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Synthesis and Reactivity of α-Diazo-β-Keto Sulfoxides: Scope and Synthetic Potential

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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

Naomi M. Buckley, B.Sc.

A Thesis Presented for the Degree of
Doctor of Philosophy
to
THE NATIONAL UNIVERSITY OF IRELAND, CORK

Department of Chemistry
University College Cork

Supervisors: Prof. Anita R. Maguire and Dr. Stuart G. Collins
Head of Department: Prof. Michael Morris

January 2013

Contents

DECLARATION BY CANDIDATE

I declare that this thesis contains my own work and has not been submitted for another degree, either at University College Cork, or elsewhere.

_____

Naomi M. Buckley

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Naomi M. Buckley

Abstract

The research described in this thesis focuses on the design and synthesis of stable α-diazosulfoxides and investigation of their reactivity under a variety of conditions (transition-metal catalysis, thermal, photochemical and microwave) with a particular emphasis on the synthesis of novel heterocyclic compounds with potential biological activity. The exclusive reaction pathway for these α-diazosulfoxides was found to be hetero-Wolff rearrangement to give α-oxosulfine intermediates.

In the first chapter, a literature review of sulfines is presented, including a discussion of naturally occurring sulfines, and an overview of the synthesis and reactivity of sulfines. The potential of sulfines in organic synthesis and recent developments in particular are highlighted.

The second chapter discusses the synthesis and reactivity of α-diazosulfoxides, building on earlier results in this research group. The synthesis of lactone-based α-diazosulfoxides and, for the first time, ketone-based benzofused and monocyclic α-diazosulfoxides is described. The reactivity of these α-diazosulfoxides is then explored under a variety of conditions, such as transition-metal catalysis, photochemical and microwave, generating labile α-oxosulfine intermediates, which are trapped using amines and dienes, in addition to the spontaneous reaction pathways which occur with α-oxosulfines in the absence of a trap. A new reaction pathway was explored with the lactone based α-oxosulfines, involving reaction with amines to generate novel 3-aminofuran-2(5*H*)-ones *via* carbophilic attack, in very good yields. The reactivity of ketone-based α-diazosulfoxides was explored for the first time, and once again, pseudo-Wolff rearrangement to the α-oxosulfines was the exclusive reaction pathway observed. The intermediacy of the α-oxosulfines was confirmed by trapping as cycloadducts, with the stereochemical features dependant on the reaction conditions. In the absence of a diene trap, a number of reaction fates from the α-oxosulfines were observed, including complete sulfinyl extrusion to give indanones, sulfur extrusion to give indanediones, and, to a lesser extent, dimerisation. The indanediones were characterised by trapping as quinoxalines, to enable full characterisation. One of the overriding outcomes of this thesis was the

provision of new insights into the behaviour of α-oxosulfines with different transition metal catalysts, and under thermal, microwave and photolysis conditions.

A series of 3-aminofuran-2(5*H*)-ones and benzofused dihydro-2*H*-thiopyran *S*-oxides were submitted for anticancer screening at the U.S. National Cancer Institute. A number of these derivatives were identified as hit compounds, with excellent cell growth inhibition. One 3-aminofuran-2(5*H*)-one derivative has been chosen for further screening.

The third chapter details the full experimental procedures, including spectroscopic and analytical data for the compounds prepared during this research. The data for the crystal structures are contained in the attached CD.

For Mum and Dad

‘The best way to have a good idea is to have lots of ideas’
Linus Pauling

Chapter 1

Introduction

Contents

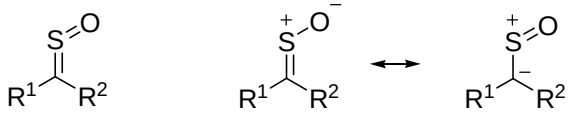
Sulfine Review

Abstract

Sulfines (thiocarbonyl *S*-oxides) are non-linear, tetravalent sulfur centred heterocumulenes. They are formally derived from sulfur dioxide, in which one oxygen atom is replaced by a carbon atom. In this review, highlights of the properties, synthesis and reactivity of sulfines are presented. The first section concerns naturally occurring sulfines, especially those occurring in the onion *(Allium cepa).* A subsequent section discusses the synthesis of sulfines, with particular focus on more recent discoveries and developments. Finally, the scope of sulfine reactivity is reviewed, including nucleophilic additions, Diels-Alder cycloadditions and decomposition. A number of reviews of sulfine chemistry have appeared in the literature, most recently by Zwanenburg.[1-4]

1.1 Introduction

The name 'sulfine' was first proposed by Sheppard and Dieckmann in 1964 to indicate the structural relationship with thiocarbonyl *S*-dioxides, known as sulfenes.[5] Sulfines are the *thio* analogues of carbonyl oxides (the intermediates in the ozonolysis of alkenes). Although the name sulfine corresponds to the non-classical structure (i) below, sulfines are alternatively viewed in terms of charge-separated resonance structures (ii) and (iii), where (ii) can be interpreted as the oxide of a thiocarbonyl compound (*cf.* both structures, Figure 1.1). Although many authors prefer the structure (i), most theoreticians do not regard the participation of sulfur d-orbitals as high, therefore the resonance structures (ii) and (iii) might actually be considered more accurate representations.[6] This resonance hybrid constitutes a 1,3-dipole.



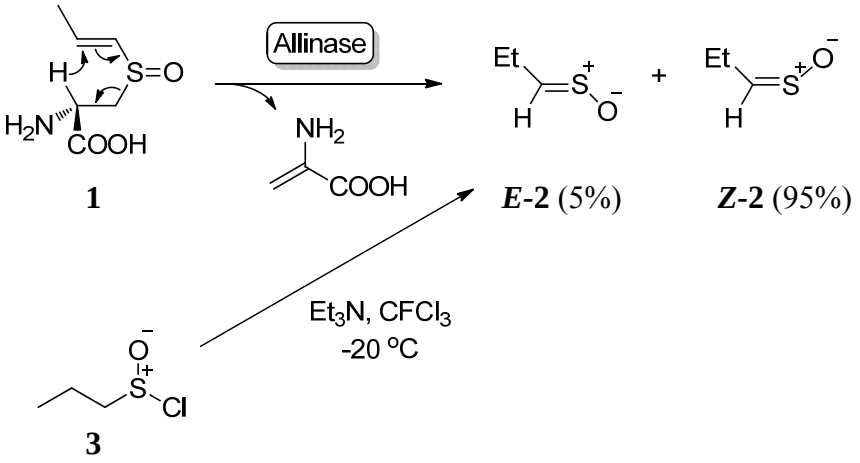
(i) (ii) (iii)

Figure 1.1

A consequence of the non-linear structure of sulfines is that they exist as geometrical isomers, provided that the substituents at the sulfine carbon are different. The non-linearity of the C=S=O system has been established by X-ray crystallography (C-S, 1.62 Å; S-O, 1.46 Å; CSO angle, 114°).[7] The S=O bond length of the sulfine is closer to that of the typical S=O double bond length of 1.43 Å, rather than the sulfoxide S-O single bond length of 1.53 Å.[8,9] The ability of most sulfines to exist as *E*- and *Z*- isomers allows for the formation of isomerically distinct products on treatment with nucleophiles and 1,3-dienes (Sections 1.4.1-1.4.3).

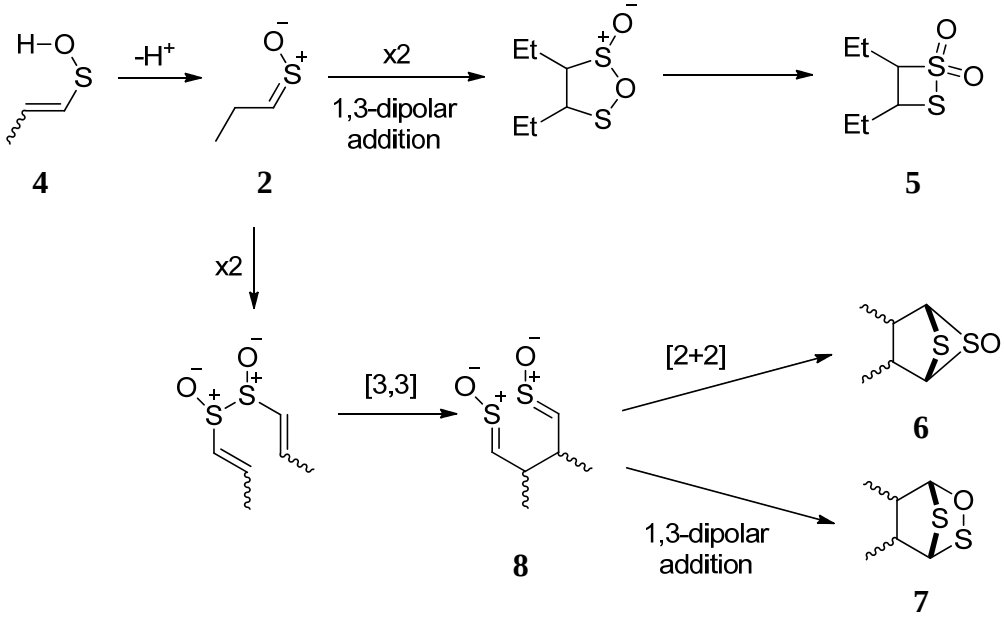
1.2 Sulfines in Nature

The interesting pathways for sulfine formation and their scope for reactivity can be illustrated by examining the few known naturally occurring sulfines. In 1961, recent advances in the understanding of organosulfur compounds of the onion (*allium cepa*) allowed Virtanen *et al.* to demonstrate that *trans*-(+)-*S*-1-propenyl-L-cysteine *S*-oxide **1** is the precursor of the principal lachrymatory factor of onions.[10] Virtanen also showed that onion allinase was the enzyme responsible for the conversion.[11] At the same time, Wilkens independently isolated and described the structure of this lachrymatory factor as the sulfine (*Z*)-propanethial *S*-oxide **2**.[12] The discovery of the first naturally occurring sulfine certainly stimulated the early development of sulfine chemistry throughout the 1960s and 70s. The biological mechanism for its formation, was provided by Brodnitz and Pascale in 1971 (Scheme 1.1). The authors also spectroscopically confirmed Wilkins' assignment by synthesising propanethial *S*-oxide **2** from dehydrochlorinating propanesulfinyl chloride **3** (Scheme 1.1).[13] Finally, the *Z*-stereochemistry was confirmed by Block *at al*.[14] Recent advances in DART-MS has also allowed the detection of naturally occurring butanethial *S*-oxide from a related plant, *allium siculum*.[15]



Scheme 1.1

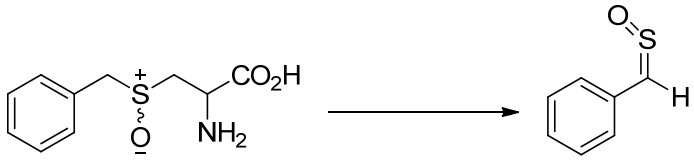
The reactivity of the labile and naturally occurring compounds 1-propenesulfenic acid **4** and (*Z*)-propanethial *S*-oxide **2** attracted the attention of Block *et al.* and led to the isolation of a number of unusual and interesting heterocyclic compounds **5-7** by the routes shown in Scheme 1.2. Notably, the sulfine *Z*,*Z*-(±)-2,3-dimethylbutanedithial *S*,*S*'-dioxide **8** is formed *via* a [3,3]-sigmatropic rearrangement.[16]



Scheme 1.2

More recently in 2003, Kubec *et al.* isolated the lachrymatory factor from the root of *Petiveria alliacea*, a perennial shrub found widely in South and Central America, as *Z*-thiobenzaldehyde *S*-oxide **9** (Figure 1.2).[17] The *E*-isomer was not

found and the mechanism of its formation remains unclear, although the authors suggest *S*-benzylcysteine sulfoxide (petiveriin) **10** as its precursor. Interestingly, the authors also reported moderate antimicrobial activity of the sulfine, which was tested against a panel of gram positive and gram negative bacteria.[17]



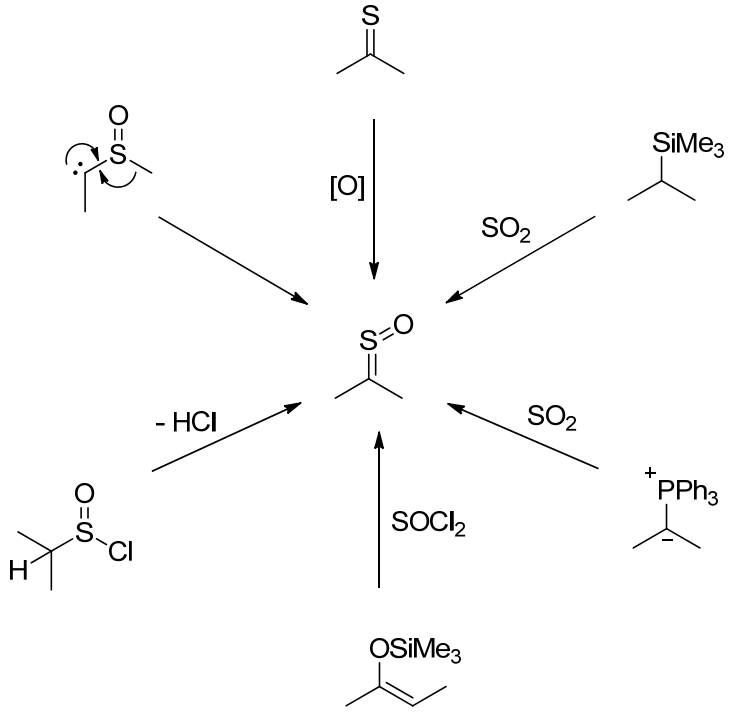
10 **9**

Figure 1.2 *Z-Thiobenzaldehyde S-oxide* ***9****, the principal lachrymatory factor of* petiveria alliacea

The lability of these compounds presumably explains the relatively few examples of naturally occurring sulfines which have been isolated to date.

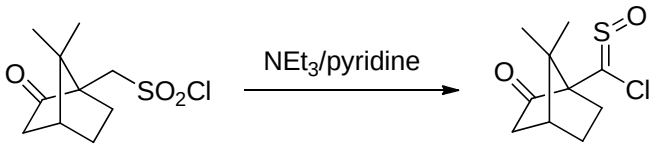
1.3 Synthesis of Sulfines

Sulfines are readily prepared using a variety of methods, some of which are illustrated in Scheme 1.3. The synthesis of sulfines has been reviewed a number of times in the literature,[1,3] most recently by Zwanenburg.[4]



Scheme 1.3

In 1923, Wedekind described the first preparation of a stable sulfine from the reaction of camphor-10-sulfonyl chloride **11** with pyridine or triethylamine to form 'chlorosulfoxid-camphor' **12** (Scheme 1.4).[18] Forty years later, King and Durst confirmed the sulfine structure using spectroscopic methods. These authors also discovered the non-linear structure of sulfines, confirming they can exist as geometrical isomers.[19]



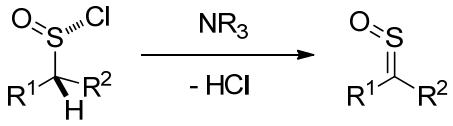
11 **12**

Scheme 1.4

The renewed interest in the chemistry of sulfines dating from the 1960's led to the development of several routes towards the synthesis of sulfines. The principal methods are discussed below.

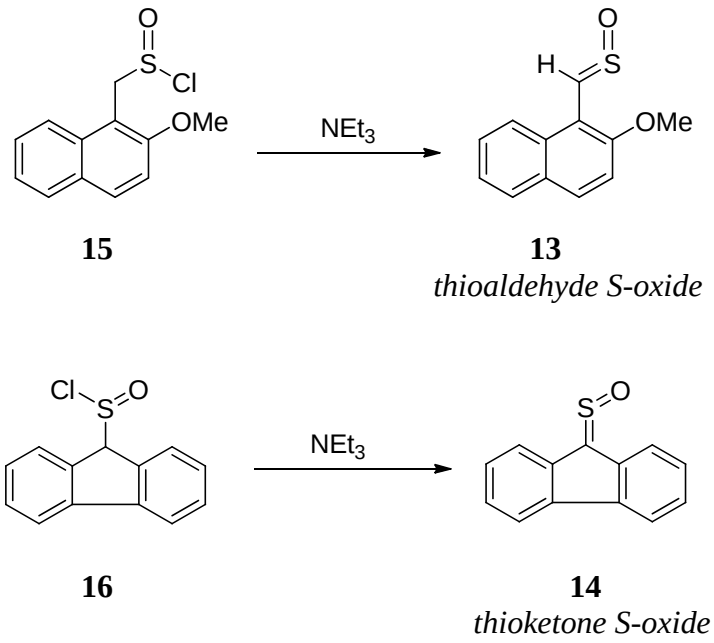
1.3.1 1,2-Dehydrohalogenation of sulfinyl halides

One of the first methods developed in the preparation of sulfines involved the elimination of hydrogen chloride from sulfinyl chlorides bearing an α-hydrogen (Scheme 1.5).



Scheme 1.5

Notably, the first thioaldehyde *S*-oxide **13** and the first thioketone *S*-oxide **14** were prepared by this method (Scheme 1.6). Zwanenburg and workers prepared the first thioaldehyde *S*-oxide **13** in 1964,[20] the same year in which Dieckmann and Sheppard prepared fluorenethione *S*-oxide **14**,[5] employing the same dehydrochlorination method.

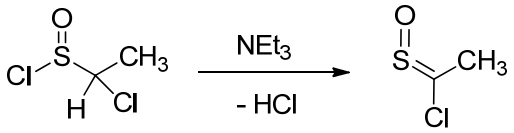


15 **13**
thioaldehyde S-oxide

16 **14**
thioketone S-oxide

Scheme 1.6

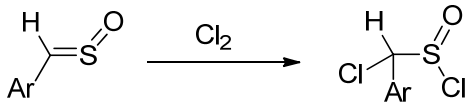
As discussed in Section 1.2 above, the lachrymatory factor of freshly cut onions, propanethial *S*-oxide **2**, has also been synthesised from dehydrochlorinating propanesulfinyl chloride **3** (Scheme 1.1).[13] This method has been especially successful in the synthesis of aliphatic sulfines,[5,21-23] as illustrated by Carpino's work with sulfinyl chlorides (Scheme 1.7).[23] However, because aromatic sulfinyl chloride precursors are more difficult to prepare, the method has not been used extensively for aromatic substituted sulfines.[5,20]



17 **18**

Scheme 1.7

Conversely, for sulfines which are too unstable for convenient handling, conversion to 2-chlorosulfinyl chlorides **19** has been used to form isolable derivatives (Scheme 1.8).[5,23,24]

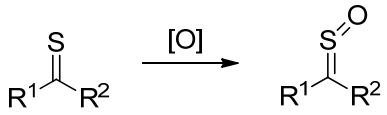


20 **19**

Scheme 1.8

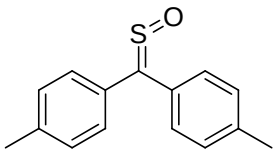
1.3.2 Oxidation of thiocarbonyl compounds

A versatile and established synthesis of sulfines involves the oxidation of thiocarbonyl compounds (Scheme 1.9). The oxidation of thiocarbonyl compounds to give sulfines has been efficiently performed using both peroxycarboxylic acids (e.g. *m*-CPBA) and milder oxidants such as dimethyl dioxirane (DMDO).[24,25,3]

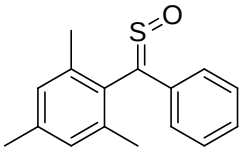


Scheme 1.9

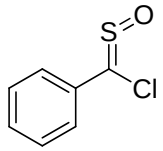
Early reports in the literature on the oxidation of thioketones to give immediate formation of the corresponding ketones initially discouraged work into the development of this method as a route towards sulfines.[26] However, following initial reports by Zwanenburg that careful treatment of fused aromatic thioketones with monoperphthalic acid gave the corresponding sulfines in excellent yields,[24,25] the oxidation method has been elaborated to a general and convenient method for the synthesis of a large variety of sulfines. Zwanenburg treated thioketones with DMDO to produce the corresponding *S*-oxides in high yield (Figure 1.3).[3] Significantly, this proved a departure from the previously held assumption that only sulfines derived from non-enethiolizable thiocarbonyls (**21**, **22**, **23**), and not sulfines derived from enethiolizable thiocarbonyl compounds (**24**, **25**, **26**), would yield sulfines on oxidation.[1,2] It has been found that the mechanism is very similar to that of the oxidation of sulfides, involving a nucleophilic attack by sulfur on the the peroxycarboxylic acid. Due to the greater polarizability of the C=S function, it was also found that thiones are about ten times as reactive towards this transformation as comparable sulfides.[24]



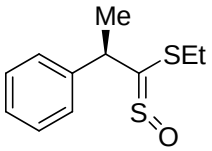
21
98%



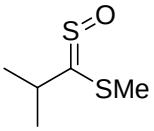
22
>98%, *E:Z* = 7:3



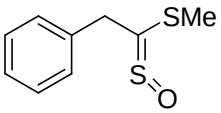
23
64%, *E:Z* = 1:1



24
>98%, *E:Z* = 1:2



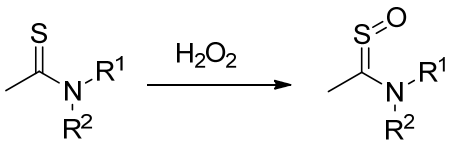
25
74%, *E:Z* = 1:1



26
>98%, *E:Z* = 1:2

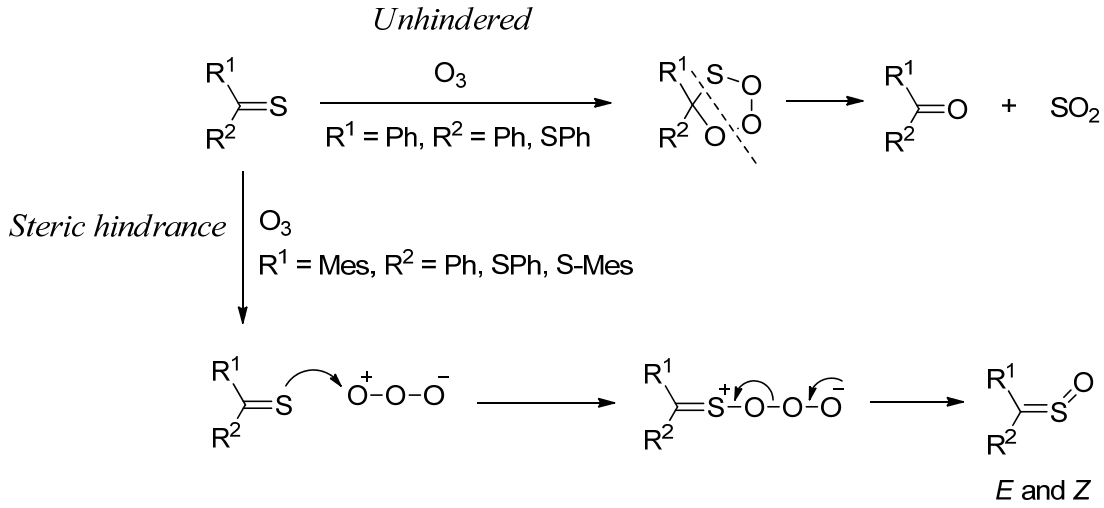
Figure 1.3

An extensive study by Walter has shown that a variety of thioamides can be converted into the corresponding *S*-oxides by oxidation with hydrogen peroxide (Scheme 1.10).[27,28] The amino function has a considerable stabilising effect on sulfines, particularly when an NH present can form a hydrogen bond with the sulfine oxygen.[27]



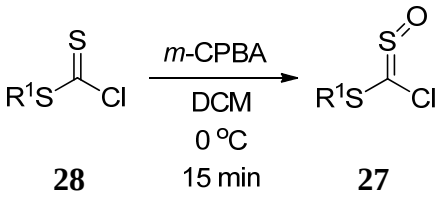
Scheme 1.10

The use of ozone as an oxidising agent for this transformation has led to interesting results. While it has been found that sterically hindered thiocarbonyl compounds successfully produced sulfines upon treatment with ozone, unhindered thiocarbonyls gave the corresponding carbonyl compounds (Scheme 1.11).[29] Zwanenburg rationalised these results by theorising that unhindered thiocarbonyls undergo cycloaddition with ozone, with subsequent loss of SO_2, to yield carbonyl compounds. However, the same cycloaddition would be much more difficult with a sterically hindered sulfine, instead resulting in nucleophilic attack of the thiocarbonyl sulfur on ozone, with elimination of molecular oxygen giving the sulfine (Scheme 1.11).[29]



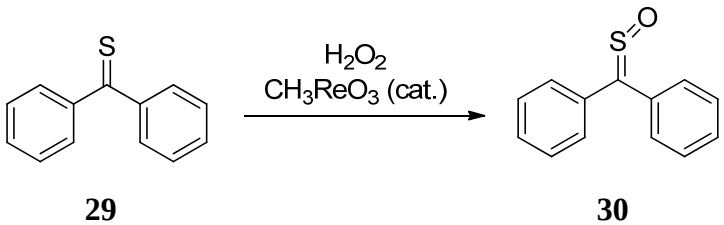
Scheme 1.11

More recently, chlorosulfines **27** were synthesised in quantitative yield by oxidation of chlorodithioformates **28** using *m*-CPBA (Scheme 1.12).[30] The oxidation was found to occur only at the thiocarbonyl sulfur and the reaction proceeded stereoselectively to produce the *Z*-isomer only. Furthermore, the sulfines were stable in aqueous conditions and could be stored for several months at room temperature without decomposition.



Scheme 1.12

A new oxidation route towards sulfines was described by Huang and Espenson, who used hydrogen peroxide and catalytic methyltrioxorhenium, CH_3ReO_3 (MTO), to oxidise thiobenzophenones **29** to their sulfines **30** (Scheme 1.13).[31]



Scheme 1.13

The chemistry of this highly effective method is summarised in Figure 1.4. The sulfine is formed by nucleophilic attack of the sulfur atom on the electron deficient oxygen atom of the peroxorhenium complexes that are the active intermediates in the reaction.

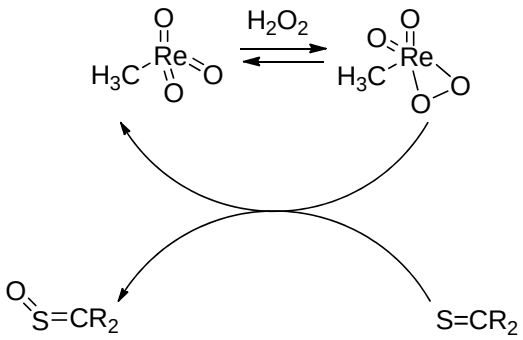
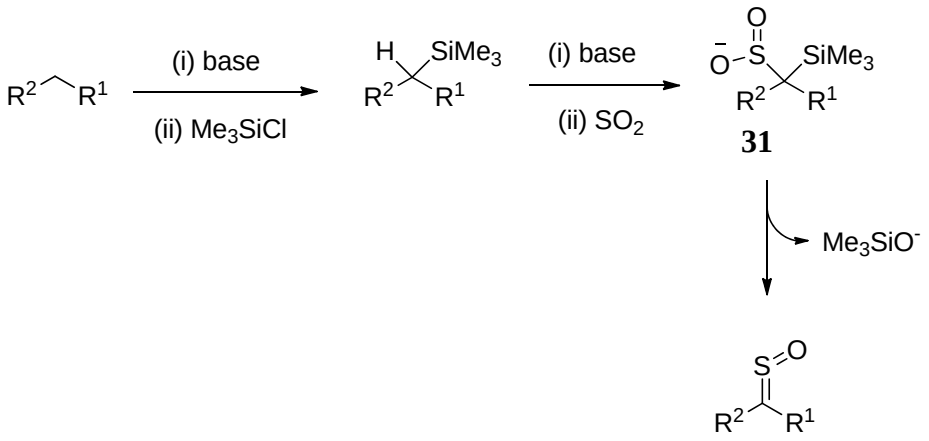


Figure 1.4

1.3.3 Alkylidenation reaction of sulfur dioxide

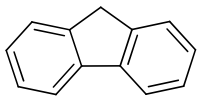
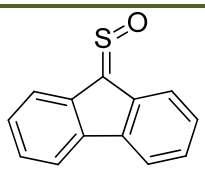
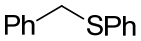
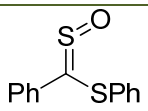
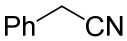
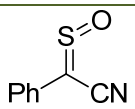
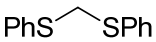
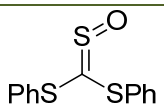
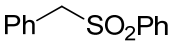
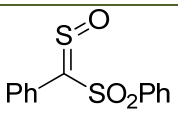
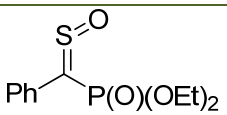
Sulfines can be considered as the alkylidene derivatives of sulfur dioxide. It was first reported by Peterson that alkylidenation of α-silyl carbanions with sulfur dioxide is an attractive route towards sulfines,[32] especially in those cases where the corresponding thiocarbonyl compounds are not available.[1,33-35] The primary formed adduct is an α-silylsulfinate **31**, which smoothly eliminates trimethylsilanolate to give the C=S bond (Scheme 1.14). This sequence can thus be referred to as a modified Peterson olefination reaction.[32]



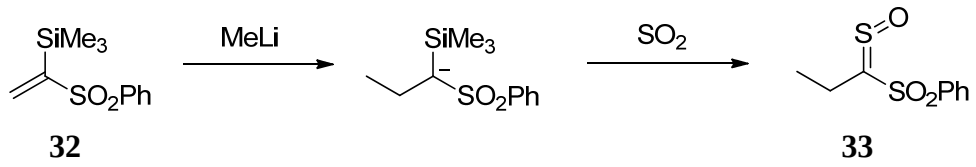
Scheme 1.14

An advantage of this route, is the ready availability of active methylene compounds for the α-silyl carbanions **31**. Because this opens up the synthesis of sulfines to substrates which are not accessible *via* the oxidation of thiocarbonyl compounds, the modified Peterson method is a powerful tool in the synthesis of a wide range of sulfines. Furthermore, the reaction can be performed without the isolation of intermediate products in a simple, one-pot procedure. The scope of the Peterson method is illustrated in Table 1.1.[33]

Table 1.1 Generation of sulfine using the Peterson method reported by Zwanenburg.[33]

Entry	Starting material	Sulfine	% Yield
1			75
2			55
3			20
4			80
5			70
6			65

An alternative method of generating α-silyl carbanions involves the β-addition of certain nucleophiles such as organolithium compounds to vinylsilanes **32**. Subsequent reaction with sulfur dioxide then gives the required sulfine **33**, such as the reaction reported by Zwanenburg and illustrated in Scheme 1.15.[33,34]

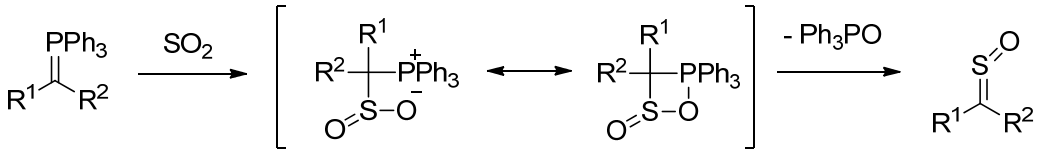


32 **33**

Scheme 1.15

Another approach involves the Wittig-alkylidenation of sulfur dioxide with phosphonium ylides. Diarylsulfines have been prepared in moderate to good yields on reaction of (diarylmethylene)triphenylphosphoranes with excess sulfur dioxide, in apolar solvents such as benzene (Table 1.2).[36]

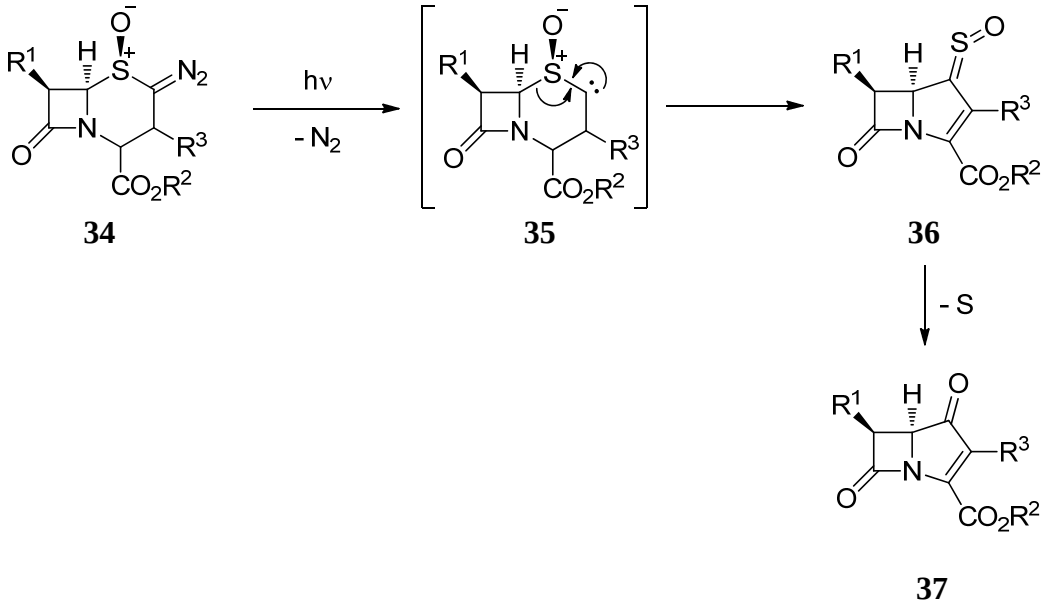
Table 1.2 Sulfines generated via Wittig-alkylidenation of sulfur dioxide with phosphonium ylides.[36]



Entry	R^1	R^2	Yield %
1	Ph	Ph	50
2	*p*-MeC_6H_4	*p*-MeC_6H_4	58
3	Ph	SPh	53

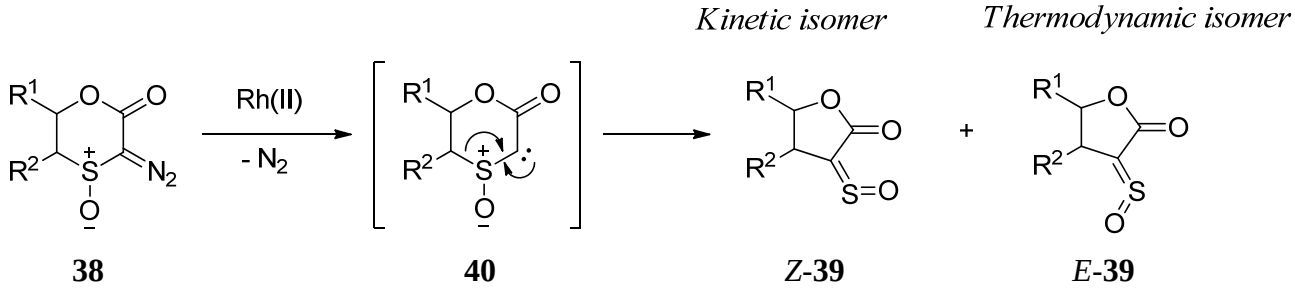
1.3.4 Rearrangement of sulfinyl carbenes

A particularly interesting method of sulfine formation involves a hetero-Wolff rearrangement of a sulfinyl carbene. Studies carried out by Rosati *et al.* on the reactivity of cephalosporinates **34** under photochemical conditions resulted in Wolff rearrangement of the carbene intermediates **35** to form the sulfines **36** (Scheme 1.16). This route was used in the formation of carbapenem products **37**.[37,38]



Scheme 1.16

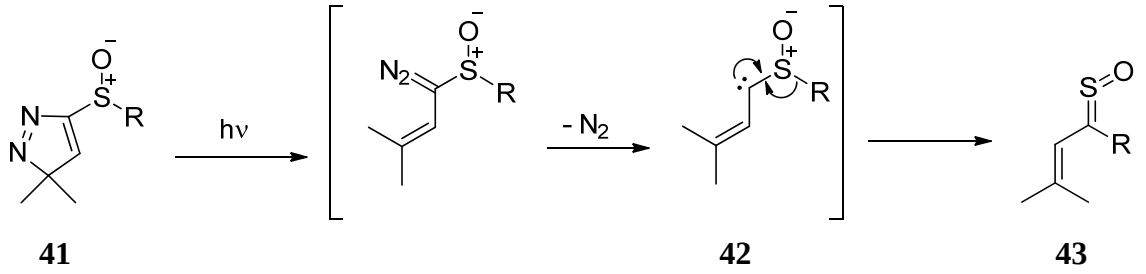
Recent reports by Maguire *et al.* have demonstrated rhodium carboxylate or carboxamide-catalysed decomposition of cyclic α-diazosulfoxide precursors **38** results in formation of both (*E*)- and (*Z*)-α-oxosulfines **39** *via* this method of ring contraction (Scheme 1.17).[39-42] The authors have also demonstrated for the first time that the *Z*-sulfine is the kinetically formed isomer, and the *E*-sulfine is the thermodynamically formed isomer (Section 1.4.3).[40-42] These α-oxosulfines have been detected in argon matrices, and in some instances, can be isolated and characterised directly from transition metal catalysed decomposition.[41,42]



Scheme 1.17

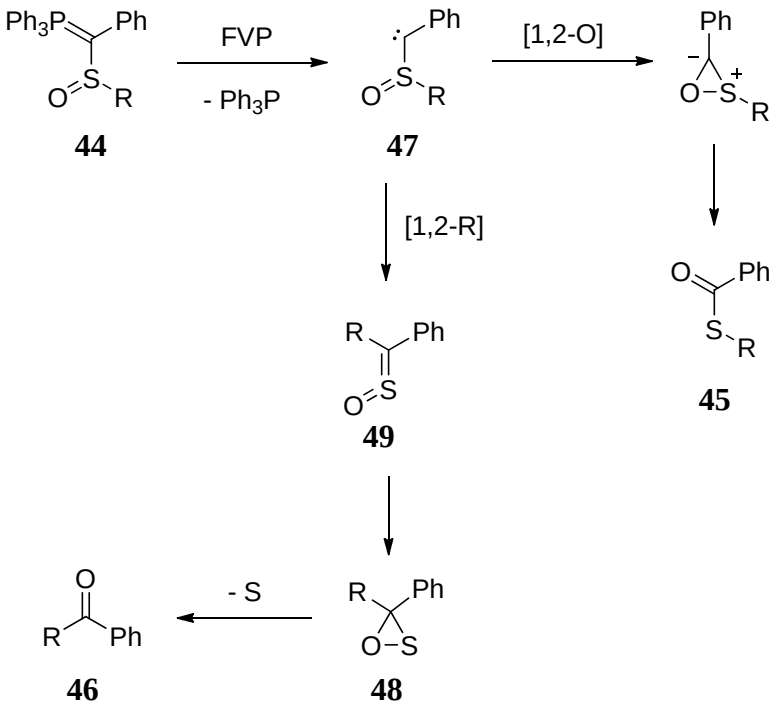
This route, while currently limited at this stage to cyclic derivatives, is a useful tool in the preparation of α-oxosulfines. Recently, efficient Wolff-rearrangement of α-diazosulfoxides to α-oxosulfines has been reported under microwave conditions in the absence of a transition metal catalyst.[40] The outcome of the transformation was very similar to the outcome under thermal conditions, with no evidence of specific microwave effects.[40]

Photolysis of sulfinyl pyrazoles **41** generated the vinylsulfinyl carbene intermediates **42** which formed the sulfines **43** (Scheme 1.18). The sulfines **43** however were reported as quite unstable compounds and readily decomposed *via* desulfurisation.[43]



Scheme 1.18

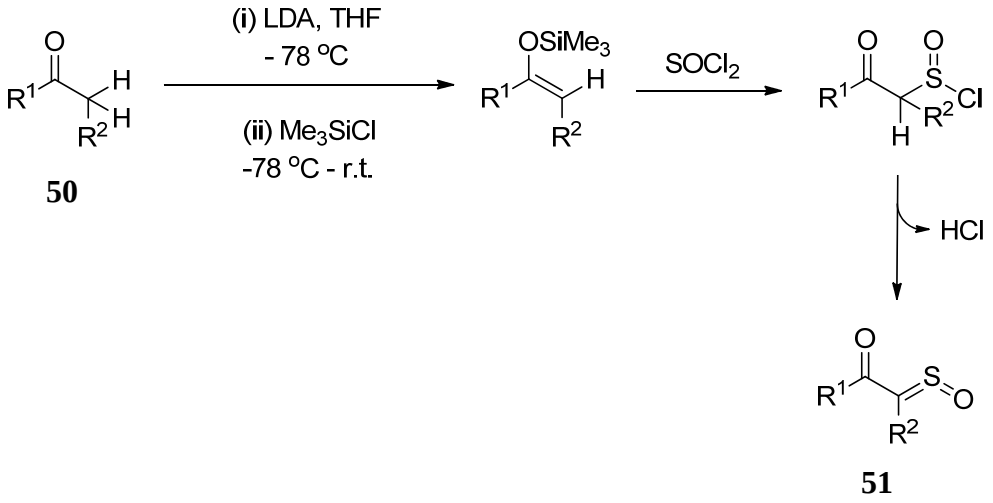
Aitken and co-workers carried out flash vacuum pyrolysis of α-sulfinyl phosphorus ylides **44** (500 °C, 10^{-2} Torr) and found that triphenylphosphine, as opposed to triphenylphosphine oxide, was mainly extruded from these compounds.[44] While formation of thioesters **45** was one of the main pathways observed, the ketones **46** were also observed. Wolff rearrangement of the sulfinyl carbenes **47** and the subsequent formation of ketones **46** was attributed to extrusion of sulfur from oxathiiranes **48** which had been formed by electrocyclisation of the sulfines **49** (Scheme 1.19).



Scheme 1.19

1.3.5 Reaction of silyl enol ethers with thionyl chloride

An efficient route towards α-oxosulfines was developed by Zwanenburg using readily available methylene ketones. A variety of silyl enol ethers have been treated with thionyl chloride to give α-oxosulfines in good yields.[45,46] As for the modified Peterson method discussed above, this route has the advantage of allowing the synthesis of sulfines from substrates which are not available for thiocarbonyl oxidation (Scheme 1.20). Notably however, the route is limited to ketones which bear an active α-methylene site.



Scheme 1.20

The range of labile α-oxosulfines which were prepared by Zwanenburg using this method are illustrated in Figure 1.5.[44,45]

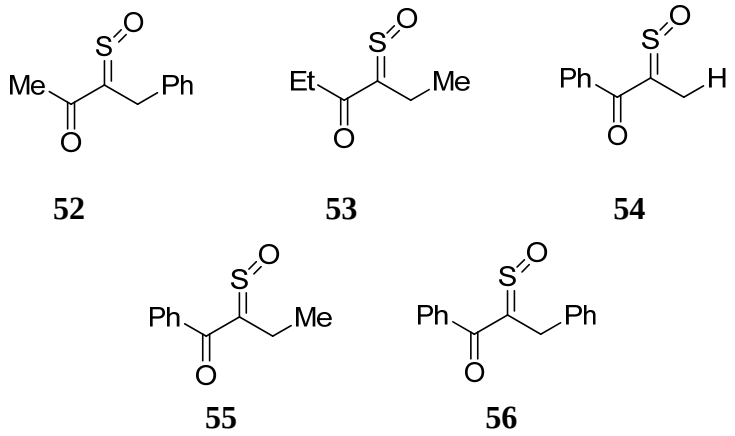


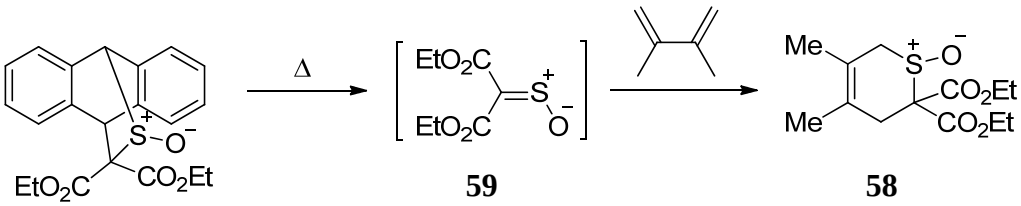
Figure 1.5

1.3.6 Miscellaneous methods

There are numerous other methods for the preparation of sulfines in the literature, some of which are isolated reports and limited in scope. A selection of some recent literature is presented below.

Retro-Diels-Alder reactions of appropriate precursors can afford sulfine products. Kirby and McGregor heated the anthracene cycloadduct **57** in the presence of 2,3-dimethyl-1,3-butadiene.[47] The isolation of cycloadduct **58** as a product of the

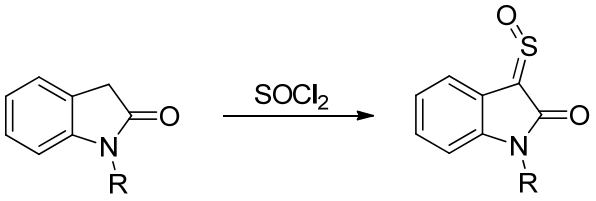
reaction provided evidence that the sulfine **59** had been formed as an intermediate by retro-Diels-Alder reaction of **57** (Scheme 1.21).



57 **59** **58**

Scheme 1.21

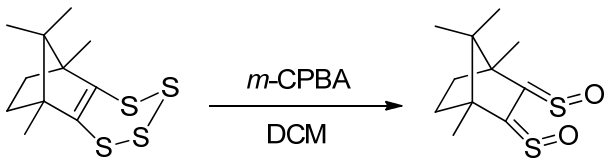
The oxindoles **60** and **61** were recently found to react readily with thionyl chloride to give the sulfines **62** and **63** in excellent yield (Scheme 1.22). Unusually, activation of the methylene group was not required.[48]



R = H **60** R = H **62** 95%
R = Me **61** R = Me **63** 78%

Scheme 1.22

An unusual class of sulfines, α-disulfines were recently prepared by treating thiocamphor derived tetrathiins, such as **64**, with *m*-CPBA (Scheme 1.23). Spectroscopic analysis indicated the α-disulfine **65** existed in the *E*,*Z*-form.[49]



64 **65**

Scheme 1.23

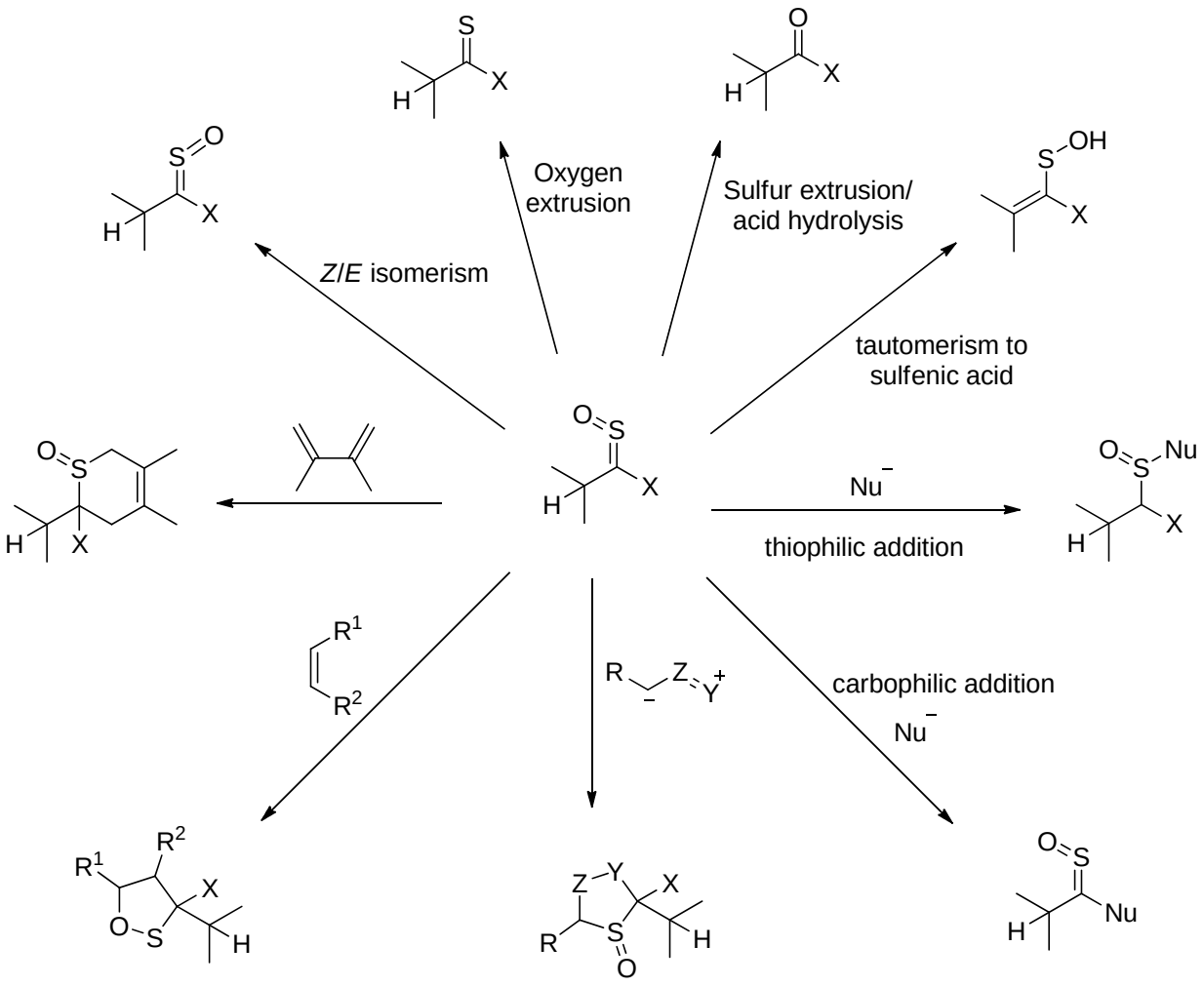
In summary, there are many routes available towards the synthesis of sulfines. Several methods have been developed which allow accessibility from a wide range of precursors. A number of important routes have been discussed,

including oxidation of thiocarbonyl compounds, 1,2-dehydrohalogenation of sulfinyl halides and alkylidenation reaction of sulfur dioxide. Some recent developments have introduced new routes towards sulfines, including retro-Diels-Alder reactions, rearrangement of sulfinyl carbenes from α-diazosulfoxides and reaction of oxindoles with thionyl chloride.

The harsh conditions of many of these routes are not compatible with the formation of labile sulfines, including α-oxosulfines. Notably however, the more recent reports of sulfinyl carbene rearrangements from α-diazosulfoxides, represent one of the mildest routes for the formation of sulfines, allowing for the generation of even labile lactone-based α-oxosulfines for the first time.[39-42]

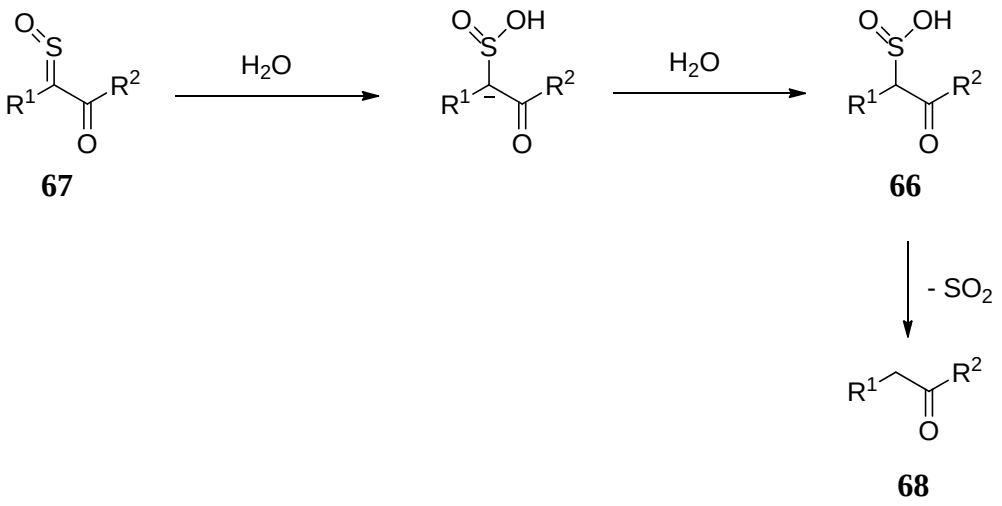
1.4 Reactivity of sulfines

The reactivity of sulfines has been reviewed in detail[1-4] and typical pathways are summarised in Scheme 1.24. Sulfines are highly reactive, very labile systems which have been used as reactive intermediates in a wide variety of transformations. The scope of sulfine reactivity includes cycloadditions, nucleophilic addition at carbon or sulfur, acid-catalysed hydrolysis of the carbonyl compound, tautomerism and isomerism. Loss of elemental sulfur is also a well-known reaction of sulfines which can take place under both thermal and photochemical conditions, *via* an oxathiirane intermediate which is formed by electrocyclisation of the sulfine (Section 1.4.5).



Scheme 1.24

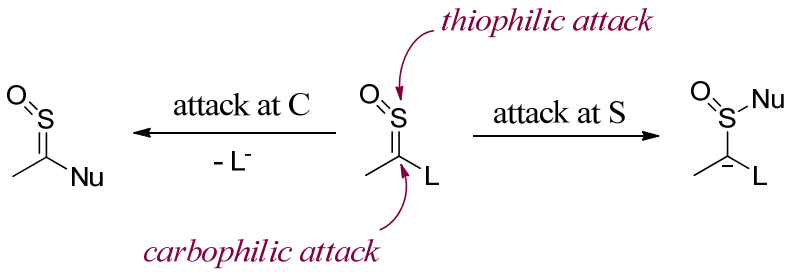
α-Oxosulfines, which bear an electron-withdrawing carbonyl group, can undergo reductive hydrolysis which results in the CSO moiety being replaced by CH_2 (Scheme 1.25).[50] The hydrolysis proceeds *via* a sulfinic acid intermediate **66**.



Scheme 1.25

1.4.1 Thiophilic additions

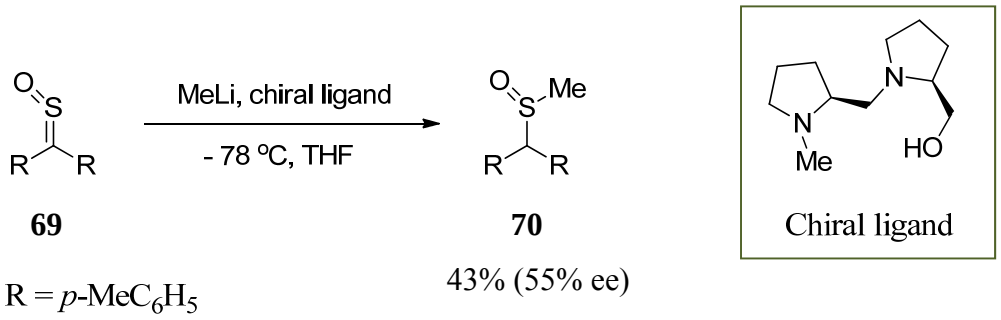
The reactivity of sulfines with nucleophiles has attracted interest because attack of the nucleophile can either occur in a thiophilic or carbophilic fashion, depending on the nature of the sulfine. Nucleophilic reactions at the partially positively charged sulfur atom are observed in quite a number of cases, as described below. Carbophilic addition with nucleophiles are less frequently encountered and appear to be generally limited to sulfines bearing a leaving group at the sulfine carbon atom. The two principal modes of addition are outlined in Scheme 1.26.



Scheme 1.26

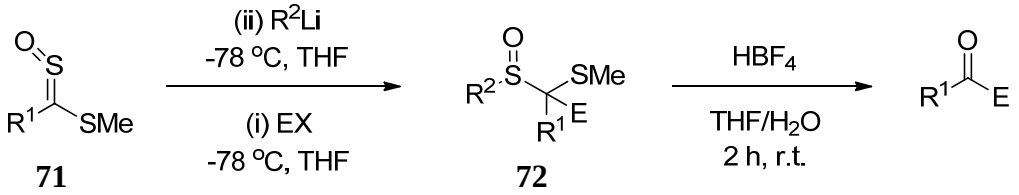
The most frequently encountered thiophilic addition in the literature is that involving alkyllithium reagents resulting in sulfoxides. The first evidence for the electrophilic character of the sulfur atom of sulfines in the reaction with organolithiums was reported by Schlessinger and Schultz.[51] A notable example of this type of reactivity is the formation of diphenylmethyl alkyl sulfoxides from

diphenylsulfine by Zwanenburg *et al.*[52] Optically active sulfoxides were also obtained when the reaction was conducted in the presence of a chiral ligand, albeit in a moderate optical yield (Scheme 1.27).



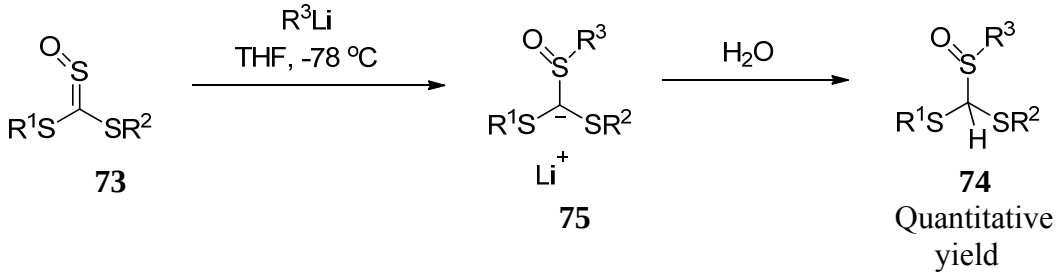
Scheme 1.27

More recently, Metzner *et al.* generated enethiolisable sulfines **71** by oxidation of dithioesters and reacted them with organolithiums (Scheme 1.28).[53-55] The reaction followed a selective thiophilic course, leading to stabilised dithioacetal oxide carbanions, which were then treated with electrophiles (H_2O, D_2O, MeI). The resulting dithioacetal oxides **72** were readily transformed into aldehydes or spontaneously to ketones, with cleavage of disulfides.



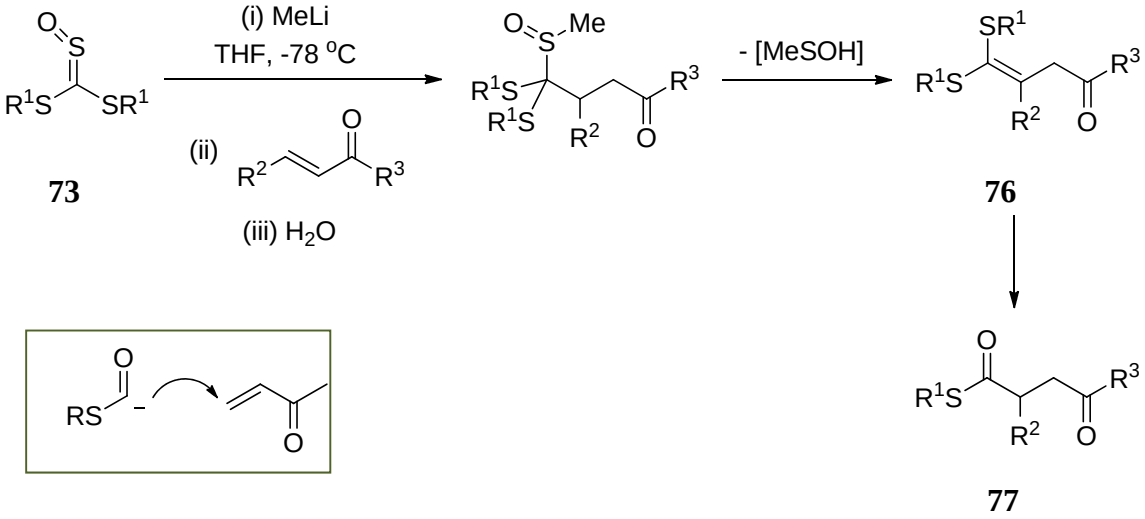
Scheme 1.28

The addition of organolithiums to trithiocarbonate oxides **73** afforded trithioorthoester oxides **74** in quantitative yield (Scheme 1.29).[56] The cryogenic reaction conditions and rapid additions demonstrated that sulfines are highly reactive towards alkyllithiums.



Scheme 1.29

The authors also treated the intermediates **75** with electrophiles other than water. 1,4-Addition with conjugated α-enones followed by elimination of methanesulfenic acid gave the β-ketone dithioacetals **76** (Scheme 1.30).[56] The ketene dithioacetal moiety was readily converted to a thiolester group, affording 1,4-dicarbonyl compounds **77**. The overall sequence allowed for the use of an alkylthiocarbonyl anion synthon for Michael addition in polarity reversal reactions. The authors were interested in the *Umpolung* aspect of this chemistry, which involved the generation of a carbanion using an addition reaction, and not a deprotonation.

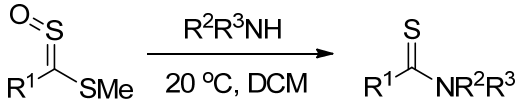


Scheme 1.30

1.4.2 Carbophilic additions

Nucleophilic attack at the sulfine carbon generally only takes place when that carbon bears a potential leaving group. Metzner *et al.* first reported carbophilic activity when sulfines were treated with amines.[57] The reaction, the sole example of carbophilic addition of a nucleophile in the absence of a leaving group, provided new access to thioamides and proceeded smoothly at room temperature (Table 1.3).

Table 1.3 Reaction of dithioester sulfines **71** with amines by Metzner[57]

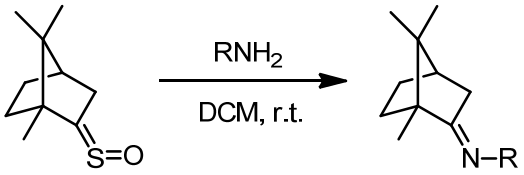


71 **78**

R^1	R^2	R^3	Time	% Yield
Pr^i	Me	H	15 min	82
Pr^i	Me	Me	15 min	56
Pr^i	Morpholino		24 h	25
Bu^i	Me	H	24 h	53
Bu^i	Me	Me	24 h	52

The authors also investigated the behaviour of a chiral sulfine **79**, derived from a thioketone, with the aim of preparing new chiral sulfinamides. However, the sulfine **79** obtained from (-)-thiochamphor, when treated with primary amines, instead gave easy access to enantiopure imines **80** with ready elimination of [HSOH], as summarised in Table 1.4.[57]

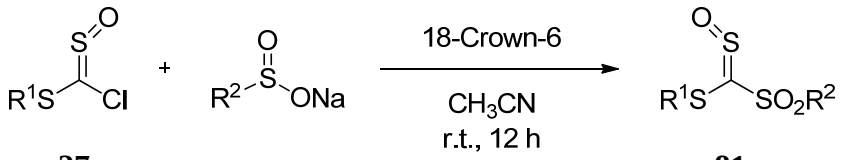
Table 1.4 Reaction of sulfine **79** with amines to give chiral imines **80**



79 **80**

R	Time	Yield %
Me	45 min	80
Et	45 min	83
n-Bu	12 h	61
^{i}Pr	48 h	70

More recently, nucleophilic reactions of arylsulfinates with chlorosulfines **27** have been investigated and have been revealed to proceed with complete inversion of stereochemistry (Scheme 1.31).[30] The route represents ready access to substituted sulfonylsulfines **81**.

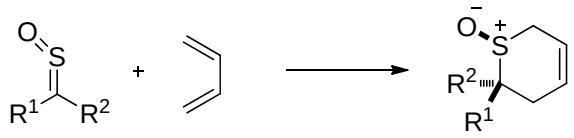


27 **81**

Scheme 1.31

1.4.3 [4+2] Cycloadditions

[4+2] Cycloadditions are an important transformation of sulfines and unstable sulfines are often formed in the presence of a diene in order to isolate the corresponding cycloadduct. The Diels-Alder cycloaddition with 1,3-dienes is a well-documented reaction,[1-3] which generally proceeds with retention of the sulfine stereochemistry in the cycloadduct **82** (Scheme 1.32).

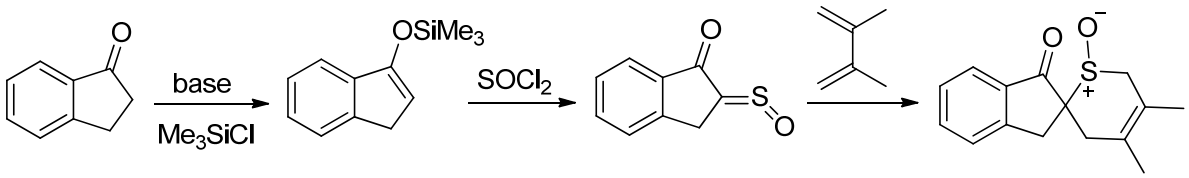


82

Scheme 1.32

The dienophilicity of sulfines is dependent on their substituents. Electron withdrawing substituents enhance reactivity, while sterically bulky groups have a strong retarding effect. Hence, α-oxosulfines rapidly undergo cycloaddition. For less reactive sulfines, Lewis acid catalysts have been shown to enhance reaction rate considerably, especially $SnCl_4$.[45] The cycloadducts derived from these reactions, dihydro-2*H*-thiopyran *S*-oxides **82**, are of synthetic value and can be used as precursors for the synthesis of bioactive compounds.[58-61]

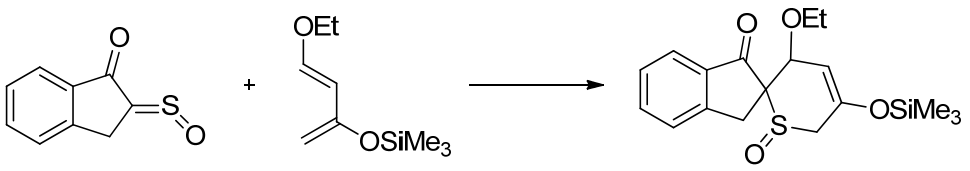
The group of Zwanenburg has undertaken considerable research in this area. The α-oxosulfine **83** was prepared from 1-trimethylsilyloxy-1-indene **84** and treated with 1,3-dimethyl-2,3-butadiene in a Diels-Alder fashion to form the dihydro-2*H*-thiopyran *S*-oxide **85** in good yield (Scheme 1.33). The issue of potential formation of diastereomers was not mentioned in this early report.[46] The reaction also proceeded smoothly in a one-pot procedure.



84 **83** **85**
75%

Scheme 1.33

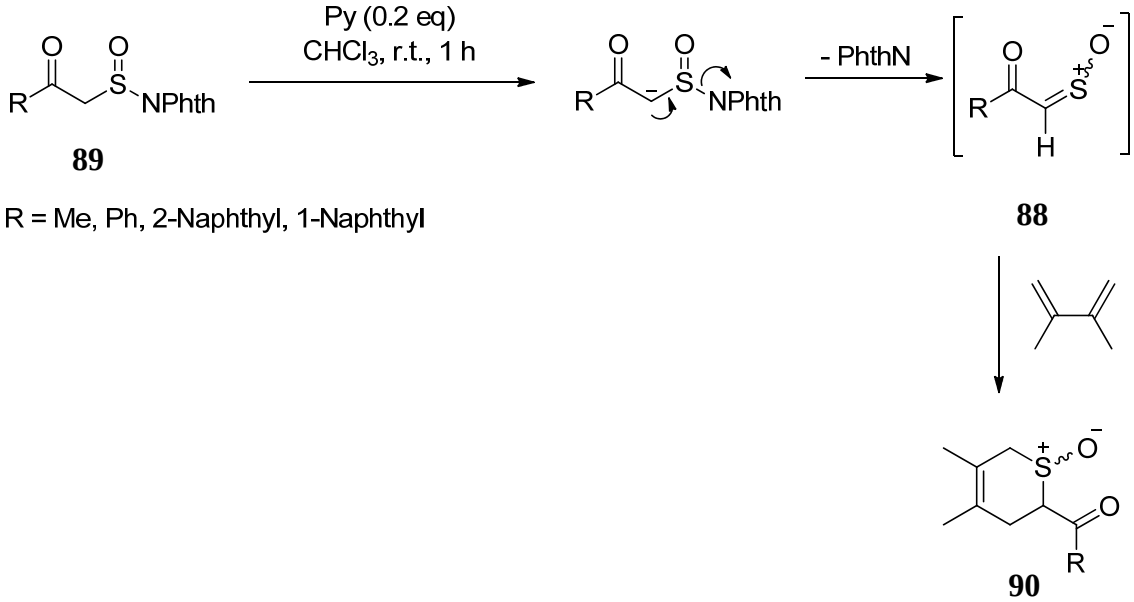
Rewinkel and Zwanenburg reported a regioselective cycloaddition of α-oxosulfine **83** and 1-ethoxy-3-trimethylsilyloxy-1,3-butadiene **86** with the cycloadduct **87** formed as the major product (Scheme 1.34).[62] Analysis of the reaction in terms of the HOMO/LUMO energy gap between both π systems allowed the authors to propose that the substituents on the sulfine have a strong effect on the regiochemistry of the Diels-Alder reaction.



83 **86** **87**

Scheme 1.34

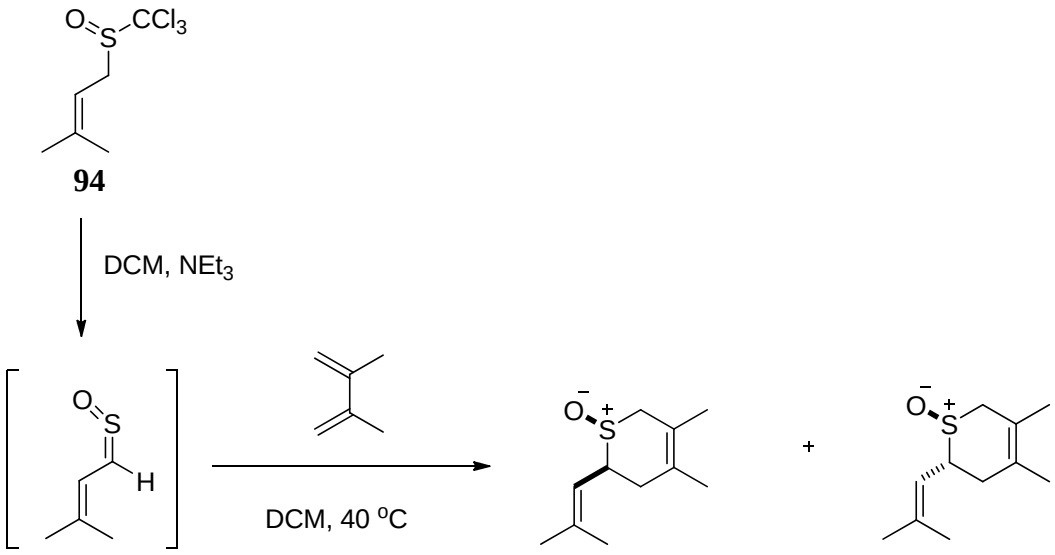
Labile α-oxothioaldehyde *S*-oxide intermediates **88** have also been efficiently trapped as electron-poor dienophiles.[63] Deprotonation of *N*-phthalimidesulfinamides **89**, followed by 1,2-elimination at sulfur gave the transient sulfines **88** which were trapped as the stable cycloadducts **90** under mild conditions and in good yields (Scheme 1.35).



89 **88** **90**

Scheme 1.35

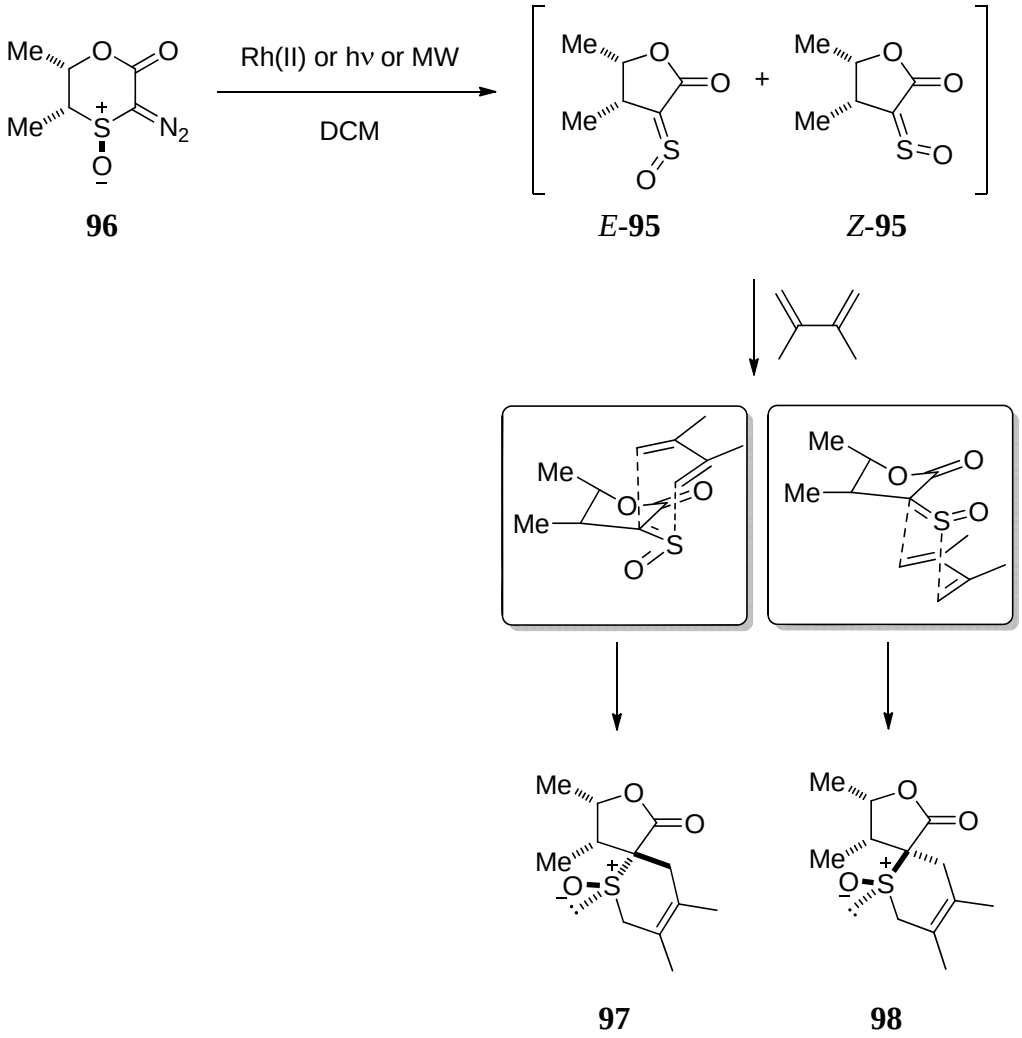
As previously discussed, the stereochemistry of the sulfine is generally retained in the cycloadduct. However, mixtures of diastereomers are sometimes formed and this can be rationalised through rapid thermal isomerism of the *Z*-sulfine to the *E*-sulfine prior to cycloaddition. Bonini and workers initially reported the rapid intramolecular conversion of **91**,[64] with further work by Braverman and Gottlieb giving a mixture of two diastereomeric cycloadducts **92** and **93** (1:4.5) from the conjugated vinyl *Z*-sulfine **91**, which was generated *in situ* from the sulfoxide **94** (Scheme 1.36).[65]



Scheme 1.36

The authors ruled out the possibility of epimerisation in the presence of base after cycloaddition by performing a control experiment where each pure diastereomer **92** and **93** was independently subjected to the initial reaction conditions. No further reaction was observed, demonstrating that the stereochemistry is established prior to, and not after, cyclisation.[65]

Work within the group of Maguire has demonstrated that sulfine interconversion occurs, with *Z*-sulfines as the kinetically formed isomers, and *E*-sulfines as the thermodynamically formed isomers. This has been confirmed by undertaking cycloaddition reactions of sulfines *E*-**95** and *Z*-**95** generated from the α-diazosulfoxide **96** under various reaction conditions (Scheme 1.37).[39-42] Notably, these cycloadducts can also be formed under microwave and photochemical conditions, in the absence of a transition-metal catalyst, with the stereochemical outcome of the sulfines *E*-**95** and *Z*-**95** sensitive to the reaction conditions employed.



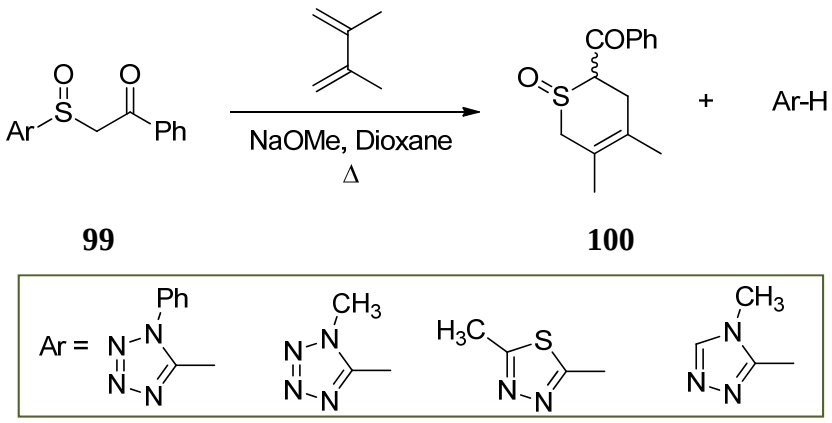
MW:	1	:	5
$Rh_2(OAc)_4$:	1	:	3.5
hν:	1	:	1.6

Scheme 1.37

The rationale for the stereoselectivity is that with efficient *in situ* diene trapping, the principal cycloadduct **98** is derived from approach of the diene from below to the *Z*-isomer of the α-oxosulfine **95**, which is the initially formed kinetic product of the Wolff rearrangement. In the absence of a diene trap, the (*Z*)-oxosulfine **95** isomerises to the more thermodynamically stable (*E*)-oxosulfine **95** over time (<10 min).[40] Direct evidence for this was obtained by initially forming the (*E*)-oxosulfine **95** as a single product from the α-diazosulfoxide **96**. *E*-**95** was subsequently reacted with 2,3-dimethyl-1,3-butadiene to generate the cycloadduct **97**

derived from approach of the diene from above to the *E*-isomer, thus confirming the α-oxosulfine interconversion.[40]

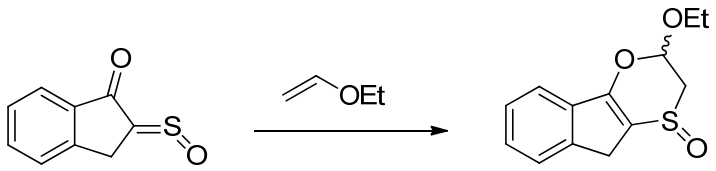
Thermolysis of sulfoxides **99** bearing heterocycles such as thiadiazoles, triazoles and tetrazoles in the presence of 2,3-dimethyl-1,3-butadiene in dioxane has led to efficient trapping of transient sulfine intermediates as 6-substituted-5,6-dihydro-3,4-dimethyl-2*H*-thiapyran *S*-oxides **100** (Scheme 1.38).[66]



99 **100**

Scheme 1.38

Interestingly, it has also been demonstrated that α-oxosulfines can behave as the 4π unit in Diels-Alder cycloadditions. The α-oxosulfine **83** was employed as an electron-poor diene in an inverse electron demand Diels-Alder reaction by Zwanenburg (Scheme 1.39).[46]

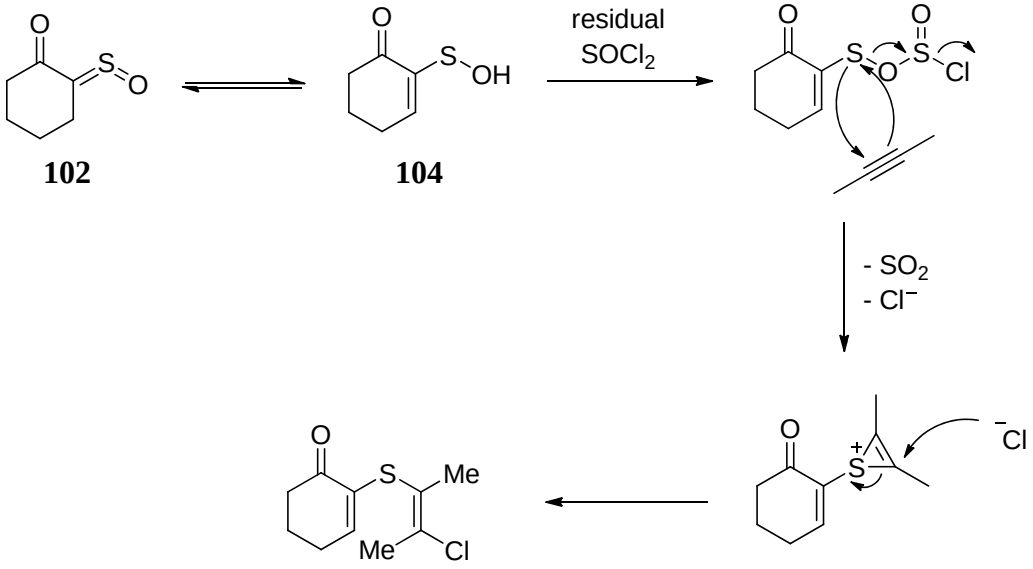


83 **101**

Scheme 1.39

Still and Wilson also attempted Diels-Alder cycloadditions where the α-oxosulfine **102** was used as a heterodiene in a reaction with dienophiles. The α-oxosulfine **102** was initially prepared from a silyl enol ether with thionyl chloride.[67] However, when the α-oxosulfine **102** was treated with several alkenes and alkynes as dienophiles, the products formed did not exhibit the expected spectral

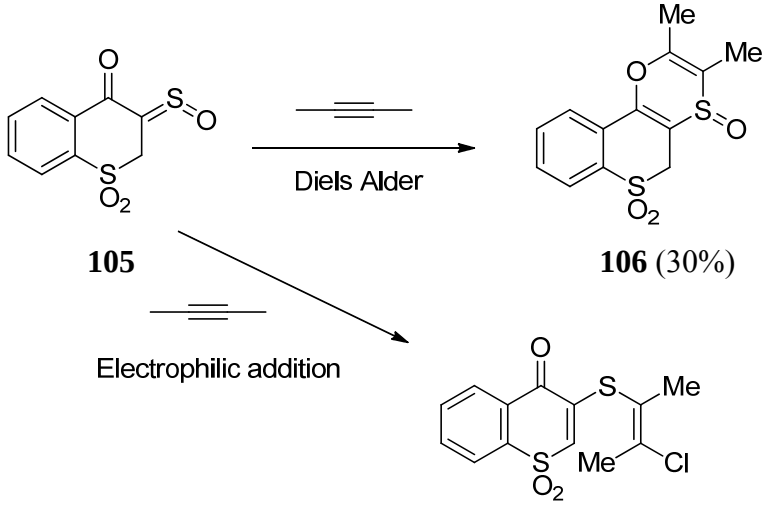
characteristics for the Diels-Alder products (Scheme 1.40). X-Ray crystallographic analysis revealed that **103** was an electrophilic addition product, which formed *via* the sulfenic acid tautomer **104** in the presence of residual thionyl chloride.



102 **104** **103**

Scheme 1.40

Subsequent investigations by the authors with the α-oxosulfine **105** resulted in the formation of the Diels-Alder product **106**, accompanied by the electrophilic addition product **107**, albeit in lesser yields (Scheme 1.41).[68]



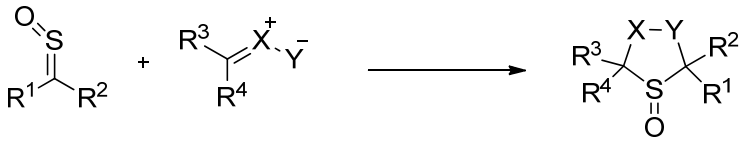
105 **106** (30%)

107 (14%)

Scheme 1.41

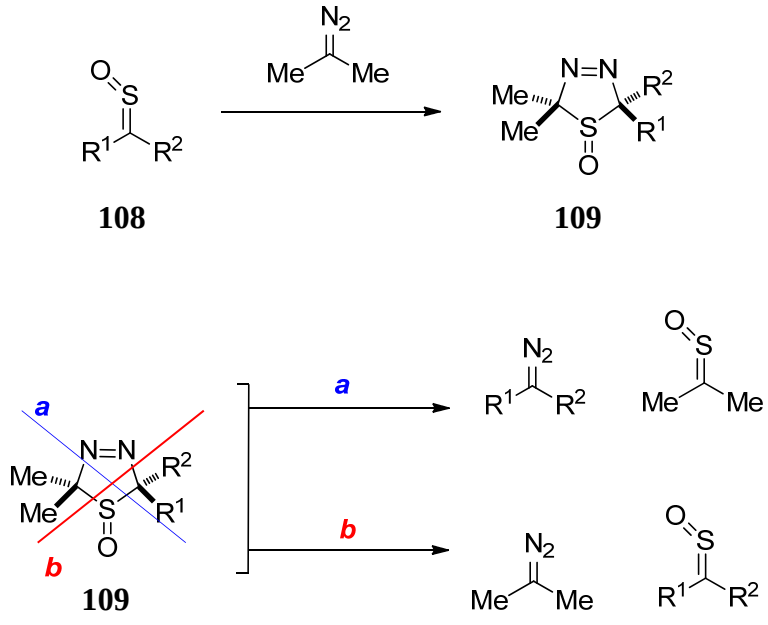
1.4.4 1,3-Dipolar [3+2] Cycloadditions

Sulfines are known to participate in 1,3-dipolar cycloadditions, usually as dipolarophiles (Scheme 1.42). Again, the stereochemistry of the sulfine is retained in the cycloadduct.



Scheme 1.42

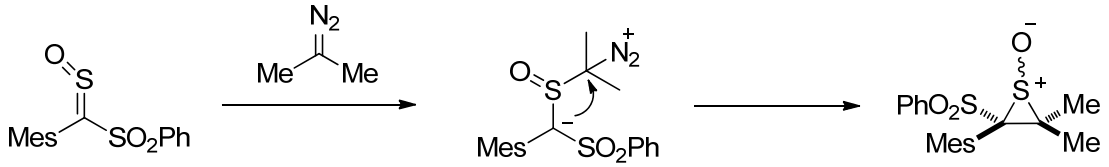
Considerable attention has been given to reactions of sulfines with diazo compounds. In particular, 1,3-dipolar cycloadditions of 2-diazopropane with aryl sulfines **108** has been studied to give thiadiazoline adducts **109** in a regio- and stereospecific manner (Scheme 1.43).[69] Diazomethane was found to react much more sluggishly with sulfines than 2-diazopropane. However, the cycloadducts **109** were thermally unstable, with slow decomposition occurring even below 0 °C. In solution, cycloreversion reactions were observed, with two modes of ring cleavage possible, as illustrated in Scheme 1.43.[69]



Scheme 1.43

Interestingly, sulfines with sterically demanding substituents, for example, *Z*-mesityl phenylsulfonyl sulfine **110**, react with 2-diazopropane to give the

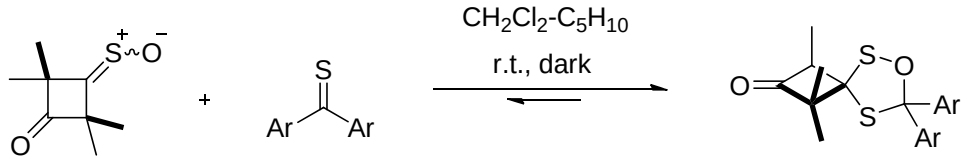
episulfoxides **111** as a mixture of diastereomers in a non-concerted reaction *via* a zwitterionic intermediate **112** (Scheme 1.44).[70] The bulky substituents hamper the 1,3-dipolar cycloaddition reaction to form a five-membered ring.



110 **112** **111**

Scheme 1.44

Evidence of sulfines behaving as 1,3-dipoles in dipolar cycloadditions was not obtained until the 1990's, when the first unequivocal 1,3-dipolar cycloaddition of sulfines were reported by Huisgen and co-workers.[71] They found that the oxadithiolane **113** was formed when a thioketone **114**, which they regard as a 'superpolarophile', was treated with the sulfine **115**, thereby causing the sulfine to deviate from its usual behaviour (Scheme 1.45).

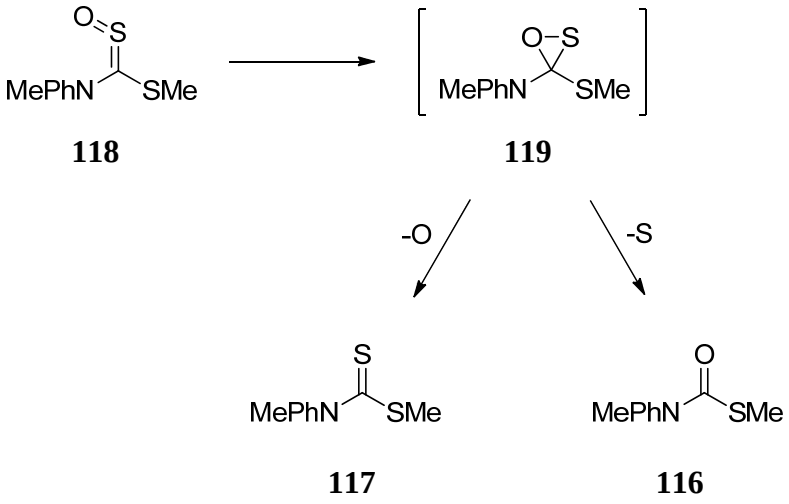


115 **114** **113**

Scheme 1.45

1.4.5 Rearrangements

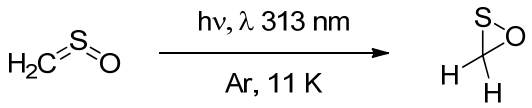
A characteristic behaviour of many sulfines is loss of elemental sulfur to give ketones under thermal and photolytic conditions.[51,72-75] Deoxygenation of sulfines has also been reported in the literature.[24,75,76] The proposed mechanism involves rearrangement to an oxathiirane intermediate, as illustrated in the example provided in Scheme 1.46, reported by Metzner.[75] The thiocarbamate **116** was generated by extrusion of sulfur from the oxathiirane ring, while the dithiocarbamate **117** was formed *via* extrusion of oxygen.



118 **119** **117** **116**

Scheme 1.46

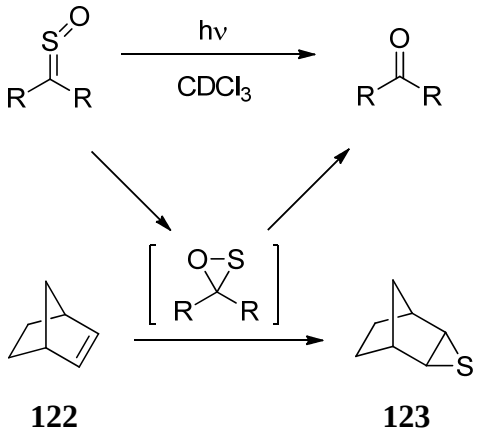
Oxathiiranes are unstable species which have been invoked as reactive intermediates in a variety of sulfine transformations. The electrocyclisation of sulfines to oxathiiranes has been widely reported.[2,77] Oxathiiranes have proven elusive intermediates, and the photochemical generation and matrix isolation of the first experimentally observable oxathiirane **120** from thioformaldehyde *S*-oxide **121** was only recently reported by Schreiner *at al*. (Scheme 1.47).[78]



121 **120**

Scheme 1.47

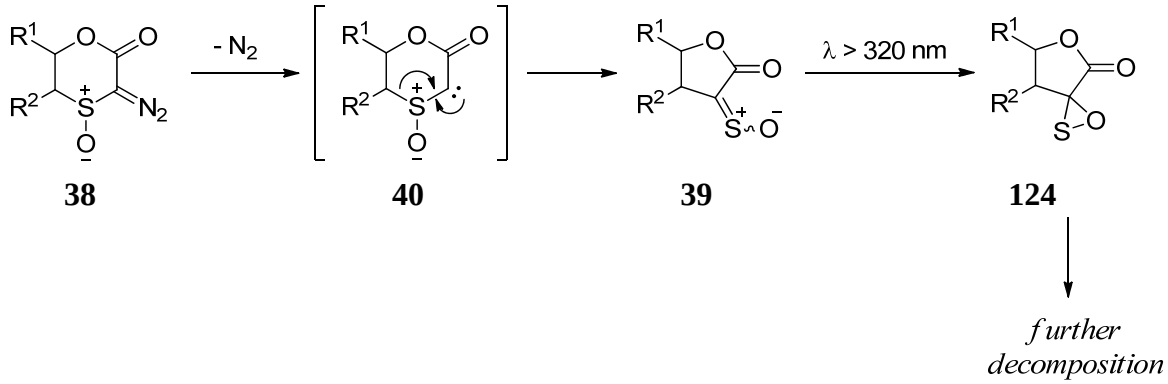
Adam *et al.* reported that oxathiiranes can be used as highly stereoselective sulfur-transferring agents and successfully employed oxathiiranes generated by the photolysis of sulfines to thioepoxidise strained cyclic alkenes **122** (Scheme 1.48).[79] Enhanced sulfur transfer efficiency was observed when planar fluorene- and xanthene-derived sulfines were used for the transformation.



122 **123**

Scheme 1.48

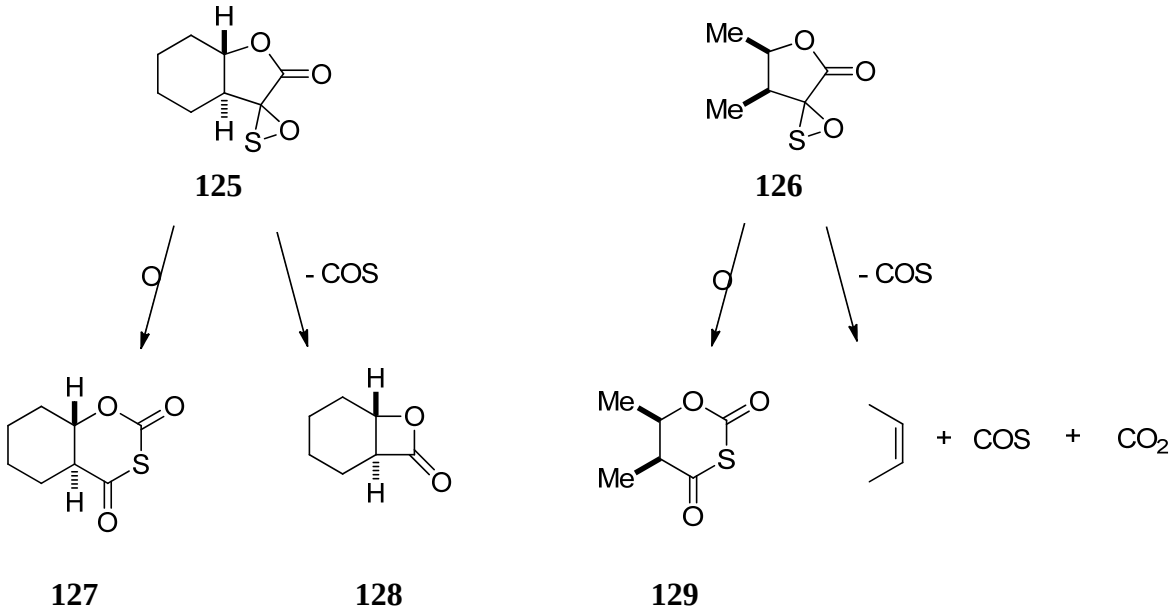
The photochemistry of α-diazosulfoxides **38** in solid argon at 10 K by IR and UV/Vis spectroscopy has been investigated within the groups of Maguire and Sander and definitively confirmed the intermediacy of α-oxosulfine intermediates **39**.[41,42] Photochemically induced hetero-Wolff rearrangement of sulfinyl carbenes **40** gave α-oxosulfines **39** (Scheme 1.49). Irradiation at λ > 320 nm resulted in decomposition of the α-oxosulfines **39** *via* oxathiirane intermediates **124**.



38 **40** **39** **124**

Scheme 1.49

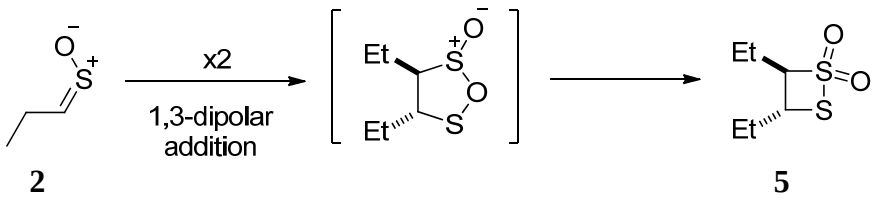
The matrix-isolated species shown in Scheme 1.50, formed by photochemically induced rearrangement of these oxathiiranes **125** and **126**, were identified by the authors by comparison of experimental and calculated IR spectra, providing excellent insight into the nature of sulfine decomposition under cryogenic conditions.[41,42]



Scheme 1.50

1.4.6 Sulfine dimerisation

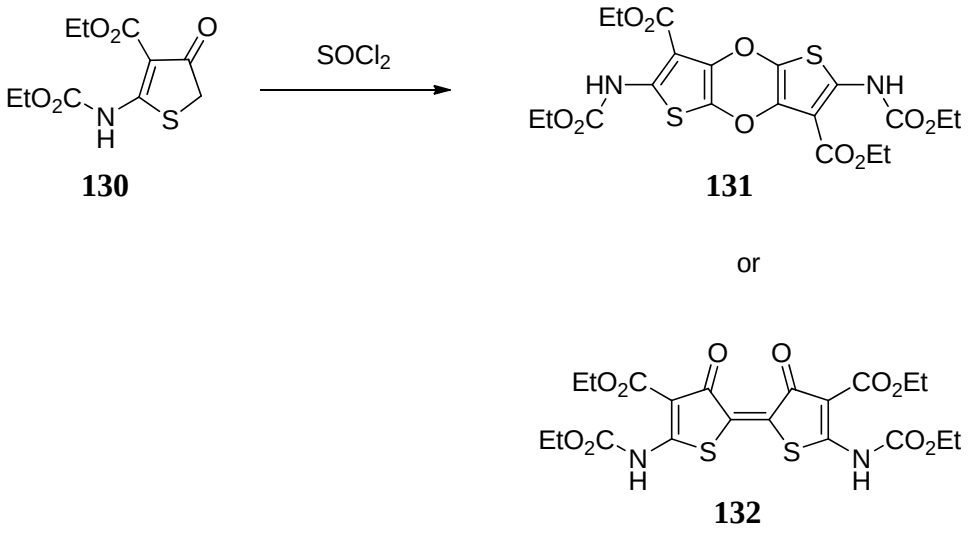
The dimerisation of sulfines to give 1,3-dithietane *S*-oxides was initially suggested by Wilkens,[12] who reported that onion lachrymatory factor **2** dimerised to give 2,4-diethyl-1,3-dithietane-1,3-dioxide **5** (Section 1.2). Block subsequently investigated the dimerisation in more detail and found that the product was, in fact, a 1,2-dithietane which was formed by a cycloaddition of the sulfine **2**, acting both as a 1,3-dipole and dipolarophile, followed by rearrangement of the unstable cyclic sulfenyl sulfinate ester (Scheme 1.51).[14]



Scheme 1.51

Notably, when Faull and Hull reacted a dihydrothiophene **130** with thionyl chloride in an attempt to generate the sulfine, they isolated the unexpected products **131** or **132** (Scheme 1.52).[80] The authors suspected oxidative condensation of **130** to give either the dioxane **131** or the alkene dimer **132**. Zwanenburg later confirmed

that a sulfine is indeed formed as an unstable intermediate by carrying out the reaction in the presence of 2,3-dimethyl-1,3-butadiene.[81]



130 **131**

132

Scheme 1.52

1.5 Conclusion

Sulfines are very interesting intermediates, both structurally and from a reactivity perspective. Furthermore, their non-linear structure and their ability to exist as two isomers mean that they are synthetically useful compounds for stereoselective synthesis. Notably, the high reactivity generally associated with sulfines presents a challenge to both successfully control and exploit the potential of these compounds as reactive intermediates.

From the 1970s, the group of Zwanenburg has led the development in this field, with significant contributions by the groups of Metzner, Capozzi and Block in more recent years. Most recently, work within the group of Maguire has demonstrated that *Z-E* sulfine intraconversion can be flexibly exploited in diastereoselective cycloaddition reactions, in addition to a new synthetic route to α-oxosulfines involving mild neutral condition, thus introducing fresh possibilities in the reactivity of sulfines in organic synthesis.

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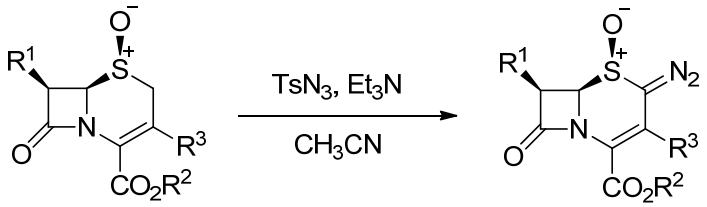
Chapter 2

Results and Discussion

Contents

2.1 Background

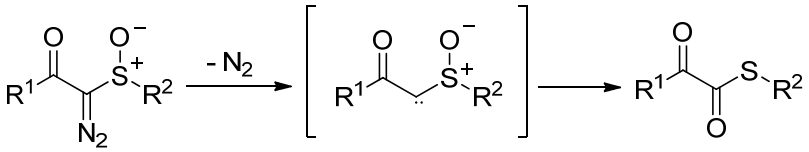
Work within our group began on the synthesis and reactivity of α-diazosulfoxides in the early 1990's by Maguire and Kelleher. Prior to this, the only stable α-diazosulfoxides which had been isolated were the cephalosporin derviatives **1**, by the groups of Campbell[1,2] and Rosati[3], with the general structure as depicted in Scheme 2.1. While diazo transfer to the (*R*)-sulfoxides was found to be unsuccessful, the (*R*)-diazosulfoxides were isolated. The authors suggested that this was due to steric effects. However, neither group commented on the significance of these compounds as the only examples of stable α-diazosulfoxides in the literature.



1

Scheme 2.1

Other isolated reports described α-diazosulfoxides as unstable intermediates.[4,5] Hodson and Holt[23] attempted diazo transfer to β-keto sulfoxides. However, they were only able to isolate the thiol esters **2**. They suggested a decomposition mechanism involving oxygen transfer from sulfur to the carbene centre of **3**, subsequent to, or concerted with, the loss of nitrogen, as illustrated in Scheme 2.2.

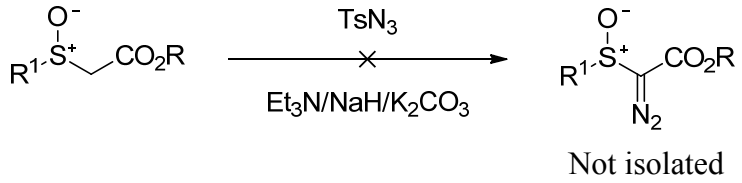


4 **3** **2**

Scheme 2.2

Workers within this group have proposed two factors which lead to the unusual stability of the α-diazosulfoxide derivatives **1**.[6] Firstly, the vinylic conjugation to the ester group in these compounds may lend stability to these diazo compounds. The compounds that had previously been explored were derived from ketones[4] and sulfinyl chlorides.[5] A second, and more plausible, reason is that the

rigid fused bicyclic system could be envisaged to provide kinetic stability to the compounds by reduced conformational mobility, thus reducing the possibility of spontaneous diazo decomposition by the proposed oxygen transfer mechanism. Both proposals were investigated. While it was envisaged that the ester conjugation was unlikely to provide an increase in stability that was sufficient to rationalize the isolation of these compounds, a preliminary exploration of diazo transfer to acyclic α-sulfinyl esters was undertaken without success (Scheme 2.3).[6]



Scheme 2.3

To explore the second hypothesis that conformational restriction was essential for the stability of the cephalosporin based α-diazosulfoxides **1**, a series of bicyclic and monocyclic sulfoxide lactones were designed and synthesised. It was found that successful diazo transfer to these systems could indeed be effected (Figure 2.1), thus confirming the second proposal. While the majority of α-diazosulfoxides synthesised to date have been lactone derivatives, Collins also successfully generated a series of lactam α-diazosulfoxides (Scheme 2.4).[7]

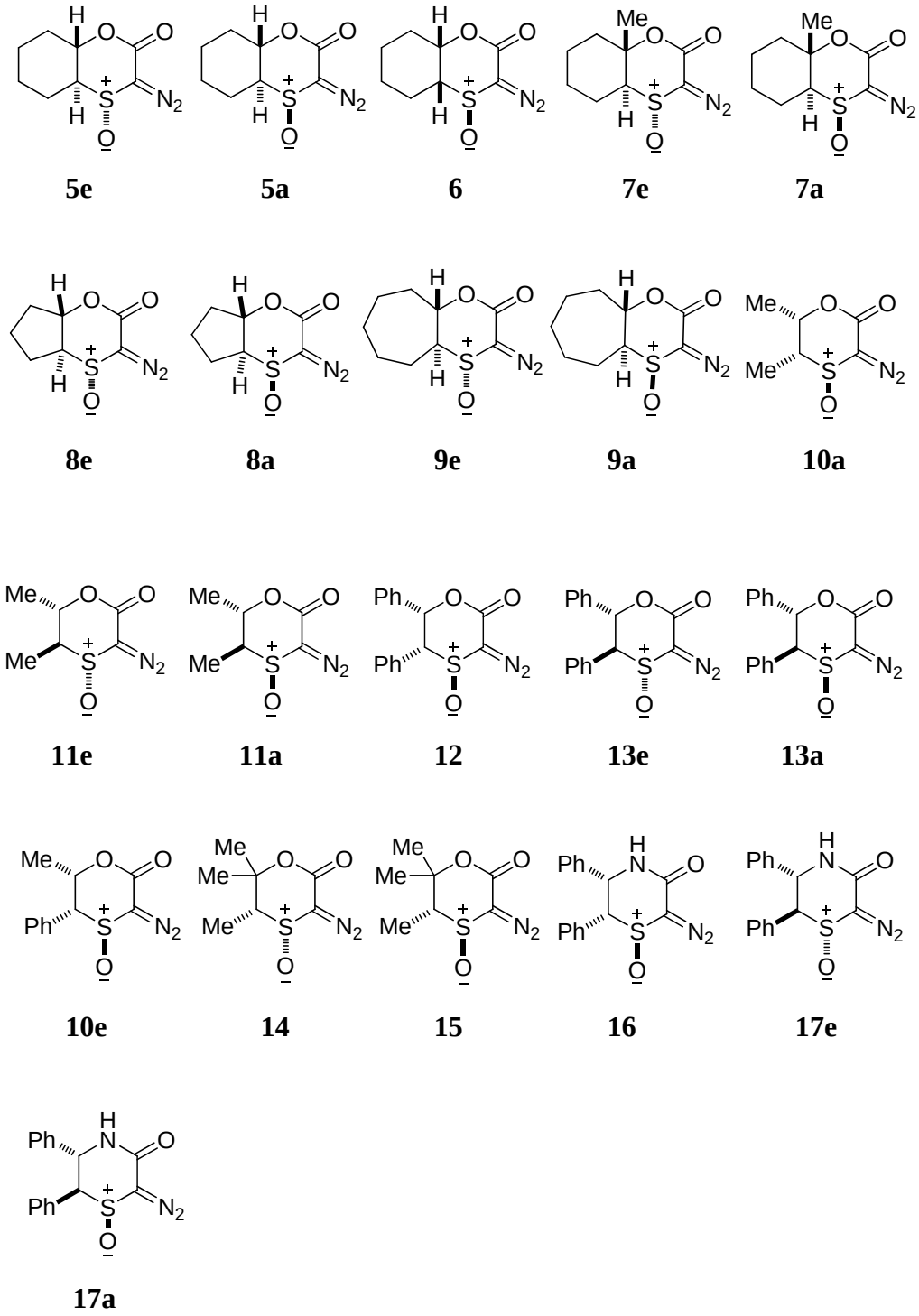
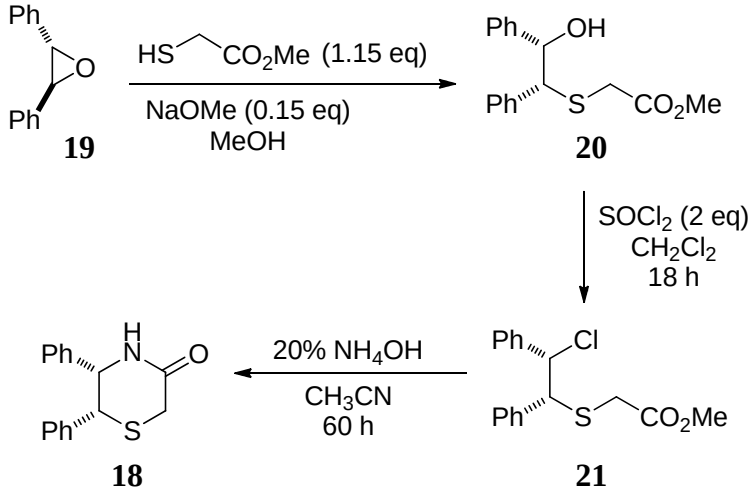


Figure 2.1

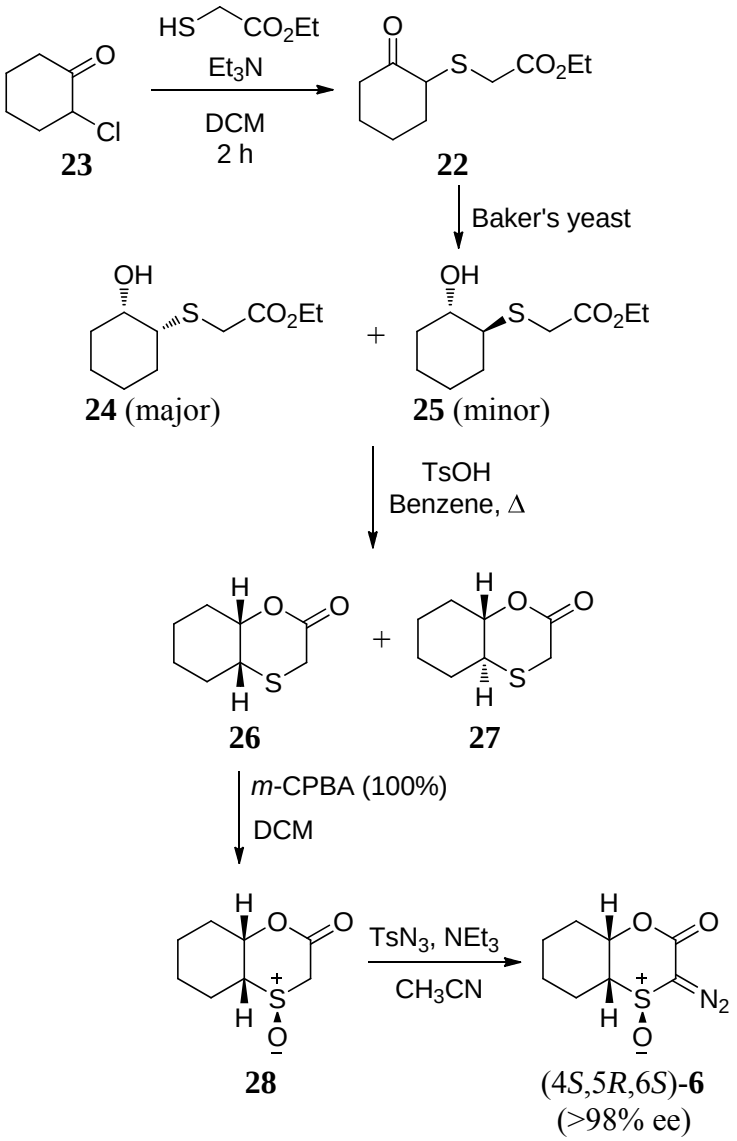
A number of lactone based α-diazosulfoxides were synthesised during this project, and the synthetic route is discussed in Section 2.3. The route towards lactam sulfides such as **18** explored by Collins[7] follows a slightly different route (Scheme 2.4), while the final sulfoxidation and diazo transfer steps to form the diazo

derivatives **16**, **17e** and **17a** are similar to those employed for the lactone based α-diazosulfoxides **5-15**.[7]



Scheme 2.4

The asymmetric synthesis of α-diazosulfoxides has also been investigated using chemoenzymatic methods. Baker's yeast (*Saccharomyces cerevisiae*) has previously been used successfully within the group for the reduction of cycloalkanones and was employed by Collins to carry out an asymmetric reduction of the ketosulfide **22** (Scheme 2.5). Using this method, the α-diazosulfoxide **6** was generated with >98% ee.[8]



Scheme 2.5

2.2 Objectives

An important objective of this project was to further expand the series of α-diazosulfoxides synthesised within our group. Earlier work within this group has been restricted to lactone and lactam derivatives. Diazo transfer to acyclic β-oxo sulfoxides with functionalities such as esters, phosphonates and imidazoles had previously been attempted within the group without success.[6,7] Attempts to synthesise cyclic β-keto sulfides and sulfimides did not lead to substrates for diazo transfer.[9] New approaches towards the synthesis of a novel class of ketone based α-diazosulfoxides (referred to as α-diazo-β-keto sulfoxides in this thesis) were

investigated in this project. Exploration of these routes led to a better understanding of the structural features which are essential to enable the isolation of stable α-diazosulfoxides. The synthetic procedures are discussed in Sections 2.5 and 2.6.

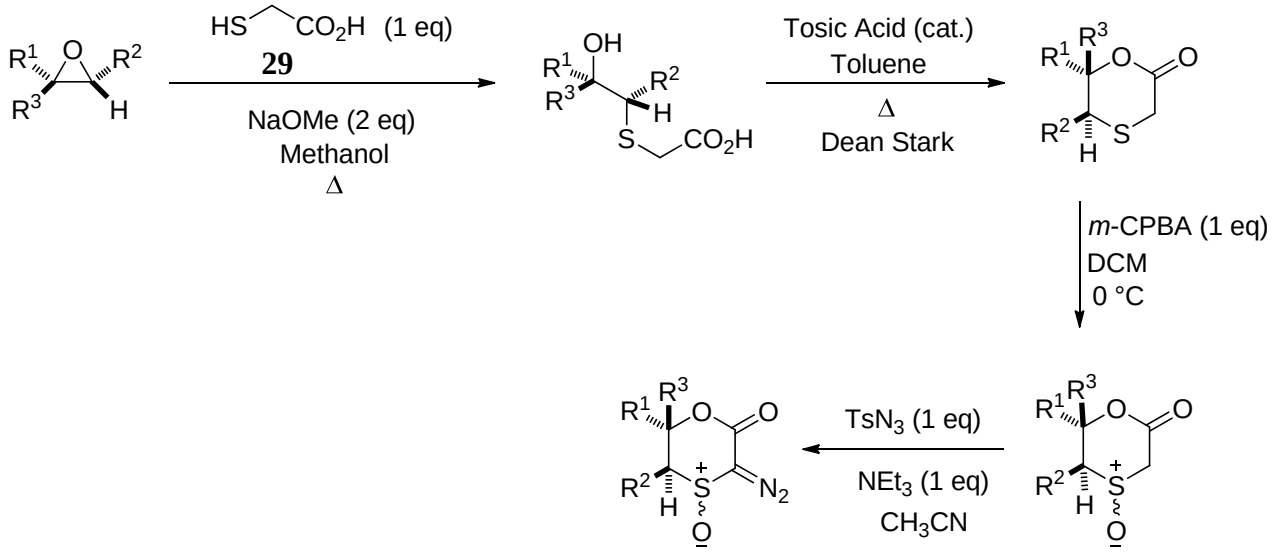
Previous work within the group has focused on cycloaddition and decomposition studies of α-oxosulfine generated from α-diazosulfoxides, therefore another objective was to expand the scope of reactivity of α-diazosulfoxides to include nucleophilic reactions with carbon, sulfur and nitrogen nucleophiles. Novel routes towards 2-substituted furanones were envisaged, leading to interesting heterocyclic systems.

Another objective in this work was to investigate the reactivity of novel α-diazosulfoxide derivatives prepared under a variety of reaction conditions, including transition metal catalysis, microwave and photolysis conditions in order to further enhance our understanding of the reactivity of α-oxosulfine intermediates. Trapping of new α-oxosulfines as dihydro-2*H*-thiopyran *S*-oxides was also envisaged, extending the work undertaken by previous members within the group.

A number of the lactone based α-diazosulfoxides were synthesised according to procedures employed by Kelleher,[10] Collins[7] and O'Sullivan,[9] and efforts were made to further optimise these routes in the course of this work. The synthetic route is discussed in Secion 2.3.

2.3 Lactone Based α-Diazosulfoxides

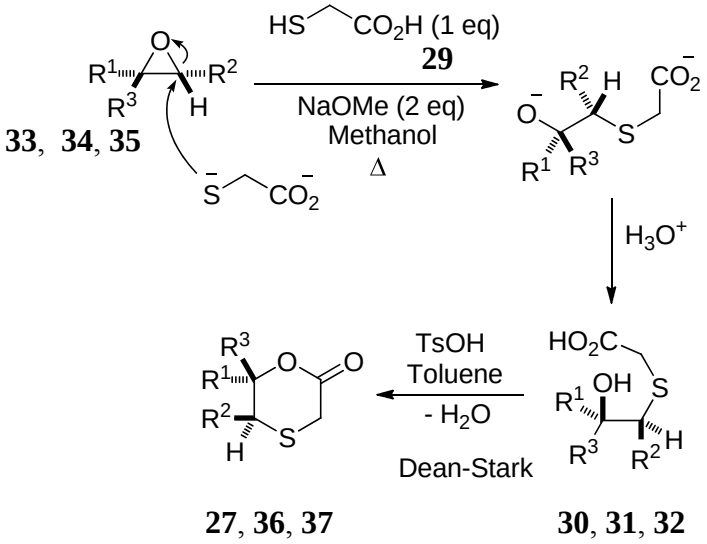
The synthesis of lactone based α-diazosulfoxides from cyclic β-keto sulfide precursors has been explored in depth by previous workers within the group. Detailed discussions regarding the synthetic route and spectroscopic details are available.[7,9,10] Herein, a brief summary of the synthesis of the lactone based α-diazosulfoxides **5a**, **5e**, **7a**, **7e** and **10** synthesised in this project will be given. The overview of the synthetic route is shown in Scheme 2.6.



Scheme 2.6

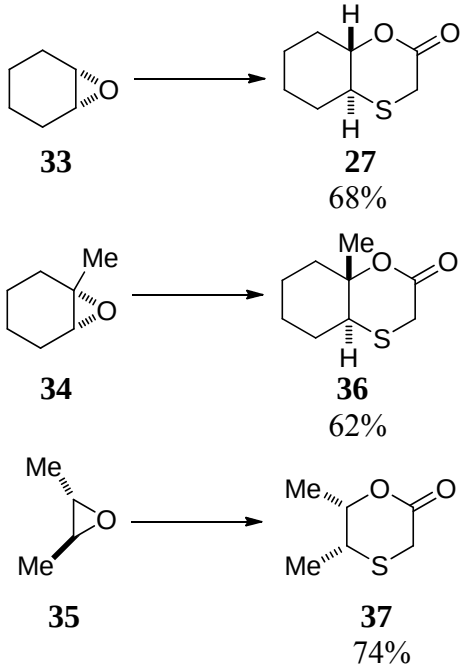
2.3.1 Synthesis of Sulfides

The first step of the reaction pathway involves nucleophilic ring-opening of the epoxide by the thioglycolate dianion. This results in inversion of stereochemistry at the site of attack (Scheme 2.7). Although the deprotonated thioglycolic acid has two nucleophilic sites, only attack by the stronger sulfur anion is observed. After 2.5-3 h under reflux, the reaction is complete by TLC and yields the hydroxy acid after work-up. Analysis of the hydroxy acid is generally not obtained, as the ^{1}H NMR spectra are not readily assigned due to partial spontaneous cyclisation. Instead, the hydroxy acids **30**, **31** and **32** are generally carried directly onto the next step and cyclised in the presence of a catalytic amount of *p*-toluenesulfonic (tosic) acid in toluene using a Dean-Stark trap.



Scheme 2.7

The sulfides **27**, **36** and **37** synthesised by this method and the yields obtained are summarised in Scheme 2.8. The yields and spectroscopic details were in agreement with previous data reported by workers within the group.[7,9,10]

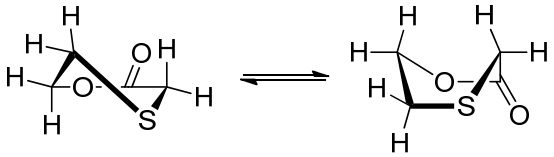


Scheme 2.8

The sulfides were isolated after washing with saturated sodium bicarbonate followed by water, to remove all of the tosic acid. There was no significant difference in the yield, compared to reactions carried out without a sodium

bicarbonate wash, indicating that ring-opening of the lactone in the presence of bicarbonate is not an issue. However, when saturated KOH solution was used during the work-up, the yields obtained were appreciably lower, indicating that the stronger base resulted in partial ring opening of the lactone.

The cyclic sulfides generated *via* this method are 1,4-oxathianones. They contain a planar ester functionality and a puckered C-S-C-C part of the ring. Rather than adopting the conventional chair conformation, NMR studies carried out on the conformational properties of 1,4-oxathianones by Koskimies have demonstrated that these rings can adopt two possible structures – the half chair or the boat conformation, or may exist as an equilibrium mixture of forms (Figure 2.2).[11]



half-chair boat

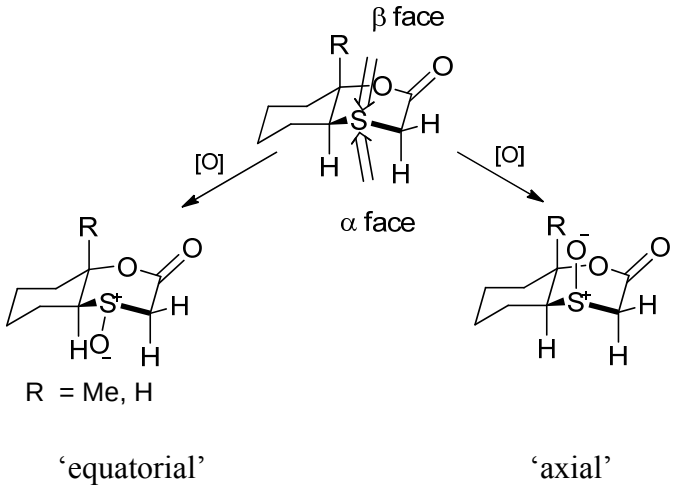
Figure 2.2

2.3.2 Synthesis of Sulfoxides

The oxidation of sulfides to sulfoxides has been widely reported[12] and there are a variety of suitable oxidants available.[13] Collins and Kelleher have explored and optimised a wide range of oxidants for sulfides, including the sulfides **27**, **36**, **37** used in this project.[7,10] The sulfoxides described in this section are stable, white crystalline solids which can be stored at room temperature without decomposition for extended periods of time. Unlike their sulfide precursors, they are not malodorous.

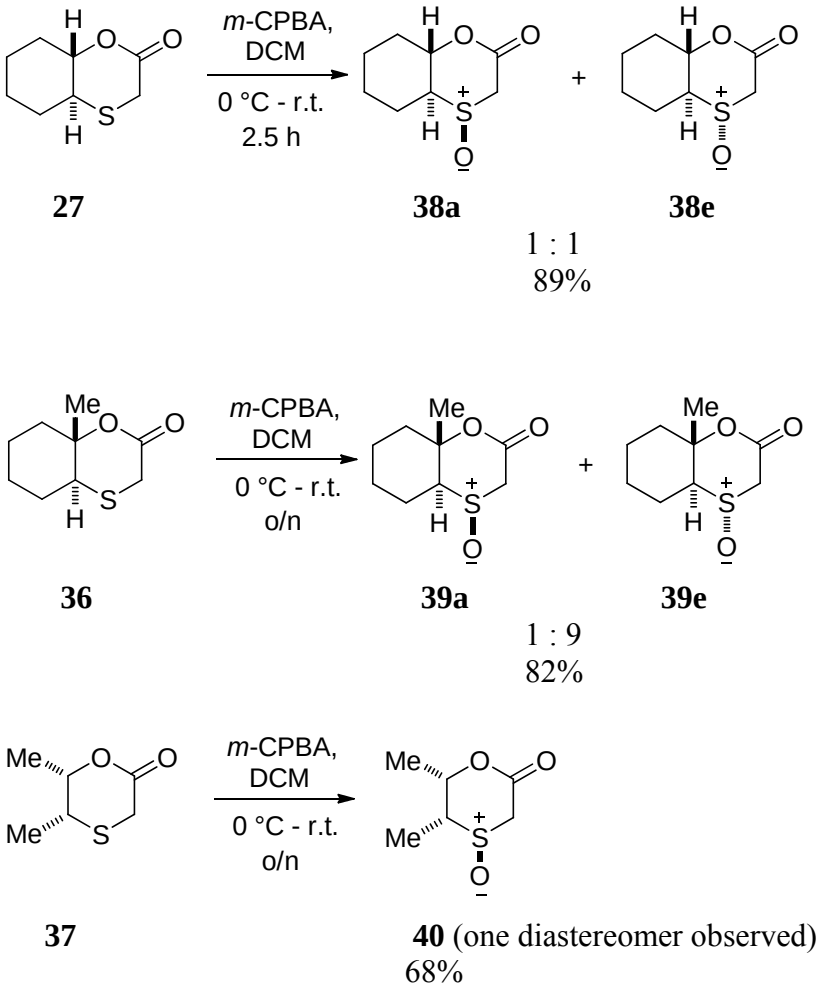
Commercial *m*-CPBA (~77% pure) was employed for oxidation to the sulfoxides **38a**, **38e**, **39a**, **39e** and **40** (Scheme 2.10). Due to the reported explosive hazard associated with this chemical in the pure state,[14] *m*-CPBA was not purified and was instead used as obtained commercially. Instead, the active oxygen content of each batch was determined by iodometric titration prior to use.[14]

Because the oxidant can approach the sulfide from either face, two sulfoxides can be formed which are diastereomeric at sulfur (Scheme 2.9). For convenience in this research programme, 'axial' is used to indicate that the sulfinyl oxygen lies on the β face and 'equatorial' is used to indicate that the sulfinyl oxygen lies on the α face. To maintain consistency with the bicyclic series, the designation of 'axial' and 'equatorial' in the case of monocyclic sulfoxides and α-diazosulfoxides is also used.



Scheme 2.9

The stereoselectivity of the oxidation is strongly dependant on the sulfide structure. Oxidation of the bicyclic sulfide **27** gave an essentially equimolar diastereomeric mixture of sulfoxides **38a** and **38e**. For the sulfide **36**, the methyl bridgehead group sterically hinders the approach of the oxidant from the β face, leading to pronounced diastereoselectivity for the sulfoxides **39a** and **39e** (1:9). For the sulfide **37**, only oxidation to the sulfoxide **40** ('axial' diastereomer) was observed, due to the steric hindrance caused by the two *cis*-dimethyl groups. However, it should be noted that O'Sullivan has demonstrated that some sulfoxidation on the opposite face can occur and is only detected when the reaction is scaled up appreciably.[9]

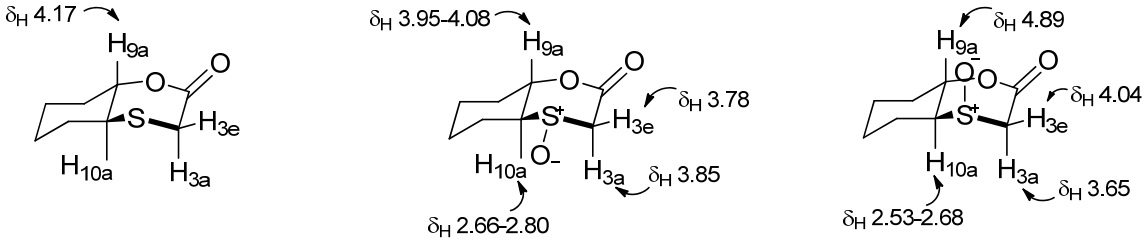


Scheme 2.10

Collins reported improved yields for the oxidation of **37** to the sulfoxide **40** with Oxone®.[7] However, attempts to reproduce this result during this project were unsuccessful and *m*-CPBA was used instead. In order to prevent over oxidation to the sulfone, only one equivalent of *m*-CPBA was employed and careful control of the reaction was maintained by TLC. The yields obtained are in agreement with those reported by Collins.[7]

The assignments of the chemical shifts in the ^{1}H NMR spectra for the bicyclic sulfoxides **38e** and **38a** were based on assignments made by Evans on similar systems and on the expected shielding and deshielding effects of the electronegative heteroatoms in the ring.[15,16] There exists an effect known as the "*syn*-axial" effect in ^{1}H NMR spectra of cyclic sulfoxides and this leads to a dramatic deshielding (0.5-1.0 ppm) of the β-protons which are in a *syn* diaxial orientation relative to the S-O bond. The most important factor in the "*syn*-axial" effect seems to

be the Van der Waals interaction between the negatively charged O atom and the syn β-protons. Thus the C-9 proton in the sulfoxide **38a** at δ_H 4.89 is deshielded because of this "*syn*-axial" effect. This proton is in a *syn* diaxial orientation with the lone pair when the sulfinyl oxygen is in the equatorial position **38e** and is shielded at δ_H 3.95-4.08 relative to the sulfide **27** at 4.17 ppm (Figure 2.3). Detailed NMR studies on the assignment of stereochemistry of the bicyclic sulfoxides **38e** and **38a** have previously been undertaken,[7,10] which served as model compounds to enable characterisation of other derivatives. The diastereomeric ratios and ^{1}H NMR data reported are in agreement those previously reported. [7,9,10]



27 **38e** **38a**

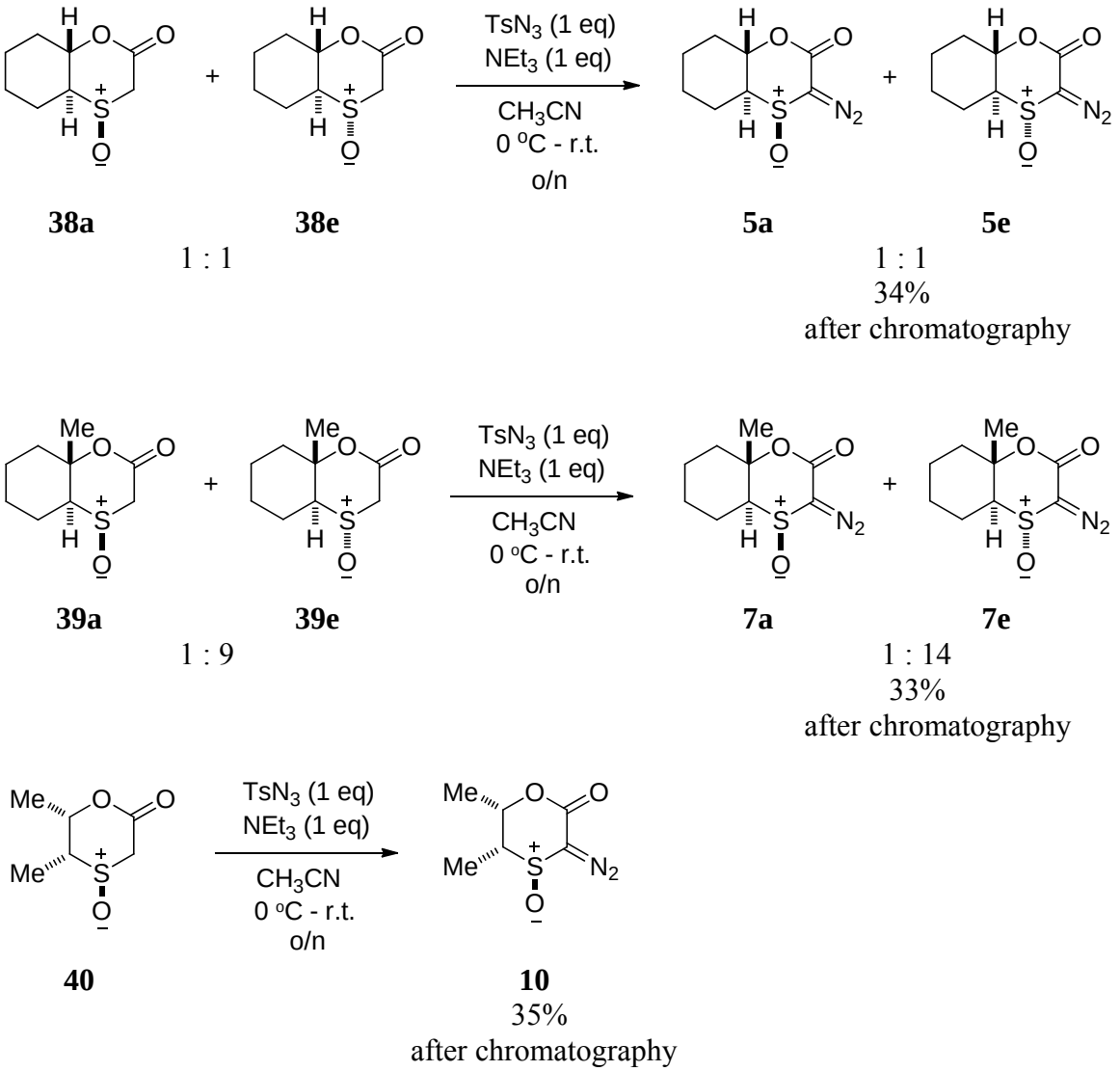
Figure 2.3

2.3.3 Synthesis of α-Diazosulfoxides

Diazo transfer to the sulfoxides **38a**, **38e**, **39a**, **39e** and **40** was readily achieved during this work using reaction conditions previously optimised within the group.[7,9,10] Diazo transfer is a well-established technique which has been employed to synthesise α-diazocarbonyl, α-diazophosphoryl and α-diazosulfonyl compounds.[17,18] The reaction involves the transfer of a diazo group from a donor species, usually a sulfonyl azide, to an accepter molecule which generally has an activated methylene site. Therefore, the reaction is dependent on the use of a suitable base. Tosyl azide **41** is the diazo transfer reagent most commonly employed,[19] and the reagent which has been found most suitable for the synthesis of α-diazosulfoxides.[10] Multigram batches were prepared during this work following procedures discussed in more detail in Section 2.5.4. Optimisation has resulted in the use of triethylamine as the most suitable base, in conjunction with acetonitrile solvent.[10]

The reaction involved the use of triethylamine base to deprotonate the sulfoxide in acetonitrile. The reaction mixture was stirred for 5 min and then a solution of tosyl azide **41** in acetonitrile was added dropwise to the reaction mixture under a nitrogen atmosphere. To ensure complete diazo transfer, the reaction mixtures were stirred overnight. The colour of the solutions gradually changed from pale yellow to orange, darkening overnight to yield a dark red solution. The crude products were extremely viscous, insoluble, dark red oils. Purification using flash chromatography was difficult, given the highly polar nature of the α-diazosulfoxides. Adsorption onto Celite® was necessary, and a 1:1 mixture of hexane/ethyl acetate was used as eluent. Sometimes it was necessary to run a second column in order to remove residual sulfonamide; this inevitably led to a significant loss in yield.

