University of St. Andrews

Oxime Oxalate Amides as Tin Free Precursors for the Radical Mediated Synthesis of Lactams

A thesis presented by Eoin M. Scanlan to the University of St. Andrews in application for the degree of Doctor of Philosophy

December 2003

Declarations

I, Eoin Martin Scanlan hereby certify that this thesis has been composed by myself, that it is a record of my own work and that it has not been accepted in partial or complete fulfilment of any other degrees or professional qualification

Signed Date 10/12/2003

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on 1st October 2000 and as a candidate for the degree of PhD. On 1st October 2001.

Signed Date 10/12/2003

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the degree of PhD.

Signed Date 10 Dec 2003

Declaration

In submitting this thesis to the University of St. Andrews, I understand that I am giving permission for it to be made available in accordance with the regulations of the University library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and abstract will be published and that a copy of the work may also be made and supplied to any *bona fide* library or research worker.

Table of Contents

Acknowledgements

Many people have provided me with assistance and guidance over the course of the last three years. First and foremost I wish to express my sincere gratitude to my supervisor Prof. Walton for giving me the opportunity to carry out my PhD studies here in St. Andrews. Without his support this PhD would not have been possible.

I would also like to thank the people I have worked with over the last three years. These are the people whose presence added a unique personality to lab 410. They are Leon Jackson, Patricia Minin, Franco Bella, Mark Roydhouse and James Lymor.

I would also like to express my gratitude to all my friends and colleges in St. Andrews. In particular I would like to thank my closest friends Steve and "Tiny" and all the people of Gannochy House and The Chimes for putting up with me!!

My final acknowledgement goes to my parents and my brother for all the support and encouragement that they have shown me over the last three years.

Abbreviations and Symbols

AIBN	2,2-Azobisisobutyronitrile
bp	Boiling point
DCM	Dichloromethane
DMSO	Dimethyl sulfoxide
DMF	Dimethyl formamide
EPR	Electron Paramagnetic Resonance
ESR	Electron Spin Resonance
Ether	Diethyl ether
GC/MS	Gas chromatography/Mass Spectroscopy
GHz	Gigahertz
hfs	Hyperfine splitting
mp	Melting Point
MHz	Megahertz
M eq	Molar equivalent
NMR	Nuclear Magnetic Resonance
OOA	Oxime oxalate amide
PMAP	*Para*-methoxy acetophenone
s, d, t, q	singlet, doublet, triplet, quartet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
UV	Ultra violet

Abstract

A summary of the use of radicals in organic synthesis and in particular the preparation of azetidinone rings is provided. This is followed by four chapters describing our efforts to develop new clean free radical precursors and to apply them to the preparation of useful organic molecules. The kinetics of 4-*exo* ring closure is also examined.

A general synthetic route to oxime oxalate amides was developed and applied to the preparation of molecules incorporating suitably unsaturated side chains. It was demonstrated by ESR spectroscopy that the oxime oxalate amides dissociated to give the corresponding iminyl and carbamoyl radicals when photolysed with 4-methoxyacetophenone as a photosensitizer.

Carbamoyl radicals derived from *N*-alk-3-enyl oxime oxalate amides underwent ring closure to afford pyrrolidine-2-ones. The analogous *N*-alkyl-2-enyl precursors afforded azetidin-2-ones. Reactions of the cyclohexenyl and cinnamyl oxime oxalate amides afforded a bicyclic β-lactam and a 3-benzyl-substituted β-lactam respectively. Both products were isolated as hydroxylated compounds. The kinetics of cyclisation onto an oxime ether was also examined.

Oxime oxalate amides incorporating a thiazolidine ring with an unsaturated group at the C-2, position were also prepared. These were expected to undergo 4-*exo* cyclisation to give penicillins and GC-MS evidence indicated that some penicillin may have been formed.

Dioxime oxalates were also investigated as precursors for iminyl radicals. The precursors were examined by ESR spectroscopy and precursors were designed which could undergo 5-*exo* cyclisation to give the corresponding pyrroles.

Chapter 1.

Introduction

1.1 Radicals in Organic Synthesis

Radical chemistry dates back to 1900 when Gomberg[1] investigated the formation and the reactions of the triphenylmethyl radical. Organic synthesis using free radicals dates back to 1937 when Hay and Waters[2] described the phenylation of aromatic compounds by benzoyl peroxide as a radical precursor.

The last two decades have seen huge advances in the role of radical chemistry in organic synthesis and a number of books and reviews have been published on the topic.[3,4,5-7] These reactions involve the homolytic cleavage of covalent bonds with the production of highly reactive intermediates which possess an unpaired electron.

The high level of interest in radical chemistry in organic synthesis results from the fact that radical based synthetic methods usually involve neutral conditions and also that the reactive species seldom attack functional groups, therefore allowing key steps to be carried out without the need for protecting groups.

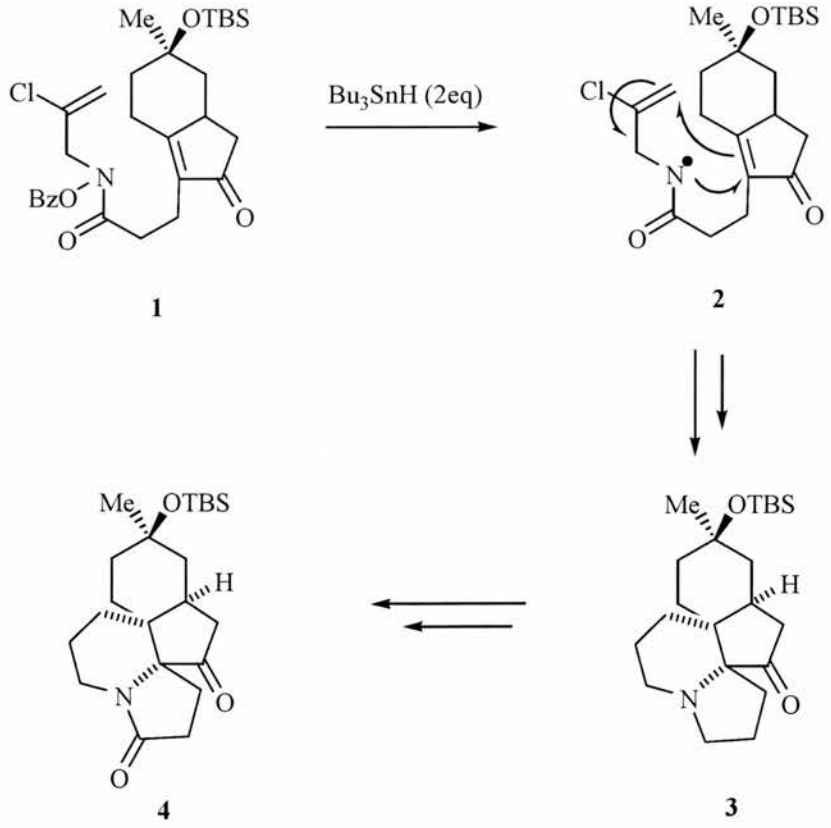
One of the most fundamental reactions in synthetic organic chemistry is the formation of carbon-carbon bonds. Free radicals do this readily,[6] and in good yield, and have now become an important tool for synthetic organic chemistry.

The aim of this introduction is to demonstrate how free radical chemistry is used in organic synthesis. In particular it will focus on the use of radical cyclisations in the preparation of ring systems and the use of acyl and carbamoyl radicals in the preparation of lactams.

1.2 Natural product synthesis

Although highly reactive species, free radicals are fast becoming popular in the total synthesis of natural products. Their ability to ring close and participate in cascade reactions has led to elegant syntheses of complex natural products. Some of the most recent successes include the synthesis of (+/-)-13-deoxyserratine **4** by Zard[8] and Murphy's[9] preparation of (+/-)-horsfiline **9**.

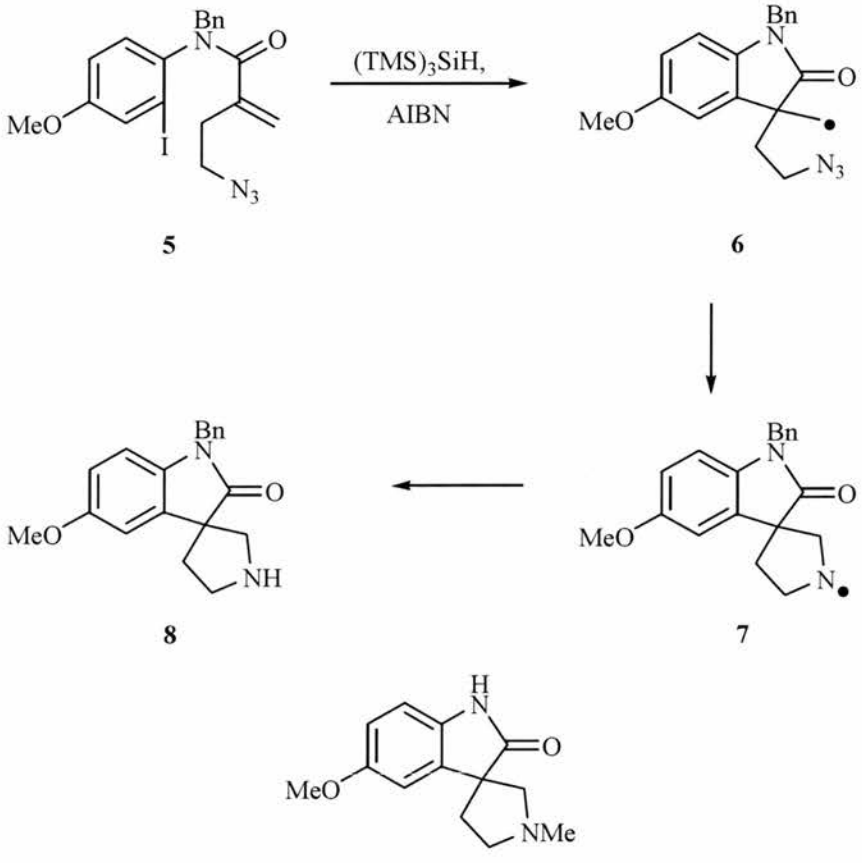
In Zard's synthesis, a [3 + 2] annulation has been used to prepare (+/-)-13-deoxyserratine **4** via a homoallyl radical (Scheme 1). The amidyl radical **2** was generated from the chloroallyl analog of *O*-benzoyl-*N*-allylhydroxylamine **1** by reaction with Bu_3SnH. The amidyl radical undergoes a 5-*exo* cyclisation onto the double bond followed by a "cascade", 6-*endo* ring closure onto the chloroallyl group. This gives the cyclised species **3** in a 52 % yield. The annulation takes place onto the less hindered face giving some stereo control over the end product.



1 **2** **3** **4**

Scheme 1

In the total synthesis of (+/-) horsfiline **9** (Scheme 2), Murphy incorporated a tandem cyclisation onto an azide in order to form a heterocyclic ring. From the indoarene precursor **5**, an aryl radical was generated using $(TMS)_3SiH$ in the presence of AIBN. The aryl radical underwent a 5-*exo*-cyclisation onto an adjacent alkene to give the alkyl radical **6**. This alkyl radical then underwent cyclisation onto the azide group which lost N_2 to give an aminyl radical **7** which was reduced by the tris(trimethylsilyl)silane to give the spirocyclic product **8** in 60 % yield.



5 **6** **7** **8**

9 (+/-) Horsfiline

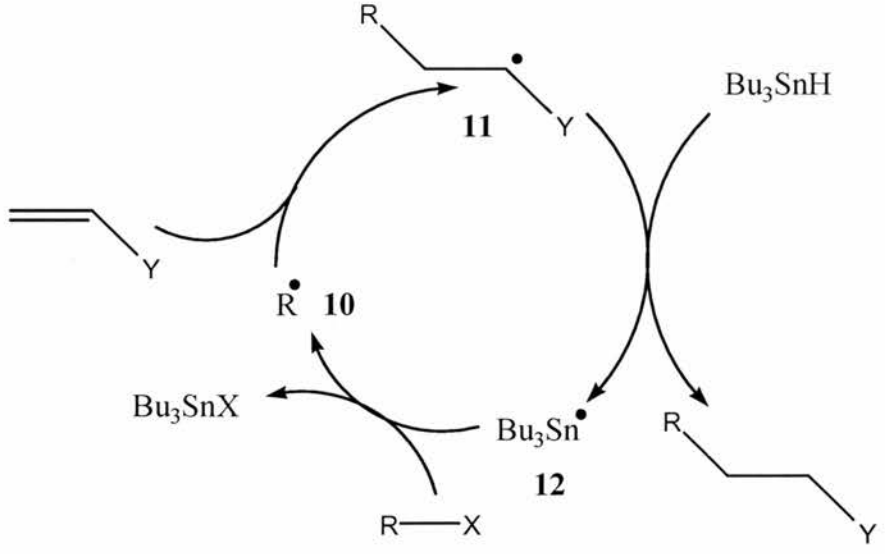
Scheme 2

It is obvious from these examples that free radicals are indeed extremely useful in organic synthesis, however, their application to the pharmaceutical industry has been hampered by a heavy reliance on tin hydrides.

1.3 Clean free radical precursors

Tributyltin hydride is still the most widely used reagent in radical chain methodology. It was discovered in the 1960's that the reduction of alkyl halides with trialkyl and triaryl tin hydrides resulted in the formation of alkyl radicals which could undergo classic radical reactions.[10] The use of tin hydrides in radical chemistry became widespread after work by Giese in the 1980's.[11,12] His research involved the addition of radicals to olefins in the preparation of C-C bonds.

The use of tin hydrides is a chain process, requiring only a small quantity of radical initiator (Scheme 3). The radicals **10-12**, react with non-radicals (alkenes, tributyltin hydride) to give new radicals.



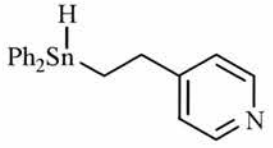
Scheme 3

This simple chain process is extremely efficient. The formation of a strong tin-halogen bond and the rapid hydrogen atom abstraction by the alkyl radical from the weak tin-hydrogen bond lead to constant regeneration of the chain carrying tin-centered radical and hence to good yields of the final product.

The downside of tin hydrides is their toxicity and the difficulty in handling and removal of tin compounds. For years, this toxicity has kept radical chemistry from being implemented in the production of medicines and food stuffs. Because of the

obvious synthetic applications of free radicals, much research is now being undertaken to discover new tin-free "clean" radical precursors.

One solution to the tin problem is the development of alternative tin compounds which encompass all the advantages of tin hydrides but which are easier to remove. For example pyridylstannane **13**, prepared from 4-vinyl pyridine affords products in good yield.[13] The advantage of this reagent is that the organotin halide by-products have R_f values of approximately zero for elution with ethyl acetate/hexane, and this enables products to be isolated relatively easily.



13

It is however, most desirable not to incorporate tin at all in the synthetic process. For this reason other metal-hydrides have been investigated as potential tin hydride replacements. In the process of this research, silicon and germanium have evolved as potential tin replacements.

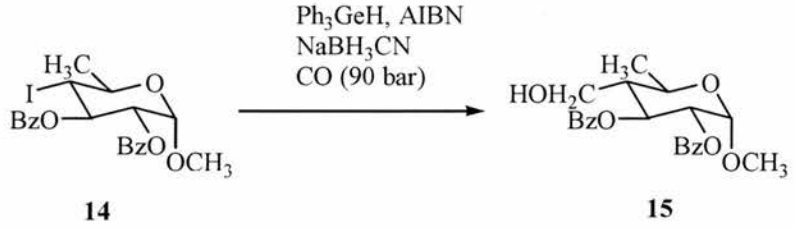
The silicon-hydrogen bond in simple triorganosilanes is too strong for ready hydrogen transfer, and therefore the chain process can often remain incomplete. Although triethylsilane[14-16] and diphenylsilane[17] have been used as alternatives to organotin hydrides, the range of amenable substrates is limited and the reaction temperature is often high (120-140 °C).

The most successful and widely used replacement for organotin hydride is tris(trimethylsilyl)silane.[18-20] Not only does this reagent present no toxic threat but it also produces far fewer by-products of direct reduction because its Si-H bond is about 5 kcal mol^{-1} stronger then the Sn-H bond. This has often allowed radical processes to be accomplished with a stoichiometric amount of the silane in the initial reaction mixture instead of the tedious slow-addition, high-dilution, techniques associated with tin hydrides. It was postulated that the low bond energy of the Si-H bond was due to a

bonding interaction between β-silicon d orbitals and the semi occupied p orbital on the central silicon atom in the corresponding silyl radical.[21]

The downside of tris(trimethylsilyl)silane is the propensity of the $(Me_3Si)_3Si\bullet$ radical to add to multiple bonds. In fact tris(trimethylsilyl)silane is an efficient reagent for hydrosylating alkenes and alkynes.[22] Other disadvantages are the cost and the necessity to handle under argon.

Tributylgermanium hydride has a relatively strong Ge-H bond and therefore direct substrate reduction is not usually significant.[23,24] An example of the use of germanium hydrides is illustrated in Scheme 4. It was necessary to prepare the monosaccharide **15** for a mechanistic study of the complex natural product calicheamicin. Attempts to replace the iodine atom of **14** with a hydroxymethyl sustituent using ionic reagents failed. Attention therefore turned to the free radical chemistry of Ryu which involved the addition of CO to alkyl radicals under high pressure.[25,26] The technique proved to be ineffective when tin hydrides were used as the reduction medium but significant yields of the desired monosaccharide were obtained when germanium hydride was used.

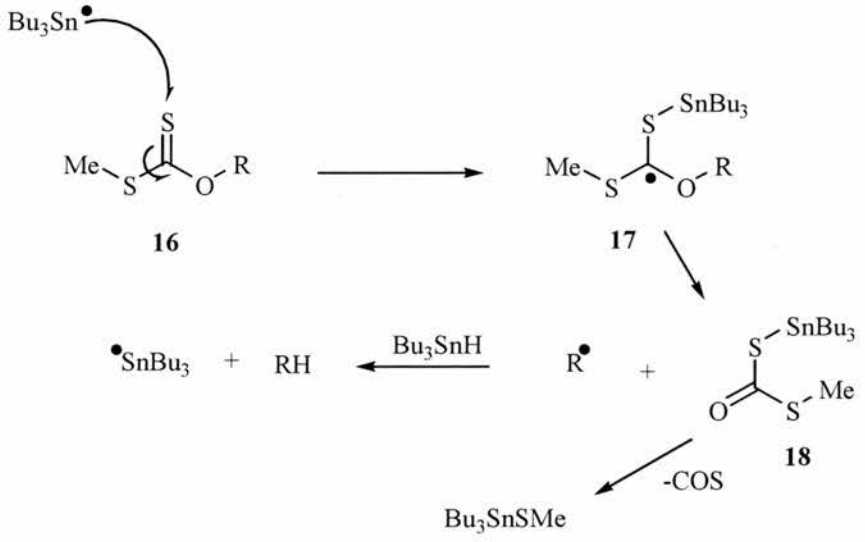


Scheme 4

Tris(trimethylsilyl)germane $(Me_3Si)_3GeH$ reduces a variety of functional groups in high yield.[27] However, the rate of hydrogen abstraction from $(Me_3Si)_3GeH$ by a primary alkyl radical was found to be even faster than from tributyltin hydride[28] and this limits the reagent's usefulness. The downside of germanium hydrides is again the cost and the difficulty in handling these compounds.

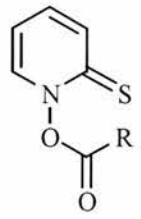
In order to break away from the use of metals entirely, numerous "metal free" radical precursors have been investigated. Of these, the most successful have been the xanthates,[27] and the Barton esters.

The most widely known radical reaction involving xanthates is the Barton-McCombie reaction for deoxygenating secondary alcohols.[29,30] This reaction has had a major impact on organic synthesis, especially for the modification of carbohydrates and as a convenient source of free radicals from alcohols in general. Scheme 5 illustrates the original Barton-McCombie mechanism.



Scheme 5

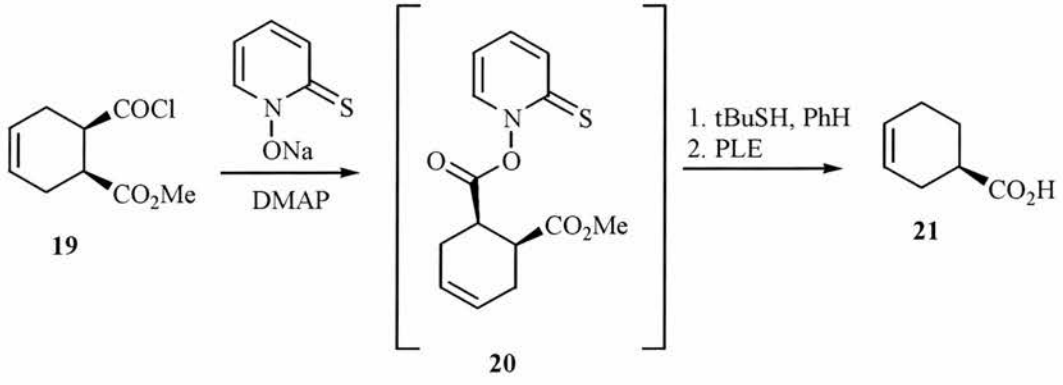
The Barton–McCombie methodology was further modified to allow functional group transformation on carboxyl groups. Barton esters, or *o*-acyl thiohydroxamates can be readily prepared by esterification with an acid chloride and a sodium salt. Barton esters allow reductive decarboxylation to be carried out in the presence of AIBN and tributyltin hydride. It was also found that the Barton esters can function as photochemical precursors for carbon centered radicals.



The Barton Ester

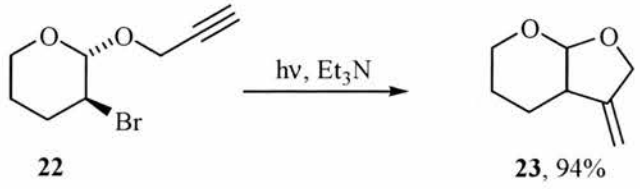
Although the original Barton chemistry was carried out in the presence of organotin hydrides, these can be replaced with a thiol (usually 2-methylpropane-2-thiol) with very little loss of efficiency. The success of this methodology is due to the susceptibility of the thionyl functionality to the addition of tin- and sulphur- centered radicals, the weakness of the N-O bond and the use of aromatization as a favourable thermodynamic driving force.

Since the introduction of the Barton methodology numerous applications have been reported. For example, the conversion of carboxylic acids into thiols[31], cyanides[32] and isothiocyanides[32] and the generation of oxygen-centered radicals.[33] The methodology works particularly well for reductive decarboxylations. For example (*R*)-3 cyclohexenecarboxylic acid **21** was required as the starting point for the total synthesis of the natural product FK506 (Scheme 6).[34] The acid chloride **19** was converted into the corresponding thiohydroxamic ester which underwent decarboxylation with 2-methyl-2-propane-2-thiol in benzene to give the required product after enzymic hydrolysis.



Scheme 6

Several new metal-free systems for the generation of radicals and the managing of homolytic systems have recently been discovered. It was found that, on photolysis, and in the presence of an excess of triethylamine, alkyl bromides and iodides yield C-centered radicals.[35,36] This procedure was utilized in ring closure reactions and the bicyclic ether **23** was isolated in almost quantitative yield (Scheme 7).



22 **23**, 94%

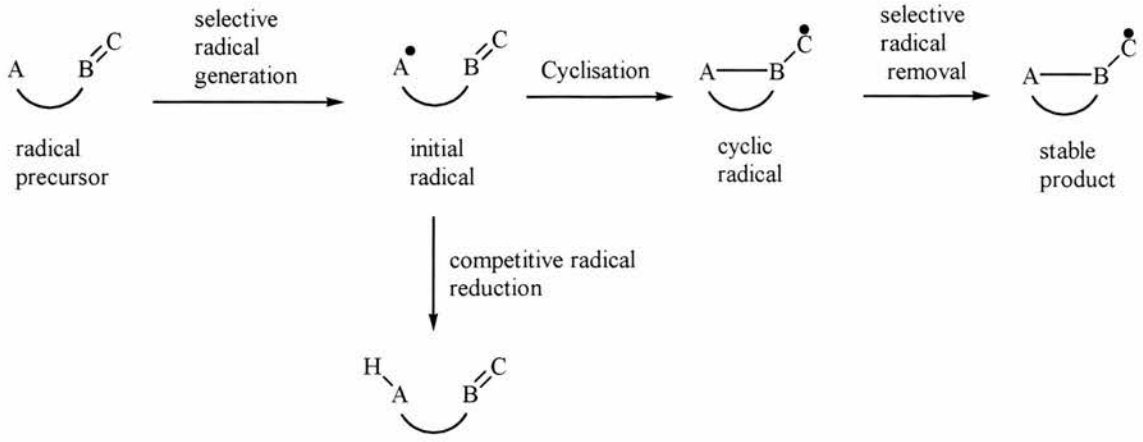
Scheme 7

Other examples of metal-free precursors include the 2-naphthyl thioesters[37] which have been introduced as sources of acyl radicals and diphenylphosphine, whose P-H bond is weak enough to sustain a radical chain process.[38]

In order for free radical chemistry to be fully incorporated into mainstream organic synthesis it is obvious that the dependence on tin hydride and other metal based systems must be overcome. For this reason it is necessary to continue research into the development and optimisation of novel "clean" free radical precursors.

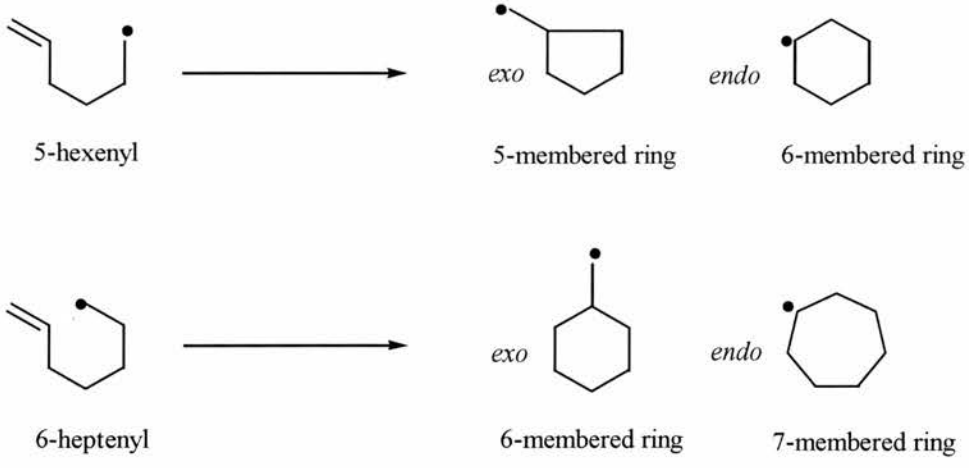
1.4 Radical Cyclisations

One of the most important reactions in radical chemistry and indeed organic synthesis is the formation of rings. Most antibiotics and natural products contain at least one ring and many are bicyclic or tricyclic systems. Free radicals are advantageous in that they quite readily undergo ring closure reactions to give a range of carbon rings and heterocycles. Radicals readily cyclise onto a range of functional groups including carbon-carbon multiple bonds, carbonyl groups and imines. In general intramolecular addition is much faster than intermolecular addition. The general scheme to conduct a selective radical cyclisation is summarised below (Scheme 8).



Scheme 8

Radical cyclisations are most often applied to the synthesis of 5-membered rings. There are a number of reasons for this. The first is that *exo*-cyclisations are usually faster for the formation of 5-membered rings[39] than for any other ring size. The simple 5-hexenyl radical[40-43] cyclises 20 times faster than the 6-heptenyl radical (Scheme 9). 5-Membered rings are therefore less subject to competitive formation of reduced, uncyclised by-products.

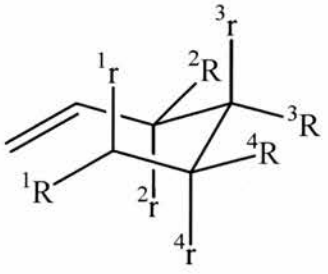


Scheme 9

The second reason is that the regioselectivity for 5-*exo* cyclisation is often outstanding.[40-43] Of the two possible cyclisations, *exo* and *endo,* generally the *exo* is preferred. For the parent 5-hexenyl radical, 5-*exo*-cyclisation is 50 times faster than 6-

endo cyclisation, at room temperature. This is in agreement with Baldwin's rules of cyclisation[44] which state that 5-*exo*-cyclisation is a favoured process whereas 6-*endo*- is not.

A third reason why 5-*exo*-cyclisations are so common is that the formation of 5-membered rings by radical cyclisation can also be highly stereoselective. The major product of a 5-*exo* cyclisation can generally be predicted using the Beckwith-Houk transition state model[45] (Scheme 10).

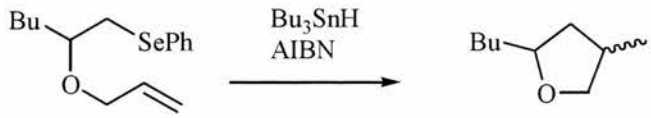


R = location of substituent in major diastereoisomer
r = location of substituent in minor diastereoisomer

Scheme 10

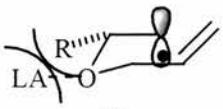
The Beckwith-Houk model is a good representation of the lowest energy transition state, and it predicts the major cyclisation product by placing a chain substituent in an equatorial-like orientation. The early transition state of a 5-*exo* radical cyclisation, resembling a cyclohexane ring, prefers the chair over the boat conformation and prefers that substituents be pseudo-equatorial rather than pseudo-axial. Simple model studies show that substitution at C_1 or C_3 of the 5-hexenyl radical gives primarily *cis*-disubstituted cyclopentanes, whereas substitution at C_2 and C_4 gives primarily *trans*-disubstituted cyclopentanes. Selectivity is highest for C_1 and C_4 substituted systems. Theoretical treatments and experimental results aid in planning highly steroselective reactions and allow exceptions to Beckwith's guidelines to be anticipated.

Diastereocontrol can be obtained using trialkylaluminiums in the synthesis of tetrahydrofurans *via* radical cyclisation.[46,47] An example of the cyclisation of phenylselanide precursor, **24**, to give a 2,4-disubstituted tetrahydrofuran **25** is illustrated in scheme 11.



24 **25**

(cis : trans = 5.1 : 1)



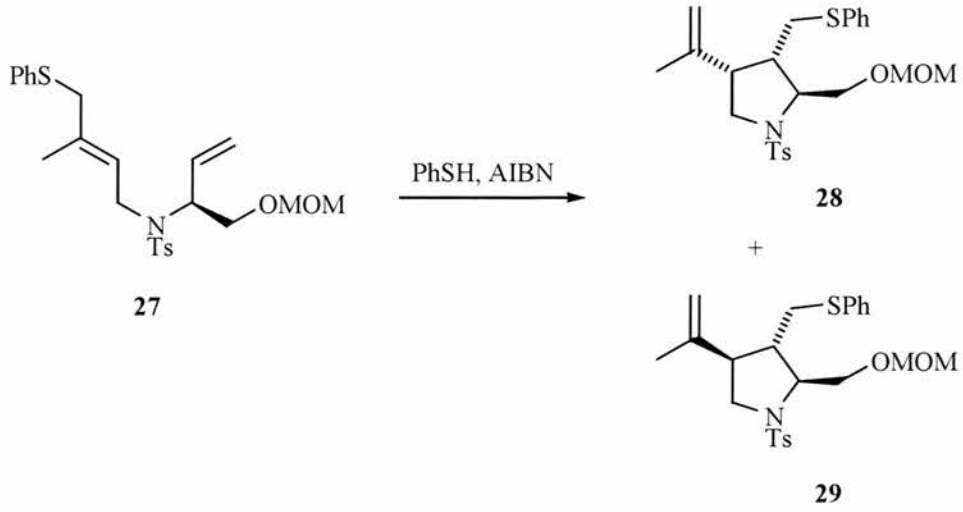
26

(Beckwith-Houk TS)

Scheme 11

A variety of Lewis acids were used in order to control diastereoselectivity. Of these, Et_3Al proved to be the most effective in terms of yield and diastereocontrol. Due to clashes with the steric bulk of the complexed Lewis acid as shown in intermediate **26**, the substituent is forced into the axial or twist boat conformation in the transition state. This highly diastereoselective cyclisation strategy resulted in the formation of 2,3,4- and 2,3,4,5-substituted furan rings.[48] Excellent levels of 2,4-*trans* selectivity were observed in accordance with the Beckwith-Houk transition state model for 5-*exo* radical cylisations.

One example of a 5-*exo*-cyclisation is in the preparation of (-)-kainic acid[49] (Scheme 12). The protocol involves the use of a phenylthiyl radical (PhS•). The thiyl radical adds to the β-alkene of the precursor **27** followed by a 5-*exo*-trig cyclisation and PhS• elimination to form the pyrrolidines **28** and **29** in 95 % yield (1:1.5 ratio of diastereoisomers). The diastereoisomer **28** was further elaborated to give a formal total synthesis of (-)-kainic acid.

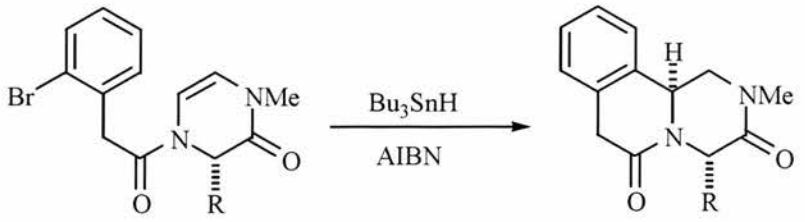


27 **28** **29**

Scheme 12

6-Membered ring radical cyclisations are less general than cyclisations leading to 5-membered rings. However, they still have an important place in synthesis. Cyclisation of the 6-heptenyl radical is possible although it is less regio-selective than cyclisation of the 5-hexenyl radical. The rate for 6-*exo*-cyclisation at 25 °C ($k_C = 5.10^3$ s^{-1}, k_C = rate constant of cyclisation) is much slower than that of 5-*exo*- cyclisation.[50] Cyclisation can be accomplished if low concentrations of trapping agents are used.

One example of a preparation involving 6-*exo* cyclisation is the formation of novel amino acid derived heterocycles which can be used as peptidomimetic scaffolds[51] (Scheme 13). Amino acids were used to synthesise a range of enamido radical precursors **30 a-c.** The aryl radicals were generated using Bu_3SnH and these cyclised with 6-*exo* selectivity to yield the peptide mimics **31a-c** in good yield. Only one diastereoisomer was obtained in each case and this was explained by the radical approaching from the opposite face of the amino acid side chain. The anthelmentic drug praziquantel was also synthesised according to this protocol.

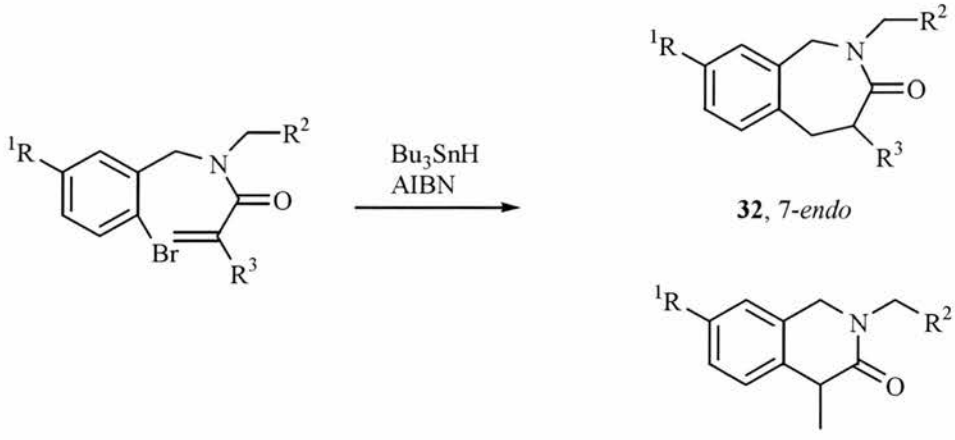


30a, R = Bn
30b, R = *i*-Pr
30c, R = Me

31a, R = Bn, 80%
31b, R = *i*-Pr, 70%
31c, R = Me, 71%

Scheme 13

Radical cyclisations to give 7-membered rings have also been carried out. In a very recent example, Kamimura et al.[52] have incorporated a 7-*endo* cyclisation into the preparation of 2-benzapines **32** (Scheme 14). In some cases mixtures of the 7-*endo* and 6-*exo* product **33** were obtained. Exclusive formation of the desired *endo* product was observed when an alkyl group was present in position R^3. This was probably a steric effect which only allowed the disfavoured *endo* cyclisation.



32, 7-*endo*

33, 6-*exo*

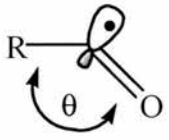
Scheme 14

4-Membered rings, including lactams and lactones have also been prepared through radical methodology but these will be discussed in a later section.

1.5 Acyl Radicals

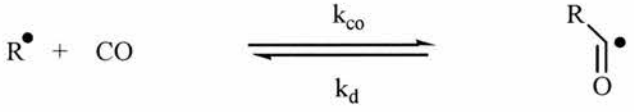
Acyl radicals are synthetically useful.[53] A wide range of precursors for acyl radicals have been developed and acyl radicals have been used in the preparation of some complex organic molecules. A recent review on acyl radicals by Chatgilaloglu *et al*[53] illustrates the huge developments in acyl free radicals in the last ten years.

It has been established by both experiment and theory that the radical centre in acyl radicals is bent (Scheme 15) and that the unpaired electron occupies an orbital with substantial 2s character. This species can therefore be considered as being a sigma type radical.



Scheme 15

The most well known reactions involving acyl radicals are the addition of an alkyl radical to carbon monoxide (carbonylation) and its reversal (decarbonylation) as shown in Scheme 16.



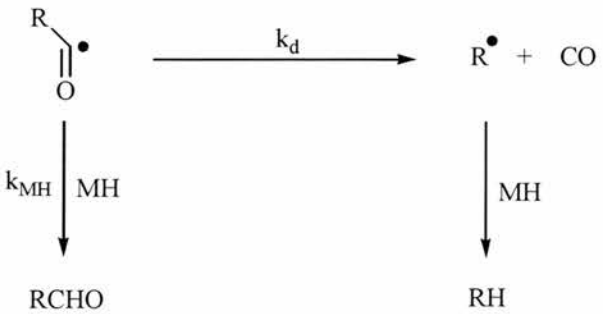
Scheme 16

The kinetics of both these processes have been studied in detail. The first kinetic data for carbonylation reactions appeared in the 1970's. The gas phase reactions of the methyl and ethyl radicals with CO were studied by Watkins et al. [54,55] It was found that the rate of carbonylation of the methyl radical in the gas phase was 6.3×10^3 $M^{-1} s^{-1}$ and that the rate of carbonylation of the ethyl radical in the gas phase was 1.7×10^5 $M^{-1} s^{-1}$. The rate constant for the of addition of a primary alkyl radical to CO with benzene as the solvent has recently been found to be 6.3×10^5 $M^{-1}s^{-1}$ at 80 °C.[56] This is in agreement with the gas phase value for the ethyl radical. The rate constant for the

reaction of the methyl radical with CO in aqueous solution was found to be 2.0 x 10^6 M^{-1} s^{-1}. This value is 2-3 orders of magnitude greater then that of the gas phase reported by Watkins.[55] This large increase in going from the gas phase to the liquid phase is thought to be due to stabilisation of the acetyl radical by dipolar interactions with the solvent.[56] It may also be that the large difference is due to errors arising from the gas phase measurements.

Decarbonylation has been investigated much more thoroughly and is better understood than carbonylation. The first kinetic studies for decarbonylation were carried out in the 1930's.[57,58] Since then several studies have been conducted on the decarbonylation system (Scheme 16). In 1987 Fischer and Paul collected and analysed all the data in the literature concerning the decarbonylation reaction.[59,60] They found that the rate constants, which depend heavily on the group R, covered almost 15 orders of magnitude.

Recently, the kinetics of decarbonylation of primary, secondary and tertiary alkyl substituted acyl radicals in competition with hydrogen abstraction from Bu_3SnH or $(TMS)_3SiH$ have been measured[61,62] (Scheme 17).



Scheme 17

It was assumed that the rate of hydrogen abstraction for a particular reducing agent by the R(CO•) radical is independent of the nature of the alkyl substituent R. The results then suggested that the entropy changes on the approach to the transition state are negligible and that the large variation in rates observed for decarbonylation is in fact caused by activation energies. A combination of the relative kinetic data with the Arrhenius parameters for the propanoyl radical decarbonylation allows corresponding

data from the decarbonylation of secondary and tertiary alkyl-substituted acyl radicals to be obtained. For the acetyl radical in the gas phase the rate of decarbonylation was found to be 4.0 s^{-1}. For the ethyl acetyl radical the rate was determined to be 2.1 x 10^2 s^{-1}.

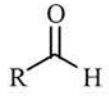
Recent laser flash photolysis studies either by UV[63] or IR[64] detection allowed the rate constant of decarbonylation of the pivaloyl radical to be measured directly at room temperature. It was determined to be 8.3 x 10^5 s^{-1} at 296 K. This value compared favourably with the rate constants estimated from the Arrhenius expression of tertiary alkyl-substituted acyl radicals.

The effect of solvent on decarbonylation has also been studied. Initial work was carried out by Ingold and co-workers who observed that the rate of decarbonylation of the $PhCH_2C(O)\bullet$ radical is slightly influenced by the polarity of the solvent. For example, at 296K the rate constant was 8.1 x 10^6, 7.0 x 10^6 and 4.1 x 10^6 s^{-1} in isooctane, tetrahydrofuran and methanol respectively.[65] These rate constants were calculated from the corresponding Arrhenius expressions and some were found to have large errors. More recently, Fischer and co workers studied the solvent effects on the rates of decarbonylation of acyl radicals in detail.[63] They found that the phenylacetyl radical dissociates with rate constants of 8.3, 4.2 and 1.4 x 10^5 s^{-1} in hexane , methanol and acetonitrile respectively. It was postulated that since acyl radicals have an appreciable dipolar moment, they should be stablilised with increasing solvent polarity and therefore the rate constants are decreased by increasing the activation energy.

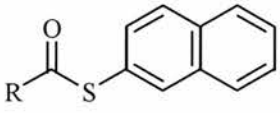
As was mentioned earlier, acyl radicals are a synthetically useful species. In order to apply acyl radicals to synthesis, it was first necessary to develop suitable precursors. Three different methods have been employed for the generation of acyl radicals. The first and most widely used of these is homolytic cleavage of a RC(O)-X bond. The second involves the carbonylation of a carbon-centered radical with CO and the third involves fragmentation of a C(O)-C bond as, for example, in the loss of CO_2 from an α–ketocarboxyl radical.

A Generation of acyl radicals by homolytic cleavage

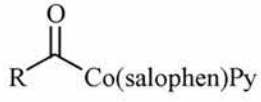
Generation of acyl radicals through the homlytic cleavage of an RC(O)-X bond has been heavily investigated and a number of suitable precursors have been developed. The X moiety may be any group susceptible to homolytic rupture of the C-X bond, namely hydrogen, halogen, chalcogen and various metals. Scheme 18 illustrates the diversity of precursors which are now available.



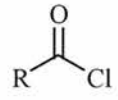
aldehyde



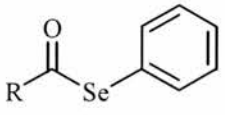
thioesters



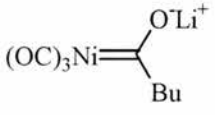
acylcobalt(III) derivatives



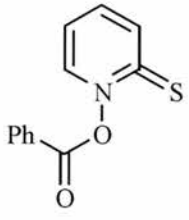
acyl chloride



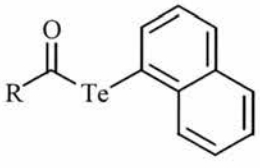
acyl selenides



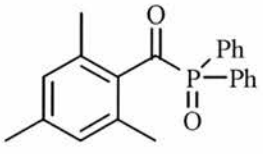
metal carbene complexes



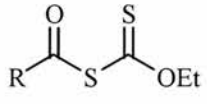
O-benzoyl thiahydroxamate



acyl telluroesters



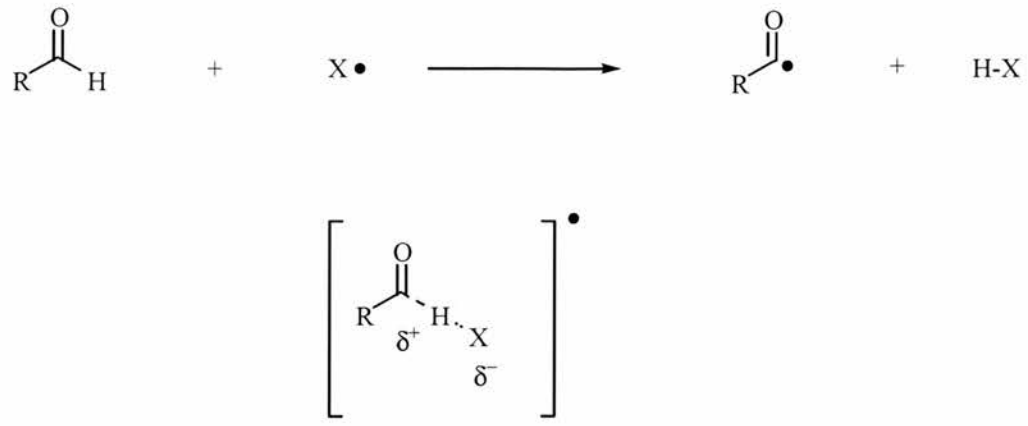
acyl phosphine oxides



dithiacarbonates

Scheme 18

The simplest source of acyl radicals through homolytic cleavage of RC(O)-X occurs when X=H ie. aldehydes. When the abstracting radical, X•, is electrophilic then the induced homolysis is readily achieved. However, when the abstracting radical is nucleophilic the abstraction step is relatively slow. This suggests a polarized transition state **34** for the reaction (Scheme 19).

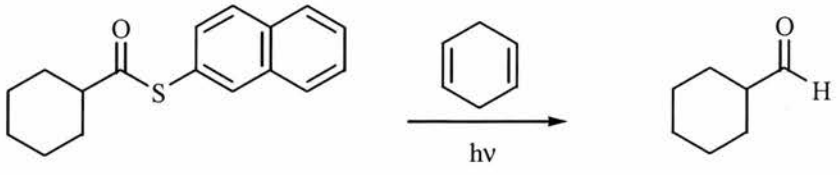


34

Scheme 19

Acyl chlorides have been used as sources of acyl radicals. However the stannane-mediated reduction of acyl chlorides to aldehydes via acyl radicals is plagued by the formation of by-products, in particular esters. Early workers studying the reduction of benzoyl chloride observed benzyl benzoate.[66-68] There was much discussion about the mechanism of ester formation until Ingold[69,70] convincingly demonstrated that it involved over reduction of the aldehyde by a polar mechanism and reaction of a stannyl alkoxide with the acyl chloride. This and other complications meant that studies involving acyl chlorides as acyl radical precursors are quite limited.

Thioesters have proved to be much more successful sources of acyl free radicals. In the early 1990's, following reports of the successful photochemical and thermal homolytic cleavage of the acyl-SPh bond in S-phenylthiobenzoate,[71,72] Penn and Liu introduced thioesters as convenient sources of acyl radicals.[37] They found that white light photolysis of these substances in the presence of cyclohexa-1,4-diene as a hydrogen donor resulted in excellent yields of the corresponding aldehydes for a range of aromatic derivatives (Scheme 20).

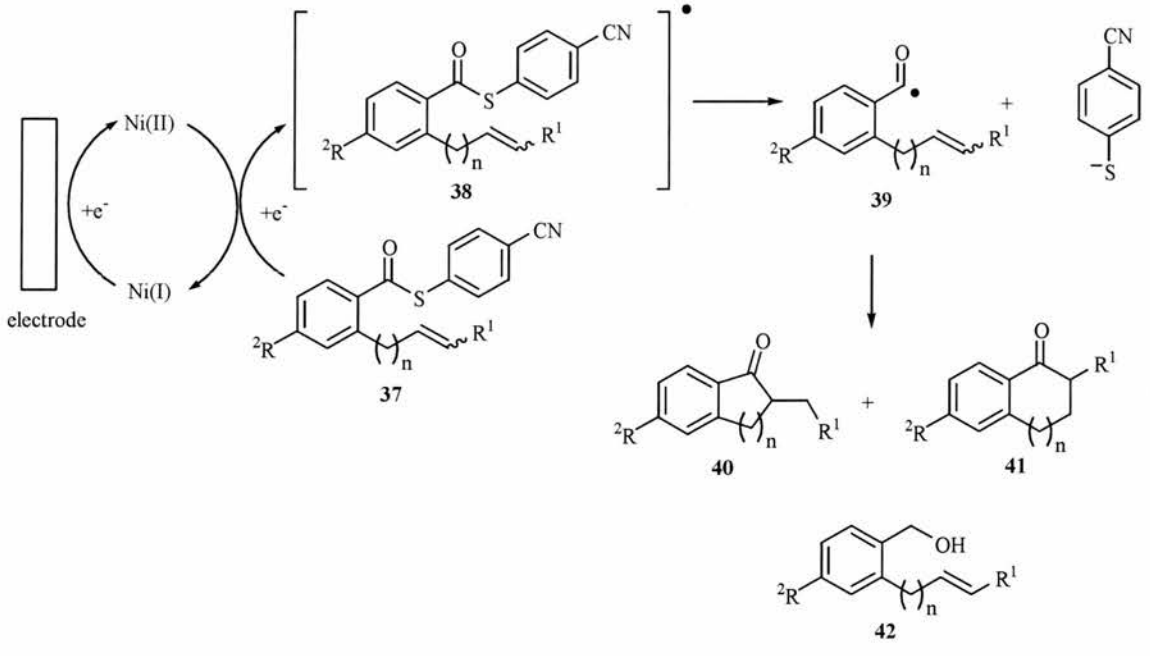


35 **36** 84%

Scheme 20

It was determined by both Bodger[73] and Crich[74] that simple *S*-phenyl thioesters were unreactive toward Bu_3Sn• radicals, which prevented their use as sources of acyl radicals in stannane mediated chain sequences. This problem can be overcome however through the use of an addition propagation step involving intramolecular cyclisation onto the sulphur.[75,76]

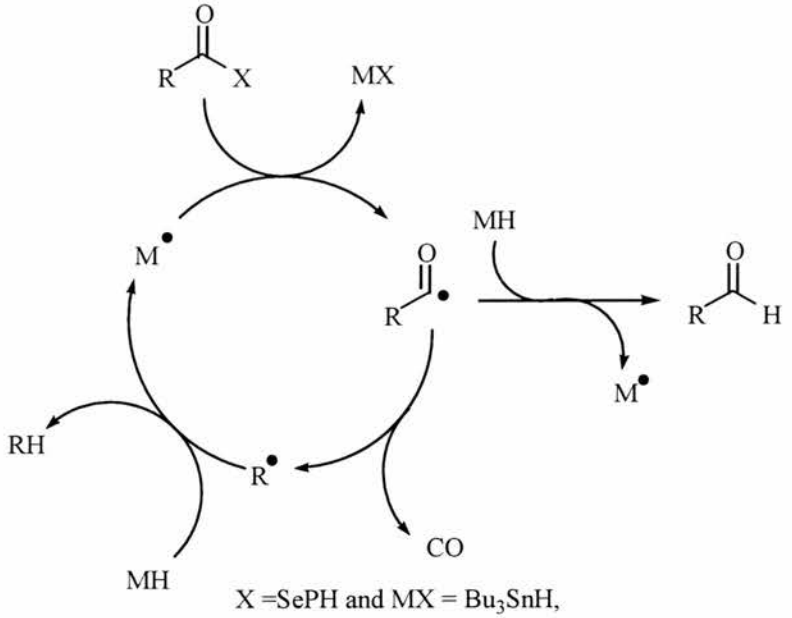
Webster and Bond recently reported that electrochemical reduction of thioesters can be used for the generation of acyl radicals.[77] This has been further developed by Ozaki *et al.*[78,79] who have used a nickel complex catalysed electroreductive method in order to generate acyl radicals from S-(4-cyano)phenyl thioesters **37** (Scheme 21).



Scheme 21

The acyl radical **39** gave products of both 5-*exo* (major) and 6-*endo* (minor) cyclisation. The acyl radical suffered further electroreduction followed by attack from residual water in DMF to also give the alcohol **42**.

A number of metal based precursors for acyl radicals have been developed. For example acyl selenoesters, which have a weaker RCO-SeR' bond than thioesters, have been found to react readily with stannyl radicals to give acyl radicals. Selenoesters can be isolated and purified by silica gel column chromatography and display none of the over reduction problems which plague the reaction of acyl chlorides with stannanes. The initial research was carried out by Graf *et al.* who investigated the reactions of selenoesters with tributyltin hydride.[80,81] It was demonstrated that selenoesters derived from tertiary carboxylic acids gave acyl radicals which underwent smooth decarbonylation in high yield. Selenoesters derived from primary acids were reluctant to undergo decarbonylation. Selenoesters derived from secondary acids displayed intermediate behaviour. The mechanism for the reaction of selenoesters with metal hydrides is illustrated in Scheme 22.

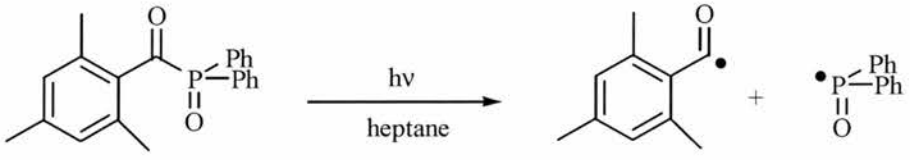


Scheme 22

The stability and smooth reactivity of selenoesters toward stannane and tris(trimethylsilyl)silyl radicals has led to their widespread adaptation as the precursor of choice for the generation of acyl radicals.

Other metal-containing reagents which have been used in the generation of acyl radicals include telluroesters and acylcobalt(III) derivatives. Telluroesters of aryl and vinyl carboxylic acids provide acyl radicals on photolysis.[82,83] These have been trapped by thiols and the absolute rate constants for addition of isopropanoyl and benzoyl radicals to PhSH have been determined.[84] The use of acyl cobalt derivatives in the formation of acyl (and carbamoyl) radicals will be discussed in a later section.

Acyl phosphine oxides have also emerged as a source of acyl radicals. Photolysis of benzophosphine oxides **43** yields benzoyl radicals **44** and phosphonyl radicals **45** with high quantum efficiency[85] (Scheme 23). The problem with these precursors is that the phosphonyl radical **45** is 1-2 orders of magnitude more reactive then the benzoyl radical toward unsaturated substrates and this severely limits acyl phosphine oxides as preparative sources of acyl radicals.



43 **44** **45**

Scheme 23

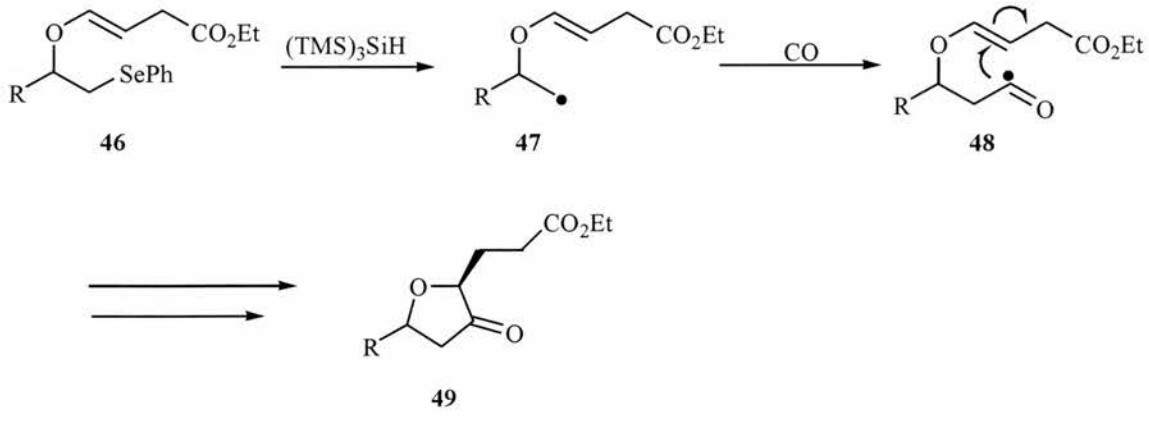
B Generation of acyl radicals by carbonylation

The carbonylation of alkyl, aryl and vinyl radicals to generate acyl radicals is a well investigated process which dates from 1939 when Faltings observed formation of acetone on UV irradiation of ethane under CO pressure.[86] Most of the early work was hampered by low yields and inefficient reactions and has been summarised in a review by Ryu.[87] The modern era of radical carbonylation began in 1990 when it was

demonstrated that alkyl halides could be carbonylated under moderate pressure of CO (70-90 atm) in benzene at 80 °C in the presence of tributyltin hydride and AIBN.

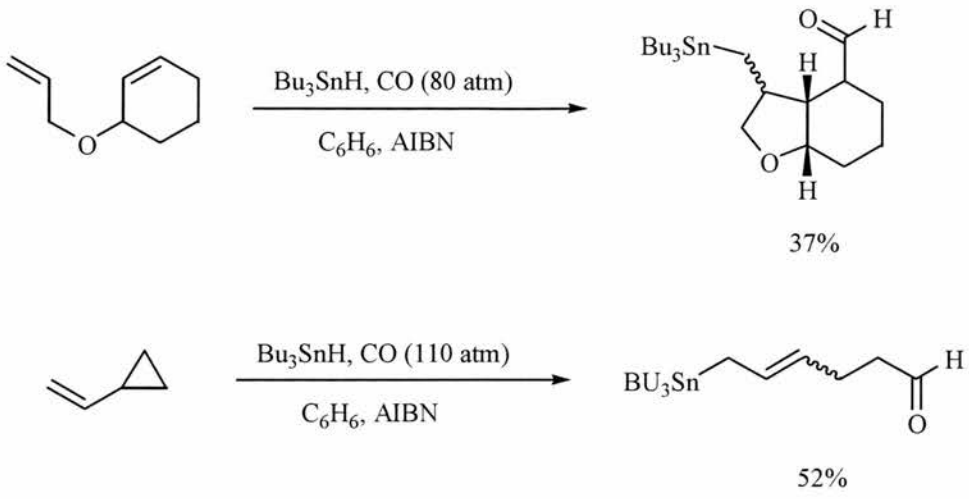
The success of the carbonylation step is of course a function of the equilibrium constant (K) which, assuming steady state conditions, is given by $K=k_{co}[CO]/k_d$. The equilibrium constant is inversely proportional to the rate of decarbonylation and hence any abnormally high rate of decarbonylation (i.e. leading to a resonance stabilised radical) will upset the equilibrium constant and the reaction will be unsuccessful. Also any side reaction which rapidly removes the acyl radical will drive the equilibrium in the forward direction whereas any which uses up the original alkyl radical is detrimental to the carbonylation process.

The carbonylation process has recently been used in the preparation of tetrahydrofuran-3-ones **49**.[88] Phenylselanyl precursors **46** have been used as precursors for the initial alkyl radical **47**. This is then carbonylated using high pressure CO to give the acyl radical **48** which undergoes 5-*exo*-trig cyclisation onto vinyl ethers with electron withdrawing groups (Scheme 24).



