CYCLISATION REACTIONS OF AROMATIC FREE RADICALS GENERATED BY FLASH VACUUM PYROLYSIS

by

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Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

University of Edinburgh

DECLARATION

I declare that this thesis is my own composition, that the work that is described has been carried out by myself, unless otherwise stated, and that it has not been submitted in any previous application for a higher degree.

This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. Hamish McNab, since 1st October, 1989, the date of my admission as a research student.

Signed

Date

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr. Hamish McNab for his encouragement, advice, enthusiasm and patience over the last three years.

I am grateful to Dr. I.H. Sadler and Dr. D. Reed for specialised NMR spectroscopy, Dr. A.J. Blake and Dr R.O. Gould for crystal structure determination and the technical services staff of the Chemistry Department, in particular Mr. J.R.A. Millar and Miss. H. Grant (NMR) and Mr. A. Taylor and Miss. E. Stevenson (mass spectrometry).

I would like to thank British Petroleum p.l.c. for financial support.

LECTURE COURSES

The following lecture courses were attended during the period of research.

Organic Research Seminars and Colloquia, The University of Ediuburgh, Chemistry Department (3 years attendance).

Current Developments in Organic Chemistry - Prof. R. Ramage *et al.* (2 years attendance).

Aspects and applications of NMR Spectroscopy - Dr. I. Sadler, Dr. D. Reed and Dr. J. Parkinson (5 lectures).

Free Radical Chemistry - Dr. I. Gosney (5 lectures).

Pesticide Chemistry - Dr. H. McNab (5 lectures).

Royal Society of Chemistry, Perkin Division, Heterocyclic Group:-
Postgraduate Symposia (3 years attendance).
Lakeland Colloquium, Grasmere, 1991.
Joint Meeting with Società Chimica Italiana, Sciacca, Italy, 1992.

Recent Advances in the Synthesis and Activity of Agrochemicals- Schering Agrochemicals (5 lectures).

Medicinal Chemistry - Merck, Sharpe and Dohme (2 years attendance).

ABSTRACT

The work described in this thesis involves the generation and cyclisation reactions of novel oxygen, nitrogen, carbon and sulphur centred free radicals in the gas phase using Flash Vacuum Pyrolysis. The two main areas of study involved attack on alkene systems which incorporated a carboxylic ester as a free radical leaving group and the first systematic study of intramolecular attack by radicals on the pyrrole ring system.

A new strategy for the synthesis of benzofurans was extended to cases with substituents on the 2-,3-,5- and/or 6-positions. This involved pyrolysis of 2-allyloxycinnamate esters to generate oxygen centred radicals which cyclise with loss of carbon dioxide and an alkyl radical. Small amounts of substituted coumarin by-products were identified in some cases and their formation rationalised mechanistically.

This work was extended in four ways. Firstly the use of 2-*t*-butylthiocinnamate ester, which generates a sulphur centred radical on pyrolysis, leads to benzothiophene in adequate yield. Secondly when the base benzene ring was replaced by thiophene the preparation of the unusual thieno[3,2-*b*]furan ring system was achieved. The attempted extension to seven membered ring formation by pyrolysis of 2-substituted-aryl pyrroleacrylates gave instead six membered ring products. Finally the attempted synthesis of pyrrolizine by cyclisation of *N*-pyrrolylmethyl radicals failed to give any products, although the precursors were successfully prepared.

The intramolecular attack of phenoxyl, aminyl, benzyl and thiophenoxyl radicals on ortho disposed pyrrole rings was studied systematically. In the case of the unsubstituted pyrrole ring phenoxyl and

aminyl radicals did not cyclise: products showed that 1,5-aryl shifts were taking place following hydrogen atom capture. Benzyl and thiophenoxyl radicals both led to good syntheses of fused tricyclic systems and an investigation of the chemistry of the little known pyrrolo[2,1-*b*] benzothiophene system was undertaken. 2,5-Dimethyl substituents on the pyrrole ring led to a variety of products in all cases studied (phenoxyl, benzyl and thiophenoxyl). These arose either by direct attack on the pyrrole ring or by an interesting radical transfer, cyclisation sequence from the methyl group. Finally, the radical transfer, cyclisation sequence was again observed when a phenoxyl radical reacted with 2,5-diphenyl substituents on the pyrrole ring. The corresponding thiophenoxyl radical gave a number of products which were separated and identified using a variety NMR techniques, one of which was a dibenzopyrrolothiazepine, the first example of seven membered ring formation by this method.

CONTENTS

INTRODUCTION

A. PREAMBLE

This thesis concerns gas-phase radical cyclisation reactions in which the radical either attacks a heteroaromatic (normally pyrrole) ring, or forms a heterocycle.

The synthetic use of radicals in solution or in the gas phase has increased dramatically over the last decade. Recent progress in radical chemistry has been thoroughly reviewed from the stand-point of structure, reactivity and synthetic methods.[1-7]

This introduction will attempt to provide an overview of three areas that are relevant to this thesis. The first section will cover the generation of free radicals, in solution and in the gas phase, but only where applicable to radical cyclisation reactions. There have however been comparatively few reaction methods in which a radical cyclises onto a heteroaromatic ring. The second section will examine such reactions in detail. Finally, the third section will consider the reaction of free radicals with the pyrrole nucleus. [8,9]

B. FREE RADICAL GENERATION

Although there a large number of radical generation methods, only a very few are used, in practice, for cyclisation reactions. Solution phase methods will be considered first and then gas phase methods.

B.1. Free Radical Generation in Solution Phase

B.1.a. Tin hydride methodology

Tributyltin hydride **1** [6] is the reagent that is used most frequently to conduct free-radical cyclisation reactions. An organic halide **3** (normally a bromide or an iodide) is reduced by means of a controlled chain reaction. (Scheme 1).

Initiation

$$Me_2(CN)C-N=N-C(CN)Me_2 \xrightarrow[\text{or } h\nu]{\Delta} Me_2(CN)C\cdot + N_2$$

AIBN

$$Bu_3SnH \xrightarrow{Me_2(CN)C\cdot} Bu_3Sn\cdot$$

1 **2**

Bu_3SnH = tributyltin hydride

Propagation

$$Bu_3Sn\cdot + R\text{-}X \longrightarrow R\cdot + Bu_3SnX$$

2 **3** **4**

X = Br or I

$$R\cdot + Bu_3SnH \longrightarrow Bu_3Sn\cdot + R\text{-}H$$

5

Scheme 1

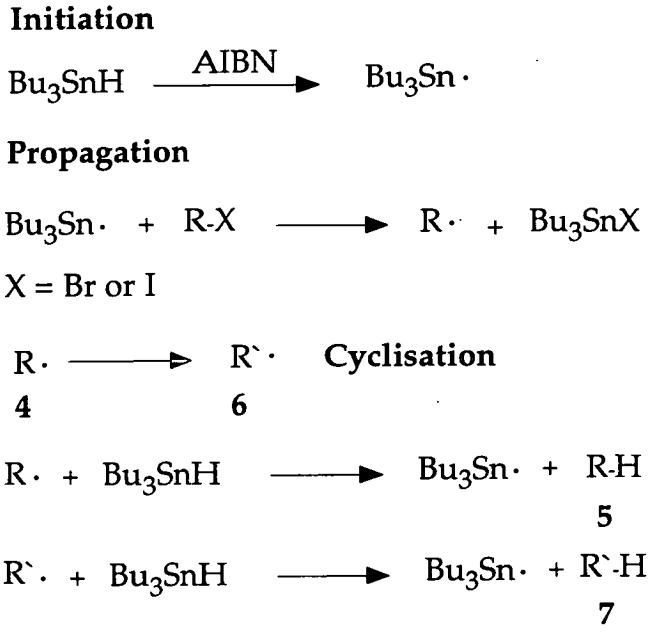
Reaction is initiated by thermal or photochemical decomposition of azoisobutyronitrile. The resulting radicals extract a hydrogen atom from the hydride **1** to give the tributyltin radical **2**. Extraction of an atom or group X from an organic substrate **3** by a tributyltin radical **2** generates a site specific radical **4**. Tin hydride then reduces the radical R· to generate the product **5** and to regenerate Bu_3Sn·. The exchange of an R-X bond for the strong R-H bond, and the exchange of a Sn-H bond for a relatively strong Sn-X bond provides the driving force for the overall reaction. Vinyl and aryl radicals are most susceptible to reaction with Bu_3SnH; benzyl and allyl are least susceptible. Very little difference is observed in the reactivity of primary, secondary and tertiary alkyl radicals towards tin hydride. No hard evidence exists to support the assumption that carbonyl- or heteroatom-substituted radicals react with tin hydride at similar rates to alkyl radicals.

To be useful in cyclisation reactions a radical **4** must undergo addition, normally to multiple bonds, faster than hydrogen atom abstractions (Scheme 2).

This generates a new radical **6**. If intramolecular radical addition by R· is faster than hydrogen abstraction then the initial radical **4** is indirectly converted to R`H **7** via R`· **6**. If radical addition (or cyclisation) is competitive with hydrogen atom abstraction from R· mixtures of RH **5** and R`H **7** result.

A limitation of this method is that tin hydride is by nature a reducing agent. Under normal conditions both a C-X functional group and a carbon-carbon π bond are sacrificed. Complete removal of tin containing by-products from desired products is frequently a problem, and several available solutions are discussed in reviews.[6] A potentially useful substitute for tin hydride is tris(trimethylsilyl)silicon hydride [Chatgilialoglu's

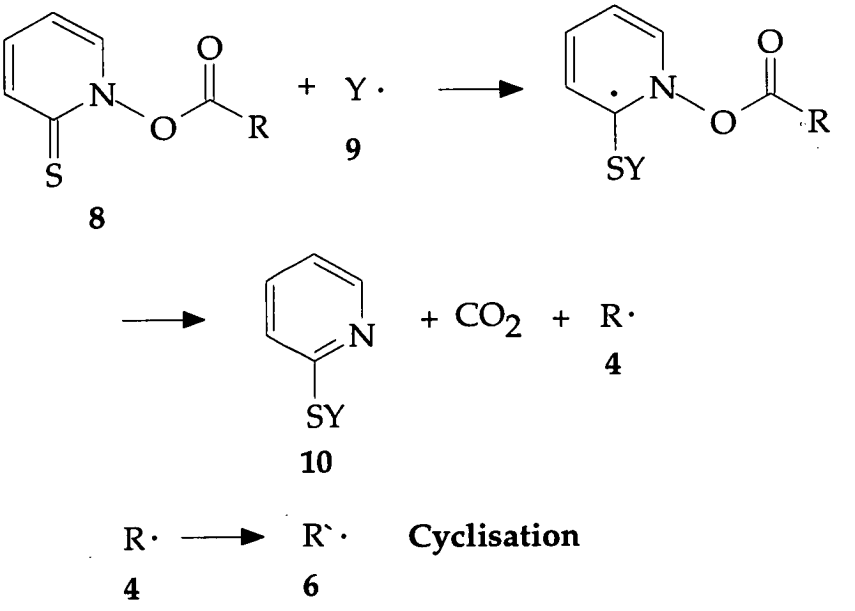
reagent].[10]



Scheme 2

B.1.b. Thiohydroxamate ester method

This method was developed by Barton.[11] A possible propagation sequence (Scheme 3)[12] involves addition of an alkyl radical Y· **9** generated by an initiator, to the thiohydroxamate ester **8**, which then fragments to produce the thioether **10**, CO_2, and a radical **4**. This may then cyclise to produce R`· **6**. This then reacts with Y-H to regenerate Y· **9**.



Scheme 3

B.2. Free Radical Generation in the Gas Phase

Free radicals generated in dilute gas phase conditions[13] have the advantage that they are obtained without an excess of substrate, product or solvent molecules. Hence intramolecular reactions are highly favoured. Experimentally, this is carried out by distillation or sublimation of a suitably designed precursor through a furnace under very low pressure, (Typically 650-750 ^{o}C and 10^{-2} Torr) so that individual molecules experience only a short time (10-100 ms) in the hot zone. This allows most functional groups to survive unchanged. These conditions are described as Flash Vacuum Pyrolysis. (F.V.P.).[14] (See Experimental Section Page 173 for a diagram of apparatus).

There are two types of processes that are of interest in free radical generation.

1. Homolysis of the weakest single bond. (e.g. ethers, thioethers).[15]
2. Homolytic cleavage of small molecules. (e.g. CO_2 from oxalate esters).[16]

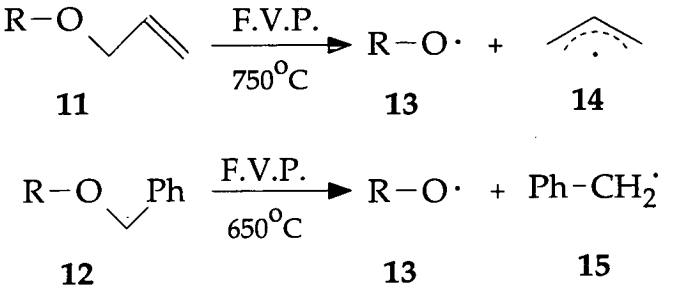
B.2.a. Oxygen and Sulphur centred radicals

These radicals are normally generated by single bond homolysis using similar starting materials.

Oxygen centred radicals[17] **13** are obtained by the homolysis of specifically designed weak bond of an allyl ether **11** or benzyl ether **12** (Scheme 4).

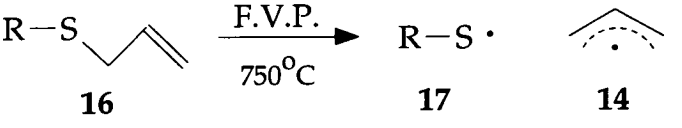
Each has its own advantages. From the allyl ether **11**, the allyl radical

14 produces low molecular weight by-products that are usually lost during work up; however allyl ethers may be subject to thermal Claisen rearrangement before volatilisation. Benzyl ethers **12** may be used where either H atom abstraction or Claisen rearrangement presents a problem; however the co-formed benzyl radical **15** can dimerise and contaminate the desired product with bibenzyl.



Scheme 4

Sulphur centred radicals[18] **17** are generally formed from thioethers **16** (Scheme 5). Again work-up is simplified as the co-formed allyl radical **14** gives essentially no by-products.

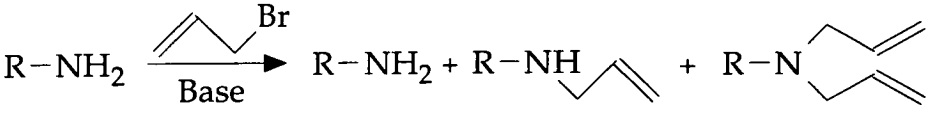


Scheme 5

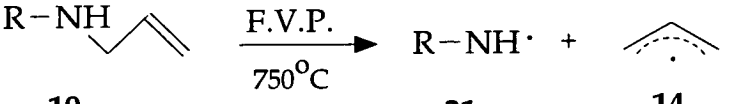
B.2.b. Nitrogen centred radicals

Generation of nitrogen centred radicals[19] **21** by cleavage of an allyl radical **14** presents slightly more difficulty in the preparation of the precursor (Scheme 6). This is because alkylation normally gives a mixture of unreacted starting amine **18** and dialkylated amine **20** along with the

desired product **19**. These must then be separated by chromatography. Otherwise pyrolysis takes place in the same way as for oxygen and sulphur centred radicals.



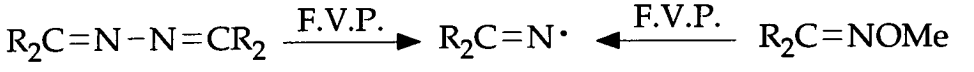
18 **18** **19** **20**



19 **21** **14**

Scheme 6

Iminyl radicals **23** may be generated from azines **22** or from oxime derivatives (Scheme 7). Azines **22** give rise to few by-products and are the precursors of choice for low molecular weight iminyl radicals. For larger molecules, oxime ethers[20] **24** are more volatile and alkoxy radicals give no problem by-products.



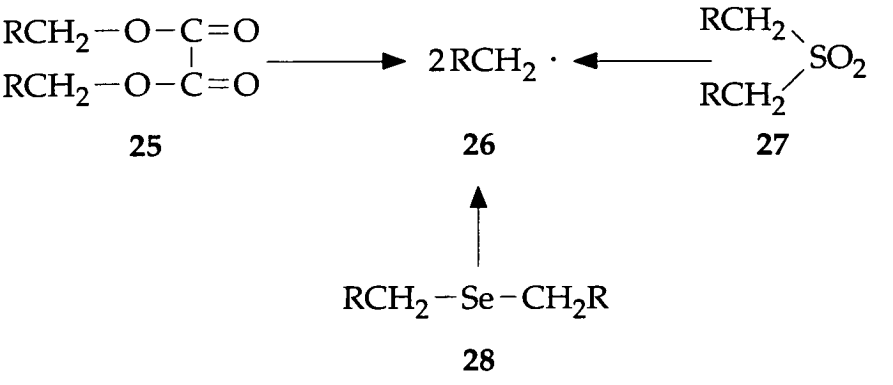
22 **23** **24**

Scheme 7

B.2.c. Carbon centred radicals

Alkyl radicals **26** are most conveniently obtained from oxalate esters[17] **25** or alternatively sulphones **27** and selenides **28** (Scheme 8). Oxalates **25** are easier to obtain, but there may be volatility problems if R is large or contains

polar groups. The CO_2 that is expelled again presents no by-product problems.



25 **26** **27**

28

Scheme 8

C. RING FORMATION

Almost all that is known about radical ring formation is the result of studies in tributyltin hydride chemistry. Extensive physical studies, have given an understanding of the absolute rates, and the structural factors that affect the rates and stereochemistry of simple radical cyclisations.[21] Rational planning of such free radical reactions has come from a knowledge of the rates with which a radical R· is generated, cyclises to R`· and is trapped by tin hydride. Tin hydride must react with R`· fast enough to maintain effective chain reaction, but at the same time it must not trap R· before cyclisation. The method can be used to form a variety of ring sizes. The factors that influence these processes have been summarised by Beckwith.[22] In general radical cyclisation are most often applied to the construction of 5-membered rings. There are three good reasons for this.

1. **Cyclisations are usually faster for the formation of 5-membered rings than any other ring size.**

   The simple 5-hexenyl radical cyclises 20 times faster than does the 6-heptenyl radical.[21] Five membered ring forming reactions are thus least subject to competitive formation of reduced, uncyclised by-products.

2. **The regioselectivity for 5-exo cyclisations is often outstanding.**[21]

   For the parent 5-hexenyl radical, 5-exo cyclisation is 50 times faster than 6-endo cyclisation. Substituted examples often show higher selectivities.

3. **Radical cyclisations giving 5-membered rings can be highly**

stereoselective.[21,23]

The major product in a 5-exo radical cyclisation can generally be predicted by using the Beckwith transition state model.[23] According to this model, the early transition state of a 5-exo radical cyclisation resembles a cyclohexane ring, prefers the chair over the boat form and prefers substituents to be pseudo-equatorial rather than pseudoaxial.[21,23] Simple model studies show that substitution at C-1 or C-3 of the 5-hexenyl radical gives primarily cis-disubstituted products, whereas substitution at C-2 or C-4 gives primarily trans-disubstituted cyclopentanes. Stereoselectivity is highest for C-1 and C-4 substituted systems. A body of theoretical treatments[21] and experimental results now aid in the planning of highly stereoselective reactions, and allow exceptions to be anticipated.

D. RADICAL CYCLISATION REACTIONS

D.1. Formation of 5-Membered Rings

D.1.a. Attack on 5-membered rings

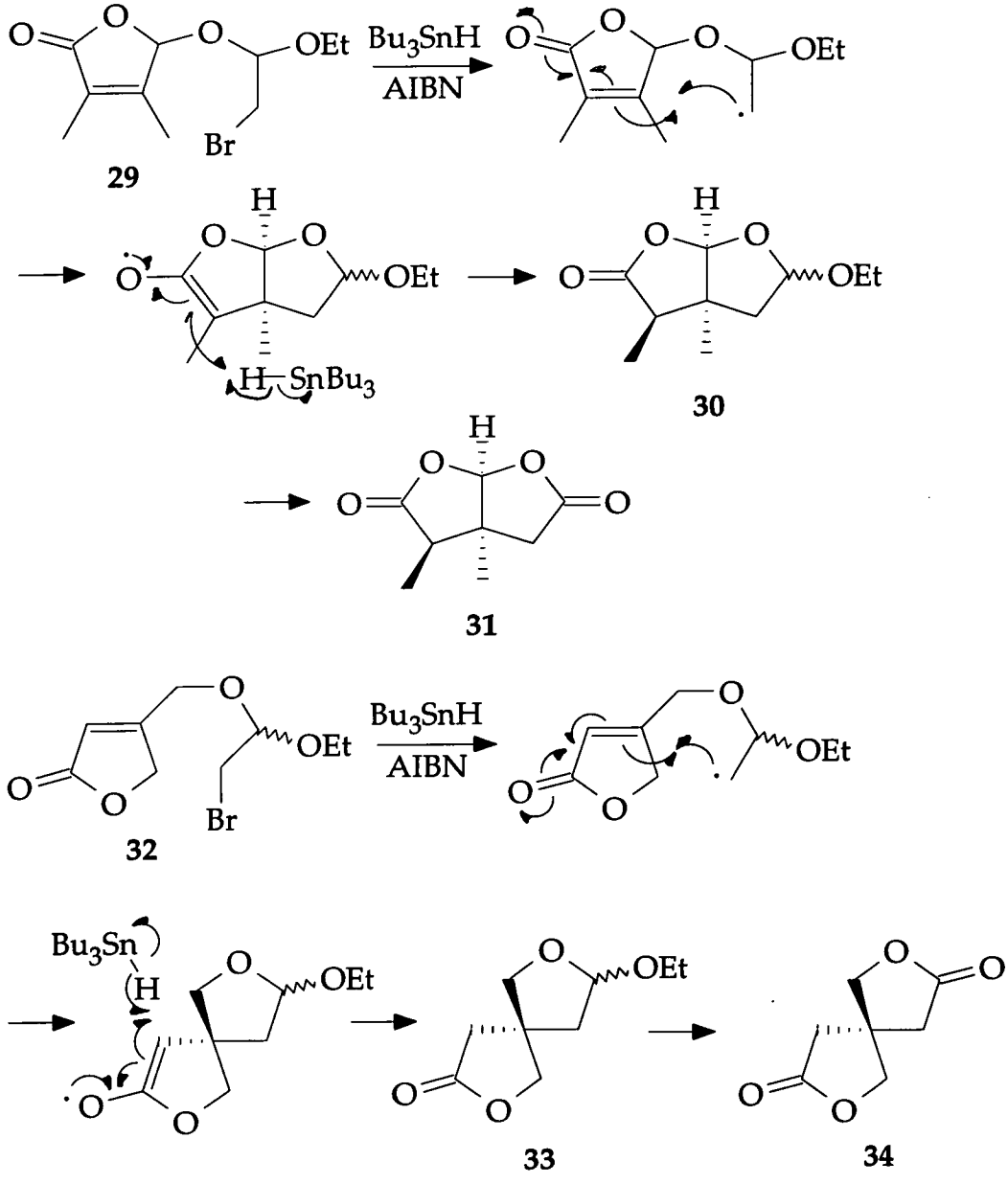
Within this section, a five membered ring, either carbocyclic or heterocyclic, is formed by radical cyclisation onto a 5-membered heterocyclic ring. There are examples of the newly formed ring containing only carbon atoms or one oxygen or one nitrogen atom, but no example where the ring formed contains a sulphur atom. The ring attacked may contain either oxygen or nitrogen but again no sulphur containing examples could be found. Both alkyl and aryl radicals have been employed.

Most work in this area appears to have been directed towards the use of radical cyclisations in natural product synthesis, rather than model studies on basic ring systems.

Intramolecular cyclisations involving alkyl radical centres, and the 2(5*H*)-furanones or related compounds were used by Pattenden and co-workers[24] in a facile synthesis of spiro and linear fused γ-lactone ring system related to the "ginkgolides" (Scheme 9). The methodology allows a facile synthesis of the ring fused lactones **31** and **34** from easily available precursors.

The synthesis of the unusual fused acetal bis-lactone **31** was achieved by controlled reduction of readily available 2,3-dimethylmaleic anhydride, to 4-hydroxy-2-butenolide which was treated with 1,2-dibromoethyl ether to give a 1:1 mixture of diastereomers of the bromoacetal **29**. Treatment of **29** with tributyltin hydride and a catalytic amount of AIBN in refluxing

benzene afforded a mixture of diastereomers of the linear fused lactone **30** (80%) resulting from 5-*exo* trigonal cyclisation. Finally oxidation of **30** led to the acetal bis-lactone **31**.

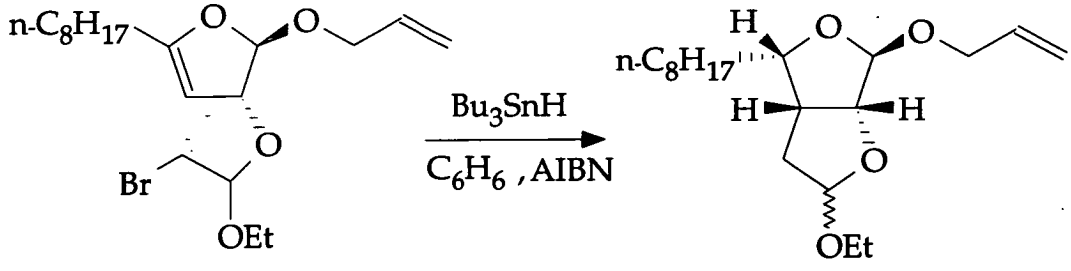


Scheme 9

The spiro fused bis-lactone **34** was synthesized by 5-*exo* trigonal radical cyclisation onto the 2(5*H*)-furanone double bond in the intermediate **32** in

88% yield. None of the alternative 6-*endo* trigonal cyclisation product was observed. Intermediate **32** was itself synthesised by treatment of 3-hydroxymethyl 2-butenolide with bromine in ethyl vinyl ether in the presence of triethylamine. Conversion of the spiro system **33** to the bis lactone **34** was accomplished by Jones oxidation.

As part of a total synthesis of (-)-Isovenaciolide, Dugger and McDonald[25] employed the radical cyclisation of the related bromoacetal **35** to give the bicycle **36** (Scheme 10). Radical cyclisation was accomplished by the tin hydride method; the overall yield for this and the previous formation of the bromoacetal was 76%. As with the formation of **31** (Scheme 9) the octyl side chain was exclusively endo; this would be predicted from approach of the bulky Bu_3SnH from the least sterically hindered face of the intermediate radical in the final H atom transfer step.

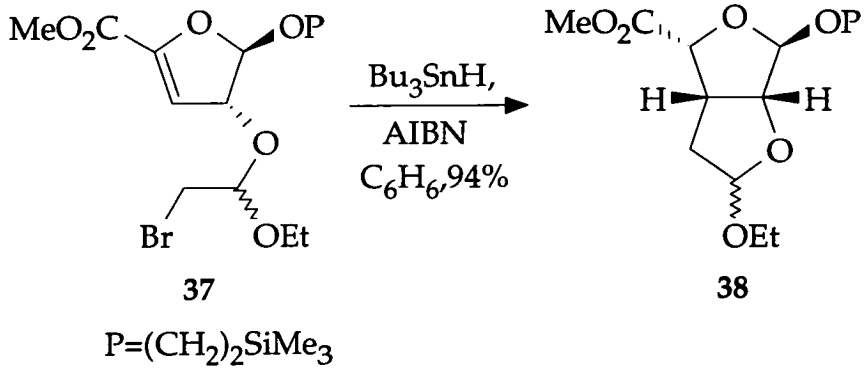


35 **36**

Scheme 10

Parallel to this work, Wee[26] also employed radical cyclisation of a bromoacetal **37** to form a bisacetal **38** (Scheme 11) as part of a total synthesis of the mould metabolites (-)-Isovenaciolide and (-)-Ethisolide. This cyclisation was again mediated by tributyltin hydride and gave a high yield of the bicyclic esters **38** as a mix of diastereomers. The increase in yield may be attributed to the presence of an electron-withdrawing group at the 2-position of the dihydrofuran, as the stereochemical consequences are

otherwise similar to Scheme 10.



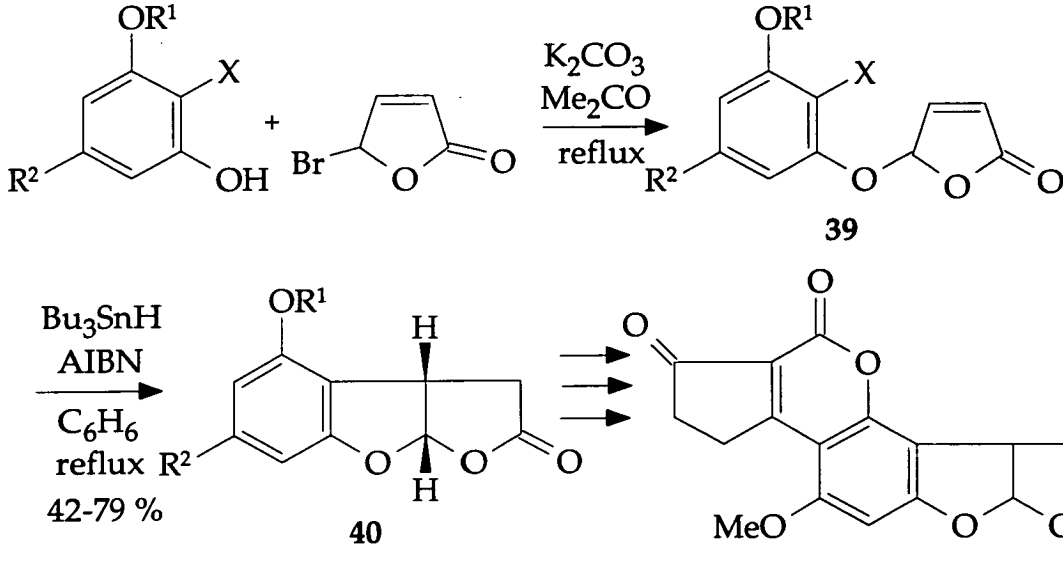
37

P=$(CH_2)_2SiMe_3$

38

Scheme 11

Moving from cyclisation of alkyl radicals to the cyclisation of aryl radicals, Snieckus *et al* [27] employed the radical cyclisation of butenolide ethers **39** in the synthesis of furobenzofurans **40** as an early step in the synthesis of Aflatoxin B_1 **41** and Aflatoxin B_2 **42** (Scheme 12).



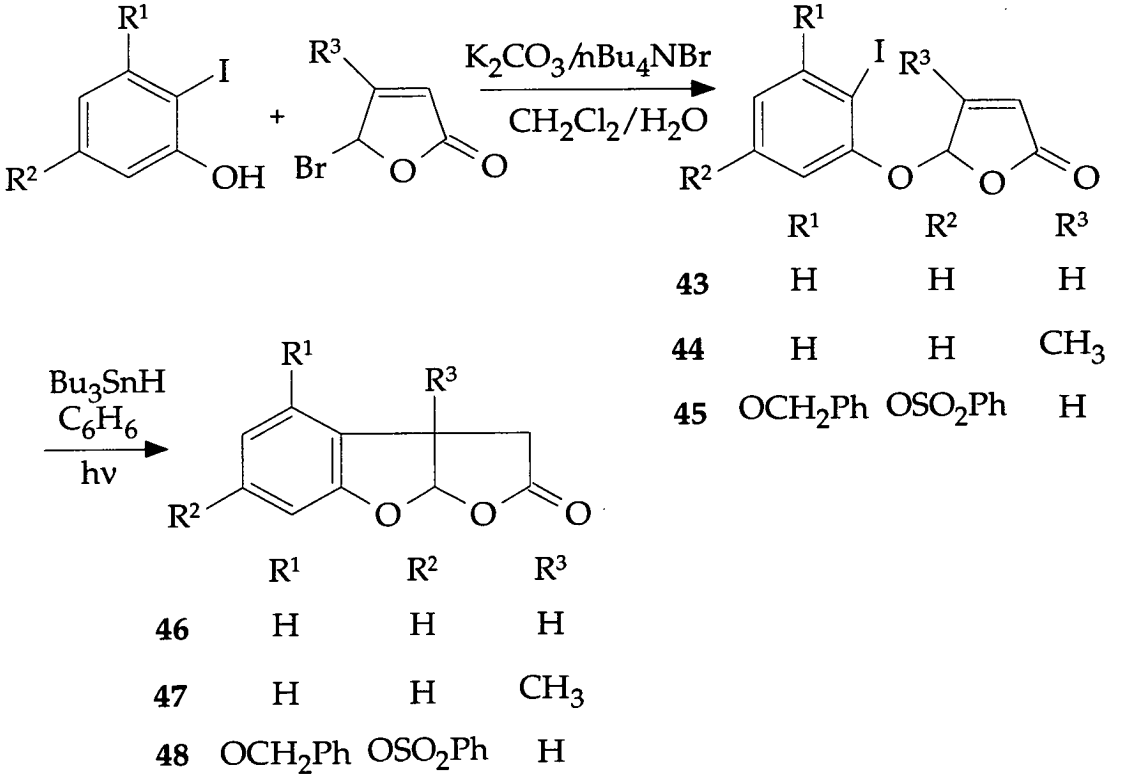
41 AFLATOXIN B_1

42 AFLATOXIN B_2 (2,3-dihydro)

Scheme 12

This may be regarded as an aryl radical equivalent of Scheme 9. The butenolide ether **39** was prepared by condensation of the appropriate iodomethoxyphenol with bromobutenolide. This was then treated with tributyltin hydride which induced ring closure and furnished the benzodifuran **40**, which could then be further elaborated to Aflatoxins by known routes.

Work on the synthesis of Aflatoxins by radical ring closure was also carried out by Hoffmann and Wolff.[28] They used basically the same chemistry as Snieckus, including tributyltin hydride mediated cyclisation, however the radical chain reaction was photochemically induced in some cases.(Scheme 13).



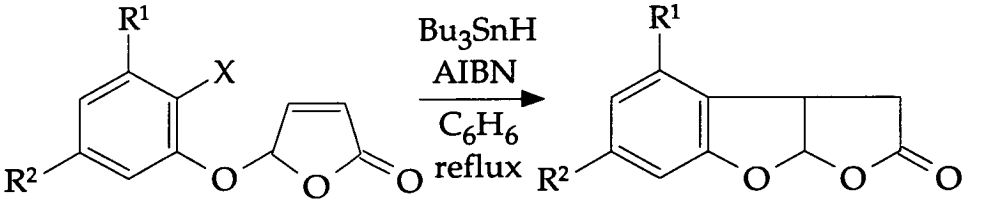
	R^1	R^2	R^3
43	H	H	H
44	H	H	CH_3
45	OCH_2Ph	OSO_2Ph	H

	R^1	R^2	R^3
46	H	H	H
47	H	H	CH_3
48	OCH_2Ph	OSO_2Ph	H

Scheme 13

Precursors **43-45** were prepared by coupling of the appropriately

functionalised *o*-iodophenol with a bromobutenolide. For the model compound **43**, photochemical activation achieved an 86% yield of the furobenzofuran **46**. When the butenolide contained a methyl group **44**, the yield of the desired cyclised product **47** dropped to 56%; with a tin containing by-product isolated in 13% yield. When photochemical initiation of the natural product precursor **45** was attempted, none of the desired product **48** was obtained. Even with slow addition of Bu_3SnH a mixture of tin containing compounds and the desired product **48** was obtained in 28% yield, but could not be separated. In a later paper,[29] Hoffmann is critical of the work of Snieckus[27] as follows: "Whereas the simple model **49**, was reported to cyclise to **52** in 42% yield the more **highly** oxygenated **50** and **51**, was reported to cyclise to **53** and **54** in 79% and 74% yield respectively" (Scheme 14).



43,45,49-51 **46,48,52-54**

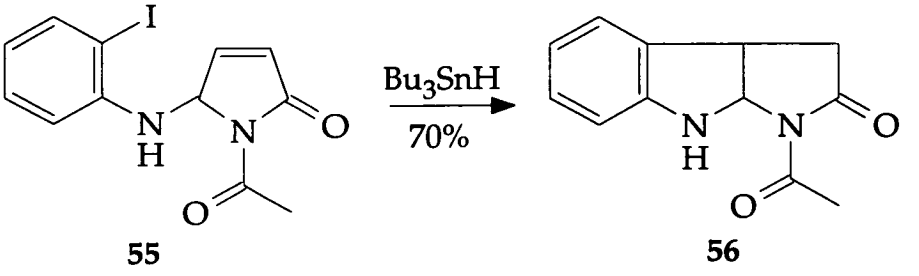
	R^1	R^2	X		% Yield
49	OMe	H	I	**52**	42
50	$MeOCH_2O$	H	I	**53**	79
51	$MeOCH_2O$	MeO	Br	**54**	74
43	H	H	I	**46**	86
45	OCH_2Ph	OSO_2Ph	I	**48**	28

Scheme 14

However in his own experiments[29] Hoffmann has found that the more oxygen substituents present on the aromatic ring, (cf. **43** vs. **45**) the more difficult the radical cyclisation becomes. It is thought that the oxophilicity of

tin may interfere. Hoffmann then adds "Bromophenol ethers are always more difficult to cyclise than the corresponding iodophenols". Hence "In the absence of further experimental detail the reports by Snieckus *et al*, should be regarded with reserve".

Hoffmann[29] then goes on to describe formation of other benzoannulated heterodiquinanes. (Scheme 15). The precursor aminal **55** was prepared by coupling of *o*-iodoaniline with an acetyl protected 5-bromo-4-methylpyrrolin-2-one.



55 **56**

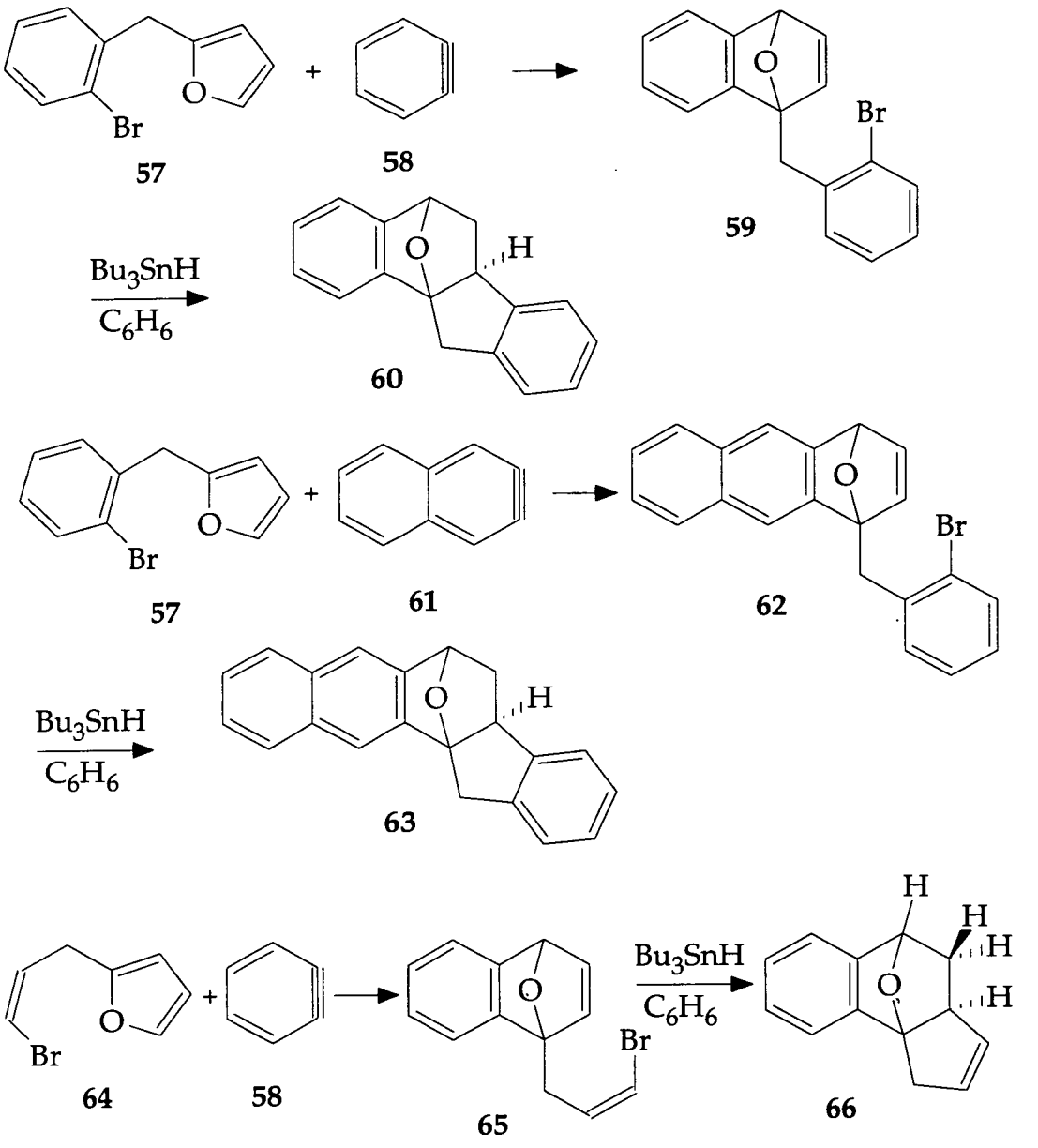
Scheme 15

The aminal **55** was then cyclised to the desired tricycle **56** with tributyltin hydride in 70% yield. Hence the presence of nitrogen atoms does not affect the efficiency of cyclisation.

Ghosh and Hart[30] employed tandem cycloaddition/ radical cyclisation in the assembly of a wide variety of ring systems. (Scheme 16 and later schemes covering other ring sizes). The idea is simple. One of the cycloaddition partners carries an appropriately located radical generation site. In the cycloaddition step a new double bond is formed, then the radical is generated and cyclises onto the new double bond forming another new ring.

Reaction between furan **57** and benzyne **58** or napthyne **61** gave the cycloadducts **59** and **62** respectively. These were then cyclised using tin

hydride methodology (67-80% yield) to give single cyclised products **60** and **63** respectively.



Scheme 16

The ^1H NMR showed these to be a single stereoisomer but did not allow unambiguous assignment of the stereochemistry. This was done by a X-ray crystal structure of **63**. Stereochemistry of **60** was assigned by analogy.

This showed that radical cyclisation occurred with exclusively *exo* stereochemistry. The vinyl analogue **64** was also prepared and reacted with benzyne **58** to give cycloadduct **65**, which was then cyclised by tin methodology to give the bridged tricycle **66**. By analogy with the ^{1}H NMR spectra of **60** and **63** the methine proton of **66** is placed *endo*.

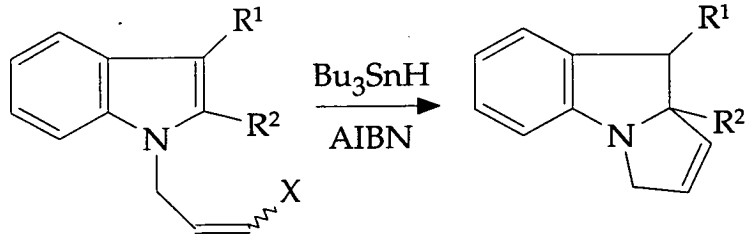
Finally we move to the formation of rings by attack on five membered rings containing nitrogen atoms. This example involves the only example of attack on fully aromatic heterocyclic systems. This cyclisation forms part of a new route to 9,9a-dihydro-3*H*-pyrrolo[1,2-a]indoles by Ziegler and Jeronic.[31] The products were of interest as a substructure of the mitomycin antibiotics, and the method was based on the cyclisation of terminal vinyl radicals onto the heterocyclic ring of an indole.

The simple derivative **67** was treated with Bu_3SnH and AIBN by slow addition to give the desired dihydropyrroloindole **75** in 48-56% yield (Scheme 17) along with the uncyclised direct reduction product *N*-allylindole (20-25%). Other reducing agents, e.g. Ph_3SnH, Bu_3GeH and $(Me_3Si)_3SiH$ were also attempted, but these were found to be less efficient. When the iodide **68** was cyclised under optimum conditions, the yield of **75** was improved to 65%.

The effect of substitution at the site of radical attack, the indole 2-position, was examined by cyclising ester **69**. The desired product **76** was obtained in 61% yield along with 17% of the uncyclised reduction product. Hence, increasing the steric hindrance at the site of attack has little effect on the course of reaction.

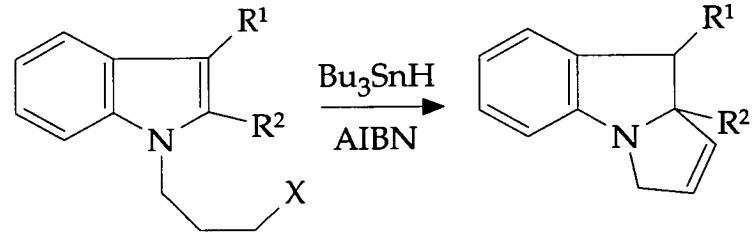
Substitution at the indole 3-position was examined by cyclising the esters **70-72**. All gave the desired products **77-78** in moderate yield (31-55%) as 1:1 mixtures of diastereomers along with some reduction products. When

the indole starting material was 2,3-disubstituted **73** a 2:1 mixture of diastereomers **79** was produced along with a product formed by cyclisation then loss of the 2-position ester group (12%) and the uncyclised reduction product (16%). Finally a radical was generated at an sp^3 centre **74** as opposed to an sp^2 centre previously. This cyclised in 50% yield to give product **80**, but this also gave significant amounts of reduction products.



67-73 **75-79**

	R^1	R^2	X		% Yield
67	H	H	Br	**75**	48-58
68	H	H	I	**75**	65
69	H	CO_2Me	Br	**76**	61
70	CH_2CO_2Me	H	Br	**77**	55
71	CO_2Me	H	Br	**78**	33-42
72	CO_2Me	H	I	**78**	31
73	CO_2Me	CO_2Me	Br	**79**	32(exo) 16(endo)

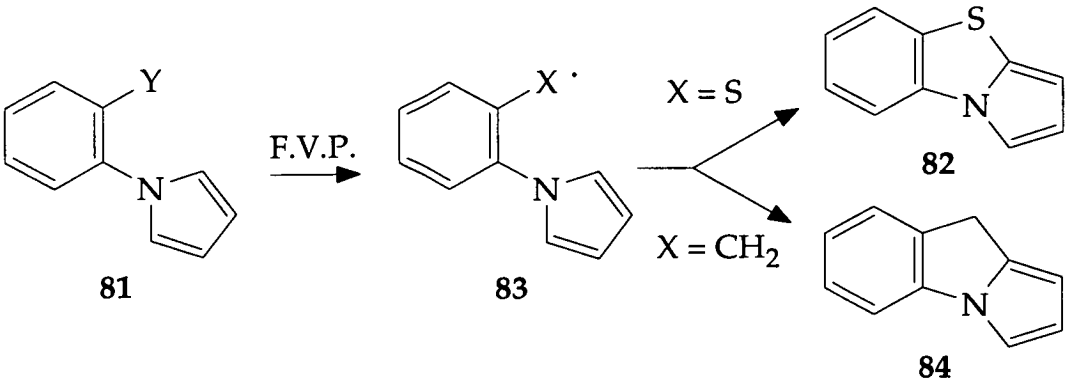


	R^1	R^2	X		% Yield
74	H	H	Br	**80**	50

Scheme 17

Flash Vacuum Pyrolysis has also given very efficient routes to pyrrolo[2,1-*b*]benzothiazole **82** and 9*H*-pyrrolo[1,2-*a*]indole **84** from a radical

81 produced by a specially designed precursor 83 (Scheme 18). These will be discussed later in this thesis.



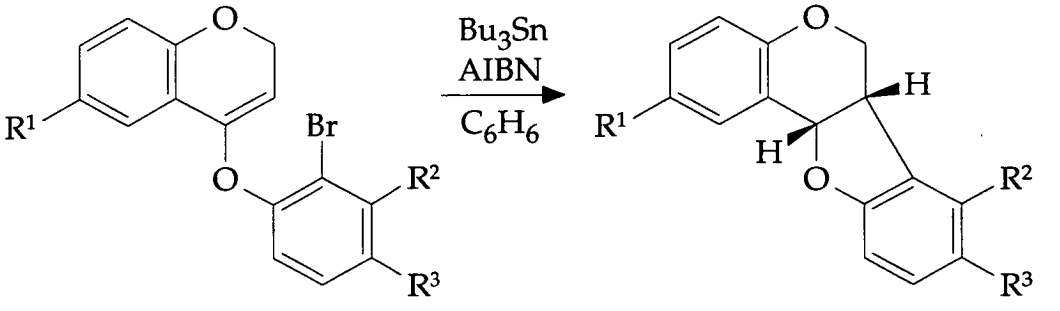
81 83 82 84

Scheme 18

D.1.b. Attack on 6-membered rings

The variety of rings formed, includes those with only carbon atoms, or those with oxygen, nitrogen and sulphur atoms. Rings attacked include one oxygen containing example, while the others are exclusively nitrogen containing.

As part of a synthesis of Pterocarpans, Balasubramanian and Gopalsamy,[32] employed the tributyltin hydride mediated cyclisation of 4-(*o*-bromophenoxy)-2*H*-1-benzopyrans **85-87** (Scheme 19).



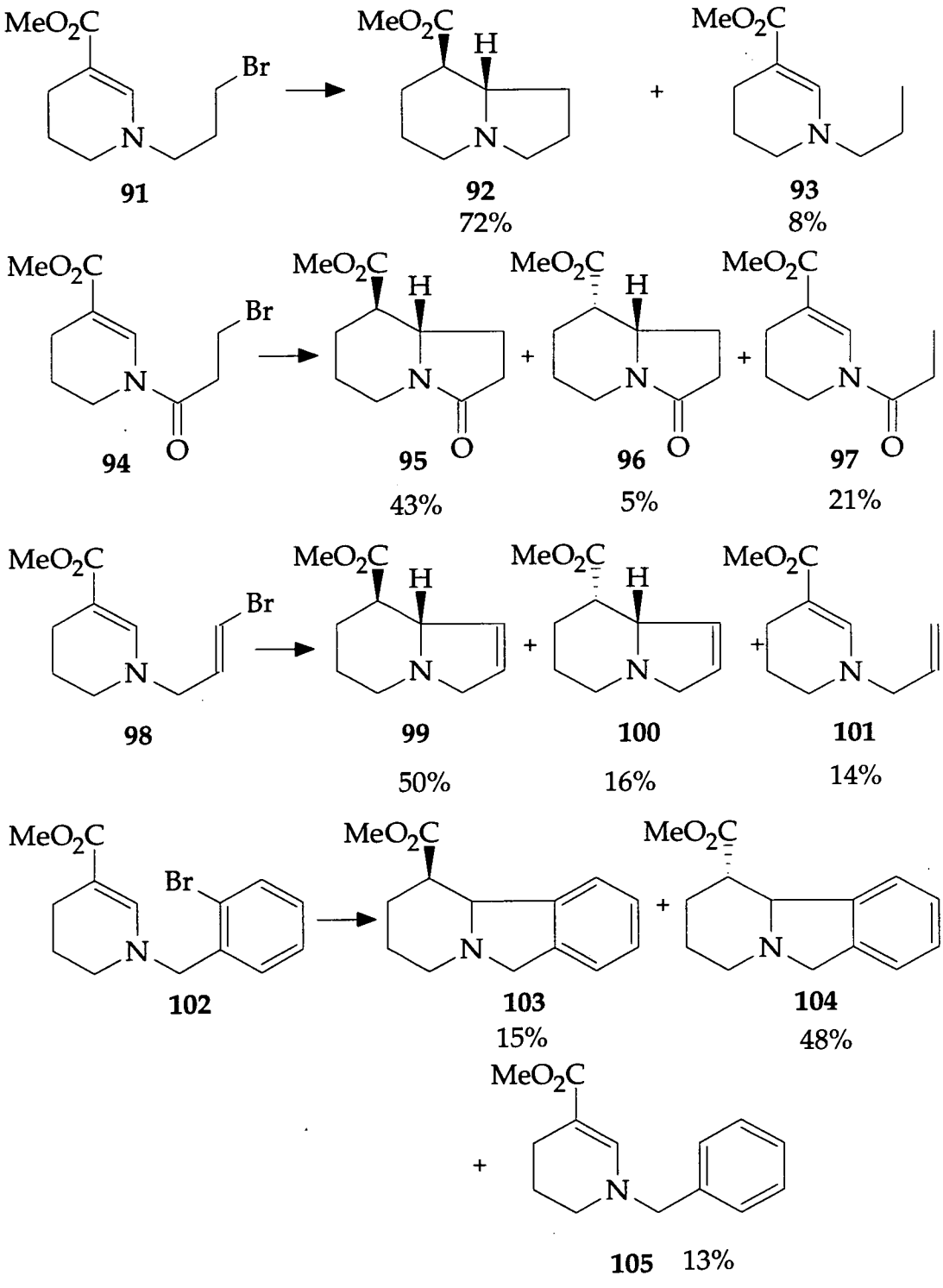
85-87 **88-90**

	R^1	R^2	R^3		% Yield
85	H	H	H	**88**	82
86	OMe	—CH=CH–CH=CH—		**89**	90
87	Cl	—CH=CH–CH=CH—		**90**	88

Scheme 19

The cyclisation proceeded smoothly in all cases to give the products **88-90** exclusively. None of the *trans* isomers and no reduction products were found.

Intramolecular cyclisation of 4-aza-6-methoxycarbonyl-5-hexenyl radicals (Scheme 20) in the work by Beckwith and Westwood[33] resulted in the formation of bicyclic amines.

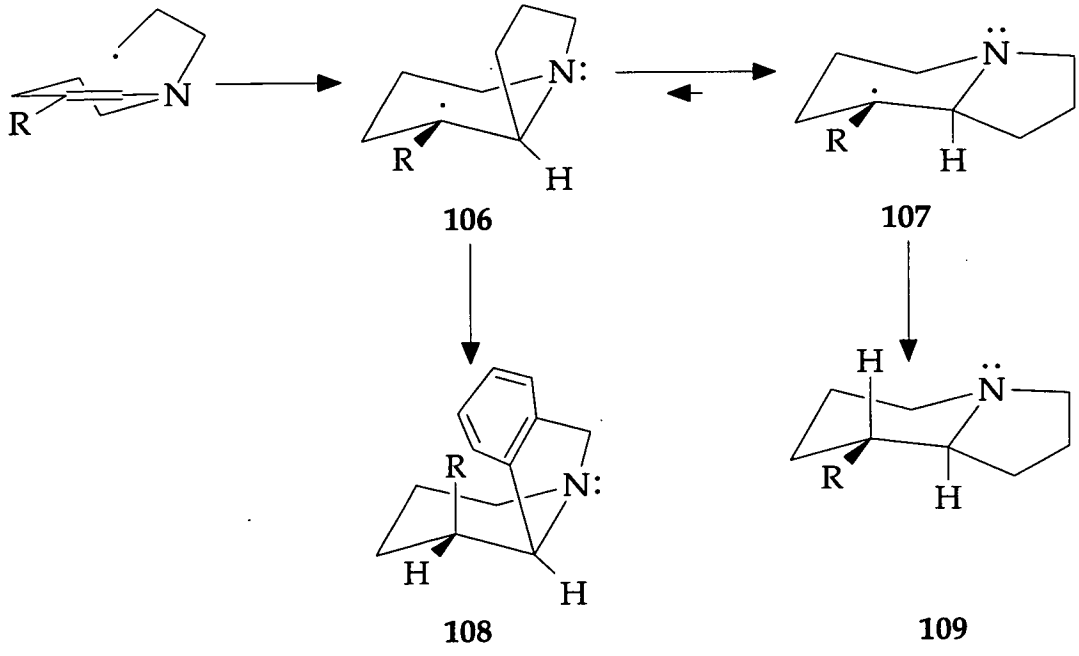


Scheme 20

Alkyl **91**, **94**, alkenyl **98** and aryl **102** radicals all underwent cyclisation successfully but in all cases 10-20% of the simple uncyclised reduction

products **93, 97, 101, 105** were observed.

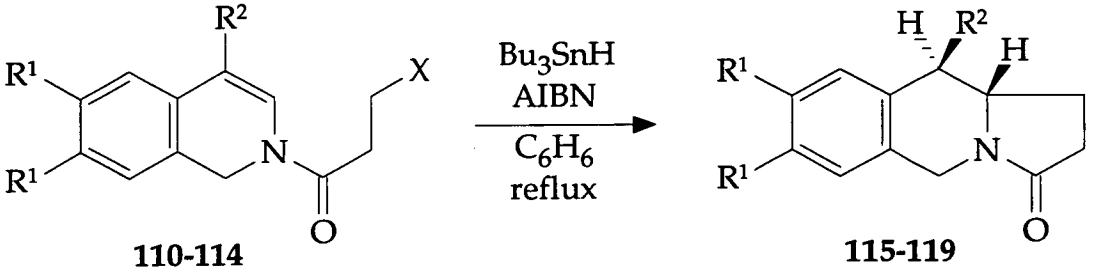
All reactions were stereoselective. In the reactions of alkyl **91, 94** and alkenyl **98** radicals the favoured product was the *anti*-isomer **92, 95, 99** (With respect to the new bond formed to give the trans fused five membered ring and the ester group). However, for the aryl radical **102** the stereoselectivity changes and the *syn*-isomer **104** is now favoured. It is thought that initial cyclisation is a *cis*-addition to the double bond to give intermediate radical **106** (Scheme 21) (*cf.* Scheme 19). In the case of alkyl **91, 94** and alkenyl radicals **98** this intermediate undergoes rapid nitrogen inversion to the *trans*-isomer **107** which reacts with tributyltin hydride in the normal manner to yield the *anti*-product **109**.



Scheme 21

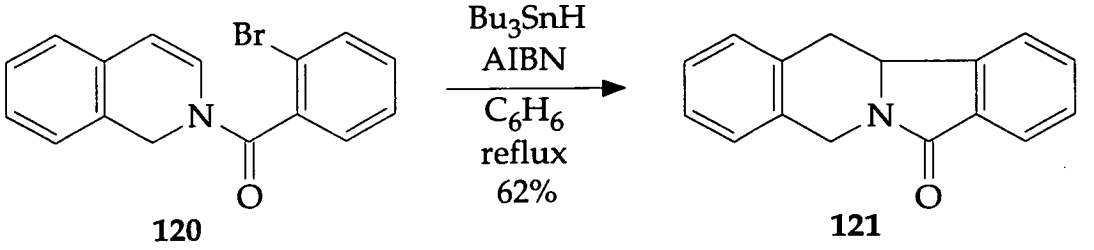
In the case of the aryl radical **102**, this inversion is slowed sufficiently that the *syn*-product **108** predominates, as is normally the case in the carbocyclic series.

Further work on the formation of fused rings with a nitrogen bridgehead was carried out by Yamaguchi *et al.*[34] Here they cyclised 2-(β-haloacyl)-1,2-dihydroisoquinolines **110-114** by means of tin hydride to form the benzo[*f*]indolizine system **115-119** (Scheme 22). Cyclisation proceeded in moderate to good yield. The reaction appears to be diastereoselective and the *anti*-isomers **117** and **118** are formed. Beckwith's mechanism (Scheme 21) accounts for this stereochemistry. The work was extended to 12,12a-dihydroisoindolo[2,3-*b*]isoquinoline **121** by cyclisation of 2-(*o*-bromobenzoyl)-1,2-dihydroisoquinoline **120**.



110-114 **115-119**

	R^1	R^2	X		% Yield
110	H	H	I	**115**	62
111	H	H	Br	**116**	45
112	H	CN	I	**117**	81
113	H	CO_2Me	I	**118**	73
114	OMe	H	I	**119**	62

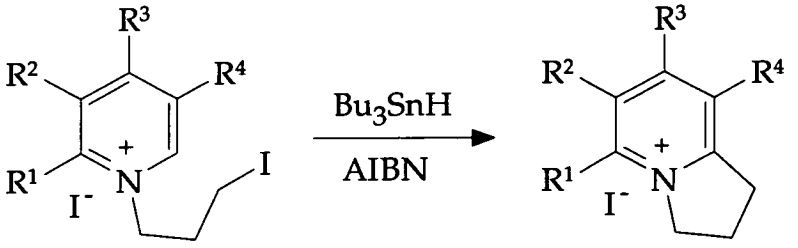


120 **121**

Scheme 22

Alkyl radicals have also been cyclised by Murphy and Sherburn,[35] where the species attacked were quaternary pyridinum salts, resulting in

indolizinium salts (Scheme 23).



122-125 **126-129**

	R^1	R^2	R^3	R^4		% Yield
122	H	H	H	H	**126**	65
123	Me	H	H	H	**127**	65
124	H	H	Me	H	**128**	
125	H	Me	H	Me	**129**	

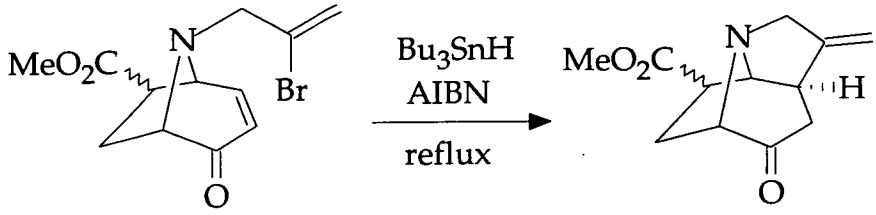
Scheme 23

Cyclisation of **122 and 123** using a full equivalent of AIBN led to efficient formation of the trihydroquinolizium salt **126 and 127.** However with **124** and **125,** although the products **128** and **129** were produced efficiently, there was contamination with the corresponding *N*-propylpyridinum salts, the product of reductive deiodination. No dihydropyridine was seen; it was assumed that the intermediate dihydropyridine was easily oxidised on exposure to air. Alternatively, a single electron transfer (SET) mechanism which avoids the fortuitous oxidation step has been proposed by Bowman and Heaney.[36]

One further example from the work of Gosh and Hart[30] is relevant here (Scheme 24). Cyclisation of **130** took place to give **131** in 63% overall yield.

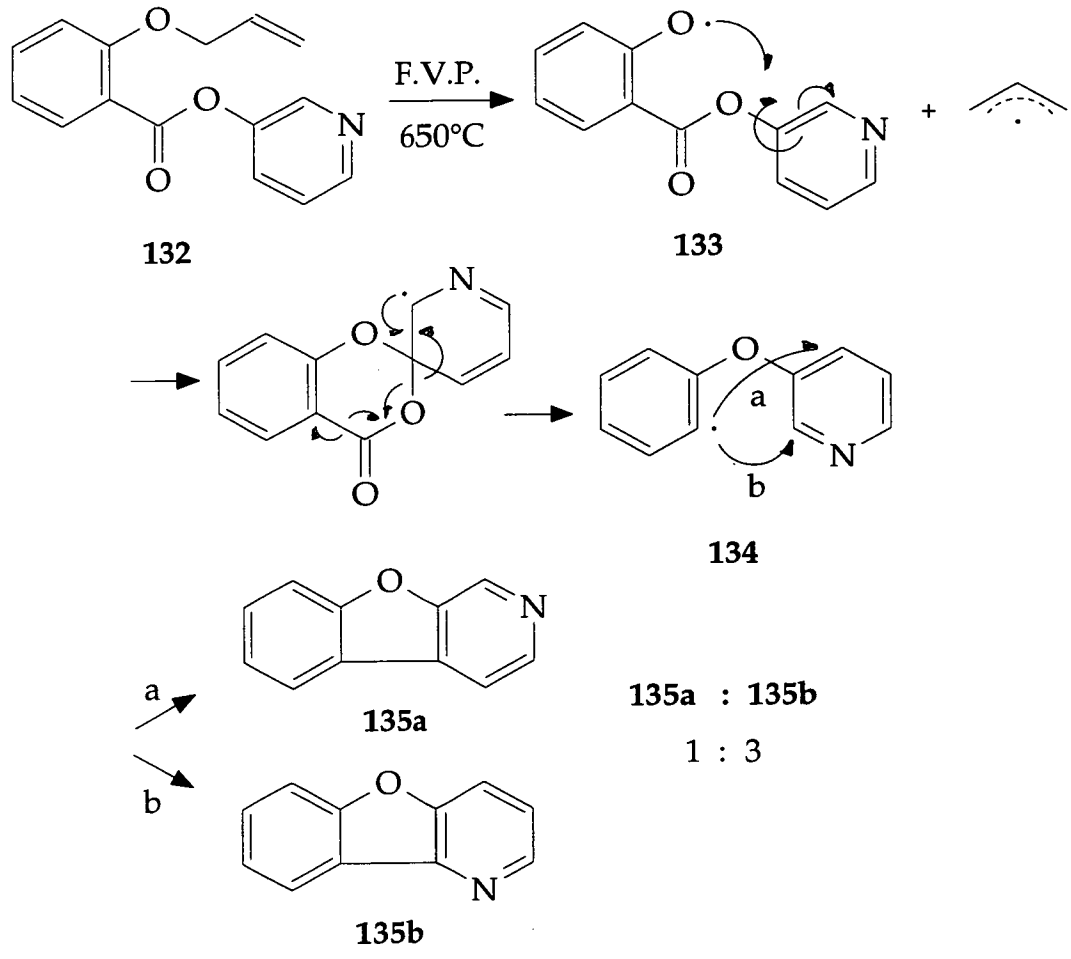
We now move to work which employed gas-phase pyrolysis techniques to generate the radical intermediate.

Firstly Black[37] prepared an isomeric mixture of benzofuropyridines **135a** and **135b** (Scheme 25).



130 **131**

Scheme 24



132 **133**

134

135a **135b**

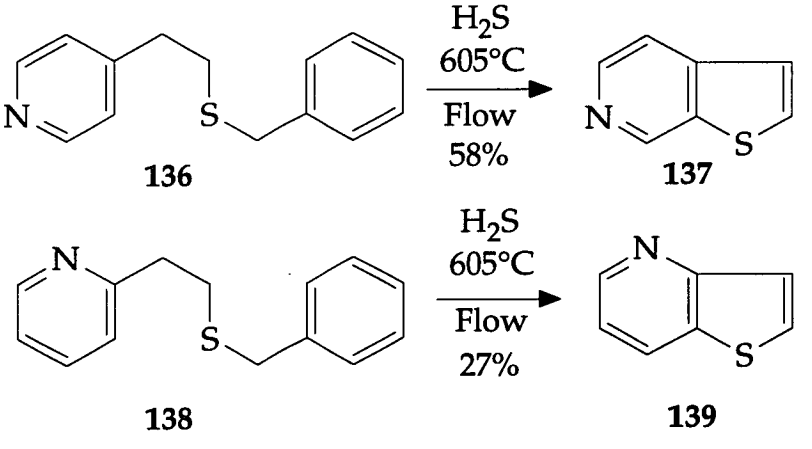
135a : 135b

1 : 3

Scheme 25

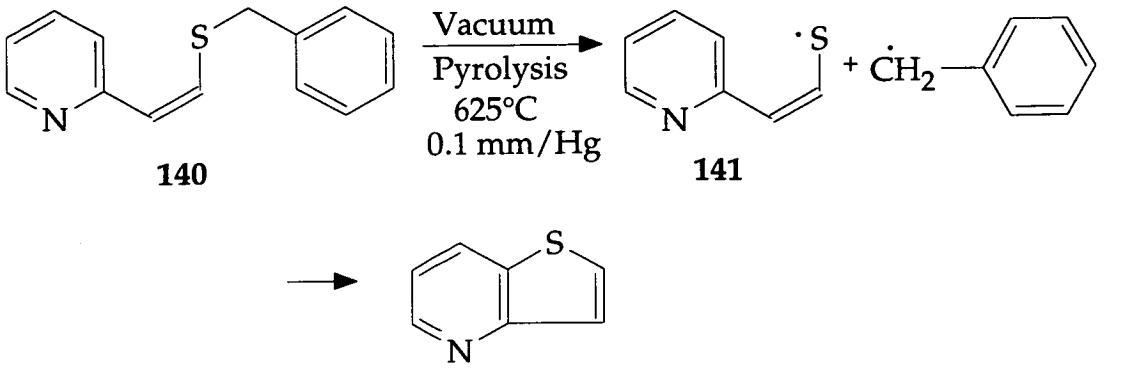
The initial oxygen centred radical **133** was generated by cleavage of an allyl ether **132** to give a stabilised allyl radical as co-product. Spiro cyclisation followed by CO_2 extrusion lead to the radical **134**. This then readds to the pyridine ring, exhibiting a 3:1 selectivity for the 2-position relative to the 4-position.

Similar work, leading to radical attack on a pyridine ring has been carried out by Klemm and Louris.[38] Initially they used flow thermolysis to synthesise two thienopyridines **137** and **139** (Scheme 26). The $PhCH_2$-S bond in the starting materials **136** and **138** cleaves to generate the sulphur centred radical, which cyclises to form a new five membered ring. Aromatisation then takes place because of the harshness of the experimental conditions.



Scheme 26

Later this methodology was improved[39] by the use of vacuum pyrolysis and a better designed starting material **140** (Scheme 27). Vacuum pyrolysis cleaves a stable benzyl radical to generate sulphur centred radical **141**. The only product observed is by attack at the pyridine 3-position to give thienopyridine **139** in 69% isolated yield.



140 **141** **139**

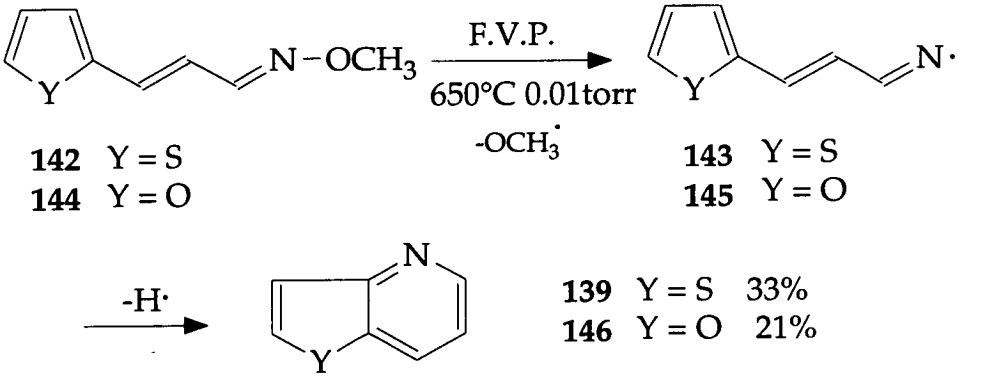
Scheme 27

D.2. Formation of 6-Membered Rings

D.2.a. Attack on 5-membered rings

There are very few examples to be found in this area.

Hickson and McNab[40] prepared thieno[3,2-*b*]pyridine **139** and furo[3,2-*b*]pyridine **146** by the gas phase cyclisation of iminyl radicals (Scheme 28). Flash vacuum pyrolysis of a suitable precursor, in this case *O*-alkyl oximes, **142** and **144** generate the iminyl radicals **143** and **145**, which cyclise to give the fused pyridine in moderate yield. Klemm has also prepared **139** by a complementary route (Scheme 27).