The α-diazosulfoxides synthesised during this work are summarised in Scheme 2.11.



Scheme 2.11

The diastereomeric ratios and modest yields obtained are in agreement with those previously reported by Collins.[7] O'Sullivan reported a diastereomeric ratio for **5a** and **5e** of 1:1.7 after chromatography.[9] However, as the equatorial diastereomer **5e** is the less polar of the two α-diazosulfoxides, this may have been due to partial separation of the diastereomers on the column, rather than an issue with diazo transfer. For the α-diazosulfoxides **7a** and **7e**, the diastereomeric ratio of 1:14 obtained is again probably indicative of a difference in polarity and partial separation on the column, rather than differences in the diazo transfer to the sulfoxides **7a** and **7e**. Due to the small quantity of **7a** relative to **7e**, some may have been lost during column chromatography. While Kelleher had originally thought that there was a difference in stability between the axial and equatorial diastereomers **5a** and **5e**,[10]

based on subsequent work by Collins,[7] O'Sullivan[9] and this work, it is now believed that there is no substantial evidence of a difference in stability between the two diastereomers.

While the α-diazosulfoxides **5-10** have been previously described within the research group, during this work the synthetic procedures have been optimised to the level where it is now possible to routinely synthesise up to a gram of these derivatives within approximately one week.

Spectral details were in agreement with those previously reported.[7,9,10] By ^{1}H NMR spectroscopy, the diazo transfer is immediately apparent by the disappearance of the characteristic $SOCH_2$ AB quartet observed for the sulfoxide precursors.

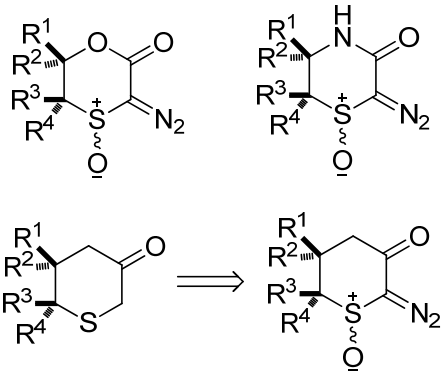
2.4 Design and Synthesis of α-Diazo-β-keto Sulfoxides

During the course of this project, one of the principal objectives was to extend the series of α-diazosulfoxides to include thian-3-one derivatives (Figure 2.4). As described in Section 2.1, the majority of α-diazosulfoxides previously synthesised had contained a lactone functionality, with some success in lactam derivatives by Collins.[7,9,10] Very preliminary investigations into diazo transfer to acyclic β-oxo sulfoxides with functionalities such as esters, phosphonates and imidazoles had previously been attempted within the group without success.[6,7] Further attempts to synthesise cyclic β-keto sulfides and sulfimides did not lead to substrates for diazo transfer.[9]

In this project, different approaches were taken towards a new class of diazocarbonyl compounds. These novel derivatives would contain an α-diazoketone functionality, as opposed to the α-diazolactone and α-diazolactam functionalities present in the previously studied α-diazosulfoxide series. The properties, stability and reactivity of α-diazoketones are distinctly different to those of α-diazoesters and diazo compounds derived from carboxylic acid derivatives in general. Typically, α-diazoketones are more labile than α-diazoesters.[20]

In this project, novel β-keto sulfoxides were designed and synthesised as substrates for diazo transfer, with a view to obtaining, for the first time, α-diazo-β-

keto sulfoxides, which would prove interesting from both a mechanistic and synthetic perspective.



thian-3-one

Figure 2.4

Within this work, the very simple monocyclic β-keto sulfide **42** was a target for investigation. Based on our earlier work, the conformationally constrained fused β-keto sulfide **43** was also identified as an important substrate more likely to lead to isolable diazo derivatives. The exploration into the synthesis of these novel α-diazosulfoxides is discussed in the following sections. The synthesis of aromatic isothiochroman-4-one **43** derivatives (Figure 2.5) is described in Section 2.5, the monocyclic dihydro-2*H*-thiopyran-3(4*H*)-one **42** derivatives (Figure 2.5) in Section 2.6, and the unsuccessful synthetic routes investigated are discussed in Section 2.8.

42 isothiochroman-4-one

43 dihydro-2*H*-thiopyran-3(4*H*)-one

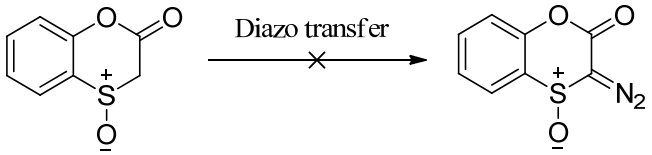
Figure 2.5

2.5 Synthesis of Benzofused α-Diazo-β-keto Sulfoxides

Isothiochroman-4-ones (Figure 2.5) are a class of compounds which have recently been investigated as precursors towards potential anti-HIV, antitubercular and antitumoral drugs.[21-23] Based on the bicyclic structure and the β-position of the

sulfur relative to the carbonyl group, these were identified as suitable precursors for the synthesis of novel α-diazo-β-keto sulfoxides.

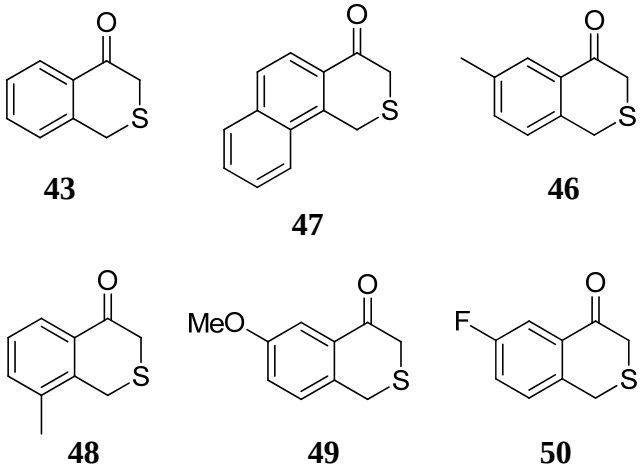
Benzofused lactone systems were not widely investigated during this programme as Collins found the benzofused lactone **44** to be unsuitable for diazo transfer (Scheme 2.12).[7] Diazo transfer to **44** was found challenging from two perspectives. Firstly, the ability of the precursor to readily undergo ring opening, and secondly, in a single attempt at diazo transfer, the diazo derivative was not isolated.



44 **45**

Scheme 2.12

A number of isothiochroman-4-one derivatives were investigated as targets in the design and synthesis of benzofused α-diazo-β-keto sulfoxides, and these are illustrated in Figure 2.6.



43 **47** **46**

48 **49** **50**

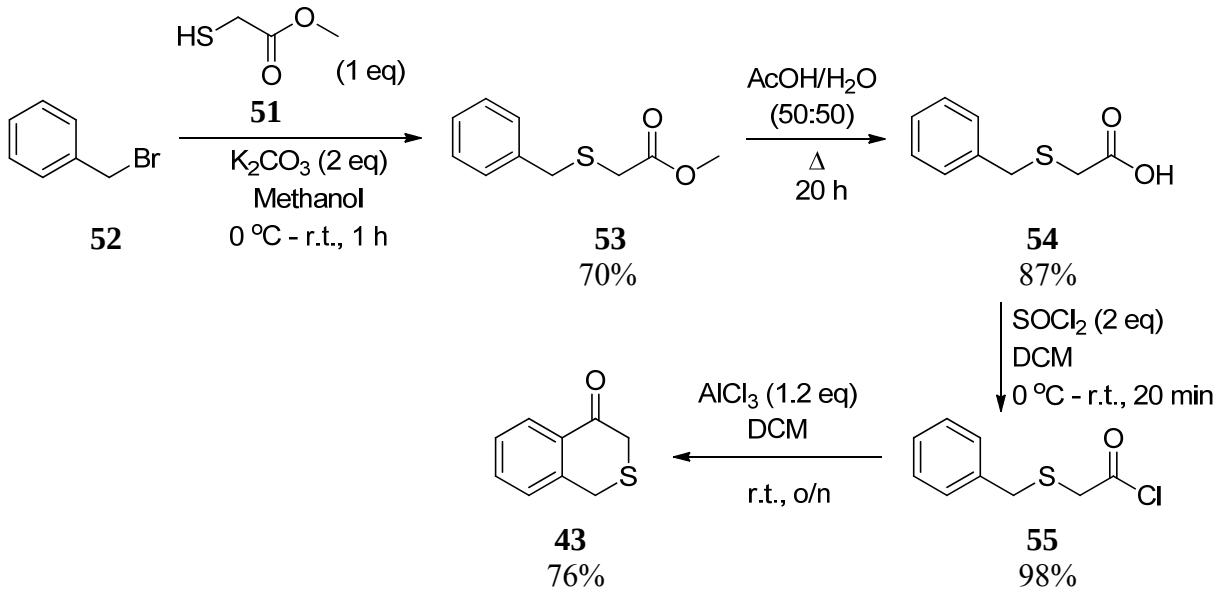
Figure 2.6

2.5.1 Synthesis of Isothiochroman-4-ones

2.5.1.1 Isothiochroman-4-one 43

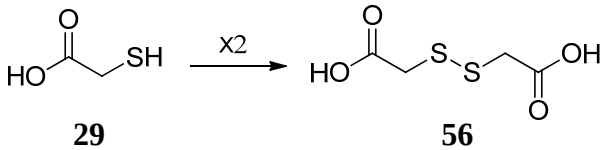
The isothiochroman-4-one **43** was first prepared in 1923 from 2-(benzylthio)acetyl chloride with aluminium trichloride in nitrobenzene.[24] Synthetic

improvements led to the use phosphorus pentoxide on 'Hyflosupercel' in benzene,[25] and then aluminium trichloride in dichloromethane.[22] The route used for the synthesis of isothiochroman-4-one **43** is a modified procedure to that described by Akkurt[22] and is shown in Scheme 2.13.



Scheme 2.13

The first step in this route involved benzylation of the methyl thioglycolate anion **51** in the presence of potassium carbonate. The reaction was complete after 1 h at room temperature to give the ester **53** after aqueous work-up as a clear oil and in 70% yield. Spectral details were in agreement with those reported in the literature, and with the IR spectrum showing the characteristic carbonyl stretch of an ester at 1736 cm^{-1}. Methyl thioglycolate **51** was used instead of thioglycolic acid **29**, which would have conveniently given the carboxylic acid **54** directly and avoided the ester hydrolysis step, due to the fact that a small amount of thioglycolic acid **29** sometimes dimerised to give the disulfide **56**, resulting in an impure batch of the acid **54** (Scheme 2.14).



Scheme 2.14

Heating the ester **53** under reflux in 50:50 acetic acid and water overnight gave the carboxylic acid **54** as a white solid in 87% yield after aqueous work-up.

Successful hydrolysis of the ester was evident in the ^{1}H NMR spectrum by the disappearance of the CH_3 singlet at 3.71 ppm and in the IR spectrum by the expected shift of the carbonyl absorbance from 1736 cm^{-1} to 1708 cm^{-1}. Several water washes were usually required to remove the acetic acid from the product, even so, most batches contained at least a small quantity of acetic acid, evident in the ^{1}H NMR spectrum with the CH_3 singlet at 2.28 ppm. Hydrolysis of the ester was also successful by routine saponification with aqueous sodium hydroxide.

The next step involved formation of the acyl chloride **55** using excess thionyl chloride in dichloromethane at room temperature. Due to the exothermic nature of the reaction, the thionyl chloride was added dropwise over 10 min at 0 °C, and the reaction mixture was then stirred for a further 20 min while returning to room temperature. The acyl chloride **55** was isolated as a yellow oil in a 98% yield. Characteristic spectral features of the acylated product included a shift of the carbonyl absorbance from 1708 cm^{-1} of the acid to 1791 cm^{-1} in the IR spectrum.

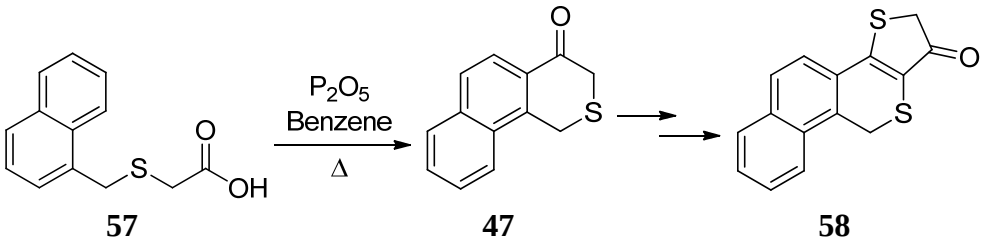
The acyl chloride **55** was cyclised to isothiochroman-4-one **43** by an intramolecular Friedel-Crafts acylation in the presence of a stoichiometric quantity of anhydrous aluminium chloride. Isothiochroman-4-one **43** was obtained as a dark brown solid in 76% yield after aqueous work-up and without the need for further purification. The IR spectrum indicated the distinctive shift in the carbonyl absorbance to that of a cyclised ketone at 1673 cm^{-1}. The aromatic proton β-to the carbonyl group of the new bicyclic system also showed a distinct downfield shift to 8.09 ppm in the ^{1}H NMR spectrum of the cyclised product.

Notably, the multistep sequence outlined in Scheme 2.13 is readily conducted on a multigram scale, without requiring purification at any of the stages and leading to the sulfide **43** in sufficiently pure form to use in further transformations.

2.5.1.2 1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene 47

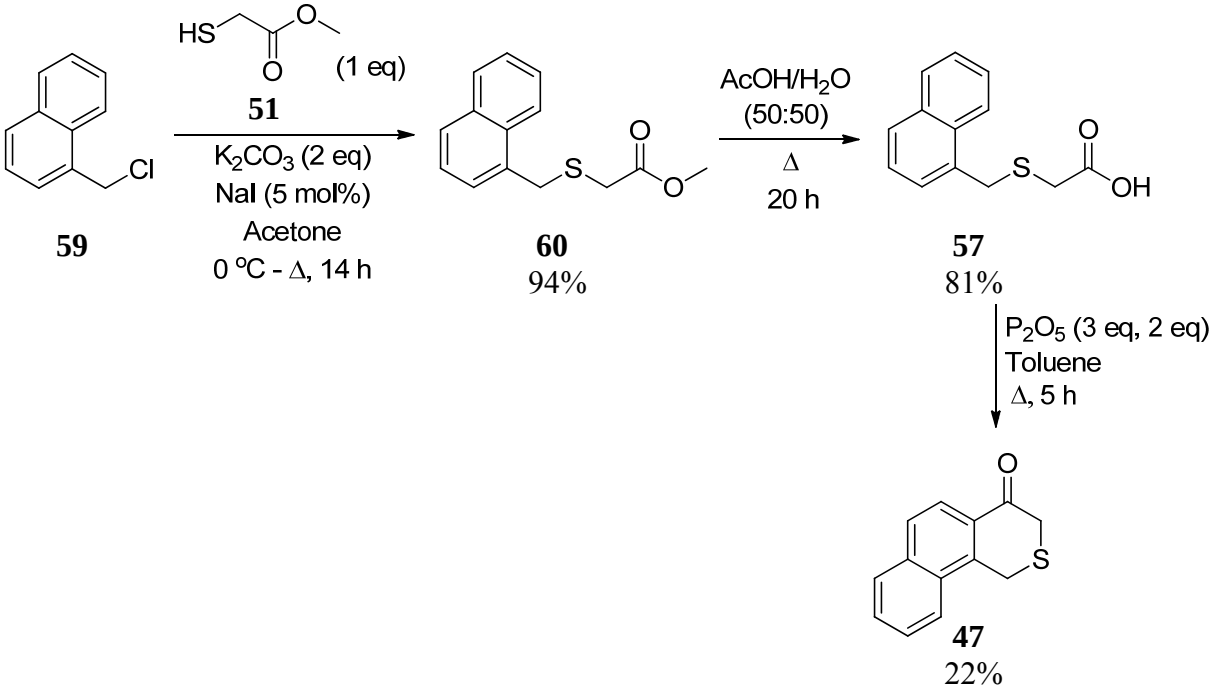
1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** was prepared using a modified procedure from the literature,[26] similar to that described for isothiochroman-4-one **43** above. Ramadas prepared the sulfide **47** *via* an intramolecular Friedel-Crafts reaction of the carboxylic acid **57** with phosphorus

pentoxide by heating under reflux in benzene, *en route* towards the thiasteroid **58** (Scheme 2.15).[26]



Scheme 2.15

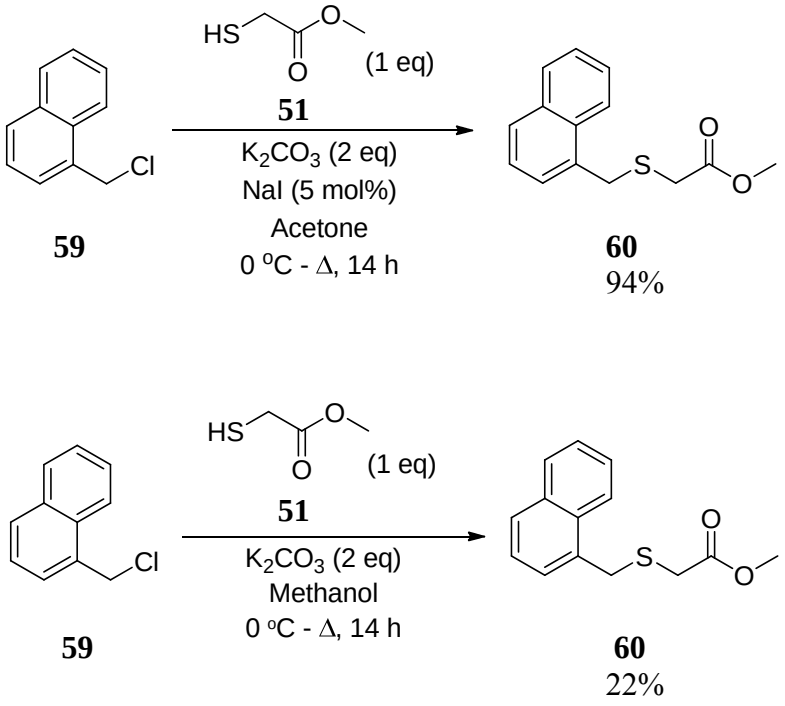
The route used towards the synthesis of the sulfide **47** in this work is shown in Scheme 2.16 and involves a modification of the literature procedure described by Ramadas.[26] 1-Chloromethylnaphthalene **59** is a low melting point solid, and difficult to handle at room temperature. It was found that melting the solid in a warm water bath and syringing the liquid directly into the reaction vessel was the most efficient method of handling the compound.



Scheme 2.16

The first step, involving benzylation of the methyl thioglycolate anion **51** with 1-chloromethylnaphthalene **59**, was optimised using a procedure found in the literature to yield the ester **60** in a yield of 94% after aqueous work-up.[27] The addition of a catalytic quantity of sodium iodide and replacing the solvent with acetone worked to improve the S_N2 reaction between the benzyl chloride and methyl

thioglycolate **51** by forming 1-iodomethylnaphthalene **61** *via* an efficient Finkelstein reaction. By contrast, the reaction in methanol, and without catalytic sodium iodide, gave **60** in a significantly lower yield of 22% (*cf*., Scheme 2.17). The spectral data for the ester **60** were readily assigned, with the characteristic carbonyl stretch of the ester appearing at 1732 cm^{-1} in the IR spectrum.



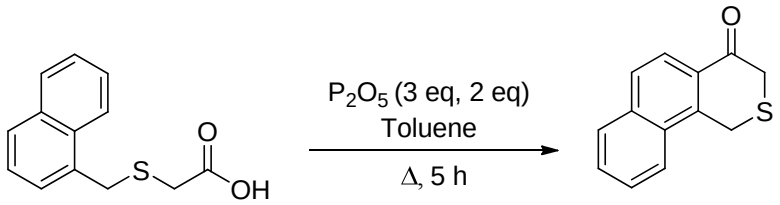
Scheme 2.17

The carboxylic acid **57** was then formed as a white solid in 81% yield by hydrolysing the ester **60** under reflux conditions in acetic acid and water (50:50) overnight. Spectral details were in agreement with literature values,[26] including the expected shift of the carbonyl stretch to 1704 cm^{-1} in the IR spectrum. The CH_3 singlet of the methyl ester **60** at 3.71 ppm was replaced with the broad COOH singlet of the carboxylic acid **57** at 11.20 ppm.

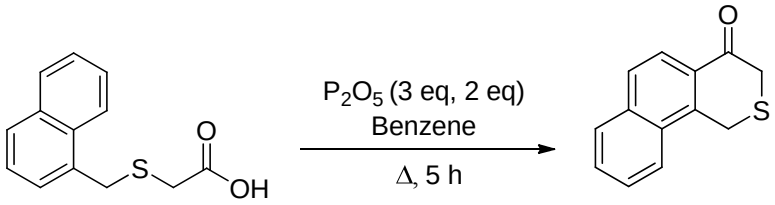
A number of procedures were investigated to optimise the final cyclodehydration step, which involved an intramolecular Friedel-Crafts reaction of the carboxylic acid **57** directly to the sulfide **47**. Although Ramadas had reported refluxing benzene as a suitable solvent,[26] it was found during this work that the use of toluene gave a very similar yield for **47** (24% in benzene, 22% in toluene), without the hazards associated with handling benzene. The use of excess phosphorus pentoxide in the reaction resulted in the formation of a thick, brown gum, which

collected at the bottom of the reaction vessel and was difficult to keep mobile using the magnetic stirring pellets. In order to ensure the presence of active phosphorus pentoxide throughout the reaction time, the addition was divided into two stages, with 3 equivalents of phosphorus pentoxide initially added to the reaction mixture, followed by another 2 equivalents after 3 hours of reflux conditions, and this was then stirred under reflux for a further 2 hours. Due to the excess phosphorus pentoxide, the aqueous work-up was difficult and time consuming. The solution was filtered slowly to remove from the brown gum, which was washed several times with toluene. Concentration of the toluene solution gave a brown solid. The pure sulfide **47** was purified by recrystallisation from 95% ethanol as a bright yellow solid in 22% yield (Scheme 2.18).

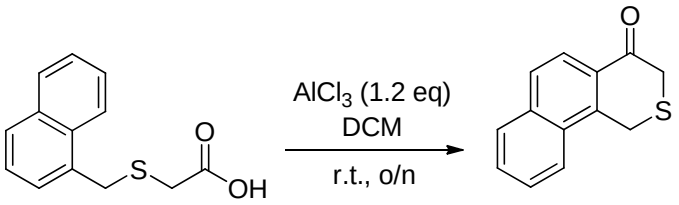
In an attempt to avoid the handling difficulties associated with phosphorus pentoxide as a reagent, aluminium chloride was investigated as a suitable Lewis acid for the cyclisation of the carboxylic acid **57** to the sulfide **47**. However, although the pure sulfide **47** was obtained after column chromatography, the yield was much lower at 13% (Scheme 2.18).



57 **47**
22%



57 **47**
24%



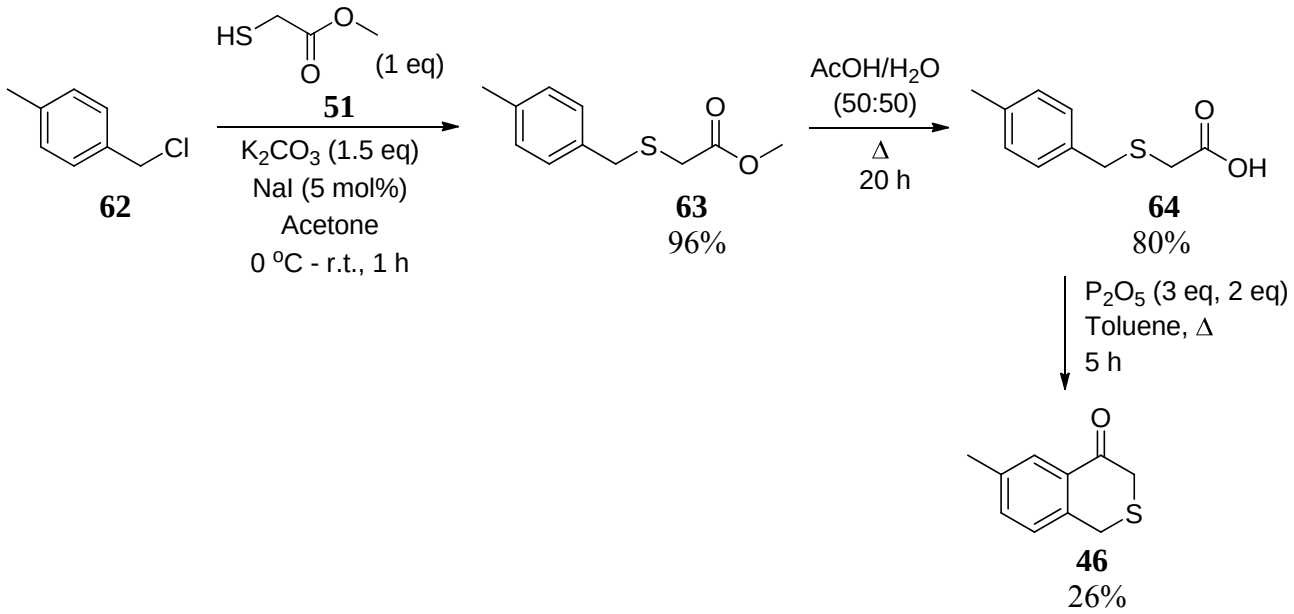
57 **47** 13%

Scheme 2.18

Spectral details for **47** agreed with those reported in the literature,[26] including the typical carbonyl stretch of the cyclic ketone at 1678 cm^{-1}. The quaternary C=O of the cyclic ketone appeared in the ^{13}C NMR spectrum at 191.2 ppm.

2.5.1.3 6-Methylisothiochroman-4-one 46

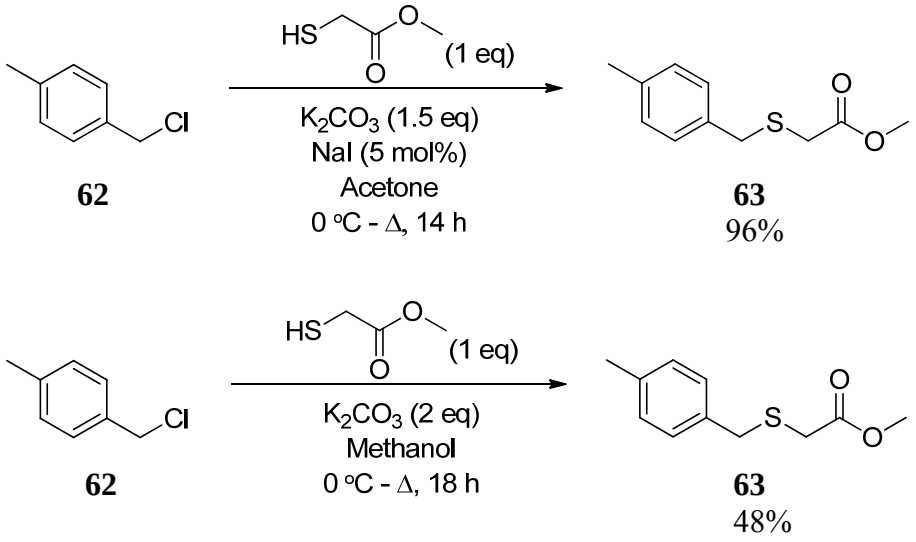
The synthesis of 6-methylisothiochroman-4-one **46** followed the modified route as described by Ramadas.[26] The procedure is shown in Scheme 2.19 below.



62 **63** 96% **64** 80% **46** 26%

Scheme 2.19

The ester **63** was formed in 96% yield as a clear oil from 4-methylbenzyl chloride **62**. As described for the naphthyl ester **60** above, the yield for the *p*-methyl ester **63** was optimised by the addition of a catalytic amount of sodium iodide in acetone to the reaction mixture (Scheme 2.20).

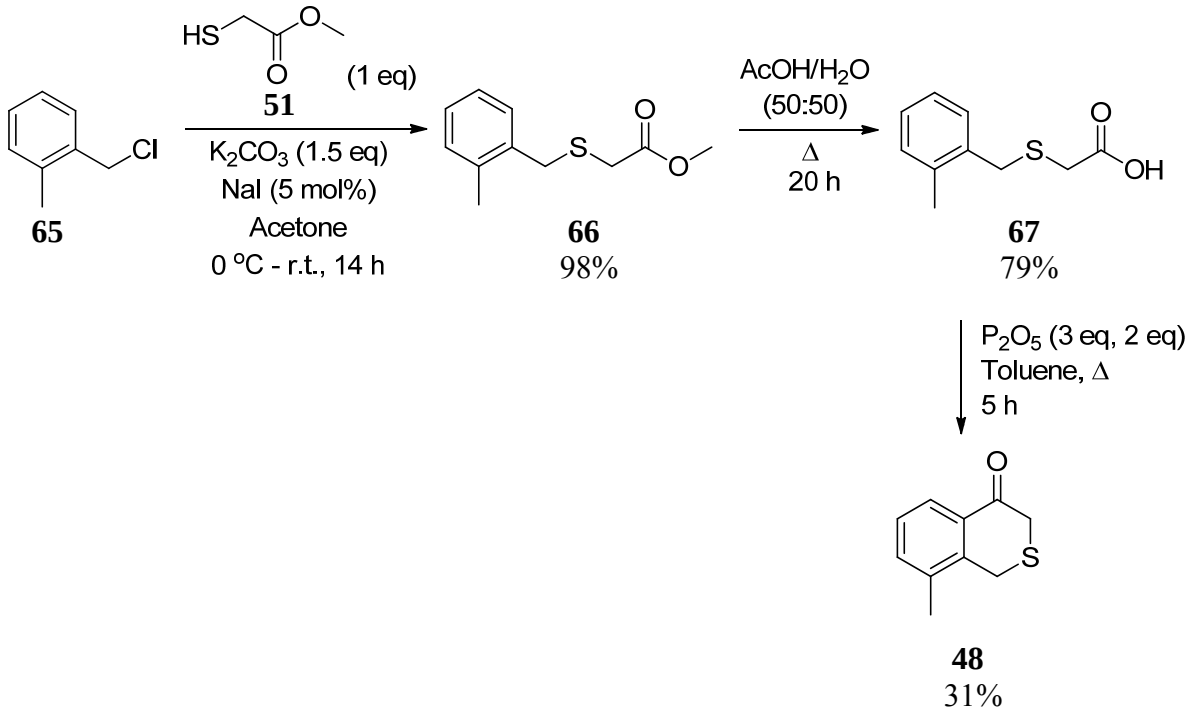


Scheme 2.20

Hydrolysis of the ester **63** gave the carboxylic acid **64** as a white solid in 80% yield by hydrolysing the ester **63** under reflux in acetic acid and water (50:50) overnight. The intramolecular Friedel-Crafts reaction of the carboxylic acid **64** to 6-methylisothiochroman-4-one **46** was achieved using the same procedure as for the naphthyl sulfide **47** by heating under reflux with phosphorus pentoxide in toluene for 5 hours. Only one product could be formed due to the symmetric *para*-methyl substitution on the benzyl ring. The 6-methyl sulfide **46** was obtained in a yield of 26% after column chromatography and as a bright yellow solid. While a straightforward recrystallisation was a suitable form of purification of the naphthyl sulfide **47**, the 6-methyl sulfide **46** was not successfully purified by recrystallisation. The poor yield obtained is a reflection of the difficulty in separating the impurities and starting material from the product by column chromatography. Although generally only one column was required, sometimes a second column was required in order to obtain a pure sample of the 6-methyl sulfide **46**. The spectral data obtained correlated favourably with that which we obtained for the sulfide **43**. The sulfide **46** is a known compound, although no spectroscopic data is available in the literature.[28]

2.5.1.4 8-Methylisothiochroman-4-one 48

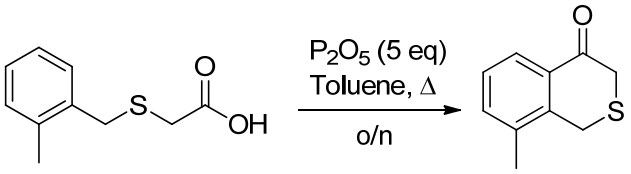
Following the successful synthesis of 6-methylisothiochroman-4-one **46**, 8-methylisothiochroman-4-one **48**, was next prepared (Scheme 2.21):



Scheme 2.21

Again, the modified version of the procedure as described by Ramadas was used.[26] Reaction of methyl thioglycolate **51** and 2-methylbenzyl chloride **65** in the presence of catalytic sodium iodide gave the *o*-methyl ester **66** in a yield of 98% and as a pale yellow oil. The was hydrolysed to the corresponding carboxylic acid **67**, which was obtained as an off-white solid and in 79% yield. An intramolecular Friedel-Crafts reaction with phosphorus pentoxide as described for the naphthyl sulfide **47** gave the 8-methyl sulfide **48** in a yield of 31% as a yellow solid. Again, recrystallisation did not purify the mixture successfully, and the low yield is reflective of the difficulty in separating the pure product from impurities and starting material by column chromatography. The sulfide **48** is a known compound, although no spectroscopic data is available in the literature.[28] When the cyclisation reaction was allowed to proceed overnight in an attempt to improve the yield (Scheme 2.22), the 8-methyl sulfide **48** appeared to decompose under the harsh conditions and very little product was detected by ^{1}H NMR analysis (~8%).

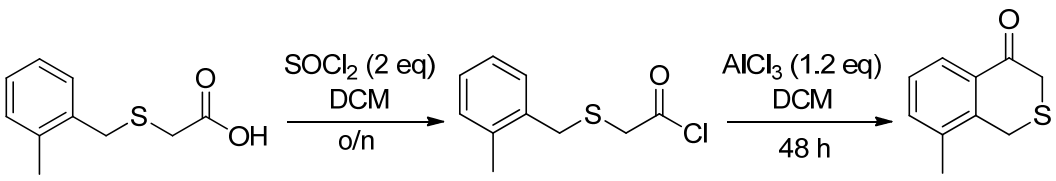
While shorter reaction times might lead to enhanced recovery of the sulfide **48**, TLC evidence indicated the complete cyclisation required 5 hours at reflux in toluene.



67 **48**
~8%
in a very complex mixture

Scheme 2.22

It was also attempted to reproduce the procedure used for preparation of isothiochroman-4-one **43** by forming the acyl chloride **68** first and cyclising to the 8-methyl sulfide **48** with aluminium chloride. The acyl chloride **68** was prepared from the carboxylic acid **67** using excess thionyl chloride in dichloromethane at room temperature and was obtained as a pale yellow oil in 96% yield (Scheme 2.23). Again, the characteristic spectral features of the acylated product included a shift of the carbonyl stretch from 1706 cm^{-1} of the acid to 1775 cm^{-1} in the IR spectrum. The acyl chloride was then treated with aluminium chloride in dichloromethane as described for isothiochroman-4-one **43** (Scheme 2.23). The reaction was monitored by TLC for the appearance of **48** and worked up after 48 hours, resulting in isolation of only a trace quantity of the cyclised 8-methyl sulfide **48**, probably due to extended exposure to stoichiometric amounts of aluminium chloride.

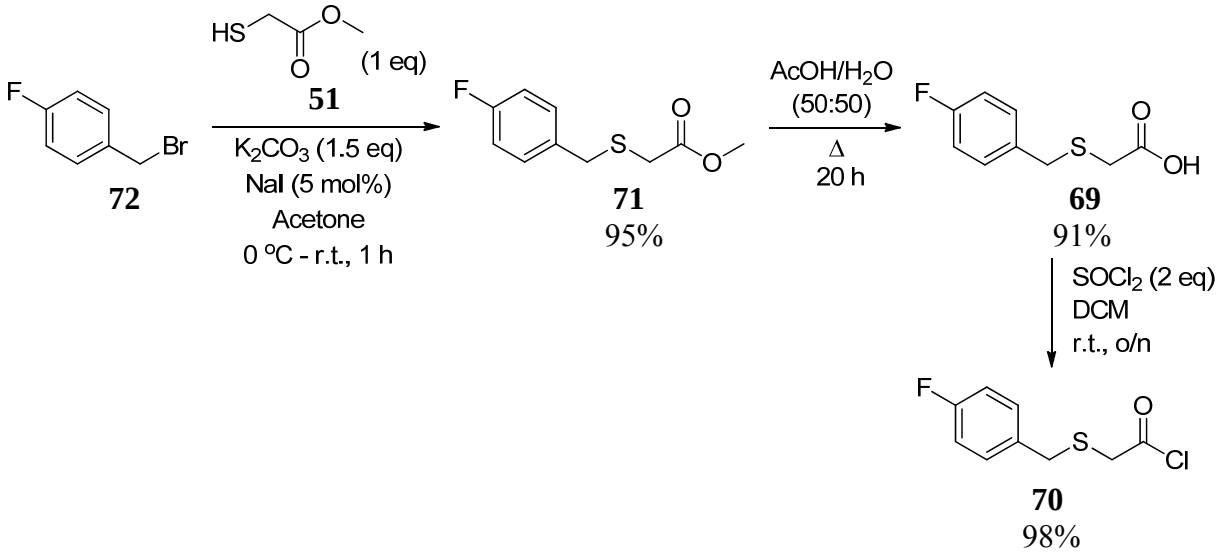


67 **68**
96%
48
small quantity

Scheme 2.23

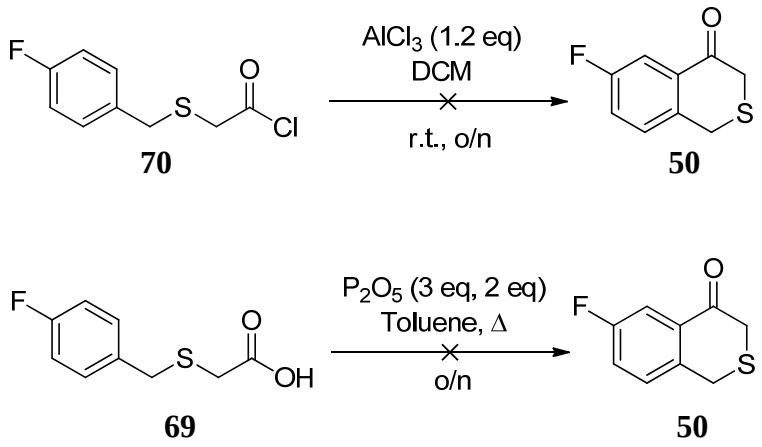
2.5.1.5 Attempted synthesis of 6-fluoroisothiochroman-4-one 50

At this stage, we decided to prepare isothiochroman-4-ones substituted with electron withdrawing groups. 6-Fluoroisothiochroman-4-one **50** was investigated as a suitable derivative. The *p*-fluoro carboxylic acid **69** and acyl chloride **70** were prepared as summarised in Scheme 2.24. The *p*-fluoro ester **71** was obtained as a clear oil in 95% yield from 4-fluorobenzyl bromide **72**. Hydrolysis with acetic acid and water gave the *p*-fluoro carboxylic acid **69** as an off-white crystalline solid in 91% yield. Chlorination of the acid gave the *p*-fluoro acyl chloride **70** as an orange oil in 98% yield.



Scheme 2.24

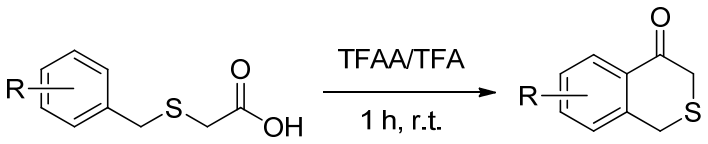
Preparation of the 6-fluoro isothiochroman-4-one **50** was attempted using the methods summarised in Scheme 2.25. However, the previous results could not be reproduced for this derivative. For both reactions, a complex mixture of unidentifiable compounds was formed and it was difficult to distinguish any signals corresponding to the cyclised product **50**. Two possible explanations can be envisaged. Firstly, the presence of the fluoro-substituent deactivates the aromatic ring towards the Friedel-Crafts acylation. Secondly, the sulfide **50** may, in retrospect, have been labile under the harsh reaction conditions involving prolonged exposure to aluminium chloride or phosphorus pentoxide. Further investigation of this is warranted.



Scheme 2.25

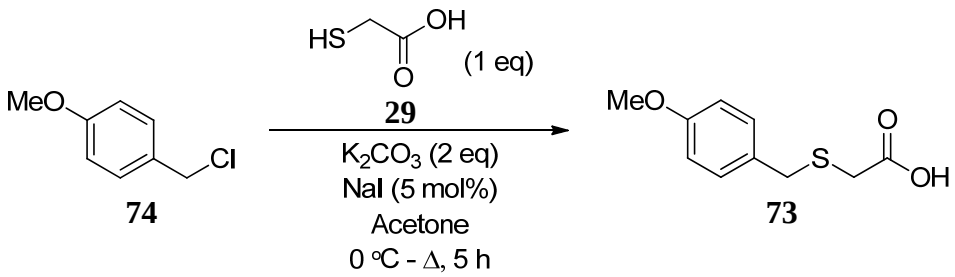
2.5.1.6 Attempted synthesis of 6-methoxyisothiochroman-4-one 49

Although two methyl substituted isothiochroman-4-one derivatives **48** and **46** had been prepared, it was decided to also investigate strongly electron donating substituents. The synthesis of a *para*-methoxy substituted isothiochroman-4one was next attempted. A search of the literature led us to a report by Bertenshaw *et al.* where methoxy and methyl substituted isothiochroman-4-ones were prepared by cyclisation using trifluoroacetic anhydride (TFAA) in trifluoacetic acid (TFA).[29] Typically, the carboxylic acid (10 mmol) in TFA (50 mL) and TFAA (20 mL) was stirred at room temperature or reflux. For benzene rings containing an election donating substituent (methoxy or methyl), the reaction was complete within 1 h at room temperature. (Scheme 2.26).[29]



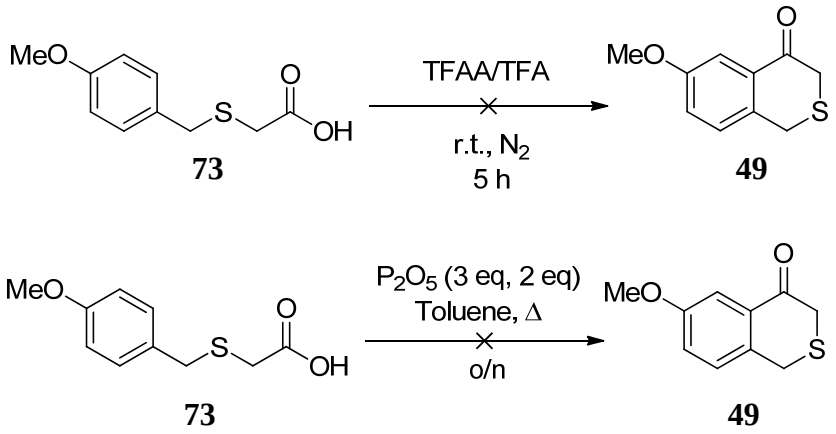
Scheme 2.26

The *p*-methoxy carboxylic acid **73** was prepared as shown in Scheme 2.27. Direct use of thioglycolic acid **29** was employed in this case, due to the limited quantity of the benzyl chloride starting material **74** available.



Scheme 2.27

The cyclisation of the *p*-methoxy carboxylic acid **73** was attempted using the reaction conditions as described by Bertenshaw.[29] However, after base work-up, a complex mixture of unidentifiable compounds was isolated (Scheme 2.28). Although the CH_2 singlet of the carboxylic acid **73** at 3.09 ppm had disappeared, there was no evidence found for the formation of the desired product **49**. Cyclisation was also attempted using phosphorus pentoxide in toluene under reflux conditions overnight. Again, only a complex mixture of compounds was recovered (Scheme 2.28).

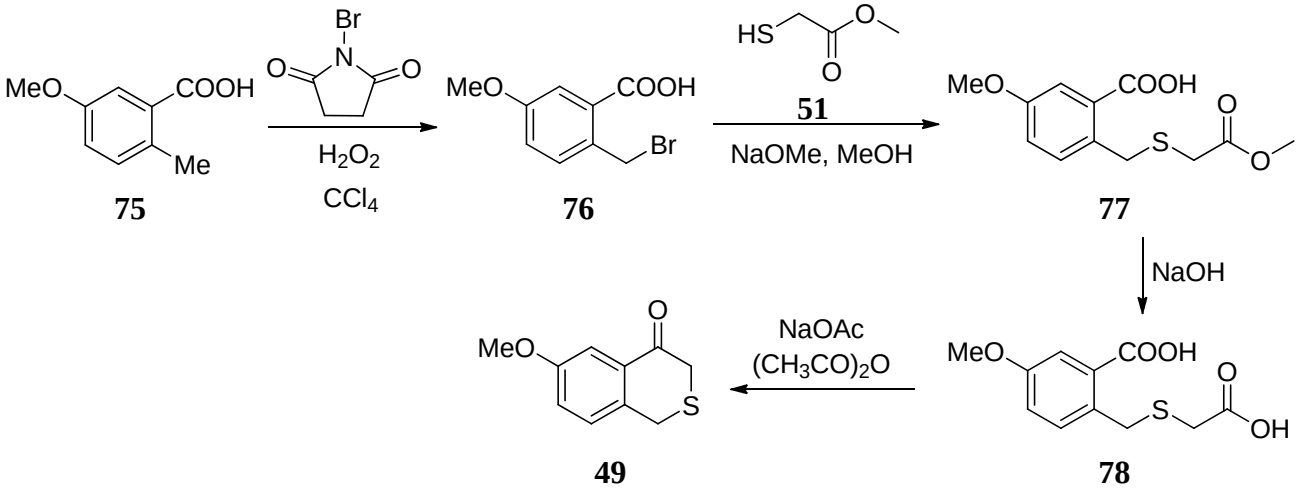


Scheme 2.28

In retrospect, exploitation of milder conditions for the cyclisation of the carboxylic acids is warranted to avoid decomposition of the isothiochroman-4-ones under the reactions for the cyclisation.

While this method of generating isothiochroman-4-ones with strongly electron withdrawing or donating groups was not successful, another has since come to light which may be worthy of future investigation. Canalini *et al.* prepared a range of isothiochroman-4-ones, including 6-methoxyisothiochroman-4-one **49**, using the

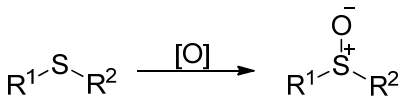
method summarised in Scheme 2.29.[30] This may open a route towards new α-diazosulfoxides with strongly electron donating substituents.



Scheme 2.29

2.5.2 Synthesis of Isothiochroman-4-one *S*-Oxides

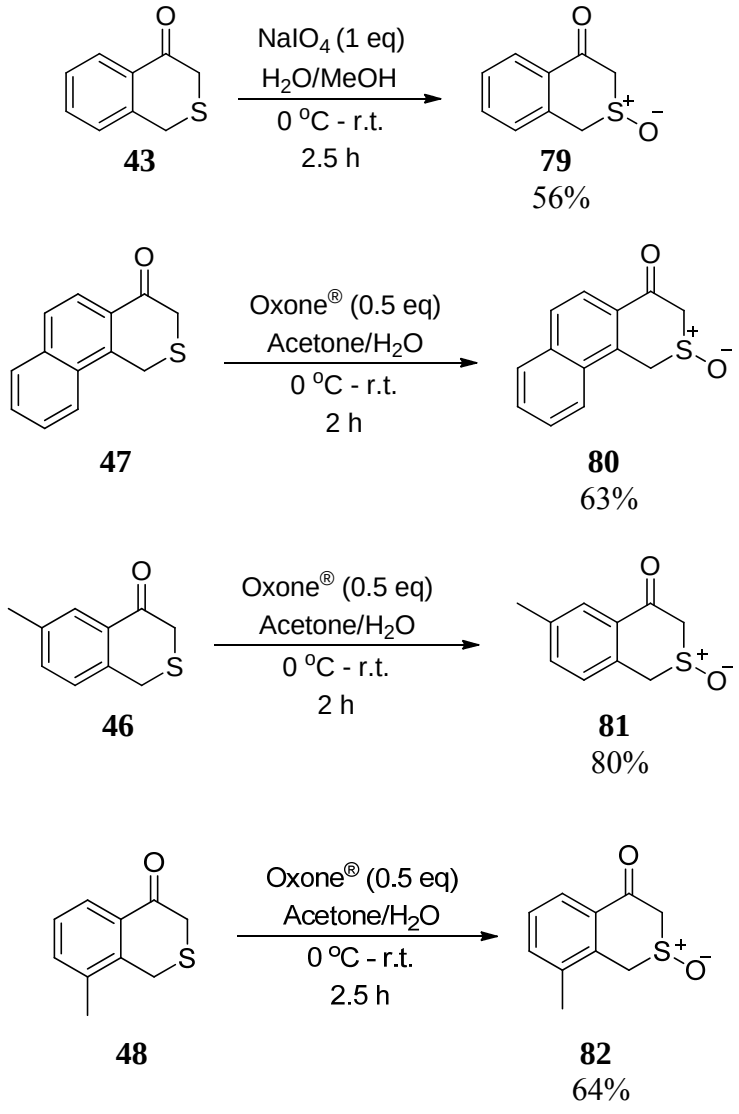
Sulfoxides are widely used in organic synthesis, and are frequently prepared by oxidation of the corresponding sulfides (Scheme 2.30). A variety of oxidants are available for this transformation.[12,13,31-33] Among the more commonly employed oxidants are *meta*-chloroperoxybenzoic acid (*m*-CPBA),[34] cumene hydroperoxide (CHP),[35] sodium *meta*-periodate,[36] magnesium monoperphthalate (MMPP),[37] Oxone®,[38] hydrogen peroxide,[13] and potassium permanganate.[39]

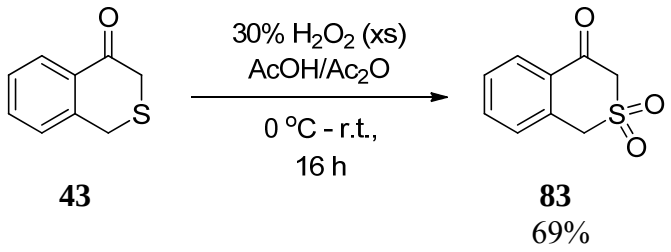


Scheme 2.30

During this work, the isothiochroman-4-one *S*-oxide **79** was formed by periodate oxidation. The optimised method employed in the synthesis of the benzofused sulfoxides **80**, **81** and **82** was Oxone® oxidation of the sulfide precursors. Other oxidising agents investigated were *m*-CPBA, hydrogen peroxide, and polystyrene supported periodate resin.[40] The asymmetric sulfoxidation of isothiochroman-4-one **43** was also briefly investigated, and is discussed in Sections 2.5.6 and 2.5.7.

Unlike the lactone β-ketosulfides discussed in Section 2.3.1, sulfoxidation of the planar isothiochroman-4-ones did not yield two sulfoxides diastereomeric at sulfur. Only one diastereomer exists in each case, and this greatly simplified spectroscopic analysis. The yields and reaction conditions for the formation of the sulfoxides **79**, **80**, **81** and **82** are shown in Scheme 2.31. While the sulfoxides **80**, **81** and **82** are novel and were fully characterised during the course of this work, the sulfoxide **79** has been previously synthesised.[41,42] The sulfoxides described here are all white, stable solids, which can be easily stored at room temperature over several months without decomposition. It was possible to prepare these sulfoxides in gram quantity, although the scale was limited by the amount of available sulfide starting material. A sample of the sulfone **83** was also synthesised,[43] for comparison with the sulfoxide **79** in order to ensure that over oxidation was not occurring.



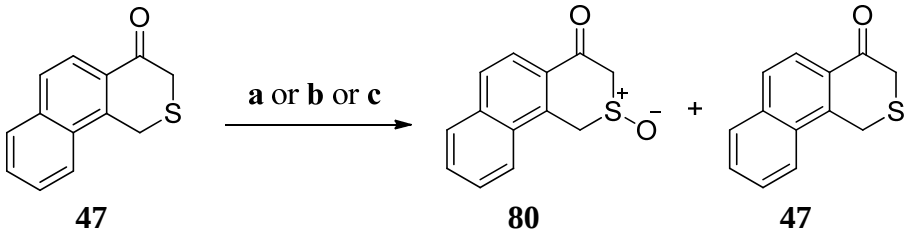


43 **83** 69%

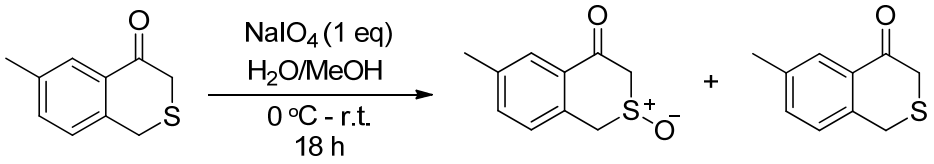
Scheme 2.31

Sulfoxidation was generally complete after 2-2.5 hours and, with the exception of the sulfoxide **79**, which was recrystallised, the crude products were purified by column chromatography in good yields, with no evidence for over oxidation to the sulfone (Scheme 2.31). Due to their high polarity, it was found that 100% ethyl acetate was required as a suitable solvent to elute the sulfoxides from the column. The use of sodium metaperiodate was successful for the complete sulfoxidation of the sulfide **43**. The moderate yield of 56% compared favourably with previous reports in the literature.[41,42] This oxidising agent was initially the reagent of choice, as periodate is reported to oxidise sulfur selectively to the sulfoxide level and avoid over-oxidation.[44,45]

The successful use of sodium metaperiodate was not extended to the sulfides **47** and **46**. For the naphthyl sulfide **47**, the reaction only went ~10% to completion, even after 24 h (Scheme 2.32). This was possibly due to the unsuitable mixed solvent system, with the less polar naphthyl derivative having a low solubility in methanol/water.[44] For the 6-methyl sulfide **46**, the reaction proceeded ~83% to completion after 18 h, with the methyl substituent on the aromatic ring also preventing sufficient solubility for complete conversion to the sulfoxide **81** (Scheme 2.32). Both *m*-CPBA and hydrogen peroxide were also investigated as suitable oxidising agents for the naphthyl sulfide **47**. With *m*-CPBA however, even after stirring overnight, a significant quantity of sulfide **47** remained, with the reaction having gone ~75% to completion. Hydrogen peroxide was initially investigated as a metal-free approach towards sulfoxidation.[33] However, after stirring overnight, a small quantity of the sulfide **47** still remained in the reaction mixture (~14%).

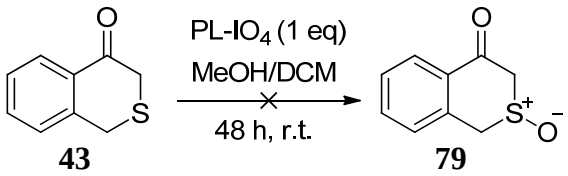


a. $NaIO_4$, MeOH/H_2O, 24 h 1 : 9
b. *m*-CPBA, DCM, o/n 3 : 1
c. H_2O_2, AcOH, o/n 6.1 : 1



Scheme 2.32

The oxidation of the sulfide **43** was also attempted using commercially obtained PL-IO_4 resin obtained from Varian. However, the reaction was unsuccessful and only starting material was recovered (Scheme 2.33).



Scheme 2.33

The resin is a polymer supported form of *meta*-periodate (Figure 2.7), and has been used with success for the oxidation of sulfides to sulfoxides in high yields by Hodge,[40] and for the oxidation of thioethers to sulfoxides.[46] Hodge reported the reaction to be highly solvent dependant, and found methanol to be the most suitable for efficient sulfoxidation.[40] However, in this work, use of this oxidant did not prove effective.

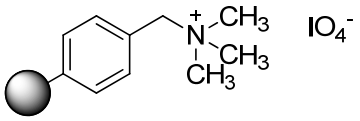
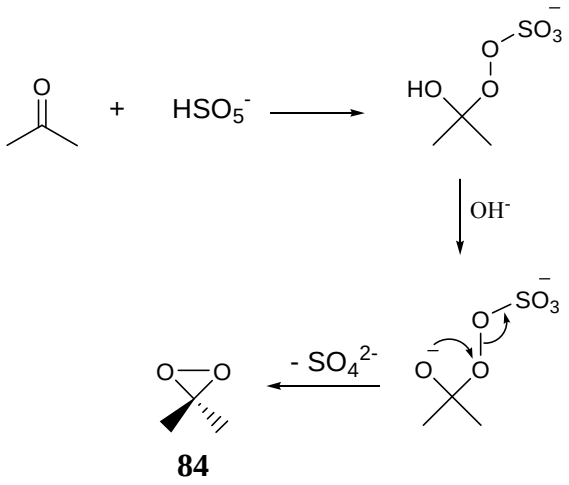


Figure 2.7

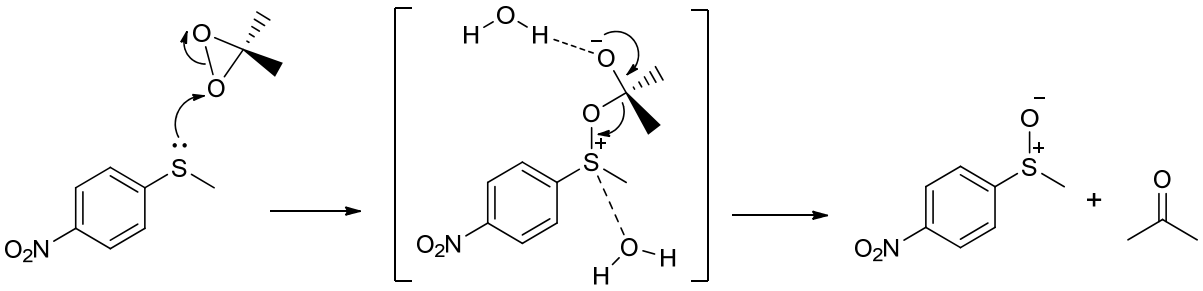
In this instance, the reason for the exceptional success of Oxone® as a sulfoxidating agent could be due to solvation effects. Oxone®, a stoichiometric commercially available oxidising agent, was first reported by Kennedy and Stock in 1960 and consists of two moles of potassium peroxymonosulfate, one mole of potassium bisulfite and one mole of potassium sulfate.[47] Potassium peroxymonosulfate reacts with acetone to produce dimethyldioxirane **84**, which is a very effective oxygen transfer reagent (Scheme 2.34).[48]



84

Scheme 2.34

A recent mechanism for the oxidation of sulfides such as **85** using dimethyldioxirane, generated *in situ* from Oxone® and acetone, has been described by Hanson.[49] The mechanism involves nucleophilic attack of the sulfur on the dioxirane **84** to give an intermediate (Scheme 2.35). When the reaction is performed in aqueous acetone, specific solvation of the intermediate by water, through hydrogen bonding to the partial negative charge on oxygen in the dioxirane **84**, and electron pair donation to the partial positive charge on the sulfur, leads to an increase in the reaction rate. Subsequent elimination of acetone from the intermediate affords the sulfoxide **86**.[49]



85 **86**

Scheme 2.35

2.5.3 Spectroscopic Details of Isothiochroman-4-one *S*-Oxides

The carbonyl stretching frequency of the sulfoxides appears in the region of ~1680 cm^{-1}, which is very similar to that of the sulfides (Section 2.5.1). Another characteristic absorption in the IR spectra of these compounds is the sulfoxide stretching vibration. Sulfoxide aborptions are reported to appear in the 1070-1030 cm^{-1} region,[50] and the sulfoxide stretches were observed as strong bands within the range 1024-1048 cm^{-1} for the iosthiochroman-4-one *S*-oxides.

The ^1H NMR spectra for the sulfoxides were relatively straightforward. The most striking difference between the sulfoxides and their sulfide precursors is the presence of an AB quartet corresponding to the diastereotopic hydrogens of both α-CH_2 groups in the sulfoxides. For each sulfoxide, the benzylic CH_2 protons are more deshielded than the CH_2 protons α-to the keto group by ~0.4 ppm. The ^1H NMR data for the sulfoxides are summarised in Figure 2.8. For comparison, the ^1H NMR data for the sulfide **43** and the sulfone **83** are also given.

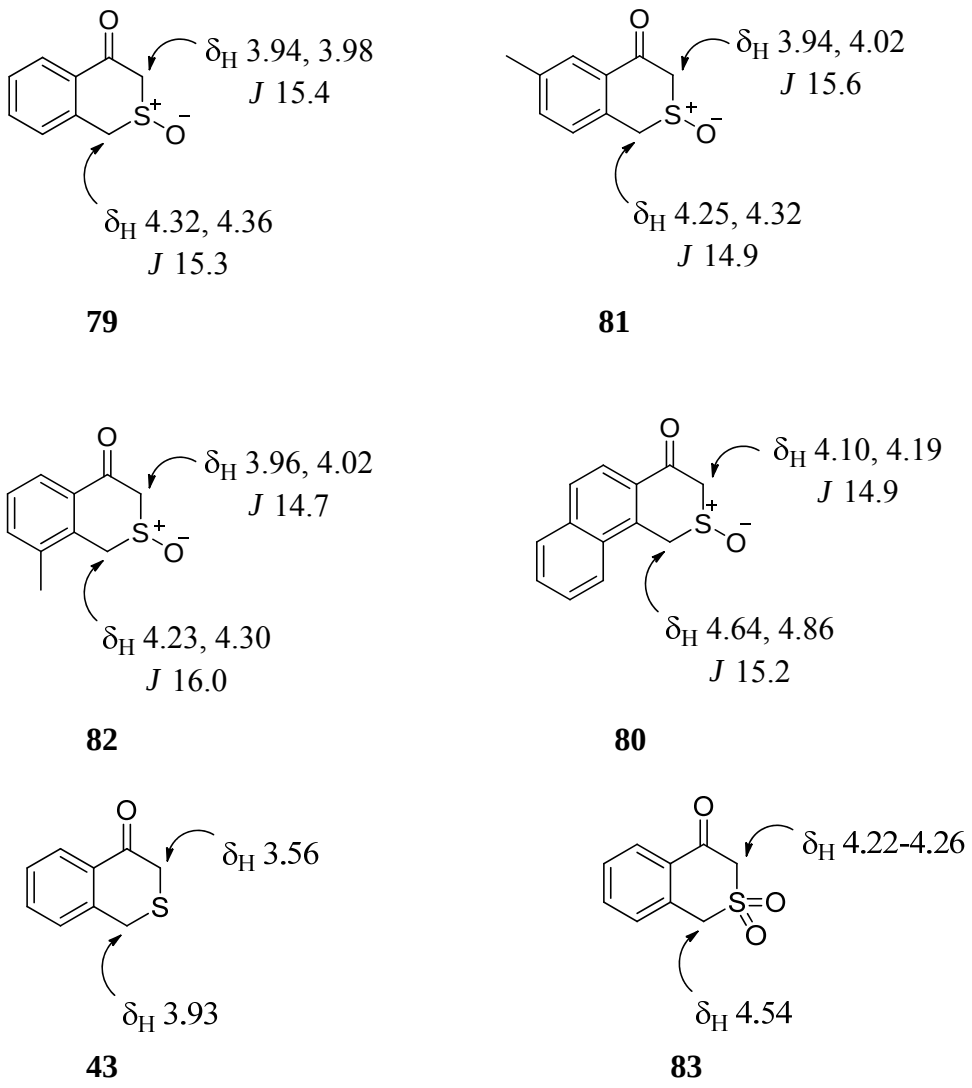


Figure 2.8 *Characteristic ^{1}H NMR signals for benzofused sulfoxides **79**, **81**, **82**, **80**, the sulfide **43**, and the sulfone **83** ($CDCl_3$, 400MHz).*

The ^{13}C NMR spectra of the sulfoxides were also readily assigned. For each sulfoxide, the benzylic CH_2 carbon is less deshielded than the CH_2 carbon α-to the keto group by ~7 ppm. The ^{13}C NMR spectral details are summarised in Figure 2.9.

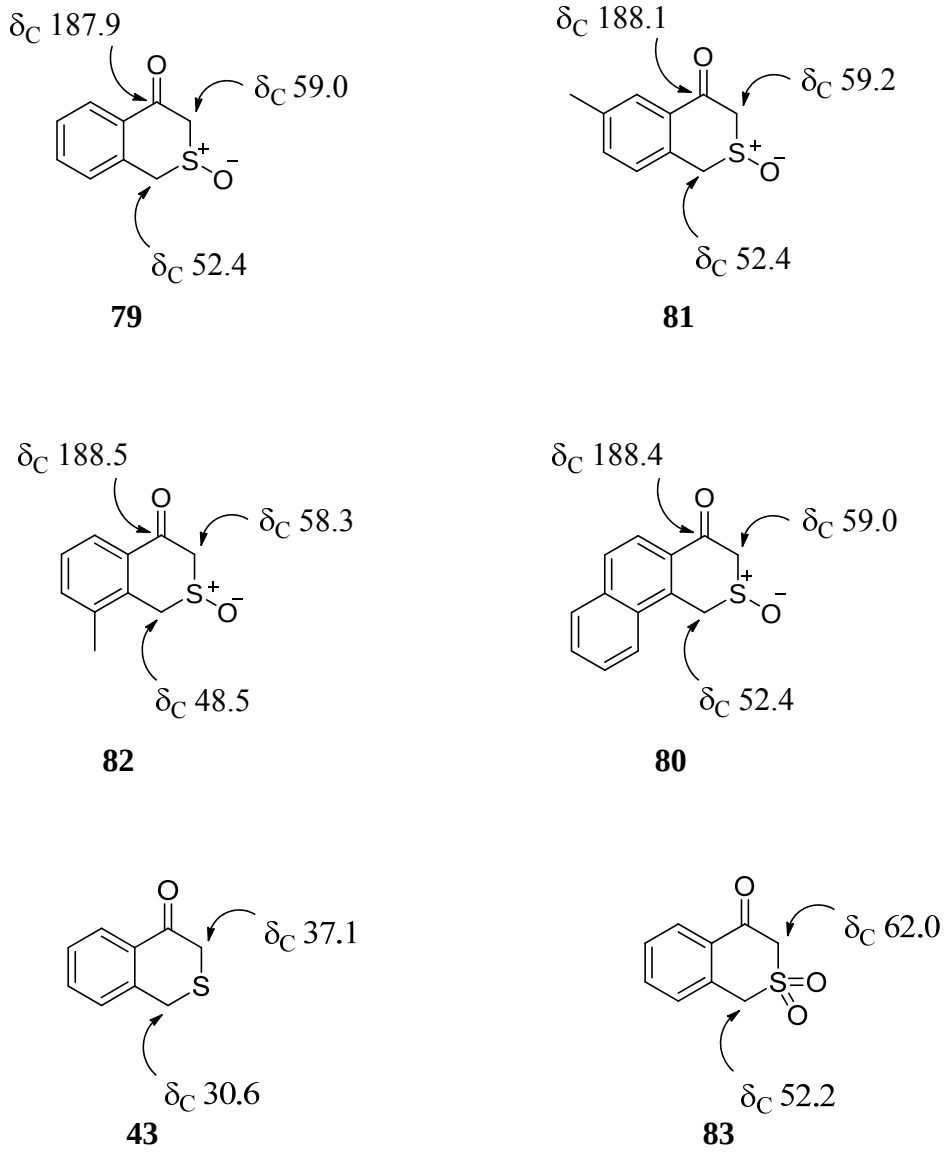
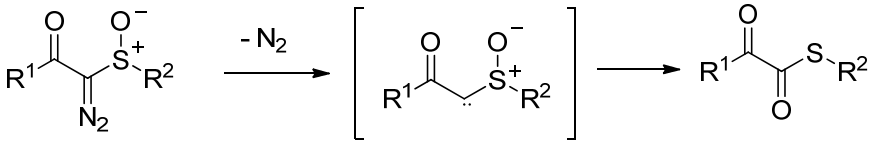


Figure 2.9 *Characteristic ^{13}C NMR signals for benzofused sulfoxides **79**, **81**, **82**, **80**, the sulfide **43**, and the sulfone **83** ($CDCl_3$, 75.5 MHz).*

2.5.4 Synthesis of 3-Diazoisothiochroman-4-one *S*-Oxides

Having synthesised a range of isothiochroman-4-one *S*-oxides, the next step was to investigate whether diazo transfer could be facilitated. As discussed in Section 2.1, prior to work within our group, it had been proposed that α-diazo-β-keto sulfoxides **4** are intrinsically unstable and that decomposition occurs by oxygen transfer from sulfur to carbon *via* carbene intermediates **3** leading to thiol esters **2** (Scheme 2.36).



Scheme 2.36

An alternative suggestion for the instability of simple acyclic α-diazosulfoxides has been suggested by workers within this group as being due to overlap of the sulfinyl lone pair of electrons with the unsaturated diazo moiety. This would facilitate loss of the diazo group as illustrated below (Figure 2.10).

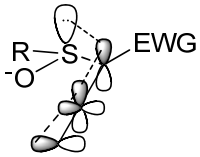
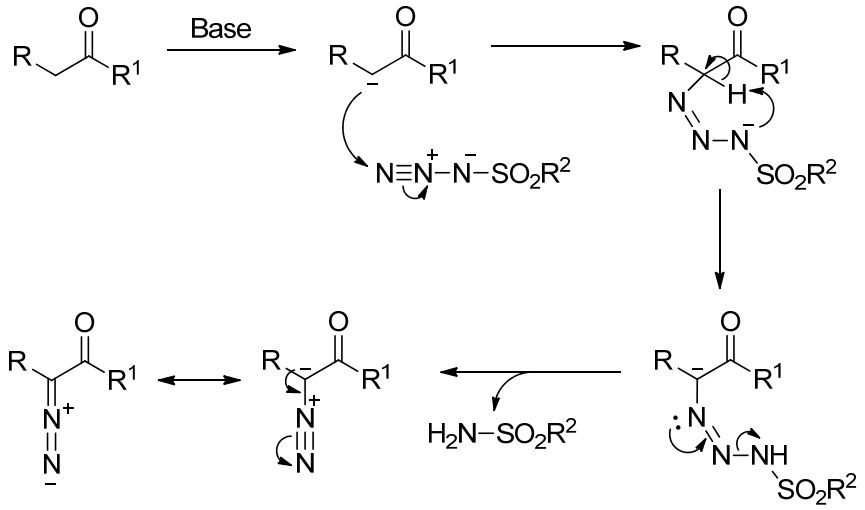


Figure 2.10

It was subsequently shown that cyclic α-diazosulfoxides with a lactone functionality can be formed as stable and isolable compounds, and it was proposed that by restricting the conformational mobility of the system in mono and bicyclic ring system then the ease of electron donation from the sulfinyl lone pair is decreased and accordingly the stability of the α-diazosulfoxide increases.[6] However, it was not known whether this would also be true for cyclic α-diazo-β-keto sulfoxides. Notably, α-diazoketones in general are more labile than α-diazoesters.[20]

Comprehensive reviews of the routes towards α-diazocarbonyl compounds are described by Maas,[51] and earlier by McKervey.[17] The Arndt-Eistert synthesis is the single most important route towards the synthesis of terminal α-diazoketones and involves the acylation of diazomethane with an acid chloride. However, the most useful method to obtain non-terminal or cyclic α-diazocarbonyl compounds employs diazo transfer reactions.[19] This method refers to the transfer of a complete diazo group from a donor (generally a sulfonyl azide) to an acceptor, which for α-diazocarbonyl compounds must be an acid or ketone derivative.[20] The general mechanism is shown in Scheme 2.37.



Scheme 2.37

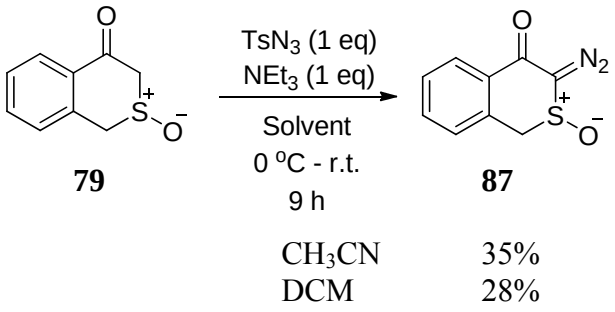
Diazo transfer to the lactone based sulfoxides **38a**, **38e**, **39a**, **39e** and **40**, discussed in Section 2.3.3, was achieved using reaction conditions previously optimised within the group.[7,9,10] Although tosyl azide **41** is the diazo transfer reagent which is most commonly employed,[19] Bollinger and Tuma have noted that there is no single diazo transfer reagent which is suitable for all diazo transfer reactions.[52] The factors affecting selection are low explosive potential, cost, availability of starting material, ease of separation of the product from the sulfonamide byproduct and efficient diazo transfer. The hazards associated with diazo transfer reagents have been assessed by Bollinger and co-workers.[52,53] Within our group, we have found tosyl azide **41** to be generally the most efficient diazo transfer agent.

Tosyl azide **41**, although offering a good diazo transfer yield, has been found to possess low impact sensitivity. Therefore, during the course of this work, several safety precautions were taken. Tosyl azide **41** was stored in the freezer, and while it is a liquid at room temperature, it forms a solid at low temperatures (m.p. 21-22 °C). Therefore, before use, tosyl azide **41** was gently melted by standing it in a shallow bath of lukewarm water. Bollinger and Tuma have stated that, in general, shock sensitivity can be eliminated when a sample is in liquid or in solution. If the compound is not completely dissolved, it retains its shock sensitivity.[52] The diazo transfer reagent was transferred carefully using a Pasteur pipette which did not have any sharp edges. In the interest of safety, the sash of the fumehood was kept closed during the synthesis of the tosyl azide **41**, both while the reaction was taking place

and while the reaction mixture was being concentrated on the safety rotary evaporator.

In this work, tosyl azide **41** was synthesised in ~10 g batches by reaction of *p*-toluenesulfonyl chloride with sodium azide in acetone,[54] which is one of the most common routes towards sulfonyl azides. While tosyl azide **41** was the diazo transfer reagent employed for the synthesis of 3-diazoisothiochroman-4-one *S*-oxides, many alternative transfer reagents are available.[19]

Diazo transfer was attempted to the sulfoxide **79** initially using the conditions successfully employed for the synthesis of the lactone α-diazosulfoxides.[7,9,10] The reaction involved the use of triethylamine and tosyl azide **41** in acetonitrile solution at 0 °C (Scheme 2.38). The reaction mixture was stirred under the inert atmosphere while returning slowly to room temperature.



79 **87**

CH_3CN	35%
DCM	28%

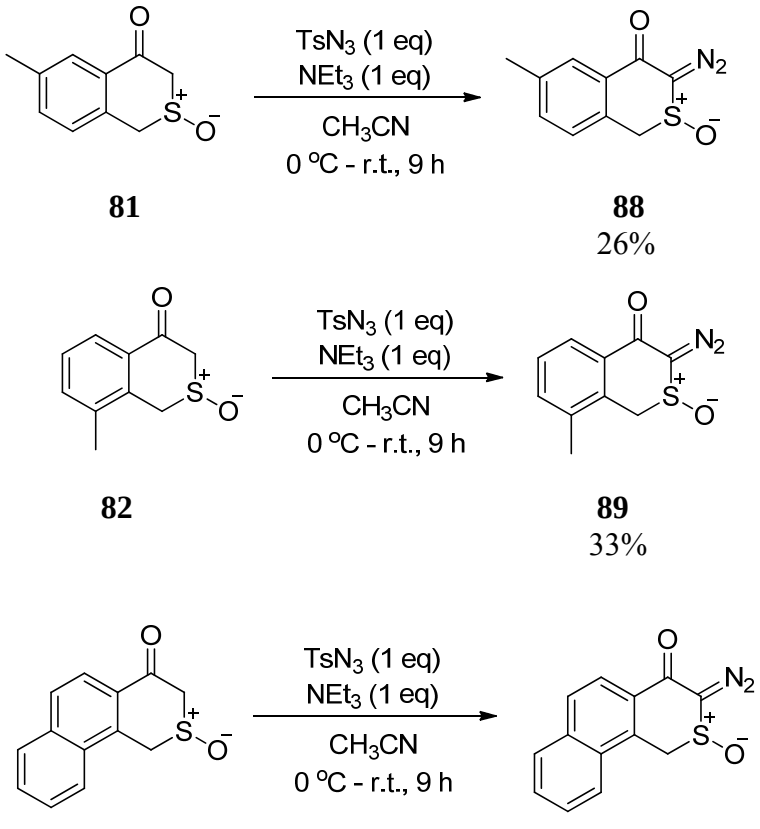
Scheme 2.38

The progress of the reaction mixture was monitored by TLC. The polar sulfoxide **79** appeared by TLC with UV light and as a strong blue spot by vanillin at the baseline of the TLC plate in 50:50 hexane/ethyl acetate eluent. After approximately 1 hour, a second spot was visualised with UV light and by vanillin (R_f = 0.12), just above the sulfoxide spot. Encouragingly, the second spot became more intense over time, with the sulfoxide **79** spot decreasing in intensity. After 9 hours a ^{1}H NMR spectrum of the crude oil was obtained. We were pleased to observe the complete absence of the α-keto CH_2 AB quartet belonging the sulfoxide **79** in the ^{1}H NMR spectrum and the appearance of a diazo stretch at 2120 cm^{-1} in the IR spectrum. The benzylic CH_2 was visible as a finely split AB quartet at 4.32 ppm. Purification of the diazo product **87** by column chromatography on silica gel gave a brown solid in 35% yield (Scheme 2.38). It is believed that partial loss of the diazo

product on the silica gel resulted in the modest yield obtained, as diazo transfer was essentially clean and quantitative by ^{1}H NMR analysis, with a good mass recovery of the crude product. TLC analysis of a pure sample of **87** was conducted on a "square" TLC plate,* with no evidence for decomposition observed.

The reaction was repeated in dichloromethane solvent using the same reaction conditions. We were interested to see whether dichloromethane would be to be a suitable solvent for diazo transfer, as previous workers within the group reported slightly lower yields for diazo transfer to lactone based sulfoxides in dichloromethane.[10] The reaction was found to be complete by TLC after 18 h. The α-diazosulfoxide **87** was obtained in a lower yield of 28% after chromatography.

Encouraged by these results, diazo transfer to the sulfoxides **81**, **82** and **80** was examined using the same reaction conditions employed for the sulfoxide **79** (Scheme 2.39).



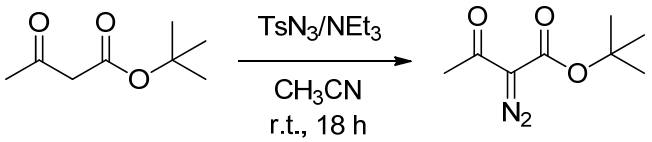
Scheme 2.39

* This refers to a TLC plate run in two orthogonal directions in order to assess sensitivity to silica gel.

The diazo products **88** and **89** were isolated as brown solids after chromatography in moderate yields (Scheme 2.39). However, decomposition of the naphthyl diazo product **90** resulted in isolation of a very small quantity of an impure sample (~43 mg from 630 mg **80**) which could not be fully characterised (Scheme 2.39). ^{1}H NMR spectra of the crude products of **87**-**89** showed that they were essentially the α-diazosulfoxides. However, the ^{1}H NMR spectrum of the crude product of the naphthyl derivative was much more complex, with only minor amounts of signals corresponding to **90** visible, most notably the AB quartet at 4.35 and 5.20 ppm. As there is no evidence for remaining sulfoxide **80**, it is believed that the α-diazosulfoxide is labile and decomposes readily to a complex mixture of unidentifiable products. The purity of the sulfoxide starting material was rechecked based on the poor outcome of the diazo transfer and was found to be pure by ^{1}H NMR analysis.

After the initial addition of tosyl azide **41** to the colourless reaction mixtures, a colour change to pale pink was observed, which darkened to a deep red within a few hours. In general, after stirring over 9 hours with TLC monitoring, the reaction mixtures developed into a dark brown colour. Similar to the lactone α-diazosulfoxides discussed in Section 2.3.3, the crude products were extremely viscous oils which were insoluble in the eluent and consequently had to be adsorbed onto Celite® before purification. The α-diazosulfoxides that are formed are very polar compounds, albeit slightly less polar than their sulfoxide precursors, which appear as strong spots on the TLC when visualised with UV light and give dark, almost black spots when stained with vanillin. The α-diazosulfoxides also appear as strong spots when visualised with UV light and give blue spots when stained with vanillin. The sulfonamide byproduct gave a yellow colour which quickly faded when stained with vanillin. It was found that by adding charcoal to a solution of the brown diazo products in dichloromethane and filtering, the brown colour could be removed to leave a pale yellow solution, albeit with loss in yield. Evaporation of the solvent left the pure diazo products as yellow crystals. The α-diazosulfoxides **87, 88** and **89** are quite stable and there was no evidence for their decomposition after storage at 4 °C for several months. Notably, the α-diazosulfoxides decompose on melting. In this work, it was possible to prepare these α-diazosulfoxides up to 1 gram quantity, with the scale mainly limited by the amount of available sulfoxide starting material.

Due to the moderate yield of pure α-diazosulfoxide **87** obtained after chromatography, an alternative method of purification was explored. Previous workers within the group had had some success with a base work-up involving a 9% KOH wash to remove the sulfonamide byproduct (Scheme 2.40),[55] as outlined initially by Regitz.[56]



91 **92**

95% (after base wash)

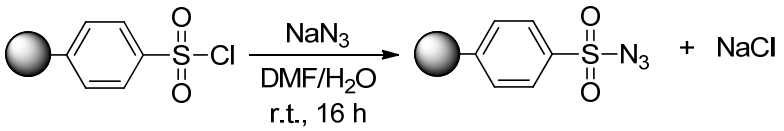
Scheme 2.40

The diazo transfer reaction to **79** was repeated as outlined in Scheme 2.38. TLC indicated complete consumption of the sulfoxide **79** and the acetonitrile was removed under reduced pressure. The resulting brown oil was dissolved in dichloromethane and then washed twice with 9% potassium hydroxide and once with water to give a brown residue. The ^{1}H NMR spectrum indicated the absence of the sulfonamide byproduct. However, a very low yield of ~11% was obtained, indicating that this method of purification is unsuitable for these α-diazosulfoxides, perhaps due to ring opening under basic conditions.

Researchers within the group have made significant progress towards 'greener' diazo transfer chemistry.[55] The primary reason diazo transfer reactions are not routinely carried out on large scale in industry is due to the hazardous nature of the transfer reagents. There are a number of reviews in the literature concerning the hazardous nature of diazo transfer reagents,[52,53] as well as some incident reports.[57,58] As discussed above, traditional diazo transfer reagents are inherently unstable and the utmost care must be taken when handling these reagents. Recently, safer alternatives have been developed,[59-61] including polystyrene supported benzenesulfonyl azide **93**, which could increase the attraction and potential of diazo chemistry.[62]

Polystyrene supported benzenesulfonyl azide **93** was prepared in one step using commercially available polystyrene benzenesulfonyl chloride **94** (100-200 mesh, 1.5-2.0 mmol/g) and sodium azide, as described by Green (Scheme 2.41).[62]

The amount of sodium azide used was calculated based on the estimated loading of the sulfonyl chloride.

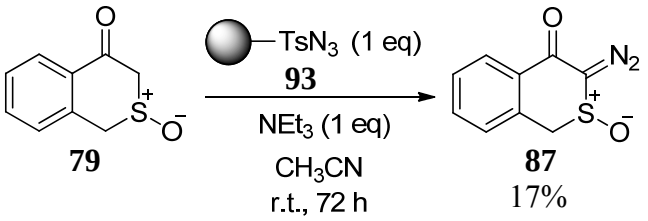


94 **93**

Scheme 2.41

The reaction was stirred overnight and the resin isolated and washed with water, dimethylformamide and dichloromethane.[63] The light brown resin was easily dried by gravity filtration and stored at 4 °C. There are a number of advantages to using polystyrene supported benzenesulfonyl azide **93**. The preparation does not require an aqueous work-up and there is no concentration of solutions containing tosyl azide **41**. The impact sensitivity of tosyl azide **41** is thus substantially reduced. Also, the polystyrene supported sulfonamide byproduct is readily removed by filtration.

Diazo transfer to the sulfoxide **79** was achieved following a modified procedure as described by Green,[62] using acetonitrile solvent instead of dichloromethane based on previous results. The reaction procedure involved stirring the benzenesulfonyl azide resin **93** (estimated as 1 mole equivalent) in acetonitrile for 10 min, followed by addition of the sulfoxide **79** and 1 equivalent of triethylamine. After 72 h with TLC monitoring to watch the disappearance of the starting material, TLC and ^{1}H NMR analysis indicated that complete diazo transfer had occurred to give the α-diazosulfoxide **87** which was isolated in 17% yield after column chromatography (Scheme 2.44). There were no other unidentifiable products in the crude product and it is believed that the low yield is associated with the lability of the α-diazosulfoxide in the reaction medium over the extended reaction time.



Scheme 2.44

The immobilised sulfonamide byproduct was easily removed by gravity filtration. Despite the lengthy reaction time (72 h instead of 9 h), successful diazo transfer to a β-ketosulfoxide using immobilised benzenesulfonyl azide **93** represents an important preliminary result in this project. The scope of this reactivity should be investigated further. Future investigation of this diazo transfer approach, including variation of the solvent or increasing the reaction temperature to decrease the reaction time, is warranted.

2.5.5 Spectroscopic Details of 3-Diazoisothiochroman-4-one *S*-Oxides

The success of the diazo transfer reactions is immediately apparent from a diazo group stretch observed in the region 2111-2120 cm^{-1} of the IR spectrum. In the case of the α-diazosulfoxide **87**, a splitting of the diazo group stretch meant that two bands were observed at 2120 and 2131 cm^{-1}, and for the 6-methyl α-diazosulfoxide **88**, a splitting of the diazo group gave two bands at 2111 and 2097 cm^{-1}. This was probably due to environmental effects within the KBr disc.[9]

A significant change to the ^1H NMR spectrum is also observed after diazo transfer has taken place. As the two diastereotopic α-keto hydrogens have been replaced by the diazo functionality, one of the characteristic AB quartets observed for the sulfoxides no longer appears in the spectrum. ^1H NMR data for the α-diazosulfoxides **87**, **88, 89** and **90** are given in Figure 2.11. For the α-diazosulfoxides **87** and **88**, the benzylic CH_2 is a very finely split AB quartet which essentially appears as a singlet. For the 8-substituted α-diazosulfoxide **89** and naphthyl α-diazosulfoxide **90**, however, the two protons appear as a distinct AB quartet with coupling constants of 15.5 and 15.8 Hz, respectively. The alteration in the appearance of the AB quartet in the diazo transfer highlights the alteration in

conformation on diazo transfer, with the C(3) carbon moving from sp^3 to sp^2 hybridisation.

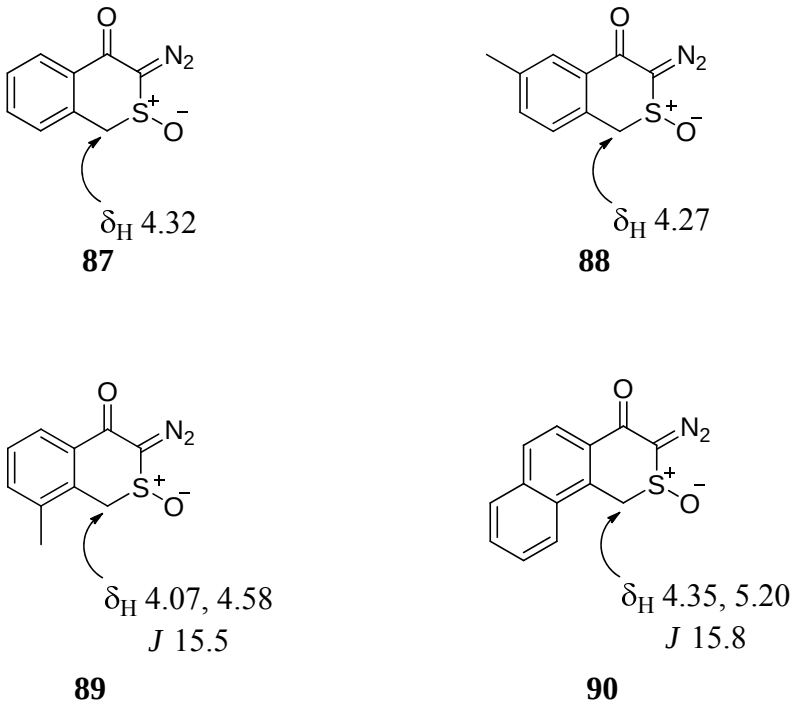
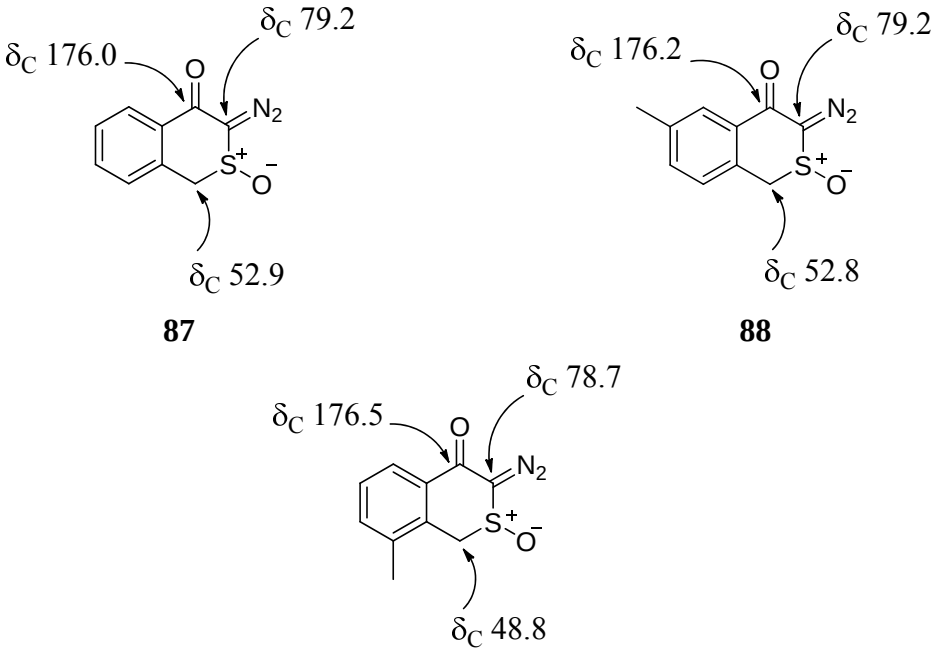


Figure 2.11 *Characteristic ^1H NMR signals for benzofused α-diazosulfoxides ($CDCl_3$, 400 MHz)*

^{13}C NMR data for the α-diazosulfoxides **87, 88** and **89** are summarised in Figure 2.12. Unlike the lactone α-diazosulfoxides discussed in Section 2.3.3, the signal corresponding to the carbon bonded to the diazo group ($C=N_2$) for the α-diazosulfoxides **87**, **88** and **89** were observed at ~79 ppm.



87 **88** **89**

Figure 2.12 *Characteristic ^{13}C NMR signals for benzofused α-diazosulfoxides ($CDCl_3$, 75.5 MHz)*

Unambiguous structural confirmation of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** by X-ray crystallography proved possible, indicating the relative stability of the diazo derivative and providing conclusive proof for the isolation of the novel α-diazo-β-keto sulfoxides (Figure 2.13).

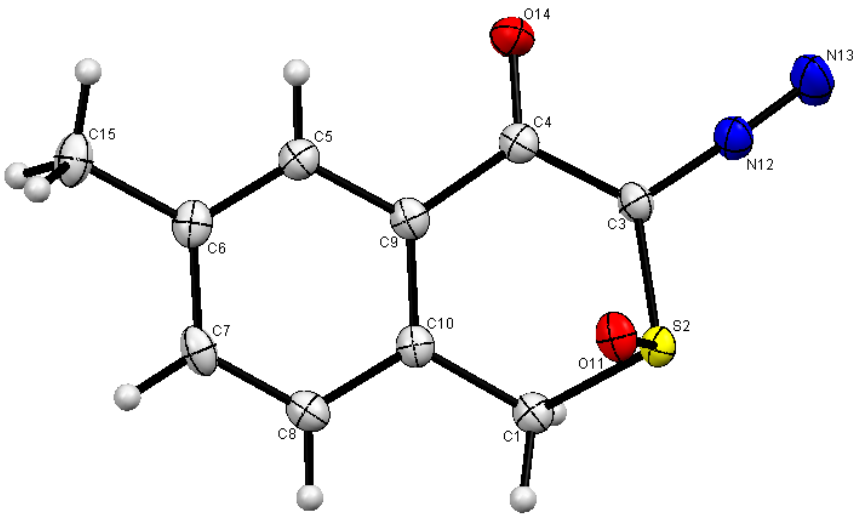
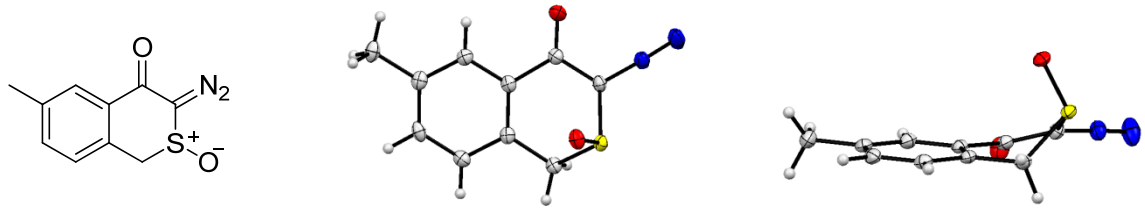


Figure 2.13 *X-ray crystal structure of 3-diazo-6-methylisothiochroman-4-one S-oxide **88**. Structure is displayed using the Mercury 2.3 (Build RC4) package.*

This three-dimensional crystal structure of α-diazosulfoxide **88** is illustrated using a front-face view (i) and side view (ii), as shown in Figure 2.14. The molecule was rotated using the Mercury 2.3 (Build RC4) package. The conformation of the 6-membered ring is clearly shown, with the sulfoxide group puckered upwards in (ii).



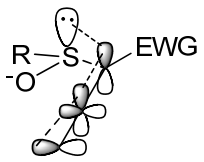
88

(i)

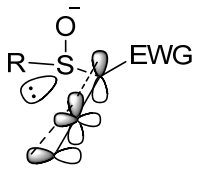
(ii)

Figure 2.14 *X-ray crystal structure of the α-diazosulfoxide **88** in a front-face view (i) and a side view(ii). Structures are displayed using the Mercury 2.3 (Build RC4) package.*

The conformational properties of the α-diazosulfoxide **88** provides further evidence for the suggested explanation for the stability of cyclic α-diazosulfoxides proposed by workers within this group, and which was discussed in Section 2.1. The conformation of the puckered sulfoxide group results in the lone pair of electrons lying in plane with the unsaturated diazo moiety and orthogonal to the π-orbitals of the diazo group. This prevents overlap with the π-orbitals which would facilitate loss of the diazo group, as illustrated in (ii) of Figure 2.15.



(i)



(ii)

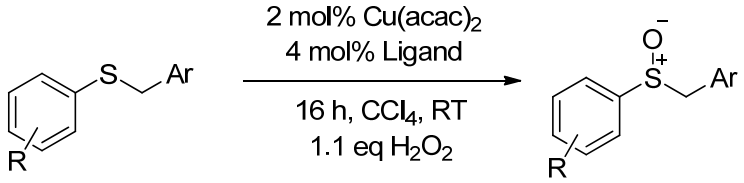
Figure 2.15

In conclusion, isolation of stable α-diazo-β-keto sulfoxides represents a significant advance in this research programme. For the first time, ketone derivatives

of the α-diazosulfoxides are provided for investigation, thereby providing enhanced mechanistic understanding, in addition to expanded synthetic utility.

2.5.6 Attempted Asymmetric Sulfoxidation of Isothiochroman-4-one 43

α-Diazosulfoxides are envisaged to have potential in stereoselective synthesis and therefore we wished to extend this work to the enantiomerically enriched series, so that access to the rhodium(II) catalysed decomposition products in enantioenriched form could also be achieved. The asymmetric synthesis of sulfoxides is an important transformation in organic synthesis. Enantiopure sulfoxides are used in the pharmaceutical industry due to their important biological activity, and the sulfinyl group has also been shown to be an effective chiral auxiliary.[64] Recently, there has been some success within the group in the area of copper catalysed asymmetric sulfoxidation of sulfides (Scheme 2.45).[65]



up to 93% ee

Scheme 2.45

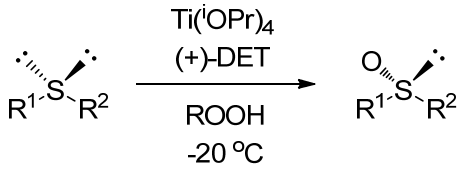
In this work, a brief investigation into the asymmetric sulfoxidation of isothiochroman-4-one **43** was undertaken. The reactions which were carried out are discussed below (Scheme 2.46).

(i) *The Kagan Oxidation*

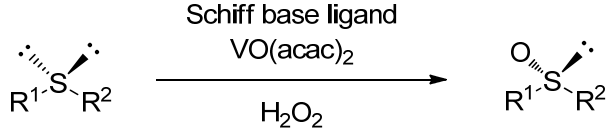
(ii) *The Bolm Oxidation*

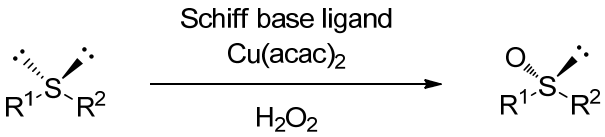
(iii) *Copper(II) catalysed Oxidation*

(i)



(ii)

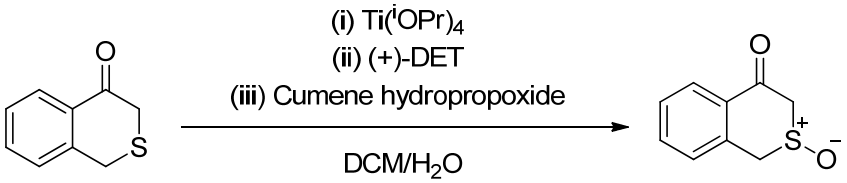


(iii) 

Scheme 2.46

Developed as a modification of the Sharpless asymmetric oxidation, the Kagan oxidation has been widely reported in the literature for the asymmetric oxidation of prochiral sulfides to sulfoxides with good enantioselectivity.[35,66-68] Although the Kagan method has been widely reported for the asymmetric sulfoxidation of aryl methyl sulfides,[31,32,69] its scope is somewhat limited and there is little evidence in the literature for its use with cyclic β-ketosulfides, such as the isothiochroman-4-ones investigated in this work. The procedure involves the preparation of a chiral complex formed between titanium isopropoxide and (+)-diethyl tartrate with a carefully controlled quantity of water added. The reaction is conducted at -20 °C for up to 20 hours, using cumene hydroperoxide or *t*-butyl hydroperoxide as oxidant.

In this work, oxidation of the sulfide isothiochroman-4-one **43** under the standard Kagan conditions was explored, even though the compound does not contain the standard aryl methyl moiety. TLC analysis indicated complete conversion of the sulfide **43** and the 2-phenyl propan-2-ol was removed by column chromatography. At this point, the ^{1}H NMR spectrum of the product indicated complete conversion to the sulfoxide isothiochroman-4-one *S*-oxide **79**, albeit in a very low yield of 12% (Scheme 2.47). One possible explanation for the low recovery is that the highly polar sulfoxide **79** may have been partially soluble in water. A chiral HPLC assay had been developed for analysis of the enantiopurity of the sulfoxide using a racemic sample (See Appendix I for conditions). However, the sample of the sulfoxide **79** isolated from the Kagan conditions was essentially racemic, indicating limited enantioselectivity with the titanium reagent in this instance, as expected based on literature precedent. To the best of our knowledge, oxidation of β-keto sulfides using the Kagan method has not previously been reported.

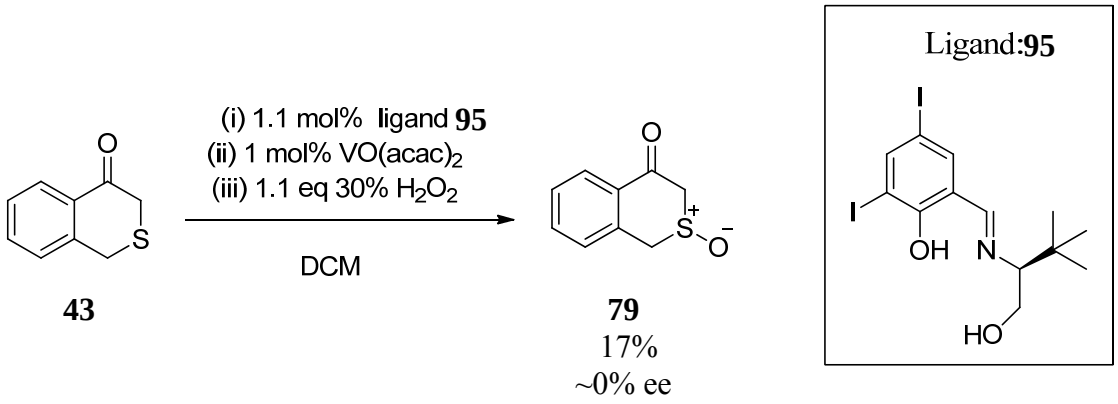


43 **79** 12% ~0% ee

Scheme 2.47

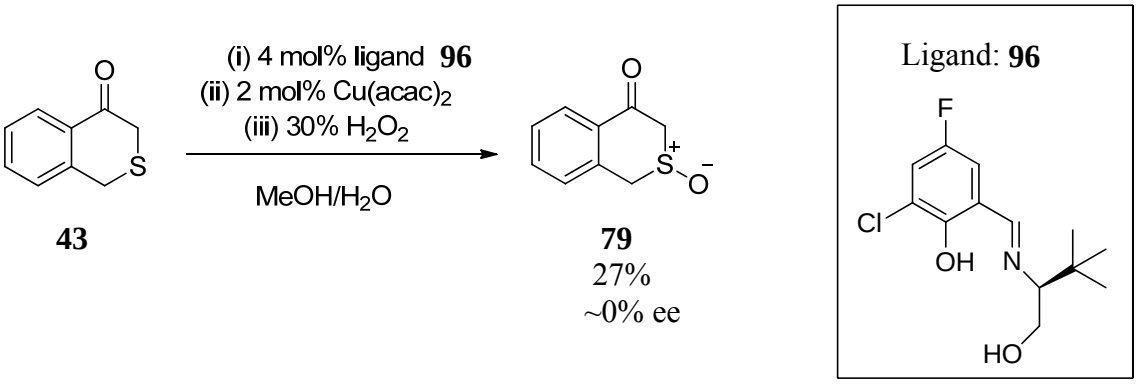
The Bolm oxidation was first reported in 1995 as a landmark vanadium Schiff base catalysed sulfide oxidation.[70] The mild conditions employed using this oxidation method and the high enantioselectivity reported make this a very attractive method for the asymmetric preparation of sulfoxides. Notably, the Bolm oxidation can be carried out under atmospheric conditions as the reaction is not sensitive to either moisture or oxygen. This is significant from a practical point of view, as many other oxidation methods, such as the titanium-catalysed Kagan oxidation, are extremely sensitive to moisture and must be carried out under an inert atmosphere. The method involves the initial preparation of a vanadium Schiff base complex *in situ*, from a Schiff base ligand such as **95** previously used within the group,[71,72] which is then mixed with the sulfide. Once again, the scope of this oxidation appears to be limited, largely to aryl methyl and aryl benzyl derivatives.[31,32,71-73] However, the simplicity and effectiveness of this oxidation method make it a very attractive and practical route for the oxidative preparation of enantioenriched sulfoxides and it was explored for the asymmetric oxidation of isothiochroman-4-one **43**.

The sulfide **43** was oxidised in the presence of the optimum Schiff base ligand **95** using this method for 16 hours. Following work-up, the crude product was isolated as a mixture of the sulfide **43** and sulfoxide **79** (2:1). The pure sulfoxide **79** was obtained in a low yield of 17% after chromatography (Scheme 2.48), and again in this instance the sample was essentially racemic by chiral HPLC (Appendix I). Once again, the low yield is indicative of the water solubility of the sulfoxide **79**.



Scheme 2.48

Recent work within the group has led to asymmetric sulfoxidation of aryl benzyl and aryl alkyl sulfides under copper(II) catalysed conditions with up to 93% ee and 30% yield.[74] It was decided to investigate the optimised conditions reported for this method in the sulfoxidation of **43** in this work. The optimum Schiff base ligand which was used is illustrated in Scheme 2.49.[75] However, while the sulfoxide **79** was isolated in a yield of 27% in this instance, once again the sulfoxide **79** was racemic by chiral HPLC (Appendix I).

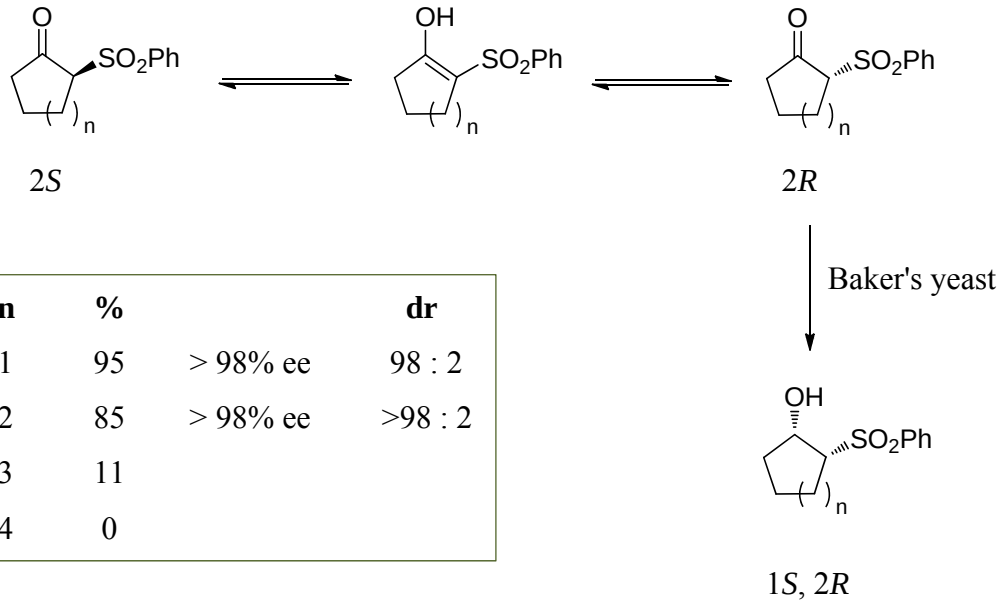


Scheme 2.49

Interestingly, while the sulfide **43** is unsymmetrically substituted, differentiation between approach of the oxidant to each of the two enantiofaces is very poor, resulting in the formation of essentially racemic samples of the sulfoxide **79** in each case.

2.5.7 Attempted Asymmetric Synthesis Using Baker's Yeast

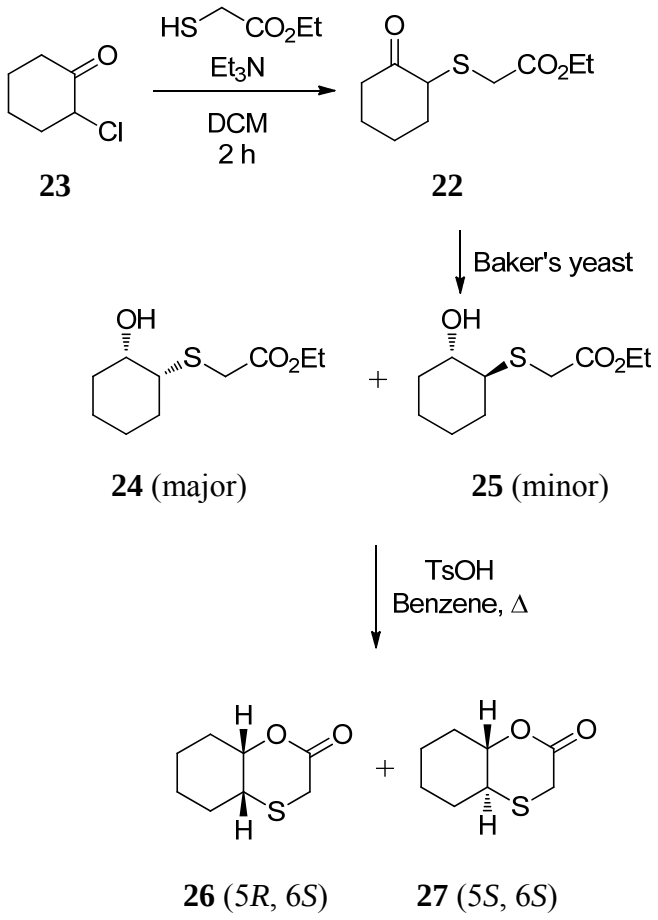
Based on previous experience within the group in baker's yeast (*Saccharomyces cerevisiae*) mediated reduction of cycloalkanones bearing sulfur substituents at the α-position,[8,76-79] it was envisaged that this methodology could be employed for the asymmetric synthesis of the isothiochroman-4-one *S*-oxide **79**. Work within this group has demonstrated that efficient dynamic kinetic resolution of 2-benzenesulfonylcyclopentanones and -cyclohexanones can be achieved using baker's yeast (Scheme 2.50).[80]



n	%		dr
1	95	> 98% ee	98 : 2
2	85	> 98% ee	>98 : 2
3	11		
4	0		

Scheme 2.50

As discussed in Section 2.1, Collins has reported the asymmetric synthesis of *cis*- and *trans*-fused lactones using baker's yeast reduction of the β-ketosulfide **22** (Scheme 2.51).[8]



Scheme 2.51

The baker's yeast reduction of carbonyl containing derivatives to give enantiomerically enriched alcohols generally proceed with excellent enantioselectivity,[79,81,82] following Prelog's rule[83] with approach of the hydride from the *re* face of the carbonyl to give the *S*-enantiomer of the alcohol (Figure 2.16).

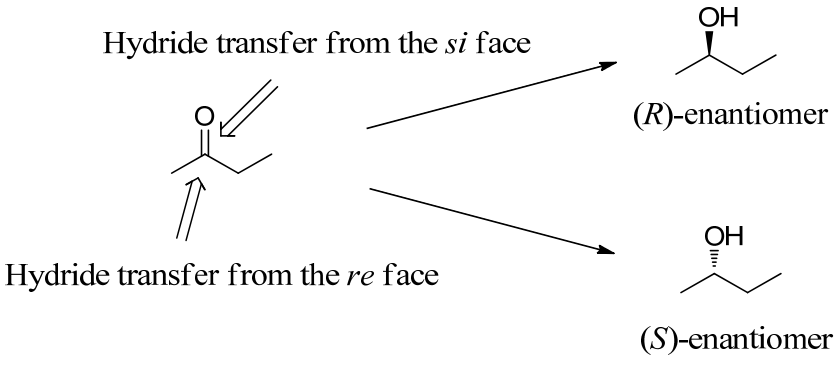
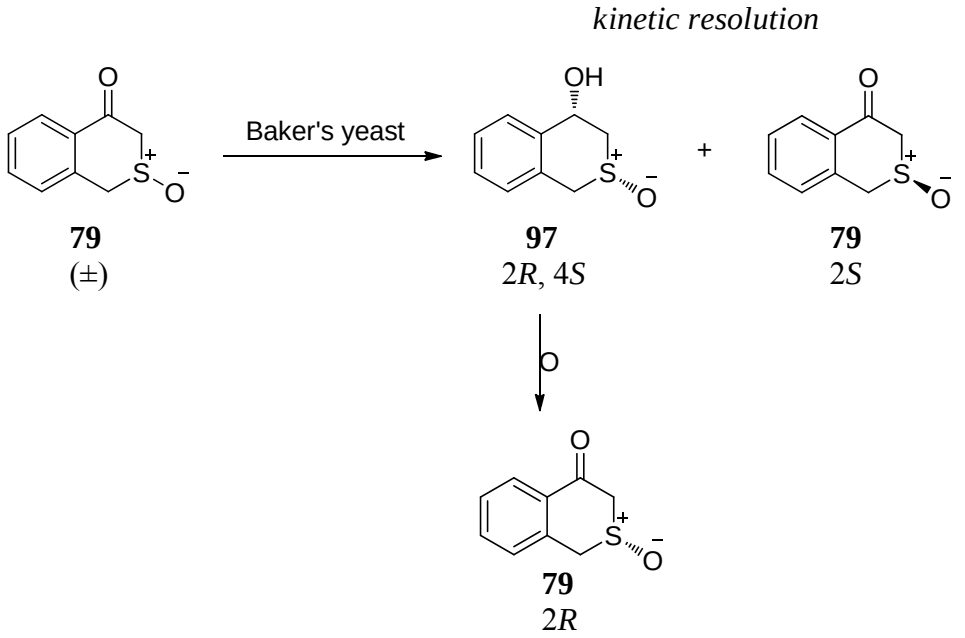


Figure 2.16

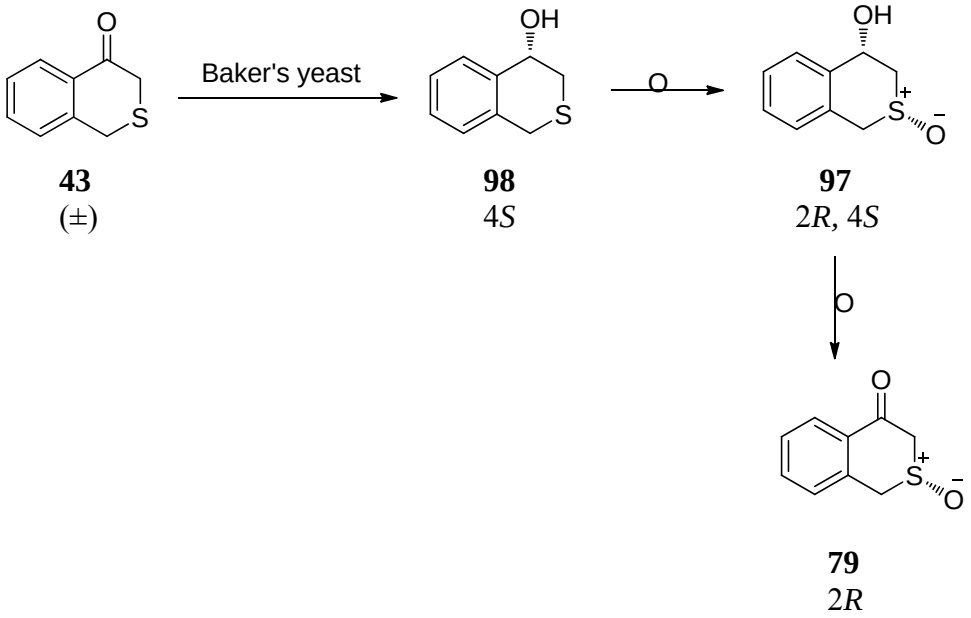
Using this methodology, the baker's yeast reduction of each of the sulfide **43** and the sulfoxide **79** was attempted in order to generate the enantioenriched

sulfoxide **79**. Firstly, kinetic resolution of the baker's yeast reduction of the racemic sulfoxide **79** was envisaged to yield an enantiopure alcohol **97** and ketone **79**. Subsequent oxidation of the alcohol would then provide the opposite enantiomer of the sulfoxide **79** (Scheme 2.52).



Scheme 2.52

Secondly, baker's yeast reduction of the sulfide **43** was envisaged to form the enantiopure carbinol **98**. Diastereoselective oxidation of the enantioenriched carbinol **98** to produce the sulfoxide **97**, and on further oxidation the ketone **79** in enantioenriched form, was envisaged (Scheme 2.53).



43
(±)

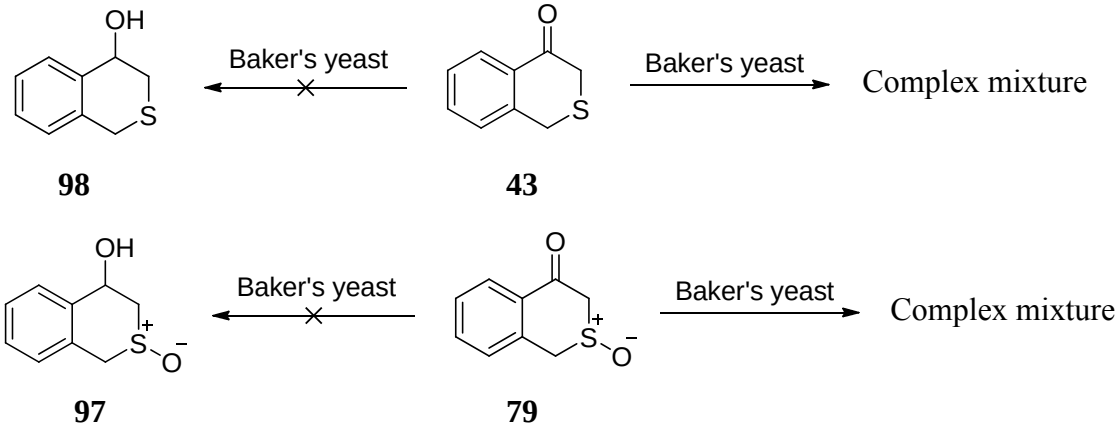
98
4*S*

97
2*R*, 4*S*

79
2*R*

Scheme 2.53

The baker's yeast reduction of each of the sulfide **43** and the sulfoxide **79** was attempted using a procedure adapted from Seebach involving a low yeast concentration,[84] and which has previously been successfully used within the group for the baker's yeast reduction of β-ketosulfides.[8] The solutions were agitated for ~1 hour, after which time TLC analysis indicated the absence of starting material. However, both TLC analysis and the ^{1}H NMR spectra of the crude products indicated the presence of a complex mixture of unidentifiable impurities for both reactions (Scheme 2.54).



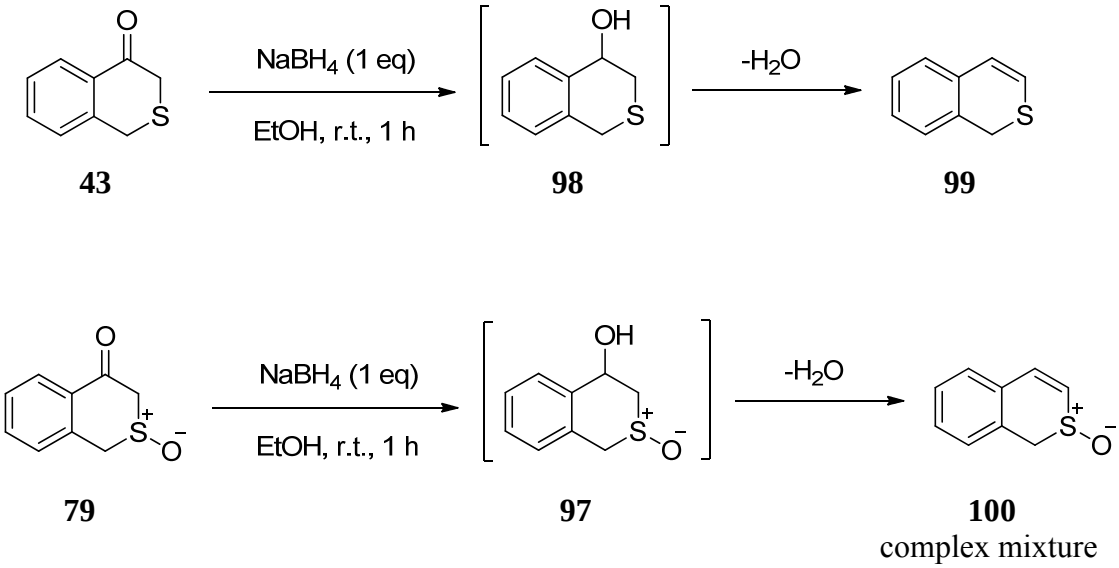
98 **43**

97 **79**

Scheme 2.54

As the baker's yeast reduction of the two isothiochroman-4-one systems was unsuccessful, it was decided to investigate the stability of the benzylic alcohols **98**

and **97** by undertaking racemic reductions of each of the sulfide **43** and the sulfoxide **79** in the presence of sodium borohydride (1 eq) in ethanol. The progress of the reactions was monitored by TLC. Once again, the carbinols **98** and **97** were not isolated, and instead dehydration occurred to give the isothiochromenes **99** and **100** among complex mixtures of unidentifiable compounds (Scheme 2.55). These results indicated that the benzylic alcohols **98** and **97** are very labile compounds. The relative stability of of the isothiochromenes **99** and **100** can be attributed to the extended conjugation associated with the formation of the alkene bonds on dehydration.



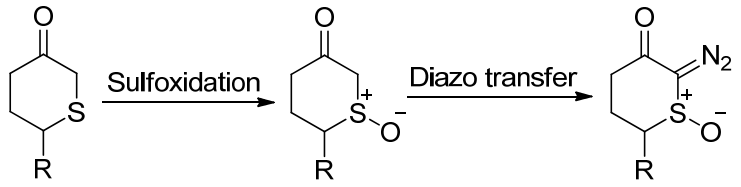
Scheme 2.55

As the baker's yeast mediated reduction of both the sulfide **43** and the sulfoxide **79** proved unsuitable for generating the carbinols **98** and **97**, this method was not pursued further. Interestingly however, the synthesis of 1*H*-isothiochromenes is of considerable synthetic interest, particularly with regard to pharmacological activity.[85] Therefore, this method may warrant further exploration in the future.

2.6 Synthesis of Monocyclic α-Diazo-β-keto Sulfoxides

The synthesis of bicyclic benzofused α-diazo-β-keto sulfoxides as a novel class of diazo compounds represented a major achievement in the course of this work. We were eager to see whether stable monocyclic α-diazo-β-keto sulfoxide derivatives could also be prepared. Although it was initially suggested that the bicyclic system for the lactone based α-diazosulfoxides played an important role in the stabilisation of the diazo system, several monocyclic α-diazosulfoxides have been prepared within this group to date, as illustrated in Figure 2.1, Section 2.1.[7,9,10]

A search of the literature led us to the simplest monocyclic β-keto sulfide, dihydro-2*H*-thiopyran-3(4*H*)-one **42**, which has been prepared as a useful synthetic precursor by a number of workers.[86,87] We decided to explore this compound as a suitable precursor for diazo transfer initially, with the potential to prepare a series of derivatives by introducing alkyl substituents on the ring as shown (Scheme 2.56).



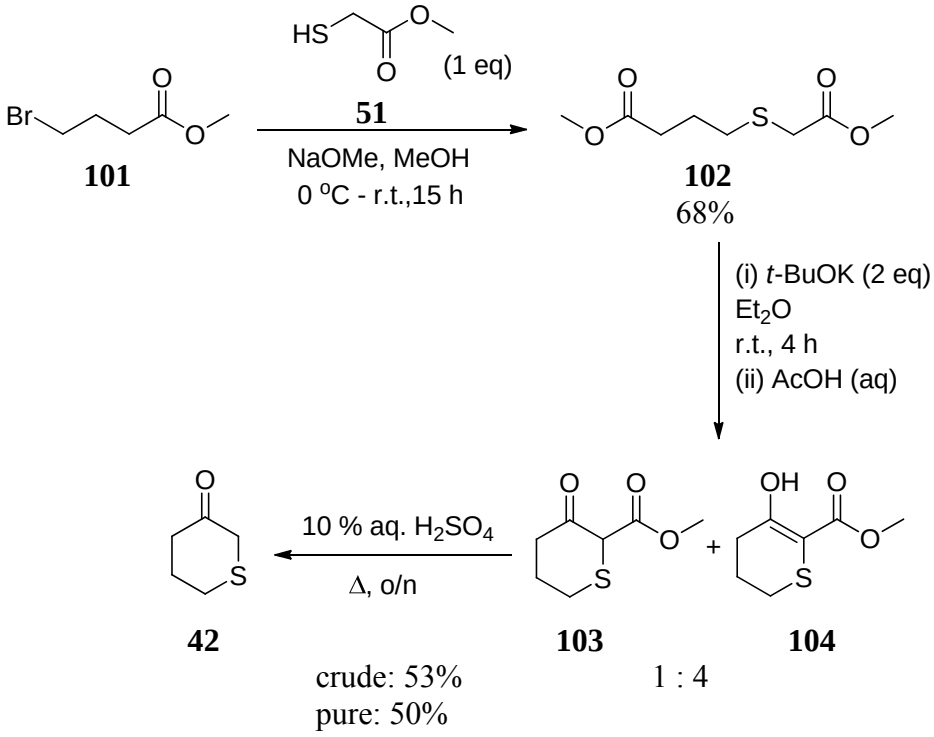
42: R = H

Scheme 2.56

2.6.1 Synthesis of Dihydro-2*H*-thiopyran-3(4*H*)-ones

2.6.1.1 Dihydro-2H-thiopyran-3(4H)-one 42

Dihydro-2*H*-thiopyran-3(4*H*)-one **42** was prepared following a modified procedure as described by Hamon[87] and summarised in Scheme 2.57.



Scheme 2.57

The first step of the sequence involved alkylation of the methyl thioglycolate anion with methyl 4-bromobutanoate **101** to give the diester **102** in 68% yield, as a pale yellow oil after aqueous work-up. The diester **102** was next treated with potassium *t*-butoxide in a Dieckmann condensation to give a 6-membered ring which proceeded smoothly to completion within 4 h by TLC. The solution was then neutralised with aqueous acetic acid. Cyclisation gave the β-keto ester **103** and the enol ester **104** in a 1:4 mixture as a yellow oil. The ^{1}H NMR spectrum of the mixture was complex, and not particularly instructive. However, a number of key signals could be recognised and were used for estimating the ratio of β-keto ester **103** to enol ester **104**. In particular, the CH signal of the β-keto ester appeared at 4.00 ppm, and the methyl ester signal appeared at 3.80 ppm. The broad OH singlet of the enol ester **104** was visible at 12.17 ppm and the methyl ester appeared at 3.81 ppm.

It should be noted, that while the Dieckmann condensation of a diester is a well-known and relatively straightforward reaction, finding suitable conditions for this particular substrate was not trivial. Hamon reported the successful use of sodium ethoxide in ethanol for the cyclisation of the analogous ethyl diester.[87] However, a range of bases, solvents and conditions were investigated before complete cyclisation was achieved; these are summarised in Table 2.1. Interestingly, cyclisation was not achieved with either sodium methoxide or sodium hydride as a base in a variety of solvents. However, the use of potassium *t*-butoxide led to efficient cyclisation with complete conversion evident following 4 hours in diethyl ether (Entry 10, Table 2.1).

Table 2.1 Influence of base and reaction conditions investigated for the Dieckmann Condensation of methyl 4-[(2-methoxy-2-oxomethyl)thio]butanoate **102**

Entry	Base	Eq.	Solvent	Conditions	Time	Conversion[a]
1	NaOMe	1	MeOH	RT	o/n	None
2	NaOMe	2	MeOH	RT	o/n	None
3	NaOMe	2	MeOH	Δ	o/n	None
4	NaOMe[b]	2.2	Et_2O	RT	2 h	None
5	NaH	1.4	Et_2O	RT	o/n	None
6	NaH	1.2	DCM	RT	o/n	None
7	*t*-BuOK[c]	1.1	THF	RT	2 h	Trace
8	*t*-BuOK[c]	1	Et_2O	Δ	2 h	66%
9	*t*-BuOK[c]	1	Toluene	Δ	o/n	60%
10	***t*-BuOK[c]**	**2**	**Et_2O**	**RT**	**4 h**	**100%**

a. Amount of product was estimated by ^{1}H NMR analysis by monitoring the presence of the C*H* of the cyclised β-keto ester at 4.10 ppm, and the O*H* of the cyclised enol at 12.20 ppm.
b. For entry 4, NaOMe 95% reagent grade powder was obtained from Sigma-Aldrich.
c. Potassium *t*-butoxide was used as commercially obtained from Aldrich without sublimation.

Hydrolysis of the ester and thermal decarboxylation was then achieved by heating under reflux conditions in 10% aqueous sulfuric acid overnight, followed by neutralisation with 10% aqueous sodium hydroxide to pH 7. The sulfide **42** was obtained as a black oil in 53% yield which was easily handled, without odour and very stable. The ^{1}H NMR spectrum of the crude product showed it to be remarkably pure, although chromatography to remove the colour gave a yellow oil in 50% yield. Spectral details were in agreement with the literature reports.[60] The IR spectrum showed the characteristic carbonyl stretch of a cyclic ketone at 1708 cm^{-1}. The ^{1}H NMR spectrum was quite straightforward, with the CH_2 singlet of the β-keto sulfide at 3.21 ppm deshielded relative to other CH_2 signals (Figure 2.17).

Notably, the sulfide **42** is prepared in a three-step sequence without requiring purification at any stage, providing ready access to the sulfide **42** in multigram scale for use in subsequent investigations.