Scheme 24

If the rate of cyclisation is faster than the rate of carbonylation then the cyclisation step will proceed and an aldehyde will be formed. This is the case in Ryu's early tin hydride method.[89,90] (Scheme 25).

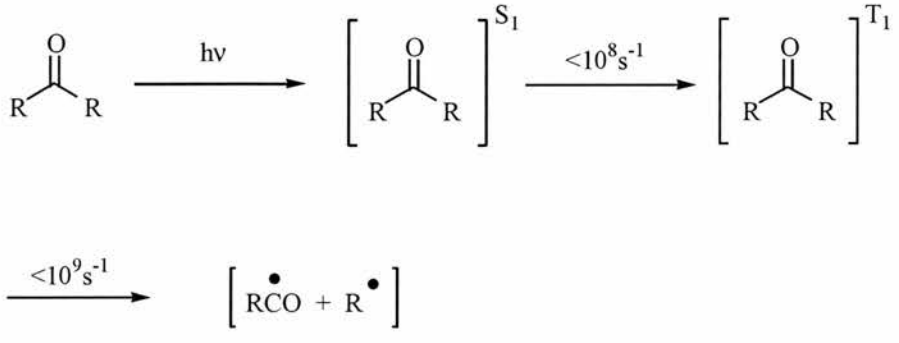


Scheme 25

In a very recent development Ryu *et al.*[91] have applied tin hydride mediated carbonylation chemistry to the preparation of α-stannylmethylene lactams from azaenynes. This has resulted in the preparation of 4, 5, 6, 7 and 8 membered rings in good yields. Use of acyl radicals in the preparation of lactams will be discussed in a later section.

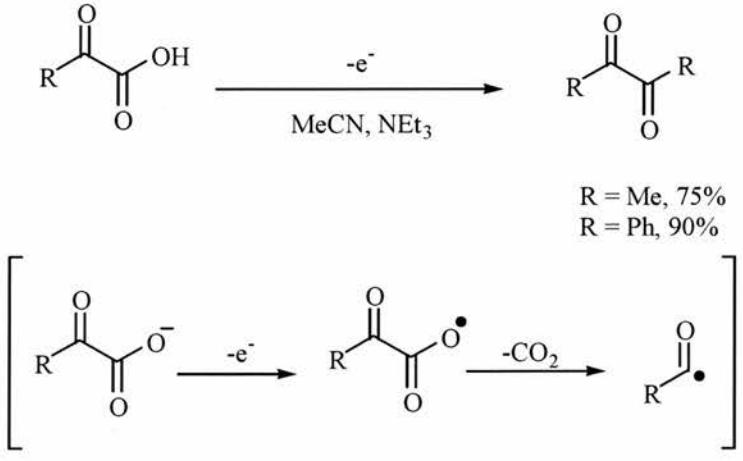
C Generation of acyl radicals by fragmentation of CO-C bonds.

One of the best known methods for the formation of acyl radicals through C-C bond cleavage is the Norrish type I photocleavage reaction.[92] This is one of the cleanest methods for the generation of acyl radicals for spectroscopic studies and has been widely used in this context. The photolyses of di-*tert*-butyl and dibenzyl ketones are classical type I cleavage reactions and follow the general Scheme 26.



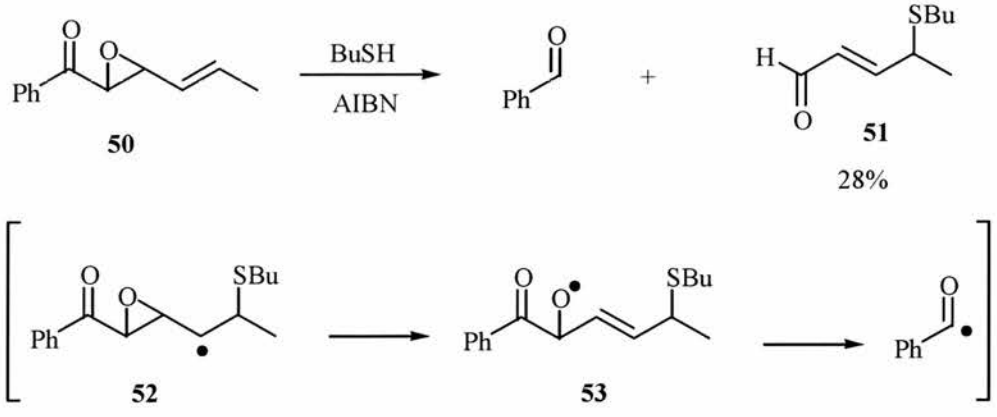
Scheme 26

Loss of CO_2 from α-ketocarboxyl radicals provides acyl radicals. In the context of the Kolbé reaction, electrolysis of the corresponding acids can lead to formation of α-diketones in good yield by coupling of acyl radicals (Scheme 27).



Scheme 27

Another source of acyl radicals through the cleavage of C-C bonds has recently been developed by Murphy. α-Acylalkoxyl radicals **53** have been generated through the cleavage of oxiranylcarbinyl radicals **52**. These radicals are obtained through the addition of thiyl radicals to alkenes **50** (Scheme 28).

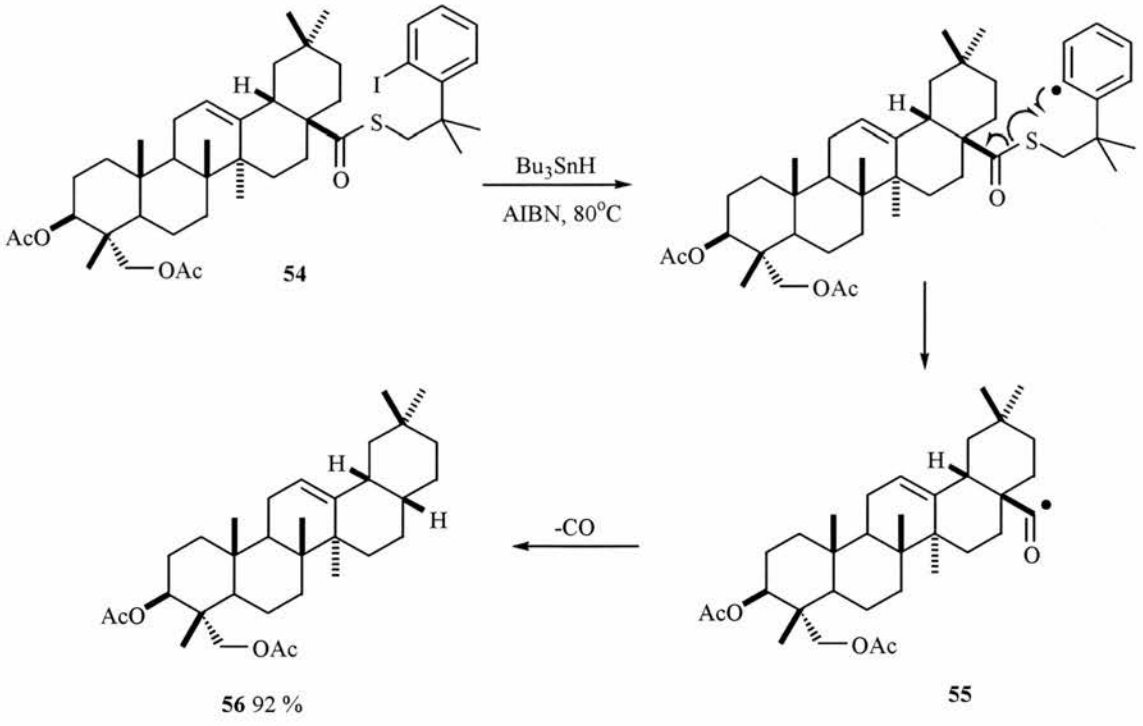


Scheme 28

D Synthetic applications of acyl radicals

Acyl radicals have been used widely in synthetic organic chemistry.[93] They can undergo decarbonylation to give alkyl radicals which are synthetically useful (see section 1.2) or they can undergo direct addition (coupling) or cyclisation reactions to give lactams and ketones. If the conditions are favourable they can also undergo reduction reactions to give aldehydes. All of these features of acyl radicals have been applied to organic synthesis and some examples are discussed below.

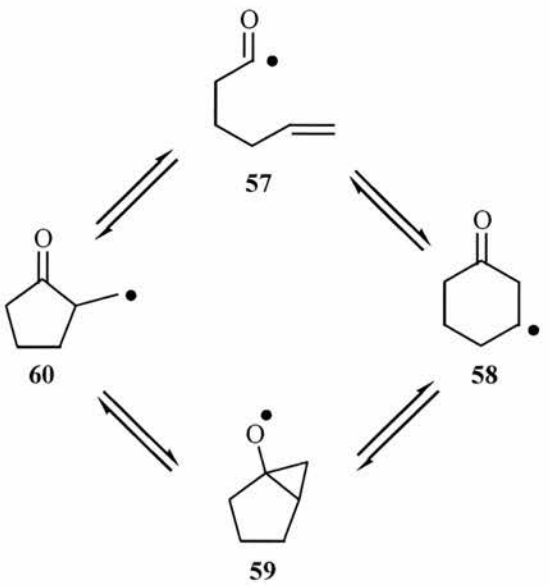
Decarbonylation reactions are the most widely used synthetic application of acyl radicals. For example Crich *et al.* have used thioesters (with an additional intramolecular propagation step) in the preparation of some complex organic systems. Scheme 29 illustrates the stannane mediated preparation of a hederagenin diacetate derivative **56**.[76]



Scheme 29

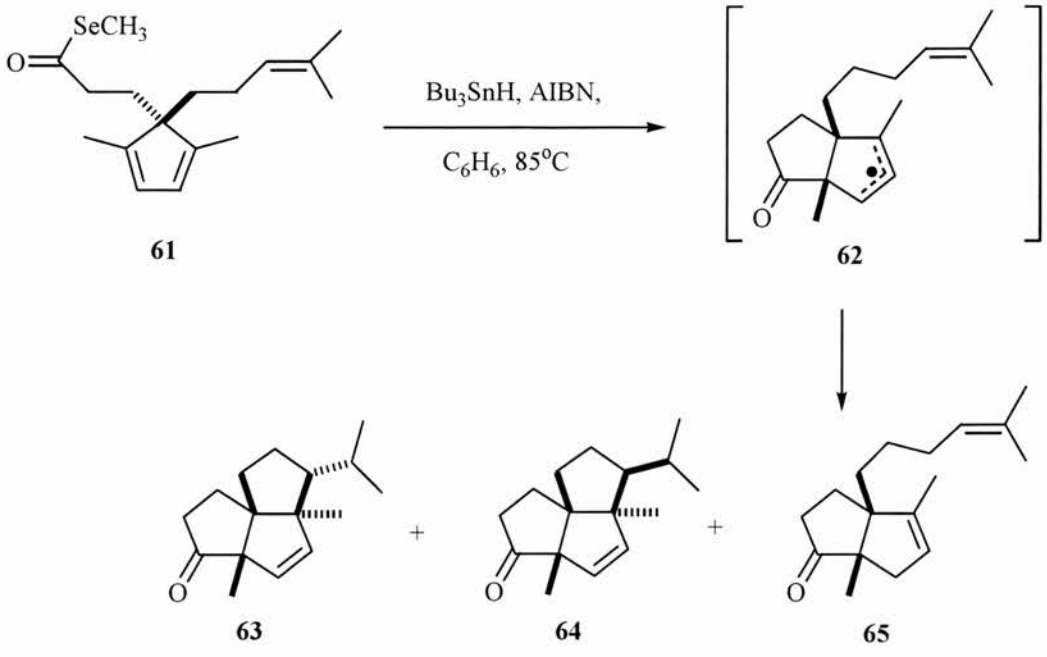
The controlled cyclisation of acyl radicals onto carbon-carbon double bonds constitutes a very useful synthesis of cycloalkanones. The main problem with acyl cyclisation is the formation of regioisomeric mixtures. The reason for these mixtures

has been heavily investigated and the discussion has expanded to encompass the rearrangement via a cyclopropyloxyl radical **59** as a possible intermediate (Scheme 30).



Scheme 30

Much research has been undertaken to understand and predict the regeoslectivity of acyl cyclisation and now both 5-*exo* and 6-*endo* modes of cyclisation have been used in the preparation of natural products. Curran and Schwartz have investigated a tandem 5-*exo* cyclisation reaction of an acyl radical for the construction of the congested triquinane portion of the tetraquinane, *Crinipillin*.[94] This tandem cyclisation strategy is unique in that it involves a 1,4-functionalisation of a cyclopentadiene nucleus via, 1,3-transposition of an allylic radical resulting from the first 5-*exo* cyclisation (Scheme 31). It produces two diastereomeric triquinanes **63** and **64** in a 1:5.5 ratio along with a bicyclic ketone **65** as a by-product.

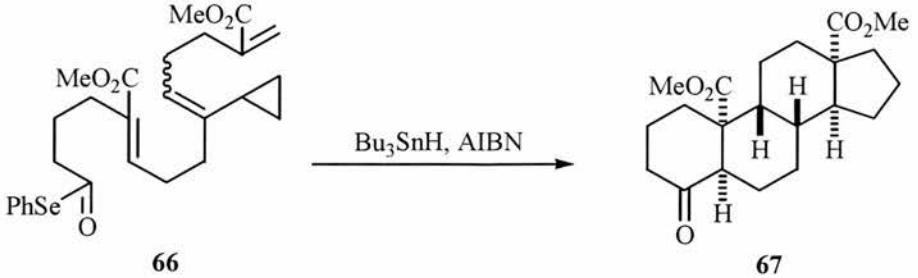


61 **62** **63** **64** **65**

62 % 1:5:2

Scheme 31

There are more examples of polycyclisation reactions involving 6-*endo* cyclisations than 5-*exo*. This is mainly due to the fact that 6-*endo* cyclisations can be used in the formation of fused polycyclic rings whereas 5-*exo* cannot. One of the most remarkable examples of fused polycyclic syntheses involving acyl radical, 6-*endo* cyclisations is Pattenden's approach to steroid ring construction.[95-97] Scheme 32 shows the cascade sequence which involves a 6-*endo*, 6-*endo*, 1,4-transposition, 9-*endo* and 5-*exo* cyclisation. It was necessary to incorporate two carboxylate ester moieties into the precursor in order to obtain the tetracyclic steroid ring **67** with success.



66 **67**

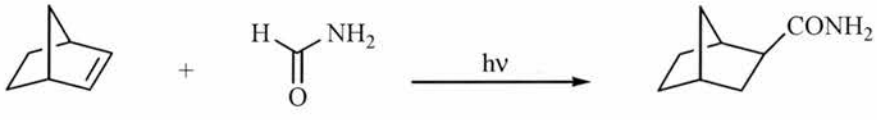
45%, cis, anti, cis, anti, cis

Scheme 32

An example of radical cyclisation followed by carbonylation for the preparation of tetrahydrofuran-3-ones **49** was earlier illustrated in scheme 24.

1.6 Carbamoyl Radicals

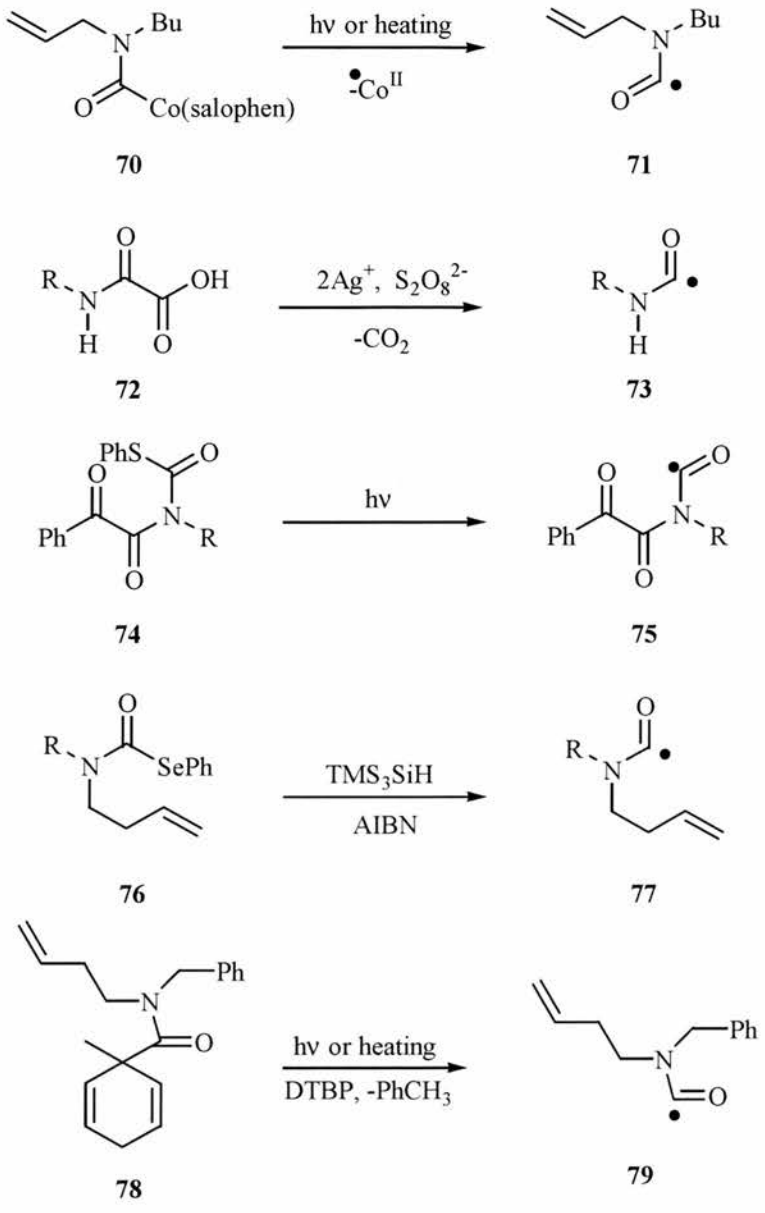
Carbamoyl radicals (aminoacyl radicals) have been studied only in the last 30 years and are less well understood then the analogous acyl radicals. The photogeneration of carbamoyl radicals from alkyl amides is quite an inefficient process.[98] Elad and Rokach demonstrated that the radical species produced from the photolysis of formamide added to both terminal and non-terminal alkenes.[99,100] The addition to norbornene **68** was stereospecific in that only *exo*-norbornenylcarboxyamide **69** was formed[101] (Scheme 33).



68 **69** *exo*-amide 87%

Scheme 33

Precursors for carbamoyl radicals are quite scarce and only a limited number of examples exist in the literature. Pattenden and co-workers reported the generation of carbamoyl radicals by thermally or photochemically induced homolysis of carbamoylcobalt salophens **70**.[102,103] The Minisci group have shown that carbamoyl radicals can be generated from the treatment of the monoamides of oxalic acid **72** by persulfate, catalysed by metal salts.[104,105] Sakamoto and co-workers[106] have demonstrated that irradiation of thiocarbamates **74** in solution results in the formation of carbamoyl radicals. Se-Phenylselenocarbamates **76** have been used as a source of carbamoyl radicals.[107] Refluxing of the selenocarbamate in TMS_3SiH in the presence of AIBN gives very efficient homolytic cleavage of the C-Se bond. Recently, Walton *et al.*[108], have developed cyclohexadiene derivatives **78** as sources of carbamoyl radicals. Examples of the known precursors for carbamoyl radicals and their modes of initiation are illustrated in Scheme 34.



Scheme 34

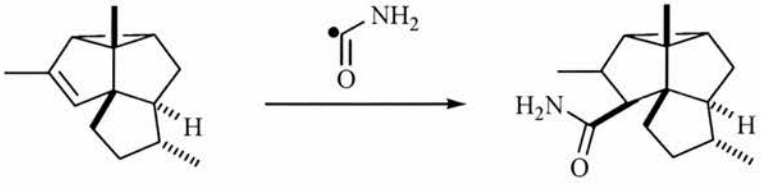
It can be seen from Scheme 34 that there are a range of precursors for carbamoyl radicals. Some of these are metal-dependent, either in their initial structure or in their mode of initiation and propagation. Others are true "clean" sources and do not rely on metals or organotin hydrides.

Carbamoyl radicals have been observed by ESR spectroscopy[109] and subsequent work has demonstrated that *N*-alkyl-carbamoyl radicals exist in both E- and Z-conformations.[110] *N*-Arylcarbamoyl radicals (ArNHC•=O), where the aromatic ring is

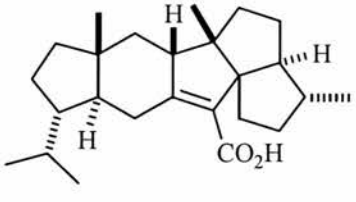
almost coplanar with the amide plane, are known only as transient species since decarbonylations are rapid to give the more persistent aminyl (ArN$^{\bullet}$H) and nitroxyl (ArNH-O$^{\bullet}$) radical species. Coplanarity is no longer attainable in N-aryl-N-alkyl-carbamoyl radicals and these species are sufficiently persistent to be detected by ESR.[111]

Carbamoyl radicals are synthetically extremely useful. Like acyl radicals, they have the ability to undergo *inter*- and *intra*-molecular additions but, unlike acyl radicals, the presence of the adjacent nitrogen heteroatom results in the formation of amides and lactams. The use of free radicals and in particular, carbamoyl radicals in the preparation of lactams will be discussed in the next section. Unlike acyl radicals, carbonylation and decarbonylation reactions are not used in the preparative reactions of carbamoyl radicals.

Wender and Singh have employed a formamide derived radical in their novel synthesis of the pentacyclic sesterterpene (-)-retigeranic acid, a lichen metabolite[112] (Scheme 35).



80 **81**

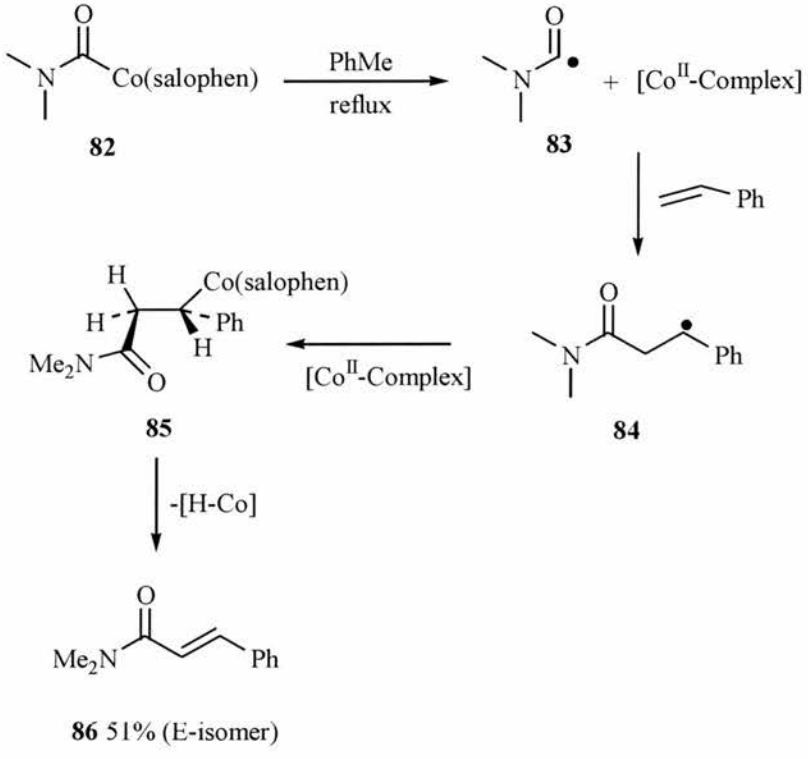


Retigeranic Acid

Scheme 35.

Carbamoylcobalt salophens **70** have recently been employed by Pattenden[103,113] in the generation of carbamoyl radicals and have been used in the synthesis of a range

of cyclic and acyclic compounds including β- and γ-lactams. Organocobalts have a weak metal-carbon bond which readily undergoes homolytic cleavage to give carbamoyl radicals which can be trapped by an alkene to give an amide, or by intramolecular reactions to give lactams. Scheme 36 illustrates the overall reaction scheme for the generation of a carbamoyl radical **83** from the organocobalt **82**. The carbamoyl radical was trapped by the styrene to give the intermolecular addition product **84**. The addition product was trapped by the cobalt(II) salophen species to give **85** which was then added to refluxing toluene in order to release the cinnamide **86**.



Scheme 36

The intramolecular reactions of carbamoyl radicals and, in particular, their use in the preparation of lactams will be discussed in the next section.

1.7 Use of Free Radicals in the Preparation of Lactams

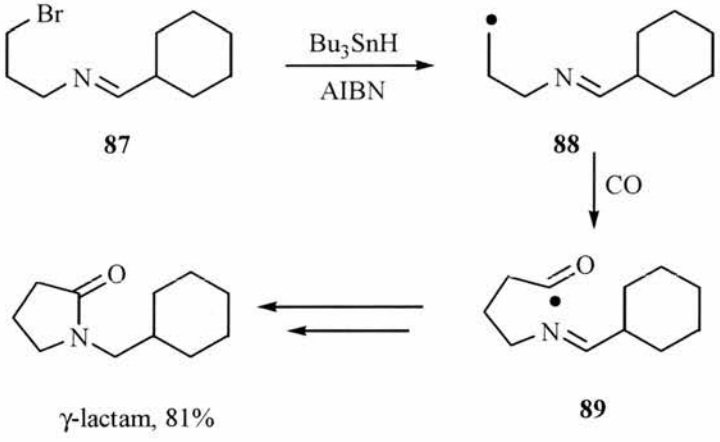
Lactams are well known to be essential constituents in a diverse range of natural and unnatural products of chemotherapeutic interest. In particular, β-lactams have been thoroughly investigated for their potent antibiotic properties.[114] The preparation of

lactams has always provided a challenge for the synthetic organic chemist and free radical chemistry has been employed successfully in the preparation of both β- and γ-lactams.

1.7.1 Free radical routes to γ-lactams.

The preparation of γ-lactams by intramolecular radical reactions has been well investigated. Both 5-*exo* and 4-*endo* cyclisations have been used. Cyclisation of carbamoyl and acyl radicals have been applied and both metal free and metal based free radical precursors have been used.

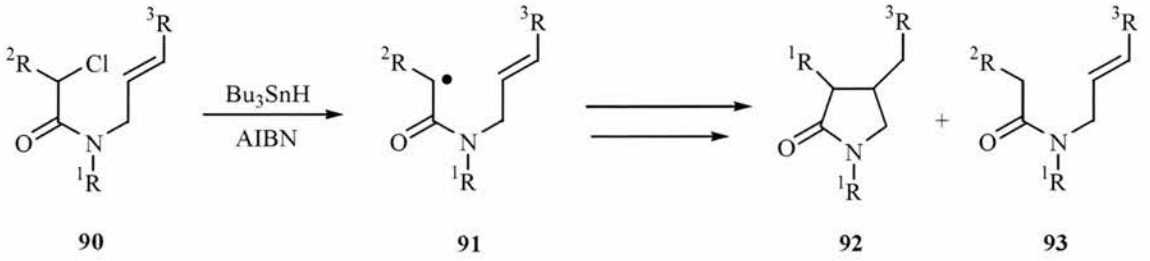
Ryu and co-workers have used acyl radicals in the preparation of lactams.[115] The alkyl radical **88** was generated from the halogenated precursor **87** using tributyltin hydride and AIBN. Using the carbonylation chemistry described earlier, followed by a 5-*exo* cyclisation of the resulting acyl radical **89** onto an iminyl group, the γ-lactam was obtained in 81 % yield (Scheme 37).



Scheme 37

An alternative strategy for the formation of γ-lactams, and one which has received much interest in the last few years is the generation of radicals β- to the nitrogen atom and their subsequent cyclisation onto alkenes.[116,117]

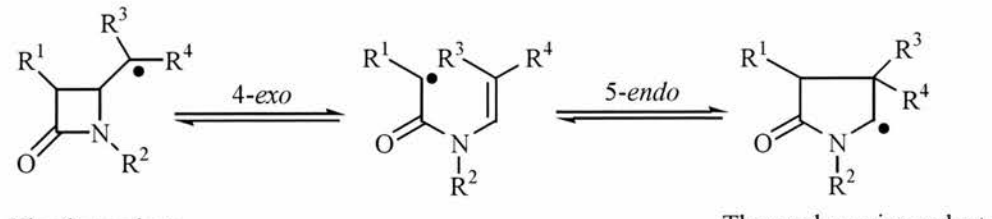
When an unsaturated haloamide **90** was treated with tributyltin hydride in the presence of AIBN, the alkyl radical **91** was formed. This could then undergo 5-*exo* cyclisation to give the lactam **92**. In this case the γ-lactam was isolated along with the uncyclised, direct reduction product **93**. Further work has been carried out by Parsons and co-workers and it has been revealed that yields of the cyclisation product are directly affected by the nature of the *N*-protecting group (R^1) and the substituents attached to the site of radical generation (R^2). As with most radical cyclisations it was found that the nature of the group at the acceptor double bond (R^3) also affected yields.



90 **91** **92** **93**

Scheme 38

It has been demonstrated that γ-lactams can also be prepared via a disfavoured 5-*endo–trig* mode of cyclisation.[118,119] Parsons and co-workers have shown that the carbamoylmethyl radical generated from halo-enamides prefers to form the γ-lactam rather than undergo the more favourable 4-*exo*-trig cyclisation to give the β-lactam.[120] These results have been explained on the basis of a reversible cyclisation mechanism, whereby the 4-*exo* mode of cyclisation produces the kinetically favoured β-lactam **95** while the 5-*endo* cyclisation produces the thermodynamically more stable γ-lactam **96**[121] (Scheme 39).



Kinetic product **95** **94** Thermodynamic product **96**

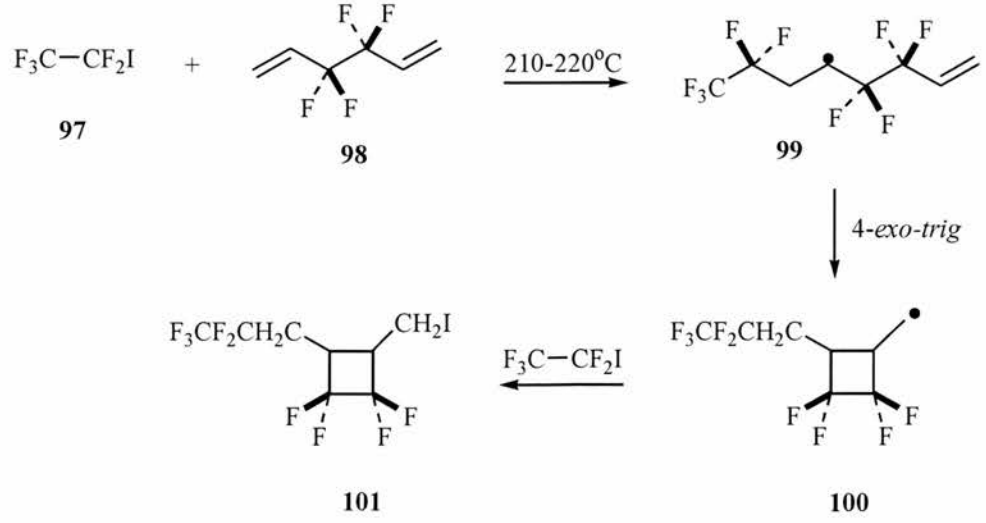
Scheme 39

Cyclisations of enamides have also been carried out under tin-free conditions. Parsons and co-workers have investigated the cyclisation of enamides using copper(I) chloride/bipyridine or dichlorotris(triphenylphosphine)ruthenium(II).[122,123] Very good yields of dienes were obtained via 5-*endo* cyclisations.

1.7.2 Free radical routes to β-lactams.

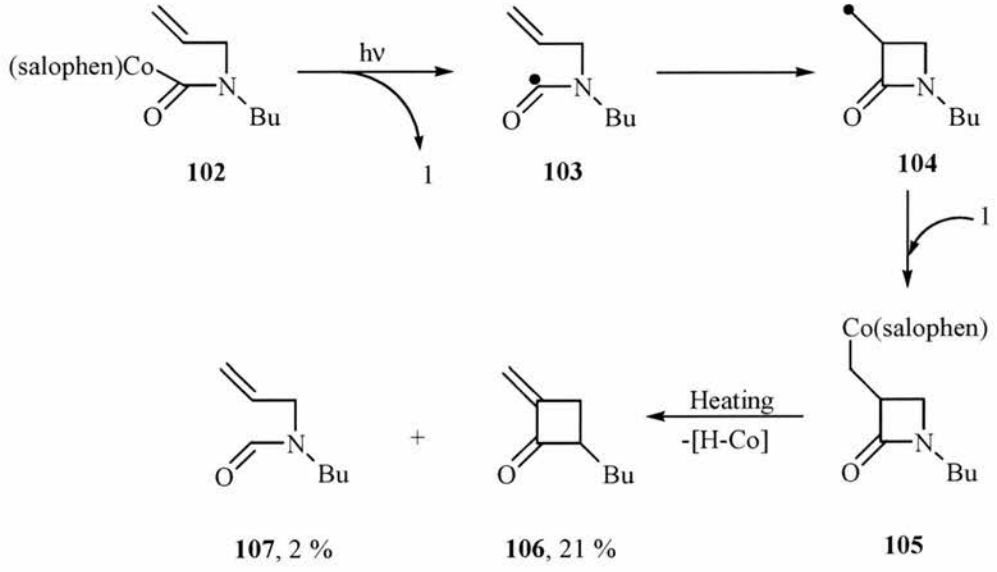
The use of radical cyclisations for the preparation of β-lactams has been well investigated and many examples exist in the literature. The major problem with the preparation of β-lactams via radical cyclisations is the tendency for cyclobutyl radicals to undergo ring opening reactions.[124-126] As was mentioned earlier the 4-*exo-trig* cyclisation is a kinetically favoured process but unless the cyclised species is specially stabilised, then ring opening is quite likely.

The first reported preparation of 4-membered rings by radical cyclisation is Piccardi and co-workers' preparation of cyclobutanes.[127,128] They found that pentafluoroiodoethane **97** reacts at 210-220 °C with 3,3,4,4-tetrafluoro-1,5-diene **98** to give the cyclobutane derivative **101** as a mixture of isomers in good yield (Scheme 40). It has been proposed by Pattenden[113] that this cyclisation is a "special case" due to the high degree of fluorine substitution.



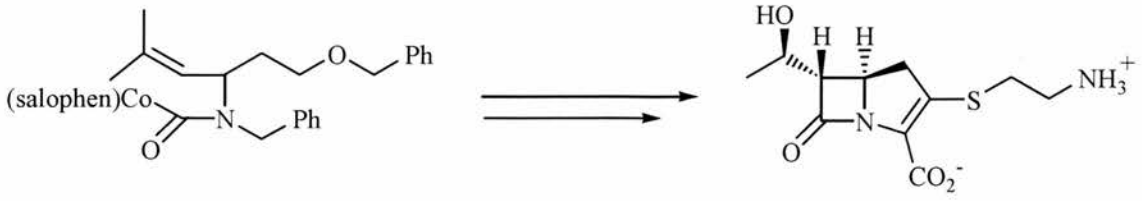
Scheme 40

Many of the precursor types used in the preparation of γ-lactams can also be used in the preparation of β-lactams. For example, the Co(salophen) chemistry developed by Pattenden as precursors for carbamoyl radicals has been applied to the preparation of β-lactams.[103,113] Scheme 41 illustrates how the carbamoyl radical **103** can ring-close via a 4-*exo-trig* cyclisation to generate the β-lactamidomethyl radical **104**, which is then trapped by the cobalt(II) salophen species to give **105**. The Co(salophen) is removed by adding the cyclised product to boiling toluene. This gave the lactam **106** in a yield of 21 %. The uncyclised formamide **107** was also isolated as a by-product in a yield of 2 %.



Scheme 41

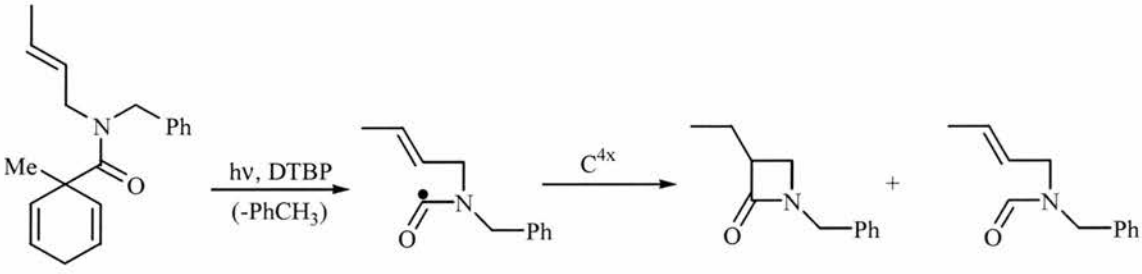
A number of other more complicated β-lactams have been prepared by Pattenden and co-workers. Of particular interest is the total synthesis of (+/-) thienamycin **109** where the key step is a 4-*exo*-trig cyclisation of a carbamoyl radical onto an alkene (Scheme 42).



108 **109**

Scheme 42

As was previously mentioned, cyclohexadiene derivatives have been developed by Walton and co-workers as "clean" precursors for carbamoyl radicals.[108] These carbamoyl radicals have been applied to the preparation of β-lactams.[129] Scheme 43 shows the cyclohexadiene precursor which on photolysis in the presence of DTBP gives the carbamoyl radical (with loss of toluene). The carbamoyl radical can undergo 4-*exo trig* cyclisation to give the β-lactam in 34 % yield. Some of the uncyclised formamide was also isolated (31 %).

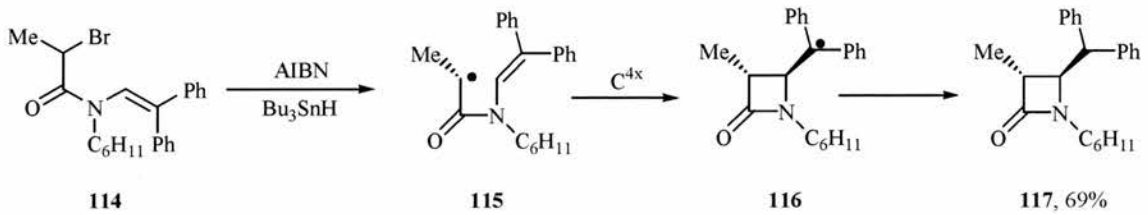


110 **111** **112**, 34 % **113**, 31 %

Scheme 43

The use of enamides as precursors for the preparation of γ-lactams via 5-*endo* cyclisations has been discussed in an earlier section. It was mentioned at the time that the competing cyclisation was a 4-*exo* cyclisation, but thermodynamic factors favoured formation of the 5-*endo* product. Since this discovery, much research has been carried out to try and understand the factors which control the regioselectivity of enamide cyclisation[130,131] and now a number of systems have been developed which give the 4-*exo* product exclusively.

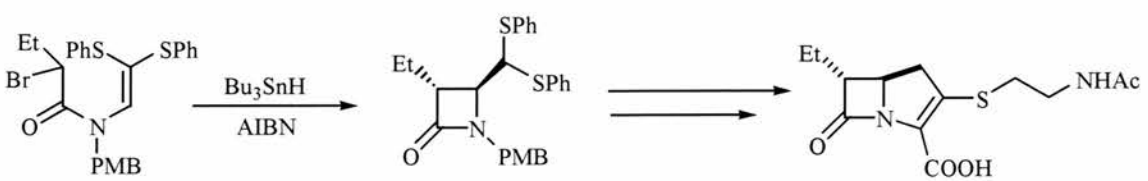
It was quickly realised that in order for enamides to undergo the thermodynamically less favoured 4-*exo* route, it would be necessary to stabilise the cyclised radical. Work undertaken by Belletire and co-workers[132] demonstrated that the introduction of a simple diphenyl group onto the vinyl terminus **114** resulted in exclusive formation of the β-lactam **117** in good yield (Scheme 44).



114 **115** **116** **117**, 69%

Scheme 44

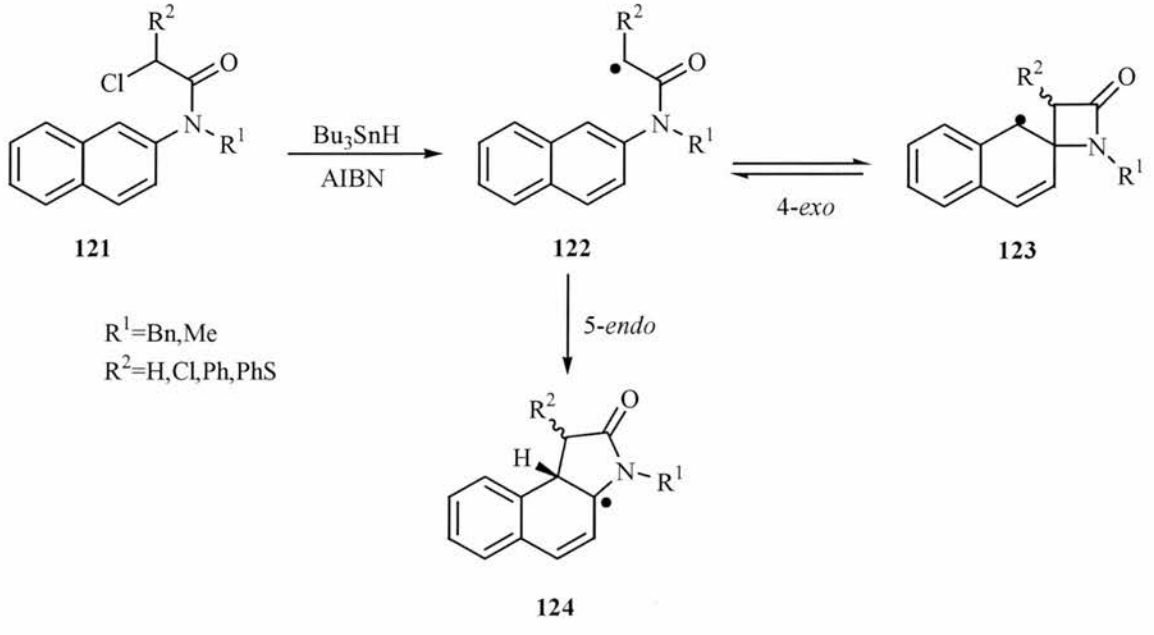
Much of the research into control of regioselectivity (and indeed stereoselectivity) of enamide cyclisation has been carried out by Ikeda and co-workers.[130,131,133-135] Most of their initial research also focussed on stabilisation of the cyclised radical in order to promote the 4-*exo trig* process. One of the most successful approaches was stabilisation through the use of sulphur substituents.[131] In an analogous approach to Belletire's work, phenylthio groups were incorporated into the vinyl terminus and this gave the β-lactam **119** in 70 % yield. They then applied this methodology to the total synthesis of PS-5 **120** which is a carbapenam antibiotic, effective against bacteria including β–lactamase producing organisms.[136] Scheme 45 illustrates the total synthesis of PS-5 **120** where the key step is a 4-*exo-trig* cyclisation of an alkyl radical onto a carbon-carbon double bond.



118 **119** **120**

Scheme 45

After investigating the effect of varying substituents on the vinyl group, Ikeda and co workers then turned their attention to the substituents attached directly to the site of radical formation. Ikeda demonstrated that by varying the nature of the group attached to the initially formed carbamoylmethyl radical it was possible to influence the regioselectivity of the cyclisation step. It was found that when R^2 = H or Cl in **121**, the formation of the β-lactam was favoured, however when the substituent was replaced by one that aided radical stabilisation, such as methyl or thiophenyl, then the γ-lactam was favoured.

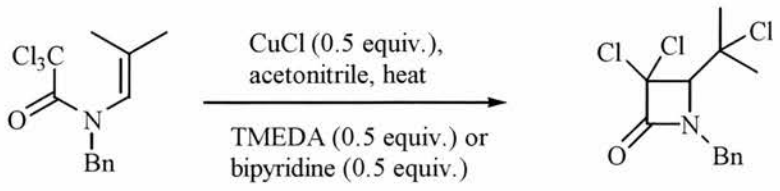


Scheme 46

The reason for this substituent effect is again based on the known reversibility of the 4-*exo-trig* cyclisation. The 4-*exo-trig* cyclisation in Scheme 46 is favoured since the resulting radical **123** is resonance stabilised by the adjacent benzene ring. When R^2 = H or Cl, the subsequent reduction of this radical intermediate is faster than the ring opening step and hence the β-lactam is formed. However, when the substituent R^2 is a radical stabilising group then the rate of ring opening is much faster and therefore reduction takes place after the thermodynamically more stable 5-*endo-trig* product **124** has been formed.

Parsons and co-workers have also investigated the factors which promote the 4-*exo-trig* mode of cyclisation of enamides.[120] It was found that when trichloro-enamide

125 was reacted with copper(I) chloride/bipyridine or copper(I) chloride/TMEDA in boiling acetonitrile, only the β-lactam **126** was formed in 85-86 % yield (Scheme 47).

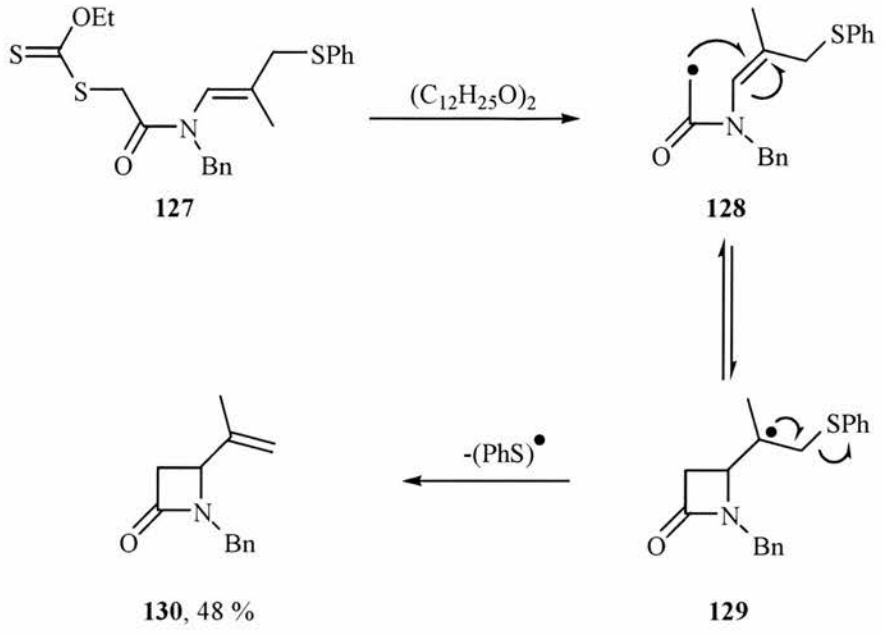


125 **126**, 85-86 %

Scheme 47

The change in regioselectivity of the cyclisation is once again attributed to the reversibility of the 4-*exo-trig* cyclisation. In this case the determining factor is not the nature of the substituents but the solubility of the oxidising agent. The copper complex is soluble in acetonitrile, and so fast oxidation can occur. The 4-*exo*-product is kinetically favoured and so forms first. Oxidation to give **126** is rapid and occurs faster than ring opening. This results in a high yield of the β-lactam. The experiment was repeated in toluene. In this case the oxidising agent is only sparingly soluble and oxidation is slow. In this case the thermodynamically more stable γ-lactam was formed.

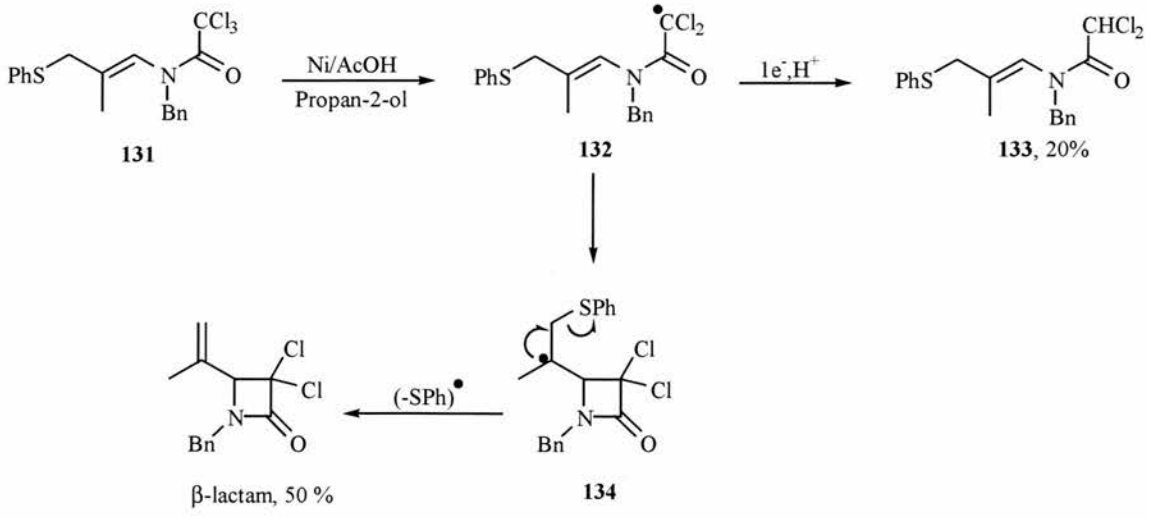
Zard and co-workers[137,138] have applied their xanthate chemistry to the preparation of β-lactams. The xanthate method has a number of advantages. In particular the long life time of the intermediate radical (by being continuously regenerated) allows it to undergo difficult cyclisations or additions to unactivated olefins. Scheme 48 illustrates how the xanthate precursor **127** can be used in the preparation of a β-lactam. When the N-alkenylacetamide **127** is initiated using lauroyl peroxide, the xanthate group is displaced to give the carbamoylmethyl radical **128**. This can then participate in a 4-*exo-trig* cyclisation, which is pushed to completion through loss of a phenylthiyl radical to give the β-lactam **130** in good yield (48 %).



127 **128** **129** **130**, 48 %

Scheme 48

Zard and co-workers have also prepared β-lactams using nickel powder as the radical initiator. The nickel powder method of radical formation is a reductive process. The main difficulty in reductive methodology is in finding a system which is able to readily transfer one electron to the radical precursor, while having a second electron transfer which remains sufficiently slow to allow the radical intermediate to undergo cyclisation. Recent studies by Zard and co-workers have highlighted the use of nickel powder as such a system.[138] Scheme 49 illustrates the mode of action of nickel powder and how it has been used to prepare β-lactams.

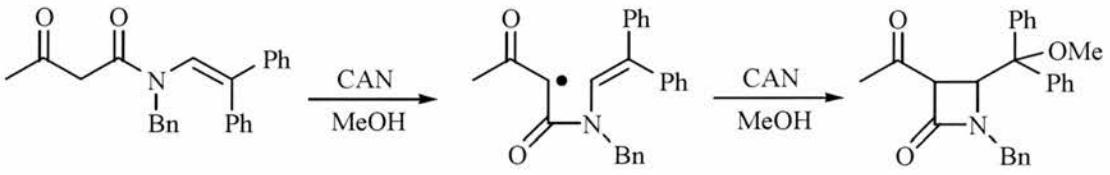


131 **132** **133**, 20% **134** β-lactam, 50 %

Scheme 49

The methodology for promoting 4-*exo-trig* cyclisation in this case was the same as for the xanthate example. Loss of the phenylthiyl radical promoted formation of the 4-*exo* prodct and none of the 5-*endo* product was observed.

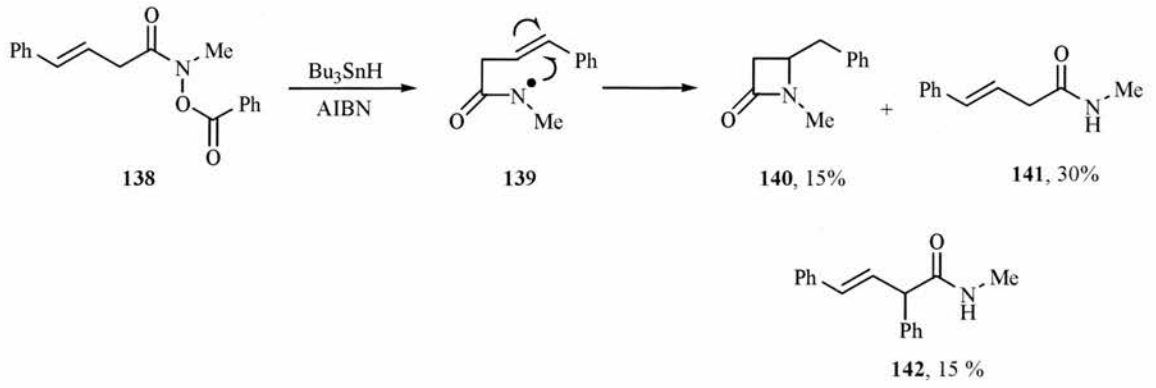
The use of cerium(IV) ammonium nitrate (CAN) in oxidative radical generation was first investigated by Heiba and Dessau.[139] Recent studies by Trogolo and co-workers have shown how this methodology can be applied to the preparation of β-lactams.[140-142] The oxidative process uses metal salts with adjacent, stable, oxidation states to remove an electron from a dicarbonyl radical precursor **135** in order to generate the carbon centered radical **136**, which is immune to further oxidation due to its electrophilic nature. The radical then undergoes a 4-*exo* cyclisation to furnish the β-lactam which is more susceptible to oxidation. The cyclised species **137** is finally attacked by a nucleophile or loses a proton to yield an alkene (Scheme 50).



135 **136** **137**, 48 %

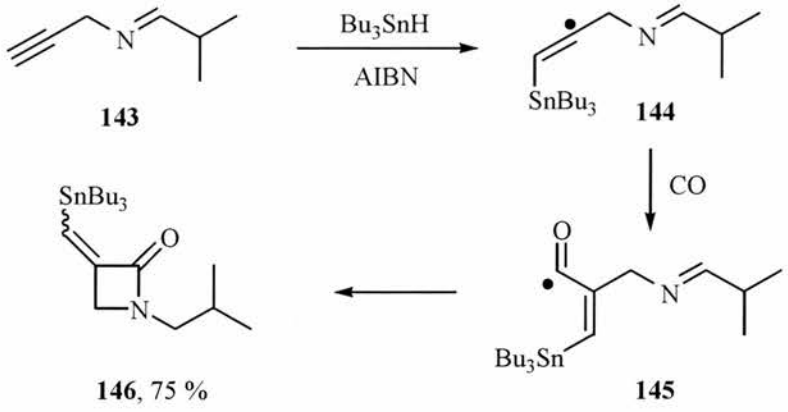
Scheme 50

Recently Clark and Peacock have investigated the 4-*exo* cyclisations of amidyl radicals.[143] Using Zard's procedure for the generation of amidyl radicals from *O*-benzoyl hydroxamic acid derivatives[144] they observed the formation of β-lactams via a 4-*exo-trig* cyclisation, albeit in low yields. By-products including the reduced product **141** and a rearranged product **142** were also isolated. Attempts to optimise the methodology did not result in greatly improved yields of the desired β-lactam **140** (Scheme 51).



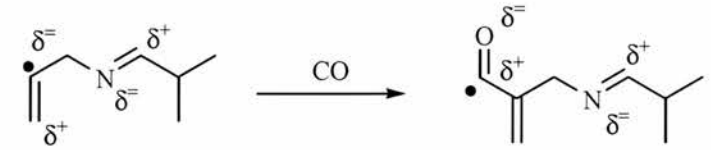
Scheme 51

In a very recent study,[91] Ryu and co-workers have illustrated how carbonylation of acyl radicals can also be applied to the preparation of β-lactams. Using the free radical mediated stannylcarbonylation of azaenynes, a number of α-stannylmethylene lactams were prepared. The azaenyne **143**, on treatment with tinhydride and AIBN gave the carbon centered radical **144**. Carbonylation gave the acyl radical which then underwent 4-*exo*-*trig* cyclisation onto the imine to give the β-lactam in good yield.



Scheme 52

Ryu has suggested that cyclisation onto the imine is promoted by polarity matching. Cyclisation of vinyl radicals onto N=C double bonds is highly inefficient, due to polarity mismatching, however when carbon monoxide is added the system becomes polarity matched and cyclisation is more favourable (Scheme 53).



Polarity mismatched Polarity matched

Scheme 53

It is obvious from these examples that free radicals are useful in the preparation of β-lactams and have established themselves as extremely useful tools for organic synthesis. It is also obvious however that a keen understanding of all factors involved is necessary before useful results can be obtained. A modern technique which is now becoming widespread for the monitoring of free radicals is ESR spectroscopy.

1.8 Electron Spin Resonance Spectroscopy (ESR)

Electron spin resonance spectroscopy (ESR), also known as electron paramagnetic resonance (EPR), is related to the study of species containing one or more unpaired electrons and therefore can be applied to the study of free radicals. The technique was first developed in 1945[145] and since then has found many applications in physics, chemistry and biology. The technique is extremely sensitive and can be used to detect radicals down to concentrations of 10^{-8} M.

The principles of ESR are closely related to those of NMR spectroscopy. Just like the proton in NMR spectroscopy, the electron spin in ESR has an associated magnetic moment. Consequently, the electron will have two distinct energy levels in an applied magnetic field and will undergo transitions between spin states if energy of the correct frequency is applied.

ESR records the magnetic resonance spectrum of unpaired electrons. The ESR spectrum of a paramagnetic compound in an external magnetic field B can be described using a Hamiltonian operator (Eqn 1)

$$\mathbf{H} = \mathbf{H}_{EZ} + \mathbf{H}_{NZ} + \mathbf{H}_{EN} + \mathbf{H}_{Q} \qquad \text{Eqn 1}$$

$\mathbf{H}_{EZ}$ is the electronic Zeeman operator, which represents the interaction between the electron spin **S** and the external field **B**. Unpaired electrons have a non-classical intrinsic angular momentum called spin. The spin is characterised by the quantum number $M_S = (+/-)1/2$, that gives two spin states differing in M_S.

$$M_S = +\ 1/2\text{: spin up } (\uparrow) \text{ or } \alpha$$
$$M_S = -1/2\text{: spin down } (\downarrow) \text{ or } \beta$$

The magnetic moment μ is is derived from the spin state using the equation $\mu = -g\beta M_s$, where M_s is the electron spin, β is the Bohr magneton ($eh/4\pi m$ = 9.2733E-24 JT^{-1}, where e and m are the charge and mass of the electron and h = 6.624E-27 is the Planck constant), and g is a dimensionless number whose value for a free electron is 2.0023. The interaction of this magnetic moment and the applied magnetic field can therefore be described by (Eqn 2).

$$\mathbf{H}_{EZ} = -\mu.\mathbf{B} = g\beta M_S.\mathbf{B} \qquad \text{Eqn 2}$$

In the absence of a magnetic field the two spin states are degenerate, i.e. they have the same energy. When the magnetic field B, is applied it interacts with the magnetic moment and the spin states are no longer degenerate. This is known as the Zeeman effect and the difference in energy between the levels is given by the equation $\Delta E = g\beta B$. If electromagnetic radiation of a frequency equivalent to this value of ΔE is applied, absorption takes place and transitions from the lower energy state to the higher energy state and vice-versa can occur (Figure 1). In a field of 3400 Gauss, the Larmor frequency of a free electron will be 9.2 GHz, therefore EPR spectra are recorded in the microwave region of the electro-magnetic spectrum.