142 Y = S
144 Y = O

143 Y = S
145 Y = O

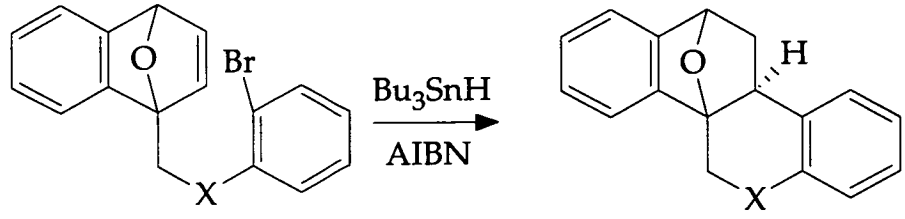
139 Y = S 33%
146 Y = O 21%

Scheme 28

The cycloaddition/radical cyclisation work of Gosh and Hart[30] contains a number of related examples of cyclisation by an aryl radical to a 2,5-dihydrofuran ring that are relevant here (Scheme 29).

Radical cyclisation of **147** and **148** gave a single stereoisomer. The similarity of the aliphatic protons in the ^{1}H NMR spectrum of **150** and **151** to that of **60** and **63** (Scheme 16) is consistent with cyclisation to the *exo* face of the double bond. Hence the stereochemical result is the same as for

5-membered ring formation, despite the greater conformational freedom in the present example. Sulphoxide **149** was cyclised as an unequal mixture of diastereomers giving **152**. That the isomerism was due to the sulphoxide moiety was proved by reduction to a single sulphide. The ^1H NMR data for this sulphide further confirmed that these six membered ring radical cyclisations occur stereospecifically from the *exo* face.

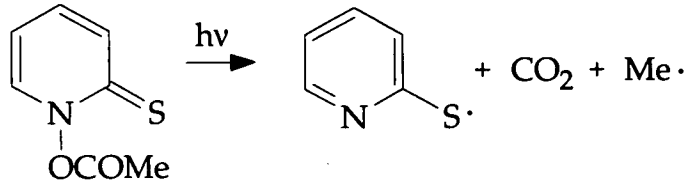


147 X = O
148 X = NCH_3
149 X = SO

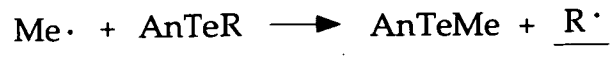
150 X = O 76%
151 X = NCH_3 54%
152 X = SO 67%

Scheme 29

One of the few examples of radical chain reactions mediated by a method other than tributyltin hydride was the work of Barton *et al*,[41] who used a radical exchange process based on the thiohydroxamate ester method (See Section B.1.b). In this case methyl radicals were generated by the photochemical breakdown of *N*-acetoxy-2-thiopyridine **153** (Scheme 30).



153

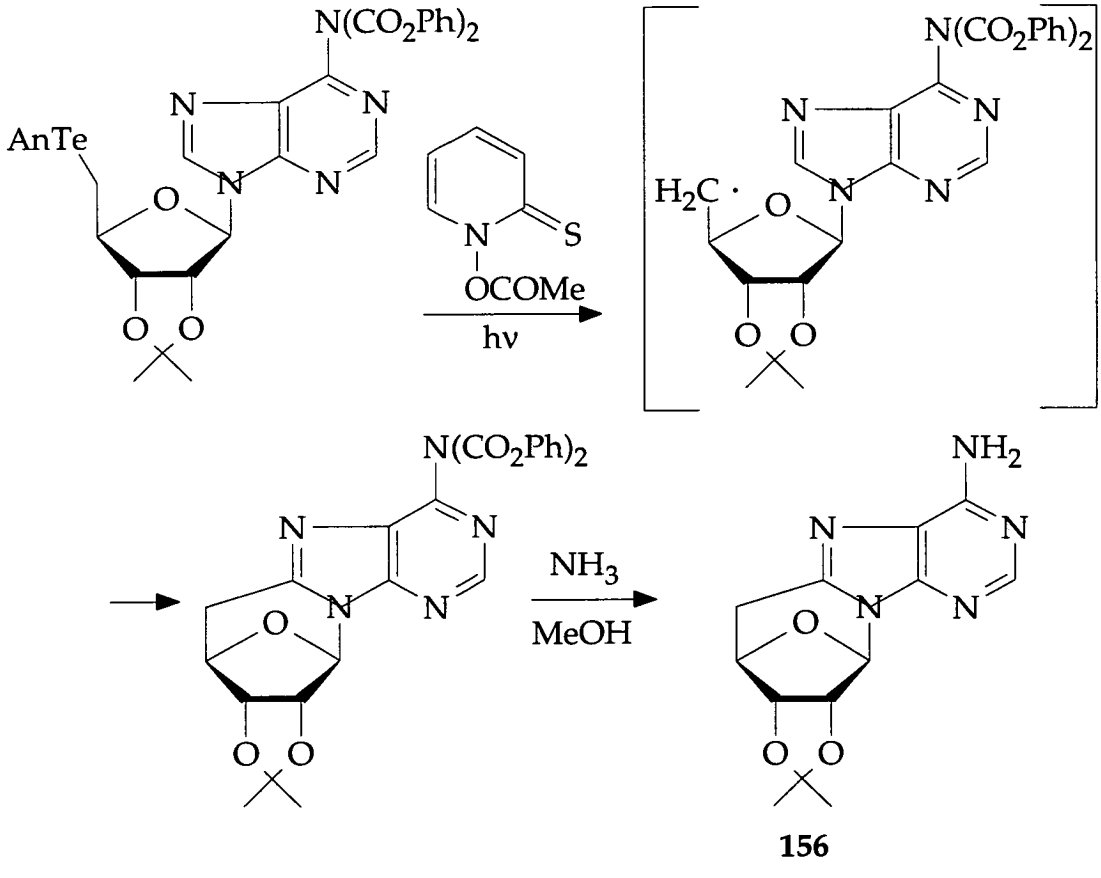


154 **155** **4**

Scheme 30

These react with an anisyl telluride derivative **154** affording anisylmethyl telluride **155** and the desired radical **4**.

This procedure was applied to the synthesis of the 5`,8-cycloadenosine **156** (Scheme 31). The cyclisation to prepare **156** proceeds in 60% yield, which is higher than previously reported. In this case the product is the result of oxidative cyclisation.



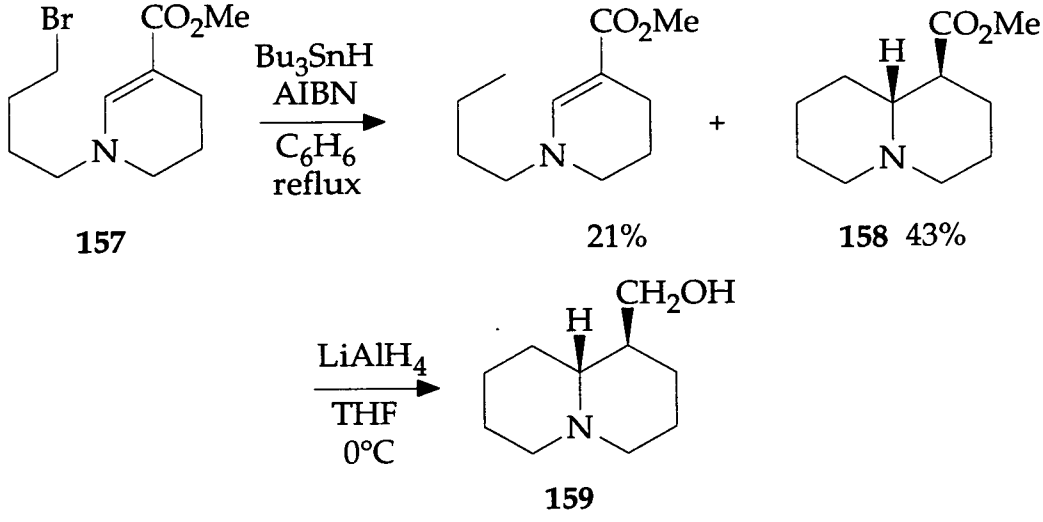
156

Scheme 31

D.2.b. Attack on 6-membered rings

In this section, rings formed contain oxygen or nitrogen atoms, while the heterocyclic ring may contain oxygen or nitrogen atoms. Again the predominant method of radical formation involves tributyltin hydride.

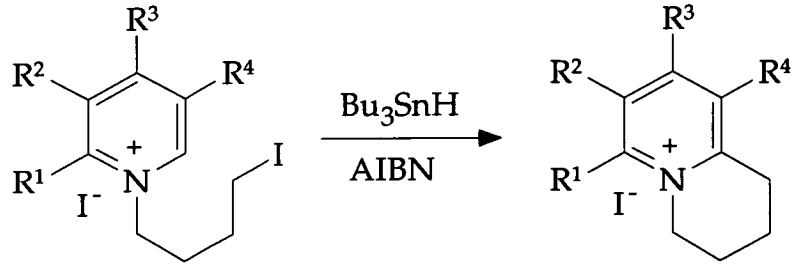
Cyclisation of alkyl radicals was used in a variant of previously considered work (Section D.1.b) by Beckwith and co-workers[33] in the synthesis of the quinolizidine alkaloid Epilupinine **159** (Scheme 32).



Scheme 32

In the step of interest, treatment of **157** with tributyltin hydride stereospecifically produces the saturated ester **158** in 43% yield. The stereoselectivity of ring formation is the same as for 5-membered ring formation (Scheme 20), and similar factors are presumably responsible (*cf.* Scheme 21).

Alkyl radicals have also been cyclised by Murphy and Sherburn[35] where the species attacked were quaternary pyridinum salts, resulting in good yields of tetrahydroquinolizinium salts (Scheme 33).



159-164 **165-170**

	R^1	R^2	R^3	R^4		% Yield
160	H	H	H	H	**166**	60
161	Me	H	H	H	**167**	58
162	H	H	Me	H	**168**	58
163	H	Me	H	Me	**169**	67
164	Me	H	Me	H	**170**	No isolable product
165	H	Me	H	H	**171**	Inseparable mixture

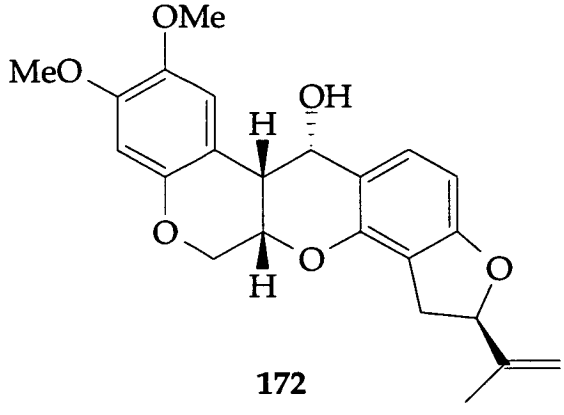
Scheme 33

Cyclisation of **160** using a full equivalent of AIBN led to efficient formation of the tetrahydroquinolizinium salt **166**. No dihydropyridine was seen; it was assumed that the intermediate dihydropyridine was easily oxidised on exposure to air. The substituted pyridines **161-165** were then cyclised as shown. Interestingly the cyclisation of the 2-methylpyridine derivative **161** was regiospecific to give **167**; no product was detected from addition of the initially formed carbon radical to the 2-position of the pyridinum salt and the yield of the bicyclic product was of the same order as for other cases. However, when *N*-iodobutyl-2,6-dimethylpyridinum iodide **164** was reacted, no product could be isolated but all the starting material was consumed. This is consistent with the addition of the radical to the pyridinum salt, but being unable to progress further toward aromatic products it formed a reactive dihydropyridine that decomposed during reaction or attempted isolation. When 3-methyl pyridine **165** was used it gave rise to what appeared to by ^{1}H NMR to be a mixture of two possible

aromatic products, but these could not be separated.

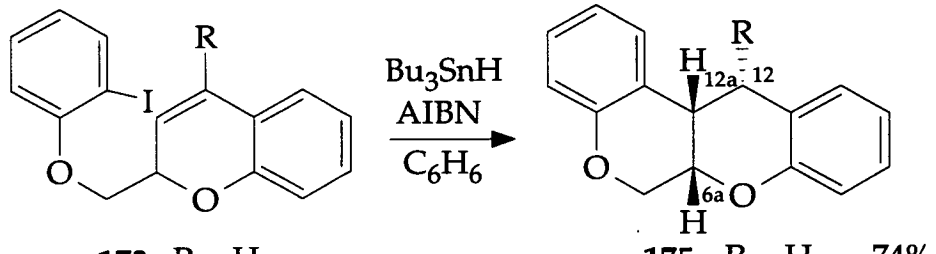
Cyclisation of aryl radicals was carried out by Ahmand-Junan and Whiting to form a variety of related four ring systems.

Firstly, the core structure of the insecticidal rotenoid alcohol **172** was synthesised by a 6-*exo* addition to deliver the necessary *cis,cis*-stereochemistry.[42]



172

Cyclisation of the chromene **173** with tributyltin hydride gave the tetracycle **175** as a single stereoisomer (Scheme 34).



173 R = H
174 R = OAc

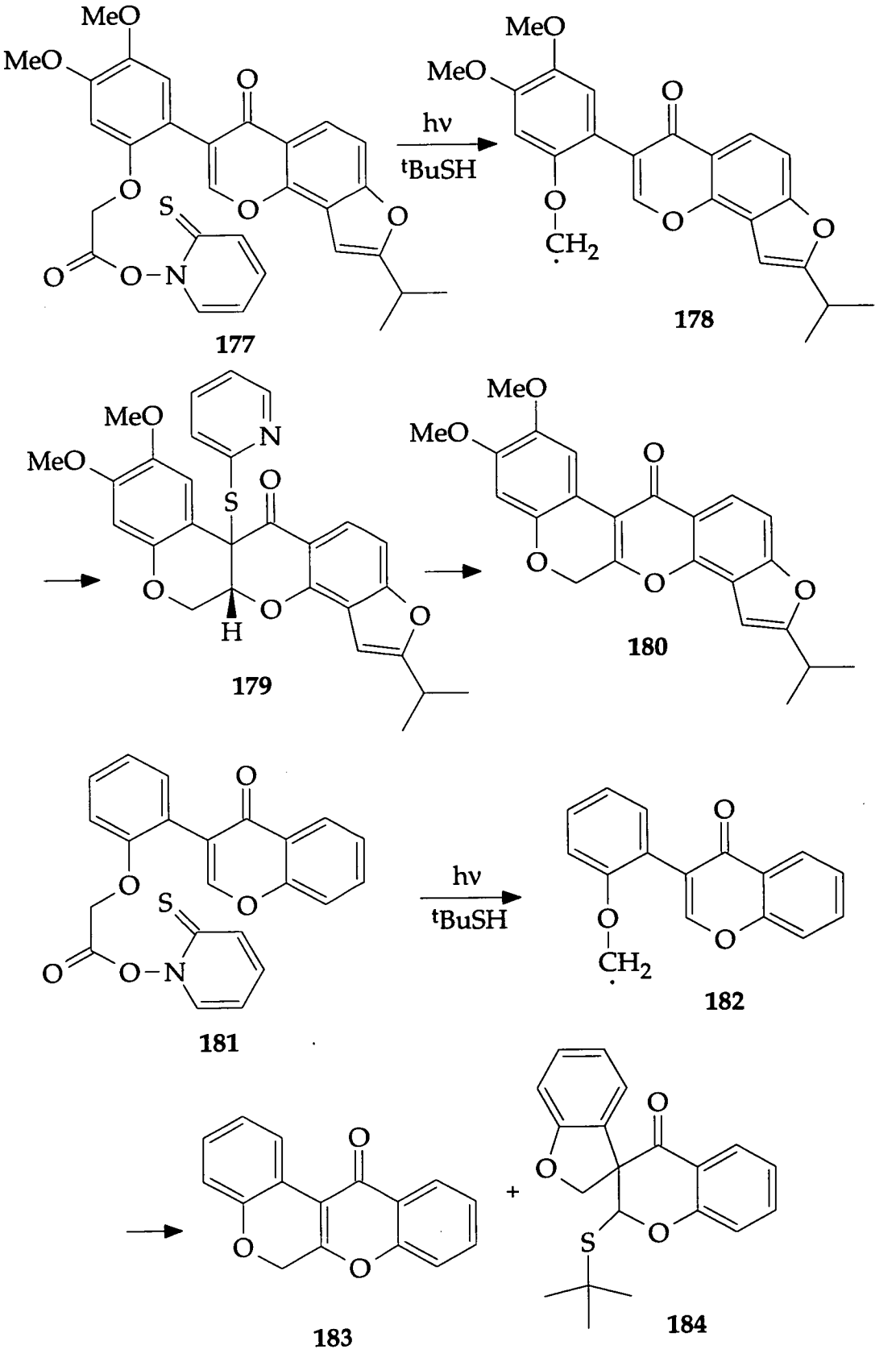
175 R = H 74%
176 R = OAc 62%

Scheme 34

The *cis*-stereochemistry of the ring junction was demonstrated by ^{1}H NMR ($J_{6a,12a}$4.4Hz, *cf.* $J_{6a,12a}$4.8Hz in the parallel *cis*-compound derived from natural rotenone, and $J_{6a,12a}$9.5Hz for its *trans*-counterpart), and is expected

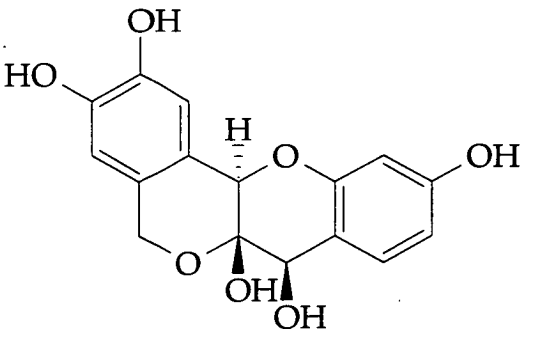
from previous results. Reaction of **174** by slow addition of tin hydride gave the acetate derivative **176**. Again the stereochemistry was demonstrated by ^{1}H NMR ($J_{6a,12a}$5.0Hz, $J_{12,12a}$4.6Hz). Stereocontrol of delivery of a hydrogen atom to C-12 by the least hindered face approach allows the setting up of three adjacent *cis* hydrogen atoms in this kinetic process.

In a second example[43], (aryloxy)methyl radicals **178** and **182** were generated by the thiohydroxamate ester method (Scheme 35). The thiohydroxamate ester **177** was prepared *in situ* and the radical was generated by irradiation in the presence of t-butylthiol. Cyclisation occurred, giving one major product, dehydroisorotenone **180** in 60% yield. Under the experimental conditions, the initially formed radical cyclises, then abstracts a pyridinethio moiety to form **179**, which then undergoes thermal elimination to form **180**. This shows that radicals of type **177** do undergo 6-*endo* cyclisation to form the rotenoid ring-B. The isoflavanone hydroxamate **181** was also investigated. Irradiation gave two major products. The desired 6a,12a-didehydrorotoxen-12-one **183** (25%) and the thioacetal **184** (11%). The explanation for product **184** is not, 5-*exo* cyclisation as opposed to 6-*endo* cyclisation, but that the initial radical is trapped by a thiopyridyl moiety, and this product reacts with t-butylthiol *via* polar conjugate addition with subsequent anionic displacement of 2-mercaptopyridine.


MeO
MeO
O
O
S
O
O-N
O
hν
tBuSH
MeO
MeO
O
O
O
CH2
O
177
178
MeO
MeO
N
S
O
O
O
H
O
MeO
MeO
O
O
O
O
179
180
O
O
S
O
O-N
O
hν
tBuSH
O
O
CH2
181
182
O
O
O
O
O
+
O
S
183
184

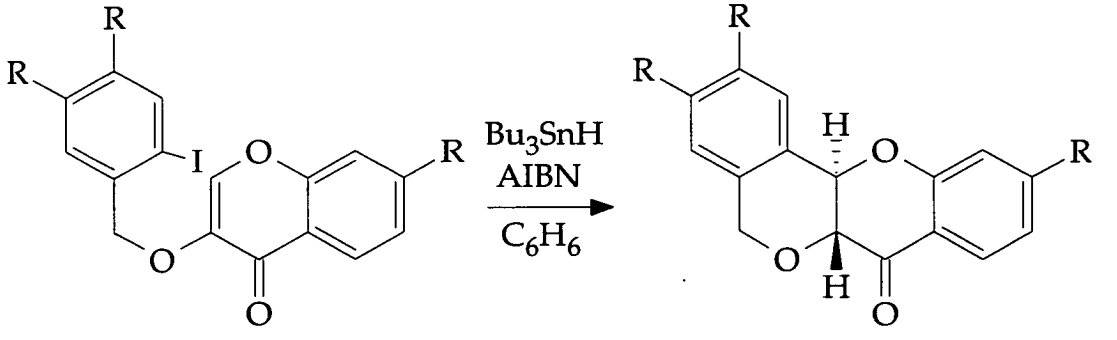
Scheme 35

Attention then turned to the closely related ring system found in (+)-peltogynol **185**.



185

The (±)-trimethyl ether of this unusual heterocycle (**189**;R=OMe) and its ring skeleton (**188**;R=H) were synthesized *via* a 6-*endo* radical cyclisation[44] (Scheme 36). The ether **186** cyclised smoothly to yield the B/C-*trans* tetracycle **188** (48%). The B/C-*cis*-isomer was also isolated (12%). The ether **187** was cyclised in a similar manner to afford trimethylpeltogynone **189** (42%), again with a minor quantity of its stereoisomer. It is not known whether *trans*-fusion represents the thermodynamically stable product, since attempted epimerisation by acid and base leads to ring opened material.

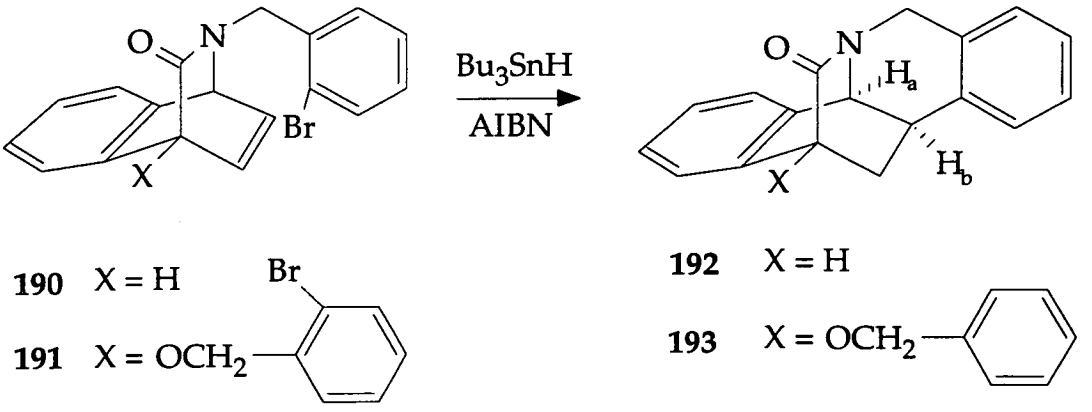


186 R = H
187 R = OMe

188 R = H
189 R = OMe

Scheme 36

The tandem cycloaddition/radical cyclisation work of Gosh and Hart[30] also provides some examples in this section (Scheme 37).



190 X = H

191 X = OCH_2

192 X = H

193 X = OCH_2

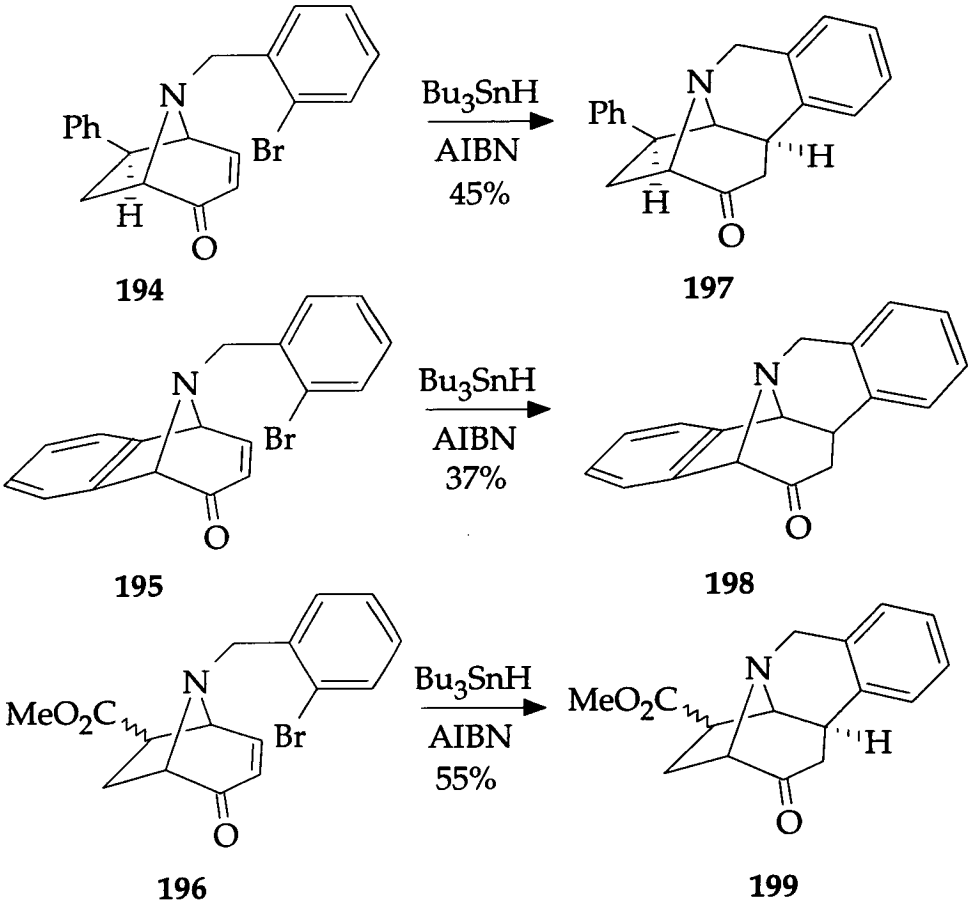
Scheme 37

Radical cyclisation of the cycloadduct **190** gave a single product **192** in 73% yield. Bridgehead proton H_a appears as a doublet at δ 4.72 with only a small coupling to H_b at δ 3.27, confirming the *endo* geometry of the latter.

Radical cyclisation of **191** with two equivalents of Bu_3SnH to reduce both bromine atoms gave **193** as major product (45%). Only a trace of alternative cyclisation was seen by ^1H NMR spectroscopy.

Cyclisation of the radical tethered to the bridgehead was disfavoured as a consequence of increased strain in the resulting six membered ring, and a reflection of that difference in the two transition states. A variety of cycloadducts of 3-hydroxypyridine **194-196** (Scheme 38) similarly gave the products **197-199** respectively under standard conditions.

This methodology of cycloaddition/radical cyclisation was also employed by Finch, Harwood *et al*[45] in a concise approach to the morphinan **200** skeleton.

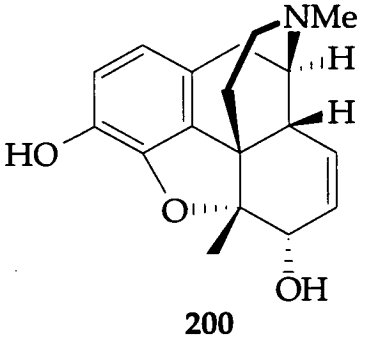


194 197

195 198

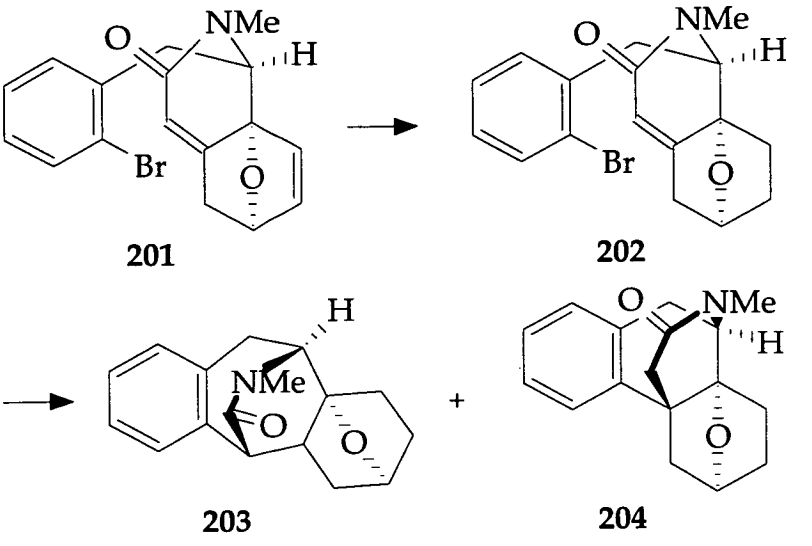
196 199

Scheme 38

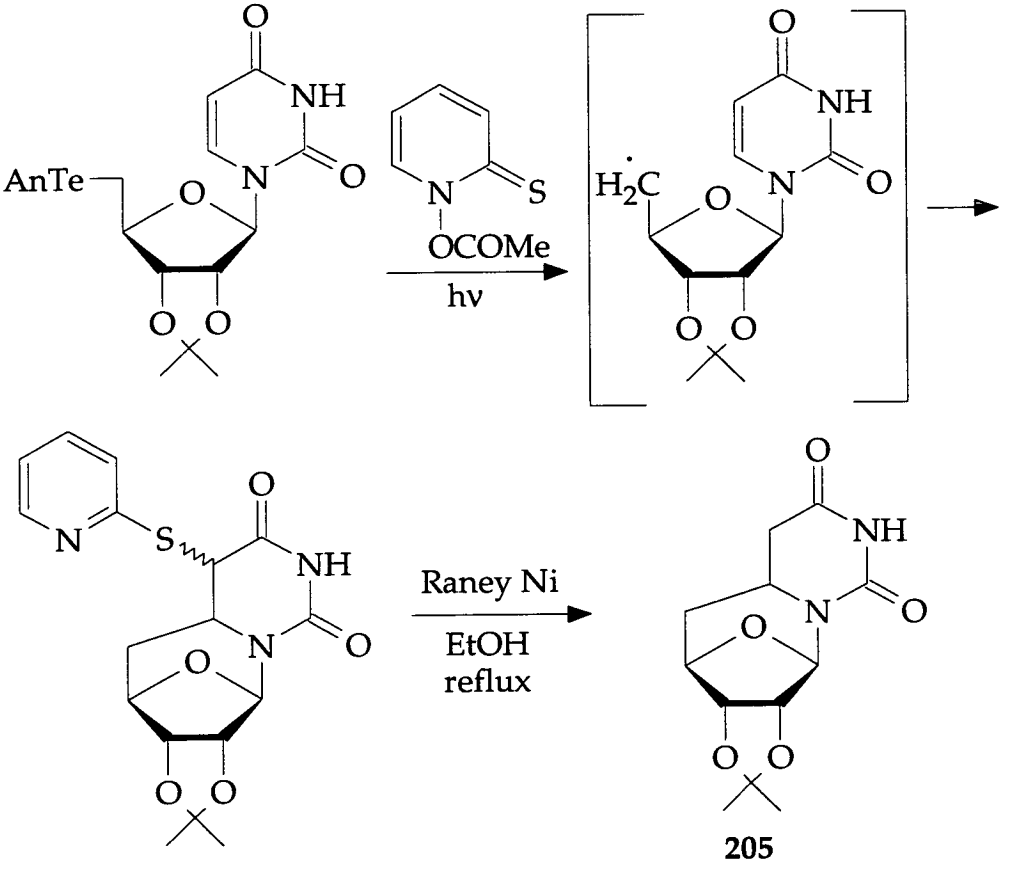


200

This proved only partially successful (Scheme 39). Firstly, the initial cycloadduct **201** had to be reduced to **202**, to avoid interference by the 3,4-bond of the dihydrofuran in the radical cyclisation. Secondly, two products were observed in this process, one resulting from 7-*endo* cyclisation **203** and the desired product of 6-*exo* cyclisation **204** in the ratio 3:2.



Scheme 39

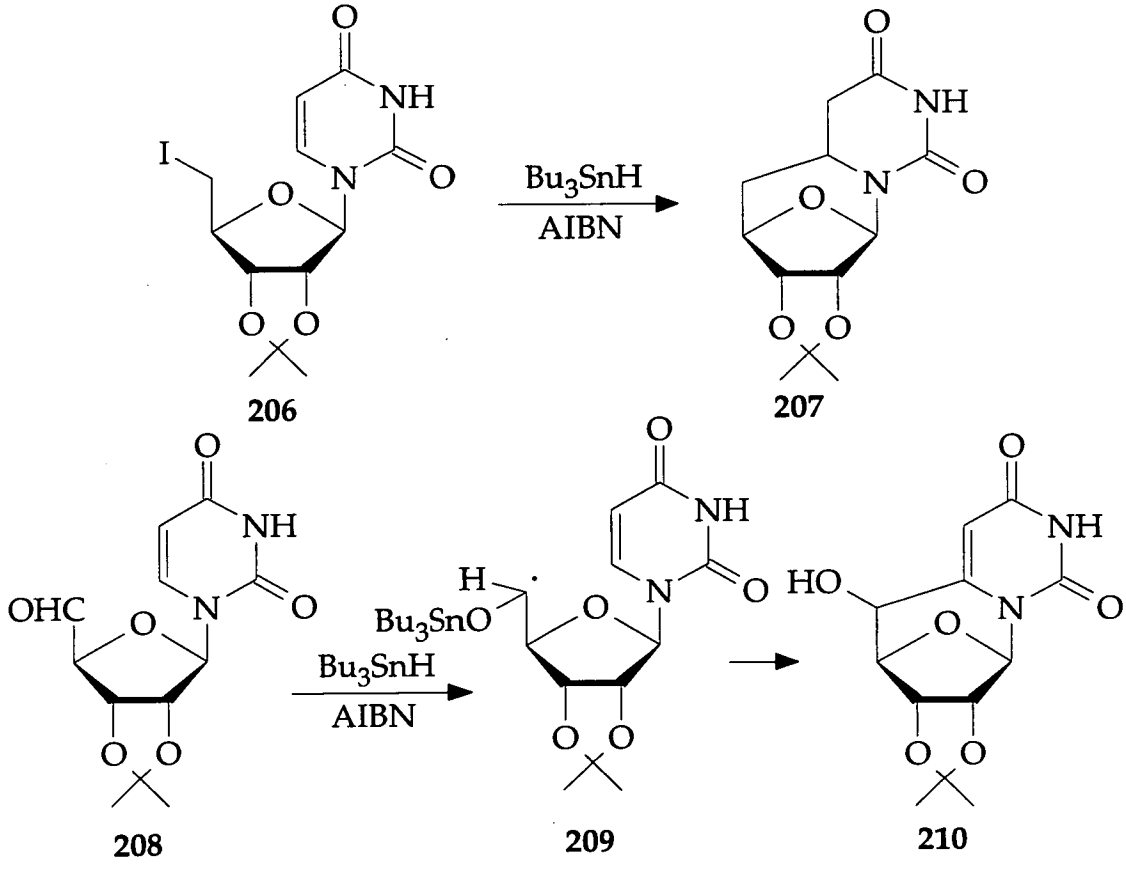


Scheme 40

The work of Barton *et al*[41] (See Section D.1.b) has an example that is relevant here. Again radicals are generated by an exchange process (See Scheme 30).

This procedure was applied to the synthesis of the cyclo-5,6-dihydrouridine **205** (Scheme 40). Preparation of **205** requires a final reduction step to remove the thiopyridyl group, which arises by termination (*i.e.* reaction with a thiopyridyl radical) or propagation (*i.e.* reaction with *N*-acetoxy-2-thiopyridine).

One other example from nucleic acid chemistry could be found in the work of Sugawara and co-workers[46] (Scheme 41).

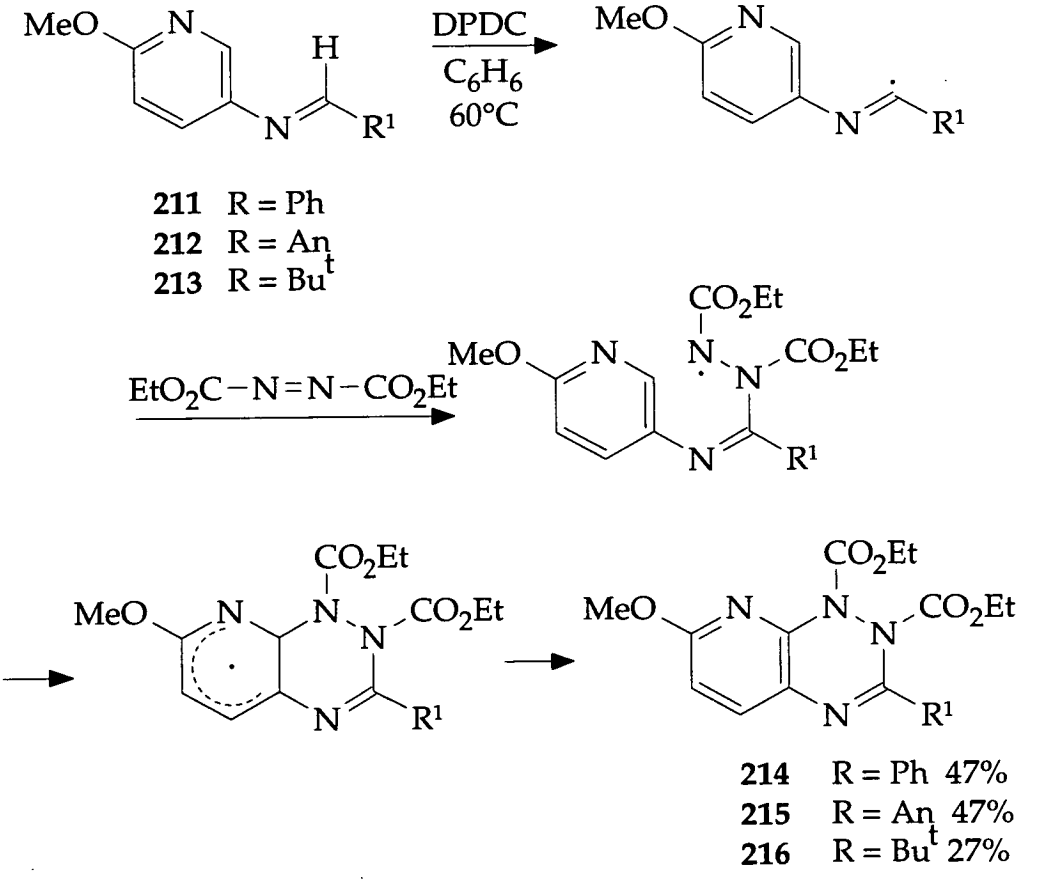


Scheme 41

The iodo compound **206** cyclises to give the

(6S,5`S)-6,5`-cyclonucleoside **207** in the usual manner. However, in the aldehyde example **208** the stannyl radical attacks carbonyl oxygen atom to form the tributylstannyloxymethine radical **209** which then cyclises to the double bond. Final conversion to the product **210** may involve hydrogen abstraction from tributyltin hydride, as more than one equivalent of this reagent is required.

A stepwise reaction, which ultimately resulted in the formation of a six membered ring, was homolytic annulation by reaction of arylimidoyl radicals with diethyl azodicarboxylate carried out by Nanni *et al*[47] (Scheme 42).

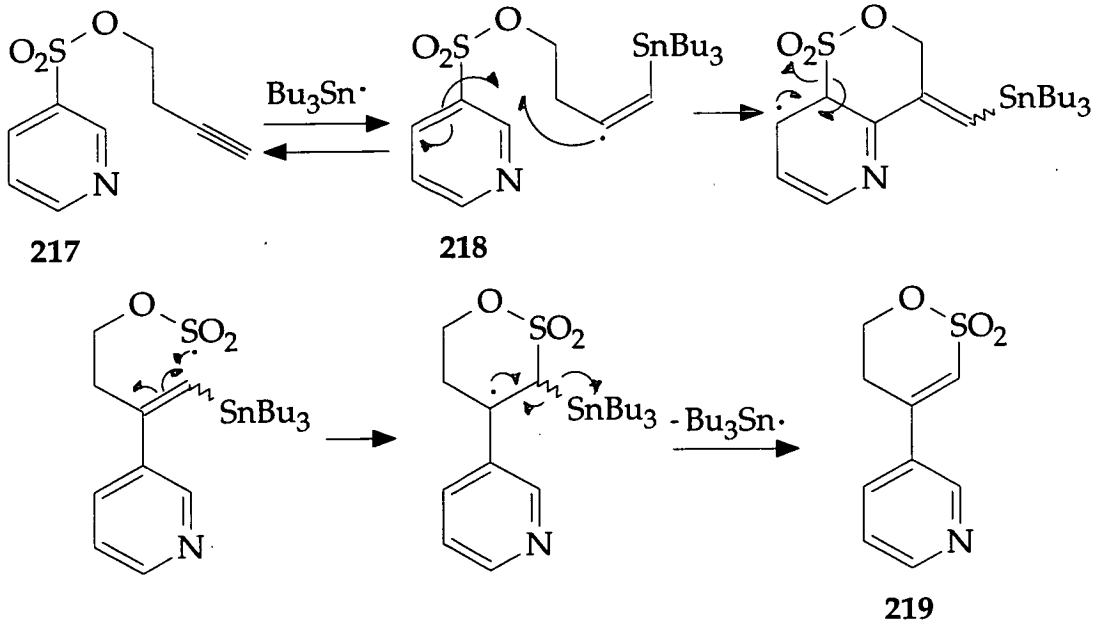


Scheme 42

The initial radicals were generated from imines **211-213** by H-atom

abstraction using di-isopropyl peroxydicarbonate (DPDC). This reaction was claimed to be the first example of homolytic annulation *via* an intramolecular free radical addition to the azo group. Notably, products **214-216** are the only ones observed, with no trace of possible isomers that would result from attack at the pyridine 4-position.

A final example in this section comes from the work of Motherwell and co-workers[48] who carried out a study on the cyclisation of radicals **218** formed by the reversible addition of tributyltin radicals to an arenesulphonate ester of a homopropargyl alcohol **218** (Scheme 43). The expected pathway was [1,6] *ipso*-substitution and subsequent loss of sulphur dioxide to furnish functionalised vinyl stannanes. However, loss of SO_2 is sufficiently slow to permit alternative 6-*endo* addition to give **219** as shown.

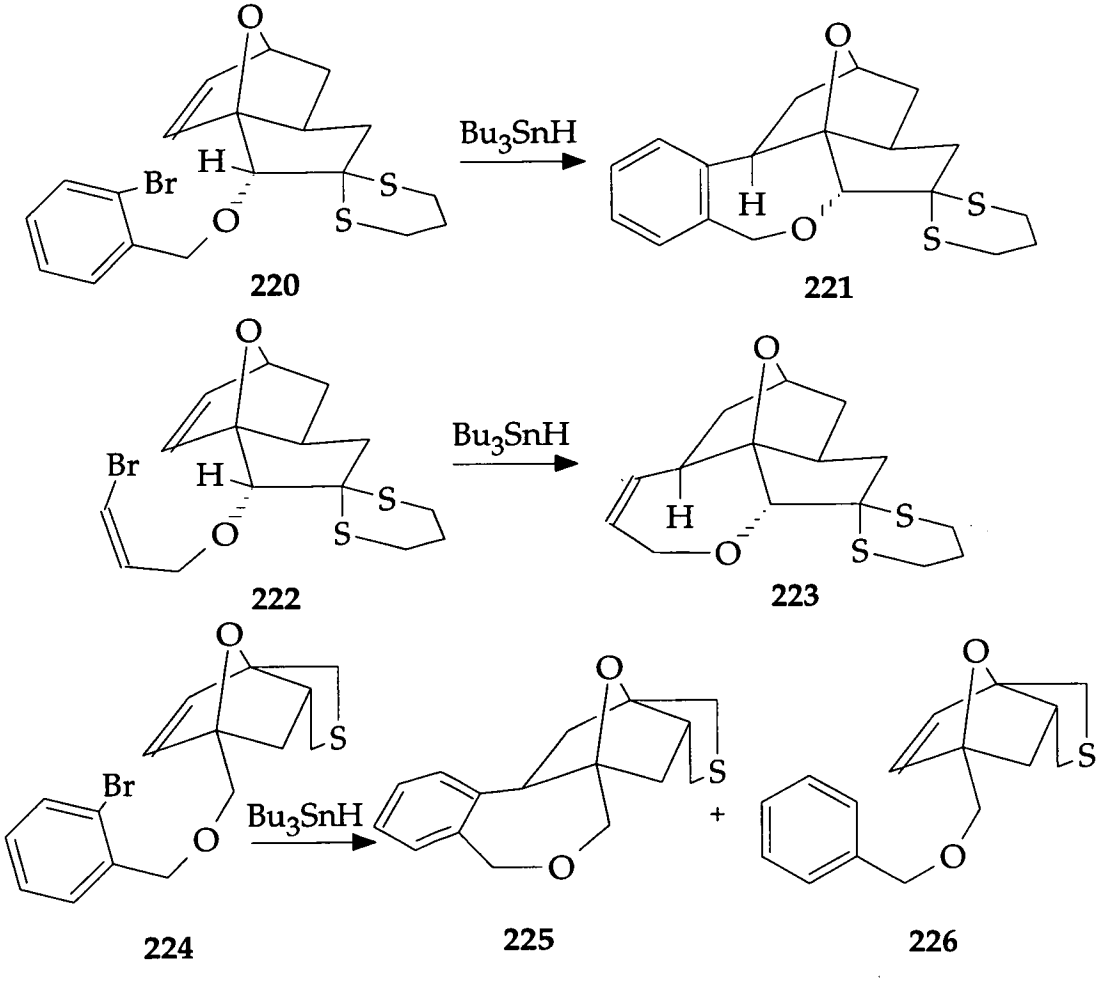


Scheme 43

D.3. Formation of 7-Membered and Larger Rings

Larger rings are mainly formed in the same way as has been described previously, but of course with an extended chain between the site where the radical was generated and the possible position of attack.

Gosh and Hart[30] have two examples of formation of seven membered rings while attacking five membered rings (Scheme 44).

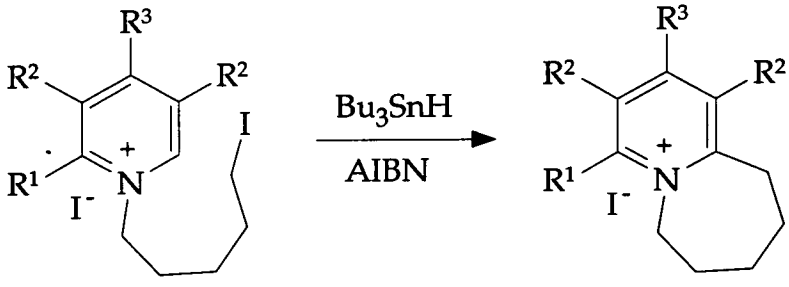


Scheme 44

Cyclisation of **220** gave the seven membered benzoxepin ring **221**, formed with complete stereocontrol. The structure was verified by X-ray analysis,

which confirmed that the aromatic ring was *exo* as found for formation of other ring sizes. None of the other possible isomers was found by ^1H NMR. Cyclisation of **222** gave **223** in a similar manner. The desired product **225** was obtained, along with the reduction product **226** in a 3:4 ratio when **224** was cyclised.

Murphy and Sherburn[35] extended the scope of their previous work (See Schemes 23 and 33) to seven membered rings (Scheme 45). Cyclisation of the quaternary pyridinium salts **227-230**, resulted in good yields of pyridoazepinium salts **231-234**.

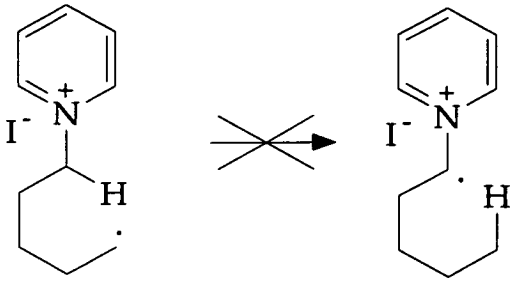


227	R^1,R^2,R^3=H	**231**	R^1,R^2,R^3=H	58%
228	R^1=Me R^2,R^3=H	**232**	R^1=Me R^2,R^3=H	58%
229	R^1,R^2=H R^3=Me	**233**	R^1,R^2=H R^3=Me	79%
230	R^1,R^3=H R^2=Me	**234**	R^1,R^3=H R^2=Me	66%

Scheme 45

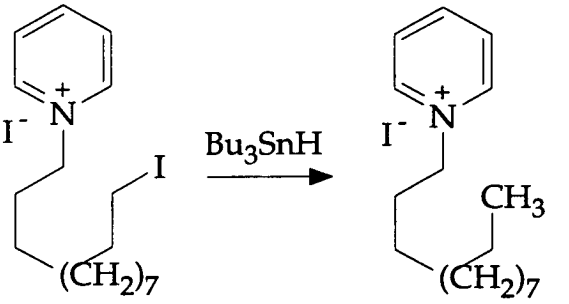
Here, there is a possible problem of H atom transfer by the primary radical **235** (Scheme 46) to give **236**. However, this is not sufficiently rapid to interfere with the desired reaction.

Finally, macrocyclisation to form a 12-membered ring was attempted by cyclisation of **237** (Scheme 47). This led only to reductive deiodination to give **238**



235 **236**

Scheme 46



237 **238**

Scheme 47

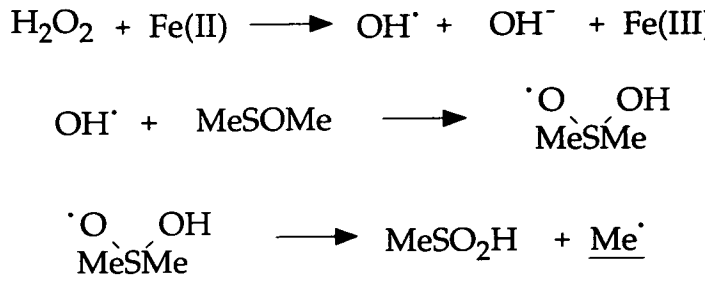
E. THE FREE RADICAL CHEMISTRY OF PYRROLE

Although pyrrole is a relatively simple compound, and much of its chemistry has been explored,[8,49] there has been very little systematic work on its reactions with free radicals.

The present survey covers alkylation, arylation and halogenation reactions. In general, few of these methods are of preparative importance - in contrast to some cyclisation reactions reported in this thesis - but certain mechanistic conclusions can be drawn. In addition certain oxidation processes may involve radical intermediates.[50] These range from simple adduct formation with molecular O_2, to the polymerisation with hydrogen peroxide to give "pyrrole blacks".[51] Because products and mechanisms are poorly defined, these will not be considered further here.

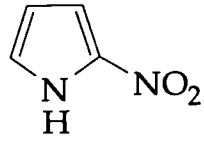
E.1. Alkylation

No systematic study has been made of alkylation reactions of radicals with pyrrole, except in the case of perfluoroalkylation. Only a few examples of simple alkylation reactions could be found. Thus Rudquist and Torssell[52] methylated 2-nitropyrrole **239** by the DMSO-hydrogen peroxide method (Scheme 48).

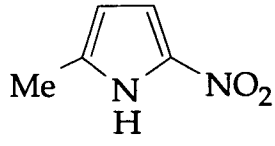


Scheme 48

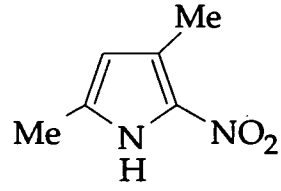
They obtained two products, 5-methyl-2-nitropyrrole **240** (30%) and 3,5-dimethyl-2-nitropyrrole **241** (12%). This result is in contrast to the corresponding 2-nitrothiophene, which gave mostly the 3-methylated product.



239



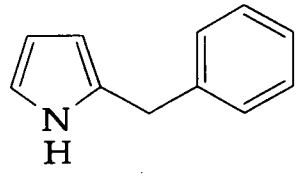
240



241

Homolytic substitution by carbon centred radicals generated in DMSO by Fe^{2+}/H_2O_2 (Scheme 48) followed by radical exchange with α-cyano, α-carbonyl and α,α-dicarbonylalkyl iodides, was carried out by Baciocchi, Muragalia and Sleiter.[53] This resulted in moderate to high yields of 2-substituted pyrroles (Table 1). Attempts to change the substitution position by using bulky *N*-substituents have proved unsuccessful.

Bass and Nababsing[54] have selectively homolytically benzylated pyrrole in acidic solution. Resonance stabilised benzyl radicals generated by decomposition of dibenzylmercury yielded 2-benzylpyrrole **242** in unspecified yield.



242

A benzyl type radical may also be generated when an *H*-atom is abstracted from the methyl group of *N*-methylpyrrole[55] **243** (Scheme 49).

The product is mainly tar from which 1,2-di(1-pyrryl)ethane **245** (by dimerisation) and 1-methyl-3-(1-pyrrylmethyl)pyrrole **246** (by attack of the radical **244** at the 1-methylpyrrole 3-position) could be isolated in very low yield (>0.5%).

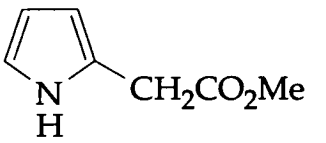
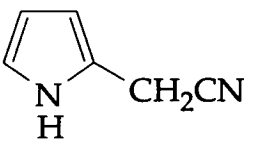
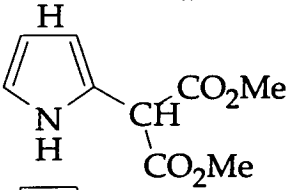
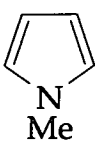
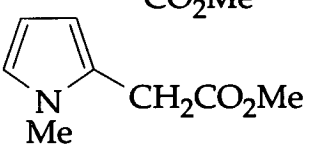
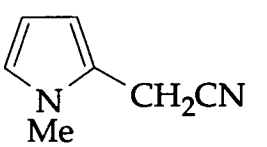
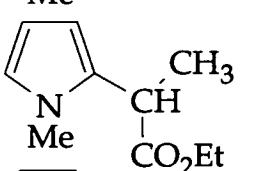
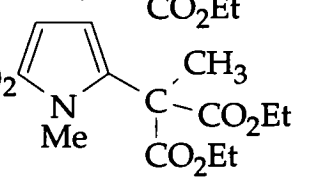
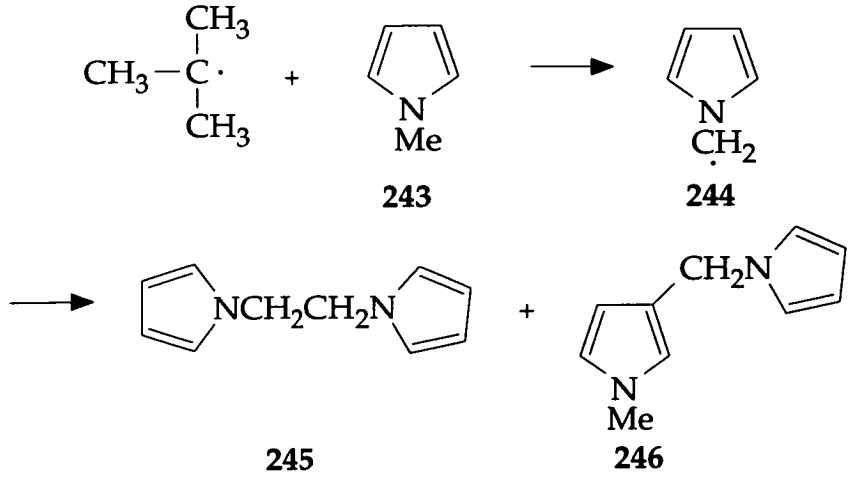
Substrate	Radical Source (RI)	Product	Yield (%)
	ICH_2CO_2Me		59%
	ICH_2CN		73%
	$ICH(CO_2Me)_2$		55%
	ICH_2CO_2Me		87%
	ICH_2CN		88%
	$ICH(CH_3)CO_2Et$		55%
	$IC(CH_3)(CO_2Et)_2$		89%

Table 1

Of note here is the variation in regioselectivity of the reactions. A benzyl radical would normally be considered nucleophilic in nature[55] and attack the 3-position of a pyrrole ring in a similar fashion to the

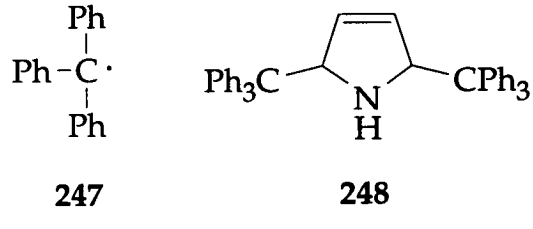
N-pyrrylmethyl radical **244** (Scheme 49).



Scheme 49

Under acidic conditions however, protonation takes place at the pyrrole 5-position, directing attack from the 3-position to the 2-position leading to the observed product **242**.

An interesting product was obtained when pyrrole **238**, was reacted with the triphenylmethyl radical **247**. Connant and Chow[56] report that in this case pyrrole reacts like butadiene to give the 1,4-adduct, 2,5-dityrityl-3-pyrrolene **248** (60%).



247 **248**

Perfluoroalkylation reactions have recently been reviewed by McClinton and McClinton.[57] Pyrrole itself has been photochemically trifluoromethylated by Kobayashi and co-workers,[58] using trifluoromethyl iodide as the radical source (Scheme 50). 2-Trifluoromethylpyrrole **249** was

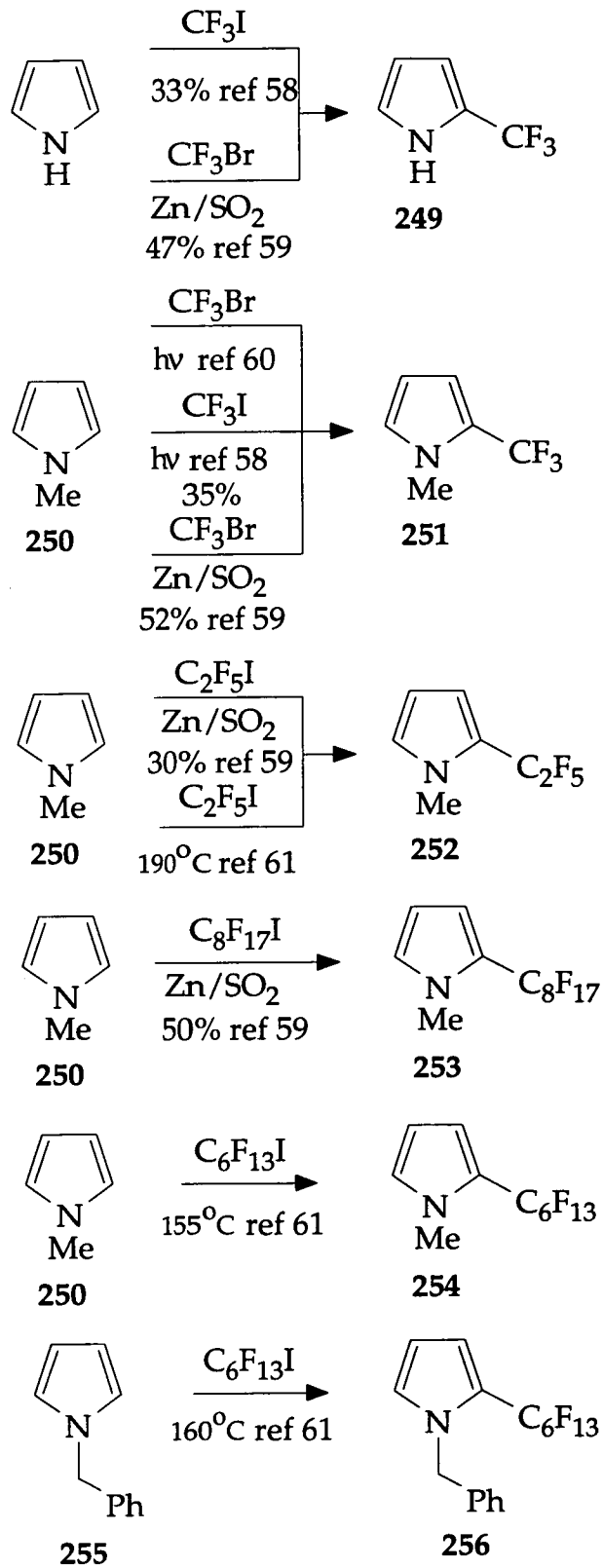
the only product isolated in 33% yield. The trifluoromethyl radical was also used by Tordeux *et al*,[59] in this case generated from trifluoromethyl bromide with zinc and sulphur dioxide as coreactant. Again the electrophilic nature of the trifluoromethyl radical directed reaction towards the 2-position (47%).

1-Methylpyrrole **250** has been perfluoroalkylated by a number of groups using a variety of straight chain perfluoroalkyl radicals.

The poorest results were obtained by Akiyama and co-workers[60] who photochemically generated trifluoromethyl radicals from trifluoromethyl bromide (Scheme 50) achieving only a 6.5% yield of 2-trifluoromethyl-1-methylpyrrole **251**. A simple change to trifluoromethyl iodide by Kobayashi *et al* [58] improved the yield of **251** to 35%. Best results were obtained by Tordeux *et al* [59] who achieved a 52% yield using trifluoromethyl bromide with zinc and sulphur dioxide as radical generators. They then extended the work, using pentafluoroethyl iodide and perfluorooctyl iodide to prepare *N*-methyl-2-pentafluoroethylpyrrole **252** and *N*-methyl-2-perfluorooctylpyrrole **253** in 30 and 50% yield respectively.

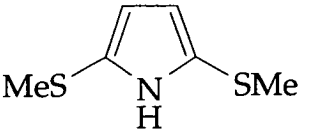
Work with straight chain perfluoroalkyl radicals has also been carried out by Catacuzene *et al.*[61] Pentafluoroethyl and perfluorohexyl radicals were thermally generated from the corresponding iodides to synthesise *N*-methyl-2-pentafluoroethylpyrrole **252** and *N*-methyl-2-perfluorohexyl pyrrole **254** in 30 and 45% yield respectively.

A final example from this group gave *N*-benzyl-2-perfluorohexylpyrrole **256** in 30% yield by thermal reaction of *N*-benzylpyrrole **255** with perfluorohexyl iodide.

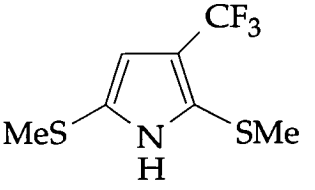

CF3I
33% ref 58
CF3Br
Zn/SO2
47% ref 59
249
CF3Br
hν ref 60
CF3I
hν ref 58
35%
CF3Br
Zn/SO2
52% ref 59
250
251
C2F5I
Zn/SO2
30% ref 59
C2F5I
190°C ref 61
252
C8F17I
Zn/SO2
50% ref 59
253
C6F13I
155°C ref 61
254
C6F13I
160°C ref 61
255
256

Scheme 50

In all cases the electrophilic nature of the perfluoroalkyl radical has directed reaction exclusively towards the 2-position. When this position is blocked,[62] as in 2,5-bis(methylthio)pyrrole **257**, radical trifluoromethylation results in a low yield of the 3-substituted product **258**.



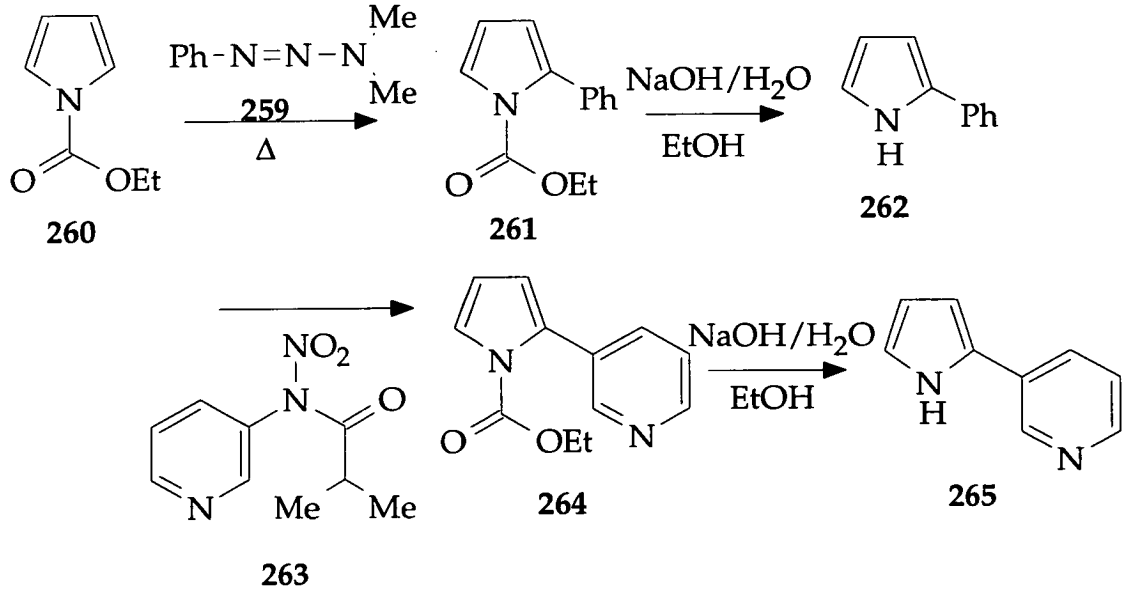
257



258

E.2. Arylation

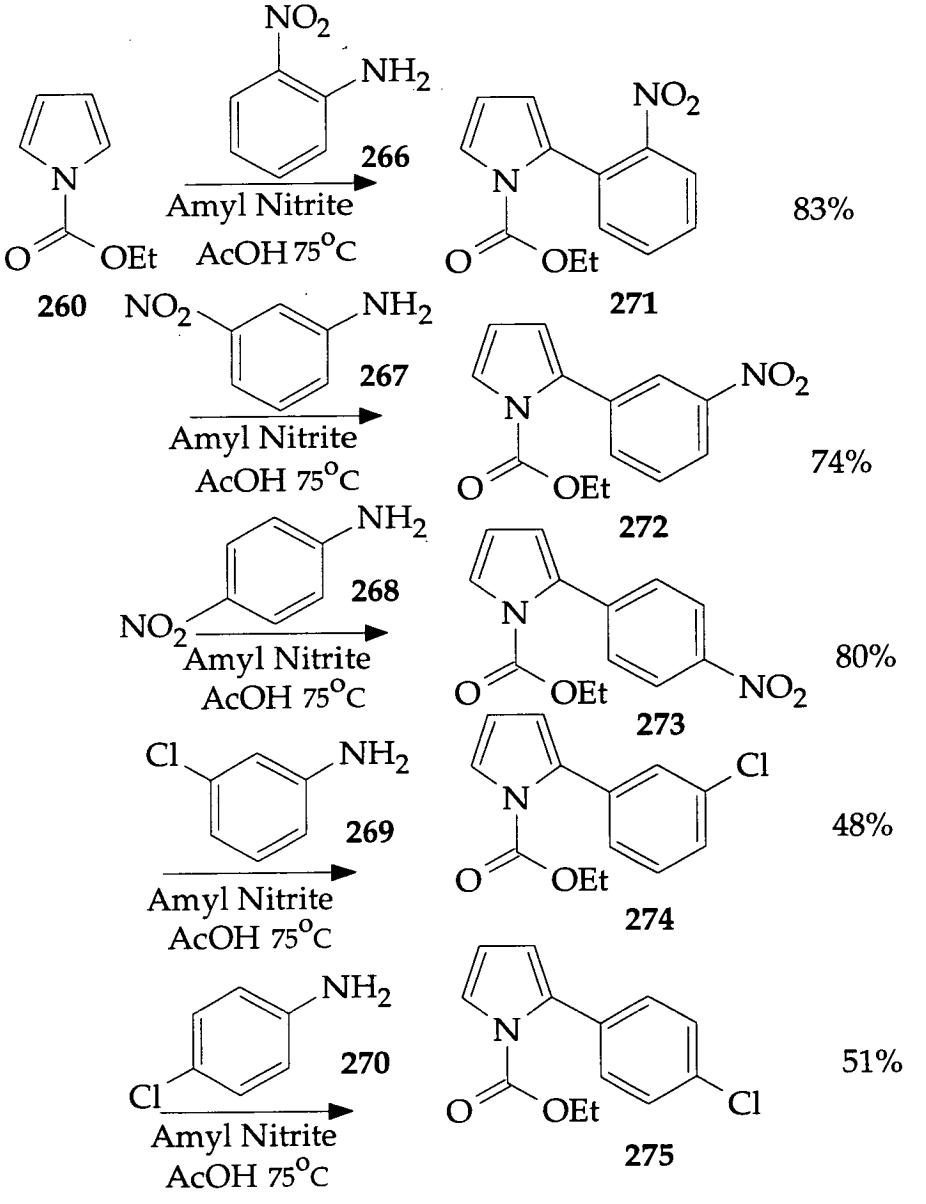
There are only a few examples of radical arylation of pyrrole. Rapoport and Look[63] have generated phenyl radicals from 3,3-dimethyl-1-phenyltriazine **259**.



260 **261** **262** **263** **264** **265**

Scheme 51

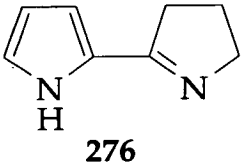
These then react with 1-carbethoxypyrrole **260** exclusively at the 2-position to give 2-phenyl-1-carbethoxypyrrole **261**. Subsequent hydrolysis of the carbethoxy group gave 2-phenylpyrrole **262** (Scheme 51). In an analogous manner pyridyl radicals were prepared by decomposition of *N*-nitroso-*N*-(3-pyridyl)isobutyramide **263**. These react exclusively at the 2-position of 1-carbethoxypyrrole **260** to yield 2-(3-pyridyl)-1-carbethoxypyrrole **264**. Hydrolysis of this then gave the deprotected 2-(3-pyridyl)pyrrole **265**.



Scheme 52

Arylation of pyrrole and 1-methylpyrrole **250** in a pseudo-Gomberg reaction proved unsuccessful.[64] However, Saeki and co-workers were successful in effecting substitution when 1-carbethoxypyrrole **260** was employed. Hence, *o*-, *m*- and *p*-nitroaniline **266-268**, gave 2-(2-nitrophenyl)carbethoxypyrrole **271**, 2-(3-nitrophenyl)carbethoxypyrrole **272** and 2-(4-nitrophenyl)carbethoxypyrrole **273**. *m*- and *p*-Chloroaniline **269-270** gave 2-(3-chlorophenyl)carbethoxypyrrole **274** and 2-(4-chlorophenyl) carbethoxypyrrole **275** respectively, in moderate to good yield (Scheme 52). The only drawback being the large excess (10 equivalents) of the pyrrole necessary to ensure high conversion.

Pyrrole itself reacts with *tert*-butoxyl radicals.[55] A hydrogen atom is abstracted from the 2-position and the resulting product in very low yield is 2-(2-pyrryl)-Δ^1-pyrroline **276**, formed by attack at the diene system of another pyrrole molecule.