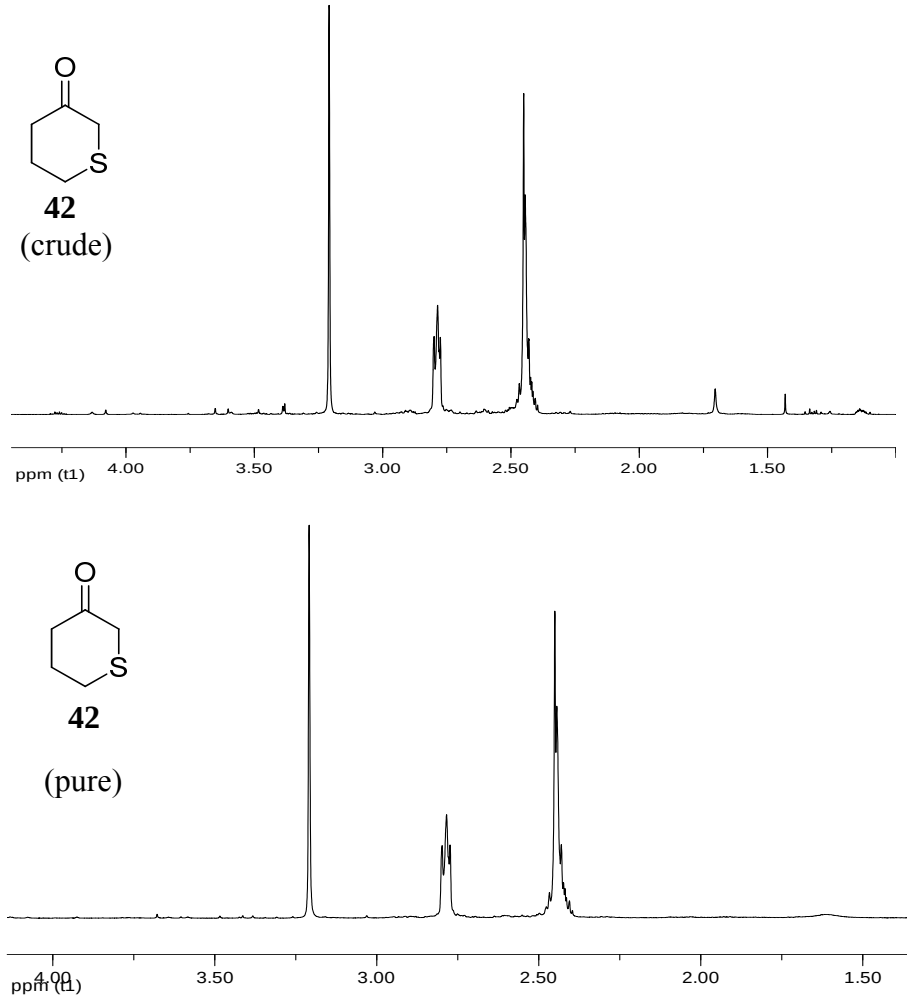


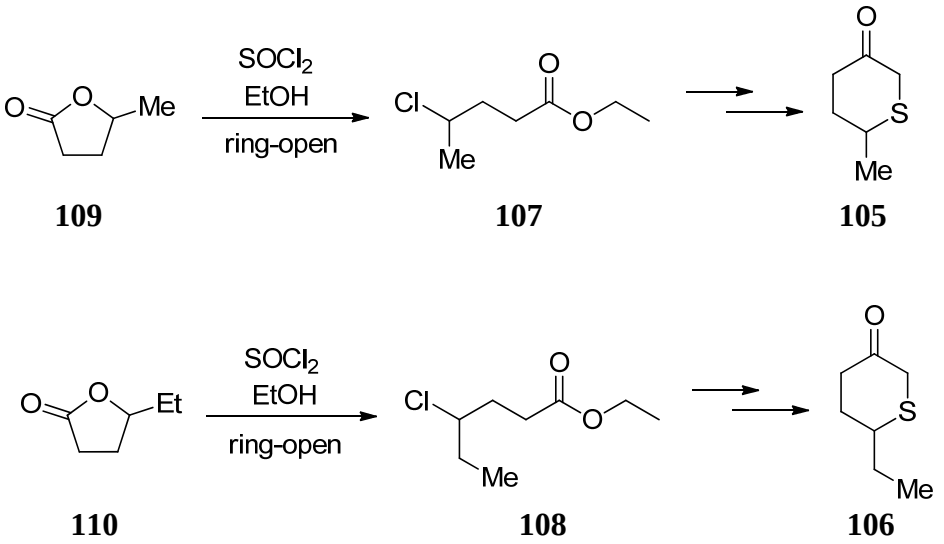
Figure 2.17 *Top: ^{1}H NMR spectra of crude sulfide **42**; bottom: pure sulfide **42** (400 MHz, $CDCl_3$).*

2.6.1.2 Alkyl substituted dihydro-2H-thiopyran-3(4H)-ones

Having prepared the unsubstituted monocyclic sulfide **42**, it was decided to synthesise the alkyl substituted analogues **105** and **106**, to explore the effect, if any, alkyl substitution would have on sulfoxidation or diazo transfer. While the sulfide **105** is mentioned in the literature, its synthesis and characterisation have not been fully described.[88] The methyl substituted sulfide **105** and the ethyl substituted sulfide **106** were synthesised following the procedure employed for the preparation of the unsubstituted monocyclic sulfide **42**. However, the secondary alkyl chlorides **107**

and **108** required for the synthesis of **105** and **106** were not commercially available, and accordingly, their synthesis was explored (Scheme 2.58).

A literature review revealed that γ-lactones undergo ring opening with thionyl chloride to generate γ-chloro esters.[89-91] Therefore, it was decided to employ a strategy beginning with γ-lactones, whereby ring-opening of γ-valerolactone **109** would give ethyl 4-chloropentanoate **107** and ring-opening of γ-caprolactone **110** would give ethyl 4-chlorohexanoate **108** (Scheme 2.58).

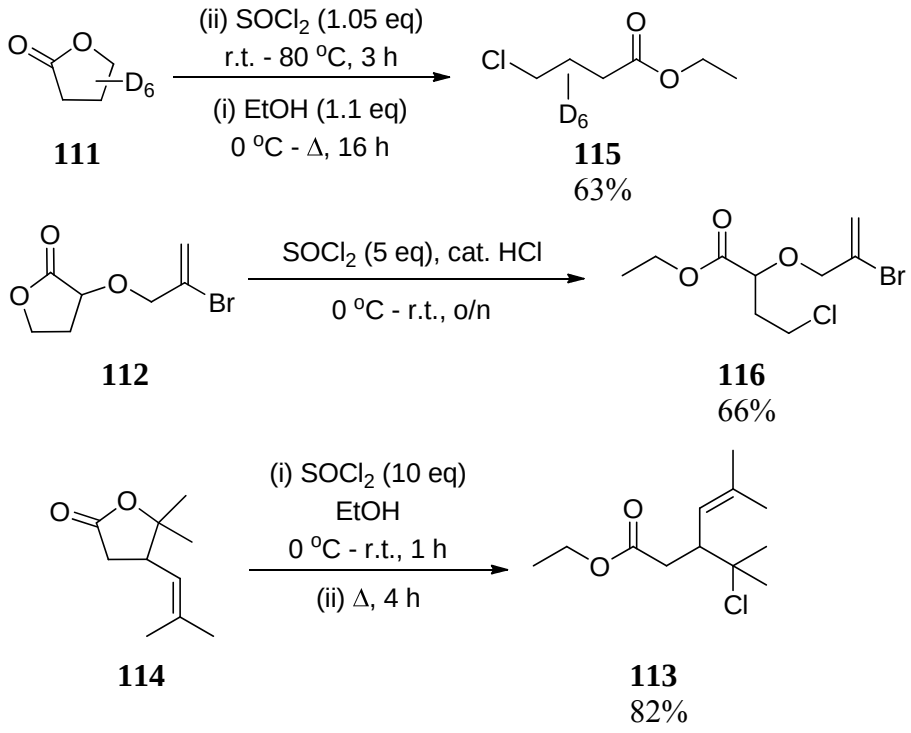


109 **107** **105**

110 **108** **106**

Scheme 2.58

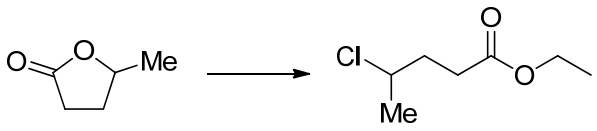
Three similar methods involving the use of thionyl chloride were found in the literature and are summarised in Scheme 2.59. Von Seebach *et al.* described the ring-opening of [D_6]-γ-butyrolactone **111** in 63% yield.[89] Molander and Harris reported a ring-opening procedure of the allyloxy lactone **112** in 66% yield,[90] and Takeda *et al.* formed the ester **113** in 82% yield from the lactone pyrocin **114**.[91]



Scheme 2.59

Based on these reports, investigation into the ring opening of the γ-lactone **109** to the ester **107** was explored, while recognising the potential difference in forming a secondary rather than a primary alkyl halide. Beginning with γ-valerolactone **109**, each method was investigated and the procedure reported by von Seebach was found to be the most suitable for our substrate (Entry 1, Table 2.2). Following work-up, the ^{1}H NMR spectrum of the crude reaction mixture indicated the presence of a mixture of γ-valerolactone **109** and ethyl 4-chloropentanoate **107** (1.6 : 1). The ester was purified by chromatography as a pale yellow oil in 53% yield. Although the yield for this reaction was moderate, most of the unreacted γ-valerolactone **109** starting material was recovered after chromatography and the corrected yield based on starting material consumed was in practice 89%.

Table 2.2 Investigation into suitable reaction conditions for the ring-opening of γ-valerolactone **109** to form ethyl 4-chloropentanoate **107**

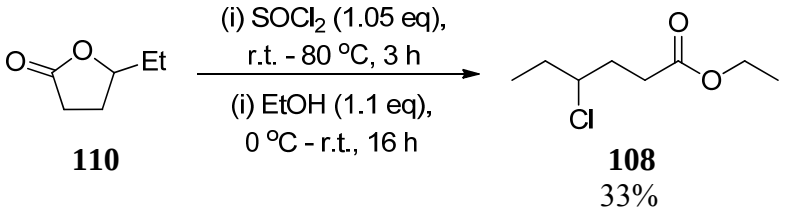


109 **107**

Entry	Reaction Conditions[a]	Crude product[b]	Pure product[c]
1	(i) $SOCl_2$ (1.05 eq), r.t. – 80 °C, 3 h (ii) EtOH (1.1 eq), 0 °C – r.t., 16 h	**109** : **107** (1.6 : 1)	**107** 53%
2	$SOCl_2$ (5 eq), cat. HCl 0 °C – r.t., o/n	**109** : **107** (9 : 1)	-
3	(i) $SOCl_2$ (10 eq), EtOH, 0 °C – r.t., 1 h (ii) Δ, 4 h	**109** : **107** (2 : 1)	-

a. Reaction conditions as described by von Seebach *et al.* (Entry 1),[89] Molander and Harris (Entry 2),[90] Takeda *et al.* (Entry 3).[91]
b. The ratios were estimated by ^{1}H NMR analysis of the crude reaction mixture.
c. The crude mixture was purified by column chromatography on silica gel.

The best conditions used for γ-valerolactone **109** were also employed for the ring-opening of γ-caproactone **110** (Scheme 2.60). Following work-up, the ^{1}H NMR spectrum of the crude reaction mixture showed the presence of γ-caproactone **110** and ethyl 4-chlorohexanoate **108** (2:1). The ester was purified by chromatography to give a pale yellow oil in a yield of 33%.

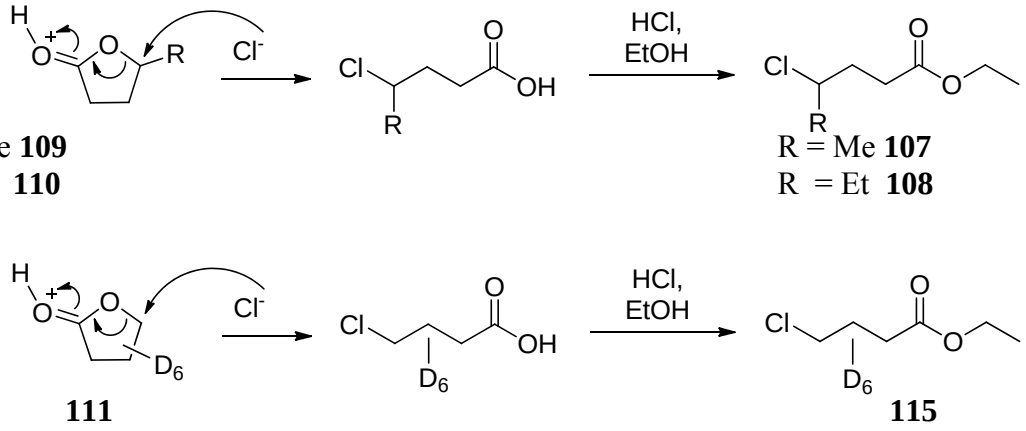


110 **108**
33%

Scheme 2.60

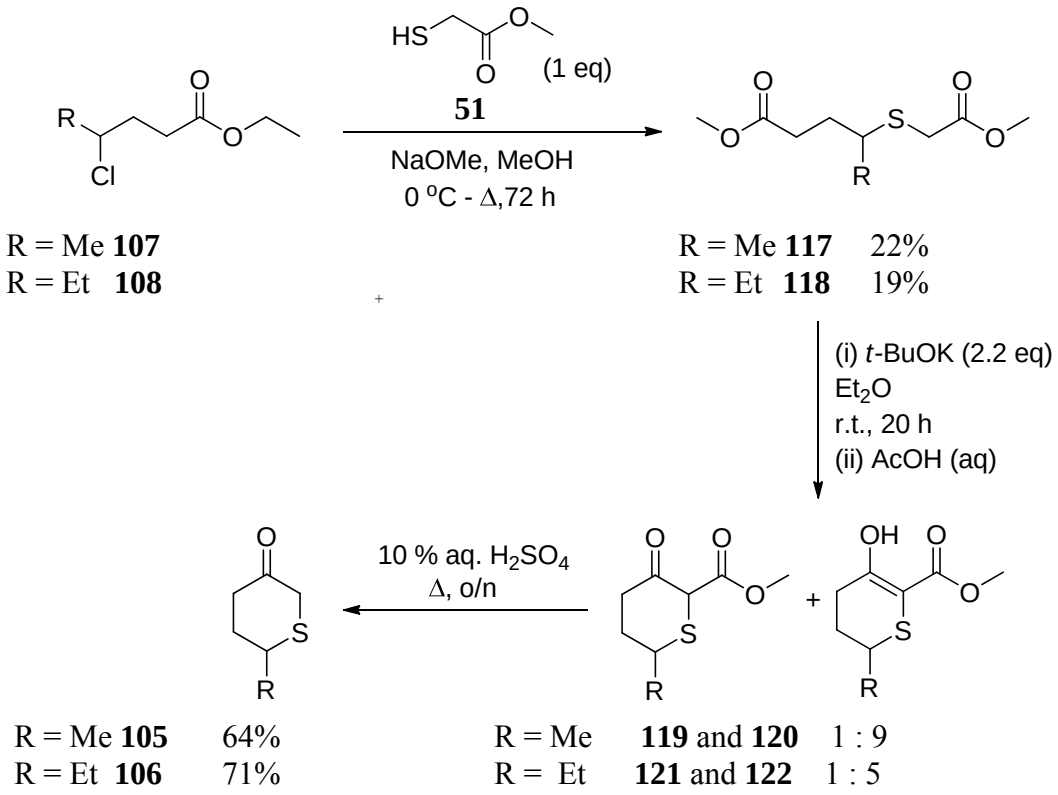
The rate of reaction to yield a secondary alkyl chloride appears to be slower than the reported process by von Seebach leading to the primary alkyl chloride **115**,[89] presumably due to the decreased rate of nucleophilic attack of chloride at the

secondary position, as illustrated in Scheme 2.61. As sufficient amounts of the chloro esters could be achieved, no further attempts to optimise the process were made at this stage.



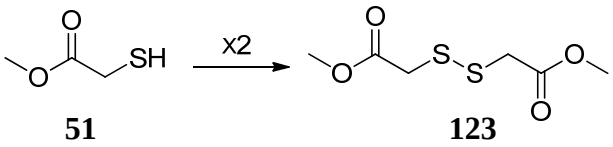
Scheme 2.61

The alkyl substituted sulfides **105** and **106** were then prepared following the modified Hamon procedure,[87] as summarised in Scheme 2.62.



Scheme 2.62

Reaction of methyl thioglycolate **51** with the secondary alkyl chlorides gave the diesters 19-22% yield after Kugelrohr distillation. The sluggish reaction at the more hindered secondary alkyl halide required the use of harsh reaction conditions under reflux over 72 hours, with no reaction under the milder conditions employed for **42**. Competing partial dimerisation of the methyl thioglycolate **51** led to the disulfide, methyl bis(thioacetate) **123** (Scheme 2.63). Even after distillation, all of the disulfide was not removed, and the diesters were obtained as mixtures with the disulfide **123**. The yields reported are corrected for the presence of the disulfide. Although this was inconvenient for characterisation, the presence of the disulfide **123** did not pose a problem for the remainder of the procedure, as it was removed during the Dieckmann condensation in the presence of potassium *t*-butoxide.



51 **123**

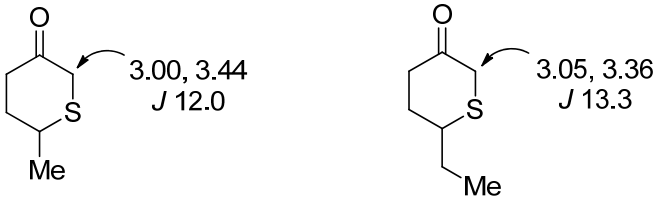
Scheme 2.63

Treatment of the diesters **117** and **118** with potassium *t*-butoxide resulted in a Dieckmann condensation to give the cyclised β-keto ester and the enol ester mixtures as orange oils after work-up. Although the ^{1}H NMR spectra were complex, a number of key signals could be assigned, including the β-keto ester CH singlets at ~3.88 ppm and the broad OH signal of the enol esters at ~12.20 ppm. Hydrolysis of the esters by heating under reflux in 10% sulfuric acid and thermal decarboxylation, followed by neutralisation with 10% aqueous sodium hydroxide to pH 7 gave the methyl and ethyl substituted sulfides **105** and **106** in good yields of 64 and 71%, respectively, over the two steps.

Once again, the reaction sequence from the diesters was remarkably efficient, providing the sulfides **105** and **106** without purification at either stage. The limitation in the syntheses of these sulfides is access to the secondary alkyl chlorides and the diesters. The cyclisation and decarboxylation stages are unaffected by the presence of the alkyl substituents.

Spectroscopic details were in agreement with those reported in the literature.[88] The IR spectra showed the typical carbonyl stretch of a cyclic ketone at 1713-1714 cm^{-1}. Notably, the ^{1}H NMR spectra were significantly more complex than

the unsubstituted monocyclic sulfide **42**, discussed in Section 2.6.1.1. The introduction of an alkyl group resulted in the diastereotopic CH_2 protons of the β-keto sulfide appearing as distinct AB quartets (Figure 2.18).

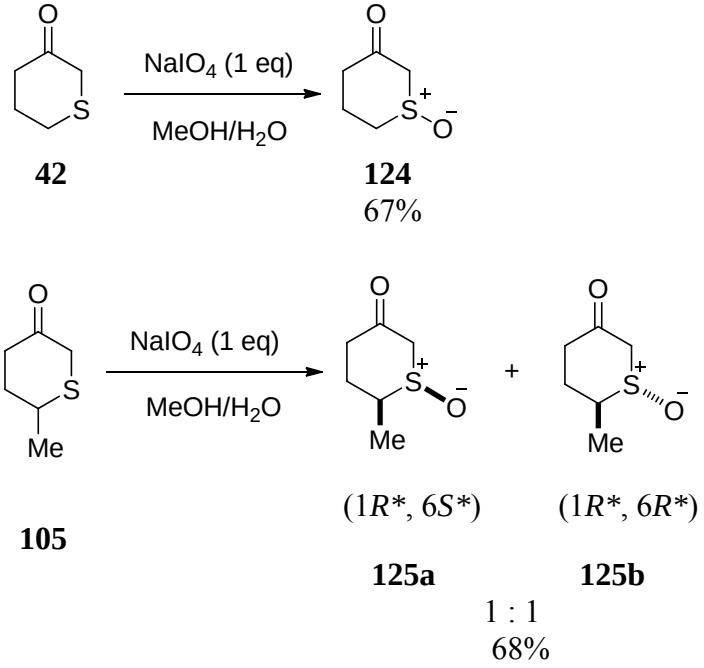


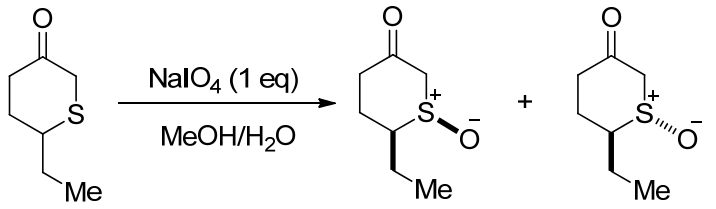
105 **106**

Figure 2.18

2.6.2 Synthesis of Dihydro-2*H*-thiopyran-3(4*H*)-one *S*-Oxides

Various oxidants suitable for the oxidation of sulfides are discussed above in Section 2.5.2. Oxidation of the monocyclic β-keto sulfides **42**, **105** and **106** was achieved using sodium metaperiodate, according to literature procedure.[92] The sulfoxides **124**, **125** and **126** are quite polar compounds which were obtained in good yields without requiring purification (Scheme 2.64).





106 (1*R**, 6*S**) **126a** (1*R**, 6*R**) **126b**

(major:minor, 1 : 0.9)*

67%

*relative stereochemistry not assigned

Scheme 2.64

The unsubstituted monocyclic sulfide **42** was oxidised to the sulfoxide **124** in a yield of 67%. Similar to the lactone sulfoxides discussed in Section 2.3.2, the oxidant can approach the sulfides **105** and **106** from either face, meaning two sulfoxides can be formed which are diastereomeric at sulfur. Therefore, for the methyl sulfide **105** and the ethyl sulfide **106**, two diastereomers were formed. Little or no diastereoselectivity was evident in the sulfide oxidation of **106** to the sulfoxides **126a** and **126b**. However, in the absence of definitive structural information, it is not possible to assign the relative stereochemistry of the two diastereomers, although it is clear that the sulfoxides **125a** and **126a** have the same stereochemistry, and **125b** and **126b** have the same stereochemistry.

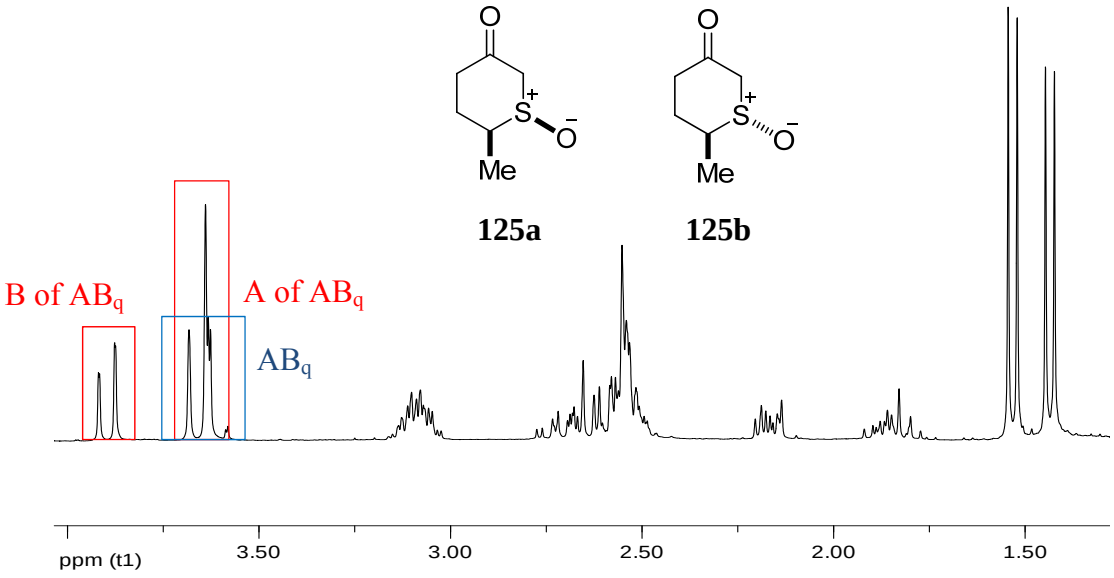
The sulfoxides **124-126** were isolated as pale yellow crystalline solids without the need for further purification. While no problems were detected in storing the sulfoxides, in general these compounds were used within 24 hours for diazo transfer. The sulfoxides were prepared on a scale of 100-400 mg, although this was limited only by the accessibility of the sulfide precursors. Preliminary attempts were made to separate the sulfoxide diastereomers by TLC or by recrystallisation, however these were not successful.

2.6.3 Spectroscopic Details of Dihydro-2H-thiopyran-3(4*H*)-one *S*-Oxides

The carbonyl stretching frequency of the sulfoxides appears in the range 1715-1718 cm^{-1} (typically ~1730 cm^{-1})[50] in the IR spectrum, which is similar to the range of 1708-1714 cm^{-1} observed for the sulfides discussed in Section 2.6.1. The sulfoxide stretching vibration is another characteristic absorption in the IR spectra of these compounds. These were observed at 1011-1018 cm^{-1}.

For the sulfoxide **124**, the most notable change relative to **42** in the ^1H NMR spectrum on oxidation is that the CH_2 signal of the β-keto sulfoxide now appears as a distinct AB quartet with a coupling constant of 13.3 Hz, in place of a singlet at 3.21 ppm for **42**. The ^1H NMR data for the sulfoxides **125** and **126** are illustrated in Figure 2.19. For the diastereomeric pairs of sulfoxides **125a** and **125b**, and **126a** and **126b**, it is not known which signals correspond to which diastereomer.

The most characteristic features of the spectra are the two distinct AB quartets which overlap in the region 3.5-4.0 ppm, as illustrated in Figure 2.19. It is clear that the conformational features of the two diastereomeric sulfoxides are quite different, leading to the two distinctly different AB quartets for the α-CH_2 protons. However, the similarity between the features of **125a/125b**, and **126a/126b** highlight clearly that these pairs have the same relative stereochemistry.



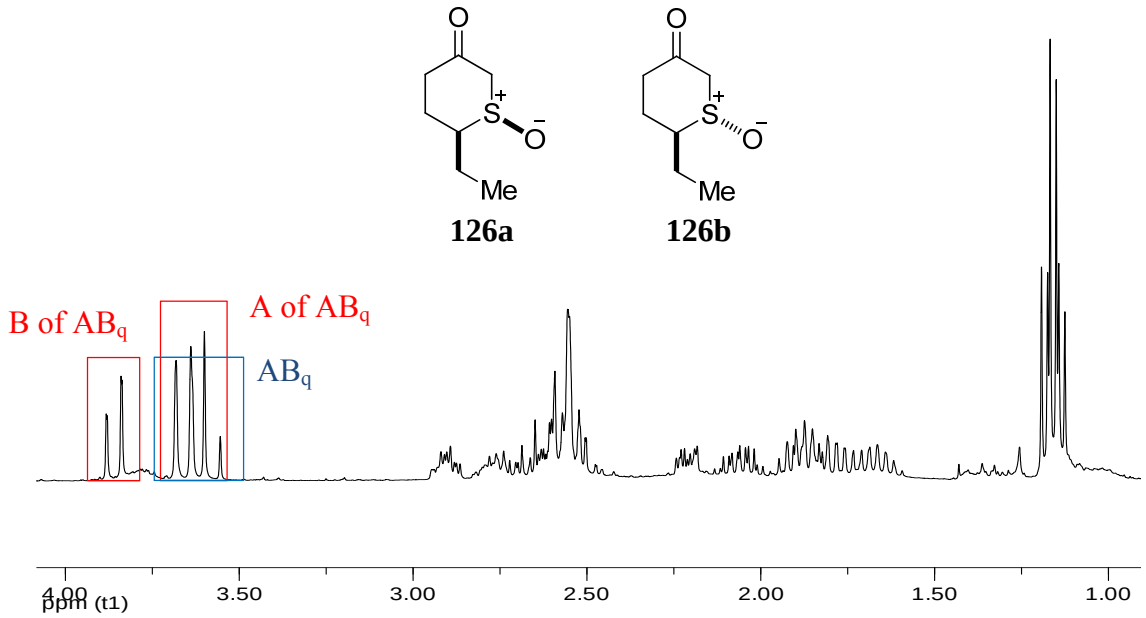
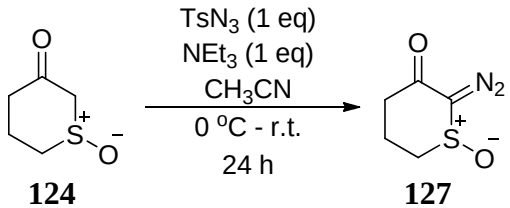


Figure 2.19 *Top: ^{1}H NMR spectrum of diastereomeric sulfoxides **125a** and **125b**; bottom: ^{1}H NMR spectrum of diastereomeric sulfoxides **126a** and **126b** (300 MHz, $CDCl_3$)*

2.6.4 Synthesis of 2-Diazo-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-Oxides

Having synthesised the monocyclic sulfoxides **124-126**, diazo transfer to these substrates was next examined, to determine if these would provide stable diazo derivatives. Diazo transfer to the monocyclic sulfoxide **124** was initially attempted using tosyl azide **41** as the transfer reagent and triethylamine as the base in acetonitrile (Scheme 2.65). The progress of the reaction was monitored by TLC, and after 24 h, ^{1}H NMR analysis indicated that the reaction had gone ~60% to completion, with some remaining sulfoxide still present.



~60% to completion

Scheme 2.65

Purification of the crude brown oil by chromatography in 90:10 dichloromethane/methanol gave the α-diazosulfoxide **127** and sulfonamide byproduct as a clean mixture (~40:60 by ^{1}H NMR) and a yellow crystalline solid which was quite stable for ~24 hours. However, multiple attempts to remove the sulfonamide byproduct by chromatography led to only impure samples of the α-diazosulfoxide **127** in very low yield. Two possible reasons are suggested for this. Firstly, although successful diazo transfer to the sulfoxide **124** was achieved, the resulting α-diazosulfoxide **127** is stabilised by the presence of the sulfonamide. This may due to hydrogen bonding interactions between the sulfoxide of the diazo compound and the amide of the sulfonamide. Stabilisation of the sulfoxide bond adjacent to a diazo group could delay a decomposition pathway *via* the proposed oxygen transfer mechanism, as discussed in Section 2.1. Secondly, prolonged contact between the α-diazosulfoxide **127** and the silica gel while trying to remove the sulfonamide may have led to decomposition on the column. The purified α-diazosulfoxide **127** is a relatively unstable compound, isolated as a sticky brown solid, which decomposes at room temperature over 24 hours to a complex mixture of unidentifiable compounds.

The IR spectrum showed the presence of the diazo group stretch at 2118 cm^{-1}. Furthermore, the absence of the CH_2 AB quartet in the ^{1}H NMR spectrum, and absence of the CH_2 signal at 59.8 ppm in the ^{13}C NMR spectrum are also indicators of successful diazo transfer. The ^{1}H NMR spectrum of the α-diazosulfoxide **127** and sulfonamide mixture and the ^{1}H NMR spectrum of the separated α-diazosulfoxide **127** are given in Figure 2.20 for comparison.

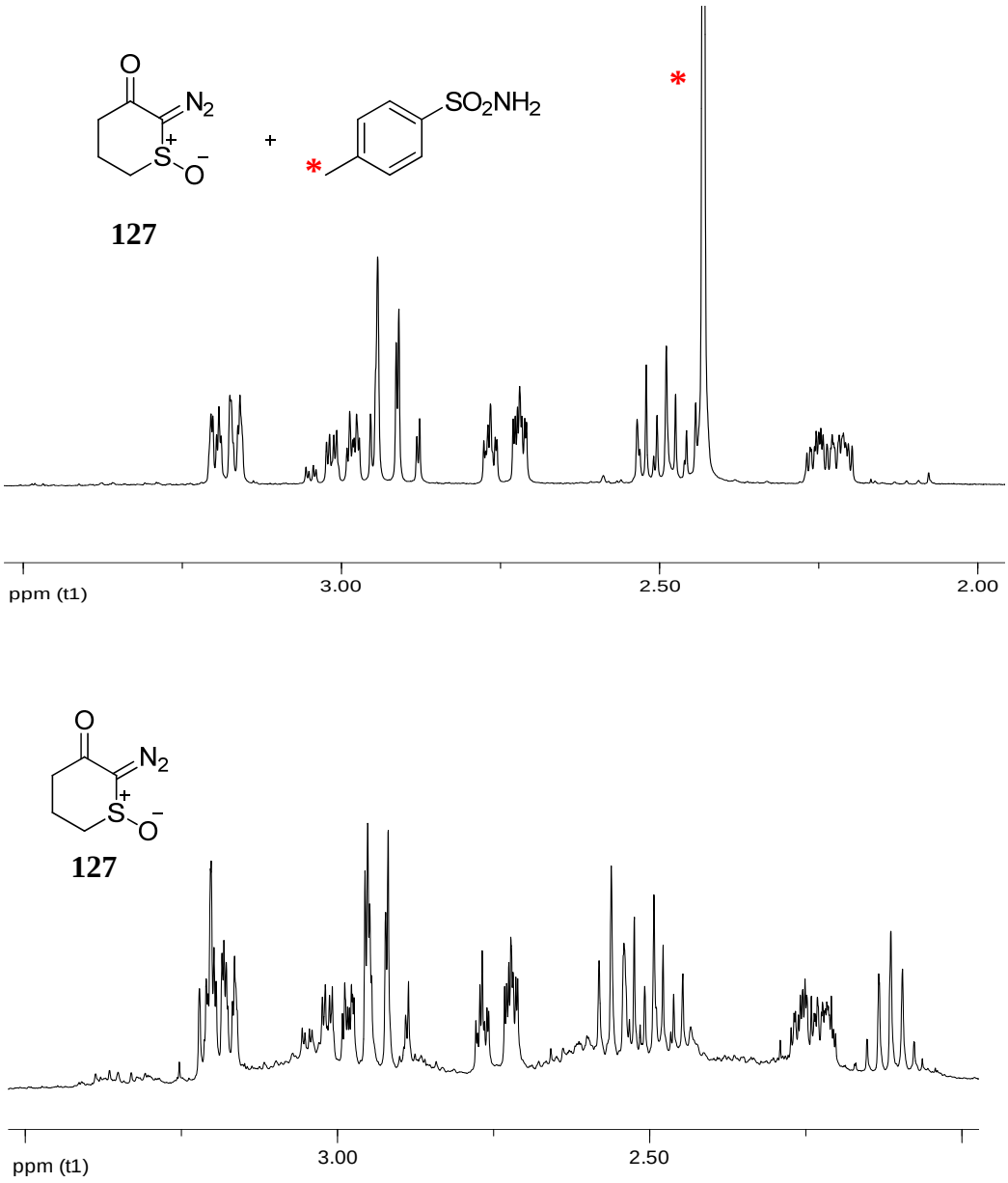
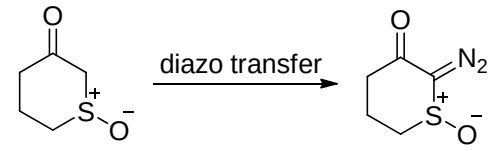


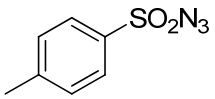
Figure 2.20 *Top: ^{1}H NMR spectrum of the α-diazosulfoxide **127** and sulfonamide mixture; bottom: ^{1}H NMR spectrum of the separated α-diazosulfoxide **127** (400 MHz, $CDCl_3$)*

The decrease in quality evident on attempted purification by chromatography led us to explore alternative reaction conditions for the diazo transfer (Table 2.3) with a view to overcoming prolonged chromatographic purification.

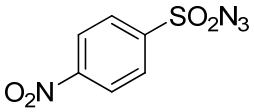
Table 2.3 Optimisation of diazo transfer conditions for the synthesis of **127**



124 **127**



41
TsN_3



128
p-NBSA

Entry[a]	Base	Diazo Transfer Reagent	Time	Product[b]
1	K_2CO_3 (1.1 eq)	TsN_3 (1 eq)	20 h	-
2	DBU (1.5 eq)	TsN_3 (1.1 eq)	o/n	-
3	*t*-BuOK (1.1 eq)	TsN_3 (1 eq)	48 h	**127** (<10%)
4	DBU (1.5 eq)	*p*-NBSA (1 eq)	o/n	-

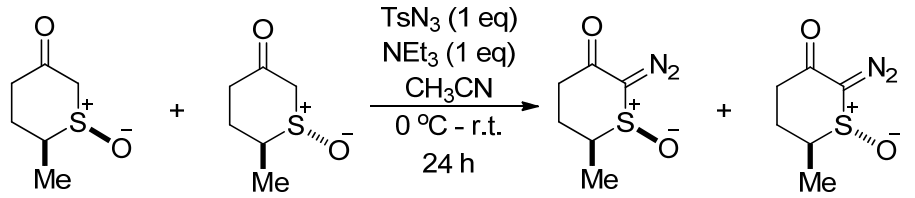
a. All reactions were carried out in HPLC grade acetonitrile and were stirred under a nitrogen atmosphere at room temperature

b. Estimated from the ^{1}H NMR spectrum of the crude material. For entries 1,3 and 4, no diazo transfer was observed. For entry 2, a small quantity of **127** was detected by TLC.

Potassium carbonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were ineffective as bases for the transformation and no diazo transfer could be detected either by TLC or ^{1}H NMR analysis, with unreacted starting material obtained in good recovery. However, with potassium *t*-butoxide, a very small quantity of the α-diazosulfoxide **127** could be detected in the reaction mixture by TLC and the quantity was estimated by comparing the tosyl azide **41** and sulfonamide CH_3 singlets in the ^{1}H NMR spectrum of the crude material. *p*-Nitrobenzenesulfonyl azide (*p*-NBSA) **128** was employed as a diazo transfer reagent in an attempt to isolate the α-diazosulfoxide **127** from the sulfonamide, which was predicted to have a very different polarity. However, no diazo transfer was detected in the ^{1}H NMR spectrum of the crude material. Having conducted this preliminary investigation, the

optimum conditions to date involve the use of tosyl azide **41** and triethylamine, although further optimisation is required.

Having achieved diazo transfer to the monocyclic β-keto sulfoxide **124**, we turned to the methyl substituted β-keto sulfoxide derivatives **125a** and **125b**. Diazo transfer was carried out using the reaction conditions as summarised in Scheme 2.66. The reaction mixture was stirred overnight and monitored by TLC. The crude product was isolated as a black oil and the ^{1}H NMR spectrum was complex. A number of signals could be identified, including the sulfoxide starting materials, sulfonamide and remaining tosyl azide **41** (**125a**:**125b**:**129**:**41** 1:1:5:3). TLC analysis seemed to indicated the presence of a diazo product, directly above the sulfoxides. An impure sample of the α-diazosulfoxides **130a** and **130b** was obtained after chromatography (major:minor 1:0.6, relative stereochemistry not assigned) in a very low yield (~6%).* As it was difficult to estimate the percentage conversion from the ^{1}H NMR spectrum of the crude material, this low yield may have been due to decomposition on the silica gel, or in the reaction vessel, or both.



(1*R**, 6*S**) **125a** | (1*R**, 6*R**) **125b** — 1 : 1

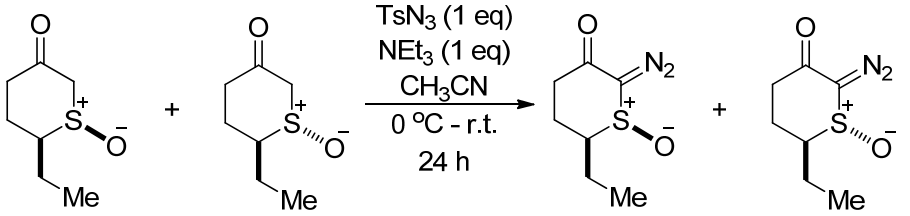
(1*R**, 6*R**) **130a** | (1*R**, 6*S**) **130b** — (major:minor 1: 0.6*) ~6%

Scheme 2.66

Evidence for at least partial diazo transfer came from the diazo group stretch, which was present in the IR spectrum at 2129 cm^{-1}, although we were unable to quantify this. However, significant decomposition of the material occurred overnight, and many signals in the ^{13}C NMR spectra could not be assigned. While access to the methyl substituted α-diazosulfoxide compounds **130a** and **130b** was achieved, the synthetic utility is limited by the low yield.

* Although in this case the diazo products were readily separated from the sulfonamide, in comparison to α-diazosulfoxide **127**.

Diazo transfer to the ethyl substituted β-keto sulfoxides **126a** and **126b** was next investigated, using the reaction conditions as summarised in Scheme 2.67. The reaction mixture was stirred overnight and the crude product was obtained as a viscous brown oil. ^{1}H NMR analysis indicated the presence of a complex mixture of compounds, including the sulfoxide starting materials **126a** and **126b**, tosyl azide **41** and sulfonamide. The presence of a diazo product could also be observed by TLC. Purification of the mixture by chromatography gave the α-diazosulfoxides **131a** and **131b** in a yield of ~12%, along with sulfonamide and a small quantity of the sulfoxide starting materials (~5%). The ethyl substituted α-diazosulfoxides **131a** and **131b** were stable enough to allow complete ^{13}C NMR analysis.



(1*R**, 6*S**) (1*R**, 6*R**) (1*R**, 6*R**) (1*R**, 6*S**)

126a **126b** **131a** **131b**

(major:minor, 1 : 0.9)* 1 : 1

~12%

Scheme 2.67

The diazo group stretch was observed at 2113 cm^{-1} in the IR spectrum, showing at least partially successful diazo transfer. The characteristic AB quartet seen for both the sulfides and the sulfoxides was no longer visible, further indicating successful diazo transfer.

In conclusion, diazo transfer to monocyclic β-keto sulfoxides to form isolable, conformationally flexible monocyclic α-diazosulfoxides is possible. Due to the low efficiencies obtained to date and associated challenges in obtaining pure samples, the synthetic utility of these novel compounds is restricted at this stage, although optimisation could potentially lead to these diazo derivatives as useful synthetic intermediates. The decomposition of these derivatives leads to a complex mixture of unidentifiable products.

The contrast with the benzofused α-diazosulfoxides discussed in Section 2.5.4 is striking. The bicyclic derivatives were stable and easily isolated and purified in contrast to the more labile monocyclic derivatives. This observation is in line with our model that the stability of α-diazosulfoxides is directly linked to conformational restriction, with stability decreasing as conformational flexibility increases. Further study into the necessary structural and conformational features for stable cyclic α-diazo-β-keto sulfoxides is required. In particular, it would be interesting to explore bicyclic, non-aromatic, derivatives. Attempts during the course of this project to prepare such bicyclic β-keto sulfide derivatives were unsuccessful, and are discussed in Section 2.8.

2.7 Conclusion

Successful diazo transfer to β-keto sulfoxides has been achieved for the first time in this work, with fused bicyclic derivatives proving substantially more stable than the simpler monocyclic systems. Diazo transfer using immobilised polystyrene-supported benzenesulfonyl azide has also been achieved for the first time with α-diazosulfoxides. The synthetic routes developed are relatively flexible and can be used to generate a series of these compounds in the future. The link between stability and conformational flexibility supports our earlier theory that the stability of α-diazosulfoxides is entirely dependent on conformational constriction. Furthermore, the crystal structure of **88** supports our previously articulated proposal that overlap of the sulfur lone pair with the π-orbitals of the diazo moiety is responsible for the lability of these systems, rather than interaction of the sulfoxide oxygen with the diazo carbon, as proposed by Hodson and Holt.[4]

2.8 Attempted Syntheses of Bicyclic β-Ketosulfides

2.8.1 *Lansbury Method:*[93] Intramolecular Alkylation of 2-Chloroalk-1-enes*

It was envisaged during this work that the series of α-diazo-β-keto sulfoxides would be expanded to include the design and synthesis of novel bicyclic β-ketosulfide derivatives, hexahydro-2*H*-thiochromen-3(4*H*)-ones. These compounds would complement the novel benzofused and monocyclic α-diazo-β-keto sulfoxides derivatives, the syntheses of which are discussed in Sections 2.5 and 2.6. The hexahydro-2*H*-thiochromen-3(4*H*)-one **132** illustrated in Figure 2.21 was investigated as a direct analogue to the lactone based α-diazosulfoxide **36**, which has been studied in depth within the group.

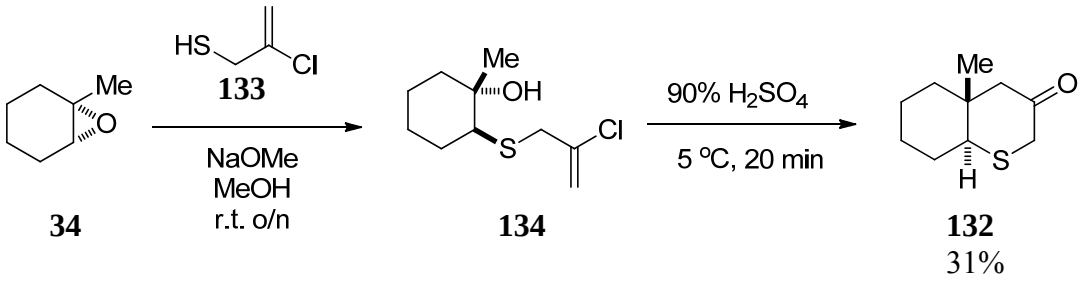
132 **36**

Figure 2.21

The lactone based sulfide **36** was efficiently prepared by cyclisation of hydroxy acids in the presence of catalytic *p*-TSA and a Dean-Stark trap, as discussed in Section 2.3.1. The synthesis of the ketone-based sulfide **132** required an alternative method of preparation. O'Sullivan had previously conducted unsuccessful preliminary investigations[9] into a report by Lansbury *et al.* which described the successful synthesis of thianone derivatives,[93] including compound **132**. A more in-depth investigation was undertaken in this work to reproduce the results reported by Lansbury. The route involved ring-opening of methylcyclohexene oxide **34** with 2-chloroallyl mercaptan **133** followed by cyclisation of the resulting hydroxy sulfide **134** under acidic conditions to give the target β-ketosulfide **132** in 31% yield with the *trans* stereochemistry as shown (Scheme 2.68).

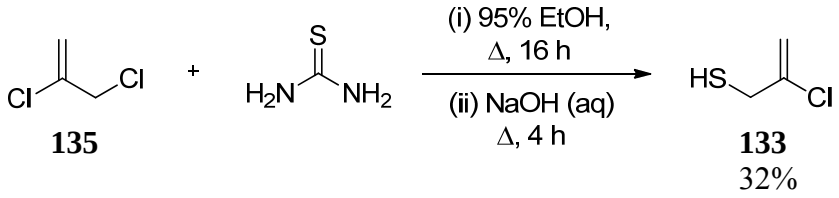
**Note:* The reactions performed in this section involved the formation of extremely malodorous products. Care was taken to soak all glassware in a bleach bath for several days.

The key step was the intramolecular nucleophilic attack of the vinylic chloride with loss of the hydroxy group (2-chloroalk-1-ene annulation) in the presence of aqueous mineral acid.[93-96]



Scheme 2.68

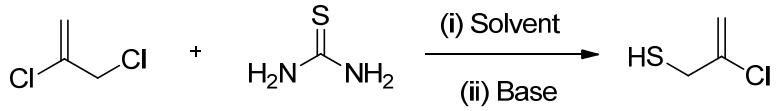
The first step involved synthesis of 2-chloroallylmercaptan **133**. The reaction conditions reported by the authors are shown in Scheme 2.69.



Scheme 2.69

Initially, the reaction was carried out by strictly adhering to the published procedure.[93] Commercially available 2,3-dichloropropene **135** and thiourea (freshly recrystallised from distilled water) were heated under reflux in ethanol overnight followed by treatment with aqueous sodium hydroxide for 4 hours under reflux and an aqueous acid work-up. The reaction was repeated on several occasions, but each time the product was isolated as a malodorous mixture of an oil and a solid. The crude mixture was purified by Kugelrohr distillation (80 Torr, 60 °C) to give the thiol **133** and unidentifiable impurities in a very low yield. The reaction was repeated by varying the conditions and base employed, but the yield was not improved (Table 2.4, with the best outcome in Entry 5).

Table 2.4: Variation of reaction conditions as described by Lansbury[93] in the attempted synthesis of 2-chloroallyl mercaptan **133**

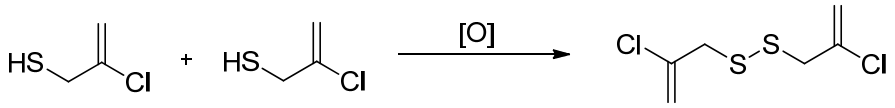


135 **133**

Entry	Solvent	Base	Conditions	Time[a]	Product[b]
1	EtOH	NaOH	Δ	(i) 5 h (ii) 4 h	Mixture
2	EtOH	$LiAlH_4$	Δ	(i) 16 h (ii) 4 h	Mixture (<50% **133**)
3	EtOH	NaOMe	Δ	(i) 16 h (i) 4 h	Mixture (<40% **133**)
4	MeOH	KOH	Δ	(i) 16 h (i) 4 h	Mixture (<50% **133**)
5	**EtOH**	**NaOH**	**Δ**	**(i) 16 h (i) 4 h**	**Mixture (>80% 133)**

a. Length of time the reaction mixture (i) was heated under reflux in solvent and (ii) heated under reflux with aqueous base.
b. The quantity of 2-chloroallyl mercaptan **133** among a complex mixture of unidentifiable compounds was estimated by ^{1}H NMR analysis of the crude reaction mixtures.

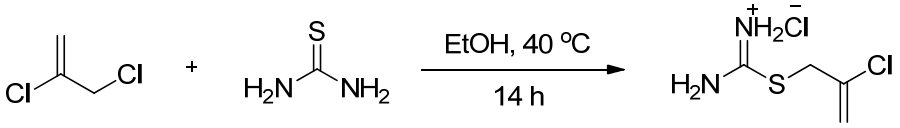
The low yield of 2-chloroallyl mercaptan **133** obtained indicate that this thiol is an unstable compound, and it is possible that partial dimerisation to the disulfide **136** occurred (Scheme 2.70), although it was difficult to confirm this in the complex ^{1}H NMR spectra. Furthermore, a search of the literature did not lead us to any report where 2-chloroallyl mercaptan **133** was synthesised and isolated, apart from the isolated report by Lansbury *et al.*.[93]



133 **133** **136**

Scheme 2.70

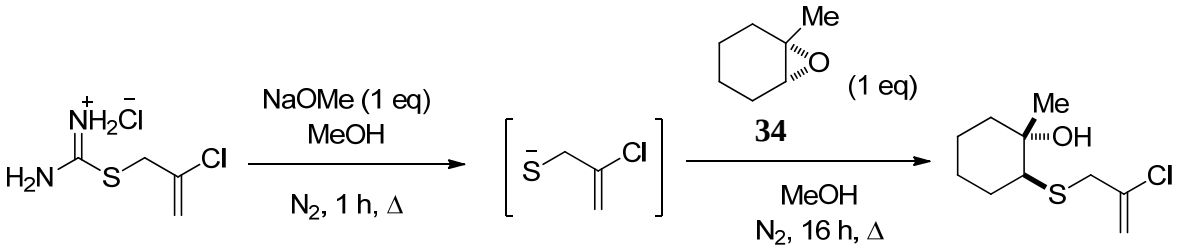
Due to the apparent instability of 2-chloroallyl mercaptan **133** and the difficulties in isolating it, our next approach involved generation of the thiolate anion of **133** as an intermediate and reacting it with methylcyclohexene oxide **34** in a one-pot method. Workers within this group have reported the formation of benzyl thioethers using a similar procedure.[97] This method would obviate the need for isolation of the malodorous thiol and form the hydroxy sulfide **134** in one step. Firstly, the isothiuronium salt **137** was generated from 2,3-dichloropropene **135** and freshly recrystallised thiourea in 96% yield (Scheme 2.71).



135 **137**
96%

Scheme 2.71

The isothiuronium salt was then treated with a base under a nitrogen atmosphere, followed by addition of the epoxide **34** after 1 hour. The procedure which was used is illustrated in Scheme 2.72.



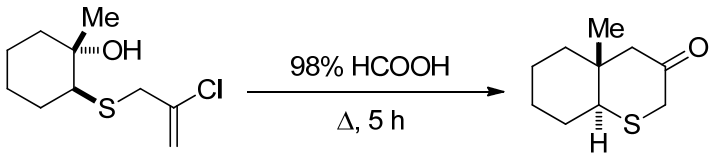
137 **133** **134**
30%

Scheme 2.72

The hydroxy sulfide **134** was successfully synthesised as a malodorous orange oil, along with unidentified impurities in a yield of 30% (~70% pure).

Although the product was not purified, the ^{1}H NMR spectrum showed distinct signals corresponding to the hydroxy OH at 3.01 ppm and the vinylic protons as two doublets at 5.30 ppm and 5.39 ppm. The OH stretching vibration was also visible in the IR spectrum at 3426 cm^{-1}. Lansbury *et al.* reported spectral details in agreement with those recorded in this work, albeit at 60 MHz.[93]

Cyclisation of the hydroxy acid **134** was investigated using the chloroalkene annulation method described by Lansbury *at al*.[93-96] The crude hydroxy sulfide **134** was treated with 98% formic acid under reflux conditions for 5 hours (Scheme 2.73).

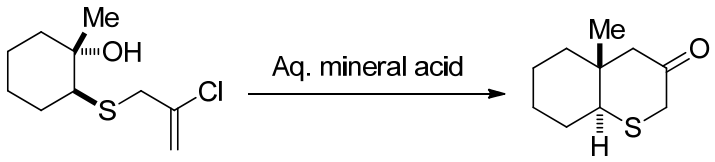


134 **132**
very small quantity

Scheme 2.73

The crude product was isolated after aqueous work-up as a malodorous, black oil. Although the ^{1}H NMR spectrum of the crude product indicated the presence of a complex mixture of unidentifiable compounds, the IR spectrum showed a strong carbonyl stretching vibration at 1711 cm^{-1}, indicative of a cyclised ketone. The mixture was purified by chromatography and a small quantity of a compound tentatively assigned as the β-ketosulfide **132** was isolated together with impurities in the second fraction. Two AB quartets could be distinguished, corresponding to the two CH_2 signals of the β-ketosulfide ring. The quantity of the β-ketosulfide **132** isolated was quite disappointing, as the authors reported the synthesis of **132** in a pure yield of 35%.[93] Therefore, the reaction was repeated a number of times, using 90% sulfuric acid, which the authors had also used with success. The results of these attempts are summarised in Table 2.5.

Table 2.5: Variation of reaction conditions as described by Lansbury[93] in the attempted cyclisation of the hydroxy acid **134** to the β-ketosulfide **132**.



134 **132**

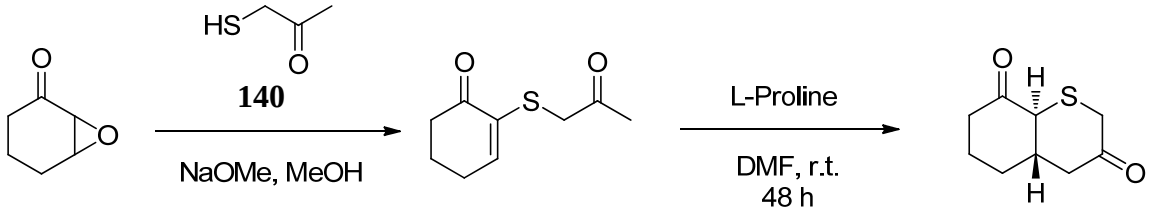
Entry	Acid[a]	Conditions	Time	Product[b]
1	98% Formic acid	Δ	1 h	Mixture (<50% **132**)
2	98% Formic acid	RT	o/n	Mixture unidentifiable compounds
3	90% H_2SO_4	Δ	20 min	Mixture unidentifiable compounds
4	90% H_2SO_4	0 - 5 °C	30 min	Mixture (<10% **132**)

a. Aqueous mineral acids used as described by Lansbury.
b. For entries 2 and 3, the ^{1}H NMR spectra of the crude reaction mixtures indicated the presence of a complex mixture of unidentifiable compounds. For entries 1 and 4, ^{1}H NMR spectra indicated the presence of **132** among a complex mixture of unidentifiable compounds.

Disappointingly, the yields obtained by Lansbury *et al.* were not reproduced in this work and the quantity of the β-ketosulfide **132** obtained was too low to be synthetically useful.[93] Although it was possible to prepare the hydroxy sulfide **134** in an appreciable yield using a one-pot method, the harsh aqueous mineral acid conditions described for the chloroalkene annulation appear unsuitable for the synthesis of β-ketosulfides. A milder method was sought, and an examination of the literature led us an interesting report on the synthesis of optically active thiadecalindiones using L-proline (Section 2.8.2).[98]

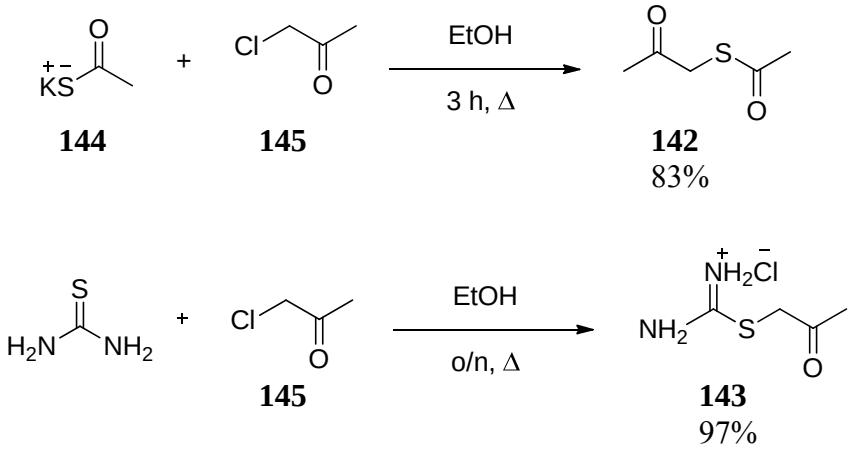
2.8.2 *Kozikowski Method*:[98] Thiadecalins *via* Intramolecular Michael Reaction

Kozikowski and Mugrage reported the preparation of *trans*-thiadecalindione **138** from the α-thio enone **139** by an L-proline catalysed intramolecular Michael process (Scheme 2.74).[98] Although the authors obtained a relatively modest 18% ee, we were interested in this synthetic route principally as an approach towards bicyclic α-diazo-β-keto sulfoxides.



Scheme 2.74

They reported that the α-thio enone **139** was formed *via* nucleophilic attack of mercaptoacetone **140** at 2,3-epoxycyclohexanone **141**. The authors referred to a synthesis of mercaptoacetone (frequently described in the literature as thioacetone) using chloroacetone and hydrogen sulfide.[99] However, due to the toxic and flammable nature of hydrogen sulfide, this was considered an undesirable synthesis for our work. As an alternative route, it was decided to generate the anion of mercaptoacetone **140** *in situ* from a stable precursor, with addition of the epoxide **141** in a one pot method. Two stable thiolate precursors were prepared, the known compound 1-acetylthio-2-propanone **142** and a novel salt, 2-acetylthio isothiouronium chloride **143**, which was fully characterised in this work (Scheme 2.75).

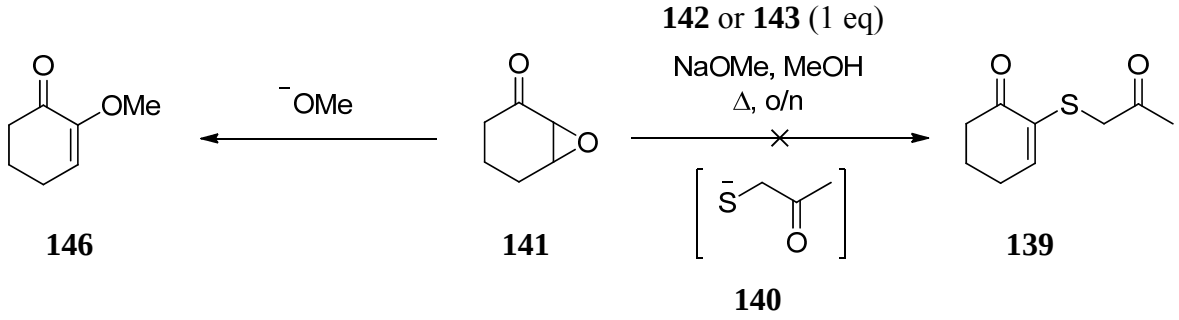


144 **145** **142** 83%

145 **143** 97%

Scheme 2.75

Two parallel reactions were then conducted, where the thiolate precursors were treated with sodium methoxide under reflux conditions for 1 hour, followed by addition of the epoxide **141**. The solutions were stirred overnight under reflux. ^{1}H NMR analysis of the crude products indicated that the α-thio enone **139** had not been formed in either case. Instead, nucleophilic attack of the methoxide anion led to the undesired known compound, 2-methoxycyclohex-2-enone **146** as the major product (Scheme 2.76).[100]



146 **141** **140** **139**

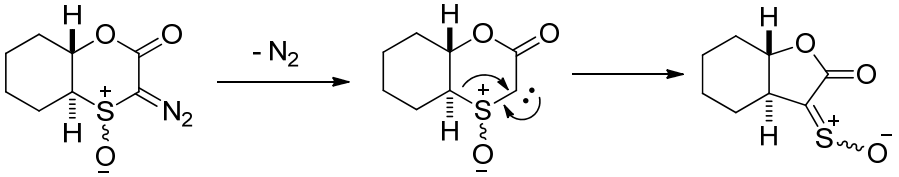
Scheme 2.76

Although preliminary investigations into this methodology proved unsuccessful, the generation of the α-thio enone **139** *via* a one-pot reaction from the epoxide **141** represents a promising and mild route which is worthy of future study, particularly through the use of non-nucleophilic bases.

2.9 Reactivity of Lactone Based α-Diazosulfoxides

2.9.1 Background

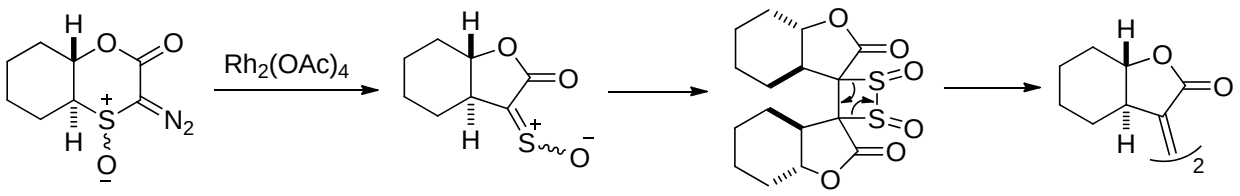
The reactivity of lactone based α-diazosulfoxides has been studied in depth by previous workers within this group.[6,7,9,10] Studies have been carried out under transition metal catalysis, microwave and photolysis conditions. Further work has been carried out using low temperature matrix isolation techniques.[101,102] These α-diazosulfoxides, for example **5**, are known to undergo a hetero Wolff-rearrangement of a carbene **147** which is formed on loss of the diazo group. This results in formation of an α-oxosulfine intermediate **148**, as shown in Scheme 2.77 (For a comprehensive review of the preparation and reactivity of sulfines, see Section 1.3).



5 **147** **148**

Scheme 2.77

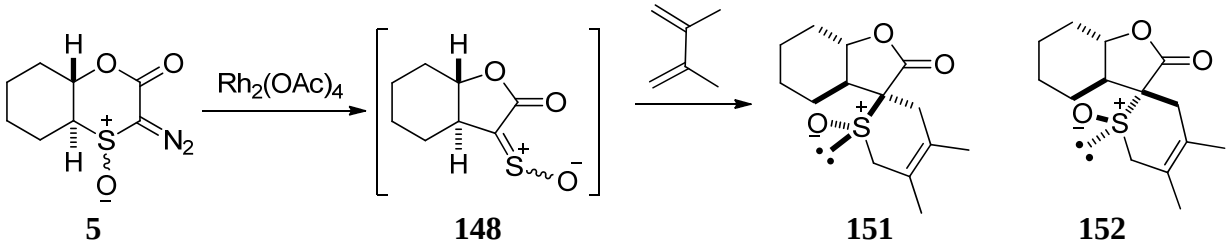
Kelleher first investigated the reactivity of the α-diazosulfoxide **5** under rhodium(II) catalysed conditions.[103] Surprisingly, the sole product from the reaction in toluene was the sterically congested alkene dimer **149** (Scheme 2.78). It was postulated that the most likely mechanism for this reaction involves Wolff rearrangement of the carbene **147** to form the sulfine **148** which dimerises to form a tricyclic intermediate **150**. Disproportionation and fragmentation of the intermediate would give the alkene dimer **149**.[103]



5 **148** **150** **149**

Scheme 2.78

Sulfines are known to readily undergo Diels-Alder cycloaddition in the presence of a diene (Section 1.4.3). Therefore, in order to verify the formation of the α-oxosulfine intermediate, Kelleher carried out reactions in the presence of dienes such as 2,3-dimethyl-1,3-butadiene to trap the sulfine **148** as Diels-Alder cycloadducts (Scheme 2.79). The cycloadduct **151** was successfully isolated and characterised.[103] A minor cycloadduct **152** was later isolated and characterised by Collins.[7]

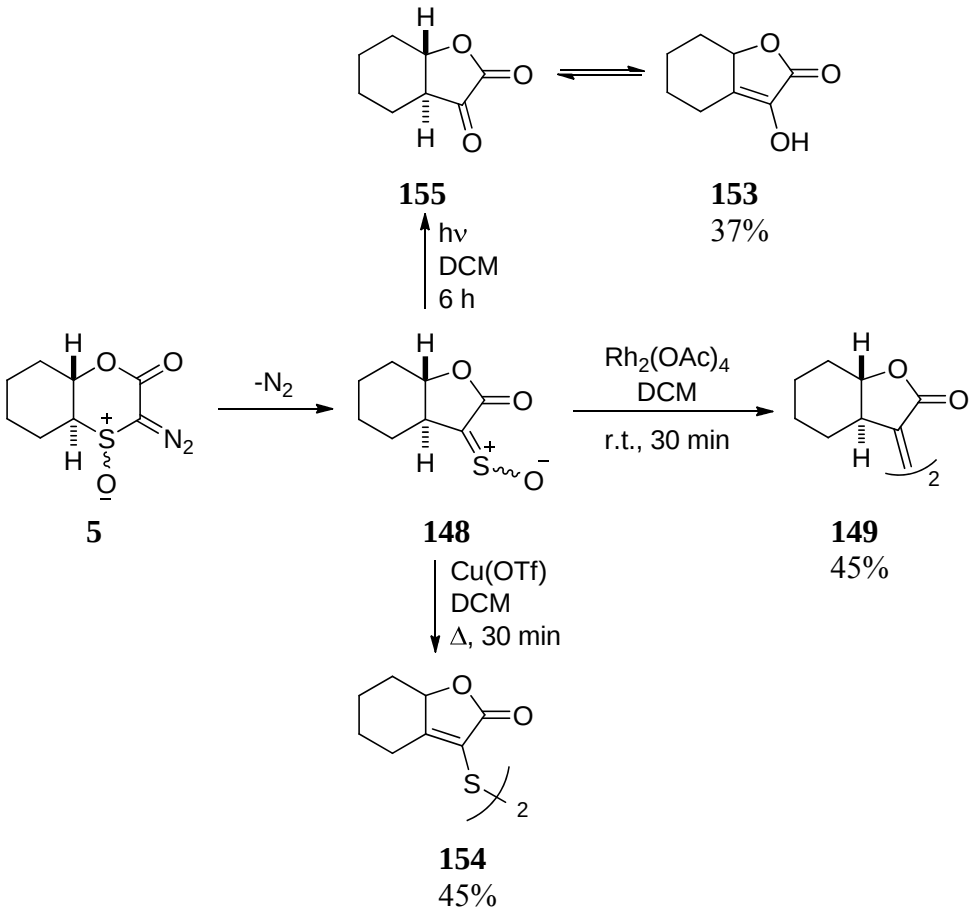


5 **148** **151** **152**

6 : 1

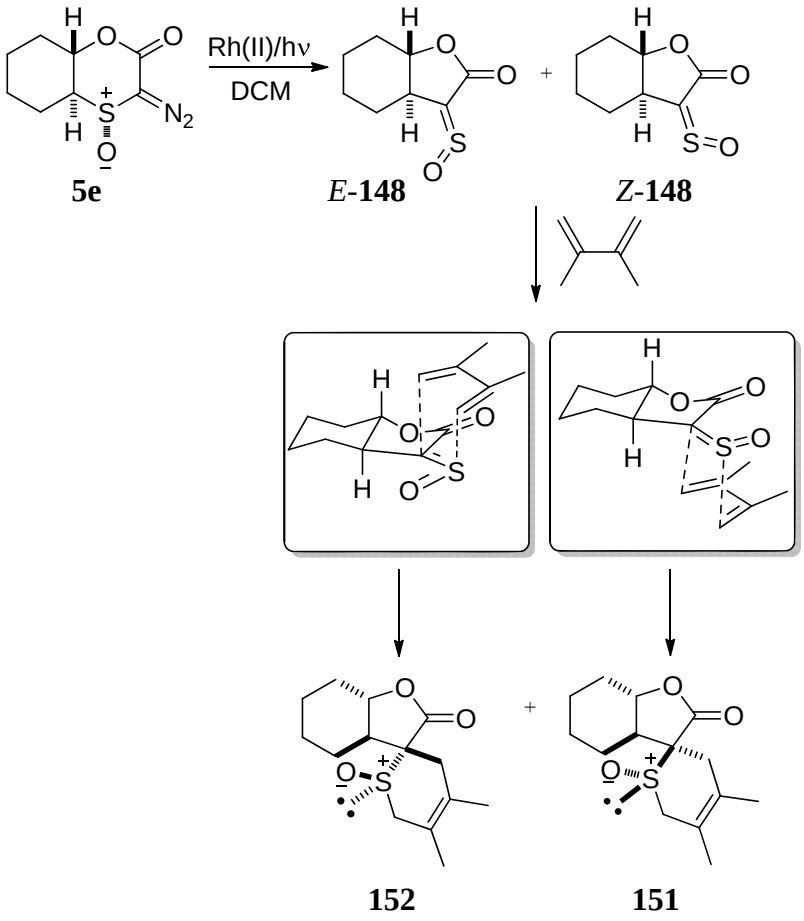
Scheme 2.79

From this foundation, a range of lactone based α-diazosulfoxides have been synthesised (Figure 2.1) and their reactivity has been studied. This is best illustrated using the α-diazosulfoxide **5** as an example, as shown in Scheme 2.80. In the absence of a diene trap, the decomposition of α-diazosulfoxides has led to a number of interesting compounds. These products (alkene dimer **149**, enol **153** and disulfide **154**) can be accessed as the major reaction products by simply altering the reaction conditions.[7,103]



Scheme 2.80

The ability of sulfines to undergo [4+2] Diels-Alder cycloadditions in the presence of dienes has been well studied. A number of cycloadducts have been synthesised within the group to date.[7,9,10,103] Additionally, it has been demonstrated that by varying the reaction conditions for Diels-Alder cycloadditions of α-oxosulfines carried out in the presence of 2,3-dimethyl-1,3-butadiene, the ratio of cycloadducts formed can be controlled. An example of a study carried out by Collins with the α-diazosulfoxide **5** summarises this, as illustrated in Scheme 2.81.[7]

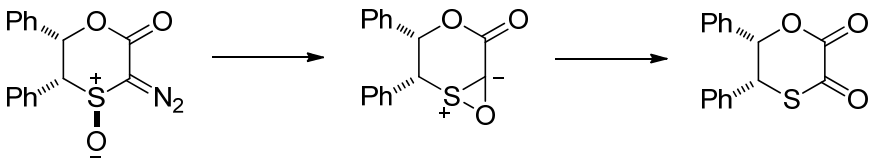


$Rh_2(OAc)_4$	1 : 6
Hg lamp (hν 254 nm)	5 : 1

Scheme 2.81

When the reaction was carried out in the presence of 1 mol% rhodium(II) acetate, the cycloadduct **6** was the major product. The X-ray crystal structure obtained revealed that this cycloadduct is derived from the *Z*-sulfine **148**. However, when the reaction was carried out under photochemical conditions, cycloadduct **6** was the minor product with the cycloadduct **7**, from the *E*-sulfine, as the major product of the reaction.

While formation of the α-oxosulfines has been the dominant pathway seen in this programme to date, in one instance oxygen-transfer from sulfur to the diazo carbon was observed to give the keto ester **156** (Scheme 2.82),[9] reminiscent of Rosati's work with cephalosporin derivatives.[3]



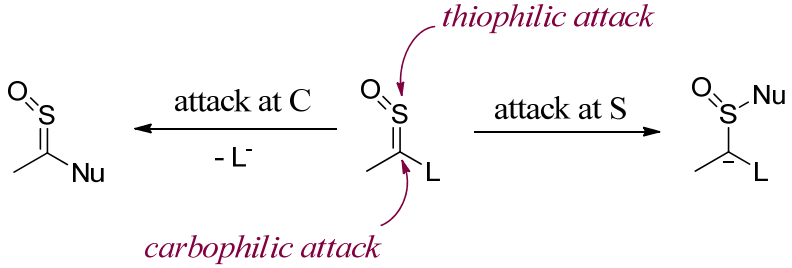
12 **157** **156**

Scheme 2.82

The synthetic and mechanistic properties of these α-diazosulfoxides has been explored extensively.[6,7,9,10] A detailed picture of the reactivity of the corresponding α-oxosulfines has been formed, based on decomposition studies and cycloadditions. However, as illustrated in Scheme 1.24, sulfines are capable of a wide range of reactivity. In particular, reports in the literature on the reactivity of sulfines with nucleophiles have revealed interesting results (Sections 1.4.1 and 1.4.2). Thus, a main objective of this project was to take these α-oxosulfines, and investigate their reactivity in the presence of a range of nitrogen and carbon nucleophiles. In doing so, we anticipated new routes toward interesting and novel heterocyclic systems.

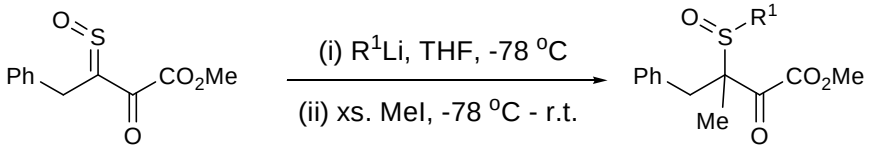
2.9.2 Reactivity with Nitrogen Nucleophiles

Literature reports on the reactivity of sulfines with nucleophiles have already been discussed in detail in Chapter 1 (Sections 1.4.1 and 1.4.2). An interesting property of sulfines allows nucleophilic attack to occur by two approaches, carbophilic attack at the carbon of the sulfine group, or thiophilic attack at the sulfur of the sulfine group (Scheme 2.83). Addition preferably takes place at the partially positively charged sulfur. Reports of carbophilic attack are encountered much less frequently, and appear to be limited to sulfines which bear a leaving group at the sulfine carbon atom.[104]



Scheme 2.83

Nucleophilic reactions with α-oxosulfines, however, have been investigated in only a small number of cases. Notably, De Laet treated α-oxo sulfines with *n*-butyllithium and LDA to obtain sulfoxides and sulfinamides, respectively, as a mixture of diastereomers in low to moderate yields.[105] Importantly, exclusive chemoselectivity through thiophilic addition with both carbon and nitrogen nucleophiles was observed in each case; carbophilic additions or reaction with the ester functionality did not occur.



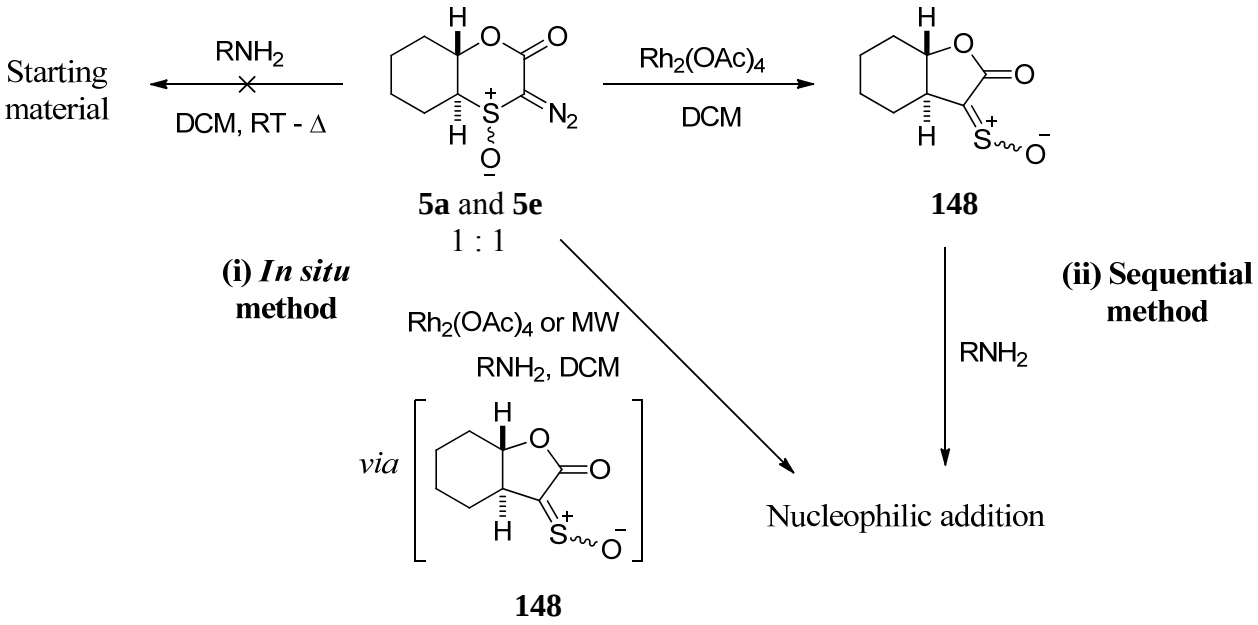
R^1 = *n*-Bu, 40%

R^1 = (*i*-Pr)$_2$N, 10%

Scheme 2.84

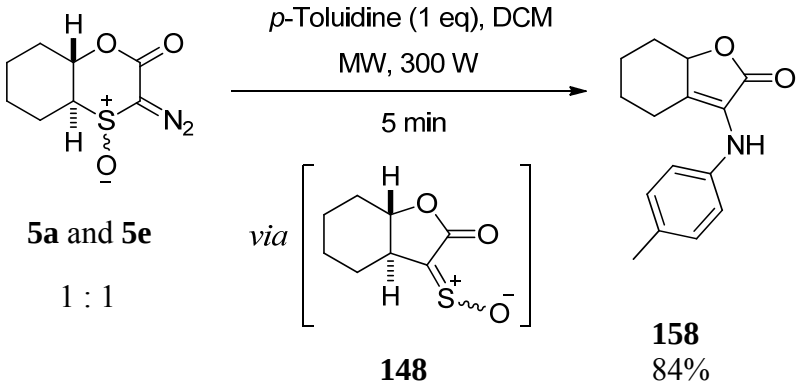
During this work, α-oxosulfines were prepared from α-diazosulfoxides and their reactivity in the presence of neutral amines was investigated. We were particularly interested in studying the chemoselective features of the additions and whether stable heterocyclic products could be isolated.

The nucleophile addition reactions were conducted using two methods. Firstly, for the *in situ* reactions, the amine nucleophile was added to the α-diazosulfoxides **5a** and **5e**, either in the presence of rhodium(II) acetate at room temperature, or under microwave conditions without a catalyst, with generation of the α-oxosulfine **148** and subsequent addition of the nucleophile in a one-pot method (Scheme 2.85). Secondly, for the sequential reactions, the α-oxosulfine **148** was formed and isolated from the α-diazosulfoxides **5a** and **5e** in the presence of rhodium(II) acetate at room temperature, and then reacted with the nucleophile in a two-step method (Scheme 2.85).



Scheme 2.85

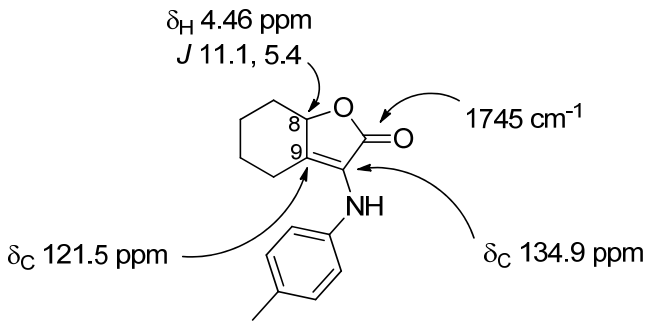
An initial reaction was carried out using the *in situ* method under microwave conditions. The reactivity of the sulfine **148** generated from the α-diazosulfoxides **5a** and **5e** was explored, with *p*-toluidine employed as a suitable amine nitrogen nucleophile. *p*-Toluidine was added to a solution of the α-diazosulfoxides **5a** and **5e** (1:1) in dichloromethane and the solution was irradiated with microwaves at 300 W for 5 minutes. Purification of the crude mixture by column chromatography gave the novel 3-aminofuran-2(5*H*)-one **158** as a brown solid in 84% yield (Scheme 2.86) which was fully characterised during this work to confirm its structure.



Scheme 2.86

A number of interesting spectral features allowed us to suggest this structure for the addition product. Firstly, although the C(8)H bridgehead proton was visible

in the ^{1}H NMR spectrum as a doublet of doublets at 4.46 ppm, the C(9)H signal of the bridgehead protons in the diazo precursors **5a** and **5e** was absent (typically 2.80-3.00 ppm), indicating the formation of an alkene bond at this position. This was confirmed by the presence of two quaternary carbons at 121.5 and 134.9 ppm in the ^{13}C NMR spectrum. Secondly, the S-O stretch typical for sulfines and sulfoxides was not observed in the IR spectrum and the characteristic carbonyl stretch of an unsaturated γ-lactone was present at 1745 cm^{-1}, confirming ring contraction (Figure 2.22). The elemental composition was also confirmed by elemental analysis, highlighting the loss of sulfur from the compound.



158

Figure 2.22

A stacked comparison of the ^{1}H NMR spectra for the sulfine **148** and 3-aminofuran-2(5*H*)-one **158** is illustrated in Figure 2.23. The characteristic downfield shift of the CHO signal on formation of the 3-aminofuran-2(5*H*)-one **158** is evident.

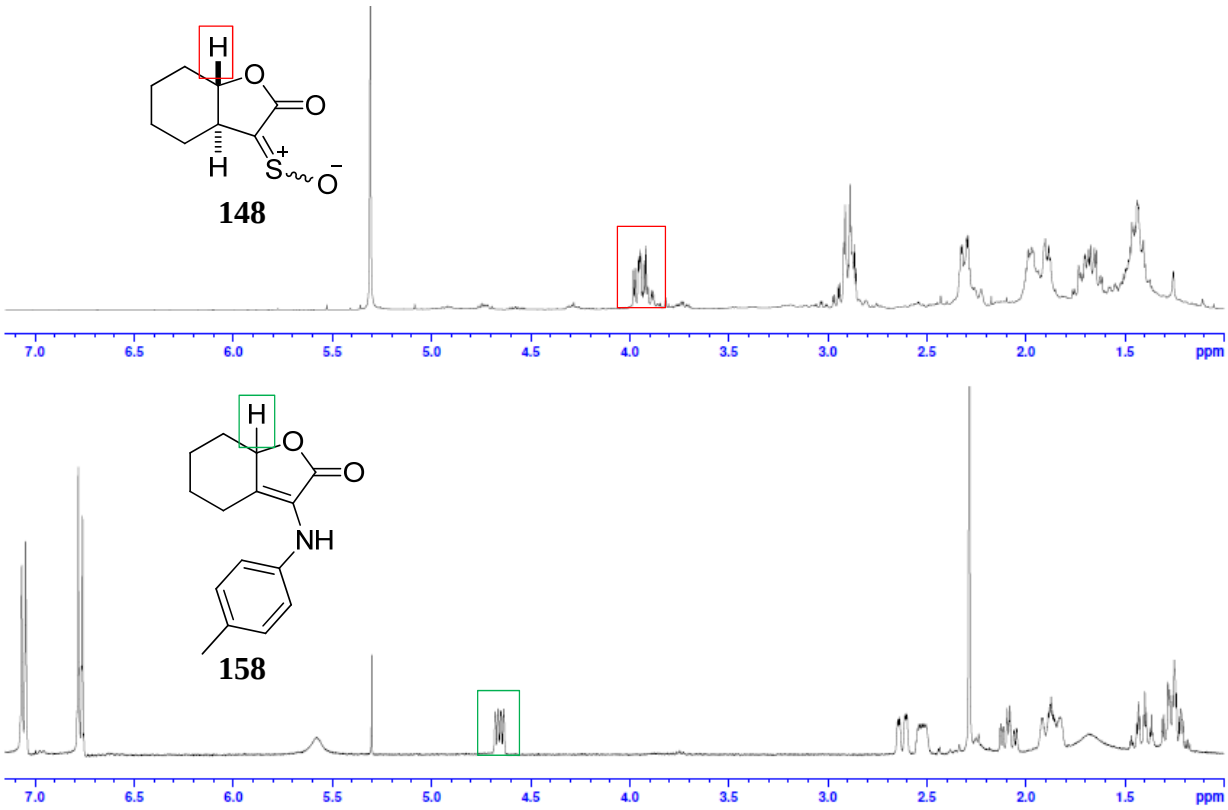
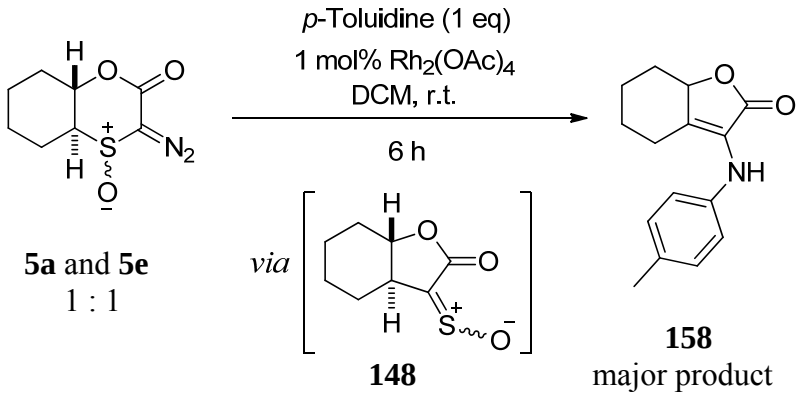


Figure 2.23 *Top ^{1}H NMR spectrum: sulfine **148**. Bottom ^{1}H NMR spectrum: 3-aminofuran-2(5*H*)-one **158** ($CDCl_3$, 400 MHz).*

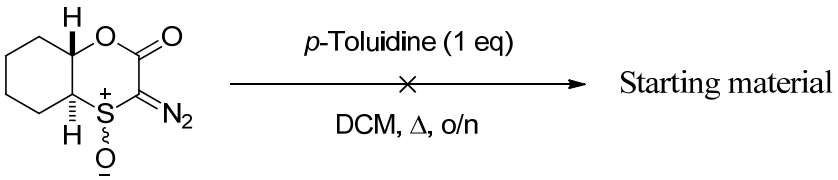
The nucleophilic addition was also undertaken *in situ* at room temperature, in the presence of 1 mol% rhodium(II) acetate in dichloromethane (Scheme 2.87). The progress of the reaction was monitored by TLC analysis, which indicated complete consumption of starting material after 6 hours. Again, the 3-aminofuran-2(5*H*)-one **158** was the main product from the reaction, with a very clean ^{1}H NMR spectrum of the crude material obtained that was not purified.



Scheme 2.87

The sequence of addition for the *in situ* reaction at room temperature was addition of the amine to a stirring solution of the α-diazosulfoxides **5a** and **5e** in dichloromethane followed immediately by addition of 1 mol% rhodium(II) catalyst. On addition of the catalyst, the initially pale green solution turned orange, suggesting possible coordination of the amine to the rhodium(II) catalyst. The isolation of the 3-aminofuran-2(5*H*)-one **158** from this reaction, whereby the amine nucleophile was present from the outset, was rather unexpected, as poisoning of the rhodium(II) catalyst through complexation to the amine was the likely anticipated outcome.

A control experiment was also conducted with the α-diazosulfoxides **5a** and **5e** and *p*-toluidine under reflux conditions in dichloromethane overnight, but in the absence of the rhodium(II) acetate catalyst (Scheme 2.88). Only the unreacted starting material was recovered, thus confirming the catalytic activity of rhodium(II) acetate in the nucleophilic addition reaction at room temperature.

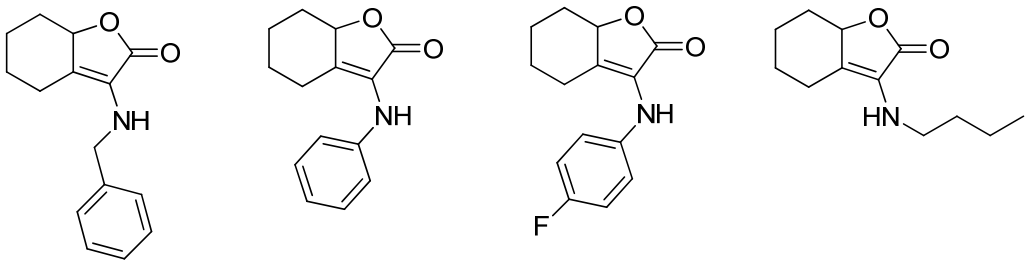


5a and **5e**

1 : 1

Scheme 2.88

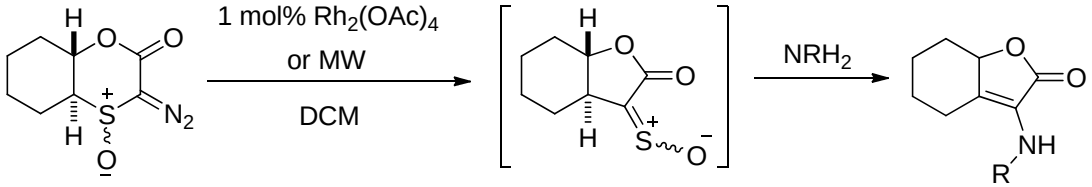
The nucleophilic addition was next employed in the preparation of a range of novel 3-aminofuran-2(5*H*)-ones using the sulfine **148** generated from the α-diazosulfoxides **5a** and **5e** (Figure 2.24). The effect of varying the amine group was investigated by exploring different aromatic and benzyl amines. It was necessary to demonstrate that nucleophilic addition did indeed take place with the sulfine **148**, therefore the reactions were undertaken using both *in situ* reactions under microwave and room temperature conditions, and the sequential method at room temperature. A summary of these reactions is given is Table 2.6.



159 **160** **161** **162**

Figure 2.24

Table 2.6 Reaction of sulfine **148** derived from α-diazosulfoxide **5a** and **5e** with amines



5a and **5e**
1 : 1

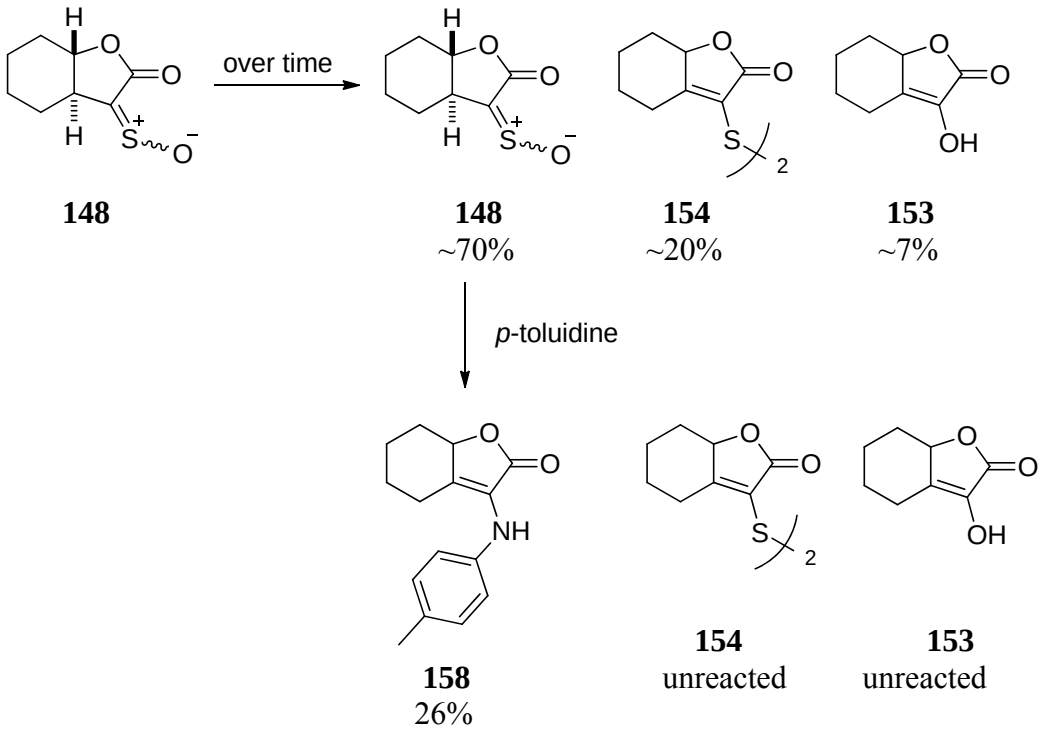
148

Entry	Amine	*in situ*/ sequential	Reaction conditions	R	3-aminofuran-2(5*H*)-one	% Yield[a]
1	*p*-toluidine	no catalyst	Δ, o/n	-	-[b]	-
2[c]	*p*-toluidine	*in situ* no catalyst	MW, 300 W, 5 min	*p*-tol	**158**	84
3[d]	*p*-toluidine	*in situ*	RT, 6 h	*p*-tol	**158**[f]	Not purified
4[e]	*p*-toluidine	sequential	(i) RT, 15 min (ii) RT, 5 h	*p*-tol	**158**	26
5[e]	benzylamine	sequential	(i) RT, 15 min (ii) RT, 5 h	Bn	**159**	29
6[d]	benzylamine	*in situ*	RT, 6 h	Bn	**159**	32[g]

7[c]	benzylamine	*in situ* no catalyst	MW, 300 W, 5 min	Bn	**159**	70[d]
8[d]	aniline	*in situ*	RT, 6 h	Ph	**160**	72
9[d]	*p*-fluoroaniline	*in situ*	RT, 6 h	*p*-F(C_6H_4)	**161**	62
10[d]	*n*-butylamine	*in situ*	RT, 6 h	*n*-Bu	**162**	Not purified[h]

a. Yield after column chromatography.
b. No product was formed in the absence of a catalyst under room temperature or reflux conditions. Clean starting material was recovered.
c. The reaction was carried out *in situ*, with addition of the amine directly to the α-diazosulfoxides **5a** and **5e** (1:1). The solution was heated to 100 °C and irradiated to 300 W for 5 min, with a 3 min ramp-time, in a sealed 10 mL vessel and in the absence of rhodium(II) catalyst.
d. The reaction was carried out *in situ* at room temperature over 6 h, with addition of the amine directly to the α-diazosulfoxides **5a** and **5e** (1:1).
e. (i) The reaction conditions under which the sulfine **148** was generated from the α-diazosulfoxides **5a** and **5e** (1:1); (ii) The reaction conditions for addition of the amine to the sulfine **148**.
f. The 3-aminofuran-2(5*H*)-one **158** was the major product in this reaction, although purification was not undertaken.
g. Contained small quantity of amide impurity **163**.
h. Attempts to purify the 3-aminofuran-2(5*H*)-one **162** were unsuccessful.

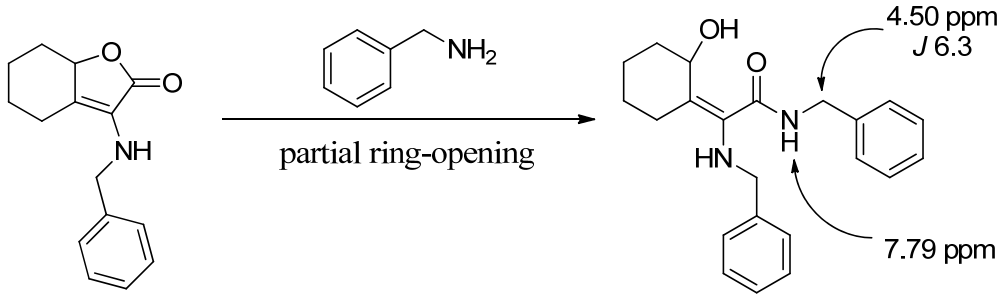
It can been seen from Table 2.6 above that the best procedures for the synthesis of the 3-aminofuran-2(5*H*)-ones employ the *in situ* methods under microwave conditions or at room temperature in the presence of rhodium(II) acetate, rather than the sequential method at room temperature in the presence of rhodium(II) acetate. Notably, nucleophilic addition to the α-oxosulfine **148** generated under microwave conditions provides a metal catalyst-free route towards the 3-aminofuran-2(5*H*)-ones. The low yields obtained using the sequential method can be explained by considering the instability of the sulfine **148**. The sulfine **148** has been studied in detail by previous workers within the group, and is known to decompose readily at room temperature, as discussed in Section 2.9.1. Thus, although 1 equivalent of the amine is added to a solution of the sulfine **148**, in actual fact, the solution contains the sulfine **148** along with small quantities of a mixture of decomposition compounds including **154** and **153**, which were observed in the ^{1}H NMR spectrum of the sulfine **148**. (Scheme 2.89). This also ensures that purification is more difficult, and inevitably leads to a significant decrease in the yield of the product.



Scheme 2.89

The 3-aminofuran-2(5*H*)-ones **158-161**, derived from aryl or benzyl amines, were obtained as stable solids and purified by chromatography in very good yields from the *in situ* methods. When required, analytically pure samples were obtained by slow recrystallisation from hexane/dichloromethane. However, although ^{1}H NMR analysis indicated formation of the *n*-butyl 3-aminofuran-2(5*H*)-one **162** derived from the primary alkyl amine, the ^{1}H NMR spectrum of the crude material was significantly more complex and we were unable to obtain a pure sample by chromatography. Furthermore, a very low quantity was obtained.

It is worth noting that the nucleophilic additions with benzylamine led to a small quantity of an impurity identified as **163** (Scheme 2.90) which was difficult to remove by chromatography, along with the 3-aminofuran-2(5*H*)-one **159**. As benzylamine is a stronger nucleophile than the aromatic amines, partial ring-opening of the lactone is readily rationalised, to give the amide **163**. The compound was identified by a distinctive CH_2 doublet at 4.50 ppm and amide NH broad singlet at 7.79 ppm (Scheme 2.90).

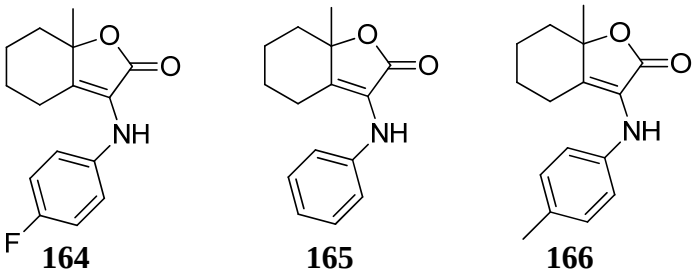


159 **163**

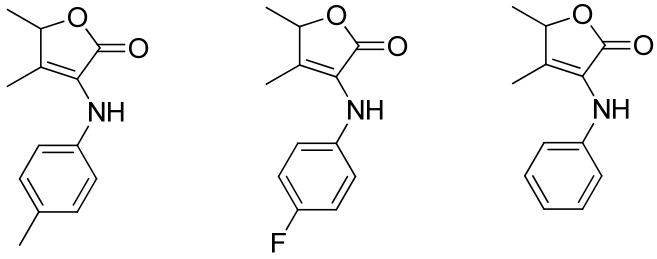
Scheme 2.90

The reactivity trends based on the electronic properties of the primary amines employed as nucleophiles are noteworthy. While the primary alkyl amine was the most powerful nucleophile studied, this led to the least efficient transformation to the 3-aminofuran-2(5*H*)-one **162**, presumably due to competing reaction pathways. The less reactive benzyl and aryl amines led to isolation of 3-aminofuran-2(5*H*)-ones in moderate to good yields. Interestingly, the isolation of amide **163** in the presence of benzylamine supports the theory of further reaction in the presence of the more reactive amine, butylamine. Comparable amides were not detected with the aryl amines, which are the least reactive nucleophiles.

Our library of 3-aminofuran-2(5*H*)-ones was next expanded to include further derivatives, using the same methodology as employed above. The novel compounds which were prepared are illustrated in Figure 2.25.



164 **165** **166**

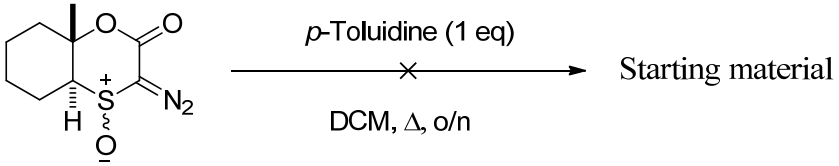


167 **168** **169**

Figure 2.25

The 3-aminofuran-2(5*H*)-ones **164-166** were prepared from the methyl bridgehead sulfine **170** in good yields, using both the *in situ* method under microwave conditions and sequential method in the presence of rhodium(II) acetate (Table 2.7). The methyl bridgehead α-diazosulfoxides **7e** and **7a** are more stable than the α-diazosulfoxides **5e** and **5a**, and require more forcing conditions to be converted to the α-oxosulfine **170**, as observed by previous members within the group.[7,9] Notwithstanding this, the α-oxosulfine **170** can be cleanly generated and is more stable than the α-oxosulfine **148.** The α-oxosulfine **170** was formed in the sequential method by heating the α-diazosulfoxides **7e** and **7a** (14:1) under reflux conditions in dichloromethane in the presence of 1 mol% rhodium(II) acetate for one hour. The sulfine was then treated with the amine in dichloromethane at room temperature. The progress of the reaction was monitored by TLC analysis, which indicated complete consumption of starting material within 6 hours. For the *in situ* reaction under microwave conditions, *p*-toluidine was added directly to a solution of the α-diazosulfoxides **7e** and **7a** in dichloromethane and the solution was irradiated with microwaves for 20 minutes. This sulfine **170** has been studied by previous members within the group and is significantly more stable than the bicyclic sulfine **148**.[7,102] The methyl bridgehead sulfine **170** can be stored overnight at 4 °C without any noticeable decomposition and this allowed for the preparation of the 3-aminofuran-2(5*H*)-ones **164-166** in good yields using both the sequential method in the presence of rhodium(II) acetate and the *in situ* method under microwave conditions. A summary of these reactions is given in Table 2.7.

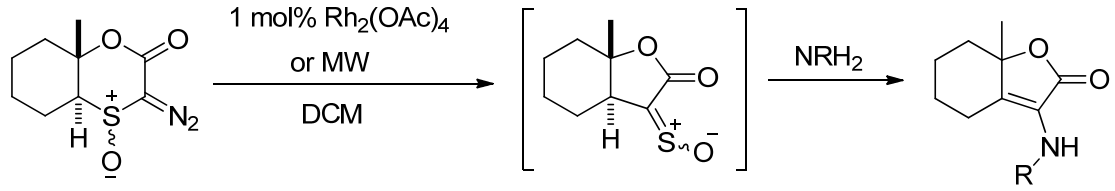
A control experiment, similar to Scheme 2.88 above, was conducted with the α-diazosulfoxides **7e** and **7a** and *p*-toluidine under reflux conditions overnight, but with the absence of the rhodium(II) acetate catalyst (Scheme 2.91). Again, only the unreacted starting material was recovered.



7e and **7a**
14 : 1

Scheme 2.91

Table 2.7 Reaction of sulfine **170** derived from α-diazosulfoxides **7e** and **7a** with amines



7e and **7a**

14 : 1

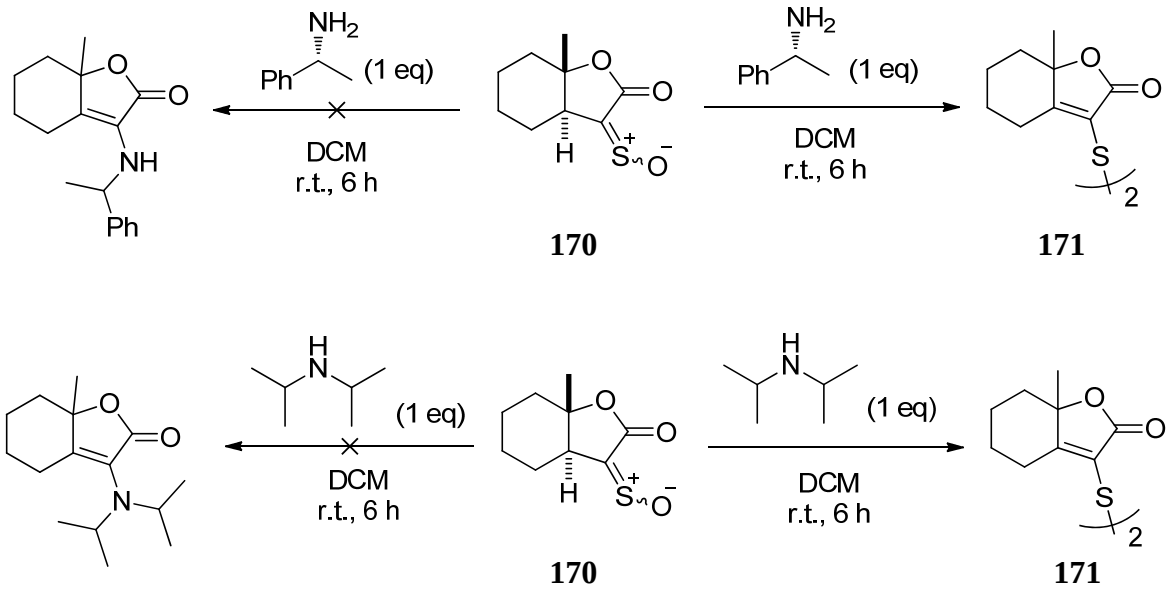
170

Entry	Amine	*in situ*/ sequential	Reaction conditions	R	3-aminofuran-2(5*H*)-one	% Yield[a]
1	*p*-toluidine	no catalyst	Δ, o/n	-	- [b]	-
2[c]	*p*-toluidine	sequential	(i) Δ, 1 h (ii) RT, 6 h	*p*-tol	**166**	72
3[d]	*p*-toluidine	*in situ* no catalyst	MW, 300 W, 20 min	*p*-tol	**166**	52
4[c]	aniline	sequential	(i) Δ, 1 h (ii) RT, 6 h	Ph	**165**	69
5[c]	*p*-fluoroaniline	sequential	(i) Δ, 1 h (ii) RT, 6 h	*p*-F(C_6H_4)	**164**	64
6[c]	(*R*)-(α)-methylbenzyl amine	sequential	(i) Δ, 1 h (ii) RT, 6 h	-	- [e]	-
7[c]	diisopropyl amine	sequential	(i) Δ, 1 h (ii) RT, 6 h	-	- [e]	-

a. Yield after chromatography.
b. No product was formed in the absence of a catalyst under reflux conditions. Clean starting material was recovered.
c. (i) The reaction conditions under which the sulfine **170** was generated from the α-diazosulfoxides **7e** and **7a** (14:1), (ii) The reaction conditions for addition of the amine to the sulfine **170**.
d. The reaction was carried out *in situ*, with addition of the amine directly to the α-diazosulfoxides **7e** and **7a** (14:1). The solution was heated to 100 °C and irradiated to 300 W for 10 min, with a 3 min ramp-time, in a sealed 10 mL vessel and in the absence of rhodium(II) catalyst.
e. No addition product was detected.

Nucleophilic addition of *p*-fluoroaniline, aniline and *p*-toluidine gave the 3-aminofuran-2(5*H*)-ones **164**-**166**. However, attempted reactions with more sterically

hindered (*R*)-(α)-methylbenzyl amine and diisopropyl amine did not lead to any addition products. Instead, decomposition of the sulfine **170** occurred, leading to the disulfide **171** shown in Scheme 2.92.



Scheme 2.92

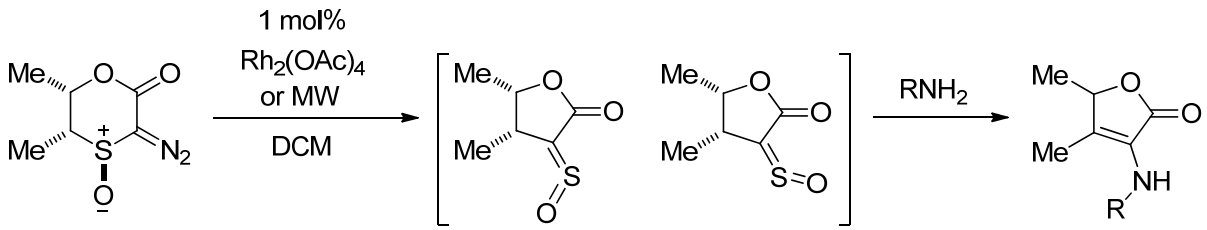
Two possible explanations for these unsuccessful reactions can be envisaged. Firstly, that the amine is not involved at all, but **170** is spontaneously decomposing to the disulfide **171** under the reaction conditions. Alternatively, reaction of the sulfines with either the primary or secondary amine leads to the disulfide **171**. Based on our observations to date, we believe the former explanation to be more likely.

While the lack of reaction between the hindered diisopropyl amine with the sulfine **170** is readily understood on the basis of steric hindrance, the contrast between benzylamine in reaction with α-diazosulfoxides **5a** and **5e** (entries 5-7, Table 2.6) and (*R*)-(α)-methylbenzyl amine with α-diazosulfoxides **7e** and **7a** (entry 6, Table 2.7) is particularly interesting and warrants further investigation.

The 3-aminofuran-2(5*H*)-ones **167**-**169** were prepared from the *cis*-dimethyl sulfines *E*-**172** and *Z*-**172** using both the *in situ* method under microwave conditions and sequential method in the presence of rhodium(II) acetate (Table 2.8). The *cis*-dimethyl sulfines *E*-**172** and *Z*-**172** were generated from the α-diazosulfoxide **10** by heating under reflux in dichloromethane with 1 mol% rhodium(II) acetate overnight.

Each isomer can be distinguished by ^{1}H NMR analysis. Extensive isomerisation studies have been undertaken by O'Sullivan[9] and one of the most important findings from her studies was the direct observation of isomerisation of the *Z*-sulfine ***Z*-172** to the *E*-sulfine ***E*-172** under rhodium(II) catalysed conditions over time. During this work for the sequential method, the sulfines ***E*-172** and ***Z*-172** were generated by heating under reflux overnight for approximately 18 hours, although this varied slightly. As such, the ratios of these sulfines also varied from experiment to experiment. Because the relative stereochemistry is lost during the nucleophilic addition, this had no effect on the stereochemical outcome of the overall reaction. A summary of the 3-aminofuran-2(5*H*)-ones prepared from the sulfines ***E*-172** and ***Z*-172** is given in Table 2.8.

Table 2.8 Reaction of sulfines *E*-**172** and *Z*-**172** derived from α-diazosulfoxide **10** with amines



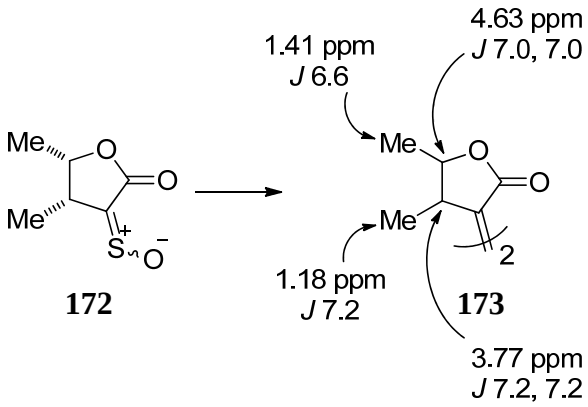
10 *E*-**172** *Z*-**172**

Entry	Amine	*in situ*/ sequential	*E* : *Z*	Reaction conditions	R	3-Amino furan-2(5*H*)-one	% Yield[a]
1[b]	*p*-toluidine	sequential	3 : 1	(i) Δ, o/n (ii) RT, o/n	*p*-tol	**167**	~44%[e]
2[c]	*p*-toluidine	*in situ*	-	(i) RT, 18 h (ii) Δ, 36 h	*p*-tol	-[f]	-
3[b]	*p*-fluoroaniline	sequential	*E* only	(i) Δ, o/n (ii) RT, o/n	*p*-F(C_6H_4)	**168**	67
4[d]	*p*-fluoroaniline	*in situ* no catalyst	-	MW, 300 W, 10 min	*p*-F(C_6H_4)	**168**	88
5[b]	aniline	sequential	11 : 1	(i) Δ, o/n (ii) RT, o/n	Ph	**169**	65

a. Yield after chromatography or recrystallisation.
b. (i) The reaction conditions under which the sulfines *E*-**172** and *Z*-**172** were generated from the α-diazosulfoxide **10** in the presence of 1 mol% rhodium(II) acetate; (ii) The reaction conditions for addition of the amine to the sulfines *E*-**172** and *Z*-**172**.
c. The reaction was carried out *in situ*, with addition of the amine to the α-diazosulfoxide **10**, followed by 1 mol% rhodium(II) acetate.
d. The reaction was carried out *in situ*, with addition of the amine directly to the α-diazosulfoxide **10**. The solution was heated to 100 °C and irradiated to 300 W for 45 min, with a 3 min ramp-time, in a sealed 10 mL vessel and in the absence of rhodium(II) catalyst.
e. The 3-aminofuran-2(5*H*)-one **167** was isolated with a small quantity of the alkene dimer **173** (10:1).
f. No addition product was detected. The ^{1}H NMR spectrum of the crude material indicated the presence of α-diazosulfoxide **10**, disulfide **174** and alkene dimer **173** (1: 0.5: 0.1)

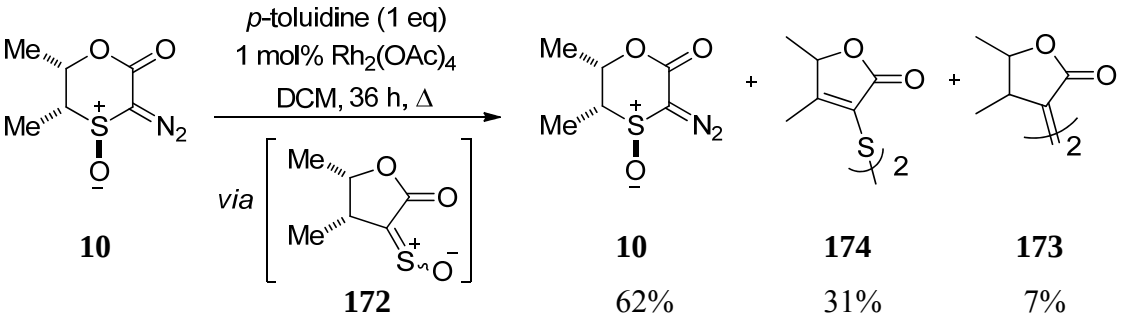
The 3-aminofuran-2(5*H*)-ones **167-169** derived from aryl amines were prepared and isolated in good yields after chromatography or recrystallisation. Analytically pure samples could be obtained by slow recrystallisation using hexane/dichloromethane.

For the sequential reaction in the presence of 1 mol% rhodium(II) acetate and the attempted *in situ* microwave reaction undertaken with *p*-toluidine (entries 1 and 2, Table 2.8), a small quantity of a compound tentatively assigned as the alkene dimer **173** was detected in the ^{1}H NMR spectra of the crude product. The spectral details identified are summarised in Scheme 2.93. Further evidence from the nominal mass spectrum indicated the presence of the molecular ion $[M+H]^{+}$ peak at 225. During decomposition studies carried out by previous members of the group, the alkene dimer **149**, generated from the bicyclic sulfine **148**, had been isolated and characterised (Section 2.9.1).[103] However, the *cis*-dimethyl alkene dimer **173** has not previously been detected and this represents the first evidence for its formation. Further work is required in order to obtain an analytically pure sample of this compound for full characterisation.



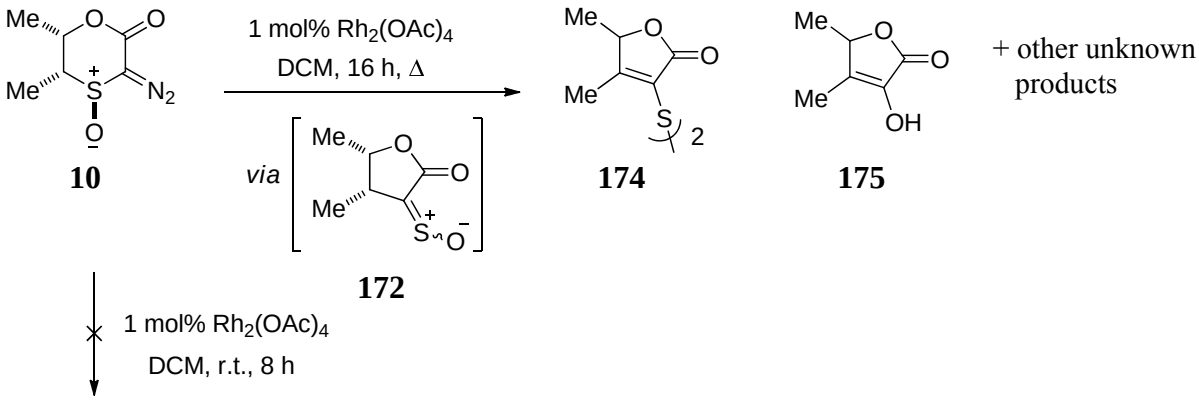
Scheme 2.93

The *in situ* reaction undertaken with *p*-toluidine (entry 2, Table 2.8) was unsuccessful. The reaction mixture was initially stirred at room temperature for 18 hours. ^{1}H NMR analysis of the mixture indicated the presence of the α-diazosulfoxide **10** and *p*-toluidine starting materials, with no evidence for any nucleophilic addition. The reaction mixture was stirred under reflux for a further 36 hours. The ^{1}H NMR spectrum showed that partial decomposition of the α-diazosulfoxide **10** had occurred, giving the disulfide **174** and the alkene dimer **173** (1 : 0.5 : 0.1, Scheme 2.94).



Scheme 2.94

Previous work has demonstrated that the α-diazosulfoxide **10** does not decompose in the presence of rhodium(II) acetate at room temperature over 8 hours. During work undertaken by Collins, fresh addition of catalyst followed by stirring under reflux conditions for a further 16 hours gave a number of products, with complete consumption of the α-diazosulfoxide **10** (Scheme 2.95).[7] Notably, further studies undertaken by O'Sullivan demonstrated that the monocyclic lactone derivatives are much less reactive than the bicyclic systems,[9] which would also be consistent with the observation in this case of reduced activity of the catalyst in the presence of the amine. It is likely that the reduced reactivity of the α-diazosulfoxide **10** gave sufficient time for complexation between *p*-toluidine and rhodium(II) acetate, resulting in catalyst poisoning to the extent that **10** did not react with *p*-toluidine.



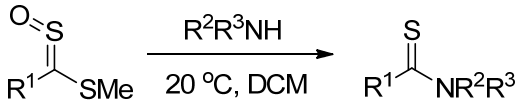
Scheme 2.95

Notably, this reaction was the only example in his work where poisoning of the rhodium(II) catalyst may have occured. The complexation of amines to

rhodium(II) to give rhodium(III) complexes has been well documented in the literature.[106,107] Significantly however, for every other nucleophilic addition undertaken in the presence of rhodium(II) acetate in this work, no evidence for poisoning of the catalyst through complexation to the amine was obtained.

The isolation of these 3-aminofuran-2(5*H*)-ones was not anticipated. Previous accounts in the literature claim the necessity for a leaving group adjacent to the sulfine for carbophilic addition to occur.[104] Rather, thiophilic attack at the sulfine, resulting in a sulfinamide product, had been expected. The only previous report in the literature of nucleophilic addition reactions of sulfines with nitrogen nucleophiles was an isolated reaction by Metzner on the reaction of dithioester sulfines **176** with amines.[108] The authors were surprised to isolate thioamides **177** (Table 2.9).

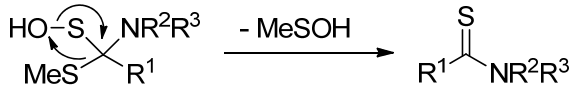
Table 2.9 Reaction of dithioester sulfines **176** with amines by Metzner[108]



176 **177**

R^1	R^2	R^3	Time	% Yield
Pr^i	Me	H	15 min	82
Pr^i	Me	Me	15 min	56
Pr^i	Morpholino		24 h	25
Bu^i	Me	H	24 h	53
Bu^i	Me	Me	24 h	52

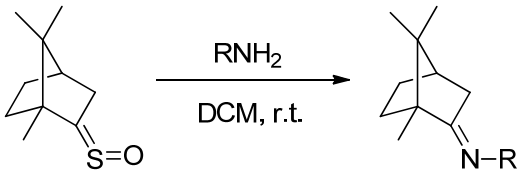
The authors explained the formation of the thioamides **177** by a carbophilic attack followed by elimination of methanesulfenic acid from a tetrahedral intermediate **178** (Scheme 2.96).



178 **177**

Scheme 2.96

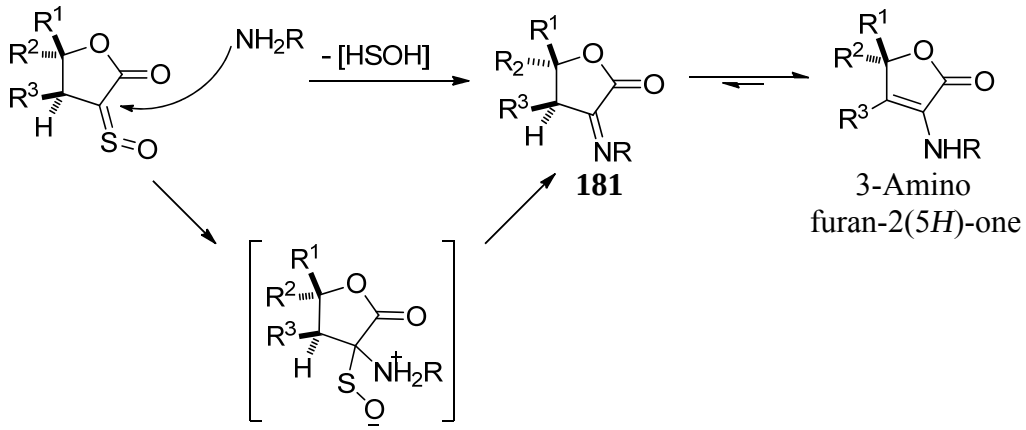
Interestingly, the authors also investigated the behaviour of a chiral sulfine **179** derived from (-)-thiocamphor with primary amines.[108] Carbophilic attack, followed by ready elimination of [HSOH], gave enantiopure imines **180** (Scheme 2.97). The reaction occurred readily at room temperature.



179 **180**

Scheme 2.97

When considering the mechanism of formation for the 3-aminofuran-2(5*H*)-ones prepared in this work, it is suggested that carbophilic attack of the amine would lead to loss of the sulfine group and give the imine **181**, as observed by Metzner in the formation of chiral imines.[108] However, due to the stability associated with conjugated furanones, tautomerism of the imine **181** to the more stable enamine leads to the final observed product.

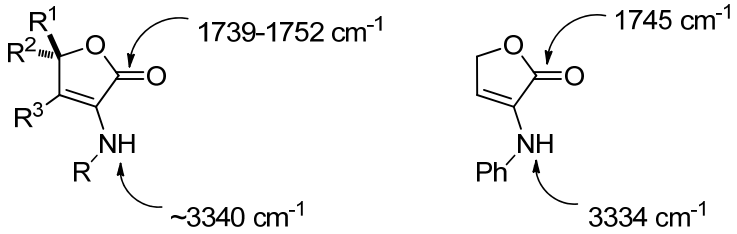


Scheme 2.98

According to the literature, this method of nucleophilic addition to sulfines is quite uncommon. Thiophilic attack of nucleophiles at sulfines is usually reported with carbon and sulfur nucleophiles unless there is a halide leaving group on the sulfur.[104,109,110] This study demonstrates predominant carbophilic attack of amines at sulfines, in line with the single report by Metzner. In addition to being interesting from a mechanistic perspective, this transformation provides a novel synthetic route towards an important class of heterocyclic compounds (Section 2.12.2.2).[111-113] Each of the 3-aminofuran-2(5*H*)-ones prepared in this work is a solid which can be readily purified and stored at room temperature for a number of months without decomposition.

2.9.3 Spectral Characteristics of 3-Aminofuran-2(5*H*)ones

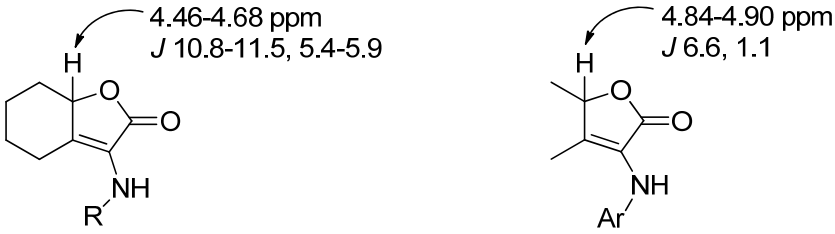
The carbonyl stretching frequency of the 3-aminofuran-2(5*H*)-ones appears in the range of 1739-1752 cm^{-1} in the IR spectra, which is a characteristic region for 5-membered unsaturated γ-lactones.[50] Another characteristic absorption in the IR spectra of these compounds is the amine N-H stretching vibration. These bands were observed in the region ~3340 cm^{-1}. The IR bands for these derivatives are in agreement with those reported in the literature for similar 3-aminofuran-2(5*H*)-ones. For example, the preparation of 3-phenylaminofuran-2(5*H*)-one **182** was described by Payette and Yamamoto *via* nitrosobenzene mediated oxidative decarboxylation.[114] The carbonyl stretching frequency was reported at 1745 cm^{-1} and the NH band was reported at 3334 cm^{-1} (Figure 2.26, *cf.* derivatives prepared in this work).



182

Figure 2.26 *Characteristic IR bands observed for the compounds in this work (left); IR bands reported by Payette and Yamamoto for 3-phenylaminofuran-2(*5H*)-one **182**[114] (right).*

For the bicyclic 3-aminofuran-2(5*H*)-ones **158-162**, the signal for the C(H)O proton was visible as a distinctive doublet of doublets in the region 4.46-4.68 ppm with coupling constants of 10.8-11.5 Hz and 5.4-5.9 Hz. For the *cis*-dimethyl 3-aminofuran-2(5*H*)-ones **167-169**, the signal for the C(H)O proton was visible as a doublet of quartets in the region 4.84-4.90 ppm with coupling constants of 6.6 and 1.1 Hz, the latter due to long-range coupling to the C(4)-Me (Figure 2.27).



158-162 **167-169**

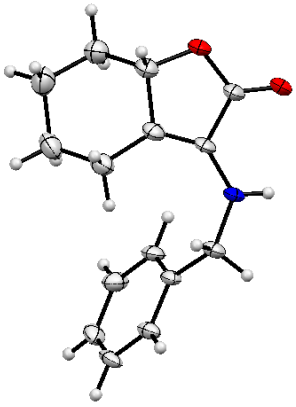
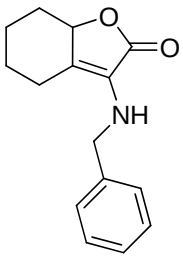
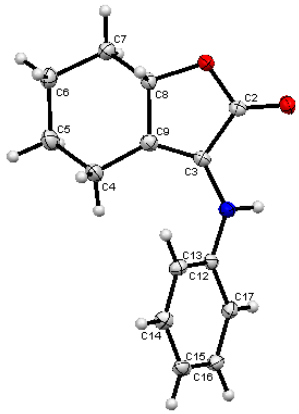
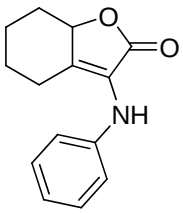
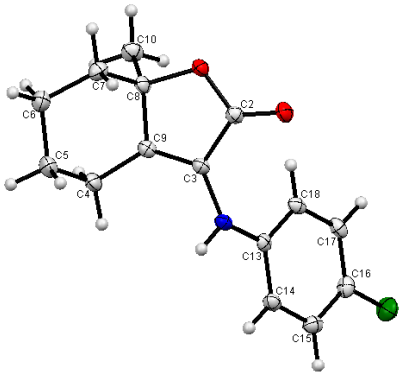
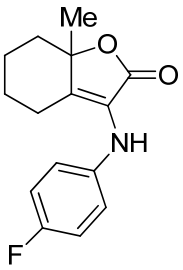
R = *p*-Tol **158**, Bn **159**, Ph **160**, *p*-F(C_6H_4) **161**, *n*-Bu **162**.

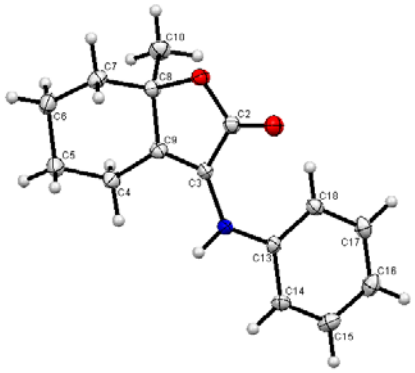
R = *p*-Tol **167**, *p*-F(C_6H_4) **168**, Ph **169**.

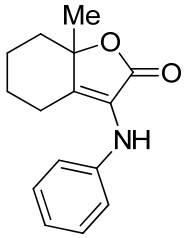
Figure 2.27

A number of 3-aminofuran-2(5*H*)-ones were recrystallised from hexane/dichloromethane and it was possible to unambiguously confirm their structures by X-ray crystallography. These structures are illustrated in Figure 2.28. The 3-aminofuran-2(5*H*)-ones **159**, **160**, **164** and **165** crystallised in centrosymmetric space groups, i.e. as a racemic crystal, while the 3-aminofuran-2(5*H*)-one **169** crystallised in a non-centrosymmetric space group, i.e. as an enantiopure crystal,

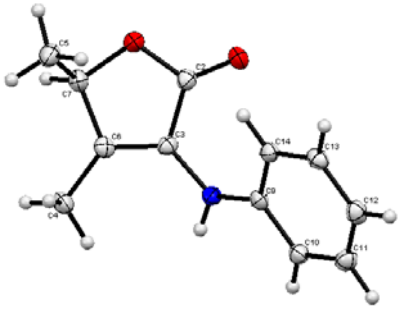
indicating spontaneous resolution. As expected, the furanone ring is essentially completely planar. It can also be seen that sp^2 hybridisation on the NH nitrogen results in planar rather than tetrahedral stereochemistry, enabling the lone pair of electrons to delocalise into the furanone ring system.

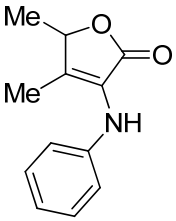
Crystal Structure	3-Aminofuran-2(5*H*)-one
	 **159**
	 **160**
	 **164**





165





169

Figure 2.28 *X-ray crystal structures obtained in this work of 3-aminofuran-2(5*H*)-ones. Structures are displayed using the Mercury 2.3 (Build RC4) package.*

The structures **159**, **160**, **164** and **165** contain intermolecular hydrogen-bonding, between the NH of the amine and the neighbouring carbonyl group. Phenyl derivatives **160**, **164** and **165** form infinite C(5) chains, while the benzyl derivative **159** forms $R_2^2(10)$ dimers. An example is illustrated in Figure 2.29, showing hydrogen bonding (broken lines) between two 3-aminofuran-2(5*H*)-ones **159**.

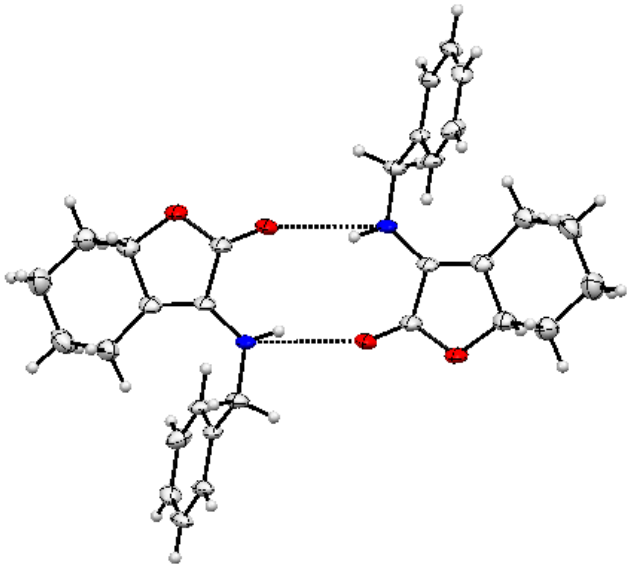
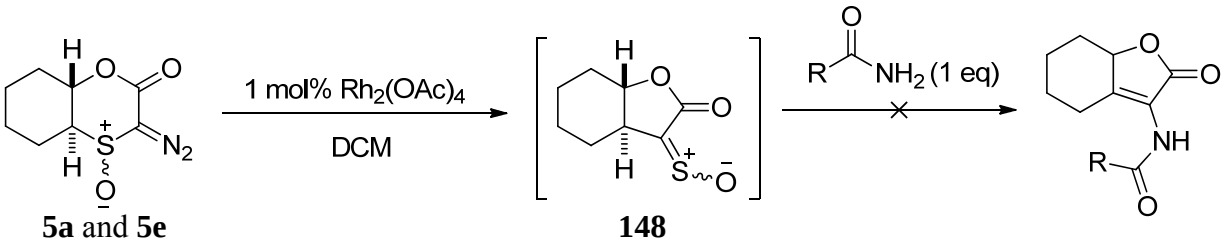


Figure 2.29 *X-ray crystal structure illustrating intermolecular hydrogen-bonding for 3-aminofuran-2(5*H*)-one **159**. Structure is displayed using the Mercury 2.3 (Build RC4) package.*

2.9.4 Attempted Reactions with Amide Nucleophiles

In the earlier studies using amines as nucleophiles, the best results were obtained with less nucleophilic amines. Accordingly, it was decided to investigate whether amides would also behave as suitable nitrogen nucleophiles towards sulfines. A number of reactions were attempted, using acetamide and benzamide, without success. Evidently, the amides were insufficiently nucleophilic to generate addition products in the presence of sulfines. Instead, decomposition of the sulfine occurred over time, with no evidence by ^{1}H NMR analysis for nucleophilic addition. The reactions were carried out *in situ*, with addition of the amide directly to the solution of α-diazosulfoxides **5a** and **5e**, followed immediately by rhodium(II) acetate. The reaction conditions are summarised in Table 2.10.