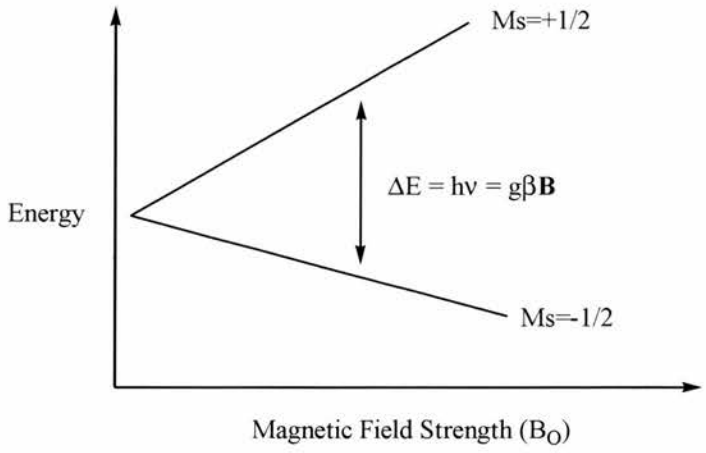


Fig 1

The spin state of a free electron is influenced by its local atomic environment, which in turn affects the g-value of the electron and its magnetic moment. In a magnetic field the unpaired electron possesses, in addition to its spin angular momentum, a small amount of extra orbital angular momentum. It is the interaction between these, called spin-orbit coupling which results in electrons having a different effective magnetic moment from that of the free electron. Since the equation for energy required for resonance is dependent on the magnetic moment, this implies that radicals of differing g-values will resonate at different field strengths.

The nuclear Zeeman operator, $\mathbf{H}_{NZ}$ represents the interaction between the nuclear spin and the external magnetic field $\mathbf{B}_0$. This value is very small and is often negligible as the nuclear magneton is approximately 1836 times smaller than the Bohr magneton. As a result the Zeeman energy is very much smaller than its electronic counterpart and can often be ignored.

The term $\mathbf{H}_{EN}$ describes the interaction between the electron spin and the local nuclear spins. Hyperfine splitting into a number of distinct lines can occur when there is an interaction between the electron magnetic moment and the magnetic moment of neighbouring magnetic nuclei and, analogous to NMR, the number of lines arising from hyperfine splitting is dependent on the number of nuclear spin orientations.

If a paramagnetic compound contains one magnetic nucleus in close proximity to the free electron, the unpaired electron will experience a local magnetic field arising from the magnetic nucleus. For example, the proton spin has two possible orientations which are parallel and antiparallel to the electron. There are four possible transitions but since the nuclear spin quantum number (M_I) cannot change during a transition, only two transitions are allowed. For this reason the hydrogen atom will therefore give a spectrum of two lines of equal intensity. The separation between the two lines is known as the hyperfine splitting and in general can be used to deduce structural information about a free radical. As a general rule the spectrum will contain $(2nI+1)$ lines where I is the spin quantum number of the nucleus and n is the number of equivalent nuclei present.

$\mathbf{H_Q}$ describes the nucleur quadrupolar energy. This occurs when some nuclei with spins of 1 or more possess an electric quadrupole moment, as the distribution of charge density within the nucleus is not spherical. This does not occur in the organic molecules described in this thesis and can be ignored.

The net result of eliminating these operations from the Hamiltonian operator given in (Eqn 1), gives a simplified equation for the spectrum observed using ESR (Eqn 3).

$$H = g\beta \mathbf{B}oS_Z + aS_ZI_Z \qquad \text{Eqn 3}$$

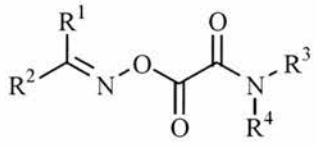
In solids the radicals are fixed and can be orientated in any direction with respect to the applied magnetic field. This means that the α- and g-valves can take on a number of different values. However in solution phase ESR, molecular tumbling averages the values of α and g resulting in simplified spectra.

As was mentioned earlier, a deep understanding of the kinetics of radical cyclisation is necessary for the planning and understanding of radical reactions. ESR has been applied to the study of both dissociation and cyclisation kinetics and has provided valuable information for planning synthetic strategies.

1.9 Research Aims and Objectives

It is clear from the material covered in this introduction that free radicals are a powerful tool for synthetic organic chemistry and have been used to prepare an impressive range of complex organic molecules. However it is also clear that the dependence on tin-hydride and other metal based chemistry is holding back its application to general synthesis.

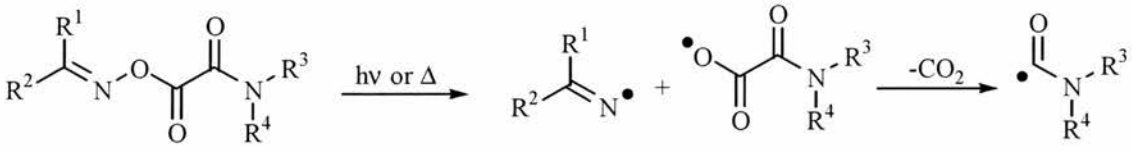
This PhD project had a number of aims and objectives, of which, the primary aim was the development of a novel "clean" free radical precursor. The system envisaged was the oxime oxalate amide **147**.



147

The first aim was to find an efficient, versatile, synthetic route to oxime oxalate amides. Once the precursor molecule had been prepared it was hoped to test it as a source of free radicals both thermally and photochemically.

The oxime oxalate amide was designed to act as a precursor for both iminyl **149** and carbamoyl **151** radicals (Scheme 54).

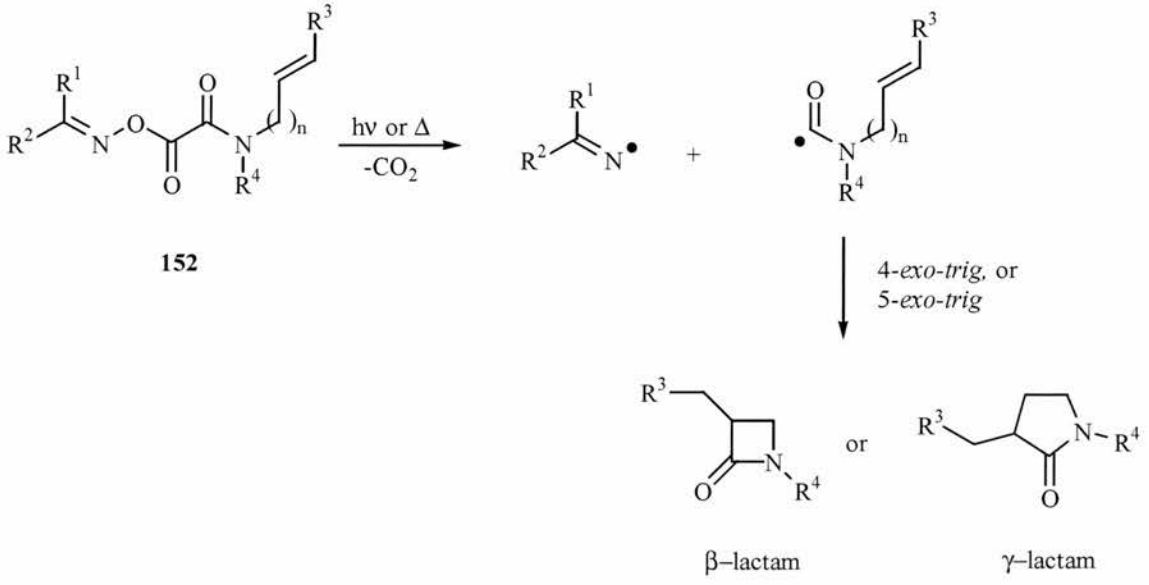


148 **149** **150** **151**

Scheme 54

The second aim of the project was to investigate the photochemistry of these compounds using ESR spectroscopy and end product analysis.

The third aim was to design and prepare oxime oxalate amides which had a proximate double bond suitable for ring closure of the carbamoyl radical. It was hoped in this way to prepare some novel β- and γ-lactams (Scheme 55).

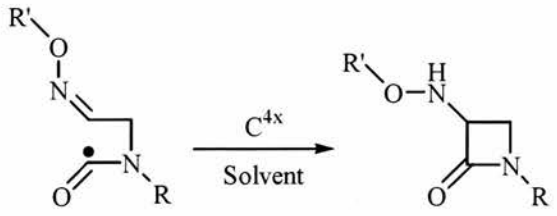


Scheme 55

The preparation of lactams could then be used to optimise conditions and to determine the ideal conditions for photolysis.

It was also an aim of this project to monitor the photochemistry of these systems and to characterise the radicals using ESR spectroscopy. At low temperature it was expected that the iminyl and carbamoyl radicals would be detected, whereas at higher temperatures it was expected that the cyclised species would predominate. These ESR studies would serve to validate proposed mechanisms and might also provide some useful kinetic data.

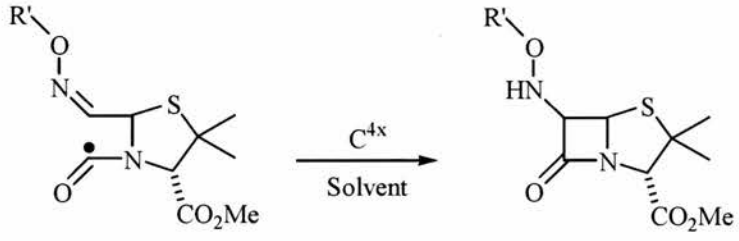
Another aim of the project was to observe cyclisation of carbamoyl radicals onto groups other than C-C double bonds. Oxime ethers in particular were expected to aid cyclisation and also to introduce nitrogen functionality into the cyclised species (Scheme 56).



153 **154**

Scheme 56

The final aim of the project was to use carbamoyl radicals in the preparation of some β-lactam containing natural products. In particular it was envisaged that cyclisation of a carbamoyl radical onto an oxime ether attached to a thiazolidine ring could provide a novel radical route to penicillins (Scheme 57).



155 **156**

Penicillin

Scheme 57

1.10 References

(1) M. Gomberg, *J. Am. Chem. Soc.*, 1900, **22**, 757.

(2) D. H. Hay and W. A. Waters, *Chem. Rev.*, 1937, **21**, 169.

(3) P. Renaud and M. P. Sibi *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.

(4) W. B. Motherwell and D. Crich *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: San Diego, 1992.

(5) D. P. Curran, *Synthesis,* 1988, 417 and 489.

(6) B. Geise *Radicals in Organic Synthesis; Formation of Carbon-Carbon bonds*; Pergamon Press: Oxford, 1986.

(7) J. C. Walton and P. A. Baguley, *Angew. Chem. Int. Ed.*, 1998, **37**, 3073.

(8) J. Cassayre, F. Gagosz and S. Z. Zard, *Angew. Chem. Int. Ed.*, 2002, **41**, 1783.

(9) S. Z. Zhou, S. Bommezijn and J. A. Murphy, *Organic Lett.*, 2002, **4**, 443.

(10) H. G. Kuivila, L. W. Menapace and C. R. Warner, *J. Am. Chem. Soc.*, 1962, **84**, 3584.

(11) B. Giese, J. A. Gonzalez-Gomez and T. Witzel, *Angew. Chem.*, 1984, **96**, 51.

(12) B. Giese, J. A. Gonzalez-Gomez and T. Witzel, *Angew. Chem Int. Ed.*, 1984, **23**, 69.

(13) D. L. J. Clive and W. Yang, *J. Org. Chem.*, 1995, **60**, 2607-2609.

(14) K. Nishiyama and M. Oba, *Tetrahedron Lett.*, 1993, **34**, 3745-3748.

(15) D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1991, **32**, 7187-7190.

(16) C. Chatgilialoglu, C. Ferreri and M. Lucarini, *J. Org. Chem.*, 1993, **58**, 249-251.

(17) D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *49,* 1993, 7193-7214.

(18) C. Chatgilialoglu, D. Griller and M. Lesage, *J. Org. Chem.*, 1988, **53**, 3641-3642.

(19) B. Giese, B. Kopping and C. Chatgilialoglu, *Tetrahedron Lett.*, 1989, **30**, 681-684.

(20) C. Chatgilialoglu, *Acc. Chem. Res.*, 1992, **25**, 188-194.

(21) C. Chatgilialoglu and S. Rossini, *Bull. Soc. Chim. Fr.*, 1988, 298.

(22) B. Kopping, C. Chatgilialoglu, M. Zehnder and B. Giese, *J. Org. Chem.*, 1992, **57**, 3994-4000.

(23) P. Pike, S. Hershberger and J. Hershberger, *Tetrahedron,* 1988, **44**, 6295-6304.

(24) P. Pike, S. Hershberger and J. Hershberger, *Tetrahedron Lett.,* 1985, **26**, 6289-6290.

(25) I. Ryu, K. Kusano, A. Ogawa, N. Kambe and N. Sonoda, *J. Am. Chem. Soc.,* 1990, **112**, 1295.

(26) I. Ryu, K. Kusano, N. Masumi, H. Yamazaki, A. Ogawa and N. Sonoda, *Tetrahedron Lett.,* 1990, **31**, 6887.

(27) S. Z. Zard, *Angew. Chem. Int. Ed.,* 1997, **36**, 672-685.

(28) C. Chatgilialoglu and M. Ballistri, *Organometallics,* 1995, **14**, 5017-5018.

(29) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1,* 1975, 1574-1585.

(30) D. H. R. Barton *Half a Century of Free Radical Chemistry*; Cambridge University Press: Cambridge, 1993.

(31) D. H. R. Barton, E. Castagnino and J. C. Jaszberenyi, *Tetrahedron Lett.,* 1994, **30**, 6057-6060.

(32) D. H. R. Barton, J. C. Jaszberenyi and E. A. Theodorakis, *Tetrahedron,* 1992, **48**, 2613-2626.

(33) D. H. R. Barton, J. C. Jaszberenyi and A. I. Morell, *Tetrahedron Lett.,* 1991, **32**, 311-314.

(34) P. Kocienski, M. Stocks, D. Donald and M. Perry, *Synlett.,* 1990, 38-39.

(35) J. Cossy, J. L. Ranaivosata and V. Bellosta, *Tetrahedron Lett.,* 1994, **35**, 8161-8162.

(36) C. K. Sha, K. C. Santhosh, C. T. Tseng and C. T. Lin, *Chem. Commun.,* 1998, 397-398.

(37) J. H. Penn and F. Liu, *J. Org. Chem.,* 1994, **59**, 2608-2612.

(38) J. E. Brumwell, N. S. Simpkins and N. K. Terrett, *Tetrahedron Lett.,* 1993, **34**, 1215-1218.

(39) J. M. Surzur *In Reactive Intermediates*; Plenum Press: New York, 1980.

(40) K. N. Houk, M. N. Paddon-Row, D. C. Spellmeyer, N. G. Rondan and S. Nagase, *J. Org. Chem.,* 1986, **51**, 2874.

(41) D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.,* 1987, **52**, 959.

(42) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron Lett.,* 1985, **26**, 373.

(43) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron,* 1985, **41**, 3925.

(44) J. Baldwin, *Chem. Commun.,* 1976, 734, 736 and738.

(45) A. L. J. Beckwith, C. J. Easton, T. Lawrence and A. K. Serelis, *Aust. J. Chem,* 1983, **36**, 545.

(46) C. Ericsson and L. Engman, *Org. Lett.,* 2001, **3**, 3459.

(47) M. Besev and L. Engman, *Org. Lett.,* 2002, **4**, 3023.

(48) M. P. Sibi, T. R. Rheault, H. Miyabe, K. Patil and C. P. Jesperse, *C. R. Acad. Sci. Ser IIc: Chim.,* 2001, **4**, 581.

(49) O. Miyata, Y. Ozawa, I. Ninomiya and T. Naito, *Tetrahedron,* 2000, **56**, 6199.l.

(50) A. L. J. Beckwith, *Chem. Commun.,* 1974, 472.

(51) E. W. Della and S. D. Graney, *Tetrahedron Lett.,* 2000, **41**, 7987.

(52) A. Kamimura, Y. Taguchi, Y. Omata and M. Hagihara, *J. Org. Chem.,* 2003, **68**, 4996-4998.

(53) C. Chatgilialoglu, D. Crich and I. Ryu, *Chem. Rev.,* 1999, **99**, 1991.

(54) K. W. Watkins and W. W. Word, *Int. J. Chem. Kinet.,* 1974, **6**, 855.

(55) K. W. Watkins and W. W. Thompson, *Int. J. Chem. Kinet.,* 1973, **5**, 791.

(56) A. Bakac and J. H. Espenson, *Chem. Commun.,* 1991, 1497.

(57) E. Gorin, *J. Phys. Chem.,* 1939, **7**, 256.

(58) D. S. Herr and W. A. Noyas, *J. Am. Chem. Soc.,* 1940, **62**, 2052.

(59) H. Fischer and H. Paul, *Acc. Chem. Res.,* 1987, **20**, 200.

(60) J. K. Vollenweider and H. Paul, *Int. J. Chem. Kinet.,* 1986, **18**, 791.

(61) C. Chatgilialoglu and M. Lucarini, *Tetrahedron Lett.,* 1995, **36**, 1299.

(62) C. Chatgilialoglu, C. Ferreri, M. Lucarini, P. Pedrielli and G. F. Pedulli, *Organometallics,* 1995, **14**, 2672.

(63) Y. P. Tsentalovich and J. H. Fischer, *J. Chem. Soc., Perkin Trans. 2,* 1994, 729.

(64) M. E. Jacox, *Chem. Phys.,* 1982, **69**, 407.

(65) L. Lunazzi, K. U. Ingold and J. C. Scaiano, *J. Phys. Chem.,* 1983, **87**, 529.

(66) G. J. M. van.der.Kerk, J. G. Noltes and J. G. A. Luijten, *J. Appl. Chem.,* 1957, **7**, 356.

(67) H. G. Kuivila, *Adv. Organomet. Chem.,* 1964, **1**, 47.

(68) E. J. Kupchik and R. J. Kiesel, *J. Org. Chem.,* 1966, **29**, 3690.

(69) J. Lusztyk, E. Lusztyk, B. Maillard and K. U. Ingold, *J. Am. Chem. Soc.,* 1984, **106**, 2923.

(70) J. Lusztyk, E. Lusztyk, B. Maillard and K. U. Ingold, *J. Am. Chem. Soc.,* 1983, **105**, 4475.

(71) J. R. Grunwell, N. A. Marron and S. I. Hanhan, *J. Org. Chem.,* 1973, **38**, 1559.

(72) H. Tomioka, Y. Takimoto, M. Kawabata, M. Harada, J. P. Fouassier and D. Ruhlmann, *J. Photochem. Photobiol.,* 1990, **53**, 359.

(73) D. L. Bodger and R. J. Mathvink, *J. Org. Chem.,* 1988, **53**, 3377.

(74) D. Crich and S. M. Fortt, *Tetrahedron,* 1989, **45**, 6581.

(75) D. Crich and Q. Yao, *J. Org. Chem.,* 1996, **61**, 3566.

(76) D. Crich, J. T. Hwang and H. Yuan, *J. Org. Chem.,* 1996, **61**, 6189.

(77) R. D. Webster and A. M. Bond, *J. Org. Chem.,* 1997, **62**, 1779.

(78) S. Osaki, M. Adachi, S. Sekiya and R. Kamikawa, *J. Org. Chem.,* 2003, **68**, 4586-4589.

(79) S. Osaki, H. Yoshinaga, E. Matsui and M. Adachi, *J. Org. Chem.,* 2001, **66**, 2503-2505.

(80) J. Pfenninger, C. Henberger and W. Graf, *Helv. Chim. Acta.,* 1980, **63**, 2328.

(81) J. Pfenninger and W. Graf, *Helv. Chim. Acta.,* 1980, **63**, 1562.

(82) C. Chen and D. Crich, *Tetrahedron Lett.,* 1993, **34**, 1545.

(83) C. Chen, D. Crich and A. Papadatos, *J. Am. Chem. Soc.,* 1992, **114**, 8313.

(84) C. E. Brown, A. G. Neville, D. M. Rayner, K. U. Ingold and J. Lusztyk, *Aust. J. Chem.,* 1995, **48**, 363.

(85) T. Sumiyoshi, W. Schnabel, A. Henne and P. Lechkten, *Polymer,* 1985, **26**, 141.

(86) K. Faltings, *Ber.,* 1939, **72B**, 1207.

(87) I. Ryu and N. Sonoda, *Angew. Chem. Int. Ed.,* 1996, **35**, 1050.

(88) S. Berlin, C. Ericsson and L. Engman, *Org. Lett.,* 2002, **4**, 3.

(89) I. Ryu, T. Niguma, S. Minakata, M. Komatsu, S. Hadida and D. P. Curran, *J. Org. Chem.,* 1994, **59**, 7570.

(90) S. Tsunoi, I. Ryu, H. Muraoka, M. Tanaka, M. Komatsu and N. Sonoda, *Tetrahedron Lett.,* 1996, **37**, 6729.

(91) I. Ryu, H. Miyazato, H. Kuriyama, K. Matsu, M. Tojino, T. Fukuyama, S. Minakata and M. Komatsu, *J. Am. Chem. Soc.,* 2003, **125**, 5632-5633.

(92) N. Turro *Modern Molecular Photochemistry*; Benjamin/Cummins: Menlo Park, 1978.

(93) C. Chatgilaloglu, D. Crich and I. Ryu, *Chem. Rev.,* 1999, **99**, 1991.

(94) C. E. Schwartz and D. P. Curran, *J. Am. Chem. Soc.,* 1990, **112**, 9272.

(95) G. Pattenden, L. Roberts and W. S. Li, *Tetrahedron Lett.,* 1996, **37**, 4191.

(96) G. Pattenden, L. Roberts and A. J. Blake, *J. Chem. Soc., Perkin Trans. 1,* 1998, 863.

(97) S. Handa and G. Pattenden, *Chem. Commun.,* 1998, 311.

(98) P. H. Mazzocchi and M. J. Bowen, *J. Org. Chem.,* 1976, **41**, 1279.

(99) D. Elad and J. Rokach, *J. Org. Chem.,* 1964, **29**, 1855.

(100) D. Elad and J. Rokach, *J. Org. Chem.,* 1965, **30**, 3361.

(101) D. Elad and J. Rokach, *J. Chem. Soc.,* 1965, 800.

(102) G. Bryon.Gill, G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1,* 1994, 369-378.

(103) G. B. Gill, G. Pattenden and S. J. Reynolds, *Tetrahedron Lett.,* 1989, **33**, 3057.

(104) F. Minisci, F. Fontana, F. Coppa and Y. M. Yan, *J. Org. Chem.,* 1995, **60**, 5430-5433.

(105) F. Minisci, *Synthesis,* 1973, 1.

(106) M. Sakamoto, M. Takahashi, T. Fujita, T. Nishio, I. Iida and S. Watanabe, *J. Org. Chem.,* 1995, **60**, 4683.

(107) J. H. Rigby, D. M. Danca and J. H. Horner, *Tetrahedron Lett.,* 1998, **39**, 8413-8416.

(108) A. F. Bella, L. V. Jackson and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2,* 2002, 1839-1843.

(109) T. Yonezawa, I. Noda and T. Kawamura, *Bull. Chem. Soc. Jpn.,* 1969, **42**, 650.

(110) R. Sutcliffe and K. U. Ingold, *J. Am. Chem. Soc.,* 1981, **103**, 7686.

(111) L. Grossi, *Chem. Commun.,* 1989, 1248-1250.

(112) P. A. Wender and S. K. Singh, *Tetrahedron Lett.,* 1990, **31**, 2517.

(113) G. B. Gill, G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1,* 1994, 369-378.

(114) A. G. Brown and S. M. Roberts *Recent Advances in the Chemistry of β-Lactam Antibiotics*; Royal Society of Chemistry: London, 1984.

(115) I. Ryu, K. Matsu, S. Minikata and M. Komatsu, *J. Am. Chem. Soc.,* 1998, **120**, 5838.

(116) J. S. Bryans, J. M. Large and A. F. Parsons, *J. Chem. Soc., Perkin Trans. 1,* 1999, 2897-2904.

(117) A. F. Parsons and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1,* 1994, 1945.

(118) S. R. Baker, K. I. Burton, A. F. Parsons, J. F. Pons and M. J. Wilson, *J. Chem. Soc., Perkin Trans. 1,* 1999, 427-436.

(119) S. R. Baker, K. Goodall, A. F. Parsons and M. J. Wilson, *J. Chem. Res.*, 2000, 312-313.

(120) J. S. Bryans, N. E. A. Chessum, A. F. Parsons and F. Ghelfi, *Tetrahedron Lett.*, 2001, **42**, 2901-2905.

(121) M. Ikeda, S. Ohtani, T. Yamamoto, T. Sato and H. Ishibishi, *J. Chem. Soc., Perkin Trans. 1,* 1998, 1763-1768.

(122) D. T. Davies, N. Kapur and A. F. Parsons, *Tetrahedron. Lett,* 1999, **40**, 8615-8618.

(123) D. T. Davies, N. Kapur and A. F. Parsons, *Tetrahedron,* 2000, **56**, 3941-3949.

(124) C. Walling and M. S. Pearson, *J. Am. Chem. Soc.,* 1964, **86**, 2262-2266.

(125) C. Walling, J. H. Cooley, A. A. Ponaras and E. J. Racah, *J. Am. Chem. Soc.,* 1966, **88**, 5361-5363.

(126) M. Julia, *Acc. Chem. Res.,* 1971, 386-392.

(127) P. Piccardi, M. Modena and L. Cavalli, *J. Chem. Soc.,* 1971, 3959-3966.

(128) P. Picardi, P. Massardo, M. Modena and E. Santoro, *J. Chem. Soc., Perkin Trans. 1,* 1973, 982.

(129) L. V. Jackson and J. C. Walton, *Chem. Commun.,* 2000, 2327-2328.

(130) H. Ishibashi, N. Nakamura, T. Sato, M. Takenuchi and M. Ikeda, *Tetrahedron Lett.,* 1991, **32**, 1725-1728.

(131) H. Ishibashi, C. Kameoka, H. Iriyama, K. Kodama, T. Sato and M. Ikeda, *J. Org. Chem.,* 1995, **60**, 1276.

(132) S. L. Fremont, J. L. Belletire and D. M. Ho, *Tetrahedron Lett.,* 1991, **32**, 2335-2338.

(133) H. Ishibashi, C. Kameoka, A. Yoshikawa, R. Ueda, K. Kodama, T. Sato and M. Ikeda, *Synlett.,* 1993, 649-650.

(134) H. Ishibashi, C. Kameoka, T. Sato and M. Ikeda, *Synlett.,* 1994, 445-446.

(135) H. Ishibashi, C. Kameoka, K. Kodama and M. Ikeda, *Tetrahedron,* 1996, **52**, 489-502.

(136) K. Okamura, S. Hirata, A. Koki, K. Hori, N. Shibamoto, Y. Okamura, M. Okabe, R. Okamoto, K. Kouno, Y. Fukagawa, Y. Shimauchi and T. Ishikura, *J. Antibiot.,* 1979, **32**, 262.

(137) B. Quiclet-Sire, J. B. Saunier and S. Z. Zard, *Tetrahedron Lett.,* 1996, **37**, 1397-1400.

(138) J. Cassayre, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron,* 1998, **54**, 1029-1040.

(139) E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.,* 1972, **94**, 2888.

(140) A. D'Annibale, S. Resta and C. Trogolo, *Tetrahedron Lett.,* 1995, **36**, 9039-9042.

(141) A. D'Annibale, A. Pesce, S. Resta and C. Trogolo, *Tetrahedron,* 1997, **53**, 13129-13138.

(142) A. D'Annibale, A. Pesce, S. Resta and C. Trogolo, *Tetrahedron Lett.,* 1997, **38**, 1829-1832.

(143) A. J. Clark and J. L. Peacock, *Tetrahedron Lett.,* 1997, **39**, 1265-1268.

(144) J. Boivin, A. C. Callier-Dublanchet, B. Quiclet-Sire, A. M. Schiano and S. Z. Zard, *Tetrahedron,* 1995, **51**, 6517.

(145) E. J. Zavoissky, *J. Phys.,* 1945, **9**, 211.

Chapter 2

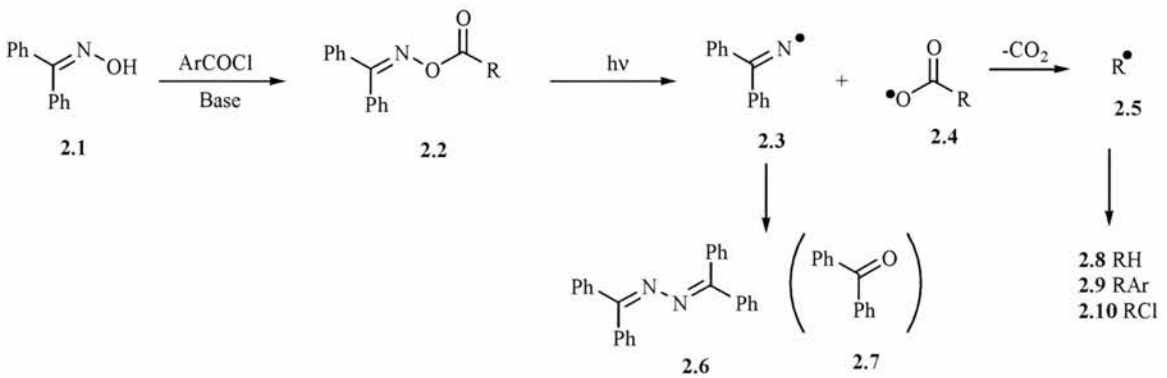
Oxime Oxalate Amides; Their Preparation and Photochemistry.

2.1.0 Introduction

The importance of free radicals in organic synthesis and the necessity for the development of clean free radical precursors has been discussed in Chapter 1. Apart from peroxides and azo-compounds, the range of molecules suitable for direct photolysis and thermolysis is quite limited.

2.1.1 Oxime Esters as Photochemical Radical Precursors

In the 1980's Hasebe and co-workers demonstrated that benzophenone oxime esters **2.2** could readily be photolysed to generate alkyl radicals **2.5** together with the diphenyl iminyl radical **2.3**[1-3] (Scheme 1).

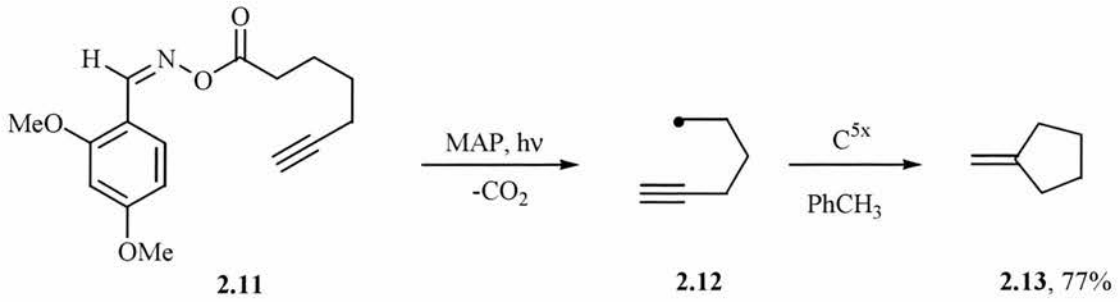


Scheme 1

The photolysis reactions were carried out in benzene or carbon tetrachloride. The diphenyliminyl radical either dimerised to give the benzophenone azine **2.6** or else abstracted hydrogen to give an imine which was subsequently hydrolysed to the corresponding ketone **2.7**. The radical R$^{\bullet}$ **2.5** could then undergo classic free radical chemistry to give alkanes **2.8**, alkyl aromatics **2.9** and alkyl chlorides **2.10**.[4]

The homolytic chemistry of oxime esters **2.2** was further investigated by Walton and co-workers.[5] It was determined that the efficiency of oxime ester photolysis could be improved through the incorporation of methoxy substituents into the aromatic ring

and through the use of photosensitisors. The oxime esters were also used in the preparation of cyclopentane rings **2.13** in good yield (Scheme 2).



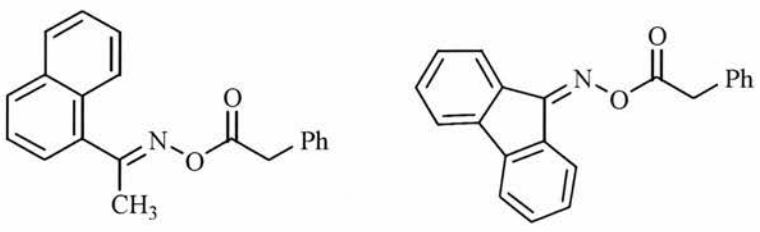
2.11 **2.12** **2.13**, 77%

Scheme 2

The oxime ester **2.11** on photolysis, cleaves at the NO bond giving the iminyl and the acyloxyl radical which rapidly loses CO_2 to give the alkyl radical **2.12**. This can then undergo a 5-*exo* cyclisation, followed by hydrogen abstraction from the solvent to give methylenecyclopentane **2.13** in 77 % yield.

Recently a study of the photochemistry of *O*-acyloximes has been completed by Lalevée et al.[6] A number of *O*-acyloximes were prepared and their photochemistry was studied by laser and fluorescence experiments. In particular, the influence of molecular structure on bond dissociation was investigated.

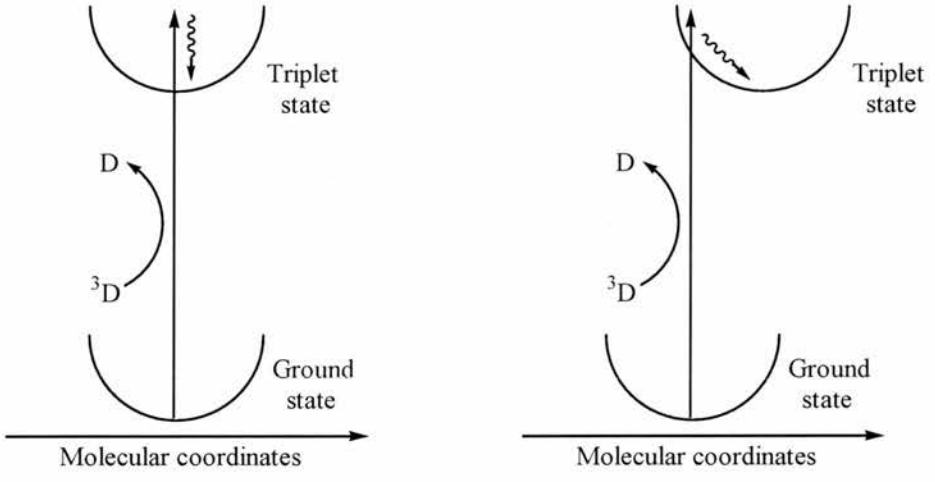
The two oxime esters **2.14** and **2.15** were prepared and their photochemistry compared. It was found that compound **2.15** was stable under irradiation but that **2.14** was characterised by a high quantum yield of photolysis. The two molecules differ only in the nature of the functionality attached to the oxime. Compound **2.15** is rigid whereas compound **2.14** has some degree of mobility (Scheme 3).



2.14 **2.15**

Scheme 3

Both compounds have similar relaxed triplet energy levels. Because they have such differing photochemical behaviour it was assumed that the dissociation did not take place from the relaxed triplet state. The spectroscopic triplet energy levels of each molecule, were determined by phosphorescence in a glassy matrix. At 77 K it was found that **2.15** had a spectroscopic triplet energy level of about 230 kJ mol^{-1}, whereas **2.14** had an energy level of 246 kJ mol^{-1}.The difference is attributed to the fact that **2.15** exhibits clear vertical behaviour whereas **2.14** exhibits nonvertical behaviour due to the flexibility of the molecule. In the case of **2.14** the geometry of the excited state is different to that of the relaxed state (Scheme 4). It is proposed that during the relaxation process, the excited flexible molecule **2.14**, explores more different geometries than the non-flexible molecule and therefore is more likely to reach the transition state for dissociation. This suggests that the high photodissociation efficiency of **2.14** is dependent on the changes in geometry during dissociation.[6]



D=Donor molecule
^{3}D=Donor molecule (triplet state)

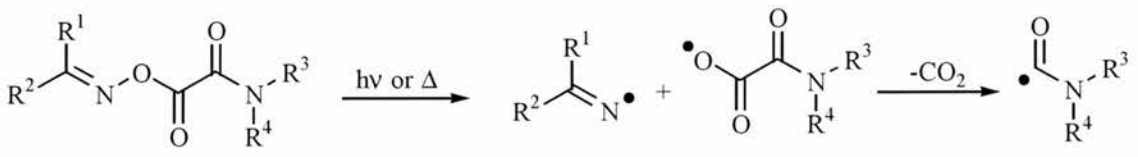
Scheme 4

These findings lead Lalevée and co-workers to propose that molecular structure was a major factor in the efficiency of the sensitised dissociation of *O*-acyloximes. The nature of the substituents was also found to be important.

2.2.0 Results and Discussion

2.2.1 Preparation of Simple Oxime Oxalate Amides

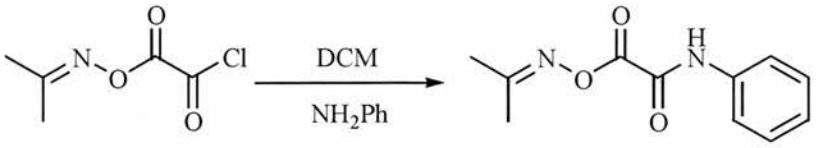
It was apparent from the work of Hasebe[1-3] and Walton[5] that the oxime functionality was a suitable radical precursor for iminyl and alkyl radicals. For this project we proposed to study oxime oxalate amides (OOAs) **2.16**. The oxime oxalate amide still incorporates the weak N-O oxime bond and should function as a radical precursor. The resulting acyloxyl radical **2.18** would then lose CO_2 to give the carbamoyl radical **2.19** (Scheme 5).



2.16 **2.17** **2.18** **2.19**

Scheme 5

A literature survey revealed only one reference where oxime oxalate amides of the type **2.16** had previously been prepared. In their investigation into the Beckmann rearrangement of *O*-(chlorooxalyl)oximes, Jochims and co-workers[7] prepared the oxime oxalate amide **2.21** through the reaction of acetone *O*-(chlorooxalyl)oxime **2.20** with two molar equivalents of aniline in DCM at rt (Scheme 6). The amide was prepared in 69 % yield.

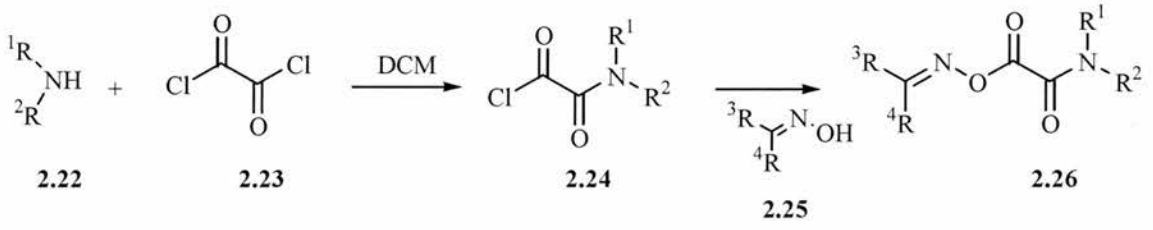


2.20 **2.21**, 69%

Scheme 6

The reaction was only carried out as a characterisation method for the preceding oxime oxalyl chloride **2.20** and no further investigation into the properties of the compound was carried out. The major problem with Jochims' preparation was the loss of one molar equivalent of the amine, through formation of the hydrochloride salt. We were aware that in the preparation of more complex oxime oxalate amides the loss of 50 % of the starting amine would be unacceptable.

Our initial synthetic strategy employed for the preparation of oxime oxalate amides, involved an attempt to prepare the monoamides of oxalyl chloride **2.24** followed by subsequent reaction with the starting oxime **2.25** (Scheme 7).



2.22 **2.23** **2.24** **2.25** **2.26**

Scheme 7

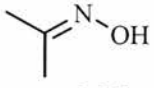
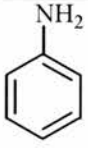
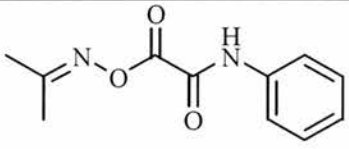
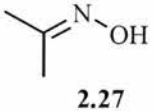
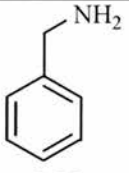
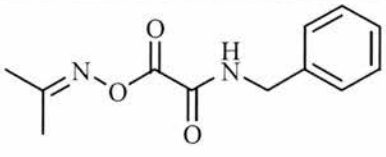
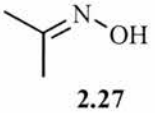
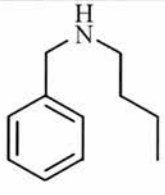
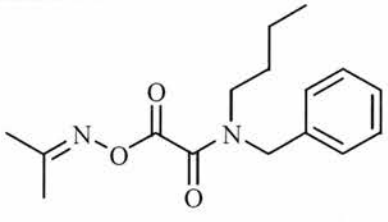
We chose a readily available 2° amine, *N*-benzyl-*N*-butylamine and attempted to react it with oxalyl chloride **2.23**. However, the reaction yielded only a complex mixture of products including the starting amine and the corresponding hydrochloride salt. The reaction was repeated at a higher temperature for a longer time but the amine oxalyl chloride **2.24** was not observed.

After this initial attempt failed, we turned our attention to Jochims' methodology. We decided to investigate if the method used by Jochims for the preparation of **2.21** could be applied to other amines and oximes. Acetone *O*-(chlorooxalyl)oxime **2.20** was prepared according to the procedure of Jochims.[7]

We first carried out the reaction with aniline **2.28** to prepare the compound **2.21**. Although this had previously been prepared by Jochims *et al.*, its photochemistry had not been investigated. It was quickly determined that the Jochims methodology, although satisfactory for aniline and benzylamine **2.29** was quite limited in its

application. It worked extremely well for simple primary amines but when *N*-benzyl-*N*-butylamine **2.31** was used the expected hydrochloride salt did not form and the oxime oxalate amide was not isolated. A modification of the procedure, using just one molar equivalent of the amine did however give the target oxime oxalate amide **2.32** in moderate yield. Table 1 illustrates the simple oxime oxalate amides prepared using Jochims' methodology.

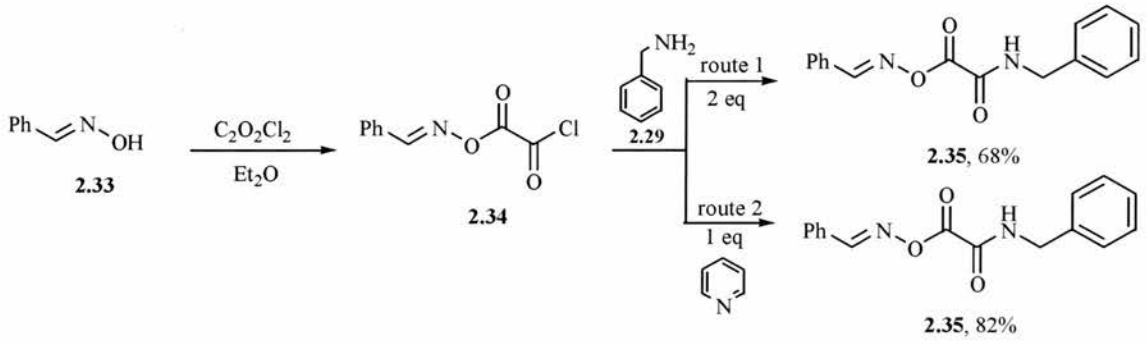
Table 1

Oxime	Amine	Oxime Oxalate Amide
 **2.27**	 **2.28**	 **2.21**, 65% lit[8]=69%
 **2.27**	 **2.29**	 **2.30**, 95%
 **2.27**	 **2.31**	 **2.32**, 54%

These compounds were found to be colourless crystalline solids or viscous liquids and were relatively stable at rt.

In order to increase the range of precursors available it was first necessary to prepare some other oximes. *syn*-Benzaldoxime **2.33** was prepared according to its literature procedure[8] through the reaction of benzaldehyde with hydroxylamine hydrochloride at rt. The oxime was isolated as a colourless oil via Kugelrohr distillation. The corresponding oxime oxalyl chloride **2.34** was prepared and isolated as a colourless, highly unstable, powder, according to the method of Jochims et al.[7] This oxime oxalyl chloride was reacted with benzylamine using two molar equivalents of

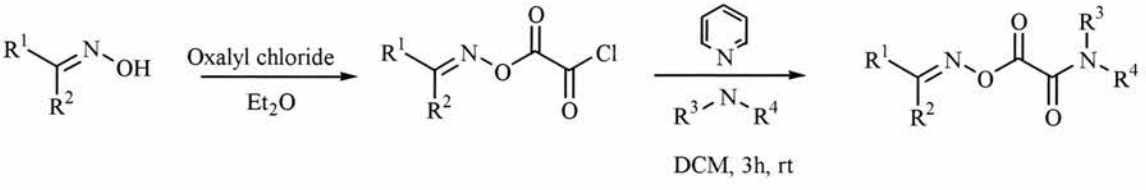
benzylamine, and the oxime oxalate amide **2.35** was isolated as a colourless powder in 68 % yield. In order to conserve the starting amine it was decided to attempt a preparation whereby only one equivalent of the amine was used and pyridine was added to act as an HCl scavenger. The reaction was carried out in DCM and the pyridine hydrochloride formed an insoluble ppt. which could easily be filtered off. This procedure resulted in formation of the oxime oxalate amide **2.35** in 82 % yield. Scheme 8 illustrates the two synthetic routes.



Scheme 8

The pyridine method (route 2) has a number of advantages over Jochims' methodology. First of all it requires only one molar equivalent of the precursor amine and all the amine used is converted into the final product. Secondly, it gives an improved yield. It may be that pyridine is a more effective scavenger for HCl and drives the equilibrium towards formation of the oxime oxalate amide. Finally, this method is suitable for all amines and does not depend on the ability of the amine to form an insoluble hydrochloride salt in DCM. This methodology was used for the preparation of all other oxime oxalate amides in this thesis.

The general procedure for the preparation of oxime oxalate amides is shown in Scheme 9.



Scheme 9

The benzaldehyde derivatives are characterized by an oximinyl proton peak around 8.5 ppm in the proton NMR. Although two possible isomers are available only one peak was observed in the NMR of **2.35**. It was presumed that the two carbonyl groups were *trans* to each other and this was later proved true by examining the cystal structure of an oxime oxalate amide. The conformation of oxime oxalate amides will be further discussed in Chapter 4.

Following the successful preparation of a number of simple oxime oxalate amides and the development of a general route to their preparation, it was decided to investigate the photochemistry of these compounds via ESR spectroscopy.

2.2.2 ESR Spectroscopy of Simple OOA's

ESR spectroscopy is a very powerful tool for the investigation of free radicals. In this project, ESR was used to determine the structures of radical intermediates and hence to validate the mechanism of their photodissociation. The spectrometer used for these studies was a Bruker EMX 10/12 operating at 9.5 GHz. Samples were photolysed in the resonant cavity by light from a 500 W super pressure Hg lamp.

Samples were prepared by taking 20 mg of the starting oxime oxalate amide and dissolving it in *t*-butylbenzene (*ca.* 500 µl). To this was then added one molar equivalent of the photosensetizer, *para*-methoxyacetophenone (MAP). The sample was deaerated under N_2 and then sealed in a 4 mm od quartz ESR tube.

The sample was placed in the resonant cavity of the ESR spectrometer and photolysed by light from the 500 W UV lamp. Figure 1 shows the triplet of septets ESR spectrum obtained from **2.21** at 320 K. This is the signal expected for the iminyl radical **2.36**. The nitrogen-atom splitting gives rise to the triplet a(N) = 9.80 G, and each triplet is split into a septet by the six equivalent hydrogens of the dimethyl group, a(H)= 1.37 G. Scheme 10 shows the expected radicals formed on the photolysis of **2.21**.

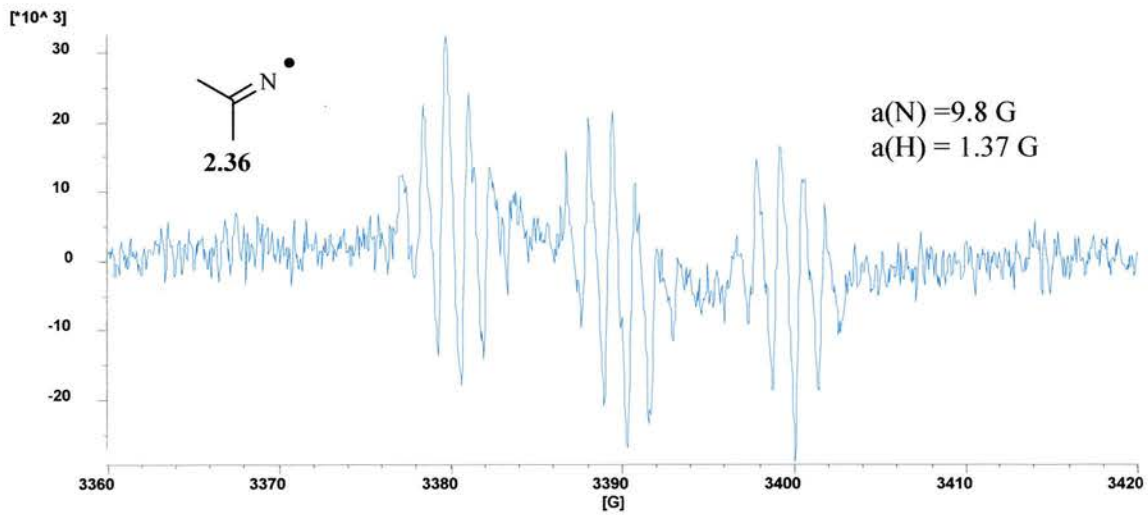
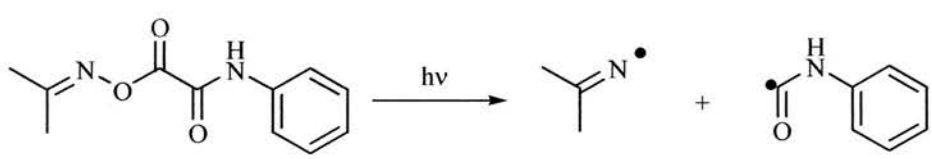


Fig 1. 9.4 GHz ESR spectrum showing iminyl radical **2.36,** formed on photolysis of a solution of **2.21** and MAP in *tert*-butylbenzene at 320 K.

Spectra were obtained at a range of temperatures but the iminyl spectrum shown in Figure 1 was the only signal observed. There were no peaks observed which could be attributed to the carbamoyl radical **2.37**. The hyperfine splittings (hfs) expected for an iminyl radical of this type are a(N) = 9.6 or 9.7 at 223 K and a(H) = 1.4 or 1.3 at 300 K.[9] The ESR parameters determined for the radical **2.36** at 250 K (see above) compared quite favourably to the expected values for a radical of type **2.36** and suggest that the spectrum in Figure 1 is indeed that of the iminyl radical **2.36**.



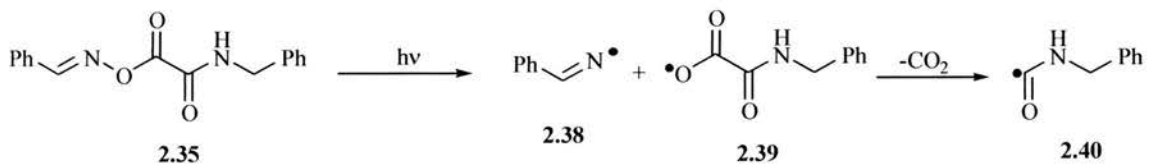
2.21 **2.36** **2.37**

Scheme 10

The presence of the iminyl radical proved that homolytic N-O bond cleavage was occurring. The absence of any nitroxyl radicals indicated that C-O homolytic cleavage did not occur. The absence of the carbamoyl radical was attributed to the persistence of the stabilised iminyl radical and may also be due to the rate of CO_2 loss and the rate of termination of the carbamoyl radical **2.37**.

ESR spectra of the acetone derived oxime oxalate amides **2.30** and **2.32** were also obtained. These samples gave signals identical to those obtained from **21** at a range of temperatures and once again only the iminyl radical was observed.

The oxime oxalate amide **2.35** was also investigated using ESR spectroscopy. The sample was prepared in the usual manner and ESR spectra were obtained at a range of temperatures. Scheme 11 shows the expected radicals generated on photolysis of the oxime oxalate amide **2.35**.



Scheme 11

Unlike the ESR spectrum derived from the analogous acetone derivative **2.30**, the spectrum from the oxime oxalate amide **2.35** gave a more complex signal. Figure 2 shows the ESR spectrum obtained at 220 K.

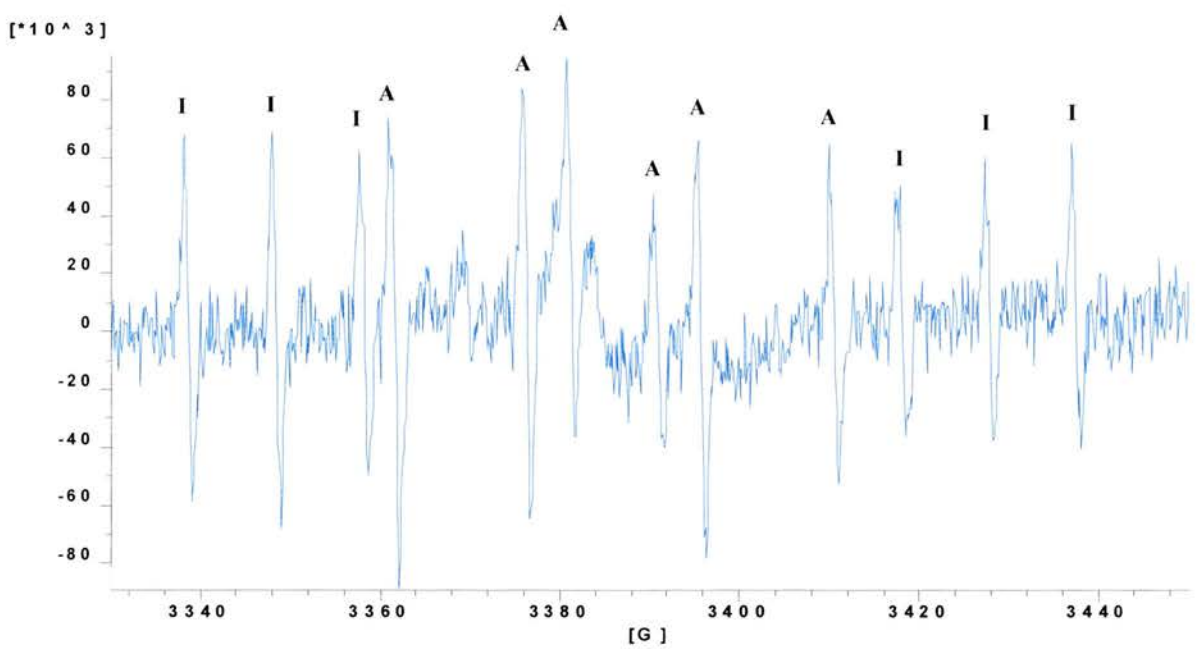


Fig 2. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **2.35** and MAP in *tert*-butylbenzene at 220 K. I; iminyl, A; carbamoyl **2.40**.

The two groups of three lines at the extreme left and right ends of the spectrum (marked I in Figure 4) are due to the iminyl radical **2.38**. The iminyl nitrogen gives a triplet which is split into a wide doublet by the adjacent oximinyl hydrogen. The doublet of triplets (marked A) is due to the carbamoyl radical **2.40**. From the ESR spectrum, it was possible to determine the ESR parameters for the radicals in *tert*-butylbenzene at 320 K, iminyl (I) g = 2.0034, a(N) = 9.7, a(H) = 79.3 G; carbamoyl (A) g = 2.0046, a(N) = 14.6, a(H) = 19.6 G (1mT = 10 G). The ESR spectrum demonstrates therefore, that scission of the N-O bonds of oxime oxalate amides occurs cleanly and that this is followed by rapid CO_2 loss to afford the carbamoyl radical **2.40**. The absence of the oxylacyl radical **2.39** suggests that decarboxylation occurs rapidly on photolysis. The absence of an aminyl radical proves that the carbamoyl radical does not undergo loss of carbon monoxide. The ESR spectra at higher temperatures showed identical peaks but the peak strength began to diminish as temperature was increased.

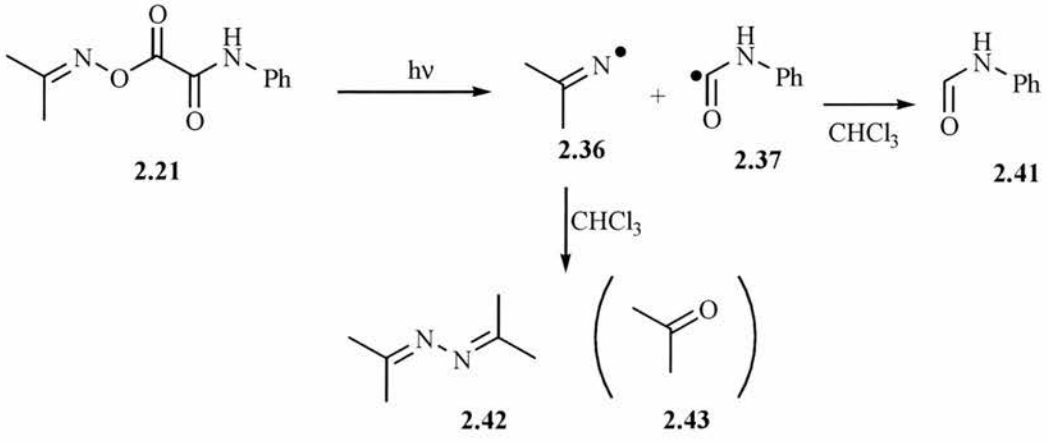
The benzaldoxime derived oxime oxalate amide had a number of advantages over the acetone oxime derived analog. Firstly, the aminoacyl radical was observed from compound **2.35** but not for the acetone derivatives. This suggests a high photochemical efficiency for the benzaldoxime derivative. Secondly the ESR spectrum of the iminyl radical **2.38** leaves a "window" at the centre of the spectrum which allows other radicals to be observed without overlap. For these reasons all other oxime oxalate amides prepared in this thesis are the benzaldoxime derivatives.

The ESR study proved that both iminyl and carbamoyl radicals could be generated on photolysis of oxime oxalate amides. In order to determine the fate of the radicals it was decided to carry out some preparative experiments followed by end product analysis.

2.2.3 Preparative Study of Simple OOA's

In order to prove the formation of the carbamoyl radical for the acetone derived oxime oxalate amides, it was decided to conduct some preparative experiments. The oxime oxalate amide **2.21** was used since this gave the strongest ESR signals.

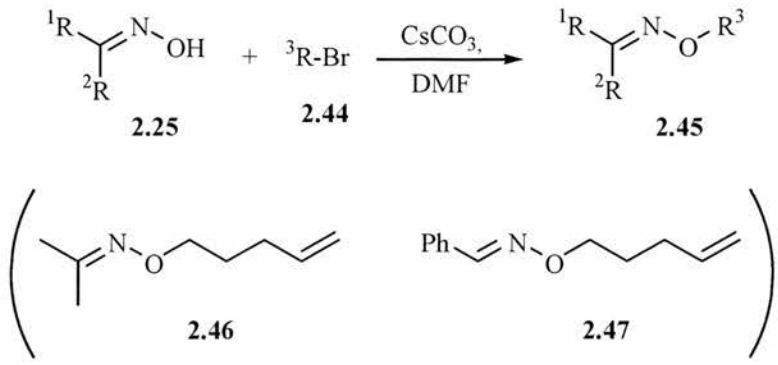
The first experiment carried out was the simple preparation of the formamide **2.41** through the direct photolysis of **2.21** (Scheme 12). The sample (20 mg) was photolysed in chloroform in the presence of 1eq. of MAP at rt for 2 h. The sample was evaporated to dryness and submitted for GC/MS analysis. The chromatogram displayed a major peak of the correct molecular weight for the formamide **2.41** and also a peak corresponding to acetone **2.43** (none of the dimerized imine **2.42** was observed). Some minor chlorinated products were also observed.