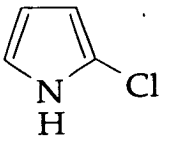


276

E.3 Halogenation

Free radical halogenation of pyrrole appears not to have been reported. This is probably due to the instability of 2-halogenopyrroles,[65] the expected products. 2-Chloropyrrole **277** decomposes in 10 seconds to 55 minutes depending on impurities: 2-bromopyrrole **278** decomposes in under 60 seconds. There is some evidence that chlorination with sulphuryl chloride in ether proceeds by a free radical or electrophilic mechanism[49] and under controlled conditions 2-chloropyrrole can be obtained. In this case the

chlorine atom would be electrophilic in nature as it attacks the 2-position.



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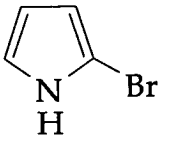


278

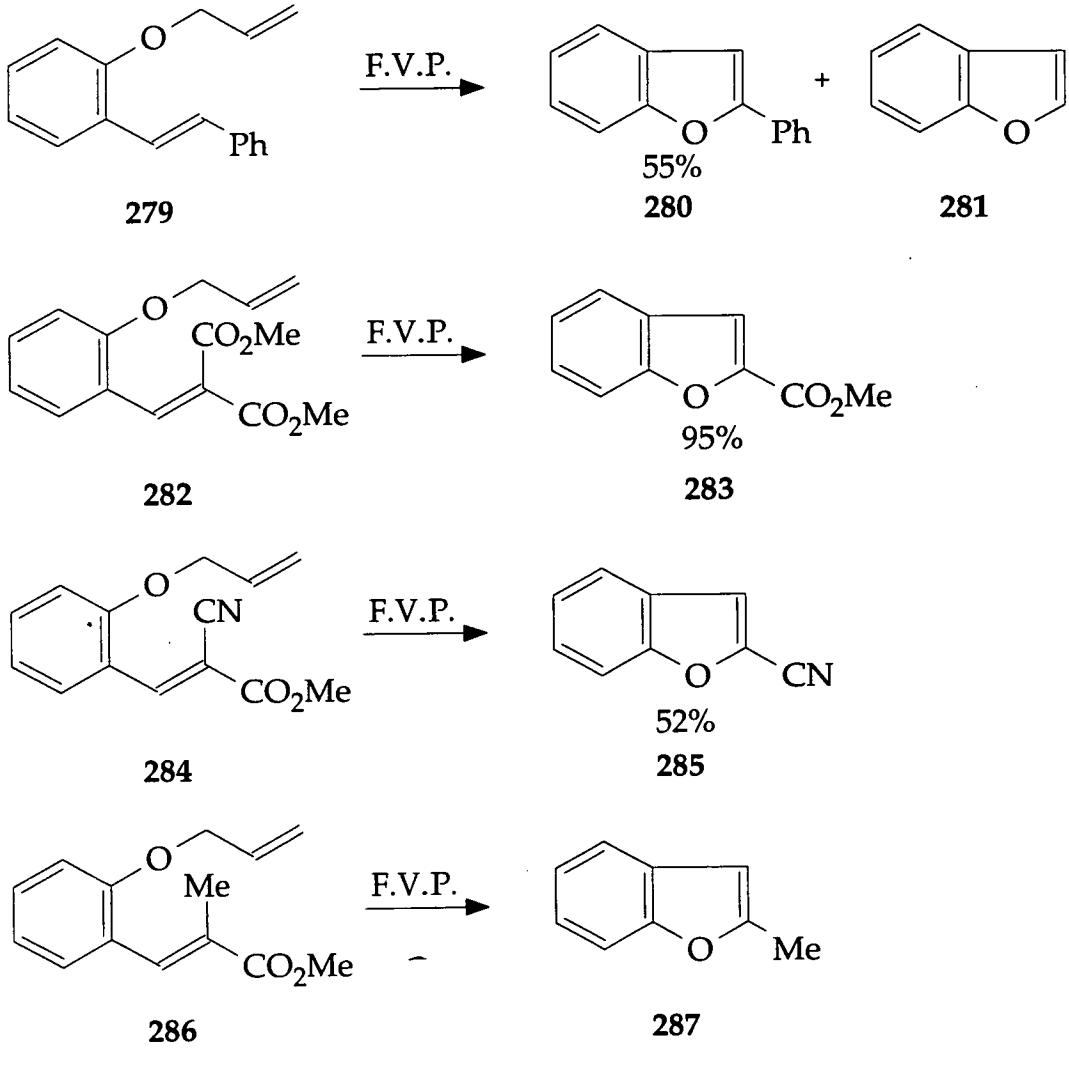
In conclusion, although there has been little systematic study of the free radical reactions of pyrrole the following general trends can be noted. A radical that is electrophilic in nature will prefer to attack the more electron rich 2-position, while a nucleophilic radical will attack the less electron rich 3-position. Steric bulk around the nitrogen cannot be used to direct reaction away from the 2-position.

DISCUSSION

A. THE USE OF AN ESTER FUNCTION AS A FREE RADICAL LEAVING GROUP IN THE FORMATION OF BENZOFURANS

A.1. Introduction

During the work of Black,[37] the pyrolysis reactions of a number of substituted 2-vinyl-1-allyloxybenzene compounds **279 282 284 286** were studied (Scheme 53).



Scheme 53

As would be expected, on generation of the phenoxyl radical by pyrolysis of the phenyl substituted compound **279** there was cyclisation followed by competitive loss of either a phenyl radical or hydrogen atom to give a mixture of 2-phenylbenzofuran **280** and benzofuran **281**. When a very high yield of 2-(carbomethoxy)benzofuran **283** was observed on pyrolysis of dicarbomethoxy compound **282**, this gave an indication that the carbomethoxy group was also a possible radical leaving group. An investigation into the efficiency of this reaction pathway was carried out by pyrolysing methyl 3-[2-(allyloxy)phenyl]-2-cyanopropenoate **284** which gave 2-cyanobenzofuran **285** specifically and 3-[2-(allyloxy)phenyl]-2-methylpropenoate **286** which, very surprisingly, gave exclusively 2-methylbenzofuran **287**. The carbomethoxy group being expelled even in preference to a methyl radical, which is a common radical leaving group[66] proved its utility as a radical leaving group.

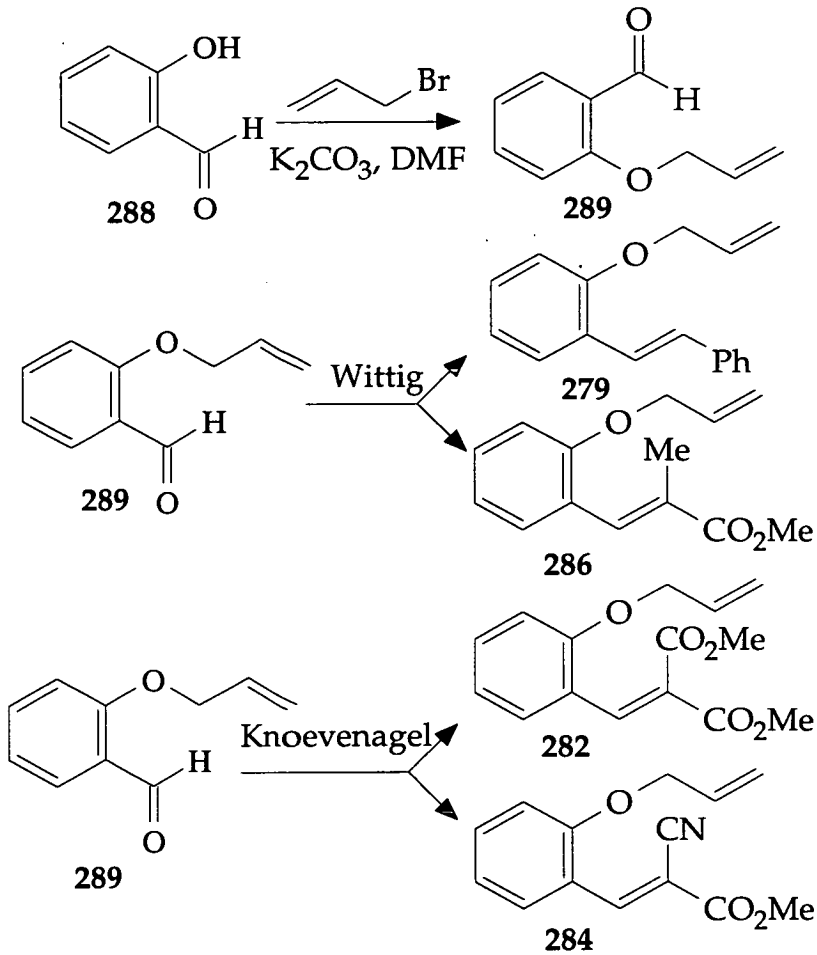
Since it was possible to examine only a few substrates in the previous work[37] it was decided to study further examples to exploit this reaction as a general preparative route to benzofurans, benzothiophenes and other fused furans. The effect of substituents in the benzene ring and at both positions of the acrylate are also investigated, together with fused and heterocyclic analogues.

A.2. Preparation of Radical Precursors: Methyl 3-[2-(Allyloxy)phenyl]propenoate 299, Methyl 3-[2-(Allyloxy)-5-chlorophenyl]propenoate 300, Methyl 3-[2-(Allyloxy)-5-nitrophenyl]propenoate 301, Ethyl 2-Methyl-3-[2-(allyloxy)phenyl]propenoate 302, Ethyl 2-Methyl-3-[2-(allyloxy)-5-chlorophenyl]propenoate 303, Methyl 3-[2-(Allyloxy)naphth-1-yl]propenoate 304, Ethyl 2-Methyl-3-[2-(allyloxy)naphth-1-yl]propenoate 305 Methyl 3-[2-(Isopropyloxy)naphth-1-yl]propenoate 306, Methyl 3-[2-(Benzyloxy)naphth-1-yl]propenoate 307 and Ethyl 3-[2-(Benzyloxy)phenyl]but-2-enoate 310

When preparing the radical precursor a choice of routes is available. The normal starting materials are commercially available compounds with an aromatic ring containing *ortho* disposed hydroxy and aldehyde or ketone groups. The two conversions which must be accomplished are alkylation of the hydroxy group to provide a radical generator and conversion of the carbonyl to an acrylate group using Wittig or Knoevenagel reactions.

The route with initial alkylation was investigated in the work of Black,[37] who first alkylated salicylaldehyde **288** (Scheme 54) to give 2-(allyloxy)benzaldehyde **289**. This removed the possibility of the acidic OH interfering with the next stage of the preparation. The 2-(allyloxy)benzaldehyde **289** was then reacted under Wittig conditions to give **279** and **286**, or Knoevenagel conditions to give **282** and **284**. The unoptimised Wittig reactions provided low to moderate yields of the desired products, while the Knoevenagel reactions gave good yields. In addition the preparation of methyl 2-(triphenylphosphoranylidene)propionoate *en route*

to **286** was time consuming and inefficient.

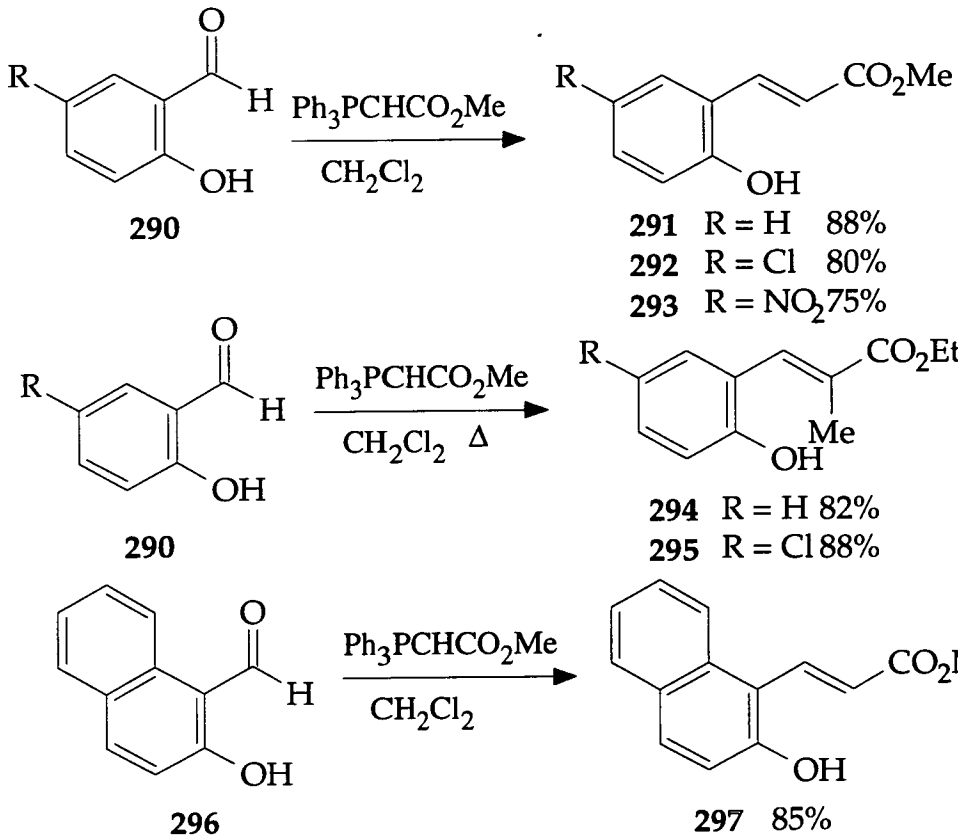


Scheme 54

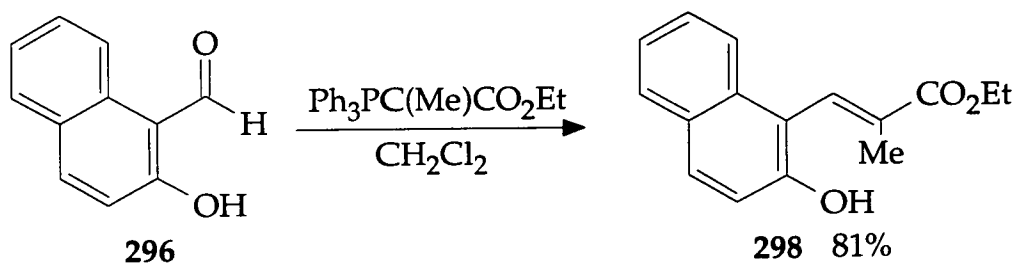
The use of the Wittig reaction on free 2-hydroxybenzaldehydes **290** and 2-hydroxynaphthaldehyde **296** as the initial step has been investigated (Scheme 55) by Cartwright[67] as part of a synthesis of fused pyranones. He found that the reaction proceeded under mild conditions giving high yields without the need for protection of the phenol group.

In view of the above results and in the knowledge that alkylation of phenols normally proceeds in high yield it was decided that the route to prepare the majority of the desired radical precursors would be, firstly Wittig reaction of the aldehyde (*eg.* Scheme 56) followed by alkylation of the

OH (Scheme 57).



Scheme 55

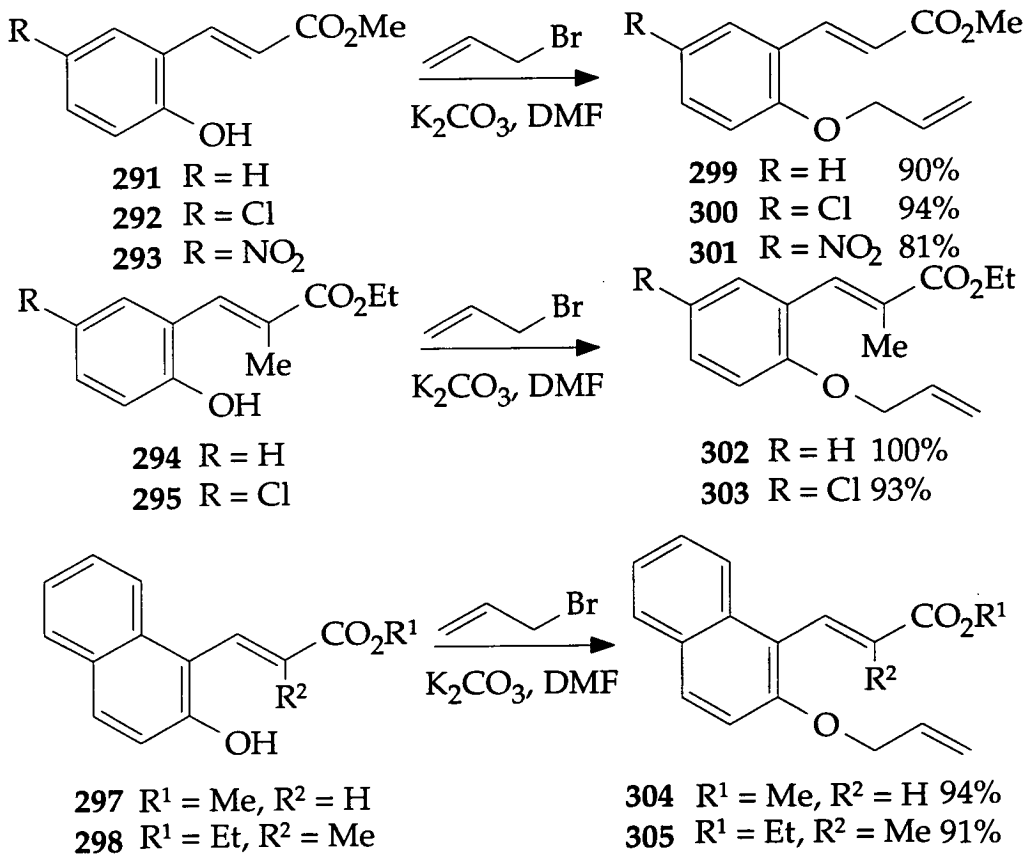


Scheme 56

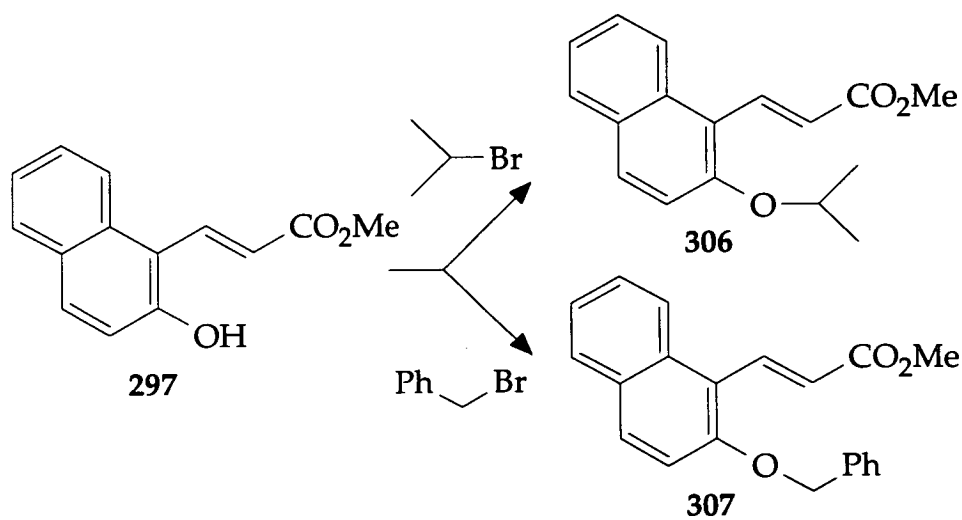
The preparation of the ethyl ester **298** was facilitated by the commercial availability of the Wittig reagent.

Alkylations were performed using potassium carbonate in dimethylformamide to generate the anion and the appropriate alkyl bromide

as alkylating agent (Schemes 57). Thus the allyl compounds **299-305** were obtained in 81-100% yield.



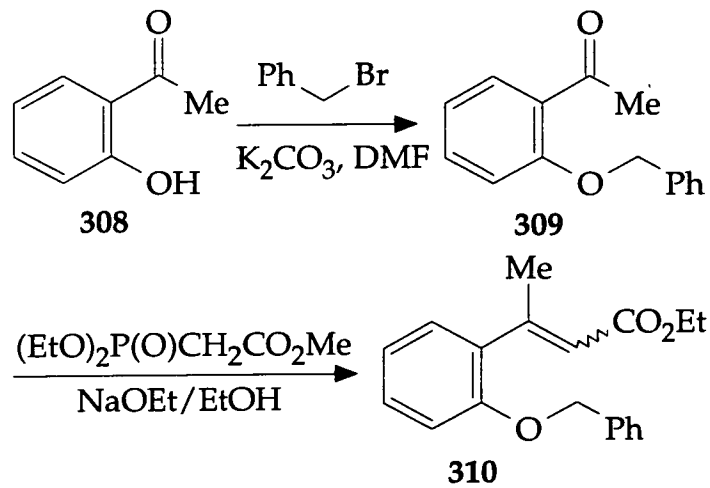
Scheme 57



Scheme 58

In the few cases where problems were encountered alternative radical generators were explored and the isopropyl compound **306** and the benzyl derivative **307** were made in 76 and 85% yield respectively.

Finally, when 2-hydroxyacetophenone **308** proved unreactive to the above Wittig reaction conditions, the acrylate was prepared by Wittig-Horner methodology (Scheme 59). To circumvent any possible rearrangement of an *O*-allyl group under basic conditions a benzyl ether was employed as a radical generator. To facilitate the olefination reaction the phenolic OH of **308** was first protected to give 2-(benzyloxy)acetophenone **309** by the standard alkylation procedure (Scheme 59).



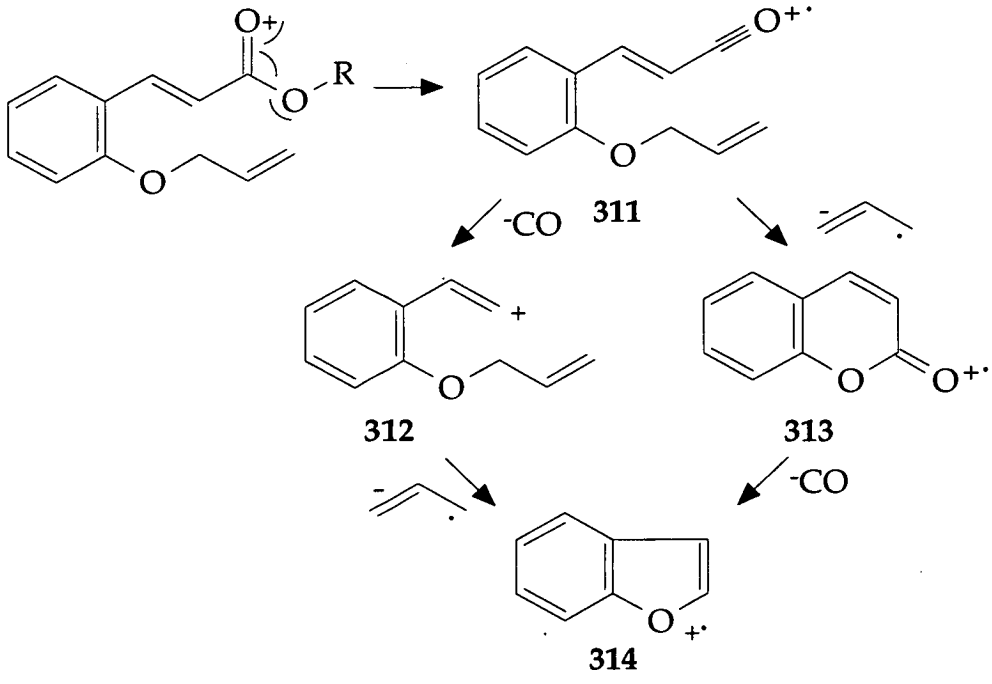
308 **309** **310**

Scheme 59

Wittig-Horner reaction of **309** with methyl diethylphosphonoacetate and sodium ethoxide in ethanol gave a good yield of ethyl 3-[2-(benzyloxy)phenyl]but-2-enoate **310** (Scheme 59) as a 3 : 1 ratio of *trans* to *cis* isomers. During heating under reflux, in sodium ethoxide in ethanol the methyl ester was exchanged for an ethyl ester.

A.3. Mass spectra of Radical Precursors: 299-307 and 310

The mass spectrua of compounds **299, 300, 301, 302, 303, 304, 305, 306, 307** and **310** shows a fragmentation patterns which are different from the expected thermal breakdown pattern of cleavage of the *O*-allyl bond. Hence, there appear to be two competing breakdown pathways (Scheme 60).



Scheme 60

The first step in both involves ionisation at the carbonyl followed by loss of a methoxy or ethoxy group to give an intermediate **311** with peaks at M-31 or M-45. The next step involves decarbonylation (to give **312**) and then loss of the allyl group (to give **314**), showing peaks at M-59 or M-73 and M-100 or M-114. Alternatively, the allyl group may be lost first (to give **313**), followed by decarbonylation (to give **314**) giving rise to peaks at M-72 or M-84 and M-100 or M-114 respectively (Scheme 60). The loss of methoxy or

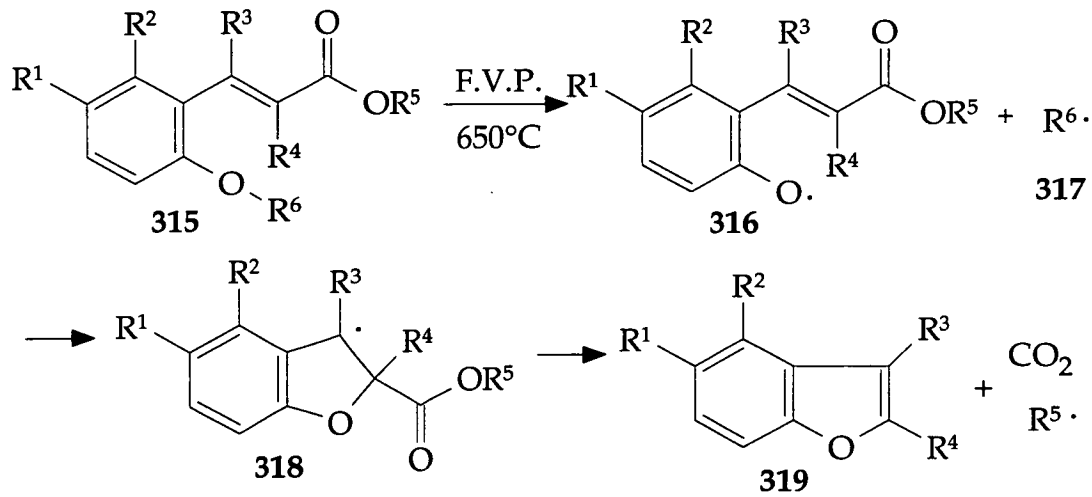
ethoxy, followed by decarbonylation is a common breakdown for ester groups.[68] With compound **306**, the isopropyl is lost first but the same base peak at M-102 for intermediate **314** is reached: with **310** the benzyl fragment (*m/z* 91) is the dominant peak in the spectrum. Further evidence for the formation of the benzofuran like intermediate **314** is found by comparison of the mass spectra of the acrylates with those of the corresponding benzo and naphthofurans. It is observed in a number of cases that the breakdown patterns of the benzo and napthofurans are broadly similar to those of the acrylates below the M-100 or M-114 peaks.

A.4. Pyrolysis of Radical Precursors: 299-307 and 310: Preparation of Benzofuran 281, 2-Methylbenzofuran 287, 3-Methylbenzofuran 320, 5-Chlorobenzofuran 321, 5-Chloro-2-methylbenzofuran 322, Naphtho[2,1-*b*]furan 323, 2-Methylnaphtho[2,1-b]furan 324 and 5-Nitrobenzofuran 325 and other products

The radical precursors **315** were subjected to pyrolysis at 650 °C (Scheme 61). The reaction proceeded as expected, with homolytic cleavage of the comparatively weak *O*-R^6 bond, to form an oxygen centred radical **316** and a stabilised radical **317** (Scheme 61). The oxygen centred radical then adds to the double bond to form the fused ring radical **318**. This radical then loses carbon dioxide and a methyl (or ethyl) radical to form the benzofuran **319**.

When the parent compound **299** was reacted the major product by ^1H NMR spectroscopy was benzofuran itself **281** (Table 2). The crude product was purified by a simple bulb to bulb distillation; chromatography was not

required.



Scheme 61

Radical precursor	R^1	R^2	R^3	R^4	R^5	R^6	Expected product	Yield(%)
299	H	H	H	H	Me	allyl	**281**	65
302	H	H	H	Me	Et	allyl	**287**	75
310	H	H	Me	H	Me	benzyl	**320**	67
300	Cl	H	H	H	Me	allyl	**321**	60
303	Cl	H	H	Me	Et	allyl	**322**	85
304	$-(CH)_4-$		H	H	Me	allyl	**323**	39
307	$-(CH)_4-$		H	H	Me	benzyl	**323**	55
306	$-(CH)_4-$		H	H	Me	isopropyl	**323**	59
305	$-(CH)_4-$		H	Me	Et	allyl	**324**	88
301	NO_2	H	H	H	Me	allyl	**325**	55

Table 2

The ability to introduce substituents on the furan ring was examined by pyrolysing the 2-methyl propenoate **302**, a reaction initially performed on a

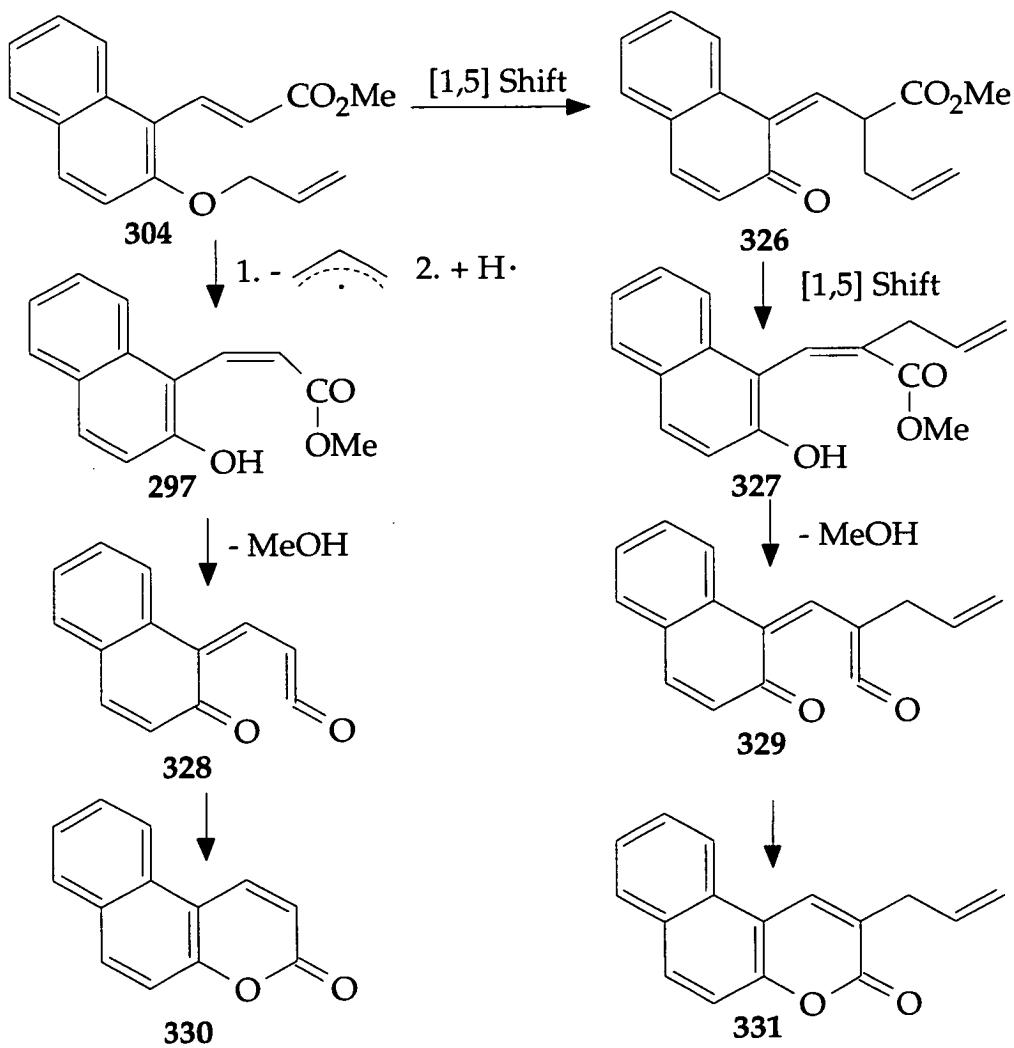
small scale by Black[37] for the corresponding methyl ester. This compound decomposed similarly to give 2-methylbenzofuran **287** in high yield, with no evidence of the possible 2-carboethoxybenzofuran by ^{1}H NMR spectroscopy: It is important to note that a possible side reaction of ethyl esters - *viz* pyrolytic *cis* elimination to give the carboxylic acid and ethylene[69] - was not observed in this case and indeed the yield of benzofurans from the ethyl ester precursors was consistently higher than from the methyl esters (Table 2). The butenoate **310** gave a high yield of 3-methylbenzofuran **320** although this had to be purified by chromatography to remove the co-formed bibenzyl, originating from dimerisation of the benzyl radical. Alternative reactions of **318** (R^3 = Me) apparently do not take place and so the synthetic route is applicable to 3-substituted benzofurans.

Moving to substitution of the benzene ring, the chloro substituted propenoates **300** and **303** gave 5-chlorobenzofuran **321** and 5-chloro-2-methylbenzofuran **322** respectively as the sole identifiable product by ^{1}H NMR spectroscopy and on a preparative scale could be conveniently purified by bulb to bulb distillation (Table 2).

When the (allyloxy)naphth-1-ylpropenoate **304** was pyrolysed however it was apparent from ^{1}H NMR spectroscopy and t.l.c that three products had been formed (Scheme 62).

Upon separation by dry flash chromatography these were identified as the expected naphthofuran **323** (39%), a naphthopyranone **330** (13%) and an allylnaphthopyranone **331** (21%) (Scheme 62). The naphthopyranone **330** was identified by comparison with spectra of an authentic sample.[67] The position of the allyl group on the allylnaphthopyranone **331** was identified by comparison of its ^{1}H NMR spectrum with **330**. Of note was the disappearance of the doublet at δ_H 6.57 corresponding to the pyranone

2-position and the loss of coupling of the 1-position proton (**330** δ_H 8.48 doublet *J* 9.8 to **331** δ_H 8.24 singlet). The pyranone **330** may arise by capture of a hydrogen atom by the initially formed radical to give the phenol **297** (Scheme 62). Such hydrogen capture reactions are well known for phenoxyl radicals under F.V.P. conditions.[17] The phenol may then ring close to the pyranone **330** by an elimination of methanol to form a ketene **328** and subsequent cyclisation.[70]

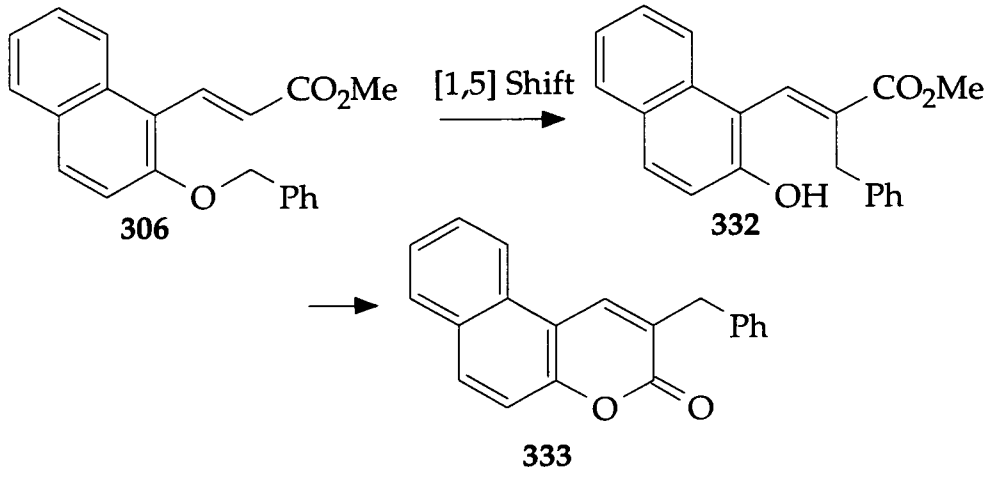


Scheme 62

The formation of the third product **331** is unprecedented in reactions of

this type. It may be explained by the occurrence of a previously unknown [1,5] shift of the allyl group to give **326** followed by a [1,5] hydrogen shift in the reverse direction to give the 2-allyl-3-(2-hydroxynaphth-1-yl)propenoate **327**. Ketene formation giving **329** and ring closure as above leads to formation of the 2-allylnaphthopyranone **331** (Scheme 62).

Hydrogen atom capture can be minimised by using benzyl rather than allyl ether precursors. Hence in an attempt to minimise the formation of the pyranone **330**, the benzyl ether **306** was pyrolysed. However, although the expected naphthofuran **323** was isolated in an improved yield of 55%, the naphthopyranone **330** was also present in 11% yield. A third product was found to be 2-benzylnaphthopyranone **333** (7%) (Scheme 63). The position of the benzyl group was determined by the same reasoning as for the allyl group of **331**, and this product can be formed by an analogous [1,5] benzyl shift to give 2-benzyl-3-(2-hydroxynaphth-1-yl)propenoate **332** as an intermediate (Scheme 63).



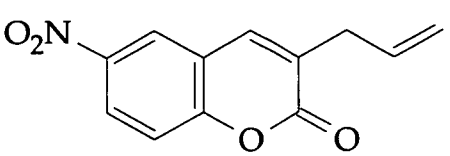
Scheme 63

The occurrence of this reaction is evidence that the initial rearrangement in the formation of the allylpyranone **330** is not a [3,5]

sigmatropic rearrangement which would not be possible with a benzyl substituent. Finally, ring closure as before gives the 2-benzylnaphtho pyranone **333** (Scheme 63).

It is known that different groups have varying migratory aptitudes[71] in sigmatropic rearrangement reactions and so in an attempt to remove the undesired 1,5 shift products the isopropyl ether **307** was pyrolysed. Only two products were obtained, the naphthofuran **323** and the naphthopyranone **330** (32%). Although the strategy was successful in eliminating one undesired product the substantial hydrogen atom flux from the coformed isopropyl radical still gave an unacceptably high level of the pyranone **330**. Nevertheless the yield of the desired naphthofuran **323** was highest by this method.

The final compound to be pyrolysed was the nitro substituted propenoate **301**. This also led to a mixture of three products which were separated and identified as the expected 5-nitrobenzofuran **325** (Table 2), a 3-allyl-6-nitrocoumarin **334** (4%) and a product which was speculatively assigned as 7-allylbenzofuran **335** (21%).



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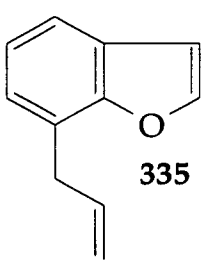


335

The allylnitrocoumarin **334** was identified by comparison with the spectra of 6-nitrocoumarin[67] and the position of the allyl group was confirmed using the same reasoning as for the allylnaphthopyranone **331**. The mechanism for formation of **334** was a [1,5] shift followed by ring closure as described

previously. The structure of the product **335** which differed from all those previously seen was mainly assigned by ^{1}H NMR spectroscopy. The presence of the furan ring was indicated by two doublets (δ 7.59 and 6.71, *J* 2.1), the presence of the *C*-allyl group was indicated by the usual peak pattern (1H at δ 6, 2H at δ 5 and 2H at δ 3.5) and the absence of the nitro group was inferred by the lack of any aromatic signals above δ 8. The position of the allyl group was inferred by the by the complexity of the aromatic pattern which ruled out 5 or 6 substitution but a 4-allyl substituent cannot be excluded by the present data.

It is of interest to consider why the allyl and benzyl rearrangement products **331, 333** and **334** were only observed in the naphthyl and nitro substituted examples **304, 306** and **301**. In the naphthyl series less aromatic character is destroyed in the initial migration product **326** than in the corresponding benzenoid compounds. With the nitro compound **301** electron withdrawal may weaken the *O*-allyl bond and facilitate migration. The anomalous product **335** is more difficult to explain and may be associated with an initial Claisen rearrangement. Although the thermal chemistry of nitro groups is well known protodenitration is unprecedented under these conditions[13] and in our apparatus nitro groups are generally unchanged at temperatures in excess of 650°C.[37] More work is required to confirm and substantiate the nature of this compound.

In conclusion this work has established that pyrolysis of *ortho O*-allyl propenoates and related compounds is a useful synthetic route to the benzofuran ring system. The reaction is compatible with a wide variety of substituents, yields are generally in the range 60-90% and in favourable cases the product can be isolated without chromatography. This methodology is extended to other fused heterocyclic systems in the next chapter.

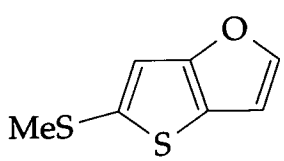
B. FORMATION OF THIENO[3,2-*b*]FURANS 352 AND THIENO[3,2-*b*]BENZOFURANS 338 AND ATTEMPTED PREPARATION OF THIENO[3,2-*b*]BENZOFURAN 338

B.1. Introduction

Three possible routes to furan rings by F.V.P. reactions of oxygen centred radicals have now been established as follows:

1. attack on *ortho* acrylates with loss of carbon dioxide and an alkyl radical.
2. attack on *ortho* aryl rings with loss of a hydrogen atom[37].
3. attack on *ortho* aryl esters with loss of carbon dioxide and a hydrogen atom[37].

Target syntheses were devised using this chemistry in an attempt to prepare three compounds 5-(methylthio)thieno[3,2-*b*]furan **336**, 2-(carbomethoxy)-5-(methylthio)thieno[3,2-*b*]furan **337** and thieno[3,2-*b*] benzofuran **338**.



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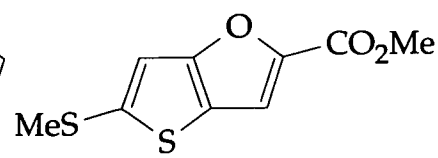

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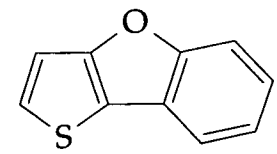
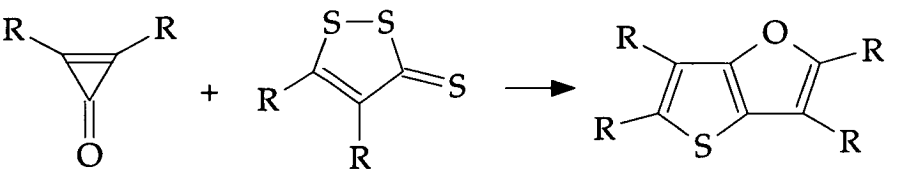


338

Very little is known of the synthesis of the thieno[3,2-*b*]furan ring system. Behringer and Meinetsberger[72] formed the polyaryl thienofuran **341** by reaction of 2,3-diarylcyclopropenones **339** with 4,5-diaryl-1,2-dithiole-3-thiones **340** (Scheme 64).

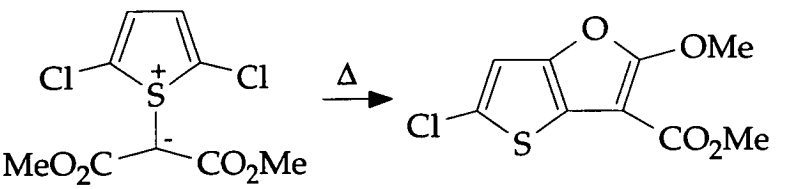
Gillespie *et al*[73] prepared 3-carbomethoxy-5-chloro-2-

methoxythieno[3,2-*b*]furan **343** by thermolysis of 2,5-dichlorothiophenium bismethoxycarbonylmethylide **342** (Scheme 65).



339 **340** **341**

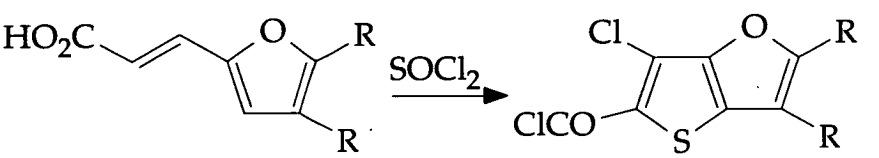
Scheme 64



342 **343**

Scheme 65

5,6-Disubstituted thieno[3,2-*b*]furans **345** were prepared in low yield by Kralovicova and coworkers[74] by treatment of 3-(fur-2-yl)propenoic acids **344** with thionyl chloride (Scheme 66)



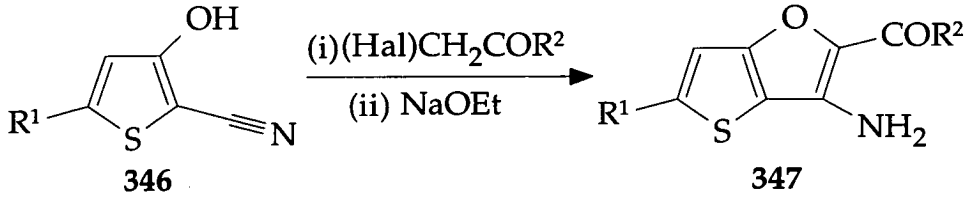
344 **345**

Scheme 66

All the above routes are unusual syntheses and are not generally applicable.

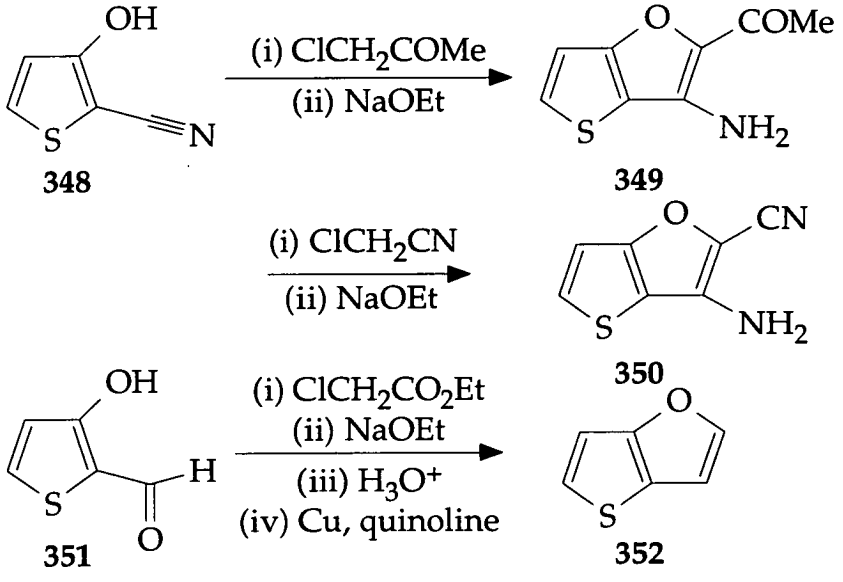
Routes which are more generally applicable begin with 2-cyano-3-hydroxythiophenes **346** and **348**, or 2-formyl-3-hydroxythiophenes **351**. The 3-hydroxy substituent is alkylated, followed by generation of a carbanion

and ring closure onto the 2-substituent to form the furan ring. This methodology was employed by Gewald and Bellmann[75] who alkylated 2-cyano-3-hydroxythiophenes **346** and then cyclised the product with sodium ethoxide to give 3-amino-2-substitutedthieno[3,2-*b*]furans **347** (Scheme 67). An extension of this reaction was also reported by Morel and co-workers[76] who prepared 3-amino-2-(carbomethoxy)thieno[3,2-*b*]furan **349** and 3-amino-2-cyanothieno[3,2-*b*]furan **350** by reacting 2-cyano-3-hydroxy thiophene **348** with 1-chloropropan-2-one and chloroacetonitrile respectively (Scheme 68).



346 **347**

Scheme 67



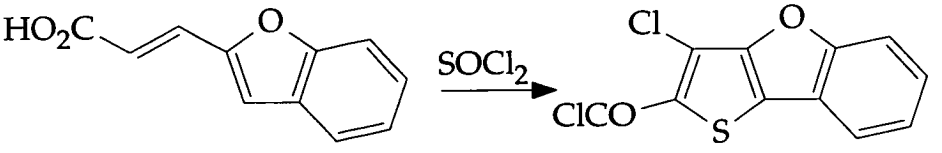
348 **349** **350** **351** **352**

Scheme 68

This group then extended this methodology[77] to prepare the parent

ring system **352** by reaction of 2-formyl-3-hydroxythiophene **351** with ethyl 2-chloroethanoate, followed by cyclisation, acid hydrolysis and decarboxylation.

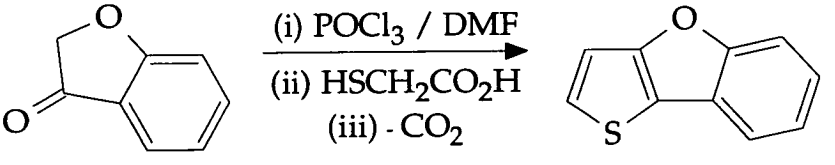
The thieno[3,2-*b*]benzofuran ring system is even less well investigated. Kralovicova and coworkers[74] extended their previous methodology (see Scheme 66) by reacting 3-(benzofur-2-yl)propenoic acid **353** with thionyl chloride to give 3-chloro-2-(carboxychloro)thieno[3,2-*b*]benzofuran **354** (Scheme 69).



353 **354**

Scheme 69

Finally Caignant and co-workers[78] prepared the parent ring system **338** and a variety of mono, di, tri and tetra methylated analogues by formylation of benzofuran-3-one **355** on the 2-position, followed by reaction with 2-thioacetic acid, cyclisation and decarboxylation to form the thiophene ring (Scheme 70).



355 **338**

Scheme 70

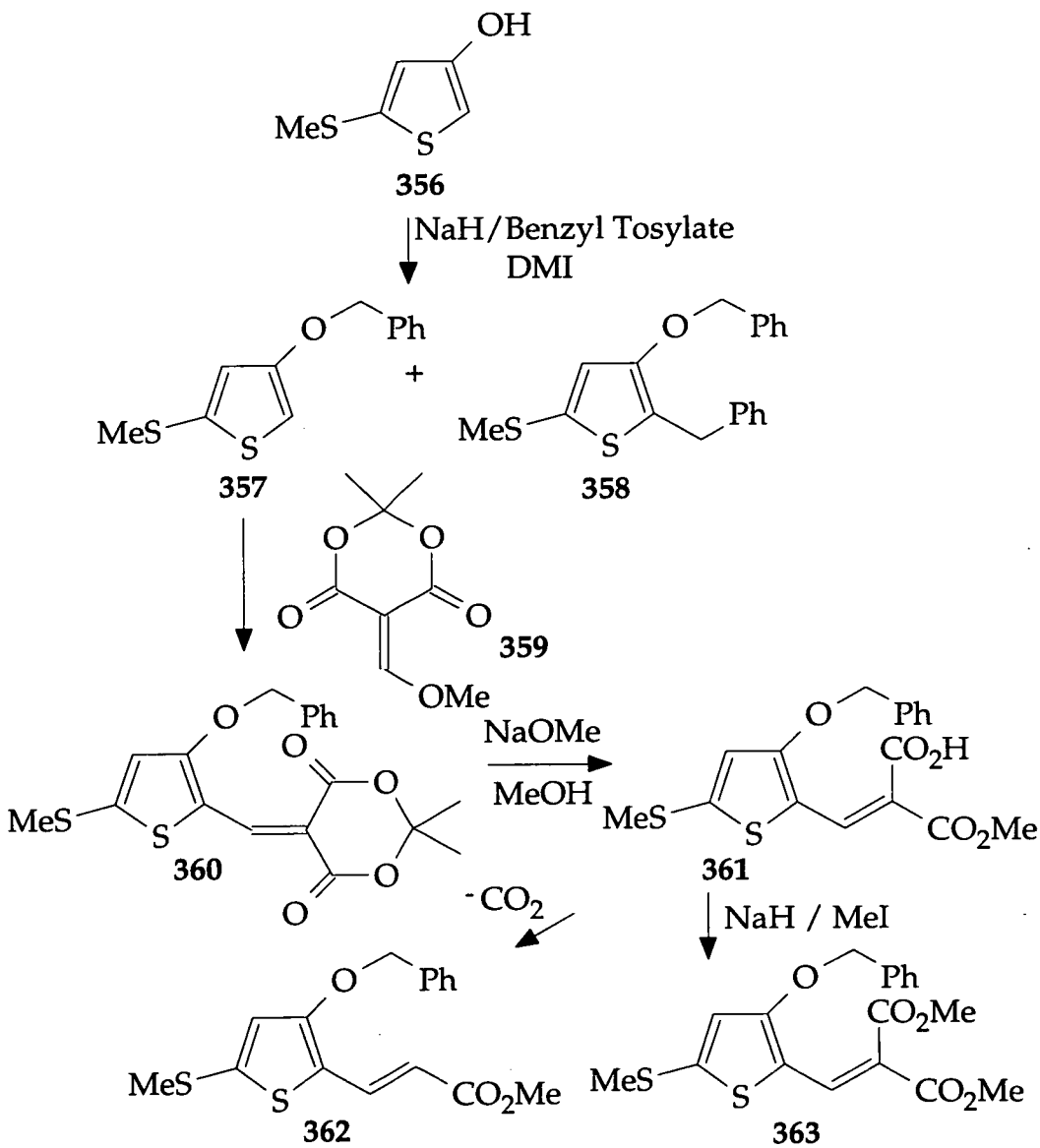
B.2. Preparation of Radical Precursors: Methyl 3-[(3-Benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate 362 and Methyl 2-Carbomethoxy-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate 363

The first preparations attempted were 5-(methylthio)thieno[3,2-*b*]furan **336** and 2-(carbomethoxy)-5-(methylthio)thieno[3,2-*b*]furan **337** using the cyclisation of oxygen centred radicals to acrylate esters, as described in the previous section. This reaction was expected to be more difficult because a fused five-five ring system is being formed with corresponding increase in the angle strain at the bridgehead atoms.[80]

3-Hydroxy-5-(methylthio)thiophene **356** (Scheme 71)[80] was available by F.V.P. of bis(methylthio)methylene Meldrum's acid.[80] Attempts to formylate this compound (Phosphoryl chloride in DMF) proved unsuccessful with only starting material being recovered. It was assumed that the 3-hydroxy group was affecting reaction so this group was *O*-benzylated. This served the twin purposes of providing a site for radical generation and protection of the thiophene hydroxyl group. When the hydroxythiophene **356** was alkylated using conditions known to direct alkylation to the oxygen,[80] (NaH/benzyl tosylate in DMI) a mixture of products was obtained. On examination by ^{1}H NMR spectroscopy these were seen to be the desired 3-(benzyloxy)-5-(methylthio)thiophene **357** and a product of dialkylation, 2-benzyl-3-(benzyloxy)-5-(methylthio)thiophene **358** (Scheme 71). These were separated by careful bulb to bulb distillation to give a moderate yield (39%) of 3-(benzyloxy)-5-(methylthio)thiophene **357**. This compound also could not be formylated ($POCl_3$ in DMF) so a different approach was attempted.

Thus, 3-(benzyloxy)-5-(methylthio)thiophene **357** was reacted with

methoxymethylene Meldrum's acid[80] **359** in acetonitrile to yield 5-{[3-(benzyloxy)-5-(methylthio)thiophen-2-yl]methylene}-2,2-dimethyl-1,3-dioxan-4,6-dione **360** (42%) (Scheme 71). This compound **360** was then treated with sodium methoxide in methanol, which resulted in ring opening of the Meldrum's acid ring and loss of acetone to give methyl 2-carboxy-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **361**.



Scheme 71

From this compound the two radical precursors could be prepared (Scheme 71), either by decarboxylation resulting from bulb to bulb distillation to give methyl 3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **362** (67%), or by conversion of the acid function to an ester function by reaction with potassium carbonate and methyl iodide to give methyl 2-(carbomethoxy)-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **363** (82%).

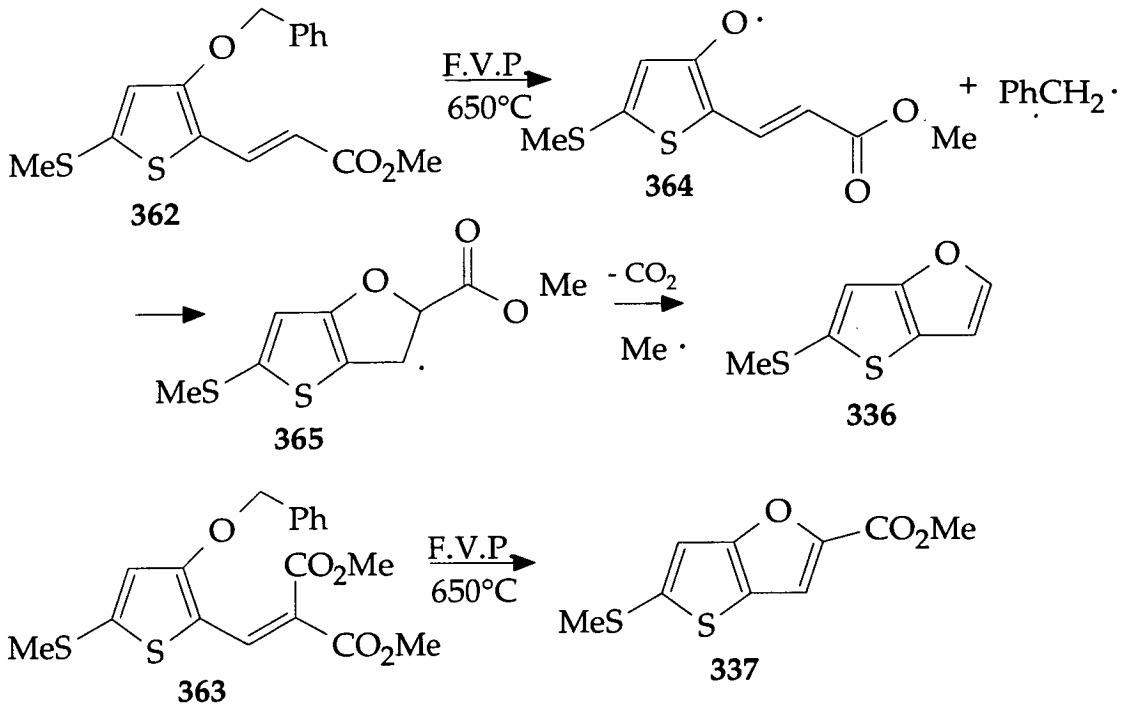
B.3. Mass Spectra of Radical Precursors: 362 and 363

Methyl 3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **362** and methyl 2-(carbomethoxy)-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl] propenoate **363** both show strong base peaks at *m/z* 91 indicating that a benzyl fragment ion is formed. The molecular ion of both compounds is very weak, but both show loss of OMe (M-31) and then decarbonylation (M-59). This is the expected breakdown of an ester group.

B.4. Pyrolysis of Radical Precursors: 362 and 363 to give 5-(methylthio)thieno[3,2-*b*]furan 336 and 2-(carbomethoxy)-5-(methylthio)thieno[3,2-*b*]furan 337

Firstly the methyl 3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl] propenoate **362** was subjected to pyrolysis (Scheme 72). Cleavage of the *O*-benzyl bond gave the desired radical **364** and a co-formed benzyl radical. The radical **364** then cyclised to the acrylate double bond to give an intermediate **365**, which then eliminated carbon dioxide and a methyl radical to form the product **336** (Scheme 72). After separation of the co-formed bibenzyl the small quantity of the major product was characterised as the

expected 5-(methylthio)thieno[3,2-*b*]furan **336** by ^{1}H NMR spectroscopy (see below). Proton chemical shifts in this compound were H-2 δ 7.54, H-3 δ 6.67 and H-6 δ 7.15 and the coupling constant were $^3J_{2\text{-}3}$ 2.0, $^5J_{2\text{-}6}$ unresolved and $^5J_{3,6}$ 0.8 Hz.



Scheme 72

Methyl 2-(carbomethoxy)-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **363** was pyrolysed in the same manner (Scheme 72) to give a product which was assigned as the expected 2-(carbomethoxy)-5-(methylthio)thieno[3,2-*b*]furan **337** by ^{1}H NMR spectroscopy. Proton chemical shifts in this compound were H-3 δ 7.41 and H-6 δ 7.09 and the coupling constant was $^5J_{3\text{-}6}$ 0.6 Hz. Both compounds were obtained in approximately 20% yield and had decomposed after 2 days in chloroform solution. Mass spectra were therefore not recorded. The low yields may be due to the reaction being unfavourable because of the angle strain in the ring

system or alternatively the products may be lost during chromatography due to their sensitivity.

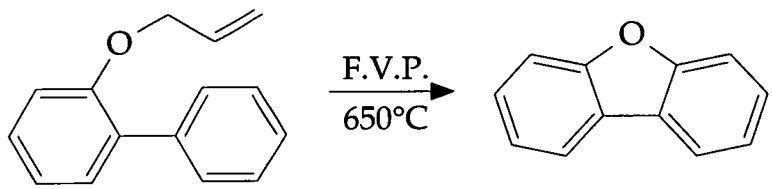
The proton chemical shifts and proton-proton coupling constants were compared with the results of Paulmier[77] who reported these values for the parent compound **352** (Chemical shifts H-2 δ 7.51, H-3 δ 6.69 and H-6 δ 7.02 and the coupling constant $^3J_{2\text{-}3}$ 2.0, $^5J_{2\text{-}6} \cong 1$ and $^5J_{3\text{-}6} \cong 0.8$).

For the 2-unsubstituted compound **336** the H-2 chemical shift is comparable with that of the parent compound **352** as is the $^3J_{2\text{-}3}$ coupling constant; however the $^5J_{2\text{-}6}$ although unresolved must be less than the 1 Hz reported by Paulmier[77]. The H-3 proton in **336** has a chemical shift almost identical with the parent compound **352** and the coupling constant $^5J_{3\text{-}6}$ is similar. In **337** the ester function at the 2-position has the effect of increasing the chemical shift of H-3 by around 0.7 ppm. This effect was also seen by Paulmeir[77] who reports that the 2-carboxylic acid derivative shows an increase of around 1.0 ppm for the chemical shift of H-3 when compared to the parent **352**. The chemical shifts of H-6 for the 5-methylthio compounds **336** and **337** were comparable with those of the parent compound **352**. It can be shown by comparing two model compounds 3-methoxythiophene and 5-(methylthio)-3-methoxythiophene[80] that the methylthio group has very little effect on the chemical shift of an adjacent proton in thiophene systems.

These results suggest that the above methodology may provide a viable route to fused five-five ring systems, having shown that the radical induced ring closure is successful if the appropriate precursor can be synthesized.

B.5. Preparation and Pyrolysis of Radical Precursors: 3-(Allyloxy)-2-phenylthiophene 369, 3-(Benzyloxy)-2-phenyl thiophene 371 and 3-(Benzyloxy)-2-(4-methylphenyl) thiophene 373

A possible route to thienobenzofuran was suggested by the work of Black[37] who prepared dibenzofuran **367** in good yield (75%) by pyrolysis of 2-(allyloxy)biphenyl **366** (Scheme 73).



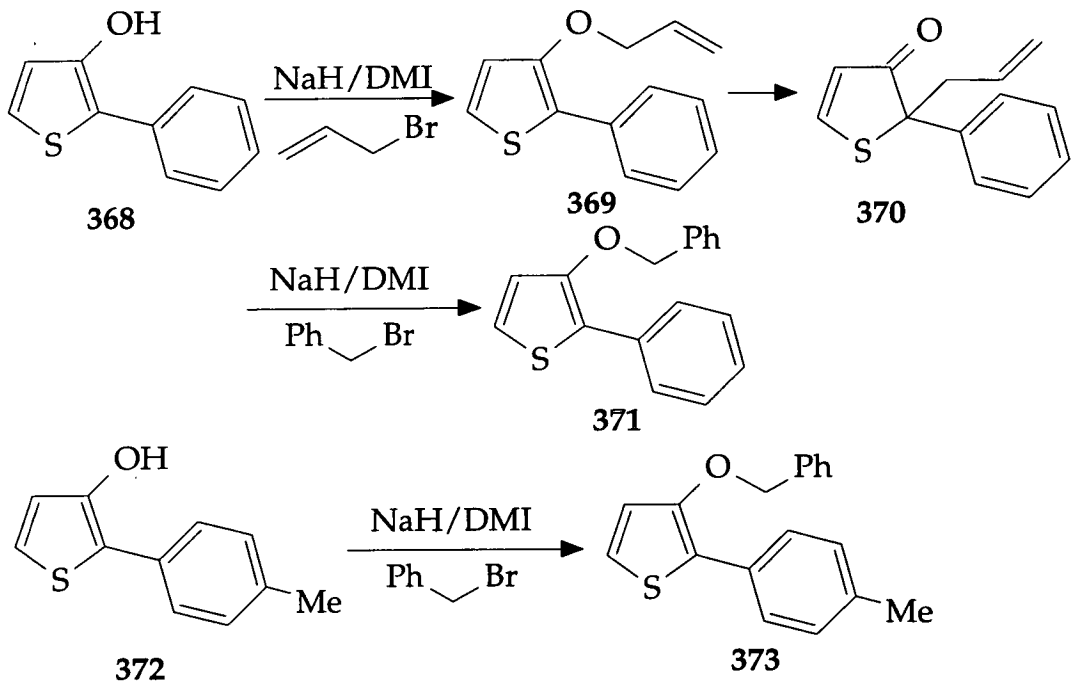
366 **367**

Scheme 73

Replacing one of the phenyl rings with a thiophene ring should give a thienofuran preparation. 3-Hydroxy-2-phenylthiophene **368** was prepared by the method of Hunter[80]. In order to form a radical generation site this compound was allylated to give 3-(allyloxy)-2-phenylthiophene **369** (Scheme 74). Upon attempted distillation this compound undergoes Claisen rearrangement to give the 2,2-disubstituted thiophenone **370**.

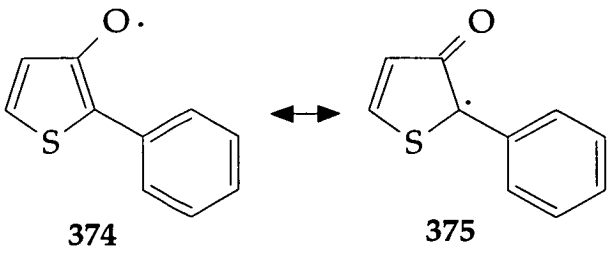
On pyrolysis under the usual conditions, no cyclised product could be found by GC-MS and analysis of the ^{1}H NMR spectrum showed the presence of the starting 3-hydroxythiophene compound **368** (50%). In an attempt to minimise the hydrogen atom flux and hence the amount of recovered 3-hydroxythiophene, 3-(benzyloxy)-2-phenylthiophene **371** was prepared (Scheme 74) and pyrolysed. This again showed no evidence of the desired cyclised material but the hydroxy compound **368** was present in

reduced (40%) yield. In an attempt to ascertain if H-atom capture was the only process taking place 3-(benzyloxy)-2-(4-methylphenyl)thiophene **373** was prepared from 3-hydroxy-2-(4-methylphenyl)thiophene **372** (Scheme 74) and pyrolysed. Analysis of the ^{1}H NMR spectrum showed the presence of a number of methyl peaks which suggests that the reaction is more complex than simple H-atom capture to regenerate the hydroxythiophene starting material, but no other products could be isolated.



Scheme 74

It is clear from these results that the (thiophen)oxyl radical as generated by pyrolysis of the *O*-allyl or *O*-benzyl derivatives, shows much less tendency to cyclise onto adjacent phenyl groups than the corresponding phenoxyl radicals. This may be due to resonance stabilisation between the radical **374** and the 3-oxothiophen-2-yl radical **375** (Scheme 75) which is captodatively stabilised and perhaps less reactive.

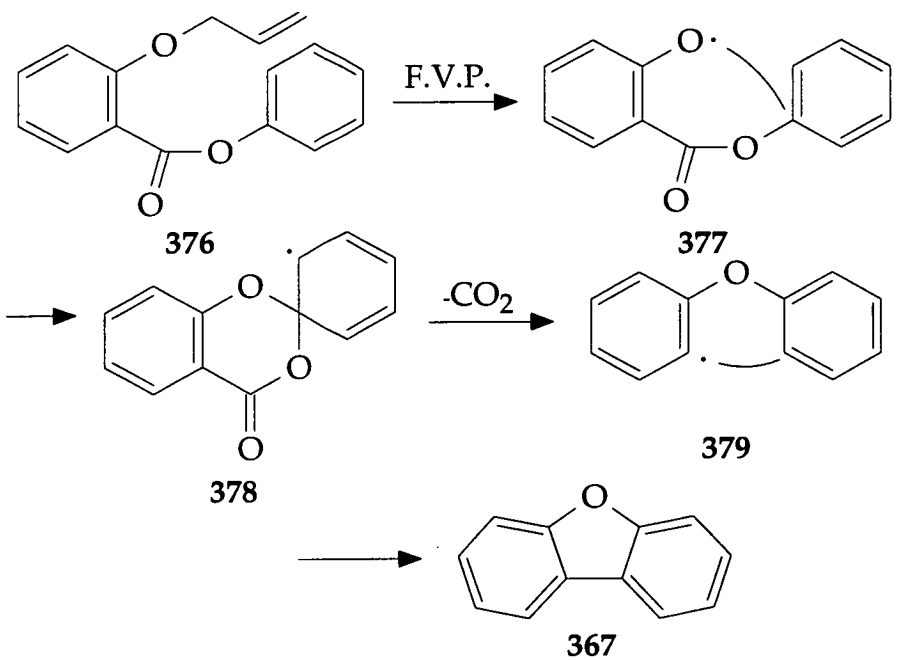


374 375

Scheme 75

B.6. Preparation and Pyrolysis of Radical Precursor: [5-(methylthio)thiophen-3-yl] 2-(allyloxy)benzoate 382

The final attempted method for the preparation of thienobenzofuran also came from the work of Black[37] who prepared dibenzofuran **367** by pyrolysis of **376**, to give the initial radical **377** which cyclises to give a spiro intermediate **378**. This intermediate **378** then loses carbon dioxide to form the radical **379** which then cyclises to form dibenzofuran **367** (Scheme 76).

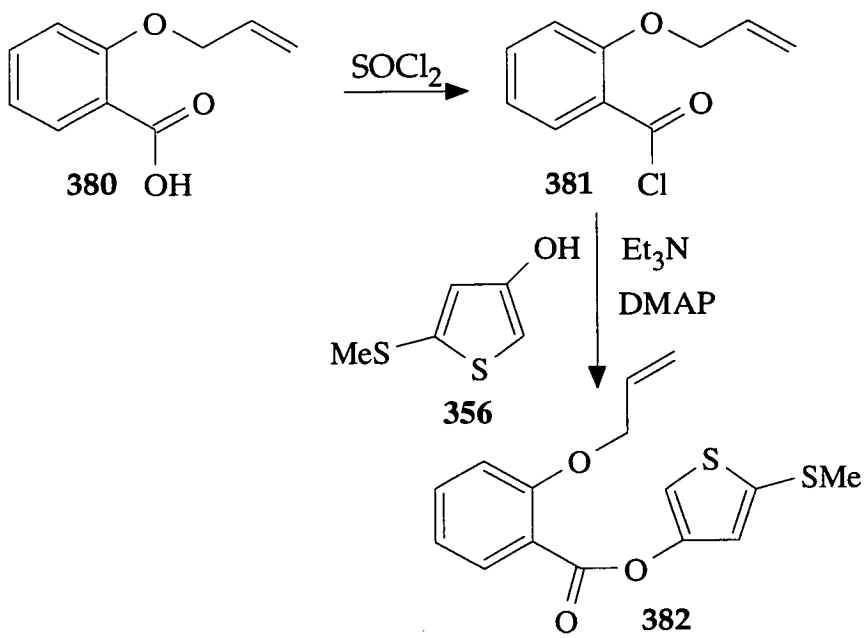


376 377 378 379 367

Scheme 76

Replacing either of the phenyl rings with a thiophene provides possible routes to thienofurans. However, replacement of the phenol portion of the ester in **376** has the advantage that a phenoxyl radical, which is known to cyclise is formed initially.