Table 2.10 Summary of attempted reactions between sulfine **148** generated from α-diazosulfoxide **5a** and **5e** with amides



5a and **5e**

1 : 1

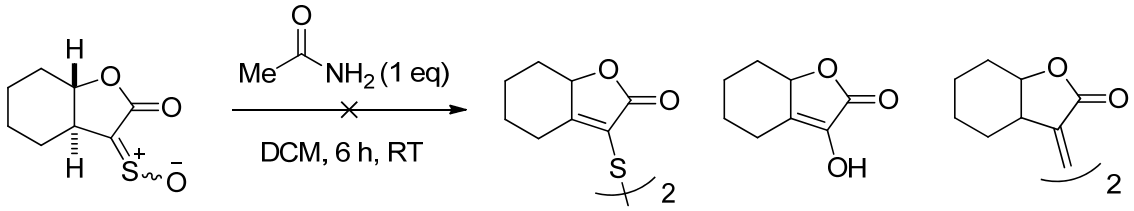
148

Entry	Amide	Reaction conditions	Product[a]
1	acetamide	6 h, RT, DCM	-
2	acetamide	6 h, RT, CH_3CN	-
3	benzamide	5 h, RT, DCM	-

a. Analysed by ^{1}H NMR spectroscopy. No addition products were detected, decomposition of the sulfine **148** occurred.

b. *In situ* addition of the amide to the α-diazosulfoxides **5a** and **5e** followed by addition of 1 mol% rhodium(II) acetate at room temperature. The reactions were allowed to stir for 5-6 hours at room temperature.

For each reaction mixture, ^{1}H NMR analysis indicated the presence of unreacted amide, and a mixture of decomposition products, as illustrated in Scheme 2.99 for entry 1, Table 2.10.



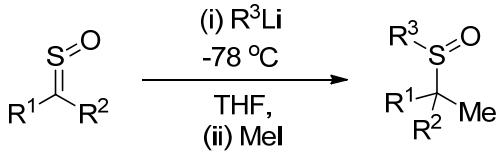
148 **154** 35% **153** 22% **149** 43%

Scheme 2.99

The profile of the decomposition products appeared very similar to the pattern which would be seen in the absence of the amide, indicating that the amide does not take part in the reaction.

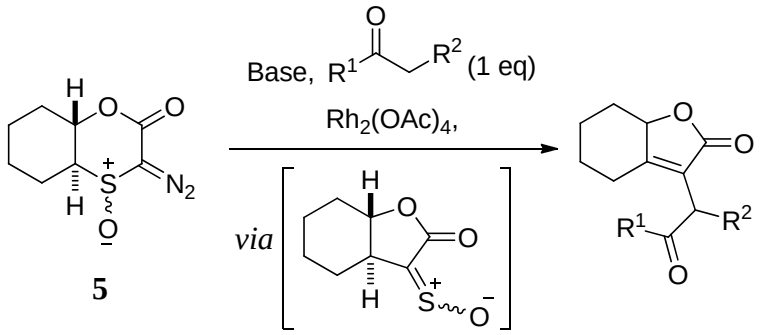
2.9.5 Reactivity with Carbon Nucleophiles

We were interested to understand how carbon nucleophiles would behave in the presence of the α-oxosulfines generated from α-diazosulfoxides in this work. There are a number of reports in the literature which examine nucleophilic addition of carbon nucleophiles to sulfines (Sections 1.4.1 and 1.4.2). The majority of these deal exclusively with the addition of alkyllithiums, resulting in sulfoxides **183** (Scheme 2.100).[109,115-117]



Scheme 2.100

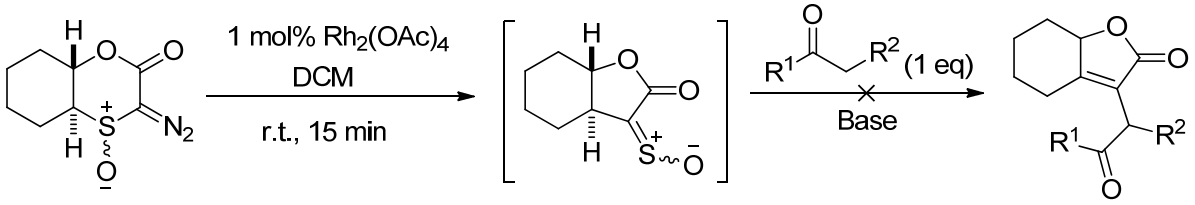
Interestingly, there have been no reports of carbophilic addition of carbon nucleophiles to sulfines without the presence of a good leaving group, such as a halide, adjacent to the sulfine group.[104] Within this project, having generated a series of novel 3-aminofuran-2(5*H*)-ones from carbophilic attack of nitrogen nucleophiles at sulfines (Section 2.9.2), we next explored the possibility of extending this methodology to include carbon nucleophiles, with the prospect of discovering a new route towards carbon-carbon bond formations (Scheme 2.101).



Scheme 2.101

A search of the literature indicated that, while substantial work had been carried out with alkyllithiums,[109,116-120] to the best of our knowledge, there have been no studies carried out on the nucleophilic addition of stabilised enolates at sulfines. Thus, a series of stabilised enolates, easily generated in the presence of a base, was initially investigated. *n*-BuLi was also investigated. The reactions were carried out as described in the literature.[116] The enolate was prepared in the presence of a base in ethanol or THF. The pre-generated sulfine **148** (which was first formed in the presence of rhodium(II) acetate in dichloromethane over 15 minutes) was then dissolved in ethanol or THF and the enolate solution was immediately added *via* cannula at 0 °C. *n*-BuLi was directly added to the pre-generated sulfine **148** in THF or ethanol at 0 °C *via* syringe. A summary of the nucleophilic reactions attempted with the sulfine **148** is given in Table 2.11. These reactions were unsuccessful and no addition product could be identified in the ^{1}H NMR spectrum.

Table 2.11 Summary of attempted nucleophilic addition of carbon nucleophiles to sulfine **148** pre-generated from α-diazosulfoxide **5a** and **5e**



5a and **5e**

1 : 1

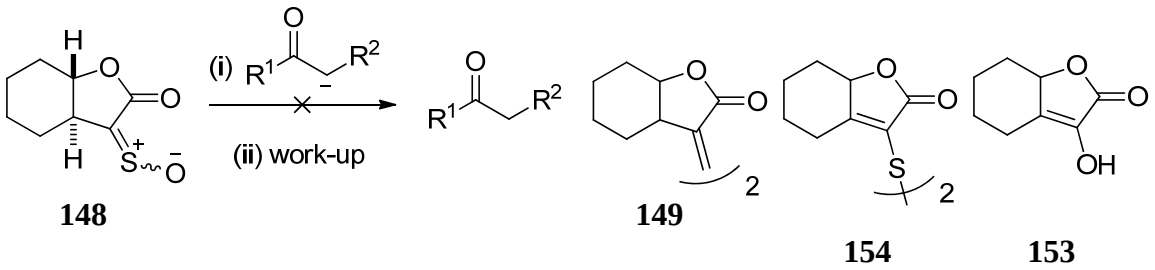
148

Entry	Nucleophile[a]	Base	Reaction conditions[b]	Product[c]
1	Ethyl cyanoacetate	NaOEt	0 °C - r.t, EtOH, 45 min	-
2	Ethyl acetoacetate	LDA	-72 °C, THF, 1 h	-
3	Meldrum's acid	LDA	-72 °C, THF, 1 h	-
4	Meldrum's acid	NaOEt	0 °C - r.t, EtOH, 1 h	-
5	*n*-BuLi	-	-78 °C, THF, 1 h	-

a. For entries 1-4, 1 eq of the carbon nucleophile was used; for entry 5, 1.2 eq of *n*-BuLi was used.
b. The sulfine **148** was pre-generated from the α-diazosulfoxide **5** in dichloromethane at room temperature over 15 min. The sulfine is known to form readily under these conditions and was not characterised, although TLC analysis indicated complete absence of the α-diazosulfoxide **5**. The rhodium(II) catalyst was removed by filteration over Celite®, the solvent was removed *in vacuo* and the sulfine was re-dissolved in EtOH or THF. The enolate was prepared in the presence of a base and directly added to the solution of the sulfine **148**.
c. For entries 1-4, analysis of the ^{1}H NMR spectrum of the crude products indicated an excess of the nucleophiles ethyl cyanoacetate or Meldrum's acid, along with a complex mixture of decomposition products formed from the sulfine **148**. For entry 5, the ^{1}H NMR spectrum of the crude products showed a complex mixture of decomposition products from the sulfine **148**.

Evidently, carbanion nucleophiles do not behave in a similar fashion to neutral amines in the presence of sulfines. Two possible explanations for these results can be considered. Firstly, the furanone products may be too labile for isolation. Secondly, the strongly nucleophilic enolates may cause ring-opening of the furanone. The latter theory agrees with the results obtained from the reactions with

amines (Section 2.9.2), where the most nucleophilic amines were the least successful. The ^{1}H NMR spectra indicated the presence of a complex mixture of compounds, however it was possible to identify a number of decomposition products generated from the sulfine **148** (Scheme 2.102). Unexpectedly, it appeared that sulfine decomposition occurred instead of reaction with the carbon nucleophiles.



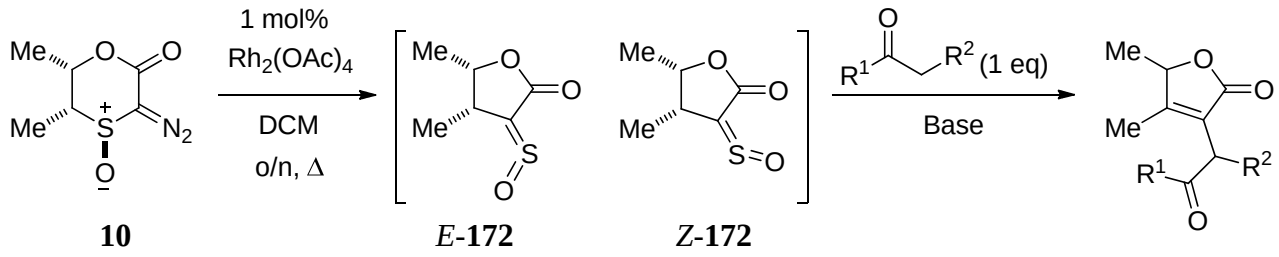
148 **149** **154** **153**

(in a complex ^{1}H NMR spectrum)

Scheme 2.102

A series of parallel reactions was also undertaken with the monocyclic *cis*-dimethyl sulfines *E*-**172** and *Z*-**172** in the presence of the stabilised enolates. The sulfines *E*-**172** and *Z*-**172** were generated from the α-diazosulfoxide **10** under reflux condition overnight in the presence of rhodium(II) acetate in dichloromethane, the catalyst was removed by filtration through Celite®, the solution was concentrated and characterised by ^{1}H NMR analysis and then subjected directly to reaction with the nucleophile. Again, the enolate was freshly formed in the presence of a suitable base in ethanol or THF. The freshly pre-generated sulfines *E*-**172** and *Z*-**172** were then dissolved in a solution of ethanol or THF and the enolate solution was immediately added at 0 °C *via* cannula. Further work has demonstrated that ethanol does not undergo nucleophilic addition with sulfines (Section 2.9.6). The results of this brief study, undertaken using different bases and reaction conditions, are summarised in Table 2.12.

Table 2.12 Summary of nucleophilic addition of carbon nucleophiles to the pre-generated sulfines *Z*-**172** and *E*-**172** derived from α-diazosulfoxide **10**

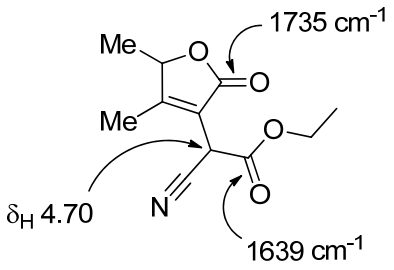


10 *E*-**172** *Z*-**172**

Entry	Nucleophile[a]	R^1	R^2	Base	Reaction Conditions[b]	Product
1	Ethyl cyanoacetate	OEt	CN	NaOEt	0 °C, EtOH, 1 h	**184** (15%)
2	Ethyl cyanoacetate	OEt	CN	LDA	0 °C, THF, 1 h	**184** (17%)
3	Ethyl acetoacetate	OEt	Ac	NaOEt	0 °C, EtOH, 1 h	-[c]
4	Diethyl malonate	OEt	CO_2Et	NaOEt	0 °C, EtOH, 1 h	-[c]

a. For each entry, 1 eq carbon nucleophile was used.
b. The sulfines *E*-**172** and *Z*-**172** were pre-generated from the α-diazosulfoxide **10** in the presence of rhodium(II) acetate under reflux conditions in dichloromethane overnight, the rhodium(II) catalyst was removed by filtration over Celite®, the solution was concentrated and characterised by ^{1}H NMR analysis. The solvent was removed *in vacuo* and the sulfines were re-dissolved in EtOH or THF. The enolate was prepared in the presence of a base and directly added to the solution of the sulfines *E*-**172** and *Z*-**172** at 0 °C.
c. For entries 3-4, analysis of the ^{1}H NMR spectrum of the crude product indicated an excess of the carbon nucleophile starting material, along with complex mixtures of decomposition products formed from the sulfines ***Z*-172** and ***E*-172**.

For the reactions undertaken in the presence of ethyl cyanoacetate and each of sodium ethoxide and LDA base (entries 1 and 2, Table 2.12), the addition product **184** was detected in the ^{1}H NMR spectrum of the crude material. Furthermore, it proved possible to isolate the pure product by chromatography, to give the furan-2(5*H*)-one **184** as a clear oil in a low yield (Figure 2.30).



184

Figure 2.30

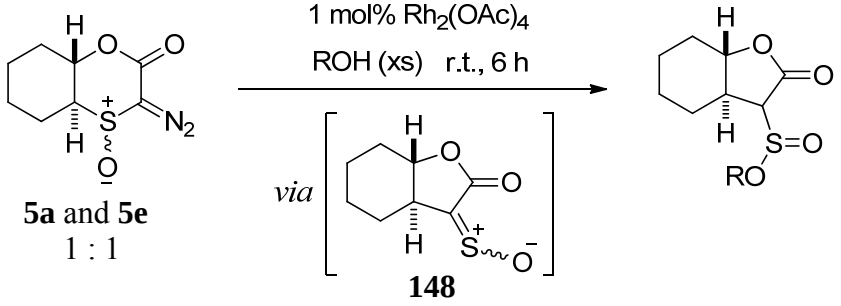
Although the isolation of just a single 3-substituted-furan-2(5*H*)-one **184** in this brief study proved possible, this result represents a significant step in the use of sulfines as reactive intermediates for carbon-carbon bond forming reactions. This is the first time that carbophilic addition of carbon nucleophiles to sulfines in the absence of a halide leaving group has been reported. Further study, particularly into milder and more suitable reaction conditions, is warranted, with a view to generating a synthetically useful procedure.

2.9.6 Reactivity with Oxygen Nucleophiles

Although nucleophilic addition of carbon nucleophiles,[104,110,117-119] and, to a lesser extent, nitrogen nucleophiles,[108] have been reported in the literature (Sections 1.4.1 and 1.4.2), there is no precedent for the addition of oxygen nucleophiles to sulfines. In this work, preliminary investigations were made into the addition of neutral oxygen nucleophiles to the α-oxosulfine **148** generated from the α-diazosulfoxides **5a** and **5e**. A series of alcohols were employed as a convenient source of neutral oxygen nucleophiles.

The reactions were carried out as summarised in Table 2.13. and were undertaken *in situ* at room temperature in the presence of 1 mol% rhodium(II) acetate. The α-diazosulfoxides **5a** and **5e** (1:1) were added directly to the neat alcohol, which also behaved as solvent for these reaction mixtures, followed immediately by addition of the rhodium(II) catalyst. The reactions were stirred at room temperature for 6 hours, after which time TLC analysis indicated complete consumption of the starting material.

Table 2.13 *In situ* reactions of α-oxosulfine **148** derived from α-diazosulfoxides **5a** and **5e** with alcohol nucleophiles

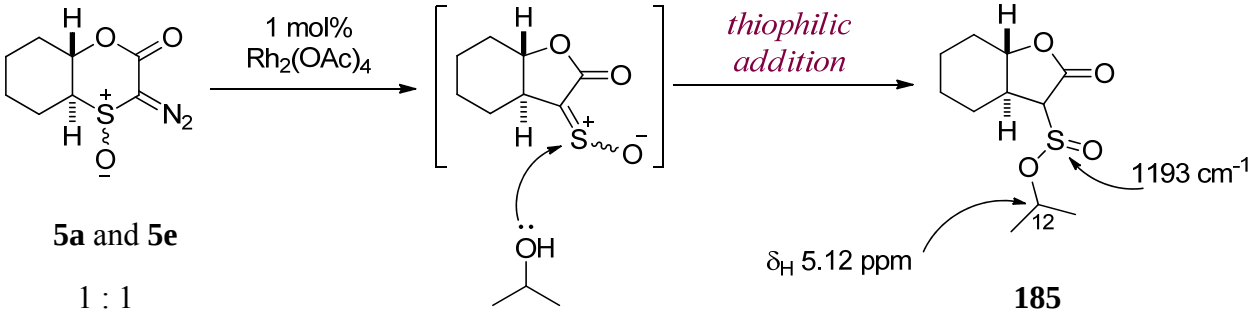


Entry	Alcohol nucleophile[a]	Reaction conditions[b]	Product[c]
1	Isopropyl alcohol	RT, 6 h	**185** (small quantity)[d]
2	Ethanol	RT, 6 h	Complex mixture
3	*t*-Butanol	RT, 6 h	Complex mixture
4	Phenol	RT, 6 h	Complex mixture

a. Excess alcohol nucleophile was employed for each reaction, with the alcohol also behaving as solvent. The reactions were carried out on a ~40 mg scale, with 1 mol% rhodium(II) acetate in ~10 mL alcohol.
b. Reactions were carried out *in situ* at room temperature over 6 hours, with addition of the α-diazosulfoxides **5a** and **5e** (1:1) to the alcohol, immediately followed by 1 mol% rhodium(II) acetate.
c. Products were determined by ^{1}H NMR analysis. No addition products were detected for entries 2-4. Complex mixtures of unidentifiable compounds were detected by ^{1}H NR analysis.
d. The crude product was purified by chromatography and a very small quantity of **185** (~4 mg) was obtained.

No evidence of nucleophilic addition for the reactions carried out with ethanol, *t*-butanol or phenol was detected (Table 2.13, entries 2-4). The ^{1}H NMR spectra indicated the presence of a complex mixture of unidentifiable compounds, indicating that decomposition of the α-oxosulfine **148** most likely occurred, with no addition product detected. For the reaction undertaken with isopropyl alcohol however, a small quantity of an unknown product could be detected in the ^{1}H NMR spectrum of the crude material. Purification by column chromatography gave a trace quantity (~4 mg) of an impure compound, tentatively assigned as the nucleophilic addition product **185** (Scheme 2.103).

Interestingly, in contrast to the nucleophilic additions undertaken with amines and carbon nucleophiles in this work, signals in the ^{1}H NMR spectrum indicated that thiophilic addition of the isopropyl alcohol to the α-oxosulfine **148** may have occurred, possibly generating a sulfinate ester **185**. The presence of the characteristic C(9)H multiplet at 3.10-3.22 ppm indicates that the double bond of a 3-substituted furan-2(5*H*)-one was not formed. A septet assigned as the isopropyl C(12)*H* was also present at 5.12 ppm. Furthermore, the IR spectrum obtained shows a typical sulfoxide S-O absorption at 1193 cm^{-1} (Scheme 2.103). However, due to the impure sample and low quantity obtained, further characterisation of the product **185** was not possible and only a tentative suggestion of its structure can be made at this stage.



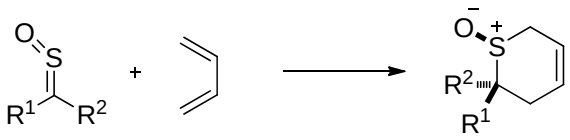
Scheme 2.103

In summary, the reaction of alcohols as neutral oxygen nucleophiles with α-oxosulfines does not lead to stable addition products. A search of the literature indicates that sulfinate esters are unstable compounds which have been reported to readily decompose at ambient conditions.[121] Further work may be warranted to oxidise the sulfinate ester to the corresponding sulfonate ester in order to generate a more stable product and thus confirm the mode of nucleophilic addition.

2.10 Cycloaddition Reactions

2.10.1 Background

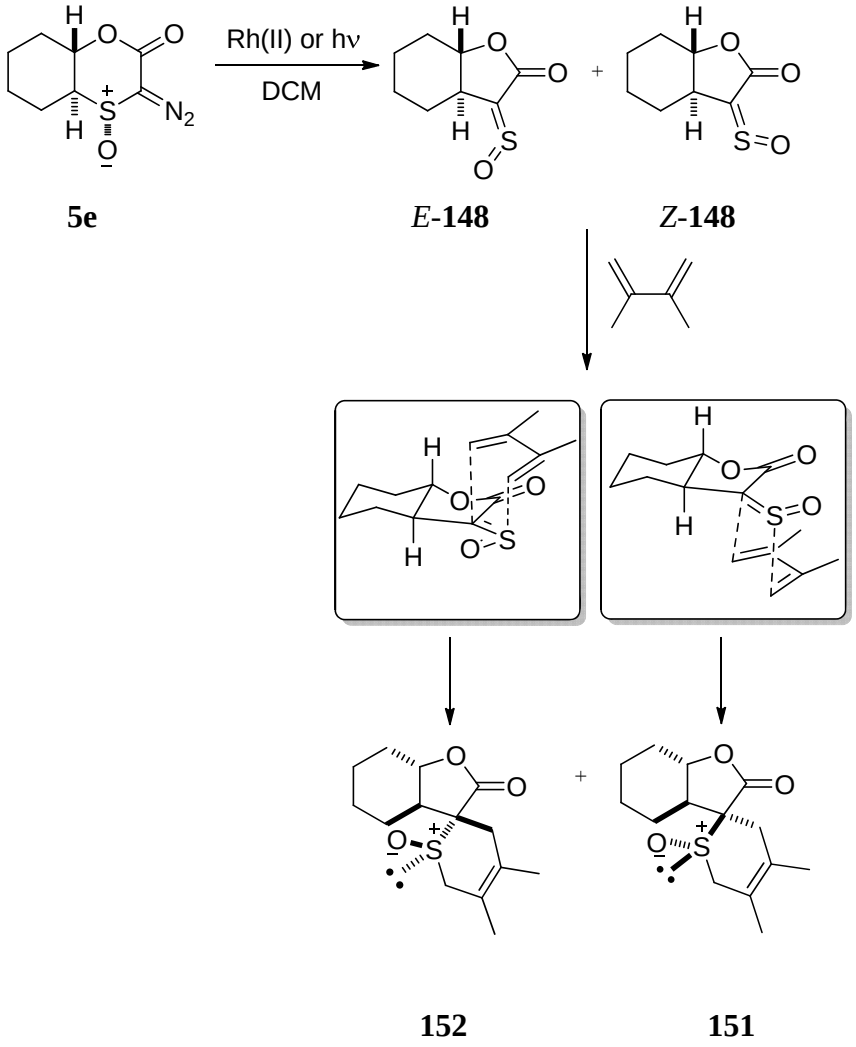
An important and well documented reaction of sulfines is the Diels-Alder cycloaddition with 1,3-dienes (Section 1.4.3).[122-125] The stereochemistry of the sulfine is retained in the cycloadduct. This stereospecific behaviour is characteristic of a concerted [4+2] cycloaddition. A variety of sulfines have been described in the literature which undergo cycloaddition with dienes to give dihydro-2*H*-thiopyran *S*-oxides **186** (Scheme 2.104), which can be used as precursors for the synthesis of bioactive molecules.[126-129]



186

Scheme 2.104

The Diels-Alder reaction plays an important role in the reactivity of α-oxosulfines, which are especially electron poor dienophiles and can be trapped *in situ* with 1,3-dienes.[130,131] As discussed in Section 2.9.1, substantial work has been done within the group on the reactivity of α-oxosulfines in the presence of 2,3-dimethyl-1,3-butadiene under various reaction conditions, including photolysis, catalysis and microwave conditions.[7,9,10,103,132] Remarkable diastereomeric control over the cycloadducts formed has been demonstrated (Scheme 2.105).



5e *E*-**148** *Z*-**148**

152 **151**

$Rh_2(OAc)_4$	1 : 6
Hg lamp (hν 254 nm)	5 : 1

Scheme 2.105

A series of novel α-diazo-β-keto sulfoxides were prepared in this project, and their synthesis is discussed in Sections 2.5 and 2.6. In this section, the reactivity of these compounds in the presence of 2,3-dimethyl-1,3-butadiene under different reaction conditions is discussed. The α-diazo-β-keto sulfoxides used for this work are illustrated in Figure 2.31.

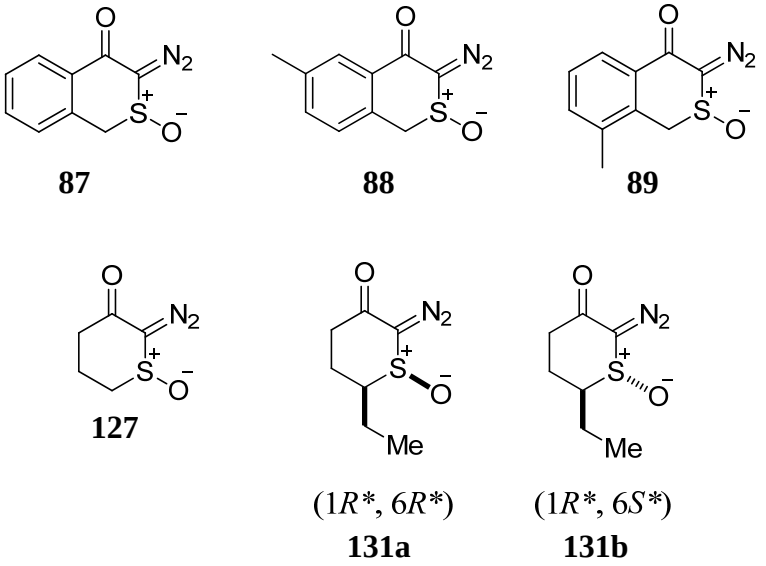


Figure 2.31

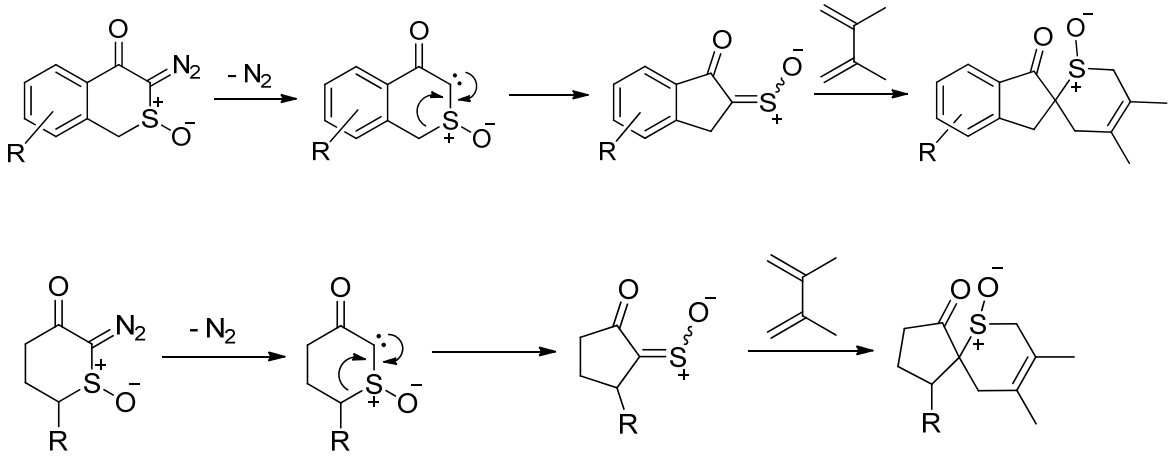
Thus, the objectives in this study were to:

(i) Generate the sulfines from the α-diazo-β-keto sulfoxides **87**-**89**, **127** and **131** and establish their formation by trapping them as cycloadducts (Scheme 2.106).

(ii) Explore isomerisation of the sulfines, and diastereoselectivity in the cycloadducts formed.

(iii) Examine the effect of catalysis, microwave and photolysis conditions on the diastereoselectivity of cycloadduct formation

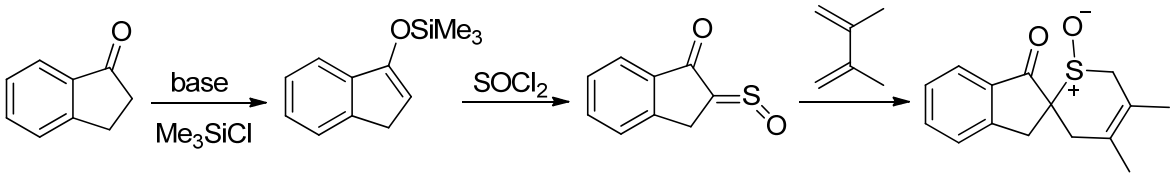
(iv) Prepare a series of novel dihydro-2*H*-thiopyran *S*-oxides



Scheme 2.106

2.10.2 Cycloadditions with Benzofused α-Diazosulfoxides

The preparation of the sulfine **187a** and its cycloaddition with 2,3-dimethyl-1,3-butadiene has been studied by Zwanenburg.[130] The α-oxosulfine **187a** was prepared by the reaction of thionyl chloride with an α-methylene ketone. The α-oxosulfine **187a** then reacted smoothly with the diene to give the dihydro-2*H*-thiopyran *S*-oxide **188*** (Scheme 2.107). The issue of diastereoselectivity was not mentioned and the sulfine was described as one isomer, albeit characterised with ^{1}H NMR at 60 MHz.



189 **187a** **188**

Scheme 2.107

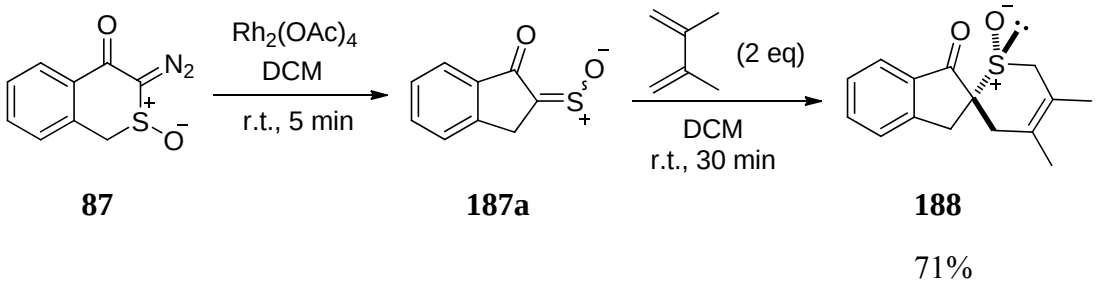
Firstly, we wished to show that the sulfine **187a** can be generated from the novel α-diazosulfoxide **87**. Forming the sulfine **187a** and then trapping it in a sequential cycloaddition reaction would allow us to establish that the decomposition of these novel diazo derivatives occurs *via* a Wolff rearrangement mechanism, as illustrated above in Scheme 2.106. The α-diazosulfoxide **87** was stirred with rhodium(II) acetate in dichloromethane at room temperature for 5 minutes. On addition of the catalyst, the solution was observed to effervesce almost immediately. The solution was filtered through Celite®,** then concentrated and the ^{1}H NMR spectrum of the sulfine **187a** indicated a slight shift of the CH_2 singlet from 4.32 to 4.26 ppm.*** The IR spectrum also indicated the disappearance of the diazo group stretch. The sulfine **187a** was then redissolved in dichloromethane and treated with 2,3-dimethyl-1,3-butadiene in dichloromethane for 30 minutes.

* The cycloadduct formed by Zwanenburg is believed to be **188**, although we do not have sufficient evidence to conclude this. Based on our results, it is expected that the *E*-sulfine is trapped as the thermodynamic cycloadduct.

** The solution was filtered through Celite® as it is believed to remove the rhodium(II) acetate. The green colour of the catalyst remains on top of the pad of Celite®.

*** The ^{1}H NMR spectrum also indicated the presence of small quantities of decomposition products, which are not relevant in this study. See section 2.11.

^{1}H NMR analysis of the product showed the presence of one diastereomer in a very clean spectrum. Purification by chromatography gave the cycloadduct **188** as a pale brown crystalline solid in 71% yield (Scheme 2.108).

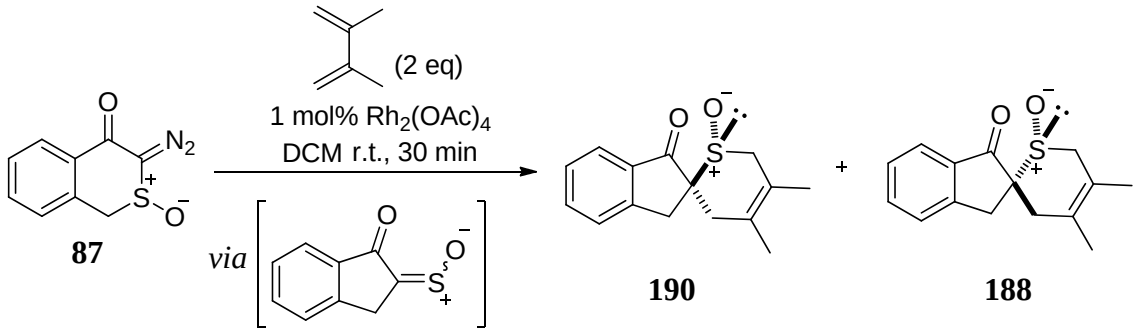


87 **187a** **188**

71%

Scheme 2.108

The reaction was repeated *in situ*, this time with addition of the diene directly to the diazosulfoxide **87** followed by 1 mol% rhodium(II) acetate in dichloromethane. Again, effervescence of the solution could be observed almost immediately after addition of the catalyst. The solution was stirred at room temperature for 30 minutes. Interestingly, this time the ^{1}H NMR spectrum of the product indicated a clean mixture of two diastereomers **190**:**188** (~7:1). The major cycloadduct **190** was separated from the minor cycloadduct **188** by chromatography, followed by preparative TLC, in a yield of 35% as a brown solid (Scheme 2.109).



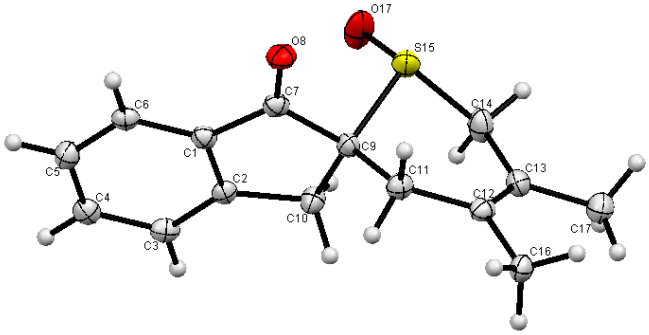
87 **187a** **190** **188**

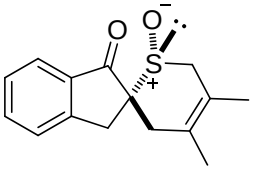
crude 6 : 1
purified **190** (35%)

Scheme 2.109

The results of these two experiments gave us an interesting insight into the formation and isomerisation of the sulfine **187a**. In order to determine the relative stereochemistry of the cycloadducts **188** and **190**, X-ray crystal structures were obtained from recrystallised samples, as illustrated in Figure 2.32. A study of these

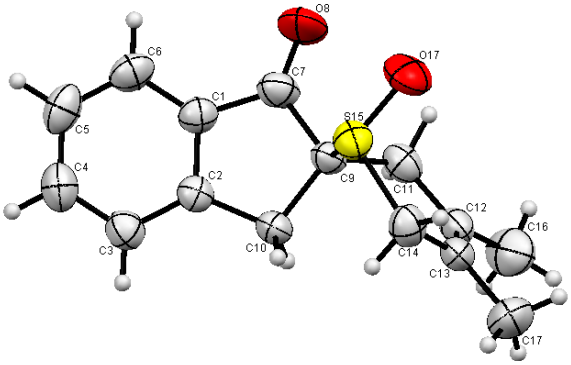
structures allowed us to propose two modes of addition of the diene, and thus explain the resulting stereochemistry of the cycloadducts.

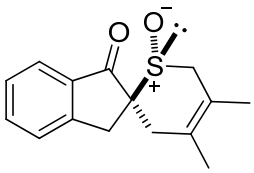




(9*R**, 15*R**)

188





(9*R**, 15*S**)

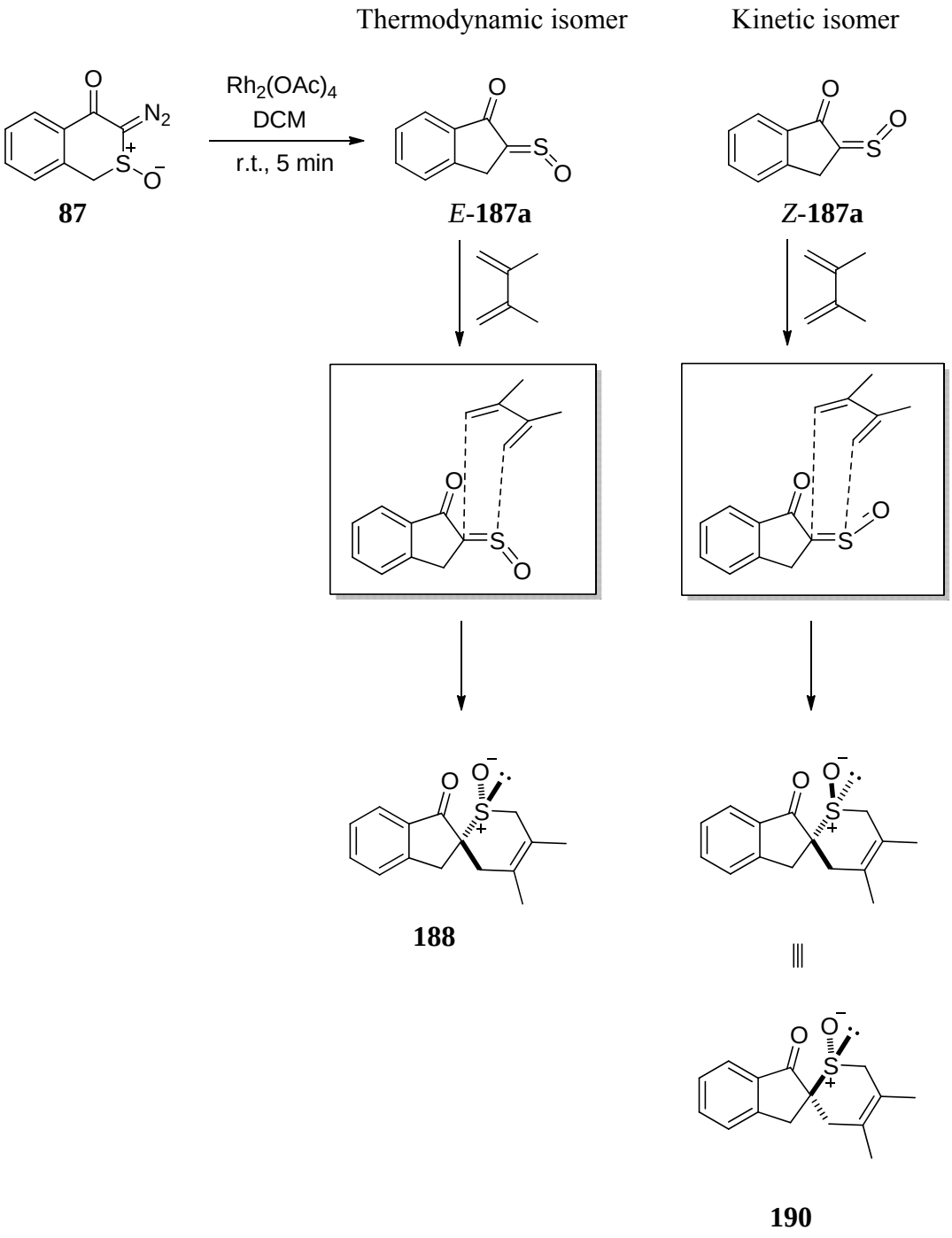
190

Figure 2.32 *X-ray crystal structures of the cycloadducts **188** and **190**. The top structure is the cycloadduct **188** formed during the sequential reaction, and the bottom structure is the major cycloadduct **190** formed during the* in situ *reaction. Structures are displayed using the Mercury 2.3 (Build RC4) package.*

Examination of the relative orientation of the C9-C7 bond and the C9-C10 bonds allowed us to conclude that the cycloadduct **188** was formed on reaction of the diene with the *E*-isomer of the sulfine **187a** (Scheme 2.110). The cycloadduct **190** is formed from the reaction of the diene with the *Z*-isomer of the sulfine **187a** (Scheme 2.110).

The sulfines *E*-**187a** and *Z*-**187a** differ in S-O orientation of the sulfinyl group only. The planar indanone system ensures that the direction of approach of the diene does not affect the stereochemistry of the cycloadduct. It should be noted that

although a crystal structure of each diastereomer was obtained, these are of the *opposite enantiomers* for each diastereomer. Therefore, it is difficult to visualise the different stereochemistry of **188** and **190**. The cycloadducts **188** and **190** are thus represented in this work as the same enantiomer, to emphasise that the only difference in stereochemistry occurs at the relative orientation about the spiro C(9) centre. In Scheme 2.110 below, both enantiomers of the cycloadduct **190** are represented for clarity.

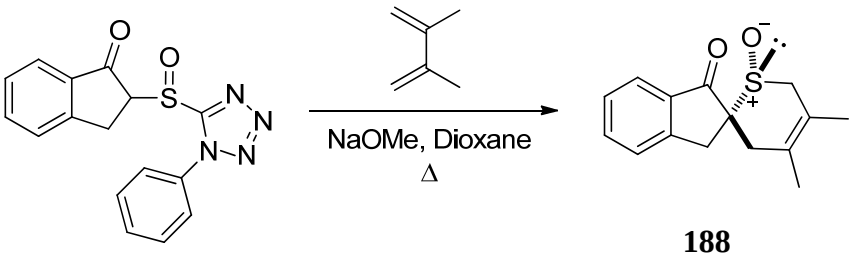


Scheme 2.110 *Cycloaddition reactions of sulfines* E-***187a*** *and* Z-***187a*** *with retention of stereochemistry. For the cycloadduct* ***190****, both enantiomers are illustrated for clarity. Structures are displayed using the Mercury 2.3 (Build RC4) package.*

Collins, Kelleher and O'Sullivan previously explored cycloadditions with lactone based α-oxosulfines[7,9,10,103,132] and found that the *Z*-sulfine is the kinetic product, with isomerisation to the more stable *E*-sulfine over time. Based on the reactions of the novel α-diazo-β-keto sulfoxides, it was envisaged that the *Z*-sulfine

187a is the initially formed kinetic product of the Wolff rearrangement, with isomerisation over time to give the more thermodynamically stable *E*-sulfine **187a** (Scheme 2.110).[101,102] Indeed, the cycloaddition reactions described above appear to support this. The *in situ* cycloaddition allows trapping of the kinetically formed *Z*-sulfine **187a** as the major cycloadduct **190**, with only a small quantity of the *E*-sulfine **187a** trapped as the minor cycloadduct **188**. However, when the cycloaddition is carried out using the sequential method, the *Z*-sulfine **187a** had time to completely isomerise to the *E*-sulfine **187a** (< 10 min), giving the cycloadduct **188** as the only product.

Interestingly, the cycloadduct **188** has been described by Morita *et al.* as a product in the trapping of sulfines from elimination reactions of heteroaromatic sulfoxide compounds.[133] Although the authors fail to comment on the relative stereochemistry of the cycloadduct, detailed ^{1}H and ^{13}C NMR data provided allowed us to identify the compound as **188**. Thermolysis of the tetrazole bearing sulfoxide **191** in the presence of 2,3-dimethyl-1,3-butadiene gave **188** (Scheme 2.111). This report can be explained as trapping the thermodynamically formed *E*-sulfine **187a** intermediate. Notably however, the cycloadduct **190** is novel, and to the best of our knowledge, represents the first time that the kinetically formed *Z*-sulfine **187a** has been trapped.



191 **188** 33%

Scheme 2.111

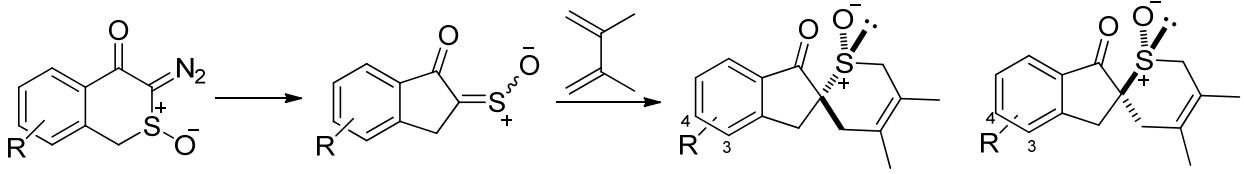
At this stage, definitive evidence had been provided for the formation of the sulfine **187a** *via* Wolff rearrangement of the α-diazosulfoxide **87** under rhodium(II) acetate catalysis. Significantly, selective access to either of the two diastereomers **188** and **190** can be achieved simply by conducting the cycloadditions *in situ* or in a sequential manner, substantially enhancing the synthetic utility of this process. Based on this success, extension of this cycloaddition methodology to provide novel

cycloadducts derived from 6-methyl and 8-methyl α-diazosulfoxides **88** and **89** was undertaken. Furthermore, we were interested in exploring transition metal-free conditions for the cycloaddition reactions. Previous work within the group had demonstrated a variation in diastereoselectivity under metal-free conditions using microwaves and photolysis.[7,9,132] The diastereoselective control reported by Collins has already been discussed in Section 2.10.1.

A series of reactions were undertaken with the α-diazosulfoxides **87**, **88** and **89** under various different reaction conditions, the results of which are summarised in Table 2.14.

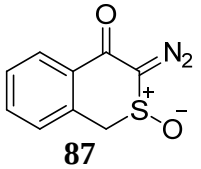
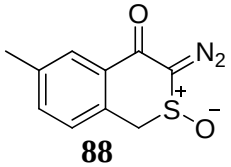
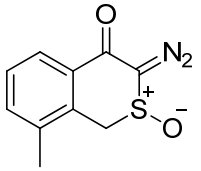
Table 2.14 Summary of cycloaddition reactions of α-oxosulfines generated from α-diazosulfoxides **87**, **88** and **89** with 2,3-dimethyl-1,3-butadiene.

From *E*-sulfine From *Z*-sulfine



87-89 **187a-c** **188**, **192**, **193** **190**, **194**, **195**

R = H, **188**, **190**
R = 4-Me **192**, **194**
R = 3-Me **193**, **195**

Entry	α-Diazosulfoxide	RT Sequential[a] $Rh_2(OAc)_4$	Photolysis *in situ*[b] Metal-free	RT *in situ*[c] $Rh_2(OAc)_4$	MW *in situ*[d] Metal-free
1	 **87**	**188** (71%)	**188**	**190**: **188** (7 : 1) (**190**: 35%)	**190**: **188** (24 : 1)
2	 **88**	**192** (76%)	**192**	**194**: **192** (6 : 1)[f]	**194**: **192** (9 : 1)
3	 **89**	**193** (84%)	**193**[e]	**195**: **193** (25 : 1) (**195**: 29%)	**195**

a. Sulfines were generated from α-diazosulfoxides using 1 mol% rhodium(II) acetate for 5 min at room temperature in DCM and then reacted with 2 eq 2,3-dimethyl-1,3-butadiene for 30 min in a sequential reaction. Purified yields are given.
b. Reactions were carried out *in situ* and reaction mixtures were irradiated in a Pyrex® vessel with a 90 W mercury lamp for 4 h in DCM. The isolated crude products were not purified.
c. Reactions were carried out *in situ* for 30 min at room temperature in DCM, with addition of 2 eq of 2,3-dimethyl-1,3-butadiene directly to the α-diazosulfoxide followed by 1 mol% rhodium(II) acetate. For entries 1 and 3, purified yields are given.
d. Reactions were carried out *in situ* and heated to ~135 °C and irradiated to 300 W for 2-3 min in a sealed 10 mL vessel in the absence of rhodium(II) catalyst in DCM. The isolated crude products were not purified.
e. The ^{1}H NMR spectrum indicated the presence of some remaining sulfine **187** (~20%).
f. Difficulties in separating the major cycloadduct **194** from the minor cycloadduct **192** resulted in only a very small, impure quantity of the cycloadduct **194** being isolated.

When the cycloadditions were carried out using the sequential method as described in Scheme 2.108, it can be clearly seen that the thermodynamically formed *E*-sulfines were trapped to give the cycloadducts **188**, **192** and **193** as the *only* products from the reaction. The ^{1}H NMR spectra of these products were remarkably clean, and were easily purified by chromatography to give the cycloadducts **188**, **192** and **193** in very good yields of 71-84%. In contrast, the ^{1}H NMR spectra of the more labile γ-lactone based cycloadducts studied by previous workers within the group were much less clean.[7,9,10]

Photolysis reactions were carried out in a Pyrex® flask containing a solution of the α-diazosulfoxide in dichloromethane and fitted with a reflux condenser, with the flask positioned as close to the mercury lamp as possible and the whole apparatus covered with aluminium foil. The reaction mixture was then irradiated under a nitrogen atmosphere for 4 hours and the reaction was monitored by TLC. This procedure was developed by Collins, and he noted that Pyrex® filters wavelengths below 300 nm and that the transmission limit of dichloromethane is 245 nm so it was unlikely that the 254 nm wavelength was involved in the decomposition of α-diazosulfoxides.[7] Nevertheless, as a mercury lamp is a polychromatic light source, it is clear that sufficient irradiation at an appropriate wavelength was emitted which triggered diazo decomposition.

The *in situ* photolysis of the α-diazosulfoxides in the presence of a diene produced the same cycloadducts **188**, **192** and **193** as for the sequential reactions, with no evidence for the formation of other diastereomeric products. This indicates that irradiation from the mercury lamp has a strong influence on the stereochemical outcome of the reaction.

The cycloadditions carried out *in situ* allowed trapping of the kinetically formed *Z*-sulfines as the major cycloadducts **190**, **194** and **195**, with only small quantities of the *E*-sulfines trapped as the minor cycloadducts **188**, **192** and **193**. It was possible to purify samples of the cycloadducts **190** and **195** for complete analysis in moderate yields of 35 and 29%, respectively. However, difficulties in isolating a pure sample of the major cycloadduct **194** from the minor cycloadduct **192** resulted in only a very small, impure quantity of the cycloadduct **194** being isolated.

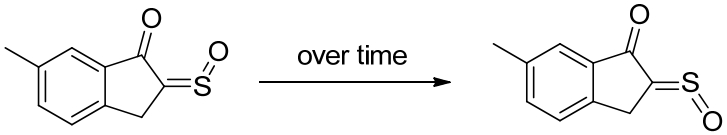
The *in situ* microwave-induced reactions carried out in the presence of 2,3-dimethyl-1,3-butadiene gave the cycloadducts **190** and **194** as the major products, and **195** as the only product. As can be seen from Table 2.14, these results were very similar to those obtained from the reactions carried out *in situ* at room temperature with rhodium(II) acetate. Interestingly, it appears that the high temperature and pressure conditions of the microwave vessel do not increase the rate of isomerisation of the *Z*-sulfines to the *E*-sulfines. Thus, there is no evidence for specific microwave effects in the Wolff-rearrangement and subsequent cycloaddition. There has been considerable debate in the literature relating to specific microwave effects, with the current view indicating that these do not exist, with the microwave effects operating exclusively through efficient heating.[132,134-140]

Overall, the cycloadditions outlined in Table 2.14 have given a clear insight into the mechanism of sulfine formation and subsequent trapping. A critical feature of the cycloaddition reactions is that the ratio of products differs dramatically depending on the reaction conditions employed. While the reactions performed using the sequential and photolysis methods gave the thermodynamic cycloadducts **188**, **192** and **193** as the only products, the reactions performed *in situ* with rhodium(II) acetate or under microwave conditions gave the kinetic cycloadducts **190**, **194** and **195** as the major products. It should also be noted that variation of the concentrations of the reaction mixtures does not appear to affect the ratio of diastereomers. No competition between intramolecular isomerisation and intermolecular trapping was apparent. The diastereoselective control exhibited during this work is significantly more efficient than that exhibited for the lactone based derivatives previously studied, although the bicyclic structures meant that up to four diastereomers could be formed in a mixture.[7,9,10]

In order to obtain further evidence that the variation in cycloadducts depends on isomerisation from the *Z*- to the *E*-sulfine, a brief time study was undertaken with the α-diazosulfoxide **88** (Table 2.15). In a number of parallel reactions, the addition of rhodium(II) acetate to a stirring solution of the α-diazosulfoxide **88** was followed by the addition of 2,3-dimethyl-1,3-butadiene. The results summarised in Table 2.15 clearly illustrate that the greater the amount of time which elapses between the addition of rhodium(II) acetate and the addition of 2,3-dimethyl-1,3-butadiene, the

greater the amount of the thermodynamic cycloadduct **192** relative to the kinetic cycloadduct **194**. When the diene is added after 5 minutes has elapsed, only the thermodynamic diastereomer **192** is observed (Entry 4, Table 2.15). The ^{1}H NMR spectra of these reactions are stacked in Figure 2.33.

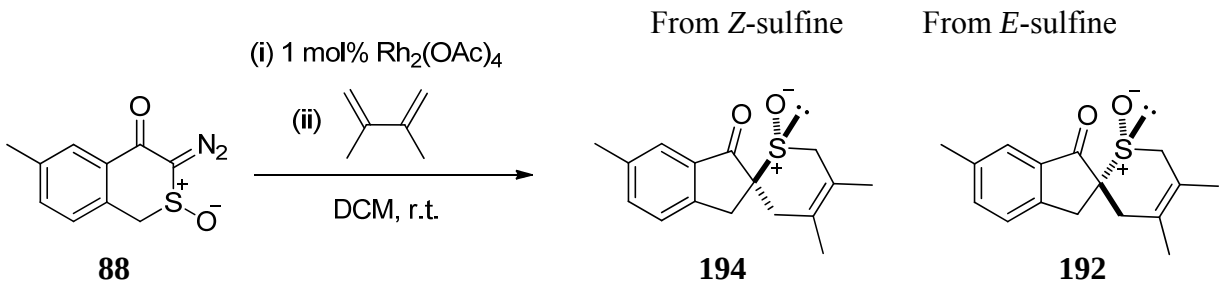
The observation that the *E*-sulfine only has been detected by ^{1}H NMR analysis is readily rationalised by the rapid interconversion of the kinetic product, the *Z*-sulfine, to the thermodynamic product, the *E*-sulfine (Scheme 2.112).



Z-**187b** *E*-**187b**

Scheme 2.112

Table 2.15 Indication of isomerisation of the sulfine *Z*-**187b** to sulfine *E*-**187b** over time



88 **194** **192**

Entry	Time[a]	**194**: **192**[b]
1	0 s	2.5:1
2	1 min	4:3
3	2 min	1:2
4	5 min	100% **192**

a. For entries 2-4, refers to time elapsed between addition of 1 mol% $Rh_2(OAc)_4$ catalyst and then 2 eq 2,3-dimethyl-1,3-butadiene **196** to α-diazosulfoxide **88** in DCM solution. For entry 1, the diene was added immediately *before* the catalyst.

b. Product ratios were determined by ^{1}H NMR ($CDCl_3$).

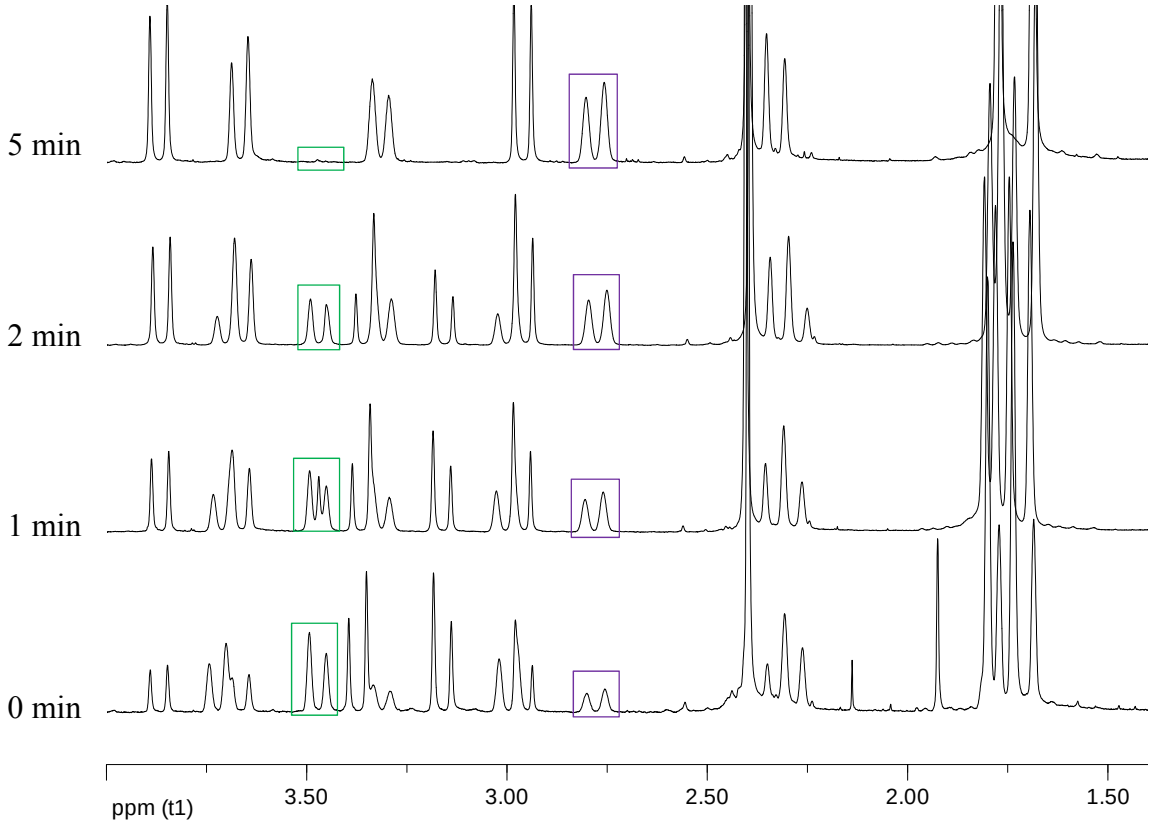
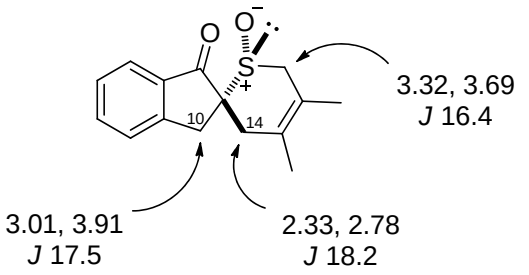


Figure 2.33 *Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$) for the mixtures of cycloadducts **194** and **192**, illustrating isomerisation of the sulfine Z-**187b** to the sulfine* E-***187b*** *over time. The decreasing A of AB_q signal for the $SOCH_2$ of **194** is highlighted in green. The increasing B of AB_q signal for the $C(14)H_2$ of **192** is highlighted in purple.*

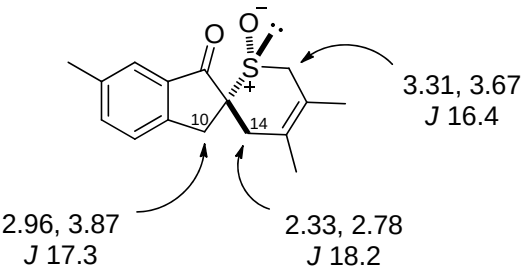
2.10.3 Spectral Characteristics of Dihydro-2*H*-thiopyran *S*-Oxides

The stereochemistry of the cycloadducts formed by reaction of the sulfines derived from α-diazosulfoxides with 2,3-dimethyl-1,3-butadiene is governed by the stereochemistry of the sulfine which is approached by the diene. While two cycloadducts have been isolated and characterised from each α-diazosulfoxide **87-89**, two crystal structures have been obtained which definitively reveal the stereochemistry of the cycloadducts **188** and **190**. However, the ^{1}H NMR spectra of the cycloadducts contain characteristic signals which allow us to assign the stereochemistry of each cycloadduct by analogy.

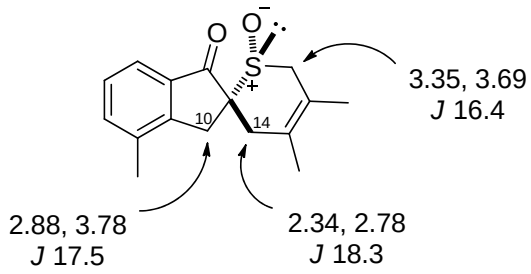
The cycloadducts **188**, **192** and **193** formed on trapping of the thermodynamic *E*-sulfine exhibit very similar ^{1}H NMR spectral features, and the cycloadducts **190**, **194** and **195** formed on trapping the kinetic *Z*-sulfine also have similar spectra (Figure 2.34). The key diagnostic signals are the three characteristic AB quartets corresponding to the C(14)H_2, C(10)H_2 and the SOCH_2 protons, as illustrated in the stacked ^{1}H NMR spectra in Figures 2.35 and 2.36. The signals corresponding to the C(14)H_2 and the SOCH_2 protons are broadened due to long range, unresolved coupling with the hydrogens of the vinylic methyl groups.



188



192



193

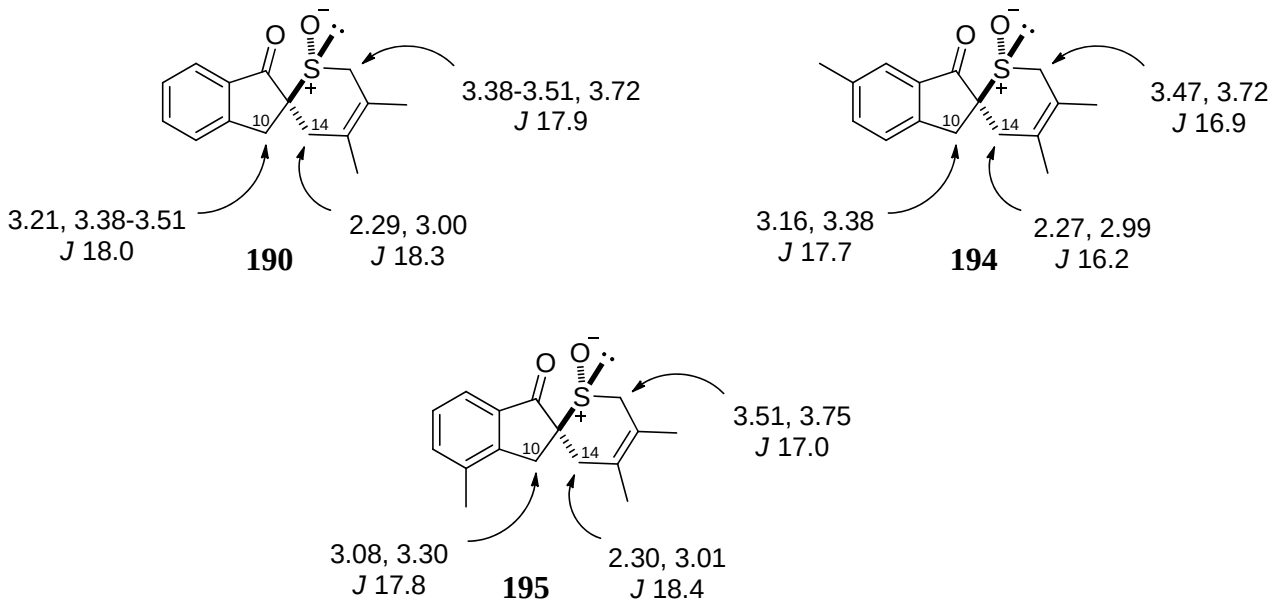


Figure 2.34

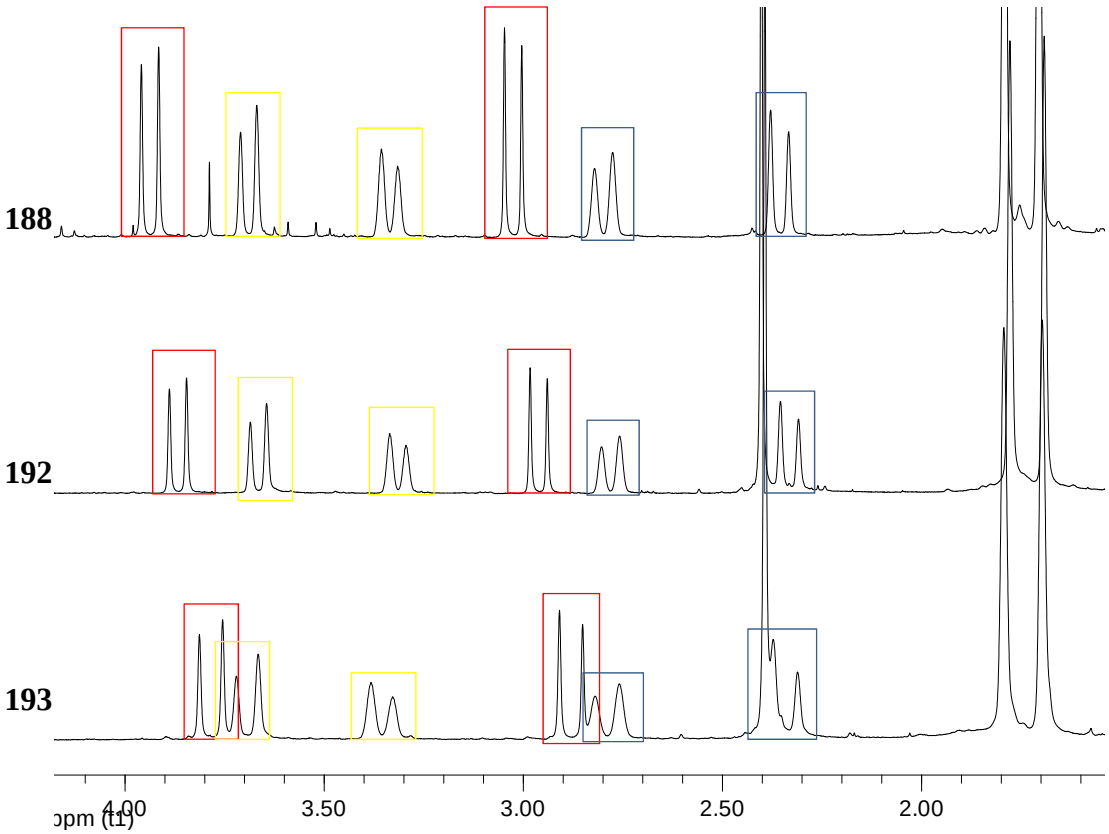


Figure 2.35 *Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$) for the cycloadducts **188** (top), **192** (middle) and **193** (bottom). The C(14)H_2 signals are marked in blue, the C(10)H_2 signals are marked in red, and the SOCH_2 signals are marked in yellow.*

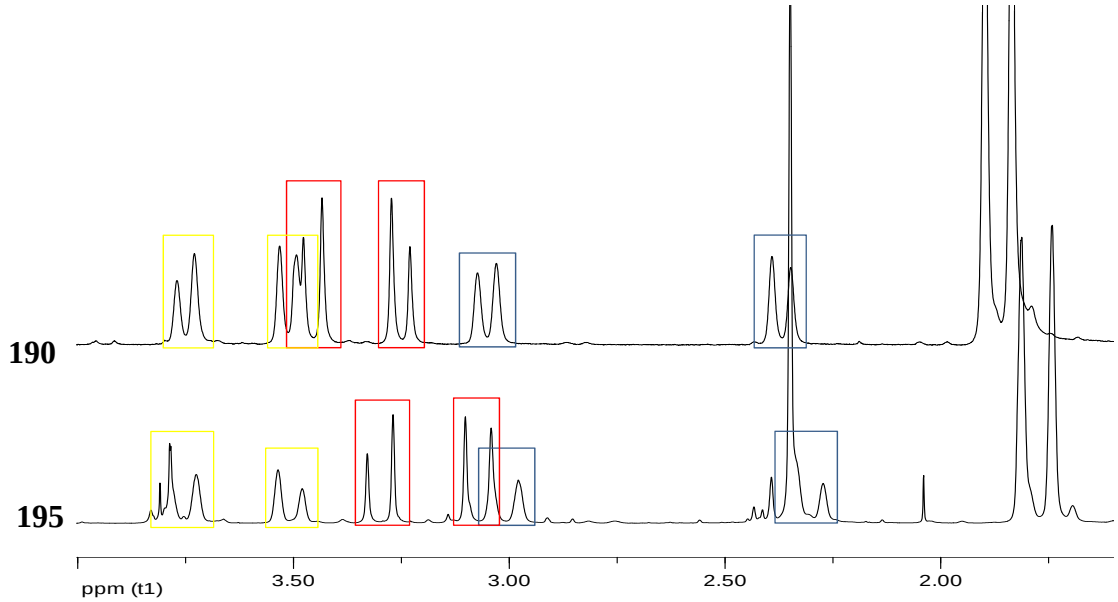
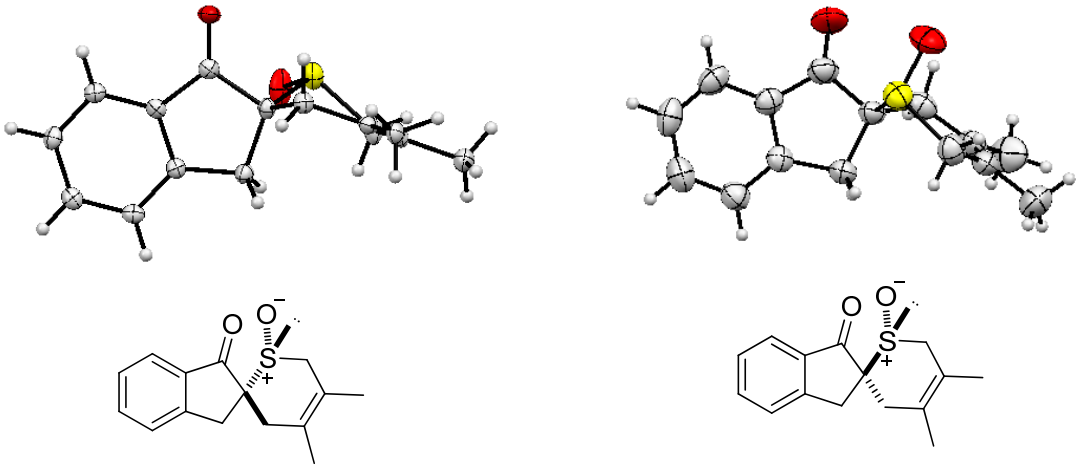


Figure 2.36 *Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$) for the cycloadducts **190** (top) and **195** (bottom). The C(14)H_2 signals are marked in blue, the C(10)H_2 signals are marked in red, and the SOCH_2 signals are marked in yellow.*

By comparing the stacked ^{1}H NMR spectra for the cycloadducts **190** and **195** with the spectra for the cycloadducts **188**, **192** and **193**, it can be clearly seen that the AB quartets of the C(10)H_2, C(14)H_2 and SOCH_2 protons are in different electronic environments. This can be attributed to the relative stereochemistry at S of the sulfoxide group. The three-dimensional structures of the cycloadduct **188** and the cycloadduct **190** are illustrated in Figure 2.37 and the relative positions of the sulfoxide oxygen can be compared. The sulfoxide lies into the plane for **188** and points upwards for **190**. Both cycloadducts crystallised in a centrosymmetric space group, i.e. a racemic crystal, one enantiomer of which is illustrated for both.



188 **190**

Figure 2.37 *X-ray crystal structures of the cycloadducts **188** (left) and **190** (right). Structures are displayed using the Mercury 2.3 (Build RC4) package.*

The difference in the relative stereochemistry at S of the sulfoxide group can also be illustrated with the ^{13}C NMR spectra of the cycloadducts **188** and **190**. The quaternary spiro C(9) appears at 68.5 ppm and 63.7 ppm, respectively (Figure 2.38).

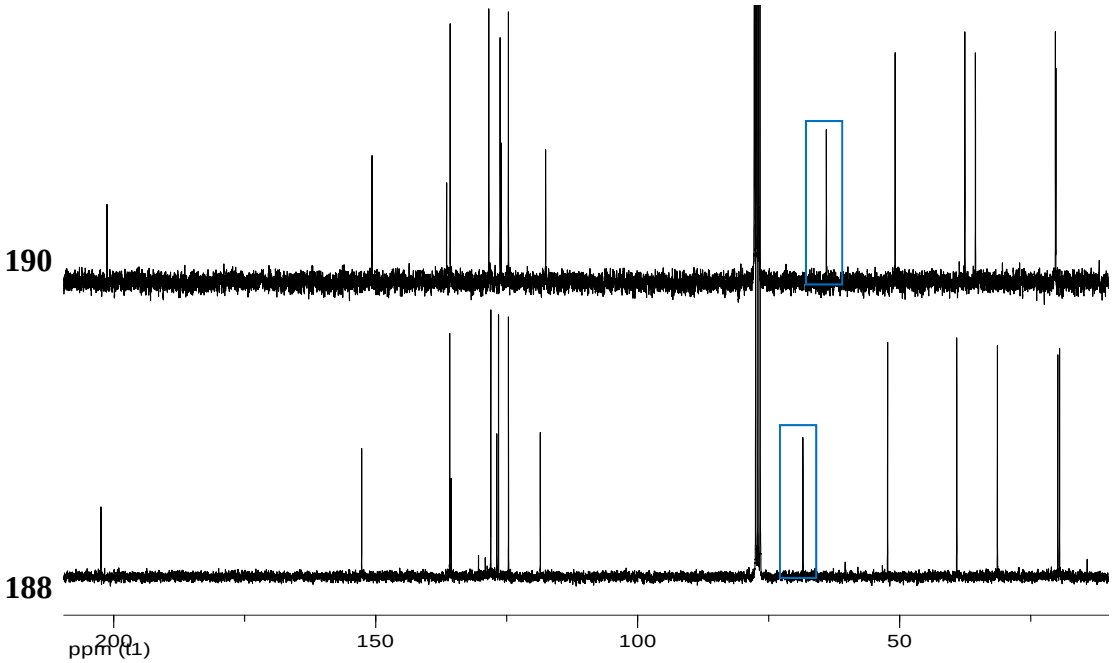
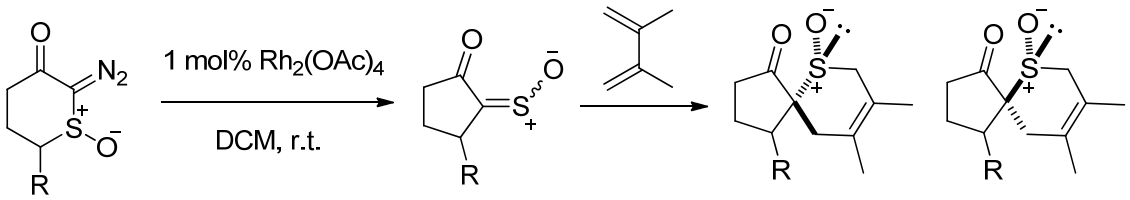


Figure 2.38 *Stacked ^{13}CNMR spectra of cycloadduct **188** (bottom) and **190** (top). The quaternary C(9) signals are highlighted in blue ($CDCl_3$, 75.5 MHz).*

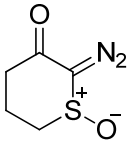
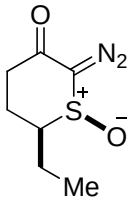
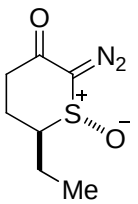
2.10.4 Cycloadditions with Monocyclic α-Diazosulfoxides

The synthesis of the monocyclic α-diazosulfoxides **127**, **131a** and **131b** has been described in Section 2.6. While synthetic access to these monocyclic α-diazosulfoxides was challenging, with overall low yields, cycloaddition reactions with the α-diazosulfoxides **127**, **131a** and **131b** were successfully undertaken in this work, to see if we could effect the Wolff rearrangement to form a sulfine intermediate which could be trapped as a cycloadduct. These reactions are summarised in Table 2.16.

Table 2.16 Summary of cycloaddition reactions of sulfines generated from α-diazosulfoxides **127**, **131a** and **131b** with 2,3-dimethyl-1,3-butadiene.



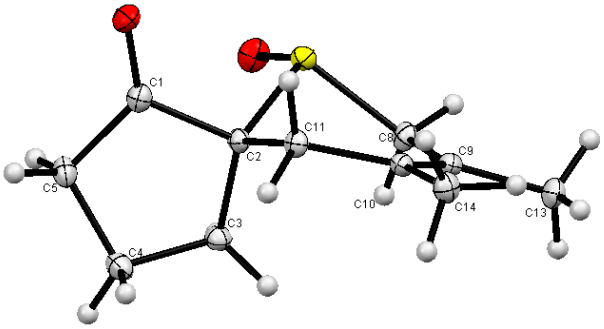
127, **131a**, **131b** **197**, **198** **199**, **200**
R = H **197**, **199**
R = Et **198**, **200**

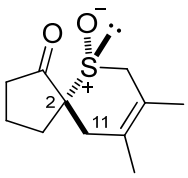
Entry	α-Diazosulfoxides	One-pot, stepwise[a]	*in situ*[b]
1	 **127**	**197**: **199** (19%) (9 : 1)	**199**: **197** (49%) (1 : trace)
2	 (1*R**, 6*R**)  (1*R**, 6*S**) **131a**, **131b**[c] 1 : 1	**198**: **200** (~3:1) separated: (**198**: 24%) (**200**: 9%)	**200** (20%)

a. The α-diazosulfoxides were stirred in the presence of 1 mol% rhodium(II) acetate in DCM for 15 min at room temperature, followed by addition of 2 eq 2,3-dimethyl-1,3-butadiene without isolation of the sulfine intermediate. Purified yields are given.
b. Reactions were carried out *in situ* for 30 min at room temperature in DCM, with addition of the diene directly to the α-diazosulfoxide in the presence of 1 mol% rhodium(II) acetate. Purified yields are given.
c. Relative stereochemistry not assigned.

Encouragingly, it appeared that the more labile monocyclic α-diazosulfoxides followed the same reaction sequence to that described for the benzofused derivative described in Section 2.10.2, leading to novel spiro cycloadducts.

A crystal structure was obtained for the cycloadduct **197**, thereby confirming relative stereochemistry (Figure 2.39),* and it was possible to also assign the same stereochemistry for the cycloadduct **198**, based on comparison of the very similar ^{1}H NMR spectra.



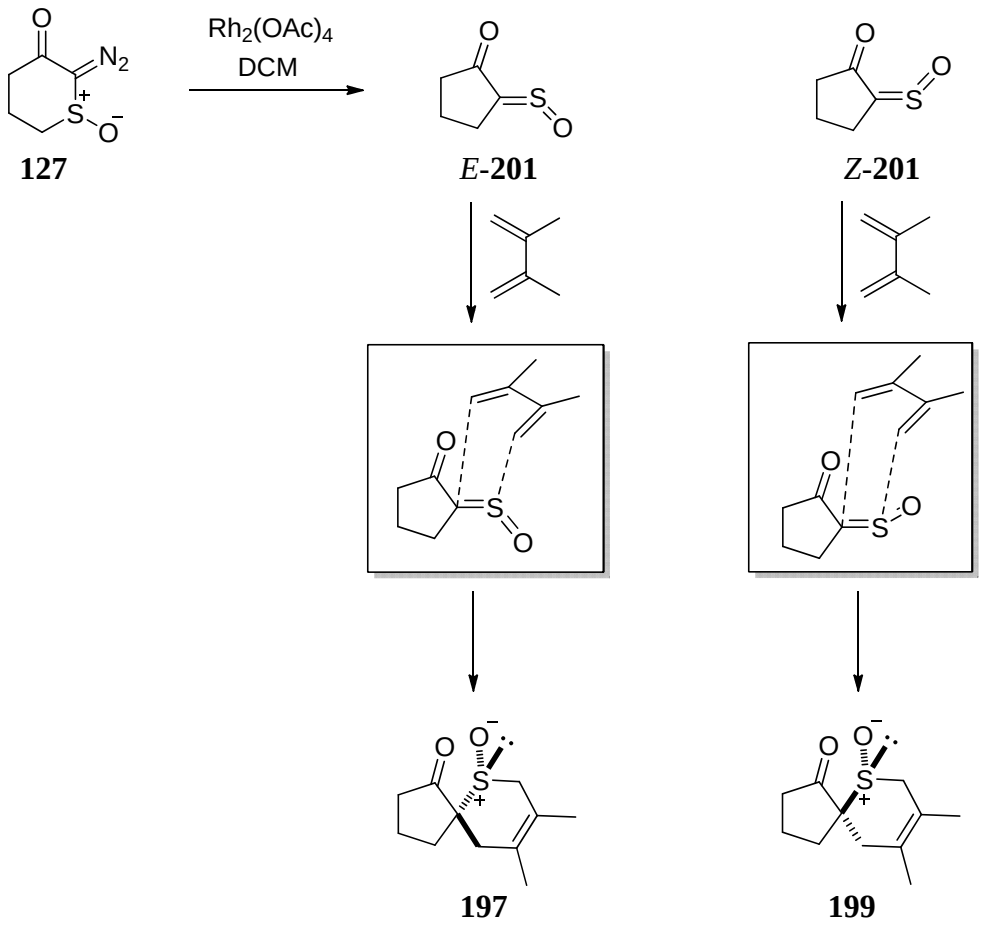


197

Figure 2.39 *X-ray crystal structure of the cycloadduct **197** formed during the sequential reaction of the diene with the α-diazosulfoxide **127**. Structure is displayed using the Mercury 2.3 (Build RC4) package.*

The cycloadduct **197** is the major product formed from the sequential reaction of the diene with the α-diazosulfoxide **127**. It was concluded from the relative orientation of the C2-C3 bond and the C2-C1 bond that this was formed on reaction of the diene with the *E*-sulfine **201** (Scheme 2.113). Based on the results obtained previously, we expect that the *Z*-isomer of the sulfine **201** gave the cycloadduct **199** as the major product from the *in situ* reaction (Scheme 2.113).

* It should be noted that, although it is likely the crystal structure obtained is that of the major cycloadduct **197**, the sample from which the crystal was generated also contained a small quantity of the minor cycloadduct **199** (~10%).

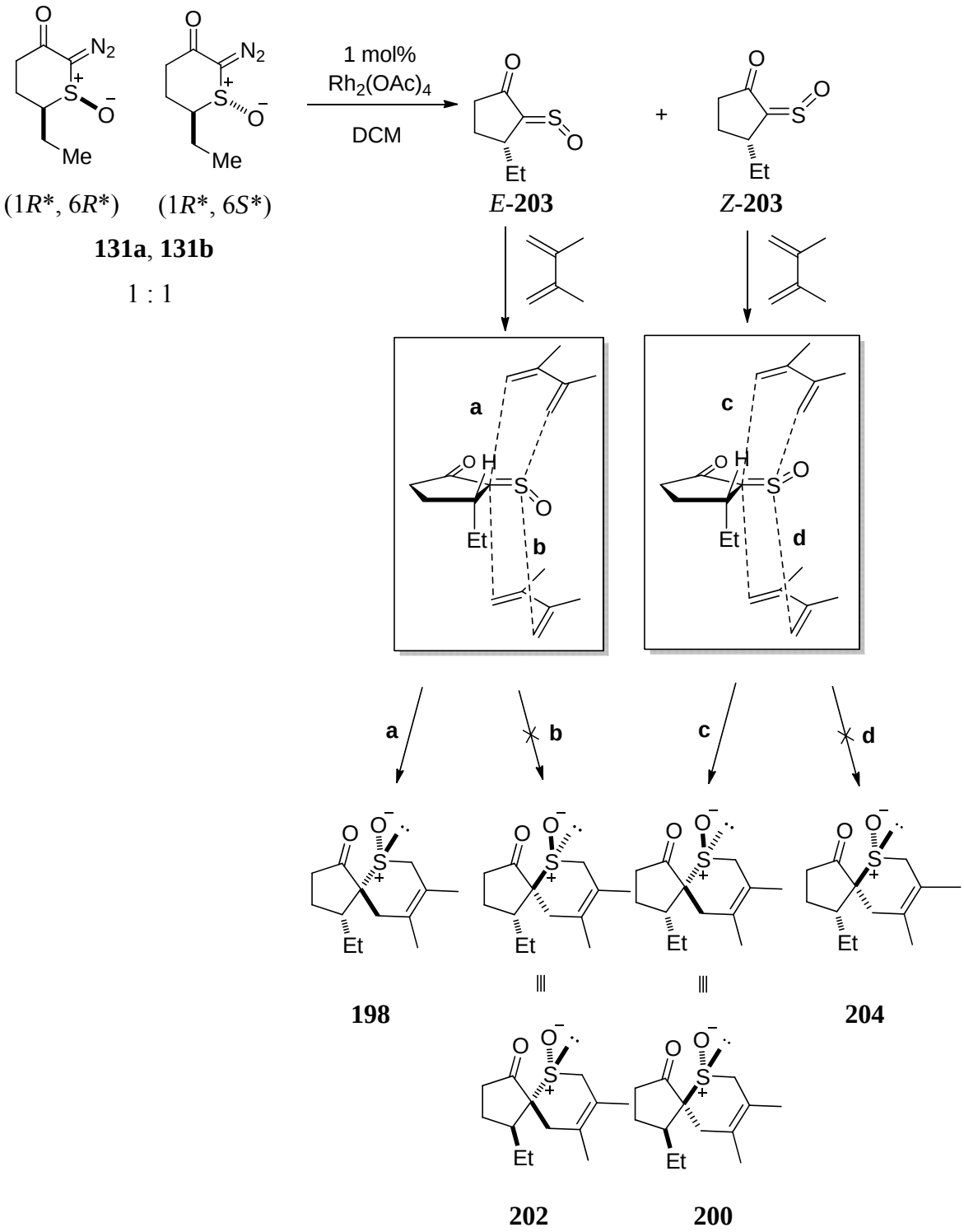


Scheme 2.113

The ^{1}H NMR spectra of these cycloadducts **197**/**198** and **199/200** contain characteristic signals depending on the stereochemistry of the adduct, which clearly indicate the same relative stereochemistry of **197**/**198** and **199/200**, in relation to the spiro and sulfur stereogenic centres. In particular, the C(2)H_2 and the SOCH_2 AB quartets offer diagnostic signals which, by analogy to the structure of **197**, allow us to tentatively assign the relative stereochemistry of the ethyl substituted cycloadducts **198** and **200**. Furthermore, TLC analysis of **197**/**198** and **199/200** showed very similar polarities (the cycloadducts **197**/**198** were more polar), giving further evidence that these cycloadducts have the same relative stereochemistry.

It should be noted that although only two ethyl cycloadducts **198** and **200** were isolated, there are four possible diastereomers, and therefore the stereochemistry at the C(3) position of the cycloadducts **198** and **200** directs diastereofacial approach of the diene to the sulfines. Indeed, the ^{1}H NMR spectra of the crude cycloadducts were complex, possibly indicating the formation of more than

two cycloadducts. Although the stereochemistry of the cycloadducts **198** and **200** was not determined, it is likely that the ethyl substituent directs the approach of the diene to the opposite face of the planar sulfine, as illustrated in Scheme 2.114. For clarity, both enantiomers of the cycloadducts **202** and **200** are illustrated.



Scheme 2.114

A summary of the ^{1}H NMR data for the cycloadducts is illustrated in Figure 2.40. Stacked ^{1}H NMR spectra for the cycloadducts **197/198** and **199/200** are illustrated in Figure 2.41 and Figure 2.42, respectively.

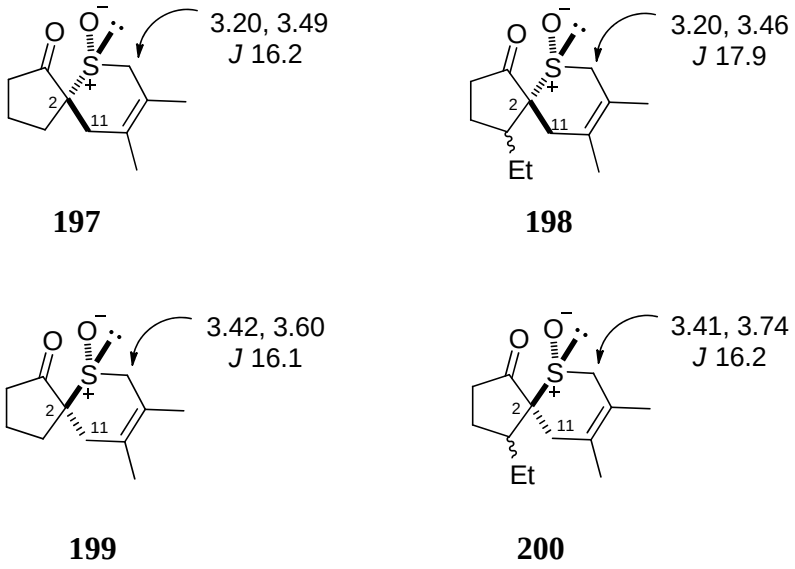


Figure 2.40

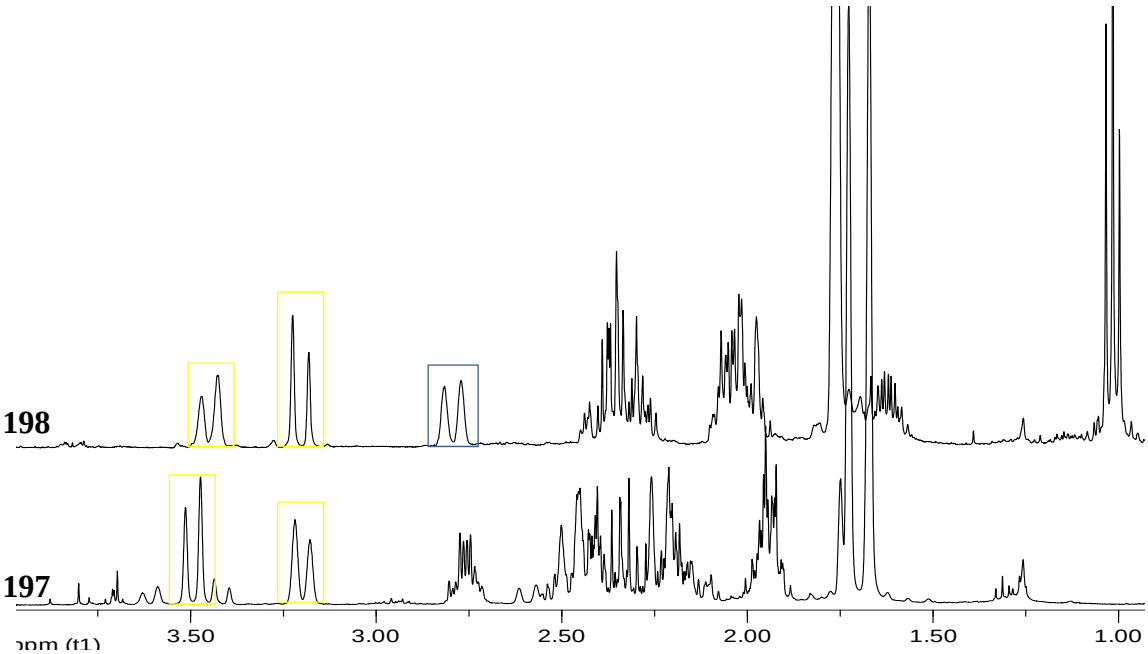


Figure 2.41 *Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$) for the cycloadduct **197** (bottom) and the cycloadduct **198** (top). The distinguishable C(11)H_2 signal is marked in blue, and the SOCH_2 signals are marked in yellow.*

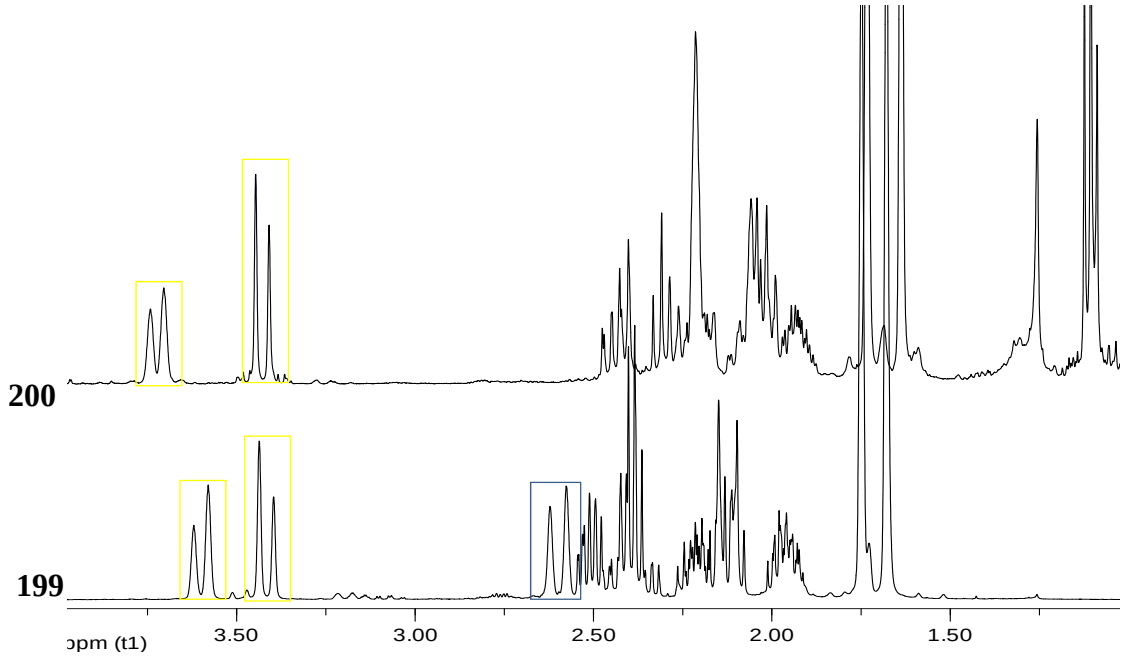
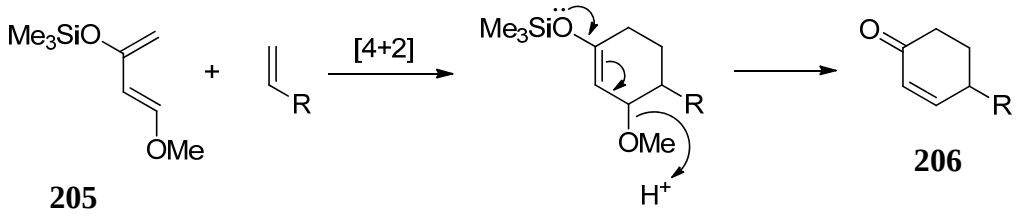


Figure 2.42 *Stacked ^{1}H NMR spectra (400 MHz, $CDCl_3$) for the cycloadduct **199** (bottom) and the cycloadduct **200** (top). The distinguishable C(11)H_2 signal is marked in blue, and the SOCH_2 signals are marked in yellow.*

In conclusion, it has been revealed for the first time that α-diazo-β-keto sulfoxides behave as suitable precursors towards α-oxosulfine intermediates which can be trapped as dihydro-2*H*-thiopyran *S*-oxides. Excellent diastereoselectivity in cycloaddition reactions of sulfines has been demonstrated, based on trapping the *E*- or *Z*-isomers of the sulfines. For the monocyclic α-diazosulfoxides **131a** and **131b**, the presence of a second stereogenic centre at C(3) directs diastereofacial approach of the diene to the sulfines, allowing for the formation of up to four diastereomeric cycloadducts, with the isolation of just two diastereomers in this work. A series of novel and stable adducts have been prepared in good yields, which are quite stable over prolonged periods of time at room temperature. This route provides ready access to a class of unusual spiro-centred heterocycles, which in turn have potential as useful precursors in organic synthesis.[126-129]

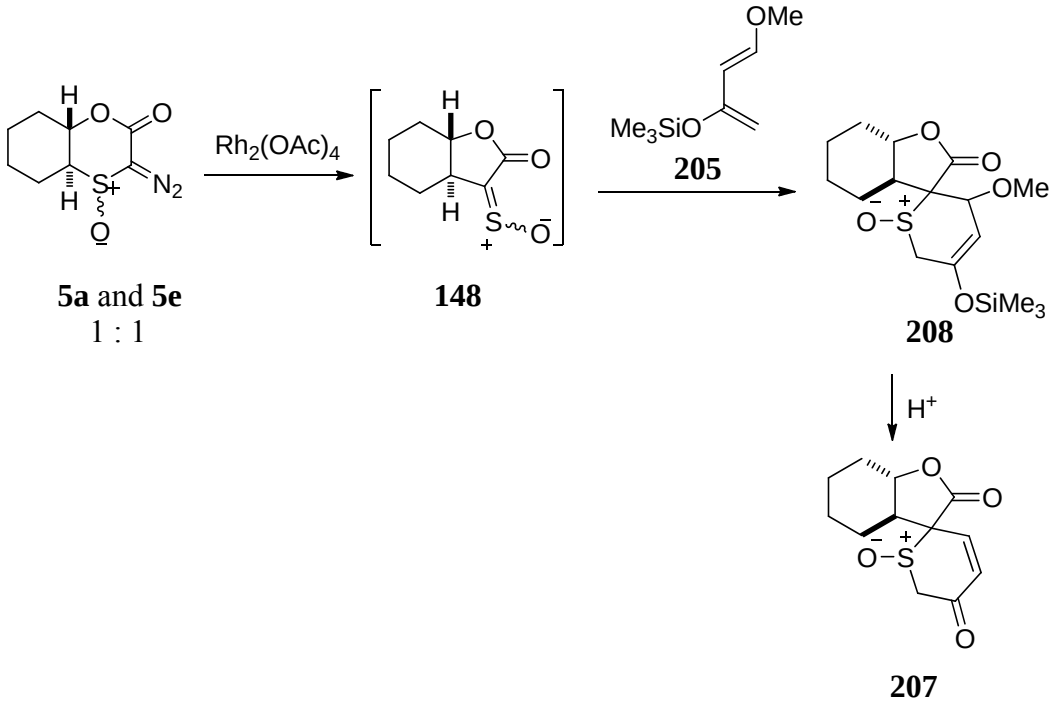
2.10.5 Decomposition of α-Diazosulfoxides 5a and 5e in the Presence of *E*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene 205

In the early stages of this work, a new series of cycloadducts were envisaged, by investigating [4+2] cycloadditions in the presence of *E*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **205** (Danishefsky's diene). Danishefsky's diene is a well-known and very reactive diene frequently used in Diels-Alder reactions for its high regiospecificity, due to the electron rich methoxy group.[141] Furthermore, convenient loss of the silyl and methoxy groups under mildly acidic conditions to form the enone cycloadduct **206**, made it a potentially useful reagent in this work (Scheme 2.115).



Scheme 2.115

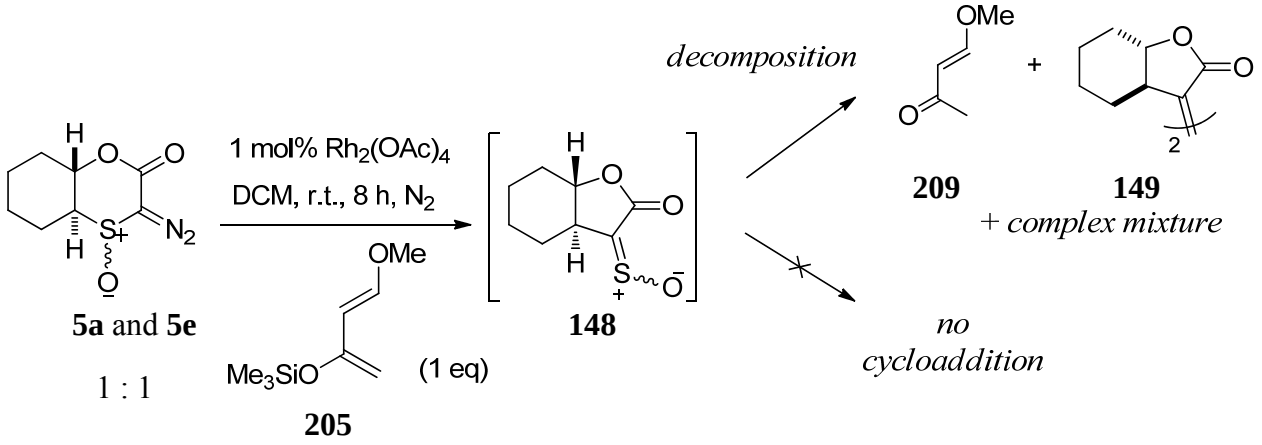
It was envisaged that the diene **205** would be sufficiently reactive to form a cycloadduct with the α-oxosulfine **148** derived from the α-diazosulfoxides **5a** and **5e**, resulting in the stable cycloadduct **207**. The regiochemistry is predicted to be as shown in Scheme 2.116.[142]



Scheme 2.116

The reaction was carried out *in situ*, with addition of one equivalent of the diene **205** to a solution of the α-diazosulfoxides **5a** and **5e** in dichoromethane at room temperature under a nitrogen atmosphere. The rhodium(II) acetate catalyst was added immediately following addition of the diene, and the solution was stirred at room temperature under the inert atmosphere. After 8 hours, TLC analysis indicated complete consumption of starting material.

However, despite the high reactivity of the diene **205** in the presence of dienophiles, it is also known to decompose to the enone **209** when exposed to air over time (Scheme 2.117).[141] In this work, no evidence for reaction between the diene **205** and the α-oxosulfine **148** was observed, despite carrying out the reaction under a nitrogen atmosphere.* Complete decomposition of the diene **205** occured instead, resulting in the enone **209**, and with decomposition of the α-oxosulfine **148** giving the alkene dimer **149** among a complex mixture of unidentifiable compounds (Scheme 2.117).



Scheme 2.117

Considering the well documented reactivity of Danishefsky's diene **205** in the presence of dienophiles,[143,144] this result was somewhat unexpected. Interestingly, cycloaddition reactions of sulfines and Danishefsky's diene have not previously been reported.

***** *E*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene **205** is commercially available in a sealed glass vial under an inert atmosphere. The purity of the diene was determined by ^{1}H NMR analysis as ~95% (~5% enone **209**) immediately prior to the reaction. The reaction was carefully carried out under a nitrogen atmosphere, in the absence of air and moisture, in an attempt to minimise decomposition of the diene.

Clearly, cycloaddition of Danishefsky's diene **205** with the α-oxosulfine **148** does not compete effectively with the individual reaction pathways, to provide the alkene dimer **149** from the α-oxosulfine **148** and the enone **209** from hydrolysis of the diene **205**. The rationale for the absence of cycloaddition may be steric and/or electronic in origin.

Although no cycloaddition product was detected in the ^{1}H NMR spectrum of the crude material, the mixture was purified by column chromatography on silica gel. One product was isolated, the alkene dimer **149**, formed on decomposition of the α-oxosulfine **148**. The alkene dimer **149** was isolated in this instance as orange crystals. ^{1}H NMR analysis indicated that this product had been isolated to a degree of purity not previously achieved within this project, as illustrated in Figure 2.43.

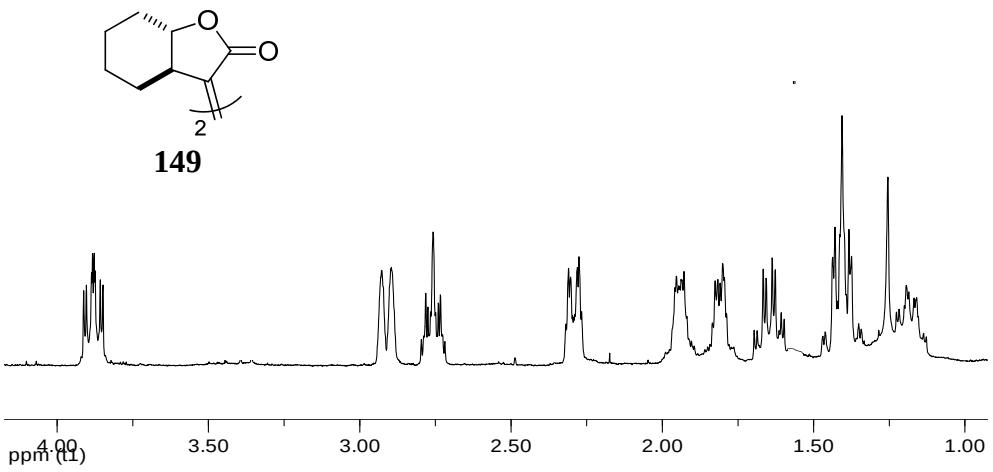
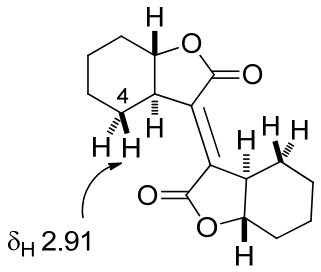
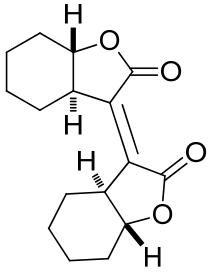


Figure 2.43 *^{1}H NMR spectrum of the alkene dimer **149** ($CDCl_3$, 300 MHz)*

Since the early 1990's, a series of researchers within the group have exhaustively attempted to grow crystals of the dimer **149** suitable for X-ray structure determination.[6,7,9,10] We were reasonably confident that the alkene had *E*-stereochemistry on the basis of ^{1}H NMR spectroscopy, with one of the C(4)H protons appearing as a deshielded broad doublet at 2.91 ppm, due to spatial proximity with the carbonyl group (Figure 2.44).

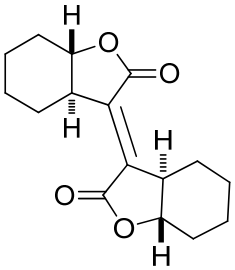


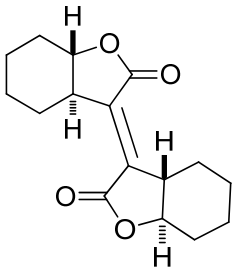


E-alkene dimer **149** *Z*-alkene dimer **149**

Figure 2.44

Trans fusion in each of the lactone units was expected to have been retained in the Wolff rearrangement step. However, the relative stereochemistry of the two bicyclic lactones, *i.e.* C_2 symmetry or centrosymmetric, had not been definitively identified prior to this work (Figure 2.45). Compound **149** forms white needle-like crystals which prove unsuitable for structural determination by X-ray crystallography.



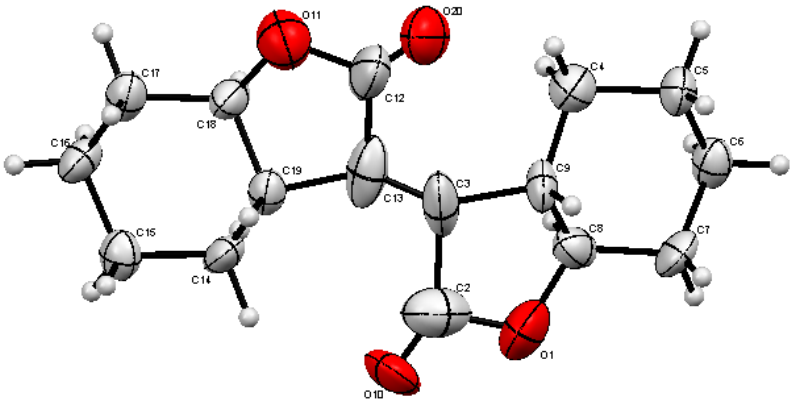


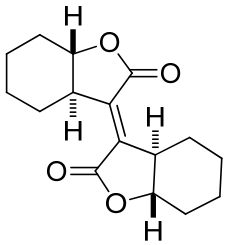
C_2 Symmetry Centrosymmetric

Figure 2.45

However, during this work, small orange crystals of **149** were grown from dichloromethane/hexane. It is believed that the different morphology of the crystals obtained in this work is related to the formation of the compound in a different reaction medium. In this case, the dimer is generated in the presence of Danishefsky's diene **205**, and while the ^{1}H NMR spectrum is clean, the orange colour in the crystals is indicative of the presence of a trace impurity (potentially a trace amount of chloride, from trimethylsilyl chloride). For the first time in a 20 year programme of research, it has proved possible to definitively identify the structure of the dimeric alkene by X-ray crystallography, shown in Figure 2.46. It is clearly illustrated that the compound has *E*-stereochemistry at the alkene and C_2 symmetry,

rather than a centre of symmetry. Thus, this has solved a longstanding problem in this research program. Interestingly, despite the tetrasubstitution around the alkene, the double bond lies flat in the plane of the alkene dimer.





149

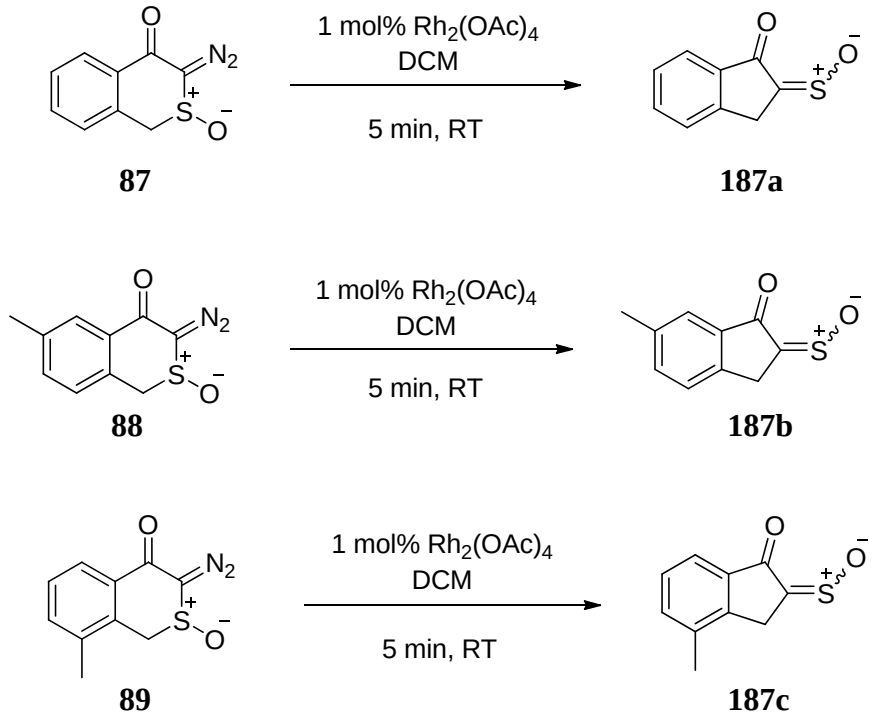
C_2 symmetry

Figure 2.46 *X-ray crystal structure of the alkene dimer* ***149*** *illustrating the* trans *fusion and* E*-stereochemistry. Structure is displayed using the Mercury 2.3 (Build RC4) package.*

2.11 Decomposition Reactions of Benzofused α-Diazosulfoxides

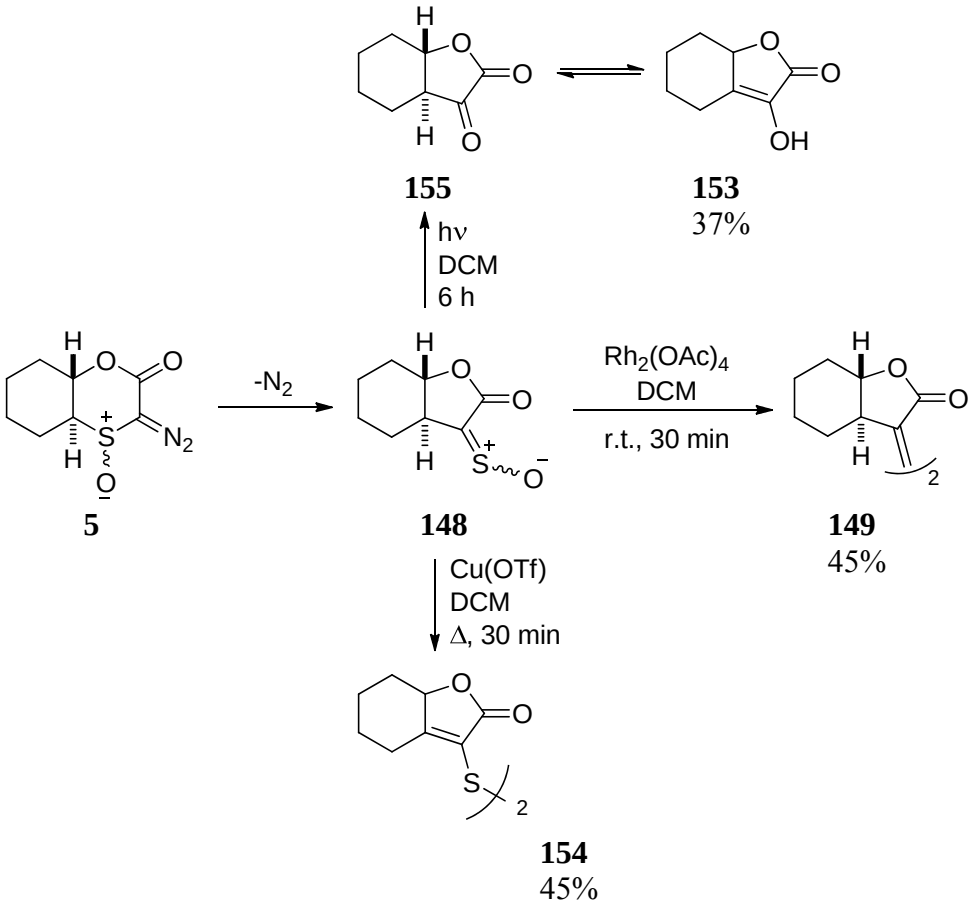
2.11.1 Background

The synthesis of the benzofused α-diazosulfoxides **87**, **88** and **89** has been discussed in Section 2.5. The decomposition of these diazo compounds *via* Wolff rearrangement to give the corresponding α-oxosulfines **187a-c** was established in Section 2.10.2 by trapping the reactive intermediates in cycloaddition reactions.



Scheme 2.118

The reactivity of α-oxosulfines generated from lactone based α-diazosulfoxides under transition metal catalysis, photolysis and microwave conditions has been explored in depth within the group and was discussed in Section 2.9.1.[7,101-103,132] In the absence of a diene trap, the decomposition of α-diazosulfoxides has led to a number of interesting compounds. These products, for example the alkene dimer **149**, enol **153** and disulfide **154** from the α-diazosulfoxide **5**, can be accessed as the major reaction products by simply altering the reaction conditions (Scheme 2.119).[7,103]

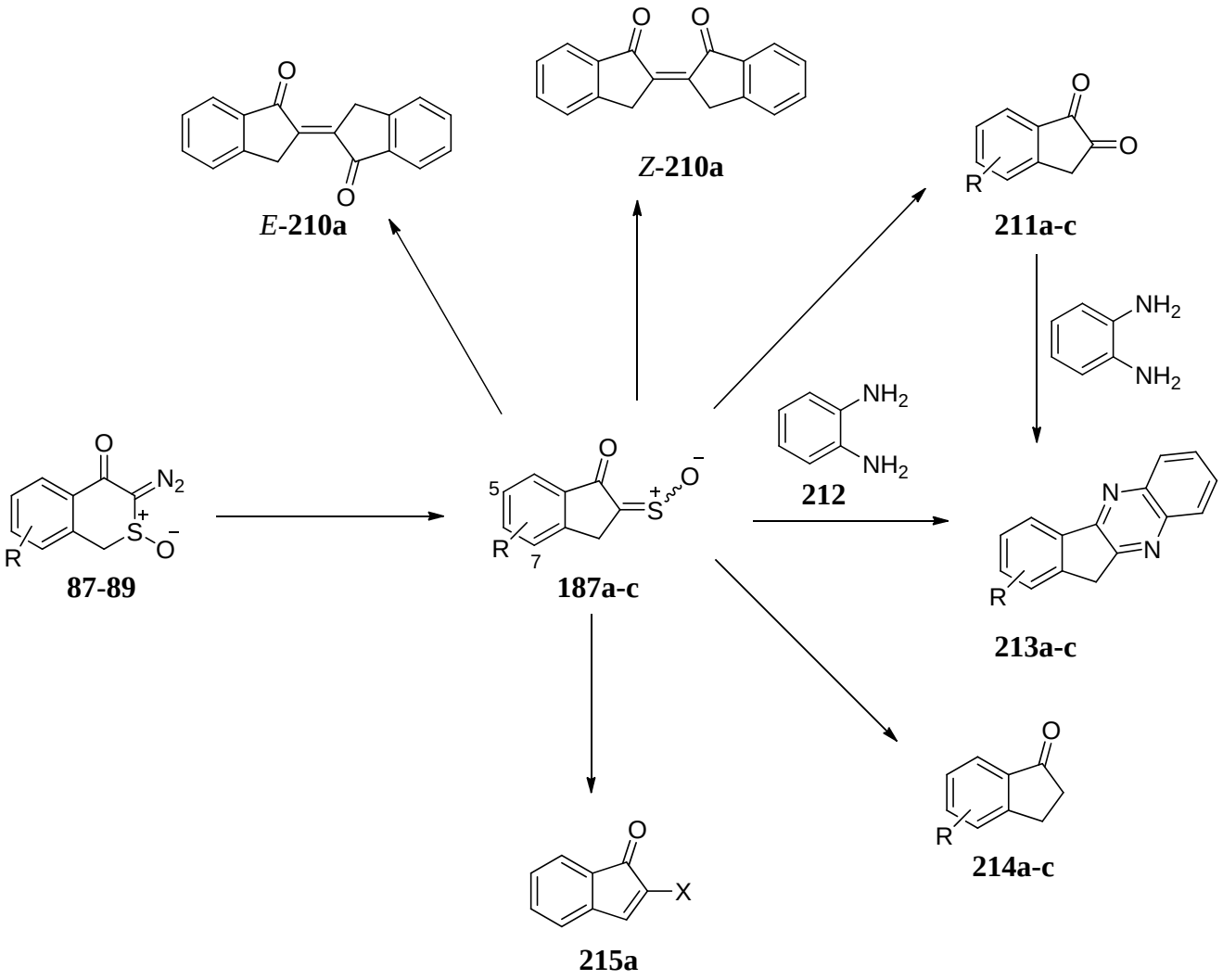


Scheme 2.119

Work carried out thus far has established that the critical step in the reactivity of α-diazosulfoxides is the loss of nitrogen and Wolff rearrangement to form α-oxosulfine intermediates. As outlined above, it has been reported that there are a number of pathways for reactivity of the α-oxosulfine.

In this work, the decomposition of the α-diazosulfoxides **87**-**89** was explored under transition metal catalysis, microwave and photolysis conditions. A number of reaction pathways were observed, leading to isolation of a series of interesting novel compounds. A summary of these compounds is illustrated in Scheme 2.120. The following discussion relates to the various reaction conditions explored and the optimum conditions determined for the formation of each of these compounds. In Section 2.11.3 mechanistic implications are then considered as well as the synthetic utility of these reactions.

2.11.2 Decomposition reactions

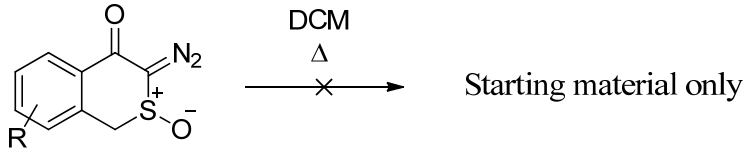


a	R = H	*E*-**210a**, *Z*-**210a**, **213a**, **214a**, **215a**
b	R = 5-Me	**211b**, **213b**, **214b**
c	R = 7-Me	**211c**, **213c**, **214c**

Scheme 2.120 *Series of decomposition products formed from the α-oxosulfines* ***187a-c****.* ***a****: R = H,* ***b****: R = 5-Me,* ***c****: R = 7-Me. The products* ***210b/c*** *were not isolated but were detected on occasion in the* ^{1}*H NMR spectra of the crude products.*

Initially, blank experiments were carried out in order to investigate how labile the α-diazosulfoxides **87-89** were, and to what extent they would decompose in solution in the absence of a transition metal catalyst. As a precaution, glassware which had been cleaned in aqua regia was used for these control reactions, to preclude the possibility that any catalyst residues adhering to the Pyrex® surface would have an influence on the reaction. Fortuitously, it was found that the α-diazosulfoxides **87-89** are stable compounds that do not decompose at room temperature in solution and there was no decomposition of the starting material detected even on heating under reflux in dichloromethane for up to 48 hours. These results are summarised in Table 2.17. However, it should be noted that when samples of the α-diazosulfoxides **87-89** were allowed to stand in deuterated chloroform at room temperature for up to 4 days, decomposition occurred, with formation of the corresponding α-oxosulfines in increasing quantities overtime. These results are summarised in Tables 3.6, 3.9, and 3.11 in Chapter 3. The instability of these compounds in deuterated chloroform, as opposed to dichloromethane, may be attributed to acidic nature of chloroform, which catalysed loss of the diazo group and decomposition *via* the Wolff rearrangement to give the α-oxosulfines.[20]

Table 2.17 Investigation of the reactivity of the α-diazosulfoxides **87-89** in the absence of a metal catalyst



87-89

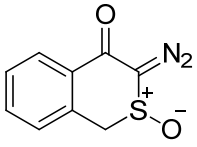
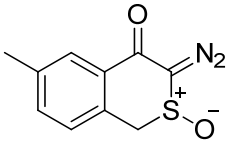
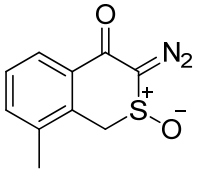
Entry	Starting material	Solvent	Conditions[a]	Time	Product[b]
1	**87**	DCM	Δ	24 h	**87**
2	**88**	DCM	Δ	48 h	**88**
3	**89**	DCM	Δ	24 h	**89**

a. The solutions were stirred under reflux conditions and a nitrogen atmosphere in DCM. No catalyst was employed.

b. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. No decomposition of the α-diazosulfoxides occurred.

Having established the stability of the α-diazosulfoxides **87-89** in dichloromethane and in the absence of a transition metal catalyst, an investigation into the reactivity of these compounds could now be undertaken. The results of this investigation are summarised in Table 2.18.

Table 2.18 Summary of decomposition reactions of α-diazosulfoxides **87**-**89** under various reaction conditions.

Entry	Reaction conditions[a,b,c]	 **87**	 **88**	 **89**
1	Cu(I)OTf, 8 h, RT, DCM	*crude* **214a** : **211a** 5 : 1 *pure* **214a** (50%)		
2	Cu(I)OTf, 20 h, Δ, DCM		*crude* **214b** : **211b** : **187b** 1 : 0.6 : trace *pure* **214b** (41%)	
3	Cu(I)OTf, 48 h, Δ, DCM			*crude* **214c** : **187c** 1 : 1.8 *pure* **214c** (30%)
4	hν, 4 h DCM	*crude* **214a** : *E*-**210a** : **187a** 2.8 : 1 : 0.5 *pure* **214a** (24%)	*crude* **214b**	*crude* **214c** : **211c** : *E*-**210c** 1 : 0.2 : 0.05
5[d]	MW, 20 min, 90 °C, DCM	*crude* **211a** : *E*-**210a** : **214a** 6 : 1 : trace *pure E*-**210a** : *Z*-**210a** 1 : trace (21%)		
6	$Rh_2(OAc)_4$, toluene, o/n, Δ	*crude* **211a** : *E*-**210a** : *Z*-**210a** 2 : 1: trace *pure E*-**210a** : *Z*-**210a** 21 : 1 (19%)		
7	$Rh_2(OAc)_4$, Δ, DCM, 72 h		*crude* **187b** : **211b** : *E*-**210b** 0.6 : 1 : 0.1	*crude* **187c** : **211c** : *E*-**210c** : **214c** 1 : 2 : 0.1 : trace

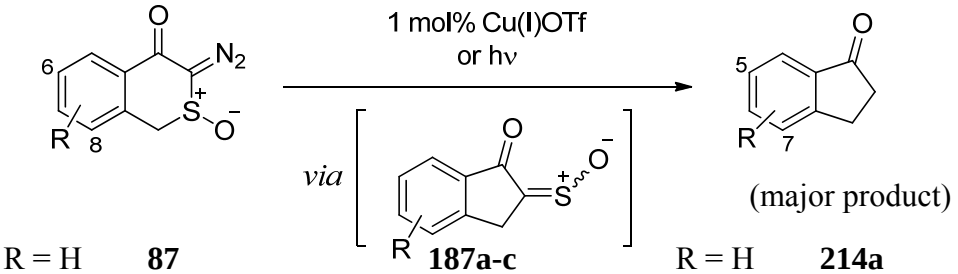
			211b : *E*-**210b** very small quantities	
8[e]	**212**, MW, 45 min, 90 °C, DCM	*crude* **213a** : **214a** 1 : trace **213a** (70%)	*crude* **213b** *pure* **213b** (75%)	*crude* **213c** : **214c** 1 : 0.2 **213c** (62%)
9[e]	(i) MW, 30 min, 90 °C, DCM (ii) **212**, RT, 1 h	*crude* **213a** : *E*-**210a** : **214a** 7 : 1 : trace		
10	$Rh_2(OAc)_4$, H_2O, o/n	**215a**		
11	$Rh_2(OAc)_4$, o/n, Δ, DCM	**216**		
12	Cu(0), 48 h, Δ, DCM	**216**	*crude* **187b** : **211b** 1 : 0.2	*crude* **187c** : **211c** : **214c** : *E*-**210c** 1 : 0.1 : 0.1 : 0.05

a. Where described, 1 mol% catalyst loading was used.
b. Microwave reactions were heated to 90 °C in a sealed, 10 mL vessel, with a ramp time of ~2 min. Photolysis reactions were carried out with a 90W mercury lamp.
c. Crude product ratios were determined by integration of signals in the ^{1}H NMR spectrum.
d. The crude reaction mixture was stored at room temperature for ~12 weeks before purification.
e. *o*-Phenylenediamine **212** was used to trap the diketones **211a-c** as quinoxalines **213a-c**. Entry 8 refers to addition of **212** to the α-diazosulfoxides *in situ* under mircrowave conditions. Entry 9 refers to sequential reaction, with formation of the indanediones first under microwave conditions, followed by addition of **212** at room temperature.

A number of interesting results were obtained from this study which warrant discussion. For most reactions, a mixture of up to four products was formed. It should be noted that reactions were only performed once and therefore optimisation studies should be undertaken in future work. Notably, however, distinct trends for the formation of major products depending on the reaction conditions employed can be identified.

Decomposition of the α-diazosulfoxides **87-89** in the presence of 1 mol% copper triflate and under photolysis conditions gave the known indan-1-ones **214a-c** as the major products (entries 1-4, Table 2.18).[145-147] These could be separated from the mixtures by chromatography in moderate yields. For the α-diazosulfoxides **88**

and **89**, the reaction progress appeared to be quite sluggish, even under reflux conditions. The photolysis reactions were complete after 4 hours, with complete consumption of starting material indicated by TLC. For the decomposition of the α-diazosulfoxide **88** under photolysis conditions, the indan-1-one **214b** was essentially the only product formed, in a very clean ^{1}H NMR spectrum. For entries 2 and 3, small quantities of α-oxosulfine remained the reaction mixture, indicating that decomposition of the α-diazosulfoxides **87**-**89** to the indan-1-ones **214a-c** most likely occurs *via* Wolff rearrangement to the α-oxosulfine intermediates **187a-c** (Scheme 2.121).



R = H **87**
R = 6-Me **88**
R = 8-Me **89**

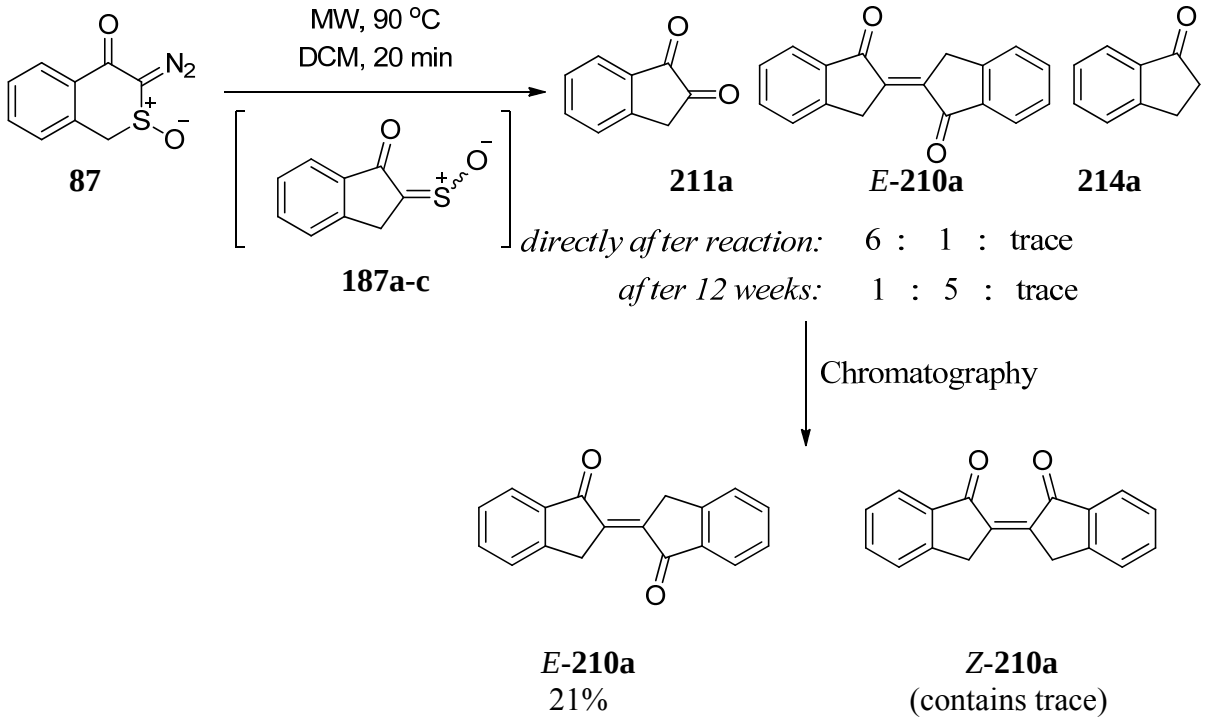
187a-c

R = H **214a**
R = 5-Me **214b**
R = 7-Me **214c**

Scheme 2.121

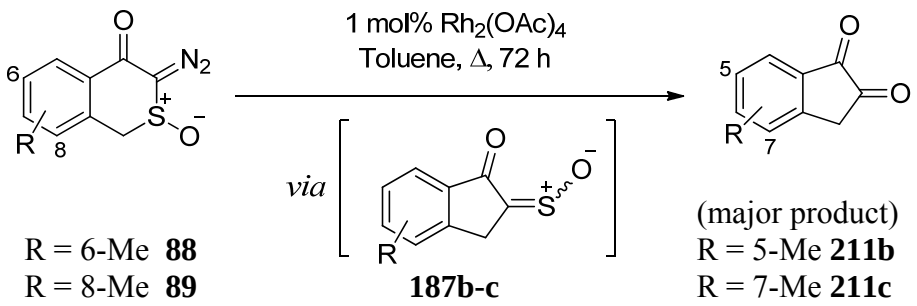
The decomposition of the α-diazosulfoxide **87** under microwave conditions led to the formation of a compound tentatively identified as the indanedione **211a** as the major product, along with the alkene dimer *E*-**210a** and a trace quantity of the indan-1-one **214a** (entry 5, Table 2.18). The indanedione **211a** is a known compound, and was identified by the distinctive CH_2 singlet at 3.64 ppm, which is shifted upfield from the corresponding CH_2 singlet of the α-diazosulfoxide **87** (4.32 ppm) and the α-oxosulfine **187a** (4.26 ppm). However, aryl 1,2-diketones are well known as compounds which are difficult to isolate and purify.[148] Attempted purification of the indanedione **211a** from the reaction mixture instead gave the sterically congested *E*-alkene dimer *E*-**210a**,[149] along with a trace quantity of the *Z*-alkene dimer *Z*-**210a** in 21% yield. It should be noted however, that this particular crude product was stored at room temperature for ~12 weeks before purification by chromatography was undertaken. After this time, ^{1}H NMR analysis indicated that significant decomposition of the indanedione **211a** had occurred, leaving the alkene dimer *E*-**210a** as the major product (Scheme 2.122). This is discussed further in

Section 2.11.3. The alkene dimers **210b** and **210c** were also tentatively identified in crude reaction mixtures, albeit in very small quantities.