Scheme 12

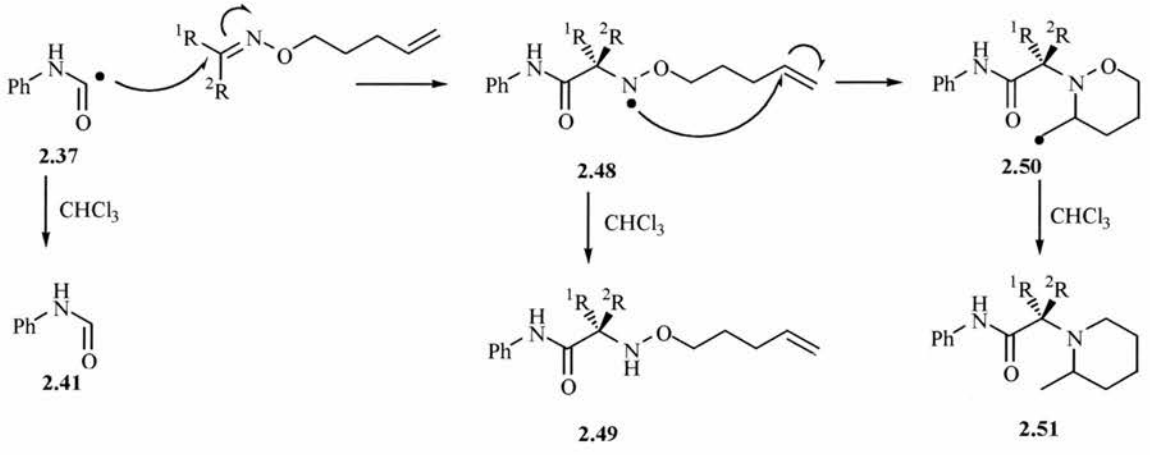
Following the successful preparation of the formamide it was attempted to determine if the carbamoyl radicals could be used to undergo intermolecular addition to oxime ethers. The addition of free radicals to oxime ethers has been well investigated and many examples exist in the literature.[10-12] (Addition reactions to oxime ethers will be discussed in detail in Chapter 3).

Oximes ethers can be easily prepared from the starting oxime through the reaction with an alkyl bromide in the presence of caesium carbonate. The two oxime ethers prepared for this study were *O*-pent-4-enyl acetone oxime **2.46** and *O*-pent-4-enyl benzaldoxime **2.47**. Both were prepared in moderate to good yield from their corresponding oximes[5] (Scheme 14).



Scheme 13

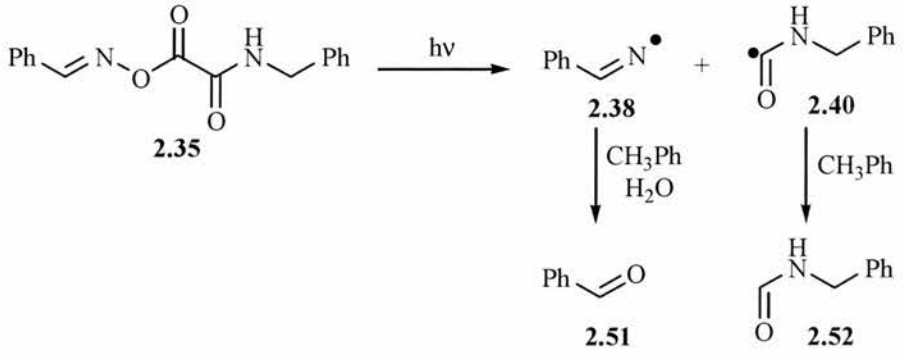
The oxime ethers prepared had an unsaturated alkyl chain so that after intermolecular addition of the carbamoyl radical, further intramolecular cyclisation could occur to give the cyclised species **2.50**. It was also possible that the addition product might be reduced before cyclisation resulting in the formation of the reduction product **2.49**. Two other possible reactions were the addition of the iminyl radical to the oxime and also direct formation of the formamide (Scheme 14).



Scheme 14

The photolysis reactions were carried out in chloroform at rt in the presence of MAP. In each case 1 M eq of the oxime ether was added. The product mixtures were submitted for GC/MS analysis. Peaks corresponding to the formamide **2.41** were observed but no addition or cyclisation products were observed. Peaks corresponding to the addition of the trichloromethyl radical ($Cl_3C^{\bullet}$) to the oxime were observed. Evidently the addition step, and/or the 6-*exo*-cyclisation step, were too slow to compete with H-abstraction from the solvent.

The final photolysis experiment carried out was a preparative scale photolysis of **2.35** in toluene. The starting oxime oxalate amide **2.35** (200 mg) was photolysed in toluene for 90 min at rt in the presence of 1 M eq of MAP (Scheme 15). After this time the sample was evaporated to dryness. Comparison of the crude ^{1}H NMR to literature values[13] showed that the formamide **2.52** had been formed in good yield. Using the MAP peaks as a reference the conversion of the formamide **2.52** was determined to be 99 %. The conversion of benzaldehyde was only 30 %. GC/MS analysis confirmed the formation of the formamide and benzaldehyde. No other significant products were observed.



Scheme 15

The extremely high yield of the formamide suggested that the quantum yield of photolysis was also very high and therefore that the oxime oxalate amides would be extremely efficient sources of both iminyl and carbamoyl radicals.

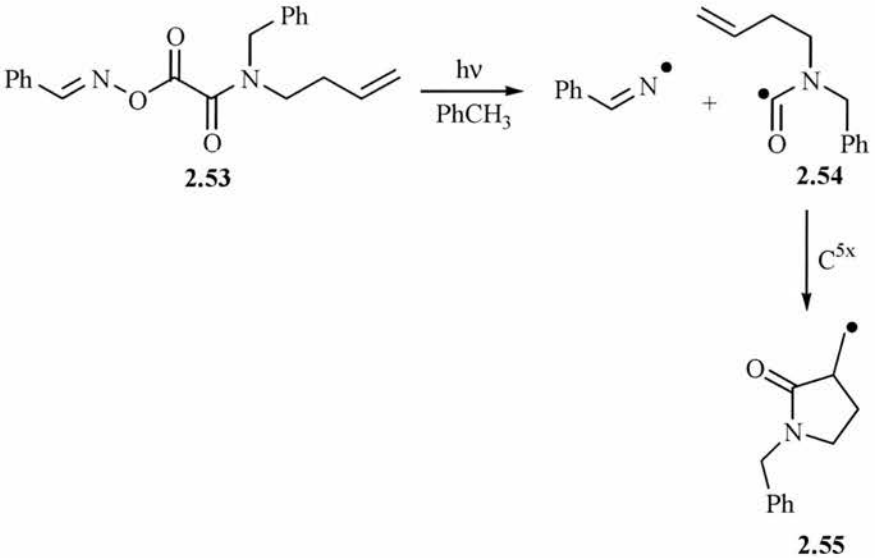
The preparative experiments demonstrated that carbamoyl radicals were generated in good yield and could be used in the preparation of formamides. Intermolecular addition to oxime ethers did not occur but this may be due to the nature of the oxime ethers.

As was discussed in Chapter 1, carbamoyl radicals are synthetically very useful and have been used in the preparation of heterocycles. It was postulated that oxime oxalate amides could be prepared which incorporated an unsaturated group suitable for ring closure reactions. The next section discusses the oxime oxalate amides prepared and their photochemistry.

2.2.4 Preparation of Synthetically Useful OOA's

Pattenden and co-workers demonstrated that carbamoyl radicals generated using cobalt salophen chemistry could undergo ring closure reactions to give lactams.[14,15] We planned to further develop the chemistry of oxime oxalate amides and to investigate if carbamoyl radicals generated using this system could be used for the preparation of lactams.

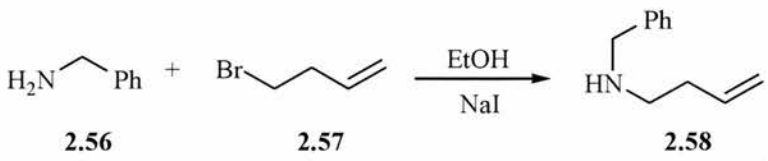
The 5-*exo-trig* cyclisation is one of the most commonly used in free radical chemistry (see introduction) and so our first objective was to design and prepare an oxime oxalate amide with a suitably unsaturated amine onto which the carbamoyl radical could undergo a 5-*exo-trig* cyclisation. The oxime oxalate amide envisaged was benzaldehyde-*O*-(*N*-benzyl-3-buten-1-ylaminooxalyl)oxime **2.53**. It was expected that on photolysis the oxime oxalate amide would dissociate with loss of CO_2 to give the iminyl and the carbamoyl radical **2.54**. The carbamoyl radical **2.54** would then undergo 5-*exo-trig* cyclisation to give the *N*-benzyl-2-oxopyrrolidinylmethyl radical **2.55** (Scheme 16).



Scheme 16

2.2.5 Benzaldehyde-*O*-(*N*-benzyl-3-buten-1-ylaminooxalyl)oxime 53

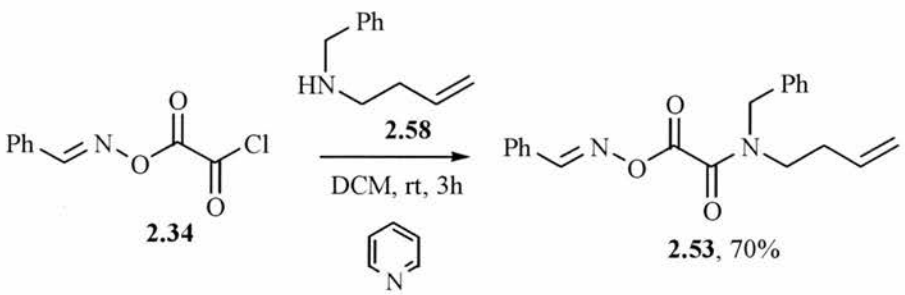
In order to prepare the oxime oxalate amide **2.53**, it was first necessary to prepare the amine **2.58**. *N*-Benzyl-buten-1-ylamine was prepared according to its literature procedure[16] through the reaction of benzylamine **2.56** with 4-bromo-1-butene **2.57** in ethanol (Scheme 17).



2.56 **2.57** **2.58**

Scheme 17

The amine was then reacted with benzaldoxime oxalyl chloride **2.34** in the presence of pyridine to give the desired oxime oxalate amide as a colourless solid in good yield (70 %, Scheme 18).



Scheme 18

The photochemical properties of this compound were first investigated using ESR spectroscopy. The sample was prepared in the usual manner, taking 20 mg of the oxime oxalate amide and combining it with 1 M eq. of MAP. The sample was irradiated with light from a 500 UV lamp and the ESR spectra were observed at a range of temperatures.

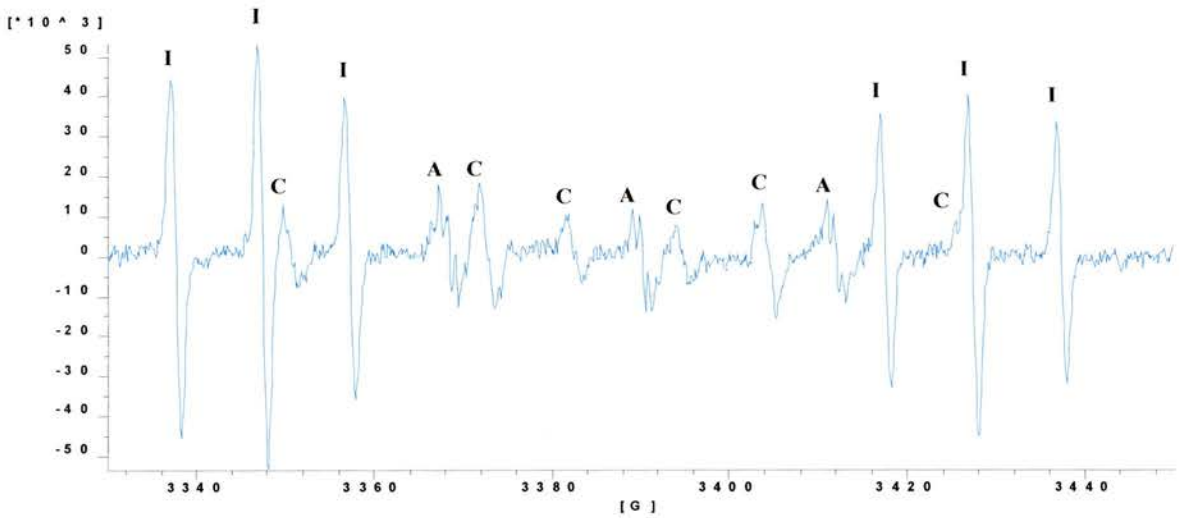
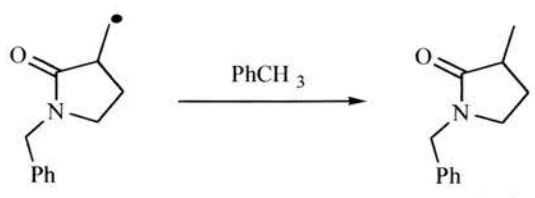


Fig 3. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **2.53** and MAP in *tert*-butylbenzene at 220 K. I; iminyl, A; carbamoyl, C; cyclised species.

Figure 3 shows the spectrum obtained on photolysis of the oxime oxalate amide **2.53** in the presence of MAP at 220 K. The 1:1:1 triplets at either extreme of the spectrum, are due to the iminyl radical **2.38**. The well spaced 1:1:1 triplet (marked A) is due to the carbamoyl radical **2.54** and the doublet of triplets (marked C) is due to the cyclised radical **2.55**. The ESR parameters for the radicals derived from **2.53** were: iminyl (I) g = 2.0034, a(N) = 9.9, a(H) = 79.9 G; carbamoyl (A) g = 2.0017, a(N) = 21.7 G; cyclised radical (C) g = 2.0025, a(2H) = 22.3, a(1H) = 31.6 G. These figures compare favourably to those expected for the carbamoyl and the cyclised radical and suggest the photochemical process occurs in accordance with Scheme 16.

The oxime oxalate amide was then used in some small scale preparative reactions in order to determine if the preparation of γ-lactams was feasible. It was anticipated that in the presence of a suitable H-atom donor, the cyclised radical **2.55** would go on to form the corresponding γ-lactam **2.59** (Scheme 19).



2.55 **2.59**

Scheme 19

The optimum conditions for the formation of the cyclised species were unknown. Unlike the preparation of the simple formamides discussed earlier, the formation of a lactam is a radical cyclisation process and a number of factors control the proportion of cyclised species formed. In this case it was necessary to find photochemical conditions which were suitable for the formation of initial radicals and which also promoted formation of the cyclised species.

A range of small scale photolysis experiments using oxime oxalate amide **2.53** was carried out, monitoring the percentage of the cyclised species by NMR spectroscopy. The factors which could be varied were time, temperature, concentration, solvent, hydrogen donor and the amount of photosensitizer added. Table 1 illustrates the results of these experiments.

Table 2

Solvent	**Time h**	**Temp °C**	**Mass of OOA/mg**	**Other conditions**	**Conversion of lactam[a]**
Toluene ($5\ cm^3$)	3	80	40	MAP (1 mol eq)	48
Toluene ($5\ cm^3$)	6	80	40	MAP (1 mol eq)	57
Toluene ($5\ cm^3$)	9	80	40	MAP (1 mol eq)	58
Toluene ($5\ cm^3$)	5	110	10	Benzil (2 mol eq)	30
Toluene ($5\ cm^3$)	5	100	5	MAP (2 mol eq)	70
Toluene ($5\ cm^3$)	5	100	5	MAP (1 mol eq)	44
Toluene ($5\ cm^3$)	5	115	10	MAP (4 mol eq)	74
Toluene ($5\ cm^3$)	5	100	10	MAP (1 mol eq)	60

Toluene ($5\ cm^3$)	5	100	10	MAP (2 mol eq)	50
Toluene ($5\ cm^3$)	5	100	5	MAP (2 mol eq)	80
Toluene ($5\ cm^3$)	5	100	5	MAP (3 mol eq)	89
Toluene ($5\ cm^3$)	5	100	5	MAP (4 mol eq)	86
Toluene (400 µl)	5	100	20	MAP (4 mol eq)	26
Toluene (400 µl)	5	100	20	MAP (1 mol eq) CHD[b] (1.5 mol eq)	15
Benzene (400 µl)	5	100	20	MAP (1 mol eq) CHD[b] (1.5 mol eq)	7
Toluene ($5\ cm^3$)	5	100	20	MAP (4 mol eq)	61
Toluene ($5\ cm^3$)	5	100	5	MAP (4 mol eq)	86

Conditions for production of 2.59 from 2.53

[a] Determined by ^{1}H NMR. [b] CHD = 1,4-cyclohexadiene.

From the results of the small scale photochemical experiments it was possible to draw a number of conclusions regarding the optimum photochemical conditions. It was found that the concentration of the photochemical precursor in the solvent was a major factor in the yield. Using 5 or 10 mg of the oxime oxalate amide in 5 cm^3 of the solvent was found to give the best yields. When the solvent was reduced to 400 µl the yields dropped below 20 %. The solvent itself was also important. Using a non hydrogen donor solvent such as benzene in the presence of a 1 mol. eq. of a facile hydrogen donor, cyclohexadiene, did not improve the yields. The length of time of photolysis and

temperature were also important. In general it was found that a longer photolysis time and a higher temperature improved the conversion. It was noted however that a higher temperature did not mean a lower photolysis time could be used. The other important factor was the quantity of photosensitizer added. It was determined that addition of 3 or 4 mol eq of the photosensetizer gave the optimum conversion of the lactam.

Once the optimum conditions for photolysis had been established the photolysis was carried out on a preparative scale. It was found that photolysis of the oxime oxalate amide **2.53**, by light from a 400 W medium pressure Hg UV lamp , in the presence of 3 M eq. of MAP at 100 °C for 5 h in toluene resulted in the formation of *N*-benzyl-3-methylpyrrolidin-2-one **2.59** in 90 % yield by NMR and in an isolated yield of 84 %. GC-MS analysis showed that formation of the *N*-formyl by-product was negligible (< 1 %).

The preparative scale NMR yield was higher than any of the small scale yields and this is thought to be due to the more efficient immersion photolysis technique employed for the preparative scale photolysis experiments. The conditions determined for the formation of the lactam were deemed to be the best photochemical conditions and were subsequently used for all other cyclisation reactions.

The high yield of the cyclised product proved that the system was an efficient source of carbamoyl radicals and that these radicals could be employed in the preparation of lactams. As was mentioned previously, the 5-*exo* cyclisation is a favoured process and therefore a good yield of the γ-lactam was expected.

2.2.6 Preparation of β-Lactams

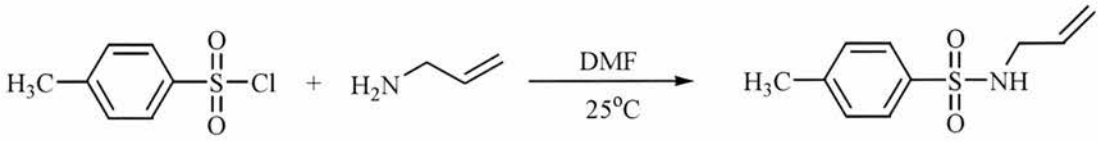
It was postulated that the system could also be applied to the preparation of β lactams. 4-*Exo* cyclisations are disfavoured and it was expected that lower yields of the cyclised product would be obtained.

This section discusses the oxime oxalate amides used for the preparation of β-lactams. Each oxime oxalate amide will be discussed individually. In each case the

preparation of the starting amine and its conversion to the oxime oxalate amide will be discussed. The photochemistry including the ESR spectroscopy will be presented, along with the final products obtained.

2.2.6a Benzaldehyde *O*-(*n*-allyl-*p*-toluene sulfonaminooxalayl)oxime 2.63

The oxime oxalate amide was derived from the amine *n*-allyl-*p*-toluene sulphonamide **2.62** which was prepared in good yield (94 %) according to the literature procedure of Piper *et al.*[17] through the reaction of *p*-toluenesulfonyl chloride **2.60** with *n*-allyl amine **2.61** in DMF (Scheme 20).

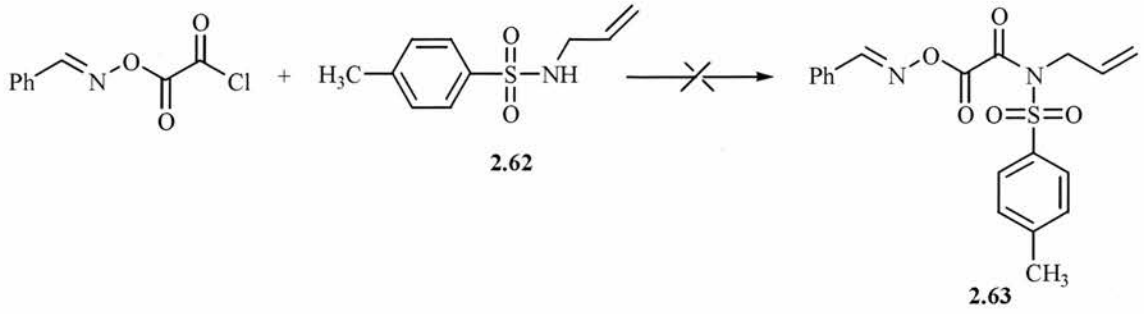


2.60 **2.61** **2.62**

Scheme 20

The amine was chosen because of the *n*-allyl side chain, which is suitable for 4-*exo* ring closure and because of the *p*-toluene sulfonyl group which is a well known protecting group and would allow further chemistry to be carried out on the lactam.

It was then attempted to convert the sulfuramide **2.62** to the oxime oxalate amide **2.63** through the usual reaction with benzaldehyde *O*-(chlorooxalyl)oxime (Scheme 21). In this case however there was no pyridine hydrochloride ppt. formed, even after addition of pentane. The crude reaction mixture was evaporated to dryness and proton NMR revealed that the starting amine had not reacted. The oximinyl hydrogen had not shifted from 8.5 ppm suggesting that the oxime oxalyl chloride had not reacted either. The reaction was repeated for a longer time but the expected oxime oxalate amide **2.63** was not formed.



Scheme 21

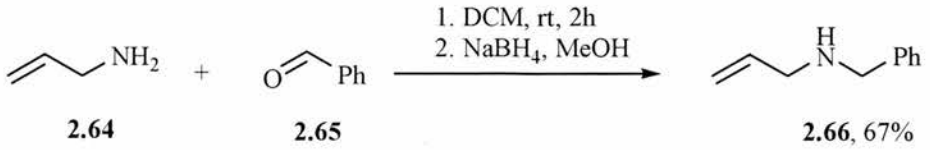
The failure of the amine **2.62** to react with the acid chloride has been attributed to the presence of the *p*-toluene-sulfonyl group. Although a useful functional group the sulfonyl group is quite bulky and in this case is probably resulting in steric hindrance which prevents reaction with the acid chloride. The protecting group is also quite electron withdrawing and since it is attached directly to the reaction centre it would make the amine less nucleophilic and hence less likely to react.

Due to the failure in preparing the oxime oxalate amide **2.63** we were unable to investigate the photochemistry of the molecule.

2.2.6b Benzaldehyde *O*-(*n*-benzyl-prop-2-enylaminooxalyl)oxime 2.67

Benzaldehyde *O*-(*n*-benzyl-prop-2-enylaminooxalyl)oxime is the *n*-benzyl derivative of the oxime oxalate amide **2.63**. The *n*-benzyl group had previously been incorporated into the preparation of the γ-lactam **2.59** and was known not to hinder the reactivity of the amine with the acid chloride. It has also been demonstrated in the literature that the benzyl group can act as a leaving group and so would allow further modifications to be carried out on the lactam.

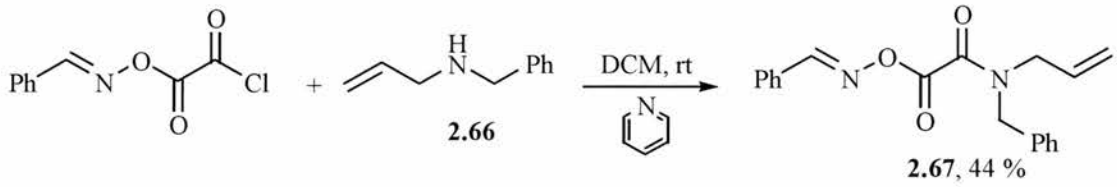
The starting amine, *n*-benzyl-prop-2-enylamine **2.66** was prepared in a moderate yield (67 %), through the reaction of prop-2-enylamine with benzaldehyde in DCM followed by reduction with sodium borohydride in methanol (Scheme 22).



2.64 **2.65** **2.66**, 67%

Scheme 22

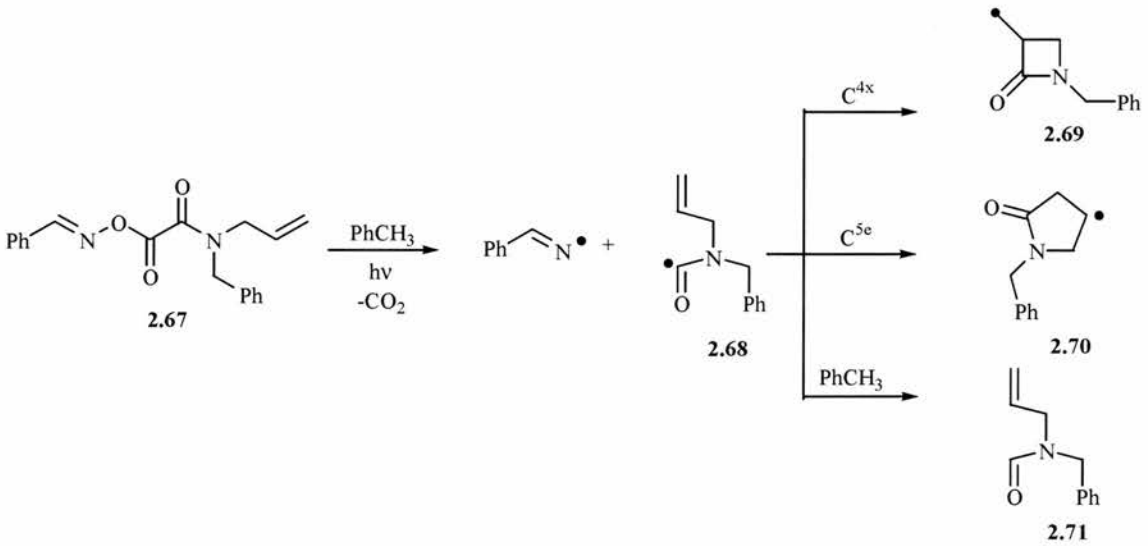
The amine was then converted to the oxime oxalate amide through reaction with benzaldehyde *O*-(chlorooxalyl)oxime. In this case there was no steric hindrance and the oxime oxalate amide was isolated as a colourless solid in a yield of 44 % (Scheme 23).



2.66 **2.67**, 44 %

Scheme 23

The system was designed so that the carbamoyl radical **2.68** could undergo a 4-*exo* cyclisation onto the proximate double bond to give the *N*-benzyl-3-methyl-azetidin-2-one radical **2.69** which could in turn, abstract a hydrogen from the solvent to give the β-lactam. As was discussed in Chapter 1, the 4-*exo* cyclisation is a disfavoured process and competitive processes include 5-*endo* cyclisation to give the γ-lactam **2.70** and direct proton abstraction by the carbamoyl radical to give the formamide **2.71** (Scheme 24).



2.67 **2.68** **2.69** **2.70** **2.71**

Scheme 24

The photochemistry of the system was initially studied using ESR spectroscopy. The sample was prepared in the usual manner and photolysed with light from a 500 W UV lamp in the presence of 1 M eq. of MAP. Spectra were obtained at a range of temperatures. Figure 4 shows the spectrum obtained at 220 K.

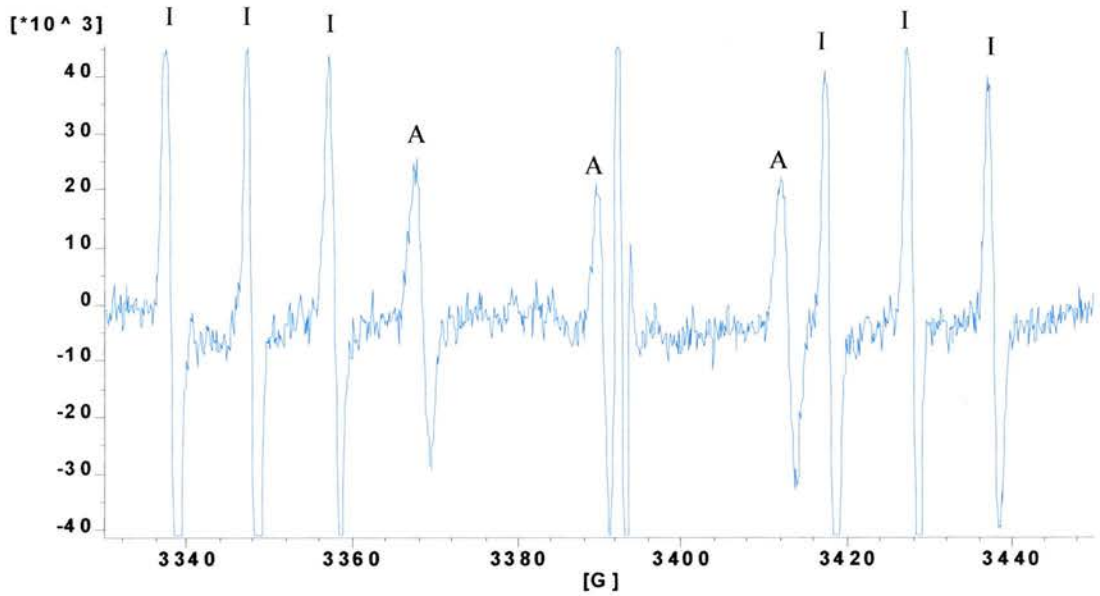
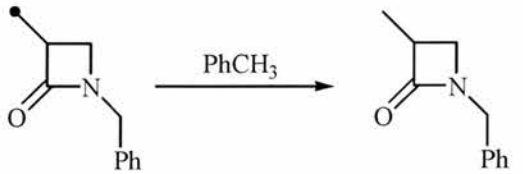


Fig 4. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **2.67** and MAP in *tert*-butylbenzene at 220 K; I; iminyl, A; carbamoyl

The spectrum clearly shows the familiar doublet of triplets which characterises the iminyl radical. The well spaced triplet (marked A) is due to the carbamoyl radical **2.68**. The ESR parameters for the radicals derived from **2.67** were: iminyl (I) g = 2.0034, a(N) = 10.0, a(H) = 80.0 G; carbamoyl (A) g = 2.0018, a(N) = 22.3 G. These parameters compare favourably with those obtained for **2.53**, suggesting that the triplet is indeed due to the carbamoyl radical **2.68**. The absence of any other peak does not mean that cyclisation does not occur. There are no examples in the literature of 4-*exo* cyclisations being observed by ESR spectroscopy and so it was unlikely that the 4-*exo* cyclisation product **2.69** would be observed. There were also no peaks corresponding to the 5-*endo* product **2.70**.

Since ESR spectroscopy could not be used to determine the fate of carbamoyl radical **2.68**, a preparative scale photolysis was carried out. The conditions used in the

preparation of the γ-lactam **2.59** were used and the yellow oil which resulted from the photolysis was purified by column chromatography. The 4-*exo* cyclisation product 1-benzyl-3-methyl-azetidin-2-one, which was formed through hydrogen abstraction from the solvent (Scheme 25), was isolated as a colourless oil in a yield of 40 %. The 5-*endo* product and the formamide **2.71** were not observed.



2.69 **2.72**, 40 %

Scheme 25

Although the yield of the 4-*exo* product was low, it compared favourably to yields for β-lactams obtained by Pattenden and co-workers using their Co-salophen methodology.[15]

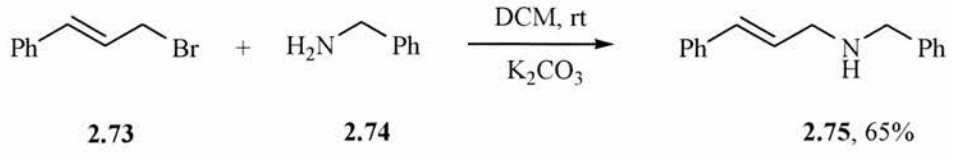
2.2.6c Benzaldehyde *O*-(*N*-cinnamyl-benzylaminooxalyl)oxime 2.76

It had been demonstrated that the oxime oxalate system could act as a free radical precursor for carbamoyl radicals which could undergo ring closure reactions to give β-lactams, albeit with low yield.

The strong ESR spectra and the high yield of the γ-lactam suggested that the photochemical step was efficient and generation of the carbamoyl radical occurred readily. The low yield therefore, was resulting from the cyclisation step. In order to promote cyclisation an amine was prepared, which incorporated a radical stabilising group attached to the vinyl group. This would promote cyclisation because the resonance stabilisation of the cyclised radical would be increased.

The amine chosen was *N*-cinnamyl-benzylamine **2.75**. This amine, on cyclisation of the carbamoyl radical would result in the formation of a secondary, benzyl stabilised radical which should have greater thermodynamic stabilisation than a primary radical such as **2.69**. The amine was prepared in a moderate yield (65 %)

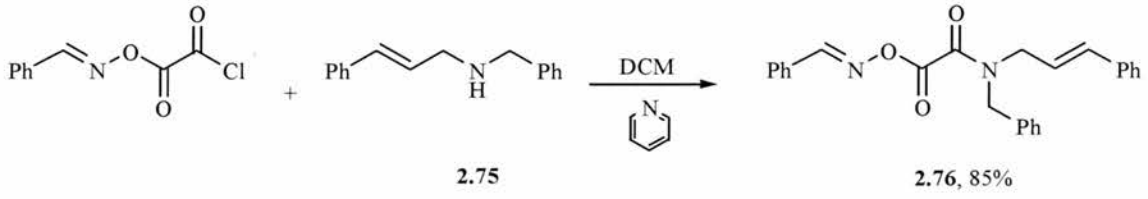
through the reaction of cinnamyl bromide with benzylamine in DCM in the presence of a base (Scheme 26).



2.73 **2.74** **2.75**, 65%

Scheme 26

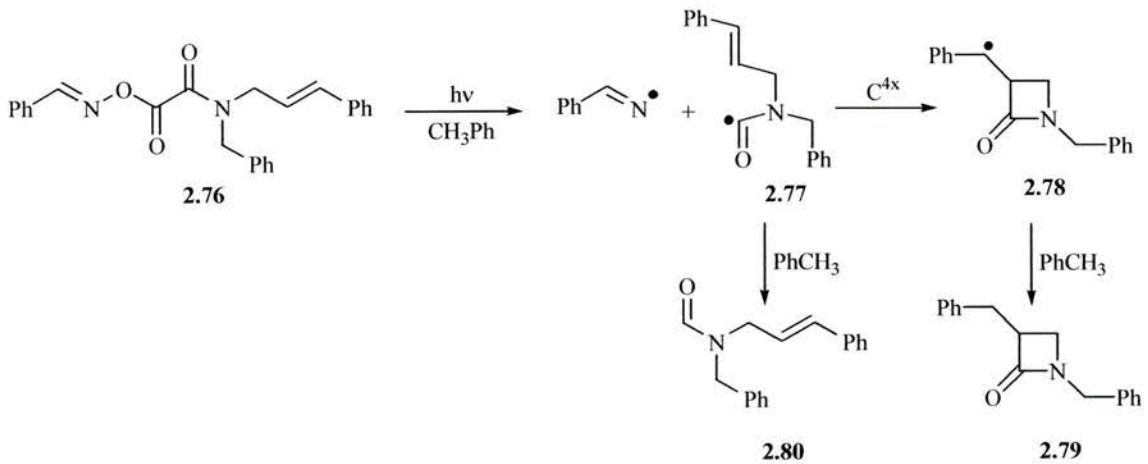
The amine **2.75** was converted to its oxime oxalate amide **2.76** through the reaction with benzaldehyde *O*-(chlorooxalyl)oxime. The oxime oxalate amide **2.76** was isolated as a colourless oil in a yield of 85 % (Scheme 27).



2.75 **2.76**, 85%

Scheme 27

It was expected that the carbamoyl radical **2.77** in this case would undergo 4-*exo* cyclisation to give the 2° benzyl stabilised radical **2.78** which would then abstract a hydrogen from the solvent to give the β-lactam **2.79** (Scheme 28). Since none of the 5-*endo* product was observed in the case of cyclisation onto an N-allyl group it was not expected to be a significant process in this case, where a 5-*endo* cyclisation would not result in formation of the benzyl stabilised radical. Direct formation of the formamide **2.80**, resulting from direct hydrogen abstraction by the carbamoyl radical **2.77** was also expected to be insignificant in this system due to the enhanced stability of the cyclised radical through benzyl stabilisation.



Scheme 28

The photochemistry of the system was first investigated by ESR spectroscopy. The sample was prepared in the usual manner and photolysed by light from the 500 W UV lamp. The ESR spectra were recorded over a range of temperatures. Figure 5 shows the ESR spectra obtained at 220K.

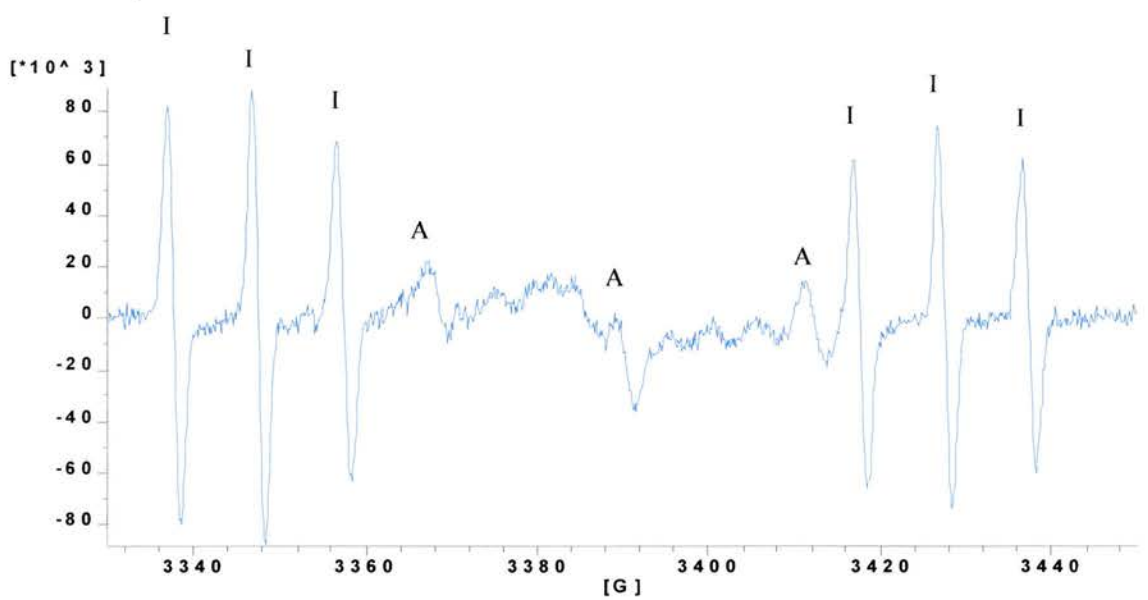


Fig 5. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **2.76** and MAP in *tert*-butylbenzene at 220 K; I; iminyl, A; carbamoyl.

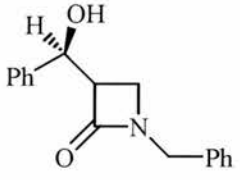
The ESR spectrum is very similar to that obtained for the *N*-allyl system. The spectrum clearly shows the familiar doublet of triplets which is characteristic of the iminyl radical. The well spaced triplet (marked A) is due to the carbamoyl radical **2.77**. The ESR parameters for the radicals derived from **2.76** at 220 K were: iminyl (I) g = 2.0034, a(N) = 10.0, a(H) = 80.0 G; carbamoyl (A) g = 2.0017, a(N) = 21.9 G. These

parameters compare favourably with those obtained for **2.53**, suggesting that the triplet is indeed due to the carbamoyl radical **2.77**.

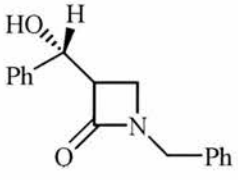
The ESR spectrum seemed to show some additional peaks in the central region which may have been the cyclised product but they were to weak to characterise.

A prep scale photolysis of the oxime oxalate amide **2.76** was carried out in order to prepare the β-lactam **2.79** and to determine if the incorporation of the cinnamyl group had resulted in an increased yield of cyclised product.

The starting oxime oxalate amide (400 mg) was photolysed for 5 h in toluene in the presence of 3 M eq of MAP at 100 °C. The yellow oil which resulted from the photolysis was purified by column chromatography and two products **2.81** and **2.82** were isolated as colourless oils. It was found that the β-lactam **2.79** had not been formed and that the product was a mixture of diastereoisomers (69 %, 3:1) of the hydroxylated lactam. The structures of the two products were determined by NMR and confirmed by COSY NMR and mass spectrometry. No other significant products were isolated (apart from benzaldehyde).

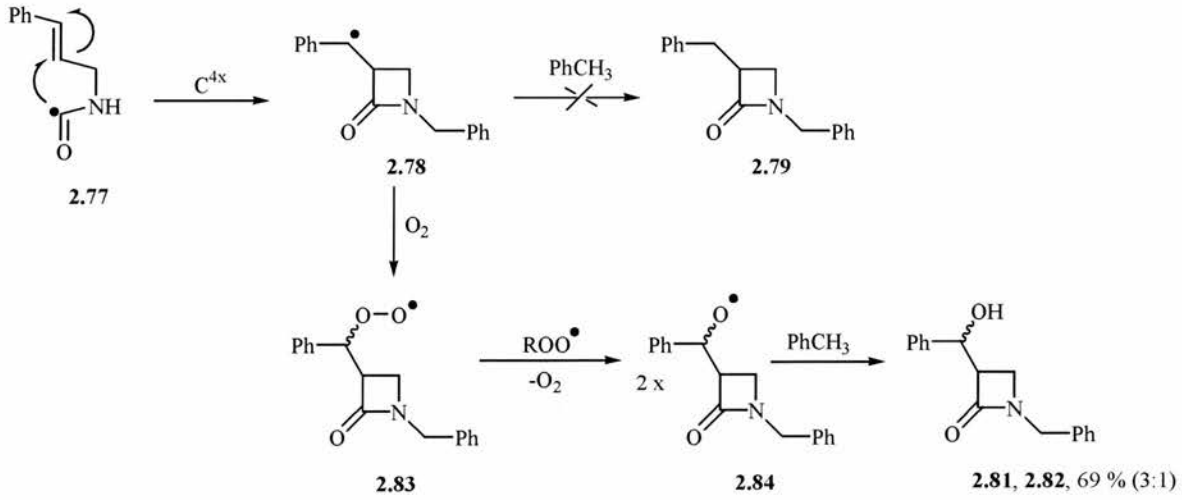


2.81



2.82

It was postulated that the rate of hydrogen abstraction from the toluene solvent was slow due to the stability of the benzylic radical **2.78** and that addition of dissolved oxygen supervened. The peroxyl radical **2.83** formed in this way would be converted to the more reactive oxyl radical **2.84** (by self coupling and O_2 loss)[18] and this would then quickly abstract a hydrogen from solution to give the hydroxylated product (Scheme 29).



Scheme 29

The yield of 69 % for the β-lactam was a significant improvement on the modest yield of 44 % obtained in the case of cyclisation onto the N-allyl group. This suggested that incorporation of a radical stabilising group such as a benzene ring could be very effective in increasing the efficiency of the ring closure step.

Formation of the hydroxylated product was unexpected, but is advantageous in that the hydroxyl group provides an additional functional group for further reactions and therefore makes the end product more synthetically useful.

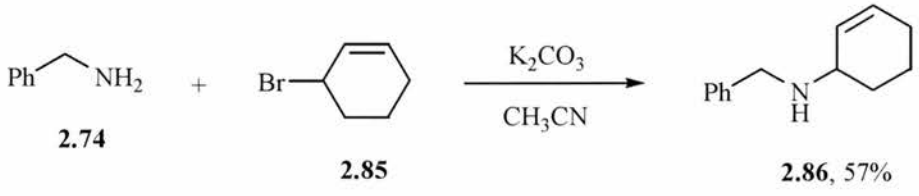
The diastereoisomers **2.81** and **2.82** had very different polarities and this allowed separation via column chromatography. It was thought that the difference in polarity may be attributed to the position of the hydroxyl group relative to the carbonyl, however molecular models of both isomers showed that a simple rotation of side chain containing the hydroxyl group would give an identical overlap for both isomers.

It had now been demonstrated that oxime oxalate amides could be used in the preparation of simple β- and γ-lactams in good yield. It was decided to further investigate the synthetic potential of the system and to determine if the oxime oxalate amides could be used in the preparation of bicyclic lactams.

2.2.6d Benzaldehyde *O*-(*n*-benzyl-2-cyclohexenyl aminooxalyl)oxime 2.87

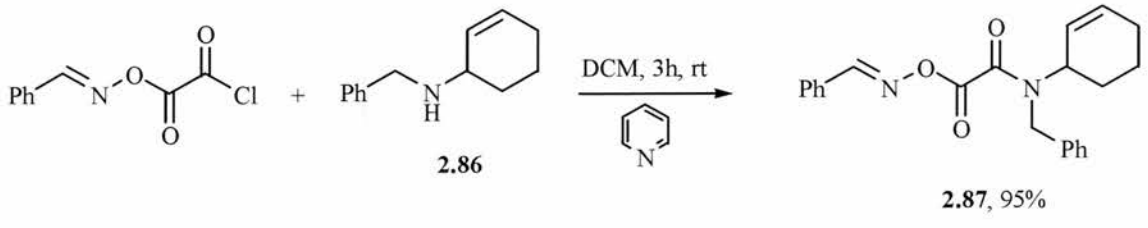
In order to prepare a bicyclic lactam it was first necessary to prepare a starting amine which incorporated an unsaturated ring suitable for ring closure. The amine prepared was *n*-benzyl-2-cyclohexenylamine **2.86** which has an unsaturated cyclohexene ring suitable for radical addition. It also incorporated the *n*-benzyl side chain which was known not to interfere with the preparation of the oxime oxalate amide.

The amine **2.86** was prepared by the literature procedure of Mori *et al.*[19] through the reaction of benzylamine **2.74** with 3-bromocyclohexene **2.85** in acetonitrile for 12 h at rt. The amine was isolated via column chromatography as a colourless liquid in 57 % yield (Scheme 30).



Scheme 30

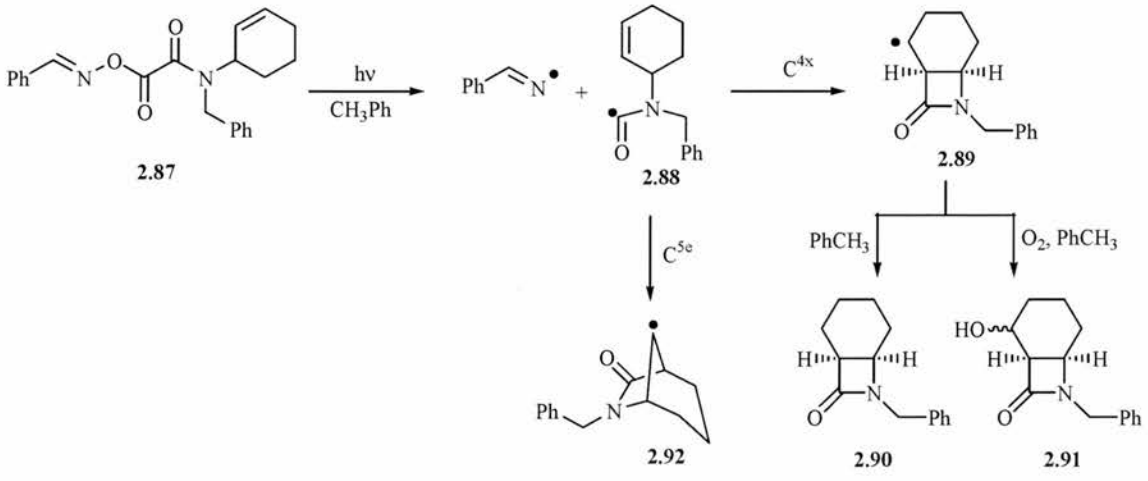
The amine was converted into the oxime oxalate amide through reaction with benzaldehyde *O*-(chlorooxalayl)oxime at rt which was isolated as colourless oil in 95 % yield (Scheme 31).



Scheme 31

It was postulated that on photolysis the system would dissociate in the usual manner to give both the iminyl and the carbamoyl radical **2.88**. In this instance, it was

predicted that the carbamoyl radical would undergo a 4-*exo* cyclisation to give the cyclohexenyl type radical **2.89**. The radical would then either, directly abstract a hydrogen from the solvent to give the β-lactam **2.90** or else it would follow the behaviour of the benzyl stabilised radical and react with dissolved O_2 to give the hydroxylated lactam **2.91**. The competing 5-*endo* process could not be ruled out in this case as it would also result in the formation of a secondary radical **2.92**. Direct hydrogen abstraction to give the formamide was not expected to be a significant process since cyclisation was favoured through formation of the stabilised 2° radical (Scheme 32).



Scheme 32

The photochemistry of the system was first investigated using ESR spectroscopy. The sample was prepared in the usual manner and photolysed with light from a 500 W UV lamp in the presence of MAP. Spectra were recorded at a range of temperatures. Figure 6 shows the ESR spectrum of oxime oxalate amide **2.87** at 220 K.

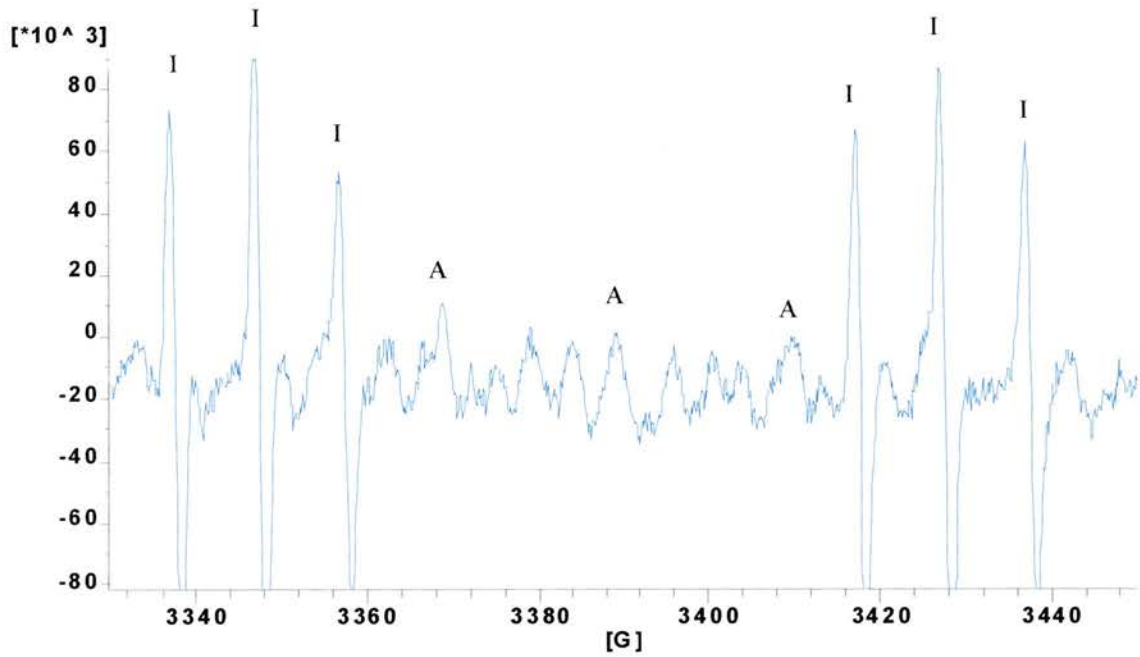


Fig 6. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **2.87** and MAP in *tert*-butylbenzene at 220 K; I; iminyl, A; carbamoyl.

The ESR spectrum obtained at 220 K was quite complex. The two groups of 3 lines towards the left and right ends of the field sweep (marked I in Figure 6) are due to the iminyl radical. The well-spaced N-triplet (marked A) is due to the carbamoyl radical **2.88**. There were a number of additional peaks remaining in the spectrum and it was possible that these may be attributed to the cyclised radical **2.89**.

The spectrum of the cyclised species **2.89** would have a radical interacting with 4 adjacent hydrogen atoms with varying hfs. This would give rise to a spectrum with 16 peaks and so it was possible that the additional peaks in figure 6 may be the cyclised species. A simulation was run using the WinEPR sofware and the remaining lines in the spectrum were well simulated (Figure 7) by a radical having g = 2.0027 and the hfs shown in Table 2.

Table 3. Experimental and computed hfs for bicyclohexyl radical **2.89**

	H_α	H^3_{ax}	H^4_{ax}	H^4_{eq}
Expt. 220K[a]	21.7	16.8	41.5	29.3
UB3LYP[b]	-20.8	16.1	41.4	28.7

[b] 6-311+G(d,p) basis set, hfs computed for the *N*-methyl analogue.

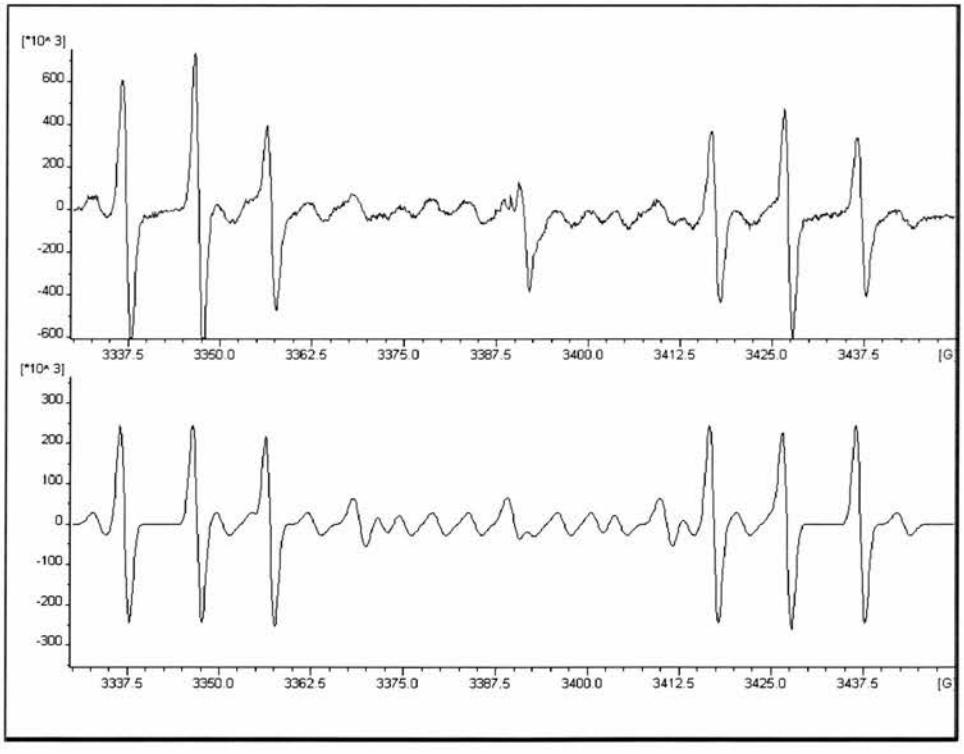


Figure 7. Experimental (top) and simulated (bottom) EPR spectra from sensitised photolysis of **2.87** in *t*-BuPh at 220 K.

The *g*-factor of this species indicated a C-centred radical and hfs from four non-equivalent H-atoms were resolved. These parameters suggested that the third radical in

figure 6 was the cyclised cyclohexenyl type radical **2.89**. It was surprising that the disfavoured *4-exo*-ring closure could be observed at 220 K. However, the experimental hfs were quite similar to those of the cyclohexyl radical in its locked conformation.[20] Furthermore, a DFT computation for the analogous N-methyl radical, UB3LYP method with a 6-311+G(d,p) basis set,[21] showed an optimised structure (Figure 8) with three non-equivalent β-H-atoms (green). Two of the H_β were axial and one equatorial.

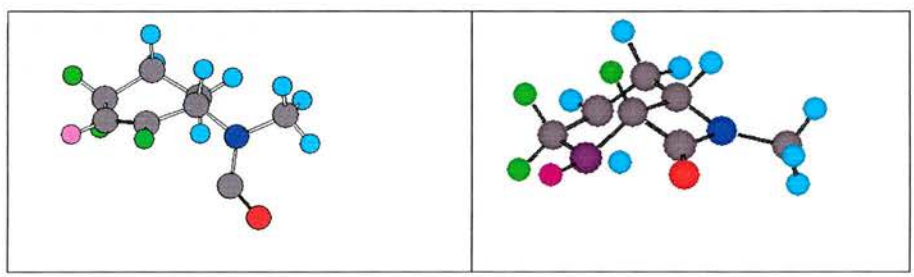


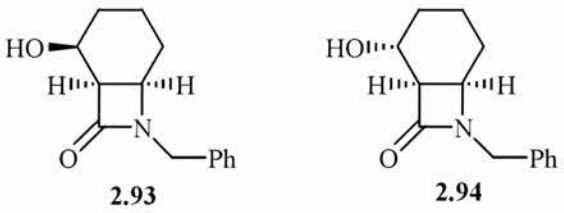
Fig 8. Structures of radicals **2.88** and **2.89** computed using the UB3LYP method with a 6-311+G(d,p) basis set.

The computed hfs in table 2 were in excellent agreement with the experimental data for the N-benzyl-bicyclohexyl radical **2.89**. The hfs for H_α (pink) was within the normal range for H-atoms adjacent to radical centres. These results confirmed our identification. We believe this to be the first EPR spectroscopic observation of a *4*-exo cyclisation. There were no peaks observed which could be attributed to the 5-*endo* product, demonstrating therefore that this was not a significant process.

Following the remarkable results of the ESR study it was predicted that the oxime oxalate amide **2.87** would give good yields of the β-lactam on prep. scale photolysis.