The acid portion of the ester **382** was to be provided by the acid chloride **381** (Scheme 77) prepared by the action of thionyl chloride on 2-(allyloxy)benzoic acid **380**. The alcohol portion of the ester **382** was 3-hydroxy-5-(methylthio)thiophene **356** (Scheme 77) which was easily prepared by the method of Hunter[80]. Treatment of a mixture of the thiophene **356** and the acid chloride **381** with triethylamine in the presence of a catalytic amount of 4-*N*,*N*-dimethylaminopyridine resulted in formation of the ester [5-(methylthio)thiophen-3-yl] 2-(allyloxy)benzoate **382** in 72% yield (Scheme 77).



Scheme 77

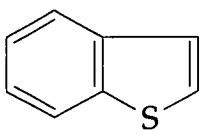
Upon pyrolysis, [5-(methylthio)thiophen-3-yl] 2-(allyloxy)benzoate **382**

did not give any of the desired cyclised product. Analysis of the ^{1}H NMR spectrum showed the the major identifiable product was the starting 3-hydroxy-5-(methylthio)thiophene **356** in 11% yield. This type of product resulting from an alternative cleavage of the ester linkage has been observed in the work of Black[37] as a minor product in most cases and as the major product in one heterocyclic example. In this case *ipso*-attack of the phenoxyl radical would give a localised radical at the thiophene 2-position instead of the delocalised radical **378** and this may be sufficient to cause the reaction to take an alternative course.

C. PREPARATION OF BENZOTHIOPHENE USING AN ACRYLATE ESTER RADICAL LEAVING GROUP

C.1. Introduction

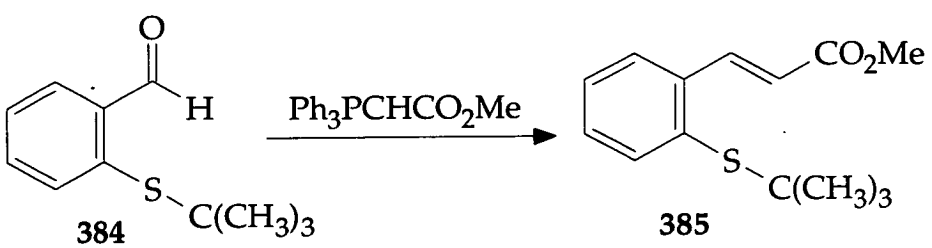
Having shown that a wide variety of benzofurans could be prepared from *ortho*-(allyloxy)acrylate esters an attempt was now made to apply this methodology to the preparation of the benzothiophene ring system **383**.



383

C.2. Preparation and X-ray Crystal Structure Determination of Radical Precursor: Methyl 3-[2-(*t*-Butylthio)phenyl] propenoate 385

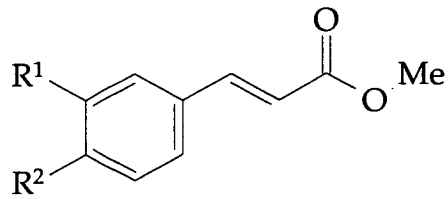
This preparation began with commercially available 2-(*t*-butylthio)benzaldehyde **384**. This compound was reacted with the Wittig reagent, methyl triphenylphosphoranylideneacetate (Scheme 78) to give 3-[2-(*t*-butyl)phenyl]propenoate **385** in high yield (95%).



384 **385**

Scheme 78

In view of this compound having two large *ortho* substituents (*t*-butylthio and methyl acrylate), a crystal structure was recorded to determine the interaction of these two groups (Figure 1). The results obtained were compared with the model compounds *m*-azoxy-*trans*-cinnamate[81] **386** and 4-(2-carboxyvinyl)-α-cyanocinnamic acid[82] **387**.



	R^1	R^2
386	$NN(O)C_6H_4CHCHCO_2Me$	H
387	H	$CH_2C(CN)CO_2Me$

Bond lengths in the acrylate group were the same as in the model compounds and those in the butylthio group were consistent with average values[83]; however the benzene ring was substantially affected with the bond between the substituents being extended from the average value[83] of 1.384 Å to 1.411(2) Å and the bonds 2,3 to both substituents shortened to 1.374(2) Å. Surprisingly, the cisoid angle between the acrylate group and the benzene ring is reduced, moving the acrylate in the direction of the butylthio group when compared with other cinnamates. The angle between the butylthio group and the benzene ring is however increased moving this group away from the *ortho* substituent. The angle between the two bonds on sulphur is smaller than tetrahedral but not unusual for sulphides in general.[84] One of the methyl groups of the butyl group forms a smaller angle between itself and the sulphur atom when compared with the two other methyl groups. There is a slight torsion of the acrylate group away from the plane of the benzene ring but not greater than expected.

X-Ray Crystal Structure of 3-[2-(t-butyl)phenyl]propenoate 385

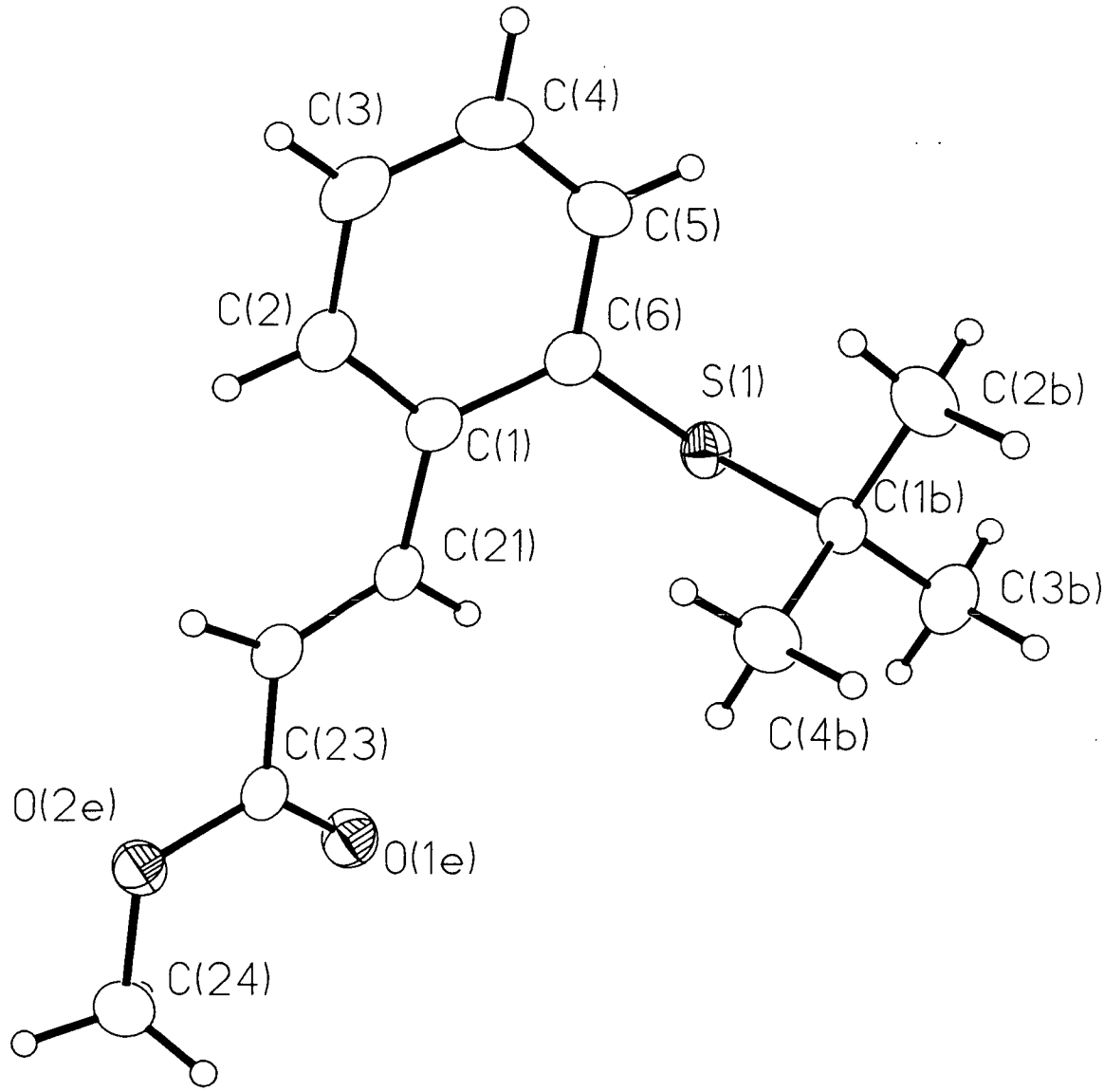


Figure 1

The most surprising feature is however the large torsion of the *t*-butyl group relative to the benzene ring, with an angle of 87° between the plane of the benzene ring and the S-*t*-butyl bond.

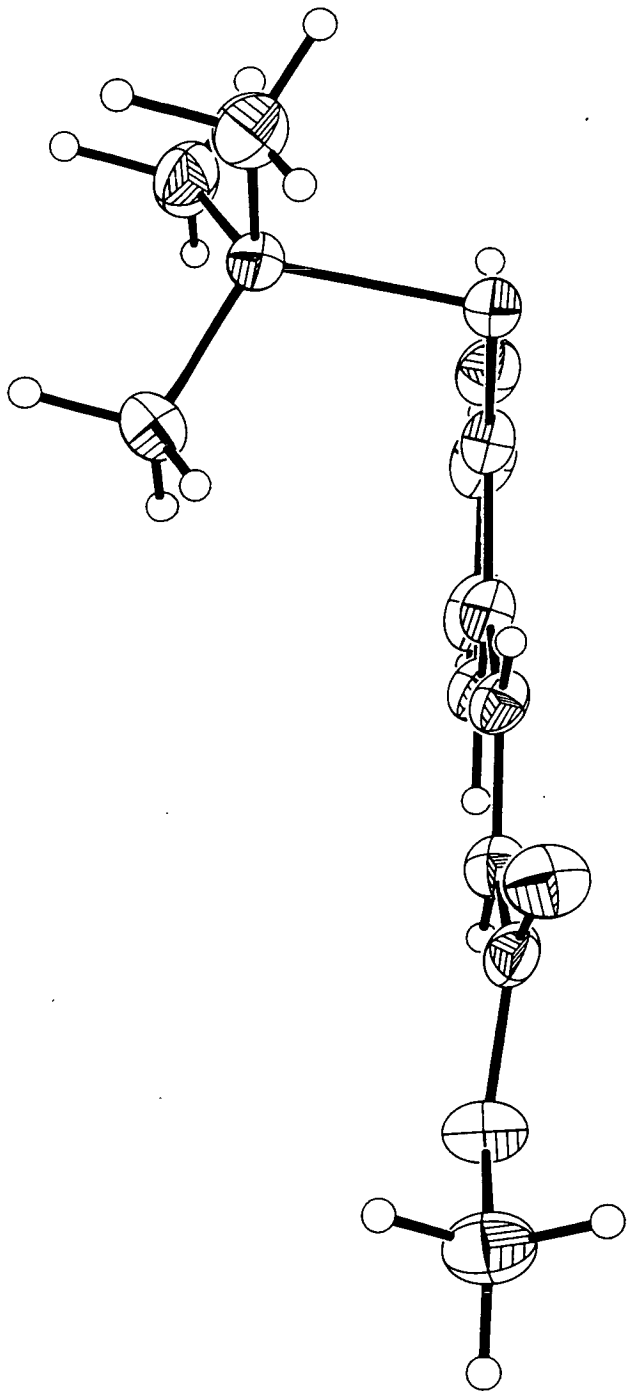


Figure 1 (continued)

Table 1. Bond Lengths(A) with standard deviations

C(1)	- C(2)	1.3992(21)	C(1b)	-C(2b)	1.5159(24)
C(1)	- C(6)	1.4110(20)	C(1b)	-C(3b)	1.5205(24)
C(1)	-C(21)	1.4646(20)	C(1b)	-C(4b)	1.5214(24)
C(2)	- C(3)	1.3741(24)	C(21)	-C(22)	1.3256(21)
C(3)	- C(4)	1.3820(25)	C(22)	-C(23)	1.4704(20)
C(4)	- C(5)	1.3739(24)	C(23)	-O(1E)	1.2066(18)
C(5)	- C(6)	1.3978(22)	C(23)	-O(2E)	1.3458(17)
C(6)	- S(1)	1.7772(15)	O(2E)	-C(24)	1.4449(21)
S(1)	-C(1b)	1.8547(15)			

Table 2. Angles(degrees) with standard deviations

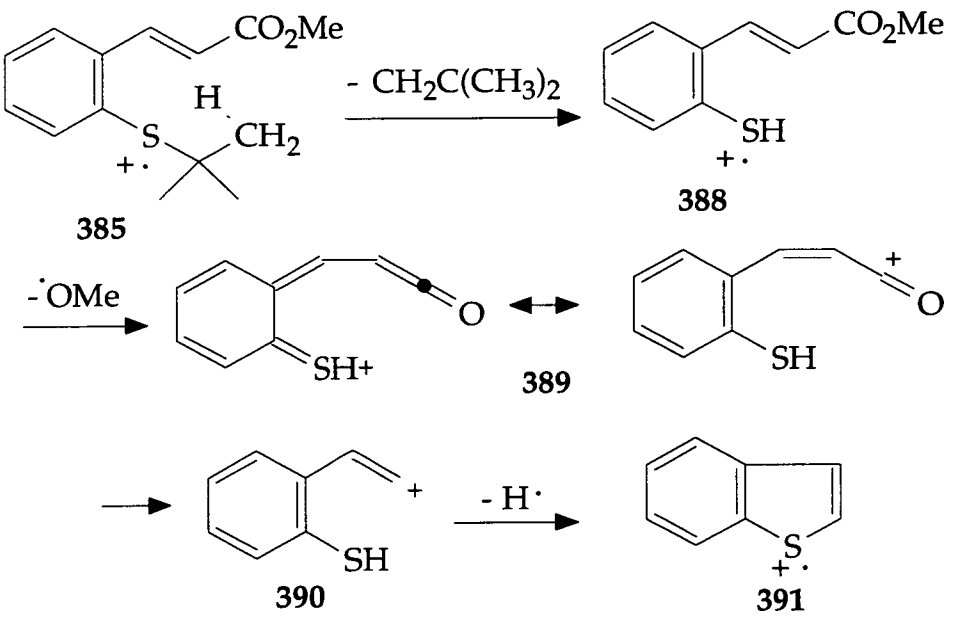
C(2)	- C(1)	- C(6)	118.09(13)	S(1)	-C(1b)	-C(3b)	110.89(11)
C(2)	- C(1)	-C(21)	120.96(13)	S(1)	-C(1b)	-C(4b)	110.70(11)
C(6)	- C(1)	-C(21)	120.93(13)	C(2b)	-C(1b)	-C(3b)	110.73(14)
C(1)	- C(2)	- C(3)	121.63(15)	C(2b)	-C(1b)	-C(4b)	110.46(14)
C(2)	- C(3)	- C(4)	119.93(16)	C(3b)	-C(1b)	-C(4b)	110.68(14)
C(3)	- C(4)	- C(5)	119.94(16)	C(1)	-C(21)	-C(22)	127.68(14)
C(4)	- C(5)	- C(6)	121.09(15)	C(21)	-C(22)	-C(23)	120.00(13)
C(1)	- C(6)	- C(5)	119.24(14)	C(22)	-C(23)	-O(1E)	125.85(13)
C(1)	- C(6)	- S(1)	122.47(11)	C(22)	-C(23)	-O(2E)	111.11(12)
C(5)	- C(6)	- S(1)	118.26(11)	O(1E)	-C(23)	-O(2E)	123.04(13)
C(6)	- S(1)	-C(1b)	103.67(7)	C(23)	-O(2E)	-C(24)	115.36(12)
S(1)	-C(1b)	-C(2b)	103.17(11)				

Table 3. Torsion angles(degrees) with standard deviations

C(6)	- C(1)	- C(2)	- C(3)	1.23(23)	C(4)	- C(5)	- C(6)	- S(1)	-179.30(13)
C(21)	- C(1)	- C(2)	- C(3)	-177.13(15)	C(1)	- C(6)	- S(1)	-C(1b)	-94.82(13)
C(2)	- C(1)	- C(6)	- C(5)	-3.05(21)	C(5)	- C(6)	- S(1)	-C(1b)	87.00(13)
C(2)	- C(1)	- C(6)	- S(1)	178.79(11)	C(6)	- S(1)	-C(1b)	-C(2b)	-179.55(10)
C(21)	- C(1)	- C(6)	- C(5)	175.32(14)	C(6)	- S(1)	-C(1b)	-C(3b)	61.88(12)
C(21)	- C(1)	- C(6)	- S(1)	-2.85(20)	C(6)	- S(1)	-C(1b)	-C(4b)	-61.38(12)
C(2)	- C(1)	-C(21)	-C(22)	-3.79(24)	C(1)	-C(21)	-C(22)	-C(23)	179.85(14)
C(6)	- C(1)	-C(21)	-C(22)	177.90(15)	C(21)	-C(22)	-C(23)	-O(1E)	-6.54(23)
C(1)	- C(2)	- C(3)	- C(4)	1.3(3)	C(21)	-C(22)	-C(23)	-O(2E)	172.79(13)
C(2)	- C(3)	- C(4)	- C(5)	-1.9(3)	C(22)	-C(23)	-O(2E)	-C(24)	-177.19(12)
C(3)	- C(4)	- C(5)	- C(6)	0.1(3)	O(1E)	-C(23)	-O(2E)	-C(24)	2.16(20)
C(4)	- C(5)	- C(6)	- C(1)	2.45(23)					

C.3. Mass Spectra of Radical Precursor: 385

The mass spectrum of methyl 3-[2-(*t*-butyl)phenyl]propenoate **385** showed a breakdown pattern which was similar to the expected thermal breakdown. Initial ionisation is believed to take place on the sulphur atom. This is followed by a rearrangement, which results in the loss of the *t*-butyl group as 2-methylpropene to give the thiol **388** at M-56 (Scheme 78). This is then followed by the usual breakdown for esters with loss of OMe to give **389** at M-87, followed by loss of CO to give **390** and a hydrogen atom to give a base peak for **391** at M-115 (Scheme 79).



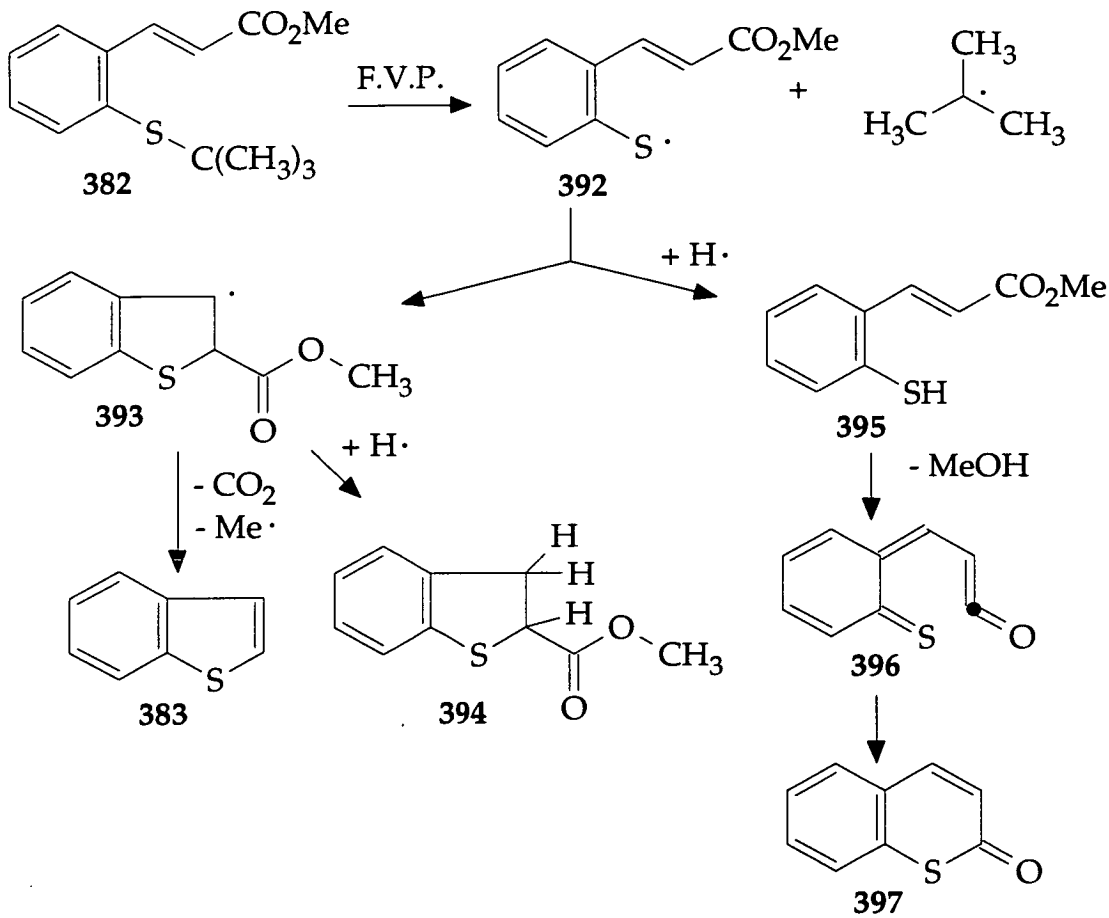
Scheme 79

A competing pathway for **385** is loss of a *t*-butyl cation giving a large peak at *m/z* 57.

C.4. Pyrolysis of Radical Precursor: Methyl 3-[2-(*t*-Butylthio) phenyl]propenoate 385: Formation of Benzothiophene 383 and other Products

Upon pyrolysis, methyl 3-[2-(*t*-butyl)phenyl]propenoate **385** gave three products which were separated by dry flash chromatography. The first to elute was identified as the expected benzothiophene **383**. The second was identified as 2-(carbomethoxy)-2,3-dihydrobenzothiophene **394** and the third as 2*H*-1-benzothiopyran-2-one **397**. Upon pyrolysis it would be expected that the S-*t*-butyl bond would homolyse to give the sulphur centred radical **389** and a *t*-butyl radical (Scheme 80). However, unlike the resonance stabilised allyl or benzyl radicals which normally dimerise the *t*-butyl radical would be expected to eliminate an H atom to form 2-methylpropene. This would produce a higher than normal H atom flux which may account for the two undesired products. The mechanism for the formation of the benzothiophene **383** would be expected to be the same as for benzofuran **281** (See Scheme 61), with cyclisation of the initial sulphur centred radical **392** (Scheme 80) to give the intermediate radical **393** which then eliminates carbon dioxide and a methyl radical to give benzothiophene **383**. If however the intermediate radical **393** captures an H atom this leads directly to 2-(carbomethoxy)-2,3-dihydrobenzothiophene **394** (Scheme 80). The formation of the 2*H*-1-benzothiopyran-2-one **397** can be explained by a similar mechanism as for the formation of benzopyranones **330** (See Scheme 62). This however involves the previously unseen capture of hydrogen atom by a sulphur centred radical to give the thiol **395**, possibly because of the increased hydrogen atom flux from the co-formed *t*-butyl radical. The thiol then eliminates methanol to give the ketene **396** which cyclises to

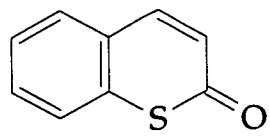
2*H*-1-benzothiopyran-2-one **397**. This hypothesis could be explored by pyrolysis of the appropriate *S*-allyl or *S*-benzyl radical precursor and showing that this gives at least reduced quantities of the 2*H*-1-benzothiopyran-2-one **397** and by pyrolysis of the thiol **395** at the same temperature to investigate if any pyranothione is formed.



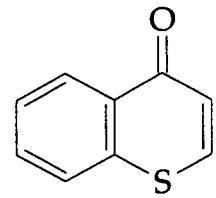
Scheme 80

While determining the structure of the 2*H*-1-benzothiopyran-2-one **394** an anomaly was discovered in the literature of this type of compound. Panetta and Rapoport[86] report having obtained 2*H*-1-benzothiopyran-2-one **394** with a melting point of 77-78 °C, but comparison of the ^{1}H NMR spectrum showed different resonances to those reported in this thesis.

Further investigation of the literature gave papers by Meth-Cohn and Tarnowski[87] and by Still and coworkers[88] which reported 2*H*-1-benzo thiopyran-2-one **397**, m.p. 79-80 °C along with ^{1}H NMR, ^{13}C NMR spectra and mass spectra which were similar to our values. Its isomer 1-benzo thiopyran-4-one **398** is also reported by Still and coworkers,[88,89] m.p. 78-80 °C along with ^{1}H NMR, ^{13}C NMR spectra and mass spectra. From this data it was concluded that the compound actually obtained by Panetta and Rappoport was in fact the 1-benzothiopyran-4-one **398**.



397



398

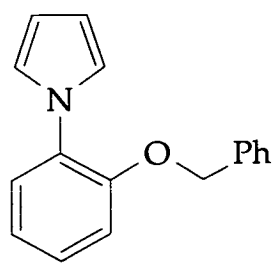
D. ATTEMPTED USE OF THE CARBOMETHOXY LEAVING GROUP IN THE PREPARATION OF SEVEN-MEMBERED RING SYSTEMS

D.1. Introduction

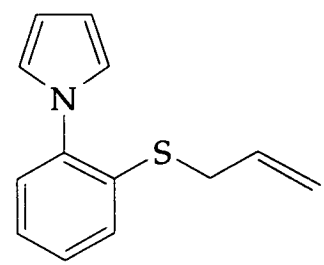
Following the successful use of the carbomethoxy group as a leaving group in the cyclisation of oxygen and sulphur centred radicals, to form five membered rings it was decided to investigate if this methodology was applicable to the formation of larger ring sizes. To this end radical precursors which could lead to seven membered rings were prepared and studied.

D.2. Preparation of Radical Precursors: Methyl 3-{*N*-[2-(Benzyloxy)phenyl]pyrrol-2-yl}propenoate 411 and Methyl 3-{*N*-[2-(Allylthio)phenyl]pyrrol-2-yl}propenoate 412

The preparations of 1-[2-(benzyloxy)phenyl]pyrrole **399** and 1-[2-(allylthio)phenyl]pyrrole **400** will be covered in Section F.2. (See Scheme 94 and 95).

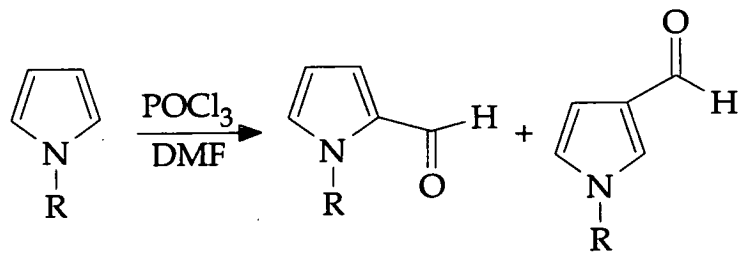


399



400

The next step in the preparation of **411** and **412** is the formylation of the pyrrole ring. Under Vilsmeier-Haack conditions formylation occurs at both the 2- and 3-positions of the pyrrole ring. Durham and Rees found that 1-phenylpyrrole **401** gave 2-formyl-1-phenylpyrrole **403** and 3-formyl-1-phenylpyrrole **405** in the ratio 14 : 1 (Scheme 81)[90]. In contrast Candy, Jones and Wright[91] found that 1-*t*-butylpyrrole **402** gave 2-formyl-1-*t*-butylpyrrole **404** and 3-formyl-1-*t*-butylpyrrole **406** in the ratio 1 : 17.5 (Scheme 81), the increase in steric bulk causing a complete reversal of the product distribution. Hence with 1-[2-(benzyloxy)phenyl]pyrrole **399** and 1-[2-(allylthio)phenyl]pyrrole **400** the presence of an *ortho* substituent on the phenyl ring might be expected to decrease to amount of the desired 2-substitution product relative to **401**.



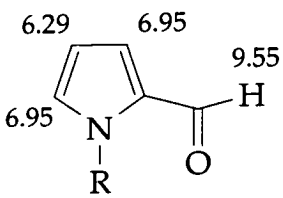
401 R = Ph **403** R = Ph **405** R = Ph
402 R = ^{t}Bu **404** R = ^{t}Bu **406** R = ^{t}Bu

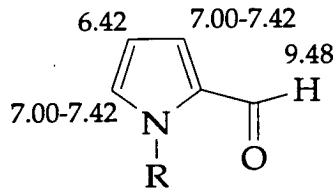
Scheme 81

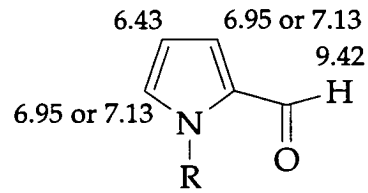
This was found in practice. Thus, when 1-[2-(benzyloxy)phenyl]pyrrole **399** was formylated (DMF / $POCl_3$) two products were obtained. These were separated by dry flash chromatography to give 1-[2-(benzyloxy) phenyl]-2-formylpyrrole **407** (77%) and 1-[2-(benzyloxy)phenyl]-3-formylpyrrole **408** (15%). Similarly, formylation of 1-[2-(allylthio)phenyl] pyrrole **400** with DMF / $POCl_3$ gave two products. These were separated by dry flash chromatography as before to give 1-[2-(allylthio)phenyl]-2-

formylpyrrole **409** (77%) and 1-[2-(allylthio)phenyl]-3-formylpyrrole **410** (23%). The position of the formyl group was determined by comparison with the ^1H NMR spectrum of 2-formyl-1-phenyl pyrrole **403** and 3-formyl-1-phenylpyrrole **405** (Scheme 81). The chemical shifts of the 2-formyl proton at δ_H *ca* 9.4-9.5 and the 3-formyl proton at δ_H *ca* 9.7-9.8 are particularly characteristic.

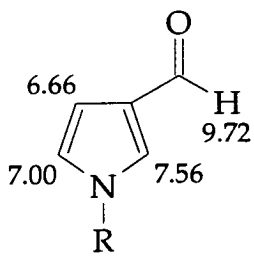
^1H NMR Chemical Shifts of Formyl Pyrroles

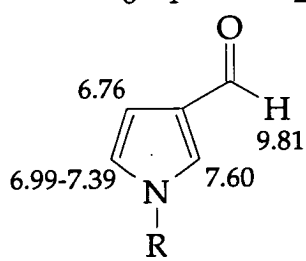


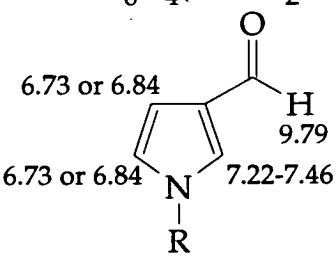




403 R = Ph **407** R = C_6H_4(2-OCH_2Ph) **409** R = C_6H_4(2-SCH_2CHCH_2)







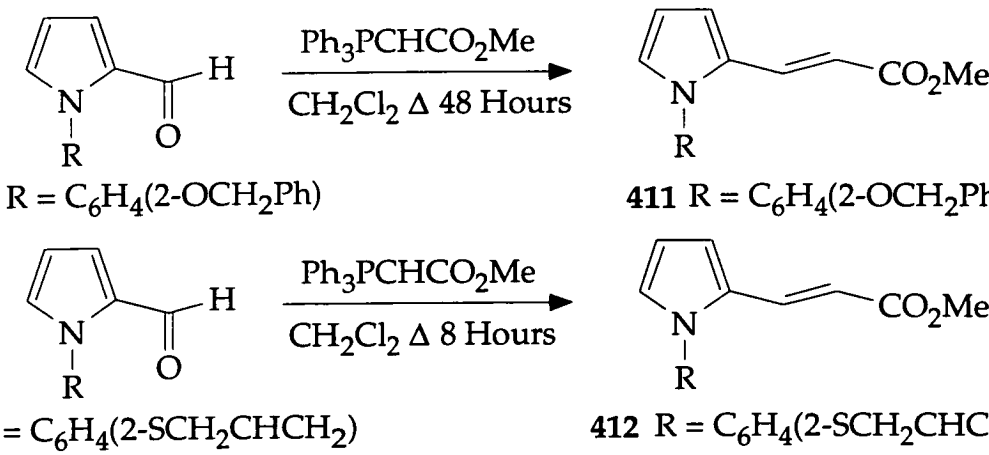
405 R = Ph **408** R = C_6H_4(2-OCH_2Ph) **410** R = C_6H_4(2-SCH_2CHCH_2)

Scheme 82

The appropriate 2-formylpyrroles were then reacted with the Wittig reagent, methyl (triphenylphosphoranylidene)acetate (Scheme 83).

Hence, 1-[2-(benzyloxy)phenyl]-2-formylpyrrole **407** gave methyl 3-{*N*-[2-(benzyloxy)phenyl]pyrrol-2-yl}propenoate **411** (45%) and 1-[2-(allylthio)phenyl]-2-formylpyrrole **408** gave methyl 3-{*N*-[2-(allylthio) phenyl]pyrrol-2-yl}propenoate **412** (60%) which were purified by chromatography. These aldehydes proved to be slightly unreactive and required prolonged heating under reflux to achieve complete conversion of

the aldehyde; this may account for the moderate yields obtained. Examination of the ^1H NMR spectra of the products **411** and **412** showed these to be single isomers.



407 R = C_6H_4(2-OCH_2Ph) **411** R = C_6H_4(2-OCH_2Ph)

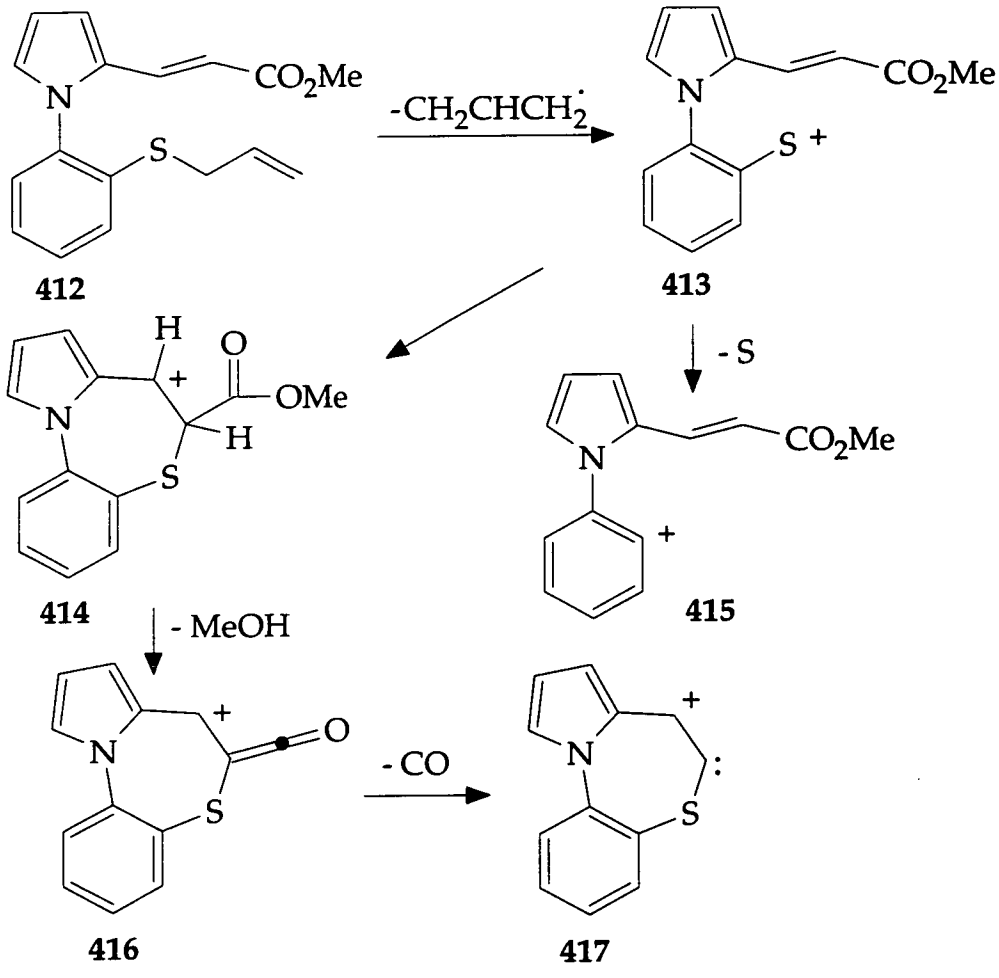
409 R = C_6H_4(2-SCH_2CHCH_2) **412** R = C_6H_4(2-SCH_2CHCH_2)

Scheme 83

D.3. Mass Spectra of Radical Precursors: 411 and 412

Examination of the mass spectra of methyl 3-{*N*-[2-(benzyloxy)phenyl]pyrrol-2-yl}propenoate **411** shows a possible breakdown associated with an methyl ester group to a give peak at (M-31) by loss of OMe· followed by decarbonylation to give a peak at (M-59). The spectrum is however dominated by a base peak at *m/z* 91 resulting from $PhCH_2$+. The spectrum of methyl 3-{*N*-[2-(allylthio)phenyl]pyrrol-2-yl}propenoate **412** is more interesting and shows an initial breakdown similar to the expected thermal process with loss of CH_2CHCH_2· to give a peak at (M-41) for **413** (Scheme 84). This is followed by the loss of a fragment of *m/z* 32, which may be explained by rearrangement to **414** and loss of methanol to give **416** or loss of a sulphur atom to give **415**, both at (M-73). The loss of methanol to give **416** seems more likely as this can then more readily explain the

subsequent loss of *m/z* 28 as CO to give **417** at (M-101). After the initial loss of allyl to give **413** (M-41) there are also smaller peaks for loss of OMe (M-72) and loss of CO (M-100) indicating a possible loss of a methyl ester.



Scheme 84

D.4. Pyrolysis of Radical Precursors Methyl 3-{*N*-[2-(benzyloxy) phenyl]pyrrol-2-yl}propenoate 411 and Methyl 3-{*N*-[2-(allylthio)phenyl]pyrrol-2-yl}propenoate 412: Identification of Products Formed

When methyl 3-{*N*-[2-(benzyloxy)phenyl]pyrrol-2-yl}propenoate **411**

was pyrolysed the t.l.c and ^{1}H NMR spectrum of the crude pyrolysate showed that a number of products had been formed. These were separated by dry flash chromatography and shown to be two major products and a number of very minor products. The first major product to elute was methyl 2-(4*H* pyrrolo[2,1-*c*][1,4]benzoxazin-4-yl)ethanoate **421**. The structure of this compound was determined by ^{1}H and ^{13}C NMR. These showed the presence of four aromatic protons and three pyrrole protons as expected along with a doublet of doublet of doublets, centred on δ 5.61 integrating for one proton and non first order signal centred on δ 2.98 integrating for two protons. A 3π/4 DEPT experiment was used to confirm that these signals were a CH_2 group.

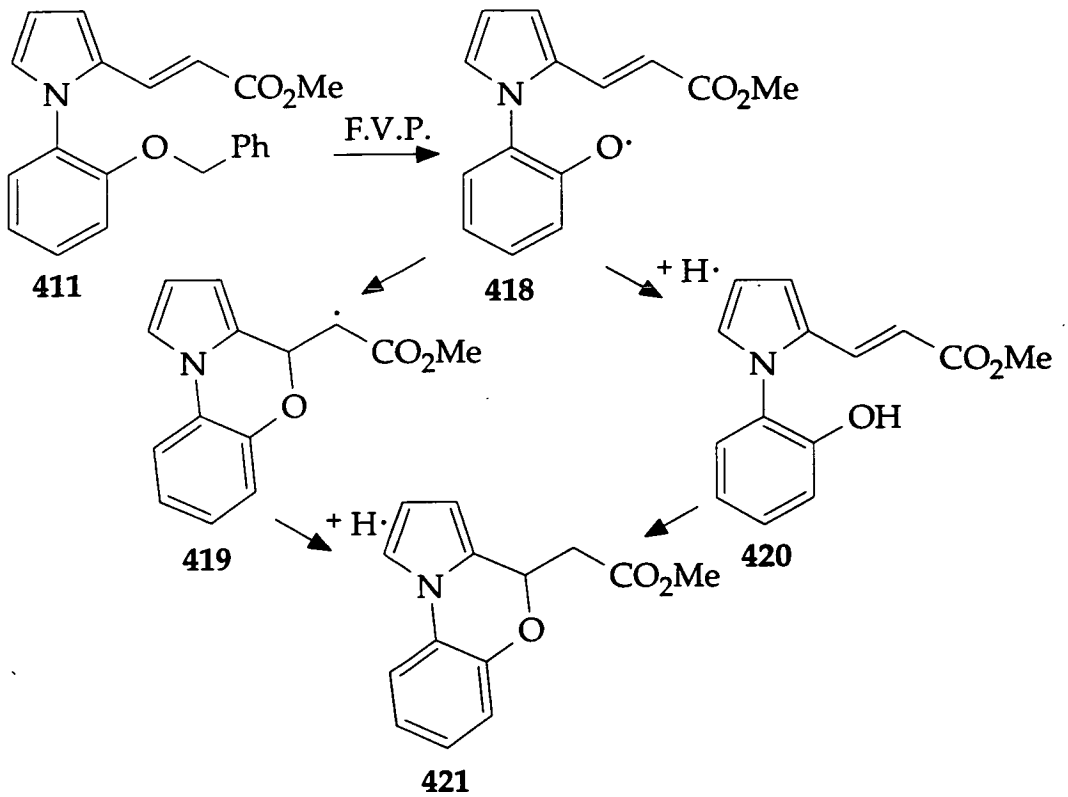
The second major product, which could not be isolated pure, was identified as methyl 3-[1-(2-hydroxyphenyl)pyrrol-2-yl]propenoate **420** by comparison of its ^{1}H NMR spectrum with an authentic sample (See below).

Compound **421** may arise by two possible routes. Initial pyrolysis gives the oxygen centred radical **418**. In the first possible mechanism *exo* attack by the oxygen radical **418** on the double bond to give the radical **419** is followed by capture of a hydrogen atom to give methyl 2-(4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-yl)ethanoate **421**. In the second mechanism, which is more in keeping with the normal behaviour of oxygen centred radicals under these conditions, the radical **418** captures a hydrogen atom to give the phenol **420**, which is then followed by a Michael addition to the double bond to give methyl 2-(4*H* pyrrolo[2,1-*c*][1,4]benzoxazin-4-yl)ethanoate **420** (Scheme 85).

This second mechanism seems more likely as the formation of the co-product **420** is also explained, but it is necessary to prove that the cyclisation of **420** to **421** is viable. This was indeed established by an independent

synthesis. Thus, 1-(2-hydroxyphenyl)pyrrole **422** was formylated ($POCl_3$ / DMF) to give a 1.6 : 1 mixture of the 2- **423** and 3-formyl **424** derivatives (Scheme 86) which were separated by dry-flash chromatography.

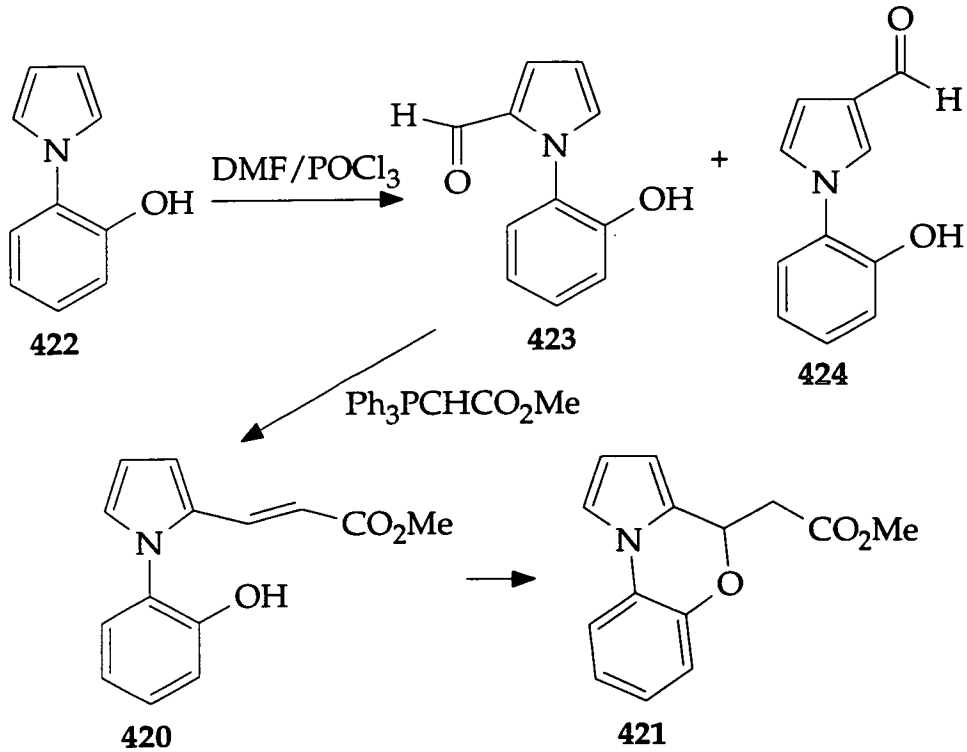
Upon reaction of the 2-formyl isomer **423** with the appropriate Wittig reagent (Scheme 86), t.l.c showed that two products had been formed. These were separated and found to be methyl 2-(4*H* pyrrolo[2,1-*c*][1,4]benzoxazin-4-yl)ethanoate **421** and methyl 3-[1-(2-hydroxyphenyl)pyrrol-2-yl]propenoate **420**. Hence, the second mechanism of Scheme 85 has been shown to be viable.



Scheme 85

Because the intramolecular Michael reaction can take place in solution it is not known whether the formation of methyl 2-(4*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-4-yl)ethanoate **421** takes place during during F.V.P or

subsequently in the cold trap or upon work-up.

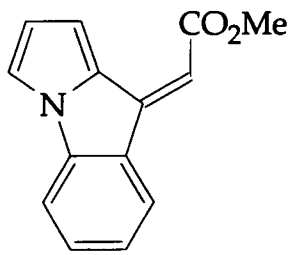


Scheme 86

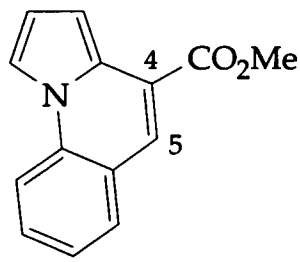
When methyl 3-{*N*-[2-(allylthio)phenyl]pyrrol-2-yl}propenoate **412** was pyrolysed ^{1}H NMR and t.l.c of the crude pyrolysate showed that one major product and a number of very minor products had been formed. The major product was purified by dry-flash chromatography and the ^{1}H NMR spectrum showed the presence of three pyrrole protons, four aromatic protons, one alkenyl proton and one methoxy group, i.e. eleven hydrogens atoms altogether. A N.O.E. experiment on the methoxy group showed it was close in space to the alkenyl proton and one of the pyrrole protons. A similar experiment on the alkenyl proton was inconclusive but no link could be made between the two rings. Decoupling experiments showed the connectivity of the pyrrole protons and the connectivity of the aromatic protons. The ^{13}C NMR spectrum showed the presence of fourteen carbon

carbon atoms in total, including five quaternaries one of which had a chemical shift which indicated it was a carbonyl, giving a basic formula of $C_{14}H_{11}NO_2$, giving a mass of 225. The mass spectrum gave a molecular ion at *m/z* 225 indicating, surprisingly that the sulphur atom was missing. Hence, assuming that no major rearrangements have taken place, two possible structures for the product **425** and **426** can be proposed.

In an effort to distinguish between the two structures, the ^{13}C NMR spectrum of the parent ring system of compound **426** was examined. For positions 4 and 5 of the ring system, the chemical shifts were 119.0 and 118.6 respectively.[92] The ^{13}C substituent effect for a methyl ester group on the *ortho* proton of a benzene ring is -0.5ppm[93] and by comparing pyridine[94] with 3-carbomethoxypyridine,[95] the substituent effect on the equivalent pyridine proton would be +1.2. Hence, the chemical shift of the 5-position of **426** might be expected at δ_C 119 ± 2 ppm. As the nearest CH resonances are at 114.1 and 123.7 it seems reasonable to conclude that there is no resonance in the region where the carbon at the 5-position would be expected and hence that compound **426** is an unlikely structure.



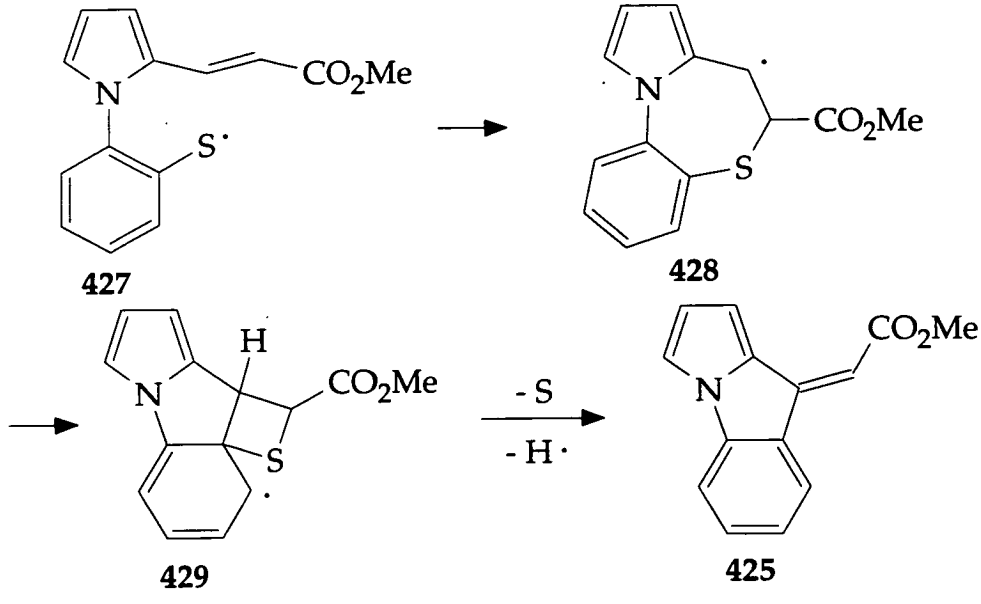
425



426

A suggested mechanism for the formation of **425** is that pyrolysis forms the initial sulphur centred radical **427**, (Scheme 87) which then cyclises to form a seven membered ring to give the radical **428**. This radical then does not eliminate CO_2 and a methyl radical as expected but instead cyclises to

give the radical **429**, forming a four and a five membered ring in the process (Scheme 87). To relieve ring strain, radical **429** then eliminates the sulphur atom and loses a hydrogen atom to form the product, 9-(carbomethoxymethylene)-9*H*-pyrrolo[1,2-*a*]indole **425** (Scheme 87). The loss of sulphur under radical F.V.P. conditions is known.[96] This mechanism also provides a possible explanation as to movement of the carbomethoxy group next to the pyrrole ring as observed in the N.O.E. experiment described earlier. As can be seen in radical **429** the carbomethoxy group is singly bound to the ring system and rotates to the point of minimum steric interaction. When the double bond reforms it does so to leave the carbomethoxy group *cis* to the pyrrole ring.



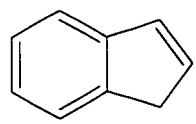
Scheme 87

Hence, although interesting products had been formed the desired seven membered rings were not available by this route.

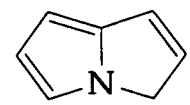
E. ATTEMPTED USE OF THE CARBOMETHOXY RADICAL LEAVING GROUP AND CARBON CENTRED RADICALS IN THE PREPARATION OF THE 3*H*-PYRROLIZINE 431 AND 2-METHYL-3*H*-PYRROLIZINE 448

E.1. Introduction

Having shown that the carbomethoxy group could be used as a radical leaving group, in the ring closure of both oxygen and sulphur centred radicals the next step was to examine the ring closure of carbon centred radicals. In view of the fact that the use of a benzene ring as the base for the radical precursor would generate the well known indene ring system **430** it was decided to employ a pyrrole ring on which to base the radical precursor for a more interesting ring system. Hence placing the carbon centred radical generator on the pyrrole nitrogen and the acrylate on the 2-position would be expected to give a synthetic route to the pyrrolizine ring system **431**.[97]

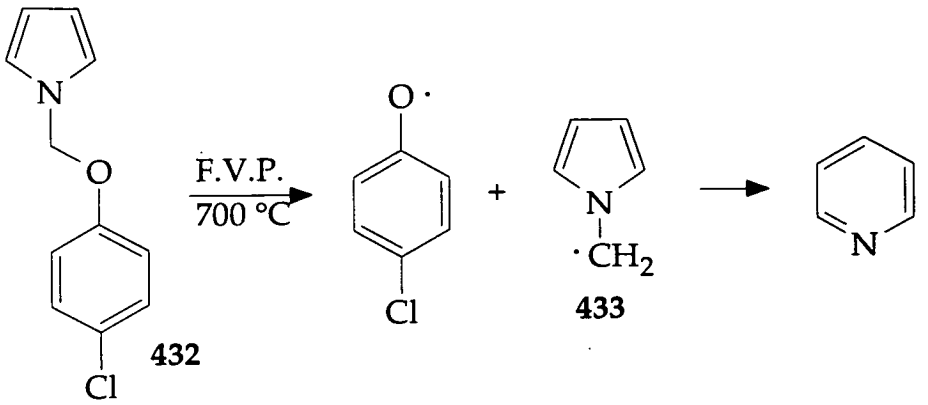


430



431

To generate the carbon centred radicals an alternative precursor to the more commonly used oxalate esters was employed. In this case the (4-chlorophenoxy)methyl derivative of the pyrrole 2-acrylic ester was used. Similar precursors *e.g.* 1-(4-chlorophenoxy)methylpyrrole **432** have been shown to generate the 1-pyrrolylmethyl radical **433** which ring expands to pyridine (Scheme 88).[98]



432 433

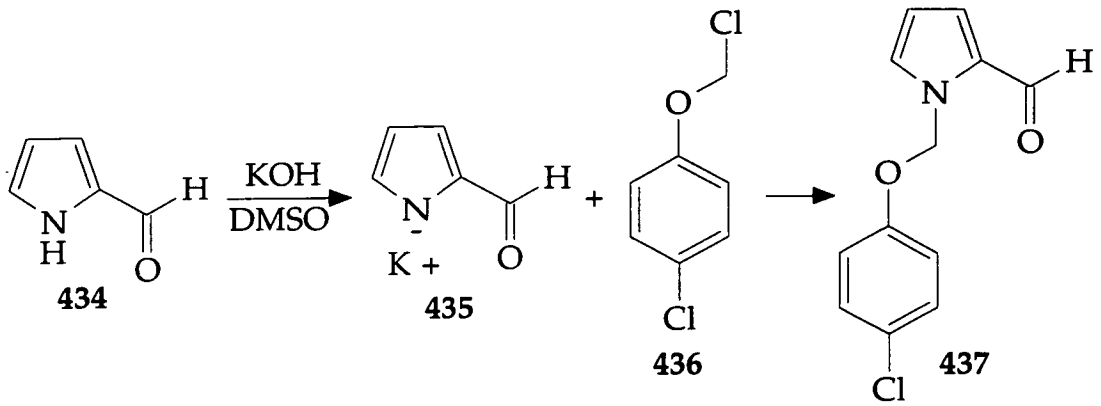
Scheme 88

E.2. Preparation of Radical Precursors Methyl 3-[1-(4-Chlorophenoxy)methylpyrrol-2-yl]propenoate 441 and Ethyl 3-[1-(4-Chlorophenoxy)methylpyrrol-2-yl]-2-methyl propenoate 442

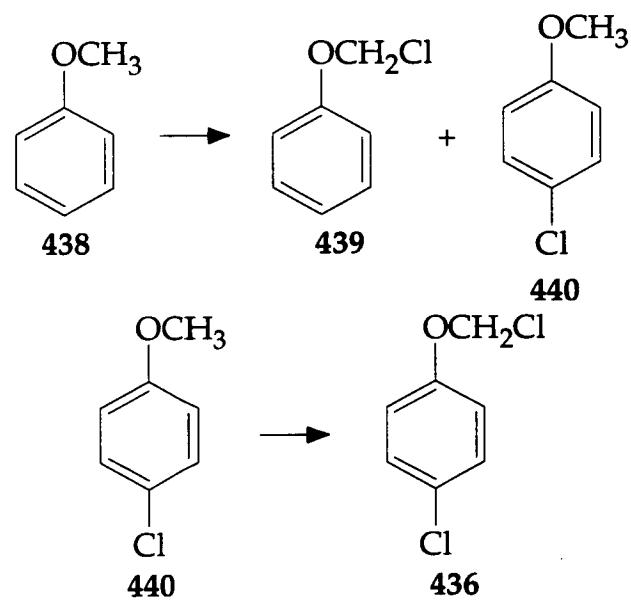
The preparation began with commercially available pyrrole-2-carboxaldehyde **434**. From this compound two routes are available, either alkylation to form the radical generator or Wittig reaction to form the vinyl ester which the radical may attack. The chosen route was to alkylate to form the radical generation site, as this route had the advantage that different Wittig reagents could then be employed to vary substitution at the site of expected radical attack. Hence, pyrrole-2-carboxaldehyde **434** was treated with potassium hydroxide to generate the anion **435** and this was then alkylated with α,4-dichloroanisole **436** to give 1-(4-chlorophenoxy)methyl-2-formylpyrrole **437** in 72% yield (Scheme 89).

The choice of α,4-dichloroanisole **436** as opposed to α-chloroanisole **439** is purely on the grounds of ease of synthesis. Upon chlorination anisole **438** yields a mixture of α-chloroanisole **439** and 4-chloroanisole **440**, whereas 4-chloroanisole **440** yields only α,4-dichloroanisole **436** (Scheme 90).

In the next stage of the synthesis a Wittig reaction was carried out upon the aldehyde. For this two different Wittig reagents were employed (Scheme 91) so that two different radical precursors were obtained.



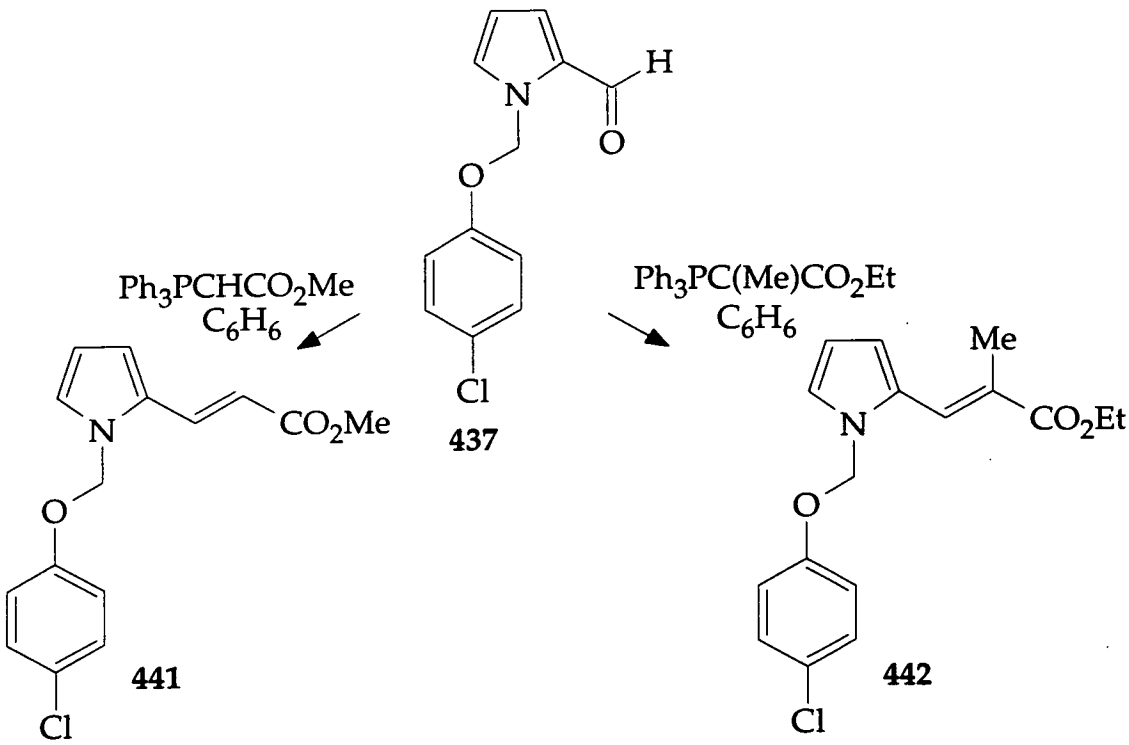
Scheme 89



Scheme 90

Hence, 1-(4-chlorophenoxy)methyl-2-formylpyrrole **437** was reacted with methyl(triphenylphosphoranylidene)acetate in dry benzene to give methyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]propenoate **441** in 72% yield after chromatography (Scheme 91) and with ethyl

2-(triphenylphosphoranylidene)propionate in dry benzene to give ethyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]-2-methylpropenoate **442** in 73% yield after chromatography (Scheme 91). In both cases exclusively the *E*-isomer was formed.

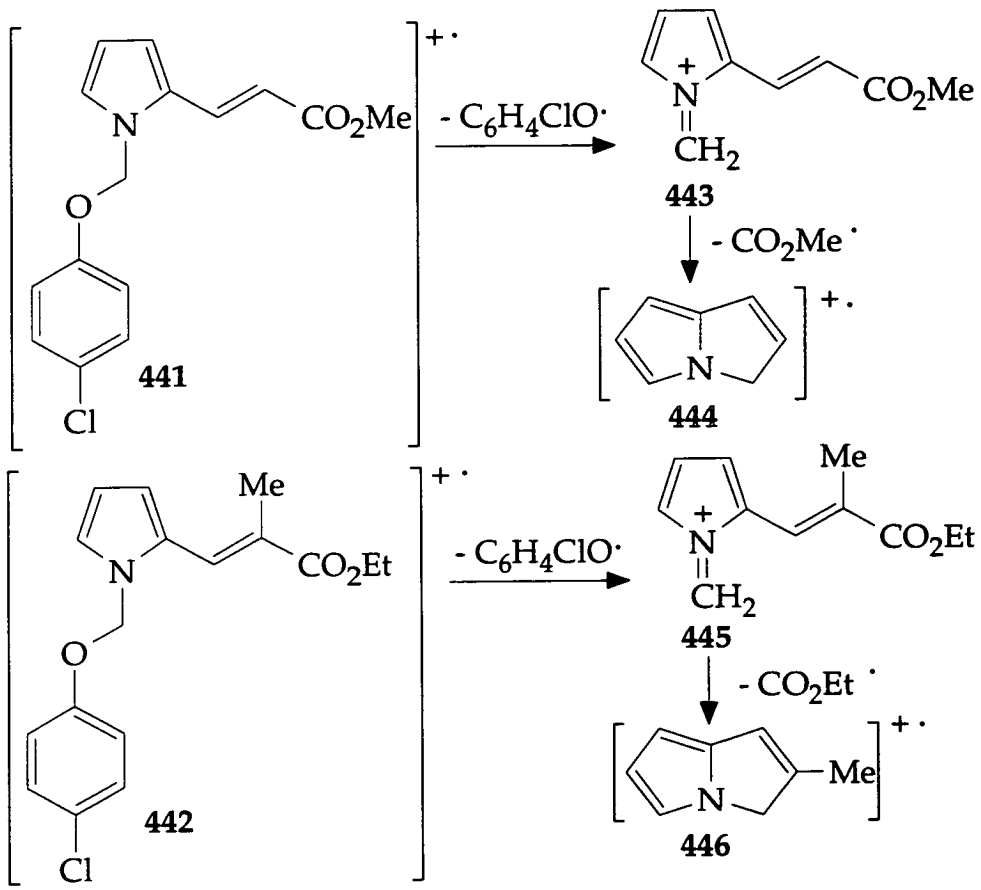


Scheme 91

E.3. Mass Spectra of Radical Precursors 441 and 442

The mass spectra of methyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]propenoate **441** and ethyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]-2-methylpropenoate **442** both show some very interesting peaks. Both show peaks which indicate that initial ionisation is followed by cleavage of the CH_2-O bond, with loss of $C_6H_4{}^{37}ClO$ to give peaks at M-129 or $C_6H_4{}^{35}ClO$ to give peaks at M-127. This leads to ions **443** from **441** and **445** from **442**

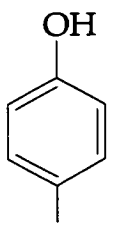
respectively (Scheme 92). This is then followed loss of the ester group, best explained by a ring closure similar to the expected thermal process to give the pyrrolizine radical ion **444** (*m/z* = 105) (M-186/188). This interpretation is supported by the presence of a strong peak at *m/z* 104: strong (M-1) peaks are common for 3*H*-pyrrolizines as indicated by Flitsch and Jones.[97] Similarly a peak at *m/z* = 119 due to **446** is found in the spectrum of the ethyl ester **442** (M-200/202) also with a strong peak at *m/z* 118 (Scheme 92).



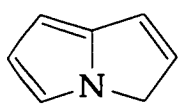
Scheme 92

E.4. Pyrolysis of Radical Precursors: Methyl 3-[1-(4-Chlorophenoxy)methylpyrrol-2-yl]propenoate 441 and Ethyl 3-[1-(4-Chlorophenoxy)methylpyrrol-2-yl]-2-methyl propenoate 442

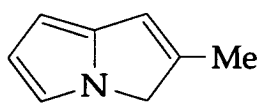
Firstly methyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]propenoate **441** was pyrolysed at 700°C, a temperature known to generate the 1-pyrrolylmethyl radical.[98] The entire pyrolysate was washed from the tube with $CDCl_3$ and examined by ^1H NMR spectroscopy. This showed the presence of 4-chlorophenol **447** as the major product and comparison with the ^1H NMR spectrum of an authentic sample of 3*H*-pyrrolizine **431**,[99] showed that none of this product had been formed. Examination by GC-MS confirmed that the major product was indeed 4-chlorophenol **447** and that none of the other minor peaks in the GC produced a mass spectrum with a molecular ion with m/z = 105. No other products were present in significant amounts.



447



431



448

Ethyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]-2-methylpropenoate **442** was then pyrolysed, also at 700°C and ^1H NMR spectroscopy of the entire pyrolysate again showed that the major product was 4-chlorophenol **447**. There were however minor peaks in the spectrum which may have coincided with those expected for 2-methyl-3*H*-pyrrolizine **448**, but GC

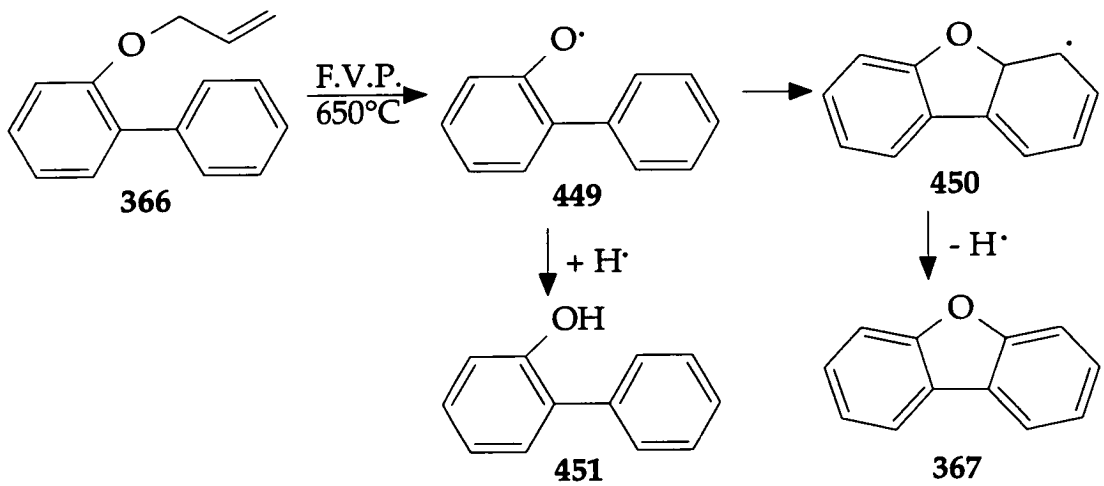
analysis showed that there were at least eight components to the mixture and GC-MS showed that one of the more minor components produced a molecular ion of *m/z* 119. Hence no further work was performed.

From these results it appears that the use of 4-(chlorophenoxy)methyl derivative to generate carbon centred radicals which may then cyclise to a vinyl carbomethoxy group does not provide a route to fused ring systems in this case. Nonetheless it was surprising that no other products - for example those from the ring expansion reaction (see Scheme 88) - could be identified. One possible reason for this is that the co-formed 4-chlorophenol is a strong enough acid to attack and destroy the products before they can be analysed.

F. GENERATION OF PHENOXYL, AMINYL, BENZYL AND THIOPHENOXYL FREE RADICALS AND INVESTIGATION OF THEIR INTRAMOLECULAR CYCLISATION REACTIONS WITH A 2-(PYRROL-1-YL) SUBSTITUENT

F.1. Introduction

As reported in a previous section, earlier work within the group had led to an investigation of the reaction which took place when 2-(allyloxy)biphenyl **366** was pyrolysed (Scheme 93).[37] Upon pyrolysis the oxygen centred radical **449** is formed and reacts to give two major products. The first is dibenzofuran (75%) **367** formed by cyclisation of **449** to give the aryl radical **450**, followed by loss of a hydrogen atom to give the product **367** (Scheme 93). The second major product is 2-hydroxyphenylbenzene (19%) **451** formed by the initial radical **449** capturing a hydrogen atom (Scheme 93).