Scheme 2.122

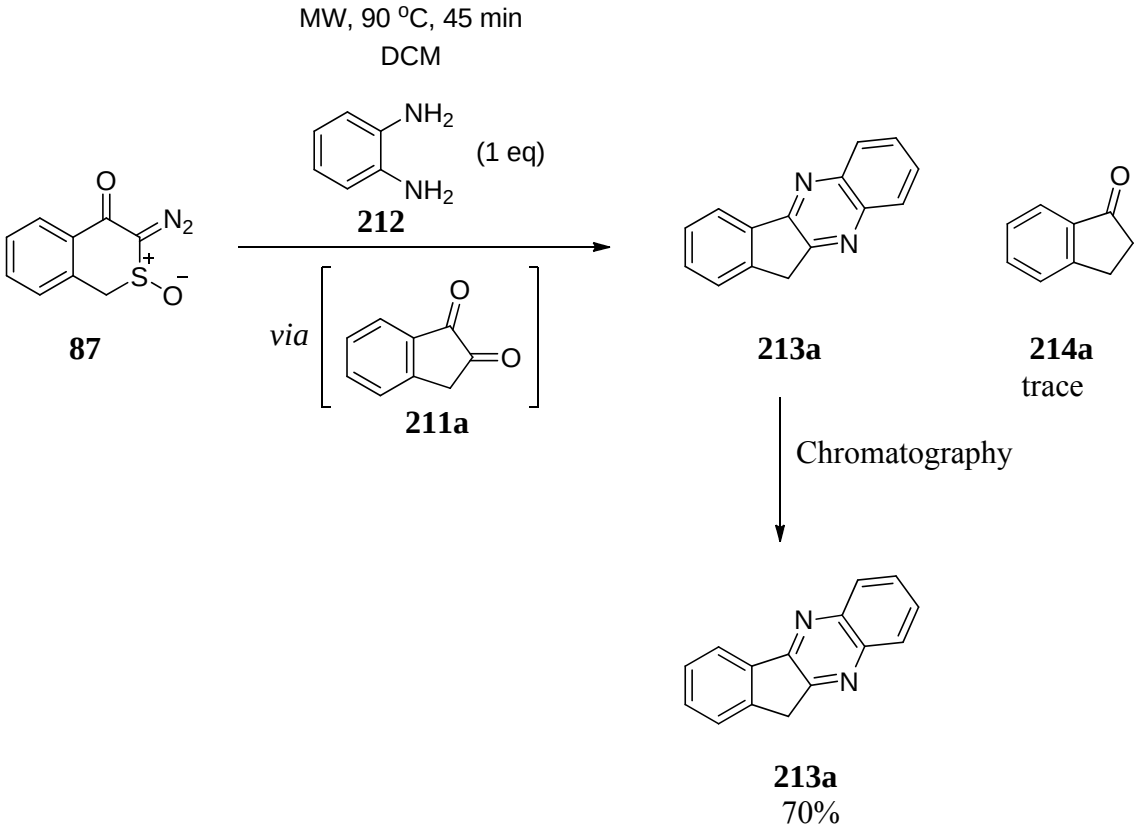
When the α-diazosulfoxide **87** was treated with 1 mol% rhodium(II) acetate under reflux conditions in toluene overnight, the indanedione **211a** was again the major product identified in the ^{1}H NMR spectrum of the crude mixture, along with a small quantity of the alkene dimer *E*-**210a** (entry 6, Table 2.18). A second attempt to immediately isolate the indanedione **211a** by chromatography was again unsuccessful. Instead, the *E*-alkene dimer *E*-**210a** and the *Z*-alkene dimer *Z*-**210a** (21:1) were again isolated as pale green crystals in 19% yield. The α-diazosulfoxides **88** and **89** were also treated with 1 mol% rhodium(II) acetate under reflux conditions in dichloromethane (entry 7, Table 2.18). After 72 hours, TLC analysis indicated the complete consumption of starting material. The CH_2 singlets of the indanediones **211b** and **211c** were detected in the ^{1}H NMR spectra of the crude mixtures as the major products (Scheme 2.123).



Scheme 2.123

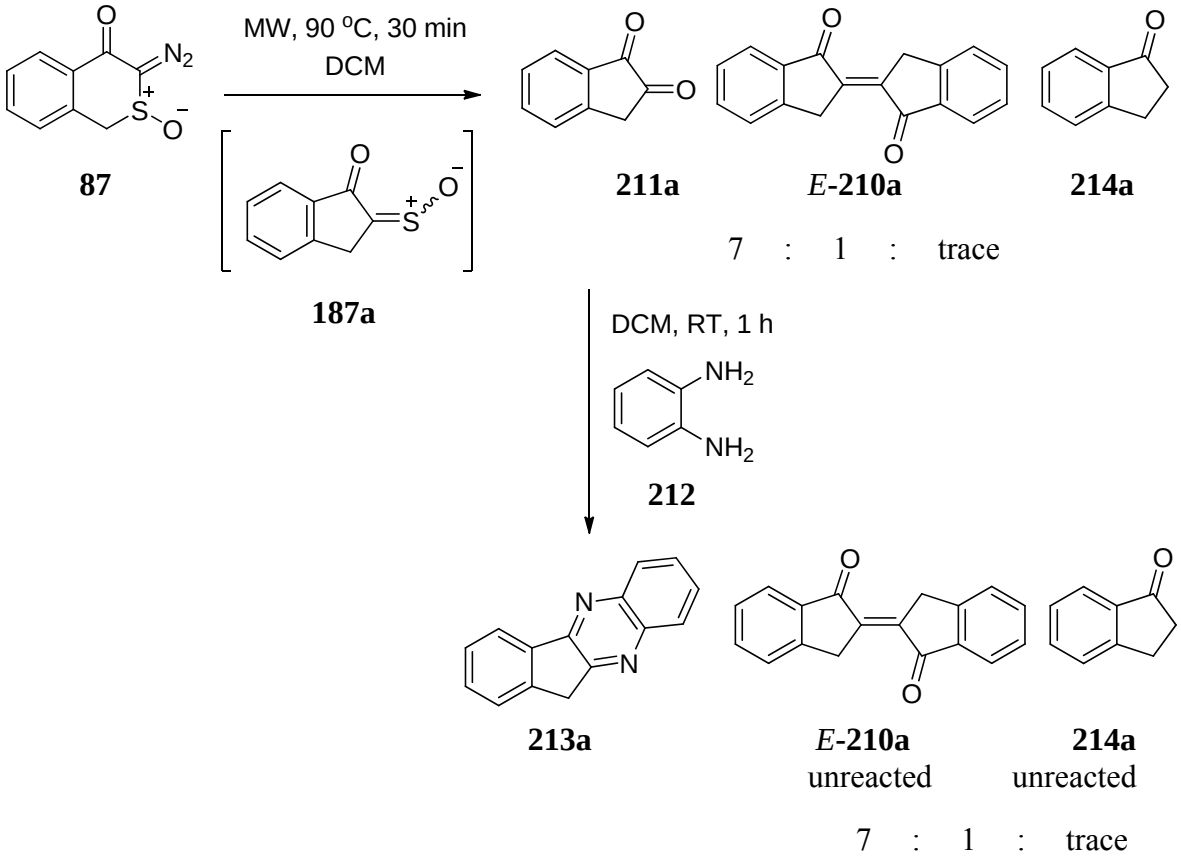
The difficulty in isolating and thus definitively proving the formation of the indanedione products **211a-c** led us to consider condensation with *o*-phenylenediamine **212** in order to form the quinoxaline derivatives as an alternative route. Condensation reactions of 1,2-diamines with diketones or glyoxal compounds have been widely reported in the literature.[17]

Beginning with the α-diazosulfoxide **87**, we decided to initially attempt an *in situ* trapping of the indanedione **211a**, with addition of *o*-phenylenediamine **212** directly to the α-diazosulfoxide **87** (entry 8, Table 2.18). The mixture was then irradiated with microwaves at 90 °C for 45 minutes. The known quinoxaline **213a** was successfully generated along with a trace quantity of the indan-1-one **214a**.[150] The quinoxaline **213a** was purified by chromatography and recrystallisation to give the pure product in a very good yield of 70% (Scheme 2.124).



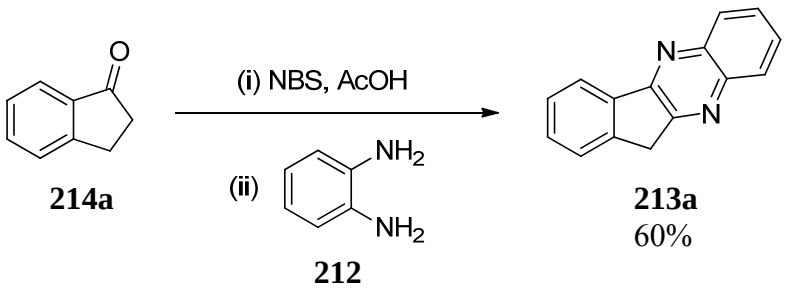
Scheme 2.124

We were interested to discover that *o*-phenylenediamine **212** appears to readily condense with the indanedione **211a** only in an efficient reaction. It is possible that **213a** is formed by competing condensation of the α-oxosulfine intermediate **187a**, leading to the same product, although no direct evidence for this was observed. In order to confirm that the condensation was indeed taking place with the indanedione **211a**, a sequential reaction was also undertaken, whereby the indanedione **211a** was initially formed from the α-diazosulfoxide **87** and isolated, together with minor amounts of *E*-**210a** and **214a** (7 : 1 : trace) and the mixture was then treated with *o*-phenylenediamine **212** in a two-step sequence (entry 9, Table 2.18). ^{1}H NMR analysis of the crude product indicated the disappearance of the indanedione **211a** CH_2 singlet at 3.64 ppm, and the formation of the quinoxaline **213a** CH_2 singlet at 4.13 ppm (Scheme 2.125).



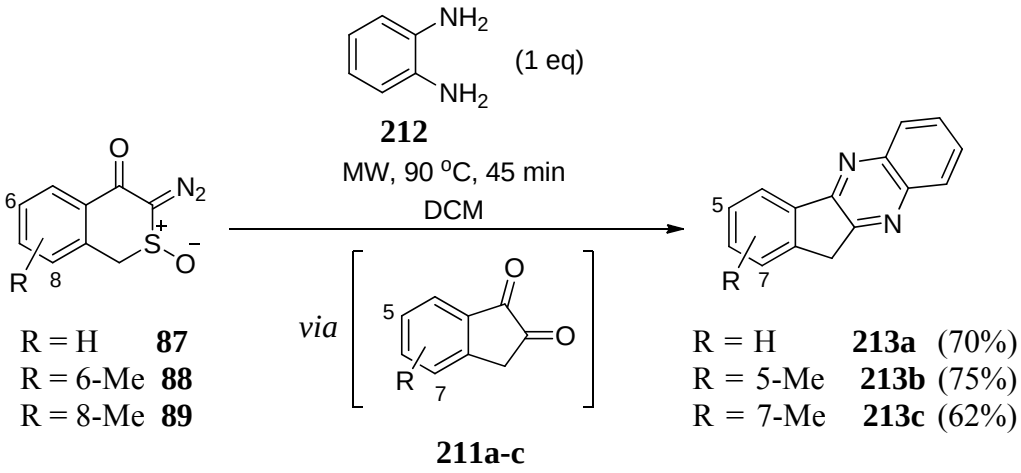
Scheme 2.125

Interestingly, the quinoxaline **213a** has previously been prepared in a yield of 60% by Chang and co-workers from **214a** by α-bromination with NBS followed by condensation of the resulting α-bromo ketone with *o*-phenylenediamine (Scheme 2.126).[150]



Scheme 2.126

The indanediones **211b-c** generated from the α-diazosulfoxides **88** and **89** were also selectively trapped *in situ*, allowing access to two novel quinoxaline derivatives **213b** and **213c** in very good yields (Scheme 2.17).



Scheme 2.127

Polycyclic quinoxaline heterocycles are important benzoheterocycles in combinatorial drug discovery libraries.[150,151] They are generally synthesised by the condensation of 1,2-dicarbonyls with 1,2-diamines in either acetic acid or ethanol under reflux conditions. Although a number of quinoxalines have been prepared using multi-step routes, new methods for their preparation are needed.[150] The method described in this work has a major advantage of elevated yields, due to the convenient, one-pot reaction.

At this point, it is worth reviewing the variety of decomposition products which have been isolated and characterised. The indan-1-ones, **214a-c** were generated as the major products from the copper triflate catalysed and photolysis reactions. The sterically congested alkene dimer *E*-**210a** and its isomer *Z*-**210a** were isolated from decomposition of the α-diazosulfoxide **87** under microwave conditions and in the presence of rhodium(II) acetate in refluxing toluene, albeit present as minor components in the crude mixtures. The major products under these conditions were the indanediones **211a-c**, which were unstable and difficult to isolate. However, efficient condensation either *in situ* or under sequential conditions with *o*-phenylenediamine **212** gave the tetracyclic quinoxalines **213a-c** in good yields. A number of these compounds are novel, and have been fully characterised in this work. Additionally, the decomposition pathways investigated represent new routes towards these compounds. A summary of this work is illustrated in Figure 2.47.

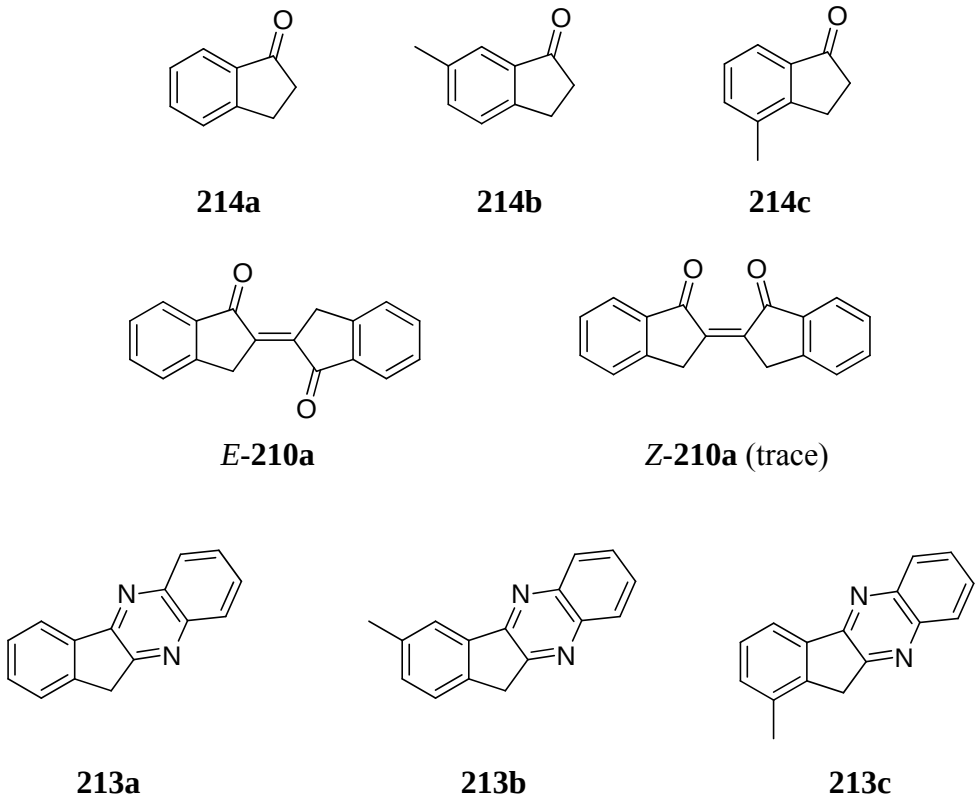
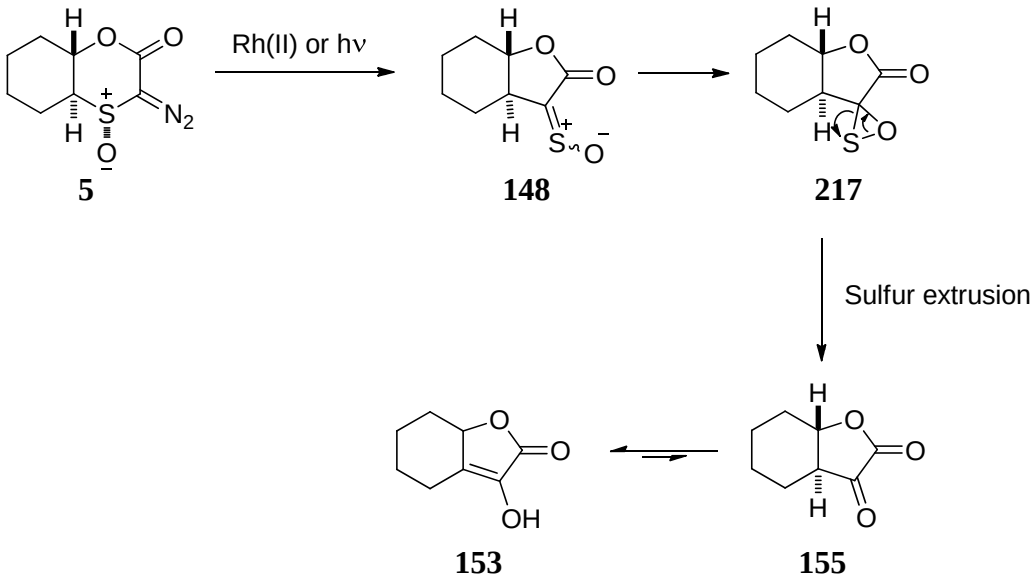


Figure 2.47 *Summary of decomposition products isolated from α-diazosulfoxides* ***87-89***

Note: For the α-diazosulfoxide **87**, a range of transition metal catalysts were screened in order to investigate their effect on its decomposition. In each case, similar mixtures of products to those obtained with rhodium(II) acetate were provided. The lack of sensitivity to the nature of the catalyst supports the view that once the α-oxosulfine is generated, the subsequent reaction pathways of this labile intermediate occur essentially independently of the catalyst. A summary of these reactions can be found in Table 3.8, Chapter 3.

2.11.3 Mechanistic considerations

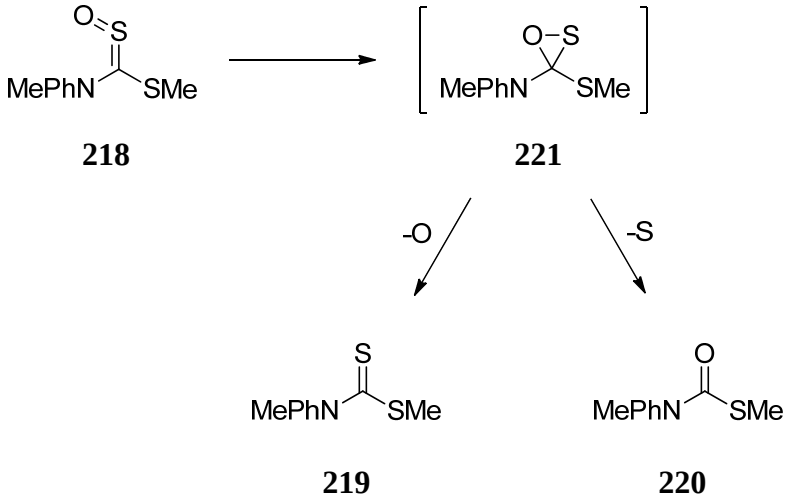
The mechanistic pathways for the formation of these products are next considered. The indanediones **211a-c** were generated as the major products under microwave conditions and in the presence of rhodium(II) acetate in refluxing toluene. Previous work within the group has demonstrated the decomposition of lactone based α-diazosulfoxides, for example **5**, to the diketone **155** followed by tautomerisation to the enol **153** (Scheme 2.128).



5 **148** **217** **153** **155**

Scheme 2.128

Indeed, sulfines have been documented in the literature to undergo loss of both sulfur and oxygen *via* similar oxathiirane intermediates, as reported by Metzner (Scheme 2.129).[152] The relative stabilities of a range of sulfines was investigated, and, as an example, the sulfine **218** was transformed after 15 days into a mixture of the dithiocarbamate **219** and the thiocarbamate **220** (1:1).

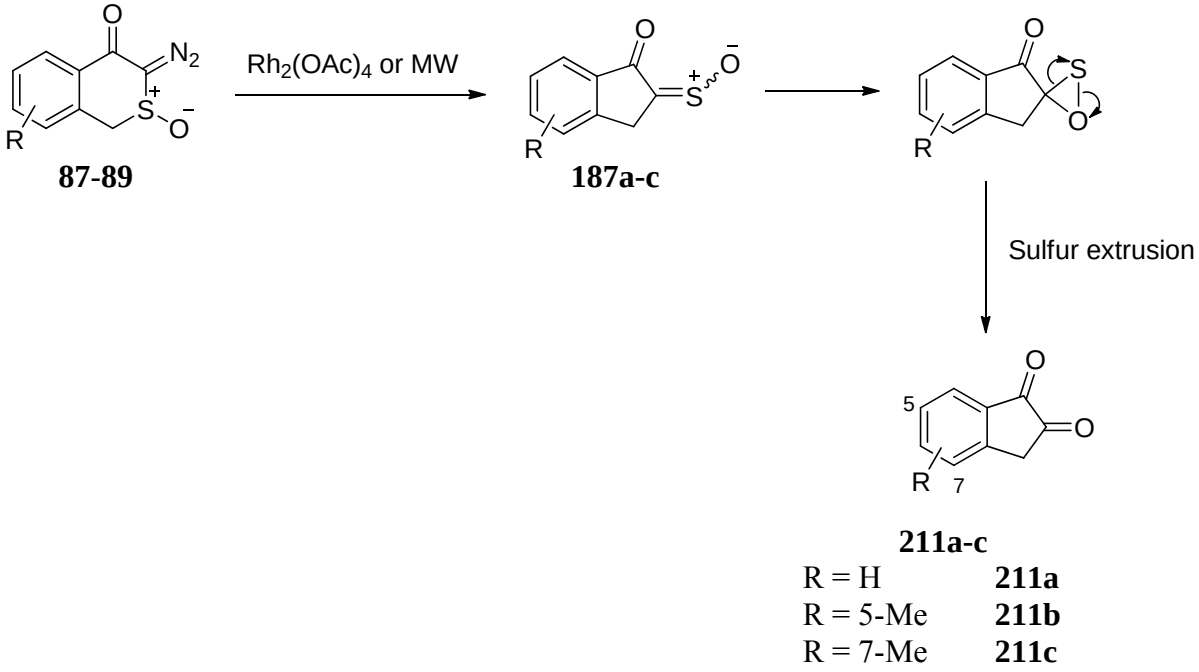


218 **221** **219** **220**

Scheme 2.129

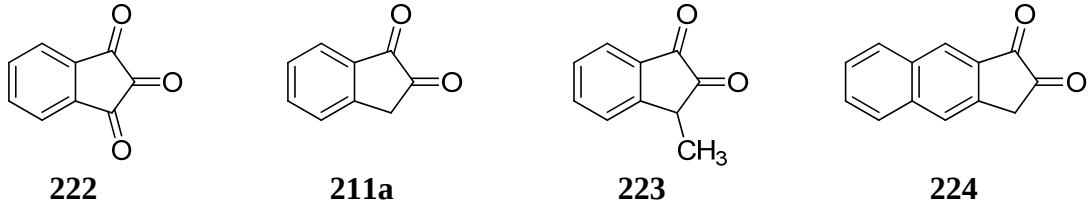
It is interesting to note that the lactone based enol **153** studied by Collins was formed under both rhodium(II) catalysed and photolysis conditions.[7] In this work however, the diketones **211a-c** were formed as the major products under rhodium(II) catalysed and microwave conditions. Photolysis resulted in the formation of the

indanones **214a-c** as the major products. The stability associated with the 3-furanone structure of **153** results in ready tautomerisation from **155**. For the benzofused derivatives prepared in this work however, the diketone form appears to be the more stable tautomer, and no evidence for the enol tautomer was found. Thus, the mechanism of formation for the indanediones **211a-c** is proposed to occur *via* electrocyclisation of the α-oxosulfines to oxathiiranes, followed by sulfur extrusion and is illustrated in Scheme 2.130.



Scheme 2.130

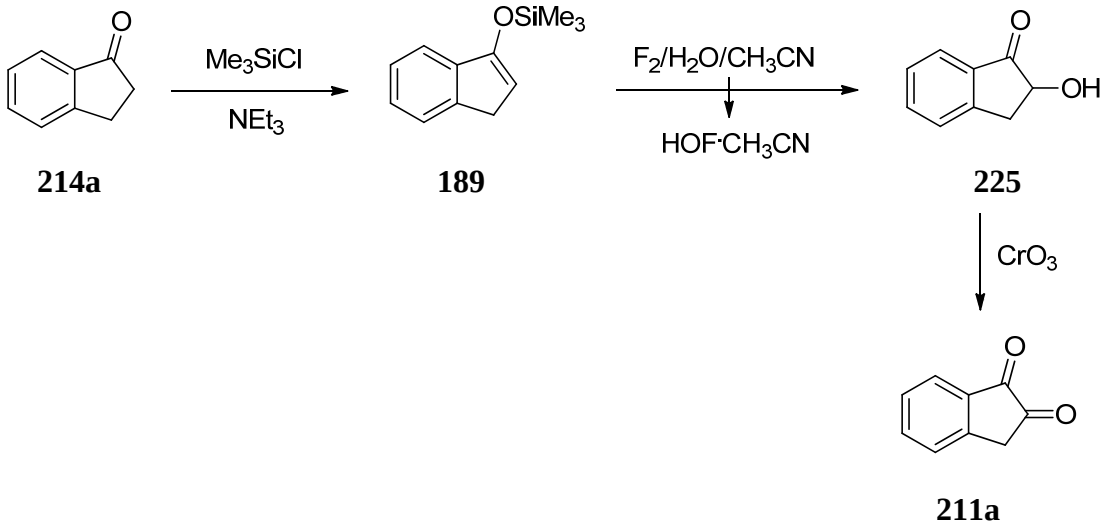
Indanediones, such as ninhydrin **222**, indanedione **211a** and its derivatives **223** and **224** (Figure 2.48) have been reported as useful tools in biochemistry and forensic science, most notably as reagents allowing the visualization of latent fingerprints by direct fluorogenic reactions.[153,154]



222 **211a** **223** **224**

Figure 2.48

Several methods for the preparation of 1,2-indanediones are described in the literature involving coupling methods,[155] oxidation of the methylene group in the 2-position using selenium dioxide,[156] hydrolysis of 2-oximino-1-indanones prepared from 1-indanone derivatives[157] and α-hydroxylation of ketones using $HOF{\cdot}CH_3CN$ complex.[153] Many of these methods involve the use of harsh reaction conditions, such as the route illustrated in Scheme 2.131, which involves the use of chromium trioxide.[153]

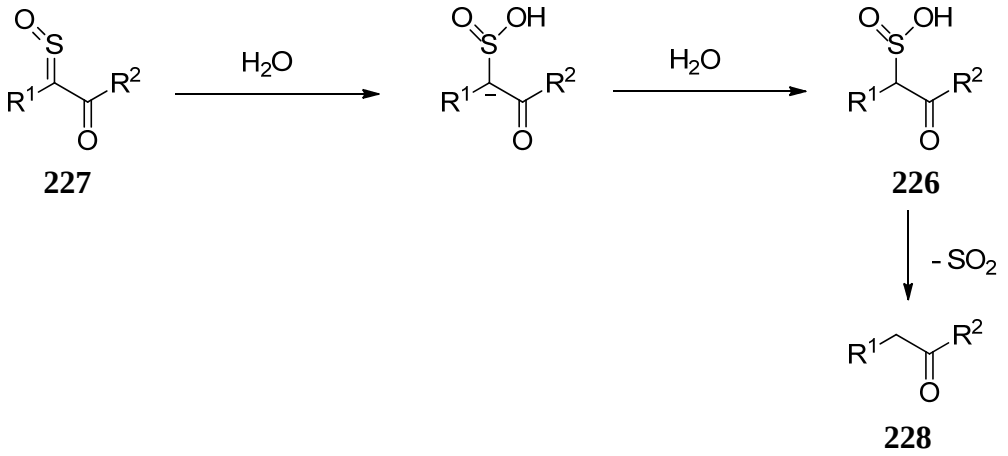


214a **189** **225** **211a**

Scheme 2.131

In contrast, the preparation of indanediones from α-oxosulfines described in this work represents a mild synthetic route towards a useful class of compounds.

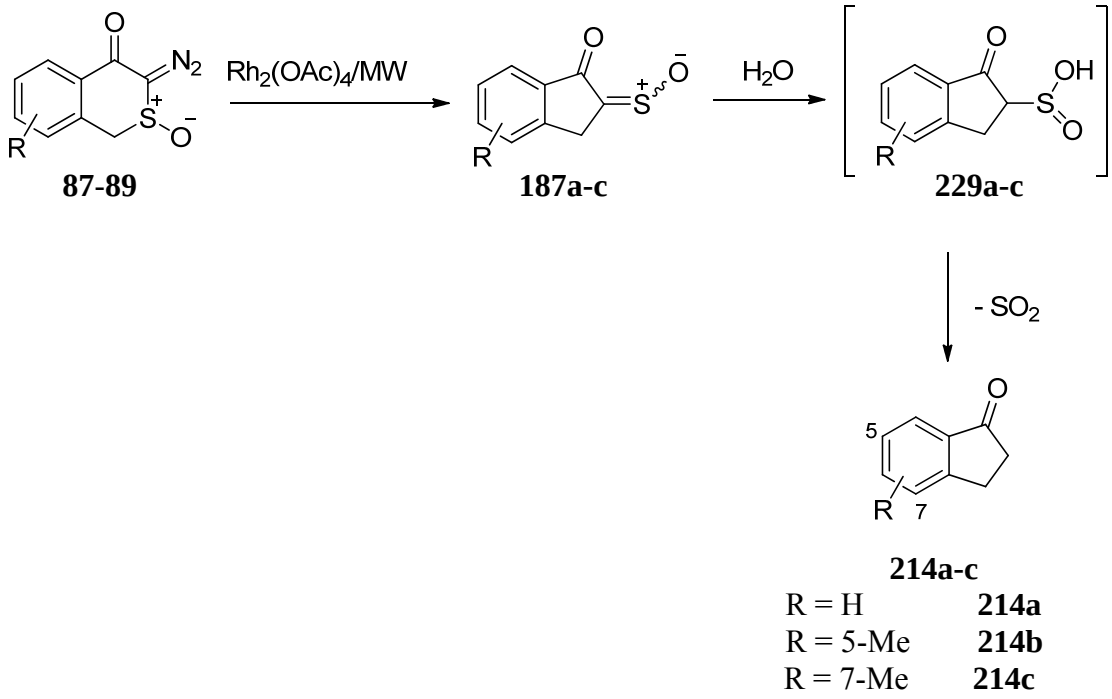
The indanones **214a-c** were formed on decomposition of the α-oxosulfines **187a-c** with complete loss of the sulfinyl group. Notably, this reaction is facilitated by the presence of copper triflate and under photolysis conditions, where the indanones **214a-c** are the major product formed in each case. This is contrast with previous work done on the reactivity of the lactone based α-diazosulfoxides, where Collins found that copper catalysis favoured oxygen extrusion, and photolysis conditions favoured sulfur extrusion.[7] Loss of both sulfur and oxygen gives the monoketone. As discussed in Section 1.4, reductive hydrolysis of α-oxosulfines has previously been reported in the literature by Zwanenburg, with replacement of the CSO moiety by CH_2.[158,159] The hydrolysis proceeded readily *via* sulfinic acid intermediates **226**, with loss of sulfur dioxide (Scheme 2.132).



227 **226** **228**

Scheme 2.132

In this work, it is also possible that replacement of the sulfinyl moiety by CH_2 takes place *via* similar sulfinic acid intermediates **229a-c** in the presence of adventitious water (Scheme 2.133). Indan-1-ones are an important class of compounds in organic synthesis, and the indanone core is present in several compounds with biological activity (Section 2.12.2.3).[160,161]



87-89 **187a-c** **229a-c**

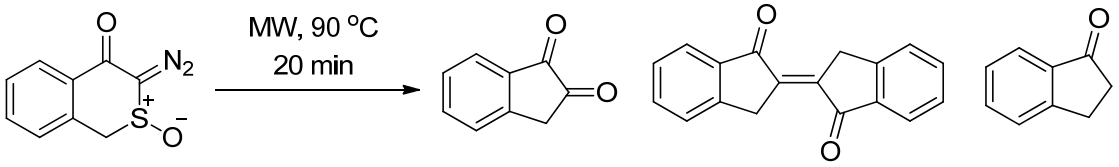
214a-c

R = H **214a**
R = 5-Me **214b**
R = 7-Me **214c**

Scheme 2.133

The alkene dimer *E*-**210a** and a trace quantity of the *Z*-alkene dimer *Z*-**210a** were isolated from the decomposition of the α-diazosulfoxide **87** under microwave conditions and in the presence of rhodium(II) acetate under reflux in toluene. The alkene dimers *E*-**210b** and *E*-**210c** were detected in the ^{1}H NMR spectra of the crude

reaction mixtures, although these were not isolated. As discussed in Section 2.11.2, it appeared that decomposition of the indanedione **211a** occurred with an increase in the relative amount of alkene dimer *E*-**210a** present in the crude product (Scheme 2.134).



87 **211a** *E*-**210a** **214a**

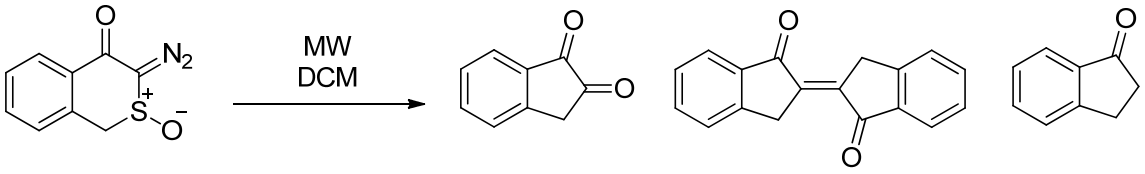
directly after reaction: 6 : 1 : 0.5

after 12 weeks: 1 : 5 : 1

Scheme 2.134

A second decomposition reaction of the α-diazosulfoxide **87** was undertaken under microwave conditions for 40 minutes, and the product ratios compared with those obtained directly after the 20 minute microwave reaction. The results are summarised in Table 2.19 and it can been seen that the ratio of indanedione **211a** to alkene dimer *E*-**210a** is significantly altered after the 40 minute reaction, with increased amounts of the dimer *E*-**210a**. One possible interpretation is that the dimer **210a** is derived from the indanedione **211a**. An alternative explanation is that the indanedione **211a** decomposes to a range of products, with no change in the amount of alkene dimer *E*-**210a** present in the mixture. However, the ^{1}H NMR spectrum of the crude mixture after 12 weeks did not indicate substantial decomposition products from the indanedione **211a**.

Table 2.19 Variation for product ratios of **211a** and *E*-**210a** based on reaction times under microwave conditions.

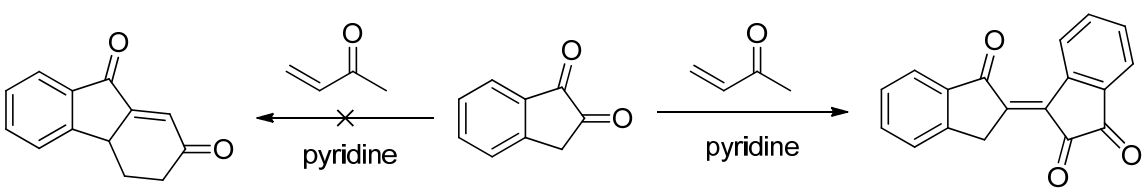


87 **211a** ***E*-210a** **214a**

Entry	Conditions[a]	Time[b]	Solvent	Products[c]
1	MW	20 min	DCM	**211a** : *E*-**210a** : **214a** (6 : 1 : 0.5)
2	MW	40 min	DCM	**211a** : *E*-**210a** : **214a** (3 : 1 : 0.4)

a. Both reactions were carried out in a sealed 10 mL vessel in DCM. Both reaction mixtures were irradiated to a temperature of 90 °C using the maximum power of 300W with a ramp time of ~1 min 10 s.
b. Time for which the set point was held.
c. The product ratios were determined based on analysis of the ^{1}H NMR spectra of the crude material. Small quantities of unidentifiable impurities were also observed.

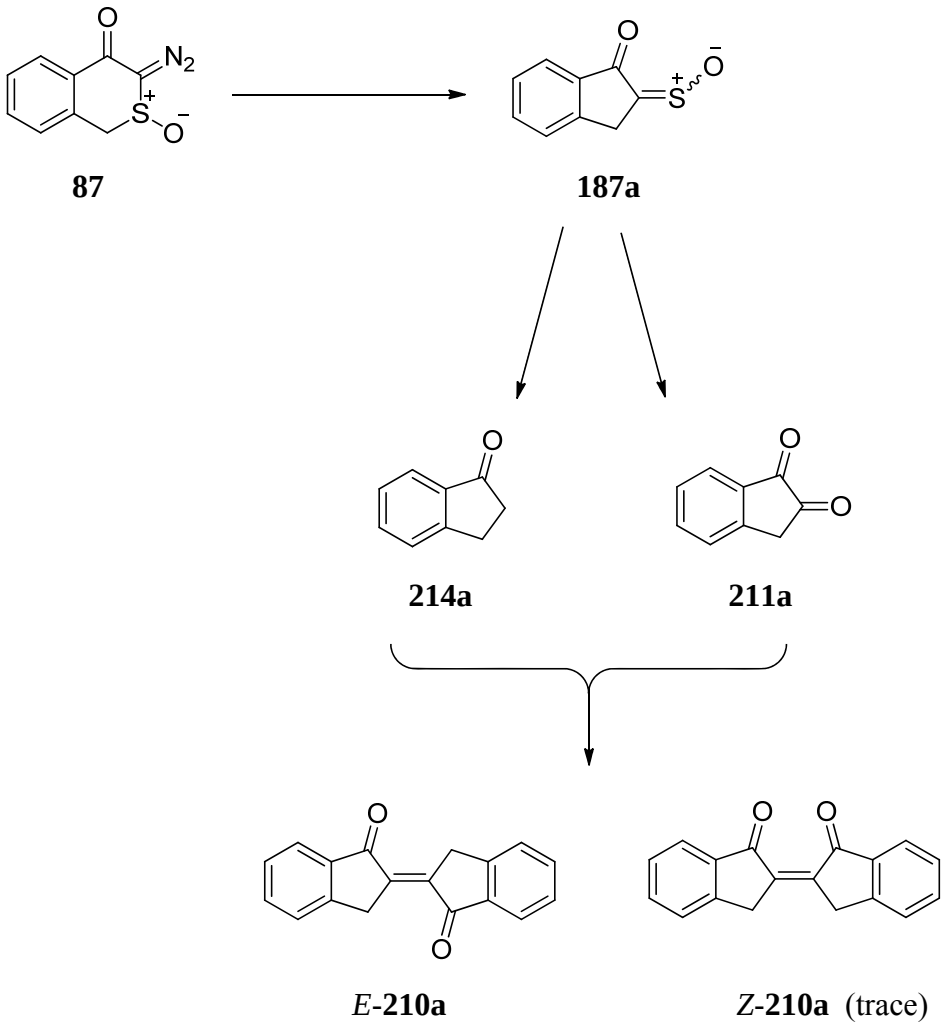
An examination of the literature revealed a significant paper by House, who described an attempted condensation of indanedione **211a** with methyl vinyl ketone.[162] However, the product obtained was the self-condensation product **230** which readily formed *via* an aldol condensation in the presence of pyridine (Scheme 2.135). The authors were able to repeat the same reaction in the absence of methyl vinyl ketone to confirm the self-condensation.



231 **211a** **230**

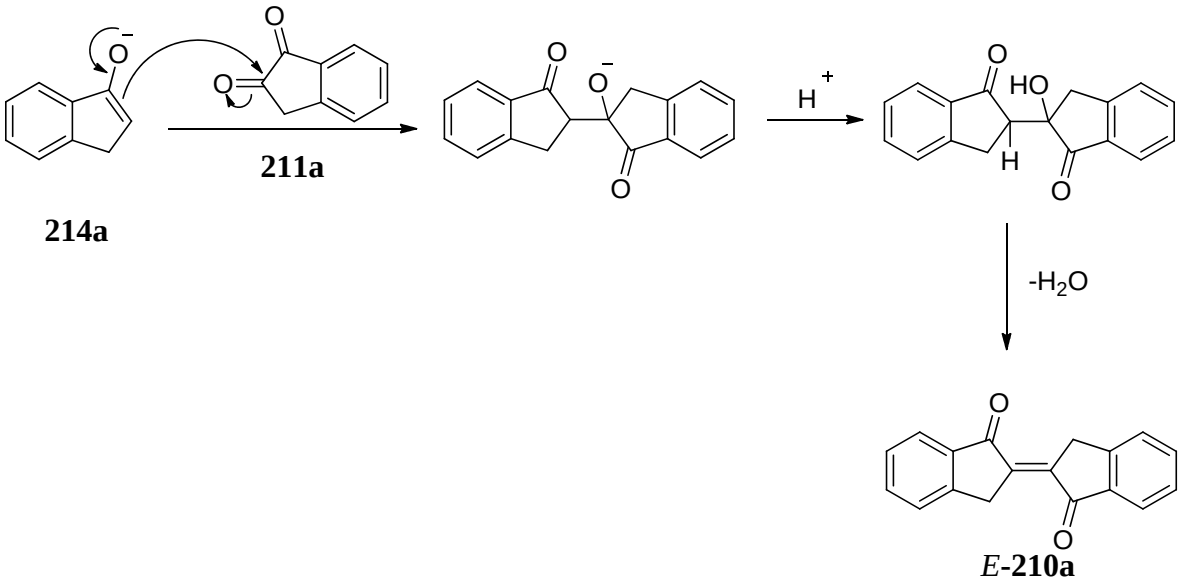
Scheme 2.135

An aldol condensation between the indanedione **211a** and the indanone **214a** could be envisaged in a similar reaction, with formation of the alkene dimer *E*-**210a** and a trace amount of the *Z*-isomer *Z*-**210a** (Scheme 2.136).



Scheme 2.136

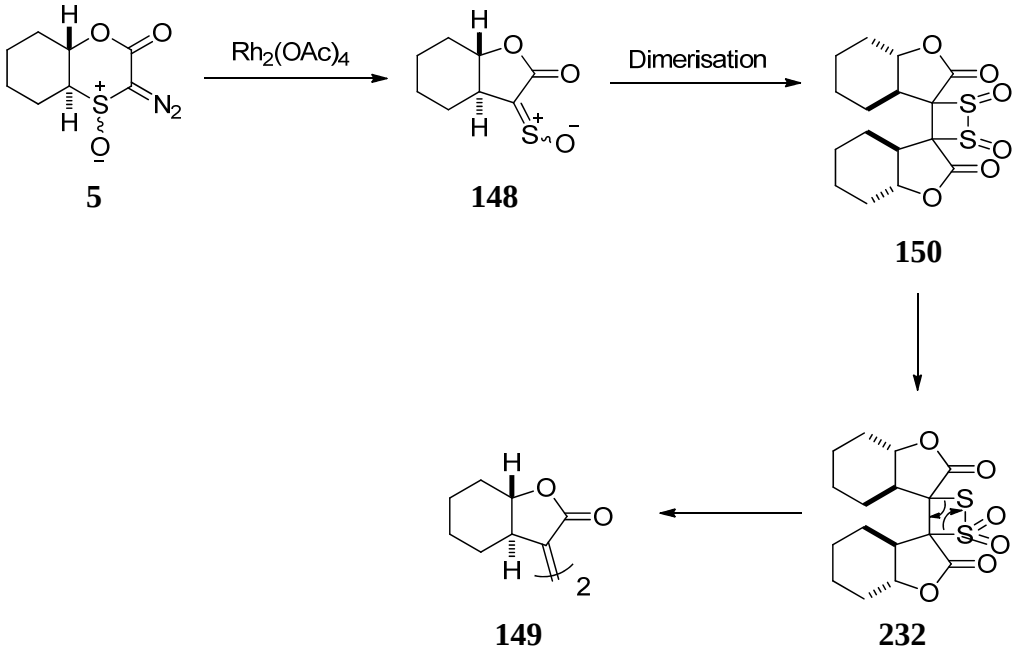
Trace amounts of the indanone **214a** were detected in the ^{1}H NMR spectra of the crude products. The key question is whether the transformation of **211a** to *E*-**210a** can be explained due to the presence of the indanone **214a** as a minor component in the reaction mixture, or alternatively as a decomposition product of **211a** through an alternative pathway. A proposed mechanism of formation for *E*-**210a** is illustrated in Scheme 2.137.



Scheme 2.137

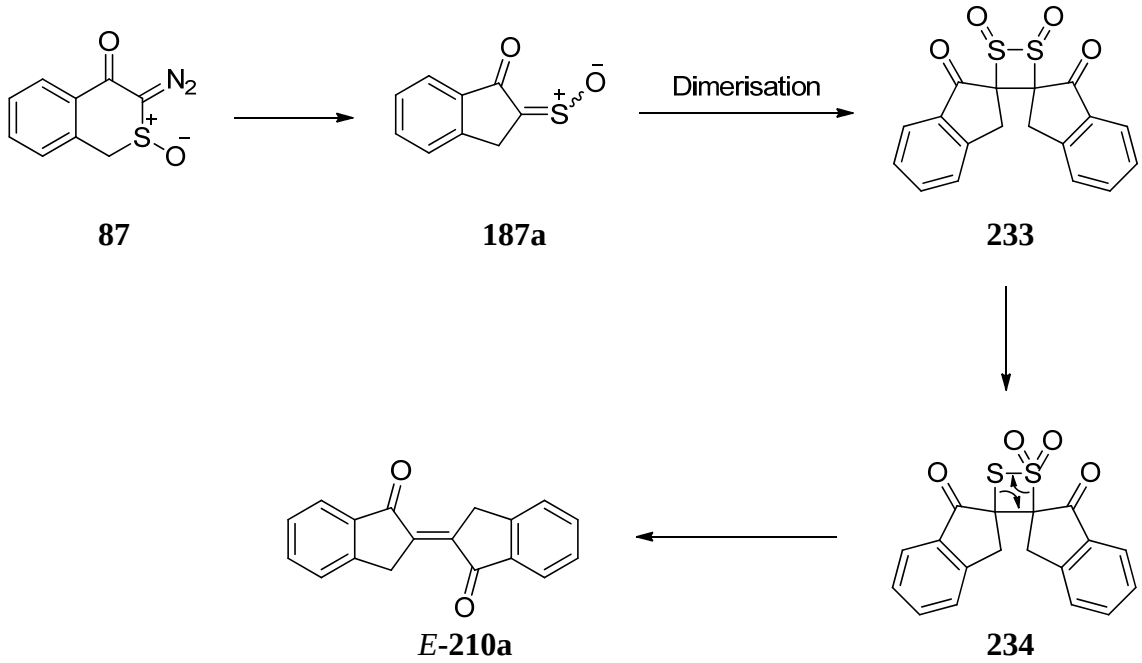
However, at this stage, the mechanistic pathway outlined above remains to be confirmed as the amounts of the dimer *E*-**210a** formed cannot be definitively correlated with the loss of the indanedione **211a**.

An alternative mechanistic pathway based on our recent results may be that dimerisation occurs *via* the α-oxosulfine **187a**. Interestingly, Kelleher suggested a mechanism for the dimerisation of the lactone based α-diazosulfoxide **5**.[10,103] Dimerisation of the α-oxosulfine **148** gives the pentacyclic intermediate **150**. This intermediate disproportionates to **232** which fragments to give the alkene dimer **149** (Scheme 2.138).



Scheme 2.138

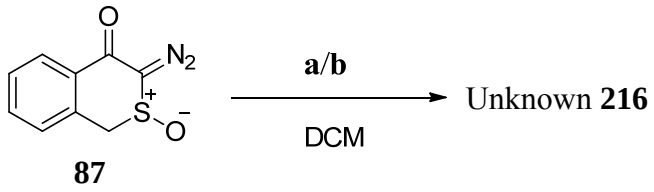
This provides an alternative pathway towards the alkene dimer *E*-**210a**, with dimerisation of the α-oxosulfine **187a** to the pentacyclic intermediate **233** as shown in Scheme 2.139. Alternatively, the pathway to *E*-**210a** may proceed *via* 1,3-dipolar addition, rather than [2+2] addition (Scheme 1.2).



Scheme 2.139

2.11.4 Additional decomposition studies

A number of additional studies carried out with the α-diazosulfoxide **87** provided unexpected results which warrant discussion here. Two transition metal catalysed reactions which were undertaken with **87** resulted in the isolation of an unexpected compound (entries 11 and 12, Table 2.18). Decomposition of **87** in the presence of 1 mol% rhodium(II) acetate or copper in dichloromethane gave a brown oil which was purified by chromatography to give an unidentified compound **216** as a yellow oil. Interestingly, while this result was reproducible for the reaction conditions described in Scheme 2.140, **216** was not detected in the crude spectra of any other reactions undertaken.

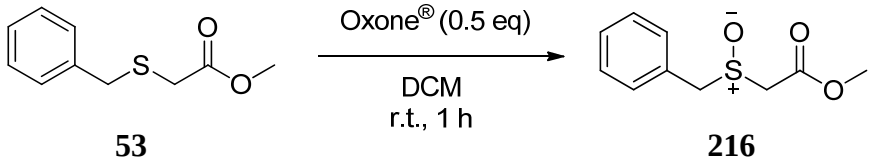


87

a = $Rh_2(OAc)_4$, Δ, o/n
b = Cu(0), Δ, 48 h

Scheme 2.140

A number of distinctive spectral features for this compound allowed us to suggest a credible structure for **216**. Firstly, the carbonyl stretching frequency in the IR spectrum was visible as a strong band at 1719 cm^{-1}, possibly indicating an ester functionality, rather than a ketone. Further evidence for this was obtained from the quaternary carbonyl which was visible at 165.7 ppm in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum obtained appeared to show one compound, which contained a number of distinctive signals, notably, two AB quartets and a CH_3 singlet characteristic of a methyl ester at 3.78 ppm (Figure 2.49). It was also worth noting that the aromatic protons were visible as a narrow multiplet in the region 7.32-7.41 ppm and that there were only three aromatic CH signals visible in the ^{13}C NMR spectrum. It is thus suggested that ring opening occurred, to give the sulfoxide **216** as a monosubstituted aromatic compound. Finally, the parent molecular ion peak $[M+H]^+$ was detected in the nominal mass spectrum at 213. The structure of **216** is given in Figure 2.49 and was confirmed by preparing an authentic sample *via* sulfoxidation of the ester **53** (Scheme 2.141).



53 **216**

Scheme 2.141

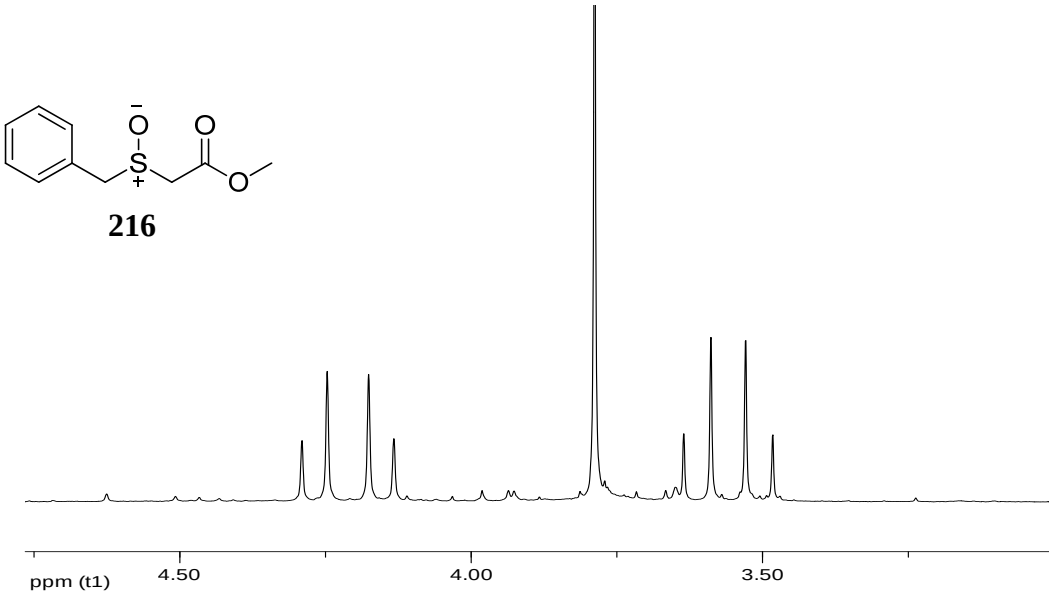
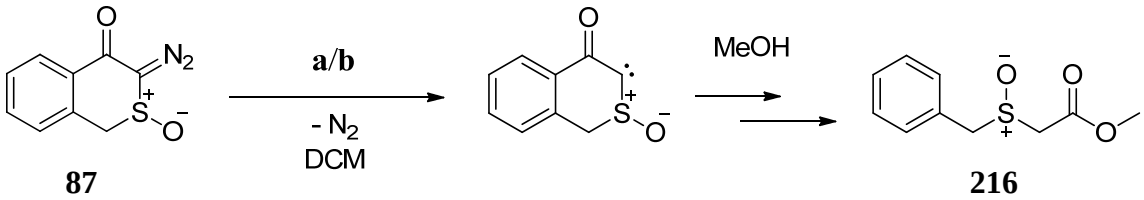


Figure 2.49 *Distinctive ^{1}H NMR signals (300 MHz, $CDCl_3$) for **216***

The isolation and characterisation of **216** represents an unexpected result. The decomposition of the α-diazosulfoxide **87** *via* reductive ring-opening of the cyclic ketone, instead of the expected Wolff rearrangement mechanism, has not been previously reported for α-diazosulfoxides (Scheme 2.142). Furthermore, the formation of the methyl ester moiety indicates that the solutions may have been contaminated with a source of MeOH. While cleavage of the C-C bond *via* a Wolff-type rearrangement could potentially be envisaged, it is not clear how this would lead to reductive cleavage at the aryl ring.

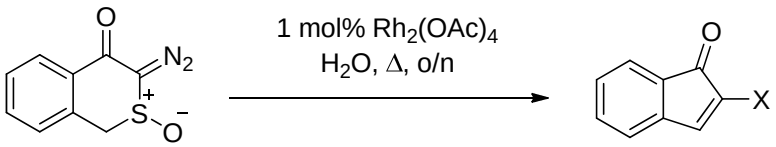


87 **216**

a = $Rh_2(OAc)_4$, Δ, o/n
b = Cu(0), Δ, 48 h

Scheme 2.142

There has been some success within the group with OH insertion reactions with α-diazocarbonyl compounds.[55] We were interested to see whether OH insertion could be facilitated with the α-diazosulfoxides in this work. The α-diazosulfoxide **87** was stirred as a suspension in the presence of 1 mol% rhodium(II) acetate in water under reflux overnight (entry 10, Table 2.18). The crude product was isolated as an oily brown solid and was purified by chromatography to give a white solid. The product was quite polar, with low solubility in deuterated chloroform. After purification by chromatography, it was possible to isolate a pure sample of an unknown compound **215** as the only product eluted from the column, and the spectroscopic data obtained has led to a number of conclusions concerning the structure of this compound. The core structure of the compound is tentatively assigned as shown in Scheme 2.143.



87 *unknown* **215**

Scheme 2.143

Firstly, the carbonyl stretch present at 1686 cm^{-1} in the IR spectrum is indicative of an α,β-unsaturated cyclic ketone. There was also an absorption at ~3400 cm^{-1}, possibly corresponding to an alcohol functional group. The ^1H NMR spectrum only shows the presence of signals in the aromatic region of 7.17-8.47 ppm (Figure 2.50). A deshielded ^1H NMR singlet at 8.47 ppm indicates the presence of an unsaturated system in conjugation with the aromatic ring. Further ^{13}C DEPT and

correlation studies show that this singlet does not interact with the four aromatic signals.

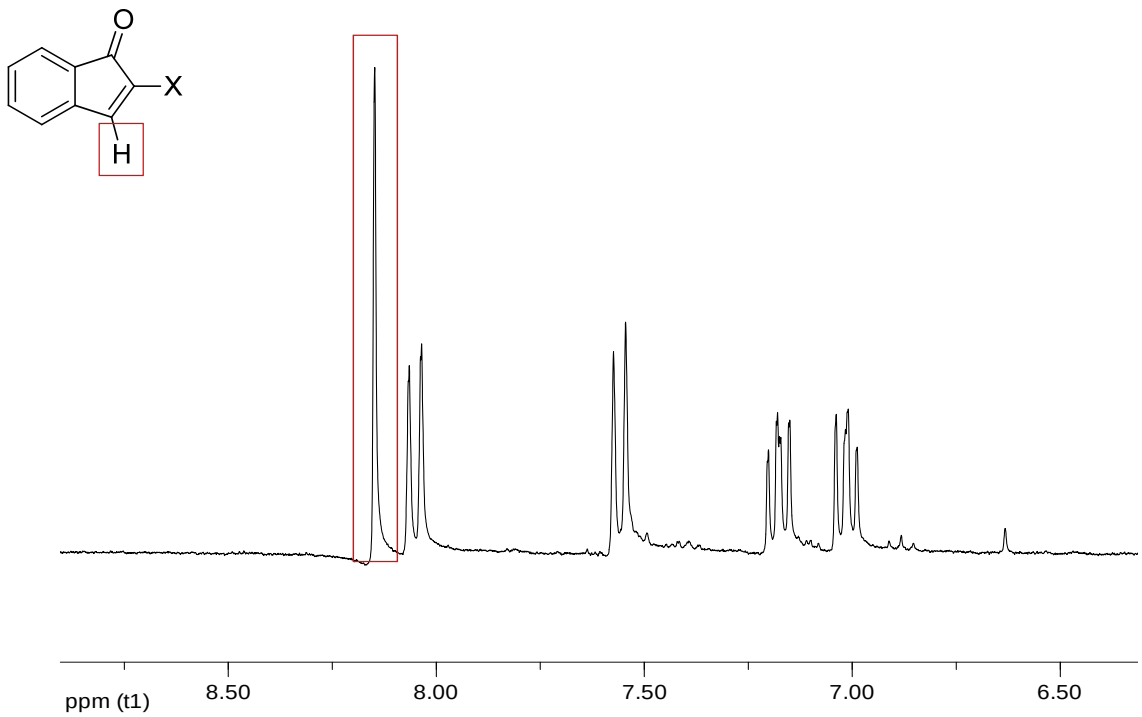
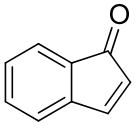


Figure 2.50 *^{1}H NMR spectrum (300 MHz, DMSO) of the unknown product **215***

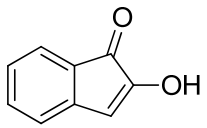
Mass spectrometric analysis of **215** did not result in a parent molecular ion being isolated, and indeed, fragmentation was not extensive. A fragment peak of 130 was detected however, which corresponds to an empirical formula of C_9H_6O. This agrees with the assignment that **215** contains the unsaturated structure shown in Figure 2.51. Although **215** could not be obtained in a completely pure state, and so an accurate microanalysis was not obtained, elemental analysis did indicate the absence of sulfur from the compound.



$C_9H_6O = 130$

Figure 2.51

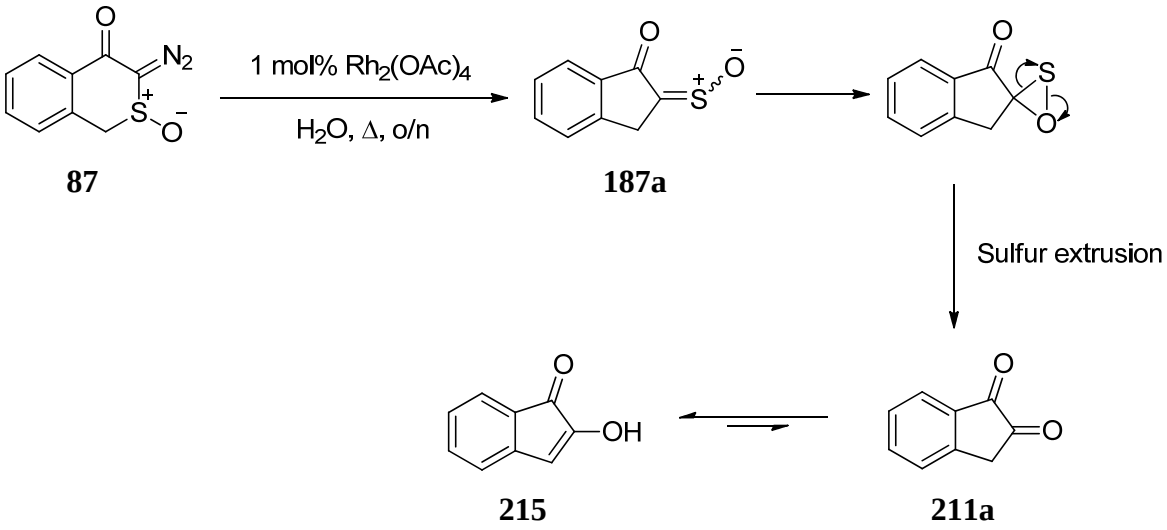
Due to the polar nature of **215** (the compound readily dissolved in DMSO), one possible structure which was considered is that of the enol **215** (Figure 2.52). It should be noted however, that no OH singlet was observed in the ^{1}H NMR spectrum.



215

Figure 2.52 *Suggested structure for the unknown decomposition product **215***

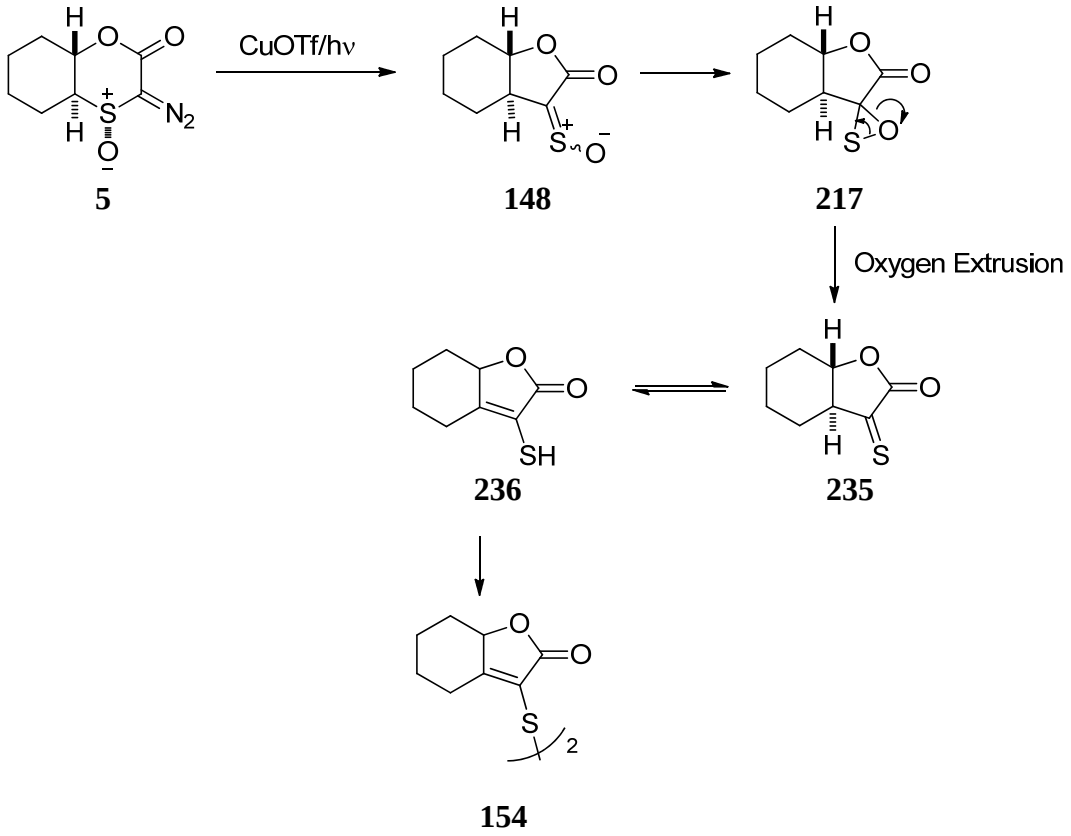
The proposed mechanism of formation for the indanedione **211a**, *via* sulfur extrusion, was discussed above (Scheme 2.130). In this case however, the effect of the water solvent system could then result in tautomerisation of the indanedione **211a** to the enol **215**, as illustrated in Scheme 2.144.



87 **187a** **215** **211a**

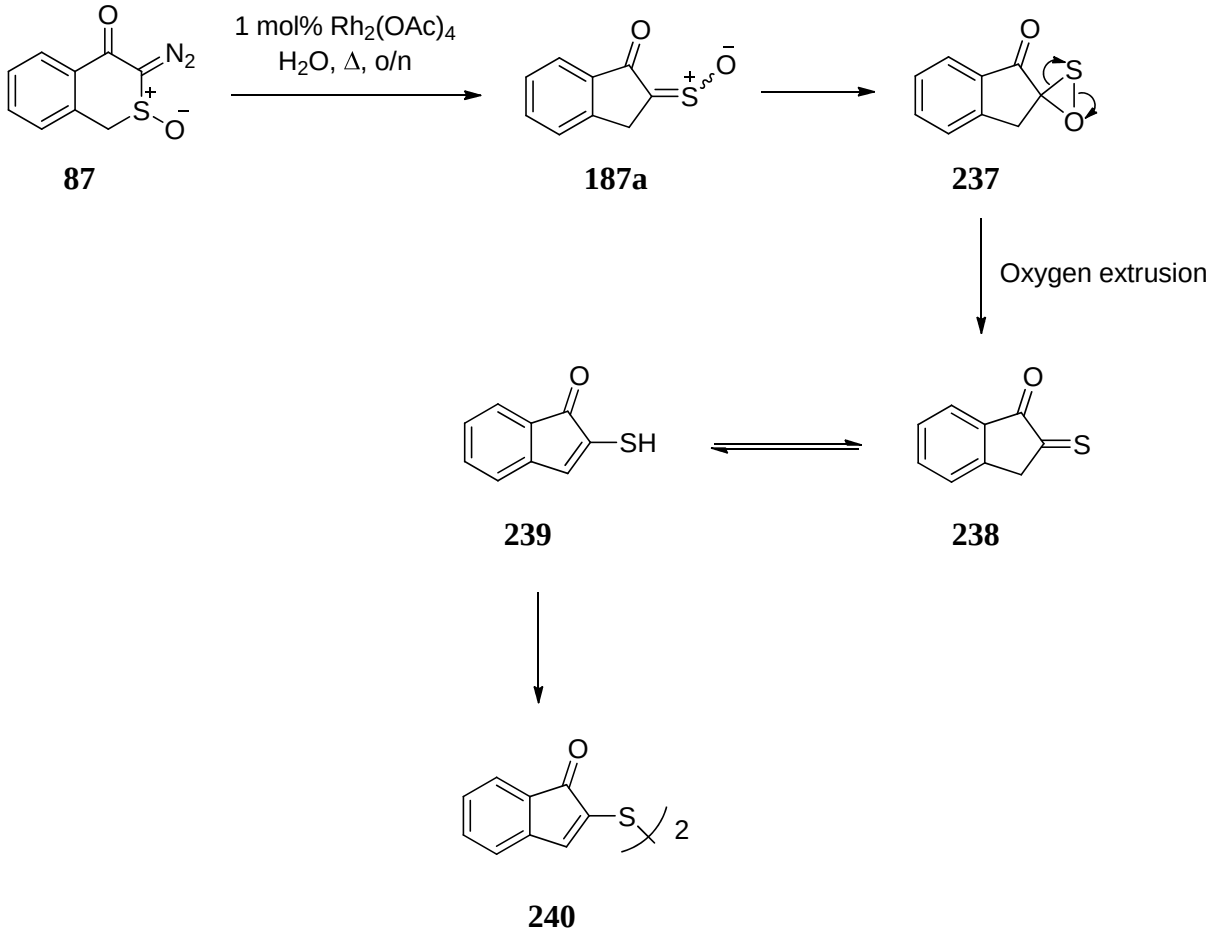
Scheme 2.144

Another possibility is that oxygen extrusion from the oxathiirane intermediate occurred, resulting in disulfide formation. Collins identified the disulfide **154** and proposed the mechanism described in Scheme 2.145, *via* electrocyclisation of the α-oxosulfine and oxygen extrusion from the oxathiirane ring **217**. Tautomerisation of the thioketone **235** to the thiol **236** is believed to facilitate dimerisation to the disulfide **154**.



Scheme 2.145

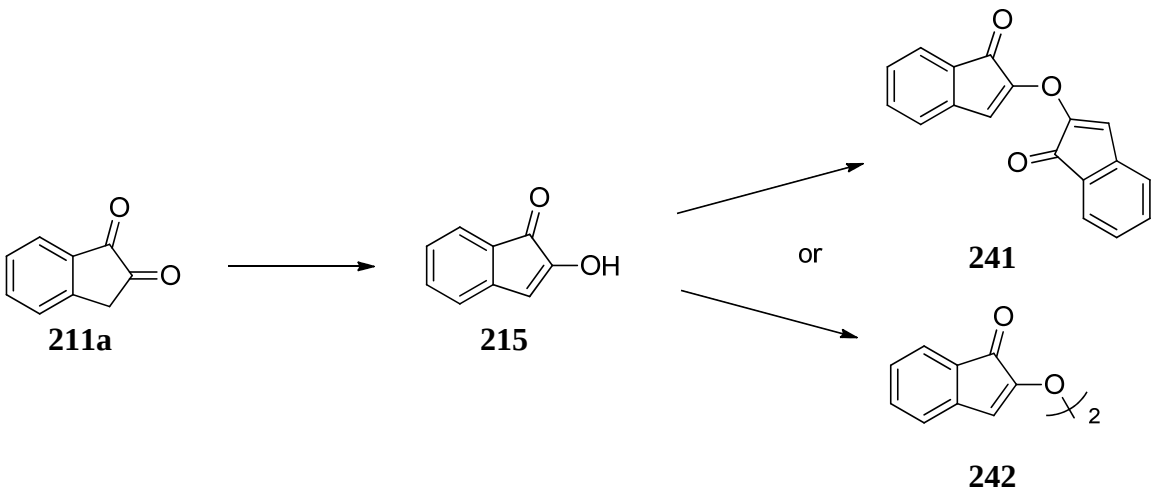
Following this precedent, formation of the disulfide could occur *via* oxygen extrusion from the oxathiirane intermediate **237**. Tautomerism of the thioketone **238** would give the thiol **239** which could also result in dimerisation to **240** (Scheme 2.146).



Scheme 2.146

A sample of the compound **215** was submitted for microanalysis. Although an accurate elemental data could not be obtained, there was no evidence found for the presence of sulfur in the compound, thus appearing to exclude the possibility of disulfide **240** formation. It appears more likely that **215** contains oxygen, although conclusive evidence has not been obtained at this stage.

Alternatively, dimerisation of the indanedione **211a** *via* the enol **215** to give either the dimeric ether **241** or the dimeric peroxide **242** as very polar solids may have occurred (Scheme 2.147). Although it is considered unlikely that the peroxide **242** would exist as a stable dimer, at this stage there is insufficient evidence is available to rule out either pathway of dimerisation.



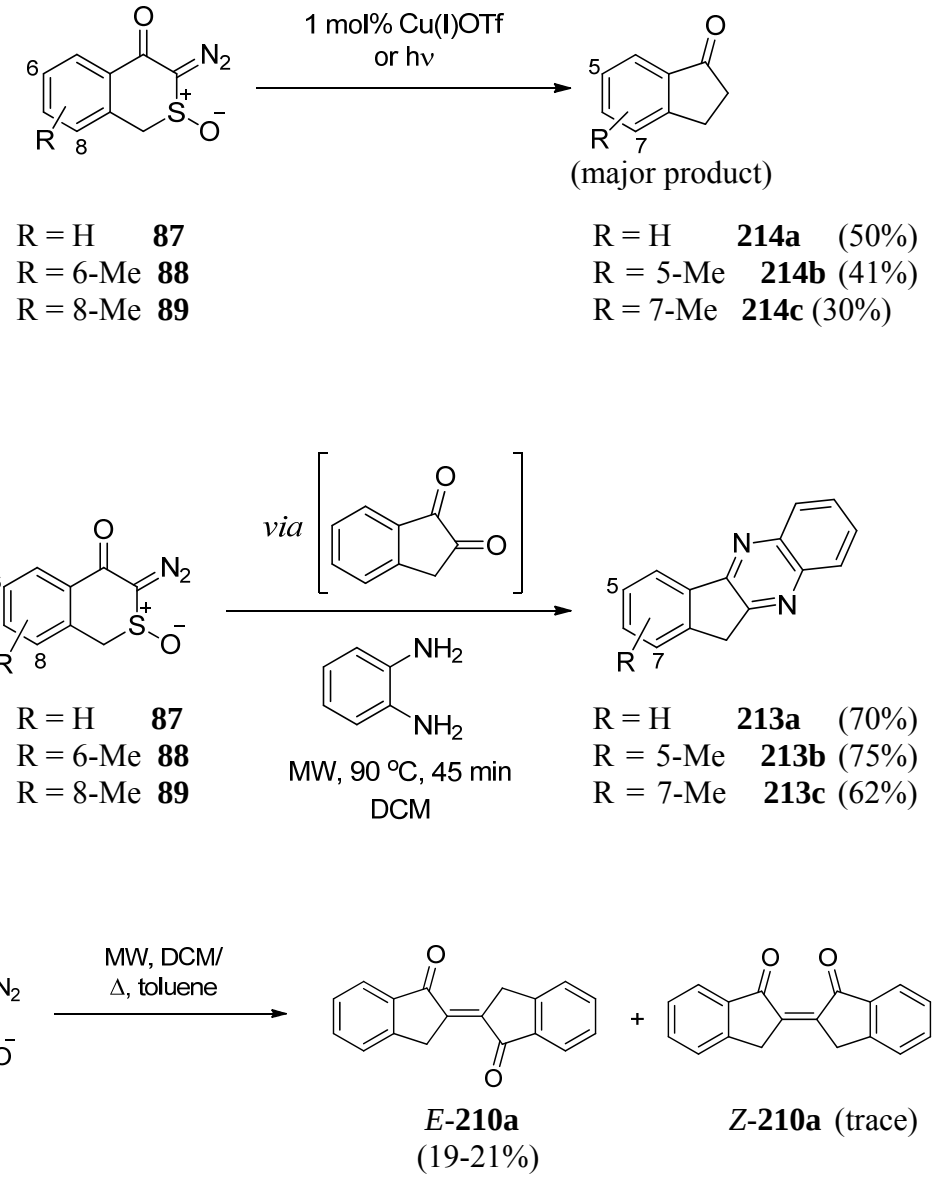
Scheme 2.147

2.11.5 Conclusions

The results discussed in this section serve to highlight the scope of reactivity of α-diazo-β-keto sulfoxides and α-oxosulfines. It has been shown that the ketone based α-diazosulfoxides **87-89** under various decomposition conditions (transition metal catalysis, photolysis, microwave) lose nitrogen to form carbene intermediates which then undergo Wolff rearrangement to form α-oxosulfines. These α-oxosulfines decompose readily to form a variety of other products, many of which can be isolated and characterised.

In the absence of a diene trap, the α-oxosulfines follow different reaction pathways depending on the conditions under which the decomposition took place. There are a number of patterns which can be observed in the chemistry of the α-oxosulfine decompositions, and it is worth briefly discussing them here. It can be stated that indan-1-ones **214a-c** were the major products formed on the decomposition of the α-diazosulfoxides under copper triflate catalysed and photolysis conditions. Each of the α-diazosulfoxides **87-89** gave the corresponding indan-1-one as the major product under these conditions. The indanediones were formed as the major products under microwave conditions and under reflux in the presence of rhodium(II) acetate. The compounds were unstable and difficult to isolate, but could be trapped as quinoxaline condensation products in good yields. Alkene dimers *E*-**210a** and *Z*-**210a** were isolated, which may have formed on

dimerisation of the indanedione **211a** *via* a proposed aldol condensation, or alternatively *via* sulfine **187a** dimerisation. A summary of the optimised routes towards these compounds is illustrated in Scheme 2.148.



Scheme 2.148

These patterns of reactivity seen with the ketone derived α-diazosulfoxides were different to those seen with the lactone α-diazosulfoxides, indicating the effect of variation of substituents on the carbene and/or the α-oxosulfine reactivity.

One or two unusual results were highlighted and discussed. Notably, the α-diazosulfoxide **87** decomposed *via* a ring-opening mechanism to give the sulfoxide **216** in an unexpected reaction pathway which has never before been reported for α-

diazosulfoxides. An unknown compound tentatively assigned as the enol **215** was obtained on decomposition of α-diazosulfoxide **87** under rhodium(II) acetate catalysed conditions in water.

2.12 Biological Evaluation

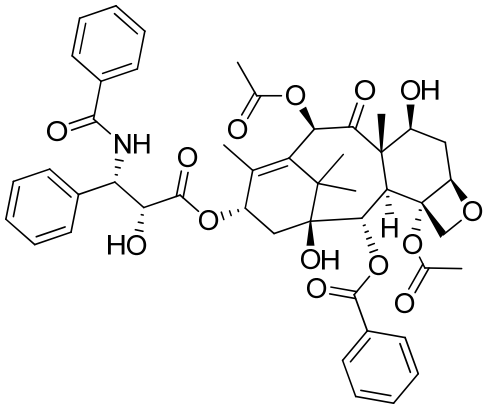
2.12.1 Introduction to NCI-60 Cancer Cell-line Screen Programme

The U.S National Cancer Institute's Developmental Therapeutics Programme (DTP) 60 human tumour cell line service (NCI-60) was developed in the late 1980's, as a strategic high-throughput screening tool for *in vitro* anti-cancer drug activity. Cytotoxicity data for in excess of 100,000 compounds across diverse cancer lines (lung, renal, colorectal, ovarian, breast, prostate, central nervous system, melanoma and hematological malignancies) has been classified, following this approach. This project is designed to screen up to 3,000 compounds per year for potential anticancer activity. Since its establishment, DTP has played a vital role in the discovery and development of more than 40 U.S. licensed chemotherapeutic agents, with the rest coming directly from the pharmaceutical industry. Some examples of these anticancer agents, developed with DTP involvement are shown in Table 2.20, adapted from the NCI website.[163-169]

Table 2.20 Anticancer agents developed with DTP involvement

Year	Drug	Year	Drug	Year	Drug
2010	Eribulin	**1988**	Ifosfamide	**1970**	Mitramycin
2009	Romidepsin	**1987**	Mitoxantrone	**1969**	Procarbazine
2004	Erbitux	**1983**	Etoposide	**1967**	Hydroxyurea
2003	Velcade	**1982**	Streptozotocin	**1966**	Thioguanine
1998	Ontax	**1979**	Daunorubicin	**1964**	Actinomycin D
1996	Topotecan	**1978**	Cisplatin	**1963**	Vincristine
1995	All-t-retinoic acid	**1977**	BCNU	**1962**	Fluorouracil
1992	Taxol	**1976**	CCNU	**1961**	Vinblastine
1991	Pentostatin	**1975**	Dacarbazine	**1961**	Chloroambucil
1990	Hevamisole	**1974**	Adriamycin	**1959**	Cyclophosphamide
1989	Carboplatin	**1973**	Bleomycin		

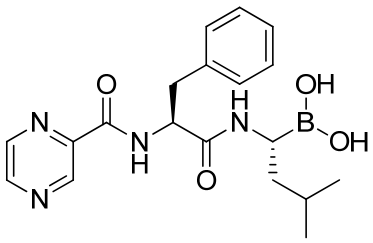
Notably, the above list contains Paclitaxel **243**, a mitotic inhibitor which is one of the most widely prescribed anticancer drugs on the market to date. Paclitaxel **243**, a natural product, was first discovered by researchers working under a joint U.S. Department of Agriculture-National Cancer Institute grant. It was a DTP contractor who formulated the drug for use in clinical trials. Paclitaxel **243** is now used to treat patients with lung, ovarian, breast, head and neck cancer, and advanced forms of Kaposi's sarcoma. Paclitaxel **243** is also used for the prevention of restenosis (Figure 2.53).[170-172]



243

Figure 2.53 *Paclitaxel (Taxol®) **243***

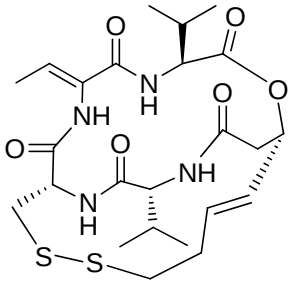
Bortezomib **244** is another DTP success story, which was screened and formulated by DTP in cooperation with its commercial sponsor (Figure 2.54). Approved by the Food and Drug Administration (FDA) in 2003, it was the first treatment in more than a decade to be approved for patients with multiple myeloma. In multiple myeloma, complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease. It took only 8 years from initial NCI-60 hit identification of the novel proteasome inhibitor bortezomib **244** - a COMPARE-negative (distinct anti-cancer mode of action) agent - in 1995 to full FDA approval.[167,168,173-177]



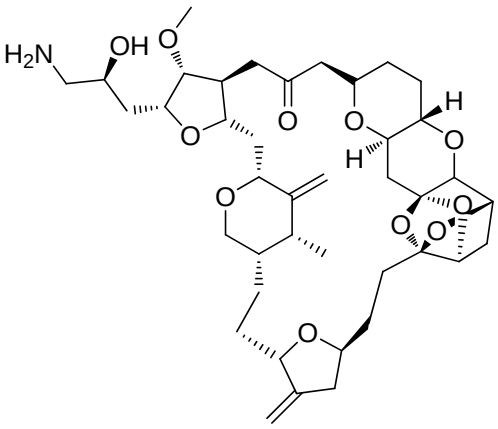
244

Figure 2.54 *Bortezomib (Velcade®) **244***

More recent successes include romidepsin **245** (approved in 2009 for cutaneous T-cell lymphoma, Figure 2.55),[178,179] and eribulin **246** (approved in 2010 for metastatic breast cancer, Figure 2.55).[180,181]



245



246

Figure 2.55 *Left: romidepsin (Istodax®) **245**, right: eribulin (Halaven®) **246***

The DTP programme has been involved in the discovery or development of more than 70% of the anticancer therapeutics on the market today.[164-166,182] The patterns of relative drug sensitivity and resistance are generated with standard anticancer drugs using three response parameters: GI_{50} (concentration at which growth of 50% of cells present is fully arrested), TGI (concentration for total inhibition or 0% cell growth) and LC_{50} (lethal concentration causing death in 50% of cells originally present).[165,182-185]

In this work, a series of novel 3-aminofuran-2(5*H*)-ones were generated from nucleophilic addition of aromatic amines with lactone based α-oxosulfines (Section 2.9.2). A series of novel benzofused dihydro-2*H*-thiopyran *S*-oxides were also

prepared from [4+2] cycloadditions of 2,3-dimethyl-1,3-butadiene with α-oxosulfines (Section 2.10.2). Fulfilling non-duplication criteria prescribed for NCI-60 compound selection, the NCI normally choose a selection of compounds as representative chemotypes for biological screening in the Developmental Therapeutics Programme. In this instance, all nine submitted compounds were accepted. These compounds were successfully investigated for initial one dose (10 μM) tumour cell line activity, and the pattern of quantifiable growth inhibition of these agents on the NCI-60 human tumour cell line panel is outlined herein.

2.12.2 Evaluation of NCI-60 Cancer Cell-line Screen Results

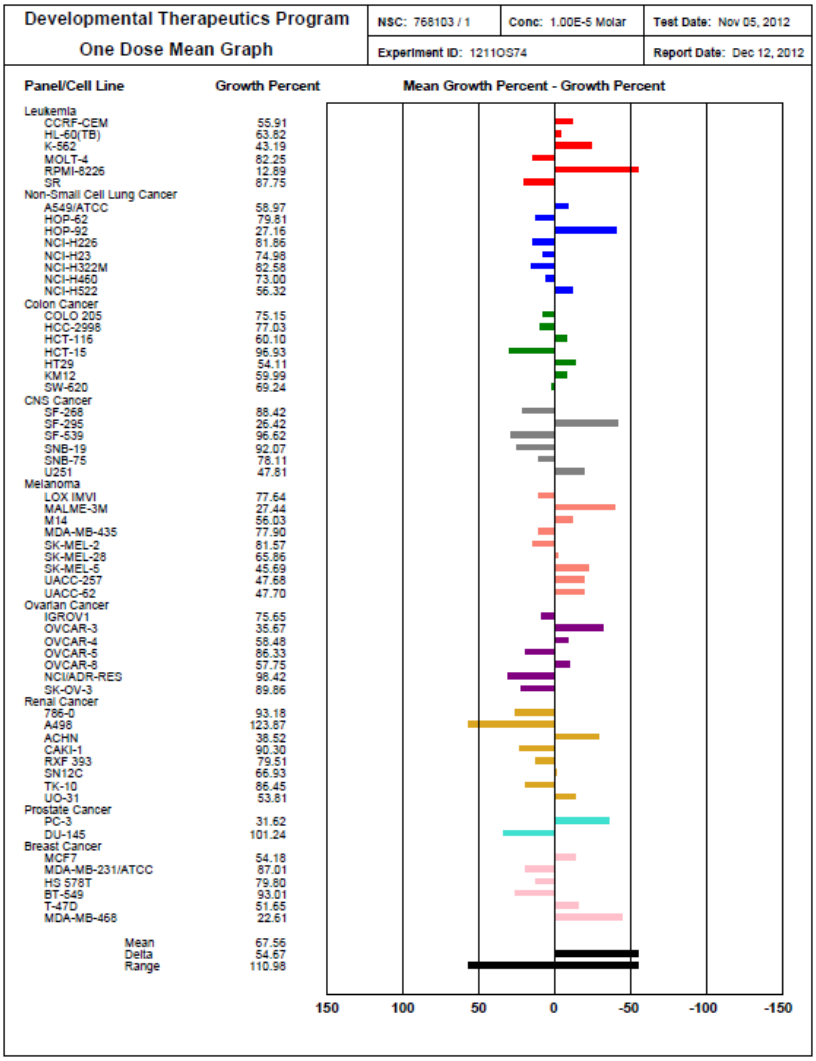
2.12.2.1 NCI-60 method of screening

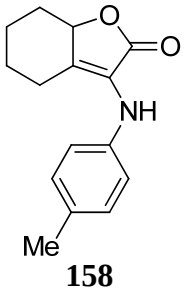
The reported methodology used for evaluation of growth inhibition within the NCI-60 cancer cell-line screen programme involves a number of steps. A 4 mM stock solution with dimethylsulfoxide (DMSO) is initially prepared, prior to the dilution into a RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine, followed by exposure to each cell line previously cultured for 24 hours.[167,173] After 48 hour incubation, sequential steps of media removal, cell fixation and sulforhodamine B (SRB) staining is performed, prior to 1% acetic acid wash, and air drying of these plates. The dye is dissolved in Tris buffer, and the colorimetric growth inhibition-dependent absorbance at 515 nm is measured and calibrated against the DMSO control.[167,186]

In vitro activity of each compound in the human tumour cell lines is displayed in the form of a 'mean graph', consisting of a series of horizontal bar graphs representing units of nominal growth-percent, deviating from the arithmetic mean growth for the entire 60 cell line panel ('0'). In each case, graphs which extend to the right (-) signify more selective cytotoxicity or positive growth inhibition, while those which extend to the left (+) of centre line indicate a chemoprotective or non-cytotoxic effect on individual cell lines. It is worth noting that a mean growth inhibition value of over 50% fits the necessary NCI-60 criteria for five dose screening. An example of a 'mean graph' is shown in Figure 2.56. Patterns of total

panel activity may also be correlated with those of over 100,000 compounds within a NCI-60 database, to reveal key mechanisms of action.

Following initial NCI-60 screening, compounds which exhibit an interesting pattern of inhibition are evaluated by the Data Review Committee, prior to a five dose investigation. This screen is performed by a 5 × 10 fold serial dilution of a 100 μM stock solution prepared at the same time as the one dose sample. The results are displayed on a graph showing the three response parameters; GI_{50}, TGI and LC_{50}. Following recommendation by the Biological Review Committee, compounds which exhibit useful activity profiles may progress to *in vivo* hollow-fibre testing in mouse models and further xenograft assays, with successful drug candidates eventually authorised by the Drug Development Group to enter NCI clinical development.





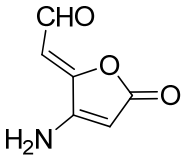
158

Figure 2.56 NCI-60 cancer cell-line screen 'mean graph' of **158**

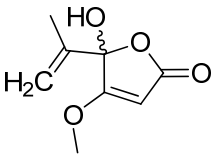
2.12.2.2 Biological Activity of 3-aminofuran-2(5H)-ones

The synthesis of 3-aminofuran-2(5*H*)-ones generated from α-oxosulfines in this work represents a novel route towards an important class of heterocyclic compounds. Furanone derivatives have been shown to exhibit different biological activities such as antibacterial, antifungal, antiviral, anticancer, anti-tubercular, and

anti-inflammatory activities.[111-113] They can thus be used as precursors in the discovery of new drug molecules. Furanone moieties have been incorporated into a wide variety of therapeutically interesting drug candidates such as Basidalin **247** and Penicillic acid **248**, butenolide natural products which show antitumour activity (Figure 2.57).[187,188]



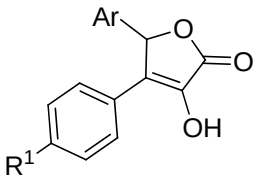
Basidalin
247



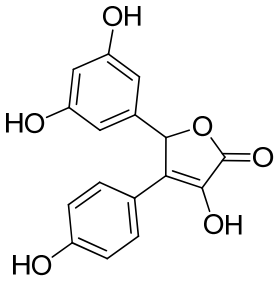
Penicillic acid
248

Figure 2.57

Bailly *et al.* prepared a series of 3-hydroxy-furan-2(5*H*)-ones substituted at the 4- and 5- positions by aryl groups **249** (Figure 2.58).[113] The antiproliferative activity of these furanones was evaluated against the human prostate carcinoma PC-3 cell line. One derivative in particular, 3-hydroxy-5-(3,5-dihydroxyphenyl)-4-(4-hydroxyphenyl)-furan-2(5*H*)-one **250**, exhibited potent antiproliferative activities (Figure 2.58).



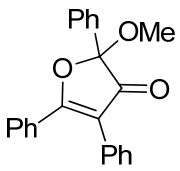
249



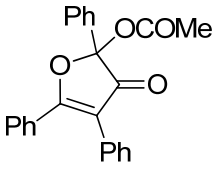
250

Figure 2.58

Rappai *et al.* synthesized two triaryl substituted 3-substituted-furan-(2*H*)-ones and their antitumor activity was evaluated.[112] The anti-proliferate effect of 2,3-dihydro-3-oxo-2,4,5-triphenylfuran-2-yl acetate **251** and 2-methoxy-2,4,5-triphenylfuran-3(2*H*)-one **252**, was studied using DLA cells. Both *in vitro* and *in vivo* experiments showed that the presence of these compounds significantly reduced the proliferation of DLA cells.



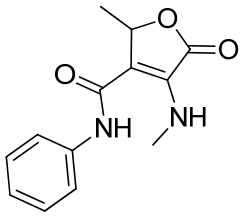
251



252

Figure 2.59

The 3-aminofuran-2(5*H*)-ones synthesised in this project are novel synthetic analogues of 3-aminofuran-2(5*H*)-ones which have been investigated as potential inhibitors of subgenomic hepatitis C virus RNA application in the replicon assay in liver cells.[111] The authors reported 2,5 dihydro-2-methyl-4-(methylamino)-5-oxo-*N*-phenylfuran-3-carboxamide **253** as the most active compound of the series. The closest analogue in the literature which exhibited biological activity was **253**. Although the electronic structure of this compound is quite different to our novel 3-aminofuran-2(5*H*)-ones, this report highlights the importance of screening for biological activity.

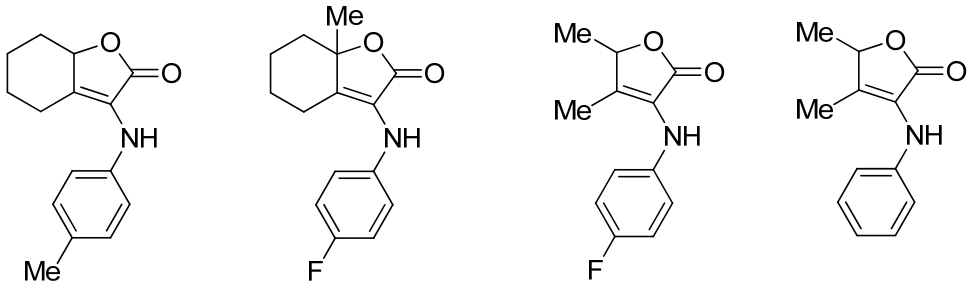


253

Figure 2.60

Recognising the potential of the novel 3-aminofuran-2(5*H*)-ones prepared within this project, it was decided to test a selection of these compounds across a range of cancer cell lines. Four compounds were chosen as representative chemotypes and submitted for NCI-60 cancer cell-line one dose screening to the Developmental Therapeutics Programme (Figure 2.61). We are interested to see how our novel 6,5-bicyclic furanone framework would behave in the anticancer studies, as an alternative to the usual diaryl derivatives **249**-**252** studied in the literature reported above.[113] The conformationally constrained 6,5-bicyclic system (**158**, **164**) could provide quite a unique steric interaction while maintaining the core furanone

and amino substituent activity as reported in the literature. It would also be interesting to compare activity on going from a bicyclic furanone system to a more flexible monocyclic system (**168**, **169**).



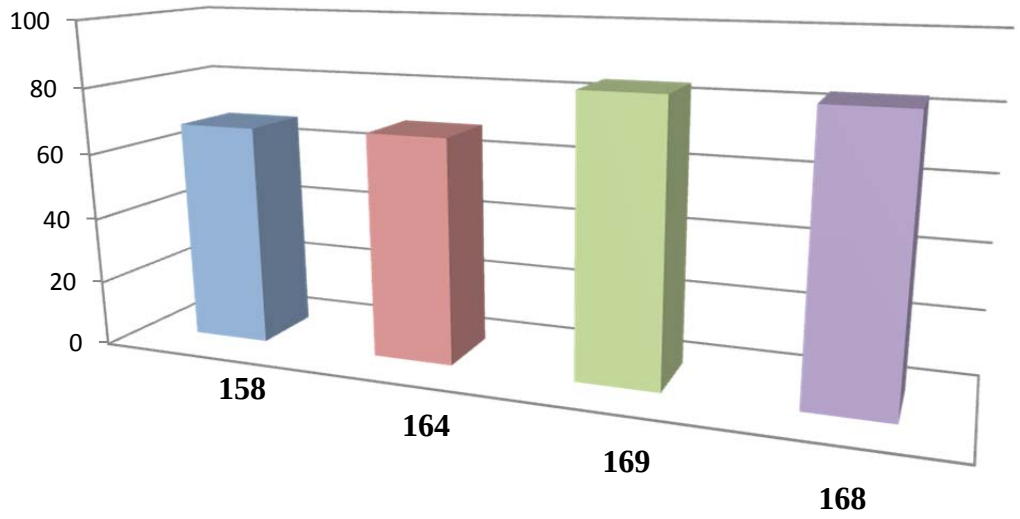
158 **164** **168** **169**

Figure 2.61 *Series of 3-aminofuran-2(*5H*)-ones submitted for NCI-60 screening in the Developmental Therapeutics Programme.*

The 3-aminofuran-2(5*H*)-ones displayed in Figure 2.61 were successfully investigated for initial one-dose (10 mM) tumour cell line activity, and the pattern of quantifiable growth inhibition of these agents on the NCI-60 human tumour cell line panel is outlined herein. It should also be noted that the bicyclic 3-aminofuran-2(5H)-one **158** exhibited a broad range of biological activity, and to our delight, has been chosen for five-dose screening by the NCI.

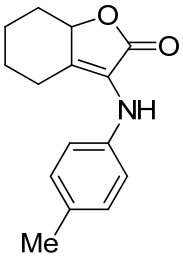
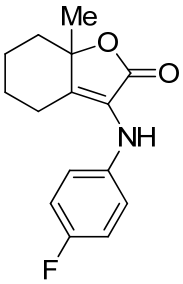
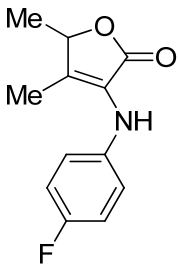
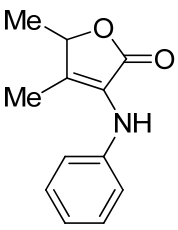
The one-dose mean graphs obtained for each of these compounds depicted in Figure 2.61 are presented in Appendix II. Evaluation of these one-dose mean graphs obtained for the 3-aminofuran-2(5*H*)-ones **158**, **164**, **168** and **169** revealed a number of interesting and distinctive patterns for biological activity. Particularly, the bicyclic and methyl bridgehead 3-aminofuran-2(5*H*)-ones **158** and **164**, which both contain the 6,5-bicyclic framework, demonstrated greater overall inhibition than the monocyclic *cis*-dimethyl 3-aminofuran-2(5*H*)-ones **168** and **169**. Graph 2.1 illustrates the enhanced growth inhibition of the 6,5-bicyclic 3-aminofuran-2(5*H*)-ones; the overall NCI-60 mean growth percent is plotted for each compound.

Graph 2.1 *Illustration of NCI-60 mean growth percent for the 3-aminofuran-2(5*H*)-ones **158**, **164**, **169** and **168**.*



The 3-aminofuran-2(5*H*)-ones exhibited distinctive biological activity for two cancer types in particular: leukaemia and melanoma. Interestingly, these compounds proved highly selective against leukaemia, revealing a remarkable pattern of growth inhibition for the six cancer cell lines. The mean growth percentage for each of the 3-aminofuran-2(5*H*)-ones remained in a similar range of 57-75%. The one-dose mean data for the six leukaemia cell lines tested is summarised in Table 2.21.

Table 2.21 One-dose screen of 3-aminofuran-2(5*H*)-ones (leukaemia cancer cell lines)

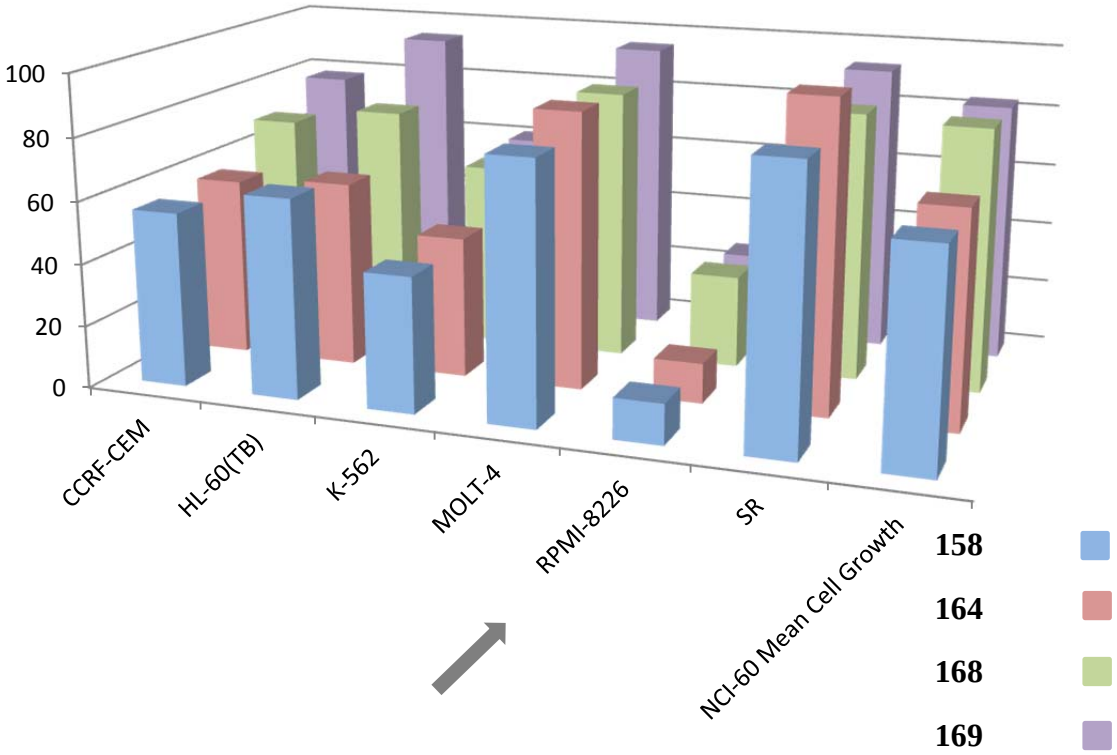
Entry	3-aminofuran-2(5*H*)-one	NCI-60 cell-lines	Tumour site	Growth percent*	Mean cell line growth
1	 **158**	CCRF-CEM	Leukaemia	55.91	57.63
		HL-60(TB)		63.82	
		K-562		43.19	
		MOLT-4		82.25	
		RPMI-8226		12.89	
		SR		87.75	
2	 **164**	CCRF-CEM	Leukaemia	57.37	60.23
		HL-60(TB)		59.56	
		K-562		45.12	
		MOLT-4		88.45	
		RPMI-8226		12.80	
		SR		98.07	
3	 **168**	CCRF-CEM	Leukaemia	69.84	67.80
		HL-60(TB)		75.48	
		K-562		59.21	
		MOLT-4		86.88	
		RPMI-8226		29.68	
		SR		85.70	
4	 **169**	CCRF-CEM	Leukaemia	78.25	74.62
		HL-60(TB)		94.30	
		K-562		60.92	
		MOLT-4		95.15	
		RPMI-8226		26.47	
		SR		92.64	

* Cultured cells were tested on RPMI 1640 medium at an initial compound concentration of 10 μM.

From evaluation of Table 2.21, it can be seen that the greatest inhibition of growth occurred in the RPMI-8226 cell line (highlighted), a multiple myeloma cell line. The bicyclic 3-aminofuran-2(5*H*)-one **158** and the methyl bridgehead 3-aminofuran-2(5*H*)-one **164**, especially, exhibited outstanding growth inhibitions to 12.80 and 12.89%, respectively. Interestingly, both of these compounds contain the 6,5-bicyclic system, while the *cis*-dimethyl monocyclic derivatives **168** and **169** displayed slightly lower inhibitions to 29.68 and 26.47%. Nevertheless, the positive selectivity of these 3-aminofuran-2(5*H*)-ones for leukaemic cancer evidenced in this screening process, and the RPMI-8226 cell line in particular, is encouraging and will be explored further in future work.

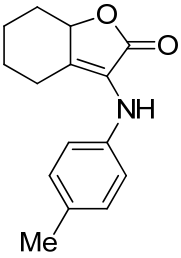
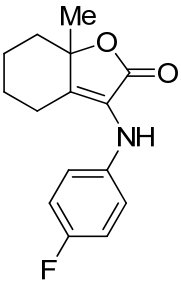
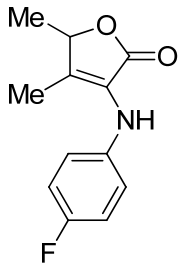
The remarkable selective inhibition exhibited in the RPMI-8226 cell line is clearly illustrated in Graph 2.2. The growth percent of the six leukaemia cell lines along with the NCI-60 mean growth are plotted for the 3-aminofuran-2(5*H*)-ones screened in this series.

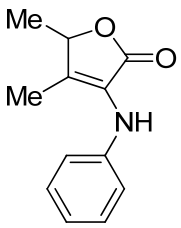
Graph 2.2 *Illustration of growth percent of six leukaemia cell lines and NCI-60 mean growth percent for 3-aminofuran-2(*5H*)-ones* ***158***, ***164***, ***168*** *and* ***169***.



Another distinctive pattern observed during the evaluation of these 3-aminofuran-2(5*H*)-ones was the inhibition of growth in melanoma cancer cell lines (Appendix II). Again, the 6,5-bicyclic 3-aminofuran-2(5*H*)-ones **158** and **164** exhibited much greater inhibition than the monocyclic *cis*-dimethyl derivatives **168** and **169**, although a similar pattern of inhibition throughout the nine melanoma cell lines can be observed for the four compounds. The one-dose mean data for the nine melanoma cell lines is summarised in Table 2.22. From evaluation of the results below, it is clear that inhibition of growth in the MALME-3M cell line is most prominent throughout the series, with a mean growth percentage for the 6,5-bicyclic 3-aminofuran-2(5*H*)-ones **158** and **164** to 27.44% and 17.51%, respectively.

Table 2.22 One-dose screen of 3-aminofuran-2(5*H*)-ones (melanoma cancer lines)

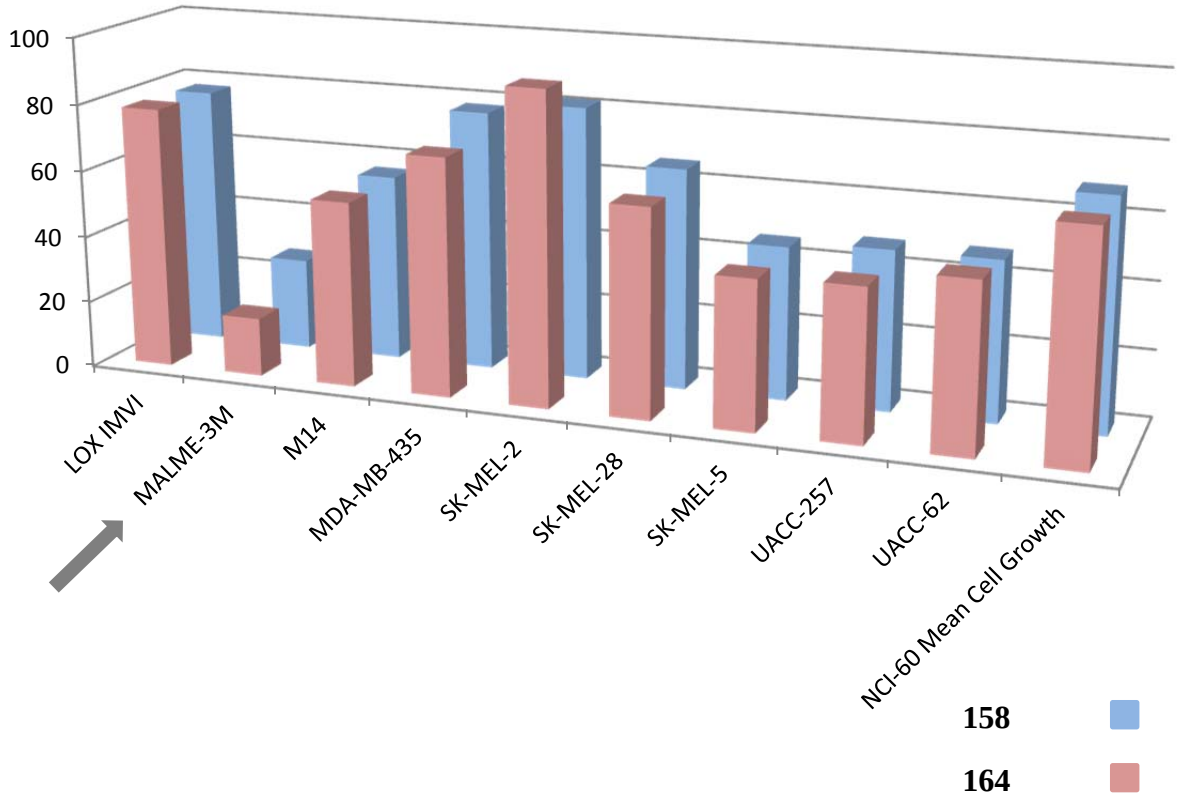
Entry	3-aminofuran-2(5*H*)-one	NCI-60 cell-lines	Tumour site	Growth percent*	Mean cell line growth
1	 **158**	LOX IMVI MALME-3M M14 MDA-MB-435 SK-MEL-2 SK-MEL-28 SK-MEL-5 UACC-257 UACC-62	Melanoma	77.64 27.44 56.03 77.90 81.57 65.86 45.69 47.68 47.70	58.61
2	 **164**	LOX IMVI MALME-3M M14 MDA-MB-435 SK-MEL-2 SK-MEL-28 SK-MEL-5 UACC-257 UACC-62	Melanoma	78.34 17.51 55.43 71.12 92.80 62.03 44.50 45.34 50.24	57.48
3	 **168**	LOX IMVI MALME-3M M14 MDA-MB-435 SK-MEL-2 SK-MEL-28 SK-MEL-5 UACC-257 UACC-62	Melanoma	90.29 53.01 79.62 98.82 101.08 84.70 71.09 81.04 72.33	71.64

4	 **169**	LOX IMVI	91.90	68.39
		MALME-3M	57.14	
		M14	75.69	
		MDA-MB-435	90.93	
		SK-MEL-2	95.39	
		SK-MEL-28	82.97	
		SK-MEL-5	66.64	
		UACC-257	80.15	
		UACC-62	70.10	
			Melanoma	

* Cultured cells were tested on RPMI 1640 medium at an initial compound concentration of 10 μM.

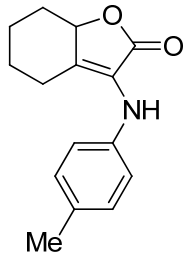
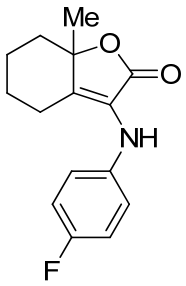
The excellent activity displayed in the MALME-3M cell line for the 6,5-bicyclic 3-aminofuran-2(5*H*)-ones **158** and **164** is further illustrated in Graph 2.3. The growth percent of the nine melanoma cell lines along with the NCI-60 mean growth percent are plotted for the two 3-aminofuran-2(5*H*)-ones **158** and **164** screened in this series. Melanoma is a dangerous form of skin cancer which begins in melanocytes and can easily spread to other parts of the body. Thus, these results are promising and warrant further work in the future.

Graph 2.3 *Illustration of growth percent of nine melanoma cell lines and NCI-60 mean growth percent for 3-aminofuran-2(*5H*)-ones **158** and **164***



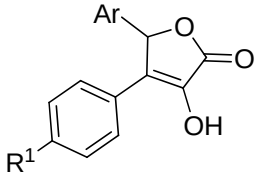
A number of other interesting results are worth mentioning here. The 6,5-bicyclic 3-aminofuran-2(5*H*)-ones **158** and **164** also exhibited notable inhibition of the non-small cell lung cancer (NSCLC) cell line HOP-92, the CNS cancer cell line SF-295 and the breast cancer cell line MDA-MB-468 (Appendix II). Although these results do not compare quite so favourably with the leukaemia and melanoma inhibition results discussed above, the pattern of results for the two 3-aminofuran-2(5*H*)-ones **158** and **164** is striking and may be improved upon in the future. These results are summarised in Table 2.23.

Table 2.23 One-dose screen of 3-aminofuran-2(5*H*)-ones **158** and **164** (HOP-92, SF-295 and MDA-MB-468 cancer cell lines)

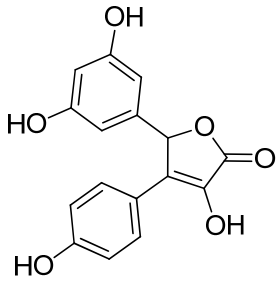
Entry	3-aminofuran-2(5*H*)-one	NCI-60 cell-lines	Tumour site	Growth percent*	Mean cell line growth
1	 **158**	HOP-92	NSCLC	27.16	58.61
		SF-295	CNS Cancer	26.42	
		MDA-MB-468	Breast cancer	22.61	
2	 **164**	HOP-92	NSCLC	29.50	57.48
		SF-295	CNS Cancer	28.33	
		MDA-MB-468	Breast cancer	23.15	

* Cultured cells were tested on RPMI 1640 medium at an initial compound concentration of 10 μM.

Interestingly, previous work by Bailly *et al.* revealed 4,5-diaryl-3-hydroxy-furan 2(5*H*)-ones **249** as cytotoxic agents in the human prostate carcinoma PC-3 cell line (Figure 2.62).[113] One derivative **250** in particular, showed an antiproliferative activity to 39% at 10 μM dose.



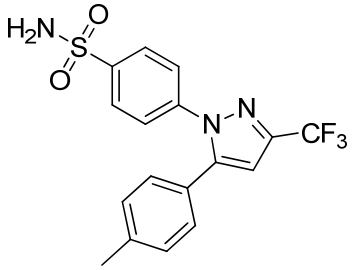
249



250

Figure 2.62

Indeed, the authors also compared the activity of their diaryl-3-hydroxy-furan-2(5*H*)-one **250** with that of the clinically used compound, celecoxib **254** (Celebrex®, 50% inhibition at 48 μM).[113]



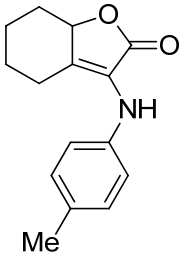
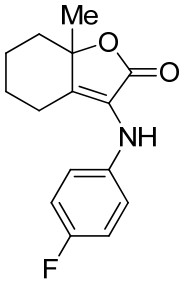
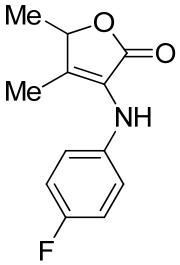
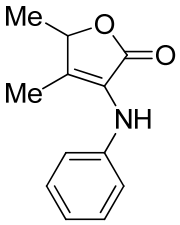
254

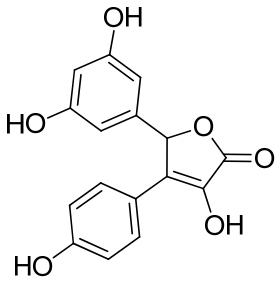
Figure 2.63 *Celecoxib **254** (Celebrex®)*

These diaryl 3-hydroxy-furan-2(5*H*)-ones are quite different in structure to the 3-aminofuran-2(5*H*)-ones examined in this work. However, it can be readily appreciated that the activities reported for the 3-aminofuran-2(5*H*)-ones compare very favourably to those reported by Bailly *et al.* (Appendix II).[113] Indeed, the 6,5-bicyclic 3-aminofuran-2(5*H*)-ones **158** and **164** in particular, exhibit antiproliferative activity for the human prostate carcinoma PC-3 cell line to 31.62% and 31.89%, respectively. These results exceed those reported by Bailly *et al.* at the same dosage and have notable potencies when compared to the clinically used compound, celecoxib **254**. During the *viva*, the link between the biological activity of these compounds and the nucleophile/electrophile dual reactivity of the α-aminoenone structure was discussed.

A summary of the one-dose mean data for the PC-3 cell line obtained with the 3-aminofuran-2(5*H*)-ones in this work, and the 4,5-diaryl-3-hydroxy-furan-2(5*H*)-one **250** reported by Bailly *et al.* is shown in Table 2.24.

Table 2.24 One-dose screen of 3-aminofuran-2(5*H*)-ones prepared in this work and 4,5-diaryl-3-hydroxy-furan 2(5*H*)-one **250** reported by Bailly *et al*. (PC-3 cancer cell line)

Entry	3-aminofuran-2(5*H*)-one	NCI-60 cell-lines	Tumour site	Growth percent*
1	 **158**	PC-3	Prostate cancer	31.62
2	 **164**	PC-3	Prostate cancer	31.89
3	 **168**	PC-3	Prostate cancer	49.04
4	 **169**	PC-3	Prostate cancer	45.96

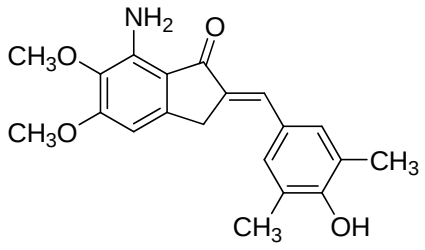
5	 **250**	PC-3	Prostate cancer	39

* Cultured cells were tested on RPMI 1640 medium at an initial compound concentration of 10 μM.

These results serve to further highlight the impressive biological activity exhibited by the 3-aminofuran-2(5*H*)-ones in this work and the need for future studies into these derivatives.

2.12.2.3 Biological Activity of Benzofused Dihydro-2H-thiopyran S-oxides

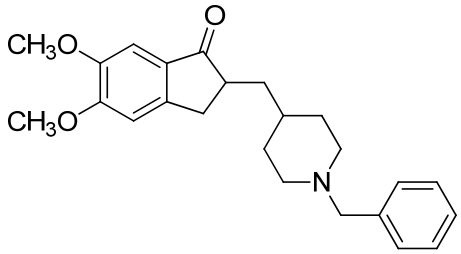
The synthesis of benzofused dihydro-2*H*-thiopyran *S*-oxides cycloadducts prepared using Diels-Alder reactions of 2,3-dimethyl-1,3-butadiene with α-oxosulfines is discussed in Section 2.10.2. These cycloadducts are indan-1-ones which contain a spiro-centre. Indanones and their related compounds are important bioactive compounds.[160] Several studies in the literature report their biological activities, including against cancer and Alzheimer's disease. Indanocine **255** and its analogues are examples of indan-1-ones which are being developed to combat drug-resistant malignancies (Figure 2.64).[160]



255

Figure 2.64

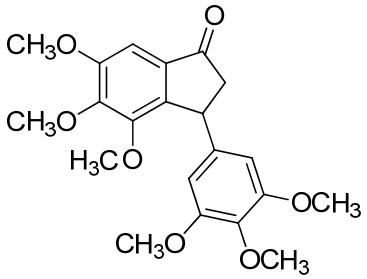
Donepezil **256** is another indanone analogue which has been approved by US-FDA for the treatment of mild to moderate Alzheimer's disease.[161] The hydrochloride salt of the drug behaves as an AChE (acetylcholinesterase) inhibitor.[189]



256

Figure 2.65

Further examples include gallic acid-based indanone derivatives, which exhibited very good anticancer activity in MTT assay against various human cancer cell lines. The most potent indanone (**257**, IC_{50} = 2.2 μM) against the MCF-7 hormone-dependent breast cancer line, showed no toxicity to human erythrocytes, even at higher concentrations (100 mg/μL, 258 μM).[85]



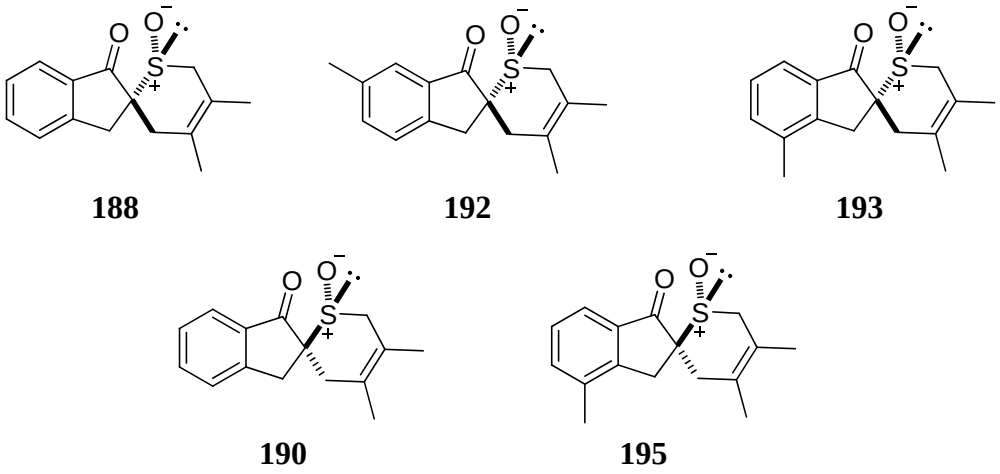
257

Figure 2.66

While the cycloadduct **188** has previously been reported by Morita *et al*.,[133] the cycloadduct derivatives **190**, **192**, **193**, **194** and **195** prepared in this work represent novel compounds which feature the core indanone structure, along with a spiro 6-membered ring adduct containing a sulfoxide moiety. There are a number of interesting features in the structure of these compounds, most notably the novel spiro substituent at the C(9) position, where this is typically an alkyl, aryl or hydroxy group.[160,161,189,190]

Thus, the potential for biological activity from these compounds is significant. Five benzofused dihydro-2*H*-thiopyran *S*-oxides were submitted for NCI-60 cancer cell-line one dose screening to the Developmental Therapeutics Programme (Figure 2.67). We were interested to learn whether the sulfoxide group whould lead to interesting electronic, steric and conformational interactions and

binding (hydrogen bonding in particular) while maintaining the core indanone activity as reported in the literature. The incorporation of a methyl substituent on the aryl ring may also lead to alternative binding, steric and electronic effects (electron donating inductive group).



188 **192** **193**

190 **195**

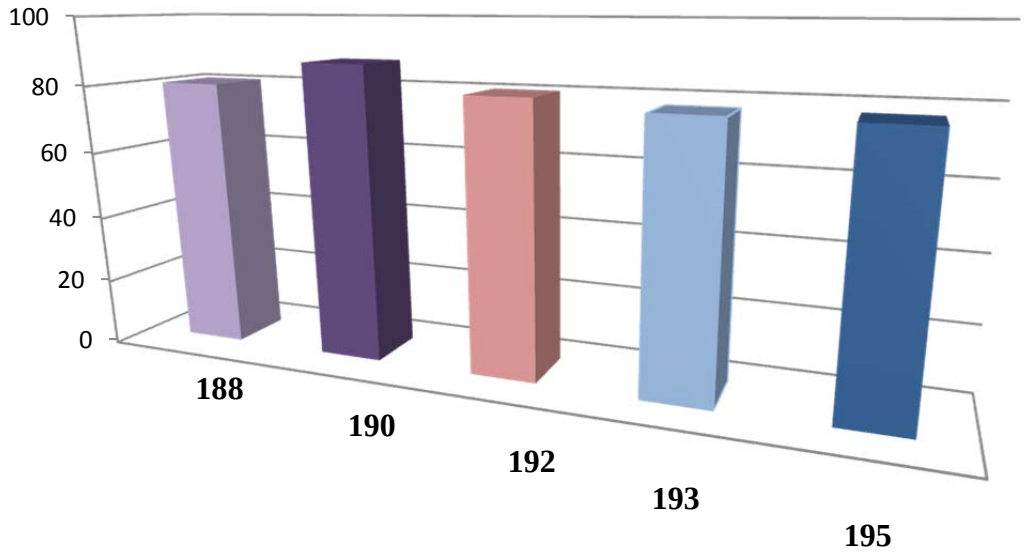
Figure 2.67 *Series of benzofused dihydro-2*H*-thiopyran* S*-oxides submitted for NCI-60 screening in the Developmental Therapeutics Programme.*

The cycloadducts displayed in Figure 2.67 were successfully investigated for initial one-dose (10 mM) tumour cell line activity, and the pattern of quantifiable growth inhibition of these agents on the NCI-60 human tumour cell line panel is outlined herein.

The one-dose mean graphs obtained for each of these compounds depicted in Figure 2.67 are presented in Appendix II. Evaluation of these graphs revealed several interesting and distinct trends, although these compounds are not as biologically active as the 3-aminofuran-2(5*H*)-ones discussed in Section 2.12.2.2. Graph 2.4 illustrates the growth inhibition exhibited for the benzofused dihydro-2*H*-thiopyran *S*-oxides **188**, **190**, **192**, **193** and **195**; the NCI-60 mean growth percent is plotted for each compound. Overall, the NCI-60 mean growth percent does not vary substantially between the five cycloadducts, and remains within a relatively narrow range of 77-87%. The cycloadducts **188**/**192**/**193** and the cycloadducts **190**/**195** have the same relative stereochemistry. However, little correlation between stereochemistry and cell growth inhibition was revealed, with a significant difference between 87.50% and 77.30% in the mean growth percent of the cycloadducts **190**/**195**, respectively. Interestingly however, the mean growth percentages for the

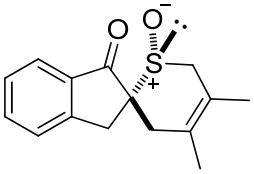
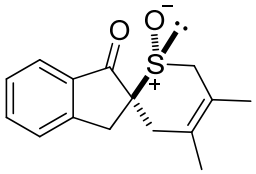
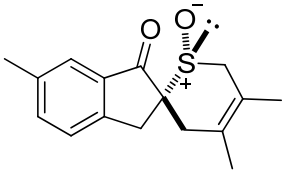
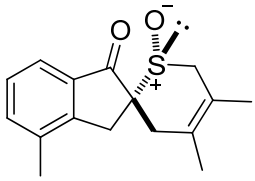
cycloadducts **193** and **195**, which both contain a methyl group at the C(3) position, were remarkably similar at 77.15% and 77.30% respectively. Thus, there appears to be a relationship between substitution on the aryl ring, particularly at the C(3) position, and improved cell growth inhibition.

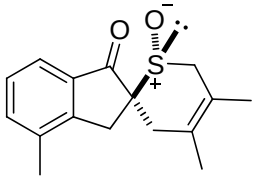
Graph 2.4 *Illustration of NCI-60 mean growth percent for the benzofused dihydro-2*H*-thiopyran* S*-oxides **188, 190, 192, 193** and **195.***



We were interested to discover that the benzofused dihydro-2*H*-thiopyran *S*-oxides exhibited notable biological activity for leukaemia, with particular selectivity for the RPMI-8226 cell line. This trend is similar to that observed for the 3-aminofuran-2(5*H*)-ones discussed in Section 2.12.2.2, and presents an interesting correlation between the two series, which are structurally quite different. The one-dose mean data for the six leukaemia cell lines tested is summarised in Table 2.25. Although little activity in the CCRF-CEM, HL-60(TB), MOLT-4 and SR cell lines was displayed, inhibition in the K-562 and the RPMI-8226 lines is clearly revealed. The mean growth percent in these cell lines for each of the benzofused dihydro-2*H*-thiopyran *S*-oxides remains in a similar range of 60-71%.

Table 2.25 One-dose screen of benzofused dihydro-2*H*-thiopyran *S*-oxides (leukaemia cancer cell lines)

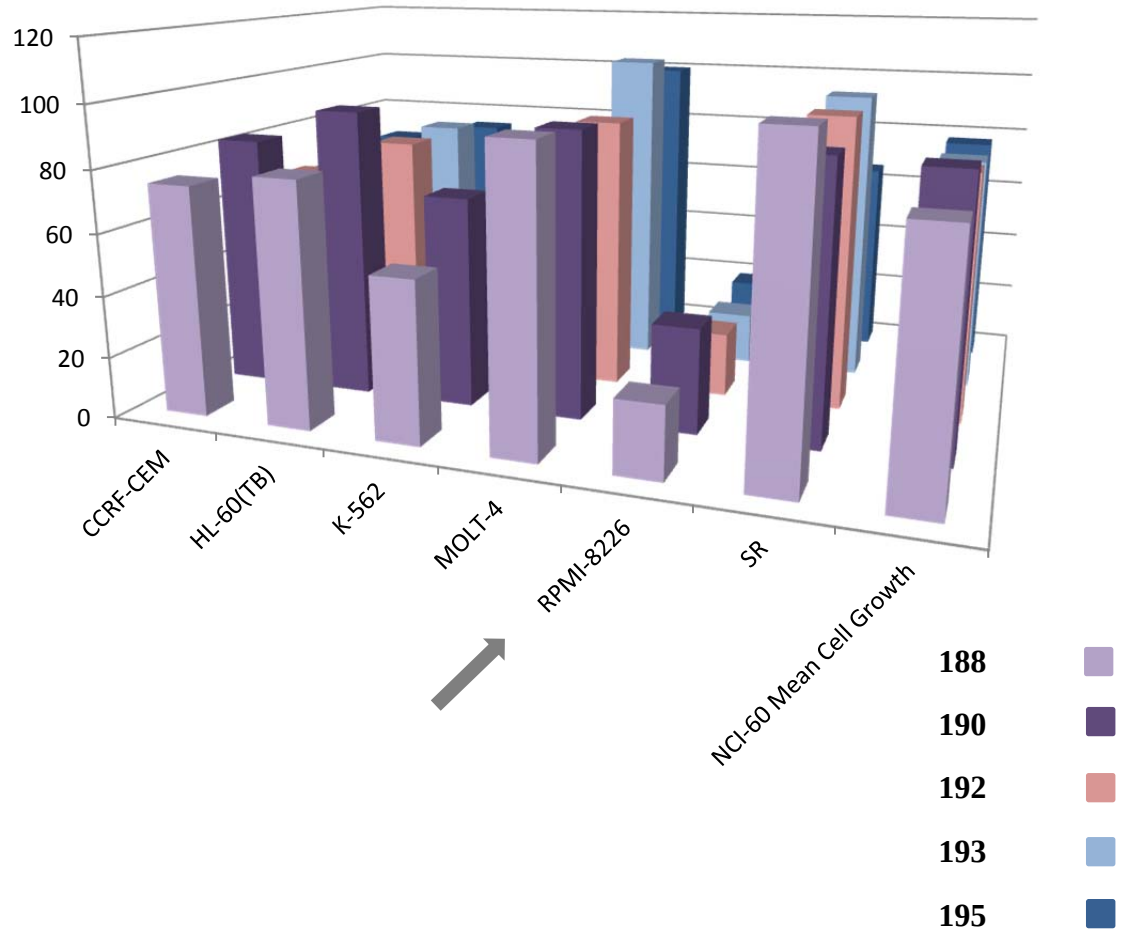
Entry	Benzofused dihydro-2*H*-thiopyran *S*-oxide	NCI-60 cell-lines	Tumour site	Growth percent*	Mean cell line growth
1	 **188**	CCRF-CEM HL-60(TB) K-562 MOLT-4 RPMI-8226 SR	Leukaemia	74.79 79.22 52.19 95.08 23.30 102.37	71.16
2	 **190**	CCRF-CEM HL-60(TB) K-562 MOLT-4 RPMI-8226 SR	Leukaemia	82.91 94.34 68.80 92.54 34.11 89.11	76.97
3	 **192**	CCRF-CEM HL-60(TB) K-562 MOLT-4 RPMI-8226 SR	Leukaemia	65.51 78.52 50.43 89.53 20.99 95.18	66.69
4	 **193**	CCRF-CEM HL-60(TB) K-562 MOLT-4 RPMI-8226 SR	Leukaemia	63.89 79.04 58.17 105.89 16.93 96.75	70.11

5	 **195**	CCRF-CEM	Leukaemia	68.30	60.67
		HL-60(TB)		74.14	
		K-562		37.73	
		MOLT-4		99.62	
		RPMI-8226		18.65	
		SR		65.59	

* Cultured cells were tested on RPMI 1640 medium at an initial compound concentration of 10 μM.

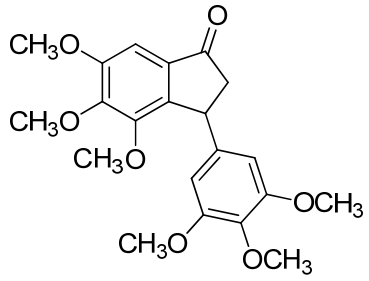
The selective inhibition exhibited in the RPMI-8226 cell line is clearly illustrated in Graph 2.5. The growth percent of the six leukaemia cell lines along with the NCI-60 mean growth are plotted for each of the benzofused dihydro-2*H*-thiopyran *S*-oxides screened in this series. The cycloadducts **193** and **195**, which both contain a methyl group at the C(3) position, exhibited the best growth inhibition for this series of compounds, again suggesting a relationship between substitution on the aryl ring at the C(3) position, and improved cell growth inhibition.