The starting oxime oxalate amide (800 mg) was photolysed by light from a 400 W UV lamp in the presence of 3 M eq. of MAP at 100 °C for 5 h. After this time the solvent was removed and the yellow oil which resulted was seperated by column chromatography. Once again two major products were isolated as colourless oils. NMR

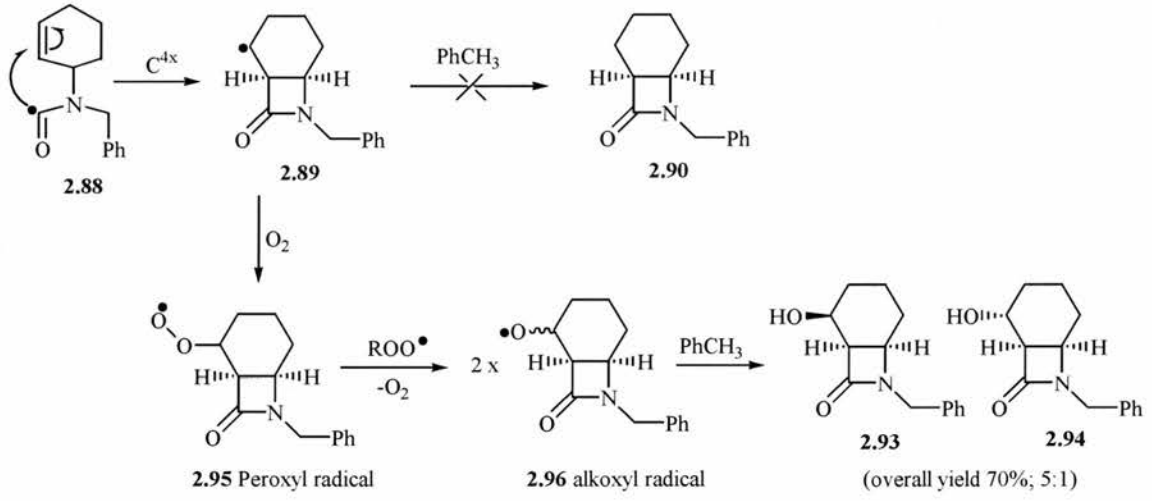
anaylsis determined that the products were isomers of the hydroxylated lactam **2.91**. These structures were verified by COSY NMR and mass spec.



2.93 **2.94**

(overall yield 70 %; 5:1)

The overall yield for the reaction was 70 % which compares quite favourably to the yield obtained from 4-*exo* cyclisation onto the cinnamyl group. Once again the rate of reaction of the 2° radical with dissolved O_2 was faster then the rate of direct hydrogen abstraction from the toluene solvent. The proposed mechanism for the formation of the hydroxylated species is illustrated in Scheme 33.



2.88 **2.89** **2.90**

2.95 Peroxyl radical **2.96** alkoxyl radical **2.93** **2.94** (overall yield 70%; 5:1)

Scheme 33

The 2° radical **2.89** reacts with dissolved O_2 to give the peroxyl radical **2.95**. This is then converted to the more reactive alkoxyl radical through self coupling and O_2 loss. The alkoxyl radical can then abstract a hydrogen atom from solution to give the hydroxylated species **2.93** and **2.94**.

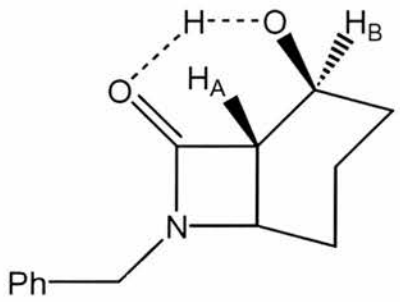
The isomers once again demonstrated significantly different polarity and the ratio of isomers was even more exaggerated then in the case of the lactams **2.81** and

2.82 (5:1 vs 3:1, in favour of the less polar isomer). The ratio of 5:1 suggests that one conformation is greatly favoured over the other.

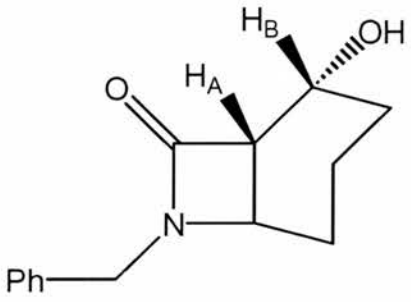
One explanation for the difference in polarity and the ratios of the isomers can be attributed the proximity of the hydroxyl group to the carbanoyl functilality.

In the case of isomers **2.93** and **2.94**, the dominant isomer was the less polar isomer where H_A and H_B are *trans* to one another. This allows a significant interaction between the ketone and the hydroxyl group which results in charge delocalisation, and an overall lowering of polarity. The interaction is also a stabilising factor and makes the *trans*- isomer the preferred conformation.

The *cis* isomer makes up less than 20 % of the overall yield of the β-lactam. The *cis* configuration of H_A and H_B orientates the hydroxyl group away from the ketone and so the interaction is reduced. The absence of any charge sharing makes the system more polar and the system is less stable overall (Scheme 34).



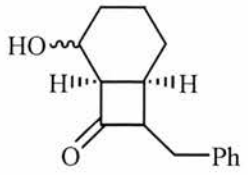
Major isomer (*Trans)*
Less Polar



Minor Isomer (*Cis*)
More Polar

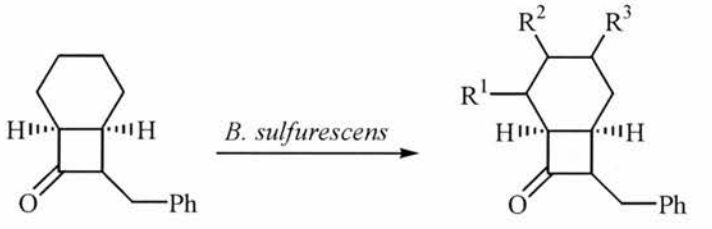
Scheme 34

It should also be noted that the geometry of the hydrogens at the ring junction was *cis* for both isomers. This is in accord with expectation since there is extra strain in the TS for *trans* ring closure and hence *cis* is favoured for radical cyclisation.



Cis -isomer

The hydroxylated bicyclic β-lactam **2.91** had previously been prepared in a 7 % yield by Furstoss *et al.*[22] through the biohydroxylation of the β-lactam by the fungus *Beauveria Sulfurescens* (Scheme 35).



2.97 **2.98**

2.98A R^1 = OH, R^2 = R^3 = H (7%)

2.98B R^2 = OH, R^1 = R^3 = H (23%)

2.98C R^3 = OH, R^1 = R^2 = H (15%)

Scheme 35

The biohydroxylation resulted in the formation of a mixture of compounds. The compound **2.98A** was isolated by column chromatography. The stereochemistry of the compound was undefined but comparison with our own work established that the less stable *cis* isomer had been isolated. The proton shifts for the ^{1}H NMR exactly matched those of compound **2.94** and this was further proof that molecules **2.93** and **2.94** were indeed the hydroxylated bicyclic β-lactams.

Once again the formamide was not observed and no traces of the 5-*endo* product were observed. The only other major product was benzaldehyde, derived from the iminyl radical.

2.3.0 Conclusions

It was demonstrated that oxime oxalate amides can be used as clean efficient radical precursors for iminyl and carbamoyl radicals. Homolytic cleavage of the N-O oxime bond occurs on photolysis and rapid loss of CO_2 gives the carbamoyl radical. The radicals could be observed by ESR spectroscopy and on no occasion was there loss of CO to give the aminyl radical.

A versatile, efficient route to oxime oxalate amides was developed and was found to work for all target molecules apart from one instance where steric factors prevented reaction.

The ESR spectra of both iminyl and carbamoyl radicals were observed and the g-factor and hyperfine splittings were measured. Through comparison of these values with known literature values it was possible to confirm the nature of the radicals observed.

The fate of the iminyl radical was determined. It was found that the iminyl radicals, instead of self coupling, abstracted a hydrogen atom from solution to give the imine which was hydrolysed on work up to give the corresponding aldehyde or ketone. In this way both acetone and benzaldehyde were observed.

The carbamoyl radicals generated were used in cyclisation reactions to prepare both β- and γ-lactams in good yields. The yields for γ-lactam were excellent once the optimum conditions for photolysis has been established. The yields for β-lactams varied depending on the nature of the functional group onto which cyclisation was occurring. Simple carbon-carbon double bonds gave low yields of the lactam whereas cinnamyl and cyclohexenyl groups led to good yields of the lactams.

Secondary stabilised radicals were found to react more quickly with dissolved O_2 rather than the solvent and isomers of hydroxylated lactams were isolated in good yields. Carbamoyl radicals were also used in the preparation of a highly strained bicyclic lactam in good yield.

ESR spectroscopy was also used to observe and characterise the products of radical cyclisations. 4-*exo* cyclisations which had never before been observed by ESR spectroscopy were observed at 220 K. ESR prediction software and computer modelling packages were used to confirm the structure of the cyclised radical. The ESR parameters were determined and compared favourably to the simulation.

2.4.0 Experimental

Instrumentation and General Techniques

1. NMR Spectroscopy:

^{1}H-NMR: Routine spectra were obtained at 300 MHz on a Bruker B-ACS60 Avance 300 or on a Varian Gemini 2000.

^{13}C-NMR: Spectra were obtained at 75 MHz on a Bruker B-ACS60 Avance 300 or on a Varian Gemini 2000.

Both the ^{1}H-NMR and ^{13}C-NMR spectra were obtained from solutions in $CDCl_3$ unless otherwise stated. All spectra were referenced to internal tetramethylsilane and the chemical shifts for all NMR spectra are expressed in parts per million to high frequency of the reference.

2. Infrared spectroscopy:

The IR spectra were obtained on a Perkin Elmer FT-IR Paragon 1000 spectrometer. Solids were run as nujol mulls and liquids were run as thin films on NaCl plates.

3. Mass Spectroscopy:

Mass spectra and accurate mass measurements were obtained on a VG Platform spectrometer by Mrs. Caroline Horsburgh. Unless otherwise stated the spectra were obtained using electron impact at 70 eV. Chemical ionisation spectra were obtained using isobutene as the ionising gas and fast atom bombardment spectra were obtained using 3-nitrobenzyl alcohol as the matrix.

4. GC/MS:

GC/MS analyses were run on a Finnigan Incos 50 quadrupole instrument coupled to a Hewlett Packard HP 5890 chromatograph fitted with a 25 m HP 17 capillary column (50 % phenyl methyl silicone).

5. Elemental Analysis:

Microanalysis was carried out for C, H and N using an EA 1110 CHNS CE instruments elemental analyser by Mrs. S. Williamson.

6. Melting Points:

Routine melting points were carried out on a Gallenkamp melting point apparatus. Melting points for new compounds were determined on a Reichert hot-stage microscope. All melting points are uncorrected.

7. Thin Layer Chromatography:

Thin layer chromatography was performed using 0.2 mm layers of silica supported on aluminium sheets (Merck, Silica Gel $60F_{254}$). The components were observed under ultraviolet light and/or stained with ninhydrin.

8. Column Chromatography:

For column chromatography Fisher silica gel and Fisher neutral alumina was used.

9. Dry Solvents:

Diethyl ether was freshly distilled from sodium benzophenone ketyl. Where dry DCM was used, it was distilled over CaH_2. DMSO was dried and distilled from CaH_2 and stored over 4 Å molecular sieves. Other organic compounds were used as received, without further drying.

10. Drying and Evaporation of Organic Solutions

Organic solutions were dried by standing over anhydrous magnesium sulfate and evaporated under reduced pressure on a rotary evaporator.

11. UV Photolysis:

Ultra Violet irradiation was carried out in quartz apparatus using a 400 W medium pressure Hg lamp.

12. X-Ray Crystallography:

Data were collected on a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined using full-matrix least squares methods. Atomic coordinates and bond lengths and angles are listed in the Appendix and the structures are shown in the discussion.

13. ESR Spectroscopy:

ESR spectra were obtained with a Bruker EMX 10/12 spectrometer operating at 9.5 GHz with 100 KHz modulation.

Acetone *O*-(chlorooxalyl)oxime[7] 20

A solution of acetone oxime **27** (2.92 g; 40 mmol) in diethylether (10 cm^3) was added dropwise under stirring to a cold (-20 °C) solution of oxalyl chloride (7.60 g; 60 mmol) in diethyl ether (10 cm^3). The mixture was stirred at –20 °C for 30 min followed by 10 min at 23 °C (after which time the initial ppt. had completely dissolved). The solvent was removed at 23 °C/13 torr to yield a colourless volatile oil, which started to turn yellow on standing at rt (6.07 g; 94 %); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 2.11, 2.12 (3H, s, CH_3).

Acetone *O*-(anilinooxalyl)oxime[7] 2.21

A solution of aniline (1.86 g; 20 mmol) in $CHCl_3$ was added dropwise under stirring to a cold (-40 °C) solution of the oxime oxalyl chloride **20** (1.62 g, 10 mmol) in $CHCl_3$ (20 cm^3). After stirring for 1 h at 23 °C, anilinium chloride was filtered off. Evaporation of the filtrate yielded a colourless powder which was purified *via*

recrystallisation from $CHCl_3$ (25 cm^3) at –20 °C (1.42 g; 65 %) mp = 175-178 °C; ν_{max}(NaCl)/cm^{-1} 1746, 1703 (C=O); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 2.16, 2.21 (6H, s, CH_3) 7.28 - 7.69 (5H, m, ArH), 8.95 (1H, br, N-H), δ_C ($CDCl_3$) 17.5, 21.9 (CH_3), 136.3, 125.6, 129.2, 119.8 (ArC), 153.3, 158.8, 167.6 (C=N, C=O)

Attempted synthesis of *N*-benzyl-*N*-butylaminoxalylchloride 2.24

N-Benzyl-*n*-butylamine (0.5 g; 3.1 mmol), was added dropwise under stirring to a solution of oxalyl chloride (0.47 g; 3.7 mmol) and triethylamine (0.31 g; 3.1 mmol) in cold (-20 °C) diethyl ether (20 cm^3). The white ppt which resulted was filtered and dried overnight in a dessicator. NMR analysis revealed that a mixture of products had been formed.

Acetone *O*-(benzylaminooxalyl)oxime 2.29

A solution of benzylamine (2.14 g; 20 mmol) in $CHCl_3$ (10 cm^3) was added dropwise under stirring to a cold (-40 °C) solution of acetone *O*-(chlorooxalyl)oxime (1.63 g; 10 mmol). After stirring for 1 h at rt the reaction mixture was left standing overnight. The reaction mixture was filtered, and the filtrate evaporated to yield a colourless powder. The product was then washed with hexane/diethyl ether and ethyl acetate, and the solution was filtered to furnish **2.29** as a colourless powder (3.14 g; 67 %); mp. 198-202 °C; ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 2.11, 2.12 (3H, s, CH_3), 4.55 (2H, d, Ar-CH_2), 7.35 (5H, s, Ar-H), 7.52-7.68 (1H, br, NH), 2.11, 2.14 (6H, s, CH_3-dioxime); δ_C ($CDCl_3$)17.9, 22.4 (CH_3), 44.4 (CH_2), 158.7, 167.9 (C=N), (C=O), 137.1, 128.5, 128.4, 129.3 (ArC); *m/z* (%),(CI) 235 (MH^+,50), 180 (100); (Found: 235.1092, $C_{12}H_{15}N_2O_3$ requires 235.1086).

Acetone *O*-(*n*-benzyl-*n*-butylaminooxalyl)oxime 2.32

A solution of *N*-benzyl-*N*-butylamine (1.86 g; 11.3 mmol) was added dropwise to a cold (-40 °C) solution of acetone *O*-(chlorooxalyl)oxime **2.20** (1.63 g;10 mmol) in $CHCl_3$ (20 cm^3). After stirring for 1 hr at -20 °C, the solvent was removed at 0 °C to yield a colourless solid **2.32** (1.57 g; 54 %). The product was then recrystallised from dry $CHCl_3$. ($CHCl_3$ was dried by passing it through an alumina column); ^{1}H NMR, (300

MHz, $CDCl_3$) δ_H 0.96 (3H, t, J 7, CH_3), 1.33 (2H, m, CH_2), 1.55 (2H, m, CH_2), 2.01 (6H, s, 2 CH_3), 3.22 (2H, t J 7, NCH_2), 4.49 (2H, s, NCH_2Ph), 7.23-7.64 (5H, m, ArH); δ_C ($CDCl_3$) 16.9 (CH_3), 21.5 (2xCH_3). 19.7 (CH_2), 29.7 (CH_2), 47.3 (NCH_2), 51.1 (NCH_2Ph), 127.9 128.5 127.4 135.5 (ArC), 161.5, 165.5, 165.7 (C=O, C=N); *m/z* (%), (CI) 291 (MH^+ 89), (164; 100).

Syn-Benzaldoxime[8] 2.33

To a solution of sodium hydroxide (14 g; 0.33 mol) in H_2O (40 cm^3) was added benzaldehyde (21 g; 20 cm^3; 0.2 mol), then hydroxylamine hydrochloride (15 g; 0.22 mol) portionwise, with vigorous stirring. On cooling and leaving overnight a crystalline mass formed. Water was added until this dissolved (~150 cm^3) and CO_2 was passed through the solution until a fine ppt had formed. The product was extracted with ether (4 x 75 cm^3), dried ($MgSO_4$), and concentrated. The product was distilled at reduced pressure (115 °C @ 0.4 mm Hg), giving a colourless liquid (11.26 g, 47 %, lit[8] = 49 %); ^1H NMR, (300 MHz, $CDCl_3$) δ_H 7.43-7.63 (5H, m, Ar-H), 8.22 (1H, s, PhCH=N), 9.55 (1H, br, NOH); m/z (%) 121 (M^+, 100 %).

Benzaldehyde _O_-(chlorooxalyl)oxime[7] 2.34

A solution of benzaldoxime (1.21 g; 10 mmol) in diethyl ether (10 cm^3) was added dropwise to a cold (-40 °C) solution of oxalyl chloride (1.90 g; 15 mmol) in diethyl ether (10 cm^3). After stirring for 1 h at –20 °C the solvent was evaporated at –10 °C/13 torr to leave a colourless temperature sensitive powder which was dried under vacuum for 2 h to remove residual diethyl ether. (2.01 g; 96 %, lit[7] = 97 %); ν_{max}(NaCl)/cm^{-1} 1791 (C=O); ^1H NMR, (300 MHz, $CDCl_3$) δ_H 7.2 -7.49 (5H, m, ArH), 8.55 (1H, s, CH) δ_C 128.2, 128.8, 129.2, 132.9 (Ar) 159.4, 160.4 (C=N,C=O). m/z (%) 211 (M^+,20 %).

Preparation of benzaldehyde _O_-(_n_-benzylaminooxalyl)oxime 2.35

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime (1.2 g; 6 mmol) in DCM (10 cm^3) at 0 °C was added a solution of pyridine (0.5 g; 6 mmol) in DCM (5

cm^3), followed by a solution of benzylamine (0.64 g; 6 mmol) in DCM (5 cm^3). The mixture was stirred at -10 °C for 10 min and then at rt for 3 h. After this time the ppt which had formed was filtered off and the solvent was removed. The product was filtered through a pad of silica and the product was recrystallised from DCM/hexane at -20 °C to give the title compound **2.35** as colourless platelets (1.38 g; 82 %) mp = 20 – 22 °C; ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 4.57 (2H, d, *J* 6, $ArCH_2$), 7.31-7.40 (5H, m, ArH), 7.43-7.55 (3H, m, ArH), 7.75-7.78 (2H, m, ArH), 8.62 (1H, s, HC=N); δ_C ($CDCl_3$) 44.7 ($ArCH_2$), 128.3, 128.4, 128.5, 129.1, 129.2, 129.3, 129.4, 132.8 (ArC), 156.0, 158.7, 159.5 (C=O, C=O, C=N); *m/z* (%), (CI), 283 (MH^+, 29 %), 269 (17), 180 (100), 160 (11), 104 (56), 57 (46); (Found: MH^+ 283.1082, $C_{16}H_{15}N_2O_3$ requires MH^+ 283.1095).

Preparation of samples for EPR analysis.

Samples were prepared by taking 20 mg of the starting oxime oxalate amide and dissolving it in *tertiary*-butylbenzene (*ca.* 500 µl). To this was then added one molar equivalent of the photosensetizor, *para*-methoxyacetophenone (MAP). The sample was degassed under N_2 and then sealed in a quartz ESR tube.

Photolysis of Acetone *O*-(anilinooxalayl)oxime 2.21

A degassed solution of *O*-(anilinooxalyl)oxime **2.21** (20 mg; 0.09 mmol) in $CHCl_3$ (1 cm^3) in the presence of 4-methoxyacetophenone (MAP) (13.7 mg; 0.09 mmol) was photolysed for two hours with light from a 400 W medium pressure UV lamp. After this time the mixture was allowed to cool and the solvent was removed. The yellow oil which resulted was submitted for analysis by GC/MS. Peak no. 82 PhNCO (5 %), m/z (%) 119 (100), 91 (43), 64 (28). Peak no. 235, PhNHCH(CO), (formamide **2.41**) (33 %), m/z (%) 121 (100), 93 (100), 107 (12), 77 (36), 66 (68). Peak no. 345 $PhNHCOCO_2H$ (2 %) m/z (%) 165 (51), 108 (100), 123 (51), 80 (18).

Synthesis of *O*-pent-4-enyl acetone oxime[8] 2.46.

To a stirred mixture of acetone oxime (2.63 g; 3 6mmol) and 5-bromo-1-pentene (4.47 g; 30 mmol) in DMF (99 cm^3) was added caesium carbonate (11.94 g; 36 mmol). The mixture was stirred overnight. Water (75 cm^3) was added and the product was extracted with ether (3 x 75 cm^3) then washed extensively with water and the organic layer dried ($MgSO_4$) and concentrated. The crude product was purified via Kugelrohr distillation which furnished **46** as a colourless oil (1.21 g; 29 %); ^1H NMR, (300 MHz, $CDCl_3$) δ_H 1.69-1.83 (2H, m, CH_2), 1.87 (6H, s, CH_3), 2.10-2.22 (2H, m, CH_2CH=), 4.02 (2H, t, J 7, OCH_2), 4.93-5.10 (2H, m, CH_2=CH), 5.75-5.90 (1H, m, CH_2=CH); δ_C ($CDCl_3$) 15.8, 22.1, 28.7, 30.5, 72.9, 114.9, 138.5, 154.5.

Synthesis of O-pent-4-enyl benzaldoxime[8] 2.47.

To a stirred mixture of benzaldoxime (4.36 g; 36 mmol) and 5-bromo-1-pentene (4.47 g; 3 0mmol) in DMF (99 cm^3) was added caesium carbonate (11.94 g; 36 mmol). The mixture was stirred overnight. Water (75 cm^3) was added and the product was extracted with ether (3 x 75 cm^3) then washed extensively with water and the organic layer dried ($MgSO_4$) and concentrated. The crude product was purified via Kugelrohr distillation which furnished **47** as a colourless oil (4.0 g; 71 %); ^1H NMR, (300 MHz, $CDCl_3$) δ_H 1.79-1.86 (2H, m, CH_2), 2.13-2.21 (2H, m, CH_2CH=), 4.18 (2H, t, J 7, OCH_2), 4.97-5.08 (2H, m, CH_2=CH), 5.80-5.89 (1H, m, CH_2=CH), 7.33-7.37 (3H, m, ArH), 7.55-7.58 (2H, m, ArH), 8.07 (1H, s, CH=N), δ_C ($CDCl_3$) 28.8, 30.5, 74.01, 115.29, 127.3, 129.0, 130.0, 132.8, 148.7.

Photochemical reaction of acetone *O*-(anilinooxalyl)oxime 2.21 in the presence of oxime ester *O*-pent-4-enylacetoneoxime 2.46.

A degassed solution of *O*-(anilinooxalyl)oxime **2.21** (20 mg; 0.092 mmol) in $CHCl_3$ (1 cm^3) in the presence of 4-methoxyacetophenone (13.7 mg; 0.092 mol) and *O*-pent-4-enylacetoneoxime (12.8 mg; 0.092 mmol) was photolysed for 2 h using a 125 W medium pressure Hg lamp, and the product mixture analysed by GC/MS. Peak no.

240, PhNHCOH *m/z* (%) 121 (M^+100), 93 (90) 66 (58). Peak no.289, chlorinated adduct, *m/z* (%) 224 (M^+16), 226 (9), 56 (100), 194 (28), 160 (17), 142 (21), 128 (15), 109 (46), 84(17), 73 (69). Peak no. 354, HOCOCONHPh, *m/z* (%) 165 (M^+, 51 %), 108 (100), 123 (53), 108(100), 93 (27), 77 (35). There was no peak corresponding to the unreacted starting oxime oxalate amide **2.21**.

Photochemical reaction of acetone *O*-(anilinooxalyl)oxime 2.21 in the presence of oxime ester *O*-pent-4-enylbenzaldoxime 2.47.

A degassed solution of *O*-(anilinooxalyl)oxime **2.21** (20 mg; 0.092 mmol) in $CHCl_3$ (1 cm^3) in the presence of 4-methoxyacetophenone (13.7 mg; 0.092 mol) and *O*-pent-4-enylbenzaldoxime (17.2 mg; 0.092 mol) was photolysed for two hours using a 125 W medium pressure Hg lamp, and the product mixture analysed by GC/MS. Peak no.346, chlorinated adduct, *m/z* (%) 224 (M^+ 76), 225(9), 227(3), 190(100), 160(53), 132(10), 122(34), 104(62), 77(83).Peak no 449, PhCONHCOPh *m/z* (%), 240(M^+ 7), 105(100), 225(19), 105(100), 77(57).

***N*-Benzylformamide 2.52**

A solution of benzaldehyde *O*-(*n*-benzylaminooxalyl)oxime (100 mg; 0.35 mmol) and MAP (53 mg; 0.35 mmol) in toluene (150 cm^3), was photolysed at rt by light from a 400 W medium pressure Hg lamp for 90 min. After this time the reaction mixture was evaporated to dryness to give a yellow oil. The yield of the formamide (100 %) was determined by NMR. ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 4.51 (2H, d, *J* 6, CH_2), 7.29-7.38 (5H, m, ArH), 8.14 (1H, s, HC=O).

Synthesis of benzaldehyde *O*-(*N*-benzyl-3-buten-1-ylaminooxalyl)oxime 2.53

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime **2.34** (1.43 g; 0.8 mmol) in DCM (15 cm^3) at 0 °C was added pyridine (0.54 g; 6.8 mmol) in DCM (8 cm^3) followed by *N*-benzyl-3-buten-1-ylamine **2.58** (1.1 g; 6.8 mmol) in DCM (8 cm^3). The mixture was allowed to reach rt and then stirred at rt for 2 h. After this time pentane (ca. 3 cm^3) was added to promote formation of the pyridine hydrochloride ppt.

The ppt. was filtered off and the filtrate was evaporated to dryness. The resulting oil was purified via flash column chromatography to give the pure product as a white solid (1.60 g; 70 %) mp 0-5 °C; ν_{max}(NaCl)/cm^{-1} 1739 (C=O), 1636 (C=N); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 2.34 (1H, q, J 7), 2.40 (1H, q, J 7) (apparent sextet), 2.32 (1H, t, J 7, N-CH_2), 2.42 (1H, t, J 7, N-CH_2), 4.55 (1H, s, Ar-CH_2), 4.69 (1H, s, Ar-CH_2), 5.00-5.13 (2H, m, =CH_2), 5.63-5.82 (1H, m, =CH), 7.30-7.70 (10H, m, ArH), 8.42 (1/2H, s), 8.50 (1/2H, s); δ_C ($CDCl_3$) 31.1, 32.5, 43.4, 46.5, 47.1, 51.8 (CH_2), 117.3 (=CH_2), 127.9, 128.3, 128.3, 128.6, 128.6, 128.8, 128.9, 132.3, (ArC), 134.9 ,135.7 (=CH), 157.7, 157.9 (C=O), 160.9, 161.2 (C=N); *m/z* (%) MH^+ (337, 24 %), 234 (92), 190 (25), 104 (77), 57 (100); (Found: MH^+ 337.1562, $C_{20}H_{21}N_2O_3$ requires MH^+ 337.1552).

Preparation of *N*-benzyl-3-buten-1-ylamine[16] 2.58

A solution of benzylamine (7.56 g; 70.4 mmol), 4-bromo-1-butene (1.92 g; 14.1 mmol), and ethanol (20 cm^3) was deoxygenated with N_2 and treated with NaI (ca. 20 mg) at rt. The resulting solution was heated at 75 °C for 4 h, cooled to rt and partitioned between DCM (100 cm^3) and 1 M KOH (100 cm^3). The aqueous phase was extracted with DCM (100 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated and the resulting residue was purified by column chromatography (hexane/DCM) to give the pure amine as a colourless oil 1.21 g (53 %); ^{1}H NMR, (300MHz, $CDCl_3$) δ_H 1.45 (1H, brs, NH), 2.25-2.30 (2H, m, CH_2), 2.70-2.78 (2H, m, NCH_2), 3.80 (2H, s, $PhCH_2$), 5.01-5.02 (2H, m, =CH_2), 5.74-5.83 (1H, m, =CH), 7.26-7.33 (5H, m, PhH). δ_C ($CDCl_3$) 34.3, 48.3, 53.9, 116.3, 126.8, 128.0, 128.3, 136.4, 140.3.

1-Benzyl-3-methyl-pyrrolidin-2-one 2.59

A solution of benzaldehyde *O*-(*N*-benzyl-3-buten-1-ylaminooxalyl)oxime **2.54** (800 mg; 2.38 mmol) and MAP (1.07 g; 7.14 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was purified via column chromatography (DCM; MeOH) to give the pure product as a colourless oil (378 mg; 84 %); ^{1}H NMR, (300MHz, $CDCl_3$) δ_H 1.25 (3H, d, J 17, CH_3) 1.6 (1H, m,

CH), 2.25 (1H, m, CH_2), 4.42 (1H, AB, J 15 and 18, CH), 4.48 (1H, AB,), 7.21-7.37 (5H, m, ArH); δ_C ($CDCl_3$) 16.4 (CH_3), 27.1 (CH_2), 36.8 (CH), 44.7 (CH_2), 46.8 (CH_2), 127.5, 128.1, 128.6, 136.7 (ArC), 177.4 (C=O); *m/z* (%) 189 (100, M^+), 174 (11), 161 (12), 91(90); (Found M^+ 189.1153, $C_{12}H_{15}NO$ requires M^+ 189.1154).

Synthesis of N-allyl-*p*-toluenesulfonamide[17] 2.62

A solution of *p*-toluenesulfonyl chloride **2.60** (7.7 g; 0.04 mol) in DMF (20 cm^3) was added dropwise to a stirred solution of allyl amine **2.61** (4.56 g; 0.08 mol) in DMF (20 cm^3) maintained at 25 °C by external cooling. After 30 min at 25-30 °C the resulting solution was warmed at 40-45 °C for 5 min, cooled and then poured onto H_2O (160 cm^3). The resulting ppt. was collected, washed with H_2O, dried and reprecipitated from an activated carbon treated, celite filtered solution in 6 % NaOH (100 cm^3) by addn. of 25 % H_2SO_4 to give the product as a white crystalline solid (7.93 g; 94 %); mp 67-69 °C; lit[17]= 68.5-69.5 °C; (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 2.44 (3H, s, CH_3), 3.59 (2H, m, CH_2), 4.42 (1H, brt, J 6, NH), 5.08-5.14 (2H, m, $=CH_2$), 5.70 (1H, m, =CH), 7.30 (2H, d, J 8, ArH), 7.76 (2H, d, J 8, ArH).

Attempted synthesis of benzaldehyde *O*-(*N*-allyl-*p*-toluenesulfonamino oxalyl)oxime 2.63

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime **2.34** (2.11 g; 10 mmol) and pyridine (1.03 g; 13 mmol) in DCM (30 cm^3) at 0 °C was added N-allyl-*p*-toluenesulfonamide **2.62** (2.11 g; 10 mmol) in DCM (10 cm^3). The mixture was allowed to reach rt and stirred for 2 h. The ppt. which formed was filtered off and the filtrate evaporated to dryness. NMR analysis of the crude material revealed that the target molecule had not been formed.

***N*-Benzyl-prop-2-enylamine 2.66**

A mixture of prop-2-enylamine **2.61** (3.2 g, 0.06 mol) and benzaldehyde **2.65** (5.9 g, 0.06 M), were stirred in DCM (25 cm^3) at rt for 2 h. After this time the solvent was evaported under reduced pressure and the residue was dissolved in MeOH (25

cm^3). Sodium borohydride (4.2 g, 0.11 mol) was added portionwise over a period of 30 min and the mixture was stirred at rt for an additional 60 min. After this time, water (25 cm^3) was added and the mixture was extracted with DCM (4 x 25 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Distillation of the residue (Kugelrohr, bulb to bulb) at 110-115 °C at 2 mmHg, yielded the pure amine **2.66** as a colourless oil (5.5 g; 67 %); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 1.62 (1H, br, NH), 3.23 (2H, d, *J* 6 , N-CH_2), 3.81 (2H, s, ArCH_2), 5.17 (2H, m, =CH_2), 5.83 (1H, m, =CH), 7.38 (5H, m, ArH); δ_C ($CDCl_3$) 51.7 (CH_2), 53.2 (Ar-CH_2), 115.9 (=CH_2), 126.9, 128.1, 128.3, 136.7 (ArC), 140.2 (C=O).

Benzaldehyde *O*-(*N*-benzyl-prop-2-enylaminooxalyl)oxime 2.67

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime (2.11 g; 10 mmol) in DCM (25 cm^3) at 0 °C was added pyridine (1.0 g; 13 mmol) in DCM (5 cm^3) followed by *N*-benzyl-prop-2-enylamine (1.5 g; 10 mmol) in DCM (10 cm^3). The mixture was allowed to reach rt and then stirred at rt for 2 h. After this time pentane (ca. 3 cm^3) was added to promote formation of the pyridine hydrochloride ppt. The ppt. was filtered off and the filtrate was evaporated to dryness to give a yellow oil. The oil was further purified via flash column chromatography to give the pure target molecule as a colourless oil which solidified on cooling (1.40 g; 44 %) mp = 0-5 °C; ν_{max}(NaCl)/cm^{-1} 1744 (C=O), 1656 (C=N); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 3.83 (1H, d, *J* 7, CH_2), 3.88 (1H, d, *J* 7, CH_2), 4.46 (1H, s, ArCH_2), 4.64 (1H, s, ArCH_2), 5.18-5.27 (2H, m, =CH_2), 5.66-5.84 (1H, m, =CH), 7.22-7.68 (10H, m, ArH), 8.41 (1/2H, s) 8.44 (1/2H, s); δ_C ($CDCl_3$) 47.8, 48.8, 50.3, 51.1 (CH_2), 119.2 (=CH_2), 127.9, 128.0, 128.1, 128.3, 128.6, 128.8, 128.9, 129.0, 129.1, 130.4, 130.6, 132.1 (ArC), 132.7 (=CH), 157.7, 157.9 (C=O), 163.3 (C=N); *m/z* (relative intensity), (CI), 323 (MH^+, 36 %), 310 (10), 220 (100), 176 (25), 122 (20), 104 (36); (Found: MH^+ 323.1392, $C_{19}H_{19}N_2O_3$ requires MH^+ 323.1395).

1-Benzyl-3-methyl-azetidin-2-one[23] 2.72

A solution of benzaldehyde *O*-(*N*-benzyl prop-2-enylaminooxalyl)oxime **2.67** (800 mg; 2.5 mmol) and MAP (1.13 g; 7.5 mmol) in toluene (400 cm^3) was photolysed

at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was evaporated to dryness and purified via column chromatography (DCM; MeOH) to give the pure product as a colourless oil (173 mg; 40 %); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 1.27 (3H, d *J* 7, Me), 2.73 (1H, dd *J* 5 and 2, CH), 3.15 (1H, m, CH), 3.26 (1H, m, CH), 4.30 (1H, d, *J* 15, CH), 4.35 (1H, d, *J* 15, CH), 7.30 (5H, m, ArH); δ_C ($CDCl_3$) 13.7 (CH_3), 44.5 (CH), 45.8 (CH_2), 46.7 (CH_2-Ph), 127.7, 128.3, 128.8, 135.9 (Ar), 171.4 (C=O).

Synthesis of *N*-Cinnamyl-benzylamine 2.75

To a stirred solution of benzylamine (1.2 g; 11 mmol) and K_2CO_3 (4.5 g) in DCM (45 cm^3) was added cinnamyl bromide (1.8 g; 11 mmol) in DCM (10 cm^3). The mixture was stirred at rt for 2 h after which time the solvent was removed. The resulting oil was purified via column chromatography to give the amine as a colourless oil (1.6 g; 65 %); ^{1}H NMR, (300MHz, $CDCl_3$) δ_H 1.64 (1H, brs, NH), 3.44 (2H, dd, *J* 1 and 6, CH_2), 3.84 (2H, s, $ArCH_2$) 6.32 (1H, dt, *J* 6 and 16, =CH), 6.54 (1H, d, *J* 16, =CH), 7.30 (5H, m, Ar); δ_C ($CDCl_3$) 51.1, 53.2 (CH_2) 126.3, 127.0, 12.4, 128.1, 128.2, 18.4, 128.5, 131.6 (ArC), 137.0, 140 (CH=).

Benzaldehyde *O*-(*N*-cinnamyl-benzylaminooxalyl)oxime 2.76

To a stirred solution of the benzaldehyde *O*-(chlorooxalyl)oxime **2.34** (1.3 g; 6.0 mmol) in DCM (20 cm^3) was added dropwise a solution of pyridine (0.62 g; 6 mmol) in DCM (5 cm^3) followed by *N*-cinnamyl-benzylamine **2.75** (1.34 g; 6 mmol) in DCM (5 cm^3). The solution was allowed to reach rt and then stirred at rt for 3 h. After this time a small amount of pentane (ca. 10 cm^3) was added in order to promote formation of the pyridine hydrochloride salt. The ppt. was filtered off and the filtrate collected. The filtrate was evaporated to dryness to give the crude product as a colourless oil. The product was purified via flash column chromatography to give the pure oxime oxalate amide as a colourless oil (2.0 g; 85 %); ν_{max}(NaCl)/cm^{-1} 1764 (C=O), 1665 (C=N); (Found C, 68.75; H, 5.48; N, 6.97 %; $C_{25}H_{22}N_2O_3$ requires C, 75.4; H 5.57; N, 7.03 %); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 3.92 (1H, d, *J* 6, N-CH_2), 4.03 (1H, d, *J* 6, N-CH_2), 4.46 (1H, s, $ArCH_2$), 4.62 (1H, s, $ArCH_2$), 5.98-6.14 (1H, m,

=CH), 6.41 (1H, d, *J* 15, =CH), 7.16-7.60 (15H, m, ArH), 8.38 (1H, s); δ_C ($CDCl_3$) 45.7, 47.1, 49.6, 51.1 (CH_2) 127.4, 128.3, 128.5, 128.7, 128.9, 129.0, 129.1, 129.3, 129.4, 129.5, (ArC), 135.3 (CH=CH), 158.1 (C=O), 161.9 (C=N).

1-Benzyl-3-(hydroxy-phenyl-methyl)-azetidin-2-one 2.81, 2.82.

A solution of **2.19** (400 mg; 0.97 mmol) and MAP (452 mg; 3.0 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was purified via column chromatography (DCM; MeOH) to give a mixture of isomers (3:1; *anti*:*syn*) as a colourless oil (169 mg; 69 %). The isomers were separated by further column chromatography (EtOAc; hexane) *anti* ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 3.04 (1H, t, *J* 5, N-CH), 3.20 (1H, dd, *J* 5 and 3, N-CH), 3.59 (1H, m, COCH), 3.81 (1H, br, OH), 4.39 (2H, AB, $ArCH_2$), 5.24 (1H, d, *J* 3, ArCH), 7.14–7.38 (10H, m, ArH); δ_c ($CDCl_3$) 40.2 (N-CH_2), 45.9 ($ArCH_2$), 56.7 (CH), 69.6 (CHOH), 127.6, 127.7, 127.9, 128.3, 128.4, 128.5, 128.7, 128.8 (ArC), 168.3 (C=O); *m/z* (relative intensity) 267 (M^+, 10 %), 176 (17), 133 (38), 105 (62), 91 (100), 84 (62), 77 (55); (M^+ 267.1267, $C_{17}H_{17}NO_2$ requires M^+ 267.1259); *syn* ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 2.99 (1H, dd, J 2 and 6, N-CH), 3.14 (1H, t, *J* 6, N-CH), 3.61 (1H, m, COCH), 3.81 (1H, br, OH), 4.35 (2H, AB, $ArCH_2$), 5.02 (1H, d, *J* 7, $ArCH_2$), 7.03 – 7.44 (10H, m, ArH); δ_C ($CDCl_3$) 41.6 (N-CH_2), 45.8 ($ArCH_2$), 56.1 (CH), 73.0 (CHOH), 127.6, 127.8, 127.9, 128.1, 128.2, 128.6, 128.8, 128.9 (ArC), 168.3 (C=O); *m/z* (relative intensity) 267 (M^+, 11 %), 176 (37), 133 (59), 105 (47), 91 (100), 77 (41); (M^+ 267.1259, $C_{17}H_{17}NO_2$ requires M^+ 267.1259).

***N*-Benzyl-2-cyclohexenyl amine[19] 2.86**

To a stirred solution of benzylamine (1.60 g; 15 mmol) and K_2CO_3 (6.0 g; 43.2 mmol) in CH_3CN (60 cm^3) was added a solution of 3-bromocyclohexene (2.0 g; 12.5 mmol) in CH_3CN (12 cm^3). The mixture was stirred overnight at rt. After this time, the solvent was removed and the resulting oil was purified via column chromatography (EtOAc/ hexane) to give the pure product as a colourless oil (1.33 g; 57 %) ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 1.34 (1H, br, CH), 1.52 (2H, m, CH_2), 1.74 (1H, m, CH), 1.90

(1H, m, CH) 1.99 (2H, m, CH_2), 3.21 (1H, br, NH), 3.84 (2H, AB, CH_2), 5.74 (2H, m, HC=CH), 7.31 (5H, m, Ar); ms (EI) relative intensity (M^+) *m/z* 187 (M^+, 56 %), 159 (65), 144(30), 91(100), 81(11), 65(17); (Found: M^+ 187.1361, $C_{13}H_{17}N$ requires M^+ 187.1359).

Benzaldehyde *O*-(*N*-benzyl-2-cyclohexenylaminooxalyl)oxime 2.87

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime **2.34** (1.13 g; 5.3 mmol) in DCM (20 cm^3) at 0 °C was added pyridine (0.42 g; 5.3 mmol) in DCM (5 cm^3) and *N*-benzyl-2-cyclohexenylamine **2.86** (0.98 g; 5.3 mmol) in DCM (5 cm^3). The mixture was allowed to reach rt and then stirred at rt for 3 h. After this time, pentane (ca. 10 cm^3) was added in order to promote formation of the pyridine hydrochloride ppt. The solution was filtered and then evaporated to dryness. The crude product was purified via flash column chromatography to give the pure product as a colourless oil (1.80 g; 95 %); ν_{max}(NaCl)/cm^{-1} 1744 (C=O), 1612 (C=N); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 1.56 (1H, m, CH), 1.63 (1H, m, CH), 1.74 (1H, m, CH), 1.97 (3H, m, CH), 4.43 (1H, d, J 15, ArCH), 4.77 (1H, d, J 15, ArCH), 5.50 (1H, m, =CH), 5.94 (1H, m, =CH), 7.24-7.76 (10H, m, ArH), 8.49 (1H, s, HC=N); δ_C ($CDCl_3$) 21.7 (CH_2), 24.7 (CH_2), 28.9 (CH_2), 45.5 ($ArCH_2$), 56.8 (CH), 126.9, 127.5, 127.8, 127.9, 128.9, 129.0, 129.4, 129.5, 132.6, 133.8, (ArC, =CH, =CH), 157.9, 158.0, 158.9 (C=O, C=O, C=N); *m/z* (relative intensity), (CI), 363 (MH^+, 11 %), 288 (22), 260 (14), 222 (89), 104 (100); (Found: MH^+ 363.1713, $C_{22}H_{23}N_2O_3$ requires MH^+ 363.1710).

7-Benzyl-2-hydroxy-7-aza-bicyclo[4.2.0]octan-2-one 2.93,2.94.

A solution of **2.87** (800 mg; 2.2 mmol) and MAP (1.0 g; 6.6 mmol) in toluene (400 cm^3) was photolysed at 100 °C by light from a 400 W medium pressure Hg lamp for 5 h. After this time the reaction mixture was evaporated to dryness. The resulting oil was purified via column chromatography (DCM; MeOH) to give a mixture of isomers as a colourless oil (330 mg, 70 %). The product exists as a mixture of *anti* and *syn* isomers (5:1) and these were separated by column chromatography (EtOAc; hexane) (35: 65); *anti* ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 1.21-1.80 (5H, m), 1.95 (1H, m), 3.23 (1H, m), 3.78 (1H, dd, J 7, 15), 4.13 and 4.53 (2H, d, *J* 15), 4.27 (1H, m, HC-OH), 7.29

(5H, m, Ar); δ_C ($CDCl_3$)15.0 (C-7), 22.9 (C-8), 28.8 (C-6), 44.4 CH_2-Ar), 50.8 (C-1), 54.9 (C-4), 65.5 (C-OH), 127.7, 128.3, 128.8, 135.8 (Ar), 168.63 (C=O) *m/z* (relative intensity), (CI), 232 (MH^+,100 %), 151 (13), 122 (21), 97 (8); (MH^+ 232.1344, $C_{14}H_{18}NO_2$ requires MH^+ 232.1338).

Syn ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 1.15-2.12 (5H, m), 2.53 (1H, m), 3.81 (1H, d, J 4), 3.95 (1H, m), 4.03 (1H, m, HC-OH), 4.09 and 4.53 (2H, d, J 15, CH_2Ar), 7.22 (5H, m, Ar); δ_C ($CDCl_3$) 15.9 (C-7), 24.4(C-8), 40.2 (C-6), 45.0 (CH_2-Ar, C-9), 51.1 (C-1), 61.7 (C-4), 77.2 (C-OH), 128.1, 128.4, 129.0, 135.0 (Ar), 160.7 (C=O).

2.5.0 References

(1) M. Hasebe, K. Kogawa and T. Tsuchiya, *Tetrahedron Lett.*, 1984, 3887.

(2) M. Hasebe and T. Tsuchiya, *Tetrahedron Lett.*, 1986, 3239.

(3) M. Hasebe and T. Tsuchiya, *Tetrahedron Lett.*, 1987, 6207.

(4) M. Hasebe and T. Tsuchiya, *Tetrahedron Lett.*, 1988, 6287.

(5) A. J. McCarroll and J. C. Walton, *Chem. Commun.*, 2000, 351.

(6) J. Lalevee, X. Allonas, J. P. Fouassier, H. Tachi, A. Izumitani, M. Sharai and M. Tsunooka, *J. Photochem and Photobiol. A: Chemistry*, 2002, **151**, 27-37.

(7) J. C. Jochims, S. Hehl and S. Herzberger, *Synthesis*, 1990, 1128-1133.

(8) B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell *Vogels Text Book of Organic Chemistry*; 5th ed.; Langman, Harlow, 1989.

(9) Landolt-Bornstein: *Magnetic Properties of Free Radicals*; Springer-Verlag: Berlin, 1979 and 1987.

(10) G. K. Friestad, *Tetrahedron.*, 2001, **57**, 5461-5496.

(11) E. J. Corey and S. J. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821.

(12) P. A. Bartlett, K. L. McLaren and P. C. Ting, *J. Am. Chem. Soc.*, 1988, **110**, 1635.

(13) A. R. Katritzky, H. X. Chang and B. Yang, *Synthesis*, 1995, 503-505.

(14) G. B. Gill, G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1994, 369.

(15) G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1994, 379.

(16) J. McCann and S. F. Overman, *J. Am. Chem. Soc.*, 1987, **109**, 6107-6114.

(17) J. R. Piper, L. M. Rose, J. P. Johnston and M. M. Grenan, *J. Med. Chem.*, 1975, **18**, 803-812.

(18) J. A. Howard *Free Radicals*; Wiley: New York, 1973.

(19) M. Mori, N. Kanda, I. Oda and Y. Ban, *Tetrahedron*, 1985, **41**, 5465-5474.

(20) R. W. Fessenden and R. H. Schuler, *J. Phys. Chem.*, 1963, **39**, 2147.

(21) R. A. Gaussian 98, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P.

Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople Pittsburgh PA, 2001.

(22) A. Archelas, J. D. Fourneron and R. Furstoss, *Tetrahedron Lett.*, 1988, **29**, 6611-6614.

(23) W.-B. Wang and E. J. Roskamp, *J. Am. Chem. Soc.*, 1993, **115**, 9417-9420.

Chapter 3

Radical Cyclisation onto Oxime Ethers; A Preparative and Kinetic Study

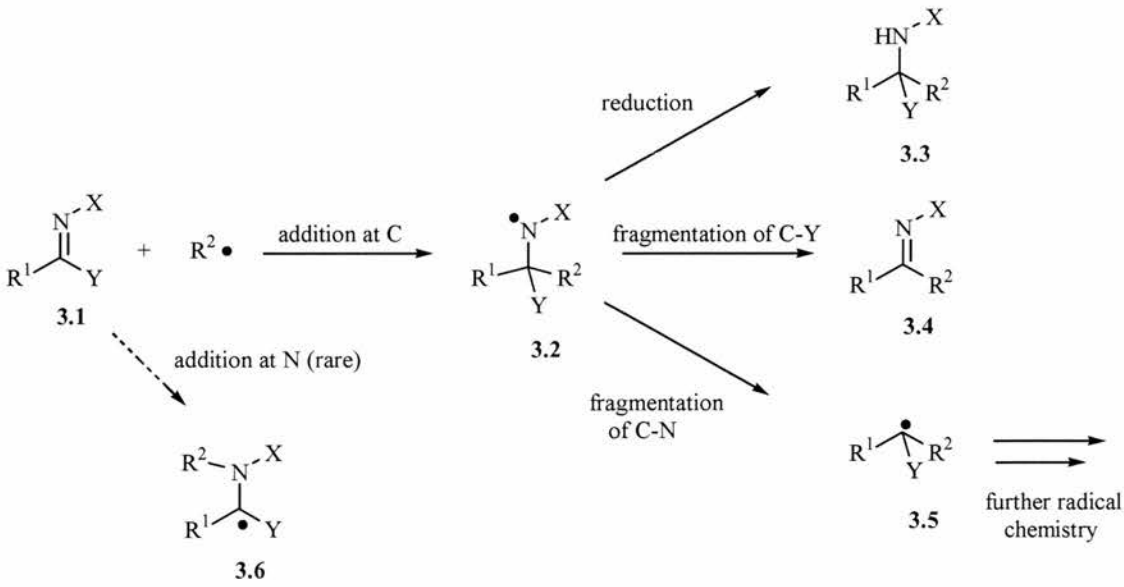
3.1.0 Introduction

3.1.1 Cyclisation onto C=N bonds

The addition of free radicals to alkenes has been thoroughly investigated and many synthetic strategies employ this methodology. However, radical addition to imines and related compounds has only emerged as a useful synthetic process since the 1980's. Friestad has compiled a recent review on addition reactions to imines and related compounds.[1]

The advantages of radical cyclisation to C=N bonds include a rapid addition rate, often two or three orders of magnitude higher than radical addition rates to simple alkenes. Furthermore a useful functional group remains available for subsequent synthetic elaboration, either via fragmentation or further radical chemistry.

Scheme 1 illustrates the various synthetic applications of radical addition to C=N bonds of imines and related compounds.



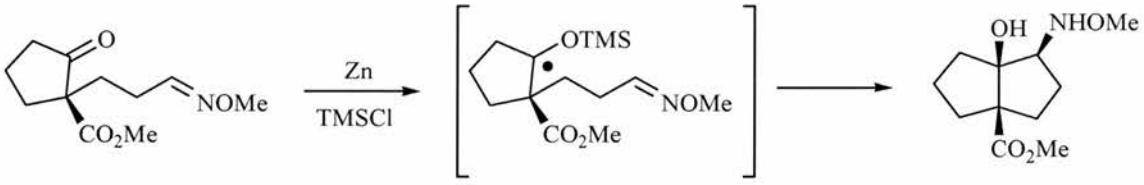
Scheme 1

Radical addition usually occurs at the C-centre but examples do exist of addition to the N of the C=N bond. The most common application of radical addition to C=N bonds is reductive addition to obtain amines **3.3**.

Oxime ethers and hydrazones are the most commonly used radical receptors among the various C=N containing functional groups used. This introduction will focus only on oxime ethers as radical receptors.

3.1.2 Cyclisation onto Oxime Ethers

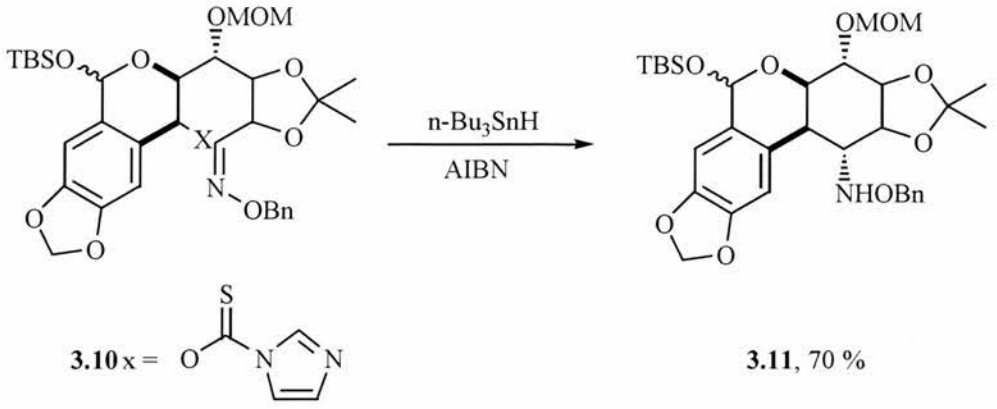
One of the first examples of a cyclisation of a carbon centered radical onto an oxime ether was reported by Corey and Pine in 1983.[2] They demonstrated the efficiency of oxime ethers as radical traps through the cyclisation of the trimethylsilyl protected ketyl radical **3.8**, generated *in situ* by treatment of a suitable cyclopentanone such as **3.7** with zinc trimethylchlorosilane, onto a methyl oxime ether functionality. The cyclisation afforded the diquinane amino-alcohol **3.9** in 84 % yield as a single diastereoisomer.



3.7 **3.8** **3.9** 84 %

Scheme 2

Since this initial work, a range of cyclisations involving radical addition to oxime ethers has been investigated.[3] Keck and co-workers[4] employed a 6-*exo* radical cyclisation of a benzylic radical onto an oxime ether to construct a highly functionalised cyclohexane nucleus **3.11** as part of their total synthesis of the tetracyclic alkaloid pancratistatin, isolated from *Amaryllidaceae* (Scheme 3).

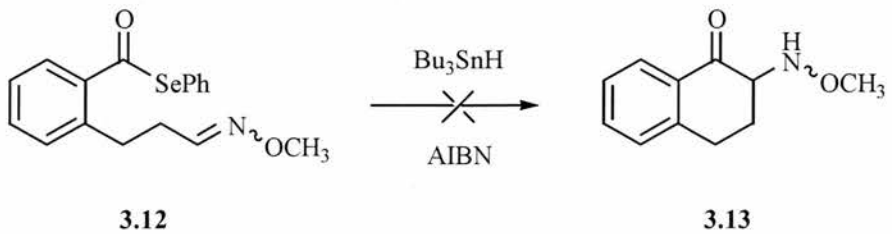


Scheme 3

Kim and co-workers[5] determined the approximate rate constants for the cyclisation of alkyl radicals onto benzyl oxime ethers. For 5-*exo* and 6-*exo* cyclisations they determined rates of 4.2 x 10^7 s^{-1} and 2.4 x 10^6 s^{-1} respectively at 80 °C. There are no examples in the literature of a value for the rate constant of a 4-*exo* cyclisation onto an oxime ether.

3.1.3 Cyclisation of Acyl radicals onto Oxime Ethers

The cyclisation of acyl radicals onto oxime ethers has not been investigated. A literature survey revealed only one example where cyclisation of an acyl radical onto an oxime ether was attempted. Boger and co-workers[6] attempted a 6-*exo* cyclisation of an acyl radical derived from the phenyl selenoester **3.12** under standard tin conditions, but none of the cyclised product **313** was observed.



3.12 **3.13**

Scheme 4

3.1.4 Kinetic ESR Spectroscopy

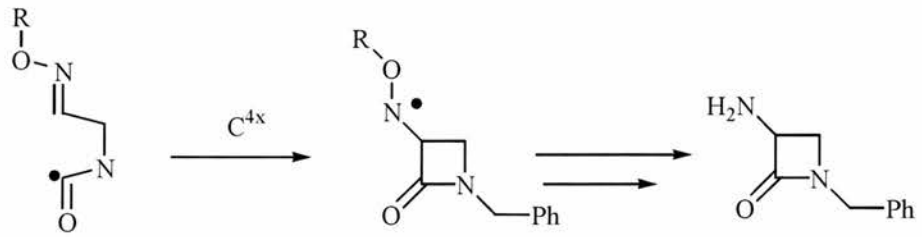
The basic principle of ESR spectroscopy was discussed in chapter 1, but ESR spectroscopy has applications outside the simple characterisation of paramagnetic substances. The determination of radical concentrations can be performed using ESR spectroscopy. The absorption intensity of the observed radical is directly proportional to the concentration of the radical and this allows determination of concentrations over a range of temperatures.

The use of ESR spectroscopy in determination of kinetic data has already been implemented by Walton and co-workers.[7] In a recent study of the rates of dissociation of 1-carbamoyl-1-methylcyclohexa-2,5-dienyl radicals, ESR spectroscopy was used to determine the concentrations of the radicals over a range of temperatures. Using the measurements for the concentrations of the initial and released radicals, rate constants and Arrhenius parameters for the dissociation of 1-carbamoyl-1-methylcyclohexa-2,5-dienyl radicals were obtained.

3.2.0 Results and Discussion

Benzaldehyde *O*-(benzylamino-acetaldehyde-*O*- benzyl oxime oxalyl)oxime 3.22

The oxime oxalate system had proved effective, for the preparation of simple β-lactams in good yield. It is well known that most biologically important β-lactams have an amine or an amide at the C_2 position. It was postulated that an efficient route to the introduction of an amine into the C_2 position would be via radical cyclisation of a carbamoyl radical onto an oxime ether (Scheme 5).

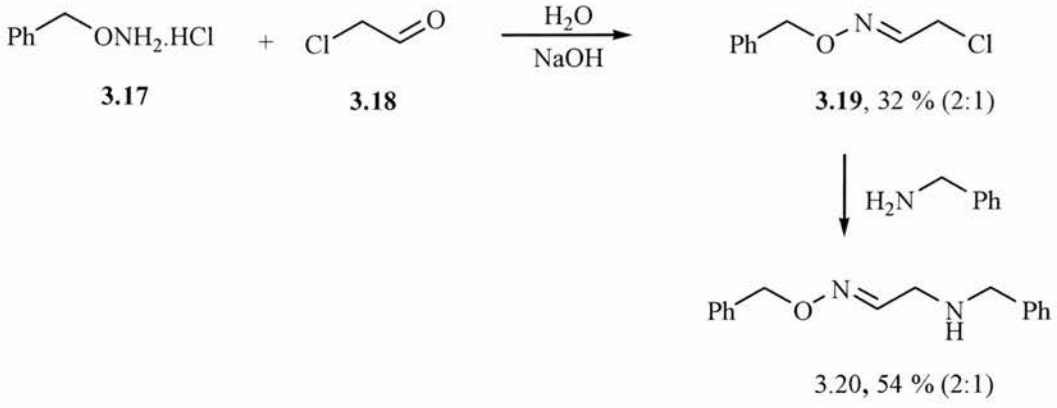


3.14 **3.15** **3.16**

Scheme 5

Radical addition to oxime ethers has been investigated, and additions occur at a rate 3 to 4 times faster than addition to carbon-carbon double bonds. It was expected that this would help to improve the efficiency of the 4-*exo* cyclisation step and therefore give improved yields of the β-lactam ring system.