366 **449** **450** **451** **367**

Scheme 93

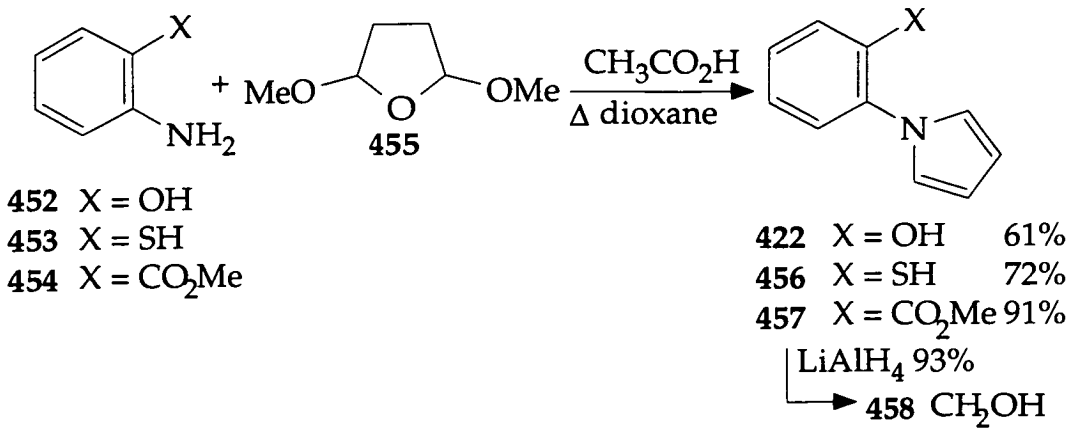
From this work it was decided to investigate the attack of oxygen, nitrogen, carbon and sulphur centred radicals on a heterocyclic ring system. This contrasts with work reported in a previous section where heteroaryloxyl radicals react with adjacent aryl rings. The ring system chosen here was the pyrrole ring attached by the nitrogen atom to the benzene ring bearing the radical. This has the major advantage that, the site of radical attack is symmetrical, hence limiting the number of possible products.

F.2. Preparation of Radical Precursors: *N*-[2-(allyloxy)phenyl]pyrrole 460, *N*-[2-(benzyloxy)phenyl] pyrrole 399, *N*-[2-(allylamino)phenyl]pyrrole 461, Bis-[2-(pyrrol-1-yl)benzyl] oxalate 462 and *N*-[2-(allylthio)phenyl]pyrrole 400

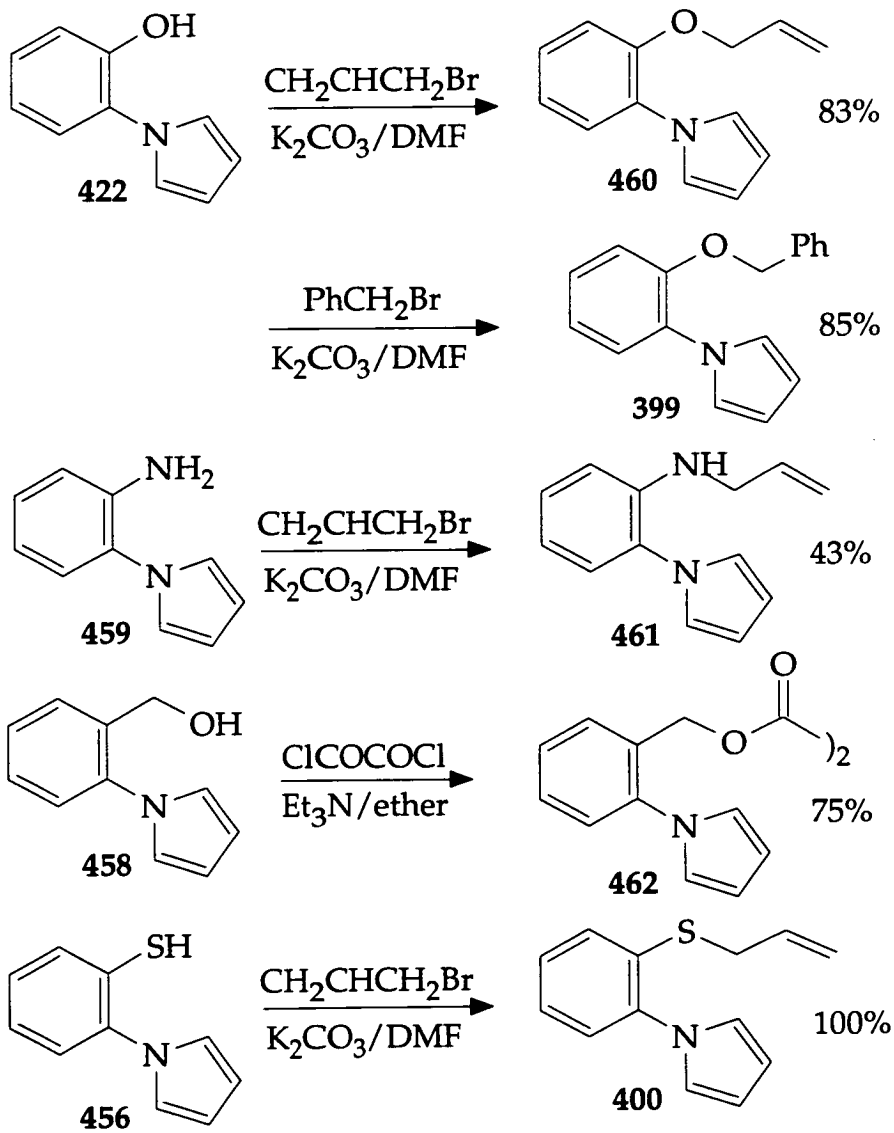
The preparation of these radical precursors was carried out in two steps, firstly by formation of the pyrrole ring, followed by conversion of the group *ortho* to the pyrrole to one suitable for radical generation. The pyrrole ring was formed by condensation of an appropriately *ortho* substituted aminophenol **452-454** with 2,5-dimethoxytetrahydrofuran **455** (Scheme 94).[100]

Reaction of the methyl ester **457**, followed by lithium aluminium hydride reduction to give **458** was employed because attempted direct reaction of 2-aminobenzylalcohol gave a poor yield.

The radical generation site was then prepared by the usual methods (Scheme 95).



Scheme 94



Scheme 95

The phenol **422** was alkylated with allyl and benzyl bromide to give the ethers **460** and **399** respectively in good yield, the two precursors being required because of hydrogen atom capture problems (see below). The thiophenol **456** was alkylated with allyl bromide to give the thioether **400** in good yield. With the aminophenol **459** problems arose because allylation gave rise to a mixture of starting amine, mono and diallylated products which required separation by chromatography to give the amine **461**. Finally the benzyl alcohol **458** required an alternative type of precursor and was converted to the oxalate ester **462** in good yield (Scheme 95). It is of interest that oxalyl chloride reacts specifically with the primary alcohol function even though it is known that it can react with pyrrole itself under very mild conditions.[101]

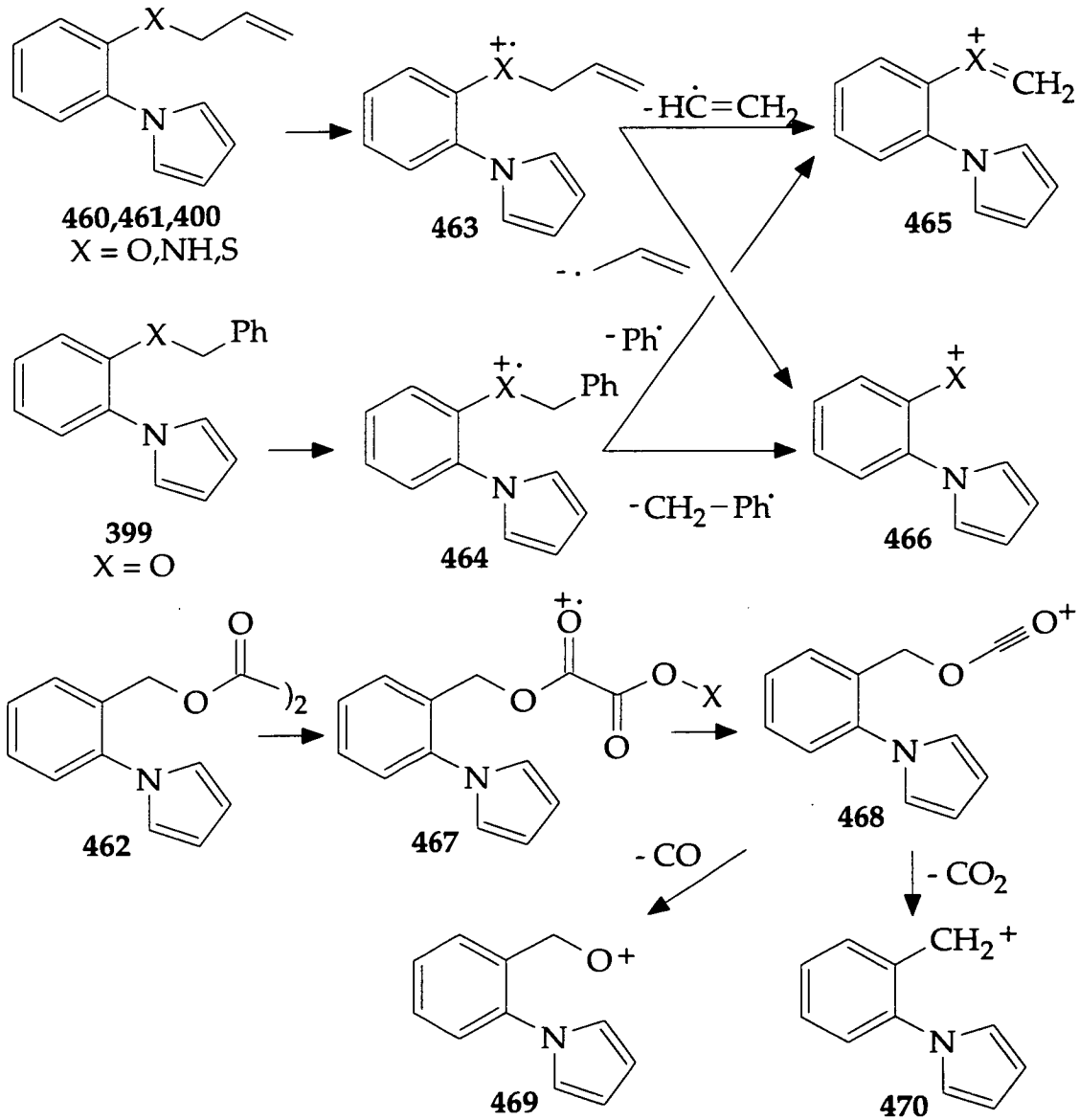
F.3. Mass Spectra of Radical Precursors: 399, 400, 460, 461 and 462

The mass spectra of the radical precursors show some breakdown patterns which are similar to the expected thermal breakdowns.

In the case of all the allyl and benzyl compounds **460, 399, 461** and **400** there appear to be two competing pathways which occur to a greater or lesser extent (Scheme 96). In both of these pathways initial ionisation occurs on the heteroatom connected to the allyl or benzyl to give the radical cation **463** or **464**. In the first pathway α-cleavage occurs with loss of a vinyl or phenyl radical to give **465** (M - 27 or 77). In the second pathway disproportionation occurs with loss of an allyl or benzyl radical to give **466** (M - 41 or 91). An interesting peak appears at M - 29 for the allyl compounds of similar intensity to the M - 27 peak. This may indicate a loss of 2 from

465, which may be associated with a cyclisation.

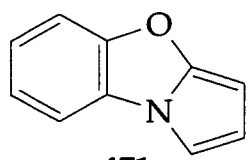
In the case of the oxalate ester **462** initial ionisation takes place at one of the carbonyls to give **467**. The oxalate then cleaves leaving one fragment with the positive charge **468**. This fragment then loses either carbon monoxide to give **469** or carbon dioxide to give **470** (Scheme 96).



Scheme 96

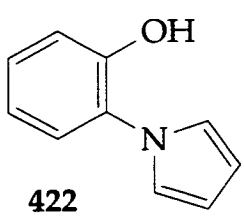
F.4. Pyrolysis of Radical Precursors: *N*-[2-(Allyloxy)phenyl]pyrrole 460, *N*-[2-(Benzyloxy)phenyl] pyrrole 399, *N*-[2-(Allylamino)phenyl]pyrrole 461, Bis-[2-(pyrrol-1-yl)benzyl] oxalate 462 and *N*-[2-(Allylthio)phenyl]pyrrole 400

The first precursor to be pyrolysed was *N*-[2-(allyloxy)phenyl]pyrrole **460**. Initially the crude pyrolysate was examined by ^{1}H NMR and GC-MS, which showed no evidence of the expected cyclisation product pyrrolo[2,1-*b*]benzoxazole **471**, *ie* no peak at *m/z* 159.

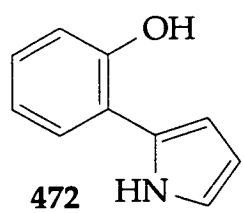


471

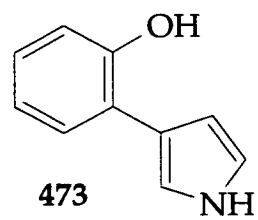
A larger scale pyrolysis was then carried out and the products were separated by dry flash chromatography. These were shown by ^{1}H NMR spectroscopy and comparison with authentic samples (see below) to be the starting phenol *N*-(2-hydroxyphenyl)pyrrole **422** and its isomer, 2-(2-hydroxyphenyl)pyrrole **472**.



422



472



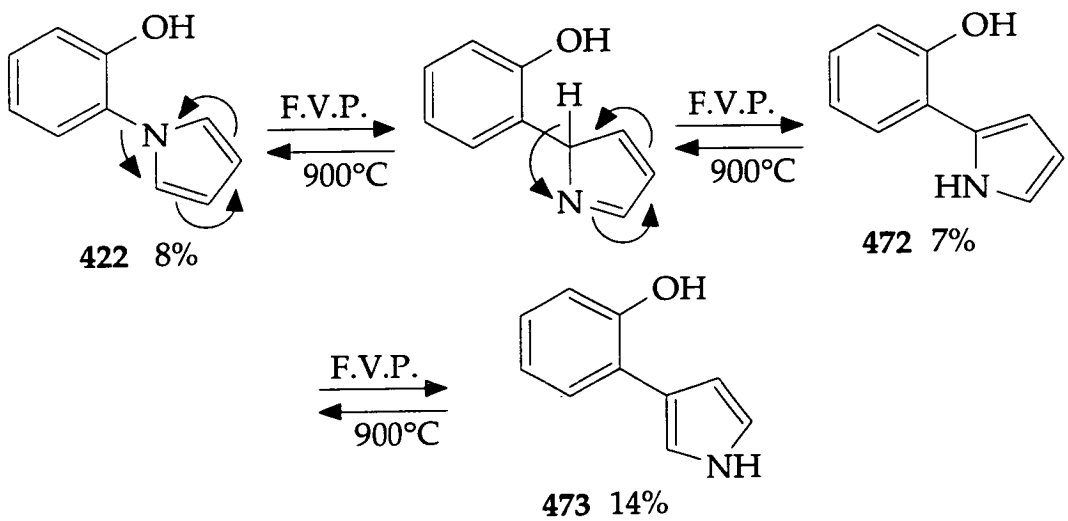
473

In the ^{1}H NMR spectrum of *N*-(2-hydroxyphenyl)pyrrole **422** the pyrrole α protons occur at δ 6.94 and the pyrrole β protons occur at δ 6.44.

Compound **472** shows pyrrole protons at δ 6.87, 6.62 and 6.38 *i.e.* 1 α and 2 β protons, while compound **473** (see below) shows pyrrole protons at δ 6.97, 6.92 and 6.44 *i.e.* 2 α and 1 β proton.

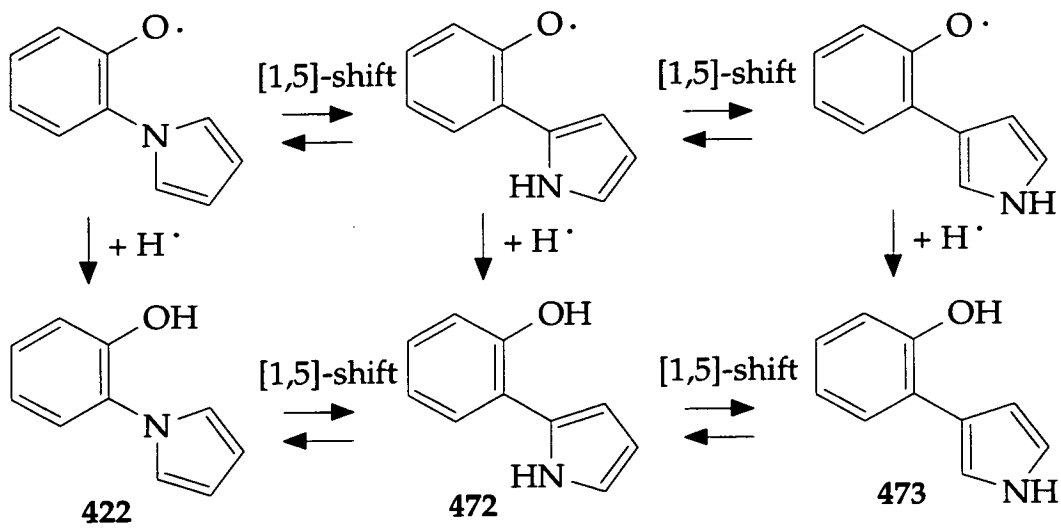
It is known that oxygen centred radicals have a strong tendency to capture a hydrogen atom and reform the phenol. In an attempt to minimise this hydrogen atom capture and perhaps favour cyclisation *N*-[2-(benzyloxy) phenyl]pyrrole **399** was pyrolysed. This however led to the same products **422** and **472** as found above, along with the other isomer 3-(2-hydroxyphenyl)pyrrole **473**.

It is also known that by pyrolysis *N*-phenylpyrrole will undergo [1,5]-shifts to form 2-phenylpyrrole and 3-phenylpyrrole[102]. Indeed this work was applied to the preparation of authentic samples of 2-(2-hydroxy phenyl)pyrrole **471** and 3-(2-hydroxyphenyl)pyrrole **472**[103] (Scheme 97). Pyrolysis of *N*-(2-hydroxyphenyl)pyrrole **422** at 750 °C showed only little conversion to the 2-isomer and none of the 3-isomer so pyrolysis was repeated at 900 °C. The ^{1}H NMR spectrum showed the presence of the desired products which were separated by dry-flash chromatography.



Scheme 97

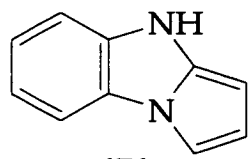
It is very difficult to decide whether the species which rearranges to the 2- and 3-isomers is the radical itself or the phenol **422**. Rearrangement of the radical precursors is clearly further advanced at 750 °C than the rearrangement of the phenol. Because of the low isolated yields, this analysis was based on the ^{1}H NMR spectra of the crude pyrolysates, but was complicated by the fact that the characteristic pyrrole resonances of phenol **422** and the 3-isomer **473** are almost coincident, however in all cases the 3-isomer appears as a shoulder on the starting phenol resonance. Thus, at 750°C the phenol **422** gives a higher ratio of the phenol **422** (plus 3-isomer **473**) to 2-isomer **472** (3.5 : 1), compared with the allyl compound **460** (1.5 : 1) and the benzyl compound **399** (1 : 1). This suggests that the radical species may be more likely to rearrange due to the extra energy in the system caused by chemical activation. However, some of the acceleration of the rearrangement may be due to the OH substituent, since the rearrangement was found to be well advanced at 900 °C whereas for *N*-phenylpyrrole itself 1000 °C was required.[102]



Scheme 98

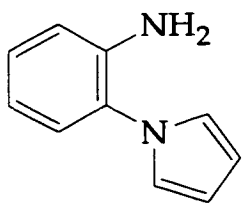
Hence possible routes to the observed products may go *via* rearrangement then hydrogen atom capture, hydrogen atom then rearrangement or a mixture of both (Scheme 98).

The second precursor to be pyrolysed was *N*-[2-(allylamino) phenyl]pyrrole **461**. The crude pyrolysate was examined by GC-MS which showed no peaks with *m/z* 156 due to the expected 4*H*-pyrrolo[1,2-*a*] benzimidazole **474**.[104] Examination of the ^{1}H NMR spectrum showed a large triplet at δ 4.51 *J* 1.9 which was removed when the sample was shaken with D_2O, however, despite repeated attempts this product could not be isolated.

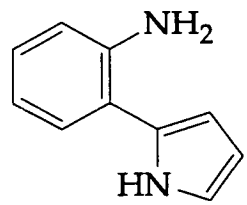


474

A larger scale pyrolysis was carried out and the mixture was separated by dry-flash chromatography. The two products isolated were shown to be recovered *N*-(2-aminophenyl)pyrrole **459** (16 %) and its isomer 2-(2-amino phenyl)pyrrole **475** (7 %). The formation of these products may be expected to occur in a similar manner to those formed for the oxygen centred radical above, with hydrogen atom capture and [1,5] shifts occurring.

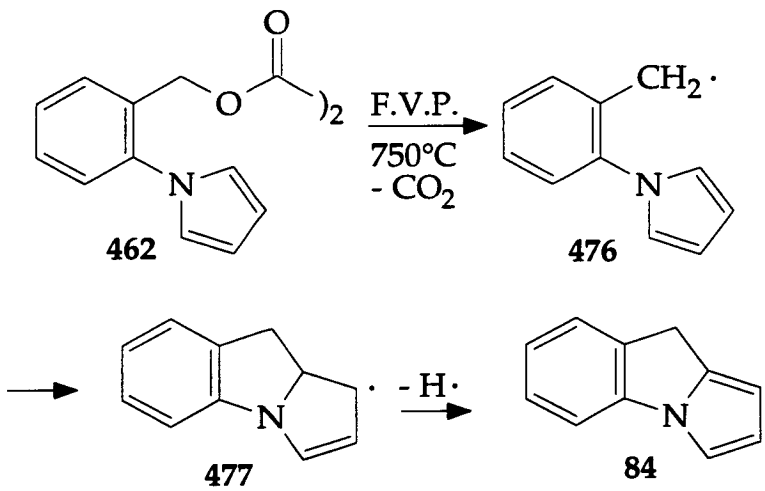


459



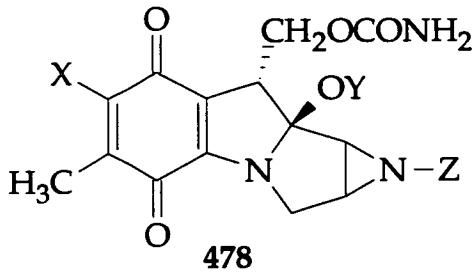
475

The next radical precursor to be pyrolysed was bis-[2-(pyrrol-1-yl) benzyl] oxalate **462**. Analysis of the crude pyrolysate by ^1H NMR spectroscopy showed that there was one major product and by comparison with literature spectra[105] this was shown to be 9*H*-pyrrolo[1,2-*a*]indole **84**, obtained in 85% yield. The proposed mechanism for formation of this compound (Scheme 99) is that the oxalate ester **462** cleaves, with loss of two molecules of carbon dioxide to give the carbon centred radical **476**. This radical cyclises to give the heteroaryl radical **477**, which forms the product by losing a hydrogen atom (Scheme 99).



Scheme 99

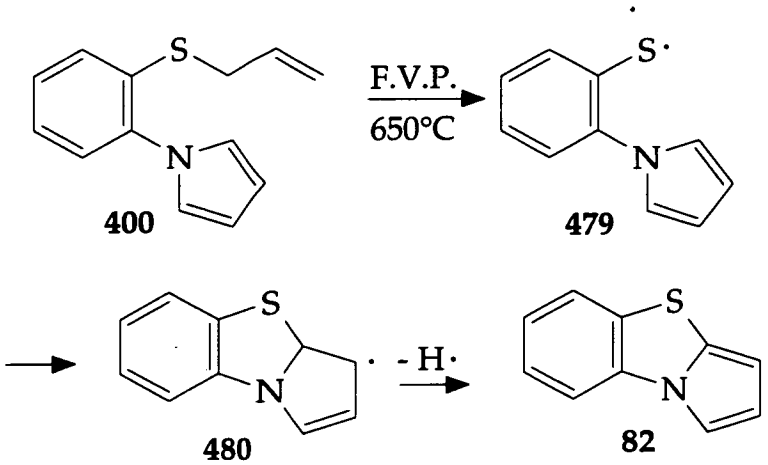
Overall this provides a very efficient synthesis of 9*H*-pyrrolo[1,2-*a*] indole **84** which is related to the mitomycin series of antibiotics **478**.[106]



478

Previously this compound had been synthesized from ethyl pyruvate in 18% yield by Bailey, Scott and Vandrevala[107] and from methyl anthranilate (as in this thesis) in 50 % yield by Mazzola, Bernady and Frank[108].

The final precursor to be pyrolysed was *N*-[2-(allylthio)phenyl]pyrrole **400**. Again the crude pyrolysate was shown by ^{1}H NMR spectroscopy to consist of one major product, which was purified by bulb to bulb distillation and later by crystallisation from which a crystal structure (Figure 2) was obtained: this conclusively proved the structure to be pyrrolo[2,1-*b*]benzothiazole **82**, obtained in 87% yield. The mechanism for formation of this product (Scheme 100) is believed to be similar to that for formation of the previous ring system (Scheme 99). In this case the allythioether **400** cleaves to generate the sulphur centred radical **479**, which cyclises to give the heteroaryl radical **480**. This then loses a hydrogen atom to form the product pyrrolo[2,1-*b*]benzothiazole **82** (Scheme 100).



Scheme 100

X-Ray Crystal structure of Pyrrolo[2,1-*b*]benzothiazole 82

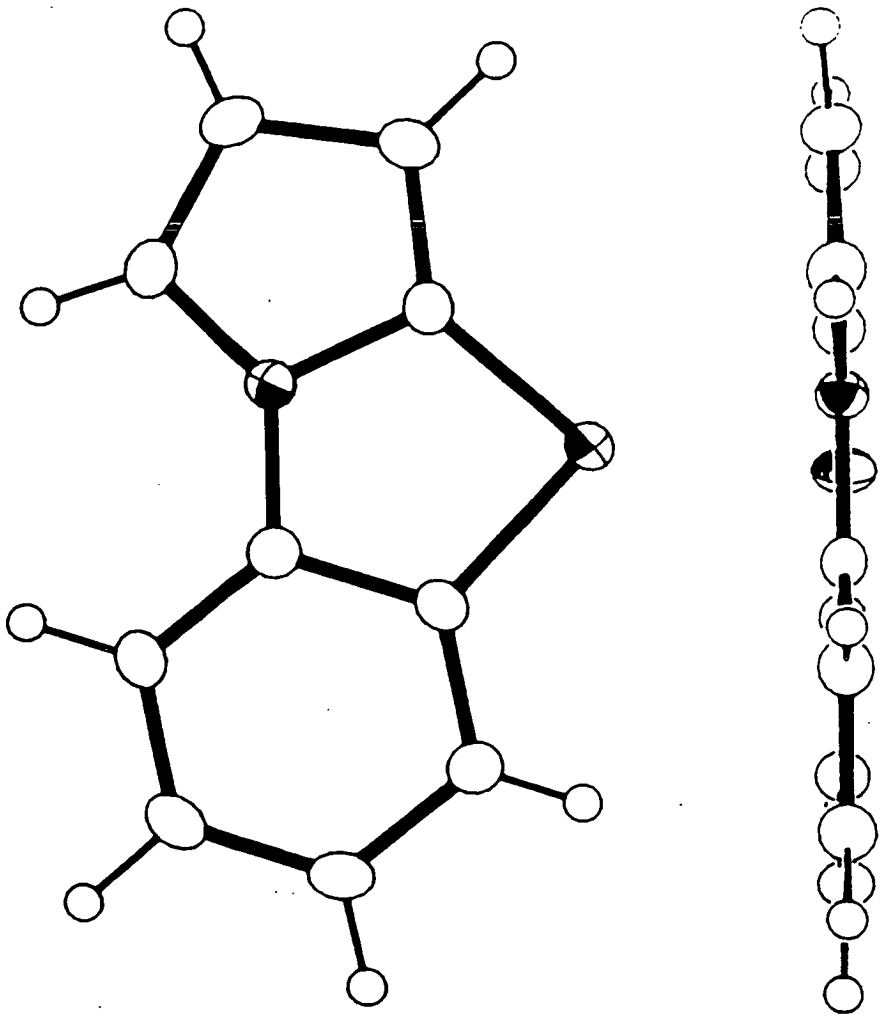


Figure 2

Table 1. Bond Lengths(Å), angles(degrees) and torsion angles(degrees) with standard deviations

C(1) - C(2)	1.3710(23)	C(5a) - C(5)	1.3845(22)
C(1) - N(9)	1.3849(20)	C(5a) -C(8a)	1.3995(21)
C(2) - C(3)	1.4241(23)	C(5) - C(6)	1.3860(23)
C(3) -C(3a)	1.3661(22)	C(6) - C(7)	1.3930(23)
C(3a) - S(4)	1.7474(16)	C(7) - C(8)	1.3842(23)
C(3a) - N(9)	1.3822(20)	C(8) -C(8a)	1.3878(22)
S(4) -C(5a)	1.7616(16)	C(8a) - N(9)	1.3954(19)

C(2) - C(1) - N(9)	106.83(14)	C(5a) - C(5) - C(6)	118.77(14)
C(1) - C(2) - C(3)	109.13(14)	C(5) - C(6) - C(7)	120.52(15)
C(2) - C(3) -C(3a)	106.06(14)	C(6) - C(7) - C(8)	121.25(15)
C(3) -C(3a) - S(4)	139.19(13)	C(7) - C(8) -C(8a)	118.04(15)
C(3) -C(3a) - N(9)	109.08(13)	C(5a) -C(8a) - C(8)	121.02(14)
S(4) -C(3a) - N(9)	111.73(11)	C(5a) -C(8a) - N(9)	111.23(13)
C(3a) - S(4) -C(5a)	89.90(7)	C(8) -C(8a) - N(9)	127.73(14)
S(4) -C(5a) - C(5)	127.16(12)	C(1) - N(9) -C(3a)	108.90(12)
S(4) -C(5a) -C(8a)	112.45(11)	C(1) - N(9) -C(8a)	136.42(13)
C(5) -C(5a) -C(8a)	120.39(14)	C(3a) - N(9) -C(8a)	114.65(12)

N(9) - C(1) - C(2) - C(3)	0.10(18)	C(8a) -C(5a) - C(5) - C(6)	-0.75(23)
C(2) - C(1) - N(9) -C(3a)	-0.10(17)	S(4) -C(5a) -C(8a) - C(8)	-179.55(12)
C(2) - C(1) - N(9) -C(8a)	-177.68(16)	S(4) -C(5a) -C(8a) - N(9)	1.68(16)
C(1) - C(2) - C(3) -C(3a)	-0.11(19)	C(5) -C(5a) -C(8a) - C(8)	1.17(23)
C(2) - C(3) -C(3a) - S(4)	179.46(15)	C(5) -C(5a) -C(8a) - N(9)	-177.60(14)
C(2) - C(3) -C(3a) - N(9)	0.08(18)	C(5a) - C(5) - C(6) - C(7)	-0.11(24)
C(3) -C(3a) - S(4) -C(5a)	-177.50(19)	C(5) - C(6) - C(7) - C(8)	0.6(3)
N(9) -C(3a) - S(4) -C(5a)	1.93(12)	C(6) - C(7) - C(8) -C(8a)	-0.14(24)
C(3) -C(3a) - N(9) - C(1)	0.11(17)	C(7) - C(8) -C(8a) -C(5a)	-0.71(23)
C(3) -C(3a) - N(9) -C(8a)	178.21(13)	C(7) - C(8) -C(8a) - N(9)	177.84(15)
S(4) -C(3a) - N(9) - C(1)	-179.58(11)	C(5a) -C(8a) - N(9) - C(1)	177.33(16)
S(4) -C(3a) - N(9) -C(8a)	-1.39(16)	C(5a) -C(8a) - N(9) -C(3a)	-0.19(18)
C(3a) - S(4) -C(5a) - C(5)	177.15(15)	C(8) -C(8a) - N(9) - C(1)	-1.3(3)
C(3a) - S(4) -C(5a) -C(8a)	-2.06(12)	C(8) -C(8a) - N(9) -C(3a)	-178.86(15)
S(4) -C(5a) - C(5) - C(6)	-179.89(12)		

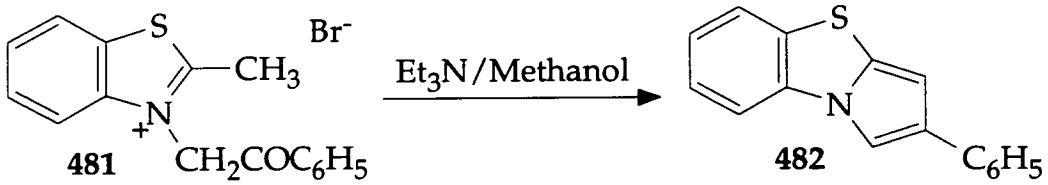
The pyrolyses of **400** and **462** show that highly efficient cyclisation reactions of thiophenoxyl and benzyl radicals can take place onto pyrrole rings in a similar fashion to reactions with aryl rings.[18] The contrast with the reactions of aminyl and in particular phenoxyl radicals where no cyclisation products onto the pyrrole ring were obtained is again evident.[19,17]

F.5. Chemistry of Pyrrolo[2,1-*b*]benzothiazole 82

F.5.a. Introduction

A search of the literature revealed that the parent compound **82** of this ring system could only previously be prepared in low yield by multistep routes and that little was known of the chemistry of substituted examples. Since the radical cyclisation reported above gave simple access to multigram quantities of **82** an investigation of its chemistry was undertaken. A brief review of the published work is now presented.

The first report of a synthesis of the pyrrolo[2,1-*b*]benzothiazole ring system is by Kröhnke and Friedrich[109] who prepared 2-phenylpyrrolo[2,1-*b*] benzothiazole **482** in 35% yield by treating compound **481** with triethylamine (Scheme 101).

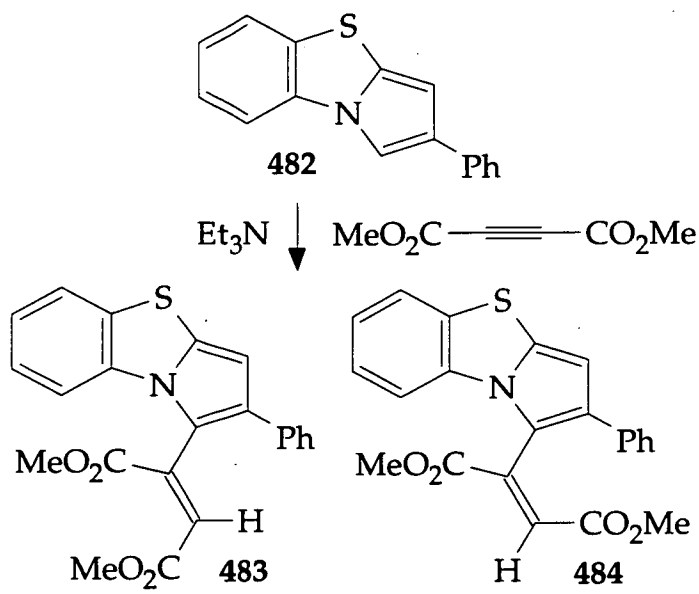


481 **482**

Scheme 101

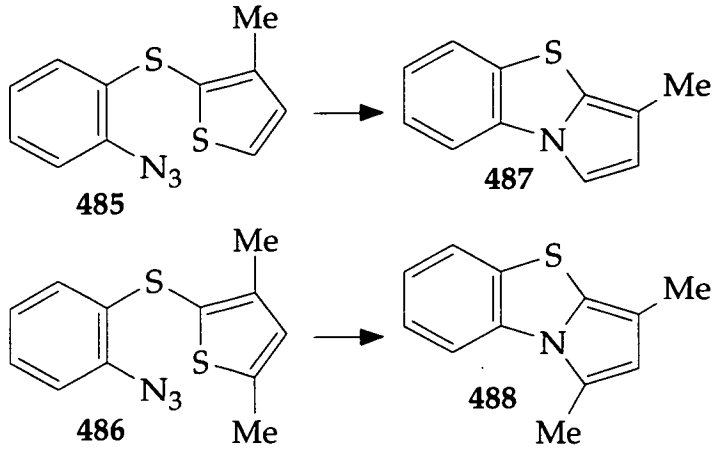
This work was repeated by Molloy, Reid and Skelton[110] who improved

the yield to 41%, and by Galera, Vaquero, Garcia Navio and Alvarez-Builla[111] who achieved a 66% yield using ethanol as solvent. and by Tsuge, Tanaka, Shimoharada and Noguchi.[112] This last group also carried out some work on the chemistry of 2-phenylpyrrolo[2,1-*b*]benzothiazole **482**. They reacted 2-phenylpyrrolo[2,1-*b*]benzothiazole **482** with dimethyl acetylenedicarboxylate in the presence of triethylamine, yielding a mixture of *Z* and *E*-isomers (47% and 39%) **483** and **484** from Michael addition at the 1-position (Scheme 102).



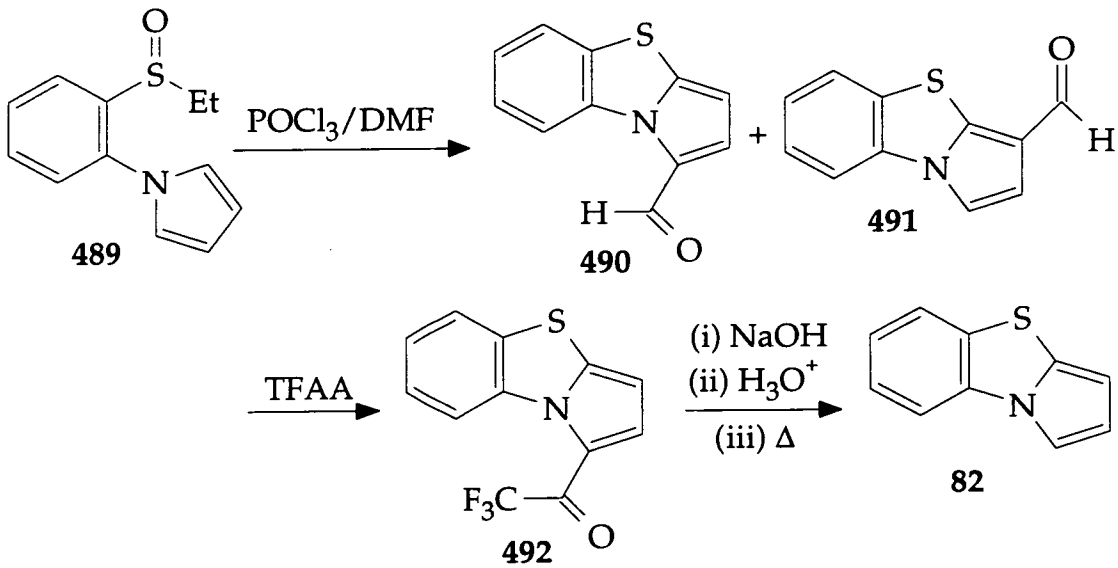
Scheme 102

Lindley, Meth-Cohn and Suschitzky[113] prepared the 3-methyl **487** and the 1,3-dimethyl compounds **488** by thermolysis of the azides **485** and **486** in 65% and 74% yield respectively (Scheme 103). The unsubstituted compound **82** could also be made in this way, but apparently in very low yield since "much purple polymer" was obtained.



Scheme 103

Finally 1-formylpyrrolo[2,1-*b*]benzothiazole **490** and 3-formylpyrrolo [2,1-*b*]benzothiazole **491** were prepared in 73% and 9% yield respectively by Bates, Sell and Pichard.[114] They employed the interrupted Pummerer reaction of compound **489** induced by two equivalents of the Vilsmeier reagent (phosphoryl chloride/DMF) (Scheme 104). The first brings about cyclisation while the second performs the formylation in the usual manner.



Scheme 104

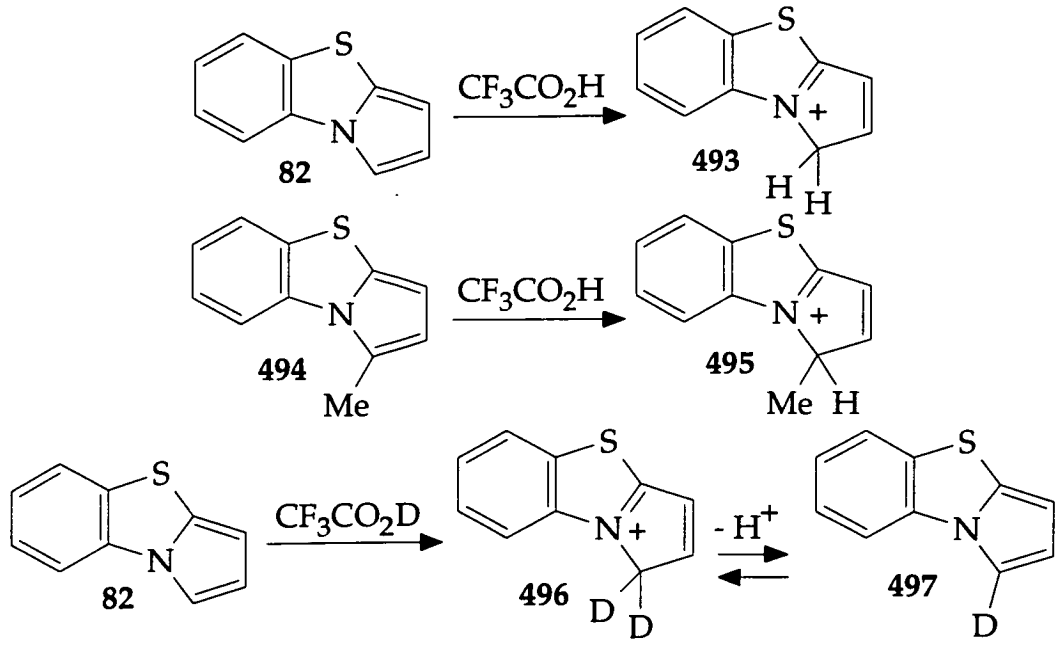
A similar cyclisation of **489** using trifluoroacetic anhydride[115] gave a 1-trifluoroacetyl derivative **492**, which could be hydrolysed and decarboxylated to give the parent compound **82** in 27% overall yield. One other preparation of **82** involved base induced decomposition of a cyanine dye derived from benzothiazole nuclei.[116]

F.5.b. Reactions of Pyrrolo[2,1-*b*]benzothiazole 82

F.5.b.i. Protonation and Deuterium exchange

When pyrrolo[2,1-*b*]benzothiazole **82** was dissolved in trifluoroacetic acid, protonation took place instantaneously at the 1-position to give the protonated compound **493** (Scheme 105). The position of protonation was determined by repeating the reaction with 1-methylpyrrolo[2,1-*b*] benzothiazole **494** which gave the protonated compound **495**; the proton at the 1-position appeared as a quartet with a large coupling of 7.2 Hz, due to coupling with methyl group on the 1-position. Compound **493** was stable in acid solution for over 2 weeks. When pyrrolo[2,1-*b*]benzothiazole **82** was dissolved in deuteriated trifluoroacetic acid, deuteriation took place immediately to give the dideuteriated compound **496**, this suggests that the initial deuteriated cation is in rapid equilibrium with the neutral species **497** (Scheme 105). Further monitoring showed the exchange of a second pyrrole proton with a half life of around 10 minutes, but this could not be assigned unambiguously. The third pyrrole proton was masked by the aromatic signal and could not be accurately observed.

These experiments show that the pyrrolo[2,1-*b*]benzothiazole is potentially very active to electrophiles.



Scheme 105

F.5.b.ii. Vilsmeier-Haack formylation

When pyrrolo[2,1-*b*]benzothiazole **82** was reacted with phosphoryl chloride in DMF two products were isolated but in very low yield. These were shown to be 1-formylpyrrolo[2,1-*b*]benzothiazole **490** (5 %) and 3-formylpyrrolo[2,1-*b*]benzothiazole **491** (7 %) by a series of N.O.E experiments (Figure 3), which further confirm the assignments of Bates *et al.*[114] A ^{1}H NMR spectrum of the crude reaction mixture showed that the ratio of 1-isomer to 3-isomer was 3 : 1, which is slightly different from the results obtained by Bates, Sell and Pichard[114] who believe that they obtained a ratio of 8 : 1 when formylation followed cyclisation (See Scheme 104).

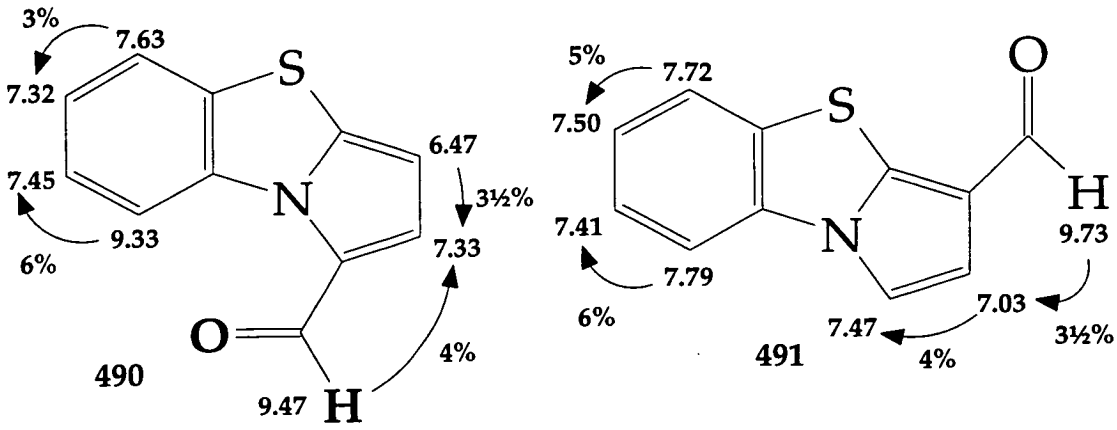


Figure 3

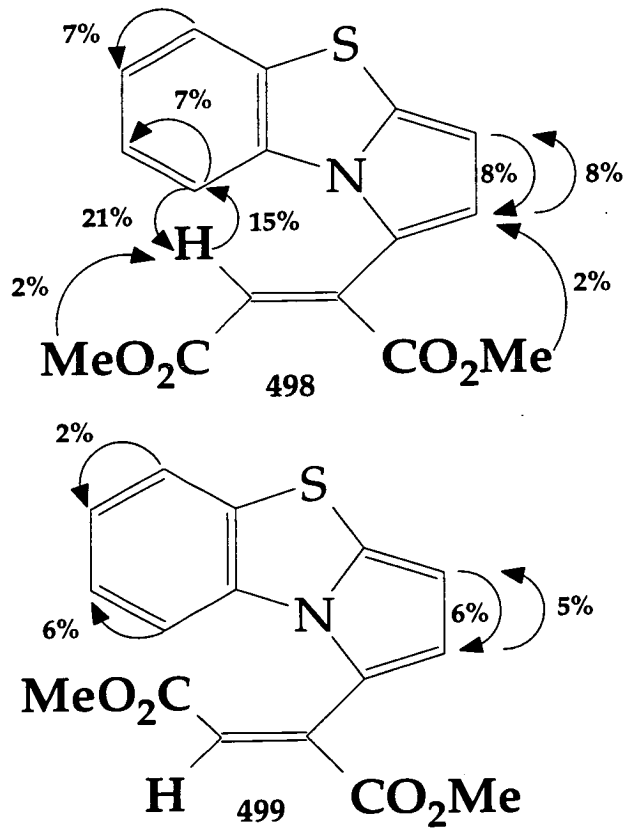


Figure 4

F.5.b.iii. Reaction with Dimethyl acetylenedicarboxylate

When pyrrolo[2,1-*b*]benzothiazole **82** was reacted with dimethyl acetylenedicarboxylate two products were obtained. These were separated

by dry-flash chromatography and shown by a series of N.O.E. experiments to be the *Z*- **498** and *E*-isomers **499** of methyl [3-(carbomethoxy) -3-(pyrrolo[2,1-*b*]benzothiophen-1-yl]propenoate, formed in 33 and 20 % yields respectively (Figure 4). This predominance of *Z*-isomer over *E*-isomer is in accordance with the result of Tsuge and co-workers[112] who obtained 47% *Z* **483** to 39% *E* **484** when they performed the same reaction on 2-phenyl pyrrolo[2,1-b]benzothiazole **482** (Scheme 102).

F.6. Conclusion

While oxygen and nitrogen centred radicals did not yield any cyclised products, the products obtained were of mechanistic interest. The carbon and sulphur centred radicals, however, provided a short, high yielding route to two fused three ring systems.

G. GENERATION OF PHENOXYL, BENZYL AND THIOPHENOXYL FREE RADICALS AND INVESTIGATION OF THEIR INTRAMOLECULAR CYCLISATION REACTION WITH A 2-(2,5-DIMETHYL PYRROL-1-YL) SUBSTITUENT

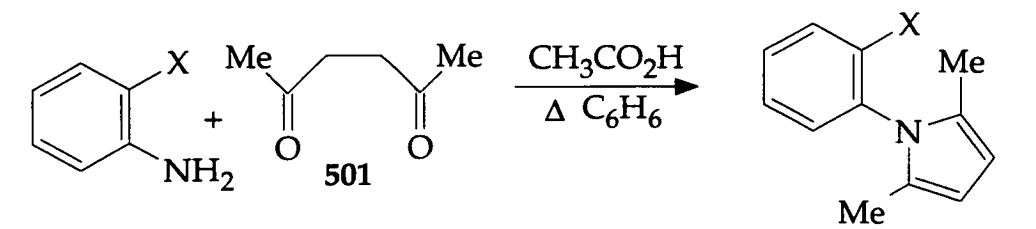
G.1. Introduction

Having carried out a study of the reactions of oxygen, nitrogen, carbon and sulphur centred radicals on an unsubstituted pyrrole ring the next investigation which we chose to undertake was the reactions of oxygen, carbon and sulphur centred radicals on the corresponding 2,5-dimethyl substituted pyrrole ring. The nitrogen centred radical system was not employed because of the difficulty in synthesizing the radical precursor and because results would be expected to be broadly similar to those of the oxygen centred radical.

G.2. Preparation of Radical Precursors: 2,5-Dimethyl-*N*-[2-(allyloxy)phenyl]pyrrole 505, Bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate 506 and 2,5-Dimethyl-*N*-[2-(allylthio) phenyl]pyrrole 507

The method of preparation of these radical precursors was similar to that employed in the previous section. In this case, however, in the formation of the pyrrole ring, hexane-2,5-dione **501** was employed to incorporate the two methyl groups at the 2- and 5-positions (Scheme 106)[117] instead of using the 2,5-dimethoxytetrahydrofuran. It is interesting that in

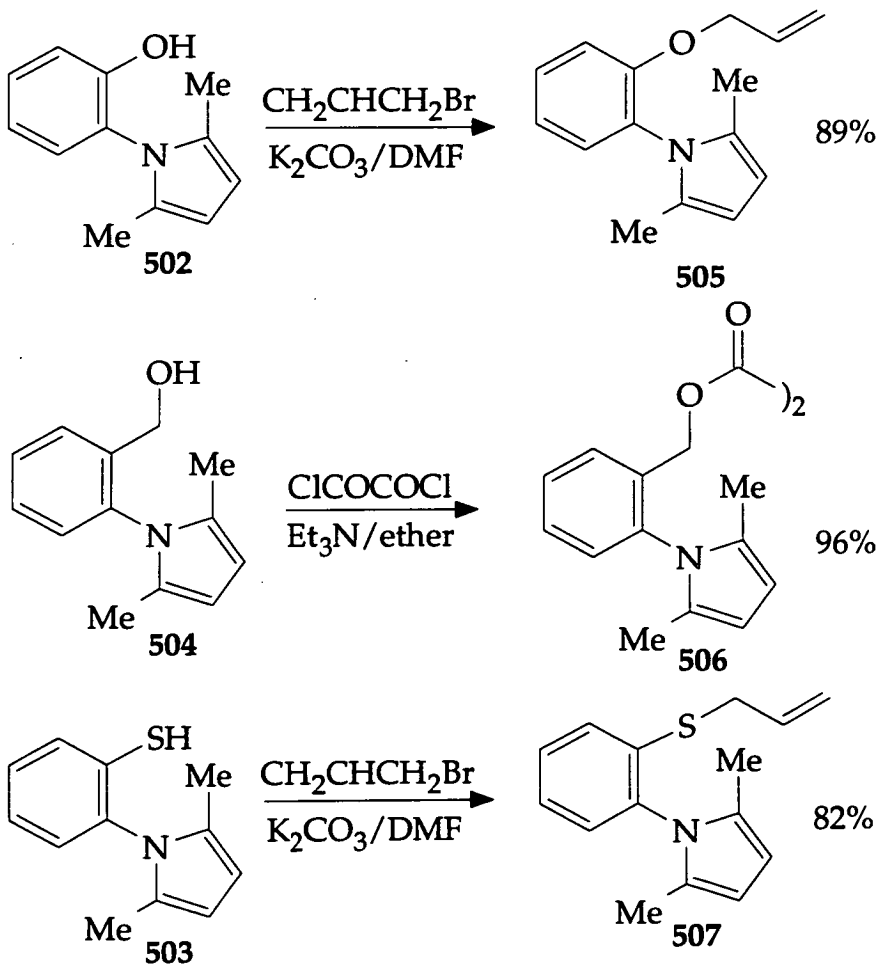
this case the amino benzyl alcohol **500** gives a high yield of the pyrrole compound **504** without the need to employ the reduction of the corresponding ester.



452 X = OH
453 X = SH
500 X = CH_2OH

502 X = OH 99%
503 X = SH 77%
504 X = CH_2OH 93%

Scheme 106



Scheme 107

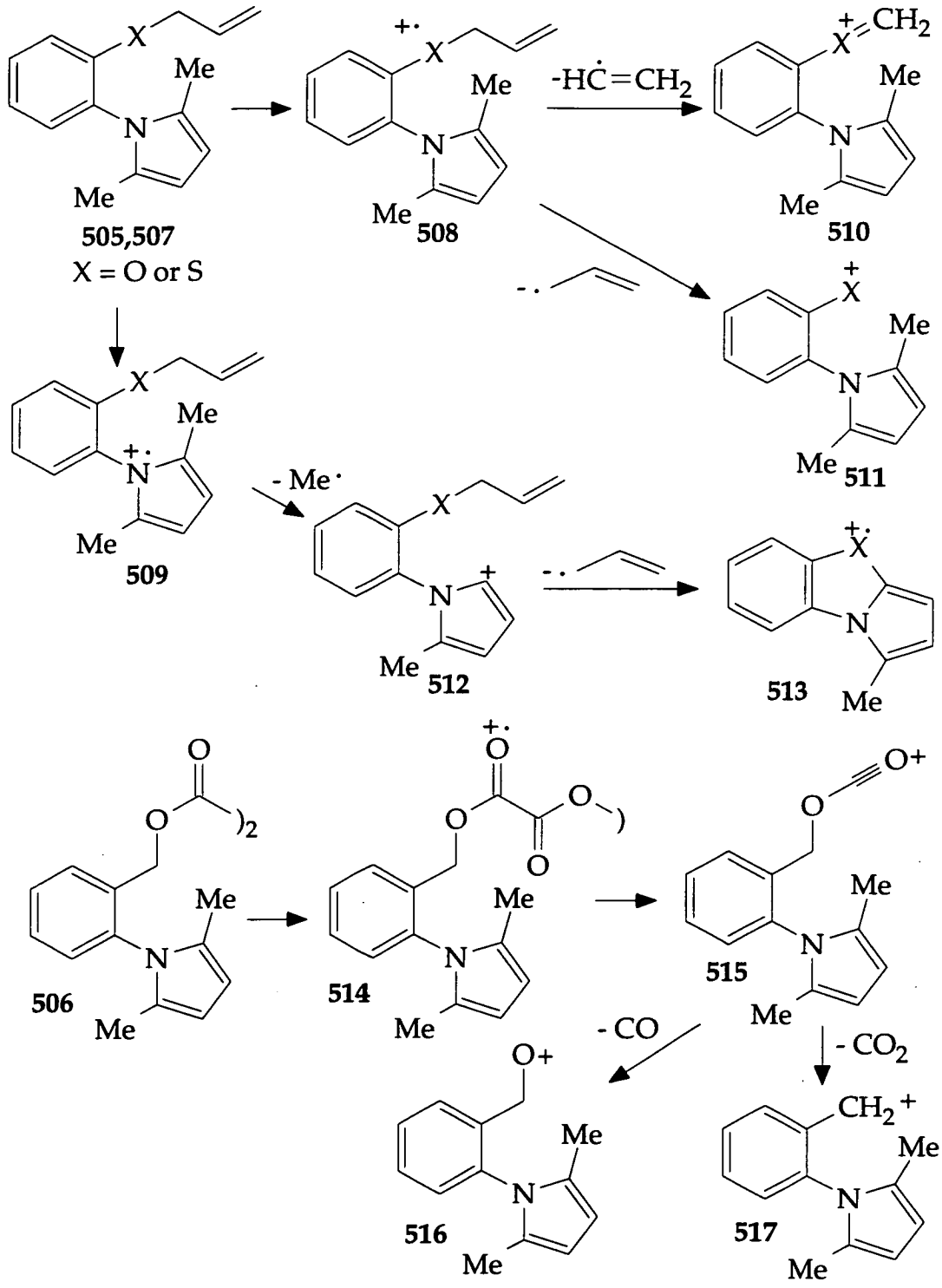
Secondly, the radical generation site was prepared in the usual manner, converting the phenol **502** to the allyl ether **505**, the thiol **504** to the allylthio ether **507** and the benzyl alcohol **503** to the oxalate ester **506** in good yield (Scheme 107).

G.3. Mass Spectra of Radical Precursors: 505, 506 and 507

The mass spectra of the radical precursors showed similar breakdown patterns to those observed for the unsubstituted examples (Scheme 96).

For the two allyl compounds **505** and **507**, initial ionisation can take place on either heteroatom to give a radical cation **508** or **509** (Scheme 108). Intermediate **508** then breaks down by either by α cleavage of a vinyl radical to give **510** (M-27) or by loss of an allyl radical to give **511** (M-41). Intermediate **509**, first loses a methyl radical to give **512** (M-15), then cyclises, losing an allyl radical to give **513** (M-57) (Scheme 108).

The oxalate ester **506** initially ionises at one of the carbonyls to give **514**. The oxalate then cleaves leaving one fragment with the positive charge **515**. This fragment then loses either carbon monoxide to give **516** or carbon dioxide to give **517** (Scheme 108). There is no evidence for loss of a methyl radical with this compound.

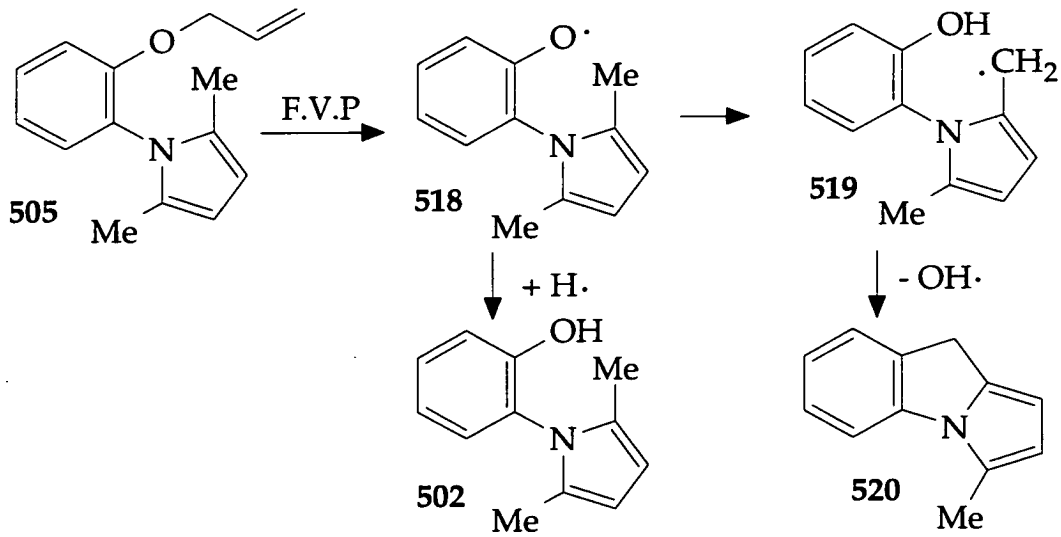

X
Me
N
Me
505,507
X = O or S
+·
-HC·=CH2
+
X=CH2
508
510
-·
511
- Me·
509
512
513
O
)2
506
514
515
O+
- CO
- CO2
516
CH2+
517

Scheme 108

G.4. Pyrolysis of Radical Precursors: 2,5-Dimethyl-*N*-[2-(allyloxy)phenyl]pyrrole 505, Bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate 506 and 2,5-Dimethyl-*N*-[2-(allylthio) phenyl]pyrrole 507

The first radical precursor to be pyrolysed was 2,5-dimethyl-*N*-[2-(allyloxy)phenyl]pyrrole **505**. This gave two major products by t.l.c., which were separated by dry flash chromatography and shown to be 3-methyl-9*H*-pyrrolo[1,2-*a*]indole **520** (29%) and 2,5-dimethyl-*N*-[2-(hydroxy)phenyl] pyrrole **502** (35%). The sample of **520** was identical with that prepared in the following experiment (see Scheme 112) by pyrolysis of the oxalate **506**.

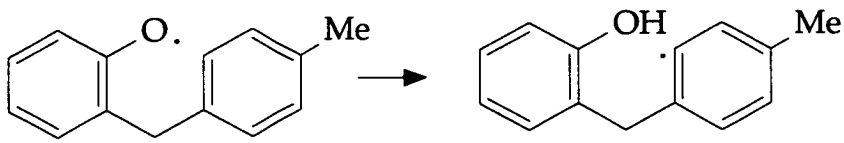
The formation of 3-methyl-9*H*-pyrrolo[1,2-*a*]indole **520** was most unexpected. The proposed mechanism for its formation follows from generation of the initial oxygen centred radical **518** (Scheme 109).



Scheme 109

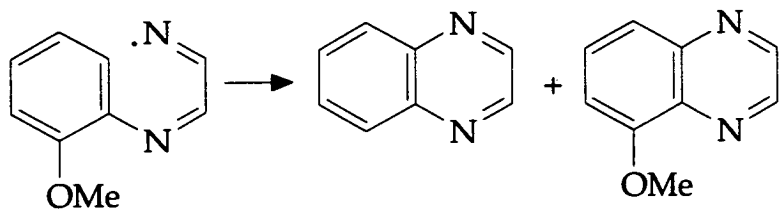
This may simply capture a hydrogen atom to form the phenol **502**, or, more interestingly the oxygen centred radical **518** may abstract a hydrogen atom

from the methyl group to form the carbon centred radical **519**. This type of reaction has been observed previously by Cadogan, Hickson and McNab[17] in the reaction of the phenoxyl radical **521** to give to give the phenyl radical **522** (Scheme 110). In this case the carbon centred radical **519** then cyclises onto the phenyl ring with exclusive loss of the hydroxy radical to give 3-methyl-9*H*-pyrrolo[1,2-*a*]indole **520**. Precedent for this preferential loss of a substituent from a phenyl ring comes from the work of McNab[118] who observed that the radical **523** exhibited a >5:1 preference for the ejection of a methoxy radical to give quinoxaline **524**, as opposed to 5-methoxyquinoxaline **525** (Scheme 111).



521 **522**

Scheme 110



523 **524** 11% **525** 2%

Scheme 111

The second of this series of radical precursors to be pyrolysed was bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate **506**. This was pyrolysed at 750 °C and gave a mixture of a number of products. These were separated and the three principal components shown to be 3-methyl-9*H*-pyrrolo [1,2-*a*]indole **520** (41%) which had spectra identical with those seen for the

previous experiment, 4,5-dihydro-2-methyl-1*H*-benz[*g*]indole **526** (7%) and 4,5-dihydro-2-methyl-3*H*-benz[*e*]indole **527** (5%). From the ^{1}H NMR spectrum of the crude pyrolysate these occurred in the ratio 7.6 : 1 : 1.3. The structures of the last two compounds were confirmed by a series of N.O.E experiments (Figure 5), which showed the connectivity between the aromatic ring, the two CH_2's and the pyrrole ring. Comparison was also made with literature spectra of 4,5-dihydro-*1H*-benz[*g*]indole[119] and 4,5-dihydro-2-phenyl-*3H*-benz[*e*]indole.[120]

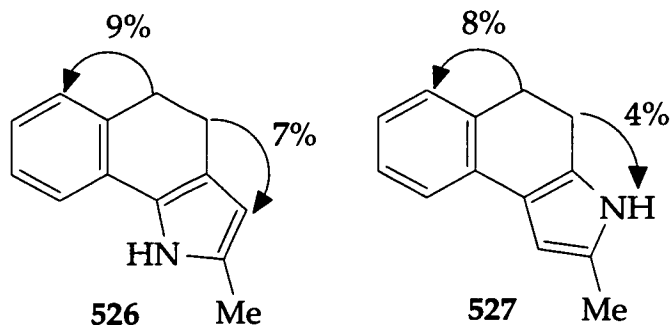
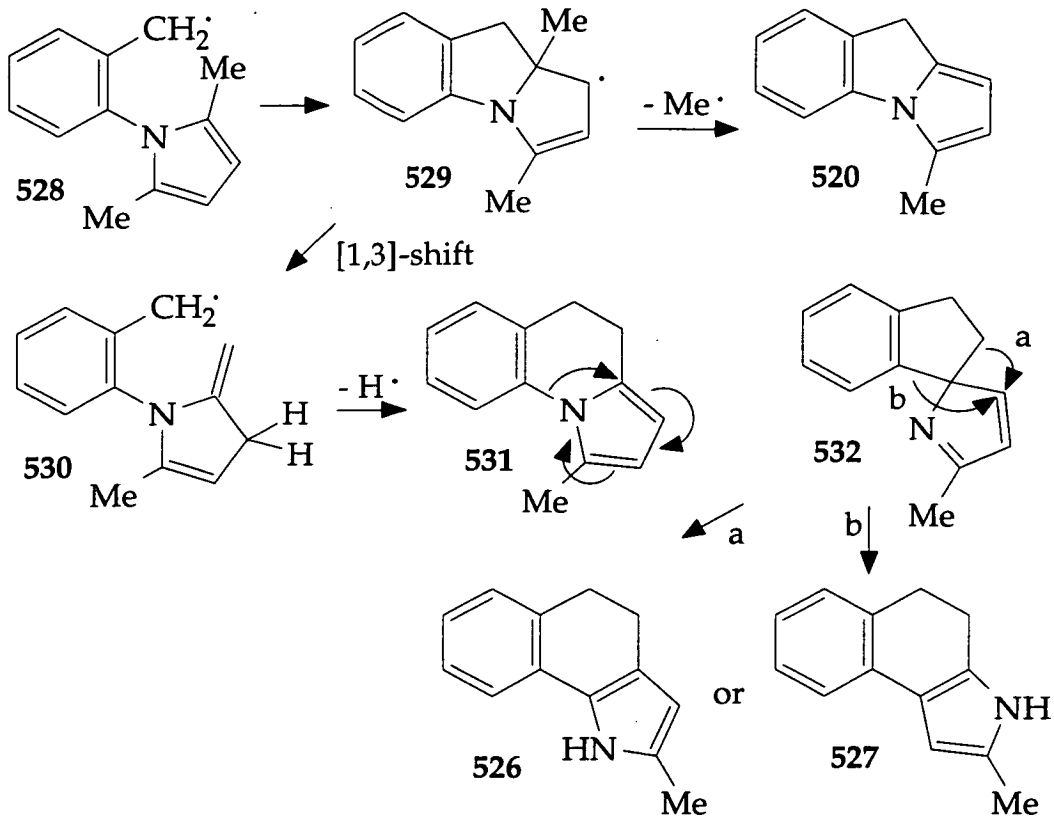


Figure 5

The proposed mechanism for formation of the observed products is that initial pyrolysis gives the carbon centred radical **528**, which then attacks the pyrrole 2-position to give the key intermediate radical **529** from which all the products can be derived. In the major pathway, the radical **529** loses a methyl radical from the 2-position to give 3-methyl-9*H*-pyrrolo[1,2-*a*]indole **520**.



Scheme 112

In the minor pathway a [1,3]-hydrogen shift and ring opening takes place to give the intermediate radical **530**, which is postulated to cyclise to give an intermediate **531** which is not seen in this case. From the ^{1}H NMR spectrum of the crude pyrolysate the level of this compound if present was estimated to be less than 1%. (However the corresponding intermediate was identified in the next section.) The two observed products may then be explained by two [1,5]-shifts. The first gives the spiro intermediate **532**, then depending on which bond shifts, either product 4,5-dihydro-2-methyl-1*H*-benz[*g*]indole **526** (route a) or 4,5-dihydro-2-methyl-3*H*-benz[*e*]indole **527** (route b) may be formed (Scheme 112).

The final radical precursor of this series to be pyrolysed was 2,5-dimethyl-*N*-[2-(allylthio)phenyl]pyrrole **507**. This was pyrolysed at

750 °C and gave a mixture which consisted of four major products. A feature of the ^{1}H NMR spectrum of the crude pyrolysate was the presence of only one significant methyl signal in the range δ 2-3. The components were separated and shown to be 1-methylpyrrolo[2,1-*b*]benzothiazole **494** (17%), by comparison with spectra of pyrrolo[2,1-*b*]benzothiazole **82**, 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazine **533** (23%), by comparison with literature,[121] 1,4-dihydrobenzothiopyrano[4,3-*b*]pyrrole **534** (3%) and 1,4-dihydrobenzothiopyrano[3,4-*b*]pyrrole **535** (3%). From the ^{1}H NMR spectrum of the crude pyrolysate these occurred in the ratio of 1.6 : 2.4 : 1.1 : 1. The connectivity between the hydrogen atoms of the last two compounds was established by N.O.E. (Figure 6).