Graph 2.5 *Illustration of growth percent of six leukaemia cell lines and NCI-60 mean growth percent for the benzofused dihydro-2*H*-thiopyran* S*-oxides* ***188***, ***190***, ***192***, ***193*** *and* ***195***



Due to the unusual structure of these benzofused dihydro-2*H*-thiopyran *S*-oxides, which contain a spiro substituent at the C(9) position and a sulfoxide group on the six-membered ring, there are few comparable compounds with similar anticancer biological activity discussed in the literature. Notably however, one report by Saxena *et al.* discusses gallic-based indanone derivatives as *in vitro* anticancer agents across various human cancer cell lines by MTT assay.[85] The most potent indanone (**257**, IC_{50} = 2.2 μM) against the hormone-dependant breast cancer cell line MCF-7, showed no toxicities to erythrocytes at higher concentrations (Figure 2.68). Although the cell growth inhibitions against this particular cell line for the benzofused dihydro-2*H*-thiopyran *S*-oxides **188**, **190**, **192**, **193** and **195** studied in

this work were lower, with the percent growth remaining in the range of 65-88% (Appendix II), this report by Saxena *et al.* highlights the potential of benzofused indanones as anticancer agents with no or low toxicities to normal cells,[85] and thus encourages future development in these derivatives.



257

Figure 2.68

2.12.3 Conclusion

The cell-based cytotoxicity assay for the novel 3-aminofuran-2(5*H*)-ones and benzofused dihydro-2*H*-thiopyran *S*-oxides generated in this work was provided by the NCI-60 human cancer screening service, with growth inhibition rendered by these compounds collated by means of a standard mean graph output (Appendix II). The biological data which has been accumulated from the NCI-60 screening has successfully provided proof of concept for anti-cancer activity within both series of 3-aminofuran-2(5*H*)-ones and benzofused dihydro-2*H*-thiopyran *S*-oxides generated in this work. Preliminary SAR suggests that the bicyclic 3-aminofuran-2(5*H*)-ones series are more promising at this stage and future molecular targets can be designed based on these. Coincidently, selective activity is seen in the same leukaemia cell line, RPMI-8226, for both series of compounds, despite the very different structural features.

Future work will focus on the strategic design of 3-aminofuran-2(5*H*)-ones analogues incorporating the core structures of the most active derivatives, which include the 6,5-bicyclic framework. The bicyclic and methyl bridgehead 3-aminofuran-2(5*H*)-ones **158** and **164** exhibited much greater inhibition across the NCI-60 cell lines than the monocyclic *cis*-dimethyl 3-aminofuran-2(5*H*)-ones **168** and **169**, with outstanding inhibition exhibited for the RPMI-8226 leukaemia cell

line. Indeed, the fact that the bicyclic 3-aminofuran-2(5*H*)-ones **158** has been chosen for five-dose screening highlights the potential of these compounds in future tumour growth inhibition studies.

The benzofused dihydro-2*H*-thiopyran *S*-oxides, although generally displaying lower activity across the NCI-60 cell lines than the 3-aminofuran-2(5*H*)-ones, nevertheless show a number of interesting and promising trends which may be enhanced in future work. The notable activity exhibited in the RPMI-8226 leukaemia cell line in particular, is worth further attention, with substitution on the aryl ring at the C(3) position appearing to increase cell growth inhibition.

2.13 Concluding Remarks

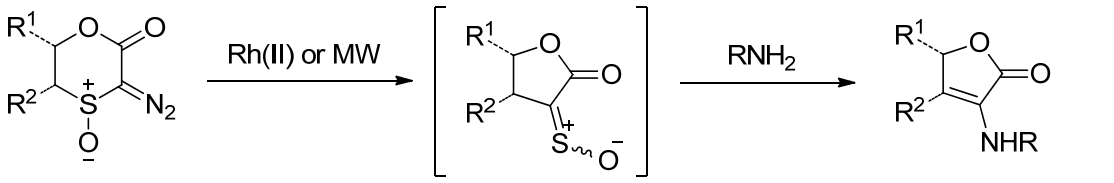
The synthesis and reactivity of α-diazosulfoxides has been studied extensively in this work under thermal, transition metal-catalysed, microwave and photochemical conditions, building on earlier results in this research group. Previous workers had synthesised α-diazosulfoxides based on lactones, and perhaps the major breakthrough in this work was the synthesis for the first time of α-diazosulfoxides derived from benzofused and monocyclic β-keto sulfoxides (Figure 2.69). Diazo transfer using immobilised polystyrene-supported benzenesulfonyl azide has also been achieved for the first time with α-diazosulfoxides.

Previous work X = O/NH

This work

Figure 2.69

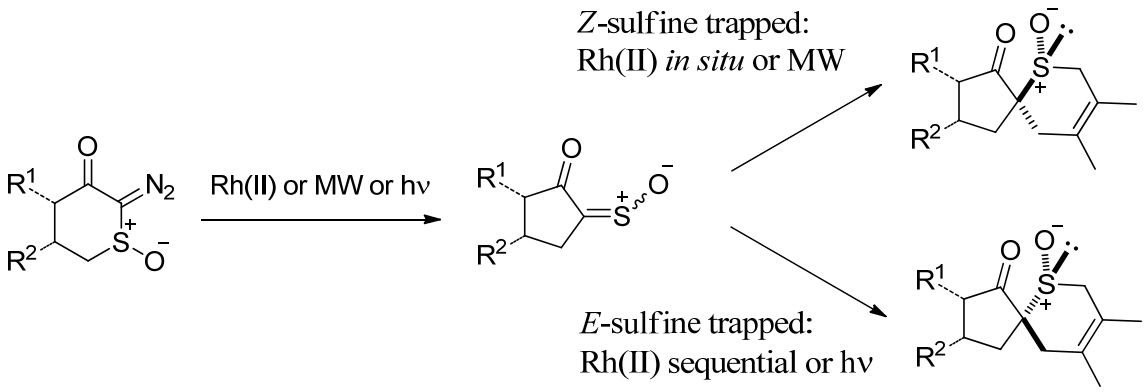
With the lactone based α-diazosulfoxides, a new and synthetically useful reaction pathway was discovered on treatment with amine nucleophiles, leading to novel 3-aminofuran-2(5*H*)-ones (Scheme 2.149). Unexpectedly, the α-oxosulfines react with the primary amines in a carbophilic approach, with complete extrusion of the sulfinyl moiety. Interestingly, this reaction pathway can be effected sequentially, whereby the α-oxosulfine is pre-generated using rhodium(II) acetate, and then reacted with the amine, or alternatively, *in situ* with the amine in place prior to generation of the α-oxosulfine with rhodium(II) acetate or with microwave irradiation. The observation that the amines do not poison the rhodium(II) catalyst was very unexpected. Preliminary investigations were also undertaken into nucleophilic addition of stabilised enolates as carbon nucleophiles. While it was not possible to generate a similar series of 3-substituted-furan-2(5*H*)-ones analogues, notably, carbophilic addition was observed for one derivative.



Scheme 2.149

The reactivity of ketone-based α-diazosulfoxides was explored for the first time during this work. In line with the lactone-based series, the primary reaction pathway was pseudo-Wolff rearrangement to generate the α-oxosulfine, with the subsequent reaction pathway depending on the reaction conditions. Generation of the α-oxosulfine intermediate, although labile, could be detected by ^{1}H NMR spectroscopy, and was confirmed by trapping as a cycloadduct with 2,3-dimethyl-1,3-butadiene.

The stereochemical features were consistent with the earlier results in the lactone series, showing that the *Z*-sulfine is the kinetic isomer formed, which can be effectively trapped *in situ* with the diene (Scheme 2.150). However, if generated in the absence of the diene, essentially complete isomerisation to the thermodynamic isomer occurs within 10 minutes, leading to trapping to form the diastereomeric cycloadduct obtained from the *E*-sulfine. From a synthetic perspective, potential access to both diastereomers simply through varying the time of diene addition, is very powerful. The generation of the α-oxosulfines and trapping as cycloadducts is also readily effected under microwave conditions and by photolysis, in addition to the rhodium(II) catalysed process, albeit with different stereochemical outcomes. The *Z*-sulfine was predominantly trapped under microwave conditions, and the *E*-sulfine was trapped under photolysis conditions.

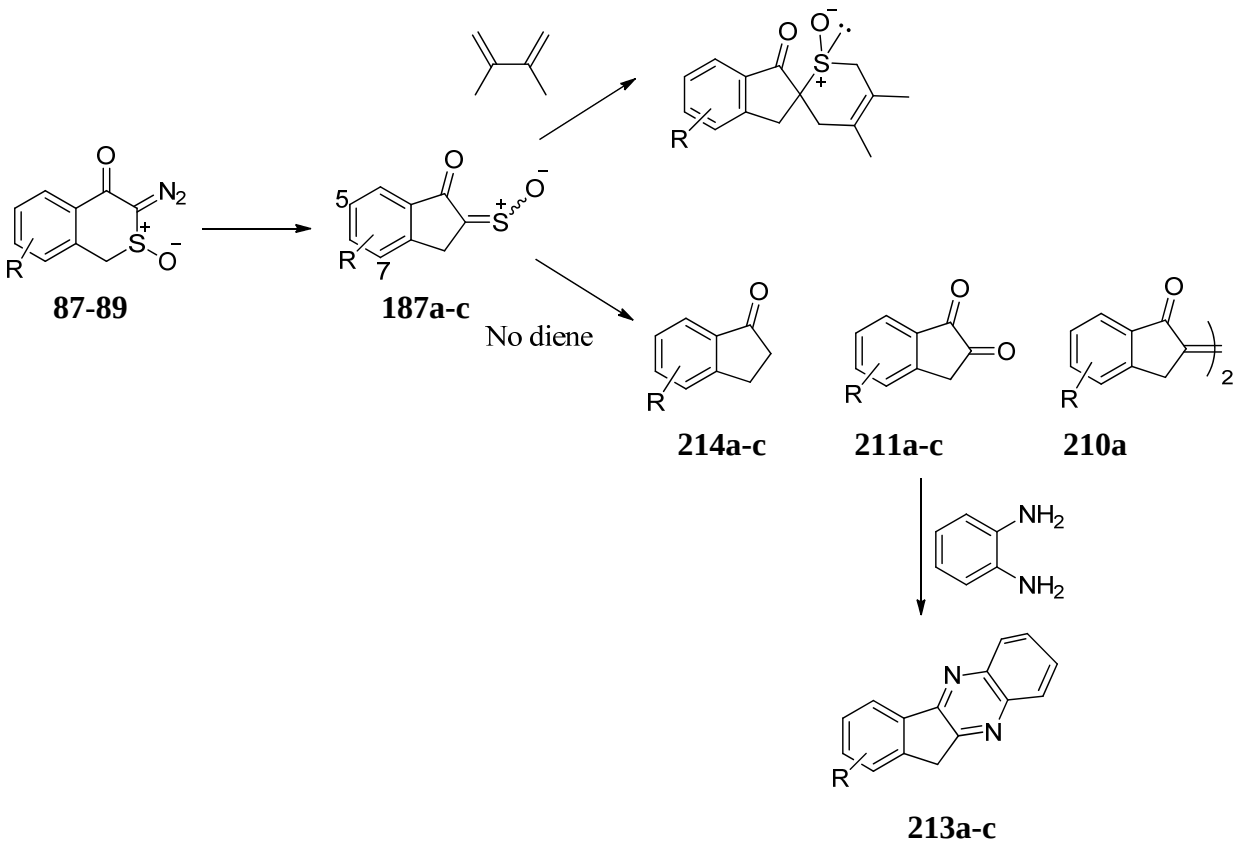


Scheme 2.150

In the absence of a diene trap, the α-oxosulfines derived from the ketone-based benzofused α-diazosulfoxides follow different reaction pathways, depending on the conditions under which the decomposition took place. These preliminary decomposition studies provide an interesting insight into the behaviour of α-oxosulfines. General trends were observed, and the most significant pathways included:

- Complete loss of the sulfinyl group to give indan-1-ones **214a-c** under copper triflate or photolysis conditions.
- Sulfur extrusion to give indanediones **211a-c** as the major pathway under rhodium(II) acetate catalysed or microwave conditions. Notably, the indanediones were quite unstable compounds, but were trapped as quinoxaline condensation products **213a-c** in good yields.
- Alkene dimer products *E*-**210a** and *Z*-**210a** were isolated, which may have formed *via* either sulfine dimerisation or aldol condensation.

A summary of the reactivity of the benzofused α-diazosulfoxides in the presence of and in the absence of a diene trap is illustrated in Scheme 2.151.



Scheme 2.151 ***a****: R = H,* ***b****: R = 5-Me,* ***c****: R = 7-Me.*

A series of 3-aminofuran-2(5*H*)-ones and benzofused dihydro-2*H*-thiopyran *S*-oxides were submitted for anticancer screening across a range of 60 cancer cell lines at the U.S. National Cancer Institute's Developmental Therapeutics Programme. A number of these derivatives exhibited excellent cell growth inhibition, particularly in the leukaemia cell lines. One 3-aminofuran-2(5*H*)-one derivative has been chosen for further five-dose screening.

Chapter 3

Experimental

3.1 General Procedures

All solvents were distilled prior to use by the following methods: dichloromethane was distilled from phosphorus pentoxide;[76] ethyl acetate was distilled from potassium carbonate;[77] acetone was distilled from potassium permanganate followed by potassium carbonate;[76] toluene was distilled from sodium benzophenone ketyl and stored over 4 Å molecular sieves;[78] and methanol was distilled from magnesium methoxide and stored over 3 Å molecular sieves.[78] Distilled diethyl ether was obtained commercially from Riedel de Haën and HPLC grade acetonitrile, available from Labscan Ltd., was used for diazo transfer reactions. All reagents were used without further purification except for 4-toluenesulfonyl chloride which was used after any tosic acid impurities had been precipitated using dichloromethane and hexane,[79] and thiourea which was recrystallised from distilled water.[76] 3-Chloroperoxybenzoic acid (77% max.) supplied by Aldrich was used without further purification unless otherwise stated; the active oxygen content was determined by iodometric titration.[27]

^{1}H (300.13 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer. ^{1}H NMR (400.13 MHz) spectra were recorded on a Bruker Avance 400 NMR spectrometer. All spectra were recorded at 20 °C in deuterated chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_H and δ_C) are reported as parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), br d (broad doublet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), qd (quartet of doublets), m (multiplet) and ABq (AB quartet). While the term AB quartet is used throughout this thesis, this is perhaps more accurately described as an AB system consisting of two doublets. ^{13}C NMR spectra were calibrated using the solvent signals *i.e.* $CDCl_3$: δ_C 77.0 ppm. All spectroscopic details for compounds previously made were in agreement with those reported unless otherwise stated. Diastereomeric ratios (d.r.) and product ratios were determined by ^{1}H NMR spectroscopy. Infra red spectra were recorded as thin films on sodium

chloride plates (oils) or KBr discs (solids) on a Perkin Elmer Paragon 1000 FT-IR spectrometer or a Perkin Elmer Spectrum One FT-IR spectrometer. Microwave-assisted synthesis was carried out using the CEM Discover Synthesiser in conjunction with ChemDriver software (Version 3.5.0) and the CEM Discover S-class Synthesiser in conjunction with Synergy software (Version 1.19). Both microwaves apply a maximum power of 300 W and reaction temperatures were measured by an IR sensor with an accuracy of ±5 °C. Melting points were measured on a Uni-Melt Thomas Hoover capillary melting point apparatus and are uncorrected. Photochemical reactions were carried out using a Philips 80ESHPLN 80 W mercury lamp (λ_{max} of 254 nm).

Wet flash column chromatography was carried out on silica gel using Kieselgel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV light detection (254 nm), vanillin staining, iodine staining and potassium permanganate staining as appropriate.

The Microanalysis Laboratory, University College Cork, performed elemental analysis using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier TOF LC-MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. In a number of cases, the exact masses are outside the acceptable limit but these were included for information purposes and have been highlighted with an asterisk.

Single crystal X-ray analysis was conducted by Dr. S. E. Lawrence and Dr. Kevin Eccles, Department of Chemistry, University College Cork using a Nonium Mach 3 diffractometer with graphite monochromatised Mo-Kα radiation (λ = 0.71069 Å). Calculations were performed on a PC with the SHELXL-97 (G.M.

Sheldrick, University of Gottingen, 1998) and Platon (A.L. Spek, University of Utrecht, 1998) suite of programs.

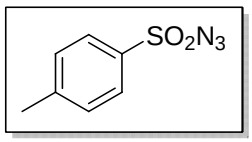
Glassware, gloves and any materials which were in contact with thioglycolic acid or any malodorous sulfur compounds were soaked for at least 24 h in a bleach bath.

3.1.1 Procedure for Generating Sodium Methoxide

Sodium metal was cut into small pieces and washed with hexane to remove any paraffin oil. The sodium was then added, slowly and in small portions, to methanol which was stirring at 0 °C under a nitrogen atmosphere. Any sodium residues which may have remained in the hexane washing were quenched with a small amount of methanol.

3.1.2 Synthesis of *p*-Toluenesulfonyl Azide 41[54]

Caution: Diazo transfer reagents are potentially hazardous reagents and extreme care should be taken in their use.[52] They are shock sensitive and in the case of *p*-toluenesulfonyl azide (tosyl azide) **41**, which is a solid below room temperature, it should not be handled as a solid. Instead, tosyl azide **41** should be allowed warm to its melting point (*ca.* 20 °C) and then pipetted from its container using a clean Pasteur pipette which has no sharp edges. The preparation or concentration of solutions containing diazo transfer reagents was carried out in a well-ventilated fumehood behind a safety shield. Tosyl azide **41** was stored in a freezer.

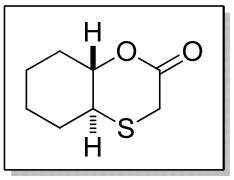


A solution of *p*-toluenesulfonyl chloride **258** (13.00 g, 63.0 mmol, 1 eq) in acetone (30 mL) was added slowly to a solution of sodium azide (4.34 g, 67.0 mmol, 1 eq) in water (15 mL) and acetone (30 mL) while stirring at 0 °C. Once the addition was complete, the reaction mixture was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo* and the aqueous solution was extracted with dichloromethane (30 mL). The organic layer was washed with water (2 × 20 mL) and brine (2 × 20 mL). The solution was dried with $MgSO_4$ and concentrated *in vacuo*, without heating the water bath, to give tosyl azide **41** as a colourless oil which crystallised to a white solid on storage at <18 °C (10.10 g, 81%); ν_{max}/cm^{-1} (film) 2128, 1595, 1371, 1167; δ_H (300 MHz) 2.50 (3H, s, C*H*$_3$), 7.20–8.00 (4H, m, 4 × Ar*H*).

3.2 Synthesis of Lactone Based α-Diazosulfoxides

3.2.1 Synthesis of Sulfides

3.2.1.1 *trans*-Hexahydrobenzo[1,4]oxathiin-2-one 27[10,191]

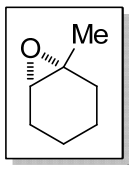


(a) A solution of thioglycolic acid **29** (***Caution:*** malodorous) (7.22 mL, 101.9 mmol, 1 eq.) in methanol (10 mL) was added slowly to a freshly prepared solution of sodium methoxide (4.70 g sodium, 203.8 mmol, 2 eq in 100 mL methanol) while stirring at 0 °C under a nitrogen atmosphere. The pale pink solution was stirred for 5 min and a solution of 1-cyclohexene oxide **33** (10.00 g, 101.9 mmol, 1 eq.) in methanol (20 mL) was added dropwise to the solution while stirring at 0 °C under a nitrogen atmosphere. The temperature was maintained at 0 °C until the addition of the epoxide was complete. The reaction mixture was then heated under reflux conditions for 3 h under a nitrogen atmosphere. The reaction mixture was cooled and the solvent removed *in vacuo* to leave a pale yellow solid which was dissolved in water (50 mL) and acidified to pH 1 with concentrated hydrochloric acid. The aqueous solution was extracted with diethyl ether (3 × 35 mL). The combined ethereal layers were washed with water (20 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave the hydroxy acid **30** (18.51 g) as a colourless oil.

(b) The crude hydroxy acid **30** was dissolved in toluene (100 mL) and a catalytic amount of tosic acid (40 mg, 0.2 mmol) was added. The reaction mixture was heated under reflux conditions for 6 h under Dean-Stark conditions. The solution was cooled and washed with sodium bicarbonate solution (10%, 3 × 30 mL), water (20 mL), brine (20 mL), and dried with anhydrous $MgSO_4$. The organic layer was then concentrated *in vacuo* to give the sulfide **27** as a pale yellow solid (5.95 g, 68% over the two steps). ^{1}H NMR analysis indicated that this compound was sufficiently pure to be carried on to the next step without further purification; m.p. 87-88 °C (lit.,[10] 87.5-88.5 °C); δ_H (400 MHz) 1.11-1.64 (4H, m, cyclohexyl ring), 1.69-1.81 (1H, m, cyclohexyl ring), 1.82-1.92 (1H, m, cyclohexyl ring), 1.96-2.12 (1H, m, cyclohexyl ring), 2.19-2.30 (1H, m, cyclohexyl ring), 3.00 (1H,

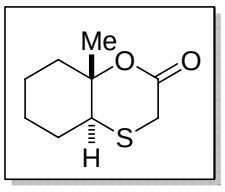
overlapping ddd, *J* 11.6, 10.4, 4.0, C*H*S), 3.23 (1H, A of ABq, *J* 14.7, one of SCH_2), 3.69 (1H, B of ABq, *J* 14.7, one of SCH_2), 4.17 (1H, overlapping ddd appears as dt, *J* 10.6, 10.6, 4.3, C*H*O). Spectral characteristics in agreement with those reported in the literature.[10]

3.2.1.2 1-Methyl-1-cyclohexene oxide 34[10]



A solution of *m*-CPBA (75%, 23.00 g, 93.0 mmol, 1 eq) in dichloromethane (150 mL) was added slowly to a solution of 1-methyl-1-cyclohexene **259** (9.00 g, 93 mmol, 1 eq) in dichloromethane (50 mL) at 0 °C. The reaction was allowed to stir for 5 h while slowly returning to ambient temperature and was then filtered to remove precipitated *m*-chlorobenzoic acid. The filtrate was washed with sodium bicarbonate solution (10%, 3 × 30 mL), water (1 × 20 mL), brine (1 × 20 mL) and dried with anhydrous $MgSO_4$. The organic layer was concentrated *in vacuo* to give the epoxide product **34** as a colourless oil (5.26 g, 58%); δ_H (400 MHz) 1.19-1.25 (1H, m, cyclohexyl ring), 1.29 (3H, s, CH_3), 1.32-1.50 (2H, m, cyclohexyl ring), 1.61-1.71 (1H, m, cyclohexyl ring), 1.80-1.94 (4H, m, cyclohexyl ring), 2.96 (1H, s, C*H*O). Spectral characteristics in agreement with those reported in the literature.[10]

3.2.1.3 8a-Methylhexahydrobenzo[1,4]oxathiin-2-one 36[7,9]

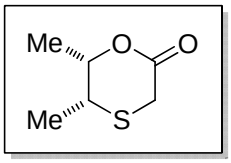


(a) A solution of thioglycolic acid **29** (5.06 mL, 72.4 mmol, 1 eq) in methanol (10 mL) was added slowly to a freshly prepared solution of sodium methoxide (3.33 g sodium, 144.7 mmol, 2 eq, in 40 mL methanol) while stirring at 0 °C under a nitrogen atmosphere. The pale pink solution was stirred for 5 min and a solution of the epoxide **34** (8.12 g, 72.4 mmol, 1 eq) in methanol (20 mL) was added dropwise to the solution, while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was then heated under reflux conditions for 3 h under a nitrogen atmosphere. The mixture was cooled and the solvent removed *in vacuo* to give a pale yellow solid which was worked up according to the procedure outlined in Section 3.2.1.1 to

produce the hydroxy acid **31** (19.32 g) as a pale yellow oil which was immediately brought on to the next step.

(b) The crude hydroxy acid **31** was dissolved in toluene (100 mL) and a catalytic amount of tosic acid (42 mg, 0.2 mmol) was added. The reaction mixture was heated under reflux conditions for 6 h using a Dean-Stark trap. The solution was cooled and washed with sodium bicarbonate solution (10%, 1 × 20 mL), water (20 mL), brine (20 mL), and dried with anhydrous $MgSO_4$. The organic layer was concentrated *in vacuo* to give the sulfide **31** as a pale yellow oil (5.95 g, 32.0 mmol, 62% over two steps); δ_H (400 MHz) 1.20-1.94 (10H, m, contains 7H of cyclohexyl ring and C*H*$_3$ s at 1.57), 2.00-2.12 (1H, m, C*H* of cyclohexyl ring), 3.12 (1H, dd, *J* 12.0, 3.8, C*H*S), 3.46 (1H, A of ABq, *J* 17.0, one of SC*H*$_2$), 3.64 (1H, B of ABq, *J* 17.0, one of SC*H*$_2$). Spectral characteristics in agreement with those reported in the literature.[7,9]

3.2.1.4 *cis*-5,6-Dimethyl[1,4]oxathian-2-one 37[7,9]

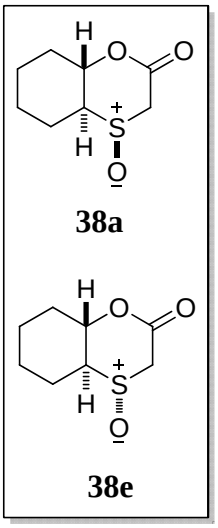


(a) A solution of thioglycolic acid **29** (7.40 mL, 106.4 mmol, 1 eq) in methanol (20 mL) was added slowly to a freshly prepared solution of sodium methoxide (4.89 g sodium, 212.7 mmol, 2 eq, in 150 mL methanol) while stirring at 0 °C under a nitrogen atmosphere. The pale pink solution was stirred for 5 min, then a solution of *trans*-2,3-epoxybutane **35** (7.67 g, 106.4 mmol, 1 eq) in methanol (20 mL) was added dropwise to the solution, while stirring at 0 °C under nitrogen. The temperature was maintained at 0 °C until the addition of epoxide was complete. The reaction mixture was then heated under reflux conditions for 4 h. The reaction mixture was cooled and the solvent was removed *in vacuo* to give an off-white solid which was dissolved in water (100 mL) and acidified to pH 1 with concentrated hydrochloric acid (37%, 15 mL). The aqueous solution was extracted with diethyl ether (3 × 30 mL). The combined ethereal layers were then washed with water (25 mL), brine (25 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give the hydroxy acid **32** (14.79 g) as a colourless oil which was immediately brought on to the next step.

(b) The crude hydroxy acid **32** was dissolved in toluene (240 mL) and a catalytic amount of tosic acid (10 mg, 0.06 mmol) was added. The reaction mixture was heated under reflux conditions for 4 h using a Dean-Stark trap. The solution was allowed to cool and washed with sodium bicarbonate solution (10%, 25 mL), water (25 mL), and brine (25 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give the sulfide **32** as a pale yellow oil (11.52 g, 74% over two steps). ^{1}H NMR analysis indicated that this compound was sufficiently pure to be carried on to the next step without further purification; δ_H (300 MHz) 1.29 (3H, d, *J* 6.9, C*H*$_3$CHS), 1.43 (3H, d, *J* 6.5, C*H*$_3$CHO), 3.21 (1H, A of ABq, *J* 14.7, one of SC*H*$_2$), 3.28 (1H, qd, *J* 6.9, 2.7, C*H*S), 3.59 (1H, B of ABq, *J* 14.7, one of SC*H*$_2$), 4.65 (1H, qd, *J* 6.4, 2.6, C*H*O). Spectral characteristics in agreement with those reported in the literature.[7,9]

3.2.2 Synthesis of Sulfoxides

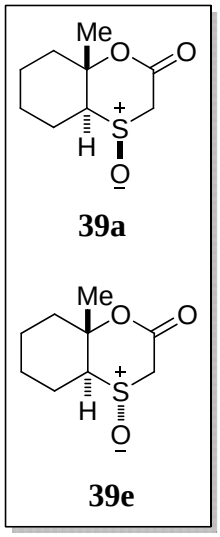
3.2.2.1 *trans*-Hexahydrobenzo[1,4]oxathiin-2-one *S*-oxides 38a and 38e[7,9]



A solution of *m*-CPBA (75%, 7.90 g, 34.4 mmol, 1 eq) in dichloromethane (30 mL) was added dropwise over 20 min to a solution of the sulfide **27** (5.94 g, 34.4 mmol, 1 eq) in dichloromethane (60 mL) while stirring at 0 °C. The reaction mixture was stirred over 2.5 h while slowly returning to room temperature. The solution was filtered to remove precipitated *m*-chlorobenzoic acid, washed with sodium bicarbonate solution (10%, 3 × 30 mL), water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to produce the crude sulfoxides as a mixture of diastereomers **38a** and **38e** (1:1) as a pale yellow solid (5.77 g, 89%). ^{1}H NMR analysis indicated that this compound was sufficiently pure to be carried on to the next step without further purification. m.p. 100-102 °C (lit.,[10] 110-116 °C); δ_H (400 MHz) 1.16-2.45 (15H, m, cyclohexyl ring of both diastereomers), 2.53-2.80 (3H, m, 2 × C*H*S of both diastereomers and C*H* of cyclohexyl ring of **38e**), 3.65 (1H, A of ABq, *J* 15.8, one of SOC*H*$_2$ of **38a**), 3.78 (1H, A of ABq, *J* 15.9, one of SOC*H*$_2$ of

38e), 3.85 (1H, B of ABq, *J* 15.9, one of SOCH_2 of **38e**), 3.95-4.08 (2H, m, contains C*H*O of **38e** overlapping with B of ABq at 4.04, *J* 15.8, one of SOCH_2 of **38a**), 4.89 (1H, ddd, appears as dt, *J* 11.0, 10.4 5.0, C*H*O of **38a**). Spectral characteristics in agreement with those reported in the literature.[7,9]

3.2.2.2 8a-Methylhexahydrobenzo[1,4]oxathiin-2-one *S*-oxides 39a and 39e[7,9]



39a

39e

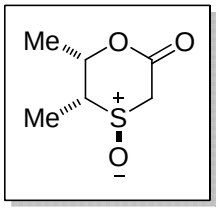
A solution of *m*-CPBA (75%, 6.74 g, 29.4 mmol, 1 eq) in dichloromethane (30 mL) was added dropwise over 20 min to a solution of the sulfide **36** (5.95 g, 29.4 mmol, 1 eq) in dichloromethane (60 mL) while stirring at 0 °C. The reaction mixture was stirred overnight while returning slowly to room temperature. The solution was filtered to remove precipitated *m*-chlorobenzoic acid. It was then washed with sodium bicarbonate solution (10%, 3 × 30mL), water (30mL) and brine (30mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude sulfoxides as a mixture of diastereomers **39a** and **39e** (1:9) as a pale yellow solid (4.88 g, 82%); m.p. 93-95 °C [lit., (1:10/**39a**:**39e**)[9] 92-95 °C]; δ_H (400 MHz) Major equatorial sulfoxide **39e**: 1.32-2.20 (10H, m, contains 7H m of cyclohexyl ring and CH_3 s at 1.41), 2.50-2.61 (1H, m appears as br d, C*H* of cyclohexyl ring), 2.88 (1H, dd, *J* 12.6, 4.2, C*H*S), 3.55 (1H, A of ABq, *J* 16.7, one of SOCH_2), 4.46 (1H, B of ABq, *J* 16.7, one of SOCH_2).

Signals observed corresponding to minor axial sulfoxide **39a**: 3.73 (1H, A of ABq, *J* 16.9, one of SOCH_2), 4.41 (1H, B of ABq, *J* 16.9, one of SOCH_2).

Spectral characteristics in agreement with those reported in the literature.[7,9]

3.2.2.3 *cis*-5,6-Dimethyl-1,4-oxathian-2-one *S*-oxide 40[7,9]

Method 1 With *m*-CPBA in dichloromethane overnight



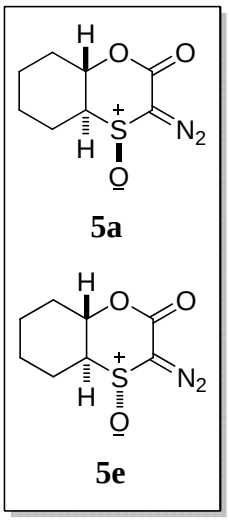
A solution of *m*-CPBA (75%, 18.18 g, 79.10 mmol, 1 eq) in dichloromethane (90 mL) was added dropwise to a solution of the sulfide **37** (11.52 g, 79.10 mmol, 1 eq) in dichloromethane (110 mL) while stirring at 0 °C. The reaction mixture was stirred overnight while returning slowly to room temperature and was then filtered to remove precipitated *m*-chlorobenzoic acid. The filtrate was washed with sodium bicarbonate solution (10%, 2 × 30 mL), water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude sulfoxide **40** as a colourless oil (5.53 g, 68%). δ_H (400 MHz) 1.20 (3H, d, *J* 7.5, C*H*$_3$CHS), 1.53 (3H, d, *J* 6.6, C*H*$_3$CHO), 2.86–2.99 (1H, symmetrical m, C*H*S), 3.45 (1H, A of ABq, *J* 16.6, one of SOC*H*$_2$), 4.06 (1H, B of ABq, *J* 16.6, one of SOC*H*$_2$), 5.41 (1H, qd, *J* 6.6, 1.5, C*H*O). Spectral characteristics in agreement with those reported in the literature.[7,9]

Method 2 With polystyrene supported periodate resin in methanol[192]

Polystyrene supported periodate resin (0.18 g, 0.22 mmol, 1 eq) was 'swollen' in methanol (5 mL) for 5 min at room temperature. Sulfide **37** (33 mg, 0.22 mmol, 1 eq) in methanol (1 mL) was added to the solution and the reaction mixture was stirred at room temperature overnight. The reaction progress was monitored by TLC analysis which indicated that no oxidation had taken place over 48 h. The resin was removed by gravity filtration and washed with methanol (3 × 3 mL). The washes were combined with the supernatant liquid and concentrated to leave a brown residue (35 mg). The ^{1}H NMR spectrum of the crude product indicated the presence of the sulfide **37**.

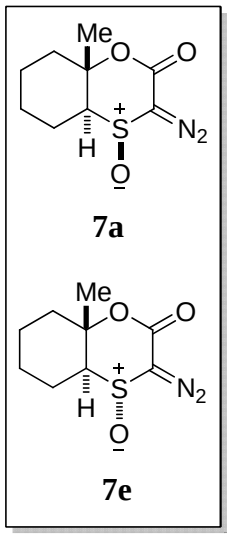
3.2.3 Synthesis of α-Diazosulfoxides

3.2.3.1 Axial and equatorial 3-diazo-*trans*-hexahydrobenzo[1,4]oxathiin-2-one *S*-oxides 5a and 5e[7,9]



A solution of triethylamine (0.24 mL, 1.7 mmol, 1 eq) in acetonitrile (20 mL) was added dropwise to the sulfoxides **38a** and **38e** (1:2, 0.33 g, 1.7 mmol, 1 eq) in acetonitrile (50 mL) while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 minutes and then a solution of tosyl azide **41** (0.33 g, 1.7 mmol, 1 eq) in acetonitrile (10 mL) was added dropwise again, while stirring at 0 °C under a nitrogen atmosphere. Once the additions were complete the ice bath was removed and the bright orange solution was stirred at ambient temperature under inert atmosphere overnight for 17 h. The solvent was evaporated to give the crude product as a viscous dark orange oil which was adsorbed onto Celite® and purified by column chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent to give a mixture of the pure diastereomeric α-diazosulfoxides **5e** and **5a** (1:1) as a bright yellow solid (0.13 g, 34 %); m.p. 84-86 °C [lit.,[10] 104-106 °C (**5a** only), 76-77 °C (**5e** only)]; δ_H (400 MHz) 1.30–1.80 (8H, m, cyclohexyl ring of both diastereomers), 1.82-1.20 (4H, m, cyclohexyl ring of both diastereomers), 2.02-2.14 (1H, m, one of cyclohexyl ring of **5a**), 2.26-2.35 (1H, m, one of cyclohexyl ring of **5e**), 2.37-2.46 (1H, m, one of cyclohexyl ring of **5a**), 2.59–2.68 (1H, m, one of cyclohexyl ring of **5e**), 2.82 (1H, qd, *J* 12.6, 10.3, 4.5, C*H*S of **5a**), 2.95 (1H, qd, *J* 12.7, 11.1, 4.6, C*H*S of **5e**), 4.03 (1H, overlapping ddd appears as dt, *J* 11.0, 11.0, 5.2, C*H*O of **5e**), 4.89 (1H, ddd appears as, *J* 10.8, 10.8, 5.3, C*H*O of **5a**). Spectral details in agreement with those reported in the literature.[7,9]

3.2.3.2 Axial and equatorial 8a-methyl-3-diazo-*trans* hexahydrobenzo[1,4]oxathiin-2-one *S*-oxides 7a and 7e[7,9]



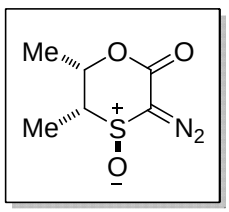
A solution of triethylamine (0.21 mL, 1.5 mmol, 1 eq) in acetonitrile (20 mL) was added dropwise to the sulfoxides **39a** and **39e** (1:9, 0.32 g, 1.5 mmol, 1 eq) in acetonitrile (50 mL) while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 minutes and then a solution of tosyl azide (0.30 g, 1.5 mmol, 1 eq) in acetonitrile (10 mL) was added dropwise, again while stirring at 0 °C under a nitrogen atmosphere. Once the additions were complete the ice bath was removed and the bright orange solution was stirred at ambient temperature under the inert atmosphere overnight. The solvent was evaporated to give the crude product as a viscous red oil which was adsorbed onto Celite® and purified by column chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent to give a mixture of the pure diastereomeric α-diazosulfoxides **7a** and **7e** as a yellow solid (1:14, 0.12 g, 33%); m.p. 94-96 °C [lit. (1:5/**7a**:**7e**),[10] 90-92 °C].

Major diastereomer **7e**: δ_H (300 MHz) 1.31–2.12 (9H, m, conatins 6H m of cyclohexyl ring and C*H*$_3$ s at 1.42), 2.50–2.64 (2H, m, C*H*$_2$ of cyclohexyl ring), 3.02 (1H, dd, *J* 12.6, 4.2, C*H*S).

Signals detected corresponding to minor diastereomer **7a**: 1.81 (3H, s, methyl group), 2.75 (1H, dd, *J* 12.6, 4.1, C*H*S)

Spectral details are in agreement with those reported in the literature.[7,9]

3.2.3.3 3-Diazo-*cis*-5,6-dimethyl-1,4-oxathian-2-one *S*-oxide 10[7,9]



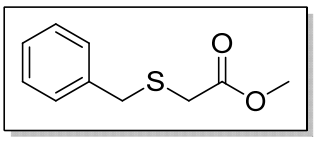
A solution of triethylamine (0.58 mL, 3.6 mmol, 1 eq) in acetonitrile (20 mL) was added dropwise to a solution of sulfoxide **40** (0.612 g, 3.6 mmol, 1 eq) in acetonitrile (30 mL) while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and a solution of tosyl azide **41** (0.732 g, 3.6 mmol, 1

eq) in acetonitrile (5 mL) was then added slowly. Once the additions were complete the ice-bath was removed and the solution was stirred at room temperature under the inert atmosphere overnight. The solvent was evaporated to yield the crude product as a viscous red oil which was adsorbed onto Celite® and purified by column chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent to give the pure α-diazosulfoxide **10** as a pale yellow solid (0.21 g, 35%); δ_H (400 MHz) 1.23 (3H, d, *J* 7.2, C*H*$_3$CHS), 1.52 (3H, d, *J* 6.6, C*H*$_3$CHO), 2.96 (1H, qd, *J* 7.2, 1.3, C*H*S), 5.39 (1H, qd, *J* 6.6, 1.3, C*H*O). Spectral details in agreement with those reported in the literature.[7,9]

3.3 Synthesis of Benzofused α-Diazo-β-keto Sulfoxides

3.3.1 Synthesis of Esters

3.3.1.1 Methyl 2-(benzylthio)acetate 53[193]

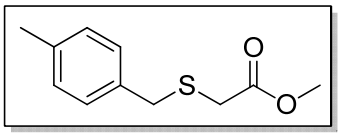


Potassium carbonate (9.30 g, 67.26 mmol, 2 eq) was slowly added to a solution of methyl thioglycolate **51** (3.01 mL, 33.63 mmol, 1 eq) in methanol (50 mL) over 5 min at 0 °C. The mixture was allowed to reach room temperature and a solution of benzyl bromide **52** (4.00 mL, 33.63 mmol, 1 eq) in methanol (8 mL) was added. The reaction mixture was stirred for 1 h and filtered to remove the inorganic salts which had precipitated. The filtrate was concentrated *in vacuo* and the residue partitioned between water (80 mL) and diethyl ether (80 mL). The aqueous layer was separated and extracted with diethyl ether (2 × 30 mL). The combined ethereal layers were washed with sat. sodium bicarbonate solution (20 mL), water (20 mL), brine (20 mL) and dried with anhydrous $MgSO_4$. The solution was concentrated *in vacuo* to give methyl 2-(benzylthio)acetate **53** as a clear oil which was used without further purification (4.58 g, 70%); ν_{max} (film)/cm^{-1} 1736 (C=O); δ_H (400 MHz) 3.08 (2H, s, C*H*$_2$), 3.71 (3H, s, C*H*$_3$), 3.82 (2H, s, C*H*$_2$), 7.18-7.47 (5H, m, Ar*H*); δ_C (75.5 MHz) 32.1 (*C*H$_2$), 36.4 (*C*H$_2$), 52.3 (*C*H$_3$), 127.3, 128.6, 129.2 (5 × aromatic *C*H), 137.2

(aromatic C_q), 170.8 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_{13}O_2S$ $[M+H]^+$, 197.0636. Found 197.0632; m/z (ESI+) 197 $[(M+H)^+$, 8%)]. Spectral details are in agreement with those reported in the literature.[193]

3.3.1.2 Methyl 2-(4-methylbenzylthio)acetate 63[30]

Method 1 Using potassium carbonate (2 eq) and sodium iodide (5 mol%) in acetone[27]



Potassium carbonate (11.59 g, 83.87 mmol, 1.5 eq) was directly added to a solution of 4-methylbenzyl chloride **62** (7.86 g, 55.91 mmol), 1 eq in acetone (40 mL). Methyl thioglycolate **51** (5.00 mL, 55.91 mmol, 1 eq) in acetone (10 mL) was added over 5 mins at 0 °C, followed by a catalytic amount of sodium iodide (0.42 g, 2.80 mmol, 5 mol%). The mixture was heated under reflux for 14 h, cooled to room temperature and concentrated *in vacuo*. The white solid was partitioned between water (40 mL) and ethyl acetate (40 mL) and the aqueous layer washed with ethyl acetate (20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give methyl 2-(4-methylbenzylthio)acetate **63** and 4-methylbenzyl chloride **62** (95:5) as a clear oil which was used without further purification (11.29 g, 96 %); ν_{max} (film)/cm^{-1} 1737 (C=O).

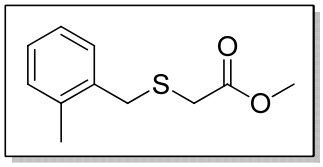
Methyl 2-(4-methylbenzylthio)acetate **63**: δ_H (400 MHz) 2.32 (3H, s, ArCH_3), 3.07 (2H, s, CH_2), 3.70 (3H, s, CH_3), 3.78 (2H, s, CH_2), 7.09-7.16 (2H, m, Ar*H*), 7.18-7.23 (2H, m, Ar*H*); δ_C (75.5 MHz) 21.1 (Ar*C*H_3), 32.1 (*C*H_2), 36.1 (*C*H_2), 52.3 (*C*H_3), 129.1, 129.2 (4 × aromatic *C*H), 134.1 (aromatic C_q), 136.9 (aromatic C_q), 170.9 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_2S$ $[M+H]^+$, 211.0793. Found 211.0784; m/z (ESI+) 211 $[(M+H)^+$, 17%)].

Signals detected for 5% 4-methylbenzyl chloride **62**: δ_H (400 MHz) 2.34 (3H, s, ArCH_3), 4.55 (2H, s, CH_2); δ_C (75.5 MHz) 21.2 (*C*H_3), 46.3 (*C*H_2), 128.6 (aromatic *C*H), 129.4 (aromatic *C*H), 134.6 (aromatic C_q), 138.3 (aromatic C_q).

Method 2 Using potassium carbonate (2 eq) in methanol

The title compound was prepared following the procedure described for methyl 2-(benzylthio)acetate **53** using 4-methylbenzyl chloride **62** (7.44 mL, 55.92 mmol, 1 eq), methyl thioglycolate **51** (5.00 mL, 55.92 mmol, 1 eq) and potassium carbonate (15.46 g, 111.84 mmol, 2 eq) in methanol (80 mL) for 18 h under reflux. Following work-up, methyl 2-(4-methylbenzylthio)acetate **63** was isolated as a pale yellow oil which was used without further purification (5.65 g, 48%). Spectral details are given in Method 1, above.

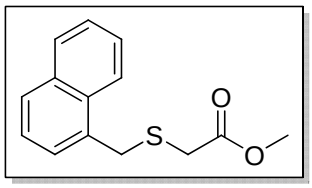
3.3.1.3 Methyl 2-(2-methylbenzylthio)acetate 66[194]



The title compound was prepared following the procedure described in Method 1 for methyl 2-(4-methylbenzylthio)acetate **63** using 2-methylbenzyl chloride **65** (4.70 mL, 35.56 mmol, 1 eq), potassium carbonate (7.37 g, 53.34 mmol, 1.5 eq), methyl thioglycolate **51** (3.18 mL, 35.56 mmol, 1 eq) and sodium iodide (0.27 g, 1.78 mmol, 5 mol%) in acetone (80 mL). Following work-up, methyl 2-(2-methylbenzylthio)acetate **66** was isolated as a pale yellow oil which was used without further purification (7.37 g, 98 %); ν_{max} (film)/cm^{-1} 1736 (C=O); δ_H (400 MHz) 2.41 (3H, s, ArC*H*$_3$), 3.11 (2H, s, C*H*$_2$), 3.74 (3H, s, C*H*$_3$), 3.82 (2H, s, C*H*$_2$), 7.07-7.23 (4H, m, Ar*H*); δ_C (75.5 MHz) 19.1 (*C*H$_3$), 32.4 (*C*H$_2$), 34.5 (*C*H$_2$), 52.4 (*C*H$_3$), 125.8, 127.6, 130.0, 130.8 (4 × aromatic *C*H), 134.8 (aromatic *C*$_q$), 137.0 (aromatic *C*$_q$), 171.0 (*C*=O); Exact mass calculated for $C_{11}H_{15}O_2S$ $[M+H]^+$, 211.0793. Found 211.0780; m/z (ESI+) 211 $[(M+H)^+$, 18%)].

3.3.1.4 Methyl 2-(naphthalen-1-ylmethylthio)acetate 60

Method 1 Using potassium carbonate (2 eq) and sodium iodide (5 mol%) in acetone[27]



The title compound was prepared following the procedure described in Method 1 for methyl 2-(4-methylbenzylthio)acetate **63** using 1-chloromethylnaphthalene* **59** (4.24 mL, 28.30 mmol, 1 eq), potassium carbonate (5.87 g, 42.45 mmol, 1.5 eq), methyl thioglycolate **51** (2.53 mL, 28.30 mmol, 1 eq) and sodium iodide (0.21 g, 1.42 mmol, 5 mol%) in acetone (80 mL). Following work-up, methyl 2-(naphthalen-1-ylmethylthio)acetate **60** was isolated as a clear viscous oil which was used without further purification (6.55 g, 94 %); ν_{max} (film)/cm^{-1} 1732 (C=O); δ_H (400 MHz) 3.12 (2H, s, C*H*$_2$), 3.71 (3H, s, C*H*$_3$), 4.29 (2H, s, C*H*$_2$), 7.35-7.57 (4H, m, Ar*H*), 7.72-7.87 (2H, m, Ar*H*), 8.13 (1H, d, *J* 8.4, Ar*H*); δ_C (75.5 MHz) 32.6 (*C*H$_2$), 34.1 (*C*H$_2$), 52.4 (*C*H$_3$), 124.0, 125.1, 125.9, 126.3, 127.8, 128.5, 128.8 (7 × aromatic *C*H), 131.4, 132.4, 134.2 (3 × aromatic C_q), 171.0 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{14}H_{15}O_2S$ $[M+H]^+$, 247.0793. Found 247.0788; m/z (ESI+) 247 $[(M+H)^+$, 5%)].

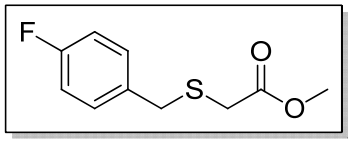
*1-Chloromethylnaphthalene **59** was melted by first heating the container to above room temperature in a water bath and adding it to warm methanol stirring in a 100 mL round bottom flask.

Method 2 Using 2 eq potassium carbonate in methanol

The title compound was prepared following the procedure described in Method 1 for methyl 2-(4-methylbenzylthio)acetate **63** using 1-chloromethylnaphthalene* **59** (4.24 mL, 28.30 mmol, 1 eq), methyl thioglycolate **51** (2.53 mL, 28.30 mmol, 1 eq) and potassium carbonate (7.82 g, 56.61 mmol, 2 eq) in methanol (90 mL). Following work-up, methyl 2-(naphthalen-1-ylmethylthio)acetate **60** was isolated as a viscous yellow oil which was used without further purification (1.51 g, 22%). Spectral details are given in Method 1, above.

*1-Chloromethylnaphthalene **59** was melted by first heating the container to above room temperature in a water bath and adding it to warm methanol stirring in a 100 mL round bottom flask.

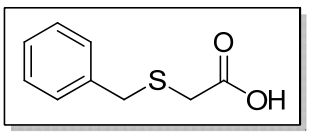
3.3.1.5 Methyl 2-(4-fluorobenzylthio)acetate 71



The title compound was prepared following the procedure described in Method 2 for methyl 2-(4-methylbenzylthio)acetate **63** using 4-fluorobenzyl bromide **72** (1.32 mL, 10.58 mmol, 1 eq), potassium carbonate (2.19 g, 15.87 mmol, 1.5 eq), methyl thioglycolate **51** (0.95 mL, 10.58 mmol, 1 eq) and sodium iodide (0.08 g, 0.53 mmol, 5 mol%). Following work-up, methyl 2-(4-fluorobenzylthio)acetate **71** was isolated as a clear oil (2.15 g, 95%); ν_{max} (film)/cm^{-1} 1737 (C=O); δ_H (400 MHz) 3.07 (2H, s, C*H*$_2$), 3.72 (3H, s, C*H*$_3$), 3.80 (2H, s, C*H*$_2$), 6.97-7.04 (2H, m, Ar*H*), 7.28-7.33 (2H, m, Ar*H*); δ_C (75.5 MHz) 32.0 (*C*H$_2$), 35.6 (*C*H$_2$), 52.4 (*C*H$_3$), 115.4 (*C*H, d, $^2J_{CF}$ 21.5, aromatic *C*H), 130.7 (CH, d, $^3J_{CF}$ 8.0, aromatic *C*H), 132.9 (C, d, $^4J_{CF}$ 3.2, aromatic C_q), 162.0 (C, d, $^1J_{CF}$ 245.8, aromatic C_q), 170.7 (*C*=O).

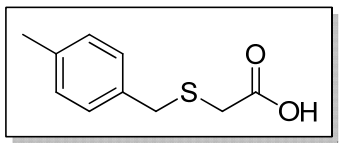
3.3.2 Synthesis of Carboxylic Acids

3.3.2.1 2-(Benzylthio)acetic acid 54[22]



Methyl 2-(benzylthio)acetate **53** (4.50 g, 22.95 mmol) was added to a solution of acetic acid and water (50:50, 100 mL). The reaction mixture was heated under reflux for 20 h and cooled to room temperature. The mixture was extracted with diethyl ether (2 × 40 mL). The combined ethereal layers were washed with water (6 × 150 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give 2-(benzylthio)acetic acid **54** as a white crystalline solid which was used without further purification (3.63 g, 87 %); m.p. 62-63 °C (lit.,[22] 64 °C); ν_{max} (KBr)/cm^{-1} 3431 (O-H) 1708 (C=O); δ_H (400 MHz) 3.10 (2H, s, C*H*$_2$), 3.86 (2H, s, C*H*$_2$), 7.21-7.48 (5H, m, Ar*H*), 10.25 (1H, br s, O*H*); δ_C (75.5 MHz) 31.9 (*C*H$_2$), 36.4 (*C*H$_2$), 127.4, 128.6, 129.2 (5 × aromatic *C*H), 136.9 (aromatic C_q), 176.7 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_9H_{11}O_3S$ $[M+O+H]^+$, 199.0429. Found 199.0430; m/z (ESI$^-$) 181 [(M-H)$^-$, 90%]. Spectral details are in agreement with those provided in the literature.[22]

3.3.2.2 2-(4-Methylbenzylthio)acetic acid 64[30]



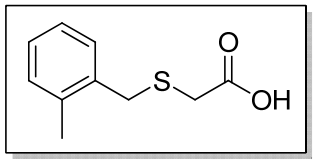
The title compound was prepared following the procedure described for 2-(benzylthio)acetic acid **54** using methyl 2-(4-methylbenzylthio)acetate **63** (11.29 g, 53.74 mmol), acetic acid and water (50:50, 110 mL). Following work-up, 2-(4-methylbenzylthio)acetic acid **64**, some remaining acetic acid (4:1) and a small quantity of methyl 2-(4-methylbenzylthio)acetate **63** (~5%) were isolated as a clear oil which solidified overnight to a white solid and was used without further purification (8.42 g, 80 %); m.p. 66-68 °C (lit.,[30] 68-70 °C); ν_{max} (KBr)/cm^{-1} 3431 (O-H), 1642 (C=O).

2-(4-Methylbenzylthio)acetic acid **64**: δ_H (400 MHz) 2.33 (3H, s, C*H*$_3$), 3.09 (2H, s, C*H*$_2$), 3.82 (2H, s, C*H*$_2$), 7.13 (2H, d, *J* 7.9, Ar*H*), 7.22 (2H, d, *J* 8.0, Ar*H*), 10.56 (1H, br s, O*H*); δ_C (75.5 MHz) 21.1 (*C*H$_3$), 32.0 (*C*H$_2$), 36.1 (*C*H$_2$), 129.1 (2 × aromatic *C*H), 129.3 (2 × aromatic *C*H), 133.8 (aromatic *C*$_q$), 137.1 (aromatic *C*$_q$), 177.1 (*C*=O).

Signals detected for 5% methyl 2-(4-methylbenzylthio)acetate **63**: δ_H (400 MHz) 3.70 (3H, s, C*H*$_3$), 3.78 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 32.1 (*C*H$_2$), 52.3 (*C*H$_3$), 129.1, 129.2 (4 × aromatic *C*H), 134.1 (aromatic *C*$_q$), 136.9 (aromatic *C*$_q$).

Signals detected for remaining acetic acid: δ_H (400 MHz) 2.11 (3H, s, C*H*$_3$); δ_C (75.5 MHz) 20.8 (*C*H$_3$), 178.0 (*C*=O).

3.3.2.3 2-(2-Methylbenzylthio)acetic acid 67[28]



The title compound was prepared following the procedure described for 2-(benzylthio)acetic acid **54** using methyl 2-(2-methylbenzylthio)acetate **66** (7.37 g, 35.08 mmol), acetic acid and water (50:50, 80 mL). Following work-up, 2-(2-methylbenzylthio)acetic acid **67**, some remaining acetic acid (4:1) and a trace amount of methyl 2-(2-methylbenzylthio)acetate **66** were isolated as an clear oil which crystallised overnight to an off-white solid and was used without further

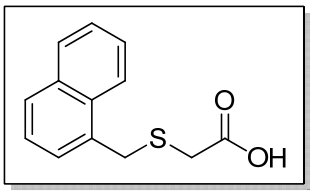
purification (5.45 g, 79 %); m.p. 42-44 °C (lit.,[28] 43.5 °C); ν_{max} (KBr)/cm^{-1} 3019 (O-H), 1706 (C=O).

2-(2-Methylbenzylthio)acetic acid **67**: δ_H (400 MHz) 2.41 (3H, s, C*H*$_3$), 3.14 (2H, s, C*H*$_2$), 3.88 (2H, s, C*H*$_2$), 7.12-7.26 (4H, m, Ar*H*), 9.50 (1H, br s, O*H*); δ_C (75.5 MHz) 19.1 (*C*H$_3$), 32.3 (*C*H$_2$), 34.5 (*C*H$_2$), 125.9, 127.8, 130.1, 130.9 (4 × aromatic *C*H), 134.5 (aromatic C_q), 137.0 (aromatic C_q), 176.9 (*C*=O). Spectral details in agreement with those reported in the literature.

Signals detected for trace amount of methyl 2-(2-methylbenzylthio)acetate **66**: δ_H (400 MHz) 3.11 (2H, s, C*H*$_2$), 3.71 (3H, s, C*H*$_3$), 3.82 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 52.5 (*C*H$_3$), 127.6 (aromatic *C*H).

Signals detected for remaining acetic acid: δ_H (400 MHz) 2.11 (3H, s, C*H*$_3$); δ_C (75.5 MHz) 20.8 (*C*H$_3$), 177.9 (*C*=O).

3.3.2.4 2-(Naphthalen-1-ylmethylthio)acetic acid 57[26]



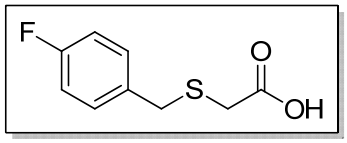
The title compound was prepared following the procedure described for 2-(benzylthio)acetic acid **54** using methyl 2-(naphthalen-1-ylmethylthio)acetate **60** (1.51 g, 6.14 mmol), acetic acid and water (50:50, 30 mL). Following work-up, 2-(naphthalen-1-ylmethylthio)acetic acid **57** and trace amounts of remaining acetic acid and methyl 2-(naphthalen-1-ylmethylthio)acetate **60** were isolated as an off-white crystalline solid which was used without further purification (1.16 g, 81 %); m.p. 110-112 °C (lit.,[28] 112 °C); ν_{max} (KBr)/cm^{-1} 3049 (O-H), 1704 (C=O).

2-(Naphthalen-1-ylmethylthio)acetic acid **57**: δ_H (400 MHz) 3.16 (2H, s, C*H*$_2$), 4.35 (2H, s, C*H*$_2$), 7.36-7.62 (4H, m, Ar*H*), 7.75-7.85 (1H, d, *J* 7.9, Ar*H*), 7.85-7.92 (1H, d, *J* 8.2, Ar*H*), 8.12 (1H, d, *J* 8.4, Ar*H*), 11.20 (1H, br s, O*H*); δ_C (75.5 MHz) 32.5 (*C*H$_2$), 34.1 (*C*H$_2$), 123.9, 125.1, 126.0, 126.3, 127.9, 128.6, 128.9 (7 × aromatic *C*H), 131.3, 132.1, 134.2 (3 × aromatic C_q), 176.3 (*C*=O); m/z (ESI$^-$) 231 [(M-H)$^-$, 100%]. Spectral details are in agreement with those reported in the literature.[26]

Signals detected for trace amount of methyl 2-(naphthalen-1-ylmethylthio)acetate **60**: δ_H (400 MHz) 3.12 (2H, s, C*H*$_2$), 3.71 (3H, s, C*H*$_3$), 4.19 (2H, s, C*H*$_2$).

Signals detected for remaining acetic acid: δ_H (400 MHz) 2.11 (3H, s, C*H*$_3$). δ_C (75.5 MHz) 20.8 (*C*H$_3$), 177.4 (*C*=O).

3.3.2.5 2-(4-Fluorobenzylthio)acetic acid 69[195]



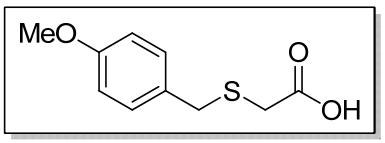
The title compound was prepared following the procedure used for 2-(benzylthio)acetic acid **54** using methyl 2-(4-fluorobenzylthio)acetate **71** (2.15 g, 10.04 mmol), acetic acid and water (50:50, 40 mL). Following work-up, 2-(4-fluorobenzylthio)acetic acid **69**, a small amount of remaining acetic acid (4.5:1) and a trace amount of methyl 2-(4-fluorobenzylthio)acetate **71** were isolated as an off-white crystalline solid and was used without further purification (1.83 g, 91%); m.p. 66-67 °C (lit.,[195] 68-69 °C); ν_{max} (KBr)/cm^{-1} 3019 (O-H), 1707 (C=O).

2-(4-Fluorobenzylthio)acetic acid **69**: δ_H (400 MHz) 3.09 (2H, s, C*H*$_2$), 3.83 (2H, s, C*H*$_2$), 6.98-7.04 (2H, m, Ar*H*), 7.28-7.33 (2H, m, Ar*H*), 9.23 (1H, br s, O*H*); δ_C (75.5 MHz) 31.9 (*C*H$_2$), 35.5 (*C*H$_2$), 115.5 (CH, d, $^2J_{CF}$ 21.5, aromatic *C*H), 130.8 (CH, d, $^3J_{CF}$ 8.0, aromatic *C*H), 132.6 (C, d, $^4J_{CF}$ 3.2, aromatic *C*$_q$), 162.1 (C, d, $^1J_{CF}$ 246.1, aromatic *C*$_q$), 176.7 (*C*=O).

Signals detected for trace amount of methyl 2-(4-fluorobenzylthio)acetate **71**: δ_H (400 MHz) 3.72 (3H, s, C*H*$_3$), 3.80 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 32.1 (*C*H$_2$), 115.4 (*C*H, d, $^2J_{CF}$ 21.5, aromatic *C*H), 130.7 (CH, d, $^3J_{CF}$ 8.0, aromatic *C*H), 132.9 (C, d, $^4J_{CF}$ 3.2, aromatic *C*$_q$), 162.0 (C, d, $^1J_{CF}$ 245.8, aromatic *C*$_q$), 170.7 (*C*=O).

Signals detected for remaining acetic acid: δ_H (400 MHz) 2.11 (3H, s, C*H*$_3$). δ_C (75.5 MHz) 20.8 (*C*H$_3$), 176.3 (*C*=O).

3.3.2.6 2-(4-Methoxybenzylthio)acetic acid 73[30]



Potassium carbonate (1.59 g, 11.49 mmol, 2 eq) was directly added to a solution of 4-methoxybenzyl chloride **74** (0.58 mL, 5.75 mmol, 1 eq) in acetone (15 mL). Thioglycolic acid **29** (0.40 mL, 5.75 mmol, 1 eq) in acetone (4 mL) was added over 5 mins at 0 °C, followed by a catalytic amount of sodium iodide (43 mg, 0.29 mmol, 5 mol%). The mixture was heated under reflux for 5 h, cooled to room temperature and concentrated *in vacuo*. The white solid was dissolved in water (20 mL) and acidified to pH 1 with concentrated hydrochloric acid (4 mL). The aqueous solution was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product as a clear oil (0.98 g). ^{1}H NMR analysis indicated the presence of 2-(4-methoxybenzylthio)acetic acid **73** along with remaining 4-methoxybenzyl chloride **74** and thioglycolic acid **29** starting material (2.3:1:1). The mixture was redissolved in acetone (20 mL) with potassium carbonate (0.50 g) and heated under reflux overnight. Following work up, the ^{1}H NMR spectrum of the crude product indicated that no further reaction had taken place (0.92 g, ~85% pure); m.p. 48-51 °C (lit.,[196] 55-56 °C); ν_{max} (KBr)/cm^{-1} 3049 (O-H), 1707 (C=O).

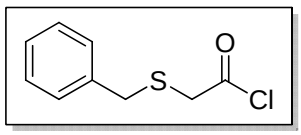
2-(4-Methoxybenzylthio)acetic acid **73**: δ_H (400 MHz) 3.09 (2H, s, C*H*$_2$), 3.80 (3H, s, C*H*$_3$), 3.82 (2H, s, C*H*$_2$), 6.83-6.88 (2H, m, Ar*H*), 7.22-7.28 (2H, m, Ar*H*), 9.29 (1H, br s, O*H*); δ_C (75.5 MHz) 31.8 (*C*H$_2$), 35.7 (*C*H$_2$), 55.3 (O*C*H$_3$), 113.9 (2 × aromatic *C*H), 128.8 (2 × aromatic *C*$_q$), 130.3 (aromatic *C*H), 158.9 (aromatic *C*$_q$), 176.9 (*C*=O).

Signals detected for thioglycolic acid **29**: δ_H (400 MHz) 2.01 (1H, t, *J* 7.9, *H*S), 3.30 (2H, d, *J* 7.9, C*H*$_2$); δ_C (75.5 MHz) 26.4 (*C*H$_2$), 170.5 (*C*=O).

Signals detected for 4-methoxybenzyl chloride **74**: δ_H (400 MHz) 3.34 (3H, s, OC*H*$_3$), 4.45 (2H, s, C*H*$_2$), 6.83-6.88 (2H, m, Ar*H*), 7.22-7.28 (2H, m, Ar*H*); δ_C (75.5 MHz) 32.2 (*C*H$_2$), 66.9 (O*C*H$_3$), 113.9 (aromatic *C*H), 114.0 (aromatic *C*H), 129.0 (aromatic *C*$_q$), 130.3 (aromatic *C*H), 130.4 (aromatic *C*H), 159.8 (aromatic *C*$_q$).

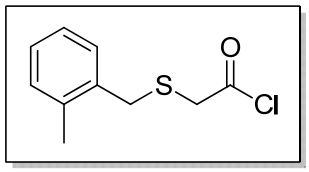
3.3.3 Synthesis of Acyl Chlorides

3.3.3.1 2-(Benzylthio)acetyl chloride 55[22]



Thionyl chloride (1.81 mL, 24.94 mmol, 2 eq) in dichloromethane (10 mL) was added dropwise to 2-(benzylthio)acetic acid **54** (2.27 g, 12.47 mmol, 1 eq) in dichloromethane (40 mL) over 10 min at 0 °C. The reaction mixture was allowed to slowly reach room temperature while stirring for 20 min. The solvent and excess thionyl chloride were removed *in vacuo* to leave 2-(benzylthio)acetyl chloride **55** as a yellow oil which was used without further purification (2.45 g, 98 %); ν_{max} (film)/cm^{-1} 1791 (C=O); δ_H (400 MHz) 3.51 (2H, s, C*H*$_2$), 3.82 (2H, s, C*H*$_2$), 7.21-7.49 (5H, m, Ar*H*); δ_C (75.5 MHz) 36.2 (*C*H$_2$), 43.6 (*C*H$_2$), 127.7, 128.8, 129.2 (5 × aromatic *C*H), 136.1 (aromatic C$_q$), 170.1 (*C*=O). Spectral details in agreement with those reported in the literature.[22]

3.3.3.2 2-(2-Methylbenzylthio)acetyl chloride 68[28]

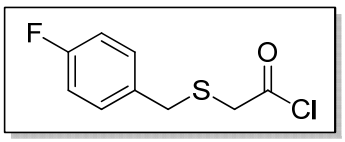


The title compound was prepared following the procedure described for 2-(benzylthio)acetyl chloride **55** using 2-(2-methylbenzylthio)acetic acid **67** (1.11 g, 5.64 mmol, 1 eq) and thionyl chloride (0.82 mL, 11.27 mmol, 2 eq) in dichloromethane (20 mL). The reaction mixture was stirred overnight and the solvent and excess thionyl chloride were removed *in vacuo* to give 2-(2-methylbenzylthio)acetyl chloride **68** and trace amount of 2-(2-methylbenzylthio)acetic acid **67** as a pale yellow oil which was used without further purification (1.16 g, 96 %); ν_{max} (film)/cm^{-1} 1775 (C=O).

2-(2-Methylbenzylthio)acetyl chloride **68**: δ_H (400 MHz) 2.40 (3H, s, C*H*$_3$), 3.55 (2H, s, C*H*$_2$), 3.84 (2H, s, C*H*$_2$), 7.13-7.23 (4H, m, Ar*H*); δ_C (75.5 MHz) 19.1 (*C*H$_3$), 34.5 (*C*H$_2$), 44.0 (*C*H$_2$), 126.0, 128.1, 130.1, 131.1 (4 × aromatic *C*H), 133.7 (aromatic *C*$_q$), 137.1 (aromatic *C*$_q$), 170.3 (*C*=O).

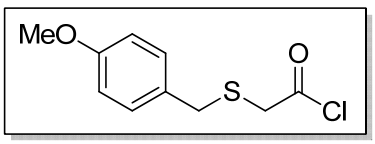
Signals detected for trace amount of 2-(2-methyl benzylthio)acetic acid **67**: δ_H (400 MHz) 3.71 (3H, s, C*H*$_3$), 3.82 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 52.5 (*C*H$_3$), 125.8, 127.8, 130.9 (aromatic *C*H).

3.3.3.3 2-(4-Fluorobenzylthio)acetyl chloride 70



The reaction was carried out following the procedure described for 2-(benzylthio)acetyl chloride **55** using 2-(4-fluorobenzylthio)acetic acid **69** (1.84 g, 9.38 mmol, 1 eq) and thionyl chloride (1.36 mL, 18.76 mmol, 2 eq) in dichloromethane (20 mL). The reaction mixture was stirred overnight and the solvent and excess thionyl chloride were removed *in vacuo* to give 2-(4-fluorobenzylthio)acetyl chloride **70** as an orange oil which was used without further purification (2.00 g, 98%); ν_{max} (film)/cm^{-1} 1774 (C=O), δ_H (400 MHz) 3.51 (2H, s, C*H*$_2$), 3.80 (2H, s, C*H*$_2$), 6.97-7.06 (2H, m, Ar*H*), 7.24-7.32 (2H, m, Ar*H*); δ_C (75.5 MHz) 35.4 (*C*H$_2$), 43.6 (*C*H$_2$), 115.7 (CH, d, $^2J_{CF}$ 21.7, aromatic *C*H), 130.8 (CH, d, $^3J_{CF}$ 8.1, aromatic *C*H), 131.8 (C, d, $^4J_{CF}$ 3.2, aromatic *C*$_q$), 162.3 (C, d, $^1J_{CF}$ 246.6, aromatic *C*$_q$), 170.0 (*C*=O).

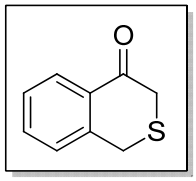
3.3.3.4 Attempted synthesis of 2-(4-methylbenzylthio)acetyl chloride 260[197]



The reaction was carried out following the procedure described for 2-(benzylthio)acetyl chloride **55** using 2-(4-methoxylbenzylthio)acetic acid **73** (**73**:**74**:**29** mixture 2.3:1:1, 0.92 g) and thionyl chloride (0.67 mL, 8.66 mmol, 2 eq) in dichloromethane (20 mL). The reaction mixture was stirred overnight and the solvent and excess thionyl chloride were removed *in vacuo* to give the crude product as a yellow residue (49 mg). ^{1}H NMR analysis indicated the presence of a complex mixture of unidentifiable products among remaining starting material (~20%).

3.3.4 Synthesis of Cyclic Sulfides

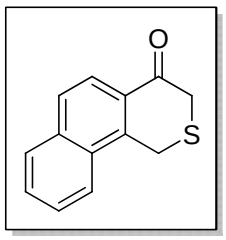
3.3.4.1 Isothiochroman-4-one 43[22]



Anhydrous aluminium chloride (1.96 g, 14.70 mmol, 1.2 eq) in dichloromethane (10 mL) was added to a solution of 2-(benzylthio)acetyl chloride **55** (2.45 g, 12.25 mmol, 1 eq) in dichloromethane (40 mL). The reaction mixture was stirred overnight at room temperature. A solution of conc. hydrochloric acid in water (50:50, 40 mL) was added and the two layers were partitioned. The organic layer was washed with sat. sodium bicarbonate solution (2 × 10 mL), water (10 mL), brine (10 mL) and dried with anhydrous $MgSO_4$. The solution was concentrated *in vacuo* to give isothiochroman-4-one **43** as a brown solid which was used without further purification (1.53 g, 76 %); m.p. 61-62 °C (lit.,[198] 60 °C); ν_{max} (KBr)/cm^{-1} 1673 (C=O); δ_H (400 MHz) 3.56 (2H, s, C*H*$_2$), 3.93 (2H, s, C*H*$_2$), 7.20 (1H, d, *J* 7.9, Ar*H*), 7.34-7.40 (1H, m, Ar*H*), 7.43-7.49 (1H, m, Ar*H*), 8.09 (1H, d, *J* 7.9, Ar*H*); δ_C (75.5 MHz) 30.6 (*C*H$_2$), 37.1 (*C*H$_2$), 127.7, 127.8, 129.0 (3 × aromatic *C*H), 131.9 (aromatic C_q), 133.0 (aromatic *C*H), 141.8 (aromatic C_q), 191.0 (*C*=O). Spectral details in agreement with those reported in the literature.[22]

3.3.4.2 1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene 47[26]

Method 1. With phosphorus pentoxide in toluene



Phosphorus pentoxide (21.33 g, 75.13 mmol, 3 eq) was directly added to a stirring solution of 2-(naphthalen-1-ylmethylthio)acetic acid **57** (5.81 g, 25.04 mmol, 1 eq) in hot toluene (60 °C, 100 mL). The mixture was stirred vigorously under reflux for 3 h, and a further 2 eq phosphorus pentoxide (14.22 g, 50.09 mmol) were then added. The mixture was stirred for an additional 2 h under reflux and cooled to room temperature. The organic solution was decanted from the brown insoluble mass, which was extracted with hot toluene (60 °C, 2 × 40 mL). The combined organic layers were washed with water (40 mL), brine (40 mL)

and dried with anhydrous $MgSO_4$. Concentration *in vacuo* gave the crude product as a light brown solid (2.33 g) which was purified by recrystallisation from 95% ethanol to give 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** and a small amount of 2-(naphthalen-1-ylmethylthio)acetic acid **57** (~4%) as a bright yellow solid (1.20 g, 22%). Found: C, 72.15; H, 4.69; S, 15.30. $C_{13}H_{10}OS$ requires C, 72.87; H, 4.69; S, 14.96%; m.p. 120-122°C (lit.,[26] 123-124 °C); ν_{max} (KBr)/cm^{-1} 1678 (C=O).

1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47**: δ_H (400 MHz) 3.60 (2H, s, C*H*$_2$), 4.39 (2H, s, ArC*H*$_2$), 7.58-7.65 (2H, m, Ar*H*), 7.81 (1H, d, *J* 8.0, Ar*H*), 7.84-7.91 (1H, m, Ar*H*), 8.00-8.11 (1H, m, Ar*H*), 8.15 (1H, d, *J* 7.9, Ar*H*); δ_C (75.5 MHz) 26.9 (*C*H$_2$), 35.6 (*C*H$_2$), 124.0, 124.1, 127.3, 127.8, 128.5, 129.0 (6 × aromatic *C*H), 129.8, 130.5, 135.3, 139.4 (4 × aromatic C_q), 191.2 (*C*=O). Spectral details in agreement with those reported in the literature.[26]

Signals detected for 4% 2-(naphthalen-1-ylmethylthio)acetic acid **57**: δ_H (400 MHz) 3.71 (3H, s, C*H*$_3$), 4.19 (2H, s, C*H*$_2$).

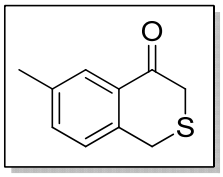
Method 2. With phosphorus pentoxide in benzene

The title compound was prepared following the procedure described in Method 1 using 2-(naphthalen-1-ylmethylthio)acetic acid **57** (4.23 g, 18.21 mmol, 1 eq), phosphorus pentoxide (15.51 g, 54.63 mmol, 3 eq for 3 h, followed by 10.34 g, 36.42 mmol, 2 eq for 2 h) in benzene (100 mL) instead of toluene. Following work-up and recrystallisation **47** was isolated as a yellow solid (0.93 g, 24%). Spectral details as described above.

Method 3: With aluminium chloride

The title compound was prepared following the procedure described for isothiochroman-4-one **43** using 2-(naphthalen-1-ylmethylthio)acetic acid **261** (5.39 g, 21.57 mmol, 1 eq), aluminium chloride (3.45 g, 25.88 mmol, 1.2 eq) in dichloromethane (50 mL). Following work-up, the crude product was isolated as a brown solid (1.73 g). Following purification by flash chromatography (80:20 hexane:ethyl acetate) and recrystallisation from 95% ethanol, **47** was isolated as a bright yellow solid (0.63 g, 13%). Spectral details as described above.

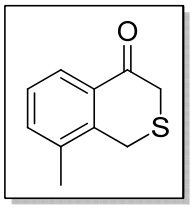
3.3.4.3 6-Methylisothiochroman-4-one 46[199]



The title compound was prepared following the procedure described in Method 1 for 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** using 2-(4-methylbenzylthio)acetic acid **64** (2.27 g, 11.58 mmol, 1 eq), phosphorus pentoxide (4.94 g, 34.74 mmol, 3 eq for 3 h, followed by 3.29 g, 23.16 mmol, 2 eq for 2 h) in toluene (50 mL). Following work-up, the crude product was isolated as a viscous yellow oil (0.85 g). ^{1}H NMR analysis indicated the presence of the desired product 6-methylisothiochroman-4-one **46** along with a small quantity of unidentifiable impurities (~60% pure). Purification by flash chromatography (90:10 hexane:ethyl acetate) gave 6-methylisothiochroman-4-one **46** as a bright yellow crystalline solid (0.53 g, 26%); m.p. 53-54 °C (lit.,[30] 52-53 °C); ν_{max} (KBr)/cm^{-1} 1678 (C=O); δ_H (400 MHz) 2.37 (3H, s, C*H*$_3$), 3.53 (2H, s, C*H*$_2$), 3.88 (2H, s, ArC*H*$_2$), 7.09 (1H, d, *J* 7.8, Ar*H*), 7.24-7.28 (1H, m, Ar*H*), 7.89 (1H, s, Ar*H*); δ_C (75.5 MHz) 21.0 (Ar*C*H$_3$), 30.3 (*C*H$_2$), 37.1 (*C*H$_2$), 127.7, 129.2 (aromatic *C*H), 131.6 (aromatic *C*$_q$), 133.9 (aromatic *C*H), 137.5, 138.9 (2 × aromatic *C*$_q$), 191.5 (*C*=O). Spectral details in agreement with those reported in the literature.[199]

3.3.4.4 8-Methylisothiochroman-4-one 48[28]

Method 1. With phosphorus pentoxide in toluene over 5 h



The title compound was prepared following the procedure described in Method 1 for 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** using 2-(2-methylbenzylthio)acetic acid **67** (2.39 g, 12.19 mmol, 1 eq), phosphorus pentoxide (4.66 g, 36.57 mmol, 3 eq for 3 h, followed by 3.10 g, 24.38 mmol, 2 eq for 2 h) in toluene (50 mL). Following work-up, the crude product was isolated as a viscous brown oil (1.45 g). Purification by flash chromatography (95:5 hexane:ethyl acetate) gave 8-methylisothiochroman-4-one **48** and a small amount of 2-(2-methylbenzylthio)acetic acid **67** (~2%) and methyl 2-(2-methylbenzylthio)acetate **66** (~3%), as a yellow solid (0.67 g, 31 %); m.p. 56-57 °C; ν_{max} (KBr)/cm^{-1} 1681 (C=O).

8-Methylisothiochroman-4-one **48**: δ_H (400 MHz) 2.31 (3H, s, C*H*$_3$), 3.46 (2H, s, C*H*$_2$), 3.83 (2H, s, ArC*H*$_2$), 7.22-7.27 (1H, m, Ar*H*), 7.33 (1H, d, *J* 6.9, Ar*H*), 7.94 (1H, d, *J* 7.8, Ar*H*); δ_C (75.5 MHz) 19.6 (*C*H$_3$), 27.5 (*C*H$_2$), 35.9 (Ar*C*H$_2$), 127.6 (aromatic *C*H), 127.7 (aromatic *C*H), 132.6 (aromatic C_q), 134.3 (aromatic *C*H), 135.4 (aromatic C_q), 139.8 (aromatic C_q), 191.1 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_{12}OS$ $[M+H]^+$, 179.0531. Found 179.0526, m/z (ESI-) 178 $[(M)^-]$.

Signals detected for 2% 2-(2-methylbenzylthio)acetic acid **67**: δ_H (400 MHz) 2.41 (3H, s, ArC*H*$_3$), 3.11 (2H, s, C*H*$_2$), 3.71 (3H, s, C*H*$_3$); δ_C (75.5 MHz) 19.1 (*C*H$_3$), 32.4 (*C*H$_2$), 34.5 (*C*H$_2$), 52.4 (*C*H$_3$), 125.8, 127.6, 130.0, 130.8 (4 × aromatic *C*H), 134.8 (aromatic C_q), 137.0 (aromatic C_q), 171.0 (*C*=O);

Signals detected for 3% methyl 2-(2-methylbenzylthio)acetate **66**: δ_H (400 MHz) 2.41 (3H, s, ArC*H*$_3$), 3.11 (2H, s, C*H*$_2$), 3.74 (3H, s, C*H*$_3$), 3.82 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 52.5 (*C*H$_3$), 127.6 (aromatic *C*H).

Method 2 With phosphorus pentoxide in toluene overnight

The reaction procedure was carried out as described in Method 1 for 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** using 2-(2-methylbenzylthio)acetic acid **67** (1.195 g, 6.095 mmol, 1 eq), phosphorus pentoxide (8.651, 30.375 mmol, 5 eq) in toluene (30 mL) overnight. Following work-up, the crude product was isolated as a black solid. ^{1}H NMR analysis indicated the presence of a complex mixture of unidentifiable compounds and the product **48** (~8 %). Spectral details for 8-methylisothiochroman-4-one **48** are given in Method 1.

Method 3 With aluminium chloride

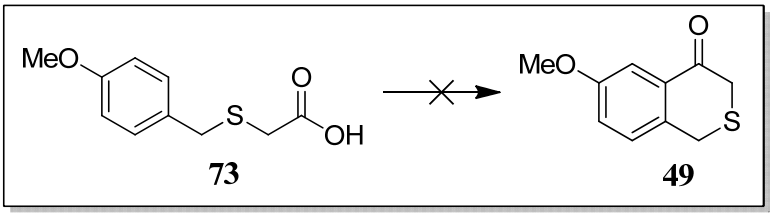
The reaction procedure was carried out as described for isothiochroman-4-one **43** using 2-(2-methylbenzylthio)acetyl chloride **68** (0.45 g, 2.12 mmol, 1 eq) and aluminium chloride (0.34 g, 2.54 mmol, 1.2 eq) in dichloromethane (25 mL) overnight. Following work-up, the crude product was isolated as a brown oil (145 mg). ^{1}H NMR analysis indicated that ~60% of the acyl chloride **68** had cyclised, along with starting material **68** and an unidentifiable signal at 4.60 ppm. The crude product was redissolved in dichloromethane (30 mL) and aluminium chloride (0.14

g, 1.02 mmol) was added to the solution. The reaction mixture was stirred for a further 18 h. Following work-up, the crude product was isolated as a brown oil (23 mg). ^{1}H NMR analysis indicated that the reaction had gone to completion. Spectral details as described above.

Method 4 With trifluoroacetic acid and trifluoroacetic anhydride

The reaction procedure was followed as described for 6-methoxyisothiochroman-4-one **49** using 2-(2-methyl benzylthio)acetic acid **67** (0.66 g, 3.37 mmol), trifluoroacetic acid (20 mL) and trifluoroacetic anhydride (8 mL) overnight. Following work-up, the crude product was isolated as a foamy orange solid (359 mg). ^{1}H NMR analysis indicated that decomposition of the starting material had occurred.

3.3.4.5 Attempted synthesis of 6-methoxyisothiochroman-4-one 49



Attempt 1 With trifluoroacetic acid and trifluoroacetic anhydride

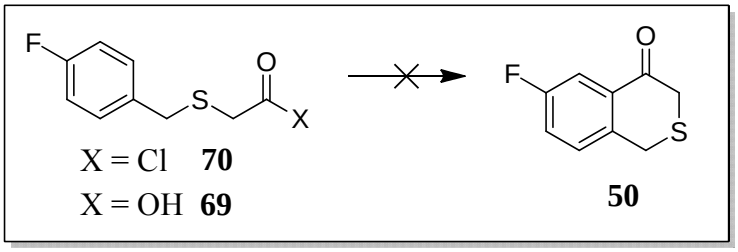
2-(4-Methoxy benzylthio)acetic acid **73** (0.85 g, 3.99 mmol) was added to a stirring solution of trifluoroacetic acid (20 mL) and trifluoroacetic anhydride (8 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature under the inert atmosphere for 5 h. The mixture was slowly poured onto aqueous potassium hydroxide (2M, 30 mL) at 0 °C and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The ethereal layer was washed with hydrochloric acid (1N, 15 mL), saturated sodium hydrogen carbonate (15 mL), water (15 mL) and brine (15 mL). The crude product was isolated as a viscous orange oil (144 mg). ^{1}H NMR analysis of the crude product demonstrated the absence of the CH_2 singlet of the carboxylic acid **73** at 3.09 ppm and a mixture of

unidentifiable compounds. Attempts to isolate the cyclised sulfide **49** by flash chromatography (diethyl ether:hexane 20:80) proved unsuccessful.

Attempt 2 With phosphorus pentoxide in toluene

The reaction was carried out as described in Section 3.3.4.2 Method 1 for 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** using 2-(4-methoxy benzylthio)acetic acid **73** (0.45 g, 2.12 mmol, 1 eq), phosphorus pentoxide (1.81 g, 6.37 mmol, 3 eq for 3 h, followed by 1.21 g, 4.24 mmol, 2 eq for 2 h) in toluene (25 mL). Following work-up, the crude product was isolated as a brown residue (37 mg). ^{1}H NMR analysis of the crude product indicated the presence of a complex mixture of compounds. Attempts were not made to isolate the cyclised sulfide **49** due to the very low yield of the crude product.

3.3.4.6 Attempted synthesis of 6-fluoroisothiochroman-4-one 50



Attempt 1 With aluminium chloride

The reaction procedure was carried out as described for isothiochroman-4-one **43** using 2-(4-fluorobenzylthio)acetyl chloride **70** (0.27 g, 1.26 mmol, 1 eq) and aluminium chloride (0.20 g, 1.51 mmol, 1.2 eq) in dichloromethane (20 mL) overnight. Following work-up, the crude product was isolated as a light brown residue (10 mg). ^{1}H NMR analysis indicated the presence of a mixture of compounds, possibly including the cyclised product **50**. Attempts were not made to purify the mixture due to the low yield of the crude product. Signals tentatively assigned as the cyclised sulfide **50**: δ_H (400 MHz) 3.05 (2H, s, CH_2), 3.70 (2H, s, CH_2).

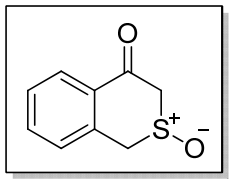
Attempt 2 With phosphorus pentoxide in toluene

The reaction was carried out as described in Method 1 for 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** using 2-(4-fluorobenzylthio)acetic acid **69** (1.60 g, 7.98 mmol, 1 eq), phosphorus pentoxide (6.80 g, 23.94 mmol, 3 eq for 3 h, followed by 4.53 g, 15.96 mmol, 2 eq for 2 h) in toluene (60 mL). Following work-up, the crude product was isolated as a yellow oil (0.77 g). ^{1}H NMR analysis of the crude product indicated the presence of a mixture of compounds, including signals indicative of the cyclised product **50**. Attempts to purify the mixture by flash chromatography (90:10 hexane/ethyl acetate) proved unsuccessful. ^{1}H NMR analysis indicated the presence of at least two unknown compounds. Signals observed: δ_H (400 MHz) 2.20 (s), 2.31 (s), 3.90 (s), 3.94 (s), 6.91-7.18 (m, Ar*H*).

3.3.5 Synthesis of Sulfoxides

3.3.5.1 Isothiochroman-4-one *S*-oxide 79[41]

Method 1 With sodium metaperiodate in methanol and water



A solution of sodium metaperiodate (0.36 g, 1.69 mmol, 1 eq) in water (5 mL) was added slowly to a solution of isothiochroman-4-one **43** (0.28 g, 1.69 mmol, 1 eq) in methanol (20 mL) while stirring at 0 °C. After 5 min, a white precipitate had formed. The reaction was monitored by TLC and stirred for 2.5 h while returning to room temperature. The precipitate was filtered and the filtrate concentrated *in vacuo* to leave the sulfoxide **79** and remaining salt mixture as a light brown solid. Dichloromethane (30 mL) was added and the mixture stirred for 10 min. The remaining solid was removed by filtration and the filtrate concentrated *in vacuo* to give isothiochroman-4-one *S*-oxide **79** as a brown solid which was recrystallised from toluene/hexane to afford light brown crystals (0.17 g, 56%); m.p. 169-171 °C (lit.,[42] 170-171 °C); ν_{max} (KBr)/cm^{-1} 1681 (C=O), 1024 (S-O); δ_H (300 MHz) 3.94 (1H, d, *J* 15.4, A of AB_q, CH_2), 3.98 (1H, d, *J* 15.4, B of AB_q, CH_2), 4.32 (1H, d, *J* 15.3, A of AB_q, ArCH_2), 4.36 (1H, d, *J* 15.3, B of AB_q, ArCH_2), 7.36 (1H, d, *J* 7.6,

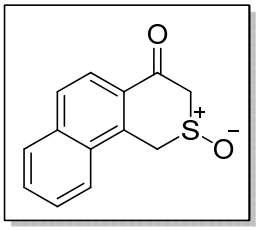
Ar*H*), 7.46-7.53 (1H, m, Ar*H*), 7.61-7.67 (1H, m, Ar*H*), 8.13 (1H, d, *J* 7.9 Ar*H*); δ_C (75.5 MHz) 52.4 (*C*H_2), 59.0 (*C*H_2), 128.3, 129.2, 131.1 (3 × aromatic *C*H), 131.4 (aromatic C_q), 131.6 (aromatic C_q), 135.4 (aromatic *C*H), 187.9 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_9H_9O_2S$ $[M+H]^+$, 181.0323. Found 181.0317, m/z (ESI$^-$) 179 [$(M-H)^-$, 10%)]. Spectral details in agreement with those reported in the literature.[41]

Method 2 Attempted oxidation with polystyrene supported periodate resin in methanol[192]

Polystyrene supported periodate resin (0.178 g, 0.224 mmol, 1 eq) was 'swollen' in methanol (8 mL) for 5 min at room temperature. Isothiochroman-4-one **43** (37 mg, 0.224 mmol, 1 eq) in dichloromethane (1 mL) was added to the solution and the reaction mixture was stirred at room temperature overnight. The reaction progress was monitored by TLC analysis which indicated that no oxidation had taken place over 48 h. The resin was removed by gravity filtration and washed with methanol (3 × 3 mL). The washes were combined with the supernatant liquid and concentrated to leave a brown residue (28 mg). The ^{1}H NMR spectrum of the crude product showed the presence of isothiochroman-4-one starting material **43** only.

3.3.5.2 1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene *S*-oxide 80

Method 1. Oxidation with Oxone®



Oxone® (0.17 g, 0.28 mmol, 0.5 eq) in water (5 mL) was added dropwise to a stirring solution of 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** (0.12 g, 0.56 mmol) in acetone (10 mL) at 0 °C. The mixture was allowed to slowly reach room temperature while stirring over 2 h. Water (10 ml) was then added to the flask to dissolve the inorganic salts. The resulting solution was extracted with dichloromethane (2 × 20 ml) and the combined organic layers washed with water (10 mL), brine (10 ml), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene *S*-oxide **80** along with trace quantities of impurities as a pale yellow solid (100 mg). The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using ethyl

acetate (100%) as eluent. The pure sulfoxide **80** was obtained as a white crystalline solid (81 mg, 63%). Found: C, 67.80; H, 4.34; S, 13.61. $C_{13}H_{10}O_2S$ requires C, 67.80; H, 4.38; S, 13.92%; m.p. 189-191 °C; ν_{max} (KBr)/cm^{-1} 1681 (C=O), 1045 (S-O); δ_H (400 MHz) 4.10 (1H, d, *J* 14.9, A of AB_q, C*H*$_2$), 4.19 (1H, d, *J* 14.9, B of AB_q, C*H*$_2$), 4.64 (1H, d, *J* 15.2, A of AB_q, ArC*H*$_2$), 4.86 (1H, d, *J* 15.2, B of AB_q, ArC*H*$_2$), 7.64-7.78 (2H, m, Ar*H*), 7.83-8.00 (2H, m, Ar*H*), 8.05-8.20 (2H, m, Ar*H*); δ_C (75.5 MHz) 48.1 (*C*H$_2$), 58.7 (*C*H$_2$), 122.8, 124.3, 128.0, 129.3, 129.3, 129.4 (6 × aromatic *C*H), 129.7, 129.9, 131.3, 136.7 (4 × aromatic C_q), 188.4 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{11}O_2S$ $[M+H]^+$, 231.0480. Found 231.0477, m/z (ESI$^+$) 231 [$(M+H)^+$, 15%)].

Method 2. Oxidation with 1 eq *m*-CPBA over 6 h

A solution of *m*-CPBA (70%, 0.14 g, 0.56 mmol, 1 eq) in dichloromethane (10 mL) was added dropwise over 5 min to a stirring solution of 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** (0.12 g, 0.56 mmol, 1 eq) in dichloromethane (10 mL) at 0 °C. The mixture was allowed to slowly reach room temperature while stirring over 6 h. The progress of the reaction was monitored by TLC analysis using hexane/ethyl acetate (80:20) as eluent. After 6 h, the solution was filtered to remove precipitated chlorobenzoic acid. The filtrate was diluted with dichloromethane (30 mL) and washed with sat. sodium bicarbonate solution (2 × 10 mL), water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product as a pale yellow solid (76 mg). ^{1}H NMR analysis indicated the presence of the sulfoxide **80** and the sulfide **47** (2:1). Spectral details for the sulfoxide **80** are given in Method 1 above. Attempts to isolate a clean sample of the sulfoxide **80** by recrystallisation from a range of solvents proved unsuccessful. Separation by flash chromatography using gradient ethyl acetate/hexane (20:80-100% ethyl acetate) led to isolation of the sulfide only (18 mg).

Method 3. Oxidation with 1.1 eq *m*-CPBA overnight

The title compound was prepared following the procedure described in Method 2 using 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** (98 mg, 0.43 mmol, 1 eq), *m*-CPBA (70%, 115 mg, 0.47 mmol, 1.1 eq) and dichloromethane (20 mL). Following work-up the crude product was isolated as a pale yellow solid (51 mg). ^{1}H

NMR analysis indicated the presence of the sulfide **47** and the sulfoxide **80** (1:3) among trace amounts of impurities. Spectral details as described above.

Method 4. Oxidation with sodium metaperiodate

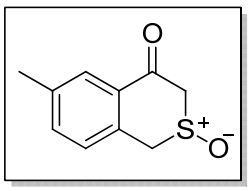
The title compound was prepared following the procedure described for isothiochroman-4-one *S*-oxide **79** using 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** (164 mg, 0.766 mmol, 1 eq), sodium metaperiodate (163 mg, 0.766 mmol, 1 eq), methanol (15 mL) and water (5 mL). The progress of the reaction was monitored by TLC analysis using hexane/ethyl acetate (80:20) as eluent. The crude product was isolated as an off-white solid following work-up after 24 h (69 mg). ^{1}H NMR analysis indicated the presence of the sulfide **47** and the sulfoxide **80** (9:1). Spectral details as described above.

Method 5. Oxidation with 1.1 eq 30% hydrogen peroxide

Acetic acid (5 mL) was added to 1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene **47** (114 mg, 0.533 mmol, 1 eq) and the mixture was brought to 0 °C until a viscous slurry was formed. Hydrogen peroxide (30% aqueous solution, 0.06 mL, 0.590 mmol, 1.1 eq) was added to the stirring slurry over 5 min at 0 °C. The reaction mixture was allowed to slowly reach room temperature and stirred for 18 h. The solution was diluted with water (30 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with sat. sodium bicarbonate solution (2 × 10 mL), water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow solid (72 mg). ^{1}H NMR analysis indicated the presence of the sulfide **47** and the sulfoxide **80** (1:6) among unidentifiable impurities. Spectral details as described above.

3.3.5.3 6-Methylisothiochroman-4-one *S*-oxide 81

Method 1. Oxidation with Oxone®



The title compound was prepared following the procedure described Method 1 for 1*H*-benzo[*h*]isothiochromen-4(3*H*)-one *S*-oxide **80** using 6-methylisothiochroman-4-one **46** (0.17 g,

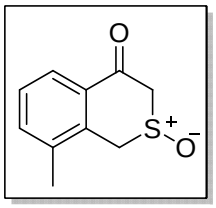
0.95 mmol, 1 eq), Oxone® (0.29 g, 0.47 mmol, 0.5 eq), water (5 mL) and acetone (10 mL). The progress of the reaction was monitored by TLC analysis (50:50 hexane:ethyl acetate) over 2 h. Following work-up, the crude sulfoxide **81** along with a small quantity of 6-methylisothiochroman-4-one **46** (~4%), was isolated as an off-white solid (150 mg, 80%). Purification by flash chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent gave pure 6-methylisothiochroman-4-one *S*-oxide **81** as a bright white crystalline solid (52 mg, 28%). Found: C, 62.10; H, 5.24; S, 16.35. $C_{10}H_{10}O_2S$ requires C, 61.83; H, 5.19; S, 16.51%; m.p. 140-142 °C; ν_{max} (KBr)/cm^{-1} 1679 (C=O), 1048 (S-O); δ_H (400 MHz) 2.41 (3H, s, C*H*$_3$), 3.94 (1H, d, *J* 15.6, A of AB$_q$, C*H*$_2$), 4.02 (1H, d, *J* 15.6, B of AB$_q$, C*H*$_2$), 4.25 (1H, d, *J* 14.9, A of AB$_q$, ArC*H*$_2$), 4.32 (1H, d, *J* 14.9, B of AB$_q$, C*H*$_2$), 7.26 (1H, d, *J* 15.6, Ar*H*), 7.46 (1H, d, *J* 15.6, Ar*H*), 7.93 (1H, s, Ar*H*); δ_C (75.5 MHz) 21.1 (*C*H$_3$), 52.4 (*C*H$_2$), 59.2 (*C*H$_2$), 128.4 (aromatic *C*$_q$), 128.6 (aromatic *C*$_q$), 129.2 (aromatic *C*H), 131.1 (aromatic *C*H), 131.4 (aromatic *C*$_q$), 136.4 (aromatic *C*H), 139.5 (aromatic *C*$_q$), 188.1 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_{12}O_2S$ $[M+H]^+$, 195.0480. Found 195.0472, m/z (ESI+) 195 $[(M+H)^+$, 95%)].

Signals identified for 4% 6-methylisothiochroman-4-one **46** in crude product: δ_H (400 MHz) 2.37 (3H, s, C*H*$_3$), 3.53 (2H, s, C*H*$_2$), 3.88 (2H, s, ArC*H*$_2$), 7.89 (1H, s, Ar*H*).

Method 2. Oxidation with sodium metaperiodate

The title compound was prepared following the procedure described for isothiochroman-4-one *S*-oxide **79** using 6-methylisothiochroman-4-one **46** (1.92 g, 11.68 mmol, 1 eq), sodium metaperiodate (2.50 g, 11.68 mmol, 1 eq), methanol (30 mL) and water (10 mL). The progress of the reaction was monitored by TLC analysis using hexane/ethyl acetate (80:20) as eluent. The crude product was isolated as an off-white solid following work-up after 18 h (1.92 g). ^{1}H NMR analysis indicated the presence of the sulfide **46** and sulfoxide **81** (1:5). Spectral details for the sulfoxide **81** are given in Method 1 above.

3.3.5.4 8-Methylisothiochroman-4-one *S*-oxide 82



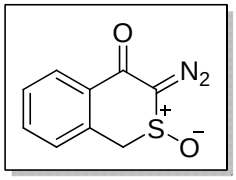
The title compound was prepared following the procedure described Method 1 for 1*H*-benzo[*h*]isothiochromen-4(3*H*)-one *S*-oxide **80** using 8-methylisothiochroman-4-one **48** (0.30 g, 1.66 mmol, 1 eq), Oxone® (0.51 g, 0.83 mmol, 0.5 eq), water (7 mL) and acetone (15 mL). The progress of the reaction was monitored by TLC analysis (100% ethyl acetate) over 2.5 h. Following work-up, the crude sulfoxide **82** along with a small quantity of 8-methylisothiochroman-4-one **48** (4%), was isolated as an off-white solid (0.27 g, 1.37 mmol, 83%). Purification by flash chromatography on silica gel using ethyl acetate (100%) as eluent gave pure 8-methylisothiochroman-4-one *S*-oxide **82** as a bright white crystalline solid (208 mg, 64%); found: C, 62.20; H, 5.13; S, 16.48. $C_{10}H_{10}O_2S$ requires C, 61.83; H, 5.19; S, 16.51%; m.p. 148-149 °C; ν_{max} (KBr)/cm^{-1} 1680 (C=O), 1047 (S-O); δ_H (400 MHz) 2.42 (3H, s, C*H*$_3$), 3.96 (1H, d, *J* 14.7, A of AB$_q$, C*H*$_2$), 4.02 (1H, d, *J* 14.7, B of AB$_q$, C*H*$_2$), 4.23 (1H, d, *J* 16.0, A of AB$_q$, ArC*H*$_2$), 4.30 (1H, d, *J* 16.0, B of AB$_q$, ArC*H*$_2$), 7.33-7.39 (1H, m, Ar*H*), 7.52 (1H, d, *J* 18.2, Ar*H*), 7.98 (1H, d, *J* 18.2, Ar*H*); δ_C (75.5 MHz) 20.0 (*C*H$_3$), 48.5 (*C*H$_2$), 58.3 (*C*H$_2$), 126.2 (aromatic *C*H), 128.4 (aromatic *C*H), 129.9 (aromatic *C*$_q$), 131.8 (aromatic *C*$_q$), 137.1 (aromatic *C*H), 138.1 (aromatic *C*$_q$), 188.5 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_{12}O_2S$ $[M+H]^+$, 195.0480. Found 195.0471, m/z (ESI+) 195 [$(M+H)^+$, 10%)].

Signals identified for 4% 8-methylisothiochroman-4-one **48** in the crude product: δ_H (400 MHz) 2.31 (3H, s, C*H*$_3$), 3.46 (2H, d, *J* 0.5, C*H*$_2$), 3.83 (2H, s, ArC*H*$_2$), 7.94 (1H, d, *J* 7.8, Ar*H*).

3.3.6 Synthesis of α-Diazo-β-keto Sulfoxides

3.3.6.1 3-Diazoisothiochroman-4-one *S*-oxide 87

Method 1. Diazo transfer with tosyl azide **41** (1.0 eq) and triethylamine (1.0 eq) in acetonitrile followed by purification with flash chromatography



A solution of triethylamine (0.60 mL, 4.29 mmol, 1 eq) in acetonitrile (5 mL) was added dropwise to a solution of isothiochroman-4-one *S*-oxide **79** (0.77 g, 4.29 mmol, 1 eq) in acetonitrile (30 mL) while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and a solution of tosyl azide **41** (0.85 g, 4.29 mmol, 1 eq) in acetonitrile (10 mL) was then added slowly while stirring at 0 °C under a nitrogen atmosphere. The solution was allowed to slowly reach room temperature while stirring under the inert atmosphere over 9 h. The solvent was removed under reduced pressure to yield the crude product as a viscous brown oil (1.45 g). The ^{1}H NMR spectrum of the crude product indicated an efficient reaction to give quantitative diazo transfer to the diazosulfoxide **87**. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent to give pure 3-diazoisothiochroman-4-one *S*-oxide **87** as a pale brown solid (0.31 g, 35%). Decolourisation of a dichloromethane solution with activated charcoal gave yellow crystals; found: C, 52.49; H, 3.08; N, 12.69. $C_9H_6N_2O_2S$ requires C, 52.42; H, 2.93; N, 13.58%; m.p. 78-79 °C (decomp.); ν_{max} (KBr)/cm^{-1} 2120 (C=N_2), 1632 (C=O), 1054 (S-O); δ_H (400 MHz) 4.32 (2H, fine AB_q appears as s, CH_2), 7.39 (1H, d, *J* 7.1, Ar*H*), 7.52-7.65 (2H, m, Ar*H*), 8.14 (1H, dd, *J* 7.6, 1.5, Ar*H*); δ_C (75.5 MHz) 52.9 (*C*H_2), 79.2 (*C*=N_2), 127.6 (aromatic *C*H), 129.4 (aromatic *C*H), 130.3 (aromatic C_q), 131.2 (aromatic C_q), 131.7 (aromatic *C*H), 133.9 (aromatic *C*H), 176.0 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_9H_7N_2O_2S$ $[M+H]^+$, 207.0228. Found 207.0228.

Method 2. Diazo transfer with tosyl azide **41** (1.0 eq) and triethylamine (1.0 eq) in acetonitrile followed by work-up as described by Regitz[56]

The title compound was prepared following the procedure described in Method 1 using isothiochroman-4-one *S*-oxide **79** (0.50 g, 2.80 mmol, 1 eq), tosyl azide **41** (0.55 g, 2.80 mmol, 1 eq), triethylamine (0.40 mL, 2.80 mmol, 1 eq) and acetonitrile (35 mL). ^{1}H NMR analysis of the crude reaction mixture indicated complete conversion of the sulfoxide **79** to the diazosulfoxide **87**. The brown oil (1.24 g) was dissolved in dichloromethane (40 mL) and washed with 9 % aqueous KOH (2 × 20 mL), water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give a brown residue (112 mg). The ^{1}H NMR spectrum of the crude material indicated the presence of 3-diazoisothiochroman-4-one *S*-oxide **87**, tosyl azide **41** and triethylamine (1:1.5:0.6). Spectral details as described above.

Method 3. Diazo transfer with tosyl azide **41** (1.0 eq) and triethylamine (1.0 eq) in dichloromethane

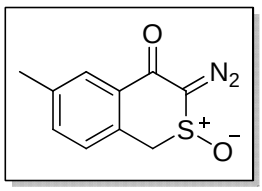
A solution of triethylamine (0.22 mL, 1.514 mmol, 1 eq) in dichloromethane (3 mL) was added dropwise to a solution of isothiochroman-4-one *S*-oxide **79** (0.31 g, 1.51 mmol, 1 eq) in dichloromethane (15 mL) while stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 5 min and a solution of tosyl azide **41** (0.30 g, 1.52 mmol, 1 eq) in dichloromethane (5 mL) was then added slowly while stirring at 0 °C under a nitrogen atmosphere. The solution was allowed to reach room temperature and stirred under the inert atmosphere overnight. The reaction progress was monitored by TLC and after 18 h, ^{1}H NMR analysis of the crude reaction mixture indicated complete conversion of the sulfoxide **79** to the diazosulfoxide **87**. The solvent was removed *in vacuo* to yield the crude product as a brown oil (0.72 g) which was adsorbed onto Celite® and purified by flash chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent to give pure 3-diazoisothiochroman-4-one *S*-oxide **87** as a pale brown solid (87 mg, 28%).

Method 4 Diazo transfer with polystyrene supported tosyl azide **93** (1.5 eq) and triethylamine in acetonitrile

Polystyrene supported tosyl azide **41** (0.15 g, 0.62 mmol, 1.5 eq) was 'swollen' by stirring in acetonitrile (5 mL) for 10 min. Isothiochroman-4-one *S*-oxide **79** (74 mg, 0.41 mmol, 1 eq) in acetonitrile (2 mL) followed by triethylamine (0.06 mL, 0.41 mmol, 1 eq) in acetonitrile (2 mL) were added dropwise at room temperature and the reaction mixture was stirred overnight. The progress of the reaction was monitored by TLC and after 24 h, an aliquot of the mixture was withdrawn and concentrated. ^{1}H NMR analysis of this sample indicated that the reaction had gone ~60% to completion. Stirring of the reaction mixture was continued at room temperature. After 72 h, TLC analysis of a second sample indicated complete consumption of the starting material. The resin was removed by gravity filtration and washed with acetonitrile (3 × 5 mL). The washes were combined with the supernatant and concentrated to leave a brown oil. The ^{1}H NMR spectrum of the crude product indicated the presence of the diazosulfoxide **87** and triethylamine. The crude reaction mixture was purified by flash chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent to give pure 3-diazoisothiochroman-4-one *S*-oxide **87** as a brown residue (21 mg, 17%).

Note: Decomposition of 3-diazoisothiochroman-4-one *S*-oxide **87** to the sulfine 1-oxo-2-thioxoindane-*S*-oxide **262a** occurred on storage in deuterated chloroform for extended periods. See Section 3.8.1.

3.3.6.2 3-Diazo-6-methylisothiochroman-4-one *S*-oxide 88

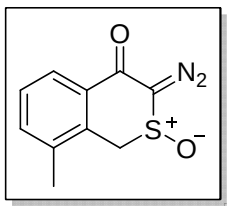


The title compound was prepared following the procedure described in Method 1 for 3-diazoisothiochroman-4-one *S*-oxide **87** using 6-methylisothiochroman-4-one *S*-oxide **81** (1.31 g, 6.73 mmol, 1 eq), tosyl azide **41** (1.33 g, 6.73 mmol, 1 eq) and triethylamine (0.93 mL, 6.73 mmol, 1 eq) in acetonitrile (25 mL). The crude product was isolated as a viscous brown oil (1.561 g). The ^{1}H NMR spectrum of the crude product indicated an efficient reaction to give clean diazo transfer to the diazosulfoxide **88**. Purification by flash chromatography on silica gel using gradient

ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent gave 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** as pale brown crystals (0.38 mg, 26%). Decolourisation of a dichloromethane solution with activated charcoal gave yellow crystals; m.p. 64-65 °C (decomp.); ν_{max} (KBr)/cm^{-1} 2111 (C=N_2), 1680 (C=O), 1084 (S-O); δ_H (400 MHz) 2.43 (3H, s, CH_3), 4.27 (2H, fine AB_q appears as s, CH_2), 7.27 (1H, d, *J* 7.7, one of Ar*H*), 7.41 (1H, dd, *J* 7.7, 1.3, Ar*H*), 7.94 (1H, unresolved d, *J* 1.1, Ar*H*); δ_C (75.5 MHz) 21.2 (*C*H_3), 52.8 (*C*H_2), 79.2 (*C*=N_2), 127.2 (aromatic C_q), 127.9 (aromatic *C*H), 130.9 (aromatic C_q), 131.6 (aromatic *C*H), 134.6 (aromatic *C*H), 139.6 (aromatic C_q), 176.2 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_9N_2O_2S$ $[M+H]^+$, 221.0385. Found 221.0378, m/z (ESI+) 221 $[(M+H)^+$, 64%], 193 $[(C_{10}H_9O_2S)^+$ 100%].

The structure was confirmed by single crystal X-ray diffraction on a crystalline sample of **88** recrystallised from dichloromethane/hexane. Crystals of **88** are triclinic, space group $P\bar{1}$, formula $C_{10}H_8N_2O_2S$, M = 220.24, a = 4.5638(10) Å, b = 7.0494(16) Å, c = 15.476(4) Å, U = 485.35(19) Å^3, F(000) = 228, μ(Mo-Kα) = 0.312 mm^{-1}, R(F_o) = 0.0389 for 1768 observed reflection with I > 2σ(I), wR_2(F^2) = 0.1204 for all 2025 unique reflections. Data in the θ range 1.35 – 26.65° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

3.3.6.3 3-Diazo-8-methylisothiochroman-4-one *S*-oxide 89



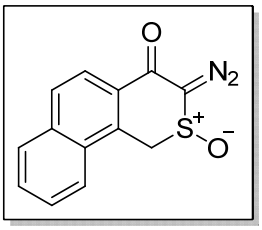
The title compound was prepared following the procedure described in Method 1 for 3-diazoisothiochroman-4-one *S*-oxide **87** using 8-methylisothiochroman-4-one *S*-oxide **82** (1.590 g, 8.189 mmol, 1 eq), tosyl azide **41** (1.612 g, 8.189 mmol, 1 eq) and triethylamine (1.14 mL, 8.189 mmol, 1 eq) in acetonitrile (30 mL). The crude product was isolated as a viscous brown oil (1.72 g). The ^{1}H NMR spectrum of the

crude product indicated an efficient reaction to give relatively clean diazo transfer to the diazosulfoxide **89**. Purification by flash chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent to give pure 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** as a pale brown solid (602 mg, 33%). Decolourisation of a dichloromethane solution with activated charcoal gave yellow crystals; m.p. 72-74 °C (decomp.); ν_{max} (KBr)/cm^{-1} 2114 (C=N_2), 1624 (C=O); δ_H (400 MHz) 2.44 (3H, s, CH_3), 4.07 (1H, d, *J* 15.5, A of ABq, one of CH_2), 4.58 (1H, d, *J* 15.5, B of ABq, one of CH_2), 7.42 (1H, t, *J* 7.7, Ar*H*), 7.49 (1H, d, *J* 7.0, Ar*H*), 8.01 (1H, d, *J* 6.9, Ar*H*); δ_C (75.5 MHz) 19.9 (*C*H_3), 48.8 (*C*H_2), 78.7 (*C*=N_2), 125.6 (aromatic *C*H), 128.6 (aromatic *C*H), 131.6 (aromatic C_q), 135.9 (aromatic *C*H), 138.5 (aromatic C_q), 176.5 (*C*=O)*. *Note:* One C_q signal was not observed in the ^{13}C NMR spectrum. HRMS (ESI+): Exact mass calculated for $C_{10}H_9N_2O_2S$ $[M+H]^+$, 221.0385. Found 221.0384, m/z (ESI+) 221 $[(M+H)^+$, 18%], 193 $[(C_{10}H_9O_2S)^+$, sulfine **263** 80%].

Note*: Due to a time lapse of 12 weeks between the dates for which ^{1}H NMR spectrum and the ^{13}C NMR spectra were obtained, small quantities of the sulfine **263 had formed on decomposition of the diazosulfoxide **89**. This was reflected in the ^{13}C NMR spectra obtained.

Signals detected for sulfine **263**: δ_C (75.5 MHz) 17.7 (*C*H_3), 32.1 (*C*H_2), 122.5 (aromatic *C*H), 129.0 (aromatic *C*H), 135.8 (aromatic C_q), 137.2 (aromatic C_q), 137.2 (aromatic *C*H), 144.4 (aromatic C_q), 184.8 (*C*=S=O), 188.9 (*C*=O);

3.3.6.4 3-Diazo-1-Oxo-3-thia-1,2,3,4-tetrahydrophenanthrene *S*-oxide 90

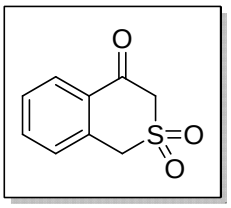


The title compound was prepared following the procedure described in Method 1 for 3-diazoisothiochroman-4-one *S*-oxide **87** using 1*H*-benzo[*h*]isothiochromen-4(3*H*)-one *S*-oxide **80** (0.63 g, 2.71 mmol, contained ~10% impurities), tosyl azide **41** (0.53 g, 2.71 mmol, 1 eq) and triethylamine (0.37 mL, 2.71 mmol, 1 eq) in acetonitrile (15 mL). The crude product was isolated as a viscous brown oil (0.82 g). ^{1}H NMR analysis of the crude product showed the presence of a complex mixture of unidentifiable compounds. Purification by flash

chromatography on silica gel using gradient ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent gave one fraction as an orange residue, which contained the diazosulfoxide **90** along with unknown products, presumably due to decomposition (43 mg). Signals indicative of 3-diazo-1-oxo-3-thia-1,2,3,4-tetrahydrophenanthrene *S*-oxide **90**: δ_H (400 MHz) 4.35 (1H, d, *J* 15.8, one of C*H*$_2$), 5.20 (1H, d, *J* 15.9, one of C*H*$_2$).

3.3.7 Synthesis of Sulfone

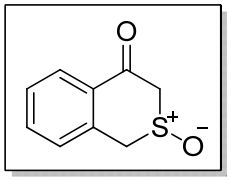
3.3.7.1 Isothiochroman-4-one 2,2-dioxide 83[43]



Hydrogen peroxide solution (30% aqueous solution, 5.0 mL, 48.91 mmol) was added to a solution of isothiochroman-4-one **43** (0.23 g, 1.42 mmol, 1 eq) in acetic acid/acetic anhydride (5:2, 14 mL) over 5 mins at 0 °C. The mixture was allowed to reach room temperature and stirred for a further 16 h. The solution was diluted with water (50 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with sat. sodium bicarbonate solution (2 × 10 mL), water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. Recrystallisation from acetone afforded isothiochroman-4-one 2,2-dioxide **83** as white crystals (0.19 g, 69 %); m.p. 155-157 °C (lit.,[42] 157-158 °C); ν_{max} (KBr)/cm^{-1} 1688 (C=O); δ_H (400 MHz) 4.23-4.24 (2H, m, C*H*$_2$), 4.54 (2H, s, ArC*H*$_2$), 7.36 (1H, d, *J* 7.6, Ar*H*), 7.55 (1H, t, *J* 7.6, Ar*H*), 7.70 (1H, td, *J* 7.5, 1.4, Ar*H*), 8.23 (1H, dd, *J* 7.9, 1.1, Ar*H*). Spectral details in agreement with those reported in the literature.[43]

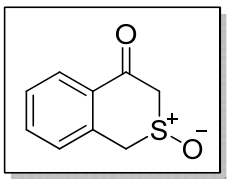
3.3.8 Attempted Asymmetric Synthesis of Isothiochroman-4-one *S*-oxide 79

3.3.8.1 Kagan Oxidation



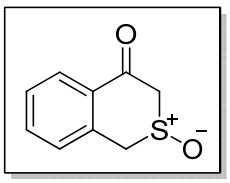
Freshly distilled titanium isopropoxide (b.p. 43-5^{o}C at 0.04 mm Hg,), (0.23 ml, 0.76 mmol, 0.5 eq) was added to a solution of (+)-diethyl tartrate (0.26 ml, 1.52 mmol, 1 eq) in freshly doubly distilled dichloromethane (6 mL) under a nitrogen atmosphere. On addition of the $Ti(O^{i}Pr)_4$, the reaction solution turned yellow. Water (14 μl, 0.76 mmol, 1 eq) was then added from a micro syringe as slowly as possible. On completion of the water addition, the reaction solution was stirred at room temperature for 25 minutes. A solution of isothiochroman-4-one **43** (250 mg, 1.52 mmol, 1 eq) in freshly doubly distilled dichloromethane (1 mL) was added and the reaction solution cooled to -30 °C. The reaction solution was maintained at -30 °C for 40 minutes, then cumene hydroperoxide (0.23 mL, 1.52 mmol, 1 eq) was added dropwise from a micro syringe. The reaction solution was stirred at – 30 °C for 5 minutes, then the reaction flask was transferred to a freezer at -21 °C. After 18 h, the flask was removed from the freezer and the contents allowed to warm to room temperature. Water (0.24 mL) was added and the solution stirred for 2 h, during which time a gel formed. The gel was removed by filtration through a bed of Celite®, which was then washed with dichloromethane (150 mL) to ensure complete recovery of the crude product. Aqueous NaOH (2M, 4.5 mL) and brine (2.2 mL) were added and the reaction mixture was stirred for 90 minutes. At this point, more brine (100 mL) was added and the phases separated. The organic layer was washed with brine (100 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give a mixture of the sulfoxide **79**, the sulfide **43**, and 2-phenylpropan-2-ol. Following flash chromatography on silica gel using ethyl acetate/hexane (50:50-100% ethyl acetate) as eluent, the sulfoxide **79** was isolated as a white crystalline solid (30 mg, 12%). The enantiomeric excess was determined by chiral HPLC (see Appendix I for conditions). Spectral characteristics for **79** as reported in Section 3.3.5.1 above.

3.3.8.2 Bolm Oxidation



$VO(acac)_2$ (2.6 mg, 0.01 mmol, 1 mol%) was added to a round bottomed flask containing the ligand (*S*)-2-(*N*-3',5'-diiodosalicylidene)-amino-3,3-dimethyl-1-butanol **95** (7.1 mg, 0.015 mmol, 0.7 mol%) in dichloromethane (2 mL). The resulting solution was stirred at room temperature for 5 min, then a solution of isothiochroman-4-one **43** (157 mg, 0.98 mmol, 1 eq) in dichloromethane (2 mL) was added. Hydrogen peroxide solution [0.12 mL (30% H_2O_2), 1.1 mmol, 1.1 eq] was added to the resulting solution. The reaction mixture was then stirred at room temperature for a further 16 hours. Water (5 mL) was added and the phases were separated; the organic layer was washed with water (2 × 5 mL) and brine (5 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product as a pale brown solid (166 mg). ^{1}H NMR analysis of the crude product indicated the presence of the sulfoxide **79** and the sulfide **43** (1:2) among small quantities of unidentifiable impurities. Following chromatography on silica gel using hexane/ethyl acetate (50:50-100% ethyl acetate), the pure sulfoxide **79** was recovered as a white crystalline solid (30 mg, 17%). The enantiomeric excess was determined by chiral HPLC (see Appendix I for conditions). Spectral details for the **79** as reported in Section 3.3.5.1 above.

3.3.8.3 Copper(II) catalysed oxidation



Copper(II) acetylacetonate (5.1 mg, 2 μmol, 2 mol%) was added to a round bottomed flask containing Schiff base ligand (*S*)-2-(*N*-3'-chloro-5'-fluorosalicylidene)-amino-3,3-dimethyl-1-butanol **96** (11.0 mg, 4 μmol, 4 mol%) and hexane/methanol (9:1, 1 mL) was added. The resulting solution was stirred at room temperature for 5 min, and then a solution of isothiochroman-4-one **43** (204 mg, 1.25 mmol, 1 eq) in hexane/methanol (9:1, 1 mL) was added. After 5 min attiring at room temperature, hydrogen peroxide solution (0.16 mL (30% H_2O_2), 1.38 mmol, 1.1 eq) was added in one portion, dropwise to the solution. The reaction mixture was stirred for a further 16 h. Water (10 mL) and dichloromethane (10 mL) were added to the reaction mixture and the phases were separated. The organic layer was washed with water (3

× 10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated under reduced pressure to give the crude product was a pale brown solid (102 mg). ^{1}H NMR analysis of the crude product indicated a mixture of the sulfoxide **79** and sulfone **83** (19:1) among small quantities of unidentifiable impurities.. The crude material was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50-100% ethyl acetate) as eluent to yield the pure sulfoxide **79** as a white crystalline solid (60 mg, 27%). The enantiomeric excess was determined by chiral HPLC (see Appendix I for conditions). Spectral details for **79** as reported in Section 3.3.5.1 above.

3.3.9 Procedure for Bakers Yeast Reduction

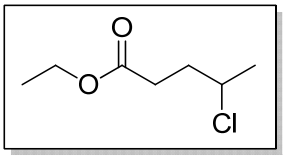
The procedure is adapted from that of Seebach[84] and has been used by Collins.[8] A mixture of baker's yeast (130 mg) and sugar (0.98 g) in water (40 mL) was incubated for 30 min, after which the substrate (**43**, 0.30 mmol) in DMSO (1 mL) was added. After agitating for ~ 1 h, TLC analysis indicated the absence of starting material. Celite® (~2 g) was added and after 10 min, the reaction was filtered. The filter cake was washed with ethyl acetate (2 × 20 mL), the filtrate was separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with water (20 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated. ^{1}H NMR analysis indicated the formation of a complex mixture of unidentifiable compounds.

3.4 Synthesis of Monocyclic α-Diazo-β-keto Sulfoxides

3.4.1 Synthesis of Ethyl Esters

3.4.1.1 Ethyl 4-chloropentanoate 107

Method 1: With thionyl chloride and ethanol as described by von Seebach[89]



γ-Valerolactone **109** (2.04 g, 20.35 mmol, 1 eq) was added directly to thionyl chloride (1.55 mL, 21.36 mmol, 1.05 eq) at room temperature. The mixture was stirred at 80 °C for 3 h and cooled to room temperature. Ethanol (1.31 mL, 22.38 mmol, 1.1 eq) was added dropwise over 5 min at 0 °C. The solution was then stirred for 16 h under reflux, cooled to room temperature, and concentrated *in vacuo* to give a brown oil (2.15 g). ^{1}H NMR analysis indicated the presence of γ-valerolactone **109** and ethyl 4-chloropentanoate **107** (1.6:1). The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (90:10) as eluent to give ethyl 4-chloropentanoate **107** as a pale yellow oil (1.77 g, 53%); ν_{max} (film)/cm^{-1} 1731 (C=O), 1334 (C-O), 1187 (C-O); δ_H (400 MHz) 1.24 (3H, t, *J* 7.0, C*H*$_3$), 1.51 (3H, d, *J* 6.1, C*H*$_3$), 1.88-1.99 (1H, m, one of C*H*$_2$), 2.02-2.16 (1H, m, one of C*H*$_2$), 2.41-2.60 (2H, m, C*H*$_2$), 4.01-4.20 (3H, m, contains 1H m of C*H*, and 2H q, *J* 7.2, of C*H*$_2$ at 4.10); δ_C (75.5 MHz) 14.2 (*C*H$_3$), 25.3 (*C*H$_3$), 31.3 (*C*H$_2$), 35.1 (*C*H$_2$), 57.7 (*C*H), 60.5 (*C*H$_2$), 172.9 (*C*=O). Spectral details in agreement with those reported in the literature.[89]

Method 2: With thionyl chloride, catalytic HCl and ethanol as described by Molander[90]

Thionyl chloride (4.06 mL, 55.94 mmol, 5 eq) was directly added to γ-valerolactone **109** (1.12 g, 11.19 mmol, 1 eq) at 0 °C under a nitrogen atmosphere. Conc. hydrochloric acid (0.10 mL, 1.12 mmol, 10 mol%) was added and the mixture was allowed to reach room temperature and stirred overnight. The solution was concentrated *in vacuo* to give an orange oil (1.32 g). The oil was redissolved in diethyl ether (25 mL) and washed with sat. sodium bicarbonate solution (2 × 10 mL),

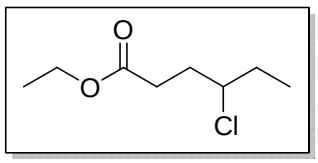
water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give an orange residue (201 mg). ^{1}H NMR analysis indicated the presence of γ-valerolactone **109** and ethyl 4-chloropentanoate **107** (9:1). Spectral details for **107** as described above.

Method 3: With thionyl chloride in ethanol solvent as described by Takeda[91]

Thionyl chloride (6.40 mL, 88.19 mmol, 10 eq) was added slowly over 10 min to a solution of γ-valerolactone **109** (0.88 g, 8.82 mmol, 1 eq) in ethanol at 0 °C. The solution was stirred while slowly returning to reach room temperature for 1 h and then heated and stirred at 60 °C for 4 h. The mixture was cooled to room temperature and concentrated *in vacuo* to give the crude product as a clear oil (0.77 g). ^{1}H NMR analysis showed the presence of γ-valerolactone **109** and ethyl 4-chloropentanoate **107** (2:1). Spectral details for **107** as described above.

3.4.1.2 Ethyl 4-chlorohexanoate 108

Method 1: With thionyl chloride and ethanol as described by von Seebach[89]



The title compound was prepared following the procedure described in Method 1 for ethyl 4-chloropentanoate **107** using thionyl chloride (11.01 mmol, 0.80 mL, 1.05 eq), γ-caproactone **110** (10.49 mmol, 1.20 g, 1 eq) and ethanol (11.54 mmol, 0.66 mL, 1.1 eq). Following work up, the crude product was isolated as a yellow oil (0.99 g). ^{1}H NMR analysis indicated the presence of ethyl 4-chlorohexanoate **108** and γ-caproactone **110** (1:2). The crude material was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (95:5) as eluent to give the pure ester **108** as a pale yellow oil (0.60 mg, 33%); ν_{max} (film)/cm^{-1} 1736 (C=O), 1179 (C-O); δ_H (400 MHz) 1.04 (3H, t, *J* 7.3, C*H*$_3$), 1.26 (3H, t, *J* 7.1, C*H*$_3$), 1.67-1.86 (2H, m, C*H*$_2$), 1.87-1.99 (1H, m, one of C*H*$_2$), 2.07-2.18 (1H, m, one of C*H*$_2$), 2.44-2.61 (2H, m, C*H*$_2$), 3.84-3.93 (1H, m, C*H*), 4.14 (2H, q, *J* 7.1, C*H*$_2$); δ_C (75.5 MHz) 10.9 (*C*H$_3$), 14.2 (*C*H$_3$), 31.3, 31.6, 33.0, (3 × *C*H$_2$), 60.5 (O*C*H$_2$), 64.6 (*C*H), 173.0 (*C*=O); m/z (ESI+) 179

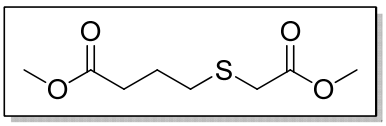
{[($C_8H_{15}{}^{35}ClO_2$)+H^+], 30%}, 181 {[($C_8H_{15}{}^{37}ClO_2$)+H^+], 15%}, [(M-HCl)$^+$, 100%]. Spectral details in agreement with those reported in the literature.[88]

Method 2: With thionyl chloride and ethanol solvent as described by Takeda[91]

The title compound was prepared following the procedure described in Method 3 for ethyl 4-chloropentanoate **107** using γ-caproactone **110** (4.99 g, 43.45 mmol, 1 eq), thionyl chloride (31.74 mL, 437.53 mmol, 10 eq) and ethanol (100 mL). The solution was concentrated *in vacuo* to give a yellow oil (7.82 g). ^{1}H NMR analysis indicated the presence of ethyl 4-chlorohexanoate **108** and γ-caproactone **110** (1:8). Spectral details for **108** as described above.

3.4.2 Synthesis of Diesters

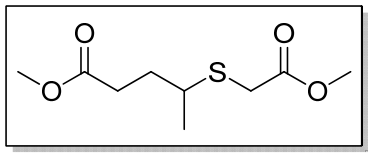
3.4.2.1 Methyl 4-[(2-methoxy-2-oxomethyl)thio]butanoate 102[200]



A solution of methyl thioglycolate **51** (5.00 mL, 55.57 mmol, 1 eq) in methanol (20 mL) was added to a solution of sodium methoxide (sodium 1.28 g, 55.57 mmol, 1 eq) in methanol (40 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 10 min and methyl 4-bromobutanoate **101** (10.82 mL, 55.5 mmol, 1 eq) in methanol (10 mL) was added slowly. The reaction mixture was stirred for 15 h at room temperature. The mixture was filtered to remove any inorganic salts which had precipitated, and the filtrate was concentrated *in vacuo* to give a yellow oil. Water (100 mL) was added to the oil and the mixture was extracted with diethyl ether (3 × 50 mL). The combined ethereal layers were washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give methyl 4-[(2-methoxy-2-oxomethyl)thio]butanoate **102** as a pale yellow oil (7.80 g, 68 %) which was used without further purification; ν_{max} (film)/cm^{-1} 1736 (C=O); δ_H (400 MHz) 1.94 (2H, quintet, *J* 7.2, CH_2), 2.45 (2H, t, *J* 7.3, CH_2), 2.68 (2H, t, *J* 7.2, CH_2), 3.23 (2H, s, CH_2), 3.66 (3H, s, CH_3), 3.74 (3H, s, CH_3); δ_C (75.5 MHz) 24.0 (*C*H$_2$), 31.8 (*C*H$_2$), 32.6 (*C*H$_2$), 33.1 (*C*H$_2$), 51.6 (O*C*H$_3$), 52.3 (O*C*H$_3$), 170.8 (*C*=O), 173.3 (*C*=O); HRMS (ESI+): Exact mass

calculated for $C_8H_{15}O_4S$ $[M+H]^+$, 207.0691. Found 207.0698; m/z (ESI+) 207 $[(M+H)^+$, 100%)].

3.4.2.2 Methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate 117



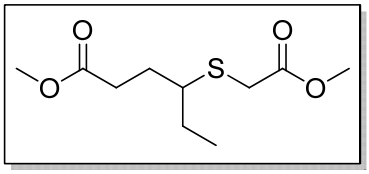
Methyl thioglycolate **51** (5.82 mL, 65.15 mmol, 1 eq) in methanol (10 mL) was added to a solution of sodium methoxide (1.50 g sodium, 65.15 mmol, 1 eq) in methanol (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 10 min and then ethyl 4-chloropentanoate **107** (9.81 g, 65.15 mmol, 1 eq) in methanol (10 mL) was added slowly. The reaction mixture was stirred for 72 h under reflux. The filtrate was concentrated *in vacuo* to give a yellow oil. Water (80 mL) was added to the oil and extracted with diethyl ether (3 × 30 mL). The combined ethereal layers were washed with water (20 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product as a pale yellow oil (10.32 g). ^{1}H NMR analysis indicated the presence of a complex mixture of compounds, including the product methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **117**, methyl bis(thioacetate) **123** and methyl 4-chloropentanoate **264** (25: 4: 5). The mixture was purified by Kugelrohr distillation. The product methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **117** and a small quantity of remaining methyl bis(thioacetate) **123** (4:1, 3.97 g, ~22%) were isolated at 175-180 °C, 15 Torr. Attempts to further purify the mixture by distillation and base extraction were unsuccessful; ν_{max} (film)/cm^{-1} 1733 (C=O).

Methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **117**: δ_H (400 MHz) 1.31 (3H, d, *J* 6.8, C*H*$_3$), 1.87 (2H, dt appears as q, *J* 7.7, C*H*$_2$), 2.47 (2H, m, C*H*$_2$), 2.95 (1H, sextet, *J* 6.7, C*H*), 3.26 (2H, fine AB$_q$ appears as s, C*H*$_2$), 3.68 (3H, s, OC*H*$_3$), 3.73 (3H, s, OC*H*$_3$); δ_C (75.5 MHz) 20.9 (*C*H$_3$), 31.1, 31.2, 32.0 (3 × *C*H$_2$), 40.2 (*C*H), 51.6 (O*C*H$_3$), 52.4 (O*C*H$_3$), 171.1 (*C*=O), 173.6 (*C*=O); m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_9H_{17}O_4S$ $[M+H]^+$, 221.0848. Found 221.0844; m/z (ESI+) 221 $[(M+H)^+$, 40 %)], 243 $[(M+Na)^+$, 62%].

Methyl bis(thioacetate) **123**: δ_H (400 MHz) 3.60 (4H, s, 2 × CH_2), 3.78 (6H, s, 2 × OCH_3); δ_C (75.5 MHz) 41.2 (2 × *C*H_2), 52.6 (2 × *C*H_3), 169.8 (2 × *C*=O).

Characteristic signal detected for methyl 4-chloropentanoate **264** in the ^{1}H NMR spectrum of crude mixture: δ_H (400 MHz) 1.54 (3H, d, *J* 7.0, CH_3).

3.4.2.3 Methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate 118



The title compound was prepared following the procedure described for methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **117** using ethyl 4-chlorohexanoate **108** (10.25 g, 62.29 mmol, 1 eq), methyl thioglycolate **51** (5.57 mL, 62.29 mmol, 1 eq), sodium (1.143 g sodium, 62.29 mmol, 1 eq) and methanol (80 mL). The reaction mixture was stirred at 0 °C and then heated under reflux for 72 h. Following work up, the crude product was isolated as a yellow oil (12.76 g). ^{1}H NMR analysis indicated the presence of a mixture of a complex mixture of compounds, including the product methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **118**, methyl bis(thioacetate) **123** and methyl 4-chlorohexanoate **265** (5: 3: 6). The crude product was purified by Kugelrohr distillation. Methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **118** and remaining methyl bis(thioacetate) **123** were isolated at 180-185 °C, 15 Torr (1.8:1, 4.60 g). Attempts to further purify the mixture by distillation and base extraction were unsuccessful. ν_{max} (film)/cm^{-1} 1736 (C=O).

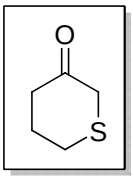
Methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **118** δ_H (400 MHz) 1.00 (3H, t, *J* 7.4, CH_3), 1.52-1.69 (2H, m, CH_2), 1.73-1.84 (1H, m, one of CH_2), 1.90-2.01 (1H, m, one of CH_2), 2.50 (2H, t, *J* 7.6, CH_2), 2.68-2.77 (1H, m, C*H*), 3.22 (2H, fine AB_q appears as s, SCH_2), 3.68 (3H, s, OCH_3), 3.73 (3H, s, OCH_3); δ_C (75.5 MHz) 11.0 (*C*H_3), 27.7, 29.1, 31.5, 32.3 (4 × *C*H_2), 47.6 (*C*H), 51.8, 52.5 (2 × OCH_3), 171.0, 173.7 (2 × *C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_{19}O_4S$ $[M+H]^+$, 235.1004. Found 235.0925; m/z (ESI+) 234 $[(M+H)^+$, tentative].

Methyl bis(thioacetate) **123**: δ_H (400 MHz) 3.60 (4H, s, 2 × C*H*$_2$), 3.78 (6H, s, 2 × OC*H*$_3$); δ_C (75.5 MHz) 41.2 (2 × *C*H$_2$), 52.6 (2 × *C*H$_3$), 169.8 (2 × *C*=O).

Characteristic signal detected for methyl 4-chlorohexanoate **265** in the ^{1}H NMR spectrum of crude mixture: δ_H (400 MHz) 0.91 (3H, t, *J* 7.3, C*H*$_3$).

3.4.3 Synthesis of Monocyclic Sulfides

3.4.3.1 Dihydro-2*H*-thiopyran-3(4*H*)-one 42[86]



(a) Potassium *t*-butoxide (15.60 g, 139.03 mmol, 2 eq) was added directly to a solution of methyl 4-[(2-methoxy-2-oxomethyl)thio]butanoate **102** (7.801 g, 69.51 mmol, 1 eq) in diethyl ether (150 mL) at 0 °C. The solution was allowed to slowly reach room temperature while stirring for 4 h. The mixture was hydrolysed with water/acetic acid solution (80:20, 60 mL). The aqueous phase was separated and extracted with diethyl ether (2 × 30 mL). The combined ethereal layers were washed with water (5 × 60 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the cyclised β-keto ester **103** and enol **104** mixture (1:4, 6.96 g) as a yellow oil which was used directly in the next step.

β-Keto ester **103**: δ_H (400 MHz) 2.41-2.53 (2H, m, C*H*$_2$), 2.60-2.69 (2H, m, C*H*$_2$), 3.05-3.3.14 (2H, m, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.00 (1H, s, C*H*). Enol **104**: δ_H (400 MHz) 2.08-2.17 (2H, m, C*H*$_2$), 2.38-2.45 (2H, m, C*H*$_2$), 2.77-2.83 (2H, m, C*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 12.17 (1H, br s, O*H*).

(b) The crude β-keto ester **103** and enol **104** mixture (1:4, 6.96 g) was stirred under reflux in aqueous sulfuric acid solution (10%, 100 mL) overnight and then cooled to room temperature. Aqueous sodium hydroxide solution (10%) was added dropwise to pH 7. The mixture was extracted with diethyl ether (3 × 40 mL). The combined ethereal layers were washed with water (20 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the crude product as a black oil (4.23 g, 53%). The ^{1}H NMR spectrum of the crude mixture showed essentially clean sulfide **42**. The crude product was adsorbed onto Celite® and

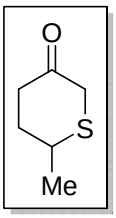
purified by flash chromatography on silica gel using ethyl acetate/hexane as eluent (50:50) to give dihydro-2*H*-thiopyran-3(4*H*)-one **42** as a yellow oil (3.97 g, 50% over the two steps); ν_{max} (film)/cm^{-1} 1708 (C=O); δ_H (400 MHz) 2.39-2.48 (4H, m, C*H*$_2$), 2.77-2.80 (2H, m, C*H*$_2$), 3.21 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 28.6, 33.4, 38.6, 41.9 (4 × C*H*$_2$), 203.9 (*C*=O); HRMS (ESI+): Exact mass calculated for C_5H_9OS $[M+H]^+$, 117.0374. Found 117.0371; m/z (ESI+) 117 $[(M+H)^+$, 8%]. Spectral details in agreement with those reported in the literature.[86]

Table 3.1 Range of bases and reaction conditions tested for the Dieckmann Condensation of methyl 4-[(2-methoxy-2-oxomethyl)thio]butanoate **102**

Entry	Base	Eq.	Solvent	Conditions	Time	Conversion[a]
1	NaOMe	2	MeOH	RT	o/n	None
2	NaOMe	2	MeOH	Δ	o/n	None
3	NaOMe[b]	2.2	Et_2O	RT	2 h	None
4	NaOMe	1	MeOH	RT	o/n	None
5	NaH	1.4	Et_2O	RT	o/n	None
6	NaH	1.2	DCM	RT	o/n	None
7	*t*-BuOK[c]	1.1	THF	RT	2 h	Trace
8	*t*-BuOK[c]	1	Et_2O	Δ	2 h	66%
9	*t*-BuOK[c]	1	Toluene	Δ	o/n	60%
10	*t*-BuOK[c]	2	Et_2O	RT	4 h	100%

a. Percentage conversion was estimated by ^{1}H NMR analysis. The C*H* of the cyclised β-keto ester at 4.10 ppm, and the O*H* of the cyclised enol at 12.20 ppm were monitored.
b. For entry 3, NaOMe 95% reagent grade powder was obtained from Sigma-Aldrich.
c. Potassium *t*-butoxide was used as commercially obtained from Aldrich without sublimation.

3.4.3.2 6-Methyl-dihydro-2*H*-thiopyran-3(4*H*)-one 105[201]

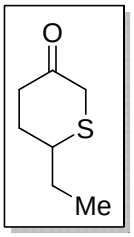


(a) Potassium *t*-butoxide (1.67 g, 14.85 mmol, 2.2 eq) was added directly to a solution of methyl 4-[(2-methoxy-2-oxoethyl)thio]pentanoate **117** (1.49 g, 6.75 mmol, 1 eq) in diethyl ether (25 mL) at 0 °C. The solution was allowed to reach room temperature and stirred for 20 h. The mixture was hydrolysed with a water/acetic acid solution (80:20, 15 mL), the aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The combined ethereal layers were washed with water (5 × 50 mL), brine (15 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the β-keto ester **119** and enol **120** mixture (1:9, 1.87 g) as an orange oil which was used directly in the next step.

Characteristic signals for β-keto ester **119**: δ_H (400 MHz) 1.22 (3H, d, *J* 6.0, C*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 3.85 (1H, s, C*H*). Characteristic signals for enol **120**: δ_H (400 MHz) 1.31 (3H, d, *J* 6.0, C*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 12.16 (1H, br s, O*H*).

(b) The β-keto ester **119** and enol **120** mixture (1:9, 1.87 g) was heated under reflux in aqueous sulfuric acid solution (10%, 50 mL) overnight and then cooled to room temperature. Aqueous sodium hydroxide solution (10%) was added dropwise to pH 7. The mixture was extracted with diethyl ether (3 × 20 mL), the combined ethereal layers were washed with water (15 mL), brine (15 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give 6-methyldihydro-2*H*-thiopyran-3(4*H*)-one **105** as a dark orange oil which was used without further purification (0.56 mg, 64% over the two steps); ν_{max} (film)/cm^{-1} 1713 (C=O); δ_H (400 MHz) 1.29 (3H, d, *J* 6.1, C*H*$_3$), 2.09-2.20 (1H, m, one of C*H*$_2$), 2.35-2.52 (3H, m, two of C*H*$_2$), 3.00 (1H, d, *J* 12.0, A of AB$_q$, one of C*H*$_2$), 3.10-3.19 (1H, m, C*H*), 3.44 (1H, d, *J* 12.0, B of AB$_q$, one of C*H*$_2$); δ_C (75.5 MHz) 20.0 (C*H*$_3$), 37.3 (C*H*), 37.7 (C*H*$_2$), 40.7 (C*H*$_2$), 40.9 (C*H*$_2$), 204.4 (*C*=O); m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_6H_{11}OS$ $[M+H]^+$, 131.0531. Found 131.0525; m/z (ESI+) 129 $[(M-H)^-$, tentative].

3.4.3.3 6-Ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one 106[87]



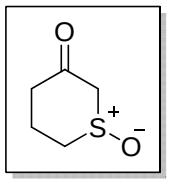
(a) Potassium *t*-butoxide (2.52 g, 22.43 mmol, 2.2 eq) was added directly to a solution of methyl 4-[(2-methoxy-2-oxoethyl)thio]hexanoate **118** (2.39 g, 10.20 mmol) in diethyl ether (50 mL) at 0 °C. The solution was allowed to reach room temperature and stirred for 8 h. The mixture was hydrolysed with a water/acetic acid solution (90:10, 30 mL), the aqueous phase was separated and extracted with diethyl ether (3 × 20 mL). The combined ethereal layers were washed with water (5 × 40 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give the cyclised β-keto ester **121** and enol **122** mixture (1:5, 1.97 g) as an orange oil which was used directly in the next step.

Characteristic signals for β-keto ester **121**: δ_H (400 MHz) 1.20 (3H, t, *J* 7.4, C*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 3.90 (1H, s, C*H*). Characteristic signals for enol **122**: δ_H (400 MHz) 1.12 (3H, t, *J* 7.4, C*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 12.20 (1H, br s, O*H*).

(b) The β-keto ester **121** and enol **122** mixture (1:5, 1.97 g) was heated under reflux in aqueous sulfuric acid solution (10%, 40 mL) overnight and then cooled to room temperature. Aqueous sodium hydroxide solution (10%) was added dropwise to pH 7. The mixture was extracted with diethyl ether (3 × 15 mL), the combined ethereal layers were washed with water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give 6-ethyldihydro-2*H*-thiopyran-3(4*H*)-one **106** (1.04 g, 71% over the two steps) and a trace amount of impurities as a viscous yellow oil which was used without further purification; ν_{max} (film)/cm^{-1} 1714 (C=O); δ_H (400 MHz) 1.04 (3H, t, *J* 7.4, C*H*$_3$), 1.57-1.68 (2H, m, C*H*$_2$), 2.06-2.19 (1H, m, one of C*H*$_2$), 2.36-2.53 (2H, m, C*H*$_2$), 2.95-3.04 (1H, m, one of C*H*$_2$), 3.05 (1H, d, *J* 13.3, A of AB$_q$, one of C*H*$_2$), 3.36 (1H, d, *J* 13.3, B of AB$_q$, one of C*H*$_2$); δ_C (75.5 MHz) 12.1 (*C*H$_3$), 27.6, 37.3, 38.0, 40.4 (4 × *C*H$_2$), 44.2 (*C*H), 204.7 (*C*=O); m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_7H_{13}OS$ $[M+H]^+$, 145.0687. Found 145.0682; m/z (ESI+) 145 [$(M+H)^+$, 43%)].

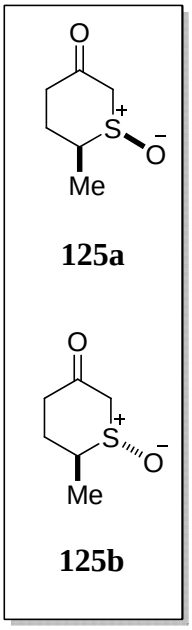
3.4.4 Synthesis of Monocyclic Sulfoxides

3.4.4.1 Dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 124[92]



A solution of sodium metaperiodate (0.92 g, 4.30 mmol, 1 eq) in water (10 mL) was added slowly to a solution of dihydro-2*H*-thiopyran-3(4*H*)-one **42** (0.50 g, 4.30 mmol, 1 eq) in methanol (50 mL) while stirring at 0 °C. After 5 min, a white precipitate had formed. The reaction was monitored by TLC and stirred for 1.5 h while returning to room temperature. The precipitate was filtered and the filtrate concentrated *in vacuo* to leave the sulfoxide **124** and remaining salt mixture as an off-white solid. Dichloromethane (40 mL) was added and the mixture stirred for 10 min. The remaining solid was removed by filtration and the filtrate concentrated *in vacuo* to give dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** as a pale yellow solid (0.38 g, 67 %), which was used without further purification; Found: C, 45.06; H, 6.14; S, 23.94. $C_5H_8SO_2$ requires C, 45.43; H, 6.10; S, 24.26%; m.p. 84-85 °C (lit.,[92] 85-88 °C); ν_{max} (KBr)/cm^{-1} 1715 (C=O); δ_H (400 MHz) 2.26-2.36 (1H, m, one of CH_2), 2.51-2.64 (2H, m, CH_2), 2.78-2.94 (1H, m, one of CH_2), 2.95-3.05 (1H, m, one of CH_2), 3.08-3.16 (1H, m, one of CH_2), 3.63 (1H, A of AB_q, *J* 13.3, one of CH_2), 3.69 (1H, B of AB_q, *J* 13.3, one of CH_2); δ_C (75.5 MHz) 19.3, 41.4, 46.6, 59.8 (4 × *C*H_2), 199.7 (*C*=O); m/z (ESI+) 133 [$(M+H)^+$, 30%)]. Spectral details in agreement with those reported in the literature.[92]

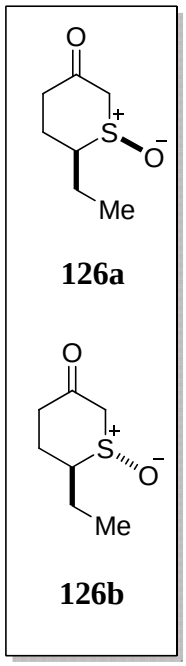
3.4.4.2 (1*R**, 6*S**)-6-Methyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 125a and (1*R**, 6*R**)-6-methyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 125b[88]



The title compounds were prepared following the procedure described for dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **42** using 6-methyldihydro-2*H*-thiopyran-3(4*H*)-one **105** (0.14 g, 1.05 mmol, 1 eq), sodium metaperiodate (0.23 g, 1.05 mmol, 1 eq), water (5 mL) and methanol (15 mL). The reaction was monitored by TLC and stirred for 3 h. Following work up, the inseparable sulfoxides **125a** and **125b** were isolated as a pale yellow crystalline solid (1:1 by ^{1}H NMR, 0.11 g, 68 %). ν_{max} (KBr)/cm^{-1} 1718 (C=O), 1011 (S-O); δ_H (300 MHz) 1.44 (3H, d, *J* 7.0, C*H*$_3$ of one diastereomer), 1.54 (3H, d, *J* 7.0, C*H*$_3$ of one diastereomer), 1.79-1.91, (1H, m, one of C*H*$_2$ of one diastereomer), 2.11-2.21 (1H, m, one of C*H*$_2$ of one diastereomer), 2.46-2.78 (6H, m, 3 × C*H*$_2$ of two diastereomers), 3.02-3.16 (2H, m, C*H* of two diastereomers), 3.61-3.70 (3H, m, containing 2H AB$_q$ of one diastereomer and 1H A of AB$_q$ of other diastereomer), 3.89 (1H, dd, *J* 12.6, 0.8, B of AB$_q$ of one diastereomer); δ_C (75.5 MHz) 14.3*, 15.5 (2 × *C*H$_3$ of two diastereomers), 25.5*, 27.5 (2 × *C*H$_2$ of two diastereomers), 39.1*, 40.9 (2 × C*H*$_2$ of two diastereomers), 51.1, 55.0* (2 × C*H* of two diastereomers), 58.1, 60.0* (2 × C*H*$_2$ of two diastereomers), 199.6*, 200.6 (2 × *C*=O of two diastereomers); m/z (ESI+) HRMS (ESI+): Exact mass calculated for $C_6H_{11}O_2S$ $[M+H]^+$, 147.0480. Found 147.0475; m/z (ESI+) 147 $[(M+H)^+$, tentative].

* Signals relating to one diastereomer as evident in ^{13}C NMR spectrum when ratio not identical.

3.4.4.3 (1*R**, 6*S**)-6-Ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 126a and (1*R**, 6*R**)-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 126b



The title compounds were prepared following the procedure described for dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** using 6-ethyldihydro-2*H*-thiopyran-3(4*H*)-one **106** (0.15 g, 1.04 mmol, 1 eq), sodium metaperiodate (0.22 g, 1.04 mmol, 1 eq), water (5 mL) and methanol (15 mL). The reaction was monitored by TLC and stirred for 3.5 h. Following work up, the inseparable sulfoxides **126a** and **126b** (major:minor 1: 0.9*, 0.11 g, 67%) and a small amount of impurities were isolated as a pale yellow crystalline solid; ν_{max} (KBr)/cm^{-1} 1718 (C=O), 1018 (S-O); δ_H (300 MHz) 1.11-1.20 (5.8H, m, contains 2 × overlapping C*H*$_3$ t of two diastereomers), 1.59-2.25 (7.7H, m, 2 × C*H*$_2$ of two diastereomers), 2.47-2.97 (5.9H, m, contains C*H*$_2$ and C*H* of two diastereomers), 3.54-3.70 (2.8H, m, contains A of AB$_q$ of major diastereomer and AB$_q$ of minor diastereomer), 3.86 (1H, B of AB$_q$, *J* 12.8, 0.8, major diastereomer); δ_C (75.5 MHz) 11.1 (*C*H$_3$ of major diastereomer), 11.8 (*C*H$_3$ of minor diastereomer), 21.5, 22.7, 23.1, 25.7 (4 × *C*H$_2$ of two diastereomers), 38.9 (*C*H$_2$ of major diastereomer), 41.1 (*C*H$_2$ of minor diastereomer), 58.0 (*C*H$_2$ of minor diastereomer), 58.2 (*C*H of minor diastereomer), 59.7 (*C*H$_2$ of major diastereomer), 61.4 (*C*H of major diastereomer), 199.7 (*C*=O of major diastereomer), 200.8 (*C*=O of minor diastereomer); HRMS (ESI+): Exact mass calculated for $C_7H_{13}O_2S$ $[M+H]^+$, 161.0636. Found 161.0634; m/z (ESI+) 161 [$(M+H)^+$, 18 %)].

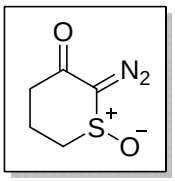
Unidentifiable signal observed, presumably due to small amount of impurities: δ_H (300 MHz) 3.71-3.84 (m).

* For the diastereomeric sulfoxides **126a** and **126b**, it is not known which is the major diastereomer and which is the minor diastereomer.

3.4.5 Synthesis of Monocyclic α-Diazo-β-keto Sulfoxides

3.4.5.1 2-Diazo-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 127

Method 1 Diazo transfer with tosyl azide **41** (1 eq) and triethylamine base (1 eq) followed by purification with flash chromatography using dichloromethane/methanol (90:10)



Triethylamine (0.22 mL, 1.59 mmol, 1 eq) was added to a solution of the dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** (0.21 g, 1.59 mmol, 1 eq) in acetonitrile (30 mL) while stirring at room temperature under a nitrogen atmosphere. The solution was stirred for 5 min and then cooled to 0 °C. A solution of tosyl azide **41** (0.31 g, 1.59 mmol, 1 eq) in acetonitrile (10 mL) was added slowly over 5 min. The reaction mixture was allowed to reach room temperature while stirring under a nitrogen atmosphere overnight to give a dark orange/brown solution. After 24 h, ^{1}H NMR analysis indicated that the reaction had gone ~60% to completion, with the presence of the remaining sulfoxide **124** distinguishable by a 2H s at 3.65 ppm. The mixture was concentrated *in vacuo* to give a brown oil (0.41 g). The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using dichloromethane/methanol (90:10) as eluent. One fraction was isolated which contained 2-diazo-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **127** and sulfonamide byproduct as a mixture (~40:60 by ^{1}H NMR, 87 mg) and as a yellow crystalline solid. Further attempts to purify the crude product by flash chromatography led to isolation of a residual quantity of the impure sample of the diazosulfoxide **127**; ν_{max} (film)/cm^{-1} 3420 (N-H of sulfonamide), 2118 (C=N_2 of diazosulfoxide **127**), 1641 (C=O of diazosulfoxide **127**), 1161 (S-O of diazosulfoxide **127**).

2-Diazo-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **127**: δ_H (400 MHz) [2.19-2.28 (1H m), 2.41-2.55 (1H, m), 2.70-2.80 (1H, sym m), 2.86-3.06 (2H, m), 3.05-3.21 (1H, m)] 3 × C*H*$_2$; δ_C (75.5 MHz) 14.5 (*C*H$_2$), 37.3 (*C*H$_2$), 48.1 (*C*H$_2$), 186.5 (*C*=O). *Note*: the quaternary *C*=N_2 was not detected in the ^{13}C spectrum; HRMS (ESI+): Exact mass calculated for $C_5H_7N_2O_2S$ $[M+H]^+$, 159.0228. Found 159.0231; m/z (ESI+) 159 $[(M+H)^+$, 22 %].

Sulfonamide: 2.40-2.55 (1H m of C*H*$_2$ of diazosulfoxide **127** and 3H s C*H*$_3$ of sulfonamide), 4.93 (2H, br s, N*H*$_2$), 7.29-7.33 (2H, m, Ar*H*), 7.79-7.83 (2H, m, Ar*H*); δ_C (75.5 MHz) 21.5 (*C*H$_3$), 126.4 (Ar*C*H), 129.7 (Ar*C*H), 139.2 (ArC_q), 143.5 (ArC_q).

Method 2 Diazo transfer with tosyl azide **41** (1 eq) and triethylamine base (1 eq) followed by purification with flash chromatography using dichloromethane/methanol (95:5)

The title compound was prepared following the procedure described in Method 1 using dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** (0.76 g, 5.74 mmol, 1 eq), triethylamine (0.80 mL, 5.74 mmol, 1 eq), tosyl azide **41** (1.13 g, 5.74 mmol, 1 eq) and acetonitrile (35 mL). The reaction mixture was stirred overnight under an inert atmosphere. ^{1}H NMR and TLC analysis indicated that the reaction had gone ~60% to completion. The mixture was concentrated *in vacuo* to give a brown oil which was purified by flash chromatography using dichloromethane/methanol (95:5) as eluent. Two fractions were eluted from the column; the first contained sulfonamide byproduct (35 mg) and the second contained the sulfoxide **124** (24 mg). The pure diazosulfoxide **127** was not eluted from the column.

Method 3 Diazo transfer with tosyl azide **41** (1 eq) and K_2CO_3 base (1.1 eq)

Dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** (0.14 g, 1.02 mmol, 1 eq) in acetonitrile (5 mL) was added to a stirring suspension of K_2CO_3 (0.16 g, 1.12 mmol, 1.1 eq) in acetonitrile (10 mL) under a nitrogen atmosphere at room temperature. The solution was brought to 0 °C and tosyl azide **41** (0.20 g, 1.02 mmol, 1 eq) in acetonitrile (2 mL) was slowly added over 5 min. The reaction mixture was allowed to reach room temperature and was stirred under a nitrogen atmosphere overnight. After 20 h, ^{1}H NMR and TLC analysis indicated that no diazo transfer had taken place. The reaction was continued for a further 20 h, and further ^{1}H NMR analysis indicated the presence of starting materials in the mixture, with partial decomposition of the sulfoxide **124**.

Method 4 Diazo transfer with tosyl azide **41** (1 eq) and *t*-BuOK base (1.1 eq)

Dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** (0.17 g, 1.30 mmol, 1 eq) in acetonitrile (5 mL) was added to a stirring suspension of *t*-BuOK (0.16 g, 1.43 mmol, 1.1 eq) in acetonitrile (10 mL) under a nitrogen atmosphere at room temperature. The solution was brought to 0 °C and a solution of tosyl azide **41** (0.25 g, 1.30 mmol, 1 eq) in acetonitrile (2 mL) was slowly added over 5 min. The reaction mixture was allowed to reach room temperature and was stirred under the nitrogen atmosphere overnight. The progress of the reaction was monitored by TLC analysis, and after 48 h, the ^{1}H NMR and IR spectra of the mixture indicated that a small quantity of 2-diazo-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **127** and sulfonamide (~8%) might be present in the mixture.

Method 5 Attempted diazo transfer with tosyl azide **41** (1.1 eq) and DBU base (1.5 eq)

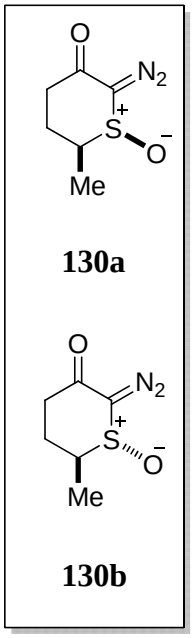
DBU (0.68 mL, 4.54 mmol, 1.5 eq) in acetonitrile (2 mL) was added to a stirring solution of dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** (0.40 g, 3.03 mmol, 1 eq) in acetonitrile (15 mL) under a nitrogen atmosphere at room temperature. The solution was brought to 0 °C and tosyl azide **41** (0.66 g, 3.33 mmol, 1 eq) in acetonitrile (5 mL) was added over 5 min. The colour of the solution immediately turned from a light brown to a black colour. The reaction mixture was allowed to reach room temperature and stirred overnight under a nitrogen atmosphere. The solution was concentrated *in vacuo* to leave a viscous black oil (1.88 g). The ^{1}H NMR spectrum of the crude mixture showed a complex mixture of unidentifiable compounds, including the starting materials DBU and tosyl azide **41**. Sulfonamide was not present in the reaction mixture.

Method 6 Attempted diazo transfer with *p*-NBSA **128** (1.1 eq) and DBU base (1.5 eq)

DBU (0.73 mL, 4.89 mmol, 1.5 eq) in acetonitrile (2 mL) was added to a stirring solution of dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **124** (0.43 g, 3.26 mmol, 1 eq) in acetonitrile (20 mL) under a nitrogen atmosphere at room temperature. The solution was brought to 0 °C and *p*-NBSA **128** (0.82 g, 3.59 mmol, 1.1 eq) in acetonitrile (8 mL) was added over 5 min. The colour of the solution

immediately turned from a light brown to a black colour. The reaction mixture was allowed to reach room temperature and stirred overnight under a nitrogen atmosphere. The solution was concentrated *in vacuo* to leave a viscous black oil (2.01 g). The ^{1}H NMR spectrum of the crude mixture showed a complex mixture of compounds, with no evidence for diazo transfer.

3.4.5.2 (1*R**, 6*R**)-2-Diazo-6-methyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 130a and (1*R**, 6*S**)-2-diazo-6-methyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 130b



130a

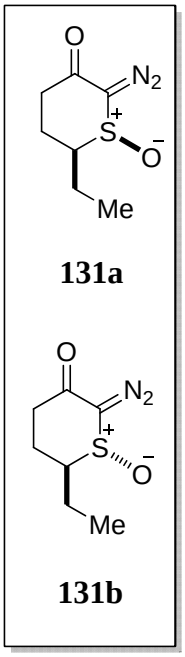
130b

The title compounds were prepared following the procedure described in Method 1 Section 3.4.5.1 using (1*R**, 6*S**)-6-methyldihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **125a** and (1*R**, 6*R**)-6-methyldihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **125b** (1:1, 0.29 g, 1.98 mmol, 1 eq), tosyl azide **41** (0.39 g, 1.98 mmol, 1 eq), triethylamine (0.27 mL, 1.98 mmol, 1 eq) and acetonitrile (20 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 24 h and concentrated *in vacuo* to leave a black oil (0.72 g). ^{1}H NMR analysis indicated the presence of sulfoxides **125a** and **125b** (1:1), tosyl azide **41**, and sulfonamide byproduct (5:3), among other unidentifiable compounds. The crude product was purified using flash chromatography with ethyl acetate/hexane eluent (gradient 90:10-100% ethyl acetate). The inseparable diazosulfoxides **130a** and **130b** (major:minor 1: 0.6*, 22 mg, 0.13 mmol, 6%) were isolated along with small quantities of unidentifiable impurities as a yellow residue. Significant decomposition of the diazosulfoxides **130a** and **130b** was observed to have occurred overnight in $CDCl_3$; ν_{max} (film)/cm^{-1} 2129 (C=N$_2$), 1718 (C=O); δ_H (400 MHz) 1.38 (1.8H, d, *J* 7.2, C*H*$_3$ of minor diastereomer), 1.47 (3H, d, *J* 6.9, C*H*$_3$ of major diastereomer), 1.88-1.95 (1H, sym m, one of C*H*$_2$ of major diastereomer), 1.97-2.06 (0.6H, sym m, one of C*H*$_2$ of minor diastereomer), 2.38-2.86 (4.8H, m, C*H*$_2$ of both diastereomers), 2.96-3.12 (1H, m, C*H* of major diastereomer), 3.23-3.31 (0.6H, m, C*H* of minor diastereomer); *Note:* Although significant decomposition occurred for the diazosulfoxides **130a** and **130b** overnight, some signals in the ^{13}C

spectrum of the mixture were distinguished: δ_C (75.5 MHz) 11.9, 16.4, 20.16, 23.1, 32.2, 37.4, 53.2, 186.5 (*C*=O of one diastereomer), 186.6 (*C*=O of one diastereomer).

* For the diastereomers **130a** and **130b**, it is not known which is the major diastereomer and which is the minor diastereomer.

3.4.5.3 (1*R**, 6*R**)-2-Diazo-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 131a and (1*R**, 6*S**)-2-diazo-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 131b



The title compounds were prepared following the procedure described in Method 1 Section 3.4.5.1 using (1*R**, 6*S**)-6-ethyldihydro-2H-thiopyran-3(4H)-one *S*-oxide **126a** and (1*R**, 6*R**)-6-ethyldihydro-2H-thiopyran-3(4H)-one *S*-oxide **126b** (major:minor 1:0.9*, 0.72 g, 4.50 mmol, 1 eq), tosyl azide **41** (0.89 g, 4.50 mmol, 1 eq), triethylamine (0.62 mL, 4.50 mmol, 1 eq) and acetonitrile (15 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 24 h and concentrated *in vacuo* without heating to leave a brown oil (0.81 g). ^{1}H NMR analysis indicated the presence of a number of compounds, including the sulfoxides **126a** and **126b** (major:minor 3:1*), tosyl azide **41** and sulfonamide byproduct (4:6). The crude product was adsorbed onto Celite® and purified using flash chromatography on silica gel using ethyl acetate/hexane eluent (gradient 50:10-100% ethyl acetate) as eluent. The inseparable diazosulfoxides **131a** and **131b**, sulfonamide (1: 1: 0.8) and a small quantity of the sulfoxide starting materials **126a** and **126b** (~5%) were isolated as a yellow oil (154 mg, ~12%). ν_{max} (film)/cm^{-1} 2113 (C=N_2), 1630 (C=O); Exact mass calculated for sulfine decomposition product **203** $C_7H_{10}O_2S$ $[M+H]^+$, 159.0480. Found 159.0481.

(1*R**, 6*R**)-2-Diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **131a** and (1*R**, 6*S**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **131b** δ_H (400 MHz) 1.16 (6H, m, overlapping 2 × C*H*$_3$ of two diastereomers), 1.54-2.14 (6H, m, C*H*$_2$ of two diastereomers), 2.43-2.80 (6H, m, C*H*$_2$ of two diastereomers), 2.96-

3.09 (2H, m, C*H* of two diastereomers); δ_C (75.5 MHz) 11.4, 11.7 (2 × *C*H_3 of two diastereomers), 18.3, 19.7, 20.6, 25.6, 32.5, 43.8 (6 × *C*H_2 of two diastereomers), 60.4, 60.5 (2 × *C*H of two diastereomers), 186.7, 187.1 (2 × *C*=O of two diastereomers);

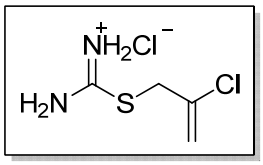
Spectral details for sulfoxides **126a** and **126b** and for sulfonamide as described above.

* It is not known which is the major diastereomer and which is the minor diastereomer.

3.5 Attempted Syntheses of Bicyclic β-Keto Sulfoxides

Part 1: Lansbury Method [93]

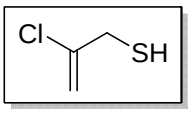
3.5.1 2-(2-Chloroallyl)isothiouronium chloride 137



A solution of 2,3-dichloropropene **135** (1.63 g, 14.7 mmol, 1 eq) in ethanol (20 mL) was added to a solution of freshly recrystallised thiourea (1.12 g, 14.7 mmol, 1 eq) in ethanol (50 mL) at 40 °C. The mixture was stirred under reflux conditions for 14 h. The solution was then cooled and the ethanol removed *in vacuo* to give 2-(2-chloroallyl)isothiouronium chloride **137** as a white crystalline solid (2.63g, 96%). An analytically pure sample was obtained by recrystallisation from 95% ethanol (1.87 g, 68%); m.p. 130-132 °C; Found: C, 25.45; H, 4.35; 40; S 17.52; Cl, 37.55. $C_4H_8Cl_2N_2S$ requires C, 25.68; H, 4.31; S, 17.14; Cl, 37.90%; ν_{max} (KBr)/cm^{-1} 3080 (N-H), 1661 (C=C); HRMS (ESI+): Exact mass calculated for $C_4H_8{}^{35}ClN_2S$ $[M\text{-}Cl]^+$, 151.0097. Found 151.0100; Exact mass calculated for $C_4H_8{}^{37}ClN_2S$ $[M\text{-}Cl]^+$, 153.0067. Found 153.0068. m/z (ESI+) 151 [($C_4H_8{}^{35}ClN_2S^+$), 100%], 153 [($C_4H_8{}^{37}ClN_2S^+$), 50%].

3.5.2 Attempted synthesis of 2-chloroallyl mercaptan 133

Attempt 1 One step formation of thiol using sodium hydroxide under reflux as described by Lansbury[93]



Caution: This compound is extremely malodorous and all glassware which is in contact with it must be soaked in a bleach bath for several days.

(***Note:*** A Teflon sleeve was used in the joint of the flask to prevent the flask and the condenser from becoming fused when refluxing the basic solution). Thiourea (1.12 g, 14.73 mmol, 1 eq) was directly added to a solution of 2,3-dichloropropene **135** (1.63 g, 14.73 mmol, 1 eq) in absolute ethanol (40 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux for 16 h and then cooled to room temperature. Aqueous sodium hydroxide (4 M, 20 mL) was added dropwise over 5 min. The reaction mixture was heated under reflux for a further 4 h and then cooled to room temperature. The aqueous solution was acidified to pH 1 with 10 % sulfuric acid and extracted with diethyl ether (2 × 30 mL). The ethereal layer was washed with water (4 × 20 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give a malodorous black oil and solid mixture (0.51 g). Purification by Kugelrohr distillation (80 Torr, 60 °C) gave one fraction as a pale yellow oil (34 mg). ^{1}H NMR and TLC analysis of the fraction appeared to indicate the possible presence of one major compound, 2-chloroallyl mercaptan **133** (~66%) and unidentifiable compounds.

Signals tentatively identified for 2-chloroallyl mercaptan **133**: δ_H (300 MHz) 2.30 (1H, s, S*H*), 3.38 (2H, unresolved d, *J* 0.8, CH_2), 5.32-5.38 (2H, m, C=CH_2).

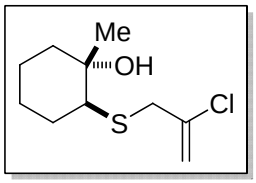
Signals corresponding to unidentifiable compounds: δ_H (300 MHz) 2.18 (s), 2.57-2.76 (m), 3.25 (s), 5.14-5.19 (m).

Table 3.2: Variation of reaction conditions as described by Lansbury[93] in the attempted synthesis of 2-chloroallyl mercaptan **133**

Entry	Solvent	Base	Conditions	Time[a]	Product[b]
1	EtOH	NaOH	Δ	(i) 5 h (ii) 4 h	Mixture
2	EtOH	$LiAlH_4$	Δ	(i) 16 h (ii) 4 h	Mixture (<50% **133**)
3	EtOH	NaOMe	Δ	(i) 16 h (i) 4 h	Mixture (<40% **133**)
4	MeOH	KOH	Δ	(i) 16 h (i) 4 h	Mixture (<50% **133**)
5	EtOH	NaOH	Δ	(i) 16 h (i) 4 h	Mixture (>80% **133**)

c. Length of time the reaction mixture (i) was heated under reflux in solvent and (ii) heated under reflux with aqueous base.
d. The quantity of 2-chloroallyl mercaptan **133** among a complex mixture of unidentifiable compounds was estimated by ^{1}H NMR analysis of the crude reaction mixtures.

3.5.3 2-[(2-Chloroallyl)thio]-1-methylcyclohexanol 134



2-(2-Chloroallyl)isothiouronium chloride **137** (1.19 g, 6.37 mmol, 1 eq) was directly to a freshly prepared solution of sodium methoxide (0.15 g sodium, 6.37 mmol, 1 eq, 15 mL methanol) under a nitrogen atmosphere. The solution was stirred for 5 min and a solution of 1-methyl-1-cyclohexene oxide **34** (0.72 g, 6.37 mmol, 1 eq) in methanol (5 mL) was added under the nitrogen atmosphere. The mixture was stirred for 16 h under reflux. The reaction mixture was cooled and the solvent removed *in vacuo* to leave a pale yellow solid which was dissolved in water (25 mL) and acidified to pH 6 with conc. hydrochloric acid. The aqueous solution was extracted with diethyl ether (3 × 10 mL), washed with water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave a malodorous

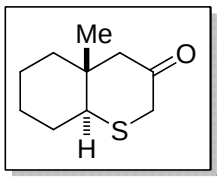
orange oil (1.07 g). ^{1}H NMR analysis of the crude product indicated the presence of 2-[(2-chloroallyl)thio]-1-methylcyclohexanol **134** as the major compound (~70% pure) among other unidentifiable impurities; ν_{max} (film)/cm^{-1} 3425 (O-H), 1627, 1448 (C=C).

2-[(2-Chloroallyl)thio]-1-methylcyclohexanol **134**: δ_H (300 MHz) 1.10-1.87 (8H, m, contains 5H m of CH_{2ring} and 3H s of CH_3 at 1.21), 1.98-2.09 (1H, m, one of CH_{2ring}), 2.60 (1H, dd, *J* 12.1, 4.1, C*H*S), 3.01 (1H, br s, O*H*), 3.39-3.54 (2H, m, SCH_2), 5.30 (1H, d, *J* 1.4, one of C=CH_2), 5.39 (1H, d, *J* 1.4, one of C=CH_2); δ_C (75.5 MHz) 22.4 (*C*H$_3$), 22.7, 26.1, 32.9, 40.6, 41.6 (5 × *C*H$_2$), 57.0 (*C*H), 72.5 (C_q), 114.7 (C=*C*H$_2$), 139.1 (C_q=CH$_2$). Spectral details in agreement with those reported in the literature.[93]

Signals detected for unidentifiable impurities: δ_H (300 MHz) 3.39-3.51 (m), 5.32 (s), 5.43 (s); δ_C (75.5 MHz) 15.2 (*C*H$_3$), 22.1 (C), 37.0 (C), 47.2 (*C*H$_2$), 65.8 (*C*H$_2$), 116.4 (*C*H$_2$), 128.1 (C), 129.7 (C), 130.0 (C), 133.0 (C), 133.1 (C), 134.5 (C), 137.4 (C), 167.8 (C).

3.5.4 *trans*-4a-Methylhexahydro-2*H*-thiochromen-3(4*H*)-one 132[93]

Method 1. Cyclisation using 98% formic acid



2-[(2-Chloroallyl)thio]-1-methylcyclohexanol **134** (0.67 g, ~70% pure by ^{1}H NMR) was dissolved in 98% formic acid (20 mL) and stirred under reflux for 5 h. The mixture was cooled to room temperature and was slowly poured into a beaker of ice-water (50 mL) over 5 min. The aqueous solution was extracted with dichloromethane (3 × 20 mL), washed with water (10 mL), brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave a malodorous, black oil (0.45 g). The infrared spectrum of the crude material showed a C=O stretch at 1711 cm^{-1} and the ^{1}H NMR spectrum indicated the presence of a complex mixture of products, including 2-[(2-chloroallyl)thio]-1-methylcyclohexanol **134** starting material and signals appearing to correspond to the desired product *trans*-4a-methylhexahydro-2*H*-thiochromen-3(4*H*)-one **132**. The crude material was adsorbed onto Celite® and purified by flash chromatography on silica gel using dichloromethane (100%) as eluent. Two fractions

were obtained, the first was obtained as a black solid and contained a complex mixture of unidentifiable compounds (65 mg), and the second was obtained as a brown oil and appeared to contain *trans*-4a-methylhexahydro-2*H*-thiochromen-3(4*H*)-one **132**, among other unidentifiable compounds (18 mg); ν_{max} (film)/cm^{-1} 1710 (C=O).

Signals corresponding to *trans*-4a-methylhexahydro-2*H*-thiochromen-3(4*H*)-one **132**: δ_H (400 MHz) 1.88 (1H, d, J 13.0, one of CH_2), 2.49-2.54 (1H, m, one of CH_2), 2.69 (1H, d, *J* 12.0, one of CH_2), 2.91 (1H, dd, *J* 12.8, 1.4, one of CH_2), 3.38 (1H, d, *J* 12.1, one of CH_2).

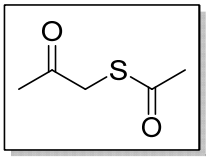
Table 3.3: Variation of reaction conditions as described by Lansbury[93] in the attempted cyclisation of 2-[(2-chloroallyl)thio]-1-methylcyclohexanol **134** to *trans*-4a-methylhexahydro-2*H*-thiochromen-3(4*H*)-one **132**

Entry	Acid[a]	Conditions	Time	Product[b]
1	98% Formic acid	RT	o/n	Mixture unidentifiable compounds
2	90% H_2SO_4	Δ	20 min	Mixture unidentifiable compounds
3	90% H_2SO_4	0 - 5 °C	30 min	Mixture (<10% **132**)
4	98% Formic acid	Δ	1 h	Mixture (<50% **132**)

c. Aqueous mineral acids were used as described by Lansbury.
d. For entries 1 and 2, the ^{1}H NMR spectra of the crude reaction mixtures indicated the presence of a complex mixture of unidentifiable compounds. For entries 3 and 4, ^{1}H NMR spectra indicated the presence of **132** among a complex mixture of unidentifiable compounds.

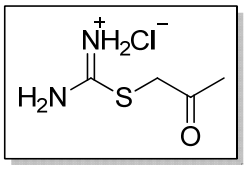
Part 2: Kozikowski Method [98]

3.5.5 1-Acetylthio-2-propanone 142[202]



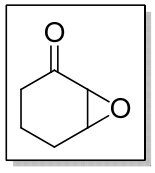
A solution of chloroacetone **145** (2.16 mL, 27.20 mmol, 1 eq) in ethanol (10 mL) was slowly added to a solution of potassium thioacetate **144** (3.10 g, 27.20 mmol, 1 eq) in ethanol (20 mL) at room temperature. The mixture was stirred overnight at room temperature. The precipitate was filtered and the filtrate concentrated *in vacuo* to give 1-acetylthio-2-propanone **142** as a yellow oil (2.97 g, 83%); ν_{max} (film)/cm^{-1} 1712 (C=O), 1694 (C=O); δ_H (300 MHz) 2.28 (3H, s, C*H*$_3$), 2.40 (3H, s, C*H*$_3$), 3.77 (2H, s, C*H*$_2$); δ_C (75.5 MHz) 28.2 (*C*H$_3$), 30.1 (*C*H$_3$), 39.7 (*C*H$_2$), 194.3 (*C*=O), 201.8 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_5H_9O_2S$ $[M+H]^+$, 133.0323. Found 133.0324; m/z (ESI+) 133 [$(M+H)^+$, 100%)]. Spectral details in agreement with those reported in the literature.[202]

3.5.6 2-Acetylthio isothiouronium chloride 143



A solution of chloroacetone **145** (1.70 mL, 21.41 mmol, 1 eq) in ethanol (10 mL) was added to a solution of freshly recrystallised thiourea (1.63 g, 21.41 mmol, 1 eq) in ethanol (20 mL) at 40 °C. The mixture was stirred under reflux for 20 h. The solution was cooled and the ethanol removed *in vacuo* to give 2-acetylthio isothiouronium chloride **143** as an off-white crystalline solid (3.50 g, 97%); m.p. 85-86 °C; Found: C, 28.56; H, 5.32; N, 16.73; S, 19.51; Cl, 20.81. $C_4H_9ClN_2OS$ requires C, 28.49; H, 5.38; N, 16.61; S, 19.01; Cl, 21.02; ν_{max} (KBr)/cm^{-1} 3305 (N-H), 1625 (C=O).

3.5.7 2,3-Epoxycyclohexanone 141

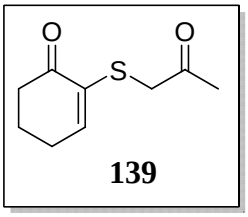


2-Cyclohexenone **266** (3.84 g, 40.00 mmol, 1 eq) in methanol (15 mL) was added to a solution of hydrogen peroxide (30% aqueous solution, 11.50 mL, 40.00 mmol, 1 eq) in methanol (30 mL) at 0 °C. After 5

min, sodium hydroxide solution (4M, 5 mL) was added dropwise over 30 min, maintaining the temperature at 0 °C. The solution was allowed to slowly return to room temperature and was stirred for a further 1.5 h. The solution was poured into water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined ethereal layers were washed with water (3 × 10 mL), brine (20 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave 2,3-epoxycyclohexanone **141** a clear oil (2.53 g, 57%); ν_{max} (film)/cm^{-1} 1711 (C=O); δ_H (300 MHz) 1.61-1.75 (1H, m, one of C*H*$_2$), 1.82-2.18 (3H, m, C*H*$_2$), 2.18-2.35 (1H, m, one of C*H*$_2$), 2.46-2.59 (1H, m, one of C*H*$_2$), 3.21 (1H, d, *J* 3.9, C*H*), 3.59-3.62 (1H, m, C*H*).

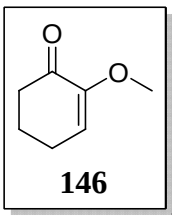
3.5.8 Attempted synthesis of 2-[(2-Oxopropyl)thio]cyclohexen-2-enone 139

Attempt 1. *In situ* formation of mercaptoacetone **140** from 1-acetylthio-2-propanone **142** and reaction with 2,3-epoxycyclohexanone **267**



139

1-Acetylthio-2-propanone **142** (1.01 g, 7.62 mmol, 1 eq), was directly added to a solution of sodium methoxide (0.18 g sodium, 7.62 mmol, 1 eq, in 25 mL methanol) at 0 °C. The solution was stirred for 1 h under reflux and 2,3-epoxycyclohexanone **141** (0.85 g, 7.62 mmol, 1 eq) in methanol (5 mL) was added dropwise over 5 min. The solution was stirred under reflux overnight. Following work-up, the crude product was obtained as a brown oil (0.900 g). Purification by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent led to the isolation of the undesired product 2-methoxycyclohex-2-enone **146** and small quantities of unidentifiable impurities as an orange oil (0.19 g, 13%).



146

2-Methoxycyclohex-2-enone **146**: ν_{max} (film)/cm^{-1} 1710 (C=O); δ_H (300 MHz) 1.98 (2H, quintet, *J* 6.1, C*H*$_2$), 2.40-2.48 (2H, m, C*H*$_2$), 2.52 (2H, t, *J* 6.4, C*H*$_2$), 3.60 (3H, s, C*H*$_3$), 5.86 (1H, t, C*H*); δ_C (75.5 MHz) 23.0, 24.4, 38.8 (3 × *C*H$_2$), 54.7 (*C*H$_3$), 116.3 (C=*C*H), 151 (*C*$_q$=CH), 195 (*C*=O).

Attempt 2. *In situ* formation of mercaptoacetone **140** from 2-acetylthio isothiouronium chloride **143** and reaction with 2,3-epoxycyclohexanone **141**

2-Acetylthio isothiouronium chloride **143** (0.49 g, 2.91 mmol, 1 eq) was directly added to a solution of sodium methoxide (0.07 g sodium, 3.20 mmol, 1.1 eq, in 10 mL methanol) at 0 °C. The solution was stirred for 1 h under reflux and 2,3-epoxycyclohexanone **141** (0.33 g, 2.91 mmol, 1 eq) in methanol (5 mL) was then added dropwise over 5 min. The reaction mixture was stirred under reflux overnight. The solution was concentrated *in vacuo* to leave a black oil. The oil was partitioned between water (10 mL) and diethyl ether (10 mL). The aqueous layer was separated and extracted with diethyl ether (10 mL). The combined ethereal layers were washed with water (5 mL), brine (5 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave a brown oil (97 mg). TLC analysis of the crude material indicated the presence of two compounds. ^{1}H NMR analysis indicated signals corresponding to 2-methoxycyclohex-2-enone **146** and a second, unknown compound, probably formed due to decomposition of the salt **143**. Signals for the unknown compound: δ_H (400 MHz) 2.19 (6H, s), 5.40 (4H, br s), 6.04 (2H, s). Spectral details for 2-methoxycyclohex-2-enone **146** as described above.

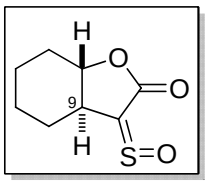
3.6 Nucleophilic Reactions with α-Oxosulfines Generated from Lactone Based α-Diazosulfoxides

Note: These reactions were carried out using two methods: sequential addition (formation and isolation of the sulfine prior to addition of the nucleophile) and *in-situ* addition (one pot reaction).

3.6.1 Nucleophilic Addition of Nitrogen Nucleophiles with 3-Diazo-*trans*-hexahydrobenzo[1,4] oxathiin-2-one *S*-Oxides 5a and 5e.

3.6.1.1 3-(Benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 159

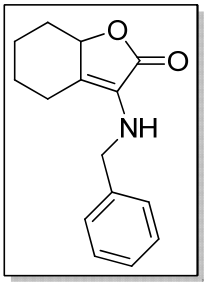
Method 1 (sequential reaction at room temperature)



Rhodium(II) acetate (1.9 mg, 4.3 μmol, 1 mol%) was added to a solution of α-diazosulfoxides **5a** and **5e** (1:1, 92 mg, 0.43 mmol, 1 eq) in dichloromethane (10 mL) and the reaction mixture was stirred for 15 min under a nitrogen atmosphere. The solvent was removed *in vacuo* without heating the water bath and the ^{1}H NMR spectrum obtained indicated formation of the sulfine **148**, the alkene dimer **149** and small quantities of unidentifiable impurities (2.5: 1, 85 mg).

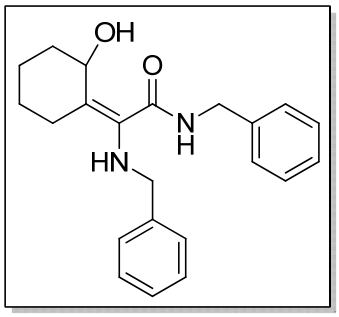
Sulfine **148**: δ_H (300 MHz) 1.30-1.74 (4H, m, CH_{2ring}), 1.76-2.07 (2H, m, CH_{2ring}), 2.17-2.39 (2H, m, CH_{2ring}), 2.83-3.01 [1H, m, C*H*(9)], 3.87-3.98 (1H, overlapping ddd appears as m, C*H*O).

Signals identified for the alkene dimer **149**: δ_H (300 MHz) 2.25-2.33 (1H, sym m, one of CH_{2ring}), 2.71-2.80 (1H, sym m, one of CH_{2ring}), 2.91 (1H, br d, *J* 12.5, one of CH_{2ring}), 3.88 (1H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).



Benzylamine (46 mg, 0.43 mmol, 1 eq) was added to a solution of the sulfine **148** (mixture containing alkene dimer **149** 2.5: 1, 85 mg) in dichloromethane (10 mL) and the reaction mixture was stirred for 5 h at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated the presence of 3-(benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **159**, the alkene dimer **149** (2.5:1) and a small quantity of the amide **163** side-product. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(Benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **159** (R_f = 0.71, red colour by vanillin stain) was isolated as a brown solid (29 mg, 29% over the two steps). m.p. 89-91 °C; ν_{max}/cm^{-1} (KBr); 3283 (N-H), 1745 (C=O), 1652 (aromatic C=C), 1496 (aromatic C=C); δ_H (400 MHz) 0.81-1.42 (3H, m, CH_{2ring}), 1.71 (1H, br d, *J* 14.7, one of CH_{2ring}), 1.81 (1H, br d, *J* 15.8, one of CH_{2ring}), 1.93-2.04 (1H, sym m, one of CH_{2ring}), 2.36-2.44 (1H, sym m, one of CH_{2ring}), 2.76-2.84 (1H, br d, *J* 11.9, one of CH_{2ring}), 4.38 (2H, s, benzylic CH_2); 4.46 (1H, dd, *J* 11.1, 5.4, C*H*O), 7.23-7.36 (5H, m, Ar*H*); δ_C (75.5 MHz) 22.8, 25.5, 26.1, 34.2 (4 × *C*H$_{2ring}$), 48.9 (benzylic *C*H$_2$), 79.4 (*C*HO), 125.8 (C_q), 126.9, 127.3 (2 × aromatic *C*H), 128.2 (C_q), 128.7 (aromatic *C*H), 139.1 (C_q), 171.4 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{17}NO_2$ $[M+H]^+$, 244.1338. Found 244.1342; m/z (ESI+) 244 $[(M+H)^+$, 98%].

The structure was confirmed by single crystal X-ray diffraction on a crystalline sample of **159** recrystallised from dichloromethane/hexane. Crystals of **159** are monoclinic, space group *C*2/*c*, formula $C_{15}H_{17}NO_2$, M = 243.30, a = 18.006(3) Å, b = 6.8172(11) Å, c = 21.597(4) Å, U = 2535.9(7) Å^3, F(000) = 1040, μ(Mo-Kα) = 0.084 mm^{-1}, R(F_o) = 0.0546 for 1887 observed reflection with I > 2σ(I), wR_2(F^2) = 0.1415 for all 2544 unique reflections. Data in the θ range 1.97 – 26.27° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.



Distinctive signals identified for the amide **163** side-product in the ^{1}H NMR spectrum of the crude product: δ_H (400 MHz) 4.50 (d, *J* 6.3, NHC*H*$_2$), 7.79 (1H, br s, N*H*CO).

Method 2 (*in-situ* reaction at room temperature)

Rhodium(II) acetate (1.9 mg, 4.2 μmol, 1 mol%) was added to a stirring solution of benzylamine (45 mg, 0.42 mmol, 1 eq) and the α-diazosulfoxides **5a** and **5e** (1: 1, 90 mg, 4.2 mmol, 1 eq) in dichloromethane (10 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 6 h. The solvent was removed *in vacuo* to leave the crude product as a brown oil. The ^{1}H NMR spectrum obtained indicated the presence of 3-(benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **159** among excess benzylamine and the amide **163** side-product (4: 1: 0.6). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. One fraction was isolated, which contained 3-(benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **159** as a brown solid, along with the amide **163** side-product (1.6: 1, 49 mg, ~32%). Spectral details for **159** as described above.

Distinctive signals identified for the amide **163** side-product: δ_H (400 MHz) 4.50 (d, *J* 6.3, NHC*H*$_2$), 7.79 (1H, br s, N*H*CO).

Method 3 (*in situ* reaction under microwave conditions)

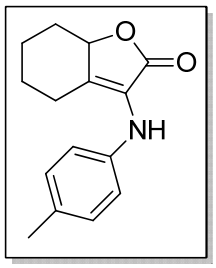
Benzylamine (57 mg, 0.53 mmol, 1 eq) was added to a solution of the α-diazosulfoxides **5a** and **5e** (1: 1, 114 mg, 0.53 mmol, 1 eq) in dichloromethane (3 mL) and the mixture was irradiated with microwaves at 300 W. The reaction settings were set for the reaction mixture to reach a temperature of 100˚C using a 3 min ramp-time and a 5 min hold-time. The mixture was then cooled and concentrated *in vacuo* to leave the crude product as a dark orange oil (162 mg). The ^{1}H NMR spectrum obtained indicated the presence of 3-(benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **159**, among excess benzylamine, the enol **153**, the

alkene dimer **149** and the amide **163** side-product (1: 1: 0.7: 0.8). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(Benzylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **159**, the amide **163** and the alkene dimer **149** were isolated as a brown solid, (1: 0.1: 0.3, 68 mg, ~70%). Spectral details as described above.

Distinctive signals identified for the amide **163** side-product: δ_H (400 MHz) 4.50 (d, *J* 6.3, NHCH_2), 7.79 (1H, br s, N*H*CO). Signals detected for enol **153** in the ^{1}H NMR spectrum of the crude material: δ_H (300 MHz) 2.90–3.00 (1H, m, one of CH_{2ring}), 4.59 (1H, dd, *J* 11.1, 6.4, C*H*O). Signals identified for the alkene dimer **149**: δ_H (300 MHz) 2.91 (1H, br d, *J* 12.5, one of CH_{2ring}), 3.88 (1H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).

3.6.1.2 3-(*p*-Tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 158

Method 1 (*in situ* reaction under microwave conditions)



p-Toluidine (38 mg, 0.35 mmol, 1 eq) was added to a solution of the α-diazosulfoxides **5a** and **5e** (1:1, 75 mg, 0.35 mmol, 1 eq) in dichloromethane (3 mL) and the solution was irradiated with microwaves at 300 W. The reaction settings were set for the reaction mixture to reach a temperature of 100˚C using a 3 min ramp-time and a 5 min hold-time. The mixture was then cooled and concentrated *in vacuo* to leave the crude product as an orange oil (94 mg). The ^{1}H NMR spectrum obtained indicated the presence of 3-(*p*-tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **158** among excess *p*-toluidine (4:1) and trace quantities of unidentifiable compounds. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(*p*-Tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **158** along with trace amounts of impurities as a brown solid (72 mg, 84%). An analytical sample was prepared by slow recrystallisation from hexane/dichloromethane to give 3-(*p*-tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **158** was isolated as a pale brown crystalline solid (51 mg, 60%); Found: C, 73.82; H, 6.90; N, 5.61. $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%; m.p. 94-96 °C; ν_{max}/cm^{-1} (KBr); 3343 (N-H), 1741 (C=O); δ_H (400 MHz) 1.20-1.48 (3H, m, CH_{2ring}), 1.80-1.94 (2H, m, CH_{2ring}), 2.05-2.15 (1H, m, one

of CH_{2ring}), 2.28 (3H, s, ArCH_3), 2.48-2.56 (1H, m, one of CH_{2ring}), 2.58-2.66 (1H, sym m, one of CH_{2ring}), 4.65 (1H, dd, *J* 10.8, 5.5, C*H*O), 5.56 (1H, br s, N*H*), 6.77 (2H, d, *J* 8.4, Ar*H*), 7.06 (2H, d, *J* 8.2, Ar*H*); δ_C (75.5 MHz) 20.6 (Ar*C*H$_3$), 22.6, 25.5, 26.9, 34.0 (4 × *C*H$_{2ring}$), 79.3 (*C*HO), 118.0, (aromatic *C*H), 122.6 (C_q), 129.6 (aromatic *C*H), 131.1 (C_q), 135.5 (C_q), 139.1 (C_q). *Note:* the quaternary carbon of the carbonyl group was not observed in the ^{13}C NMR spectrum; HRMS (ESI+): Exact mass calculated for $C_{15}H_{17}NO_2$ $[M+H]^+$, 244.1338. Found 244.1330; m/z (ESI+) 244 $[(M+H)^+$, 82%], 245 (16%).

Method 2 *(in situ* reaction at room temperature):

The reaction was carried out following the procedure described in Method 2 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 90 mg, 0.43 mmol, 1 eq), *p*-toluidine (46 mg, 0.43 mmol, 1 eq) and rhodium(II) acetate (1.8 mg, 4.2 μmol, 1 mol%) in dichloromethane (10 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 6 h. The solvent was removed *in vacuo* to leave the crude product as a dark orange solid which crystallised overnight (90 mg, 91%). The ^{1}H NMR spectrum obtained indicated the presence of 3-(*p*-tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **158**, among excess *p*-toluidine (1: 0.2) and trace amounts of unidentifiable impurities.

Method 3 (*sequential* reaction at room temperature):

The reaction was carried out following the procedure described in Method 1 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 125 mg, 0.58 mmol, 1 eq) and rhodium(II) acetate (2.6 mg, 5.8 μmol, 1 mol%). The sulfine **148** was isolated as a mixture with the enol **153** and disulfide **154** (1: 0.3: 0.1, 114 mg).

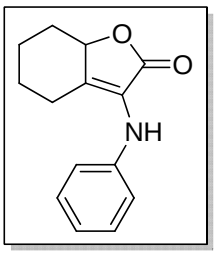
Spectral details for sulfine **148** as described above. Signals detected for enol **153**: δ_H (300 MHz) 2.90–3.00 (1H, m, one of CH_{2ring}), 4.59 (1H, dd, *J* 11.1, 6.4, C*H*O). Signals detected for disulfide **154**: δ_H (300 MHz) 3.11 (2H, br d, *J* 12.5, CH_{2ring}), 4.73 (2H, dd, *J* 11.1, 6.3, C*H*O).

p-Toluidine (125 mg, 0.58 mmol, 1 eq) and the sulfine **148** (in a mixture as described above, 114 mg) were stirred in dichloromethane (12 mL) at room temperature under a nitrogen atmosphere for 5 h. The solvent was removed *in vacuo*

and ^{1}H NMR analysis of the crude product indicated formation of 3-(*p*-tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **158**, among the disulfide **154** and excess *p*-toluidine (1: 0.1: 5, 151 mg). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(*p*-Tolylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **158** (R_f = 0.78, red colour by vanillin stain) was isolated as a pale brown solid (28 mg, 26% over the two steps). Spectral details as described above.

3.6.1.3 3-(Phenylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 160

In situ at room temperature



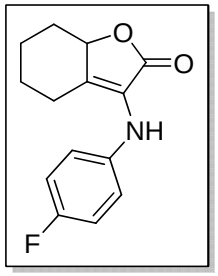
The reaction was carried out using the procedure described in Method 2 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 76 mg, 0.35 mmol, 1 eq), aniline (33 mg, 0.35 mmol, 1 eq), rhodium(II) acetate (1.5 mg, 3.5 μmol, 1 mol%) and dichloromethane (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 6 h at room temperature under the inert atmosphere. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated formation of 3-(phenylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **160**, along with the presence of aniline, the enol **153**, alkene dimer **149** and the disulfide **154** (1: 1: 0.2: 0.3: 0.4, 92 mg). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(Phenylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **160** (R_f = 0.89, red colour by vanillin stain) was isolated as a brown solid (73 mg, 72%). An analytically pure sample was obtained by slow recrystallisation from hexane/dichloromethane to give the pure product **160** as a pale brown crystalline solid (26 mg, 25%); m.p. 103-105 °C; ν_{max}/cm^{-1} (KBr); 3377 (N-H), 1744 (C=O); δ_H (400 MHz) 1.18-1.32 (2H, m, C*H*$_{2ring}$), 1.37-1.48 (1H, m, one of C*H*$_{2ring}$), 1.80-1.94 (2H, m, C*H*$_{2ring}$), 2.07-2.18 (1H, m, one of C*H*$_{2ring}$), 2.48-2.56 (1H, sym m, one of C*H*$_{2ring}$), 2.60-2.68 (1H, m, one of C*H*$_{2ring}$), 4.68 (1H, dd, *J* 11.1, 5.9, C*H*O), 5.75 (1H br s, N*H*), 6.81-6.85 (2H, m, Ar*H*), 6.88-6.93 (1H, m, Ar*H*), 7.20-7.26 (2H, m, Ar*H*); δ_C (75.5 MHz) 22.6, 25.5, 27.1, 34.0 (*C*H$_{2ring}$), 79.3 (*C*HO), 117.3 (aromatic *C*H), 121.3 (aromatic *C*H),

122.2 (C_q), 129.1 (aromatic *C*H), 137.4 (C_q), 141.8 (C_q), 171.4 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{14}H_{15}NO_2$ $[M+H]^+$, 230.1181. Found 230.1180; m/z (ESI+) 230 $[(M+H)^+$, 99%].

The structure was confirmed by single crystal X-ray diffraction on a crystalline sample of **160** recrystallised from dichloromethane/hexane. Crystals of **160** are orthorhombic, space group *P*bca, formula $C_{14}H_{15}NO_2$, M = 229.27, a = 11.431(3) Å, b = 9.593(2) Å, c = 21.116(5) Å, U = 2315.53 $Å^3$, F(000) = 976, μ(Mo-Kα) = 0.088 mm^{-1}, $R(F_o)$ = 0.0596 for 2896 observed reflection with $I > 2\sigma(I)$, $wR_2(F^2)$ = 0.0548 for all 2564 unique reflections. Data in the θ range 1.93-27.15° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

3.6.1.4 3-(4-Fluorophenylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 161

In situ at room temperature



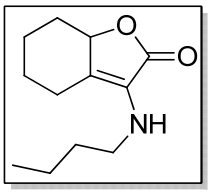
The reaction was carried out using the procedure described in Method 2 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 89 mg, 0.41 mmol, 1 eq), *p*-fluoroaniline (45 mg, 0.41 mmol, 1 eq), rhodium(II) acetate (1.8 mg, 4.1 μmol, 1 mol%) and dichloromethane (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 6 h at room temperature under the inert atmosphere. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated formation of 3-(4-fluorophenylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **161** and the presence of the disulfide **154**, enol **153**, alkene dimer **149** and excess *p*-fluoroaniline (1: 0.1: 0.15: 0.1: 2, 108 mg). Slow recrystallisation from hexane/dichloromethane gave 3-(4-fluorophenylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **161** and a trace amount of impurities as an off

white crystalline solid (64 mg, 62%); m.p. 100-102 °C; ν_{max}/cm^{-1} (KBr) 3344 (N-H), 1740 (C=O) 1682 (C=C), 1508 (C=C); δ_H (400 MHz) 1.09-1.25 (2H, m, CH_{2ring}), 1.27-1.42 (1H, m, CH_{2ring}), 1.74-1.88 (2H, m, CH_{2ring}), 1.94-2.05 (1H, m, CH_{2ring}), 2.39-2.52 (2H, m, CH_{2ring}), 4.68 (1H, dd, *J* 10.8, 5.4, C*H*O), 5.51 (1H, br s, N*H*), 6.71-6.81 (2H, m, Ar*H*), 6.85-6.93 (2H, m, Ar*H*); δ_C (75.5 MHz) 21.5, 24.5, 25.7, 33.0 (4 × *C*H_{2ring}), 78.3 (*C*HO), 114.7 (CH, d, $^2J_{CF}$ 21.9, aromatic *C*H), 118.5 (CH, d, $^3J_{CF}$ 8.0, aromatic *C*H), 121.7 (C_q, *C*=C), 134.9 (C_q, C=*C*), 136.7 (C, d, $^4J_{CF}$ 2.1, aromatic C_q), 157.0 (C, $^1J_{CF}$ 244.0, aromatic C_q), 170.3 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{14}H_{14}FNO_2$ $[M+H]^+$, 248.1087. Found 248.1084; m/z (ESI+) 248 $[(M+H)^+$, 95%].

Signals detected for enol **153** in the ^{1}H NMR spectrum of the crude material: δ_H (300 MHz) 2.90–3.00 (1H, m, one of CH_{2ring}), 4.59 (1H, dd, *J* 11.1, 6.4, C*H*O). Signals detected for disulfide **154** in the ^{1}H NMR spectrum of the crude material: δ_H (300 MHz) 3.11 (2H, br d, *J* 12.5, CH_{2ring}), 4.73 (2H, dd, *J* 11.1, 6.3, C*H*O). Signals identified for the alkene dimer **149** in the ^{1}H NMR spectrum of the crude material: δ_H (300 MHz) 2.71-2.80 (1H, sym m, one of CH_{2ring}), 2.91 (1H, br d, *J* 12.5, one of CH_{2ring}), 3.88 (1H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).

3.6.1.5 3-(Butylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 162

In situ at room temperature



The reaction was carried out following the procedure described in Method 2 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 75 mg, 0.35 mmol, 1 eq), *n*-butylamine (26 mg, 0.35 mmol, 1 eq), rhodium(II) acetate (1.5 mg, 3.5 μmol, 1 mol%) and dichloromethane (10 mL). The reaction mixture was stirred for 6 h under a nitrogen atmosphere. The solvent was removed *in vacuo* and the ^{1}H NMR spectrum of the crude product indicated formation of 3-(butylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **162** along with the presence of the disulfide **154**, enol **153** and alkene dimer **149** (1: 0.2: 0.1: 0.3, 83 mg). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(Butylamino)-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **162** and the

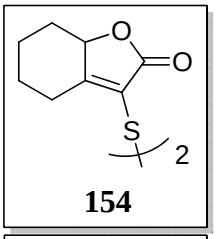
alkene dimer **149** (1: 0.15, 11 mg) were isolated as a yellow residue; ν_{max}/cm^{-1} (film) 3372 (N-H), 1751 (C=O); δ_H (300 MHz) 0.82-2.49 (14H, m, contains 7H m CH_{2ring}, 2 × CH_2, and CH_3 of *n*-butyl chain), 2.91-3.05 (1H, m, one of CH_{2ring}), 3.16 (2H, td, *J* 7.0, 1.4, CH_2 of *n*-butyl chain), 4.48 (1H, dd, *J* 11.3, 5.6, C*H*O).

Characteristic signals detected for the alkene dimer **149**: δ_H (300 MHz) 2.25-2.33 (1H, sym m, one of CH_{2ring}), 2.70-2.81 (1 H, sym m, one of CH_{2ring}, 3.88 (1H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).

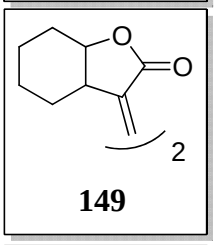
Signals detected for disulfide **154** in the crude ^{1}H NMR spectrum: δ_H (300 MHz) 4.73 (2H, dd, *J* 11.1, 6.3, C*H*O). Signals detected for enol **153** in the crude spectrum: δ_H (300 MHz) 2.90–3.00 (1H, m, one of CH_{2ring}), 4.59 (1H, dd, *J* 11.1, 6.4, C*H*O).

3.6.1.6 Attempted nucleophilic reactions with acetamide

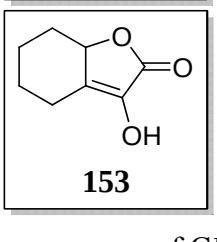
Method 1 (*in situ* at room temperature in dichloromethane)



154



149

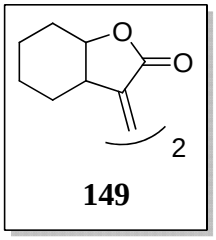


153

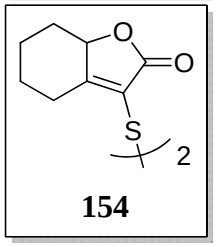
The reaction was carried out following the procedure described in Method 2 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 105 mg, 0.49 mmol, 1 eq), acetamide 29 mg, 0.49 mmol, 1 eq), rhodium(II) acetate (2.17 mg, 4.9 μmol, 1 mol%) and dichloromethane (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 6 h at room temperature. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated a complex mixture of compounds, including excess acetamide **268**, the alkene dimer **149**, the disulfide **154** and the enol **153** (1: 0.8: 0.5, 35 mg).

Characteristic signals detected for the alkene dimer **149**: δ_H (400 MHz) 2.25-2.33 (1H, sym m, one of CH_{2ring}), 2.71-2.80 (1 H, sym m, one of CH_{2ring}), 2.91 (1H, br d, *J* 12.5, one of CH_{2ring}), 3.88 (1H, ddd, *J* 11.6, 11.6, 3.6, C*H*O). Characteristic signals detected for the disulfide **154**: δ_H (400 MHz) 4.73 (1H, dd, *J* 11.1, 5.8, C*H*O), 3.11 [2H, d, *J* 11.8, axial C(4)H_{2ring}]. Characteristic signals detected for enol **153**: δ_H (400 MHz) 4.56 (1H, dd, *J* 11.2, 6.2, C*H*O).

Method 2 (*In situ* at room temperature in acetonitrile)



149



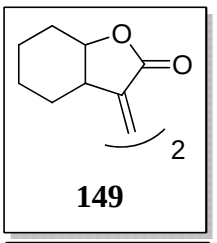
154

The reaction was carried out following the procedure described in Method 2 Section 3.6.1.1 using α-diazosulfoxides **5a** and **5e** (1:1, 97 mg, 0.43 mmol, 1 eq), rhodium(II) acetate (2.00 mg, 4.3 μmol, 1 mol%), acetamide (25 mg, 0.43 mmol, 1 eq) in acetonitrile (8 mL) for 6 h at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated the presence of the alkene dimer **149** and a trace amount of the disulfide **154** (39 mg). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. Two fractions were obtained. The first contained a mixture of the disulfide **154** and the alkene dimer **149** (1: 2.2, 9 mg) and the second fraction contained the disulfide **154** (6 mg).

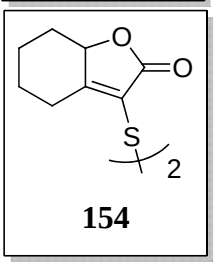
Characteristic signals detected for the disulfide dimer **154**: δ_H (400 MHz) 3.11 [2H, d, *J* 11.8, axial C(4)H_{2ring}], 4.73 (1H, dd, *J* 11.1, 5.8, C*H*O). Characteristic signals detected for the alkene dimer **149**: δ_H (400 MHz) 2.25-2.33 (2H, sym m, CH_{2ring}), 2.71-2.80 (2H, sym m, CH_{2ring}), 2.91 (2H, br d, *J* 12.5, CH_{2ring}), 3.88 (2H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).

3.6.1.7 Attempted nucleophilic reaction with benzamide

In situ reaction at room temperature



149



154

Rhodium(II) acetate (4.05 mg, 1.03 μmol, 1 mol%) was added to a solution of benzamide (125 mg, 1.03 mmol, 1 eq) and the α-diazosulfoxides **5a** and **5e** (1:1, 223 mg, 1.03 mmol, 1 eq) in dichloromethane (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred for 5 h at room temperature under the inert atmosphere. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated a mixture of benzamide, the alkene dimer **149** and a trace quantity of the disulfide dimer **154** (1:1, 305 mg). The crude product was

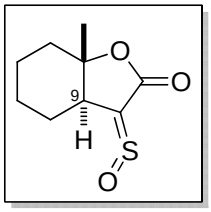
purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. One fraction was obtained which contained mainly the alkene dimer **149**, and a small amount of the disulfide dimer **154** (9.6:1, 54 mg).

Characteristic signals detected for the alkene dimer **149**: δ_H (400 MHz) 2.25-2.33 (2H, sym m, CH_{2ring}), 2.71-2.80 (2H, sym m, CH_{2ring}), 2.91 (2H, br d, *J* 12.5, CH_{2ring}), 3.88 (2H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).

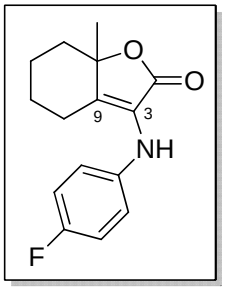
3.6.2 Nucleophilic Addition of Nitrogen Nucleophiles with 8a-Methyl-3-diazo *trans*-hexahydrobenzo[1,4] oxathiin-2-one *S*-Oxides 7a and 7e.

3.6.2.1 3-(4-Fluorophenylamino)-7a-methyl-5,6,7,7a tetrahydrobenzofuran-2(4*H*)-one 164

Sequential reaction with formation of sulfine **170** under reflux conditions and addition of *p*-fluoroaniline at room temperature



Rhodium(II) acetate (2.1 mg, 4.7 μmmol, 1 mol%) was added to a solution of α-diazosulfoxides **7e** and **7a** (14:1, 106 mg, 0.47 mmol, 1 eq) in dichloromethane (10 mL) and the reaction mixture was stirred under reflux for 1 h under a nitrogen atmosphere. The solvent was removed *in vacuo* and the ^{1}H NMR spectrum obtained indicated formation of the sulfine **170** (92 mg); δ_H (300 MHz) 1.39 (3H, s, CH_3), 1.40-1.64 (2H, m, CH_{2ring}), 1.74-1.96 (3H, m, CH_{2ring}), 2.00-2.19 (1H, sym m, one of CH_{2ring}), 2.79 (1H, br d, *J* 14.0, one of CH_{2ring}), 3.02 [1H, dd, *J* 11.9, 2.7, C(9)*H*]. Spectral details in agreement with those reported in the literature.



The reaction was carried out following the procedure described Section 3.6.1.1 using the sulfine **170** (92 mg, 0.46 mmol, 1 eq), *p*-fluoroaniline (52 mg, 0.47 mmol, 1 eq) and dichloromethane (12 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the orange crude product indicated formation of 3-(4-fluorophenylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **164** along with the presence of the disulfide **171**, excess *p*-fluoroaniline

(3: 1: 10, 143 mg) and small quantities of unidentifiable impurities. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(4-Fluorophenylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **164** was isolated as a pale brown solid (83 mg, 64% over the two steps). Found: C, 68.12; H, 6.50; N, 5.20. $C_{15}H_{16}FNO_2$ requires C, 68.42; H, 6.89; N, 5.32 %; m.p. 106-109 °C; ν_{max}/cm^{-1} (KBr) 3337 (NH), 1745 (C=O), 1680 (C=C), 1511 (aromatic C=C); δ_H (400 MHz) 1.18-1.33 (1H, m, one of CH_{2ring}), 1.42-1.53 (5H, m, contains 2H m of CH_{2ring} and 3H CH_3 s at 1.52), 1.80-1.94 (2H, m, CH_{2ring}), 2.01-2.15 (1H, m, one of CH_{2ring}), 2.27 (1H, br d, *J* 8.6, one of CH_{2ring}), 2.47-2.57 (1H, sym m, one of CH_{2ring}), 5.61 (1H, br s, N*H*), 6.75-6.82 (2H, m, Ar*H*), 6.90-6.98 (2H, m, Ar*H*); δ_C (75.5 MHz); 22.7 (*C*H_{2ring}), 23.6 (*C*H_3), 25.8 (*C*H_{2ring}), 26.4 (*C*H_{2ring}), 39.6 (CH_{2ring}), 84.4 (C_q), 115.7 (CH, d, $^2J_{CF}$ 22.6, aromatic *C*H), 118.9 (CH, d, $^3J_{CF}$ 8.0, aromatic *C*H), 122.0 (C_q), 137.9 (C, d, $^4J_{CF}$ 2.4, aromatic C_q), 140.9 (C_q), 157.9 (C, d, $^1J_{CF}$ 240.0, aromatic C_q), 170.5 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{16}NO_2F$ $[M+H]^+$, 262.1243. Found 262.1240; m/z (ESI+) 262 [$(M+H)^+$, 100%], 303 (42%), 263 (18%).

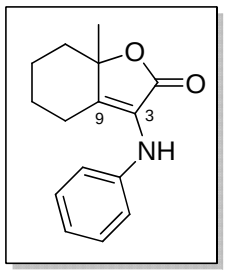
The structure was confirmed by single crystal X-ray diffraction on a crystalline sample of **164** recrystallised from dichloromethane/hexane. Crystals of **164** are triclinic, space group $P2_1/c$, formula $C_{15}H_{16}FNO_2$, M = 260.28, a = 10.9894(4) Å, b = 14.8717(5) Å, c = 7.9182(3) Å, U = 1275.40(8) $Å^3$, F(000) = 548, μ(Mo-Kα) = 0.100 mm^{-1}, $R(F_o)$ = 0.0248 for 3185 observed reflection with I > 2σ(I), $wR_2(F^2)$ = 0.0428 for all 3185 unique reflections. Data in the θ range 2.33-28.40° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

Spectral characteristics detected for disulfide **171** in the crude product: δ_H (400 MHz) 3.00 (2H, dt, *J* 13.7, 2.1, CH_{2ring}).

3.6.2.2 3-(Phenylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 165

Sequential reaction with formation of sulfine **170** under reflux conditions and addition of aniline at room temperature

The sulfine **170** was prepared following the procedure described in Section 3.6.2.1 using α-diazosulfoxides **7e** and **7a** (14:1, 51 mg, 0.23 mmol, 1 eq), rhodium(II) acetate (1.0 mg, 2.3 μmol, 1 mol%) and dichloromethane (10 mL). The solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum obtained indicated formation of the sulfine **170**. Spectral details as described above.



The reaction was carried out following the procedure described Section 3.6.1.1 using the sulfine **170** (46 mg, 0.23 mmol, 1 eq), aniline (21 mg, 0.23 mmol, 1 eq) and dichloromethane (10 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the orange crude product (60 mg) indicated formation of 3-(phenylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **165** and the disulfide **171** (5:1) among excess aniline. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(Phenylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **165** was obtained as a pale yellow solid (39 mg, 69% over the two steps); m.p. 108-110 °C; ν_{max}/cm^{-1} (KBr) 3339 (NH), 1739 (C=O); δ_H (400 MHz) 1.10-1.23 (1H, m one of CH_{2ring}), 1.38-1.51 (5H, m, contains CH_{2ring} and CH_3 s at 1.47), 1.72-1.86 (2H, m, CH_{2ring}), 2.01-2.13 (1H, m, one of CH_{2ring}), 2.19-2.24 (1H, m, one of CH_{2ring}), 2.50-2.59 (1H, sym m, one of CH_{2ring}), 5.59 (1H, br s, N*H*), 6.70-6.75 (2H, m, Ar*H*), 6.80-6.86 (1H, m, Ar*H*), 7.13-7.20 (2H, m, Ar*H*); δ_C (75.5 MHz) 21.7 (*C*H$_{2ring}$), 22.6 (*C*H$_3$), 25.1, 25.4 (2 × CH_{2ring}), 38.6 (*C*H$_{2ring}$), 83.4 (C_q), 115.8, 120.0, 128.1 (3 × aromatic *C*H), 140.9 (C_q,), 141.3 (C_q), 169.6 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{17}NO_2$ $[M+H]^+$, 244.1338. Found 244.1339; m/z (ESI+) 244 $[(M+H)^+$, 100%], 245 (18%), 285 (24%).

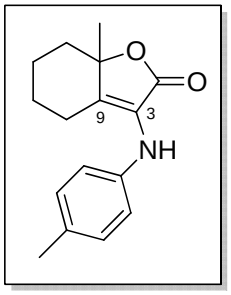
The structure was confirmed by single crystal X-ray diffraction on a crystalline sample of **165** recrystallised from dichloromethane/hexane. Crystals of **165** are monoclinic, space group $P2_1/c$, formula $C_{15}H_{17}NO_2$, M = 243.30, a =10.640(5) Å, b = 14.934(7) Å, c = 8.041(4) Å, U = 1252.3(10) $Å^3$, F(000) = 520, μ(Mo-Kα) = 0.086 mm^{-1}, $R(F_o)$ = 0.0334 for 2588 observed reflection with I > 2σ(I), $wR_2(F^2)$ = 0.0403 for all 3094 unique reflections. Data in the θ range 1.95-28.23° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

Spectral characteristics detected for disulfide **171** in the crude product: δ_H (400 MHz) 3.00 (2H, dt, *J* 13.7, 2.1, CH_{2ring}).

3.6.2.3 3-(*p*-Tolylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one 166

Method 1 (Sequential reaction with formation of sulfine **170** under reflux conditions and addition of *p*-toluidine at room temperature)

The sulfine **170** was prepared following the procedure described in Section 3.6.2.1 using α-diazosulfoxides **7e** and **7a** (14:1, 50 mg, 0.23 mmol), rhodium(II) acetate (1.0 mg, 2.3 μmol, 1 mol%) and dichloromethane (10 mL). The solvent was removed from the cooled reaction mixture *in vacuo* and the ^1H NMR spectrum obtained indicated formation of the sulfine **170** (48 mg). Spectral details as described above.



The reaction procedure was carried out as described in Section 3.6.1.1 using the sulfine **170** (48 mg, 0.23 mmol, 1 eq), *p*-toluidine (69.6 mg, 0.65 mmol, 1 eq) and dichloromethane (10 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the orange crude product indicated formation of 3-(*p*-tolylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **166** and excess *p*-toluidine (1:1, 142 mg). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 3-(*p*-Tolylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **166** (R_f = 0.69, red colour by vanillin stain) was obtained as a light orange solid (122 mg, 72% over the two steps). An analytical sample was obtained by slow recrystallisation from dichloromethane/hexane to give pale brown crystals (62 mg, 38%); Found: C, 74.92; H, 7.48; N, 5.71. $C_{16}H_{19}NO_2$ requires C, 74.68; H, 7.44; N, 5.44%; m.p. 110-112 °C; ν_{max}/cm^{-1} (KBr) 3339 (NH), 1739 (C=O), 1682 (C=C), 1602, 1497 (aromatic C=C); δ_H (300 MHz) 1.10-1.31 (1H, m one of C*H*$_{2ring}$), 1.39-1.52 (5H, m, contains C*H*$_{2ring}$ and C*H*$_3$ s at 1.53), 1.74-1.91 (2H, m, C*H*$_{2ring}$), 2.05-2.23 (1H, m, one of C*H*$_{2ring}$), 2.19-2.32 (4H, m, contains one of C*H*$_{2ring}$ and ArC*H*$_3$ s at 2.28), 2.54-2.64 (1H, sym m, one of C*H*$_{2ring}$), 5.55 (1H, br s, N*H*), 6.73 (2H, d, *J* 8.4 Ar*H*), 7.04 (2H, d, *J* 8.0 Ar*H*); δ_C (75.5 MHz) 20.6 (*C*H$_3$), 22.8 (*C*H$_{2ring}$), 23.6 (*C*H$_3$), 26.0, 26.4 (2 × *C*H$_{2ring}$), 39.6 (*C*H$_{2ring}$), 83.4 (*C*$_q$O), 117.5 (aromatic *C*H), 121.8 (C$_q$), 129.6 (aromatic *C*H), 130.8 (*C*$_q$), 139.2 (*C*$_q$), 140.4 (*C*$_q$), 170.7 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{19}NO_2$ $[M+H]^+$, 258.1494. Found 258.1498; m/z (ESI+) 258 $[(M+H)^+$, 100%], 259 (20%).

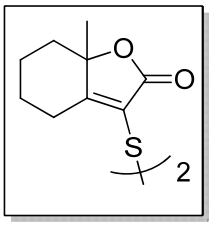
Method 2 (*In situ* reaction under microwave conditions)

p-Toluidine (43 mg, 0.40 mmol, 1 eq) was added to a solution of the α-diazosulfoxides **7e** and **7a** (14:1, 87 mg, 0.40 mmol, 1 eq) in dichloromethane (3 mL) and the mixture was irradiated with microwaves at 300 W. The reaction settings were set for the reaction mixture to reach a temperature of 100˚C using a 3 min ramp-time and a 10 min hold-time. The reaction mixture was cooled and TLC analysis indicated the presence of some unreacted sulfine **170**. The mixture was irradiated with microwaves at 300 W for a further 10 min. The solvent was removed *in vacuo* to leave a brown oil (112 mg). The ^{1}H NMR spectrum of the crude material indicated the presence of 3-(*p*-tolylamino)-7a-methyl-5, 6, 7, 7a-

tetrahydrobenzofuran-2(4*H*)-one **166**, excess *p*-toluidine and the disulfide **171** (1: 2: 0.4). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. Two fractions were isolated, the first contained pure 3-(*p*-tolylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **166** (54 mg, 52%) and the second fraction contained a mixture of 3-(*p*-tolylamino)-7a-methyl-5, 6, 7, 7a-tetrahydrobenzofuran-2(4*H*)-one **166** and the disulfide **171** (1: 0.4, 24 mg). Spectral details as described above.

3.6.2.4 Attempted reaction with (*R*)-(+)-(α)-methylbenzyl amine

The sulfine **170** was prepared following the procedure described in Section 3.6.2.1 using α-diazosulfoxides **7e** and **7a** (14:1, 82 mg, 0.36 mmol, 1 eq), rhodium(II) acetate (1.59 mg, 3.6 μmol, 1 mol%) and dichloromethane (10 mL). The solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum obtained indicated formation of the sulfine **170** (72 mg). Spectral details as described above.

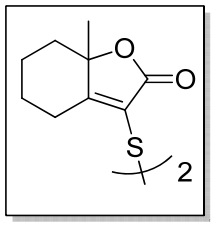


The reaction procedure was carried out as described in Section 3.6.1.1 using the sulfine **170** (72 mg, 0.36 mmol, 1 eq), (*R*)-(+)-(α)-methylbenzyl amine (43 mg, 0.36 mmol, 1 eq) and dichloromethane (12 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the orange crude product indicated the presence of (*R*)-(α)-methylbenzyl amine and the disulfide **171** (1: 0.8, 110 mg). Attempts to isolate a product by flash chromatography (hexane/ethyl acetate 20:80) gave the disulfide **171** as a pale yellow residue (12 mg); δ_H (300 MHz) 1.40-2.15 (16H, m, contains 10H m of CH_{2ring} and 2 × CH_3 s at 1.50), 2.20-2.35 (4H, m, CH_{2ring}), 3.01 (2H, dt, *J* 13.7, 2.1, CH_{2ring}).

3.6.2.5 Attempted reaction with diisopropylamine

The sulfine **170** was prepared following the procedure described in Section 3.6.2.1 using α-diazosulfoxides **7e** and **7a** (14:1, 80 mg, 0.36 mmol, 1 eq), rhodium(II) acetate (1.59 mg, 3.6 μmol, 1 mol%) and dichloromethane (10 mL). The

solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum obtained indicated formation of the sulfine **170** (71 mg). Spectral details as described above.

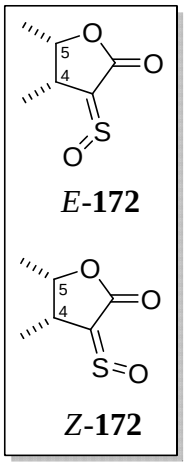


The reaction procedure was carried out as described in Section 3.6.1.1 using the sulfine **170** (71 mg, 0.36 mmol, 1 eq), diisopropylamine (36 mg, 0.36 mmol, 1 eq) and dichloromethane (10 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the orange crude product indicated the presence of diisopropylamine and the disulfide **171** (2:1, 98 mg). Attempts to isolate a product by flash chromatography (hexane/ethyl acetate 20:80) gave the disulfide **171** as a pale yellow residue (15 mg). Spectral details for the disulfide **171** as described above.

3.6.3 Nucleophilic Addition of Nitrogen Nucleophiles with *cis*-3-Diazo-5,6-dimethyl-[1,4]oxathian-2-one *S*-Oxide 10

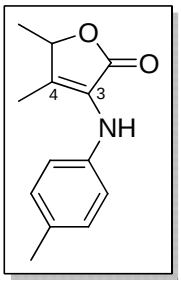
3.6.3.1 4,5-Dimethyl-3-(*p*-tolylamino)furan-2(5*H*)-one 167

Method 1 (Sequential reaction with formation of sulfines *Z*-**172** and *E*-**172** under reflux conditions and addition of *p*-toluidine at room temperature)



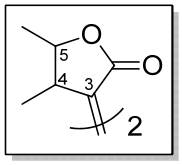
Rhodium(II) acetate dimer (2.51 mg, 6.5 μmol, 1 mol%) was added to a solution of the α-diazosulfoxide **10** (107 mg, 0.65 mmol, 1 eq) in dichloromethane (10 mL). The reaction mixture was stirred for 18 h under reflux and a nitrogen atmosphere. The solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum obtained indicated formation of the sulfines *E*-**172** and *Z*-**172** (3:1, 89 mg). Sulfine *E*-**172**: δ_H (300 MHz) 1.34-1.43 (6H, m, contains overlapping 2 × C*H*$_3$ d), 3.96 [1H, overlapping dq appears as quintet, *J* 7.1, 7.1, C(4)*H*], 4.79 [1H, overlapping dq appears as quintet, *J* 6.6, 6.6, C(5)*H*O]. Sulfine *Z*-**172**: δ_H (300 MHz) 1.34-1.43 (6H m, contains overlapping 2 × C*H*$_3$ d), 3.69 [1H, overlapping dq

appears as quintet, *J* 6.9, 6.9, C(4)*H*], 4.75 [1H, overlapping dq appears as quintet, *J* 6.5, 6.5, C(5)*H*O].



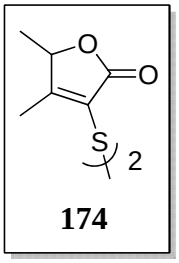
The sulfines *E*-**172** and *Z*-**172** (3:1, 89 mg, 1 eq) were dissolved in dichloromethane (10 mL) and a solution of *p*-toluidine (61 mg, 0.57 mmol, 1 eq) in dichloromethane (5 mL) was added. The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. The solvent was removed *in vacuo* and ^{1}H NMR analysis of the orange crude product indicated the presence of a mixture of compounds, including 4,5-dimethyl-3-(*p*-tolylamino)furan-2(5*H*)-one **167** and unreacted *p*-toluidine. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. Two fractions were isolated, the first contained 4,5-dimethyl-3-(*p*-tolylamino)furan-2(5*H*)-one **167** and a small quantity of the alkene dimer **173** (10:1), obtained as a light orange solid (54 mg, ~44%). The second fraction was a mixture of unreacted *p*-toluidine and 4,5-dimethyl-3-(*p*-tolylamino)furan-2(5*H*)-one **167** (12.5:1, 56 mg). Attempts to obtain an analytically pure sample of 4,5-dimethyl-3-(*p*-tolylamino)furan-2(5*H*)-one **167** by recrystallisation were unsuccessful. m.p. 85-89 °C; ν_{max}/cm^{-1} (KBr) 3368 (N-H), 1750 (C=O).

4,5-Dimethyl-3-(*p*-tolylamino)furan-2(5*H*)-one **167**: δ_H (400 MHz) 1.48 (3H, d, *J* 6.6, C*H*$_3$), 1.71 (3H, d, *J* 1.1, C*H*$_3$), 2.27 (3H, s, ArC*H*$_3$), 4.90 (1H dq, *J* 6.6, 1.1, C*H*O), 5.26 (1H, br s, N*H*), 6.74 (1H, d, *J* 7.9, Ar*H*), 6.89-6.94 (1H, m, Ar*H*), 7.10-7.19 (2H, m, Ar*H*); δ_C (75.5 MHz) 12.4 (*C*H$_3$), 17.8 (ArCH$_3$), 19.0 (*C*H$_3$), 79.0 (*C*HO), 118.0, 122.1 (2 × aromatic *C*H), 125.6 (*C*=C), 126.3 (aromatic *C*H), 128.1 (*C*$_q$), 130.7 (aromatic *C*H), 135.4 (C=*C*), 139.7 (*C*$_q$), 171.1 (C=O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{15}NO_2$ $[M+H]^+$, 218.1181. Found 218.1182; m/z (ESI+) 218 $[(M+H)^+$, 100%].

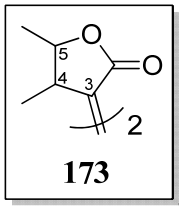


Signals detected for alkene dimer **173**: δ_H (400 MHz) 1.18 (6H, d, *J* 7.2, C*H*$_3$), 1.41 (6H, d, *J* 6.6, C*H*$_3$), 3.77 [2H, overlapping dq appears as quintet, *J* 7.2, 7.2, C*H*(4)], 4.63 [2H, overlapping dq appears as quintet, *J* 7.0, 7.0, C(5)*H*]; δ_C (75.5 MHz) 12.5, 13.8, 15.3, 78.3 [*C*(5)HO], 135.2 [*C*(3)=C]; m/z (ESI+) 225 $[(M+H)^+$, 20%].

Method 2 (Attempted *in situ* reaction with *p*-toluidine)



174



173

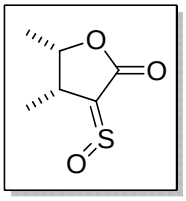
A solution of *p*-toluidine (57.5 mg, 0.54 mmol, 1 eq) in dichloromethane (5 mL) was added to a solution of rhodium(II) acetate (2.37 mg, 5.4 μmol, 1 mol%) and α-diazosulfoxide **10** (101 mg, 0.54 mmol, 1 eq) in dichloromethane (10 mL). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 18 h. The solvent was removed *in vacuo* to leave the crude product as a light brown residue (164 mg). The ^{1}H NMR spectrum indicated that no reaction had taken place and only clean α-diazosulfoxide **10** and *p*-toluidine were detected.* The reaction mixture was dissolved in dichloromethane (15 mL), a further 1 mol% rhodium(II) acetate catalyst was added and the solution was heated under reflux for 36 h. The solvent was removed *in vacuo* to leave the crude product as a dark brown residue (162 mg). The ^{1}H NMR spectrum of the crude mixture indicated that no reaction with the amine had taken place and that partial decomposition of the α-diazosulfoxide **10** to the disulfide **174** and alkene dimer **173** had occurred (1: 0.5: 0.1) along with small quantities of unidentifiable compounds.

^{1}H NMR signals detected for the disulfide **174**: 2.17 (3H, s, C*H*$_3$), 4.96 (1H, q, *J* 6.9, C*H*O). ^{1}H NMR signals detected for alkene dimer **173**: δ_H (400 MHz) 1.18 (6H, d, *J* 7.2, C*H*$_3$), 3.77 [2H, overlapping dq appears as quintet, *J* 7.2, 7.2, C*H*(4)], 4.63 [2H, overlapping dq appears as quintet, *J* 7.0, 7.0, C(5)*H*].

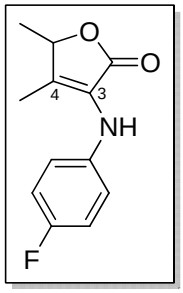
Note:* There was a slight upfield shift in the ^{1}H NMR signals for the C*H*S and C*H*O of the diazosulfoxide **10. The C*H*S and C*H*O signals for **10** are normally detected at 2.95 and 5.40, respectively. In the sample recorded in this experiment, the C*H*S qd was detected at 5.39, and the C*H*S qd was detected at 2.93. This may have been due to complexation with the unreacted *p*-toluidine. For full ^{1}H NMR spectral details of **10**, see Section 3.2.2.3.

3.6.3.2 4,5-Dimethyl-3-(4-fluorophenylamino)furan-2(5*H*)-one 168

Method 1 (Sequential reaction with formation of sulfines *Z*-**172** and *E*-**172** under reflux conditions and addition of *p*-fluoroaniline at room temperature)



The sulfine *E*-**172** (43 mg) was prepared following the procedure described in Section 3.6.3.1 using α-diazosulfoxide **10** (44 mg, 0.27 mmol, 1 eq), rhodium(II) acetate (1.19 mg, 2.7 μmol, 1 mol%) and dichloromethane (10 mL). Spectral details as described above. *Note*: The sulfine *Z*-**172** was not detected in the ^{1}H NMR spectrum for this particular reaction.



The reaction was carried out as described in Section 3.6.1.1 using the sulfine *E*-**172** (42 mg, 0.27 mmol, 1 eq), *p*-fluoroaniline (32 mg, 0.27 mmol, 1 eq) and dichloromethane (15 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated the presence of 4,5-dimethyl-3-(4-fluorophenylamino)furan-2(5*H*)-one **168** among excess *p*-fluoroaniline and a small amount of alkene dimer **173** (1: 0.3: 0.1, 53 mg). The crude product was purified by slow recrystallisation from hexane/dichloromethane to give pure 4,5-dimethyl-3-(4-fluorophenylamino)furan-2(5*H*)-one **168** as a light orange solid (39 mg, 67 % over the two steps). Found: C, 64.59; H, 5.38; N, 5.81. $C_{12}H_{12}FNO_2$ requires C, 65.15; H, 5.47; N, 6.33 %; m.p. 89-91 °C; ν_{max}/cm^{-1} (KBr) 3340 (NH), 1747 (C=O); δ_H (400 MHz) 1.47 (3H, d, *J* 6.6, C*H*$_3$), 1.75 (3H, d, *J* 1.1, C*H*$_3$), 4.90 (1H, qd, *J* 6.6, 1.1, C*H*O), 5.61 (1H, br s, N*H*), 6.77-6.83 (2H, m, Ar*H*), 6.93-7.00 (2H, m, Ar*H*); δ_C (75.5 MHz) 12.5 (*C*H$_3$), 19.0 (*C*H$_3$), 79.1 (*C*HO), 115.7 (CH, d, $^{2}J_{CF}$ 22.6, aromatic *C*H), 120.1 (CH, d, $^{3}J_{CF}$ 8.0, aromatic *C*H), 125.6 (*C*=C), 135.4 (C=*C*), 137.5 (C, d, $^{4}J_{CF}$ 2.4, aromatic C_q), 158.2 (C, d, $^{1}J_{CF}$ 240.5, aromatic C_q), 171.2 (*C*=O); Exact mass calculated for $C_{12}H_{13}FNO_2$ $[M+H]^+$, 222.0930. Found 222.0933; m/z (ESI+) 222 $[(M+H)^+$, 100%].

Signals detected for trace amount of alkene dimer **173** in the crude material: δ_H (400 MHz) 1.18 (6H, d, *J* 7.2, C*H*$_3$), 1.41 (6H, d, *J* 6.6, C*H*$_3$), 3.77 [2H, overlapping dq appears as quintet, *J* 7.2, 7.2, C*H*(4)], 4.63 [2H, overlapping dq appears as quintet, *J* 7.0, 7.0, C(5)*H*].

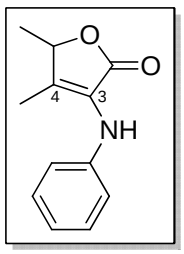
Method 2 (*In situ* reaction under microwave conditions)

p-Toluidine (32 mg, 0.17 mmol, 1 eq) was added to a solution of the α-diazosulfoxide **10** (28 mg, 0.17 mmol, 1 eq) in dichloromethane (3 mL) and the mixture was irradiated with microwaves at 300 W. The reaction settings were set for the reaction mixture to reach a temperature of 100˚C using a 3 min ramp-time and a 45 min hold-time. The reaction mixture was cooled and ^{1}H NMR analysis of the crude material indicated the presence of 4,5-dimethyl-3-(4-fluorophenylamino)furan-2(5*H*)-one **168** and trace quantities of impurities, including the alkene dimer **173** (54 mg, 88%). Spectral details as described above.

3.6.3.3 4,5-Dimethyl-3-(phenylamino)furan-2(5*H*)-one 169

Sequential reaction with formation of sulfines *Z*-**172** and *E*-**172** under reflux conditions and addition of aniline at room temperature

The sulfines *Z*-**172** and *E*-**172** were prepared following the procedure described in Section 3.6.3.1 using α-diazosulfoxide **10** (73 mg, 0.39 mmol), rhodium(II) acetate (1.72 mg, 3.9 μmol, 1 mol%) and dichloromethane (14 mL). The solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum indicated the presence of the sulfines *E*-**172** and *Z*-**172** (11:1, 63 mg). Spectral details as described above.



The reaction was carried out as described in Section 3.6.1.1 using the sulfines *E*-**172** and *Z*-**172** (63 mg, 0.39 mmol, 1 eq), aniline (36 mg, 0.39 mmol, 1 eq) and dichloromethane (15 mL). The solvent was removed *in vacuo* and ^{1}H NMR analysis of the crude product indicated the presence of 4,5-dimethyl-3-(phenylamino)furan-2(5*H*)-one **169**, unreacted aniline, alkene dimer **173** and small quantities of unidentifiable compounds (92 mg). The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. 4,5-Dimethyl-3-(phenylamino)furan-2(5*H*)-one **169** and a trace amount of impurities were isolated as a light orange solid (51 mg, 65%). An analytically pure sample was prepared by slow recrystallisation from hexane/dichloromethane (18 mg, 23%); m.p. 85-86°C, ν_{max}/cm^{-1} (KBr) 3341 (N-H), 1752 (C=O); δ_H (300 MHz) 1.42 (3H, d, *J*

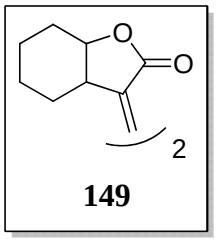
6.6, C*H*$_3$), 1.74 (3H, d, *J* 1.1, C*H*$_3$), 4.84 (1H, qd, *J* 6.6, 1.1, C*H*O), 5.54 (1H, br s, N*H*), 6.71-6.76 (2H, m, Ar*H*), 6.84-6.90 (1H, m, Ar*H*), 7.16-7.22 (2H, m, Ar*H*); δ_C (75.5 MHz) 11.8 (*C*H$_3$), 18.0 (*C*H$_3$), 78.0 (C*H*O), 116.8 (2 × aromatic *C*H), 120.4 (aromatic *C*H), 124.1 (*C*=C), 128.1 (2 × aromatic *C*H), 136.0 (C=*C*), 140.6 (aromatic *C*$_q$), 170.2 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{14}NO_2$ $[M+H]^+$, 204.1025. Found 204.1022; m/z (ESI+) 204 $[(M+H)^+$, 100%].

The structure was confirmed by single crystal X-ray diffraction on a crystalline sample of **169** recrystallised from dichloromethane/hexane. Crystals of **169** are monoclinic, space group $P2_12_12_1$, formula $C_{12}H_{13}NO_2$, M = 203.23, a = 8.2737 (2) Å, b = 10.0564 (2) Å, c = 12.2653(3) Å, U = 1020.52(4) Å^3, F(000) = 432, μ(Mo-Kα) = 0.732 mm^{-1}, R(F$_o$) = 0.0267 for 6632 observed reflection with I > 2σ(I), wR$_2$(F^2) = 0.0276 for all 1766 unique reflections. Data in the θ range 1.95-28.23° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

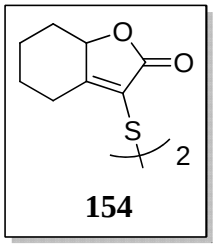
Signals detected for alkene dimer **173** in the crude material: δ_H (400 MHz) 1.18 (6H, d, *J* 7.2, C*H*$_3$), 1.41 (6H, d, *J* 6.6, C*H*$_3$), 3.77 [2H, overlapping dq appears as quintet, *J* 7.2, 7.2, C*H*(4)], 4.63 [2H, overlapping dq appears as quintet, *J* 7.0, 7.0, C(5)*H*].

3.6.4 Nucleophilic Addition of Carbon Nucleophiles with 3-Diazo-*trans*-hexahydrobenzo[1,4] oxathiin-2-one *S*-Oxides 5a and 5e.

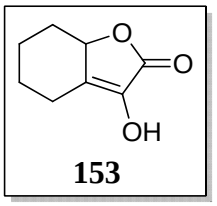
Attempt 1. Attempted nucleophilic addition of ethyl cyanoacetate using sodium ethoxide as base



149



154

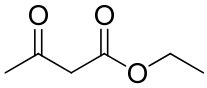
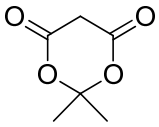
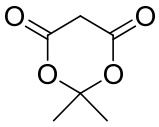


153

Ethyl cyanoacetate (53 mg, 0.47 mmol, 1 eq) was added to a freshly prepared solution of sodium ethoxide (11 mg sodium, 0.47 mmol, 1 eq in 8 mL ethanol) at 0 °C under a nitrogen atmosphere and stirred for 15 min. In a separate reaction vessel, rhodium(II) acetate (2.1 mg, 4.8 μmol, 1 mol%) was added to the α-diazosulfoxides **5a** and **5e** (16:1, 101 mg, 0.48 mmol, 1 eq) in dichloromethane (8 mL). and allowed to stir at room temperature under a nitrogen atmosphere for 10 min. The solvent was removed *in vacuo* to leave a brown residue which was redissolved in ethanol (5 mL). The enolate solution was then added to the solution of the sulfine **148** at 0 °C and allowed to stir for 45 min while slowly returning to room temperature. The reaction was quenched with water (20 mL), dichloromethane (20 mL) was added and the two phases were separated. The organic layer was washed with brine (5 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave a brown oil (102 mg). ^{1}H NMR analysis of the crude product indicated the presence of a complex mixture of compounds, including excess ethyl cyanoacetate, the disulfide **154**, the enol **153**, the alkene dimer **149**, with no evidence for the presence of an addition product.

Characteristic signals detected for the disulfide **154**: δ_H (400 MHz) 4.73 (1H, dd, *J* 11.1, 5.8, C*H*O), 3.11 [2H, d, *J* 11.8, axial C(4)H_{2ring}]. Characteristic signals detected for enol **153**: δ_H (400 MHz) 4.56 (1H, dd, *J* 11.2, 6.2, C*H*O). Characteristic signals detected for the alkene dimer **149**: δ_H (400 MHz) 3.88 (1H, ddd, *J* 11.6, 11.6, 3.6, C*H*O).

Table 3.4 Summary of attempted nucleophilic addition of carbon nucleophiles to sulfine **148** derived from 3-diazo-*trans*-hexahydrobenzo[1,4] oxathiin-2-one *S*-oxides **5a** and **5e**

Entry	Nucleophile[a]	Base	Reaction[b] conditions	Product[c]
1		LDA	-72 °C, THF, 1 h	No reaction
2		LDA	-72 °C, THF, 1 h	No reaction
3		NaOEt	0 °C, EtOH, 1 h	No reaction
4	*n*-BuLi	-	-78 °C, THF, 1 h	No reaction

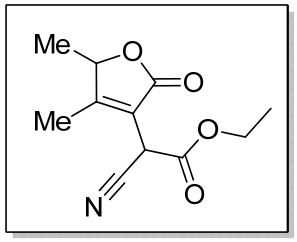
d. For entries 1-3, 1 eq of the carbon nucleophile was used, for entry 4, 1.2 eq of *n*-BuLi was used.
e. Reaction conditions as decribed in Method 1, above.
f. Analysis of the ^{1}H NMR spectrum of the crude product indicated an excess of the nucleophiles ethyl acetate and Meldrum's acid, along with small quantities of decomposition products formed from the sulfine **148**.

3.6.5 Nucleophilic Addition of Carbon Nucleophiles with *cis*-3-Diazo-5,6 dimethyl-[1,4]oxathian-2-one *S*-Oxide 10

3.6.5.1 Nucleophilic reaction with ethyl cyanoacetate

Method 1. Using sodium ethoxide as base

The sulfines *Z*-**172** and *E*-**172** were prepared following the procedure described in Section 3.6.3.1 using α-diazosulfoxide **10** (0.46 g, 2.44 mmol), rhodium(II) acetate (10.7 mg, 24.4 μmol, 1 mol%) and dichloromethane (25 mL). The solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum indicated the presence of the sulfines *E*-**172** and *Z*-**172** (10:1, 0.24 g, 2.61 mmol, 99%). ^{1}H NMR details for the sulfines *E*-**172** and *Z*-**172** are given in Section 3.6.3.1, above.



Ethyl cyanoacetate (116 mg, 1.03 mmol, 1 eq) was added to a freshly prepared solution of sodium ethoxide (24 mg sodium, 15 mL ethanol) at 0 °C under a nitrogen atmosphere and stirred for 30 min. This enolate solution was then added to a solution of the sulfines *E*-**172** and *Z*-**172** (10:1, 95 mg, 1.03 mmol, 1 eq) in ethanol (6 mL). The reaction mixture was stirred for 1 h while slowly returning to room temperature and quenched with water (20 mL). Dichloromethane (30 mL) was added and the two phases were separated. The organic layer was washed with brine (10 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to leave a brown oil (181 mg). ^{1}H NMR analysis of the crude product indicated the presence of a complex mixture of compounds, including excess ethyl cyanoacetate and the furanone **184**. The product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. The pure furanone **184** was isolated as a clear oil (37 mg, 15%); ν_{max}/cm^{-1} (film) 1735 (C=O), 1638 (C=O); δ_H (400 MHz) 1.33 (3H, t, *J* 7.1, ethyl C*H*$_3$), 1.49 (3H, d, *J* 6.4, C*H*$_3$), 2.20 (3H, s, C*H*$_3$), 4.26-4.35 (2H, m, C*H*$_2$), 4.70 (1H, s, C*H*CN), 4.93-5.01 (1H, sym m, C*H*O); δ_C (75.5 MHz) 12.4 (*C*H$_3$), 13.9 (ethyl *C*H$_3$), 17.7 (*C*H$_3$), 32.5 (*C*H), 63.9 (*C*H$_2$), 80.5 (*C*HO), 113.4 (C_q), 117.7 (C_q), 162.9 (C_q), 167.6 (*C*=O, ester), 170.7 (*C*=O, lactone); HRMS (ESI+): Exact mass calculated for

$C_{11}H_{13}NO_4$ $[M+H]^+$, 224.0923. Found 224.0925; m/z (ESI+) 224 $[(M+H)^+$, 50%], 222.1 $[(M-H)^-$, 25%].

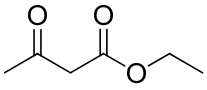
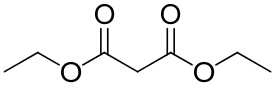
Method 2. Using LDA as base

The sulfines *Z*-**172** and *E*-**172** were prepared following the procedure described in Section 3.6.3.1 using α-diazosulfoxide **10** (0.46 g, 2.44 mmol), rhodium(II) acetate (10.7 mg, 24.4 μmol, 1 mol%) and dichloromethane (25 mL). The solvent was removed from the cooled reaction mixture *in vacuo* and the ^{1}H NMR spectrum indicated the presence of the sulfines *E*-**172** and *Z*-**172** (10:1, 0.24 g, 2.61 mmol, 99%). ^{1}H NMR details for the sulfines *E*-**172** and *Z*-**172** are given in Section 3.6.3.1, above.

DIPA (0.12 mL, 0.77 mmol, 1.1 eq) was added to a dry flask containing THF (5 mL). The stirred solution was cooled to 0 °C and *n*-butyllithium (0.34 mL, 1.6 M in hexane, 0.84 mmol, 1.2 eq) was syringed in dropwise. After 20 min, ethyl cyanoacetate (0.08 mL, 0.70 mmol, 1 eq) was added and the reaction mixture was stirred for a further 20 min. A solution of the sulfines *Z*-**172** and *E*-**172** (65 mg, 0.70 mmol, 1 eq) in THF (5 mL) was added dropwise. After 1 h, the reaction was quenched with saturated ammonium chloride (10 mL). Dichloromethane (10 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (2 × 5 mL) and the combined organic layers were washed with saturated sodium bicarbonate (2 × 5 mL), water (5 mL), brine (5 mL), dried with anhydrous $MgSO_4$ and concentrated *in vacuo* to give an orange oil (90 mg). ^{1}H NMR analysis of the crude product indicated the presence of a complex mixture of compounds, including excess ethyl cyanoacetate and the furanone **184**. The product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. The pure furanone **184** was isolated as a clear oil (20 mg, 17%).

Note: The above nucleophilic addition of ethyl cyanoacetate was attempted using a variety of carbon nucleophiles (**Table 3.5**), however the result was not reproducible.

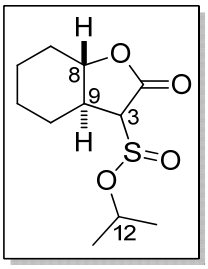
Table 3.5 Summary of attempted nucleophilic addition of carbon nucleophiles to sulfines *Z*-**172** and *E*-**172** derived from *cis*-3-diazo-5,6-dimethyl-[1,4]oxathian-2-one *S*-oxide **10**

Entry	Nucleophile[a]	Base	Reaction conditions[b]	Product[c]
1		NaOEt	0 °C, EtOH, 1 h	No reaction
2		NaOEt	0 °C, EtOH, 1 h	No reaction

d. For each entry, 1 eq carbon nucleophile was used.
e. Reaction conditions as described in Method 1, above.
f. Analysis of the ^{1}H NMR spectrum of the crude product indicated an excess of the carbon nucleophile starting material, along with trace quantities of decomposition products formed from the sulfines ***Z*-172** and ***E*-172**.

3.6.6 Nucleophilic Addition of Oxygen Nucleophiles with 3-Diazo-*trans*-hexahydrobenzo[1,4] oxathiin-2-one *S*-Oxides 5a and 5e.

Attempt 1 Attempted nucleophilic addition of isopropyl alcohol

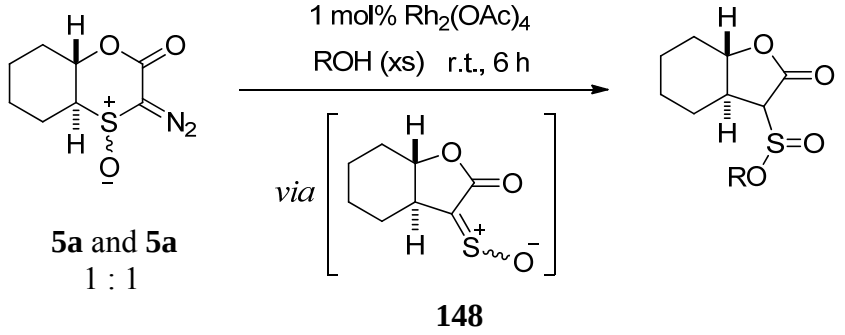


Rhodium(II) acetate (2.1 mg, 4.7 μmol, 1 mol%) was added to a solution of α-diazosulfoxides **5a** and **5e** (1:1, 48 mg, 0.22 mmol, 1 eq) in isopropyl alcohol (8 mL) under a nitrogen atmosphere. The reaction mixture was stirred under the inert atmosphere at room temperature for 6 h. The solvent was removed *in vacuo* giving the crude product as a pale yellow residue. ^{1}H NMR analysis indicated the presence of a complex mixture of unidentifiable compounds, including a small quantity of a compound tentatively assigned as the sulfinate ester **185**. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1) as eluent. One fraction was isolated from the column, an impure sample of the sulfinate ester **185** which was isolated as a pale yellow residue (~4 mg); ν_{max}/cm^{-1} (film) 1763 (C=O), 1193 (S-O); δ_H (300 MHz) 1.20-2.62 (14 H, m, cyclohexyl ring including 2 ×

3 H s at 1.35 and 1.37, 2 × isopropyl methyl CH_3), 3.10-3.22 [1H, m, C(9)*H*], 4.30-4.45 [1H, sym m, C(8)*H*], 4.82-4.94 [1H, m, C(3)*H*], 5.12 [1H, sept, *J* 14.0, 9.3, 4.0 C(12)*H*].

A number of further nucleophilic additions were attempted in the presence of alcohols, using the conditions described above for isopropyl alcohol. A summary of these unsuccessful reactions is illustrated in Table 3.6.

Table 3.6 *In situ* reactions of α-oxosulfine **148** derived from α-diazosulfoxides **5a** and **5e** with alcohol nucleophiles



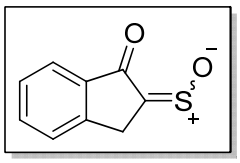
Entry	Alcohol nucleophile[a]	Reaction conditions[b]	Product[c]
1	Isopropyl alcohol	RT, 6 h	**185** (small quantity)[d]
2	Ethanol	RT, 6 h	Complex mixture
3	*t*-Butanol	RT, 6 h	Complex mixture
4	Phenol	RT, 6 h	Complex mixture

a. Excess alcohol nucleophile was employed for each reaction, with the alcohol also behaving as solvent. The reactions were carried out on a ~50 mg scale, with 1 mol% rhodium(II) acetate in ~10 mL alcohol.
b. Reactions were carried out *in situ* at room temperature over 6 hours, with addition of the α-diazosulfoxides **5a** and **5a** (1:1) to the alcohol, immediately followed by 1 mol% rhodium(II) acetate.
c. Products were determined by ^{1}H NMR analysis. No addition products were detected for entries 2-4. Complex mixtures of unidentifiable compounds were detected by ^{1}H NR analysis.
d. The crude product was purified by chromatography and a very small quantity of **185** (~4 mg) was obtained.

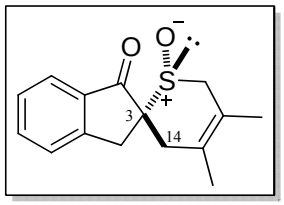
3.7 [4+2] Cycloadditions

3.7.1 Cycloadditions with 3-Diazoisothiochroman-4-one *S*-Oxide 87

3.7.1.1 Rhodium(II) acetate-catalysed decomposition of 3-diazoisothiochroman-4-one *S*-oxide 87 to α-oxosulfine 187a and subsequent cycloaddition with 2,3-dimethyl-1,3-butadiene



Rhodium(II) acetate dimer (2.10 mg, 4.76 μmol, 1 mol%) was added to a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (98 mg, 0.48 mmol, 1 eq) in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 min. The solvent was removed by evaporation and ^{1}H NMR spectral analysis of the crude product indicated the formation of the α-oxosulfine **187a** and a small amount of 1*H*-indene-1,2(3*H*)-dione **211a** (10:1, 83 mg, ~98%). Spectral details are given in Section 3.8.2.

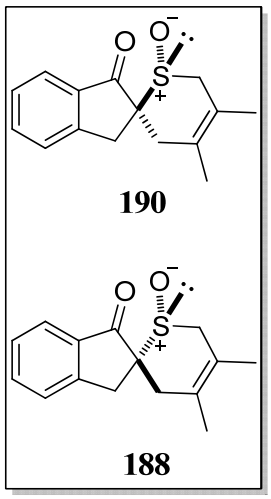


The sulfine **187a** was redissolved in dichloromethane (10 mL) and 2,3-dimethyl-1,3-butadiene (0.11 mL, 0.94 mmol, 2 eq) in dichloromethane (3 mL) was added under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 30 min. The solution was concentrated under reduced pressure to give a pale brown crystalline solid (141 mg). ^{1}H NMR analysis of the crude solid indicated the presence of one cycloadduct, along with trace impurities. The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. The pure cycloadduct **188** was isolated as a pale brown crystalline solid (86 mg, 71%, over the two steps). Found: C, 69.11; H, 6.07; S, 12.24. $C_{15}H_{16}O_2S$ requires C, 69.20; H, 6.19; S, 12.32%; m.p. 155-156 °C (lit.,[130] 154-156 °C); ν_{max} (KBr)/cm^{-1} 1707 (C=O); δ_H (400 MHz) 1.69 (CH_3), 1.78 (CH_3), 2.33 [1H, d, *J* 18.2, A of AB$_q$, C(14)H_2], 2.78 [1H, d, *J* 18.2, B of AB$_q$, C(14)H_2], 3.01 [1H, A of ABq, *J* 17.5, A of AB$_q$, C(10)H_2], 3.32 (1H, d, *J* 16.4, A of AB$_q$, SOCH_2), 3.69 (1H, d, *J* 16.4, B of AB$_q$, SOCH_2), 3.91 [1H, B of ABq, *J* 17.5, B of AB$_q$, C(10)H_2], 7.37-7.44 (1H, m, Ar*H*), 7.51 (1H, d, *J* 7.7, Ar*H*), 7.61-7.65

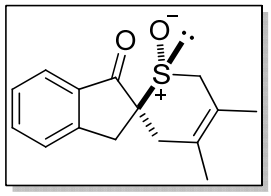
(1H, m, Ar*H*), 7.78 (1H, d, *J* 7.7, Ar*H*); δ_C (75.5 MHz) 19.5 (*C*H_3), 19.8 (*C*H_3), 31.3 [*C*(10)H_2], 39.1 [*C*(14)H_2], 52.3 (SO*C*H_2), 68.5 (C_q), 118.6 (*C*=C), 124.6, 126.6, (2 × aromatic *C*H), 126.9 (C=*C*), 128.0 (aromatic *C*H), 135.6 (aromatic C_q), 135.9 (aromatic *C*H), 152.7 (aromatic C_q), 202.4 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{17}O_2S$ $[M+H]^+$, 261.0949. Found 261.0938; m/z (ESI+) 261 $[(M+H)^+$, 20%], 521 $[(2M+H)^+$, 81%]. Spectral details in agreement with those reported in the literature.[130,133]

The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **188** recrystallised from dichloromethane/hexane. Crystals of **188** are monoclinic, space group *C*12/*c*1, formula $C_{15}H_{16}O_2S$, M = 260.34, a = 18.15(5) Å, b = 6.12(16) Å, c = 23.27(4) Å, U = 2546.6(11) $Å^3$, F(000) = 1104, μ(Mo-Kα) = 0.245 mm^{-1}, R(F_o) = 0.0420 for 1777 observed reflection with I > 2σ(I), wR_2(F^2) = 0.1166 for all 2576 unique reflections. Data in the θ range 1.90 – 26.51° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

3.7.1.2 *In situ* trapping of α-oxosulfine 187a derived from 3-diazoisothiochroman-4-one *S*-oxide 87 and rhodium(II) acetate with 2,3-dimethyl-1,3-butadiene

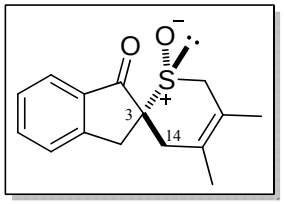


2,3-Dimethyl-1,3-butadiene (0.12 mL, 1.07 mmol, 2 eq) in dichloromethane (5 mL) was added to a stirring solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (110 mg, 0.53 mmol, 1 eq) in dichloromethane (20 mL) under nitrogen at room temperature. Rhodium(II) acetate dimer (2 mg, 5.33 μmol, 1 mol %) was then added to the reaction mixture and stirring was continued for 30 min. The solution was concentrated under reduced pressure to give a pale brown crystalline solid (141 mg). ^{1}H NMR analysis of the crude solid indicated the formation of two cycloadducts **190** and **188** (6:1), along with trace impurities.



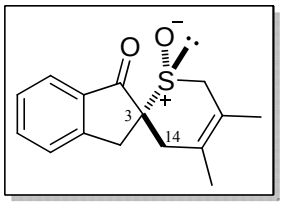
The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. One fraction was isolated, which contained the pure cycloadducts **190** and **188** (128 mg, 7:1). The major cycloadduct **190** was isolated from this mixture by preparative TLC as a pale brown solid (49 mg, 35%). Found: C, 68.89; H, 6.06; S, 12.11. $C_{15}H_{16}O_2S$ requires C, 69.20; H, 6.19; S, 12.32%; m.p. 131–134 °C, ν_{max} (KBr)/cm^{-1} 1708 (C=O); δ_H (400 MHz) 1.67, (3H, s, CH_3), 1.73 (3H, s, CH_3), 2.29 [1H, d, *J* 18.3, A of AB_q, C(14)H_2], 3.00 [1H, d, *J* 18.3, B of AB_q, C(14)H_2], 3.21 [1H, d, *J* 18.0, A of AB_q, C(10)H_2], 3.38-3.51 [2H, m, containing 1H, d, B of AB_q, C(10)H_2, and 1H, d, A of AB_q, SOCH_2], 3.72 (1H, d, *J* 17.9, B of AB_q, SOCH_2), 7.38-7.48 (2H, m, Ar*H*), 7.60-7.67 (1H, m, Ar*H*), 7.79 (1H, d, *J* 7.7, Ar*H*); δ_C (75.5 MHz) 19.8 (*C*H$_3$), 19.9 (*C*H$_3$), 35.2 [*C*(14)H$_2$], 37.2 [*C*(10)H$_2$], 50.5 (SO*C*H$_2$), 63.7 (*C*$_q$), 117.4 (*C*=C), 124.5 (aromatic *C*H), 125.9 (C=*C*), 126.1, 128.2, 135.6 (3 × aromatic *C*H), 136.3 (aromatic *C*$_q$), 150.6 (aromatic *C*$_q$), 201.3 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{17}O_2S$ $[M+H]^+$, 261.0949. Found 261.0940; m/z (ESI+) 261 $[(M+H)^+$, 16%], 521 $[(2M+H)^+$, 99%].

The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **190** recrystallised from dichloromethane/hexane. Crystals of **190** are monoclinic, space group *P*121/*c*1, formula $C_{15}H_{16}O_2S$, M = 260.34, a = 7.710(11) Å, b = 10.47(11) Å, c = 16.60(2) Å, U = 1319.3(3) $Å^3$, F(000) = 552, μ(Mo-Kα) = 0.236 mm^{-1}, $R(F_o)$ = 0.0491 for 1588 observed reflection with I > 2σ(I), $wR_2(F^2)$ = 0.1283 for all 2683 unique reflections. Data in the θ range 1.90 – 26.36° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.



Minor cycloadduct **188**, characteristic signals detected in the crude ^{1}H NMR spectrum of mixture: δ_H (400 MHz) 1.69 (C*H*$_3$), 1.78 (C*H*$_3$), 2.78 [1H, d, *J* 18.2, B of AB$_q$, C(14)*H*$_2$], 3.32 (1H, d, *J* 16.4, A of AB$_q$, SOC*H*$_2$), 3.91 [1H, B of ABq, *J* 17.5, B of AB$_q$, C(10)*H*$_2$]. Complete spectral and analytical data for minor cycloadduct **188** given above.

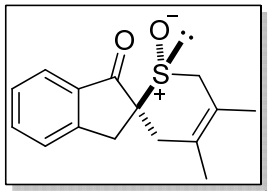
3.7.1.3 Photochemically induced decomposition of 3-diazoisothiochroman-4-one *S*-oxide 87 in the presence of 2,3-dimethyl-1,3-butadiene



A Pyrex® flask containing a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (62 mg, 0.30 mmol, 1 eq) and 2,3-dimethyl-1,3-butadiene (0.08 mL, 0.60 mmol, 2 eq) in dichloromethane (10 mL) was fitted with a condenser and an 90 W mercury lamp was placed as close as possible to the flask. The entire apparatus was wrapped in aluminium foil and the reaction mixture was irradiated for 4 h under a nitrogen atmosphere. The solvent was removed *in vacuo* to give a brown residue (86 mg). ^{1}H NMR analysis of the crude residue indicated complete consumption of the diazo starting material with formation of the

cycloadduct **188** among unidentifiable impurities. The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. The pure cycloadduct **188** was isolated as an pale brown crystalline solid (21 mg, 27%). Spectral details as described above.