It was first necessary to prepare an amine which incorporated an oxime ether suitable for 4-*exo* cyclisation of the carbamoyl radical. The amine chosen was benzylamino-acetaldehyde *O*-benzyl-oxime **3.20** which was prepared in two steps from *O*-benzyl hydroxylamine hydrochloride **3.17** (Scheme 6).



3.17 **3.18** **3.19**, 32 % (2:1)

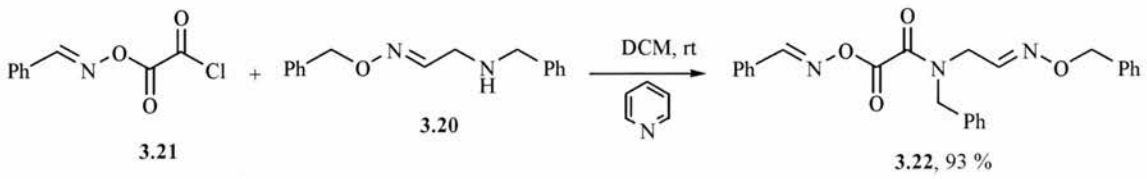
3.20, 54 % (2:1)

Scheme 6

The first step involved the condensation of *O*-benzyl hydroxylamine hydrochloride **3.17** with chloroacetaldehyde **3.18**. The reaction mixture was left standing at rt for 12 h after which time the aqueous solution was extracted with DCM and evaporated to dryness. The crude oxime was purified by distillation (130-132 °C) and the pure oxime **3.19** was isolated as a colourless liquid in a poor yield of 32 %. Proton NMR revealed that the oxime existed as a mixture of isomers in a ratio of 2:1.

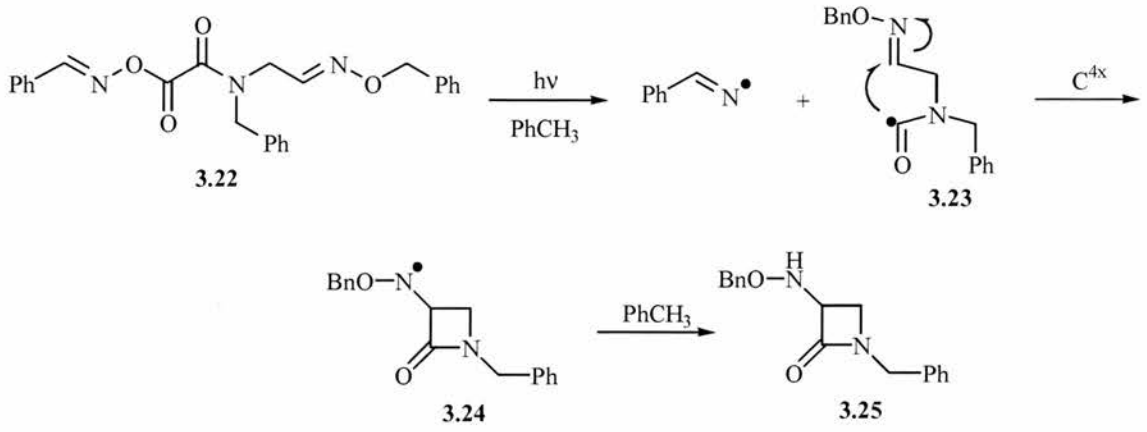
The oxime **3.19** was then reacted with benzylamine to give the amine **3.20** in moderate yield (54 %). The reaction mixture, in ethanol, was heated under reflux for 2.5 h after which time it was allowed to cool and poured onto a solution of Na_2CO_3. The product was extracted into DCM and the solvent was removed to give the crude amine. The pure amine **3.20** was isolated as a yellow oil (54 %) by column chromatography. NMR spectroscopy showed that the amine existed as a mixture of isomers in a ratio of 2:1.

Once the pure amine had been prepared it was converted to the corresponding oxime oxalate amide **3.22** through reaction with benzaldehyde *O*-(chlorooxalyl)oxime (Scheme 7). The oxime oxalate amide **3.22** was isolated as a colourless oil in good yield (93 %). ^{1}H NMR revealed that the oxime oxalate amide existed as a mixture of 4 isomers in a ratio of 2:2:1:1.



Scheme 7

The photochemistry of oxime oxalate amide **3.22** was expected to be more predictable than some of the earlier systems. The formamide had not been found in any of the previous examples and so it was considered very unlikely that it would feature in an extremely efficient cyclisation such as onto an oxime ether. The 5-*endo* cyclisation was also considered unlikely since 4-*exo* cyclisation would lead to formation of the more stable aminyl radical. The predicted photochemical decomposition of oxime oxalate amide **3.22** is shown in Scheme 8.



Scheme 8.

The carbamoyl radical **3.23** was expected to undergo rapid 4-*exo* cyclisation onto the oxime ether to furnish the aminyl radical **3.24**. The aminyl radical would then abstract a hydrogen from solution to give the lactam **3.25**. Reaction with dissolved O_2 was considered unlikely since the amine is more stable than the corresponding hydroxylamine.

ESR study of benzaldehyde *O*-(benzylamino-acetaldehyde-*O*- benzyl oxime oxalyl)oxime 3.22

The photochemistry of **3.22** was first investigated by ESR spectroscopy. The ESR samples were prepared by taking 70 mg of the starting oxime oxalate amide, 1 mol eq of MAP and dissolving them in *tert*-butylbenzene (3.5 cm^3). The solution was stirred until homogenous and this allowed the preparation of seven identical samples, each of 500 µl. The degassed sample was placed in the resonance cavity and the cavity was cooled to 220 K. Once the temperature had reached thermal equilibrium the sample was photolysed with light from a 500 W UV lamp and the ESR spectrum was recorded. The cavity temperature was then increased 10 degrees to 230 K and a fresh sample was placed in the resonant cavity. This was also photolysed and the spectrum recorded. The procedure was repeated, increasing temperature in increments of 10 K until 280 K.

The ESR spectra were unlike those observed for the oxime oxalate amides discussed in Chapter 2. On this occasion the temperature had a direct effect on radical

cyclisation and the spectrum varied significantly with temperature. Figure 1 shows the ESR spectrum obtained on photolysis of **3.22** at 220 K.

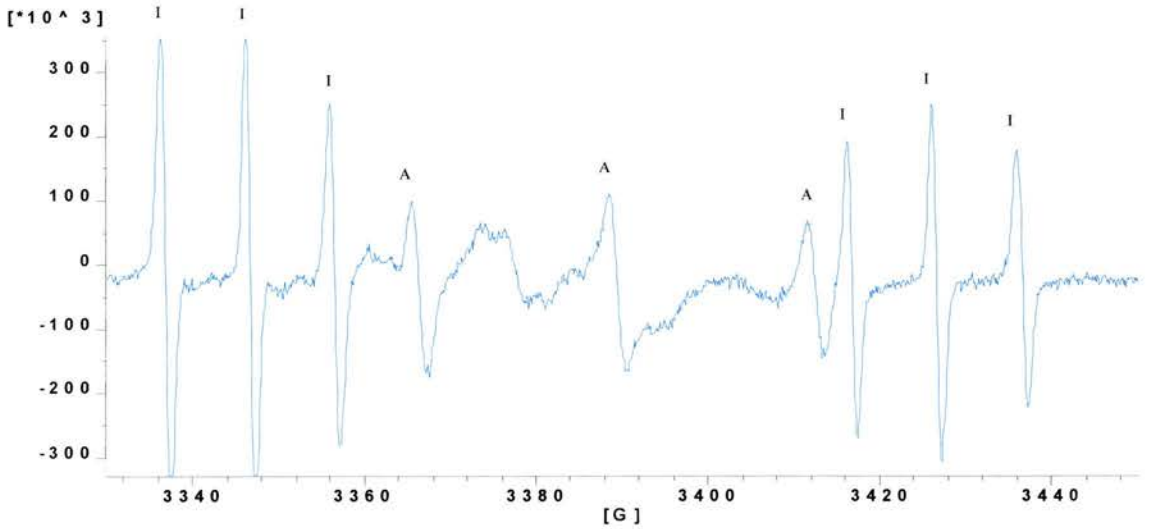


Fig 1. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **3.22** and MAP in *tert*-butylbenzene at 220 K; I; iminyl, A; carbamoyl **3.23**.

As the temperature was increased the intensity of the carbamoyl radical A began to diminish and a new spectrum started to appear. Figure 2 shows the ESR spectrum of **3.22** at 280 K.

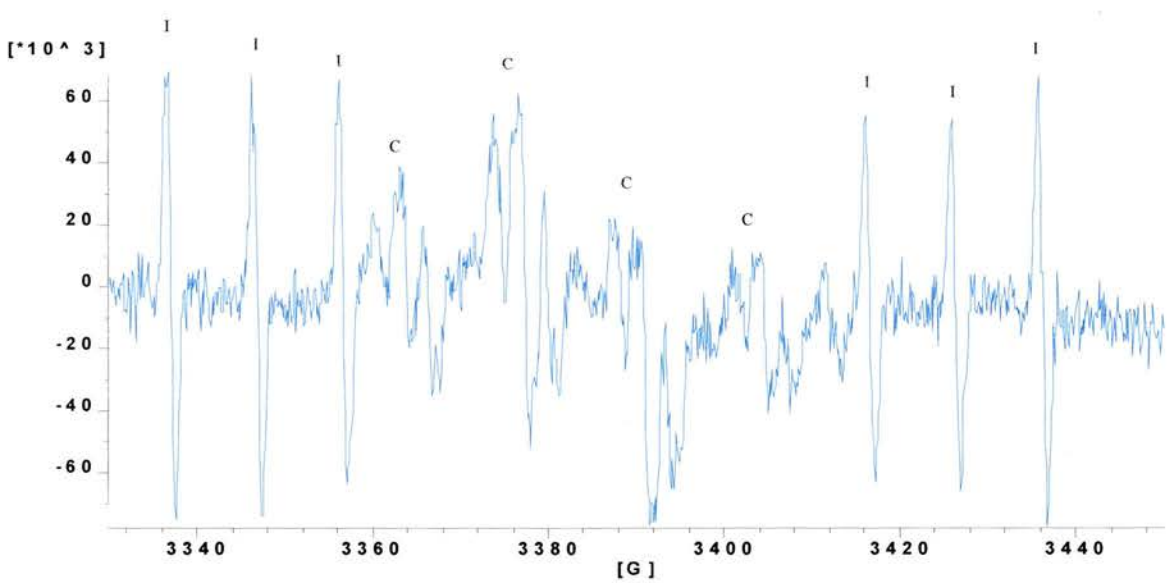
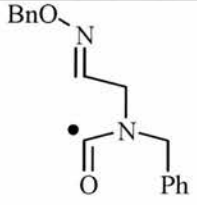
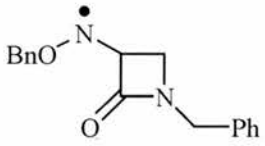


Fig 2. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **3.22** and MAP in *tert*-butylbenzene at 280 K; I; iminyl, C; cyclised radical **3.24**.

The complex ESR spectrum observed at 280 K was attributed to the presence of the cyclised species **3.24**. The ESR parameters for both the cyclised and the uncyclised radical were determined and are illustrated in Table 1.

Table 1

Radical	ESR Parameters (220 and 310 K)
 **3.23**	*a*(N) = 23.2 G g = 2.0018
 **3.24**	*a*(N) = 13.7 G *a*(1H) = 13.7 G *a*(2H) = 2.52 G *a*(2H) = 1.14 G g = 2.0049

The ESR parameters of the cyclised radical **3.24** help to explain to spectrum. The hyperfine splittings (hfs) of the nitrogen and the α-hydrogen are identical and so give an overall quartet splitting. The hfs of the γ-hydrogens are much smaller and result in a splitting of each quartet peak into a triplet of triplets.

In order to gain kinetic information using ESR, it was necessary to record measurements when both of the transient radicals could be distinguished on the same spectrum. The cavity temperature was increased in increments of 10 K, in order to determine the temperature range at which both radicals could be observed. For the oxime oxalate amide **3.22** this range was found to be from 220-280 K.

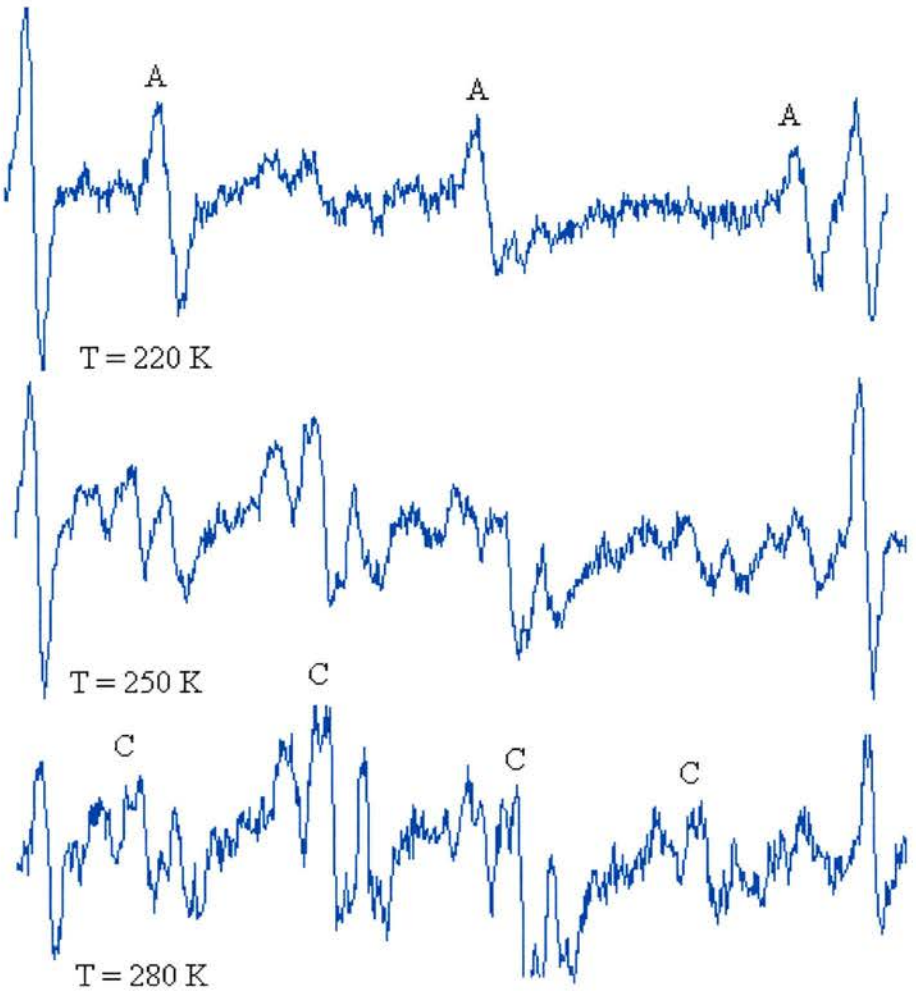


Fig 3.

Figure 3 shows the variation in the ESR spectrum of **3.22** with increasing temperature. A represents the carbamoyl radical **3.23** and C represents the cyclised species **3.24**. The ESR spectra were run over a narrower field width than usual so that only two peaks of the iminyl radical were visible at the extreme left and right.

The concentrations of the two transient radicals **3.23** and **3.24** at each temperature were determined by direct comparison of doubly integrated spectral lines to a standard DPPH spectrum. The derived values for the transient radical concentrations were placed into the steady state equation to give a value for log $k_c/2k_t$ at each temperature.

The steady state equation

Eqn 1 shows the steady state equation derived for the photolysis of oxime oxalate amide **3.22**. The derivation of this equation can be found in appendix 1.

$$k_c/2k_t = [C^\bullet] + [C^\bullet]^2/[AA] \qquad \textbf{Eqn 1}$$

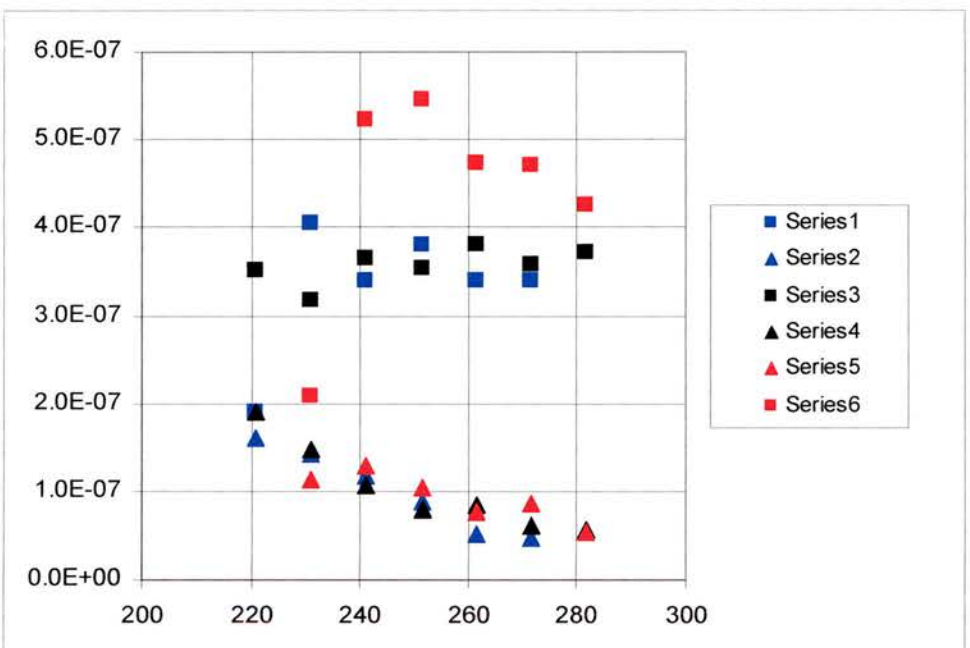
The steady state equation was derived with the assumption that the termination rates of the carbamoyl **3.23** and the cyclised radical **3.24** are diffusion controlled so that ($2k_t$) is the same for each species and is about the same as that of other small radicals such as *t*-butyl.

It did not escape our attention that in addition to the 4-*exo* cyclisation reaction to give the lactam there may be a competing ring opening reaction whereby the cyclised radical ring opens to regenerate the carbamoyl radical. Radical cyclisation to give highly strained rings is known to be reversible and therefore it was necessary to derive a second steady state equation which included a factor corresponding to ring opening. **Eqn 2** shows the steady state equation derived for the photolysis of **3.22** assuming a competing ring opening reaction. The derivation of the second steady state equation can be found in appendix 2.

$$[C^\bullet] + [C^\bullet]^2/[AA] = -k_f\,[C^\bullet]/2k_t\,[AA] + k_c/2k_t \qquad \textbf{Eqn 2}$$

A comparison of the two equations 1 and 2 shows that they differ only in one factor, k_f , which is the rate of ring opening. It can be seen that if k_f is small then **Eqn 2** simplifies to **Eqn 1**. We could not simply assume a small k_f and in order to determine if it was a significant factor we aimed to vary the concentration of the cyclised radical and the carbamoyl radical. If the rate of ring opening was significant then the values for the k_c's, determined using equation 1 would vary with radical concentration. The concentrations of the radicals were varied by lowering the concentration of the starting oxime oxalate amide and also by using a lower concentration of photosensetizer.

Figure 4 shows a plot of concentration of the radicals **3.23** and **3.24** against temperature. The concentration of the carbamoyl radical **3.23** dropped away linearly with the increase in temperature. The concentration of the cyclised radical increased rapidly with temperature but tended to reach a maximum and then level off. This is probably due to the Boltzmann factor. It was found that the change in concentration of the radicals, although small, was significant enough to demonstrate that the reverse opening reaction did not compete at the temperature of our ESR experiments.



■ concentration of cyclised radical **3.24** against temperature

▲ concentration of carbamoyl radical **3.23** against temperature

Fig 4. Plot of concentration of radicals **3.24** and **3.23** verses temperature.

Data for the diffusion-controlled rate constants of *t*-butyl radicals ($2k_t$) have previously been determined for many solvents by Fischer and co-workers.[8] This data allowed the calculated k_c values to be corrected for solvent viscosity and provided the values for log k_d used in determining the Arrhenius parameters. Tables 2, 3 and 4 show the kinetic ESR data obtained using varying concentrations of **3.22** and MAP.

Table 2. Kinetic ESR data for **3.22** (10 mg), in *t*-BuPh with 0.5 M eq MAP.

T/K	[24]	[23]	Log $k_c/2k_t$	$10^3/T$	Log $2k_c$[a] *t*-BuPh	k_c/s^{-1}
220	3.518E-07	1.893E-07	-5.997	4.530	2.638	4.34E+02
230	3.171E-07	1.467E-07	-5.998	4.330	2.835	6.84E+02
240	3.644E-07	1.060E-07	-5.791	4.147	3.212	1.63E+03
250	3.522E-07	7.981E-08	-5.720	3.979	3.431	2.69E+03
260	3.809E-07	8.305E-08	-5.672	3.824	3.605	4.03E+03
270	3.584E-07	6.173E-08	-5.613	3.681	3.775	5.96E+03
280	3.718E-07	5.716E-08	-5.554	3.548	3.930	8.51E+03

Table 3. Kinetic ESR data for **3.22** (10 mg), in t-BuPh with 0.3 M eq MAP.

T/K	[24]	[23]	Log $k_c/2k_t$	$10^3/T$	Log $2k_c$[a] *t*-BuPh	k_c/s^{-1}
230	2.094E-07	1.134E-07	-6.225	4.330	2.609	4.06E+02
240	5.235E-07	1.296E-07	-5.597	4.147	3.425	2.66E+03
250	5.456E-07	1.044E-07	-5.469	3.979	3.681	4.80E+03
260	4.743E-07	7.602E-08	-5.464	3.824	3.813	6.50E+03
270	4.704E-07	8.629E-08	-5-518	3.681	3.870	7.41E+03
280	4.260E-07	5.440E-08	-5.425	3.548	4.060	1.15E+04

Table 4. Kinetic ESR data for **3.22** (4 mg), in t-BuPh with 0.2 M eq MAP.

T/K	[24]	[23]	Log $k_c/2k_t$	$10^3/T$	Log $2k_c$[a] *t*-BuPh	k_c/s^{-1}
220	1.899E-07	1.602E-07	-6.382	4.530	2.253	1.79E+02
230	4.055E-07	1.427E-07	-5.808	4.330	3.026	1.06E+03
240	3.406E-07	1.166E-07	-5.874	4.147	3.129	1.35E+03
250	3.798E-07	8.841E-08	-5.696	3.979	3.454	2.84E+03
260	3.399E-07	5.302E-08	-5.599	3.824	3.679	4.77E+03
270	3.405E-07	4.712E-08	-5.553	3.681	3.835	6.84E+03

The variation in the rate of a chemical reaction with temperature can be represented quantitatively using the Arrhenius equation. By plotting the calculated values of log k_c against $10^3/T$ for all three sets of data, and implementing a line of best fit, it was possible to obtain the associated gradient and intercept of this line, which are related to the values of the activation energy (E_c) and the pre-exponential factor (A_c) for **3.22** (Figure 5 and Table 5).

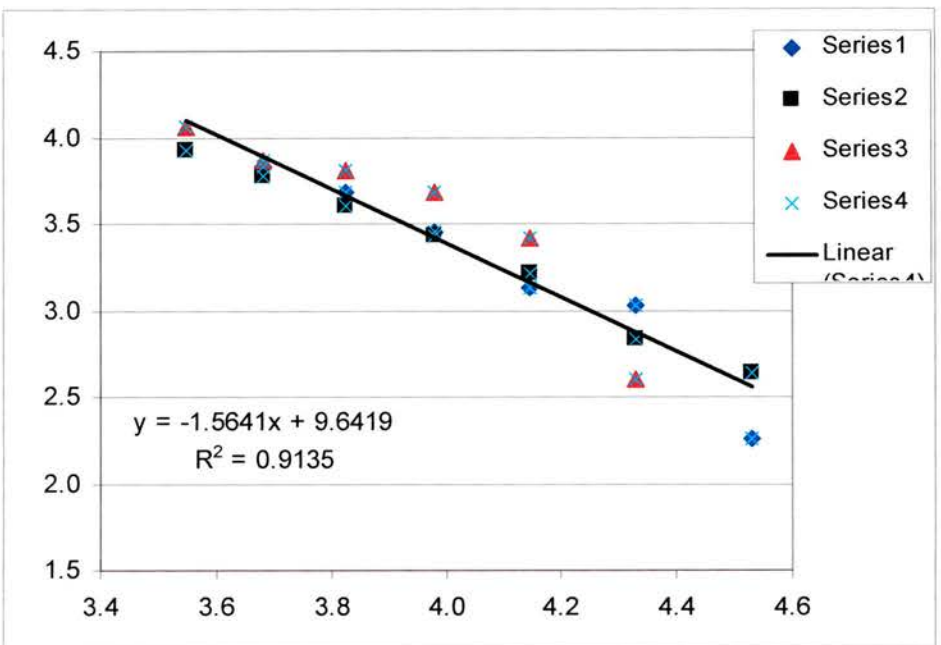


Fig 5. Plot of log k_c against $10^3/T$

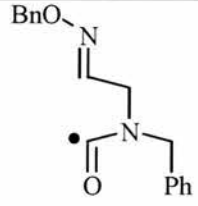
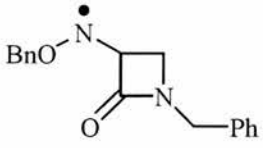
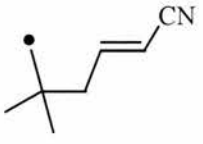
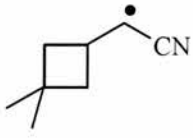
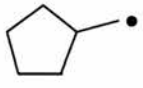
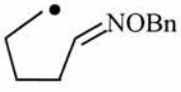
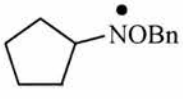
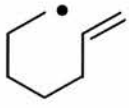
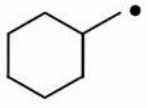
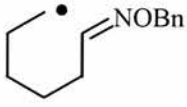
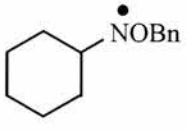
Table 5

Radical	**kc/s^{-1} (300 K)**	**Log Ac/ s^{-1}**	**E_a/ kcal mol^{-1}**
3.23 → 3.24	2.7 E+04	9.64	7.16

The rate constant of 2.7 x 10^4 s^{-1} at 300 K for ring closure of the acyl radical **3.23** would appear to be a reasonable figure for the 4-*exo* cyclisation. As was mentioned in the introduction, no kinetic data for the ring closure of acyl radicals onto oxime ethers exists, but Newcomb and co-workers[9] have determined the rate of ring closure for the alkyl radical **3.26** and found it to be in the order of 1.9 x 10^4 s^{-1} which compares favourably to the rate determined for **3.23**. Table 6 illustrates some rate constants determined for ring closure reactions. It can be seen that, in general the rates of ring closure onto oxime ethers are around 2 orders of magnitude faster then those

onto the simple carbon carbon double bonds. The rate of cyclisation determined for the acyl radical **3.23** suggests that the cyclisation should be viable for preparative purposes.

Table 6 Rates of cyclisation for carbon centered radicals

Uncyclised	Cyclised	Temp (K)[A]	Rate s^{-1}
 **3.23**	 **3.24**	300	2.7×10^4
 **3.26**	 **3.27**	323[9]	1.9×10^4
 **3.28**	 **3.29**	298[10,11]	2.5×10^5
 **3.30**	 **3.31**	353[12]	4.2×10^7
 **3.32**	 **3.33**	298[13]	5.1×10^3
 **3.34**	 **3.35**	353[12]	2.4×10^6

A = literature reference

Prep Scale Photolysis of Benzaldehyde *O*-(benzylamino-acetaldehyde-*O*- benzyl oxime oxalyl)oxime 3.22

The ESR experiments had demonstrated that the oxime oxalate amide **3.22** was an efficient source of iminyl and carbamoyl radicals and that the carbamoyl radicals could undergo 4-*exo* cyclisation onto the oxime ether functionality. We were interested in carrying out a photolysis in toluene in order to prepare the lactam **3.25**.

A solution of the oxime oxalate amide **3.22** in toluene and in the presence of MAP was photolysed by light from a 400 W UV lamp for 5 h at rt. The solvent was removed and the resulting yellow oil was analysed by ^{1}H-NMR spectroscopy. The hydrogens on C-2 of the azetidinone ring usually appear between 3.0 and 4.0 ppm.[14,15] This region of the spectrum was clear suggesting that the cyclised product **3.25** was not formed. The peaks corresponding to the benzaldoxime hydrogen had disappeared and were replaced by a singlet at 10.2 ppm corresponding to benzaldehyde. This suggested that the photodissociation does actually occur in accordance with Scheme 8 but that the final product is not the cyclised product. The remaining peaks were closely related to those of the starting amine **3.20**. In addition, the presence of a new series of peaks at around 8.2 ppm suggested that the major product was the formamide resulting from direct hydrogen abstraction by the carbamoyl radical **3.23**.

Formation of the formamide was unexpected since the ESR study had demonstrated that cyclisation occurred readily at low temperatures. The absence of the cyclised product was attributed to the activity of the iminyl radical. It was assumed that cyclisation occurred readily but the ring opening reaction was also occurring and only the carbamoyl radical could abstract a hydrogen from the solvent. The reaction was repeated at a higher temperature but once again, only the formamide was observed.

A literature survey[1] revealed that the majority of radical cyclisations onto oxime ethers were carried out in the presence of tin-hydrides and that these reduced the aminyl radical to the corresponding amine. Since the aim of this project was to exclude the use of toxic tin hydrides, we were anxious to avoid using these as reducing adgents for the aminyl radical. Other successful hydrogen donors for aminyl radicals include THF and thiols.[2,16] The photolysis was repeated in the presence of a 5 molar excess of methyl

thioglycolate in toluene and in a non hydrogen donating solvent, trifluro toluene, and also in THF as the solvent but the expected azetidinone peaks were never observed. The photolysis was also carried out in trichlorobromomethane as a solvent but a complex mixture of products was observed. A list of the potential hydrogen donors and the conditions used are illustrated in Table 7.

Table 7: Conditions attempted for the reduction of aminyl radical **3.24**

Hydrogen Donor	**Solvent**	**Time (h)**	**Additional info**	**Result**
Toluene	Toluene	5	rt	Formamide
Toluene	Toluene	5	80 0C	Formamide
Methyl thioglycolate	Toluene	3	Rt, 5 mol eq	Formamide
Methyl thioglycolate	Ph-CF_3	3	Rt, 5 mol eq	Mixture of compounds
CCl_3Br	CCl_3Br	3	rt	Mixture of compounds
THF	THF	3	rt	Mixture of compounds

3.3.0 Conclusions

A novel oxime oxalate amide incorporating an oxime ether side chain was designed, and prepared in good yield.

ESR spectroscopy was used to demonstrate that the oxime oxalate amide dissociates on photolysis to give both the iminyl and the carbamoyl radical and at higher temperatures the carbamoyl radical undergoes 4-*exo* cyclisation to give the aminyl radical.

By measuring the radical concentrations at a range of temperatures it was possible to determine the rate of cyclisation and this was found to be $2.7 \times 10^4\ s^{-1}$ at 300 K. This rate of ring closure was fast enough for preparative work and a number of attempts were made to prepare and isolate the cyclised product.

The major products in all cases were benzaldehyde, resulting from the iminyl radical and the formamide resulting from reduction of the carbamoyl radical. It was postulated that the problem was not with the cyclisation but with the reduction of the aminyl radical.

It is predicted that in the presence of a suitable hydrogen donor, that good yields of the cyclised species would be obtained and that this is worthy of further investigation

3.4.0 Experimental

Chloroacetaldehyde-*O*-benzyloxime 3.19

To a solution of NaOH (1.8 g, 45 mmol) in H_2O (200 cm^3) at rt was added an excess of chloroacetaldehyde **3.18** (20 cm^3, 40 % solution in H_2O). This was followed by the portionwise addition of *O*-benzylhydroxylamine hydrochloride **3.17** (2.4 g; 15 mmol). The mixture was left standing at rt for 12 h. After this time the mixture was extracted with DCM (4 x 25 cm^3). The DCM was dried ($MgSO_4$) and concentrated and the crude product was purified via Kugelrohr distillation (130-132 °C/ 12 mmHg) to give **3.19** as a colourless oil (840 mg; 32 %). The compound was isolated as a mixture of geometric isomers in a ratio of 2:1. (^{1}H NMR, 300 MHz, $CDCl_3$) Major isomer: δ_H 4.10 (2H, d, J 6, CH_2Cl), 5.10 (2H, s, OCH_2), 7.36 (5H, m, ArH), 7.49 (1H, t, J 6, =CH); Minor isomer: δ_H 4.26 (2H, d, J 5, CH_2Cl), 5.14 (2H, s, OCH_2), 6.90 (1H, t, J 5, =CH), 7.36 (5H, m, ArH); δ_C ($CDCl_3$) Major isomer: 40. 6 (CH_2Cl), 76.8 (OCH_2), 128.5, 128.7, 128.7, 128.9 (ArC), 146.1 (C=N); Minor isomer: 35.74 (CH_2Cl), 77.0 (OCH_2), 128.5, 128.7, 128.7, 128.9 (ArC), 146.4 (C=N); *m/z* (relative intensity), (CI), 184 (MH^+, 100 %), 148 (7), 133 (8), 91 (27); (Found: MH^+ 184.0535, $C_9H_{11}ClNO$ requires MH^+ 184.0534).

Benzylaminoacetaldehyde-*O*-benzyl oxime 3.20

To a solution of **3.19** (1.70 g, 9.3 mmol) in MeOH (35 cm^3) at 0 °C under N_2 was added a solution of benzylamine (1.72 g; 18.6 mmol) in MeOH (5 cm^3). The mixture was heated under reflux for 2.5 h. After this time the solution was allowed to cool and then poured onto a mixture of Na_2CO_3 (Aq) and DCM. The aqueous layer was extracted with DCM and the combined organic extracts were dried ($MgSO_4$) and the solvent removed. The crude amine was purified via column chromatography (EtOAc/hexane) to furnish the pure amine as a yellow oil (1.28 g; 54 %). The product was isolated as a mixture of geometric isomers in a ratio of 2:1. (^{1}H NMR, 300 MHz, $CDCl_3$) Major isomer: δ_H 3.39 (2H, d, J 5, CH_2), 3.78 (2H, s, $ArCH_2$), 5.08 (2H, s, OCH_2), 7.25- 7.37 (10H, m, ArH), 7.52 (1H, t, J 5, =CH); Minor isomer: δ_H 3.56 (2H, d, J 4, CH_2), 3.78 (2H, s, $ArCH_2$), 5.10 (2H, s, OCH_2), 6.83 (1H, t, J 5, =CH), 7.25-7.37 (10H, m, ArH);); δ_C ($CDCl_3$) Major isomer: 47.8 (CH_2NH), 53.6 (CH_2Ar), 76.2

(OCH_2), 127.5, 127.6, 128.3, 128.4, 128.6, 128.6, 128.8, 128.9 (ArC), 149.6 (C=N); Minor isomer: 44.8 (CH_2NH), 54.1 (CH_2Ar), 76.5 (OCH_2), 127.5, 127.6, 128.3, 128.4, 128.6, 128.6, 128.8, 128.9 (ArC), 152.0 (C=N);); *m/z* (relative intensity), (CI), 255 (MH^+, 100 %); (Found: MH^+ 255.1488, $C_{16}H_{19}N_2O$ requires MH^+ 255.1497).

Benzaldehyde *O*-(benzylaminoacetaldehyde-*O*-benzyloxalyl)oxime 3.22

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime (750 mg; 3.5 mmol) in DCM (15 cm^3) at 0 °C, was added a solution of pyridine (300 mg, 3.5 mmol) in DCM (5 cm^3) followed by the amine (900 mg, 3.5 mmol) in DCM (5 cm^3). The mixture was allowed to reach rt and was then stirred at rt for 3h. After this time a small quantity of pentane (ca.10 cm^3) was added in order to promote formation of the pyridine hydrochloride salt. The solution was filtered and the filtrate was collected. The solvent was removed and the crude product was purified by flash column chromatography. The pure oxime oxalate amide **3.22** was isolated as a colourless oil (1.36 g; 93 %). The compound was isolated as a mixture of four isomers in a ratio of 2:2:1:1. ν_{max}(NaCl)/cm^{-1} 1762 (C=O), 1664 (C=N); ^{1}H NMR, (300 MHz, $CDCl_3$) (major isomer 1) δ_H 3.95 (2H, d, J 6, C$\underline{H}_2$CH), 4.45 (2H, s, CH_2Ph), 5.07 (2H, s, OCH_2), 7.20-7.72 (5H, m, ArH), 7.40-7.50 (1H, m, $CH_2C\underline{H}$=N)(under aromatic peaks), 8.45 (1H, s, ArCH=N); (major isomer 2) δ_H 4.06 (2H, d, J 6, C$\underline{H}_2$CH), 4.53 (2H, s, CH_2Ph), 5.08 (2H, s, OCH_2), 7.20-7.72 (5H, m, ArH), 7.40-7.50 (1H, m, $CH_2C\underline{H}$=N)(under aromatic peaks), 8.45 (1H, s, ArCH=N); (minor isomer 1) δ_H 4.20 (2H, d, J 5, C$\underline{H}_2$CH), 4.57 (2H, s, CH_2Ph), 5.09 (2H, s, OCH_2), 6.71 (1H, t, J 5, CH_2CH=N), 7.20-7.72 (5H, m, ArH), 8.43 (1H, s, ArCH=N); (minor isomer 2) δ_H 4.25 (2H, d, J 5, C$\underline{H}_2$CH), 4.63 (2H, s, CH_2Ph), 5.09 (2H, s, OCH_2), 6.69 (1H, t, J 5, CH_2CH=N), 7.20-7.72 (5H, m, ArH), 8.43 (1H, s, ArCH=N); δc ($CDCl_3$) 42.4, 43.2, 46.2, 47.5, 48.2, 51.4, 51.5, 53.0 (CH_2N, $ArCH_2$), 76.6, 76.7, 77.0, 77.4 (OCH_2), 128.5, 128.6, 128.7, 128.8, 128.8, 128.9, 128.9, 129.0, 129.2, 129.3, 129.4, 132.8 (ArC), 144.2, 144.6, 145.0, 146.4, 146.5, 150.4, 151.3, 157.9, 157.9, 158.0 (C=O, C=N); *m/z* (relative intensity), (CI), 430 (MH^+, 100 %); (Found: MH^+ 430.1776, $C_{25}H_{24}N_3O_4$ requires MH^+ 430.1767).

Prep. scale photolysis of benzaldehyde *O*-(benzylaminoacetaldehyde-*O*-benzyloxalyl)oxime 3.22

A solution of the oxime oxalate amide **3.22** (800 mg; 1.9 mmol) in toluene (400 cm ^{3}) and in the presence of MAP (840 mg, 5.7 mmol) was photolysed by light from a 400 W UV lamp for 5 h at rt. After this time the solvent was removed and a sample was taken for ^{1}H-NMR analysis. The photolysis was repeated at 80 °C.

Small scale photolysis of benzaldehyde *O*-(benzylaminoacetaldehyde-*O*-benzyloxalyl)oxime 3.22

A solution of the oxime oxalate amide **3.22** (20 mg; 0.05 x 10^{-3} mmol) in solvent (5.0 cm^3) and in the presence of MAP (7 mg; 0.05 x 10^{-3} mmol) was photolysed by light from a 400 W UV lamp for 3 h at rt. After this time the solvent was removed and a sample was taken for ^{1}H-NMR analysis.

3.5.0 References

(1) G. K. Friestad, *Tetrahedron,* 2001, **57**, 5461-5496.

(2) E. J. Corey and S. G. Pyne, *Tetrahedron Lett.,* 1983, **24**, 2821.

(3) A. G. Fallis and I. M. Brinza, *Tetrahedron,* 1997, **53**, 17543-17594.

(4) G. E. Keck, S. F. McHardy and J. A. Murry, *J. Am. Chem. Soc.,* 1995, **117**, 7289.

(5) S. Kim, Y. Kim and K. S. Yoon, *Tetrahedron Lett.,* 1997, **38**, 2487-2490.

(6) D. L. Boger and R. J. Mathvink, *J. Org. Chem,* 1992, **57**, 1429-1443.

(7) A. F. Bella, L. V. Jackson and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2,* 2002, 1839-1843.

(8) H. Schuh and H. Fischer, *Helv. Chim. Acta,* 1987, **61**, 2130.

(9) S.-U. Park, T. R. Varick and M. Newcomb, *Tetrahedron Lett.,* 1990, **31**, 2975.

(10) A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron Lett.,* 1985, **26**, 373.

(11) A. L. J. Beckwith, C. J. Easton, T. Lawrence and A. K. Serelis, *Aust. J. Chem.,* 1983, **36**, 545.

(12) S. Kim, G. H. Joe and J. Y. Do, *J. Am. Chem. Soc.,* 1993, **115**, 3328.

(13) C. Chatgilialoglu, K. U. Ingold and J. C. Scaiano, *J. Am. Chem. Soc.,* 1981, **103**, 7739.

(14) G. Cainelli, D. Giacomini, P. Galletti and M. DaCol, *Tetrahedron Asymmetry,* 1997, **8**, 3231-3235.

(15) L. S. Hegedus, R. Imwinkelried, M. Alarid-Sargent, D. Dvorak and Y. Satoh, *J. Am. Chem. Soc.,* 1990, 1109-1117.

(16) E. A. Porter, X. Wang, H. S. Lee, B. Weisblum and S. H. Gellman, *Nature,* 2000, **404**, 565.

Chapter 4

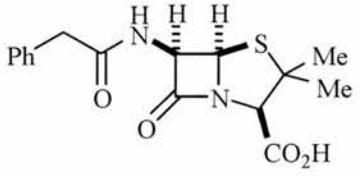
The Preparation of Penicillins

4.1.0 Introduction

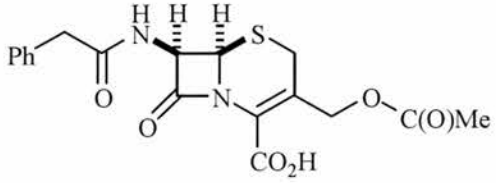
Antibiotics are an essential commodity of society. Woldwide sales of anti-bacterial substances exceed £ 7000 M per annum and of these β-lactam antibiotics account for more then 10 % of total drug sales. It is not surprising therefore that there is an international focus within both industry and academia on the development of new routes to β-lactam antibiotics.

2-Azetidinones or β-lactam antibiotics are 4-membered cyclic amides, derived from 3-amino-propanoic acids. The first member of this class was prepared by Staudinger in 1907.[1] However, the importance of β-lactam antibiotics and their application in the treatment of infection was not recognized until the discovery of penicillin by Fleming[2] in 1929.

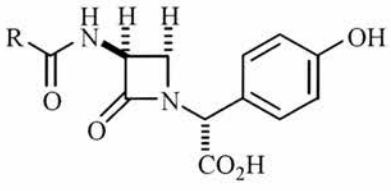
Scheme 1 illustrates some of the most important β-lactam antibiotics which have been used clinically.



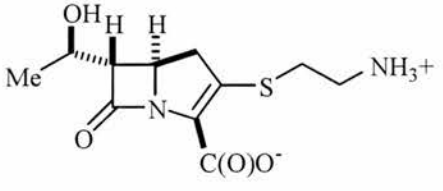
Penicillin G (1929)



Cephalosporin (1945)



Nocardicin (1976)



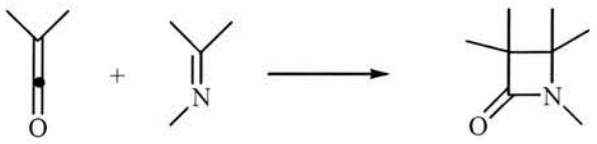
Thienamycin (1976)

Scheme 1

The core of all β-lactam antibiotics is the 4-membered azetidinone ring. Although this is a highly strained species and difficult to prepare, many synthetic routes have been developed.

4.1.1 The preparation of β-lactams.

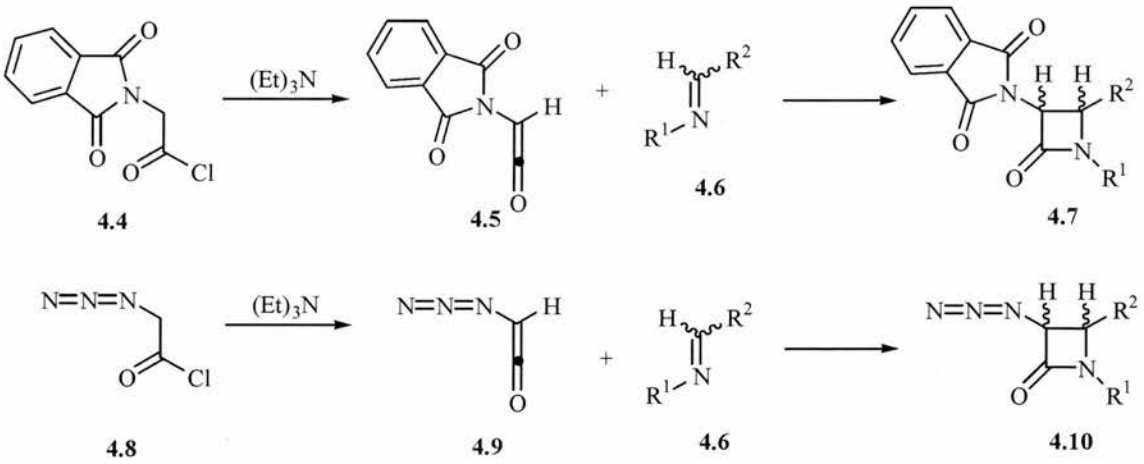
The original method for the preparation of the azetidinone ring was the Staudinger, ketene-imine, cycloaddition (Scheme 2). This method, although widely applied[3] was limited by its tendency to give a mixture of all possible stereoisomers.



4.1 **4.2** **4.3**

Scheme 2

The most widely used reagents for the formation of 3-amino-2-azetidinones are phthalimido- and azidoacetyl chlorides **4.4** and **4.8**, which upon treatment with a mild base, usually triethylamine, are converted into the corresponding ketenes **4.5** and **4.9**. The ketenes can then be used in a cycloaddition reaction with an imine to give the corresponding azetidinones **4.7** and **4.10**.



4.4 **4.5** **4.6** **4.7**

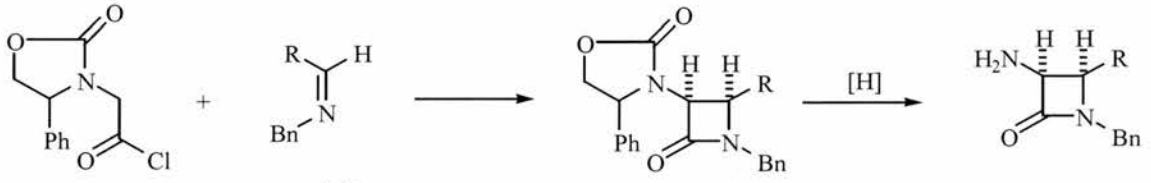
4.8 **4.9** **4.6** **4.10**

Scheme 3

In order for the Staudinger methodology to be applied to the preparation of β-lactam antibiotics it was first necessary to establish control over the stereochemistry of the cyclised product.

Bose and co-workers[4] demonstrated that for simple *N*-aryl imines the stereochemistry of the reaction with azido-ketene **4.9** could be influenced by experimental conditions. It was found, that on dropwise addition of the azidoacetyl chloride to a solution of triethylamine and the imine, the major products were the *cis*-2-azetidinones (de = 35 %). When the triethylamine was added directly to a solution of the azidoacetyl chloride and the imine, the major isomers obtained were the *trans* isomers (de = 35 %).

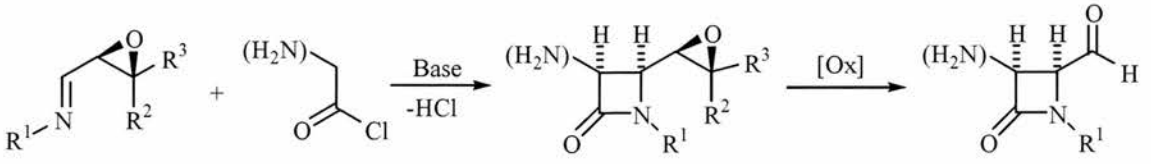
More recently a number of techniques which elicit total stereocontrol of the ketene-imine cycloaddition reaction have been developed. One of the most successful of these involves the use of chiral synthons. Evans and co-workers[5] have demonstrated that (S)-phenyloxazolidylacetyl chloride **4.11** can be employed as a homochiral ketene synthon. The advantage of this synthon is that in addition to providing excellent levels of diastereoslectivity in the cycloaddition process, the chiral oxazolidone can be reductively removed in a single step to give enantiomerically pure azetidinones **4.14** in good yield (scheme 4).



4.11 **4.12** **4.13** **4.14**

Scheme 4

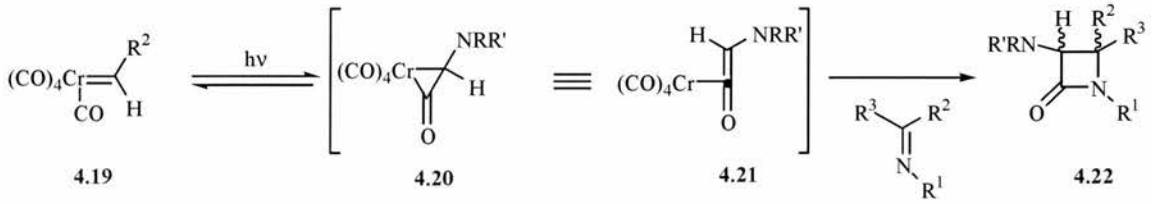
It is also possible to use the imine as the chiral synthon. Evans and Williams[6] used chiral epoxyimines **4.15**, derived from readily available α,β-epoxyaldehydes (through the Sharpless-epoxidation of substituted allylic alcohols) for the enantioselective preparation of *cis*-3-amino-4-epoxy-2-azetidinones **4.17** (Scheme 5).



4.15 **4.16** **4.17** **4.18**

Scheme 5

An interesting variation on the imine-ketene route to azetidinone preparation is the cycloaddition of metallo-carbene complexes with imines (Scheme 6). The first synthesis of 2-azetidinones via metallo-carbenes and imines was reported by Hegedus and co-workers in 1982.[7] Subsequent mechanistic studies indicated that when the starting chromium carbene was subjected to irradiation, carbon monoxide insertion into the metal-carbon double bond produces a ketene complex.



4.19 4.20 4.21 4.22

Scheme 6

Although these compounds demonstrate typical ketene-reactivity they do not proceed via free ketenes.[8] This was determined by the absence of any of the usual ketene side products which are usually present in ketene-imine cycloaddition reactions. Also good reaction yields and a high level of diastereoselectivity indicated that these were not free ketene reactions. The intermediacy of free ketenes was dismissed in favour of a pathway involving metallacyclic intermediates. Proof for the existence of a chromium coordinated ketene intermediate has been offered by Hegedus and co-workers.[8]

The metallo-carbene methodology works extremely well and a large number azetidinones have been prepared in good yield with excellent stereoselectivity.

The ketene-imine cycloaddition is the original route to azetidinone rings and has been thoroughly investigated and optimised to the point where it is regularly used in the preparation of β-lactam antibiotics. The alternative "classic" route to azetidinone rings, which was developed in parallel with the ketene-imine cycloaddition is the ester enolate-imine condensation.

Gilman and Speeter were the first to report the preparation of a β-lactam through the use of Reformatsky reagents (i.e. zinc ester enolates) with simple imines.[9]

However it was not until the 1970's when enolate chemistry had become standard for organic chemists that intensive research began in this area.[10] Of particular interest are the condensations leading to formation of 3-amino substituted azetidinones since these are intermediates for the preparation of β-lactam antibiotics.

The first attempts to prepare optically active β-lactams using ester–imine condensations were reported by Kagen and Luche. They examined Reformatsky reactions between menthyl α-bromoacetate, α-brompropionate and α-bromoisovalerate with imines and obtained racemic products.[11] Since these early studies a high degree of stereocontrol in ester-imine condensations has been achieved using both chiral imines, and chiral esters.[10]

An effective strategy for the preparation of 3-amino-substituted azetidinones is shown in Scheme 7. The amino function of the starting glycine esters is protected by an acyl or carbamate group. Treatment of the protected α-amino-esters with two equivalents of lithium amide (usually lithium di-*iso*-propylamide = LDA) gives the lithium dianions **4.23** which react with appropriate imines to give azetidinones.

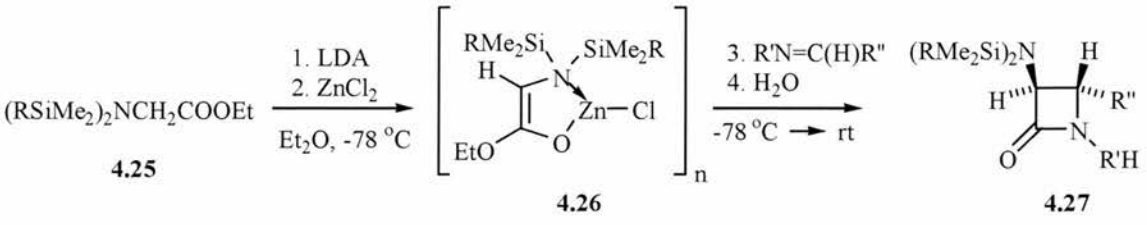
4.23 **4.24**

Scheme 7

In every case the azetidinone was obtained in good yield with exclusive *trans* stereochemistry.

Van der Steen and co-workers have described a highly stereoselective synthesis of *trans*-3-amino β-lactams using zinc enolates.[12] The zinc enolates of 2,2,5,5-tetramethyl-1-aza-2,5-disilylcyclopentane-1-acetic acid ethyl ester (STABASE) and N,N-bis(trimethylsilyl)glycine **4.26** were prepared *in situ* from the corresponding

lithium enolates, *via* transmetallation with one equivalent of zinc dichloride and were reacted with imines (Scheme 8).

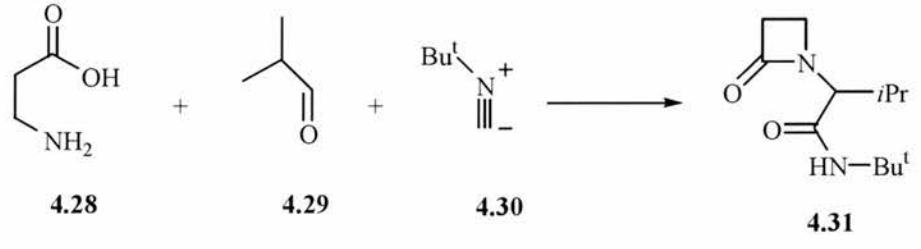


Scheme 8

Yields of the lactam were high and the *trans*-stereoselectivity was attributed to a rigid chair-like transition-state of a Z-enolate with a Z imine.

A range of other base promoted condensations of enolates with imines have been developed and oxime ethers have been employed in place of imines.[13]

The Ugi reaction employs β-aminocarboxylic acids with aldehydes and isocyanides in the preparation of β-lactams.[14] Scheme 9 shows how the difunctional aminoacid **4.28** reacts with the aldehyde **4.29** and the isocyanide **4.30** in methanol to give the β-lactam.[15]



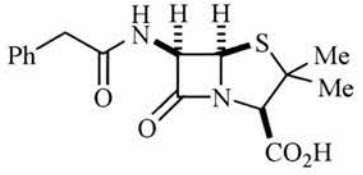
Scheme 9

Other reactions which have been used in the preparation of β-lactams include the reaction of the dianion derived from trisilylhydrazone with aldehydes[16] and the rhodium catalysed C-H insertion reactions of diazoamides.[17,18] The use of free radicals in the preparation of β-lactams has been discussed in detail in Chapter 1.

4.1.2 Penicillin

It was the discovery of the antibacterial properties of penicillin by Fleming in 1929[2] which prompted the thorough investigation of the penicillins. Because of their unique effectiveness in the treatment of bacterial infections in humans, these compounds have been investigated intensively from the chemical, microbiological and clinical points of view. The history of the development of penicillin has been charted in many books and reviews. It is the aim of this introduction to give a brief overview of some of the synthetic techniques used in the preparation of penicillins.

During the 1940's the structure of benzyl penicillin and other members of the penicillin class were studied through chemical investigations (both degradative and synthetic) and also through IR spectroscopy. The structure of penicillin-G was narrowed down to three possible structures by these methods and the structure was finally confirmed by X-ray analysis in 1945 (Figure 1).



Penicillin G

Fig 1.

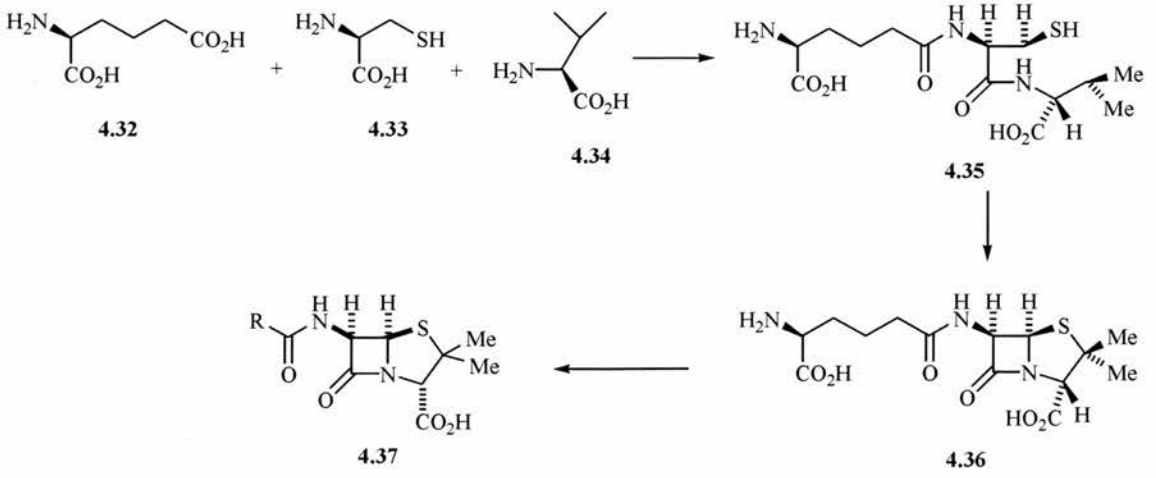
Once the core structure of penicillin had been established work could begin on its total synthesis.

4.1.2.1 Biosynthesis of Penicillins

The penicillins began as natural products and today, the most common method for preparing penicillins and their derivatives is by direct fermentation or by synthetic modification of fermentation-derived starting materials. A number of different microbial species have been found to produce penicillin but most development work has been carried out on the fungus *Penicilluim chrysogenum*.

It was recognised early on in penicillin studies that during fermentation, a series of penicillins was produced which differed at the C(6) side-chain. It was found that the composition of the mixture of products was dependent upon the composition of the medium and could be controlled by the addition of side-chain precursor acids to the fermentation medium. Today benzylpenicillin and phenoxymethylpenicillin are produced commercially with controlled fermentation media and P. chrysogenum mutants selected for their high productivity.