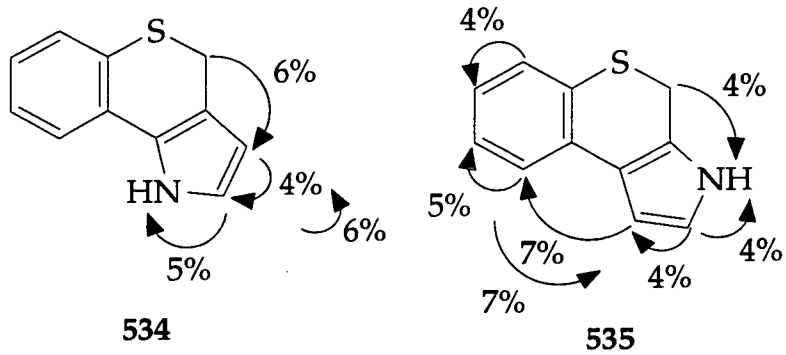
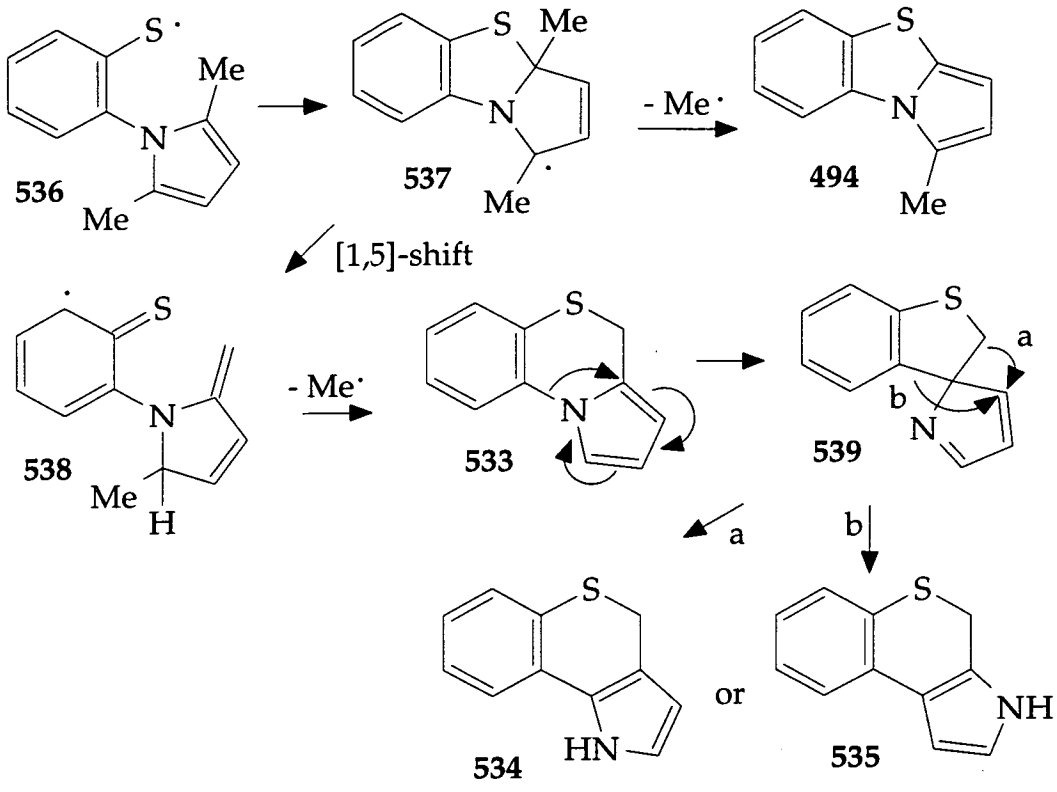


Figure 6

The proposed mechanism for the formation of the above products is similar to that for the carbon centred radical (See Scheme 112). Initial pyrolysis gives the sulphur centred radical **536**, which then attacks the pyrrole 2-position to give key intermediate radical **537** analogous to **529** in Scheme 112. In this case loss of a methyl radical from the 2-position to give 1-methylpyrrolo[2,1-*b*]benzothiazole **494** forms the minor pathway (Scheme 113).



Scheme 113

In the major pathway a [1,5]-hydrogen shift and ring opening takes place to give the intermediate radical **538** rather than the [1,3] hydrogen shift which takes place to give the corresponding benzyl radical **530**. The reasons for this dichotomy are unclear at present but may be connected with the different size of sulphur and carbon atoms. This intermediate **538** is postulated to cyclise with loss of a methyl radical to give 4*H*-pyrrolo [2,1-*c*][1,4]benzothiazine **533**: cleavage of methyl radicals rather than hydrogen atoms in such competitive situations is well known.[13] The final two observed products may then be explained as before by two [1,5]-shifts; The first gives the spiro intermediate **539**, then depending on which bond shifts, either 1,4-dihydrobenzothiopyrano[4,3-*b*]pyrrole **534** (route a) or 1,4-dihydrobenzothiopyrano[3,4-*b*]pyrrole **535** (route b) may be formed (Scheme 113). The occurrence of these [1,5]-shifts has been proved by

isolation of 4*H*-pyrrolo[2,1-*c*][1,4]benzothiazine **533** and repyrolysis to give a mixture containing 1,4-dihydrobenzothiopyrano[4,3-*b*]pyrrole **534** and 1,4-dihydrobenzothiopyrano[3,4-*b*]pyrrole **535**.

G.5. Conclusion

The inclusion of a hydrogen atom source in the 2,5-dimethyl groups has considerably extended the chemistry of these 2-pyrrolylphenoxyl and related radicals. 5-Membered ring cyclised products were obtained in all three cases, though not always in high yield. The result of the phenoxyl radical pyrolysis was particularly surprising, as a hydrogen transfer, cyclisation and ejection sequence led to a major product which did not contain oxygen. In addition 6-membered ring compounds were obtained from the benzyl and thiophenoxyl radicals and indeed formed the major products in the later case. Although superficially similar, these products differ in that those derived from the benzyl radical retain the 5-methyl group while this is lost in the products derived from the thiophenoxyl. In previous cases the properties of benzyl and thiophenoxyl in corresponding systems has been found to be similar (see previous section).

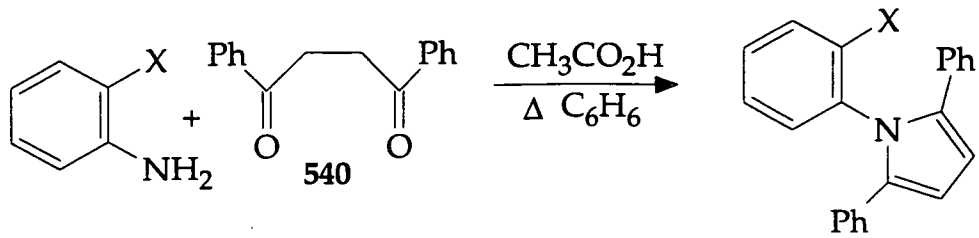
H. GENERATION OF PHENOXYL AND THIOPHENOXYL RADICALS AND INVESTIGATION OF THEIR INTRAMOLECULAR CYCLISATION REACTION WITH A 2-(2,5-DIPHENYLPYRROL-1-YL) SUBSTITUENT

H.1. Introduction

Having carried out a study of the reactions of oxygen, nitrogen, carbon and sulphur centred radicals on an unsubstituted pyrrole ring and oxygen, carbon and sulphur centred radicals on a 2,5-dimethyl substituted pyrrole ring the next investigation which we chose to undertake was the reactions of oxygen and sulphur centred radicals on a 2.5-diphenyl substituted pyrrole ring. . The decision to use only oxygen and sulphur centred radicals was taken because the previous experiments had shown that oxygen and sulphur centred radicals show reactivity at the extremes of either hydrogen atom capture or preference for cyclisation.

H.2. Preparation of Radical Precursors: 2,5-Diphenyl-*N*-[2-(allyloxy)phenyl]pyrrole 543 and 2,5-Diphenyl-*N*-[2-(allylthio)phenyl]pyrrole 544

The method of preparation of these radical precursors was similar to that employed in the previous sections. In this case, however, in the formation of the pyrrole ring, 1,2-dibenzoylethane **540** was employed in a modification of the method of Patterson and Soedigdoto[122] to incorporate the two phenyl groups at the 2- and 5-positions (Scheme 114).

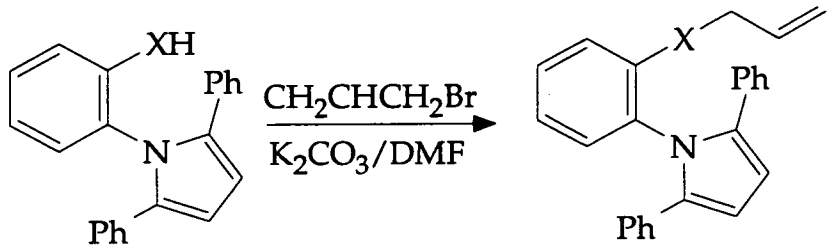


422 X = OH
456 X = SH

541 X = OH 96%
542 X = SH 98%

Scheme 114

The radical generation site was then prepared by conversion of the phenol **541** to the allyl ether **543** and the thiol **542** to the thioether **544**, both in almost quantitative yield (Scheme 115).



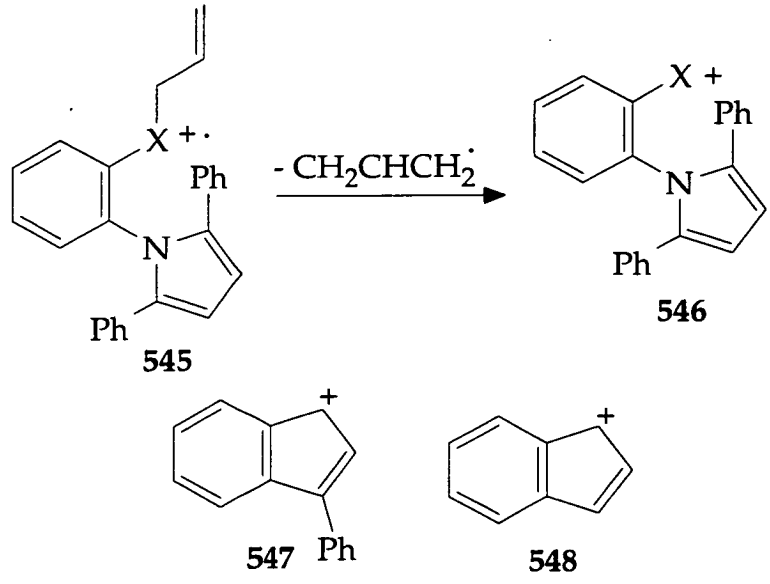
541 X = O
542 X = S

543 X = O 95%
544 X = S 96%

Scheme 115

H.3. Mass Spectra of Radical Precursors: 543 and 544

The mass spectra of the radical precursors **543** and **544** showed a breakdown pattern which is similar to the expected thermal breakdown. Initial ionisation gives a base peak **545** which then loses the allyl group to give a peak at M-41 **546** (Scheme 116). An interesting peak appears at *m/z* 191 along with a smaller peak at *m/z* 115. These may be due to **547** and **548** formed by loss of HCN or PhCN from a diphenylpyrrole like species.

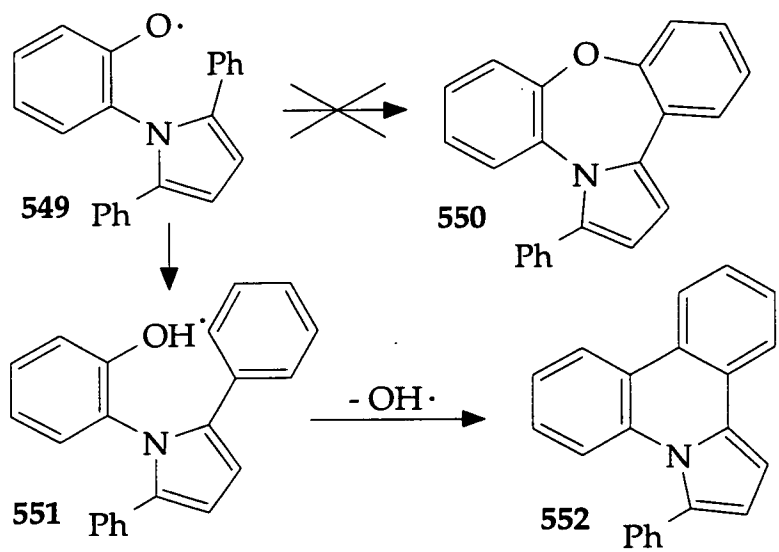


Scheme 116

H.4. Pyrolysis of Radical Precursors: 2,5-Diphenyl-*N*-[2-(allyloxy)phenyl]pyrrole 543 and 2,5-Diphenyl-*N*-[2-(allylthio)phenyl]pyrrole 544

The first radical precursor to be pyrolysed was 2,5-diphenyl-*N*-[2-(allyloxy)phenyl]pyrrole **543** at 650 °C. This gave a mixture of products which were separated by dry-flash chromatography. From this there was obtained one major product, ^{1}H NMR spectroscopy of which showed the presence of two pyrrole protons at δ 7.08 and 6.69, with a coupling constant *J* 3.9 Hz, and a complex multiplet at δ 8.34-7.09 which integrated for thirteen aromatic protons. These data were consistent with two different products; one where the initial oxygen centred radical **549** had cyclised to one of the phenyl rings to give **550** (Scheme 117), and another where the oxygen centred radical **549** abstracted a hydrogen atom to give a phenyl radical **551**, which then cyclised with loss of a hydroxy group to give 3-phenyl pyrrolo[1,2-*f*]phenanthridine **552** (Scheme 117). The latter was preferred

because of the similarity in chemical shifts with those of pyrrolo[1,2-*f*] phenanthridine which occur at δ(H–1) 6.90, δ(H–2) 6.67 and δ(H-3) 7.67 ppm, ($^3J_{1,2}$ 3.9,$^3J_{2,3}$ 2.8 and $^4J_{1,3}$ 1.3.).[123]



Scheme 117

This assignment was supported by mass spectroscopy which gave a molecular ion *m/z* 293 and accurate mass which gave a formula of $C_{22}H_{15}N$. The formation of 3-phenylpyrrolo[1,2-*f*]phenanthridine **552** was finally confirmed by an X-ray crystal structure (Figure 7).

There were two molecules unrelated by symmetry in the unit cell. There are few significant differences in the parameters of these molecules except in some of the torsion angles. As can be seen from Figure the condensed tetracycle is only approximately planar and the phenyl group is substantially twisted out of the plane. NMR data for non-planarity of phenyl groups in phenyl substituted pyrrolo[1,2-*f*]phenanthridines have been reported.[123]

X-ray crystal structure of 3-phenylpyrrolo[1,2-*f*] phenanthridine 552

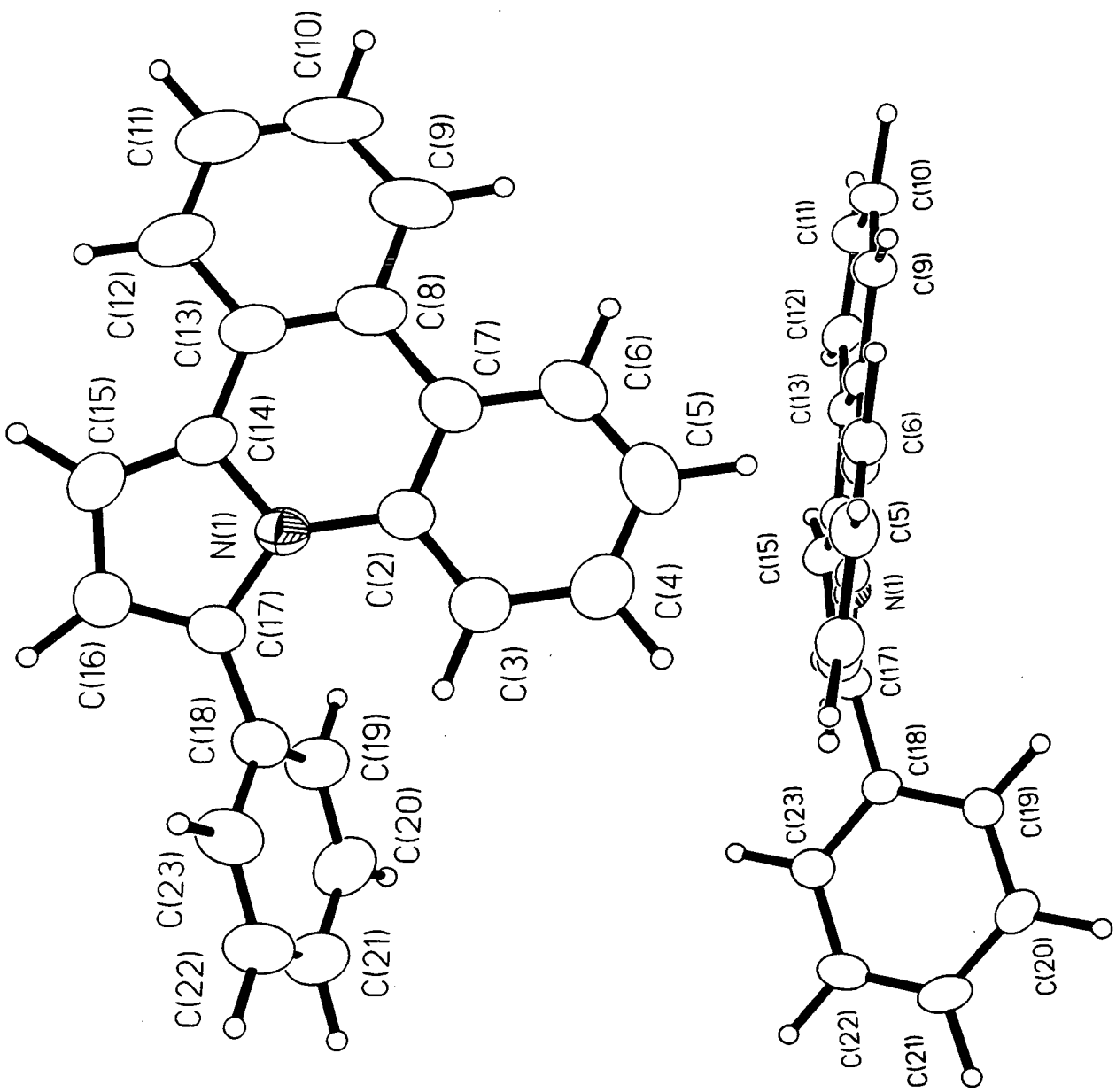


Figure 7

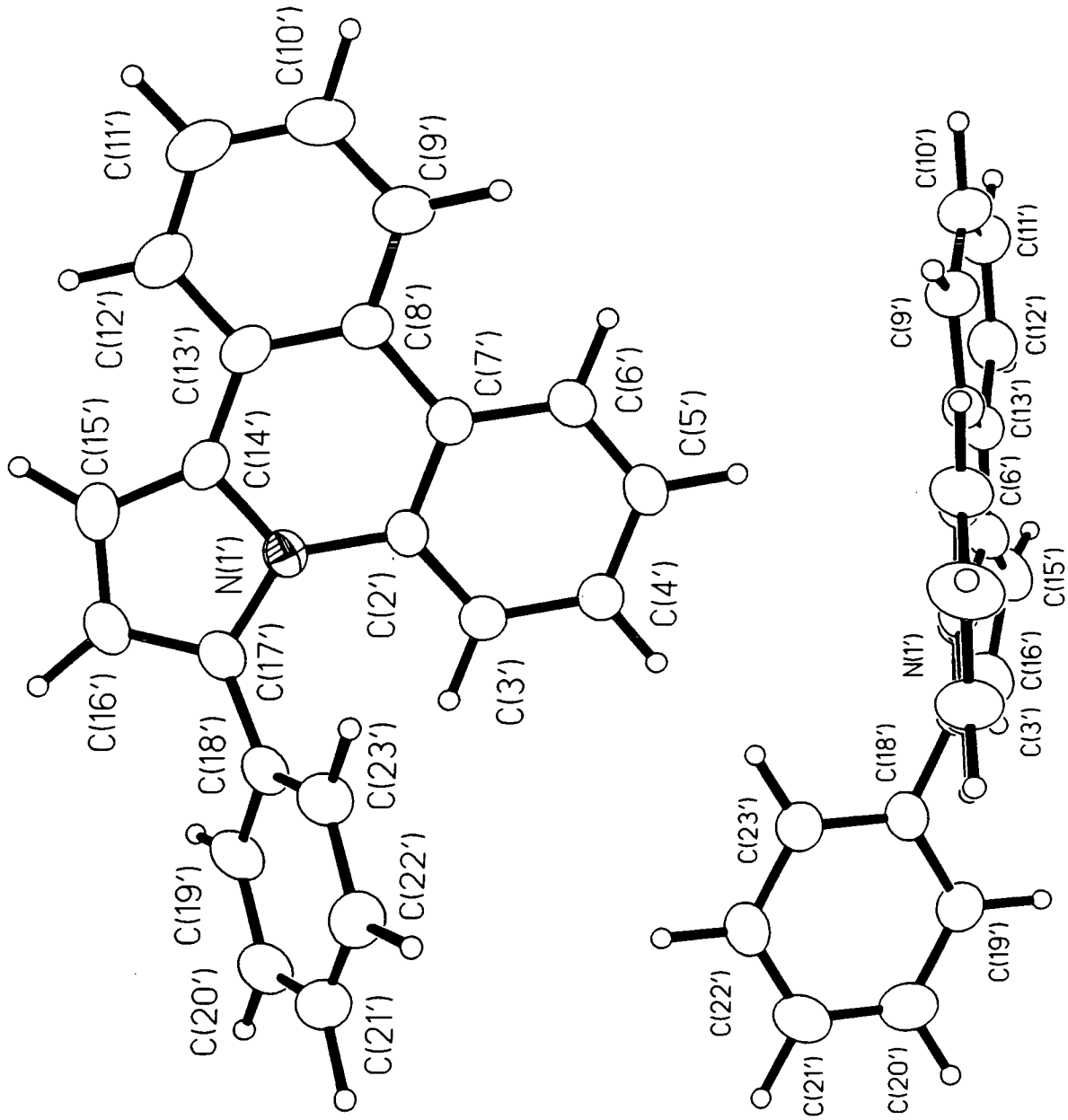


Figure 7 continued

Table 1. Bond Lengths(Å) with standard deviations

N(1)	- C(2)	1.423(4)	N(1')	-C(2')	1.415(5)
N(1)	-C(14)	1.410(4)	N(1')	-C(14')	1.402(5)
N(1)	-C(17)	1.388(4)	N(1')	-C(17')	1.403(5)
C(2)	- C(3)	1.387(5)	C(2')	-C(3')	1.394(6)
C(2)	- C(7)	1.403(5)	C(2')	-C(7')	1.408(6)
C(3)	- C(4)	1.376(6)	C(3')	-C(4')	1.373(6)
C(4)	- C(5)	1.394(6)	C(4')	-C(5')	1.392(7)
C(5)	- C(6)	1.387(6)	C(5')	-C(6')	1.369(7)
C(6)	- C(7)	1.396(6)	C(6')	-C(7')	1.389(6)
C(7)	- C(8)	1.472(6)	C(7')	-C(8')	1.476(6)
C(8)	- C(9)	1.403(6)	C(8')	-C(9')	1.404(6)
C(8)	-C(13)	1.389(6)	C(8')	-C(13')	1.393(6)
C(9)	-C(10)	1.383(7)	C(9')	-C(10')	1.390(7)
C(10)	-C(11)	1.367(7)	C(10')	-C(11')	1.381(8)
C(11)	-C(12)	1.375(7)	C(11')	-C(12')	1.385(7)
C(12)	-C(13)	1.412(6)	C(12')	-C(13')	1.394(6)
C(13)	-C(14)	1.443(6)	C(13')	-C(14')	1.446(6)
C(14)	-C(15)	1.358(6)	C(14')	-C(15')	1.372(7)
C(15)	-C(16)	1.404(6)	C(15')	-C(16')	1.398(7)
C(16)	-C(17)	1.373(6)	C(16')	-C(17')	1.377(6)
C(17)	-C(18)	1.490(5)	C(17')	-C(18')	1.467(6)
C(18)	-C(19)	1.381(6)	C(18')	-C(19')	1.387(6)
C(18)	-C(23)	1.395(6)	C(18')	-C(23')	1.392(6)
C(19)	-C(20)	1.382(6)	C(19')	-C(20')	1.387(7)
C(20)	-C(21)	1.386(6)	C(20')	-C(21')	1.374(7)
C(21)	-C(22)	1.379(6)	C(21')	-C(22')	1.378(7)
C(22)	-C(23)	1.387(6)	C(22')	-C(23')	1.389(7)

Table 2. Angles(degrees) with standard deviations

C(2)	- N(1)	-C(14)	121.4(3)
C(2)	- N(1)	-C(17)	130.5(3)
C(14)	- N(1)	-C(17)	107.6(3)
N(1)	- C(2)	- C(3)	120.7(3)
N(1)	- C(2)	- C(7)	118.0(3)
C(3)	- C(2)	- C(7)	121.3(4)
C(2)	- C(3)	- C(4)	119.7(4)
C(3)	- C(4)	- C(5)	120.8(4)
C(4)	- C(5)	- C(6)	118.7(4)
C(5)	- C(6)	- C(7)	122.1(4)
C(2)	- C(7)	- C(6)	117.2(4)
C(2)	- C(7)	- C(8)	121.1(4)
C(6)	- C(7)	- C(8)	121.6(4)
C(7)	- C(8)	- C(9)	122.7(4)
C(7)	- C(8)	-C(13)	118.6(4)
C(9)	- C(8)	-C(13)	118.7(4)
C(8)	- C(9)	-C(10)	119.9(4)
C(9)	-C(10)	-C(11)	121.4(5)
C(10)	-C(11)	-C(12)	120.0(5)
C(11)	-C(12)	-C(13)	119.8(4)
C(8)	-C(13)	-C(12)	120.3(4)
C(8)	-C(13)	-C(14)	120.6(4)
C(12)	-C(13)	-C(14)	119.1(4)
N(1)	-C(14)	-C(13)	118.9(3)
N(1)	-C(14)	-C(15)	108.3(3)
C(13)	-C(14)	-C(15)	132.7(4)
C(14)	-C(15)	-C(16)	107.7(4)
C(15)	-C(16)	-C(17)	108.7(4)
N(1)	-C(17)	-C(16)	107.6(3)
N(1)	-C(17)	-C(18)	126.0(3)
C(16)	-C(17)	-C(18)	125.9(4)
C(17)	-C(18)	-C(19)	121.9(3)
C(17)	-C(18)	-C(23)	119.0(3)
C(19)	-C(18)	-C(23)	118.8(4)
C(18)	-C(19)	-C(20)	121.0(4)
C(19)	-C(20)	-C(21)	119.6(4)
C(20)	-C(21)	-C(22)	120.4(4)
C(21)	-C(22)	-C(23)	119.5(4)
C(18)	-C(23)	-C(22)	120.7(4)

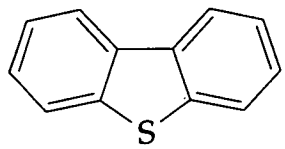
C(2')	-N(1')	-C(14')	120.7(3)
C(2')	-N(1')	-C(17')	129.0(3)
C(14')	-N(1')	-C(17')	108.5(3)
N(1')	-C(2')	-C(3')	121.6(4)
N(1')	-C(2')	-C(7')	118.5(4)
C(3')	-C(2')	-C(7')	119.7(4)
C(2')	-C(3')	-C(4')	120.6(4)
C(3')	-C(4')	-C(5')	119.9(4)
C(4')	-C(5')	-C(6')	119.5(5)
C(5')	-C(6')	-C(7')	122.2(4)
C(2')	-C(7')	-C(6')	118.0(4)
C(2')	-C(7')	-C(8')	119.9(4)
C(6')	-C(7')	-C(8')	122.1(4)
C(7')	-C(8')	-C(9')	122.5(4)
C(7')	-C(8')	-C(13')	119.0(4)
C(9')	-C(8')	-C(13')	118.4(4)
C(8')	-C(9')	-C(10')	120.4(4)
C(9')	-C(10')	-C(11')	120.6(5)
C(10')	-C(11')	-C(12')	119.5(5)
C(11')	-C(12')	-C(13')	120.4(5)
C(8')	-C(13')	-C(12')	120.6(4)
C(8')	-C(13')	-C(14')	119.7(4)
C(12')	-C(13')	-C(14')	119.6(4)
N(1')	-C(14')	-C(13')	118.9(4)
N(1')	-C(14')	-C(15')	107.5(4)
C(13')	-C(14')	-C(15')	133.4(4)
C(14')	-C(15')	-C(16')	108.2(4)
C(15')	-C(16')	-C(17')	109.0(4)
N(1')	-C(17')	-C(16')	106.7(4)
N(1')	-C(17')	-C(18')	126.1(4)
C(16')	-C(17')	-C(18')	126.0(4)
C(17')	-C(18')	-C(19')	120.0(4)
C(17')	-C(18')	-C(23')	120.8(4)
C(19')	-C(18')	-C(23')	118.8(4)
C(18')	-C(19')	-C(20')	120.4(4)
C(19')	-C(20')	-C(21')	120.5(5)
C(20')	-C(21')	-C(22')	119.7(5)
C(21')	-C(22')	-C(23')	120.1(5)
C(18')	-C(23')	-C(22')	120.4(4)

Table 3. Torsion angles(degrees) with standard deviations

C(14)	N(1)	C(2)	C(3)	163.3(3)	C(14')	N(1')	C(2')	C(3')	-158.6(4)
C(14)	N(1)	C(2)	C(7)	-13.6(5)	C(14')	N(1')	C(2')	C(7')	17.4(6)
C(17)	N(1)	C(2)	C(3)	-7.0(5)	C(17')	N(1')	C(2')	C(3')	4.2(6)
C(17)	N(1)	C(2)	C(7)	176.1(3)	C(17')	N(1')	C(2')	C(7')	-179.8(4)
C(2)	N(1)	C(14)	C(13)	13.4(5)	C(2')	N(1')	C(14')	C(13')	-20.8(6)
C(2)	N(1)	C(14)	C(15)	-170.3(3)	C(2')	N(1')	C(14')	C(15')	163.8(4)
C(17)	N(1)	C(14)	C(13)	-174.3(3)	C(17')	N(1')	C(14')	C(13')	173.2(4)
C(17)	N(1)	C(14)	C(15)	2.0(4)	C(17')	N(1')	C(14')	C(15')	-2.1(5)
C(2)	N(1)	C(17)	C(16)	169.6(3)	C(2')	N(1')	C(17')	C(16')	-161.9(4)
C(2)	N(1)	C(17)	C(18)	-18.6(6)	C(2')	N(1')	C(17')	C(18')	29.6(7)
C(14)	N(1)	C(17)	C(16)	-1.7(4)	C(14')	N(1')	C(17')	C(16')	2.5(5)
C(14)	N(1)	C(17)	C(18)	170.1(4)	C(14')	N(1')	C(17')	C(18')	-165.9(4)
N(1)	C(2)	C(3)	C(4)	179.5(4)	N(1')	C(2')	C(3')	C(4')	178.9(4)
C(7)	C(2)	C(3)	C(4)	-3.7(6)	C(7')	C(2')	C(3')	C(4')	3.1(6)
N(1)	C(2)	C(7)	C(6)	-178.3(3)	N(1')	C(2')	C(7')	C(6')	-179.2(4)
N(1)	C(2)	C(7)	C(8)	4.5(5)	N(1')	C(2')	C(7')	C(8')	-2.2(6)
C(3)	C(2)	C(7)	C(6)	4.8(6)	C(3')	C(2')	C(7')	C(6')	-3.2(6)
C(3)	C(2)	C(7)	C(8)	-172.4(4)	C(3')	C(2')	C(7')	C(8')	173.6(4)
C(2)	C(3)	C(4)	C(5)	0.3(7)	C(2')	C(3')	C(4')	C(5')	-0.9(7)
C(3)	C(4)	C(5)	C(6)	1.7(7)	C(3')	C(4')	C(5')	C(6')	-1.1(7)
C(4)	C(5)	C(6)	C(7)	-0.5(7)	C(4')	C(5')	C(6')	C(7')	0.8(7)
C(5)	C(6)	C(7)	C(2)	-2.7(6)	C(5')	C(6')	C(7')	C(2')	1.3(7)
C(5)	C(6)	C(7)	C(8)	174.5(4)	C(5')	C(6')	C(7')	C(8')	-175.7(4)
C(2)	C(7)	C(8)	C(9)	-176.4(4)	C(2')	C(7')	C(8')	C(9')	173.9(4)
C(2)	C(7)	C(8)	C(13)	4.7(6)	C(2')	C(7')	C(8')	C(13')	-9.3(6)
C(6)	C(7)	C(8)	C(9)	6.5(6)	C(6')	C(7')	C(8')	C(9')	-9.2(6)
C(6)	C(7)	C(8)	C(13)	-172.4(4)	C(6')	C(7')	C(8')	C(13')	167.7(4)
C(7)	C(8)	C(9)	C(10)	-179.9(4)	C(7')	C(8')	C(9')	C(10')	175.2(4)
C(13)	C(8)	C(9)	C(10)	-1.0(7)	C(13')	C(8')	C(9')	C(10')	-1.7(7)
C(7)	C(8)	C(13)	C(12)	178.6(4)	C(7')	C(8')	C(13')	C(12')	-176.1(4)
C(7)	C(8)	C(13)	C(14)	-5.0(6)	C(7')	C(8')	C(13')	C(14')	5.9(6)
C(9)	C(8)	C(13)	C(12)	-0.4(6)	C(9')	C(8')	C(13')	C(12')	0.9(6)
C(9)	C(8)	C(13)	C(14)	176.1(4)	C(9')	C(8')	C(13')	C(14')	-177.1(4)
C(8)	C(9)	C(10)	C(11)	1.7(8)	C(8')	C(9')	C(10')	C(11')	1.4(8)
C(9)	C(10)	C(11)	C(12)	-1.1(8)	C(9')	C(10')	C(11')	C(12')	-0.4(8)
C(10)	C(11)	C(12)	C(13)	-0.3(7)	C(10')	C(11')	C(12')	C(13')	-0.4(8)
C(11)	C(12)	C(13)	C(8)	1.0(7)	C(11')	C(12')	C(13')	C(8')	0.1(7)
C(11)	C(12)	C(13)	C(14)	-175.4(4)	C(11')	C(12')	C(13')	C(14')	176.1(4)
C(8)	C(13)	C(14)	N(1)	-3.7(6)	C(8')	C(13')	C(14')	N(1')	6.6(6)
C(8)	C(13)	C(14)	C(15)	-178.9(4)	C(8')	C(13')	C(14')	C(15')	-177.3(5)
C(12)	C(13)	C(14)	N(1)	172.7(4)	C(12')	C(13')	C(14')	N(1')	-169.3(4)
C(12)	C(13)	C(14)	C(15)	-2.5(7)	C(12')	C(13')	C(14')	C(15')	4.6(6)
N(1)	C(14)	C(15)	C(16)	-1.4(5)	N(1')	C(14')	C(15')	C(16')	0.9(5)
C(13)	C(14)	C(15)	C(16)	174.1(4)	C(13')	C(14')	C(15')	C(16')	-173.5(5)
C(14)	C(15)	C(16)	C(17)	0.4(5)	C(14')	C(15')	C(16')	C(17')	0.7(6)
C(15)	C(16)	C(17)	N(1)	0.9(5)	C(15')	C(16')	C(17')	N(1')	-2.0(5)
C(15)	C(16)	C(17)	C(18)	-171.0(4)	C(15')	C(16')	C(17')	C(18')	166.5(4)
N(1)	C(17)	C(18)	C(19)	-58.3(5)	N(1')	C(17')	C(18')	C(19')	-141.9(4)
N(1)	C(17)	C(18)	C(23)	129.0(4)	N(1')	C(17')	C(18')	C(23')	46.0(6)
C(16)	C(17)	C(18)	C(19)	112.1(5)	C(16')	C(17')	C(18')	C(19')	51.9(6)
C(16)	C(17)	C(18)	C(23)	-60.6(6)	C(16')	C(17')	C(18')	C(23')	-120.3(5)
C(17)	C(18)	C(19)	C(20)	-173.5(4)	C(17')	C(18')	C(19')	C(20')	-172.4(4)
C(23)	C(18)	C(19)	C(20)	-0.8(6)	C(23')	C(18')	C(19')	C(20')	-0.1(7)
C(17)	C(18)	C(23)	C(22)	173.4(4)	C(17')	C(18')	C(23')	C(22')	173.0(4)
C(19)	C(18)	C(23)	C(22)	0.5(6)	C(19')	C(18')	C(23')	C(22')	0.8(7)
C(18)	C(19)	C(20)	C(21)	1.2(6)	C(18')	C(19')	C(20')	C(21')	0.5(7)
C(19)	C(20)	C(21)	C(22)	-1.4(7)	C(19')	C(20')	C(21')	C(22')	-1.6(8)
C(20)	C(21)	C(22)	C(23)	1.2(7)	C(20')	C(21')	C(22')	C(23')	2.4(8)
C(21)	C(22)	C(23)	C(18)	-0.7(7)	C(21')	C(22')	C(23')	C(18')	-1.9(7)

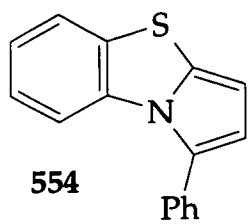
The second radical precursor to be pyrolysed was 2,5-diphenyl-*N*-[2-(allylthio)phenyl]pyrrole **544**. This was pyrolysed at 750 °C and t.l.c. showed a complex mixture from which nine fractions were separated by very careful dry-flash chromatography. Of these, three proved to be mixtures of very minor components, some of which could be identified, and six were fully characterised and their structures determined, principally by ^{1}H NMR spectroscopy.

The first fraction was identified unexpectedly as dibenzothiophene **553** (9 %)[37] from its characteristic ^{1}H and ^{13}C NMR spectra and its mass spectrum (M+ 184).



553

The second component showed a molecular ion at *m/z* 249 and is formed by loss of a phenyl radical from the initial radical **562** to give 1-phenylpyrrolo[2,1-*b*]benzothiophene **554** (5%). The ^{1}H NMR spectrum showed peaks at δ 6.52 and 6.32 with coupling of ^3J 3.7, consistent with H-2 and H-3 of this compound.



554

The electron impact spectrum of the third component showed a major peak at *m/z* 293 apparently due to loss of H· and S from the original

thiophenoxyl **562**, however the F.A.B. mass spectrum (thioglycerol matrix) showed a clear M+H peak at *m/z* 326 and this assignment was confirmed by accurate mass measurement. The most likely structure for this compound, formed by loss of H· only from the initial radical is the dibenzopyrrolothiazepine **555** (4%). In agreement with this structure ^{13}C NMR spectroscopy showed the presence of 13 methine carbon atoms (including two of double intensity due to the *ortho* and *meta* carbons of the phenyl substituent) plus seven quaternary signals. At 360 MHz eight of the thirteen chemically non equivalent protons were resolved using [$^{2}H_6$]acetone solution and the N.O.E. data shown (Figure 8) are also consistent with the assignment.

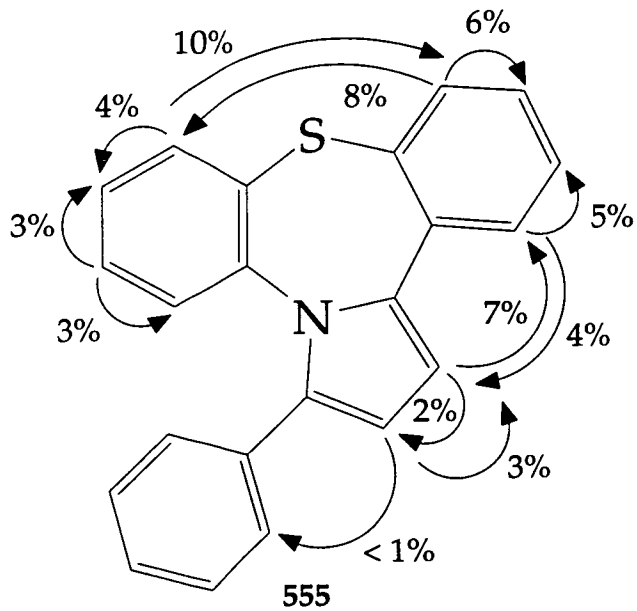
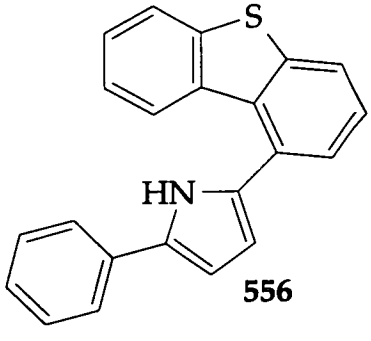


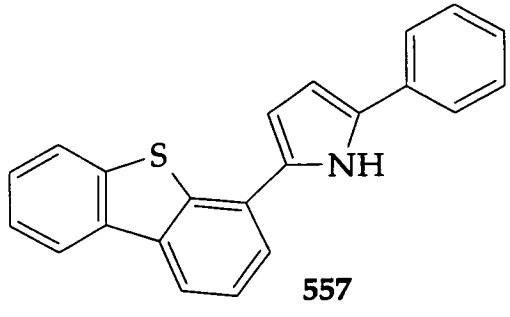
Figure 8

The fourth fraction was the major component of the mixture. The electron impact mass spectrum showed a molecular ion at *m/z* 325. Its ^{13}C NMR showed 11 methine signals, of which three were of double intensity, plus 8 quaternary signals. Two of the double intensity methine signals are

likely to be due to the *ortho* and *meta* carbons of an phenyl ring. Examination of the ^1H NMR spectrum showed two pyrrole protons [δ($CDCl_3$) 6.49 and 6.78], which appeared as double doublets, due to coupling with each other and an NH at δ($CDCl_3$) 8.68. The high frequency portion of the spectrum was best resolved in [$^2H_6$]acetone and showed evidence of one proton of a four spin system, δ 7.94 (d of d of d) and one proton of a three spin system, δ 7.99 (d of d). The latter could be related to other peaks at δ 7.54 (apparent t) and δ 7.49 (d of d) which were 1,2,3 disposed to each other from the sizes of the coupling constants. These data would be consistent with a 1- or 4-substituted benzothiophene nucleus. From N.O.E. experiments (600 MHz) (Figure 9), irradiation of the NH produced enhancements of the phenyl *ortho* protons and one other aromatic, which significantly was not part of the three spin system. This irradiation produced enhancements of the two previously assigned pyrrole protons, which suggests that these are at the 3- and 4-positions and the ring is 2,5-disubstituted. From this, structure **556** and **557** can be proposed but only **556** (24%) can show the observed N.O.E. effects between the NH and the proton δ($CDCl_3$) 7.41 which can be shown from the COSY spectrum (Figure 10) to be part of the four spin system. (The three spin system and the phenyl ring connectivity can also be seen). Other N.O.E. enhancements which support this structure are shown in Figure 9.



556



557

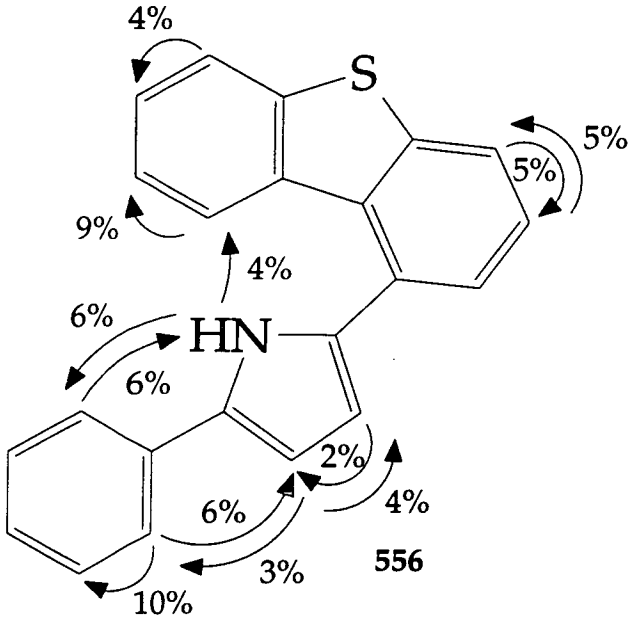


Figure 9

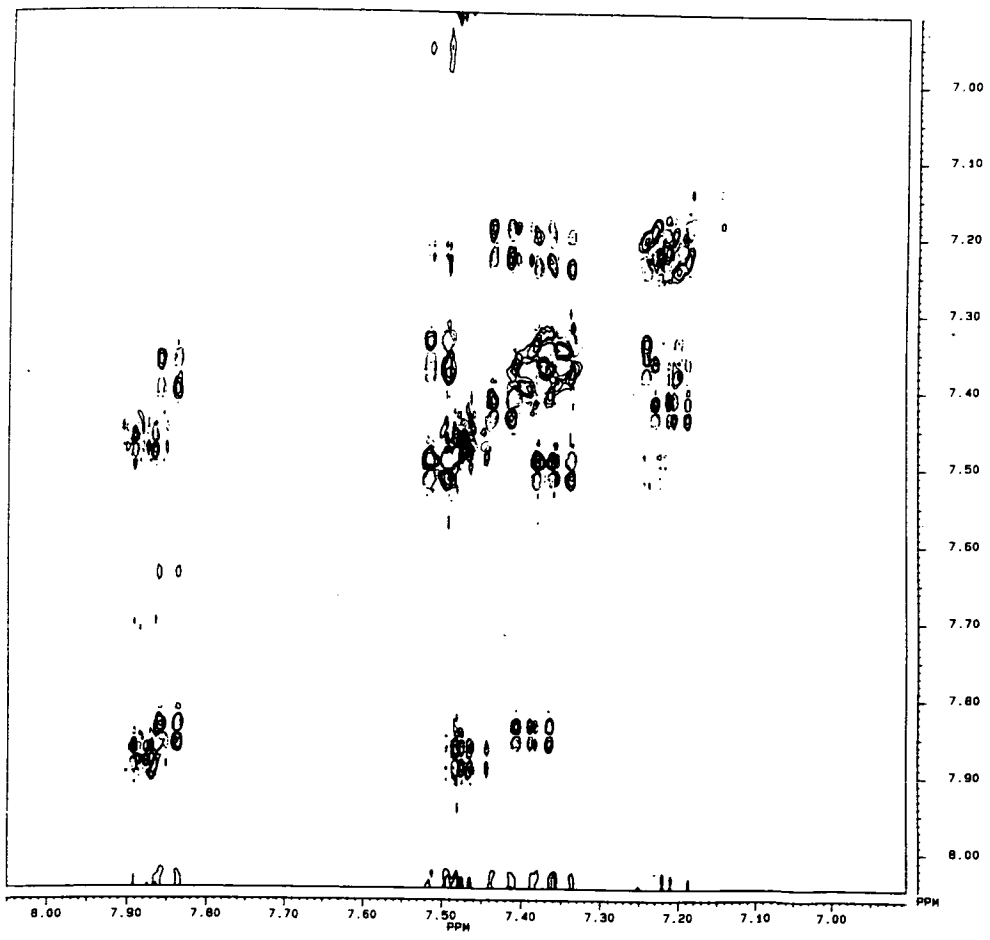
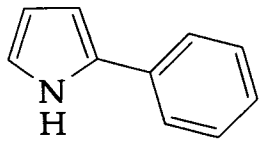


Figure 10

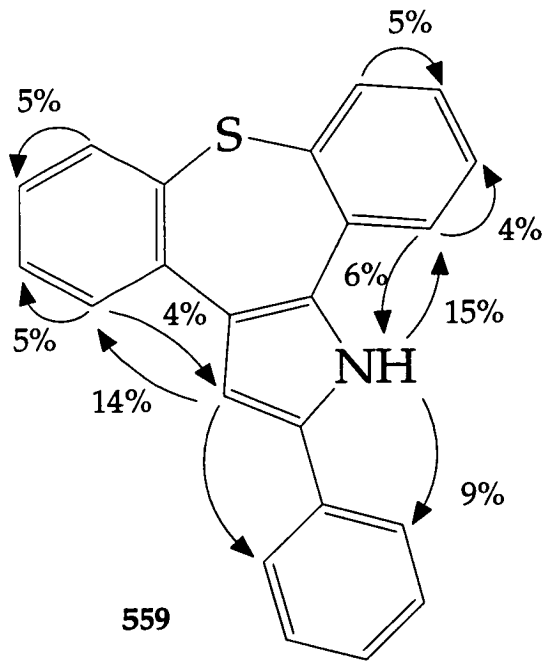
Fraction five was a mixture which was not further identified. Fraction six was also a complex mixture but from its mass spectrum (*m/z* 143) and ^{1}H NMR spectrum it appeared that 2-phenylpyrrole **558** was one of the components [δ_H 6.84(1H,m), 6.56(1H,m) and 6.32(1H,m)]. This compares with literature values of δ_H 6.84(1H,m), 6.52(1H,m) and 6.29(1H,m).[102]



558

The electron impact mass spectrum of fraction seven showed a highest mass at *m/z* 217, but it was clear from the ^{1}H and ^{13}C NMR spectra that this could not correspond to the molecular ion. Thus, the ^{1}H NMR (360 MHz) showed the presence of fifteen protons of which *ca.* ten were resolved, including an NH at δ ($CDCl_3$) 9.15. The ^{13}C NMR ([$^2H_6$]acetone) showed the presence of twelve CH signals together with at least seven quaternary signals, Apart from one methine at δ 99.38 and two quaternaries at δ 132.03 and 135.42, all of these occurred in the range δ 120-130. These data suggest that the compound is a *C,C,C*-trisubstituted pyrrole. A series of N.O.E. experiments were performed which showed the connectivities shown in Figure 11 and from these the structure of the compound **559** (19%) was assigned. The key features were the relationships between the pyrrole proton (at δ_H 7.58) with the *ortho* protons of the remaining phenyl group and one other aromatic proton. Similarly the NH is close to the *ortho* protons of the phenyl group and an other (different) aromatic proton. These data established the overall [1,3]-rearrangement of the original *N*-aryl group. The presence of the sulphur atom was inferred by the lack of any N.O.E. effect

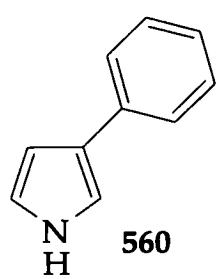
when the protons at the peri positions were irradiated. The peak in the mass spectrum at *m/z* 217 is apparently due to loss of C_6H_4S from the molecular ion.



559

Figure 11

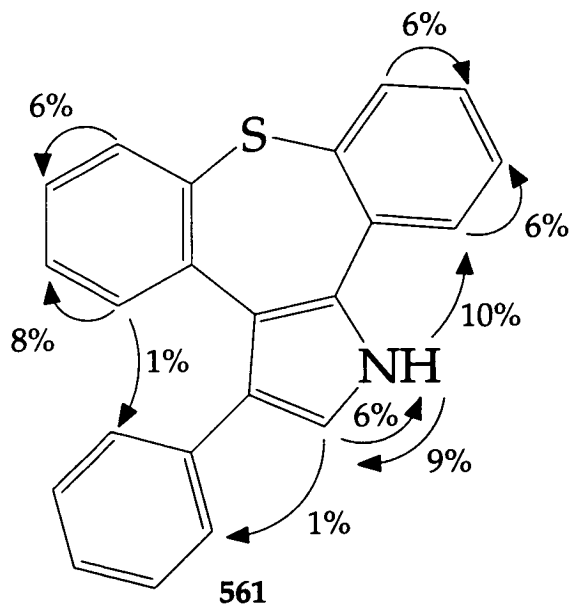
The eighth fraction contained 3-phenylpyrrole **560** as a minor component which was identified by its ^1H NMR spectrum and mass spectrum.[102] The major component of this mixture was not be assigned.



560

The electron impact mass spectrum of the final component showed a small peak at *m/z* 293 (2%), which in common with related examples (see

above), may be due to the loss of sulphur from the molecular ion. The ^{1}H NMR spectrum showed an NH at δ 9.11 and the high frequency region was very similar to **559**, see above. Significantly, one pyrrole proton doublet at δ 7.10 *J* 2.6 appeared to low frequency of the aromatics and this was enhanced (9%) when the NH was irradiated in a N.O.E. experiment (Figure 12. This suggests that the compound is a pyrrole with the 1- and 2-positions unsubstituted. Irradiation of the NH also produced enhancement of a proton δ 7.93, which was shown by the COSY spectrum (Figure 13) to be part of a four spin system. A similar proton at δ 8.12 was also part of a four spin system (Figure 13) and its irradiation in an N.O.E. experiment produced enhancement of the *ortho* protons of an isolated phenyl ring. These were also enhanced by irradiation of the pyrrole 2-position proton. The structure **561** (3%) was therefore tentatively assigned for this compound and other enhancements consistent with this interpretation are shown in Figure 12. The ^{13}C NMR spectrum could not be interpreted as all the peaks appeared in the range δ 119.5-130.



561

Figure 12

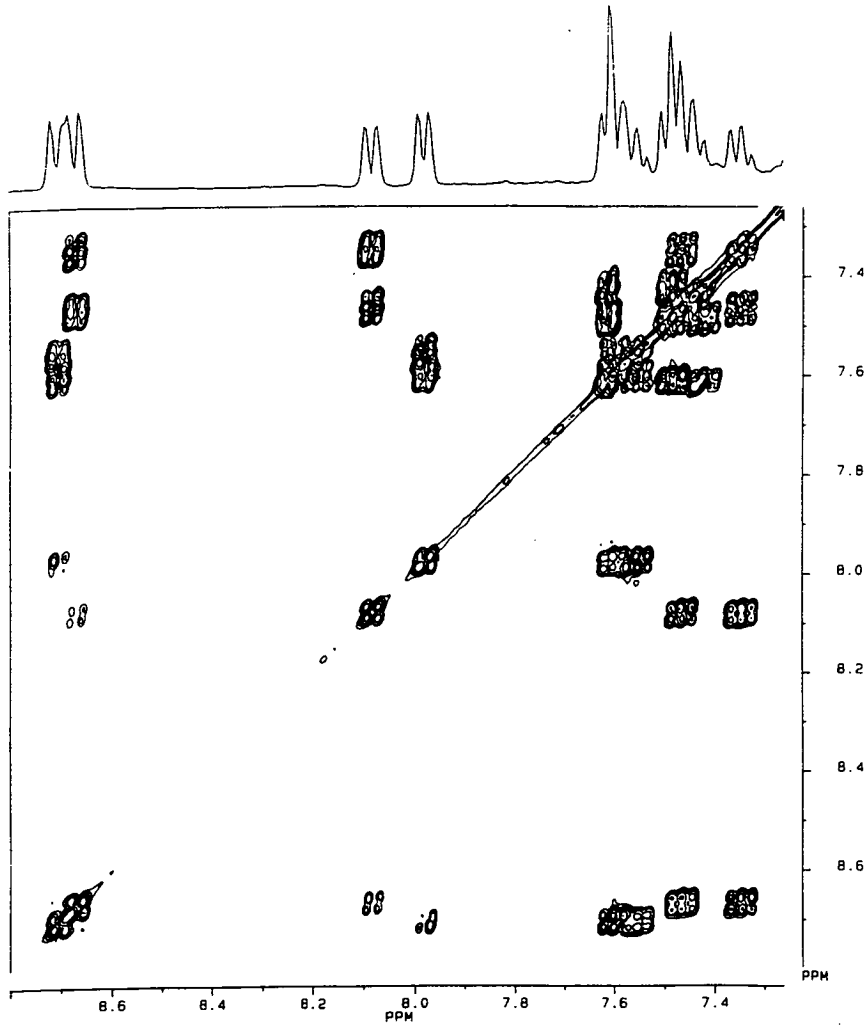
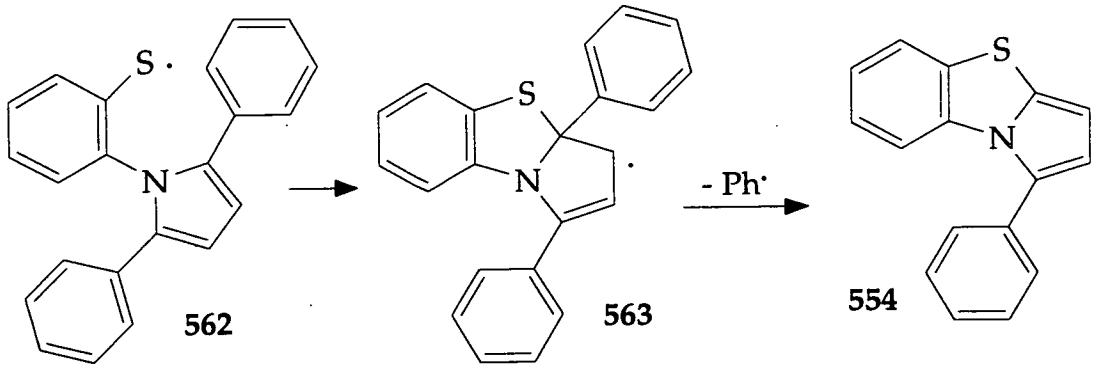
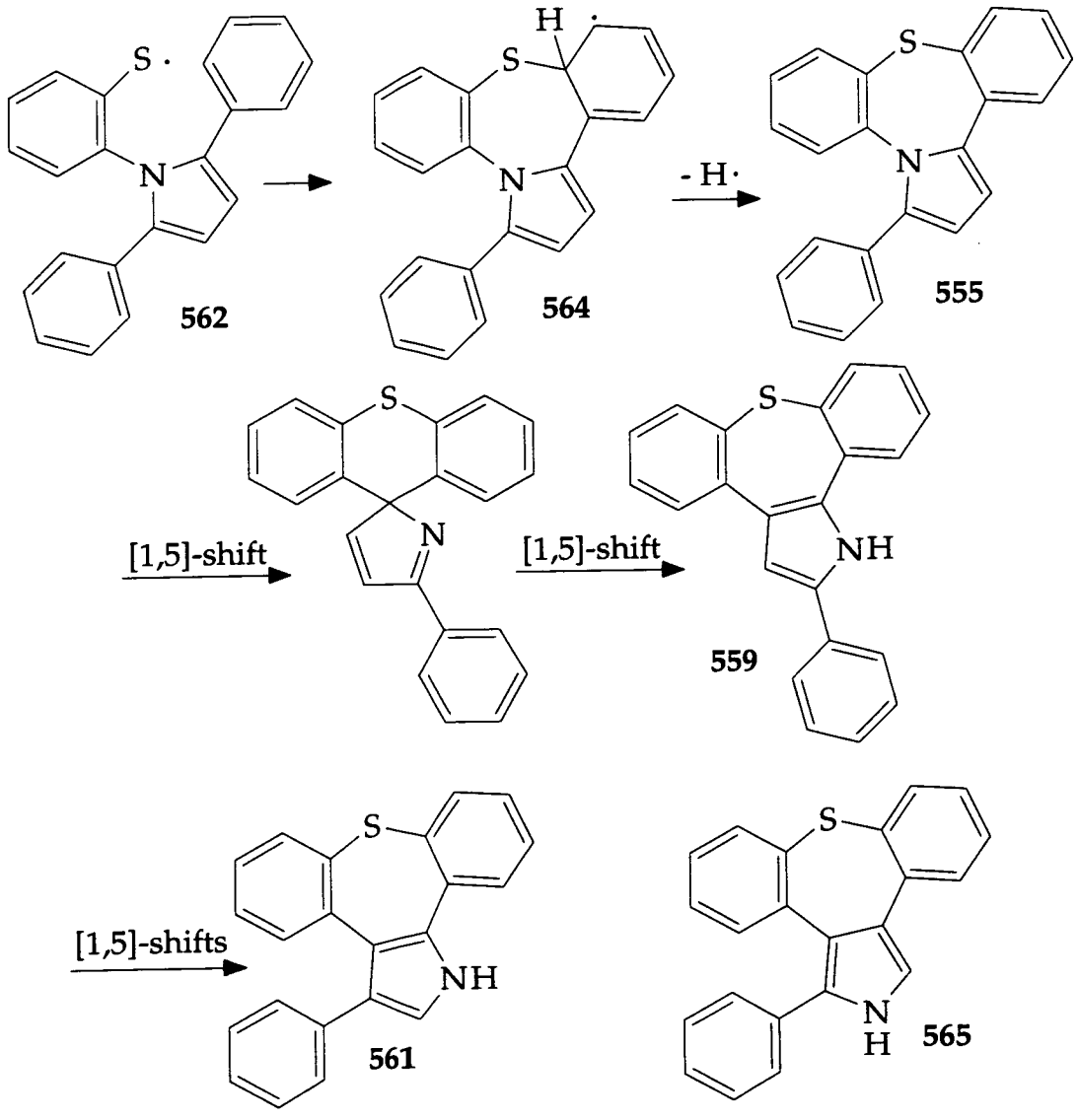


Figure 13

In a reaction as complicated as this it is very difficult to write a unifying mechanism which can easily explain all the products. Inital pyrolysis generates the sulphur centred radical **562**. The formation of 1-phenylpyrrolo[2,1-*b*]benzothiophene **554** may be explained by standard attack on the pyrrole ring and ejection of a phenyl radical **563**, as already observed for the hydrogen and methyl examples (Scheme 118) (see Scheme 100 and 113).

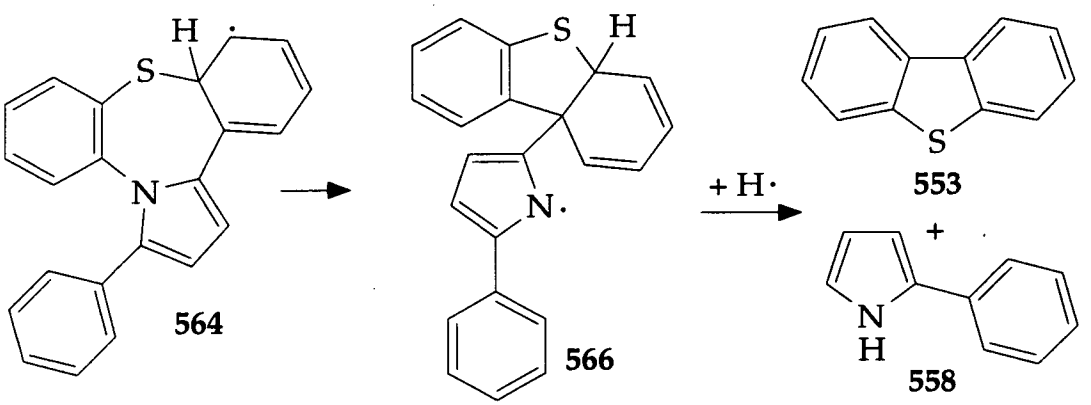


Scheme 118



Scheme 119

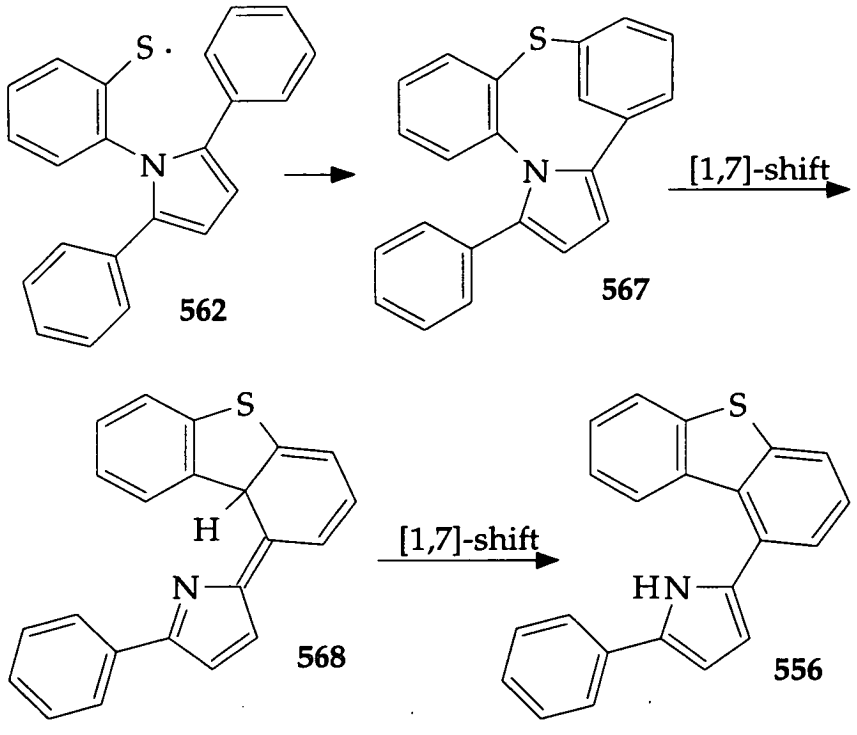
The seven membered ring products **555**, **559** and **561** may be formed by attack of the thiophenoxyl at the *ortho* position of the phenyl ring (or by attack at the *ipso* position followed by rearrangement)[18,124] to give **564**, which loses a hydrogen atom to give **555** (Scheme 119). This product is significant because it is the first example of seven membered ring formation from gas phase aromatic free radicals. The rearrangement product **559** is then easily rationalised by a sequence of [1,5]-shifts (Scheme 119 *c.f.* Scheme 113). In this context it is surprising that **565** the product of further rearrangement was not identified, although it could be present as a component of one of the minor fractions. A further series of [1,5]-shifts then leads to **561**, although its formation instead of **565** is unexpected. Cleavage of the *N*-aryl bond of radical **564** to give radical **566** may give rise to dibenzofuran **553** and 2-phenylpyrrole **558** (Scheme 20), though these could also be formed by other routes. The trace of 3-phenylpyrrole **560** is clearly formed from 2-phenylpyrrole by a [1,5]-shift sequence.



Scheme 120

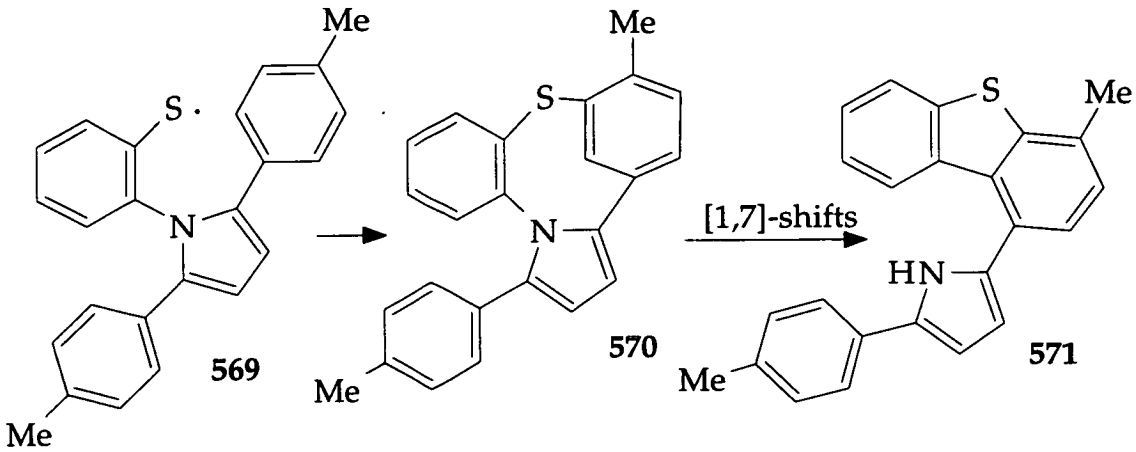
The simplest route to the pyrrolyldibenzothiophene **556** involves attack of the thiophenoxyl **562** at the *meta* position of the phenyl substituent to give intermediate **567** which establishes the connectivity of the atoms found in the

product. Ring contraction of the cyclophane **567** by [1,7]-sigmatropic shifts of the *N*-aryl group to give **568** and a hydrogen atom to give **556** (Scheme 121).



Scheme 121

Many of these mechanistic proposals are necessarily speculative but could be tested by including a *para* methyl group on the 2,5-diphenyl substituents **569**. For example the unprecedented *meta* attack invoked to explain **556** would result in the methyl group appearing at the 1-position of the product **571** (Scheme 122).



Scheme 122

H.5. Conclusion

Once again the reactions of phenoxyl radicals are dominated by hydrogen transfer, which in this case leads to an efficient synthesis of the pyrrolophenanthridene ring system and may be capable of further extension. In contrast the thiophenoxyl radical displays a dewildering array of products, some of which must be formed by unprecedented mechanisms. Clarification of the mechanisms is a goal for the future and may be accomplished by varying the substitution pattern. The reactions of the corresponding benzyl radical will also be of interest.

EXPERIMENTAL

A. INSTRUMENTATION AND GENERAL TECHNIQUES

A.1. Nuclear Magnetic Resonance Spectroscopy

^{1}H NMR spectra were recorded at 200 MHz on a Bruker WP200 (200MHz) spectrometer, unless otherwise stated. Spectra were also obtained on Bruker WP80 (80MHz), WH360 (360MHz) and Varian VXR (600MHz) instruments. Routine continuous wave spectra were obtained on a Joel PMX 60SI (60MHz) instrument. ^{13}C NMR spectra were recorded on a Bruker WP200 (50MHz) instrument

The WP200 was operated by Dr. H. McNab, Mr. J.R.A. Millar and Miss H. Grant, the WP80 by Miss H. Grant and the WH360 by Dr. D. Reed.

Spectra were recorded in [^{2}H]chloroform, unless otherwise stated; chemical shifts (δ_H, δ_C) are quoted in parts per million, relative to tetramethylsilane, and coupling constants (J) are quoted in Hz. Standard 200 MHz spectra have an accuracy of 0.3 Hz per point and are quoted as recorded.

A.2. Mass Spectroscopy

Low resolution electron impact mass spectra were recorded by Miss E. Stevenson on a A.E.I. MS902 instrument; F.A.B. mass spectra and all high resolution mass spectra were recorded by Mr A. Taylor on a Kratos MS50TC instrument. Spectra quoted were obtained by electron impact mass spectrometry unless otherwise stated.

A.3. Elemental Analysis

Microanalyses were obtained by Mrs. E. McDougall and Mrs. L. Eades on a Perkin Elmer 240 CHN Elemental Analyser, and previously on a Carlo-Erba Elemental Analyser, Model 1106.

A.4. Structure Determination

X-ray crystallographic data were obtained and refined by Dr. A.J. Blake and Dr. R.O. Gould on a Stoë STADI-4 four circle diffractometer with graphite monochromator.

A.5. Chromatography

Thin-layer chromatography was carried out on pre-coated aluminium sheets (0.2mm silica gel, Merck, grade 60) impregnated with a UV fluorescent indicator, or on pre-coated aluminium sheets (0.2mm aluminium oxide, neutral (Type E), Merck, grade 60) impregnated with a UV fluorescent indicator

Dry flash chromatography was carried out on silica gel [(Merck, grade 60, 230-400 mesh, 60 Å), or (Merck , t.l.c. grade 60)] by the method of Harwood.[125]

A.6. Solvents

Commercially available solvents were used without further purification, except for *n*-hexane and ethyl acetate which were distilled for chromatographic purposes. Ether was generally dried by storage over

sodium wire; when necessary it was dried further by distillation from sodium benzophenone ketal. All other dry solvents were obtained by storing over molecular sieve (4 Å).

B. PYROLYSIS APPARATUS AND METHODS

The apparatus used for flash vacuum pyrolysis experiments is illustrated in Figure 14, and is based on the design of W.D. Crow, Australian National University. The system is evacuated to 10^{-2}-10^{-3} mbar by an Edwards Model ED100 high capacity oil pump and the pressure is monitored between trap and the pump. For less volatile substrates, a mercury diffusion pump was used in series with the rotary oil pump (Figure 15) to increase the vacuum to a pressure of the order of 10^{-4}-10^{-5} mbar. Experiments involve heating the substrate contained in the inlet until it is volatilised. An all glass Büchi oven is generally used for heating as it allows sublimation to be easily monitored, but for inlet temperatures approaching 200°C a metal Kugelrohr oven provides more even heating and higher temperatures. The volatilised substrate passes through a silica tube (30 x 2.5 cm). The temperature of the tube is monitored by a [platinum/(platinum 13% rhodium)] thermocouple at its centre and is maintained at the required level by Stanton Redcroft laboratory tube furnace. The estimated contact time in the hot zone is 1-10 milliseconds. The products are collected at the exit of the furnace in a trap cooled in liquid nitrogen. The U-shaped trap shown in Figure 14 is used for up to 1g of substrate. To prevent blockage of the trap the larger trap shown in Figure 16 is used for larger pyrolyses.

Small scale pyrolyses refer to 10-50mg of substrate, and the entire pyrolysate was dissolved in deuteriated solvent ([^{2}H]chloroform unless otherwise stated) and examined by ^{1}H NMR spectroscopy without further purification of the products.