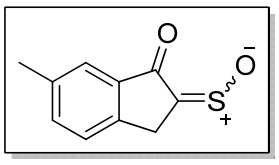
3.7.1.4 Microwave-induced decomposition of 3-diazoisothiochroman-4-one *S*-oxide 87 in the presence of 2,3-dimethyl-1,3-butadiene



2,3-Dimethyl-1,3-butadiene (0.04 mL, 0.30 mmol, 2 eq) was added to a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (31 mg, 0.15 mmol, 1 eq) in dichloromethane (3 mL) and the solution was stirred for 20 s, then irradiated to a temperature of 135 °C in the microwave. The required temperature was reached within a ramp time of 2 min 25 s and was held at the set point for 3 min 4 s. The solvent was removed *in vacuo* to give a light brown crystalline solid. ^{1}H NMR analysis indicated the formation of the cycloadduct **190**, among a small amount of the minor cycloadduct **188** (24:1, 40 mg, 98%). Spectral details as described above.

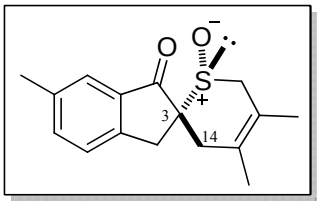
3.7.2 Cycloadditions with 3-Diazo-6-methylisothiochroman-4-one *S*-Oxide 88

3.7.2.1 Rhodium(II) acetate-catalysed decomposition of 3-diazo-6-methylisothiochroman-4-one *S*-oxide 88 to α-oxosulfine 187b and subsequent cycloaddition with 2,3-dimethyl-1,3-butadiene



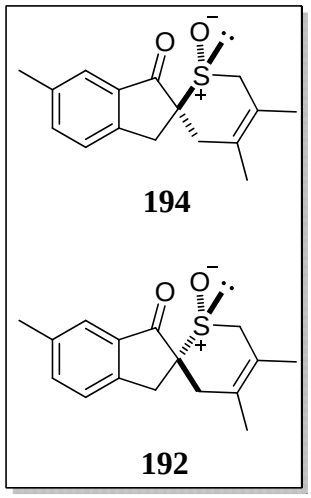
Rhodium(II) acetate dimer (1.7 mg, 3.91 μmol, 1 mol%) was added to a solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (86 mg, 0.39 mmol, 1 eq) in dichloromethane (8 mL) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 min. The solvent was removed by

evaporation and ^{1}H NMR spectral analysis of the crude product indicated the formation of the α-oxosulfine **187b** (74 mg, 96%). Spectral details are given in Section 3.9.2.

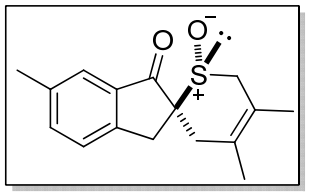


The sulfine **187b** was redissolved in dichloromethane (10 mL) and 2,3-dimethyl-1,3-butadiene (0.09 mL, 0.78 mmol, 2 eq) in dichloromethane (4 mL) was added under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 30 min. The solution was concentrated under reduced pressure to give a pale brown crystalline solid (105 mg). ^{1}H NMR analysis of the crude solid indicated the presence of one cycloadduct **192**. The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. The pure cycloadduct **192** was isolated as an off-white crystalline solid (81 mg, 76%, over the two steps). Found: C, 69.92; H, 6.58; S, 11.48. $C_{16}H_{18}NO_2S$ requires C, 70.04; H, 6.61; S, 11.69%; m.p. 139-140 °C; ν_{max} (KBr)/cm^{-1} 1708 (C=O); δ_H (400 MHz) 1.69 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.33 [1H, A of AB$_q$, *J* 18.2, C(14)*H*$_2$], 2.40 (3H, s, ArC*H*$_3$), 2.78 [1H, B of AB$_q$, *J* 18.2, C(14)*H*$_2$], 2.96 [1H, A of AB$_q$, *J* 17.3, C(10)*H*$_2$], 3.31 (1H, A of AB$_q$, *J* 16.4, SOC*H*$_2$), 3.67 (1H, B of AB$_q$, *J* 16.4, SOC*H*$_2$), 3.87 [1H, B of AB$_q$, *J* 17.3, C(10)*H*$_2$], 7.39 (1H, d, *J* 7.9, Ar*H*), 7.43-7.47 (1H, m, Ar*H*), 7.58 (1H, s, Ar*H*); δ_C (75.5 MHz) 19.5 (*C*H$_3$), 19.9 (*C*H$_3$), 21.1 (Ar*C*H$_3$), 31.0 [*C*(10)H$_2$], 39.1 [*C*(14)H$_2$], 52.2 (SO*C*H$_2$), 68.8 (*C*$_q$), 118.5 (*C*=C), 124.5 (aromatic *C*H), 126.2 (aromatic *C*H), 126.9 (C=*C*), 135.7 (aromatic *C*$_q$), 137.2 (aromatic *C*H), 138.1 (aromatic *C*$_q$), 150.1 (aromatic *C*$_q$), 202.5 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{19}O_2S$ $[M+H]^+$, 275.1106. Found 275.1095; m/z (ESI+) 273 $[(M-H)^-$, 10%], 549 $[(2M+H)^+$, 100%].

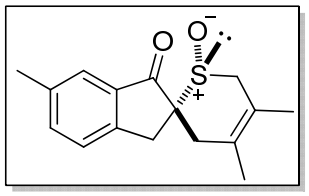
3.7.2.2 *In situ* trapping of α-oxosulfine 187b derived from 3-diazo-6-methylisothiochroman-4-one *S*-oxide 88 and rhodium(II) acetate with 2,3-dimethyl-1,3-butadiene



2,3-Dimethyl-1,3-butadiene (0.14 mL, 1.24 mmol, 2 eq) in dichloromethane (5 mL) was added to a stirring solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (136 mg, 0.62 mmol, 1 eq) in dichloromethane (20 mL) under nitrogen at room temperature. Rhodium(II) acetate dimer (3 mg, 6.18 μmol, 1 mol %) was then added to the reaction mixture and stirring was continued for 30 min. The solution was concentrated under reduced pressure to give a pale brown foamy solid (163 mg). ^{1}H NMR analysis of the crude solid indicated the formation of cycloadducts **194** and **192** (2.5:1). The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (10:90) as eluent. One fraction was isolated, which contained a mixture of the two cycloadducts **194** and **192** (68 mg, 6:1). A small, impure, quantity of the major cycloadduct **194** was isolated from this mixture by preparative TLC (~4 mg); ν_{max} (film)/cm^{-1} 1708 (C=O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{19}O_2S$ $[M+H]^+$, 275.1106. Found 275.1093; m/z (ESI+) 275 $[(M+H)^+$, 12%], 549 $[(2M+H)^+$, 100%], 550 $[(2M+2H)^+$, 30%], 551 $[(2M+3H)^+$, 15%].



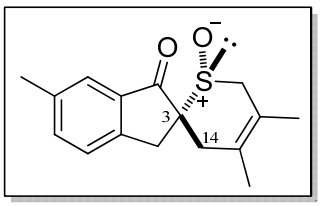
Major cycloadduct **194**: δ_H (400 MHz) 1.74 (3H, s, C*H*$_3$), 1.80 (3H, s, C*H*$_3$), 2.27 [1H, A of AB$_q$, *J* 16.2, C(14)*H*$_2$], 2.40 (3H, s, ArC*H*$_3$), 2.99 [1H, B of AB$_q$, *J* 16.2, C(14)*H*$_2$], 3.16 [1H, A of AB$_q$, *J* 17.7, C(10)*H*$_2$], 3.38 [1H, B of AB$_q$, *J* 17.7, C(10)*H*$_2$], 3.47 (1H, A of AB$_q$, *J* 16.9, SOC*H*$_2$), 3.72 (1H, B of AB$_q$, *J* 16.9, SOC*H*$_2$), 7.32 (1H, d, *J* 7.8, Ar*H*), 7.42-7.46 (1H, m, Ar*H*), 7.58 (1H, s, Ar*H*).



Minor cycloadduct **192**, characteristic signals detected in ^{1}H NMR spectrum of mixture: δ_H (400 MHz) 1.69 (3H, s, C*H*$_3$), 1.71 (3H, s, C*H*$_3$), 2.33 [1H, A of AB$_q$, *J* 18.2, C(14)*H*$_2$], 2.78 [1H, B of AB$_q$, *J* 18.2, C(14)*H*$_2$], 3.87 [1H,

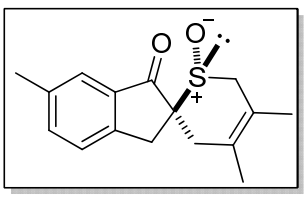
B of AB_q, *J* 17.3, C(10)H_2]. Complete spectral and analytical data for minor cycloadduct **192** given above.

3.7.2.3 Photochemically induced decomposition of 3-diazo-6-methylisothiochroman-4-one *S*-oxide 88 in the presence of 2,3-dimethyl-1,3-butadiene



The reaction procedure was carried out as described in Section 3.7.1.3 with 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (38 mg, 0.17 mmol, 1 eq), 2,3-dimethyl-1,3-butadiene (0.04 mL, 0.35 mmol, 2 eq) and dichloromethane (7 mL). After 4 h the solution was concentrated *in vacuo* to leave the crude product as a brown solid (45 mg, 92%). ^{1}H NMR spectral analysis indicated the formation of one cycloadduct **192**. Spectral details as described above.

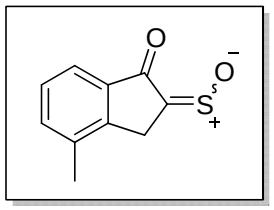
3.7.2.4 Microwave-induced decomposition of 3-diazo-6-methylisothiochroman-4-one *S*-oxide 88 in the presence of 2,3-dimethyl-1,3-butadiene



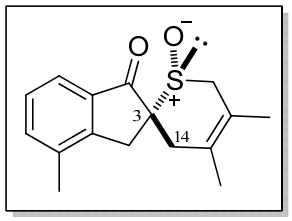
2,3-Dimethyl-1,3-butadiene (0.02 mL, 0.10 mmol, 3 eq) was added to a solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (10 mg, 0.05 mmol, 1 eq) in dichloromethane (3 mL) and the solution was stirred for 20 s, then irradiated to a temperature of 135 °C in the microwave. The required temperature was reached within a ramp time of 2 min 20 s and was held at the set point for 3 min. The solvent was removed *in vacuo* to give a light brown crystalline solid. ^{1}H NMR analysis indicated the formation of the cycloadduct **194** and a small quantity of the cycloadduct **192** (9:1, 13 mg, 99%). Spectral details as described above.

3.7.3 Cycloadditions with 3-Diazo-8-methylisothiochroman-4-one *S*-Oxide 89

3.7.3.1 Rhodium(II) acetate-catalysed decomposition of 3-diazo-8-methylisothiochroman-4-one *S*-oxide 89 to the α-oxosulfine 187c and subsequent cycloaddition with 2,3-dimethyl-1,3-butadiene



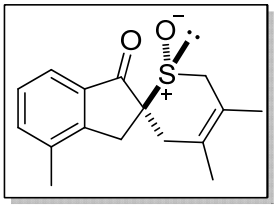
Rhodium(II) acetate dimer (3.44 mg, 7.81 μmol, 1 mol%) was added to a solution of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (78 mg, 0.35 mmol, 1 eq) in dichloromethane (10 mL) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 min. The solvent was removed by evaporation and ^{1}H NMR spectral analysis of the crude product indicated the formation of the α-oxosulfine **187c** and a small quantity of 8-methyl-1*H*-indene-1,2(3*H*)-dione **211c** (9:1, 66 mg, ~90%). Spectral details are given in Section 3.10.2.



The sulfine **187c** was redissolved in dichloromethane (10 mL) and 2,3-dimethyl-1,3-butadiene (0.09 mL, 0.94 mmol, 2 eq) in dichloromethane (3 mL) was added under a nitrogen atmosphere at room temperature. The reaction mixture was stirred for 30 min. The solution was concentrated under reduced pressure to give a pale brown foamy solid (95 mg). ^{1}H NMR analysis of the crude solid indicated the presence of the cycloadduct **193**, along with trace impurities (>95% pure). The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. The pure cycloadduct **193** was isolated as an off-white crystalline solid (86 mg, 84%, over the two steps). Found: C, 69.93; H, 6.60; S, 11.60. $C_{16}H_{18}O_2S$ requires C, 70.04; H, 6.61; S, 11.69%; m.p. 152-154 °C; ν_{max} (KBr)/cm^{-1} 1717 (C=O); δ_H (400 MHz) 1.70 (C*H*$_3$), 1.79 (C*H*$_3$), 2.34 [1H, d, *J* 18.3, A of AB$_q$, C(14)*H*$_2$], 2.39 (3H, s, ArC*H*$_3$), 2.78 [1H, d, *J* 18.3, B of AB$_q$, C(14)*H*$_2$], 2.88 [1H, d, *J* 17.5, A of AB$_q$, C(10)*H*$_2$], 3.35 (1H, d, *J* 16.4, A of AB$_q$, SOC*H*$_2$), 3.69 (1H, d, *J* 16.4, B of AB$_q$, one of SOC*H*$_2$), 3.78 [1H, d, *J* 17.5, B of AB$_q$, C(10)*H*$_2$], 7.29-7.33 (1H, m, Ar*H*), 7.45 (1H, d, *J* 7.3, Ar*H*), 7.61 (1H, d, *J* 7.6, Ar*H*); δ_C (75.5 MHz) 17.9

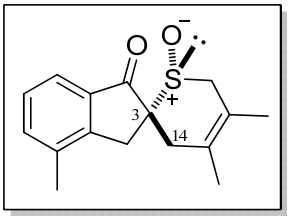
(Ar*C*H$_3$), 19.5 (*C*H$_3$), 19.9 (*C*H$_3$), 30.3 [*C*(10)H$_2$], 39.3 [*C*(14)H$_2$], 52.2 (SO*C*H$_2$), 68.3 (*C*$_q$), 118.6 (*C*=C), 122.1 (aromatic *C*H), 126.9 (C=*C*), 128.3 (aromatic *C*H), 135.3 (aromatic *C*$_q$), 135.9 (aromatic *C*$_q$), 136.4 (aromatic *C*H), 151.7 (aromatic *C*$_q$), 202.8 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{19}O_2S$ $[M+H]^+$, 275.1106. Found 275.1095; m/z (ESI+) 549 $[(2M+H)^+$, 100%].

3.7.3.2 *In situ* trapping of α-oxosulfine 187c derived from 3-diazo-8-methylisothiochroman-4-one *S*-oxide 89 and rhodium(II) acetate with 2,3-dimethyl-1,3-butadiene



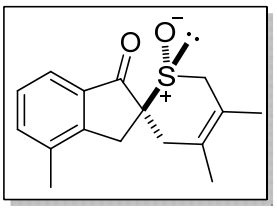
The reaction procedure was carried out as described in Section 3.7.1.2 using 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (98 mg, 0.45 mmol, 1 eq), rhodium(II) acetate dimer (1.97 mg, 4.45 μm, 1 mol%), 2,3-dimethyl-1,3-butadiene (0.10 mL, 0.89 mmol, 2 eq) and dichloromethane (15 mL). The solution was concentrated *in vacuo* to leave a brown residue (121 mg). ^{1}H NMR analysis of the crude solid indicated the presence of the cycloadduct **195** and a small quantity of the cycloadduct **193** (25:1). The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. The pure cycloadduct **195** was isolated as a pale yellow crystalline solid (35 mg, 29%). Found: C, 69.76; H, 6.50. $C_{16}H_{18}O_2S$ requires C, 70.04; H, 6.61%; m.p. 128-129 °C; ν_{max} (KBr)/cm^{-1} 1718 (C=O); δ_H (400 MHz) 1.74 (3H, s, C*H*$_3$), 1.81 (3H, s, C*H*$_3$), 2.30 [1H, d, *J* 18.4, A of AB$_q$, C(14)*H*$_2$], 2.35 (3H, s, ArC*H*$_3$), 3.01 [1H, d, *J* 18.4, B of AB$_q$, C(14)*H*$_2$], 3.08 [1H, d, *J* 17.8, A of AB$_q$ C(10)*H*$_2$], 3.30 [1H, d, *J* 17.8, B of AB$_q$, C(10)*H*$_2$], 3.51 (1H, d, *J* 17.0, A of AB$_q$, SOC*H*$_2$), 3.75 (1H, d, *J* 17.0, B of AB$_q$, SOC*H*$_2$), 7.30-7.34 (1H, m, Ar*H*), 7.43 (1H, d, *J* 7.3, Ar*H*), 7.61 (1H, d, *J* 7.6, Ar*H*); δ_C (75.5 MHz) 17.8 (Ar*C*H$_3$), 19.8 (*C*H$_3$), 19.9 (*C*H$_3$), 35.3 [*C*(14)H$_2$], 36.1 [*C*(10)H$_2$], 50.5 (SO*C*H$_2$), 63.5 (*C*$_q$), 117.4 (*C*=C), 122.0 (aromatic *C*H), 125.9 (C=*C*), 128.4 (aromatic *C*H), 135.3 (aromatic *C*$_q$), 136.0 (aromatic *C*$_q$), 136.1 (aromatic *C*H), 149.5 (aromatic *C*$_q$), 201.5 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{19}O_2S$ $[M+H]^+$, 275.1106. Found 275.1095; m/z (ESI+) 549 $[(2M+H)^+$, 100%], 550 $[(2M+2H)^+$, 44%], 551 $[(2M+3H)^+$, 22%].

3.7.3.3 Photochemically induced decomposition of of 3-diazo-8 methylisothiochroman-4-one *S*-oxide 89 in the presence of 2,3-dimethyl-1,3-butadiene



The reaction procedure was carried out as described in Section 3.7.1.3 with 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (30 mg, 0.14 mmol, 1 eq), 2,3-dimethyl-1,3-butadiene (0.03 mL, 0.27 mmol, 2 eq) and dichloromethane (5 mL). After 4 h the solution was concentrated *in vacuo* to leave the crude product as a brown solid (41 mg). ^{1}H NMR spectral analysis indicated the formation of one cycloadduct **193** and some remaining sulfine **187c** (4:1). Spectral details as described above.

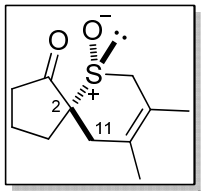
3.7.3.4 Microwave-induced decomposition of 3-diazo-8-methylisothiochroman-4-one *S*-oxide 89 in the presence of 2,3-dimethyl-1,3-butadiene



2,3-Dimethyl-1,3-butadiene (0.02 mL, 0.10 mmol, 3 eq) was added to a solution of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (11 mg, 0.05 mmol, 1 eq) in dichloromethane (3 mL), then irradiated to a temperature of 135 °C in the microwave. The required temperature was reached within a ramp time of 2 min 30 s and was held at the set point for 3 min. The solvent was removed *in vacuo* to give a light brown residue. ^{1}H NMR analysis indicated the formation of the cycloadduct **195** (14 mg, 97%). Spectral details as described above.

3.7.4 [4+2] Cycloadditions with 2-Diazodihydro-2*H*-thiopyran-3(4*H*)-one *S*-Oxide 127

3.7.4.1 Rhodium(II) acetate-catalysed decomposition of 2-diazodihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 127 and subsequent cycloaddition with 2,3-dimethyl-1,3-butadiene



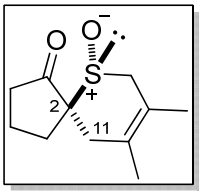
Rhodium(II) acetate dimer (1.60 mg, 3.51 μmol, 1 mol%) was added to a solution of 2-diazodihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **127** (mixture containing ~40% sulfonamide, 93 mg, 0.35 mmol, 1 eq) in dichloromethane (12 mL) and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 15 min. 2,3-Dimethyl-1,3-butadiene (0.10 mL, 0.70 mmol, 2 eq) in dichloromethane (2 mL) was added to the solution under a nitrogen atmosphere. The reaction mixture was stirred for a further 30 min at room temperature. The solution was concentrated under reduced pressure to give a brown solid (91 mg). ^{1}H NMR analysis of the crude product indicated the presence of the cycloadduct **197**, a small amount of the minor cycloadduct **199** (~9:1) along with unreacted sulfonamide and unidentifiable impurities. The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (20:80) as eluent. Slow recrystallisation from dichloromethane/hexane gave the cycloadduct **197** and a small amount of the cycloadduct **199** as an off-white crystalline solid (9:1, 12 mg, 0.06 mmol, 19%). Attempts to further purify the mixture by chromatography and recrystallisation were unsuccessful; m.p. 79-81 °C; ν_{max} (KBr)/cm^{-1} 1734 (C=O), 1047 (S-O); Major cycloadduct **197**: δ_H (400 MHz) 1.67 (3H, s, C*H*$_3$), 1.73 (3H, s, C*H*$_3$), 1.90-2.02 (2H, m, C*H*$_{2ring}$), 2.13-2.52 [5H, m, C*H*$_{2ring}$ and two of C(11)*H*$_2$], 2.71-2.81 [1H, m, one of C*H*$_2$], 3.20 (1H, d, *J* 16.2, A of AB$_q$, SOC*H*$_2$), 3.49 (1H, d, *J* 16.2, B of AB$_q$, SOC*H*$_2$); δ_C (75.5 MHz) 19.0 (*C*H$_2$), 19.4 (*C*H$_3$), 19.9 (*C*H$_3$), 25.4, 37.3, 39.3 (*C*H$_2$), 51.3 (SO*C*H$_2$), 68.1 [*C*(2)$_q$], 118.2 (*C*=C), 126.5 (C=*C*), 215.1 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{16}O_2S$ [M+H]$^+$, 213.0949. Found 213.0944; m/z (ESI+) 425 [(2M+H)$^+$, 100%].

The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **197**. Crystals of **197** are monoclinic, space

group *C*12/*c*1, formula $C_{11}H_{16}O_2S$, M = 212.30, a = 25.72(12) Å, b = 5.73(3) Å, c = 14.73(7) Å, U = 2088.38(18) $Å^3$, F(000) = 912, μ(Mo-Kα) = 0.281 mm^{-1}, $R(F_o)$ = 0.0271 for 2055 observed reflection with $I > 2\sigma(I)$, $wR_2(F^2)$ = 0.0710 for all 2169 unique reflections. Data in the θ range 1.00 – 26.52° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

Signals detected for minor cycloadduct **199**: δ_H (400 MHz) 2.58 [1H, d, *J* 18.3, B of AB_q, CH_2(10)], 3.42 (1H, d, *J* 16.1, A of AB_q, SOCH_2), 3.60 (1H, d, *J* 16.1, B of AB_q, SOCH_2); δ_C (75.5 MHz) 34.3, 36.2, 50.7, 63.6, 117.3, 126.3, 214.1. Complete spectral details for **199** as described below.

3.7.4.2 *In situ* trapping of α-oxosulfine 201 derived from 2-diazodihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 127 and rhodium(II) acetate with 2,3-dimethyl-1,3-butadiene



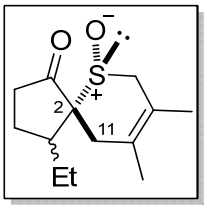
2,3-Dimethyl-1,3-butadiene (0.15 mL, 1.28 mmol, 2 eq) was added to a stirring solution of 2-diazodihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide **127** (mixture containing ~40% sulfonamide, 160 mg, 0.64 mmol, 1 eq) in dichloromethane (20 mL) under nitrogen at room temperature. Rhodium(II) acetate dimer (8.90 mg, 6.40 μmol, 1 mol%) was then added to the reaction mixture and stirring was continued overnight. The solution was concentrated under reduced pressure to give a dark orange residue (240 mg). ^{1}H NMR analysis of the crude product indicated the presence of the cycloadduct **199**, a trace quantity of the minor cycloadduct **197** along with unreacted sulfonamide. The residue was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent. Two fractions were isolated from the column. The first fraction contained unreacted sulfonamide (59 mg). The second fraction contained the pure cycloadduct **199**, along with a trace quantity of the cycloadduct **197**, and was obtained as a light orange oil

which solidified overnight (67 mg, 0.31 mmol, 49%); Found: C, 61.98; H, 7.42; S, 15.01. $C_{11}H_{16}O_2S$ requires C, 62.23; H, 7.60; S, 15.07 %; m.p. 70-72 °C; ν_{max} (film)/cm^{-1} 1733 (C=O), 1047 (S-O); δ_H (400 MHz) 1.68 (3H, s, C*H*$_3$), 1.75 (3H, s, C*H*$_3$), 1.90-2.01 (1H, m, C*H*$_{2ring}$), 2.07-2.27 (3H, m, C*H*$_{2ring}$), 2.31-2.55 [3H, m, two of C*H*$_{2ring}$ and one of C(11)*H*$_2$], 2.58 [1H, d, *J* 18.3, B of AB$_q$, C(11)*H*$_2$], 3.42 (1H, d, *J* 16.1, A of AB$_q$, SOC*H*$_2$), 3.60 (1H, d, *J* 16.1, B of AB$_q$, SOC*H*$_2$); δ_C (75.5 MHz) 18.9 (*C*H$_2$), 19.5 (*C*H$_3$), 19.9 (*C*H$_3$), 34.3, 36.2, 39.3 (*C*H$_2$), 50.7 (SO*C*H$_2$), 63.6 [*C*(2)$_q$], 117.3 (*C*=C), 126.3 (C=*C*), 214.1 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{16}O_2S$ $[M+H]^+$, 213.0949. Found 213.0949; m/z (ESI+) 425 $[(2M+H)^+$, 100%].

Signals detected for the cycloadduct **197**: δ_H (400 MHz) 3.20 (1H, d, *J* 16.2, A of AB$_q$, SOC*H*$_2$), 3.49 (1H, d, *J* 16.2, B of AB$_q$, SOC*H*$_2$); δ_C (75.5 MHz) 25.4, 37.3, 51.3, 68.1, 118.2, 126.5, 215.1. Complete spectral details for **197** as described above.

3.7.5 [4+2] Cycloadditions with (1*R**, 6*R**)-2-Diazo-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-Oxide 131a and (1*R**, 6*S**)-2-Diazo-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-Oxide 131a

3.7.5.1 Rhodium(II) acetate catalysed decomposition of (1*R**, 6*R**)-2-diazo-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 131a and (1*R**, 6*S**)-2-diazo-6-ethyl-dihydro-2*H*-thiopyran-3(4*H*)-one *S*-oxide 131b and subsequent trapping with 2,3-dimethyl-1,3-butadiene

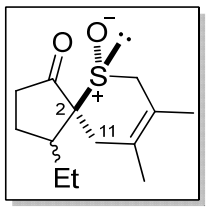


Rhodium(II) acetate dimer (1.58 mg, 3.58 μmol, 1 mol%) was added to a solution of (1*R**, 6*R**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **131a** and (1*R**, 6*S**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **131b** (1:1, 67 mg, 0.36 mmol, 1 eq) in dichloromethane (5 mL) at room temperature. The mixture was stirred for 15 min and a solution of 2,3-dimethyl-1,3-butadiene (0.8 mL, 0.72 mmol, 2 eq) in dichloromethane (2 mL) was added. The reaction mixture was stirred for a further 45 min and the solvent was removed *in vacuo* to leave an orange oil (73 mg).

^{1}H NMR analysis of the crude material indicated the presence the cycloadducts **200** and **198** (~1:3) in a complex mixture of unidentifiable compounds, potentially containing up to four cycloadducts. Purification by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent gave two fractions. The first, least polar, fraction contained the pure cycloadduct **200** as a clear residue (8 mg, 9%). The second fraction contained the pure cycloadduct **198** as a clear residue (21 mg, 24%).

Spectral details for **198**: ν_{max} (film)/cm^{-1} 1734 (C=O), 1040 (S-O); δ_H (400 MHz) 1.11 (3H, t, *J* 7.8, ethyl C*H*$_3$), 1.52-1.65 (1H, m, C*H*$_2$), 1.73 (3H, s, C*H*$_3$), 1.76 (3H, s, C*H*$_3$), 1.92-2.11 [4H, m, containing C*H*$_2$, one of C(11)*H*$_2$ and C*H*], 2.21-2.48 (3H, m, three of C*H*$_2$), 2.79 [1H, d, *J* 7.8, B of AB$_q$, C(11)*H*$_2$], 3.20 (1H, d, *J* 7.9, A of AB$_q$, SOC*H*$_2$), 3.46 (1H, d, *J* 7.9, B of AB$_q$, SOC*H*$_2$); δ_C (75.5 MHz) 12.5 (ethyl *C*H$_3$), 19.9 (overlapping 2 × *C*H$_3$), 22.9 (*C*H$_2$), 23.3 (*C*H$_2$), 31.9 [*C*(11)H$_2$], 36.3 (*C*H$_2$), 49.1 (*C*H), 49.5 (SO*C*H$_2$), 69.9 [*C*(2)$_q$], 115.3 (*C*=C), 124.5 (C=*C*), 213.1 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{21}O_2S$ $[M+H]^+$, 241.1262. Found 241.1254; m/z (ESI+) 241 $[(M+H)^+$, 60%], 481 $[(2M+H)^+$, 100%)]. Spectral details for **269** as described below.

3.7.5.2 *In situ* trapping of α-oxosulfines *E*-203 and *Z*-203 derived from (1*R**, 6*R**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide 131a and (1*R**, 6*S**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide 131b in the presence of rhodium(II) acetate with 2,3-dimethyl-1,3-butadiene

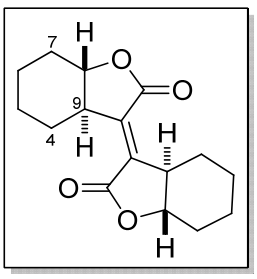


The reaction was carried out following the procedure described in Section 3.7.4.2 above using (1*R**, 6*R**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **131a** and (1*R**, 6*S**)-2-diazo-6-ethyl-dihydro-2H-thiopyran-3(4*H*)-one *S*-oxide **131b** (1:1, 88 mg, 0.47 mmol, 1 eq), 2,3-dimethyl-1,3-butadiene (0.11 mL, 0.94 mmol, 2 eq) and rhodium(II) acetate dimer (2.08 mg, 4.70 μmol, 1 mol%). The solution was concentrated *in vacuo* to leave the crude product as an orange oil (97 mg). ^{1}H NMR analysis of the crude material indicated the presence the cycloadduct **200** among a complex mixture of unidentifiable compounds, potentially containing up to four diastereomeric cycloadducts. Purification by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent gave the cycloadduct **200** and

a small amount of impurities as a clear residue (23 mg, 20%); ν_{max} (film)/cm^{-1} 1734 (C=O), 1038 (S-O); δ_H (400 MHz) 1.11 (3H, t, *J* 7.2, ethyl C*H*$_3$), 1.64 (3H, s, C*H*$_3$), 1.74 (3H, s, C*H*$_3$), 1.86-2.50 (9H, m, contains C*H* and 4 × C*H*$_2$), 3.41 (1H, d, *J* 16.2, A of AB$_q$, SOC*H*$_2$), 3.74 (1H, d, *J* 16.2, B of AB$_q$, SOC*H*$_2$); δ_C (75.5 MHz) 12.5 (ethyl *C*H$_3$), 19.0 (*C*H$_3$), 20.1 (*C*H$_3$), 23.1, 25.5, 38.5, 38.9 (*C*H$_2$), 49.6 (*C*H), 50.5 (SO*C*H$_2$), 68.2 [*C*(2)$_q$], 117.8 (*C*=C), 127.2 (C=*C*), 216.5 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{21}O_2S$ $[M+H]^+$, 241.1262. Found 241.1257; m/z (ESI+) 241 [$(M+H)^+$, 72%], 481 [$(2M+H)^+$, 100%)].

3.7.6 Microwave Induced Decomposition of α-Diazosulfoxides 5a and 5e in the Presence of *E*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene 205

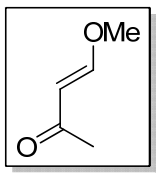
E-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene **205** (121 mg, 0.63 mmol, 1 eq) was added to solution of α-diazosulfoxides **5a** and **5e** (1:1, 136 mg, 0.63 mmol, 1 eq) in dichloromethane (3 mL) at room temperature under a nitrogen atmosphere. Rhodium(II) acetate (1 mol%) was immediately added to the solution and the reaction mixture was allowed to stir under the inert atmosphere for 8 h, after which time TLC analysis indicated complete consumption of starting material. The mixture was concentrated *in vacuo* to leave the crude product as a dark brown oil (240 mg). The ^{1}H NMR spectrum of the crude material indicated that decomposition of the starting material had occurred, giving the enone **209** among a complex mixture of unidentifiable compounds. Purification of the crude product by flash chromatography using hexane/ethyl acetate eluent (50:50) as eluent on silica gel followed by recrystallisation from dichloromethane/hexane resulted in isolation of the alkene dimer **149** as an orange crystalline solid (44 mg, 21%).



Alkene dimer **149**: ν_{max}/cm^{-1} (film); 1756 (C=O); δ_H (400 MHz) 1.11-1.24 (2H, m, C*H*$_{2ring}$), 1.36-1.45 (4H, m, C*H*$_{2ring}$), 1.59-1.71 (2H, m, C*H*$_{2ring}$), 1.76-1.86 (2H, m, C*H*$_{2ring}$), 1.88-2.01 (2H, m, C*H*$_{2ring}$), 2.25-2.33 [2 H, sym m, axial C(7)*H*$_{ring}$], 2.71-2.80 [2 H, sym m, C(9)*H*], 2.91 [2 H, br d, *J* 12.5, axial C(4)*H*$_{ring}$], 3.88 (2H, ddd, *J* 11.6, 11.6, 3.6, C*H*O). Spectral details agree with those

reported by Collins and O'Sullivan.[7,9]

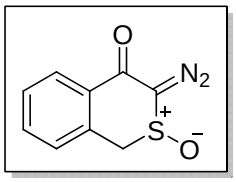
The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **149** recrystallised from dichloromethane/hexane. The crystals of **149** were needle-like and orange in colour, and are orthorhombic, space group $P2_12_12_1$, formula $C_{16}H_{20}O_4$, M = 276.32, a = 5.41(7) Å, b = 11.08(17) Å, c = 24.6(4) Å, U = 1470.0(40) $Å^3$, F(000) = 592, μ(Mo-Kα) = 0.089 mm^{-1}, $R(F_o)$ = 0.1141 for 835 observed reflection with $I > 2\sigma(I)$, $wR_2(F^2)$ = 0.304 for all 1679 unique reflections. Data in the θ range 2.52 - 17.18° were collected on a X-ray diffraction measurements were made on a Bruker APEX II DUO diffractometer using graphite monochromatised Mo-Kα radiation (λ = 0.71073 Å) and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.



^{1}H NMR spectral details for the enone **209** formed due to decomposition of **205**: δ_H (400 MHz) 2.05 (3H, s, COCH_3), 3.57 [3H, s, (O)CH_3], 5.44 (1H, d, *J* 12.8, one of allylic C*H*), 7.44 (1H, d, *J* 12.8, one of allylic C*H*).

3.8 Decomposition studies of Benzofused α-Diazo-β-keto Sulfoxides

3.8.1 Decomposition Studies of 3-Diazoisothiochroman-4-one *S*-Oxide 87



3.8.1.1 Control reaction to investigate the stability of 3-diazoisothiochroman-4-one *S*-oxide 87 in solution and in the absence of a metal catalyst

A solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (50 mg, 0.26 mmol) in dichloromethane (5 mL) was placed in a Pyrex® flask which had been cleaned with aqua regia to remove any traces of metal catalyst which may have been adhering to the surface. The reaction mixture was stirred under reflux and under a nitrogen atmosphere. The sample was analysed by TLC and ^{1}H NMR analysis. No decomposition of the diazosulfoxide **87** occurred over 24 h (Table 3.7). When the diazosulfoxide **87** was stored in $CDCl_3$ solution at room temperature, decomposition occurred over time (Table 3.7).

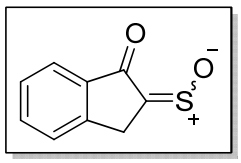
Table 3.7 Investigation of the reactivity of 3-diazoisothiochroman-4-one *S*-oxide **87** in the absence of a metal catalyst

Entry	Catalyst[a]	Solvent	Conditions[b]	Time	Product[c]
1	-	DCM	Δ	24 h	**87**
2	-	$CDCl_3$	RT	24 h	**87** (93%) **187a** (7%)
3	-	$CDCl_3$	RT	72 h	**87** (69%) **187a** (31 %)

a. No catalyst was employed.
b. For entry 1, the solution was stirred under reflux conditions and a nitrogen atmosphere. Entries 2 and 3 represent separate samples, and both solutions were allowed to stand without stirring at room temperature.
c. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

3.8.1.2 1-Oxo-2-thioxoindane-*S*-oxide 187a[130]

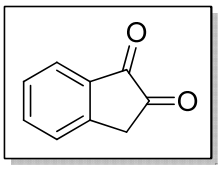
Decomposition of **87** with 1 mol% rhodium(II) acetate in dichloromethane



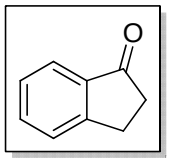
Rhodium(II) acetate dimer (2.33 mg, 5.29 μmol, 1 mol%) was added to a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (109 mg, 0.53 mmol, 1 eq) in dichloromethane (10 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 5 min after which time IR and TLC analysis indicated that the diazo starting material had been consumed. The solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave 1-oxo-2-thioxoindane-*S*-oxide **187a** and 1*H*-indene-1,2(3*H*)-dione **211a** (**187a**:**211a** 10:1, 92 mg, 94%) and a trace quantity of 2,3-dihydro-1*H*-inden-1-one **214a** and unidentifiable impurities as a pale brown crystalline solid; m.p. 126-128 °C (decomp.) (lit.,[130] 130 °C); ν_{max} (KBr)/cm^{-1} 1720 (C=O, indanedione **211a**), 1684 (C=O, sulfine **187a**).

1-Oxo-2-thioxoindane-*S*-oxide **187a**: δ_H (400 MHz) 4.26 (2H, s, C*H*$_2$), 7.45-7.54 (2H, m, Ar*H*), 7.67-7.74 (1H, m, Ar*H*), 7.86-7.91 (1H, m, Ar*H*); δ_C (75.5 MHz) 33.2 (*C*H$_2$), 125.1 (aromatic *C*H), 126.4 (aromatic *C*H), 128.7 (aromatic *C*H), 136.6

(aromatic *C*H), 137.3 (aromatic C_q), 145.5 (aromatic C_q), 184.2 (*C*=S=O); 188.6 (*C*=O). Spectral details in agreement with those reported in the literature.[7,130]



Signals detected for 1*H*-indene-1,2(3*H*)-dione **211a** in the ^{1}H NMR spectrum: δ_H (400 MHz) 3.64 (2H, s, CH_2), 7.60 (1H, d, *J* 7.5, aromatic C*H*), 7.76 (1H, t, *J* 7.5, aromatic C*H*), 7.90 (1H, d, *J* 7.5, aromatic C*H*). Signals in agreement with those reported in the literature.[203]

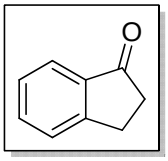


Signals detected for 2,3-dihydro-1*H*-inden-1-one **214a** in the ^{1}H NMR spectrum: δ_H (400 MHz) 2.67-2.72 (2H, m, CH_2), 3.13-3.21 (2H, m, CH_2). Full spectral details given in Section 3.8.3 below.

Note: During the time lapse of 48 h between obtaining the ^{1}H NMR and the ^{13}C NMR spectra, the indanedione **211a** decomposed in the $CDCl_3$ solution and the ^{13}C NMR signals were not detected. Signals for small quantities of unknown compounds detected in the ^{13}C NMR spectrum: δ_C (75.5 MHz) 52.9, 53.2, 58.0, 130.4, 129.1, 206.5.

3.8.1.3 2,3-Dihydro-1*H*-inden-1-one 214[204]

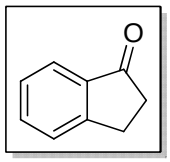
Method 1. Decomposition of **87** with 1 mol% copper(II) triflate in dichloromethane



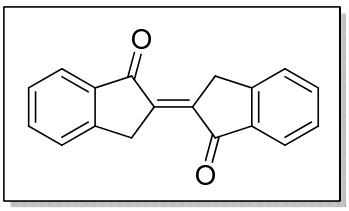
Copper(II) triflate (1.20 mg, 3.31 μmol, 1 mol%) was added to a stirring solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (68 mg, 0.33 mmol, 1 eq) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 8 h. TLC analysis indicated that the diazo starting material had been consumed at this stage. The solution was stirred overnight under a nitrogen atmosphere. The solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave a brown oil (51 mg). The ^{1}H NMR spectrum of the crude material indicated the formation of 2,3-dihydro-1*H*-inden-1-one **214a**, 1*H*-indene-1,2(3*H*)-dione **211a** (5:1) along with small quantities of unidentifiable impurities. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (96:4) as eluent to

give 2,3-dihydro-1*H*-inden-1-one **214a** as a clear oil (24 mg, 50%); ν_{max} (film)/cm^{-1} 1706 (C=O); δ_H (400 MHz) 2.67-2.72 (2H, m, C*H*$_2$), 3.13-3.21 (2H, m, C*H*$_2$), 7.35-7.40 (1H, m, Ar*H*), 7.46-7.50 (1H, m, Ar*H*), 7.56-7.61 (1H, m, Ar*H*), 7.77 (1H, d, *J* 7.7, Ar*H*); δ_C (75.5 MHz); 25.8 (*C*H$_2$), 36.2 (*C*H$_2$), 123.7 (aromatic *C*H), 126.7 (aromatic *C*H), 127.3 (aromatic *C*H), 134.6 (aromatic *C*H), 137.1 (aromatic *C*$_q$), 155.2 (aromatic *C*$_q$), 207.1 (*C*=O); HRMS (ESI+): Exact mass calculated for C_9H_9O $[M+H]^+$, 133.0653. Found 133.0655; m/z (ESI+) 132 $[(M)^+$, tentative]. Spectral details in agreement with those reported in the literature.[204]

Method 2. Photochemically induced decomposition of **87**



A Pyrex® flask containing a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (31 mg, 0.15 mmol) in dichloromethane (5 mL) was fitted with a condenser and an 90 W mercury lamp was placed as close as possible to the flask. The entire apparatus was wrapped in aluminium foil and the reaction mixture was irradiated for 4 h under a nitrogen atmosphere. The solvent was removed *in vacuo* to give a brown residue (27 mg). ^{1}H NMR analysis of the crude residue indicated the presence of 2,3-dihydro-1*H*-inden-1-one **214a**, (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a**, 1-oxo-2-thioxoindane-*S*-oxide **187a** (2.8 : 1 : 0.5), among a trace quantity of 1*H*-indene-1,2(3*H*)-dione **211a** and unidentifiable impurities. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate (96:4) as eluent to give 2,3-dihydro-1*H*-inden-1-one **214a** as a clear oil (13 mg, 24%) Spectral details as described above.

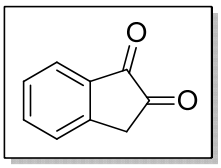


Characteristic signal detected for (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** in the ^{1}H NMR spectrum of the crude material: δ_H (400 MHz) 4.33 (4H, s, C*H*$_2$). Complete spectral details for *E*-**210a** are given in Section 3.8.4 below.

3.8.1.4 Decomposition of 87 under microwave conditions

A solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (68 mg, 0.33 mmol, 1 eq) in dichloromethane (3 mL) and irradiated to a temperature of 90 °C in the

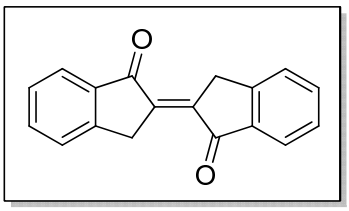
microwave. The required temperature was reached within a ramp time of 1 min 10 s and was held at the set point for 20 min. The solvent was removed *in vacuo* to give a light brown solid (61 mg). ^{1}H NMR analysis indicated the presence of 1-1*H*-indene-1,2(3*H*)-dione **211a** and (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** (6:1) along with a trace amount of 2,3-dihydro-1*H*-inden-1-one **214a** and other unidentifiable impurities (66 mg). ν_{max} (KBr)/cm^{-1}1718 (C=O).



1*H*-Indene-1,2(3*H*)-dione **211a**: δ_H (400 MHz) 3.64 (2H, s, C*H*$_2$), 7.45-7.51 (1H, m, aromatic C*H*), 7.60 (1H, d, *J* 7.5, aromatic C*H*), 7.76 (1H, t, *J* 7.5, aromatic C*H*), 7.90 (1H, d, *J* 7.5, aromatic C*H*); Signals observed in the ^{13}C NMR spectrum: δ_C (75.5 MHz) 36.6 (*C*H$_2$), 125.7, 127.5, 128.7, 137.6 (4 × aromatic *C*H), 146.5 (aromatic C_q), 199.7 (*C*=O). *Note*: The second C_q and *C*=O signals were not observed. HRMS (ESI+): Exact mass calculated for $C_9H_7O_2$ $[M+H]^+$, 147.0446. Found 147.0446; m/z (ESI+) 146 $[(M)^+$, 10%]. Spectral details in agreement with those reported in the literature.[203]

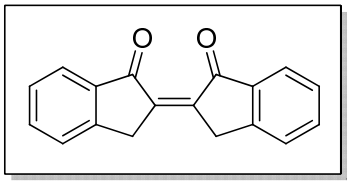
Spectral details for (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** following purification are given below.

The crude reaction mixture was stored at room temperature for 12 weeks, after which time a ^{1}H NMR spectrum was obtained which indicated the presence of the products 1-1*H*-indene-1,2(3*H*)-dione **211a** and (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** (1:5). The crude material was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent and recrystallised from hexane/toluene to give (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** and a trace amount of (*Z*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *Z*-**210a** as pale green crystals (24 mg, 21%); m.p. 160-162 °C (lit., 163 °C); ν_{max} (KBr)/cm^{-1} 1638 (C=O).



(*E*)-[2,2'-Biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a**: δ_H (400 MHz) 4.33 (4H, s, C*H*$_2$), 7.39-7.45 (2H, m, Ar*H*), 7.58 (2H, d, J 7.6, Ar*H*), 7.61-7.65 (2H, m, Ar*H*), 7.86 (2H, d, *J* 7.9, Ar*H*); δ_C (75.5 MHz) 32.4 (2 × *C*H$_2$), 124.1, 126.6, 127.6, 135.4 (8 × aromatic *C*H), 138.27 (2 × C_q), 138.28 (2 ×

C_q), 151.0 (2 × C_q), 196.9 (2 × C=O); HRMS (ESI+): Exact mass calculated for $C_{18}H_{13}O_2$ $[M+H]^+$, 261.0916. Found 261.0912. Spectral details in agreement with those reported in the literature.[149]



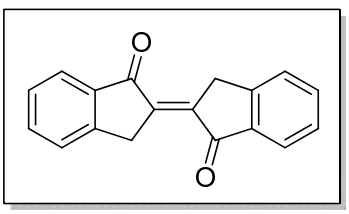
Signals detected for trace quantity of (*Z*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione ***Z*-210a**: δ_H (400 MHz) 3.84 (4H, s, CH_2); (75.5 MHz) 40.0 (2 × CH_2), 125.0, 127.9, 137.8, 148.0. Spectral details in agreement with those reported in the literature.[149]

Table 3.8 Variation for product ratios of **211a** and ***E*-210a** based on reaction times under microwave conditions.

Entry	Conditions[a]	Time[b]	Solvent	Products[c]
1	MW	20 min	DCM	**211a**, ***E*-210a**, **214a** (6: 1 : trace)
2	MW	40 min	DCM	**211a**, ***E*-210a**, **214a** (3 : 1 : trace)

a. Both reactions were carried out in a sealed vessel. Both reaction mixtures were irradiated to a temperature of 90 °C using the maximum power of 300W with a ramp time of ~1 min 10 s.
b. Time for which the set point was held.
c. The product ratios were determined based on analysis of the ^{1}H NMR spectra of the crude material.

3.8.1.5 Decomposition of 87 with 1 mol% rhodium(II) acetate in toluene

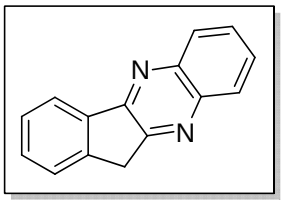


Rhodium(II) acetate dimer (1.17 mg, 2.65 μmol, 1 mol%) was added to a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (55 mg, 0.27 mmol) in toluene (15 mL) under a nitrogen atmosphere. The reaction mixture was stirred under reflux overnight and then cooled to room temperature. The solution was concentrated *in vacuo* to leave a dark green residue (54 mg). ^{1}H NMR analysis indicated the presence of 1*H*-indene-1,2(3*H*)-dione **211a** and (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione ***E*-210a** (2:1) along

with a trace amount of 2,3-dihydro-1*H*-inden-1-one **214a**. The crude material was purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent and recrystallised from hexane/toluene to give (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** and a small quantity of (*Z*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *Z*-**210a** as pale green crystals (21:1, 22 mg, 19%).

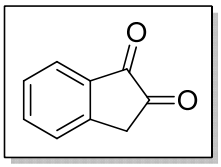
3.8.1.6 11*H*-Indeno[1,2-*b*]quinoxaline 213a[150]

Method 1. *In situ* trapping of 1*H*-indene-1,2(3*H*)-dione **211a** using one-pot addition of *o*-phenylenediamine **212** to 3-diazoisothiochroman-4-one *S*-oxide **87**

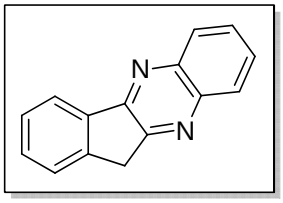


A solution of *o*-phenylenediamine **212** (50 mg, 0.47 mmol, 1 eq) in dichloromethane (2 mL) was directly added to a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (97 mg, 0.47 mmol, 1 eq) in dichloromethane (3 mL) at room temperature. The mixture was immediately irradiated to a temperature of 90 °C in the microwave. The required temperature was reached within a ramp time of 1 min 15 s and was held at the set point for 45 min. The solvent was removed *in vacuo* to give a light brown crystalline solid (109 mg). ^{1}H NMR analysis indicated the formation of 11*H*-indeno[1,2-*b*]quinoxaline **213a** among excess *o*-phenylenediamine **212** and a trace quantity of 2,3-dihydro-1*H*-inden-1-one **214a**. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent and recrystallised from dichloromethane/hexane to give pure 11*H*-indeno[1,2-*b*]quinoxaline **213a** with a trace amount of *o*-phenylenediamine **212** as a pale brown crystalline solid (72 mg, 70%); m.p. 128-130 °C (lit.,[150] 130-131 °C); ν_{max} (KBr)/cm^{-1} 1520, 1501, 1421 (aromatic C=C); δ_H (400 MHz); 4.13 (2H, s, C*H*$_2$), 7.48-7.60 (2H, m, Ar*H*), 7.63-7.66 (1H, m, Ar*H*), 7.69-7.76 (2H, m, Ar*H*), 8.05-8.11 (1H, m, Ar*H*), 8.13-8.17 (1H, m, Ar*H*), 8.23-8.8.26 (1H, m, Ar*H*); δ_C (75.5 MHz) 36.0 (*C*H$_2$), 122.7, 125.8, 128.0, 128.8, 129.0, 129.2, 129.2, 131.1 (8 × aromatic *C*H), 138.0, 141.2, 142.1, 143.5, 154.6, 159.5 (6 × aromatic C_q); HRMS (ESI+): Exact mass calculated for $C_{15}H_{11}N_2$ $[M+H]^+$, 219.0922. Found 219.0925; m/z (ESI+) 219 $[(M+H)^+$, 80%]. Spectral details in agreement with those reported in the literature.[150]

Method 2. Formation of 1*H*-indene-1,2(3*H*)-dione **211a** from **87** and sequential trapping with *o*-phenylenediazmine **212**

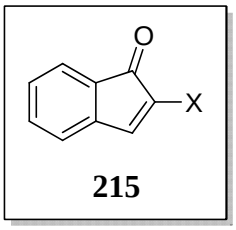


A solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (48 mg, 0.23 mmol, 1 eq) in dichloromethane (3 mL) and irradiated to a temperature of 90 °C in the microwave. The required temperature was reached within a ramp time of 1 min 10 s and was held at the set point for 30 min. The solvent was removed *in vacuo* to give a light brown crystalline solid (45 mg). ^{1}H NMR analysis indicated the presence of 1*H*-indene-1,2(3*H*)-dione **211a** and (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** (7:1) along with a trace quantity of 2,3-dihydro-1*H*-inden-1-one **214a** and other unidentifiable impurities (46 mg). Spectral details as described above.



The solid was redissolved in dichloromethane (8 mL) and a solution of *o*-phenylenediamine **212** (25 mg, 0.233 mmol, 1 eq) in dichloromethane (4 mL) was added. The reaction mixture was stirred at room temperature for 1 h. The solution was concentrated *in vacuo* to leave a foamy brown solid (55 mg). The ^{1}H NMR spectrum of the crude material contained excess *o*-phenylenediamine **212** along with 11*H*-indeno[1,2-*b*]quinoxaline **213a**, (*E*)-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione **210a** (7:1) and a trace quantity of 2,3-dihydro-1*H*-inden-1-one **214a**. Spectral details as described above.

3.8.1.7 Decomposition of 87 with 1 mol% rhodium(II) acetate in water



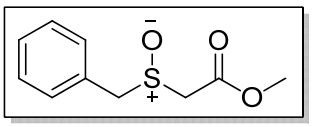
215

Rhodium(II) acetate dimer (1.59 mg, 3.67 μmol, 1 mol%) was added to a stirring suspension of 3-diazoisothiochroman-4-one *S*-oxide **87** (82 mg, 0.37 mmol, 1 eq) in water (10 mL). The reaction mixture was stirred under reflux overnight. The water was removed *in vacuo* to leave an pale brown oily solid (75 mg). The ^{1}H NMR spectrum indicated relatively clean formation of an unknown compound **215**. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using ethyl acetate/hexane (90:10) as eluent to give the unknown **215** as a white solid (54 mg, 44%); m.p. 62-64 °C (decomp.); ν_{max} (film)/cm^{-1} 1686 (C=O); δ_H (400 MHz, DMSO-d$_6$); 7.17-7.23 (2H, m, aromatic C*H*), 7.30-7.41 (2H, m, aromatic C*H*), 7.79 (2H, d, *J* 8.8, aromatic C*H*), 8.33 (2H, d, *J* 8.8, aromatic C*H*), 8.47 (2H, s, C*H*); δ_C (75.5 MHz, DMSO-d$_6$) 120.8 (C_q), 121.0, 122.9, 124.0, 127.6, 127.7 (5 × *C*H), 138.9 (C_q), 139.2 (C_q), 164.7 (*C*=O).*

Note:* During the *viva*, the ^{13}C data of **87 was discussed, and, while consistant with X=SH, appears to be inconsistent with X=OH.

3.8.1.8 Methyl 2-(benzylsulfinyl)acetate 216

Method 1. Rhodium(II) acetate-catalysed decomposition of **87** in dichloromethane



Rhodium(II) acetate dimer (3.01 mg, 6.99 μmol, 1 mol%) was added to a solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (144 mg, 0.70 mmol) in dichloromethane (12 mL) under a nitrogen atmosphere and the reaction mixture was heated under reflux. The progress of the reaction was monitored by TLC analysis over 24 h, after which time the sulfine **187a** had completely decomposed to form methyl 2-(benzylsulfinyl)acetate **216** which was isolated as a brown oil. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent to give pure **216** as a yellow oil (22 mg); ν_{max} (film)/cm^{-1} 1719 (C=O); δ_H (400 MHz) 3.51 (d, *J* 15.8, A of AB$_q$), 3.61 (d, *J*

15.8, B of AB_q), 3.78 (s), 4.15 (d, *J* 17.3, A of AB_q), 4.26 (d, *J* 17.3, B of AB_q), 7.32-7.41 (m, Ar*H*); δ_C (75.5 MHz) 52.9 (*C*H_3), 53.3 (*C*H_2), 58.0 (*C*H_2), 128.7 (aromatic *C*H), 128.9 (C_q), 129.1 (aromatic *C*H), 130.4 (aromatic *C*H), 165.7 (*C*=O); m/z (ESI+) 213 [$(M+H)^+$, 100%].

Method 2. Copper(0)-catalysed decomposition of **87** in dichloromethane

Copper bronze (0.12 mg, 1.95 μmol, 1 mol%) was added to a stirring solution of 3-diazoisothiochroman-4-one *S*-oxide **87** (43 mg, 0.20 mmol) in dichloromethane (10 mL) under a nitrogen atmosphere and the reaction mixture was heated under reflux. The progress of the reaction was monitored by TLC analysis over 48 h, after which time ^{1}H NMR analysis indicated the presence of methyl 2-(benzylsulfinyl)acetate **216**, 1-oxo-2-thioxoindane-*S*-oxide **187a** and 3-diazoisothiochroman-4-one *S*-oxide **87** (8:4:1). Purification by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent gave pure **216** as a yellow residue (10 mg). Spectral details as described above.

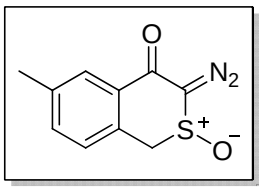
Table 3.9 Summary of decomposition reactions of 3-diazoisothiochroman-4-one *S*-oxide **87** undertaken in the presence of transition metal and lanthanide catalysts

Entry	Catalyst	Solvent	Time[a]	Crude Product Ratio[b]	Products isolated[c]
1	$Rh_2(OAc)_4$	DCM	o/n	**216**	**216**
2	$Rh_2(OAc)_4$	Toluene	o/n	**211a**, *E*-**210a** (2:1)	*E*-**210a** (22%) *Z*-**210a** (trace)
3	$Rh_2(OAc)_4$	Water	o/n	**215**	**215** (44%)
4	$Rh_2(OAc)_4$	DCM/ water	o/n	**215**	**215**

5	$Rh_2(tfa)_4$	DCM	o/n	**211a**, **214a**, ***E*-210a** (3 : 2 : trace)	Not purified
6	$Rh_2(tfacm)_4$	DCM	o/n	**211a**, **214a**, ***E*-210a** (4 : 3: 0.5)	Not purified
7	$Rh_2(pfb)_4$	DCM	o/n	**211a**, **214a**, ***E*-210a** (4 : 3: 0.2)	Not purified
8	$Rh_2(mand)_4$	DCM	o/n	**211a**, **214a** (5 : 3: 0.2)	Not purified
9	$Rh_2(cap)_4$	DCM	o/n	**211a**, **214a**, ***E*-210a** (6 : 5 : 0.5)	Not purified
10	Cu	DCM	48 h	**216**	**216**
11	Cu(I)Cl	DCM	48 h	**187a**, **211a**, **214a**, ***E*-210a** (3 : 3 : 2 : 0.4)	Not purified
12	Cu(I)(OTf)	DCM	o/n	**214a**, **211a** (5 : 1 : 1)	**214a** (25%)
13	$Gd(OAc)_3$	DCM	o/n	**187a**, **211a** (7 : 1)	Not purified
14	$Er(OTf)_3$	DCM	o/n	**87** (100%)	Not purified
15	AgOBz	DCM	o/n	**87** (100%)	Not purified

a. The progress of the reactions was monitored by TLC analysis.
b. Product ratios were determined by ^1H NMR analysis of the crude reaction mixture. For each entry, trace quantities of unidentifiable impurities were also detected.
c. Products were isolated by flash chromatography on silica gel.

3.8.2 Decomposition Studies of 3-Diazo-6-methylisothiochroman-4-one *S*-Oxide 88



3.8.2.1 Control reaction to investigate the reactivity of 3-diazo-6-methylisothiochroman-4-one *S*-oxide 88 in the absence of a metal catalyst

A solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (46 mg, 0.21 mmol) in dichloromethane (5 mL) was placed in a Pyrex® flask which had been cleaned with aqua regia to remove any traces of metal catalyst which may have been adhering to the surface. The reaction mixture was stirred under reflux and under a nitrogen atmosphere. The reaction progress was monitored by TLC analysis and ^{1}H NMR. No decomposition of the diazosulfoxide **88** occurred over 26 h (Table 3.10). When the diazosulfoxide **88** was stored in $CDCl_3$ solution at room temperature, decomposition occurred over time (Table 3.10).

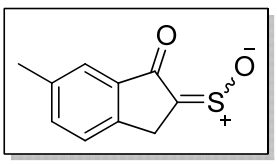
Table 3.10 Investigation into the stability of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** in solution and in the absence of a metal catalyst

Entry	Catalyst[a]	Solvent	Conditions[b]	Time	Product[c]
1	-	DCM	Δ	48 h	**88** (100%)
2	-	$CDCl_3$	RT	24 h	**88** (91%) **187b** (9%)
3	-	$CDCl_3$	RT	72 h	**88** (48%) **187b** (52%)
4	-	$CDCl_3$	RT	4 days	**88** (58%) **187b** (42%)

a. No catalyst was employed.
b. For entry 1, the solution was stirred under reflux conditions and a nitrogen atmosphere. Entries 2, 3 and 4 represent separate samples, and each solution was allowed to stand without stirring at room temperature.
c. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

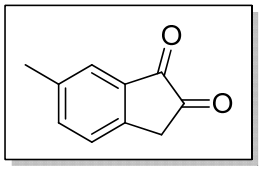
3.8.2.2 6-Methyl-1-oxo-2-thioxoindane-*S*-oxide 187b

Decomposition of **88** with 1 mol% rhodium(II) acetate in dichloromethane



Rhodium(II) acetate (2.19 mg, 4.95 μmol, 1 mol%) was added to a solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (109 mg, 0.50 mmol, 1 eq) in dichloromethane (8 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 5 min after which time IR and TLC analysis indicated that the diazo starting material had been consumed. The solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave 6-methyl-1-oxo-2-thioxoindane-*S*-oxide **187b**, a small quantity of 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** and 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (12: 1: 0.8) were isolated as a pale brown crystalline solid (92 mg, 97%); m.p. 132-134 °C (decomp.), ν_{max} (KBr)/cm^{-1} 1715 (C=O, indanedione **211b**), 1681 (C=O, sulfine **187b**).

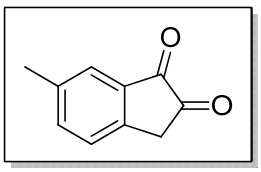
6-Methyl-1-oxo-2-thioxoindane-*S*-oxide **187b**: δ_H (400 MHz) 2.44 (3H, s, C*H*$_3$), 4.21 (2 H, s, C*H*$_2$), 7.39 (1H, d, *J* 7.9, Ar*H*), 7.49-7.53 (1H, m, Ar*H*), 7.67 (1H, s, Ar*H*); δ_C (75.5 MHz) 21.2 (*C*H$_3$), 32.8 (*C*H$_2$), 125.0 (aromatic *C*H), 126.0 (aromatic *C*H), 137.5 (aromatic C_q), 138.0 (aromatic *C*H), 139.0 (aromatic C_q), 142.8 (aromatic C_q), 184.8 (*C*=S=O). *Note*: the *C*=O quaternary carbon was not observed in the ^{13}C spectrum; HRMS (ESI+): Exact mass calculated for $C_{10}H_9O_2S$ $[M+H]^+$, 193.0323. Found 193.0332; m/z (ESI+) 193 $[(M+H)^+$, 100%].



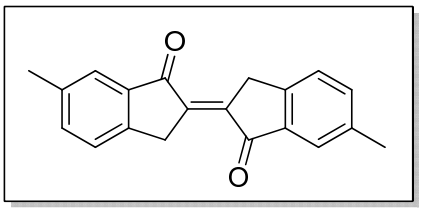
Signals detected for 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b**: δ_H (400 MHz) 2.46 (3H, s, C*H*$_3$), 3.59 (2H, s, C*H*$_2$). Complete ^{1}H NMR details are given in Section 3.9.3 below.

3.8.2.3 Decomposition of 88 with 1 mol% rhodium(II) acetate in dichloromethane

Rhodium(II) acetate dimer (1.96 mg, 4.45 μmol, 1 mol%) was added to a solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (98 mg, 0.45 mmol, 1 eq) in dichloromethane (20 mL) under a nitrogen atmosphere. The solution was stirred under reflux and the progress of the reaction was monitored by ^{1}H NMR analysis (Table 3.11). After 72 h, the ^{1}H NMR spectrum of the crude mixture indicated the presence of 6-methyl-1-oxo-2-thioxoindane-*S*-oxide **187b**, 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** and a compound tentatively assigned as (*E*)-6,6'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione ***E*-210b** (0.6: 1: 0.1). Attempts to purify the crude product by flash chromatography on silica gel using ethyl acetate/hexane (90:10) as eluent led to the isolation of two fractions. The first contained a residual amount of impure 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** among other unidentifiable impurities (~5 mg). The second fraction contained residual amount of (*E*)-6,6'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione ***E*-210b** and 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** (~4 mg, 2:1).



Signals identified for 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b**: δ_H (400 MHz) 2.46 (3H, s, C*H*$_3$), 3.59 (2H, s, C*H*$_2$), 7.49-7.54 (1H, m, aromatic C*H*), 7.54-7.59 (1H, m, aromatic C*H*), 7.70 (1H, s, aromatic C*H*); HRMS (ESI+): Exact mass calculated for $C_{10}H_9O_2$ $[M+H]^+$, 161.0603. Found 161.0598.



Signals identified for (*E*)-6,6'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione ***E*-210b**: δ_H (400 MHz) 2.44 (6H, s, C*H*$_3$), 4.27 (4H, s, C*H*$_2$). HRMS (ESI+): Exact mass calculated for $C_{20}H_{17}O_2$ $[M+H]^+$, 289.1229. Found 289.1225; m/z (ESI+) 289 $[(M+H)^+$, 20%].

Table 3.11 Progress of the reaction of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** with 1 mol% rhodium(II) acetate in dichloromethane under reflux conditions

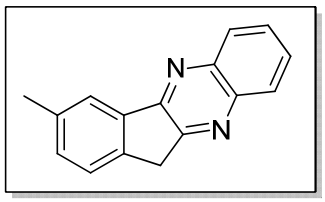
Entry	Solvent	Conditions	Time[a]	Products[b]
1	DCM	Δ	18 h	**187b**, **211b**, ***E*-210b** (4: 1: trace)
2	DCM	Δ	48 h	**187b**, **211b**, ***E*-210b** (1: 0.8: 0.1)
3	DCM	Δ	72 h	**187b**, **211b**, ***E*-210b** (0.6: 1: 0.1)

a. The progress of the reaction was monitored by removing an aliquot of the mixture and obtaining ^{1}H NMR analysis

b. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

3.8.2.4 3-Methyl-11*H*-indeno[1,2-*b*]quinoxaline 213b

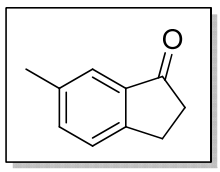
In situ trapping of 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** using one-pot addition of *o*-phenylenediamine **212** to 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88**



The title compound was prepared following the procedure described for 11*H*-indeno[1,2-*b*]quinoxaline **213a** using 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (82 mg, 0.37 mmol 1 eq), *o*-phenylenediamine **212** (40 mg, 0.37 mmol, 1 eq) and dichloromethane (3 mL). The solvent was removed *in vacuo* to leave a brown solid (108 mg). ^{1}H NMR analysis indicated the presence of 3-methyl-11*H*-indeno[1,2-*b*]quinoxaline **213b** and excess *o*-phenylenediamine **212** among trace quantities of unidentifiable impurities. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent and recrystallised from hexane/toluene to give 3-methyl-11*H*-indeno[1,2-*b*]quinoxaline **213b** as a pale brown crystalline solid (65 mg, 75%). Found: C, 82.61; H, 5.22; N, 12.19. C_8H_6N requires C, 82.73; H, 5.21; N, 12.06%; m.p. 136-137 °C; ν_{max} (KBr)/cm^{-1} 1529, 1498, 1426 (aromatic C=C); δ_H (400 MHz); 2.52 (3H, s, C*H*$_3$), 4.12 (2H, s, C*H*$_2$), 7.38 (1H, d, *J* 7.8, Ar*H*), 7.56 (1H, d, *J* 7.8, Ar*H*), 7.69-7.78 (2H, m, Ar*H*), 8.08-8.12 (2H, m, Ar*H*), 8.15-8.19 (1H, m, Ar*H*); δ_C (75.5 MHz) 21.4 (*C*H$_3$), 35.6 (*C*H$_2$), 123.0, 125.5, 128.7, 128.9, 129.1, 129.2 (6 × aromatic *C*H), 129.7 (aromatic *C*$_q$), 132.8 (aromatic *C*H), 138.1, 140.7, 141.2, 142.0, 154.8, 160.0 (6 × aromatic *C*$_q$); m/z (ESI+) Exact mass calculated for $C_{16}H_{13}N_2$ $[M+H]^+$, 233.1079. Found 233.1069; m/z (ESI+) 233 $[(M+H)^+$, 70%].

3.8.2.5 6-Methyl-2,3-dihydro-1*H*-inden-1-one 214b[205]

Method 1. Using 1 mol% copper(II) triflate in dichloromethane



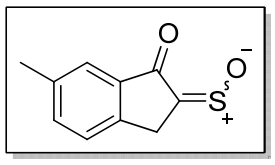
Copper(II) triflate (1.20 mg, 3.30 μmol, 1 mol%) was added to a stirring solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (72 mg, 0.33 mmol, 1 eq) in dichloromethane (8 mL). The reaction mixture was stirred under reflux for 20 h. TLC analysis indicated that the diazo starting material **88** and the sulfine **187b** had been consumed at this stage. The solution was filtered through a pad of Celite® and

concentrated *in vacuo* to leave a brown oil (66 mg). The ^{1}H NMR spectrum of the crude material indicated the formation of 6-methyl-2,3-dihydro-1*H*-inden-1-one **214b**, 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** (1:0.6) along with a trace amount of remaining sulfine **187b**. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (90:10) as eluent to give 6-methyl-2,3-dihydro-1*H*-inden-1-one **214b** as a clear oil (20 mg, 41%); ν_{max} (film)/cm^{-1} 1707 (C=O); δ_H (400 MHz) 2.40 (3H, s, C*H*$_3$), 2.66-2.72 (1H, m, C*H*$_2$), 3.10 (2H, t, *J* 6.0, C*H*$_2$), 7.36-7.42 (2H, m, Ar*H*), 7.56 (1H, s, Ar*H*); δ_C (75.5 MHz) 21.1 (*C*H$_3$), 25.4 (*C*H$_2$), 36.6 (*C*H$_2$), 123.7, 126.4, 135.9 (aromatic *C*H), 137.2 (aromatic *C*$_q$), 152.5 (aromatic *C*$_q$), 207.2 (*C*=O); m/z (ESI+) Exact mass calculated for $C_{10}H_{11}O$ $[M+H]^+$, 147.0810. Found 147.0803; m/z (ESI+) 147 $[(M+H)^+$, 100%]. Spectral details in agreement with those reported in the literature.[205]

Method 2. Photochemically induced decomposition of **88**

A Pyrex® flask containing a solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (50 mg, 0.23 mmol) in dichloromethane (5 mL) was fitted with a condenser and an 90 W mercury lamp was placed as close as possible to the flask. The entire apparatus was wrapped in aluminium foil and the reaction mixture was irradiated for 4 h under a nitrogen atmosphere. The solvent was removed *in vacuo* to give a brown residue (29 mg). ^{1}H NMR analysis of the crude residue indicated relatively clean formation of 6-methyl-2,3-dihydro-1*H*-inden-1-one **214b**. Spectral details as described above.

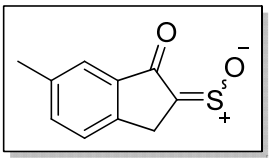
3.8.2.6 Decomposition of 88 with 1 mol% copper(I) chloride



Copper(I) chloride (0.76 mg, 8.4 μmol, 1 mol%) was added to a stirring solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (90 mg, 0.42 mmol, 1 eq) in dichloromethane (7 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux and the progress was monitored by TLC analysis. After 48 h, the solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave a brown oil (80 mg). ^{1}H NMR analysis indicated the presence of 6-methyl-1-oxo-2-thioxoindane-*S*-oxide **187b**, 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** (1:0.7),

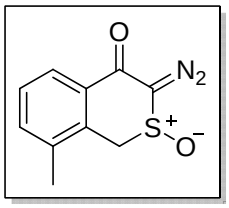
among a trace amount of 6-methyl-2,3-dihydro-1*H*-inden-1-one **214b** and other unidentifiable impurities. Spectral details as described above.

3.8.2.7 Decomposition of 88 with 1 mol% copper



Copper (0.52 mg, 8.0 μmol, 1 mol%) was added to a stirring solution of 3-diazo-6-methylisothiochroman-4-one *S*-oxide **88** (85 mg, 0.40 mmol, 1 eq) in dichloromethane (5 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux and the progress was monitored by TLC analysis. After 48 h, the solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave a brown oil (71 mg). ^{1}H NMR analysis indicated the presence of 6-methyl-1-oxo-2-thioxoindane-*S*-oxide **187b** and 6-methyl-1*H*-indene-1,2(3*H*)-dione **211b** (1: 0.2). Spectral details as described above.

3.8.3 Decomposition Studies of 3-Diazo-8-methylisothiochroman-4-one *S*-Oxide 89



3.8.3.1 Control reaction to investigate the stability of 3-diazo-8-methylisothiochroman 4-one *S*-oxide 89 in solution and in the absence of a metal catalyst

A solution of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (41 mg, 0.18 mmol) in dichloromethane (5 mL) was placed in a Pyrex® flask which had been cleaned with aqua regia to remove any traces of metal catalyst which may have been adhering to the surface. The reaction mixture was stirred under reflux conditions and under a nitrogen atmosphere over 24 h. The reaction progress was monitored by TLC analysis and ^{1}H NMR. No decomposition of the diazosulfoxide **89** occurred over 24

h (Table 3.12). When the diazosulfoxide **89** was stored in $CDCl_3$ solution at room temperature, decomposition occurred over time (Table 3.12).

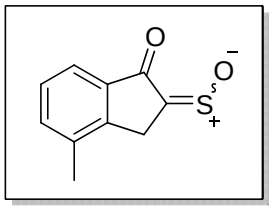
Table 3.12 Investigation of the reactivity of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** in the absence of a metal catalyst

Entry	Catalyst[a]	Solvent	Conditions[b]	Time	Product[c]
1	-	DCM	Δ	24 h	**89** (100%)
2	-	$CDCl_3$	RT	24 h	**89** (60%) **187c** (40%)
3	-	$CDCl_3$	RT	72 h	**89** (4%) **187c** (96%)

a. No catalyst was employed.
b. For entry 1, the solution was stirred under reflux conditions and a nitrogen atmosphere. Entries 2 and 3 represent separate samples, and both solutions were allowed to stand without stirring at room temperature.
c. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

3.8.3.2 8-Methyl-1-oxo-2-thioxoindane-*S*-oxide 187c

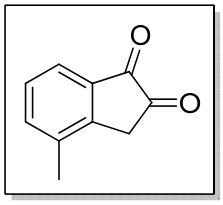
Decomposition of **89** with 1 mol% rhodium(II) acetate in dichloromethane



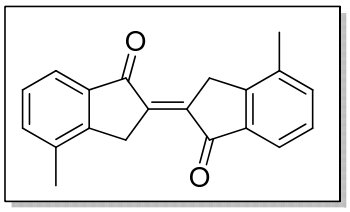
The title compound was prepared following the procedure described for 1-oxo-2-thioxoindane-*S*-oxide **187a** above using 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (90 mg, 0.41 mmol, 1 eq), rhodium(II) acetate (1.84 mg, 4.13 μmol, 1 mol%) in dichloromethane (10 mL). After 5 min, ^{1}H NMR analysis indicated the presence of the sulfine **187c** along with small quantites of 8-methyl-1*H*-indene-1,2(3*H*)-dione **211c** and a compound tentatively assigned as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210c** (5 : 0.8 : 0.6) (77 mg); m.p. 139-141 °C (decomp.), ν_{max} (KBr)/cm^{-1} 1684 (C=O).

8-Methyl-1-oxo-2-thioxoindane-*S*-oxide **187c**: δ_H (400 MHz) 2.38 (3H, s, C*H*$_3$), 4.14 (2 H, s, C*H*$_2$), 7.36-7.43 (1H, m, Ar*H*), 7.50 (1H, d, *J* 7.4, Ar*H*), 7.70

(1H, d, *J* 7.7, Ar*H*); δ_C (75.5 MHz) 17.7 (*C*H_3), 32.1 (*C*H_2), 122.5 (aromatic *C*H), 129.0 (aromatic *C*H), 135.8 (aromatic C_q), 137.2 (aromatic C_q), 137.2 (aromatic *C*H), 144.4 (aromatic C_q), 184.8 (*C*=S=O), 188.9 (*C*=O); HRMS (ESI+): Exact mass calculated for $C_{10}H_8O_2S$ $[M+H]^+$, 193.0323. Found 193.0314; m/z (ESI+) 193 $[(M+H)^+$, 100%].



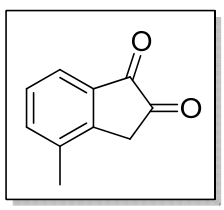
Signals observed for 8-methyl-1*H*-indene-1,2(3*H*)-dione **211c** 3.51 (2H, s, CH_2).



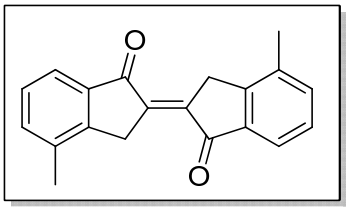
Signals observed for compound tentatively assigned as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210c**: δ_H (400 MHz) 4.21 (4H, s, 2 × CH_2).

3.8.3.3 Decomposition of 89 with 1 mol% rhodium(II) acetate in dichloromethane

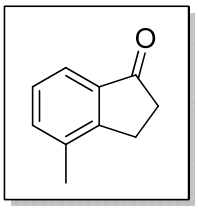
Rhodium(II) acetate dimer (1.70 mg, 3.82 μmol, 1 mol%) was added to a solution of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (83 mg, 0.38 mmol, 1 eq) in dichloromethane (10 mL) under a nitrogen atmosphere. The solution was stirred under reflux and the progress of the reaction was monitored by TLC analysis. After 72 h, the ^{1}H NMR spectrum of the crude mixture indicated the presence of 8-methyl-1-oxo-2-thioxoindane-*S*-oxide **187c**, 8-methyl-1*H*-indene-1,2(3*H*)-dione **211c**, a trace quantity of 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c** and a compound tentatively identified as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210c** (1: 2: trace: 0.1, 79 mg). Spectral details for 8-methyl-1-oxo-2-thioxoindane *S*-oxide **187c** as described above.



Signals observed for 8-methyl-1*H*-indene-1,2(3*H*)-dione **211c**: δ_H (400 MHz) 3.51 (2H, s, CH_2), 7.52 (1H, d, *J* 7.5, aromatic C*H*), 7.71 (1H, d, *J* 7.5, aromatic C*H*); HRMS (ESI+): Exact mass calculated for $C_{10}H_9O_2$ $[M+H]^+$, 161.0603. Found 161.0611.



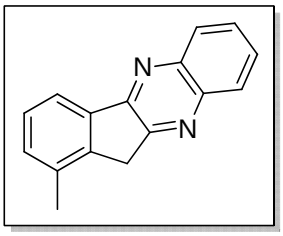
Signals observed for compound tentatively assigned as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione ***E*-210c**: δ_H (400 MHz) 4.21 (4H, s, 2 × C*H*$_2$); HRMS (ESI+): Exact mass calculated for $C_{20}H_{17}O_2$ $[M+H]^+$, 289.1229. Found 289.1230; m/z (ESI+) 289 $[(M+H)^+$, 24%].



Signals observed for 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c**: δ_H (400 MHz) 2.69-2.73 (2H, m, C*H*$_2$), 3.03 (2H, t, *J* 5.5, C*H*$_2$). Complete spectral details for **214c** are given below.

3.8.3.4 1-Methyl-11*H*-indeno[1,2-*b*]quinoxaline 213c

In situ trapping of 4-methyl-1*H*-indene-1,2(3*H*)-dione **211c** using one-pot addition of *o*-phenylenediamine **212** to 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89**

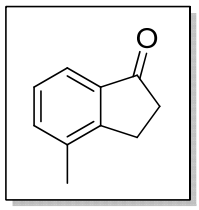


The title compound was prepared following the procedure described for 11*H*-indeno[1,2-*b*]quinoxaline **213a** using 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (97 mg, 0.44 mmol 1 eq), *o*-phenylenediamine **212** (47 mg, 0.44 mmol, 1 eq) and dichloromethane (3 mL). The solvent was removed *in vacuo* to leave a brown solid (112 mg). ^{1}H NMR analysis indicated the presence of 1-methyl-11*H*-indeno[1,2-*b*]quinoxaline **213c** and excess *o*-phenylenediamine **212** among trace quantities of 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c** (1: 0.1: 0.2) and unidentifiable impurities. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (50:50) as eluent and recrystallised from hexane/toluene to give 1-methyl-11*H*-indeno[1,2-*b*]quinoxaline **213c** as a pale brown crystalline solid (62 mg, 61%). Found: C, 82.24; H, 5.11; N, 12.27. C_8H_6N requires C, 82.73; H, 5.21; N, 12.06%; m.p. 122-124 °C; ν_{max} (KBr)/cm^{-1} 1540, 1482, 1386 (aromatic C=C); δ_H (400 MHz); 2.48 (3H, s, C*H*$_3$), 4.00 (2H, s, C*H*$_2$), 7.33 (1H, d, *J* 7.7, Ar*H*), 7.41-7.49 (1H, m, Ar*H*), 7.66-7.81 (2H, m, Ar*H*), 8.05-8.11 (2H, m, Ar*H*), 8.16-8.19 (1H, m, Ar*H*); δ_C (75.5 MHz); 18.7 (*C*H$_3$), 34.8 (*C*H$_2$), 120.1, 128.3, 128.7, 129.0, 129.1, 129.2, 132.0

(7 × aromatic *C*H), 135.1, 137.7, 141.2, 142.1, 142.5, 155.0, 159.5 (7 × aromatic C_q); m/z (ESI+) Exact mass calculated for $C_{16}H_{13}N_2$ $[M+H]^+$, 233.1079. Found 233.1073; m/z (ESI+) 233 $[(M+H)^+$, 85%].

3.8.3.5 4-Methyl-2,3-dihydro-1*H*-inden-1-one 214c

Method 1. Decomposition of **89** with 1 mol% copper(II) triflate in dichloromethane



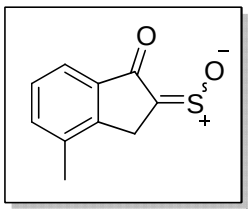
Copper(II) triflate (1.45 mg, 4.00 μmol, 1 mol%) was added to a stirring solution of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (87 mg, 0.40 mmol, 1 eq) in dichloromethane (10 mL). The reaction mixture was stirred under reflux for 48 h. The solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave a brown oil (75 mg). The ^{1}H NMR spectrum of the crude material indicated the formation of 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c** along with remaining sulfine **187c** (1:1.8) and trace quantities of unidentifiable impurities. The crude product was adsorbed onto Celite® and purified by flash chromatography on silica gel using hexane/ethyl acetate (90:10) as eluent to give 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c** as a clear oil (18 mg, 30%); ν_{max} (film)/cm^{-1} 1708 (C=O); δ_H (400 MHz) 2.36 (3H, s, C*H*$_3$), 2.69-2.73 (2H, m, C*H*$_2$), 3.03 (2H, t, *J* 5.5, C*H*$_2$), 7.28-7.32 (1H, m, Ar*H*), 7.41 (1H, d, *J* 7.2, Ar*H*), 7.61 (1H, d, *J* 7.6, Ar*H*); δ_C (75.5 MHz) 17.7 (*C*H$_3$), 24.7 (*C*H$_2$), 36.2 (*C*H$_2$), 121.1, 127.5, 135.0 (aromatic *C*H), 135.9, 136.9, 154.2 (aromatic C_q), 207.5 (*C*=O); m/z (ESI+) Exact mass calculated for $C_{10}H_{11}O$ $[M+H]^+$, 147.0810. Found 147.0803; m/z (ESI+) 293 $[(2M+H)^+$, 83%].

Method 2. Photochemically induced decomposition of **89**

A Pyrex® flask containing a solution of 3-diazo-8-methylisothiochroman-4-one *S*-oxide **89** (48 mg, 0.22 mmol) in dichloromethane (5 mL) was fitted with a condenser and an 90 W mercury lamp was placed as close as possible to the flask. The entire apparatus was wrapped in aluminium foil and the reaction mixture was irradiated for 4 h under a nitrogen atmosphere. The solvent was removed *in vacuo* to give a brown residue (30 mg). ^{1}H NMR analysis of the crude residue indicated the presence of 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c**, 8-methyl-1*H*-indene-

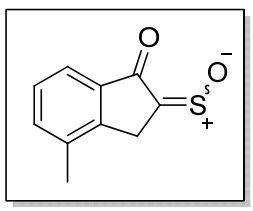
1,2(3*H*)-dione **211c**, and the compound tentatively assigned as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210c**, among unidentifiable impurities (1: 0.2: 0.05). Spectral details as described above.

3.8.3.6 Decomposition of 89 with 1 mol% copper



Copper (0.26 mg, 4.0 μmol, 1 mol%) was added to a stirring solution of 3-diazo-8-methylisothiochroman 4-one *S*-oxide **89** (42 mg, 0.20 mmol, 1 eq) in dichloromethane (5 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux and the progress was monitored by TLC analysis. After 48 h, the solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave a brown oil (71 mg). ^{1}H NMR analysis indicated the presence of 8-methyl-1-oxo-2-thioxoindane-*S*-oxide **187c**, small quantities of 4-methyl-1*H*-indene-1,2(3*H*)-dione **211c**, 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c** and the compound tentatively assigned as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210c** (1: 0.1: 0.1: 0.05), among trace quantities of unidentifiable compounds. Spectral details as described above.

3.8.3.7 Decomposition of 89 with 1 mol% copper(I) chloride



Copper(I) chloride (0.38 mg, 4.2 μmol, 1 mol%) was added to a stirring solution of 3-diazo-8-methylisothiochroman 4-one *S*-oxide **89** (44 mg, 0.21 mmol, 1 eq) in dichloromethane (7 mL) under a nitrogen atmosphere. The reaction mixture was heated under reflux and the progress was monitored by TLC analysis. After 48 h, the solution was filtered through a pad of Celite® and concentrated *in vacuo* to leave a brown oil (80 mg). ^{1}H NMR analysis indicated the presence of 8-methyl-1-oxo-2-thioxoindane-*S*-oxide **187c**, 4-methyl-1*H*-indene-1,2(3*H*)-dione **211c**, 4-methyl-2,3-dihydro-1*H*-inden-1-one **214c** and the compound tentatively assigned as (*E*)-4,4'-dimethyl-[2,2'-biindenylidene]-1,1'(3*H*, 3'*H*)-dione *E*-**210a** (1: 0.2: 0.2: 0.1), and trace quantities of unidentifiable compounds. Spectral details as described above.

3.9 Bibliography

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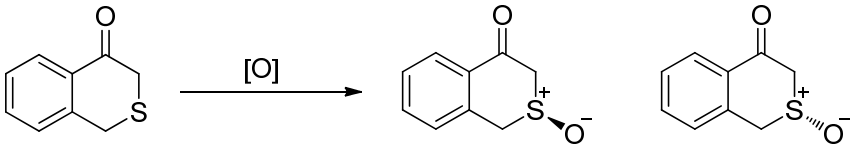
Appendix I
Chiral HPLC data

Chiral HPLC data for attempted asymmetric synthesis of isothochroman-4-one *S*-oxide **44**:



44 (*S*)-**80** (*R*)-**80**

Column/Conditions:[a] AMY-2, 30% IPA in hexane, 20 °C

Oxidation	Retention Time (min)	% ee[b]
Racemic	34.3, 40.4	0
Kagan	34.3, 40.4	~ 0
Bolm	33.4, 39.4	~ 0
Copper(II)	33.5, 39.6	~ 0

a. Column: Phenomenex Lux Amylose-2 (3μ) 250 × 4.6 mm; Flow-rate 1.0 mL/min; λ = 210 nm.
b. No enantioselectivity was detected and the enantiomers (*S*)-**80** and (*R*)-**80** were not distinguished.

Appendix II

NCI-60 One-Dose Mean Graphs

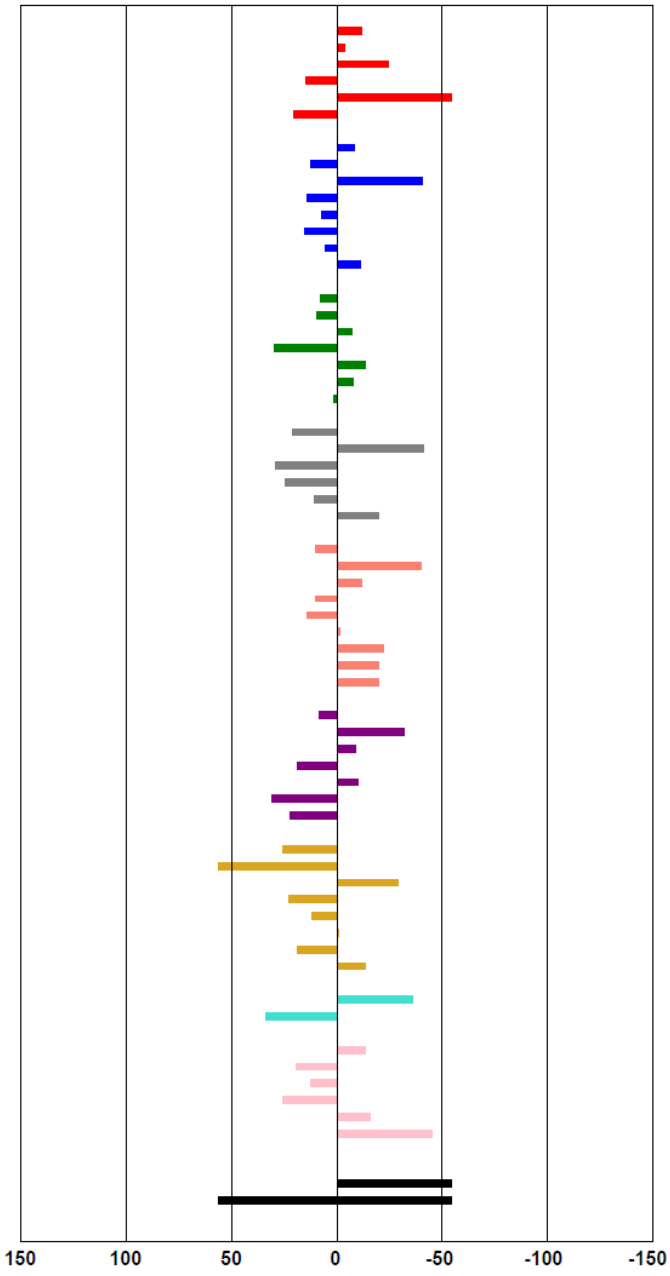
Developmental Therapeutics Program

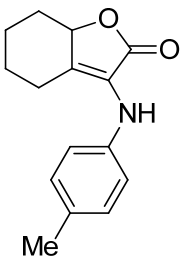
One Dose Mean Graph

NSC: 768103 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	55.91
HL-60(TB)	63.82
K-562	43.19
MOLT-4	82.25
RPMI-8226	12.89
SR	87.75
Non-Small Cell Lung Cancer	
A549/ATCC	58.97
HOP-62	79.81
HOP-92	27.16
NCI-H226	81.86
NCI-H23	74.98
NCI-H322M	82.58
NCI-H460	73.00
NCI-H522	56.32
Colon Cancer	
COLO 205	75.15
HCC-2998	77.03
HCT-116	60.10
HCT-15	96.93
HT29	54.11
KM12	59.99
SW-620	69.24
CNS Cancer	
SF-268	88.42
SF-295	26.42
SF-539	96.62
SNB-19	92.07
SNB-75	78.11
U251	47.81
Melanoma	
LOX IMVI	77.64
MALME-3M	27.44
M14	56.03
MDA-MB-435	77.90
SK-MEL-2	81.57
SK-MEL-28	65.86
SK-MEL-5	45.69
UACC-257	47.68
UACC-62	47.70
Ovarian Cancer	
IGROV1	75.65
OVCAR-3	35.67
OVCAR-4	58.48
OVCAR-5	86.33
OVCAR-8	57.75
NCI/ADR-RES	98.42
SK-OV-3	89.86
Renal Cancer	
786-0	93.18
A498	123.87
ACHN	38.52
CAKI-1	90.30
RXF 393	79.51
SN12C	66.93
TK-10	86.45
UO-31	53.81
Prostate Cancer	
PC-3	31.62
DU-145	101.24
Breast Cancer	
MCF7	54.18
MDA-MB-231/ATCC	87.01
HS 578T	79.80
BT-549	93.01
T-47D	51.65
MDA-MB-468	22.61
Mean	67.56
Delta	54.67
Range	110.98

Mean Growth Percent - Growth Percent





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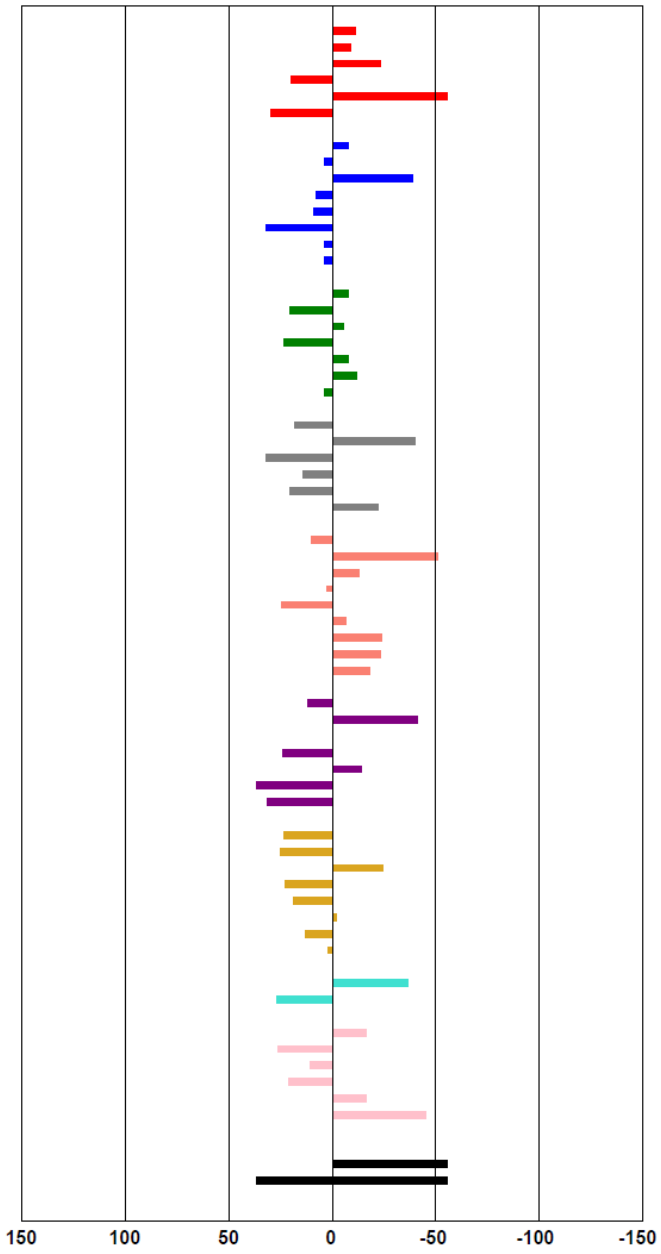
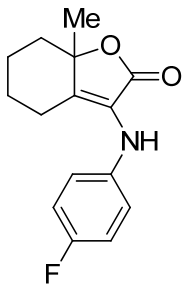
Developmental Therapeutics Program
One Dose Mean Graph

NSC: 768104 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	57.37
HL-60(TB)	59.56
K-562	45.12
MOLT-4	88.45
RPMI-8226	12.80
SR	98.07
Non-Small Cell Lung Cancer	
A549/ATCC	60.95
HOP-62	71.92
HOP-92	29.50
NCI-H226	76.34
NCI-H23	77.56
NCI-H322M	100.49
NCI-H460	72.39
NCI-H522	72.35
Colon Cancer	
COLO 205	60.62
HCC-2998	88.89
HCT-116	63.01
HCT-15	92.03
HT29	60.50
KM12	56.40
SW-620	72.38
CNS Cancer	
SF-268	86.49
SF-295	28.33
SF-539	100.15
SNB-19	82.61
SNB-75	88.71
U251	46.52
Melanoma	
LOX IMVI	78.34
MALME-3M	17.51
M14	55.43
MDA-MB-435	71.12
SK-MEL-2	92.80
SK-MEL-28	62.03
SK-MEL-5	44.50
UACC-257	45.34
UACC-62	50.24
Ovarian Cancer	
IGROV1	80.17
OVCAR-3	27.33
OVCAR-4	68.13
OVCAR-5	92.51
OVCAR-8	54.10
NCI/ADR-RES	104.81
SK-OV-3	99.85
Renal Cancer	
786-0	91.89
A498	93.62
ACHN	44.05
CAKI-1	91.36
RXF 393	87.28
SN12C	66.72
TK-10	81.45
UO-31	70.45
Prostate Cancer	
PC-3	31.89
DU-145	95.48
Breast Cancer	
MCF7	51.81
MDA-MB-231/ATCC	94.92
HS 578T	79.15
BT-549	89.73
T-47D	52.11
MDA-MB-468	23.15
Mean	68.45
Delta	55.65
Range	92.01

Mean Growth Percent - Growth Percent





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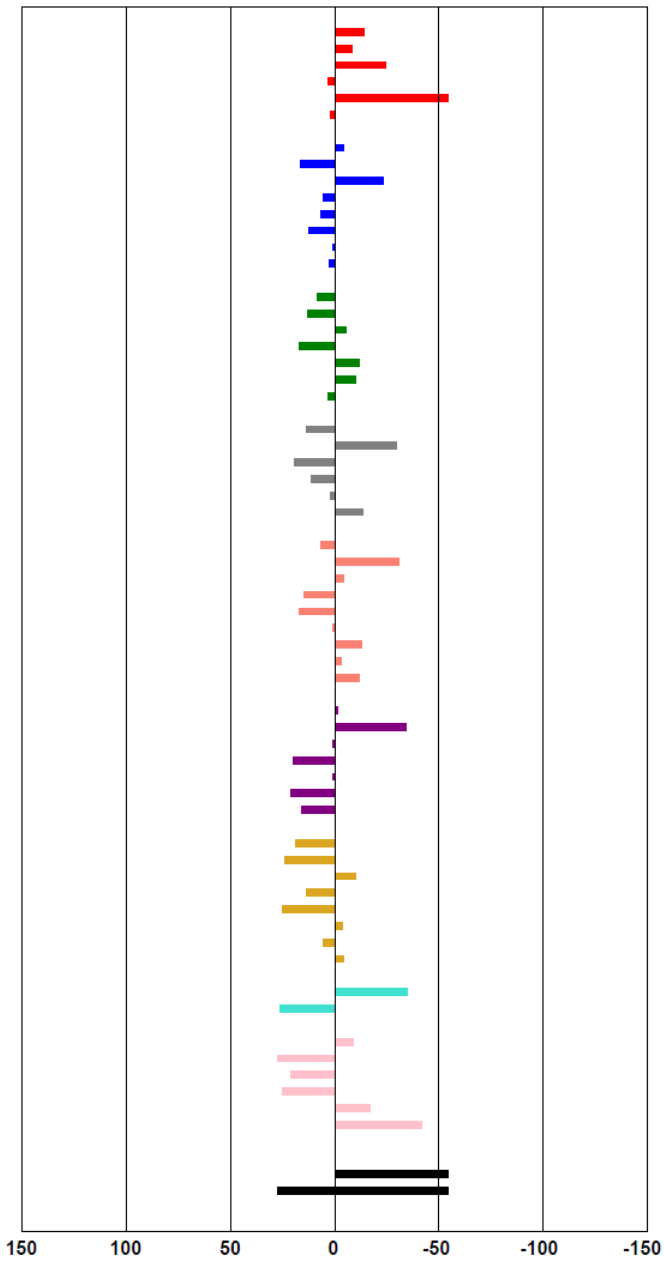
Developmental Therapeutics Program

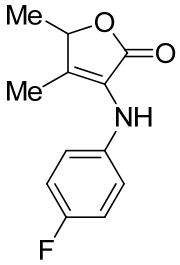
One Dose Mean Graph

NSC: 768106 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	69.84
HL-60(TB)	75.48
K-562	59.21
MOLT-4	86.88
RPMI-8226	29.68
SR	85.70
Non-Small Cell Lung Cancer	
A549/ATCC	79.39
HOP-62	100.10
HOP-92	60.36
NCI-H226	89.31
NCI-H23	90.72
NCI-H322M	96.46
NCI-H460	84.80
NCI-H522	86.60
Colon Cancer	
COLO 205	92.05
HCC-2998	96.79
HCT-116	78.65
HCT-15	100.83
HT29	71.99
KM12	73.94
SW-620	87.14
CNS Cancer	
SF-268	97.36
SF-295	54.06
SF-539	103.38
SNB-19	94.91
SNB-75	85.86
U251	70.34
Melanoma	
LOX IMVI	90.29
MALME-3M	53.01
M14	79.62
MDA-MB-435	98.82
SK-MEL-2	101.08
SK-MEL-28	84.70
SK-MEL-5	71.09
UACC-257	81.04
UACC-62	72.33
Ovarian Cancer	
IGROV1	82.58
OVCAR-3	49.88
OVCAR-4	84.99
OVCAR-5	104.01
OVCAR-8	84.73
NCI/ADR-RES	104.98
SK-OV-3	99.79
Renal Cancer	
786-0	102.36
A498	107.80
ACHN	73.79
CAKI-1	97.21
RXF 393	108.93
SN12C	80.10
TK-10	89.39
UO-31	79.51
Prostate Cancer	
PC-3	49.04
DU-145	109.91
Breast Cancer	
MCF7	74.73
MDA-MB-231/ATCC	111.29
HS 578T	104.89
BT-549	108.88
T-47D	66.68
MDA-MB-468	42.15
Mean	83.92
Delta	54.24
Range	81.61

Mean Growth Percent - Growth Percent





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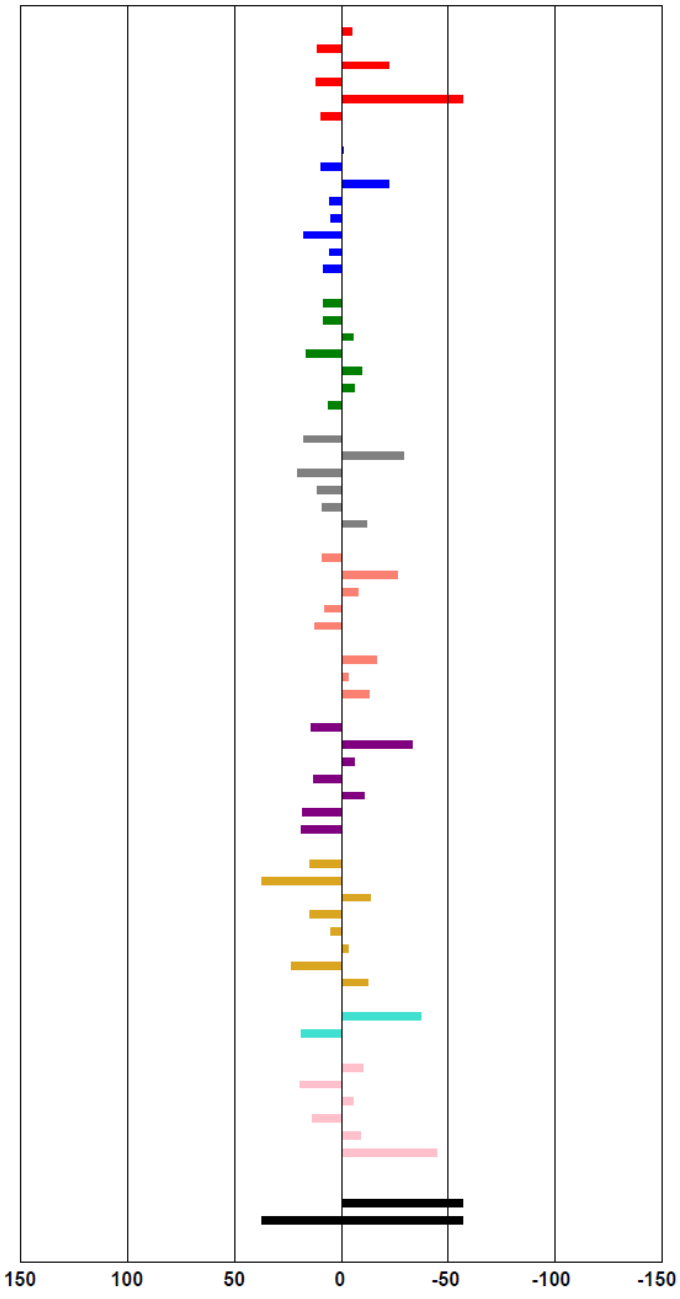
Developmental Therapeutics Program

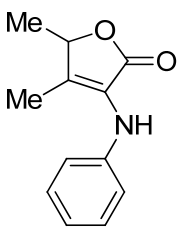
One Dose Mean Graph

NSC: 768105 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	78.25
HL-60(TB)	94.30
K-562	60.92
MOLT-4	95.15
RPMI-8226	26.47
SR	92.64
Non-Small Cell Lung Cancer	
A549/ATCC	82.47
HOP-62	93.01
HOP-92	60.85
NCI-H226	88.97
NCI-H23	88.38
NCI-H322M	100.53
NCI-H460	88.69
NCI-H522	91.84
Colon Cancer	
COLO 205	91.49
HCC-2998	91.79
HCT-116	77.71
HCT-15	99.48
HT29	73.94
KM12	76.98
SW-620	89.41
CNS Cancer	
SF-268	100.78
SF-295	53.97
SF-539	103.45
SNB-19	94.62
SNB-75	92.24
U251	71.28
Melanoma	
LOX IMVI	91.90
MALME-3M	57.14
M14	75.69
MDA-MB-435	90.93
SK-MEL-2	95.39
SK-MEL-28	82.97
SK-MEL-5	66.64
UACC-257	80.15
UACC-62	70.10
Ovarian Cancer	
IGROV1	97.46
OVCAR-3	50.01
OVCAR-4	77.10
OVCAR-5	96.43
OVCAR-8	72.86
NCI/ADR-RES	101.47
SK-OV-3	102.21
Renal Cancer	
786-0	97.69
A498	120.56
ACHN	69.72
CAKI-1	98.07
RXF 393	88.09
SN12C	79.80
TK-10	106.76
UO-31	70.80
Prostate Cancer	
PC-3	45.96
DU-145	101.70
Breast Cancer	
MCF7	73.25
MDA-MB-231/ATCC	102.45
HS 578T	77.94
BT-549	96.74
T-47D	74.23
MDA-MB-468	38.76
Mean	83.23
Delta	56.76
Range	94.09

Mean Growth Percent - Growth Percent





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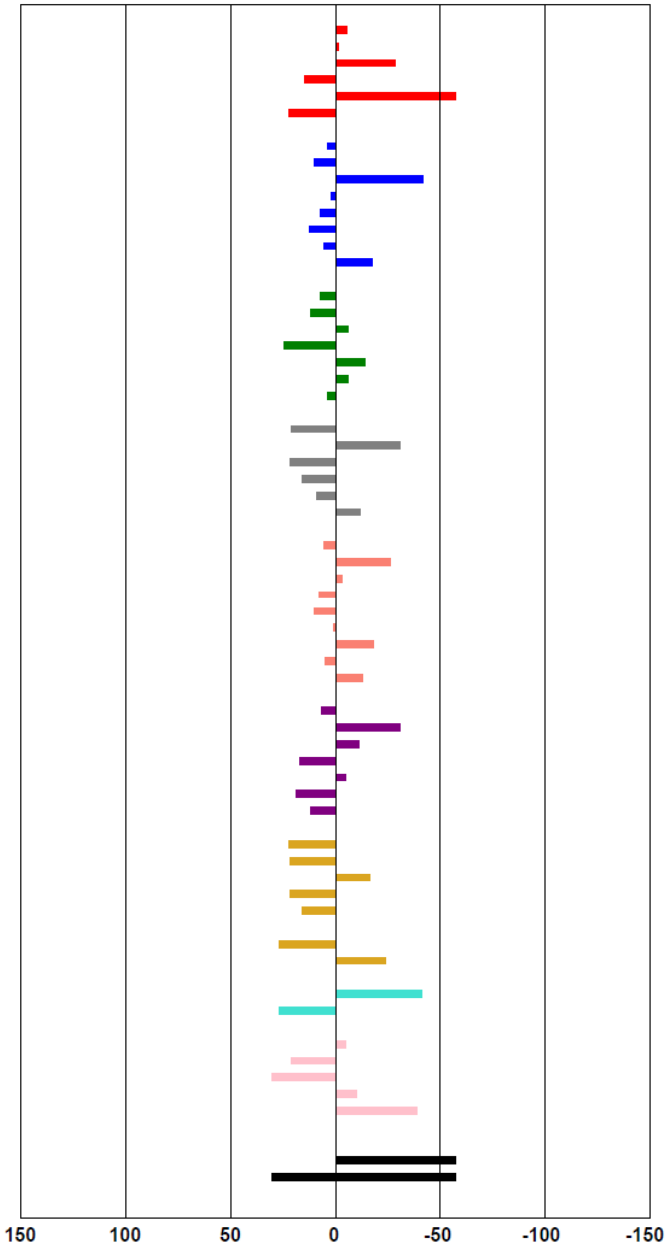
Developmental Therapeutics Program

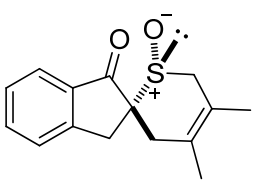
One Dose Mean Graph

NSC: 768109 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	74.79
HL-60(TB)	79.22
K-562	52.19
MOLT-4	95.08
RPMI-8226	23.30
SR	102.37
Non-Small Cell Lung Cancer	
A549/ATCC	84.24
HOP-62	90.25
HOP-92	38.55
NCI-H226	82.39
NCI-H23	87.62
NCI-H322M	92.86
NCI-H460	85.82
NCI-H522	62.93
Colon Cancer	
COLO 205	87.55
HCC-2998	92.50
HCT-116	74.15
HCT-15	104.69
HT29	66.22
KM12	74.48
SW-620	84.37
CNS Cancer	
SF-268	101.74
SF-295	49.89
SF-539	102.18
SNB-19	96.29
SNB-75	89.16
U251	68.94
Melanoma	
LOX IMVI	85.78
MALME-3M	54.21
M14	77.51
MDA-MB-435	88.30
SK-MEL-2	90.43
SK-MEL-28	81.52
SK-MEL-5	62.37
UACC-257	85.59
UACC-62	67.46
Ovarian Cancer	
IGROV1	86.93
OVCAR-3	49.72
OVCAR-4	69.40
OVCAR-5	97.44
OVCAR-8	75.71
NCI/ADR-RES	99.28
SK-OV-3	92.13
Renal Cancer	
786-0	102.47
A498	102.27
ACHN	64.18
CAKI-1	102.30
RXF 393	96.41
SN12C	80.39
TK-10	107.25
UO-31	56.63
Prostate Cancer	
PC-3	39.32
DU-145	107.37
Breast Cancer	
MCF7	75.33
MDA-MB-231/ATCC	101.60
BT-549	110.67
T-47D	70.60
MDA-MB-468	41.78
Mean	80.45
Delta	57.15
Range	87.37

Mean Growth Percent - Growth Percent





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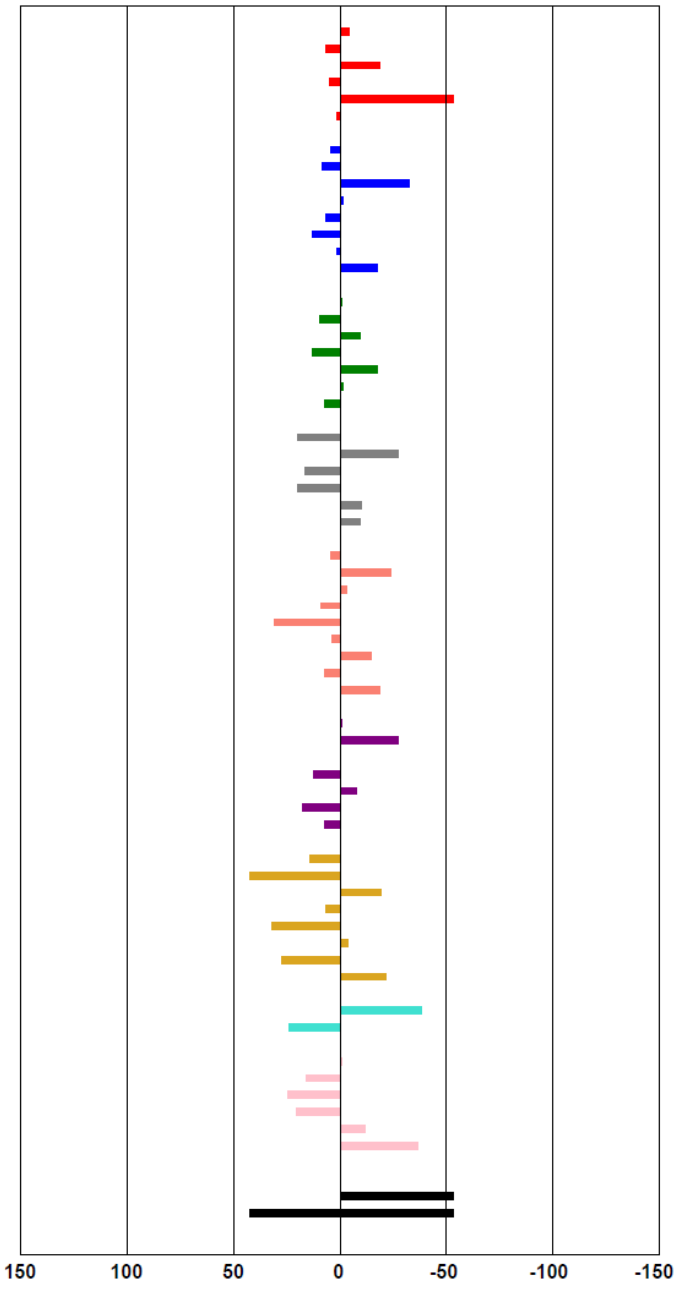
Developmental Therapeutics Program

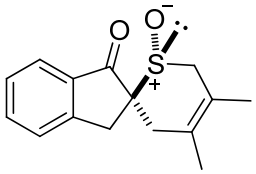
One Dose Mean Graph

NSC: 768107 / 1	**Conc:** 1.00E-5 Molar	**Test Date:** Nov 05, 2012
Experiment ID: 1211OS74		**Report Date:** Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	82.91
HL-60(TB)	94.34
K-562	68.80
MOLT-4	92.54
RPMI-8226	34.11
SR	89.11
Non-Small Cell Lung Cancer	
A549/ATCC	91.84
HOP-62	95.98
HOP-92	55.08
NCI-H226	85.94
NCI-H23	94.31
NCI-H322M	100.22
NCI-H460	89.01
NCI-H522	70.17
Colon Cancer	
COLO 205	86.62
HCC-2998	97.28
HCT-116	77.93
HCT-15	100.70
HT29	69.69
KM12	86.14
SW-620	94.67
CNS Cancer	
SF-268	107.30
SF-295	60.30
SF-539	103.91
SNB-19	107.27
SNB-75	77.44
U251	77.85
Melanoma	
LOX IMVI	91.64
MALME-3M	63.42
M14	84.07
MDA-MB-435	96.44
SK-MEL-2	118.20
SK-MEL-28	91.10
SK-MEL-5	72.70
UACC-257	94.87
UACC-62	69.00
Ovarian Cancer	
IGROV1	86.53
OVCAR-3	60.40
OVCAR-4	87.28
OVCAR-5	99.72
OVCAR-8	79.95
NCI/ADR-RES	104.84
SK-OV-3	94.46
Renal Cancer	
786-0	101.50
A498	129.74
ACHN	68.41
CAKI-1	94.40
RXF 393	119.34
SN12C	83.68
TK-10	115.04
UO-31	65.68
Prostate Cancer	
PC-3	49.48
DU-145	111.35
Breast Cancer	
MCF7	86.91
MDA-MB-231/ATCC	103.61
HS 578T	111.96
BT-549	107.90
T-47D	75.97
MDA-MB-468	51.17
Mean	87.50
Delta	53.39
Range	95.63

Mean Growth Percent - Growth Percent





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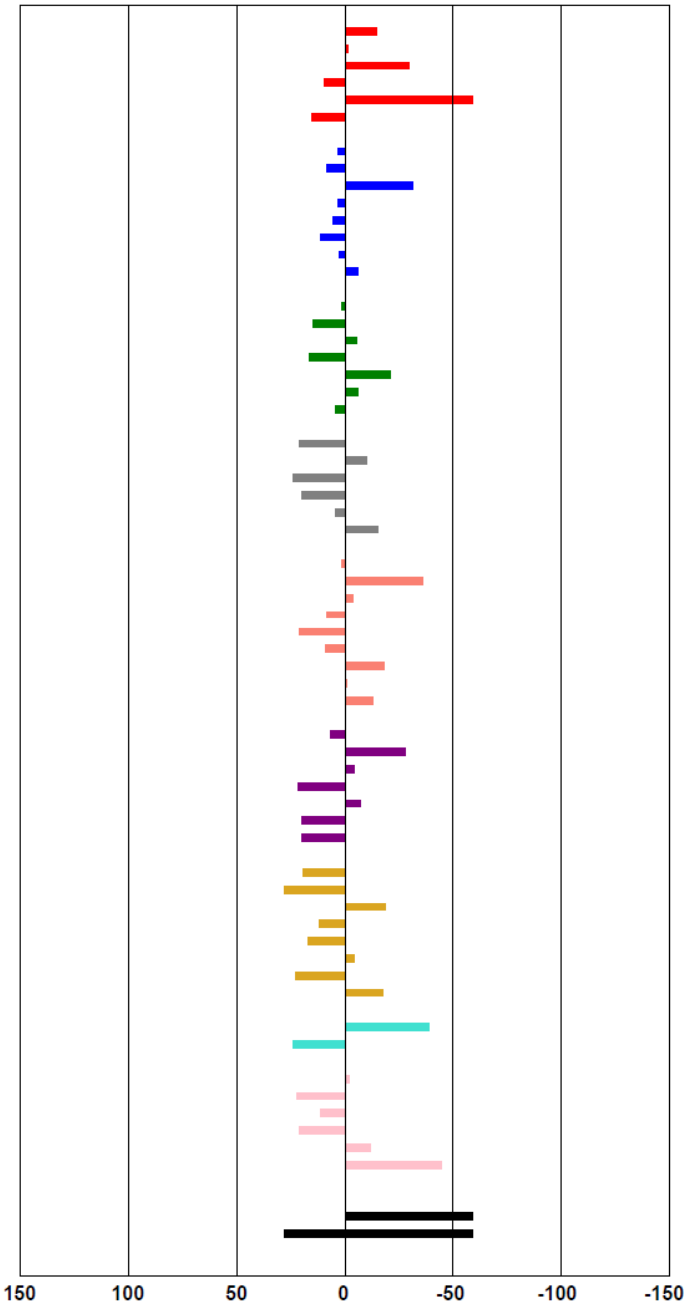
Developmental Therapeutics Program

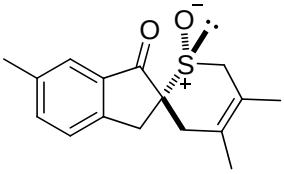
One Dose Mean Graph

NSC: 768108 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	65.51
HL-60(TB)	78.52
K-562	50.43
MOLT-4	89.53
RPMI-8226	20.99
SR	95.18
Non-Small Cell Lung Cancer	
A549/ATCC	83.08
HOP-62	88.31
HOP-92	49.00
NCI-H226	83.05
NCI-H23	85.29
NCI-H322M	91.55
NCI-H460	82.66
NCI-H522	74.09
Colon Cancer	
COLO 205	81.40
HCC-2998	94.66
HCT-116	74.68
HCT-15	96.71
HT29	59.02
KM12	73.86
SW-620	84.50
CNS Cancer	
SF-268	100.91
SF-295	69.75
SF-539	104.10
SNB-19	99.88
SNB-75	84.55
U251	64.98
Melanoma	
LOX IMVI	81.52
MALME-3M	44.14
M14	76.59
MDA-MB-435	88.56
SK-MEL-2	100.92
SK-MEL-28	88.82
SK-MEL-5	61.68
UACC-257	79.20
UACC-62	66.99
Ovarian Cancer	
IGROV1	86.86
OVCAR-3	52.14
OVCAR-4	75.91
OVCAR-5	101.94
OVCAR-8	72.91
NCI/ADR-RES	99.81
SK-OV-3	100.06
Renal Cancer	
786-0	99.53
A498	108.13
ACHN	61.23
CAKI-1	91.90
RXF 393	96.90
SN12C	75.87
TK-10	103.03
UO-31	62.31
Prostate Cancer	
PC-3	40.97
DU-145	104.07
Breast Cancer	
MCF7	78.09
MDA-MB-231/ATCC	102.44
HS 578T	91.24
BT-549	101.13
T-47D	68.06
MDA-MB-468	35.76
Mean	80.08
Delta	59.09
Range	87.14

Mean Growth Percent - Growth Percent





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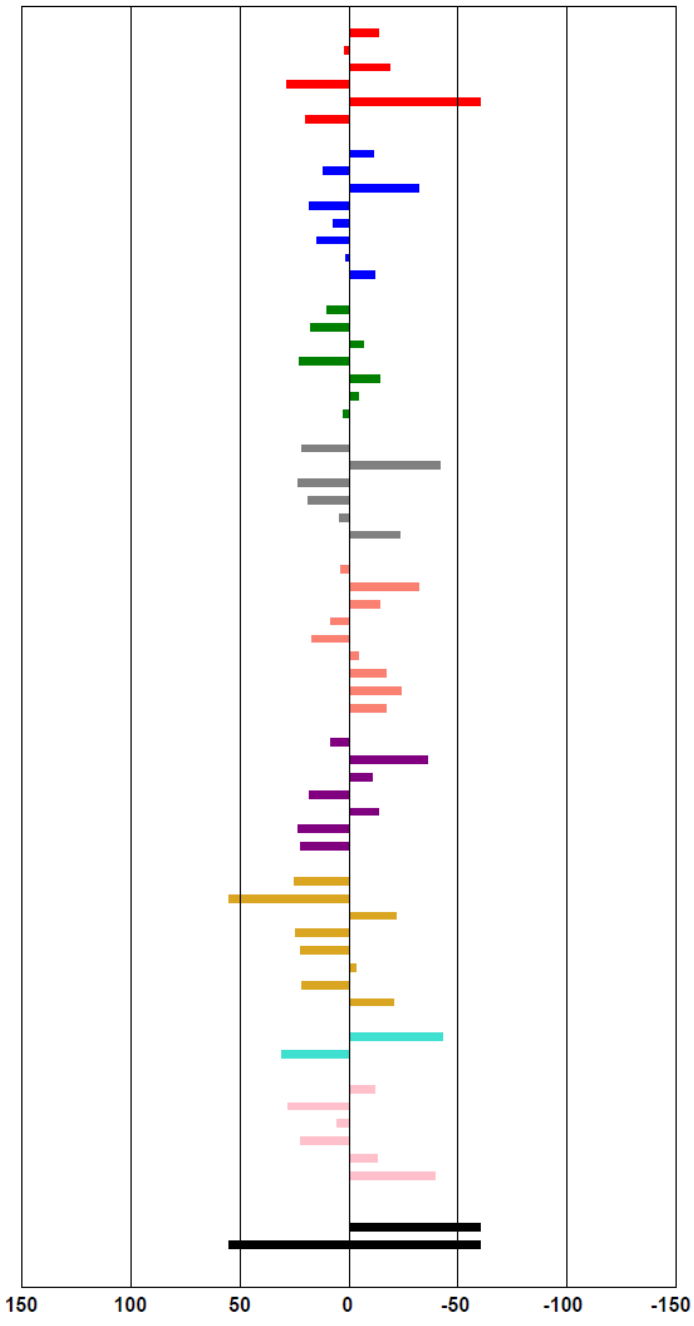
Developmental Therapeutics Program

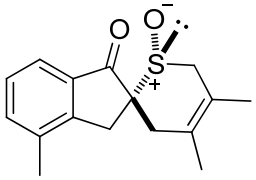
One Dose Mean Graph

NSC: 768111 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	63.89
HL-60(TB)	79.04
K-562	58.17
MOLT-4	105.89
RPMI-8226	16.93
SR	96.75
Non-Small Cell Lung Cancer	
A549/ATCC	65.88
HOP-62	88.85
HOP-92	44.95
NCI-H226	95.45
NCI-H23	84.27
NCI-H322M	92.03
NCI-H460	78.59
NCI-H522	65.14
Colon Cancer	
COLO 205	87.48
HCC-2998	94.65
HCT-116	70.35
HCT-15	100.05
HT29	63.29
KM12	72.60
SW-620	79.74
CNS Cancer	
SF-268	99.02
SF-295	35.20
SF-539	100.56
SNB-19	95.88
SNB-75	81.31
U251	53.60
Melanoma	
LOX IMVI	80.73
MALME-3M	45.41
M14	62.84
MDA-MB-435	85.50
SK-MEL-2	94.09
SK-MEL-28	72.92
SK-MEL-5	60.04
UACC-257	53.21
UACC-62	60.02
Ovarian Cancer	
IGROV1	85.67
OVCAR-3	40.91
OVCAR-4	66.74
OVCAR-5	95.04
OVCAR-8	63.48
NCI/ADR-RES	100.52
SK-OV-3	99.10
Renal Cancer	
786-0	102.01
A498	132.20
ACHN	55.53
CAKI-1	101.75
RXF 393	99.29
SN12C	73.82
TK-10	98.89
UO-31	56.52
Prostate Cancer	
PC-3	34.21
DU-145	107.99
Breast Cancer	
MCF7	65.53
MDA-MB-231/ATCC	104.83
HS 578T	82.47
BT-549	99.13
T-47D	64.40
MDA-MB-468	37.74
Mean	77.15
Delta	60.22
Range	115.27

Mean Growth Percent - Growth Percent





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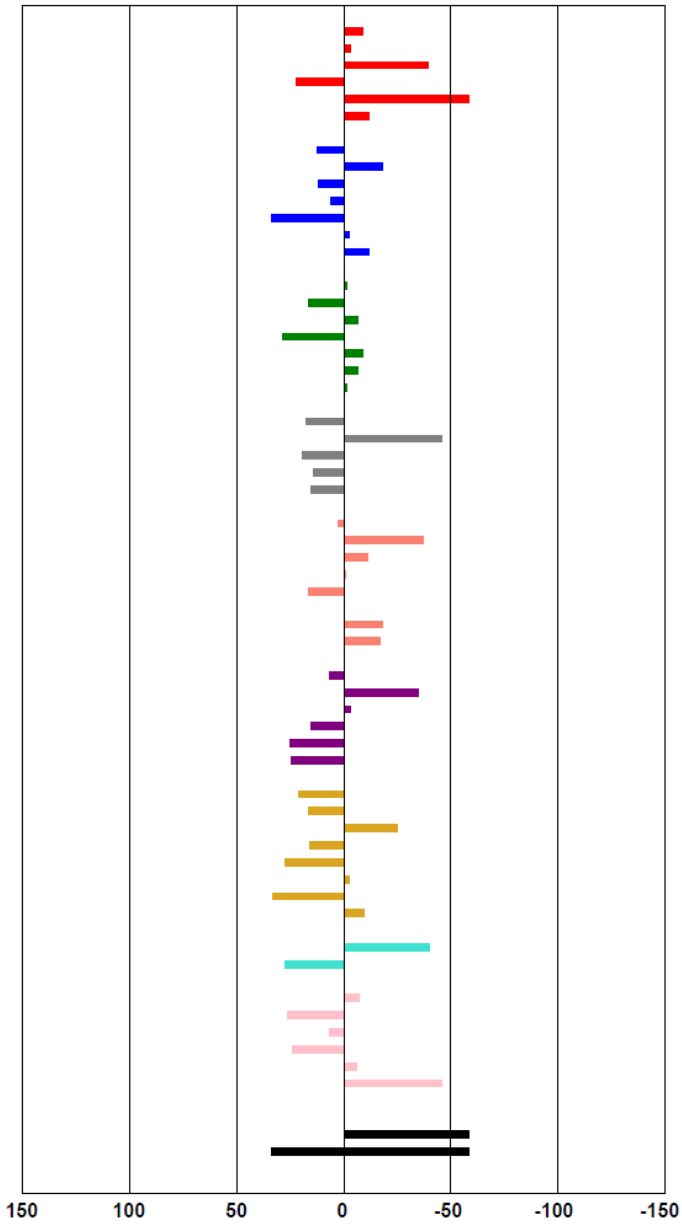
Developmental Therapeutics Program

One Dose Mean Graph

NSC: 768110 / 1	Conc: 1.00E-5 Molar	Test Date: Nov 05, 2012
Experiment ID: 1211OS74		Report Date: Dec 12, 2012

Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	68.30
HL-60(TB)	74.14
K-562	37.73
MOLT-4	99.62
RPMI-8226	18.65
SR	65.59
Non-Small Cell Lung Cancer	
HOP-62	89.42
HOP-92	59.26
NCI-H226	88.99
NCI-H23	83.41
NCI-H322M	110.89
NCI-H460	74.76
NCI-H522	65.72
Colon Cancer	
COLO 205	75.69
HCC-2998	93.79
HCT-116	70.89
HCT-15	105.89
HT29	68.21
KM12	70.87
SW-620	75.99
CNS Cancer	
SF-268	94.92
SF-295	31.42
SF-539	96.69
SNB-19	91.46
SNB-75	92.68
Melanoma	
LOX IMVI	79.63
MALME-3M	40.23
M14	66.17
MDA-MB-435	76.68
SK-MEL-2	93.75
SK-MEL-28	76.76
SK-MEL-5	58.94
UACC-62	60.11
Ovarian Cancer	
IGROV1	83.95
OVCAR-3	42.29
OVCAR-4	74.34
OVCAR-5	92.49
NCI/ADR-RES	102.40
SK-OV-3	101.62
Renal Cancer	
786-0	98.02
A498	93.70
ACHN	52.04
CAKI-1	92.96
RXF 393	104.37
SN12C	74.83
TK-10	110.36
UO-31	67.85
Prostate Cancer	
PC-3	37.24
DU-145	104.53
Breast Cancer	
MCF7	70.37
MDA-MB-231/ATCC	103.31
HS 578T	83.81
BT-549	101.18
T-47D	71.04
MDA-MB-468	31.52
Mean	77.30
Delta	58.65
Range	92.24

Mean Growth Percent - Growth Percent



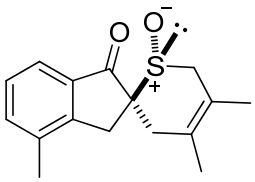


Table of Abbreviations

Å	Angstrom
ABq	AB quartet
Ac	acyl
Ar	aryl
aq.	aqueous
Bn	benzyl
br d	broad doublet
br s	broad singlet
Bu	butyl
$CHCl_3$	chloroform
$CDCl_3$	deuterated-chloroform
CH_2Cl_2	dichloromethane
^{o}	degrees
d	doublet
dd	doublet of doublets
de	diastereomeric excess
DEPT	distortionless enhancement of polarisation transfer
dq	doublet of quartets
dt	doublet of triplets
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ee	enantiomeric excess
eq	equivalents or equation where appropriate
ESI	electrospray ionisation
ESR	electron spin resonance
Et	ethyl
Ether/Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
g	gram
h	hour
H_2O_2	hydrogen peroxide
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i-	*iso*
IR	infrared
LDA	lithium diisopropyl amine
Lit.	literature
m-	*meta*
m	multiplet
M	moles litre^{-1}
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz

min	minutes
mL	millilitre
mmol	millimole
mol	moles
m.p.	melting point
MW	microwave
p-NBSA	*p*-nitrobenzenesulfonyl azide
NMR	Nuclear Magnetic Resonance
o-	*ortho*
OAc	acetate
p-	*para*
Ph	phenyl
$Rh_2(OAc)_4$	rhodium(II) acetate
$Rh_2(tfa)_4$	rhodium(II) trifluoroacetate
$Rh_2(pfb)_4$	rhodium(II) perfluorobutyrate
$Rh_2(cap)_4$	rhodium(II) caprolactamate
r.t.	room temperature
s	singlet or second where appropriate
SAR	structure activity relationship
t	triplet
t-Bu	*tert*-butyl
td	triplet of doublets
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
Vis	visible
W	Watts