The mechanism by which penicillins are synthesised biochemically has been extensively researched.[19,20] In particular Baldwin and co-workers have investigated the stereochemistry of the biosynthetic pathway. It has been proposed that the amino acids, L-α-aminoadipic acid **4.32**, L-cysteine **4.33** and L-valine **4.34** combine to form (L-α-amino-δ-adipyl)-L-cysteinyl – D-valine **4.35** which is commonly known as the Arnstein tripeptide. This is the only intermediate which has been isolated and identified between the constituent amino acids and isopenicillin *N*-(L-4-amino-4-carboxybutylpenicillin) **4.36**. During this step L-valine is converted to D-valine and this is accomplished with exchange of H(2) but without exchange of H(3) or N.[21] This is then followed by an oxidative step which is not fully understood, where **4.36** is converted into **4.37**. Of particular interest in this step is the high stereoselectivity with complete retention of stereochemistry at C(3) of cysteine, and at C(2) and C(3) of valine. In *P. chrysogenum* isopenicillin N is then converted to other penicillins depending on the composition of the fermentation medium.



Scheme 10

The number and type of different penicillins which can be produced by medium supplementation are quite limited. In general only monosubstituted acetic acids such as phenylacetic acid and *para*-hydroxy phenylacetic acid can be incorporated into the penicillin side chain. The penicillin side chains can be chemically manipulated after the core penicillin unit has been prepared by the biosynthetic pathway. In this way a large variety of penicllins could be prepared.

For this study we will focus on synthetic strategies which actually involve formation of the core penicillin unit.

4.1.2.2 Total synthesis of penicillins

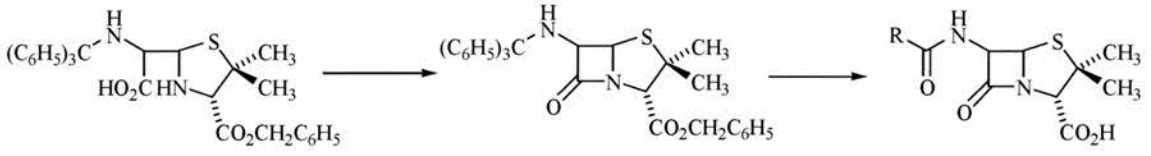
Since its discovery in 1945 the penicillin structure has provided a challenge for synthetic organic chemists. This challenge however has been met, and to date there are numerous examples in the literature of the total synthesis of penicillins.

In general the total syntheses of penicillins can be divided up into two groups. These are, synthetic schemes in which the β-lactam ring is formed late in the sequence, for example, insertion and ring contraction, and synthetic schemes in which the β-lactam ring is formed early in the sequence, for example, cycloaddition reactions and biogenetic-type closure.

Synthetic schemes in which the β-lactam ring is formed late in the sequence

A. Lactam formation.

The first example of a penicillin total synthesis was demonstrated by Sheehan and Henery-Logan[22] in 1962 and is an example of a synthetic scheme where the β-lactam is formed late in the sequence. The original total synthesis involved a carboimide cyclisation of **4.37** to **4.38** followed by a deprotection and acylation



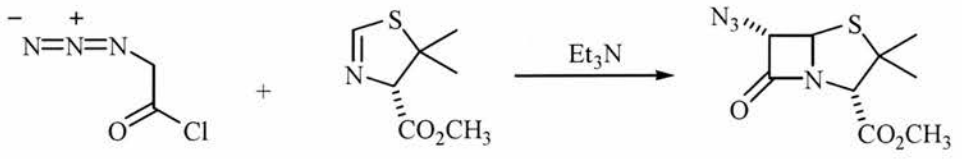
4.37 4.38 4.39

Scheme 11

The Sheehan-Harry-Logan methodology was significant in that it was the first total synthesis of a penicillin but it lacked stereospecificity. In the cyclisation reaction it was necessary to use a protecting group such as trityl because an amide carbonyl reacts preferentially to give an oxazolone rather than a β-lactam. The Sheehan carboimide cyclisation route was widely applied to the preparation of a range of penicillins including bisnor-penicillin by Hoogmartens and co-workers[23] in 1974. It was also applied to the preparation of cephalosporins.[24]

B. Cycloaddition.

The Staudinger[1] methodology used in the preparation of β-lactams can also be applied to the total synthesis of penicillins. Bose and co-workers[25] used this methodology to prepare the 6-epipenicillin precursor **4.41** in a low yield (5-8 %). The azidoketene was generated from azidoacetyl choride **4.8** in the presence of triethylamine and this underwent a 2 + 2 cycloaddition with the thiazoline **4.40** (scheme 12).



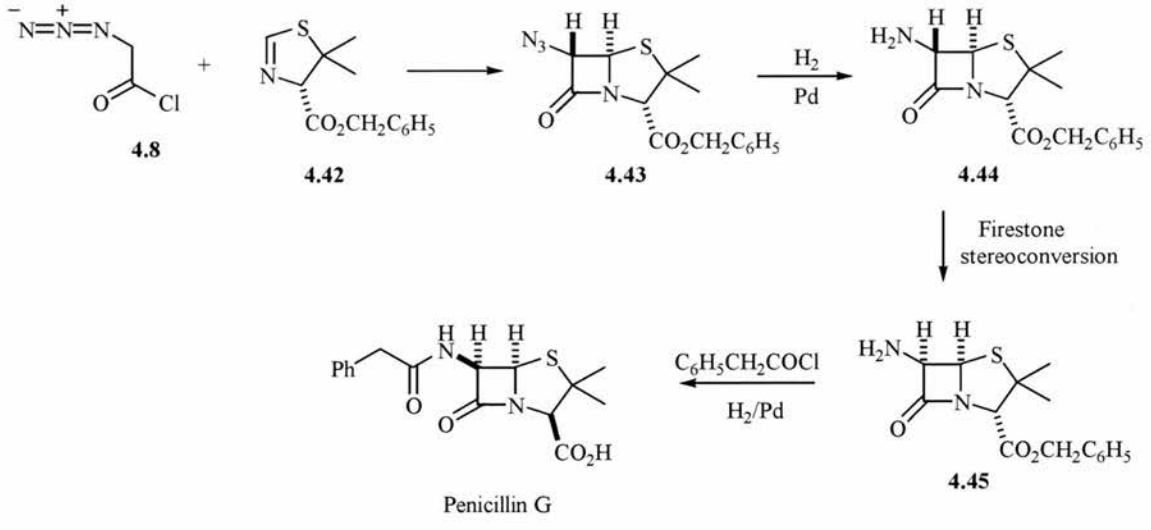
4.8 4.40 4.41

Scheme 12

The major drawback with this methodology was that the stereochemistry of the lactam hydrogens was *trans* instead of *cis*. This was the opposite stereochemistry to the natural products and it was found that the *trans* epimers were biologically inactive.[26,27]

Firestone and co-workers[28] developed a kinetically controlled methodology for the conversion of stereochemistry from the thermodynamically favoured *trans* to the less thermodynamically stable *cis* via formation of an anion at C6. Addition of a solvated proton occurred principally from the less hindered α direction resulting in 2:1 ratio of *cis* to *trans*.

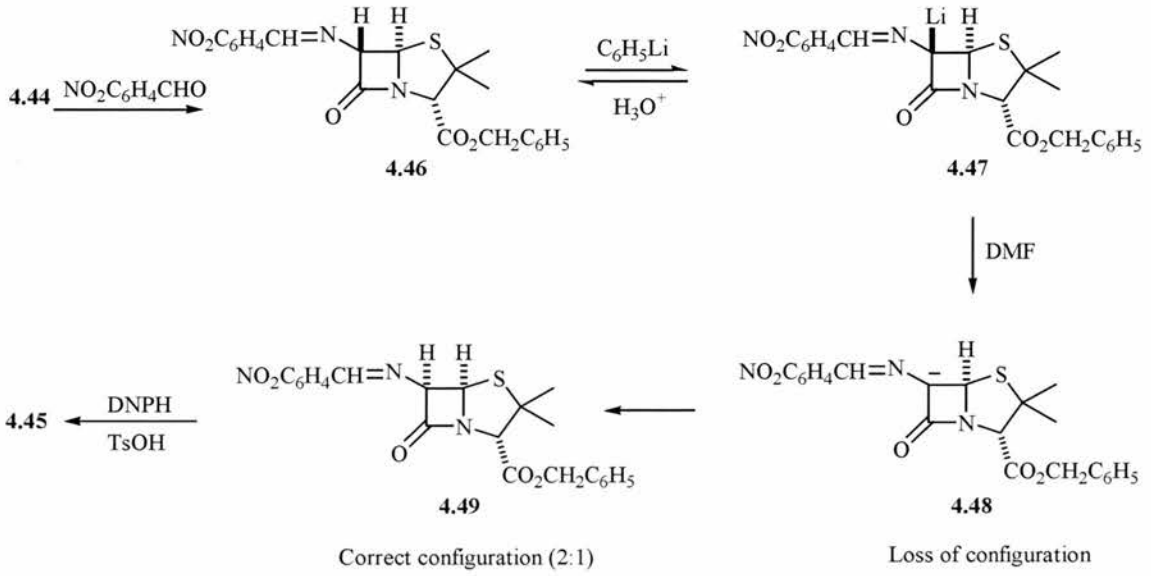
Using the chemistry of Bose and co-workers they were able to prepare the epimer **4.43**. The cyano group was converted to the free amine by catalytic hydrogenation and this then allowed the Firestone stereoconversion procedure to be carried out. Once the correct stereochemistry had been introduced then the protected penicillin was converted to Penicillin G (Scheme 13). The Firestone methodology established that the Staudinger cycloaddition could be used in the preparation of penicillins with the correct stereochemistry.



Scheme 13

The Firestone stereoconversion involved activation of the epimer **4.44** by conversion of the amine to its corresponding Schiff base **4.46**. Once activated the epimer was reacted with phenyllithium at -78 °C to give the lithiated product **4.47**. On

treatment of DMF the free anion **4.48** was formed and consequently the configuration was lost. Addition of a solvated proton occurs from the less sterically hindered α side to give the thermodynamically less favoured product **4.49**, but with the correct stereochemistry (Scheme 14).



Scheme 14

Other methods which have been applied to the preparation of β-lactam antibiotics and which involve formation of the β-lactam ring late in the scheme include insertion of carbenes and ring contraction of α-keto lactams. Since these techniques have been applied to the preparation of cephalosporins rather then penicillins they will not be discussed in this introduction.

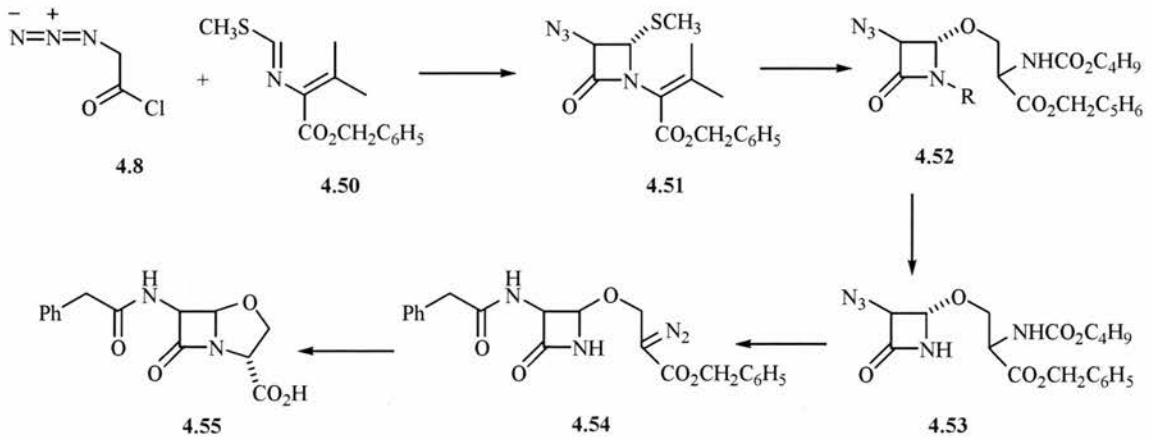
Synthetic schemes in which the β-lactam ring is formed early in the sequence.

The general approach of forming the β-lactam ring early in the preparation of antibiotics was first employed by Woodward and co-workers[29] in their preparation of cephalosporin C. Forming the β-lactam ring early in the synthetic sequence has a number of advantages over ring formation late in the sequence. The most important of these is that it allows the amide chain to be added with *cis* stereochemistry while the β-lactam ring is still relatively unreactive.

Cycloaddition

Cycloaddition reactions such as the ketene-imine cycloaddition for the preparation of β-lactams can also be used to prepare β-lactam antibiotics. It was demonstrated in Scheme 12, that the cycloaddition reaction can be used in schemes where the β-lactam ring is formed early in the sequence, however the system has also been applied to synthetic strategies whereby the β-lactam ring is formed late in the sequence.

The first successful approach to the preparation of penicillin analogs using the ketene-imine cycloaddition was developed by Cama and Christensen[30,31] at Merck. Azidoacetal chloride **4.8** was reacted with the imine **4.50** to give the *trans* β-lactam. The lactam was then converted to a mixture of *cis* and *trans* chloro derivatives which were subsequently displaced with *N-tert*-butoxycarbonylserine benzyl ester to give **4.52**. The substituent on the β-lactam nitrogen was removed by potassium permanganate oxidation **4.53** and the *cis* isomer was separated from the resulting mixture by column chromatography. After reducing the azide and acylating the resulting amine, the *tert*-butyl group was removed and the amine diazotized to give **4.54**. Cyclisation was achieved by intramolecular insertion of the carbene derived from **4.54** into the N-H bond of the β-lactam using rhodium acetate as the catalyst. Hydrogenolysis was used to release the free acid and the penicillin analog **4.55** was isolated.

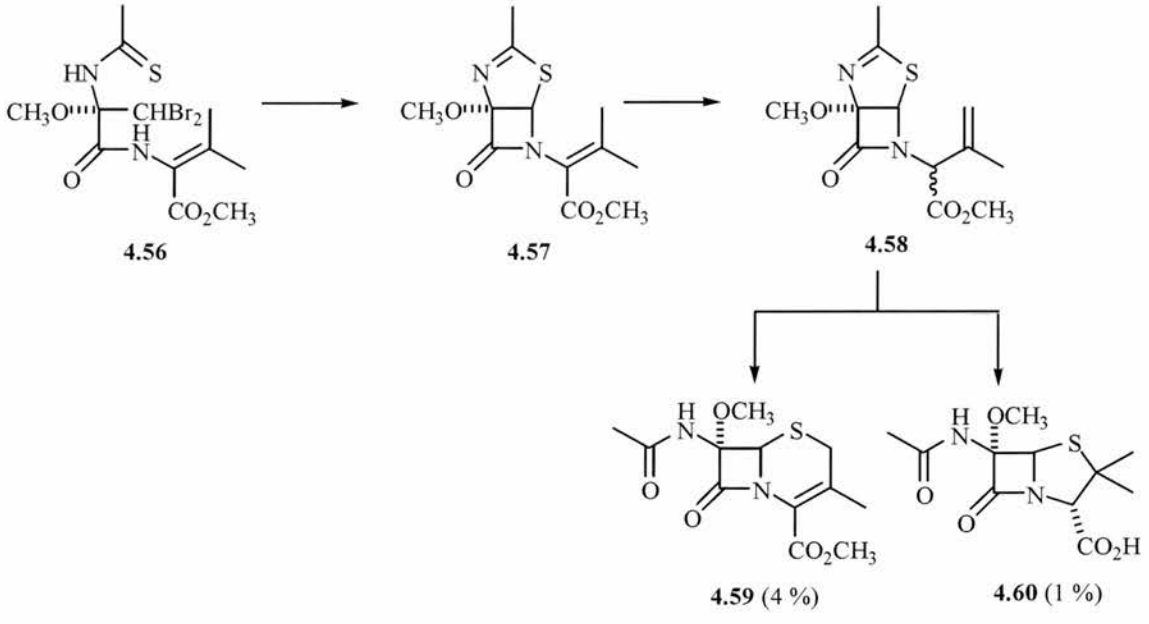


Scheme 15

Most of the β-lactam antibiotics prepared using cycloaddition chemistry are cephalosporins and will not be discussed in this introduction.

Biogenetic-Type Closure

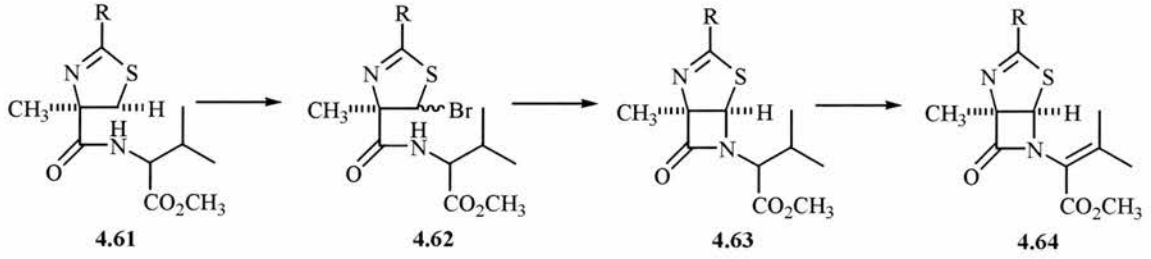
Two routes to β-lactam antibiotics, based on proposed biosynthetic pathways were developed by Kershi and co-workers.[32] The first route involved a double cyclisation of a thioamide **4.56** to give a *cis* β-lactam **4.57** in low yield. Allylic bromination followed by treatment with zinc in acetic acid gave the deconjugated olefin **4.58** as a mixture of isomers at the carbonyl position. The product with the natural or *cis* configuration was oxidised with *m*-chlorobenzoic acid in benzene containing a catalytic amount of trifloroacetic acid to yield a mixture which on treatment with phosphorus trichloride, gave low yields of the cephalosporin **4.59** (5 %) and the penicillin **4.60** (1 %).



Scheme 16

The second route which was developed, employed bromination of a thiazoline **4.61** to give a 1:1 mixture of epimeric bromides **4.62**. It was found that only one of the epimers cyclised to furnish the β-lactam **4.63** in 15 % yield on treatment with

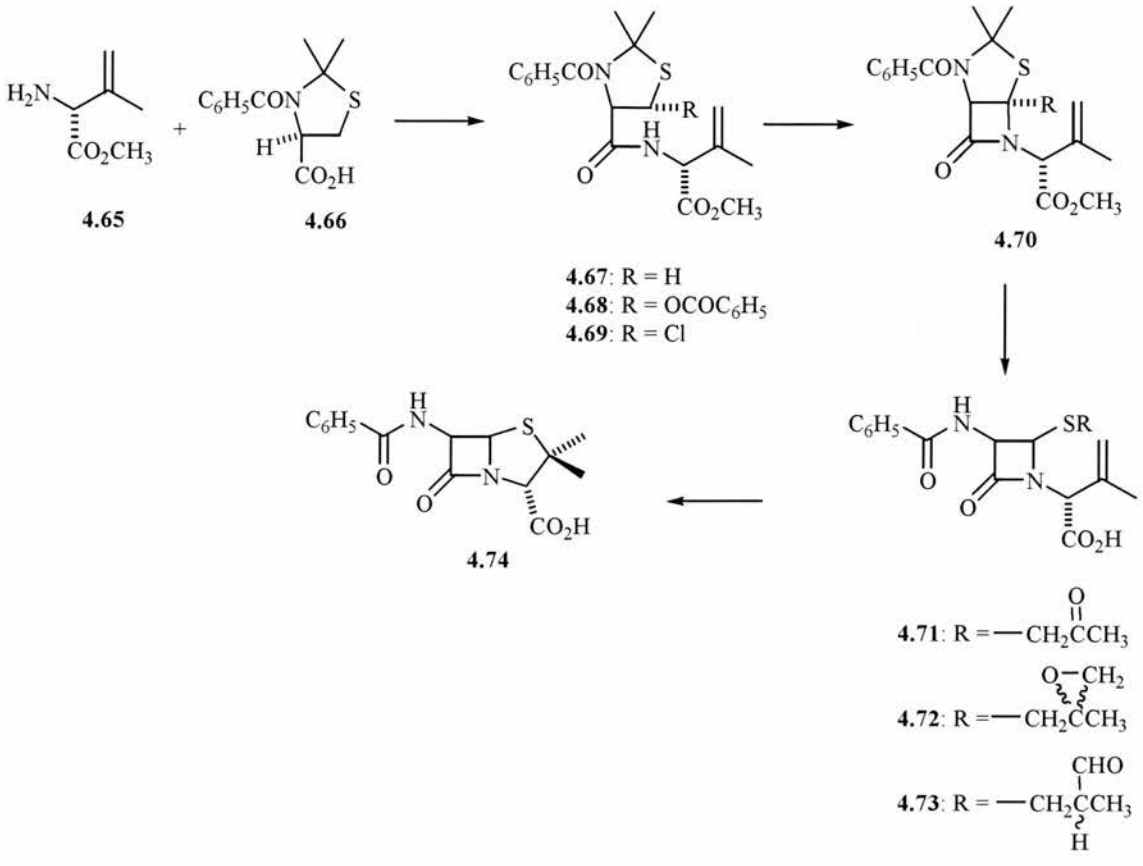
potassium hydride in THF. Bromination followed by elimination was used to introduce the olefin to give **4.64** (Scheme 17) and although it was not converted to the bicyclic β-lactam it was proposed that conversion to the corresponding penicillin and cephalosporin could be carried out by a method analogous to that shown in Scheme 16.



4.61 **4.62** **4.63** **4.64**

Scheme 17

Baldwin and co-workers[33,34] attempted a total synthesis of penicillin using a similar route. They initially prepared the D-isodehydrovaline methyl ester **4.65** in good yield from methyl 2-nitrodimethylacrylate by deconjugation of the potassium salt with aqueous HCl. The valine methyl ester **4.65** was then coupled with a thiazolidine acid **66** to give **4.67**. Stereospecific functionalisation was achieved with benzoyl peroxide and the benzoate was converted to chloride **4.69** by treatment with HCl in DCM. Addition of sodium hydride furnished the β-lactam **4.70** in a good yield of 82 %. The corresponding sulfoxide was rearranged to **4.71** by heating under acidic conditions. Epoxide formation (diazomethane) gave **4.72** which was rearranged to the aldehyde **4.73**. The corresponding sulfoxide underwent thermal *syn*-elimination of methacraldehyde to generate an intermediate sulfenic acid which afforded penicillin sulfoxide directly in 21 % yield from epoxide. Deoxygenation finally gave the penicillin **4.74** with the correct stereochemistry (Scheme 18).



Scheme 18

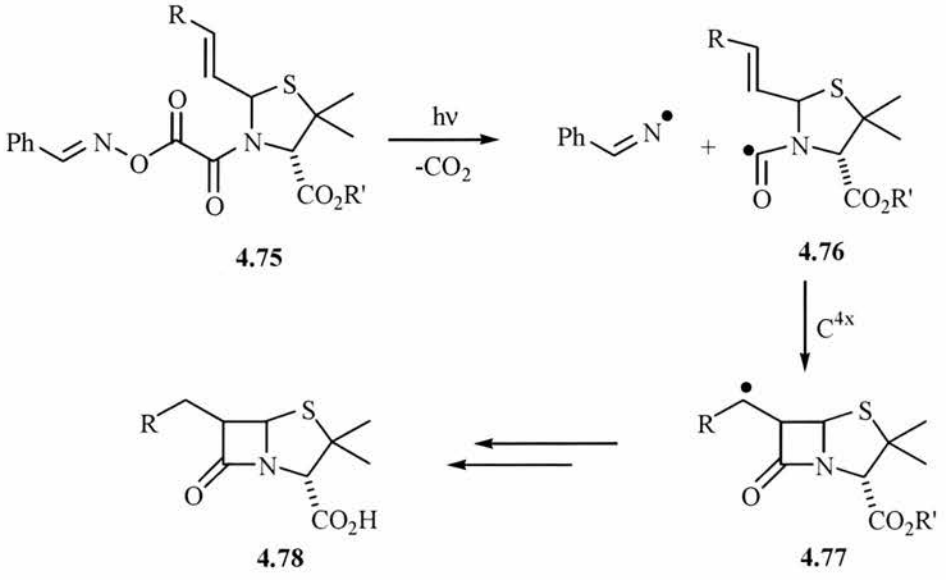
It can be seen from this introduction that a wide and varied range of synthetic procedures have been applied to the preparation of penicillins and other β-lactam antibiotics. The conditions are often harsh and the use of protecting groups is wide spread.

4.1.2.3 The preparation of penicillins *via* free radical cyclisation.

Free radical chemistry has been applied to the preparation of β-lactams and the synthetic methodology has been developed to allow preparation of some β-lactam antibiotics. In particular monocyclic β-lactam antibiotics such as nocardicins have been prepared using radical chemistry.[35] To date no successful synthesis of penicillins by free radical chemistry has been accomplished.

It was the aim of this research to investigate if the radical methodology developed for the preparation of some simple bicyclic lactams could be applied to the

preparation of penicillins. The general synthetic strategy envisaged for the preparation of simple penicillins *via* a 4-*exo* radical cyclisation is illustrated in Scheme 19.



Scheme 19

The photochemical precursor **4.75** incorporates the same oxime oxalate amide functionality as the simple precursors discussed in Chapter 2. It would therefore maintain its ability to photodissociate to an iminyl and a carbamoyl radical **4.76**. The carbamoyl radical in this instance would undergo a 4-*exo* cyclisation onto a proximate double bond to furnish the β-lactam. The thiazolidine ring is already present in the starting material and the resulting bicyclic lactam should be the penicillin **4.78**.

This is an example of a reaction scheme where the β-lactam is formed late in the sequence and, apart from the fact that it uses single electron chemistry, it bears a close resemblance to the Sheehan methodology used in the original preparation of penicillin.

4.2.0 Results and Discussion

4.2.1 The Preparation of Thiazolidines

In order to prepare oxime oxalate amides of the type **4.75** it was first necessary to prepare suitable amines. The type of amine required for ring closure was a thiazolidine ring with a double bond suitable for ring closure (Figure 2).

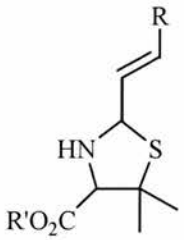
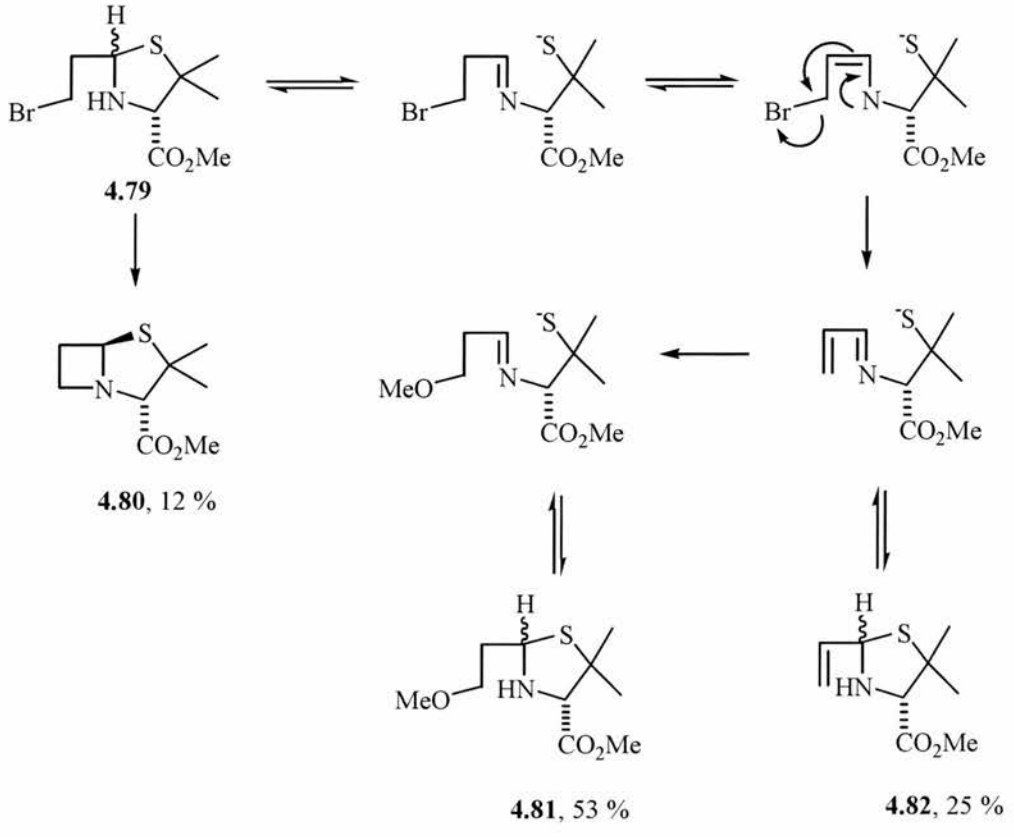


Fig 2.

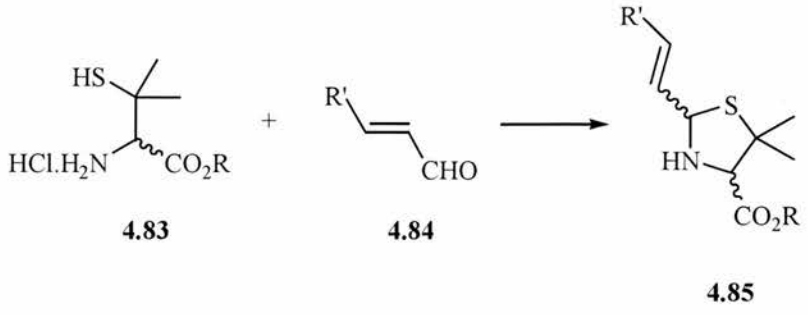
A literature survey revealed that only one thiazolidine of this type had been prepared previously. While investigating the chemistry of the reduction product of 6β-benzyloxycarbonylaminopenicillinate, Sammes and co-workers[36] isolated the thiazolidine **4.82** in 25 % yield as a byproduct from the attempted cyclisation of bromide **4.79** to the azetidine **4.80** (Scheme 20).



Scheme 20

The vinylic thiazolidine **4.82** was formed as a by-product due to an intramolecular rearrangement and this method was not considered to be a viable route for the preparation of a range of thizolidines which incorporated a double bond.

In order to prepare a range of thiazolidines of the type shown in Figure 2, it was necessary to develop a synthetic strategy which was versatile and which would easily allow variation of the side chain R. The synthetic strategy employed for the preparation of the thiazolidines was based on the well known condensation reaction of penicillamine esters with appropriate aldehydes[2,37,38] (Scheme 21).



4.83 **4.84** **4.85**

Scheme 21

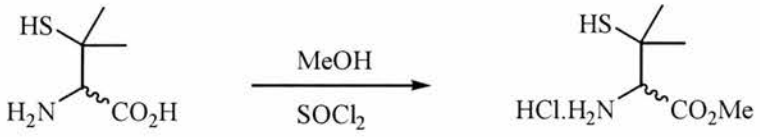
This condensation reaction had never been applied to the preparation of a vinylic thiazolidine and it was anticipated that there may be a mixture of products arising from the competing Michael addition, whereby nucleophilic attack would occur at the "softer" Michael centre of the double bond rather than at the desired aldehyde carbon.

It was realised that there were at least two plausible options available, to push equilibrium towards the desired thiazolidine condensation product, rather than the Michael product. The first was to stericially hinder the Michael addition site by using a suitably disubstituted double bond. The alternative was to incorporate an oxime ether functionality. This would serve a dual purpose. It would prevent Michael addition entirely and it would also aid cyclisation. Both of these options were explored and the results of each will be discussed in detail later in this chapter.

Prior to attempting the condensation reaction it was first necessary to protect the free acid of D,L-penicillamine. It was anticipated that the free acid group would interfere in the later reactions involving the preparation of the oxime oxalate amide.

D,L-Penicillamine methyl ester hydrochloride 4.87

The methyl ester hydrochloride of D,L-penicillamine was prepared from D,L-penicillamine according to the literature procedure of Buchanan and Clegg.[39] The starting amine was treated with thionyl chloride in methanol and stirred at rt for several days. After this time the solvent was removed and the ester was isolated as a white crystalline solid in 70 % yield. (Scheme 22).

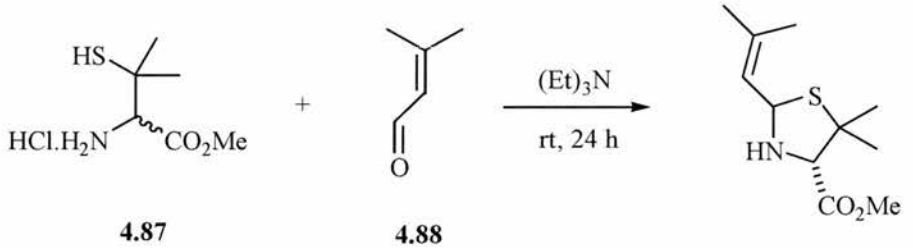


4.86 **4.87**, 70 %

Scheme 22

5,5–Dimethyl-2-(2-methyl-propenyl)-thiazolidine-4-carboxylic acid methyl ester 89

Once the penicillamine had been esterified it was attempted to prepare thiazolidine **4.89** through the condensation reaction with 3-methyl-but-2-enal **4.88** (Scheme 23). The aldehyde **4.88** was chosen because it was anticipated that the dimethyl functionalty would inhibit formation of the Michael product, and also on radical cyclisation the dimethyl functionality would stabilise the cyclised radical and therefore promote the cyclisation reaction. The aldehyde was added to a solution of the penicillamine and triethylamine in MeOH at 0 °C. The mixture was allowed to stir at rt for 24 h and after this time the sovent was removed and the thiazolidine was isolated as colourless crystals *via* column chromatography followed by recrystallisation. The yield was 25 % and only one isomer was isolated. No other significant products were isolated by column chromatography.



4.87 **4.88**

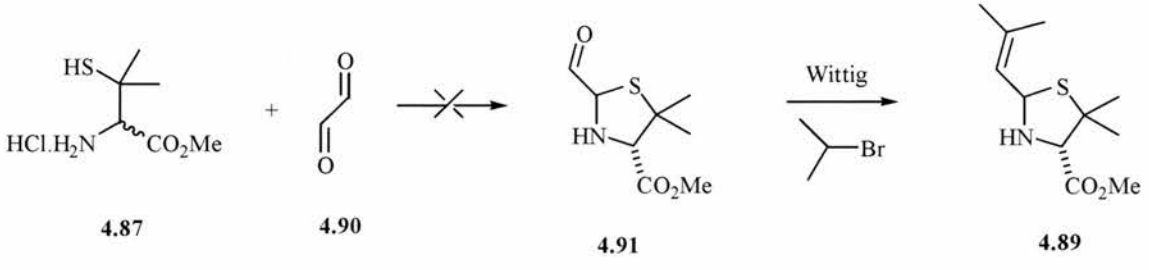
4.89, 25 %

Scheme 23

The yield of the thiazolidine **4.89** was low, but it compared favourably to the yield of the vinylic thiazolidine obtained by Sammes and co-workers.[36] It was attempted to investigate if the yield of the thiazolidine **4.89** could be improved and a number of varying synthetic strategies were employed. The initial strategy was to

repeat the synthesis under the same conditions but this resulted in isolation of the thiazolidine in an identical yield. Refluxing the reaction mixture for 2 h did not improve the yield of the thiazolidine and caused the reaction mixture to turn black. Two synthetic strategies involving formation of the thiazolidine ring followed by introduction of the double bond were also investigated.

The first strategy involved a condensation reaction of the penicillamine **4.87** with glyoxal **4.90** to give the thiazolidine **4.91**. This may then undergo a Wittig reaction with *iso*-propylbromide **4.92** to give the desired thiazolidine **4.89** (Scheme 24).

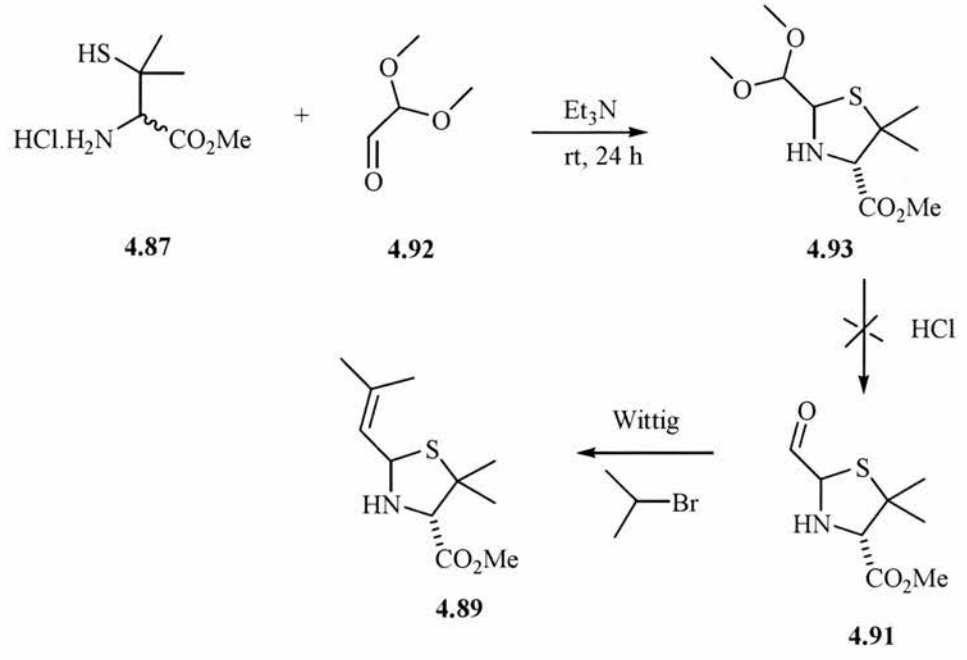


4.87 **4.90** **4.91** **4.89**

Scheme 24ester

Unfortunately the condensation reaction of the penicillamine methyl **4.87** with glyoxal **4.90** did not give any of the desired thiazolidine **4.91**. The reaction mixture quickly changed from a colourless solution to a dark black solution on the introduction of the glyoxal and no significant products were isolated by column chromatography. The reaction was carried out in EtOH at rt for 24 h and in an EtOH:H_2O (50:50) solution at rt for 4 h but the thiazolidine **4.91** was not observed.

The second strategy employed was to make use of the protected glyoxal **4.92** for the condensation step. This could then be deprotected and the Wittig reaction could be carried out on the free aldehyde **4.91** (Scheme 25).



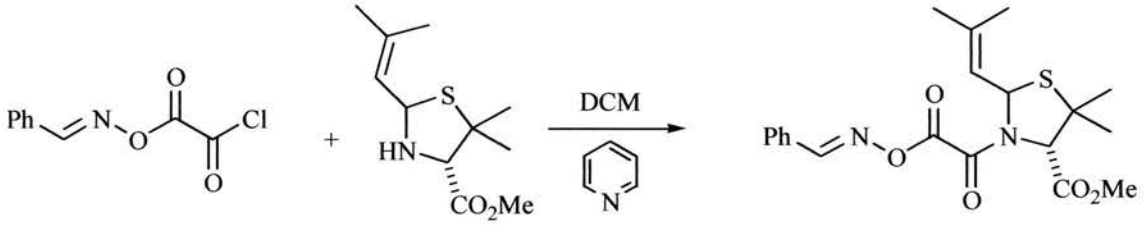
Scheme 25

The condensation reaction on this occasion was successful and the thiazolidine **4.93** was isolated in good yield as a mixture of isomers. The deprotection step however was unsuccessful. Treatment with 0.1 M, 1.0 M, 5.0 M and 6.0 M HCl over a range of temperatures failed to release the free aldehyde **4.91** and the synthetic route was abandoned.

In a final attempt to improve the yield of the thiazolidine **4.89**, the condensation reaction with 3-methyl-but-2-enal **4.88** was repeated, but instead of using D,L-penicillamine the enantiomerically pure L-penicillamine was used. The methyl ester was prepared in the same manner as for D,L-penicillamine and the condensation reaction was carried out under exactly the same conditions. The product obtained was identical to that obtained using the D,L-penicillamine but the yield was slightly improved, 28 %.

Benzaldehyde *O*-(5,5–dimethyl-2-(2-methyl-propenyl)-thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime 4.94

Following the preparation of the thiazolidine **4.89**, it was attempted to convert the amine to its corresponding oxime oxalate amide **4.94**. The methodology developed for the preparation of simple oxime oxalate amides was employed and the oxime oxalate amide **4.94** was isolated as colourless crystals in 92 % yield (Scheme 26).



4.89 **4.94**, 92 %

Scheme 26

The oxime oxalate amide was submitted for X-ray crystallography structure analysis and Figure 3 shows the crystal structure obtained.

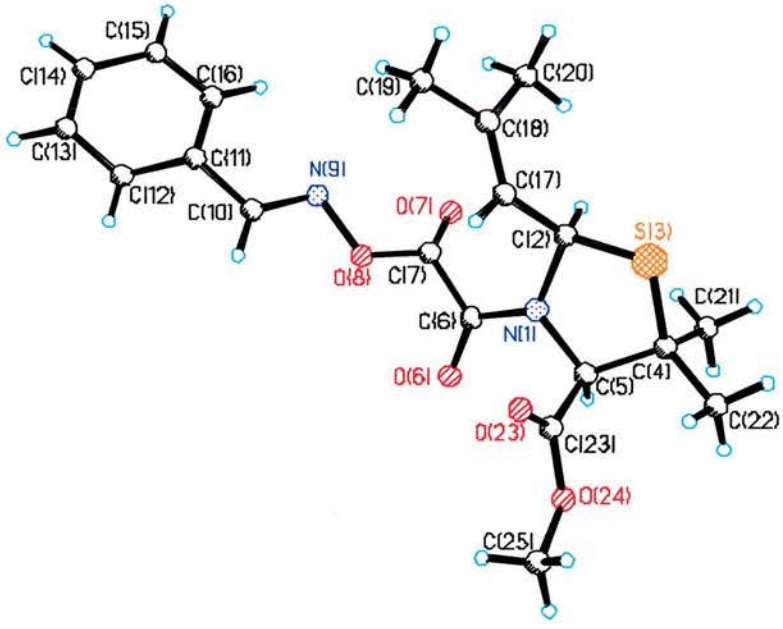
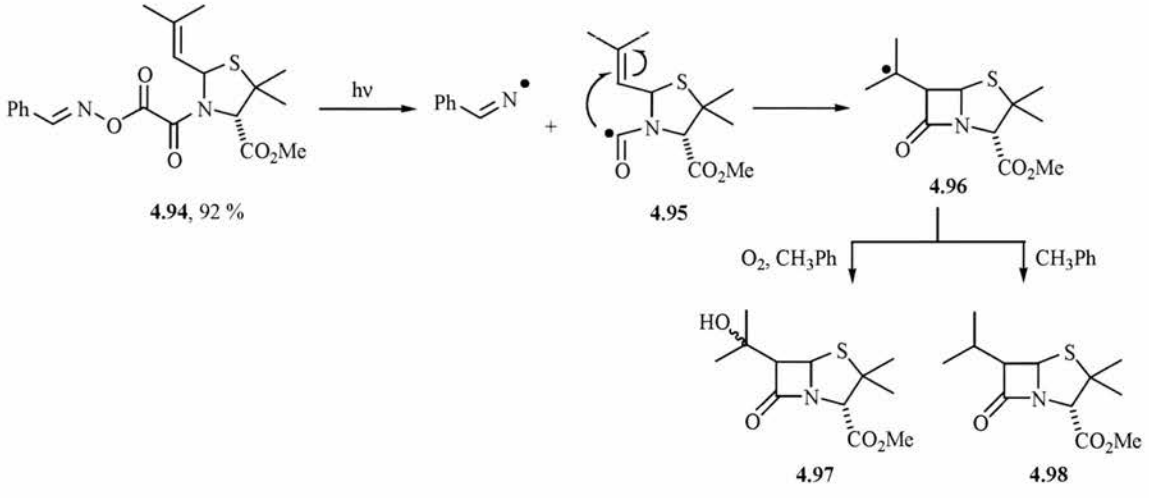


Fig 3. X-Ray structure of the oxime oxalate amide **4.94**.

The X-ray structure was useful in deducing information on the oxime oxalate amide system in general. The two oxalyl carbonyl groups are orientated *trans* to each other and as a consequence the molecule exists in an all *trans* extended conformation. The length of the N-O bond was determined to be 1.453 Å which is long for an oxime, the usual range[40] being 1.38 – 1.43 Å. This long N-O bond suggests it may be quite weak and readily undergoes homolytic cleavage on photolysis. The overall configuration is planar apart from the ring substituents. It was noted that the configuration of the methyl ester functionality was wrong for a natural penicillin.

Photochemistry of benzaldehyde *O*-(5,5–Dimethyl-2-styryl-thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime

It was expected that the photochemistry of the more complex oxime oxalate amides would not differ greatly from the simple oxime oxalate amides discussed in Chapter 2. The oxime oxalate amide **4.94** was expected to undergo homolytic cleavage of the weak N-O oxime bond to give the iminyl radical and the carbamoyl radical **4.95**. The carbamoyl radical was expected to undergo 4-*exo*-trig cyclisation to give the cyclised radical which would either abstract a hydrogen from solution to give the simple penicillin **4.98** or else react with dissolved O_2 to give the hydroxylated species **4.97** (Scheme 27).



Scheme 27

The photochemistry of the oxime oxalate amide **4.94** was first investigated using ESR spectroscopy. The sample was prepared in the usual manner, taking 20 mg of the oxime oxalate amide, 1 M eq. of MAP and dissolving it in PhBu-*t* ca. 500 µl. The sample was photolysed with light from a 500 W, high pressure UV lamp and ESR spectra were observed over a range of temperatures. At low temperature the ESR spectrum showed the iminyl radical and the carbamoyl radical. At higher temperatures both of these radicals were present but their spectra were weaker. No signal corresponding to the cyclised species was observed at any temperature. Figure 4 shows the ESR spectrum obtained at 220 K for oxime oxalate amide **4.94**.

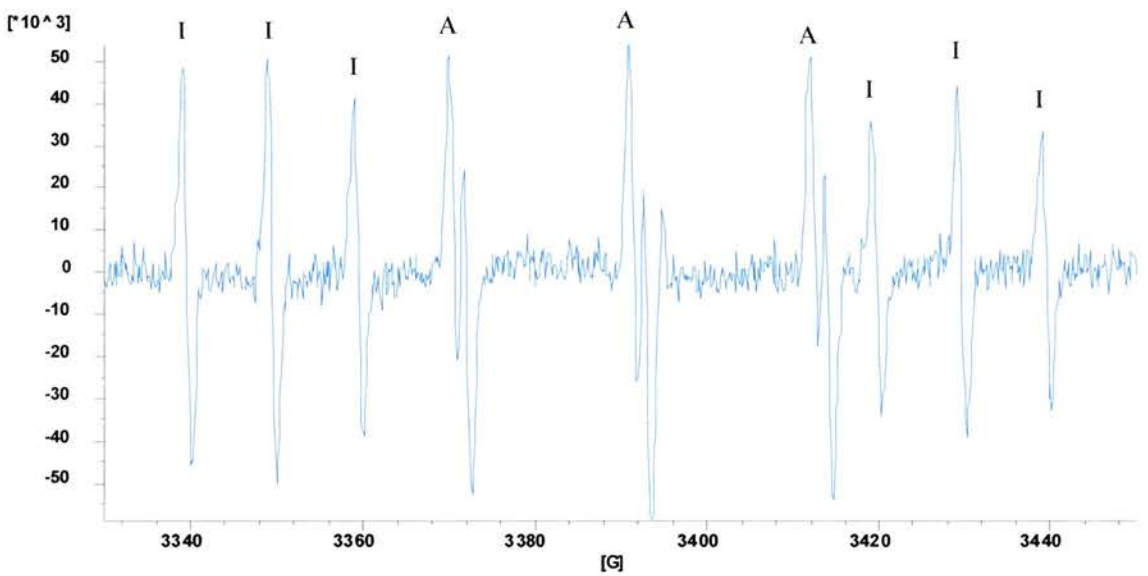


Fig 4. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **4.94** and MAP in *tert*-butylbenzene at 220 K.

The doublet of triplets arising from the iminyl radical is clearly visible at the extremes of the spectrum. The triplet at the centre of the spectrum corresponds to the nitrogen splitting of the carbamoyl radical. Each triplet was split into a doublet, probably by one of the β-hydrogens on the thiazolidine ring. The ESR parameters for the radicals derived from **4.94** were: iminyl (I) g = 2.0034, *a*(N) = 10.0, *a*(H) = 80.0 G; carbamoyl (A) g = 2.0018, *a*(N) = 21.0, *a*(1H) = 1.6 G.

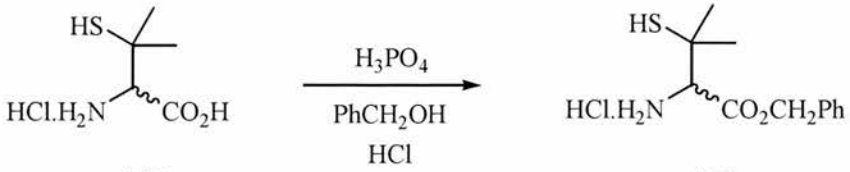
It was decided to carry out an end product analysis in order to determine if it was possible to prepare a simple penicillin *via* the oxime oxalate amide methodology. The oxime oxalate amide in the presence of MAP (3 M eq) was photolysed with light

from a 400 W UV lamp at 80 °C in toluene for 8 h. After this time the solvent was removed and the sample was investigated by NMR, GC-MS and column-chromatography. A mass peak, which may have been the penicillin, was observed by GC-MS. All the other peaks in the chromatogram were derived from the solvent or from the MAP. The molecular weight of the formamide is the same as that of the penicillin but the formamide would be expected to have a peak at m/z = 256 corresponding to loss of a hydrogen. Several attempts were made to isolate the penicillin by column chromatography and by preparative HPLC but the penicillin could not be isolated, nor were any other thiazolidine containing compounds.

D,L-Penicillamine Benzyl Ester Hydrochloride 4.99

The necessity to protect the free acid of penicillamine prior to formation of the thiazolidine ring has been discussed earlier in this chapter. Formation of the methyl ester of penicillamine occurs readily and in good yield on treatment with thionyl chloride in MeOH but deprotection to give the free acid requires harsh conditions which may hydrolyse the penicillin core unit. In order to allow the deprotection to occur in milder conditions it was decided to prepare the benzyl ester of D,L-penicillamine. The benzyl ester can be converted to the free acid via catalytic hydrogenation and this has been exploited in many penicillin total syntheses.[22,31]

The method employed for the formation of the benzyl ester was the same method used by Firestone and co-workers at Merck.[28] A solution of D,L-penicillamine **4.86**, polyphosphoric acid and benzyl alcohol was heated at 110 °C for 6 h. Once cooled the reaction mixture was added to an acidic solution of 0.6 M HCl and extracted with ether to remove the excess alcohol. The solution was then made basic and extracted with ether. The ether was evaporated to dryness to give the crude benzyl ester, which was converted to its hydrochloride salt **4.99** by saturating it with HCl in ether at 0 °C. (Scheme 28).



4.86 **4.99**

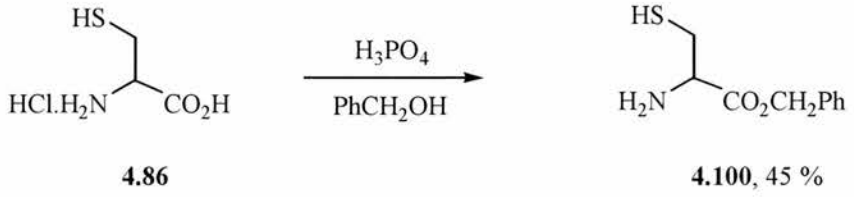
Scheme 28

After recrystallisation, only trace amounts of the benzyl ester hydrochloride were obtained. The experiment was repeated but yields of only 2-4 % of the benzyl ester hydrochloride were obtained. The reaction was repeated several times using longer and shorter reaction times, a new bottle of polyphosphoric acid and stronger acids such as HCl and H_2SO_4 but no satisfactory yields were obtained.

L-Cysteine Benzyl Ester 4.100

Due to the failure in preparing the benzyl ester of penicillamine it was attempted to prepare the benzyl ester of L-cysteine. Cysteine differs from penicillamine only in the absence of the dimethyl functionality at C2 and has been used interchangeably with penicillamine in the preparation of penams.

The L-cysteine benzyl ester was prepared according to the literature procedure of Erlanger and Hall.[41] L-Cysteine was added to a solution containing benzyl alcohol and polyphosphoric acid and stirred in an oil bath for 4 h at 105 °C. The work up was the same as the preparation of the benzyl ester of penicillamine but in this case the target benzyl ester was isolated as a colourless oil in 45 % yield (Scheme 29). The ester was not converted to its hydrochloride salt. It is not understood why the esterfication proceeded smoothly for cysteine but not for penicillamine. The dimethyl group is quite removed from the acid group where the reaction takes place and should not interfere with the reaction.

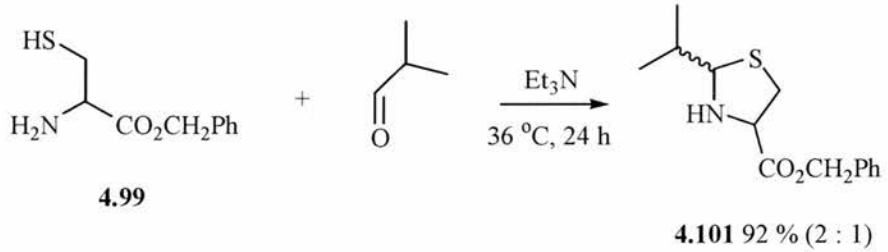


4.86 **4.100**, 45 %

Scheme 29

2-Isopropyl thiazolidine-4-carboxylic acid benzyl ester 4.101

Once the cysteine benzyl ester had been successfully prepared it was attempted to perform a condensation reaction with a saturated aldehyde. The resulting thiazolidine would not be suitable for a radical cyclisation reaction but it would be useful to investigate the stability of the thiazolidine ring under photochemical conditions. The aldehyde used was isobutyraldehyde and the condensation reaction was carried out using a Dean and Stark apparatus in refluxing pentane over 24 h. The thiazolidine was isolated as a mixture of isomers (2:1) in 92 % yield (Scheme 30).

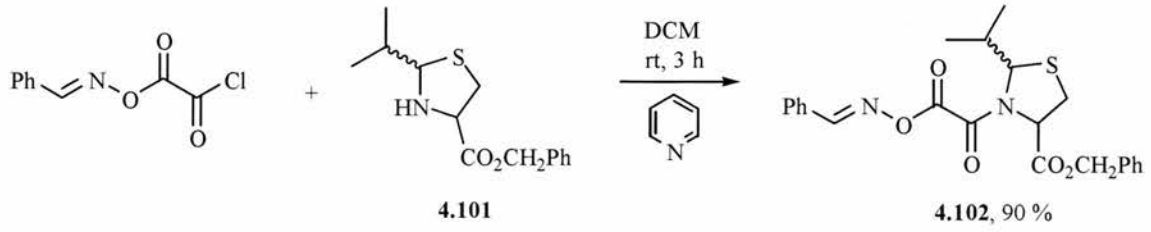


4.99 **4.101** 92 % (2 : 1)

Scheme 30

Benzaldehyde *O*-(2-isopropyl thiazolidine-4-carboxylic acid benzyl ester oxalyl) oxime 4.102

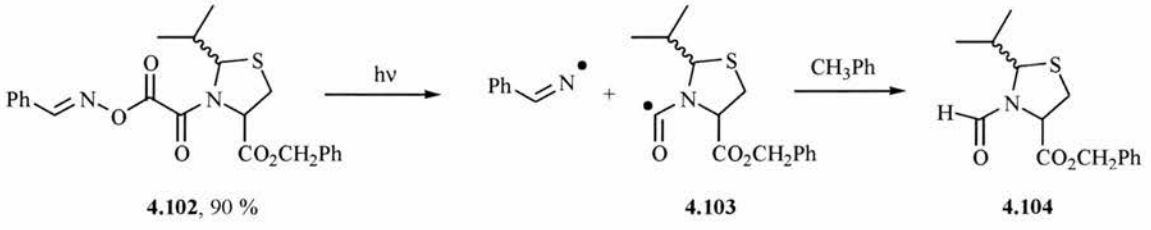
Once the pure thiazolidine **4.101** had been isolated it was converted to its corresponding oxime oxalate amide **4.102** through the reaction with benzaldehyde O-(chlorooxalyl)oxime in the presence of pyridine. The oxime oxalate amide **4.102** was isolated as a colourless oil in 90 % yield via flash column chromatography (Scheme 31).



Scheme 31

The oxime oxalate amide also existed as a mixture of isomers in a ratio of (2:1). It was predicted that the isomerism would not affect the photochemistry and would just result in the formamide existing as a mixture of isomers.

It was expected that the oxime oxalate amide **4.102** would follow the same photochemical route as the simple benzylamine derivative discussed in Chapter 2. Since there was no cyclisation step it was predicted that the carbamoyl radical **4.103** would simply abstract a hydrogen from the solvent and give the formamide **4.104** in good yield (Scheme 32).



Scheme 32

The photochemistry of the oxime oxalate amide **4.102** was first investigated by ESR spectroscopy. The sample was prepared in the usual manner, taking 20 mg of the oxime oxalate amide, 1 M eq. of MAP and dissolving it in PhBu-*t* ca. 500 µl. The sample was photolysed with light from a 500 W, high pressure UV lamp and ESR spectra were observed over a range of temperatures. At low temperature the ESR spectrum showed the iminyl radical and the carbamoyl radical. At higher temperatures both of these radicals were present but their spectra were weaker. Figure 5 shows the ESR spectrum obtained at 220 K for oxime oxalate amide **4.102**.

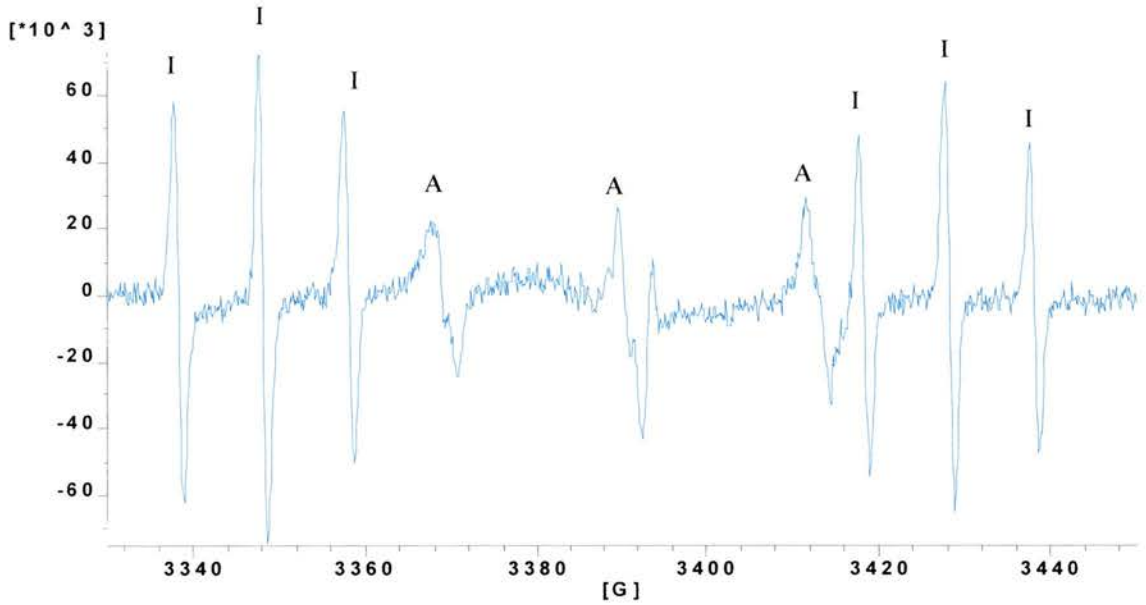


Fig 5. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **4.102** and MAP in *tert*-butylbenzene at 220 K.