Large scale pyrolyses normally refer to pyrolyses on a scale of 0.1-1g or greater. Details of the work-up are given for each example in the following chapters.

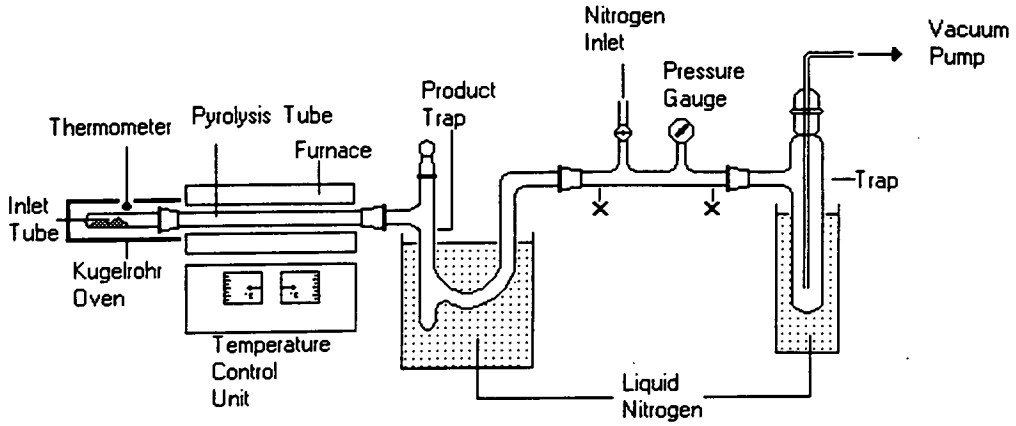


Figure 14

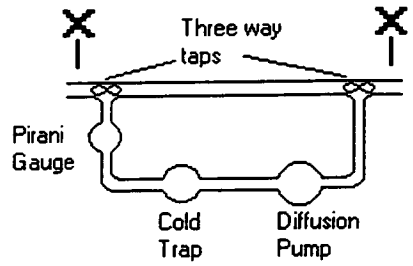


Figure 15

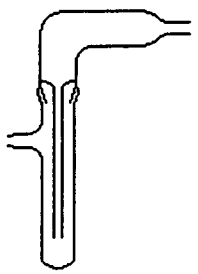


Figure 16

Pyrolysis parameters are quoted in the following order throughout this section: furnace temperature(T_f), inlet temperature(T_i), pressure(P) and the sublimation time(t).

C. THE USE OF AN ESTER FUNCTION AS A FREE RADICAL LEAVING GROUP IN THE FORMATION OF BENZOFURANS

C.1.a. Preparation of Methyl 3-(2-hydroxyphenyl)propenoate 291, Methyl 3-(2-hydroxy-5-chlorophenyl)propenoate 292, Methyl 3-(2-hydroxy-5-nitrophenyl)propenoate 293 and Methyl 3-(2-hydroxynaphth-1-yl)propenoate 297 *via* a Wittig reaction - General method[126]

The required aldehyde **288**, **290** or **296** was dissolved in dry dichloromethane. Methyl triphenylphosphoranylideneacetate was added with stirring. Reaction was continued until t.l.c. showed complete disappearance of the aldehyde. The mixture was then pre-adsorbed on to silica (5 x weight of mixture), and subjected to dry flash chromatography on silica.

The following compounds **291**, **292**, **293** and **297** were prepared by this method.

Salicylaldehyde **288** gave methyl 3-(2-hydroxyphenyl)propenoate **291**.[67]

2-Hydroxy-1-naphthaldehyde **296** gave methyl 3-(2-hydroxy naphth-1-yl)propenoate **297**.[67]

2-Hydroxy-5-chlorobenzaldehyde **290** (R=Cl) gave methyl 3-(2-hydroxy-5-chlorophenyl)propenoate **292**.[67]

2-Hydroxy-5-nitrobenzaldehyde **290** ($R=NO_2$) gave methyl 3-(2-hydroxy-5-nitrophenyl)propenoate **293**.[67]

C.1.b. Preparation of Ethyl 2-methyl-3-(2-hydroxyphenyl) propenoate 294, Ethyl 2-methyl-3-(2-hydroxy-5-chlorophenyl)propenoate 295 and Ethyl 2-methyl-3-(2-hydroxynaphth-1-yl)propenoate 298 *via* a Wittig reaction - General method

The required aldehyde **288**, **290** or **296** was dissolved in dry dichloromethane. Ethyl 2-triphenylphosphoranylidenepropionate was added with stirring. Reaction was continued until t.l.c. showed complete disappearance of the aldehyde. The mixture was then pre-adsorbed on to silica (5 x weight of mixture), and subjected to dry flash chromatography on silica.

The following compounds **294**, **295** and **298** were prepared by this method.

Salicylaldehyde **288** gave ethyl 2-methyl-3-(2-hydroxyphenyl) propenoate **294**.[67]

2-Hydroxy-5-chlorobenzaldehyde **290** (R=Cl) gave ethyl 2-methyl-3-(2-hydroxy-5-chlorophenyl)propenoate **295**.[67]

2-Hydroxy-1-naphthaldehyde **296** (0.52 g, 3 mmol) gave ethyl 2-methyl-3-(2-hydroxynaphth-1-yl)propenoate **298** as a mixture of *E* and *Z* isomers (0.62 g, 81%), m.p. 93-96 °C [lit.[127] m.p. 97-99 °C] (Found: M+ 256.1101. $C_{16}H_{16}O_3$ requires M+ 256.1099) δ_H 8.20(1H,m), 7.90-7.19(6H,m), 6.23(1H,br), 4.33(2H,q,^3J 7.1), 1.86(3H,d,^4J 1.0) and 1.39(3H,t,^3J 7.1); δ_C 167.82(q), 150.28(q), 133.07, 130.01, 128.18, 126.62, 123.81, 123.43, 117.69, 61.12, 14.57 and 14.15 quaternary signals not assigned because of the presence of *ca.* 25% of minor diastereomer; *m/z* 256(M+,31%), 211(31), 210(96), 183(38), 182(100), 181(57), 153(17), 152(31), 139(12), 91(14) and 76(18).

C.1.c. Preparation of Ethyl 3-[2-(benzyloxy)phenyl]but-2-enoate 310 *via* a Wittig-Horner reaction[128]

To a solution of sodium ethoxide [from sodium (0.25 g, 11 mmol) in ethanol (50ml)] was added methyl diethylphosphonoacetate (2.10 g, 10 mmol). After stirring for 30 minutes the mixture was cooled in ice and 2-(benzyloxy)acetophenone **309** (0.73 g, 3 mmol), (See Experimental Section C.2.c for alkylation procedure) was added dropwise. The mixture was then heated under reflux for 48 hours. (During reflux the methyl ester was exchanged to an ethyl ester). Water (100 ml) was added and the mixture was extracted with ether (3 x 50 ml). The combined extracts were washed with water (1 x 50 ml) and dried ($MgSO_4$). The crude product was pre-adsorbed onto silica (5 g) and separated by dry flash chromatography. (5% ethyl acetate/hexane : 5% gradient) This gave two products which were the *E* and *Z* isomers of *ethyl 3-[2-(benzyloxy)phenyl]but-2-enoate* **310**. *E* - isomer (0.714 g, 73%) b.p. 134-138 °C (2 Torr) (Found: M+ 296.1417. $C_{19}H_{20}O_3$ requires M+ 296.1412) δ_H 7.44-7.17(7H,m), 7.00-6.93(2H,m), 5.96(1H,q,^4J 1.3), 5.11(2H,s), 4.22(2H,q,^3J 7.1), 2.56(3H,d,^4J 1.3) and 1.32(3H,t,^3J 7.1); δ_C 166.66(q), 156.52(q), 155.33(q), 136.69(q), 133.40(q), 129.36, 128.90, 128.44, 127.75, 127.02, 120.79, 119.22, 112.43, 70.15, 59.58, 19.94 and 14.25; *m/z* 296(M+,2%), 205(8), 131(8) and 91(100). *Z* - isomer (0.240 g, 25%) b.p. 120-124 °C (2 Torr) (Found: M+ 296.1403. $C_{19}H_{20}O_3$ requires M+ 296.1412) δ_H 7.41-7.22(6H,m), 7.10-6.94(3H,m), 5.99(1H,q,^4J 1.4), 5.09(2H,s), 3.98(2H,q,^3J 7.1), 2.20(3H,d,^4J 1.3) and 1.04(3H,t,^3J 7.1); δ_C 165.39(q), 154.17(q), 153.28(q), 137.04(q), 130.65(q), 128.39, 128.17, 127.87, 127.38, 126.66, 120.40, 118.65, 112.12, 69.82, 59.25, 26.02 and 13.70; *m/z* 296(M+,3%), 204(8), 132(7), 131(9), 92(8), 91(100) and 65(9).

C.2.a. Preparation of Methyl 3-[2-(allyloxy)phenyl]propenoate 299, Methyl 3-[2-(allyloxy)-5-chlorophenyl]propenoate 300, Methyl 3-[2-(allyloxy)-5-nitrophenyl]propenoate 301, Methyl 3-[2-(allyloxy)naphth-1-yl]propenoate 304 and Ethyl 2-methyl-3-[2-(allyloxy)phenyl]propenoate 302, Ethyl 2-methyl-3-[2-(allyloxy)-5-chlorophenyl]propenoate 303 and Ethyl 2-methyl-3-[2-(allyloxy)napht-1-yl]propenoate 305 - General method

Potassium carbonate (0.152 g, 11 mmol) was added to DMF (5 ml). After stirring for 5 minutes the appropriate methyl 3-(2-hydroxy aryl)propenoates **291, 292, 293** or **297** or ethyl 3-(2-hydroxyaryl)-2-methyl propenoates **294, 295** or **298** (10 mmol) was added and the mixture was stirred for 5 minutes. Allyl bromide (0.133 g, 11 mmol) was then added dropwise and the mixture was stirred overnight. T.l.c. confirmed that all the methyl 3-(2-hydroxyaryl)propenoates **291, 292, 293** or **297** or ethyl 3-(2-hydroxyaryl)-2-methylpropenoates **294, 295** or **298** had been consumed and water (10 ml) was added. The mixture was then extracted with ether (3 x 10 ml). The combined extracts were washed with water (3 x 25 ml) and dried ($MgSO_4$). The solvent was then removed on the rotary evaporator to yield the following methyl 3-[2-(allyloxy)aryl]propenoates **299, 300, 301** and **304** or ethyl 3-[2-(allyloxy)aryl]-2-methylpropenoates **302, 303** and **305.**

Methyl 3-(2-hydroxyphenyl)propenoate **291**[67] gave *methyl 3-[2-(allyloxy) phenyl]propenoate* **299** (0.195 g, 90%) b.p. 100-105 °C (8 Torr) (Found: M+ 218.0946. $C_{13}H_{14}O_2$ requires M+ 218.0943) δ_H 8.03(1H,d,^3J 16.2), 7.48(1H,dd,^3J 7.7, ^4J 1.4), 7.30(1H,m), 6.97-6.85(2H,m), 6.52(1H,d,^3J 16.2), 6.12-5.98(1H,m), 5.45-5.26(2H,m), 4.58(2H,m) and 3.78(3H,s); δ_C 167.73(q),

157.10(q), 140.05, 132.67, 131.21, 128.68, 120.68, 118.11, 117.63, 112.27, 68.96 and 51.39, one quaternary not apparent; *m/z* 218(M+,35%), 158(27), 131(20), 118(95), 105(46), 90(34), 89(37), 59(32) and 41(100).

Ethyl 2-methyl-3-(2-hydroxyphenyl)propenoate **294**[67] gave *ethyl 2-methyl-3-[2-(allyloxy)phenyl]propenoate* **302** (0.246 g, 100%) b.p. 65-70 °C (0.08 Torr) (Found: M+ 246.1250. $C_{15}H_{18}O_3$ requires M+ 246.1256) δ_H 7.88(1H,s), 7.30-7.22(2H,m), 6.99-6.86(2H,m), 6.13-5.95(1H,m), 5.47-5.23(2H,m), 4.58-4.54(2H,m), 4.26(2H,q,^3J 7.1), 2.04(3H,d,^4J 1.4) and 1.33(3H,t,^3J 7.1); δ_C 168.55(q), 156.41(q), 134.53, 132.93, 130.09, 129.47, 128.36(q), 125.08(q), 120.12, 117.02, 111.81, 68.77, 60.55, 14.14 and 14.07; *m/z* 246(M+,73%), 201(32), 189(42), 173(40), 161(44), 160(31), 159(30), 145(26), 133(60), 132(80), 131(100), 105(67), 103(28) and 77(37).

Methyl 3-(2-hydroxynaphth-1-yl)propenoate **297**[67] gave *methyl 3-[2-(allyloxy)naphth-1-yl]propenoate* **304** (0.195 g, 94%), b.p. 100-105 °C (0.07 Torr) (Found: M+ 268.1098. $C_{17}H_{16}O_3$ requires M+ 268.1099) δ_H 8.35(1H,d,^3J 16.2), 8.16(1H,d,^3J 8.3), 7.77(2H,m), 7.53-7.32(2H,m), 7.22(1H,d,^3J 9.1), 6.78(1H,d,^3J 16.2), 6.15-6.01(1H,m), 5.47-5.27(2H,m), 4.74-4.70(2H,m) and 3.84(3H,s); δ_C 168.12(q), 155.51(q), 137.78, 132.80, 131.25, 128.40, 127.22, 123.84, 123.13, 122.91, 117.74, 113.97, 69.75 and 51.48, two quaternaries not apparent; *m/z* 268(M+,61%), 237(10), 196(22), 195(19), 168(100), 155(36), 140(22), 139(45) and 59(24).

Ethyl 2-methyl-3-(2-hydroxynaphth-1-yl)propenoate **298** gave *ethyl 2-methyl-3-[2-(allyloxy)naphth-1-yl]propenoate* **305** (0.270 g, 91%), b.p. 95-100 °C (0.1 Torr) (Found: M+ 296.1411. $C_{19}H_{20}O_3$ requires M+ 296.1412) δ_H 7.95(1H,s), 7.84-7.71(3H,m), 7.51-7.24(3H,m), 6.15-5.96(1H,m), 5.47-

5.24(2H,m), 4.69-4.65(2H,m), 4.34(2H,q,^3J 7.2), 1.77(3H,d,^4J 1.3) and 1.40(3H,t,^3J 7.1); δ_C 167.99(q), 152.93(q), 133.99, 133.23, 132.03(q), 131.92(q), 129.58, 128.74(q), 128.09, 126.53, 124.45, 123.71, 119.10(q), 117.15, 114.44, 69.74, 60.63, 14.92 and 14.23; *m/z* 296(M+,39%), 210(12), 183(34), 182(100), 181(40), 153(12) and 152(19).

Methyl 3-(2-hydroxy-5-chlorophenyl)propenoate **292**[67] gave *methyl 3-[2-(allyloxy)-5-chlorophenyl]propenoate* **300** (0.238 g, 94%), b.p. 82-87 °C (0.12 Torr) (Found: M+ 254.0517 and 252.0554. $C_{13}H_{13}{}^{37}ClO_3$ and $C_{13}H_{13}{}^{35}ClO_3$ requires M+ 254.0524 and 252.0553) δ_H 7.92(1H,d,^3J 16.2), 7.44(1H,d,^4J 2.6), 7.22(1H,dd,^3J 9.0,^4J 2.7), 6.79(1H,d,^3J 8.8), 6.74(1H,d,^3J 16.1), 6.12-5.93(1H,m), 5.43-5.26(2H,m), 4.58-4.54(2H,m) and 3.78(3H,m); δ_C 167.26(q), 155.53(q), 138.51, 132.27, 130.61, 127.98, 125.47(q), 124.94(q), 119.32, 117.98, 113.62, 69.35 and 51.52; *m/z* 254(M+,33%), 252(M+,100%), 195(13), 194(14), 193(15), 192(35), 180(30), 152(31), 113(19), 89(11) and 59(39).

Ethyl 2-methyl-3-(2-hydroxy-5-chlorophenyl)propenoate **295**[67] gave *ethyl 2-methyl-3-[2-(allyloxy)-5-chlorophenyl]propenoate* **303** (0.261 g, 93%), b.p. 110-115 °C (0.08 Torr) (Found: M+ 282.0841 and 280.0864. $C_{15}H_{17}{}^{37}ClO_3$ and $C_{15}H_{17}{}^{35}ClO_3$ requires M+ 282.0837 and 280.0866) δ_H 7.75(1H,d,^4J 0.5), 7.25-7.16(2H,m), 6.79(1H,d,^3J 8.5), 6.07-5.90(1H,m), 5.43-5.22(2H,m), 4.54-4.50(2H,m), 4.25(2H,q,^3J 7.1), 2.02(3H,d,^4J 1.4) and 1.32(3H,t,^3J 7.1); δ_C 168.19(q), 154.94(q), 133.13, 132.49, 129.60, 128.96, 126.60(q), 125.07(q), 117.32, 113.03, 69.10, 60.73, 14.11 and 14.03, one quaternary not apparent; *m/z* 282(M+,12%), 280(M+,41%), 235(16), 223(32), 207(21), 195(21), 169(16), 168(19), 167(60), 166(28), 165(100), 139(27), 131(24) and 103(26).

Methyl 3-(2-hydroxy-5-nitrophenyl)propenoate **293**[67] gave *methyl 3-[2-(allyloxy)-5-nitrophenyl]propenoate* **301** (0.212 g, 81%), unpurified m.p. 88-91 °C (Found: M+ 263.0799. $C_{13}H_{13}NO_5$ requires M+ 263.0794) δ_H 8.37(1H,d,^4J 2.7), 8.18(1H,dd,^3J 9.1, ^4J 2.7), 7.93(1H,d,^3J 16.2), 6.96(1H,d,^3J 9.2), 6.58(1H,d,^3J 16.2), 6.12-5.95(1H,m), 5.47-5.32(2H,m), 4.72-4.70(2H,m) and 3.79(3H,s); δ_C 166.88(q), 161.30(q), 141.21(q), 137.49, 131.28, 126.48, 124.11(q), 123.95, 120.91, 118.94, 112.04, 69.85 and 51.72; *m/z* 263(M+,13%), 59(11), 44(21), 41(100) and 40(90).

C.2.b. Preparation of Methyl 3-[2-(isopropyloxy)naphth-1-yl]propenoate 306 and Methyl 3-[2-(benzyloxy)naphth-1-yl]propenoate 307

Preparation and work-up were performed as in Section C.2.a., General method, but replacing allyl bromide with isopropyl bromide. Methyl 3-(2-hydroxynaphth-1-yl)propenoate **297**[67] gave *methyl 3-[2-(isopropyloxy) naphth-1-yl]propenoate* **306** (0.204 g, 76%), b.p. 107-111 °C (2 Torr) (Found: M+ 270.1243. $C_{17}H_{18}O_3$ requires M+ 270.1256) δ_H 8.37(1H,d,^3J 16.1), 8.19(1H,d,^3J 8.1), 7.82-7.75(2H,m), 7.56-7.24(3H,m), 6.82(1H,d,^3J 16.2), 6.35(1H,septet,^3J 6.1), 3.86(3H,s) and 1.41(3H,d,^3J 6.1); δ_C 168.28(q), 155.16(q), 138.12, 132.80(q), 131.17, 129.46(q), 128.37, 127.12, 123.78, 123.15, 122.61, 117.84(q), 115.45, 71.81, 51.46 and 22.27; *m/z* 270(M+,28%), 228(19), 197(25), 196(75), 169(28), 168(100), 141(16), 140(18) and 139(26).

Preparation and work-up were performed as in Section C.2.a., General method, but replacing allyl bromide with benzyl bromide. Methyl 3-(2-hydroxynaphth-1-yl)propenoate **297**[67] gave *methyl 3-[2-(benzyloxy) naphth-1-yl]propenoate* **307** (0.267 g, 85%), b.p. 135-140 °C (3 Torr) (Found: M+

318.1246. $C_{21}H_{18}O_3$ requires M+ 318.1256) δ_H 8.43(1H,d,^3J 16.2), 8.21(1H,d,^3J 8.6), 7.77(2H,d,^3J 8.8), 7.47-7.33(7H,m), 7.26(1H,d,^3J 9.2), 6.85(1H,d,^3J 16.2), 5.27(2H,s) and 3.86(3H,d,^4J 0.6); δ_C 168.14(q), 155.52(q), 137.83, 131.33, 128.55, 128.47, 127.93, 127.29, 127.02, 123.95, 123.22, 123.13, 114.25, 70.96 and 51.53, four quaternaries not assigned; *m/z* 318(M+,13%), 286(11), 196(27), 168(36), 140(10), 139(22), 92(10) and 91(100).

C.2.c. Preparation of 2-(Benzyloxy)acetophenone 309

Potassium carbonate (0.76 g, 55 mmol) was added to DMF (25 ml). After stirring for 5 minutes, 2-hydroxyacetophenone **308** (0.68 g, 50 mmol) was added and the mixture was stirred for 5 minutes. Benzyl bromide (0.94 g, 55 mmol) was then added dropwise and the mixture was stirred overnight. T.l.c. confirmed that all the 2-hydroxyacetophenone **308** had been consumed and water (25 ml) was added. The mixture was then extracted with ether (3 x 25 ml). The combined extracts were washed with water (3 x 50 ml) and dried ($MgSO_4$). The solvent was then removed on the rotary evaporator to yield *2-(benzyloxy)acetophenone* **309**. b.p. 165-170 °C (12 Torr) (Found: M+ 226.0990 $C_{15}H_{14}O_2$ requires 226.0994) δ_H 7.75(1H,dd,^3J 8.2, ^4J 2.0), 7.48-7.34(6H,m), 7.02(2H,d,^3J 7.9), 5.16(2H,s) and 2.60(3H,s); δ_C 199.77(q), 157.87(q), 136.05(q), 133.46, 130.60(q), 130.30, 128.55, 128.09, 127.42, 120.72, 112.66, 70.49 and 31.96; *m/z* 226(M+,8%), 92(11), 91(100) and 65(17). (See Section C.1.c. for Wittig - Horner reaction of this compound).

C.3.a. Pyrolysis of Radical Precursors 299,300, 301, 304, 306 and 307, to form Benzofuran 281, 5-Chlorobenzofuran 321, 5-Nitrobenzofuran 325 and Naphtho[2,1-*b*]furan 323

Methyl 3-[2-(allyloxy)phenyl]propenoate **299** (0.103 g, 5 mmol), (T_f 650 °C, T_i 80-100 °C, P 0.01 mbar, t 15min) gave benzofuran **281** (0.038g, 68%), b.p. 173-175 °C (760 Torr) [lit.[129] 97-99 °C (80 Torr)] (Found: M+ 118.0423. C_8H_6O requires M+ 118.0419) δ_H 7.69-7.22(5H,m) and 6.79(1H,dd,^3J 2.2, ^4J 0.9); *m/z* 118(M+,100%), 90(48), 89(43), 63(30), 62(12) and 39(15).

Methyl 3-[2-(allyloxy)naphth-1-yl]propenoate **304** (0.102 g, 4 mmol), (T_f 650 °C, T_i 140-160 °C, P 0.002 mbar, t 20 min) gave three products which were separated by dry flash chromatography (4% ethyl acetate / hexane; 10% gradient). Naphtho[2,1-*b*]furan **323** (0.025 g, 39%), m.p. 53-55 °C [lit.[130] 60-61 °C (from light petroleum, b.p. 80-100 °C)] (Found: M+ 168.0583. $C_{12}H_8O$ requires M+ 168.0575) δ_H 8.19-8.14(1H,m), 8.00-7.95(1H,m), 7.79-7.47(5H,m) and 7.29-7.27(1H,m); δ_C 152.38(q), 144.05, 130.18(q), 128.58, 127.68(q), 126.15, 125.03, 124.34, 123.28, 122.49(q), 112.37 and 105.44; *m/z* 168(M+,100%), 148(11), 139(35), 84(11) and 39(53). *2-Allyl-3H-naphtho[2,1-b]pyran-3-one* **330** (0.020 g, 21%) (not purified further) (Found: M+ 236.0836 $C_{16}H_{12}O_2$ requires M+ 236.0837) δ_H 8.24(1H,s), 8.21(1H,d,^3J 10.0), 7.92-7.85(2H,m), 7.70-7.49(2H,m), 7.42(1H,d,^3J 9.0), 6.15-5.95(1H,m), 5.34-5.23(2H,m) and 3.44-3.40(2H,m); δ_C 161.50(q), 152.36(q), 134.60, 133.79, 131.81, 130.14(q), 128.81, 127.79, 126.96(q), 125.72, 121.34, 118.15, 116.61, 113.25(q) and 34.75 one quaternary not apparent; *m/z* 236(M+,100%), 235(22), 221(11), 208(19), 207(25), 181(40), 178(13), 165(12), 152(27), 139(13) and 89(12). 3*H*-Naphtho[2,1-*b*]pyran-3-one[67] **329** (0.010 g, 13%) m.p. 104-106 °C [lit. [131] 117-118 °C (from ethanol)] (Found: M+ 196.0531 $C_{13}H_8O_2$ requires M+

196.0524) δ_H 8.48(1H,d,^3J 9.8), 8.22(1H,d,^3J 8.3), 8.00-7.82(2H,m), 7.72-7.42(3H,m) and 6.75(1H,d,^3J 9.8); δ_C 160.82(q), 153.77(q), 139.00, 133.02, 130.16(q), 128.90, 128.18, 125.95, 121.24, 116.96, 115.53 and 112.87, one quaternary not apparent; *m/z* 196(M+,100%), 195(11), 168(69), 139(42), 84(15), 70(12), 69(13) and 63(12).

Methyl 3-[2-(benzyloxy)naphth-1-yl]propenoate **307** (0.130 g, 4 mmol), (T_f 650 °C, T_i 140-160 °C, P 0.001 mbar, t 20 min), gave two products which were separated by dry flash chromatography (4% ethyl acetate / hexane ; 10% gradient). Naphtho[2,1-*b*]furan **323** (0.038 g, 55%), m.p. 54-56 °C [lit.[130] 60-61 °C (from light petroleum b.p. 80-100 °C)] (Found M+ 168.0576. $C_{12}H_8O$ requires M+ 168.0575) δ_H 8.19-8.14(1H,m), 8.00-7.95(1H,m), 7.80-7.47(5H,m) and 7.29-7.27(1H,m); *m/z* 168(M+,100%) and 40(85). *2-Benzyl-3H-naphtho[2,1-b]pyran-3-one* **332** (0.008 g, 7%), (Found: M+ 286.1000 $C_{16}H_{12}O_2$ requires M+ 286.0993) δ_H 8.09(1H,s), 8.04(1H,d,^3J 8.2), 7.93-7.85(2H,t), 7.61-7.29(8H,m) and 4.00(2H,s); δ_C 161.62(q), 152.38(q), 137.67(q), 135.02, 131.89, 130.12(q), 129.20, 128.79, 128.67, 128.34(q), 127.75, 126.74, 125.70, 121.26, 116.61, 113.25(q) and 36.77; *m/z* 286(M+286,100%), 258(12), 257(29) and 181(21). 3*H*-Naphtho[2,1-*b*]pyran-3-one[67] **329** (0.009 g, 11%), m.p. 106-108 °C [lit.[131] 117-118 °C (from ethanol)] (Found: M+ 196.0524. $C_{13}H_8O_2$ requires M+ 196.0524) δ_H 8.49(1H,d,^3J 9.7), 8.22(1H,d,^3J 8.4), 8.01-7.88(2H,m), 7.73-7.43(3H,m) and 6.57(1H,d,^3J 9.8); *m/z* 196(M+,79%), 168(100), 140(26), 139(59), 70(10) and 63(11).

Methyl 3-[2-(isopropyloxy)naphth-1-yl]propenoate **306** (0.148 g, 5 mmol), (T_f 750 °C, T_i 160-180 °C, P 0.001 mbar, t 20 min), gave two products which were separated by dry flash chromatography (4% ethyl acetate / hexane; 10% gradient). Naphtho[2,1-*b*]furan **323** (0.054 g, 59%) m.p. 52-55 °C

(lit.[130] 60-61 °C) (Found: M+ 168.0574. $C_{12}H_8O$ requires M+ 168.0575) δ_H 8.19-8.15(1H,m), 8.01-7.97(1H,m), 7.80-7.49(5H,m) and 7.29-7.28(1H,m); δ_C 152.41(q), 144.08, 130.23(q), 128.62(q), 127.71(q), 126.18, 125.07, 124.39, 123.32, 122.54(q), 122.41 and 105.48; *m/z* 168(M+,100%), 140(21), 139(53) and 63(11). 3*H*-Naphtho[2,1-*b*]pyran-3-one[67] **329** (0.034 g, 32%) m.p. 107-109 °C [lit. [131] 117-118 °C (from ethanol)] (Found: M+ 196.0516. $C_{13}H_8O_2$ requires M+ 196.0524) δ_H 8.39(1H,d,^3J 9.8), 8.14(1H,d,^3J 8.3), 7.93-7.83(2H,m), 7.69-7.49(2H,m), 7.37(1H,d,^3J 9.0) and 6.51(1H,d,^3J 9.8); δ_C 160.73(q), 153.62(q), 138.89, 132.92, 130.04(q), 128.82, 128.12, 125.89, 121.16, 116.80, 115.37 and 112.75(q); *m/z* 196(M+,58), 168(100), 140(16) and 139(64).

Methyl 3-[2-(allyloxy)-5-chlorophenyl]propenoate **300** (0.110 g, 4 mmol), (T_f 650 °C, T_i 120-140 °C, P 0.01 mbar, t 20 min), gave 5-chloro benzofuran **321** (0.040 g, 60%) b.p. 65-70 °C (20 Torr) (lit.[132] b.p. 215-217 °C) (Found: M+ 154.0004 and 152.0031. $C_8H_5{}^{37}ClO$ and $C_8H_5{}^{35}ClO$ requires M+ 153.9999 and 152.0029) δ_H 7.63(1H,d,^4J 2.2), 7.57(1H,dd,^4J 2.0 and 0.4), 7.44-7.39(1H,ddd,^3J 8.8,^4J 1.4 and 0.6), 7.27-7.22(1H,m) and 6.71(1H,dd,^3J 2.1,^4J 0.9); δ_C 153.19(q), 146.17, 128.64(q), 128.18(q), 124.34, 120.64, 112.21 and 106.14; *m/z* 154(M+,39%), 152(M+,100%), 89(32) and 63(13).

Methyl 3-[2-(allyloxy)-5-nitrophenyl]propenoate **301** (0.102 g, 4 mmol), (T_f 650 °C, T_i 140-460 °C, P 0.01 mbar, t 20 min), gave three products These were separated by dry-flash chromatography to give a compound which was tentatively identified as 7-allylbenzofuran **334** (0.010 g, 21%) δ_H 7.59(1H,d,^3J 2.2), 7.44-7.39(2H,m), 7.11(1H,dd) 6.71(1H,dd,^3J 2.1, ^4J 0.8), 6.00(1H,m), 5.06(2H,m) and 3.46(1H,d,^{3} 6.7); δ_C 144.99, 137.88, 124.92, 120.55, 115.38, 110.94, 106.26 and 39.96. 5-Nitrobenzofuran **325** (0.034 g, 55%) m.p. 107-109 °C [lit.[133] 116 °C (from ethanol)] (Found: M+ 163.0269. $C_8H_5NO_3$ requires

M+ 163.0269) δ_H 8.54(1H,d,^4J 2.2), 8.23(1H,dd,^3J 9.0, ^4J 2.4), 7.78(1H,d,^3J 2.3), 7.58(1H,d,^3J 9.1) and 6.92(1H,dd,^3J 2.3, ^4J 0.9); δ_C 157.55(q), 147.86, 144.04(q), 127.66(q), 120.06, 117.72, 111.63 and 107.45; *m/z* 163(M+,77%), 117(45), 89(100), 77(16), 63(75) and 62(28). *3-Allyl-6-nitrobenzopyran-2-one* **333** (0.004 g, 4%) (not purified further) (Found: M+ 231.0529 $C_{12}H_9NO_4$ requires M+ 231.0532) δ_H 8.39-8.30(2H,m), 7.58(1H,s), 7.43(1H,d,^3J 8.9), 6.01-5.85(1H,m), 5.28-5.20(2H,m) and 3.35(2H,m); δ_C(DEPT 3π/4) 137.36, 132.54, 125.42, 123.01, 119.10, and 34.38; *m/z* 231(M+,100%), 203(36), 157(45), 128(77), 127(40), 102(27), 77(28) and 63(25).

C.3.b. Pyrolysis of Radical Precursors 302, 303 and 305 to form 2-Methylbenzofuran 287, 5-Chloro-2-methylbenzofuran 322 and 2-Methylnaphtho[2,1-*b*]furan 324

Ethyl 3-[2-(allyloxy)phenyl]-2-methylpropenoate **302** (0.123 g, 5 mmol), (T_f 650 °C, T_i 100-120 °C, P 0.01 mbar, t 20 min), gave 2-methylbenzofuran **287** (0.049 g, 75%), b.p. 115-118 °C (41 Torr) [lit.[134] 192 °C (744 Torr)] (Found: M+ 132.0581 C_9H_8O requires M+ 132.0575) δ_H 7.53-7.43(2H,m), 7.27-7.19(2H,m), 6.39(1H,dq,^4J 2.1 and 1.1) and 2.48(3H,d,^4J 1.0); δ_C 155.27(q), 154.61(q), 129.05(q), 122.90, 122.27, 119.92, 110.48, 102.43 and 13.91; *m/z* 132(M+,87%), 131(100), 77(11), 51(14), 44(16) and 43(13).

Ethyl 3-[2-(allyloxy)naphth-1-yl]-2-methylpropenoate **305** (0.133 g, 0.4 mmol), (T_f 650 °C, T_i 120-140 °C, P 0.01 mbar, t 20 min), gave a mixture of products which on purification by dry-flash chromatography (4% ethyl acetate / hexane; 10% gradient) gave one major product. 2-methylnaphtho [2,1-*b*]furan **324** (0.071 g, 88%), m.p. 46-50 °C [lit.[135] m.p. 57-58 °C (from water/ethanol)] (Found: M+ 182.0731 $C_{13}H_{10}O$ requires M+ 182.0732) δ_H

8.14-8.08(1H,m), 8.00-7.95(1H,m), 7.68-7.47(5H,m), 6.89-6.87(1H,m) and 2.60(3H,s); δ_C 154.49(q), 151.77(q), 130.11(q), 128.52, 127.25(q), 125.75, 124.01, 123.63, 123.29, 111.91, 101.59 and 14.03, one quaternary not apparent; *m/z* 182(M+,100%), 181(96), 153(11), 152(30), 76(20) and 63(12).

Ethyl 3-[2-(allyloxy)-5-chlorophenyl]-2-methylpropenoate **303** (0.130 g, 5 mmol), (T_f 650 °C, T_i 100-120 °C, P 0.01 mbar, t 20 min), gave 5-chloro-2-methylbenzofuran **322** (0.066 g, 85%) b.p. 75-80 °C (20 Torr) [lit.[136] b.p. 128-130 °C (25 Torr)] (Found: M+ 168.0178 and 166.0177 $C_9H_7{}^{37}Cl$ and $C_9H_7{}^{35}Cl$ requires M+ 168.0156 and 166.0185) δ_H 7.42(1H,m), 7.30(1H,m), 7.14(1H,m), 6.31(1H,q,^4J 0.9) and 2.44(3H,d,^4J 0.9); δ_C 156.96(q), 152.95(q), 130.41(q), 127.77(q), 123.00, 119.55, 111.38, 102.20 and 13.98; *m/z* 168(M+,30%), 166(M+,100%), 165(67), 131(21), 103(13) and 51(19).

C.3.c. Pyrolysis of Ethyl 3-[2-(benzyloxy)phenyl]but-2-enoate 310, to form 3-Methylbenzofuran 320

Ethyl 3-[2-(benzyloxy)phenyl]but-2-enoate **310** (0.125 g, 0.4 mmol), (T_f 650 °C, T_i 140-160 °C, P 0.003 mbar, t 15 min), gave the crude product which was purified by dry-flash chromatography to give 3-methylbenzofuran **320** (0.042 g, 67%) b.p. 70-80 °C (12 Torr) [lit.[134] 86 °C (20 Torr)] (Found: M+ 132.0566 C_9H_8O requires M+ 132.0609) δ_H 7.60-7.46(2H,m), 7.44(1H,t,^4J 1.3), 7.37-7.28(2H,m) and 2.29(3H,d,^3J 1.4); δ_C 155.13(q), 141.24, 128.90(q), 123.93, 122.08, 119.28, 115.48(q), 111.18 and 7.76; *m/z* 132(M+,98%), 131(100), 121(67), 103(35), 91(71), 78(16), 77(45), 65(22), 63(22), 51(27) and 39(27).

D. FORMATION OF THIENO[3,2-*b*]FURANS 352 AND THIENO[3,2-*b*]BENZOFURANS 338 AND ATTEMPTED PREPARATION OF THIENO[3,2-*b*]BENZOFURAN 338

D.1. Preparation of 3-(Benzloxyl)-5-(methythio)thiophene 357

A stirred suspension of sodium hydride (0.72 g, 0.03 mol) in DMI (25 ml) under nitrogen was prepared. To this was added, dropwise a solution of 3-hydroxy-5-(methylthio)thiophene[80] **356** (1.46 g, 0.01 mol) in DMI (20 ml) and a solution of benzyl tosylate (2.62 g, 0.01 mol) in DMI (20 ml). The mixture was then stirred for 6 hours. Water (50 ml) was added and the mixture was extracted with ether (3 x 50 ml). The combined extracts were washed with water (3 x 50 ml) and dried ($MgSO_4$). Removal of the solvent gave a mixture of two products, both *O*-alkylation and *O,C*-dialkylation having taken place. These products were separated by careful bulb to bulb distillation to yield the pure *3-(benzyloxy)-5-(methylthio)thiophene* **357** (0.92 g, 39%). b.p. 120-125 °C (0.05 Torr) (Found: 236.0326. $C_{12}H_{12}OS_2$ requires 236.0330) δ_H 7.50-7.35(5H,m), 6.89(1H,d,^4J 1.8), 6.31(1H,d,^4J 1.8), 5.02(2H,s) and 2.53(3H,s); δ_C 156.25(q), 136.38(q), 128.32, 127.87, 127.35, 122.24, 99.79, 71.58 and 21.05, one quaternary not apparent; *m/z* 236(M+,10%), 123(17), 117(11), 92(100), 91(100), 89(15), 85(19), 60(13), 51(15), 45(44), 41(10) and 39(24).

D.2. Preparation of 5-{3-[(Benzyloxy)-5-(methylthio)thiophen-2-yl]methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione 360

A solution of freshly prepared 2,2-dimethyl-5-(methoxymethylene)-1,3-dioxane-4,6-dione **359** (0.65 g, 3.5 mmol) in acetonitrile (20 ml) was added to

a stirred solution of 3-(benzyloxy)-5-(methylthio)thiophene **357** (0.80 g, 30 mol) in acetonitrile (10 ml). The mixture was then stirred for 2 days. T.l.c showed that reaction was complete and the solid was filtered to give the crude product (0.87 g, 64%). This was then recrystallised from ethanol to give *5-{3-[(benzyloxy)-5-(methylthio)thiophen-2-yl]methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione* **360** (0.62 g, 42%) m.p. 206-208 °C (from ethanol) (Found: M+ 390.0608 $C_{19}H_{18}O_5S_2$ requires M+ 390.0595) (Found: C, 58.45; H, 4.70. $C_{19}H_{18}O_5S_2$ requires C, 58.45; H, 4.70%) δ_H 8.77(1H,s), 7.36(5H,s), 6.63(1H,s), 5.22(2H,s), 2.63(3H,s) and 1.70(6H,s); δ_C 168.05(q), 164.28(q), 163.44(q), 162.79(q), 141.78, 134.76(q), 128.75, 128.55, 127.18, 115.69(q), 110.74, 103.70(q), 98.37(q), 27.10 and 16.60; *m/z* 390(M+,7%), 332(22), 226(15), 225(15), 198(31), 92(12), 91(100) and 65(12).

D.3.a. Preparation of Methyl 3-[(3-Benzyloxy)-5-(methylthio) thiophen-2-yl]propenoate 362[137]

5-{3-[(Benzyloxy)-5-(methylthio)thiophen-2-yl]methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione **360** (0.20 g, 5 mmol) was dissolved in methanol (5 ml) and a solution of sodium methoxide [from sodium (0.023 g, 1 mmol) in methanol (5 ml)] was added. The reaction mixture was then stirred at room temperature for 1 hour and was poured into water (20 ml) and acidified with hydrochloric acid. The acid solution was extracted with methylene chloride (3 x 20 ml) and the combined extracts were dried ($MgSO_4$) and the solvent was removed on a rotary evaporator to give crude methyl 2-(carboxy)-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **361** (0.160 g, 88%) m.p. 115-120 °C (dec), δ_H 8.72(1H,s), 7.39(5H,s), 6.63(1H,s), 5.22(2H,s), 3.86(3H,s) and 2.63(3H,s), OH not apparent; δ_C 171.83(q), 166.65(q), 166.25(q), 161.13(q), 140.97, 135.33(q), 128.65, 128.38, 126.93(q),

115.39(q), 110.81, 101.88(q), 73.43, 52.85 and 16.60 which was used directly for the next stage;. Bulb to bulb distillation gave the decarboxylated product, *methyl 3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate* **362** (0.121 g, 76%), b.p. 120-125°C (0.05 Torr) (Found: 320.0523. $C_{16}H_{16}O_3S_2$ requires 320.0541) δ_H 7.82(1H,d,^3J 15.7), 7.38(5H,s), 6.70(1H,s), 5.99(1H,d,^3J 15.7), 5.09(2H,s), 3.74(3H,s) and 2.50(3H,s); δ_C 167.65(q), 157.37(q), 141.44(q), 135.98(q), 133.42, 128.52, 128.15, 127.20, 118.00(q), 117.23, 112.37, 73.22, 51.26 and 19.42; *m/z* 320(M+,42%), 288(10), 261(15)170(10) and 91(100).

D.3.b. Preparation of Methyl 2-(Carbomethoxy)-3-[(3-benzyloxy) -5-(methylthio)thiophen-2-yl]propenoate 363[137]

5-{3-[(Benzyloxy)-5-(methylthio)thiophen-2-yl]methylene}-2,2-dimethyl-1,3-dioxane-4,6-dione **360** (0.200 g, 0.5 mmol) was dissolved in methanol (5 ml) and a solution of sodium methoxide [from sodium (0.023 g, 0.01 mol) in methanol (5 ml)] was added. The reaction mixture was then stirred at room temperature for 1 hour. The methanol was then removed on a rotary evaporator and the residual anion dissolved in DMF (10 ml). Potassium carbonate (0.069 g, 0.5 mmol) and methyl iodide (0.07 g, 0.031 ml, 0.5 mmol) were added and the mixture stirred overnight. Water (20 ml) was added, and the mixture extracted with ether (3 x 20 ml). The combined extracts were washed with water (3 x 40 ml) and dried ($MgSO_4$). The solvent was then removed on a rotary evaporator to yield *methyl 2-(carbomethoxy)-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate* **363** (0.155 g, 82 %), b.p. 130-135 °C (0.05 Torr) (Found: 378.0594. $C_{18}H_{18}O_5S_2$ requires 378.0596) δ_H 8.15(1H,s), 7.37(5H,s), 6.64(1H,s), 5.13(2H,s), 3.88(3H,s), 3.78(3H,s) and 2.53(3H,s); δ_C 166.97(q), 165.59(q), 161.29(q), 148.15(q), 135.65(q), 133.12, 128.57, 128.22, 127.08, 114.63(q), 114.28, 73.32,

52.20, 52.07 and 18.35, one quaternary not apparent; *m/z* 378(M+,30), 302(15), 271(10), 256(10), 228(10), 111(20) and 91(100).

D.4. Pyrolysis of Methyl 3-[(3-Benzyloxy)-5-(methylthio) thiophen-2-yl]propenoate 362 and Methyl 2-Carbomethoxy-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate 363

Methyl 3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **362** (0.054 g, 0.17 mmol) (T_f 650 °C, T_i 160-180 °C, P 0.002 mbar, t 10 min) gave the crude product which was purified by dry-flash chromatography (4% ethyl acetate / hexane; 5% gradient) to remove bibenzyl and give 5-(methylthio)thieno[3,2-*b*]furan **336** (0.006 g, 21%), δ_H 7.55(1H,dd,^3J 2.0), 7.15(1H,d,^5J 0.8), 6.67(1H,dd,^3J 2.0, ^5J 0.8) and 2.60(3H,s). This compound had decomposed after 2 days in chloroform solution, so could not be further characterised.

Methyl 2-(carbomethoxy)-3-[(3-benzyloxy)-5-(methylthio)thiophen-2-yl]propenoate **363** (0.060 g, 0.16 mmol) (T_f 650 °C, T_i 160-180 °C, P 0.002 mbar, t 10 min) gave the crude product which was purified by dry-flash chromatography (4% ethyl acetate / hexane; 5% gradient) to remove bibenzyl and give 5-(methylthio)-2-(carbomethoxy)thieno[3,2-*b*]furan **337** (0.008 g, 22%), δ_H 7.41(1H,d,^6J 0.6), 7.09(1H,d,^6J 0.6), 3.23(3H,s) and 2.56(3H,s). This compound had decomposed after 2 days in chloroform solution, so could not be further characterised.

D.5.a. Preparation of 3-(Allyloxy)-2-phenylthiophene 369

To a solution of sodium hydride (0.20 g, 8.5 mmol) in DMI (5 ml) was added 3-hydroxy-2-phenylthiophene[80] **368** (0.49 g, 2.8 mol) and allyl bromide (0.41 g, 3.4 mmol). The mixture was then stirred for 2 hours, after which time ethanol (5 ml) and water (10 ml) were added. The mixture was extracted with ether (3 x 25 ml) and the combined extracts were washed with water (3 x 50 ml). The organic layer was then dried ($MgSO_4$) and the solvent was removed on a rotary evaporator to yield crude *3-(allyloxy)-2-phenylthiophene* **369** (0.49g, 100%) [During distillation the initial product undergoes Claisen rearrangement to 2-allyl-2-phenylthiophen-3(2*H*)-one **370**] b.p. 200-205°C (0.05 Torr) (Found: M+ 216.0603. $C_{13}H_{12}OS$ requires: M+216.0609); δ_H 7.83-7.77(2H,m), 7.43-7.34(2H,m), 7.26(1H,m), 7.14(1H,d,^3J 5.5), 6.91(1H,d,^3J 5.6), 6.14-5.97(1H,m), 5.48-5.25(2H,m) and 4.64-4.60(2H,m); δ_C 152.41(q), 133.45, 128.38, 127.02(q), 126.85, 126.29, 121.97, 118.52, 117.27 and 72.11 one quaternary not apparent; *m/z* 216(M+,30%), 176(15), 175(100), 147(39), 131(24), 121(36), 77(38) and 69(13).

D.5.b. Preparation of 3-(Benzyloxy)-2-phenylthiophene 371

To a solution of sodium hydride (0.17 g, 7:1 mmol) in DMI (5 ml) was added 3-hydroxy-2-phenylthiophene[80] **368** (0.414 g, 2.4 mmol) and benzyl bromide (0.44 g, 2.6 mmol). The mixture was then stirred overnight, after which time ethanol (5 ml) and water (10 ml) were added. The mixture was extracted with ether (3 x 25 ml) and the combined extracts were washed with water (3 x 50 ml). The mixture was then dried ($MgSO_4$) and the solvent was removed on a rotary evaporator to yield crude product which was purified by bulb to bulb distillation to yield *3-(benzyloxy)-2-phenylthiophene* **371** (0.45g,

71%) b.p. 160-165°C (0.005 Torr) (Found: M+ 266.0766. $C_{17}H_{14}OS$ requires M+ 266.0766); δ_H 7.83(2H,m), 7.48-7.15(8H,m), 7.14(1H,d,^3J 5.5), 6.93(1H,d,^3J 5.5) and 5.16(2H,s); δ_C 152.43(q), 137.06(q), 133.31, 128.43 (two resonances coincident), 128.13(q), 127.18, 126.90, 126.34, 122.06, 118.67 and 73.33; *m/z* 266(M+,14%), 175(16), 128(10)91(100) and 77(8) one quaternary not apparent.

D.5.c. Preparation of 3-(Benzyloxy)-2-(4-methylphenyl) thiophene 373

4-Methylbenzylmercaptan (1.52 g, 11 mmol) was added to a solution of methoxymethylene Meldrum's acid (1.86 g, 10 mmol) in acetonitrile (20 ml). The mixture was then heated under reflux for 3 hours, after which time the solvent was removed on the rotary evaporator. The crude product was washed with ethanol to give *5-[(4-methylbenzyl)thiomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione* (2.34 g, 80%), m.p. 142-144 °C (Found: C, 61.65; H,5.50; $C_{15}H_{16}O_4S$ requires C, 61.65; H, 5.50%); δ_H 9.00(1H,s), 7.19(4H,d), 4.17(2H,s), 2.34(3H,s) and 1.69(6H,s); δ_C 169.98, 160.93(q), 160.33(q), 138.12(q), 131.76(q), 129.81, 128.77, 108.51(q), 104.95(q), 41.36, 27.40 and 20.97; *m/z* 234(27), 216(7), 136(11), 129(15), 106(17) and 105(100), 292 (M+) not detected.

5-[(4-methylbenzyl)thiomethylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (1.04 g) was sublimed through a silica furnace maintained at 625 °C under a vacuum of 1 x 10^{-3} Torr. The products were collected in a trap cooled in liquid nitrogen. This gave *3-hydroxy-2-(4-methylphenyl)thiophene* (0.63 g, 95%), b.p. 138-142 °C (0.05 Torr) (Found: C, 69.55; H, 5.35, $C_{11}H_{10}OS$ requires C, 69.45; H, 5.30%); δ_H 7.49(2H,d,^3J 8.0), 7.23(2H,d,^3J 8.0), 7.08(1H,d,^3J 5.5), 6.73(1H,d,^3J 5.5), 5.28(1h,br) and 2.38(3H,s); δ_C 148.31(q), 136.72(q), 129.66, 127.21, 121.95, 120.46, 117.97(q) and 21.04.

To a stirred solution of sodium hydride (0.13 g, 4.3 mmol) in DMI (5 ml) was added 3-hydroxy-2-(4-methylphenyl)thiophene **372** (0.19 g, 1.4 mmol) and benzyl bromide (0.27 g, 1.6 mmol). The mixture was then stirred overnight. Ethanol (5 ml) and water (10 ml) were added and the mixture was extracted with ether (3 x 25 ml). The combined extracts were washed with water (3 x 50 ml), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator to yield the crude product. This was purified by bulb to bulb distillation to yield *3-(benzyloxy)-2-(4-methylphenyl)thiophene* **373** (0.29 g, 75%) b.p. 170-175 °C (0.005 Torr) (Found: C, 77.10; H, 5.90. $C_{18}H_{16}OS$ requires C, 77.10; H, 5.80%) δ_H 7.71(2H,m), 7.46-7.25(5H,m), 7.19(2H,m), 7.10(1H,d,^3J 5.5), 6.92(1H,d,^3J 5.5), 5.14(2H,s) and 2.38(3H,s); δ_C 152.03(q), 137.14(q), 136.08(q), 130.40(q), 129.11, 128.89(q), 128.40, 127.77, 127.15, 126.83, 121.48, 118.69, 73.29 and 21.06; *m/z* 280(M+,55%), 190(13), 189(88), 174(13), 161(11), 145(10), 135(16), 128(11), 91(100) and 65(11).

D.6. Pyrolysis of 3-(Allyloxy)-2-phenylthiophene, 369 3-(Benzyloxy)-2-phenylthiophene 371 and 3-(Benzyloxy)-2-(4-methylphenyl)thiophene 373

Yields of products were obtained by dissolving the crude reaction mixture in $CDCl_3$, then injecting a known quantity of cyclohexane (5 µl) and examining the ^1H NMR spectrum.

3-(Allyloxy)-2-phenylthiophene **369** (0.037 g, 0.17 mmol) (650 °C, 80-100 °C, 0.001 Torr, 20 min) gave 3-hydroxy-2-phenylthiophene **368** (50%)

3-(Benzyloxy)-2-phenylthiophene **371** (0.022 g, 0.083 mmol) (650 °C, 120-140 °C, 0.001 Torr, 20 min) gave 3-hydroxy-2-phenylthiophene **368** (40%)

3-(Benzyloxy)-2-(methylphenyl)thiophene **373** (0.058 g, 0.0207 mmol) (650 °C, 120-140 °C, 0.001 Torr, 20 min) gave 3-hydroxy-2-(4-methylphenyl)thiophene **372** (16%). The ^1H NMR spectrum of the crude pyrolysate showed the presence of 4 other methyl peaks due to other minor components which were not identified.

D.7. Preparation of [5-(methylthio)thiophen-3-yl] 2-(allyloxy) benzoate 382

A mixture of 2-(allyloxy)benzoic acid **380** (0.177 g, 1 mmol) and thionyl chloride (0.142 g, 1.2 mmol) was heated on a water bath for 30 minutes to give the acid chloride **381**, after which time the excess thionyl chloride was removed at the water pump. Dry methylene chloride (5 ml), 4-*N*,*N*-dimethylaminopyridine (0.01 g, 0.1 mmol) and a solution of 5-(methylthio)thiophen-3-one **356** (0.146 g, 1 mmol) in dry methylene chloride (5 ml) were then added. A solution of triethylamine (0.11 g, 1.1 mmol) in dry methylene chloride (5 ml) was then added dropwise over 15 minutes and the mixture was stirred for a further 2 hours. The mixture was then washed with concentrated sodium carbonate solution (2 x 25 ml), water (2 x 25 ml) and the organic phase was dried ($MgSO_4$). Removal of the solvent on a rotary evaporator gave the crude product (0.251 g, 82%) which was purified by bulb to bulb distillation to yield *[5-(methylthio)thiophen-3-yl] 2-(allyloxy)benzoate* **382** (0.222 g, 72%) b.p. 188-190 °C (0.001 Torr) (Found: M+ 306.0376 $C_{15}H_{14}O_3S_2$ requires M+ 306.0384) δ_H 7.95(1H,dd,^3J 7.5, ^4J 1.6), 7.40(1H,td,^3J 9.5 and 7.9, ^4J 1.7), 7.16(1H,d,^3J 1.8), 7.02(1H,d,^3J 1.8), 7.06-6.97(2H,m), 6.07(1H,m), 5.52(1H,m), 5.29(1H,m), 4.65(2H,m) and 2.49(3H,s); δ_C 163.13(q), 158.66(q), 146.18(q), 136.02(q), 134.13, 132.41, 132.06, 124.69,

120.33, 118.99, 117.47, 113.58, 113.12, 69.36 and 21.50; *m/z* 306(M+,22%) and 91(100)

D.8. Pyrolysis of [5-(Methylthio)thiophen-3-yl] 2-(allyloxy) benzoate 382

Yields of products were obtained by dissolving the crude reaction mixture in $CDCl_3$, then injecting a known quantity of cyclohexane (5µl) and examining the ^1H NMR spectrum.

[5-(Methylthio)thiophen-3-yl] 2-(allyloxy)benzoate **382** (0.083 g, 0.27 mmol) (650 °C, 140-160 °C, 0.001 Torr, 20 min) gave 5-(methylthio)thiophene-3-one **356** (11%)

E. PREPARATION OF BENZOTHIOPHENE USING AN ACRYLATE ESTER RADICAL LEAVING GROUP

E.1. Preparation of Methyl 3-[2-(*t*-Butylthio)phenyl] propenoate 385 *via* a Wittig reaction

2-(*t*-Butylthio)benzaldehyde **384** (1.94 g, 0.01 mol) was dissolved in dry dichloromethane (25 ml). With stirring methyl (triphenylphosphoranylidene) acetate (3.34 g, 0.01 mol) was added. Stirring was continued for 48 hours. T.l.c. showed a mixture of the product and a trace of starting aldehyde. The mixture was then preadsorbed on to silica (5 x weight of mixture), and separated by dry flash chromatography on silica. This gave *methyl 3-[2-(t-butylthio)phenyl]propenoate* **385** (2.37 g, 95%), m.p. 59-60 °C (hexane) (Found: 250.1028. $C_{14}H_{18}O_2S$ requires 250.1027) δ_H 8.56(1H,d,^3J 16.2), 7.71-7.25(4H,m), 6.37(1H,d,^3J 16.2), 3.80(3H,s) and 1.26(9H,s); δ_C 167.16(q), 144.34, 139.81(q), 139.62, 134.03(q), 129.56, 129.27, 126.54, 118.76, 51.54, 47.76(q) and 30.91; *m/z* 250(M+,6%), 195(14), 194(70), 193(25), 163(24), 161(17), 149(22), 136(13), 135(100), 134(72), 91(13), 59(13), 57(61) and 41(23).

E.2. Pyrolysis of Methyl 3-[2-(*t*-Butylthio)phenyl]propenoate 385

Methyl 3-[2-(*t*-butylthio)phenyl]propenoate **385** (0.560 g, 2.2 mmol), (T_f 700 °C, T_i 80-100 °C, P 0.01 Torr, t 15min) gave three products which were separated by dry-flash chromatography. Benzothiophene **383** (0.043 g, 15%) b.p. 90-94 °C (15 torr) (lit.[138] b.p. 221-222 °C) δ_H 8.05-7.91(2H,m) and 7.57-7.41(4H,m); δ_C 139.54(q), 139.41(q), 126.08, 124.01, 123.97, 123.64, 123.42 and

122.29; *m/z* 134 (M+,100%) and 43(48). *2-(Carbomethoxy)-2,3-dihydrobenzothiophene* **394** (0.090 g, 21%), b.p. 125-130 °C (0.1 Torr) (Found: 194.0409. $C_{10}H_{10}O_2S$ requires 194.0401) δ_H 7.22-7.01(4H,m), 4.46(1H,dd,^2J 8.8, ^3J 5.7), 3.76(3H,s), 3.67(1H,dd,^3J 5.8 and 0.8), 3.51(1H,dd,^2J 8.8, ^3J 0.9) spectra are consistent with a compound prepared by an alternative route but not fully characterised[139]; δ_C 172.04(q), 138.90(q), 138.11(q), 127.46, 124.56, 124.40, 121.43, 52.55, 48.30 and 37.98; *m/z* 194(M+,33%), 136(12), 135(100), 134(29) and 91(21). *2H*-1-Benzothiopyran-2-one **397** (0.102 g, 28%) m.p. 63-67 °C (ethyl acetate) (lit.[140] m.p. 80-80.5 °C) (Found: 162.0137. C_9H_6OS requires 162.0139) δ_H 7.69(1H,d,^3J 10.5), 7.61-7.32(4H,m) and 6.52(1H,d,^3J 10.6); δ_C 185.23(q), 143.62, 137.30(q), 131.40, 129.74, 126.28, 125.87(q), 125.67 and 123.89; *m/z* 162(M+,74%), 135(28), 134(100) and 67(11).

F. ATTEMPTED USE OF THE CARBOMETHOXY LEAVING GROUP IN THE PREPARATION OF SEVEN-MEMBERED RING SYSTEMS

F.1. Preparation of 2-Formyl-*N*-[2-(allylthio)phenyl]pyrrole 407 and 2-Formyl-*N*-[2-(benzyloxy)phenyl]pyrrole 409 - General method

A solution of the appropriate *N*-arylpyrrole (3 mmol) in DMF (5ml) was added to a solution of phosphoryl chloride (0.60 g, 3.9 mmol, 0.37 ml) in DMF (10 ml). After stirring for 1 hour a further portion of phosphoryl chloride (0.60 g, 3.9 mmol, 0.37 ml) was added and stirring continued for 1 hour. The mixture was then poured onto crushed ice, hydrolysed with 2M sodium hydroxide solution (25 ml) and then acidified to pH 6-7 with 2M hydrochloric acid. The mixture was then extracted with ether (3 x 25 ml), the organic extracts washed with water (3 x 50 ml) and dried ($MgSO_4$). T.l.c showed that formylation had occurred at both the 2- and 3-positions of the pyrrole ring, so the products were pre-adsorbed onto silica and separated by dry-flash chromatography (10% ethyl acetate / hexane: 5% gradient).

N-[2-(Benzyloxy)phenyl]pyrrole **399** (0.75 g, 3 mmol) gave *2-formyl-N-[2-(benzyloxy)phenyl]pyrrole* **407** (0.643 g, 77%), b.p. 114-118 °C (3 Torr) (Found: M+ 277.1103. $C_{18}H_{15}NO_2$ requires M+ 277.1103) δ_H 9.49(1H,s), 7.43-6.99(11H,m), 6.42(1H,dd,^3J 4.1, ^3J 2.6) and 5.05(2H,s); δ_C 178.97, 153.44(q), 136.17(q), 133.02(q), 130.98, 129.61, 128.27, 127.99, 127.61, 126.55, 120.87, 120.55(q), 113.61, 110.32 and 70.32; *m/z* 277(M+,15%), 248(23), 158(16), 91(100) and 65(12)one quaternary not apparent, and *3-formyl-N-[2-(benzyloxy)phenyl]pyrrole* **408** (0.123 g, 15%), b.p. 145-150 °C (2 Torr), (Found:

M+ 277.1103. $C_{18}H_{15}NO_2$ requires M+ 277.1103) δ_H 9.81(1H,s), 7.61(1H,t,^3J 1.7), 7.41-7.25(7H,m), 7.14-6.98(3H,m), 6.76(1H,dd,^3J 3.1 and 1.6) and 5.12(2H,s); δ_C 185.32, 151.48(q), 135.84(q), 130.74, 129.13(q), 128.74, 128.42, 127.87, 126.92(q), 126.67, 125.52, 124.85, 121.40, 114.26, 107.60 and 70.68; *m/z* 277(M+,75%), 248(12), 186(26), 172(11), 158(32), 92(20), 91(100), 77(10) and 65(30).

N-[2-(Allylthio)phenyl]pyrrole **400** (0.75 g, 3 mmol) gave *2-formyl-N-[2-(allylthio)phenyl]pyrrole* **409** (0.568 g, 77%), b.p. 124-128 °C (2 Torr) (Found: M+ 243.0713. $C_{14}H_{13}NOS$ requires M+ 243.0718) δ_H 9.42(1H,s), 7.42-7.39(2H,m), 7.28-7.24(2H,m), 7.13(1H,dd,^3J 4.0 and 1.6), 6.96-6.94(1H,m), 6.43(1H,dd,^3J 3.9 and 2.6), 5.82-5.63(1H,m), 5.16-5.02(2H,m) and 3.40-3.35(2H,m); δ_C 178.70, 137.99(q), 135.02(q), 132.84(q), 132.64, 130.84, 129.26, 129.10, 128.05, 126.29, 120.64, 118.20, 110.63 and 35.65; *m/z* 243(M+,43%), 215(12), 214(71), 186(13), 175(14), 17497), 173(59), 172(12), 171(13), 170(100) and 77(10) and *3-formyl-N-[2-(allylthio)phenyl]pyrrole* **410** (0.175 g, 23%), b.p. 136-140 °C (3 Torr) (Found: M+ 243.0726. $C_{14}H_{23}NOS$ requires M+ 243.0718) δ_H 9.79(1H,s), 7.46-7.23(5H,m), 6.85-6.83(1H,m), 6.73(1H,dd,^3J 2.7 and 1.5), 5.76-5.59(1H,m), 5.10-4.98(2H,m) and 3.32(2H,d,^3J 6.8); δ_C 185.29, 139.00(q), 132.74(q), 132.46, 130.46, 130.27, 128.82, 127.16(q), 126.85, 126.69, 124.94, 118.30, 108.00 and 36.03; *m/z* 243(M+,19%), 214(11), 203(12), 202(84), 175(19), 174(100), 173(51) and 77(9).

F.2. Preparation of Methyl 3-{*N*-[2-(Benzyloxy)phenyl]pyrrol-2-yl}propenoate 411 and Methyl 3-{*N*-[2-(Allylthio) phenyl]pyrrol-2-yl}propenoate 412 - General method

The appropriate 2-formyl-*N*-arylpyrrole (2 mmol) was dissolved in dry methylene chloride (50 ml). Methyl (triphenylphosphoranylidene)acetate (0.736 g, 2.2 mmol) was added and the mixture was then heated under reflux until t.l.c. showed that all the aldehyde had been consumed. The mixture was pre-adsorbed onto silica and purified by dry-flash chromatography (10% ethyl acetate / hexane: 10% gradient).

2-Formyl-*N*-[2-(benzyloxy)phenyl]pyrrole **407** (0.554 g, 2 mmol) (48 hours) gave *methyl 3-{N-[2-(benzyloxy)phenyl]pyrrol-2-yl}propenoate* **411** (0.300 g, 45%), b.p. 150-155 °C (0.05 Torr) (Found: M+ 333.1374. $C_{21}H_{19}NO_3$ requires M+ 333.1364) δ_H 7.42-7.20(8H,m), 7.10-7.06(2H,m), 6.93-6.90(1H,m), 6.85-6.82(1H,m), 6.40-6.36(1H,m), 6.03(1H,m,^3J 15,8), 5.05(2H,s) and 3.70(3H,s); δ_C 167.97(q), 153.71(q), 136.25(q), 133.74, 130.22, 129.71, 128.93, 128.29, 128.05(q), 127.61, 127.30, 126.58, 121.13, 114.10, 112.03, 111.73, 110.05, 70.31 and 51.14; *m/z* 333(M+,35%), 274(12), 260(10), 210(14), 183(12), 182(14), 170(34), 168(23), 154(23) and 91(100).

2-Formyl-*N*-[2-(allylthio)phenyl]pyrrole **409** (0.486 g, 2 mmol) (8 hours) gave *methyl 3-{N-[2-(allylthio)phenyl]pyrrol-2-yl}propenoate* **413** (0.342 g, 60%), b.p. 145-150 °C (0.05 Torr) (Found: M+ 299.0984. $C_{17}H_{17}NO_2S$ requires M+ 299.0980) δ_H 7.41(2H,m), 7.27-7.14(3H,m), 6.85-6.80(2H,m), 6.36(1H,dd,^3J 3.3), 5.93(1H,d,^3J 15.9), 5.81-5.64(1H,m), 5.18-5.03(2H,m), 3.67(3H,s) and 3.40(2H,d,^3J 6.6); δ_C 167.85(q), 137.36(q), 135.97(q), 133.08, 132.62, 129.88(q), 129.23, 128.88, 128.75, 127.04, 126.21, 118.24, 112.48, 112.13, 110.33, 51.20 and

35.40; *m/z* 299(M+,41%), 258(81), 227(11), 226(100), 199(44), 198(69), 197(31), 187(13), 186(53), 173(16), 167(23), 154(12), 41(22) and 39(17).

F.3. Pyrolysis of Methyl 3-{*N*-[2-(Benzyloxy)phenyl]pyrrol-2-yl} propenoate 411 and Methyl 3-{*N*-[2-(Allylthio)phenyl] pyrrol-2-yl}propenoate 412

Methyl 3-{*N*-[2-(benzyloxy)phenyl]pyrrol-2-yl}propenoate **411** (0.204 g, 6 mmol) (T_f 650 °C, T_i 140-160 °C, P 0.005 mbar, t 20 min), gave a number of products, only three of which could be separated by dry-flash chromatography. The first to elute was bibenzyl. The second was *methyl 2-(4H-pyrrolo[2,1-c][1,4]benzoxazin-4-yl)ethanoate* **421** (0.006 g, 4 %), b.p. 120-125 °C (0.05 Torr) (Found: 243.0879. $C_{14}H_{13}NO_3$ requires 243.0895) δ_H 7.33(1H,m), 7.14(1H,dd,^3J 2.9 and 1.4), 7.05-7.00(3H,m), 6.31(1H,t,^3J 3.1), 6.01(1H,m), 5.61(1H,t,^3J 6.3), 3.76(3H,s) and 2.99(2H,d,^3J 6.6); δ_C 170.26(q), 144.88(q), 126.25(q), 126.09(q), 124.98, 122.31, 118.16, 114.90, 114.57, 110.48, 104.18, 70.28, 51.89 and 38.73; *m/z* 243(M+ 30%), 171(13) and 170(100). The third product could not be isolated pure but was identified as methyl 3-[1-(2-hydroxyphenyl)pyrrol-2-yl]propenoate **420** by comparison with authentic data. (see below) δ_H 7.06-6.99(2H,m), 6.87(1H,m), 6.80(1H,m), 6.35(1H,t), 5.99(1H,d,^3J 15.8) and 3.68(3H,s) two aryl protons one alkenyl proton and OH not apparent; *m/z* 243(M+).

Methyl 3-{*N*-[2-(allylthio)phenyl]pyrrol-2-yl}propenoate **412** (0.250 g, 8 mmol) (T_f 650 °C, T_i 140-160 °C, P 0.001 mbar, t 20 min), gave one major product which was purified by dry-flash chromatography (1% Ethyl acetate / Hexane : 10% gradient) and identified as *9-(carbomethoxymethylene)-9H-pyrrolo[1,2-a]indole* **425** (see discussion) (0.084 g, 41%) b.p. 125-130 °C (0.2

Torr) (Found: 225.0784. $C_{14}H_{11}NO_2$ requires 225.0790) δ_H 7.87-7.81(3H,m), 7.70(1H,d,^3J 7.8), 7.56(1H,dt,^3J 8.3 and 1.2), 7.35-7.24(2H,m), 6.87(1H,t,^3J 3.4) and 3.99(3H,s); δ_C 165.77(q), 134.46(q), 130.28, 130.17, 127.63(q), 125.19, 123.71, 122.01(q), 120.61(q), 114.11, 113.37, 112.36, 104.99 and 52.02; *m/z* 225(M+ 100%), 194(7), 168(7), 167(63), 166(49), 140(13) and 139(12).

F.4. Preparation of 2-Formyl-*N*-(2-hydroxyphenyl)pyrrole 423

Phosphoryl chloride (1.2 g, 7.8 mmol) was dissolved in DMF (10ml). A solution of 1-(2-hydroxyphenyl)pyrrole **422** (0.318 g, 2.6 mmol) in DMF (5 ml) was then added dropwise and the mixture was stirred until t.l.c showed the disappearance of the starting material. The mixture was then poured onto ice and hydrolysed with 2M NaOH (20ml). The mixture was then neutralised (pH 7) with 2M HCl and extracted with ether (3 x 25 ml). The combined organic layers were then washed with water (3 x 50 ml) and dried ($MgSO_4$). The crude product mixture was pre-adsorbed onto silica and separated by dry flash chromatography (15% Ethyl acetate /Hexane : 5% gradient) to give two products. *2-Formyl-1-(2-hydroxyphenyl)pyrrole* **423** (0.092 g, 25%), b.p. 134-139 °C (0.2 Torr) (Found: M+ 187.0644. $C_{11}H_9NO_2$ requires M+ 187.0633) δ_H 9.42(1H,s), 7.39-6.94(4H,m) and 6.46-6.25(3H,m) OH not apparent; δ_C 178.40, 150.39(q), 131.16, 129.29, 127.26, 124.43, 120.13, 116.98, 113.92 and 110.78 two quaternaries not apparent; *m/z* 187(M+,100%), 170(28), 159(93), 158(50), 131(23), 130(55), 94(18), 78(13), 77(13) and 65(13) and *3-formyl-N-(2-hydroxyphenyl)pyrrole* **424** (0.058 g, 16%), b.p. 150-155 °C (0.5 Torr), (Found: M+ 187.0625. $C_{11}H_9NO_3$ requires M+ 187.0633) δ_H 9.69(1H,s), 7.72(1H,t), 7.30-6.91(5H,m) and 6.76(1H,dd) OH not apparent; δ_C 186.45, 149.91(q), 131.11, 129.03, 128.88(q), 128.06(q), 125.42, 124.78, 120.51,

117.41 and 108.68; *m/z* 187(M+92%), 170(40), 159(100), 158(60), 131(12), 130(32) and 94(27).

F.5. Preparation of Methyl 3-{*N*-(2-Hydroxyphenyl)pyrrol-2-yl} propenoate 420 and Methyl 2-(4*H*-Pyrrolo[2,1-*c*][1,4] benzoxazin-4-yl)ethanoate 421

2-Formyl-1-(2-hydroxyphenyl)pyrrole **423** (0.070 g, 0.37 mmol) was dissolved in dry THF (50 ml). Methyl (triphenylphosphoranylidene)acetate (0.38 g, 1.12 mmol) was added and the mixture was then heated under reflux until t.l.c. showed that all the aldehyde had been consumed (36 hours). The mixture was pre-adsorbed onto silica (1 g) and purified by dry-flash chromatography (20% ethyl acetate / hexane: 5% gradient). This gave two products *methyl 2-(4H-pyrrolo[2,1-c][1,4]benzoxazin-4-yl)ethanoate* **421** (0.031g, 34 %), b.p. 130-135 °C (0.1 Torr) (Found: M+ 243.0883. $C_{14}H_{13}NO_3$ requires M+ 243.0895) δ_H 7.33(1H,m), 7.15(1H,dd,^3J 4.3 and 1.4), 7.09-7.00(3H,m), 6.32(1H,t,^3J 3.4), 6.02(1H,m), 5.62(1H,td,^3J 7.0 and 6.0, ^4J 0.7; δ_C 170.24(q), 144.85(q), 126.24(q), 126.07(q), 124.95, 122.28, 118.12, 114.91, 114.58, 110.51, 104.15, 70.25, 51.83 and 38.72;; *m/z* 243(M+,30%), 171(15), 170(100) and 167(9), and methyl 3-[*N*-(2-hydroxyphenyl)pyrrol-2-yl]propenoate **420** (0.024 g, 27 %), b.p. 145-150 °C (0.1 Torr) (Found: M+ 243.0887. $C_{14}H_{13}NO_3$ requires M+ 243.0895) δ_H 7.33-7.12(3H,m), 7.01-6.97(2H,m), 6.87(1H,t,^3J 1.6), 6.80(1H,d,^3J 3.8), 6.38(1H,t,^3J 3.0), 6.16(1H,br), 5.97(1H,d,^3J 15.7) and 3.66(3H,s); *m/z* 234(M+ 10%), 241(13), 227(21), 226(78), 213(86), 198(100), 197(75) and 183(56). These data are identical with those reported in Section F.3..

G. ATTEMPTED USE OF THE CARBOMETHOXY RADICAL LEAVING GROUP AND CARBON CENTRED RADICALS IN THE PREPARATION OF THE 3*H*-PYRROLIZINE 431 AND 2-METHYL-3*H*-PYRROLIZINE 448

G.1. Preparation of 1-(4-Chlorophenoxy)methyl-2-formylpyrrole 437

Potassium hydroxide (0.73 g, 13 mmol) was added to DMSO (10 ml) and the mixture stirred for 5 min. Pyrrole-2-carboxaldehyde **434** (0.95 g, 0.01 mol) was added and the mixture stirred for 45 min. The mixture was then cooled in ice and a solution of α,4-dichloroanisole **436** (1.77g, 0.01 mol) in DMSO (5 ml) was added dropwise. The mixture was then stirred for a further 10 min. Water (20 ml) was added and the mixture was extracted with ether (4 x 10 ml). The combined extracts were washed with water (4 x 20 ml) and dried ($MgSO_4$). The solvent was then removed on a rotary evaporator to yield *1-(4-chlorophenoxy)methyl-2-formylpyrrole* **437** (1.68 g, 72%), m.p. 78-81 °C (hexane/ethyl acetate) (Found: 237.0347 and 235.0384. $C_{12}H_{10}{}^{37}ClNO$ and $C_{12}H_{10}{}^{35}ClNO$ requires 237.0371 and 235.0400) δ_H 9.56(1H,d,^4J 1.1), 7.26-6.82(6H,m), 6.28(1H,dd,^3J 3.9 and 2.8) and 6.20(2H,s); δ_C 179.58, 154.67(q), 130.70, 129.40, 127.69(q), 125.66, 118.07, 117.66(q), 110.93 and 75.36; *m/z* 237(M+,23%), 236(13), 235(M+,73%), 143(15), 141(47), 113(15), 111(30), 101(39), 100(100), 99(16), 80(56), 78(20), 75(19), 73(10), 63(13), 53(62), 52(13) and 51(14).

G.2. Preparation of Methyl 3-[1-(4-Chlorophenoxy) methylpyrrol-2-yl]propenoate 441 and Ethyl 3-[1-(4-Chlorophenoxy)methylpyrrol-2-yl]-2-methylpropenoate 442 - General method

1-(4-Chlorophenoxy)methyl-2-formylpyrrole **437** (0.71 g, 3 mmol) was dissolved in dry benzene (50 ml). The appropriate ylide (3.3 mmol) was then added and the mixture was stirred overnight. The mixture was then pre-adsorbed onto silica (9g), and separated by dry-flash chromatography (10 % ethyl acetate / hexane: 10 % gradient). This gave the appropriate vinyl ester.

Methyl (triphenylphosphoranylidene)acetate gave *methyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]propenoate* **441** (0.633 g, 72%) b.p. 120-125 °C (2 Torr) (Found: 293.0625 and 291.0659. $C_{15}H_{14}{}^{37}ClNO_3$ and $C_{15}H_{14}{}^{35}ClNO_3$ requires 293.0633 and 291.0662) δ_H 7.63(1H,d,^3J 15.8), 7.22(2H,d,^3J 9.1), 6.80(2H,d,^3J 9.1), 6.81-6.78(1H,m), 6.71-6.69(1H,m), 6.21(1H,d,^3J 15.7), 6.21-6.18(1H,m), 5.75(2H,s) and 3.75(3H,s); δ_C 167.64(q), 154.52(q), 131.67, 129.49, 129.13(q), 128.17(q), 126.35, 118.71, 113.96, 113.52, 110.30, 75.42 and 51.36; *m/z* 293(M+,11%), 291(31%), 165(27),164(100) 141(11), 132(27), 111(13), 110(15), 105(87), 104(39), 77(11), 59(16), 51(10) and 45(56).

Ethyl 2-(triphenylphosphoranylidene)propionate gave *ethyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]-2-methylpropenoate* **442** (0.700 g, 73%) m.p. 59-63 °C (Found: 321.0938 and 319.0965. $C_{17}H_{18}{}^{37}ClNO_3$ and $C_{17}H_{18}{}^{35}ClNO_3$ requires 321.0946 and 319.0975) δ_H 7.63(1H,d,^4J 0.6), 7.22(2H,d,^3J 9.0), 6.82(2H,d,^3J 9.0), 6.84-6.77(1H,m), 6.60-6.58(1H,m), 6.29-6.26(1H,m), 5.77(2H,s), 4.22(2H,q,^3J 7.1), 2.13(3H,d,^4J 1.3) and 1.28(3H,t,^3J 7.1); δ_C

168.42(q), 154.73(q), 129.43, 129.13(q), 128.05(q), 125.25, 124.72, 124.52(q), 118.80, 115.18, 110.05, 75.59, 60.53, 14.31 and 14.13; *m/z* 319(M+,7%), 193(14), 192(94), 164(21), 148(15), 146(16), 141(10), 134(10), 120(35), 119(100), 118(92), 117(27), 111(17), 106(10), 105(13), 104(35), 99(14), 91(18), 79(14), 78(12), 77(17), 65(18), 59(80) and 51(12).

G.3. Pyrolysis of Methyl 3-[1-(4-Chlorophenoxy)methylpyrrol-2-yl]propenoate 441 and Ethyl 3-[1-(4-Chlorophenoxy) methylpyrrol-2-yl]-2-methylpropenoate 442

Methyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]propenoate **441** (0.122 g, 0.42 mmol), (T_f 700 °C, T_i 140-160 °C, P 0.005 Torr, t 10 min) ^{1}H NMR spectroscopy showed presence of *p*-chlorophenol. G.C. (5% SE 30, 150 °C) gave 9 peaks, of which only *p*-chlorophenol was identified by GC-MS.

Ethyl 3-[1-(4-chlorophenoxy)methylpyrrol-2-yl]-2-methylpropenoate **442** (0.100 g, 0.31 mmol), (T_f 700 °C, T_i 160-180 °C, P 0.01 Torr, t 10 min) ^{1}H NMR spectroscopy showed presence of *p*-chlorophenol. G.C. (5% SE30, 150 °C) gave 11 peaks, of which only *p*-chlorophenol was identified by GC-MS.

H. GENERATION OF PHENOXYL, AMINYL, BENZYL AND THIOPHENOXYL FREE RADICALS AND INVESTIGATION OF THEIR INTRAMOLECULAR CYCLISATION REACTIONS WITH A 2-(PYRROL-1-YL) SUBSTITUENT

H.1.a. Preparation of *N*-(2-Hydroxyphenyl)pyrrole 422, *N*-(2-Hydroxy-4-methylphenyl)pyrrole, and *N*-(2-Mercapto phenyl)pyrrole 456 - General method

A mixture of the appropriate 2-(substituted)aminophenol (33 mmol), 2,5-dimethoxytetrahydrofuran (3.96 g, 30 mmol) and glacial acetic acid (15ml) in dioxane (30 ml) was heated under reflux for four hours. The volatiles were then removed on a rotary evaporator and the residue was taken up between ether (60 ml) and 3% aqueous sodium hydroxide (90 ml). The aqueous phase was separated and acidified (pH 4) and extracted with chloroform (3 x 50 ml). The combined extracts were washed with 1M sodium hydrogen carbonate (50 ml), dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. The crude product was then purified by bulb to bulb distillation.

2-Aminophenol **452** (3.60 g, 33 mmol) gave *N*-(2-hydroxy phenyl)pyrrole **422** (2.95 g, 61%), b.p. 138-140 °C (0.03 Torr) (lit.[100] m.p. 45-47 °C) [Found: M+ 159.0687. $C_{10}H_9NO$ requires M+159.0684]; δ_H 7.35-7.26 (2H,m), 7.11-6.98 (2H,m), 6.94 (2H,dd,^3J2.1) and 6.44(2H,t,^3J 2.2); δ_C 150.16(q), 128.70, 128.22(q), 126.58, 121.86, 120.79, 116.81 and 110.12; *m/z* 159(M+,100%), 158(11), 131(27), 130(41), 103(10), 51(21) and 39(11).

6-Amino-*m*-cresol (4.06 g, 33 mmol) gave N-*(2-hydroxy-4-methylphenyl)pyrrole* (1.31 g, 25%), b.p. 140 °C (0.01 Torr) (Found: C, 76.3; H, 6.5; N, 8.25. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.1%); δ_H 7.11(1H,d, ^3J 7.9); 6.85-6.74(5H,m); 6.37(2H,d,^3J 2.1); and 2.35(3H,s); δ_C 149.87(q), 139.01(q), 126.11, 125.57(q), 121.72, 121.31, 116.92, 110.01 and 20.99; *m/z* 173(M+,9%), 165(34), 147(10), 124(14), 123(100), 122(32), 94(18), 77(12), 43(12), 41(12) and 40(14).

2-Aminothiophenol **453** (6.25 g, 50 mmol scale) gave *N*-(2-mercapto phenyl)pyrrole **456** (6.28 g, 72%), b.p. 110-115 °C (0.05 Torr) [lit.[141] b.p. 119-121 °C (1.0 Torr) δ_H 7.41-7.20(4H,m); 6.85(2H,t,^3J 2.1); 6.39(2H,t,^3J 2.2) and 3.41(1H,s) spectrum identical with literature[141]; *m/z* 175(M+,6%), 174(9), 173(17), 44(25) and 40(100).

H.1.b. Preparation of *N*-[2-(Hydroxymethyl)phenyl]pyrrole 458

A mixture of methyl 2-aminobenzoate **454** (3.02 g, 20 mmol), 2,5-dimethoxytetrahydrofuran (1.98 g, 20 mmol) and glacial acetic acid (15ml) in dioxane (30 ml) was heated under reflux for 2 hours. The volatiles were then removed on a rotary evaporator and the residue azeotroped with xylene to remove any remaining acetic acid to give *N*-[2-(carbomethoxy) phenyl]pyrrole **457** (3.65 g, 91%), which was then reduced to the hydroxymethyl compound. Thus, a solution of *N*-[2-(carbomethoxy) phenyl]pyrrole **457** (6.00 g, 30 mmol) in dry ether (100 ml) was added dropwise to an ice cooled suspension of lithium aluminium hydride (1.26 g, 33 mmol) in dry ether (100 ml). The mixture was then heated under reflux for 2 hours. Wet ether (50 ml), then water (50 ml) was then added followed by 1M sodium tartrate (50ml). The solution was filtered and the ether layer

was separated. The aqueous layer was extracted with ether (2 x 50ml) and the combined organic extracts washed with water (3 x 50ml) and dried ($MgSO_4$). The solvent was removed on the rotary evaporator to yield the crude product, which was then purified by bulb to bulb distillation to yield *N*-[2-(hydroxymethyl)phenyl]pyrrole **458** (4.38 g, 85%), b.p. 155-160 °C (0.4 Torr) [lit.[142] b.p. 120 °C (0.2 Torr)] (Found: M+ 173.0846 $C_{11}H_{11}NO$ requires M+ 173.0840); δ_H 7.57-7.53(1H,m); 7.43-7.27(3H,m); 6.86(2H,t,^3J 2.1); 6.34(2H,dd,^3J 2.1); 4.53(2H,s) and 2.07(1H,br) spectrum identical with literature[142]; *m/z* 173(M+,100%), 155(16), 154(32), 144(41), 115(35), 105(25), 89(10), 77(50), 51(24), 50(14) and 39(36).

H.2.a. Preparation of *N*-[2-(Allyloxy)phenyl]pyrrole 460, *N*-[2-(Benzyloxy)phenyl]pyrrole 399, *N*-[2-(Benzyloxy)-4-methylphenyl]pyrrole and *N*-[2-(Allylthio)phenyl]pyrrole 461 - General method

A suspension of potassium carbonate (1.1 equivalents) in DMF (10 ml per gram) was stirred for 10 minutes. The appropriate *N*-arylpyrrole (1 equivalent) and the appropriate alkyl bromide (1.1 equivalents) were added and the mixture stirred until t.l.c. showed the disappearance of the *N*-arylpyrrole. Water (2ml per ml DMF) was added and the mixture was extracted with ether [3 x (volume of water/3)]. The combined extracts were washed with water [3 x (volume of ether x 2/3)] and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to yield the crude product which was purified by bulb to bulb distillation.

N-(2-Hydroxyphenyl)pyrrole **422** (2.64 g, 16.6 mmol) with allyl bromide (2.41 g, 19.9 mmol) gave N-*[2-(allyloxy)phenyl]pyrrole* **460** (2.74 g,

83%), b.p. 110-115 °C (0.005 Torr) (Found: C, 78.6; H, 6.75; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.05 %); δ_H 7.42-7.27 (2H,m), 7.16 (2H,t,^3J 2.2), 7.13-7.05(2H,m), 6.43 (2H,dd,^3J 2.3), 6.05 (1H,m), 5.40 (2H,m) and 4.61 (2H,m); δ_C 151.50(q), 132.78, 130.69(q), 127.19, 125.62, 122.00, 121.29, 117.32, 114.19, 108.77 and 69.44; *m/z* 199(M+,58%), 198(19), 184(12), 172(14), 170(14), 159(14), 158(100), 132(11), 130(12), 103(14), 80(10), 77(27), 51(17), 41(17) and 39(29).

N-(2-Hydroxyphenyl)pyrrole **422** (0.80 g, 50 mmol) with benzyl bromide (1.03 g, 55 mmol) gave N-*[2-(benzyloxy)phenyl]pyrrole* **399** (1.05 g, 85%), b.p. 160-165 °C (0.005 Torr) (Found C, 82.0; H, 6.2; N, 5.65. $C_{17}H_{15}NO$ requires C, 81.9; H 6.05; N, 5.6 %); δ_H 7.42-7.05 (9H,m), 7.15 (2H,dd,^3J 2.0), 6.42 (2H,dd,^3J 2.2) and 5.13(2H,s); δ_C 151.62(q), 136.54(q), 130.95(q), 128.38, 127.69, 127.18, 126.85, 125.69, 121.97, 121.46, 114.71, 108.70 and 70.81; *m/z* 249(M+,15%), 172(20), 158(42), 91(100), 77(23), 65(28), 63(12), 51(22) and 39(26).

N-(2-Hydroxy-4-methylphenyl)pyrrole (0.86 g, 50 mmol) with benzyl bromide (1.03 g, 55 mmol) gave N-*[2-(Benzyloxy)-4-methylphenyl]pyrrole* (1.21 g, 92%), b.p. 158-160 °C (0.05 Torr) (Found: C, 82.1; H, 6.6; N, 5.3. $C_{18}H_{17}NO$ requires C, 82.10; H, 6.5; N, 5.3 %); δ_H 7.49-7.35(5H,m); 7.29(1H,d,^3J 7.9); 7.12(2H,t,^3J 2.2); 6.98-6.89(2H,m); 6.41(2H,t,^3J 2.2); 5.12(2H,s) and 2.44(3H,s); δ_C 151.49(q), 137.44(q), 136.70(q), 128.42, 127.70, 126.89, 125.54, 122.04, 115.41, 108.58, 70.75 and 21.30 two CH coincident and one quaternary not apparent; *m/z* 263(M+,35%), 186(36), 173(15), 172(100), 115(10), 91(91), 65(17), 51(11) and 39(17).

N-(2-Mercaptophenyl)pyrrole **456** (2.00 g, 11.4 mmol) gave N-*[2-(allyl thio)phenyl]pyrrole* **400** (2.46 g, 100%), b.p. 118-120 °C (0.03 Torr) (Found C, 72.3; H, 6.2; N, 6.35. $C_{13}H_{13}NS$ requires C, 72.5; H, 6.1; 6.5 %) δ_H 7.47-7.26(4H,m), 6.91(2H,t,^3J 2.2), 6.36(2H,t,^3J 2.2), 5.84-5.68(1H,m), 5.17-5.03(2H,m) and 3.35-3.30(2H,m); δ_C 133.00, 132.78(q), 130.06, 127.50, 126.91, 126.53, 121.98, 117.87, 108.96, 108.80(q) and 35.86; *m/z* 215(M+,8%), 175(16), 174(100), 173(20), 45(9), 41(8) and 39(18).

H.2.b. Preparation of *N*-[2-(allylamino)phenyl]pyrrole 461

N-(2-Aminophenyl)pyrrole **459** (3.95 g, 25 mmol) was alkylated with allyl bromide (3.03 g, 25 mmol) as in Section H.2.a., giving a mixture of starting material, mono- and di-allylated products. These were separated by chromatography on 6% deactivated alumina using hexane as eluent. The crude product was then purified by bulb to bulb distillation to give N-*[2-(allylamino)phenyl]pyrrole* **461** (2.11 g, 43%), b.p. 145-150 °C (0.1 Torr) (Found: M+ 198.1153. $C_{13}H_{14}N_2$ requires M+ 198.1157); δ_H 7.43-7.28(2H,m); 6.98(2H,t,^3J 2.0); 6.92-6.86(2H,m); 6.53(2H,t,^3J 2.0); 6.08-5.95(1H,m); 5.41-5.26(2H,m); 4.16(1H,br) and 3.87(2H,m); δ_C 143.56(q), 134.94, 128.88, 127.30(q), 127.13, 121.90, 116.64, 116.00, 111.46, 109.55 and 45.86; *m/z* 198(M+,100%), 197(52), 183(17), 171(24), 169(39), 157(35), 156(26), 155(12), 131(12), 130(15), 118(11), 77(20), 51(15) and 41(12).

H.2.c. Preparation of Bis-[2-(pyrrol-1-yl)benzyl] oxalate 462

A solution of *N*-[2-(hydroxymethyl)phenyl]pyrrole **458** (4.00 g, 23 mmol) and triethylamine (3.03 g, 30 mmol) in dry ether (200 ml) was prepared. The solution was cooled in ice and a solution of oxalyl chloride (1.51 g, 11.5 mmol) in dry ether (20 ml) was added dropwise. The mixture was then stirred for 2 hours. Water (100 ml) was added and the mixture was extracted with methylene chloride (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed on a rotary evaporator. This gave the crude product which was recrystallised from ethanol to yield *bis-[2-(pyrrol-1-yl)benzyl] oxalate* **462** (3.51 g, 75%), m.p. 153-155 °C (ethanol) (Found: C, 71.8; H, 4.95: N, 7.0. $C_{24}H_{20}N_2O_4$ requires C, 72.0; H, 5.05; N, 7.0 %); δ_H 7.57-7.31(8H,m); 6.84(4H,dd,^3J 2.1); 6.30(4H,t,^3J 2.1) and 5.15(4H,s); δ_C 184.31(q), 156.83(q), 140.90(q), 130.70, 129.78, 127.77, 126.92, 122.43, 109.50 and 64.44; *m/z* 400(M+,7%), 399(20), 172(22), 157(16), 156(100), 155(55), 154(35), 129(11) and 128(12).

H.3. Pyrolysis of *N*-[2-(Allyloxy)phenyl]pyrrole 460, *N*-[2-(Benzyloxy)phenyl]pyrrole 399, *N*-[2-(Benzyloxy)-4-methylphenyl]pyrrole, *N*-[2-(Allylamino)phenyl]pyrrole 461, Bis-[2-(pyrrol-1-yl)benzyl] oxalate 462 and *N*-[2-(allylthio)phenyl]pyrrole 400

N-[2-(Allyloxy)phenyl]pyrrole **460** (0.200 g, 1 mmol), (T_f 650 °C, T_i 80-100 °C, P 0.005 Torr, t 10 min) gave a mixture of products. The crude pyrolysate was washed from the trap with methylene chloride and extracted with 1M sodium hydrogen carbonate. The basic fraction was then acidified with 2M hydrochloric acid and extracted with ether. The acidic products

were then separated by dry-flash chromatography. This gave *N*-[2-(hydroxy)phenyl]pyrrole **422** (0.076 g, 48%) b.p. 145-150 °C (0.05 Torr), identified by comparison of NMR spectra and *2-[(2-hydroxy)phenyl]pyrrole* **472** (0.025 g, 16 %) b.p. 140-145 °C (0.05 Torr) (Found: M+ 159.0686. $C_{10}H_9NO$ requires M+ 159.0684) δ_H 9.63 (1H,br); 7.56 (1H,dd); 7.12-6.80 (4H,m); 6.63 (1H,m) and 6.33 (1H,m) OH or NH not apparent; δ_C 151.06(q), 128.96(q), 126.92, 126.80, 121.12, 119.58(q), 118.25, 116.19, 108.96 and 105.94; *m/z* 159(M+,100%), 158(11), 131(49), 130(73), 104(13), 103(21), 102(11), 78(10), 77(30), 51(71) and 39(15) This compound has been previously reported.[143]

N-[2-(Benzyloxy)phenyl]pyrrole **399** (0.553 g, 2 mmol), (T_f 750 °C, T_i 140-160 °C, P 0.005 Torr, t 10 min) also gave a mixture of products. The crude pyrolysate was similarly washed from the trap with methylene chloride and extracted with 1M sodium hydrogen carbonate. The basic fraction was then acidified with 2M hydrochloric acid and extracted with ether. The acidic products were then separated by dry-flash chromatography. This gave *N*-[2-(hydroxy)phenyl]pyrrole **422** (0.040 g, 11%), 2-[(2-hydroxy)phenyl]pyrrole **472** (0.071 g, 20 %), b.p. 150-155 °C (0.1 Torr) (Found: M+ 159.0686. $C_{10}H_9NO$ requires M+ 159.0684) δ_H 9.43 (1H,br); 7.55 (1H,dd); 7.13-6.79 (4H,m); 6.62 (1H,m); 6.38 (1H,m) and 5.56 (1H,br) spectum identical to compound reported above; *m/z* 159(M+,100%), 158(15), 131(55), 130(76), 104(17), 103(25), 102(16), 77(30), and 51(71); and *3-2-(hydroxy)phenyl]pyrrole* **473** (0.035 g, 10 %), b.p. 155-160 °C (0.1 Torr) (Found: 159.0684. $C_{10}H_9NO$ requires M+ 159.0684); δ_H 8.50(1H,br); 7.63-6.89(6H,m) and 6.44(1H,m); δ_C 152.64(q), 129.25, 127.53, 122.59(q), 120.42, 119.43(q), 119.24, 116.34, 115.16 and 108.25; *m/z* 159(M+,79%), 131(38), 130(57), 103(37), 102(32), 86(31), 84(43), 77(100), 65(33), 63(62), 51(86) and 39(65) This compound has been previously reported.[143]

N-[2-(Benzyloxy)-4-methylphenyl]pyrrole (0.085 g, 0.32 mmol), (T_f 750 °C, T_i 140-160 °C, P 0.005 mbar, t 20 min) gave a mixture of products by ^1H NMR. GC-MS showed 6 peaks, none of which corresponded with the anticipated cyclisation product. No attempt was made to separate these although methyl signals for two major and one minor products could be seen.

N-[2-(Allylamino)phenyl]pyrrole **461** (0.511 g, 2.58 mmol), (T_f 750 °C, T_i 60-80 °C, P 0.005 Torr, t 10 min) gave a mixture of products. These were separated by chromatography on 6% deactivated alumina to give *N*-(2-aminophenyl)pyrrole **459** (0.065 g, 16%), m.p. 92-94 °C (Found: M+ 158.0843. $C_{10}H_{10}N_2$ requires M+ 158.0844); δ_H 7.20-7.12(2H,m); 6.84-6.75(4H,m); 6.35(2H,t,^3J 2.1) and 3.62(2H,br); *m/z* 158(M+,100%), 157(91), 156(13), 131(16), 130(35), 65(14), 40(11) and 39(12) and *2-[2-aminophenyl]pyrrole* **475** (0.030 g, 7%), m.p. 121-126 °C (Found: M+ 158.0843 $C_{10}H_{10}N_2$ requires M+ 158.0844) δ_H 8.70(1H,br); 7.26-7.22(1H,m); 7.13-7.04(1H,m); 6.88-6.74(3H,m); 6.44-6.41(1H,m); 6.34-6.30(1H,m) and 4.80(2H,br); δ_C 143.23(q), 129.45(q), 128.32, 127.69, 119.60(q), 118.96, 117.87, 116.35, 109.21 and 107.21; *m/z* 158(M+,100%), 157(29), 131(14), 130(81), 103(11), 77(17) and 39(11). The major product which appeared on the ^1H NMR of the crude mixture could not be isolated.

Bis-[2-(pyrrol-1-yl)benzyl] oxalate **462** (0.50 g, 1.25 mmol), (T_f 750 °C, T_i 160-180 °C, P 0.005 Torr, t 20 min) gave 9*H*-pyrrolo[1,2-*a*]indole **84**. The crude product was washed from the trap with methylene chloride and purified by bulb to bulb distillation (0.33 g, 85%), b.p. 60-65 °C (0.3 Torr), m.p. 89-91 °C (from ethanol) [lit.[108] b.p. 60-65 °C (0.2 Torr), m.p. 90-91 °C] (Found: M+ 155.0731 $C_{11}H_9N$ requires M+ 155.0735); δ_H 7.41-7.24(3H,m);

7.13-7.04(2H,m); 6.39(1H,t,^3J 3.0); 6.12(1H,m) and 3.84(2H,d,^4J 0.4); δ_C 141.06(q), 135.37(q), 134.84(q), 127.29, 125.73, 122.94, 113.01, 109.61, 101.57 and 28.92 two CH's coincident (δ 109.61); *m/z* 155(M+,81%), 154(100), 153(10), 127(12), 77(15) and 40(15).

N-[2-(allylthio)phenyl]pyrrole **400** (2.12 g, 9.87 mmol), (T_f 650 °C, T_i 100 °C, P 0.005 mbar, t 20 min) gave pyrrolo[2,1-*b*]benzothiophene **82**. The product was isolated by a similar work up as the previous example (1.47 g, 87%), b.p. 90-100 °C (0.05 Torr) m.p. 51-55 °C (from hexane/ethyl acetate) (lit.[115] 52 °C) (Found: C, 69.0; H, 4.2; N, 8.1. $C_{10}H_7NS$ requires C, 69.35; H, 4.05; N, 8.1 %); δ_H 7.61-7.16(4H,m), 7.45(1H,dd,^3J 2.9 and 1.3), 6.61(1H,dd,^3J 3.6 and 2.9) and 6.24(1H,dd,^3J 3.6 and 1.2); δ_C 134.42(q), 131.40(q), 127.49, 125.23, 123.67, 123.44, 114.57, 111.46, 110.08 and 98.62; *m/z* 173(M+,100%) and 39(34).

H.4. Preparation of 2-(2-Hydroxyphenyl)pyrrole 472 and 3-(2-Hydroxyphenyl)pyrrole 473

N-(2-Hydroxyphenyl)pyrrole **422** (0.495g, 3.1 mmol), (T_f 900 °C, T_i 80-100 °C, P 0.005 mbar, t 30 min) gave a mixture of three products which were separated by dry-flash chromatography to give *N*-(2-hydroxyphenyl)pyrrole **422** (0.042 g, 8%), 2-(2-hydroxyphenyl)pyrrole **472** (0.034 g, 7%) δ_H 9.54(1H,br), 7.56(1H,dd), 7.12-6.80(4H,m), 6.60(1H,m) and 6.34(1H,m) OH or NH not observed; *m/z* 159(M+,93%), 131(55), 130(100), 104(20), 103(28), 102(15), 78(14), 77(42) and 76(11) and 3-(2-hydroxyphenyl)pyrrole **473** (0.069g, 14%) δ_H 9.54(1H,br), 7.38-6.88(6H,m), 6.45(1H,m) and 5.40(1H,br); *m/z* 159(M+,100%), 131(36), 130(41), 103(13) and 77(16).

H.5. Reactions of Pyrrolo[2,1-*b*]benzothiophene 82

H.5.a. Formylation of Pyrrolo[2,1-*b*]benzothiophene 82

Phosphoryl chloride (2 ml) was dissolved in DMF (20 ml). A solution of pyrrolo[2,1-*b*]benzothiophene **82** (0.173 g, 1 mmol) in DMF (10 ml), was added dropwise. The mixture was stirred until t.l.c. showed the disappearance of the starting material and the appearance of two products of lower R_f value. The reaction mixture was neutralised with 2M sodium hydroxide, extracted with ether (3 x 25 ml), and the combined organic fractions were washed with water (3 x 50 ml) and dried ($MgSO_4$). The crude products were then pre-adsorbed onto silica and separated by dry-flash chromatography. This gave two products, 1-formylpyrrolo[2,1-*b*] benzothiophene **492** (0.010 g, 7%), m.p. 127-130 °C (lit.[114] 132-132.5 °C) (Found: M+ 201.0243. $C_{11}H_7NOS$ requires M+ 201.0248); δ_H 9.48(1H,s); 9.33(1H,d,^3J 8.1); 7.63(1H,dd,^3J 7.7, ^4J 0.9); 7.51-7.30(2H,m); 7.35(1H,d,^3J 4.4) and 6.47(1H,d,^3J 4.4); δ_C 175.15(q), 140.86(q), 135.72(q), 131.73, 130.65(q), 128.75(q), 126.00, 124.95, 122.89, 118.18 and 102.24; *m/z* 201(M+,100%), 200(67), 173(18), 172(32), 145(13), 128(10), 96(10), 82(11), 76(10), 75(11), 74(10), 70(10), 69(42), 63(17) and 50(25) and 3-formylpyrrolo[2,1-*b*]benzothiophene **491** (0.014 g, 7%), m.p. 128-131 °C (lit.[114] 133.5-134 °C) (Found: M+ 201.0248. $C_{11}H_7NOS$ requires M+ 201.0248); δ_H 9.83(1H,s); 7.78-7.68(2H,m); 7.52-7.34(2H,m); 7.46(1H,d,^3J 3.3) and 6.99(1H,d.^3J 3.3); δ_C 183.97(q), 132.95(q), 131.47(q), 126.37, 125.08, 124.28, 116.01(q), 115.64, 113.11, and 112.54, one quaternary not apparent; *m/z* 201(M+,86), 200(100), 192(16) 179(11), 178(34), 172(13), 128(13), 91(14), 87(11), 69(27) and 45(16).

H.5.b. Reaction of Pyrrolo[2,1-*b*]benzothiophene 82 with Dimethyl acetylenedicarboxylate

Pyrrolo[2,1-*b*]benzothiophene **82** (0.173 g, 1 mmol) was dissolved in methylene chloride (10 ml). Dimethyl acetylenedicarboxylate (0.142 g, 0.122 ml, 1 mmol) was added and the mixture was stirred until t.l.c. showed the disappearance of the starting material and the appearance of two products of lower R_f value. The crude products were then pre-adsorbed onto silica and separated by dry-flash chromatography. This gave two products, *Z-methyl [3-carbomethoxy-3-(pyrrolo[2,1-*b*]benzothiophen-1-yl] propenoate* **498** (0.063 g, 20%), b.p. 165-170 °C (0.1 Torr) (Found: M+ 315.0556 $C_{16}H_{13}NO_4S$ requires M+ 315.0565) δ_H 7.60(1H,dd,^3J 2.1 and 0.7); 7.32-7.19(3H,m); 7.11(1H,s); 6.66(1H,d,^3J 3.8); 6.31(1H,d,^3J 3.9); 3.72(3H,s) and 3.58(3H,s); δ_C 166.59(q), 165.25(q), 134.89(q), 134.30(q), 131.41(q), 130.92(q), 128.88, 125.23, 123.71, 123.38, 119.36, 118.52(q), 112.60, 99.36, 53.08 and 51.84; *m/z* 315(M+,100%), 257(17), 256(94), 255(14), 241(16), 198(13), 197(63), 196(21), and 153(10). E-*methyl [3-carbomethoxy-3-(pyrrolo[2,1-*b*]benzothiophen-1-yl]propenoate* **499** (0.103 g, 33%), b.p. 160-165 °C (0.1 Torr) (Found: M+ 315.0556 $C_{16}H_{13}NO_4S$ requires M+ 315.0565) δ_H 7.92(1H,d,^3J 8.0); 7.60(1H,dd,); 7.38-7.25(2H,m); 6.70(1H,d,^3J 4.0); 6.33(1H,d,^3J 4.0); 6.20(1H,s); 3.92(3H,s) and 3.80(3H,s); δ_C 167.17(q), 165.58(q), 138.88, 125.25, 124.14, 123.94, 121.50, 115.66, 114.00, 101.04, 52.83 and 51.88, four quaternaries not apparent: *m/z* 315(M+,100%), 257(17), 256(94), 255(14), 241(16), 198(13), 197(63), 196(21), and 153(10)

H.5.c. Protonation and deuterium exchange reactions of pyrrolo[2,1-*b*]benzothiophene 82

Pyrrolo[2,1-*b*]benzothiophene **82** was dissolved in trifluoroacetic acid. Protonation occured at the 1-position to give δ_H (80MHz) 8.27-7.84(4H,m), 7.50(1H,m), 5.54(2H,m) and 5.25(1H,s).

1-Methylpyrrolo[2,1-*b*]benzothiophene **494** was dissolved in trifluoroacetic acid. Protonation occured at the 1-position to give δ_H (80MHz) 8.20-7.81(4H,m), 7.43(1H,dd), 5.76(1H,q), 5.24(1H,s) and 1.98(3H,d).

Pyrrolo[2,1-*b*]benzothiophene **82** was dissolved in [^{2}H]trifluoroacetic acid. δ_H (80MHz). Exchange took place initially at the 1 position over a period of less than 2 minutes, followed by exchange of another proton over a period of 30-40 minutes.

I. GENERATION OF PHENOXYL, BENZYL AND THIOPHENOXYL FREE RADICALS AND INVESTIGATION OF THEIR INTRAMOLECULAR CYCLISATION REACTION WITH A 2-(2,5-DIMETHYL PYRROL-1-YL) SUBSTITUENT

I.1. Preparation of 2,5-Dimethyl-*N*-(2-hydroxyphenyl)pyrrole 502, 2,5-Dimethyl-*N*-[2-(hydroxymethyl)phenyl]pyrrole 504 and 2,5-Dimethyl-*N*-(2-mercaptophenyl)pyrrole 503 - General method[117]

A solution of the appropriate 2-(substituted)aminophenol (0.02 mol), hexane-2,5-dione (0.02 mol) and acetic acid (1 ml) in benzene (30 ml) was heated under reflux while water was removed by a Dean and Stark trap. The reaction mixture was diluted with ether (1 : 1), washed with 2M hydrochloric acid (25 ml), brine (25 ml), 1M sodium hydrogen carbonate, brine (25 ml) and dried ($MgSO_4$). Removal of the solvent gave the crude product which was purified by bulb to bulb distillation.

2-Aminophenol **452** (3.27 g, 0.03 mol) gave 2,5-dimethyl-*N*-(2-hydroxyphenyl)pyrrole **502** (5.57 g, 99%), b.p. 85-87 °C (0.05 Torr) m.p. 94-95 °C (sublimed) (lit.[144] 95-97 °C) (Found: C, 76.7; H, 7.0; N, 7.55. $C_{12}H_{13}NO$ C, 77.0; H, 6.95; N, 7.8%); δ_H 7.37-7.28(1H,m), 7.13-6.93(3H,m), 5.96(2H,s) and 1.98(6H,s), OH not apparent: δ_C 152.59(q), 129.85, 129.04, 128.96(q), 124.97(q), 120.53, 116.13, 106.61 and 12.14; *m/z* 187(M+,77%), 186(100) and 40(44).

2-Aminobenzyl alcohol **500** (2.46 g, 0.02 mol) gave 2,5-dimethyl-*N*-[2-(hydroxymethyl)phenyl]pyrrole **504** (3.74 g, 93%), m.p. 102-104 °C (from ethanol) (lit.[145] 105-107 °C) (Found: C, 77.6; H, 7.55; N, 6.9. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 6.95%) δ_H 7.62-7.16(4H,m), 5.92(2H,s), 4.29(2H,s) and 1.92(6H,s) OH not apparent; δ_C 139.33(q), 136.74(q), 129.14, 128.90, 128.66, 128.39, 128.26, 128.19, 105.67, 61.03 and 12.40; *m/z* 201(M+,100%), 200(16), 186(23), 182(25), 172(10), 170(11), 168(40), 167(14), 146(35), 105(12), 77(25) and 51(11).

2-Aminothiophenol **453** (2.28 g, 0.02 mol) gave 2,5-dimethyl-*N*-(2-mercaptophenyl)pyrrole **503** (3.14 g, 77%), b.p. 120-125 °C (0.05 Torr) [lit.[146] 100 °C (0.6 Torr) (Found: M+ 203.0777. $C_{12}H_{13}NS$ requires M+ 203.0687) δ_H 7.43-7.21(4H,m), 5.98(2H,s), 2.93(1H,s) and 1.97(6H,s); δ_C 135.78(q), 134.13(q), 129.42, 128.73, 128.52, 127.76, 125.65, 106.27 and 12.24; *m/z* 203(M+,40%), 202(100), 188(20), 187(22), 186(24) and 44(8).

I.2.a. Preparation of 2,5-Dimethyl-*N*-[2-(allyloxy)phenyl]pyrrole 505 and 2,5-Dimethyl-*N*-[2-(allylthio)phenyl]pyrrole 507 - General method

A suspension of potassium carbonate (1.1 equivalents) in DMF (10 ml per gram) was stirred for 10 minutes. The appropriate *N*-arylpyrrole (1 equivalent) and allyl bromide (1.1 equivalents) were added and the mixture was stirred until t.l.c. showed the disappearance of the *N*-aryl pyrrole. Water (2ml per ml DMF) was added and the mixture extracted with ether [3 x (volume of water/3)]. The combined organic extracts were washed with water [3 x (volume of ether x 2/3)] and dried ($MgSO_4$). The

solvent was removed on a rotary evaporator to yield the crude product which was purified by bulb to bulb distillation.

2,5-Dimethyl-*N*-(2-hydroxyphenyl)pyrrole **502** (3.74 g, 0.02 mol) gave *2,5-dimethyl*-N-*[2-(allyloxy)phenyl]pyrrole* **505** (4.05 g, 89%), b.p. 135-140 °C (0.05 Torr) (Found: M+ 227.1319 $C_{15}H_{17}NO$ requires M+ 227.1310); δ_H 7.43(4H,m), 6.04-5.85(1H,m), 5.96(2H,s), 5.34-5.18(2H,m), 4.56-4.51(2H,m) and 2.04(6H,s); δ_C 154.82(q), 132.78, 130.19, 129.07, 128.90(q), 128.13(q), 120.81, 16.94, 113.86, 105.10, 68.90 and 12.49; *m/z* 227(M+,100%), 226(26), 212(29), 200(18), 186(42), 171(15), 170(43) and 156(16).

2,5-Dimethyl-*N*-(2-mercaptophenyl)pyrrole **504** (2.02 g, 0.01 mol) gave *2,5-dimethyl*-N-*[2-(allylthio)phenyl]pyrrole* **507** (1.98 g, 82%), b.p. 135-140 °C (0.01 Torr) (Found:M+ 243.1083. $C_{15}H_{17}NS$ requires M+ 243.1082) δ_H 7.44-7.23(4H,m), 6.05(2H,s), 5.98-5.81(1H,m), 5.36-5.16(2H,m), 3.59-3.56(2H,m) and 2.07(6H,s); δ_C 137.90(q), 137.01(q), 132.97, 129.42, 128.63, 128.23, 126.86, 125.50, 117.99, 105.67, 34.24 and 12.48; *m/z* 243(M+,74%), 228(21), 203(15), 202(100), 200(14), 188(12), 187(43), 186(48).

I.2.b. Preparation of Bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate 506

A solution of 2,5-dimethyl-*N*-[2-(hydroxymethyl)phenyl]pyrrole **503** (2.00 g, 0.01 mol) and triethylamine (1.32 g, 0.013 mol) in dry ether (100 ml) was prepared. The solution was cooled in ice and a solution of oxalyl chloride (0.64 g, 0.005 mol) in dry ether (10 ml) was added dropwise. The mixture was then stirred for 2 hours. Water (100 ml) was added and the mixture extracted with methylene chloride (3 x 50 ml). The combined

extracts were dried ($MgSO_4$) and the solvent removed on a rotary evaporator. This gave the crude product which was recrystallised from ethanol to yield *bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate* **507** (2.18 g, 96%), m.p. 136-140 °C (from ethanol) (Found: C, 73.5; H, 6.2; N, 6.05. $C_{28}H_{28}N_2O_4$ requires C, 73.65; H, 6.2; N, 6.15%) δ_H 7.58-7.45(6H,m), 7.26-7.22(2H,m), 5.89(4H,s), 4.91(4H,s) and 1.90(12H,s) δ_C 156.69(q), 138.05(q), 133.34(q), 129.59, 129.55, 129.34, 128.73, 128.40, 106.02, 63.94 and 12.29; *m/z* 456(M+,18%), 455(55), 200(31), 185(19), 184(100), 183(48), 182(36), 169(15), 168(39), 167(11) and 154(24).

I.3. Pyrolysis of 2,5-Dimethyl-*N*-[2-(allyloxy)phenyl]pyrrole 505, Bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate 506 and 2,5-Dimethyl-*N*-[2-(allylthio)phenyl]pyrrole 507

2,5-Dimethyl-*N*-[2-(allyloxy)phenyl]pyrrole **505** (0.563 g, 2.48 mmol), (T_f 650 °C, T_i 60-80 °C, P 0.001 Torr, t 10 min) gave two major products which were separated by dry-flash chromatography on silica (2% ethyl acetate / hexane) to give *3-methyl-9H-pyrrolo[1,2-a]indole* **520** (0.121 g, 29%), m.p 40-45 °C (Found: M+ 169.0889 $C_{12}H_{11}N$ requires M+ 169.0891) δ_H 7.49-7.07(4H,m), 6.10-6.02(2H,m), 3.84(2H,s) and 2.63(3H,d,^4J 0.9); δ_C 141.96(q), 135.22(q), 134.37(q), 127.13, 125.77, 122.34, 111.22, 110.28, 100.51, 28.64 and 13.06 one quaternary not apparent; *m/z* 169(M+,60%), 168(39), 167(23), 155(14), 154(100), 115(11), 89(13), 55(23), 53(12), 41(33) and 39(25) and recovered 2,5-dimethyl-*N*-(2-hydroxyphenyl)pyrrole **502** (0.162 g, 35%), b.p. 95-100 °C (0.1 Torr) (Found: M+ 187.0996 $C_{12}H_{13}NO$ requires M+ 187.0997); δ_H 7.43-7.31(1H,m), 7.19-6.97(3H,m), 6.00(2H,s) and 2.02(6H,s), OH not apparent: δ_C 152.62(q), 129.90, 129.14, 128.98(q), 124.15(q), 120.59, 116.23,

106.64 and 12.23; *m/z* 187(M+,90%), 186(100), 172(31), 171(18), 170(31), 169(24), 168(16) and 154(30).

Bis-{2-[(2,5-dimethyl)pyrrol-1-yl]benzyl} oxalate **506** (0.620 g, 1 mmol), (T_f 750 °C, T_i 180-200 °C, P 0.005 Torr, t 20 min) gave three products which were separated by dry-flash chromatography on silica (2% ethyl acetate / hexane) to give 3-methyl-9*H*-pyrrolo[1,2-*a*]indole **520** (0.018 g, 41%), m.p. 38-42 °C (Found: M+ 169.0894 $C_{12}H_{11}N$ requires M+ 169.0891) δ_H 7.55-7.06(4H,m); 6.07(1H,m); 6.02(1H,m); 3.85(2H,s) and 2.63(3H,d,^4J 0.8); δ_C 141.92(q), 135.21(q), 134.39(q), 127.15, 125.79, 122.37, 111.19, 110.31, 100.49, 28.67 and 13.12 one quaternary not apparent; *m/z* 169(M+,10%), 168(11), 156(24), 155(89), 154(100), 127(16), 84(13), 78(11), 77(21), 63(10) and 51(10) spectra identical with those in above experiment, *4,5-dihydro-2-methyl-1H-benz[g]indole* **526** (0.034 g, 7%), m.p 115-120 °C (Found: M+ 183.1048. $C_{13}H_{13}N$ requires M+ 183.1048) δ_H 8.06(1H,br), 7.51-6.97(4H,m), 5.82(1H,m), 2.92(2H,dd), 2.70(2H,dd) and 2.33(3H,s); δ_C 134.25(q), 129.46(q), 128.61(q), 128.15, 126.14, 124.28, 120.72(q), 117.58, 106.17, 30.03, 21.83 and 13.19 one quaternary not apparent; *m/z* 183(M+,92%), 182(95), 181(73), 180(53), 169(11), 168(13), 167(100), 166(12), 139(13), 105(16), 90(16) and 83(21) and *4,5-dihydro-2-methyl-3H-benz[e]indole* **527** (0.025 g, 5%), m.p 125-130 °C (Found: M+ 183.1045. $C_{13}H_{13}N$ requires M+ 183.1048) δ_H 7.62(1H,br), 7.33-6.97(4H,m), 6.15(1H,dd), 3.00(2H,dd), 2.75(2H,dd) and 2.29(3H,s); δ_C 133.35(q), 132.66(q), 127.67, 126.99(q), 126.47, 123.89, 121.16, 118.31(q), 101.01, 29.61, 21.63 and 13.01 one quaternary not apparent; *m/z* 183(M+,100%), 182(98), 181(65), 180(52), 169(24), 168(55), 167(75), 92(16), 91(19), 90(19) and 84(29).

2,5-Dimethyl-*N*-[2-(allylthio)phenyl]pyrrole **507** (0.482 g, 0.002 mol), (T_f 750 °C, T_i 80-100 °C, P 0.01 mbar, t 10 min) gave four products which were separated by dry-flash chromatography on silica (2% ethyl acetate / hexane) to give *1-methylpyrrolo[2,1-*b*]benzothiazole* **494** (0.063 g, 17%), (Found: M+ 187.0455. $C_{11}H_9NS$ requires M+ 187.0456) δ_H 7.77-7.14(4H,m), 6.27-6.23(1H,m), 6.12(1H,m) and 2.72(3H,d,^4J 0.9); δ_C 126.26(q), 125.64(q), 124.90, 123.57, 123.24(q), 122.78, 113.25, 112.29, 97.45 and 14.12; *m/z* 187(M+,100%), 186(100), 176(12), 173(30), 115(16), 109(16), 108(13), 94(19), 93(16), *4H*-pyrrolo[2,1-*c*][1,4]benzothiazine **533** (0.089 g, 24%), b.p. 130-135 °C (0.2 Torr) [lit.[121] 116-118 °C (0.05 Torr)] (Found: M+ 187.0454. $C_{11}H_9NS$ required M+ 187.0456) δ_H 7.42-7.03(5H,m), 6.29(1H,t,^3J 3.3), 6.04(1H,m) and 3.93(2H,d,^4J 0.6); δ_C 135.79(q), 129.05, 126.82, 125.87(q), 124.63(q), 124.23, 117.55, 117.15, 109.81, 105.57 and 24.99; *m/z* 187(M+,69%), 186(100) and 154(12), *1,4-dihydrobenzothiopyrano[4,3-*b*]pyrrole* **534** (0.014 g, 3%), (Found: M+ 187.0450. $C_{11}H_9NS$ requires M+ 187.0456) δ_H 8.37(1H,br), 7.34(1H,m), 7.14-6.99(3H,m), 6.70(1H,t,^3J 2.8), 6.09(1H,t,^3J 2.6) and 4.00(2H,s); δ_C 130.26(q), 127.82(q), 127.48, 127.11(q), 125.69, 125.62, 119.81, 118.85, 115.10(q), 107.58 and 25.35; *m/z* 187(M+,67%), 186(100), 93(8), 92(10). and *1,4-dihydrobenzothiopyrano[3,4-b]pyrrole* **535** (0.010 g, 3%), (Found M+ 187.0454. $C_{11}H_9NS$ requires M+ 187.0456) δ_H 7.95(1H,br), 7.47-7.01(4H,m), 6.65(1H,t,^3J 2.8), 6.48(1H,t,^3J 2.8) and 3.90(2H,s); δ_C 131.94(q), 127.91(q), 126.91, 126.00, 125.16, 123.13, 122.37(q), 118.50(q), 117.34, 104.68 and 23.96; *m/z* 187(M+,20%), 186(100), 115(29), 94(16) and 93(11).

J. GENERATION OF PHENOXYL AND THIOPHENOXYL RADICALS AND INVESTIGATION OF THEIR INTRAMOLECULAR CYCLISATION REACTION WITH A 2-(2,5-DIPHENYLPYRROL-1-YL) SUBSTITUENT

J.1. Preparation of 2,5-Diphenyl-*N*-(2-hydroxyphenyl)pyrrole 541 and 2,5-Diphenyl-*N*-(2-mercaptophenyl)pyrrole 542 - General method

A solution of the appropriate 2-(substituted)aminophenol (0.013 mol), 1,2-dibenzoylethane (0.013 mol) and acetic acid (30 ml) in benzene (30 ml) was heated under reflux while water was removed by a Dean and Stark trap until t.l.c. showed the disappearance of the 1,2-dibenzoylethane. The volatiles were removed on a rotary evaporator. The residue was then dissolved in methylene chloride (100 ml) and washed with 1M sodium hydrogen carbonate (3 x 50 ml) and and the organic fraction dried ($MgSO_4$). The solvent was removed to yield the crude product. This was then purified by dry-flash chromatography.

2-Aminophenol **452** (1.42 g, 0.013 mol) gave *2,5-diphenyl*-N-*(2-hydroxyphenyl)pyrrole* **543** (3.90 g, 96%), m.p 177-181 °C (from ethanol) (Found. M+ 311.1316 $C_{22}H_{17}NO$ requires M+ 311.1310) δ_H 8.04(1H,d,^3J 7.0), 7.59-6.77(13H,m), 6.58(2H,s) and 5.32(1H,br); δ_C 136.09(q), 133.04(q), 132.18(q), 129.89, 129.84, 127.97, 127.82, 126.61, 125.74(q), 120.65, 116.28 and 110.45; *m/z* 311(M+,60%), 133(10), 105(100) and 77(32).

2-Aminothiophenol **453** (1.42 g, 0.013 mol) gave *2,5-diphenyl*-N-*(2-mercaptophenyl)pyrrole* **542** (4.16 g, 98%), m.p. 120-124 °C (from ethanol)

(Found: M+ 327.1077. $C_{22}H_{17}NS$ requires M+ 327.1081) δ_H 7.28-7.09(14H,m), 6.59(2H,s) and 3.14(1H,s); δ_C 136.44(q), 135.48(q), 133.42(q), 132.58(q), 130.73, 129.19, 128.62, 127.98, 127.82, 126.38, 125.63 and 110.05; *m/z* 327(M+,97%), 326(24), 325(11), 250(20), 115(18), 77(14) and 44(30).

J.2. Preparation of 2,5-Diphenyl-*N*-[2-(allyloxy)phenyl]pyrrole 543 and 2,5-Diphenyl-*N*-[2-(allylthio)phenyl]pyrrole 544 - General method

A suspension of potassium carbonate (1.1 equivalents) in DMF (10 ml per gram) was stirred for 10 minutes. The appropriate *N*-arylpyrrole (1 equivalent) and allyl bromide (1.1 equivalents) were added and the mixture was stirred until t.l.c. showed the disappearance of the *N*-aryl pyrrole. Water (2ml per ml DMF) was added and the mixture was extracted with ether [3 x (volume of water/3)]. The combined organic extracts were washed with water [3 x (volume of ether x 2/3)] and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to yield the crude product which was purified by bulb to bulb distillation.

2,5-Diphenyl-*N*-(2-hydroxyphenyl)pyrrole **541** (3.11 g, 0.01 mol) gave *2,5-diphenyl-*N*-[2-(allyloxy)phenyl]pyrrole* **543** (3.23 g, 95%), m.p. 106-108 °C (from ethanol) (Found: C, 85.0; H, 6.0; N, 3.95. $C_{25}H_{21}NO$ requires C, 85.45; H, 6.0; N, 4.0 %) δ_H 7.52-7.03(12H,m), 6.87-6.77(2H,m), 6.50(2H,s), 5.51(1H,m), 5.01(2H,m) and 4.16(2H,m); δ_C 154.37(q), 136.10(q), 133.51(q), 132.70, 130.69, 128.92, 128.47(q), 127.99, 127.58, 125.93, 120.48, 116.72, 113.17, 109.10 and 68.64; *m/z* 351(M+,100%), 310(12) and 191(21).

2,5-Diphenyl-*N*-(2-mercaptophenyl)pyrrole **542** (3.27 g, 0.01 mol) gave *2,5-diphenyl*-N-*[2-(allylthio)phenyl]pyrrole* **544** (3.52 g, 96%), m.p. 120-122 °C (from ethanol) (Found. C, 81.3; H, 5.6; N, 3.65. $C_{25}H_{21}NS$ requires C, 81.7; H, 5.75; N, 3.8 %) δ_H 7.27-7.05(14H,m), 6.56(2H,s), 5.63-5.50(1H,m), 5.02-4.93(2H,m) and 3.29(2H,m); δ_C 137.50(q), 137.05(q), 135.87, 133.01, 132.69, 130.74(q), 130.48, 128.64(q), 128.32, 128.11, 127.65, 126.07, 125.36, 117.68, 109.48 and 67.99; *m/z* 367(M+,100%), 327(17), 326(72), 223(15), 119(40), 115(11) and 40(12).

J.3. Pyrolysis of *N*-[2-(allyloxy)phenyl]pyrrole 543 and *N*-[2-(allylthio)phenyl]pyrrole 544

2,5-Diphenyl-*N*-[2-(allyloxy)phenyl]pyrrole **543** (0.540 g, 1.54 mmol), (T_f 650 °C, T_i 160-180 °C, P 0.01 Torr, t 20 min) gave one major product which was purified by dry-flash chromatography on silica (2% ethyl acetate / hexane) to give *3-phenylpyrrolo[1,2-f]phenanthridine* **552** (0.27 g, 60%) m.p 85-90 °C (Found: M+ 293.1211 $C_{22}H_{15}N$ requires M+ 293.1204) δ_H 8.34-8.24(2H,m), 8.06(1H,m), 7.56-7.10(10H,m), 7.07(1H,d,^3J 3.9) and 6.68(1H,d,^3J 3.9); δ_C 135.50(q), 133.84(q), 133.40(q), 131.33(q), 128.76, 128.44, 127.98, 127.24, 126.90, 126.56(q), 125.76, 125.13(q), 123.78, 123.44, 122.93(q), 122.48, 122.20, 118.85, 115.97 and 102.01; *m/z* 293(M+,100%), 292(19), 291(38) and 146(23).

2,5-Diphenyl-*N*-[2-(allylthio)phenyl]pyrrole **544** (0.98 g, 2.67 mmol), (T_f 750 °C, T_i 750 °C, P 0.01 mbar, t 40 min) gave a mixture of products, of which nine fractions were separated by dry-flash chromatography (hexane). From this six products were identified. Dibenzothiophene **553** (0.046 g, 9%) m.p 95-98 °C (lit.[37] 98-100 °C) δ_H 8.22-8.14(2H,m), 7.94-7.85(2H,m) and 7.53-

7.46(4H,m); δ_C 139.32(q), 135.43(q), 126.60, 124.25, 122.71 and 121.48; *m/z* 184 (M+,100%), 139(22), 92(38) and 79(19), *1-phenylpyrrolo[2,1-*b*]benzothiazole* **554** (0.033 g, 5%) m.p 110-113 °C (Found: M+ 249.0612 $C_{16}H_{11}NS$ requires M+ 249.0612) δ_H 7.60-7.09(9H,m), 6.52(1H,d,^3J 3.6) and 6.32(1H,d,^3J 3.6); δ_C 135.09(q), 132.79(q), 131.73(q), 129.33, 128.53(q), 128.26, 127.55, 124.62, 123.56, 123.16, 115.66, 113.46 and 99.00; *m/z* 249(M+,59%), 248(100), 125(18), 124(30) and 115(30), *1-phenyldibenzo*[b,f]*pyrrolo*[*1,2-*d]*-1,4--thiazepine* **555** (0.038 g, 4%) m.p 89-93 °C (Found: M+1+ 326.1003 $C_{22}H_{15}NS$ requires M+1+ 326.1003) δ_H 8.34-8.24(2H,m), 8.07(1H,dd), 7.57-7.11(10H,m), 7.08(1H,d,^3J 3.9) and 6.69(1H,d,^3J 3.9); δ_C 135.54(q), 133.89(q), 131.47(q), 131.38(q), 128.82, 128.50, 128.05, 127.31, 126.98, 126.62(q), 125.83, 125.19(q), 123.85, 123.52, 122.98(q), 122.54, 122.27, 118.92, 115.94 and 102.04; *m/z* (F.A.B.) 326(M+1+,100%), 325(100), 294(38) and 293(35), *4-(5-phenylpyrrol-2-yl)dibenzothiophene* **556** (0.210 g, 24%) m.p 115-118 °C (Found: M+ 325.0911 $C_{22}H_{15}NS$ requires M+ 325.0925) δ_H 8.68(1H,br), 7.88(2H,m), 7.55-7.22(10H,m), 6.78(1H,m) and 6.49(1H,m); δ_C 140.01(q), 139.50(q), 135.22(q), 133.86(q), 132.51(q), 132.42(q), 131.49(q), 130.16(q), 128.90, 128.12, 127.99, 127.72, 126.46, 126.21, 125.92, 125.75(q), 124.37, 124.30, 123.64, 122.56, 109.88 and 107.05; *m/z* 325(M+,100%), 323(23), 220(11) and 163(13), mixture containing 2-phenylpyrrole **558** (0.043 g, max 11%) (Found: M+ 143.0735 $C_{10}H_9N$ requires M+ 143.0735) δ_H 8.43(1H,br), 7.90-7.15(5H,m), 6.83(1H,m), 6.56(1H,m) and 6.33(1H,m); *m/z* 143(M+,100%), and 116(16) and 115(47), *2-phenyl-1*H-*dibenzo[2,3:6,7]thiepino[4,5-*b*]pyrrole* **559** (0.163 g, 19%) m.p 124-127 °C δ_H 9.15(1H,br), 8.69(2H,m), 8.26(1H,d), 8.04(1H,d) and 7.77-7.33(10H,m); δ_C 135.43(q), 132.30(q), 129.27(q), 128.94, 128.27(q), 127.08, 126.71, 126.47, 126.02(q), 124.60, 124.15, 123.90, 123.67(q), 123.34, 123.27, 122.79(q), 122.10(q), 119.61 and 100.37 2 CHs not apparent; *m/z* (F.A.B.) 326(M+1+,8%), ,306(17), 294(100) and 293(97) and *1-phenyl-2*H-*dibenzo[2,3:6,7]thiepino[4,5-c]pyrrole* **601**

(0.29 g, 3%) m.p 130-135 °C δ_H 9.11(1H,br), 8.73-8.65(2H,m), 8.12(1H,dd), 7.94(1H,m), 7.65-7.32(9H,m) and 7.10(1H,d,^3J 2.6); δ_C 137.02(q), 130.05, 128.88(q), 128.23, 126.72, 126.50, 126.16, 124.66, 123.76 (2 x CHs), 123.33, 122.93(q), 122.21(q), 120.97 and 119.50 (1 CH and 4 quaternaries not assigned); *m/z* 292(M+,2%), 205(6), 143(7), 98(5), 97(7), 94(27), 86(81), 84(29) and 83(34).

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Reprinted from

J. Chem. Soc., Chemical Communications

Issue 11 1993

oxylic Esters as Radical Leaving Groups: a New and Efficient Gas-phase Synthesis of zofurans

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Carboxylic Esters as Radical Leaving Groups: a New and Efficient Gas-phase Synthesis of Benzofurans

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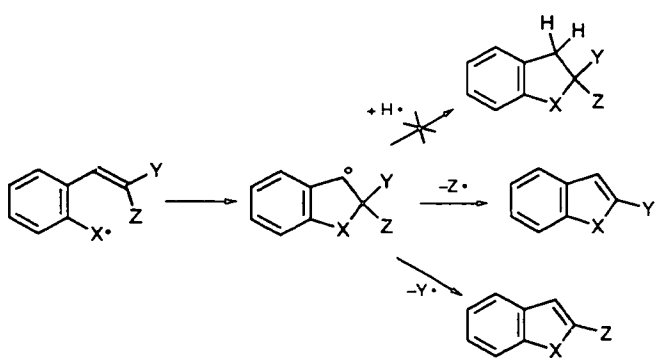
Flash vacuum pyrolysis (FVP) of *o*-allyloxycinnamate esters gives benzofurans in high yield, *via* cyclisation of a phenoxyl radical and subsequent cleavage of the carboxylic ester function; coumarins are obtained by FVP of the corresponding phenols.

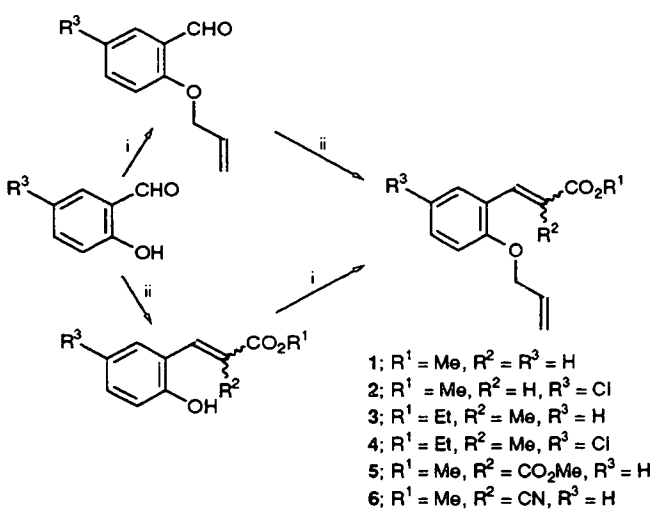
Intramolecular free-radical attack on aromatic systems under flash vacuum pyrolysis (FVP) conditions usually leads to oxidative cyclisation, in which regeneration of the benzenoid system provides the driving force for the final elimination.[1] In seeking to extend these ideas to alkene systems for which this driving force is diminished (Scheme 1) we required an efficient radical leaving group (Z) to compensate and also to ensure selectivity. We now report that the carboxylic ester function (Z = CO_2R) fulfils these criteria, and show how the methodology can be applied to a simple, versatile, and efficient synthesis of the benzofuran ring system.

The radical precursors **1–8** were easily made in two steps from salicylaldehyde derivatives, by sequential Wittig reaction (or Knoevenagel condensation) and *O*-allylation‡ (Scheme 2). These steps could be carried out in either order, and overall yields were often in excess of 80%. Because of the low reactivity of 2-hydroxyacetophenone, the precursor **9** was made by Wadsworth–Emmons reaction of the 2-benzyloxy derivative.

Flash vacuum pyrolysis of the phenoxyl radical precursors **1–9** at 650 °C (10^{-2} to 10^{-3} Torr) gave the benzofurans **10–18** respectively as the major product in each case (Table 1). Yields are generally in the range 60–90% and chromatography is not normally required in the workup. The loss of the carboxylic ester function (CO_2R^1) on cyclisation takes place quantitatively and with total specificity (Scheme 3) even in potentially competitive situations[1] [*e.g.* formation of **12**, **13** and **17** where no cleavage of methyl radicals (R^2) was observed]. In addition, there are no complications of hydrogen transfer and rearrangement processes in this series, which often limit the synthetic potential of phenoxyl radicals in the gas phase.[2] Thus, no hydrogen-transfer products were detected from the methyl-substituted precursors **3**, **4** and **9**, and the regiospecific formation of the 2,5-disubstituted

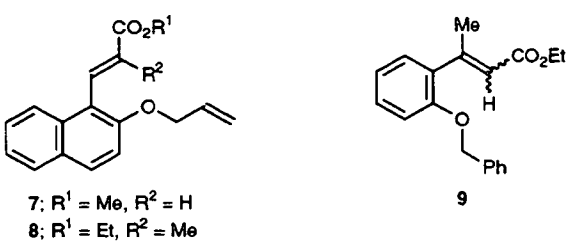


Scheme 1



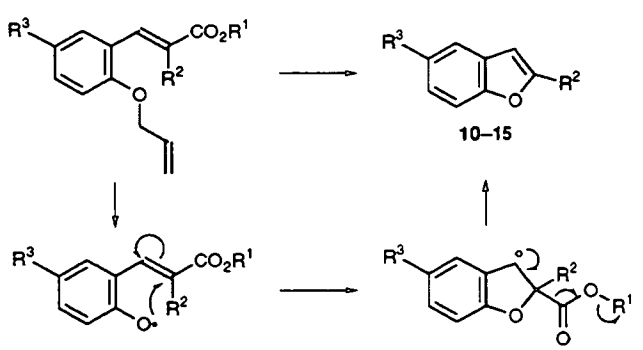
1; R^1 = Me, R^2 = R^3 = H
2; R^1 = Me, R^2 = H, R^3 = Cl
3; R^1 = Et, R^2 = Me, R^3 = H
4; R^1 = Et, R^2 = Me, R^3 = Cl
5; R^1 = Me, R^2 = CO_2Me, R^3 = H
6; R^1 = Me, R^2 = CN, R^3 = H

Scheme 2 *Reagents*: i, CH_2=$CHCH_2Br$, K_2CO_3, dimethylformamide; ii, Ph_3P=$C(R^2)CO_2R^1$, CH_2Cl_2 or $R^2CH_2CO_2Me$



7; R^1 = Me, R^2 = H
8; R^1 = Et, R^2 = Me

9



10–15

Scheme 3

Table 1 Yields of benzofurans **10–18** obtained by pyrolysis

Precursor	Product	R^2	R^3	Yield (%)
1	**10**	H	H	68
2	**11**	H	Cl	60
3	**12**	Me	H	75
4	**13**	Me	Cl	85
5	**14**	CO_2Me	H	95
6	**15**	CN	H	52
7	**16**			39
8	**17**			88
9	**18**			67

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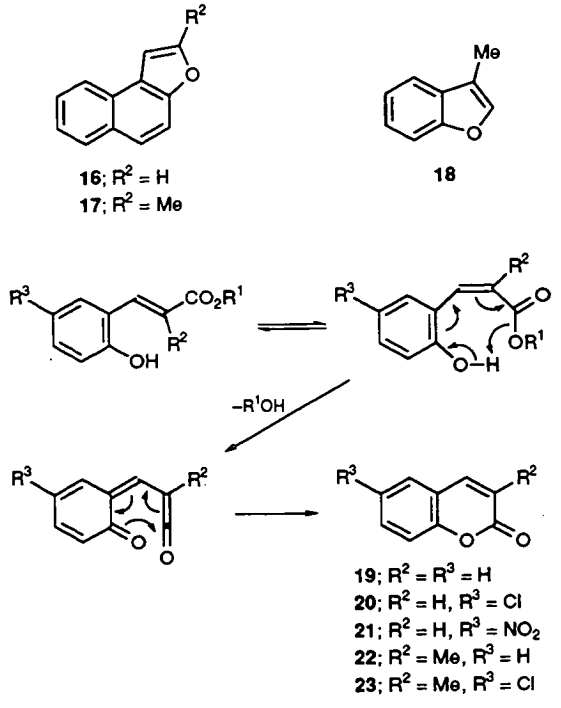
‡ All new compounds were characterised by their spectra and by elemental analysis (solids) or accurate mass measurement (liquids).



Scheme 4

product **13** confirms the absence of spiro-type rearrangements. From a synthetic point of view, the pyrolysis conditions are sufficiently mild to be compatible with most functional groups (R^3 *etc.*), and the method provides a simple, three-step route to benzofurans from salicylaldehydes, which complements our earlier gas-phase synthesis of dibenzofurans.[3]

In cases where the lower yields are obtained, coumarins are major by-products, and these may be formed by alcohol (R^1OH) elimination from the parent phenol (Scheme 4). Indeed we have found tht FVP of these compounds at 750 °C is a particularly facile means of accomplishing this transformation which avoids the use of high-boiling solvents.[4] Yields of the coumarins **19–23** were in the range 75–96%.

We are grateful to British Petroleum International Limited for Research Studentships (to M. B., G. A. C. and A. D. M.).

Received, 9th March 1993; Com. 3/01395B

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