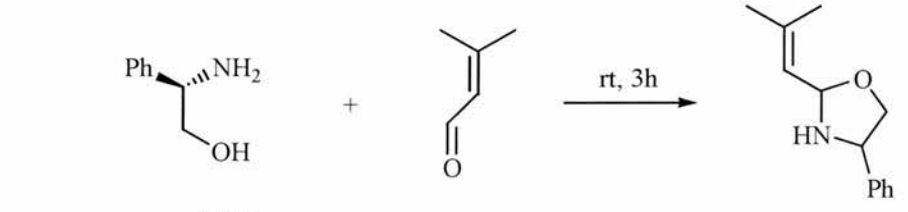
The ESR spectrum obtained for the oxime oxalate amide **4.102** was very similar to that obtained for the oxime oxalate amide **4.93**. The similarity in the spectra results from the fact that the environment of the carbamoyl radical is almost identical in each case. The ESR parameters for the radicals derived from **4.102** were: iminyl (I) g = 2.0034, a(N) = 10.0, a(H) = 80.0 G; carbamoyl (A) g = 2.0016, a(N) = 21.5 G. a(H) = 1.49 G. The ESR parameters were quite closely matched to those measured for **4.93** and suggested that the radical observed was indeed the carbamoyl radical **4.103**.

Once the formation of the carbamoyl radical had been established by ESR it was attempted to carry out a preparative study in order to determine if photolysis of **4.102** in toluene would furnish the formamide **4.104**. A solution of the oxime oxalate amide in toluene was photolysed by light from a 400 W UV lamp for 5 h at rt in the presence of MAP (3 M eq). It was noted at the time that a solid ppt. had fallen out of solution. The reaction mixture was filtered and evaporated to dryness. The yellow oil which resulted was separated by column chromatography, but only benzaldehyde and the photosensetizer (MAP) were isolated. The column was washed with 10 % MeOH in DCM but no other products were isolated. The solid ppt was insoluble in all deuterated

solvents which suggests the formation of a polymeric mass. The presence of benzaldehyde coupled with the ESR study suggests that photolysis occurs as predicted and that the carbamoyl radical is indeed generated, however the expected formamide was not formed and no other organic products were isolated.

2-(2-Methyl-propenyl)-4-phenyl-oxazolidine 106

A literature survey revealed that oxazolidines with unsaturated side-chains suitable for radical cyclisation could be prepared in good yield through the condensation reaction of a suitable amino alcohol with an aldehyde containing the unsaturated side-chain (Scheme 33).



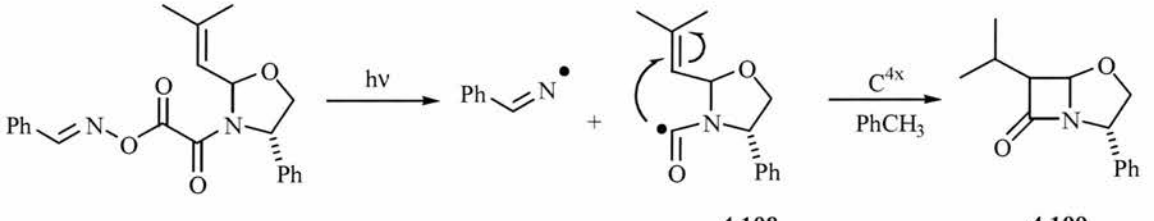
4.105
(S)-β–amninophenylethyl alcahol

4.88

4.106

Scheme 33

The methodology was analogous to that used in the preparation of thiazolidine **4.89** but the yield was greatly improved. It was postulated that incorporation of the oxazolidine into the oxime oxalate amide **4.107** would allow the preparation of penicillin analog **4.109** on photolysis (Scheme 34).



4.107

4.108

4.109

Scheme 34

The oxazolidine **4.106** was prepared in a good yield of 91 % according to the literature procedure of Waldemar and co-workers.[42]

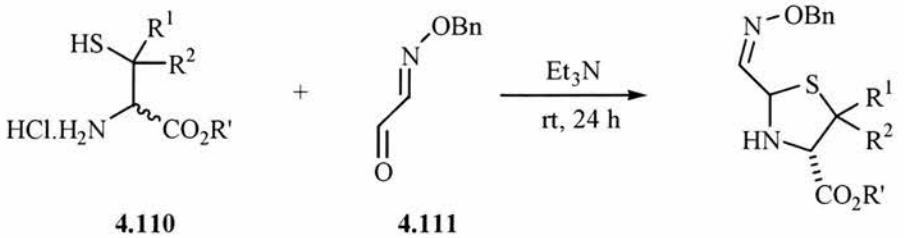
Benzaldehyde *O*-[2-(2-methyl-propenyl)-4-phenyl-oxazolidine oxalyl] oxime

Once the pure oxazolidine **106** had been prepared it was attempted to convert it to the corresponding oxime oxalate amide *via* the established synthetic strategy. However after stirring at rt for 3 h in the presence of benzaldehyde *O*-(chloroxalayl)oxime and pyridine the target oxime oxalate amide **107** was not formed and the oxazolidine **106** remained unreacted. The failure of the oxazolidine to give of the oxime oxalate amide has been attributed to the presence of the aromatic ring located adjacent to the amine. The electron-withdrawing aromatic ring would make the amine a weaker nucleophile and the physical presence of the ring would provide a steric bulk which could inhibit the reaction.

4.2.2 Thiazolidine Oxime Ethers.

The use of oxime ethers in radical cyclisation has been discussed in chapter 3 and it was demonstrated that carbamoyl radicals could undergo efficient cyclisation onto oxime ethers. It was postulated that a thiazolidine incorporating an oxime ether side chain could be prepared using the condensation methodology. These thiazolidines would have a number of advantages over the simple thiazolidines such as **4.89**. Firstly in the condensation reaction there is no possibility of a Michael addition since there is no Michael site in an oxime ether. This would improve the overall yield of the thiazolidine. Secondly, the presence of the oxime ether should encourage cyclisation of the carbamoyl radical and therefore improve the yield of the cyclised product. Finally, the oxime ether would allow the introduction of an amine at the C6 position and this would allow the preparation of natural penicillins.

A synthetic route to thiazolidines incorporating oxime ethers was devised. A condensation reaction of penicillamine or cysteine methyl or benzyl esters with glyoxal-mono-*O*-benzaldoxime was expected to furnish the corresponding thiazolidine in good yield (Scheme 35).



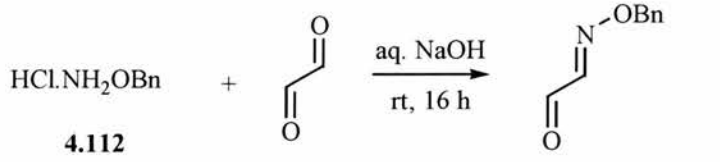
4.110 **4.111** **4.112**

$R^1 = R^2$ =Me
$R^1 = R^2$ = H
R' = Me or Bn

Scheme 35

Glyoxal-mono-*O*-benzyloxime 4.111

A literature survey revealed that the glyoxal oxime **4.111** had previously been prepared by Zimmermann and co-workers[43] through the condensation reaction of *O*-benzyl hydroxylamine hydrochloride **4.112** and glyoxal **4.90** in basic solution at rt over 16 h (Scheme 36).



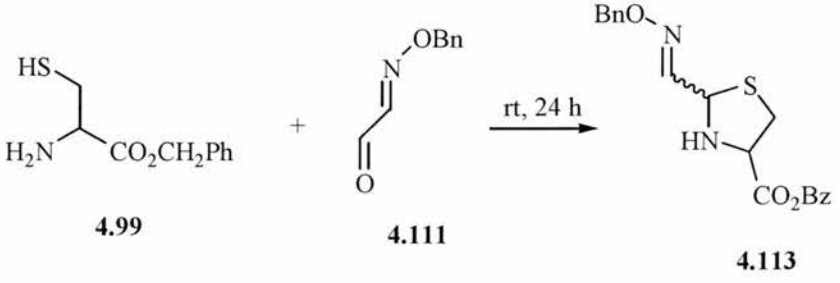
4.112 **4.90** **4.111**, 63 %

Scheme 36

The glyoxal oxime **4.111** was isolated as a pale yellow oil in 63 % yield, via Kugelrohr distillation.

2-(Benzyloxyimino-methyl)thiazolidine-4-carboxylic acid benzyl ester 4.113

The condensation reaction between the glyoxal oxime **4.111** and the benzyl ester of cysteine **4.99** was carried out using the same conditions as the preparation of the thiazolidine **4.89**. The ester was added to a solution of the oxime in EtOH and the mixture was stirred at rt for 24 h. After this time the solvent was removed and the thiazolidine was isolated as a mixture of isomers (1:1) via column chromatography. The thiazolidine was recrystallised from a solution of hexane/EtOAc and isolated as a colourless solid (Scheme 37).



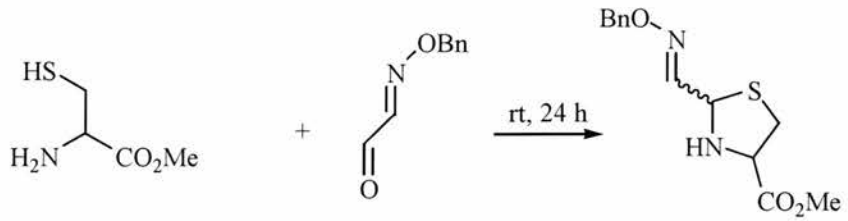
4.99 **4.111** **4.113**

Scheme 37

The ^{1}H-NMR of the thiazolidine **4.113** showed that it existed as a mixture of isomers in a ratio of 1:1. The NMR spectrum was quite complex and it was attempted to separate the isomers by column chromatography. It was found that the isomers had identical rfs for most solvent systems and it was not possible to separate the isomers by column chromatography.

2-(Benzyloxyimino-methyl)thiazolidine-4-carboxylic acid methyl ester 4.115

The methyl ester hydrochloride of cysteine **4.114** was commercially available and it was converted to its corresponding thiazolidine **4.115** in exactly the same manner as the benzyl ester. Since the hydrochloride salt was being used it was necessary to use 1 M eq of triethylamine to act as a HCl scavenger. The thiazolidine was purified by column chromatography and isolated as a colourless oil (Scheme 38).



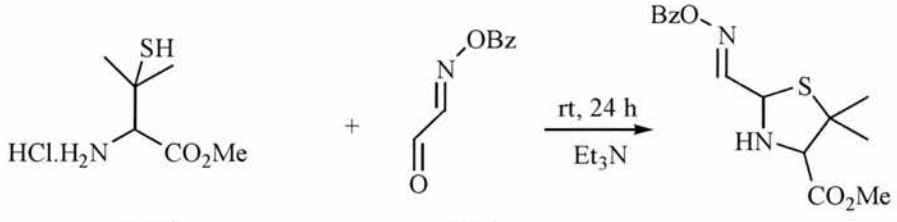
4.114 **4.111** **4.115**

Scheme 38

The ^{1}H-NMR of the thizolidine **4.115** showed that it also existed as a mixture of isomers in a ratio of 1:1. On this occasion no effort was made to separate the isomers.

2-(Benzyloxy-imino-methyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid methyl ester 4.117

The final thiazolidine oxime derivative prepared was derived from the condensation reaction of L-penicillamine with the glyoxal oxime **4.111**. The reaction proceeded smoothly in EtOH in the presence of 1 M eq of triethylamine and the thiazolidine was isolated as a colourless oil.



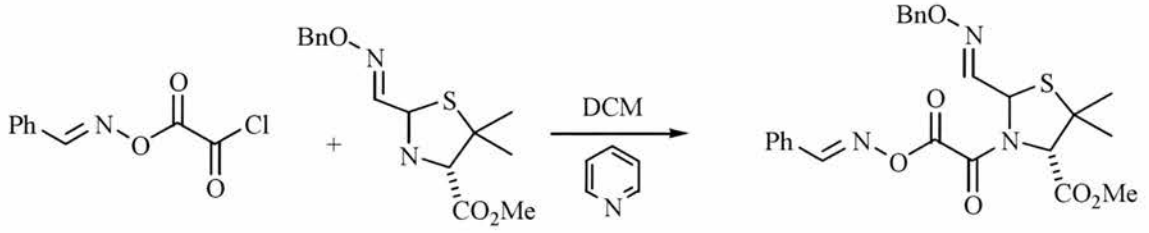
4.116 **4.111** **4.117**

Scheme 39

Once again, the ^{1}H-NMR of the thiazolidine **4.117** showed that it also existed as a mixture of isomers in a ratio of 1:1. It was noted on this occasion that on standing additional peaks began to appear in the NMR spectrum. For this reason the thiazolidine had to be freshly prepared before conversion to its corresponding oxime oxalate amide.

2.3 Oxime oxalate amides incorporating a thiazolidine with an oxime ether side chain.

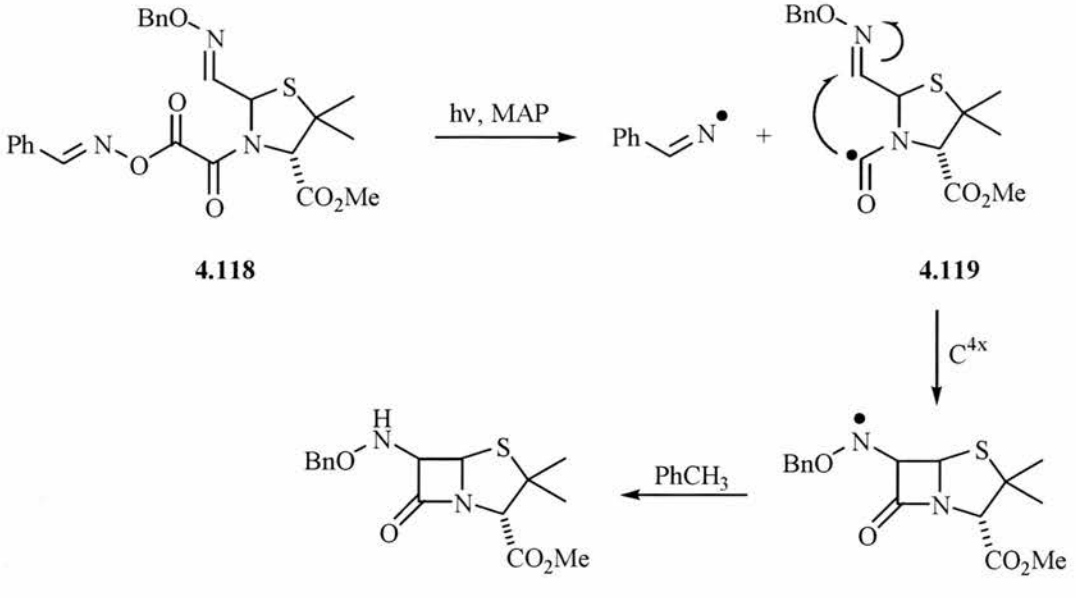
The thiazolidine **4.117** was converted into its corresponding oxime oxalate amide through the reaction with benzaldehyde *O*-(chlorooxalyl)oxime (Scheme 40). The oxime oxlate amide was isolated as a colourless oil in good yield and ^{1}H NMR showed that it existed as a mixture of isomers.



4.117 **4.118**, 90 %

Scheme 40

It was expected that the oxime oxalate amide **4.118** would follow a similar photochemical pathway to earlier oxime oxalate amides and cleave at the oxime bond with loss of CO_2 to give both the iminyl and the carbamoyl radical. The carbamoyl radical would then undergo a 4-*exo* cyclisation onto the oxime ether to give the penicillin (Scheme 41).



4.118 **4.119**

4.121 **4.120**

Scheme 41

The photochemistry of the oxime oxalate amide **4.118** was first investigated using ESR spectroscopy. A sample was prepared in the usual manner and photolysed with light from a 400 W UV lamp. ESR spectra were recorded over a range of temperatures. Figure 6 shows the ESR spectrum obtained at 220 K for oxime oxalate amide **4.118**.

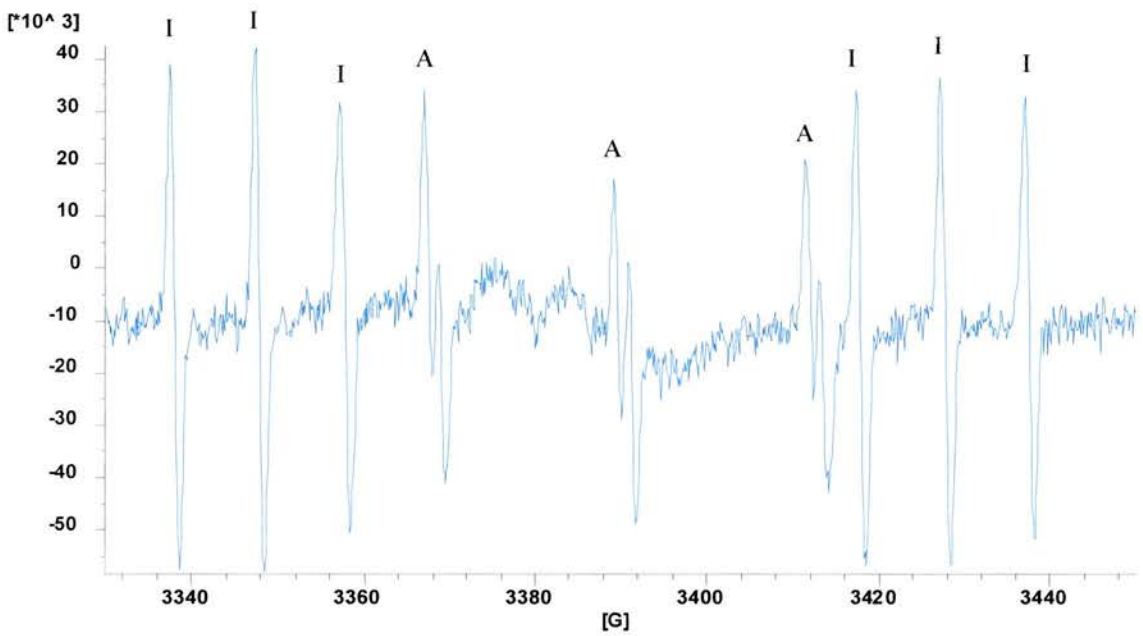


Fig 6. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **4.118** and MAP in *tert*-butylbenzene at 220 K.

The ESR spectrum obtained for the oxime oxalate amide **4.118** was very similar to that obtained for the oxime oxalate amides **4.93** and **4.102**. Once again the environment of the carbamoyl radical is almost identical in each case. The ESR parameters for the radicals derived from **4.118** at 220 K were: iminyl (I) g = 2.0034, a(N) = 9.8, a(H) = 79.7 G; carbamoyl (A) g = 2.0014, a(N) = 22.2 G. a(H) = 1.0 G. The ESR parameters were quite closely matched to those determined for similar carbamoyl radicals and suggested that the radical observed was indeed the carbamoyl radical **4.119**. Despite the presence of the oxime ether, there were no peaks corresponding to the cyclised species **4.120**.

The ESR spectrum of the oxime oxalate amide **4.118** did not show any peaks corresponding to the cyclised species. The oxime oxalate amide was stored at -20°C under nitrogen while attempts were made to determine a suitable hydrogen donor for

the cyclised aminyl radical. Studies were carried out on the analogous oxime ether containing compound discussed in Chapter 3. As was stated in Chapter 3 no suitable hydrogen donor for the aminyl radical was found. It was decided to attempt a prep scale photolysis of **4.118** in toluene in order to determine the photolysis products but a ^{1}H NMR of the oxime oxalate amide showed that a number of byproducts had formed on standing. It was attempted to purify **4.118** by flash and column chromatography but it could not be separated from the impurities. An attempt to make more of the oxime oxalate amide failed when it was found that the starting thiazolidine could not be reprepared.

4.3.0 Conclusions

The oxime oxalate amide methodology, although extremely effective for the preparation of simple β-lactams does not appear to be a suitable precursor for the preparation of penicillins

ESR spectroscopy demonstrated that the photolysis occurs according to the predicted pathway and that iminyl and carbamoyl radicals are produced but the thiazolidenyl carbamoyl radical does not appear to cyclise at the temperatures at which ESR studies were conducted.

Preparative scale experiments determined that a simple penicillin may have been prepared but the only evidence for the proposed product is mass spec data. The compound could not be isolated by conventional techniques.

Thiazolidines with suitably unsaturated sidechains were prepared in moderate to good yields and conversion to the corresponding oxime oxalate amide occurred readily for most thiazolidines.

The use of carbamoyl radicals in the preparation of penicillins requires further investigation and may provide the first free radical route to penicillins.

4.4.0 Experimental

D,L-Penicillamine methyl ester hydrochloride[39] 4.86

To a stirred solution of D,L-penicillamine (1.51 g ; 10.1 mmol) in MeOH (30 cm^3) was added an excess of freshly distilled thionyl chloride (3.0 cm^3). The reaction vessel was sealed and stirred at rt for 4-5 days. After this time the volume was reduced under vacuum to ca 15 cm^3. The volume was then made up to 100 cm^3 with diethyl ether giving the methyl ester as a white solid. Cooling of the solution resulted in formation of a heavy white ppt. which was filtered to give the pure methyl ester hydrochloride **4.86** (1.32 g; 70 %) m.p. 186-188 °C (lit[39] 185-187 °C); (^{1}H NMR, 300 MHz, D_2O) δ_H 1.24 (3H, s, CH_3), 1.50 (3H, s, Me), 1.91 (3H, s, OMe), 4.12 (1H, s, CH).

5,5–Dimethyl-2-(2-methyl-propenyl)-thiazolidine-4-carboxylic acid methyl ester 4.89

To a stirred solution of the methyl ester of penicillamine hydrochloride (4.5 g; 22.5 mmol) in MeOH (40 cm^3) at 0 °C was added a solution of triethylamine (2.3 g; 22.5 mmol) in MeOH (10 cm^3) and a solution of 3-methyl-but-2-enal (1.9 g; 22.5 mmol) in MeOH (10 cm^3). The mixture was allowed to reach rt and then stirred at rt for 24 h. The solvent was removed and the crude product was purified via column chromatography (hexane; EtOAc) (8:1). The product was recrystallised from hexane at –20 °C to give the pure product as colourless needles, mp = 52-54 °C (1.3 g; 25 %); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 1.24 (3H, s, CH_3), 1.65 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.74 (3H, s, CH_3), 2.91 (1H, br, NH), 3.63 (1H, s, 2-H), 3.77 (1H, s, OCH_3), 5.24 (1H, m, =CH), 5.39 (1H, m, =CH); δ_C ($CDCl_3$) 18.9 (CH_3), 26.0 (CH_3), 28.9 (CH_3), 29.5 (CH_3), 52.5 (OCH_3), 60.0, 65.0, 74.8 (C2, C4 and C5), 123.7 (=CH), 137.9 (=CH_3CH_3), 170.2 (C=O); m/z (relative intensity) 229 (52, M^+), 214 (11), 196 (15), 170 (20), 155 (86), 95 (100); (M^+ 229.1137, $C_{11}H_{19}NO_2S$ requires M^+ 229.1129).X-ray diffraction showed this to be the 4S stereoisomer.

2-Formyl-5,5-dimethylthiazolidine-4-carboxylic acid methyl ester 4.91

Method A: To a stirred solution of the methyl ester of penicillamine hydrochloride (2 g; 10 mmol) in MeOH (20 cm^3) at 0 °C was added a solution of triethylamine (1.0 g; 10 mol) in MeOH (5 cm^3) and 1.5 g of glyoxal (40 % in H_2O). The mixture was stirred at room temperature for 24 h and the formation of a dark brown colour was observed. The solution was filtered and evaporated to dryness. The mixture was separated by column chromatography but the target compound **4.91** was not observed.

Method B: To a stirred solution of the methyl ester of penicillamine hydrochloride (2 g; 10 mmol) in MeOH (20 cm^3) at 0 °C was added a solution of triethylamine (1.0 g; 10 mol) in MeOH (5 cm^3) and the protected glyoxal **4.92** (1.17 g; 10 mmol). The mixture was stirred at room temperature for 24 h and after this time the mixture was filtered and the solvent removed. The yellow oil which resulted was separated by column chromatography and the thiazolidine was isolated as a mixture of isomers in 81 % yield. The thiazolidine was dissolved in MeOH and treated with solutions of 0.1 M, 1.0 M, 5.0 M and 6.0 M HCl. Each solution was heated up to reflux for up to 3 h but the expected thiazolidine **4.91** was never observed.

Benzaldehyde *O*-(5,5–dimethyl-2-(2-methyl-propenyl)thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime 4.94.

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime (700 mg; 3.2 mmol) in DCM (10 cm^3) was added dropwise a solution of pyridine (0.3 g; 3.2 mmol) in DCM (5 cm^3) followed by 5,5–dimethyl-2-(2-methyl-propenyl)-thiazolidine-4-carboxylic acid methyl ester **4.89** (0.8 g; 3.2 mmol) in DCM (5 cm^3). The solution was allowed to reach rt and then stirred at rt for 3 h. After this time a small amount of pentane (ca. 10 cm^3) was added in order to promote formation of the pyridine hydrochloride salt. The ppt. was filtered off and the filtrate collected. The filtrate was evaporated to dryness and the resulting oil was filtered through a pad of silica with DCM. The product was again evaporated to dryness and recrystallised from DCM/hexane at –20 °C to give the title compound as colourless platelets, (1.2 g; 92 %);

mp = 110-112 °C; (Found C, 58.9; H, 6.4; N, 6.0 %; $C_{20}H_{24}N_2O_5S$ requires C, 59.4; H 6.0; N, 6.9 %); ν_{max}(NaCl)/cm^{-1} 1758 (C=O), 1739 (C=O), 1658 (C=N); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 1.44 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.69 (3H, s, CH_3), 3.80 (1H, s), 3.83 (3H, s, OCH_3), 5.60 (1H, m, =CH), 6.08 (1H, m, =CH), 7.42-7.50 (3H, m, Ar), 7.71-7.75 (2H, m, Ar), 8.43 (1H, s, N=CH); δ_C ($CDCl_3$) 18.2 (CH_3), 23.9 (CH_3), 25.7 (CH_3), 32.1 (CH_3), 51.6, 52.4, 60.1, 71.5 (C2, C4, C5 and OCH_3), 121.5 (=CH_3), 128.5, 128.7, 129.0, 132.1 (ArC), 140.1 (=CH_3CH_3), 157.3, 158.4 (C=O), 169.2 (C=N) m/z (relative intensity) CI 405 (100, MH^+), 302 (46), 104 (27) (MH^+ 405.1488, $C_{20}H_{25}N_2O_5S$ requires MH^+ 405.1491).

Benzaldehyde *O*-(5,5–dimethyl-2-(2-methyl-propenyl)-thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime 4.94.

Crystal data for **4.93** $C_{14}H_{17}NO_2$, M = 405.15, colourless platelets, crystal dimensions 1.0 x 1.0 x 2.0 mm, monoclinic, space group $P2_1/c$, a = 8.907 (13), b = 18.141 (3), c = 12.996 (19) Å, β = 94.95 (3)°, V = 2092.1(5) Å^3, D_c =1.284 Mg/m^3, T = 125 (2) K, R = 0.034, R_w 0.083 for 8782 reflections with I>2σ(I) and 137 variables. Data were collected on a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (α = 0.71073 Å). The structure was solved by direct methods and refined using full-matrix least squares methods. Atomic coordinates and bond lengths and coordinates are listed in Appendix (3) and the structure is shown in the discussion.

Prep scale photolysis of benzaldehyde *O*-(5,5–Dimethyl-2--(2-methyl-propenyl)thiazolidine-4-carboxylic acid methyl ester oxalyl) oxime 4.94.

To a solution of **4.93** (400 mg; 2 mmol) in toluene (400 cm^3) was added 3 M eq of MAP (890 mg; 6 mmol). The mixture was photolysed by light from a 400 W medium pressure UV lamp at 100 °C for 8 h. After this time the mixture was allowed to cool and the solvent was removed. The resulting yellow oil was submitted for analysis by GC/MS. GC/MS. Peak no. 142, PhCHNH (9 %) *m/z* (%) 103 (M^+ 100), 76 (26) 50 (15), Peak no. 174, (9 %) $PhCH_2OH$ 108 (M^+ 87), 107 (66), 79 (100), 77 (56), Peak no. 217, $OMeC_6H_4CHCH_2$ (8 %) 134 (M^+ 100), 119 (32), 91 (28), Peak no. 332, MAP (56 %) 150 (M^+ 32), 135 (100), 107 (9), 92 (14), 77 (23), Peak no. 373, $PhCH_2CH_2Ph$ (52

%) 182 (M^+ 26), 91 (100), 65 (12), Peak no. 435, $PhCHOHCH_2Ph$ (25 %) 198 (M^+ 3) 107 (82), 92 (100), 79 (60), 77(35), Peak no. 459, **4.98** (18 %), 257 (M^+ 78), 242 (16), 228 (94), 225 (86), 214 (100), 198 (31), 187 (46), 170 (54), 155 (24), 142 (46), 115 (80), 114 (46), 95 (97), 84 (43), 67 (39), (several additional unidentified compounds derived from MAP were also present).

D,L-Penicillamine benzyl ester hydrochloride[28] 4.99

A solution of D,L-penicillamnine (3.0 g; 20 mmol), 7.5 g of polyphosphoric acid and 37.5 cm^3 of benzyl alcohol was heated in an oil bath for 3-9 h at 110 °C. After this time the reaction mixture was allowed to cool and added to 300 cm^3 of 0.6 M HCl. The solution was extracted with ether (2 x 50 cm^3) and the ether was then reextracted with 1 M HCl (2 x 50 cm^3). The combined aqueous layers were brought to pH 9.6 with Na_2CO_3 and extracted with ether (5 x 50 cm^3).The ether was then dried ($MgSO_4$) and evaporated to give the crude benzyl ester. The ester was then redissolved in Ether (50 cm^3) and saturated with HCl at 0 °C. The white ppt. which resulted was collected, washed with ether and dried to give the ester **4.99** in 2-4 % yield (lit[28] = 43 %); (^1H NMR, 300 MHz, D_2O) δ_H 1.26 (3H, s, CH_3), 1.51 (3H, s, CH_3), 4.30 (1H, s, CH), 5.32 (2H, s, OCH_2), 7.2-7.4 (5H, m, ArH).

L-Cysteine benzyl ester[41] 4.100

L-Cysteine (2 g; 17 mmol) was added to a homogenous solution of benzyl alcohol (25 cm^3) and 5 g of polyphospheric acid. The mixture was stirred for 4 h at 105 °C. After this time the mixture was allowed to cool and then poured onto a solution of 0.6 M HCl (150 cm^3). The solution was extracted with ether (4 x 25 cm^3) and the ether rextracted with 1 M HCl. The combined aqueous layers were brought to pH 9.6 with Na_2CO_3 and extracted with ether (5 x 25 cm^3). The ether was dried ($MgSO_4$) and concentrated to give the benzyl ester as a colourless oil (1.61 g; 45 %); (^1H NMR, 300 MHz, $CDCl_3$) δ_H 2.85 (2H, ddd, J 4, 5, 13, CH_2), 3.68 (CH, dd J 4, 5, CH), 5.17 (2H, AB, CH_2-Ar), 7.34-7.40 (5H, m, ArH).

2-Isopropyl thiazolidine-4-carboxylic acid benzyl ester 4.101

To a stirred solution of the benzyl ester of cysteine (2.0 g; 10 mmol) in pentane (50 cm^3) was added triethylamine (2.0 g; 20 mmol) and isobutyraldehyde (1.44 g; 20 mmol). The mixture was refluxed under Dean-Stark conditions for 24 h. After this time the pentane was removed and the thiazolidine was isolated as a colourless oil via column chromatography (hexane:EtOAc) (8:2),(2.43 g, 92 %). The amine was further purified by recystallisation from hexane and the thiazolidine was isolated as colourless platelets (m.p. = 18 – 20 °C). The thiazolidine was isolated as a mixture of isomers in a ratio of 2:1. Major isomer: (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 1.06 (3H, d, J 7, $CHC\underline{H}_3$), 1.11 (3H, d, J 7, $CHC\underline{H}_3$), 1.99 (1H, m, $\underline{C}H(CH_3)_2$), 2.24 (1H, br, NH), 2.76 (1H, t, J 10, 5-HCH), 3.30 (1H, dd, J 7, 10, 5-HCH), 3.87 (1H, dd, J 7and 10, 4-CH), 4.36 (1H, d, J 7, 2-CH), 5.21 (2H, AB, CH_2-Ph), 7.36 (5H, s, ArH); ^{13}C δc 20.9, 21.1 (CH_3), 34.0 (=CH), 38.0 (C-5), 65.9 (C-4), 67.6 (CH_2-Ph),78.5 (C-2), 128.7, 128.8, 129.0, 129.1 (ArC), 171.7 (C=O); Minor isomer: (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 0.98 (3H, d, J 7, $CHC\underline{H}_3$), 1.04 (3H, d, J 7, $CHC\underline{H}_3$), 1.79 (1H, m, $\underline{C}H(CH_3)_2$), 2.24 (1H, br, NH), 3.02 (1H, dd, J 7 and 10, 5-HCH), 3.20 (1H, dd, J 7 and 10, 5-HCH), 4.13 (1H, t, J 7, 4-CH), 4.44 (1H, d, J 7, 2-CH), 5.21 (2H, AB, CH_2-Ph), 7.36 (5H, s, ArH); δc ($CDCl_3$) 20.2, 20.8 (CH_3), 35.5 (=CH), 37.7 (C-5), 64.8 (C-4), 67.5 (CH_2-Ph),77.0 (C-2), 128.7, 128.8, 129.0, 129.1 (ArC), 171.7 (C=O); m/z (relative intensity)(ElectroSpray) 288 (100, M^++Na), (M^+ 266.1219, $C_{14}H_{20}NO_2S$ requires M^+ 266.1215).

Benzaldehyde *O*-(2-isopropyl thiazolidine-4-carboxylic acid benzyl ester oxalyl) oxime 4.102.

To a stirred solution of the oxime oxalyl chloride (633 mg; 3 mmol) at 0 °C in DCM (10 cm^3) was added pyridine (237 mg; 3 mmol) in DCM (5 cm^3) and the 2-isopropyl thiazolidine-4-carboxylic acid benzyl ester **4.101** (800 mg; 3 mmol) in DCM (5 cm^3). The mixture was allowed to stir at 0 °C for 10 min and then at rt for 3 h. After this time a small quantity of pentane was added in order to promote formation of the pyridine hydrochloride salt. The mixture was filtered and the solvent removed under vacuum. The oxime oxalate amide was purified by flash column chromatography to

give the product as a colourless oil (1.18 g; 90 %); The compound was isolated as a mixture of isomers in a ratio of 2:1, ν_{max}(NaCl)/cm^{-1} 1747 (C=O), 1659 (C=N); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 0.97-1.04 (6H, m, 2 x CH_3), 1.97 (1/3H m, $\underline{CH}(CH_3)_2$), 2.15 (2/3H, m, $\underline{CH}(CH_3)_2$), 3.23-3.42 (2H, m, 5-HCH), 5.07-5.37 (2H, m, 4-CH and 2-CH), 5.30 (2H, s, OCH_2), 7.26-7.53 (8H, m, ArH), 7.69-7.77 (2H, m, ArH), 8.40 (1H, s, HC=N); δc ($CDCl_3$) 19.3, 19.5, 20.4, 20.5 (CH_3), 31.9, 33.4 (CH_2), 63.5, 64.5 (CH), 68.5, 68.8 (OCH_2), 71.9, 72.0 (CH), 128.9, 129.1, 129.1, 129.4, 132.7, 132.8 (ArC), 158.7, 165.6, 169.0 (C=O, C=N), m/z (relative intensity) CI 441 (100, MH^+); (MH^+ 441.1489, $C_{23}H_{25}N_2O_5S$ requires MH^+ 441.1485).

2-(2-Methyl-propenyl)-4-phenyl-oxazolidine[42] 4.106

To a stirred solution of (s)-β-amino-phenylethyl alcohol (1.37 g; 10 mmol) in DCM (15 cm^3) at 0 °C and in the presence of 4 Å molecular sieves was added a solution of 3-methyl-but-2-enal (840 mg; 10 mmol) in DCM (5 cm^3). The mixture was stirred at rt for 3 h after which time the solution was filtered and concentrated to give the crude product as a yellow solid. The yellow solid was recrystallised from EtOAc/Hexane to give the oxazolidine **4.106** as colourless needles (1.85 g; 91 %), mp = 70 -72 °C; (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 1.88 (3H, s, CH_3), 1.90 (1H, s, CH_3), 3.29 (1H, br, NH), 3.83 (1H, dd, J 11 and 4, CH), 3.96 (1H, dd, J 9 and 4, CH), 6.08 (1H, d, J 9, CH), 7.21-7.37 (5H, m, ArH), 8.28 (1H, d, J 9, CH); δc ($CDCl_3$) 19.1 (CH_3), 27.1 (CH_3), 68.0 (CH_2), 77.3 (CH-Ar), 125.4, 127.6, 127.7, 129.0 (ArC), 149.0 (=C), 161.9 (=CH).

Benzaldehyde *O*-[2-(2-methyl-propenyl)-4-phenyl-oxazolidine oxalyl] oxime 4.107.

To a stirred solution of benzaldehyde *O*-(chlorooxalyl)oxime (1.41 g; 6.7 mmol) in DCM (20 cm^3) at 0 °C was added a solution of pyridine (530 mg; 6.7 mmol) in DCM (5 cm^3), followed by a solution of **4.106** (1.36 g; 6.7 mmol) in DCM (20 cm^3). The mixture was stirred at 0 °C for 10 min and then at rt for 3 h. After this time a small quantity of pentane was added but no ppt was observed. The crude reaction mixture was concentrated and NMR spectroscopy revealed that the oxazolidine remained unreacted.

Glyoxal-mono-*O*-benzyloxime[43] 4.111.

O-Benzylhydroxylamine hydrochloride (800 mg; 5 mmol) was dissolved in H_2O (50 cm^3) neutralised with NaOH (3 M eq). To this was added glyoxal (7.5 g of 40 % in H_2O). The mixture was left at rt for 16 h after which time it was extracted with DCM (4 x 25 cm^3).The organic layers were collected and dried ($MgSO_4$) and the solvent removed to give the crude oxime as a yellow oil. The oxime was purified via Kugelrohr distillation (60-62 °C at 0.2 torr) and isolated as a colourless oil (515 mg; 63 %) lit[43] = 63 %; (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 5.33 (2H, s, CH_2), 7.34-7.80 (5H, m, ArH), 7.56 (1H, d, J 8, CH=N), 9.59, (1H, d, J 8, CH=O).

2-(Benzyloxyimino-methyl)thiazolidine-4-carboxylic acid benzyl ester 4.113

To a solution of the benzyl ester of cysteine **4.99** (2.11 g; 10 mmol) in ethanol (50 cm^3) at 0 °C, was added glyoxal-mono-*O*-benzyloxime **4.111** (1.63 g; 10 mmol). The mixture was stirred at rt for 24 h. After this time the solvent was removed and the crude thiazolidine was isolated as a colourless oil via column chromatography (EtOAc/hexane). The thiazolidine was further purified *via* recrystallisation from a mixture of EtOAc/ hexane to give the pure thiazolidine **4.113** as colourless needles (3.06 g; 86 %) mp =78-80 °C. The thiazolidine was isolated as a mixture of isomers in a ratio of 1:1. (Found C, 64.1; H, 5.45; N, 7.79 %; $C_{19}H_{20}N_2O_2$ requires C, 64.0; H, 5.66; N, 7.86 %); ν_{max}(NaCl)/cm^{-1} 1741 (C=O); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 2.94 (1/2 H, dd, J 7 and 10, 5-HCH), 3.02 (1/2 H, dd, J 7 and 9, 5-HCH), 3.29 (1/2 H, dd, J 7 and 10 5-HCH), 3.37 (1/2H, dd, J 7 and 10, 5-HCH), 3.95 (1/2H, dd, J 7 and 9, 4-CH), 4.11 (1/2H, t, J 6, 4-CH), 5.05 and 5.09 (2H, s, OCH_2), 5.12 (1/2H, d, J 6, HC=N), 5.20 and 5.22 (2H, s, OCH_2), 5.30 (1/2H, d, J 6, HC=N), 7.30-7.37 (10H, m, ArH), 7.33 (1/2H, NCHS, under aromatic), 7.48 (1/2H, d, J 6, NCHS); δc ($CDCl_3$) 37.9, 38.8 (C-5), 64.9, 65.7, 66.1, 66.5 (C-4 and C-2), 76.6, 76.9 (OCH_2),128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.1, 135.5 (ArC), 147.4, 149.1, 149.4, 152.3 (C=O, C=N).

2-(Benzyloxyimino-methyl)thiazolidine-4-carboxylic acid methyl ester 4.115

To a stirred solution of the methyl ester hydrochloride of cysteine (3.42 g; 20 mmol) in EtOH (25 cm^3) at – 10 °C was added a solution of triethylamine (2.02 g; 20 mmol) in EtOH (5 cm^3). The mixture was allowed to stir at – 10 °C for 10 min (until the ppt of triethylamine hydrochloride started to appear). To this was added a solution glyoxal-mono-*O*-benzyloxime **4.111** (3.26 g; 20 mmol) in EtOH (5 cm^3). The mixture was allowed to stir between -10 °C and 5 ^{0}C for 1 hr and then at rt for 24 h. After this time the reaction mixture was filtered and the solvent removed. The crude thiazolidine was purified via column chromatography (EtOAc/hexane) to give the pure thiazolidine **4.115** as a colourless oil (4.98 g; 89 %); The thiazolidine was isolated a a mixture of isomers in a ratio of 1:1; (Found C, 55.7; H, 5.76; N, 9.99 %; $C_{14}H_{17}N_2O_2$ requires C, 56.5; H 5.61; N, 10.51 %); ν_{max}(NaCl)/cm^{-1} 1753 (C=O), 1635 (C=N); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 2.95 (1/2 H, dd, J 7 and 10, 5-HCH), 3.03 (1/2 H, dd, J 6 and 10, 5-HCH), 3.24 (1/2 H, dd, J 7 and 10 5-HCH), 3.28 (1H, dd, J 6 and 10, 5-HCH), 3.78 and 3.80 (3H, s, OCH_3), 3.92 (1/2H, dd, J 6 and 9, 4-CH), 4.10 (1/2H, t, J 7, 4-CH), 5.06 and 5.10 (2H, s, OCH_2), 5.13 (1/2H, d, J 6, HC=N), 5.31 (1/2H, d, J 7, HC=N), 7.30-7.40 (5H, m, ArH), 7.38 (1/H, NCHS, under aromatic), 7.49 (1/2H, d, J 6, NCHS); δc ($CDCl_3$) 37.8, 38.7 (C-5), 53.1 (OCH_3), 64.8, 65.2, 66.0, 66.4 (C-4 and C-2), 76.6, 76.9 (OCH_2), 128.5, 128.7, 128.8, 128.9 (ArC), 147.4, 149.1, 149.2, 152.3 (C=O, C=N); m/z (relative intensity) CI 281 (45, MH^+), 108 (46), 91 (100); (MH^+ 281.0960, $C_{13}H_{17}N_2O_3S$ requires MH^+ 281.0961).

2-(Benzyloxy-imino-methyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid methyl ester 4.117

To a stirred solution of the methyl ester hydrochloride of L-penicillamine (3.03 g; 18.6 mmol) in EtOH (70 cm^3) at – 10 °C was added s solution of triethylamine (1.90 g) in EtOH (5 cm^3).). The mixture was allowed to stir at – 10 °C for 10 min (until the ppt of triethylamine hydrochloride started to appear). To this was added a solution glyoxal-mono-*O*-benzyloxime **4.111** (3.03 g; 18.6 mmol) in EtOH (5 cm^3). The mixture was allowed to stir between -10 °C and 5 ^{0}C for 1 hr and then at rt for 24 h. After this time the solvent was removed and the crude thiazolidine was purified via column

chromatography (EtOAc/hexane). The pure thiazolidine was isolated as a colourless oil (1.43 g; 25 %); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 1.21 (3H, s, CH_3), 1.63 (3H, s, CH_3), 3.72 (1H, s, NCH), 3.79 (3H, s, OMe), 5.10 (2H, s, OCH_2), 5.21 (1H, d, J 6, HC=N), 7.33-7.37 (5H, m, ArH), 7.46 (1H, d, J 6, NCHS); no further characterisation was carried out since compound was unstable.

Benzaldehyde *O*-[2-(Benzyloxy-imino-methyl)-5,5-dimethyl-thiazolidine-4-carboxylic acid methyl ester oxalyl] oxime 4.118.

To a stirred solution of benzaldehyde *O*-chlorooxalyl oxime (1.0 g; 5 mmol) in DCM (20 cm^3) at 0 °C was added a solution of triethylamine (400 mg, 5 mmol) in DCM (5 cm^3) followed by a solution of the thiazolidine **4.117** (1.43 g; 5 mmol) in DCM (5 cm^3). The mixture was allowed to stir at 0 °C for 10 min and then at rt for 3 h. After this time a small quantity of pentane was added in order to promote formation of the pyridine hydrochloride salt. The mixture was filtered and the solvent removed under vacuum. The oxime oxalate amide was purified by flash column chromatography to give the product as a colourless oil (1.97 g; 92 %); (^{1}H NMR, 300 MHz, $CDCl_3$) δ_H 1.47 (3H, s, CH_3), 1.58 (3H, s, CH_3), 3.78 (3/2H, s, OCH_3), 3.81 (3/2H, s, OCH_3), 4.73 (1/2H, s, 4-CH), 4.82 (1/2H, s, 4-CH), 4.97 (1H, s, OCH_2), 5.13 (1H, s, OCH_2), 5.95 (1/2H, d, J 7, HC=N), 6.00 (1/2H, d, J 7, HC=N), 7.17-7.73 (10H, m, ArH), 8.26 (1H, s, HC=NO) additional peaks were observed on standing at -20 °C.

4.5.0 References

(1) H. Staudinger, *Liebigs Ann. Chem.*, 1907, **51**, 365.

(2) H. T. Clarke, J. R. Johnson and R. Robertson *The Chemistry of Penicillin*; Princton University Press, 1949.

(3) R. B. Morin and M. Gorman *The Chemistry and Biology of B-lactam Antibiotics*; Acad. Press: New York, 1982.

(4) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.

(5) D. A. Evans and E. B. Sojgren, *Tetrahedron Lett.*, 1985, **26**, 3783, 3787.

(6) D. A. Evans and J. M. Williams, *Tetrahedron Lett.*, 1988, **29**, 5065-5068.

(7) M. A. McGuire and L. S. Hegedus, *J. Am. Chem. Soc.*, 1982, **104**, 5538.

(8) L. S. Hegedus, G. D. Weck and S. D'Andrea, *J. Am. Chem. Soc.*, 1988, **110**, 2122.

(9) H. Gilman and M. J. Speeter, *J. Am. Chem. Soc.*, 1943, **65**, 2255.

(10) D. J. Hart and D.-C. Ha, *Chem. Rev.*, 1989, **89**, 1447.

(11) J.-L. Luche and H. B. Kagen, *Bull. Soc. Chim. Fr.*, 1969, 3500.

(12) F. H. v. d. Steen, J. T. B. H. Jastrzebski and G. v. Koten, *Tetrahedron Lett.*, 1988, **29**, 2467.

(13) K. Ikeda, Y. Yoshinaga, K. Achiwa and M. Sekiya, *Chem. Lett.*, 1984, 369.

(14) I. Ugi, *Angew. Chem. Int. Ed. Engl.*, 1982, **21**, 2802.

(15) I. Ugi and C. Steinbruckner, *Chem. Ber.*, 1961, 2802.

(16) R. M. Adlington, A. G. M. Barrett, P. Quate and A. Walker, *J. Chem. Soc., Chem. Commun.*, 1981, 404.

(17) R. Southgate and R. J. Ponsford, *J. Chem. Soc.,Chem. Commun.*, 1979, 846.

(18) M. P. Doyle, M. S. Shanklin, S.-M. Oon, H. Q. Pho, F. R. v. d. Heide and W. R. Veal, *J. Org. Chem.*, 1988, **53**, 3386.

(19) J. E. Baldwin, E. P. Abraham, G. L. Burge and H.-H. Ting, *J. Chem. Soc.,Chem. Commun.*, 1985, 1808-1809.

(20) J. E. Baldwin; Roberts, S. M., Ed. Cambridge, 1984.

(21) J. E. Baldwin and T. S. Wan, *Tetrahedron*, 1981, **37**, 1589-1595.

(22) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, 1962, **84**, 2983.

(23) J. Hoogmartens, P. J. Claes and H. Vanderhaeghe, *J. Med. Chem.*, 1974, **17**, 389.

(24) K. Heusler *Cephalosporins and Penicillins; Chemistry and Biology*; Acad. Press.: New York, 1972.

(25) A. K. Bose, G. Spiegelmann and M. D. Manhas, *J. Am. Chem. Soc.*, 1968, **90**, 4506.

(26) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 1969, 267.

(27) J. P. Clayton, J. H. C. Naylor, R. Southgate and E. R. Stove, *J. Chem. Soc.,Chem. Commun.*, 1969, 129.

(28) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe and B. G. Christensen, *J. Org. Chem.*, 1974, **39**, 437-440.

(29) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan and H. Vorbruggen, *J. Am. Chem. Soc.*, 1966, **88**, 852.

(30) L. D. Cama and G. G. Christensen, *J. Am. Chem. Soc.*, 1974, **96**, 7582.

(31) L. D. Cama and B. G. Christensen, *Tetrahedron*, 1978, 2233.

(32) S.-I. Nakatsuka, H. Tanino and Y. Kishi, *J. Am. Chem. Soc.*, 1975, **97**, 5010.

(33) J. E. Baldwin, A. Au, M. Christie, S. B. Haber and D. Hesson, *J. Am. Chem. Soc.*, 1975, **97**, 5957.

(34) J. E. Baldwin, M. Christie, S. B. Haber and L. I. Kruse, *J. Am. Chem. Soc.*, 1976, **98**, 3045.

(35) G. B. Gill, G. Pattenden and S. J. Reynolds, *Tetrahedron Lett.*, 1989, **33**, 3057.

(36) P. G. Sammes, S. Smith and G. T. Woolley, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2603-2610.

(37) I. McMillan and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1968.

(38) H. T. Nagasawa, D. J. W. Goon, W. P. Muldoon and R. T. Zera, *J. Med. Chem.*, 1984, **27**, 591-596.

(39) I. Buchanan, C. D. Garner and W. Clegg, *J. Chem. Soc., Dalton Trans.*, 1984, 1333-1342.

(40) F. H. Allen, O. Kennard, D. G. Watson, L. Brammer and A. G. Orpen, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.

(41) B. F. Erlanger and R. M. Hall, *J. Am. Chem. Soc.*, 1954, **4**, 5781-5782.

(42) A. Waldemar, K. Peters, E.-M. Peters and S. B. Schambony, *J. Am. Chem. Soc.*, 2001, **123**, 7228-7232.

(43) B. Zimmermann, H. Lerche and T. Severin, *Chem. Ber.*, 1986, **119**, 2848-2858.

Chapter 5

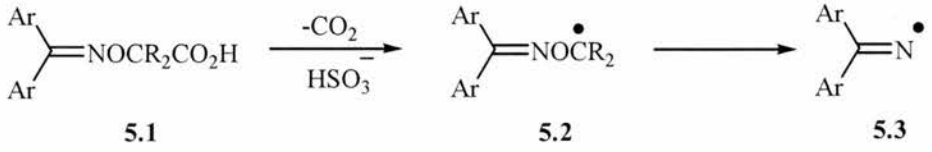
Dioxime Oxalates

5.1.0 Introduction

The synthetic potential of many nitrogen centred radicals including aminyl and amidinyl radicals has been investigated.[1-3] These species have been used in the formation of C-N bonds and in the preparation of heteroarenes. More recently iminyl radicals have emerged as useful synthetic radicals and in the last ten years their potential has been exploited for the preparation of a range of complex systems.[4]

5.1.1 Formation of Iminyl Radicals.

Early attempts to generate iminyl radicals relied on harsh conditions and this limited their synthetic application. Forrester and co-workers[5] demonstrated that iminyl radicals could be obtained from imino-oxyacetic acids **5.1** on boiling in the presence of persulfate (Scheme 1).

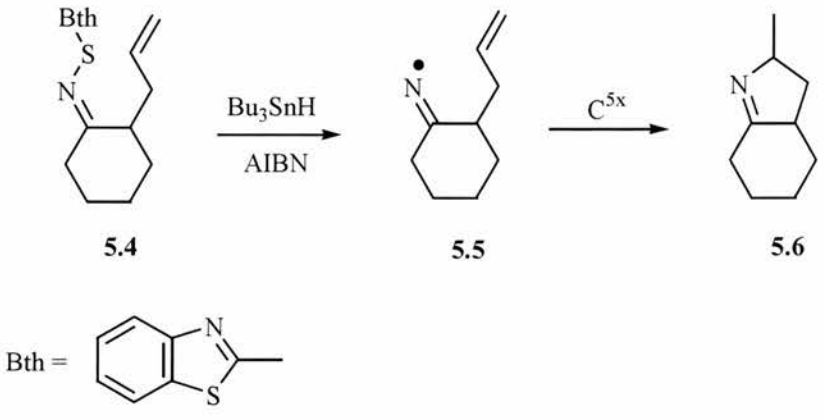


5.1 **5.2** **5.3**

Scheme 1

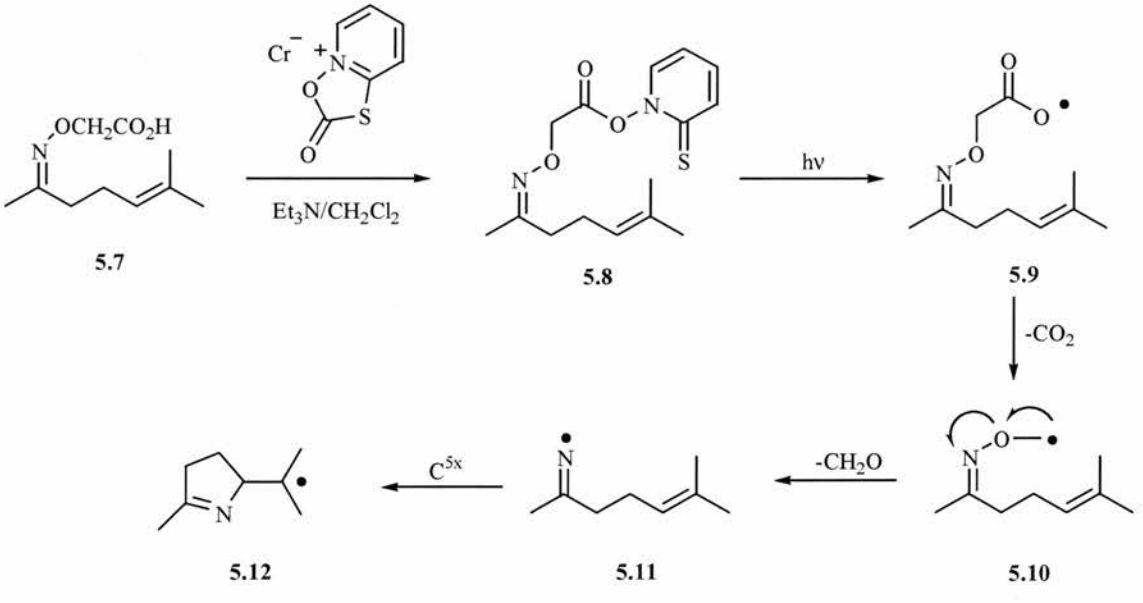
It was not until the early 1990's when Zard and co-workers conducted their intensive investigation into the chemistry of iminyl radicals that methods of generating iminyl radicals under mild conditions became available.

The original methodology employed by Zard and co-workers for producing iminyl radicals was tin-based. The precursor **5.4** was prepared via the condensation reaction of benzathiazolylsulfenamide with 2-allyl-cyclohexanone. On slow addition of tributylstannane in the presence of a small quantity of AIBN the precursor was found to give the iminyl radical **5.5** which cyclised to give the desired pyrrolenine derivative **5.6** in good yield (Scheme 2).



Scheme 2

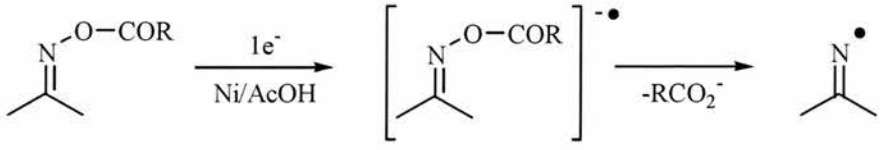
Due to the problems of tin chemistry, Zard and co-workers were anxious to develop a tin-free methodology for the generation of iminyl radicals. They examined the chemistry of Forrester[5] and attempted to replace the harsh oxidising conditions with much milder Barton chemistry. The Barton decarboxylation reaction provided a photochemical route to iminyl radicals[6] (Scheme 3).



Scheme 3

A second tin-free methodology employing nickel powder as a single electron reducing adgent[7] was developed by Zard and co-workers. The origin of the iminyl radical was based on the weak oxime N-O bond. It was postulated that a mild reducing

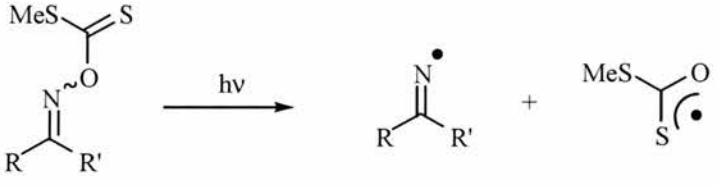
agent would break the N-O bond, resulting in formation of the iminyl radical (Scheme 4). It was necessary use a weak reducing agent such as nickel powder in order that the iminyl radical would have time to react before further reduction. For this reason strong reducing agents such as chromous acid were ruled out.



5.11 **5.12** **5.13**

Scheme 4

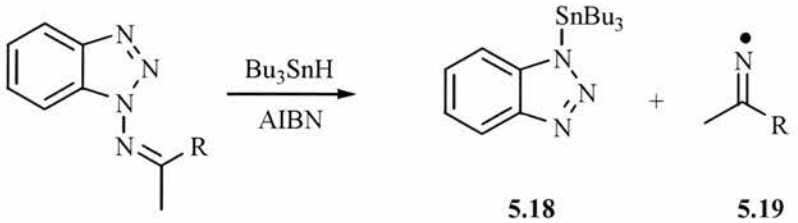
Zard has also employed ketooxime xanthates as precursors for iminyl radicals. The weak N-O oxime bond cleaves on photolysis to give the iminyl radical and the xanthate radical (Scheme 5).



5.14 **5.15** **5.16**

Scheme 5

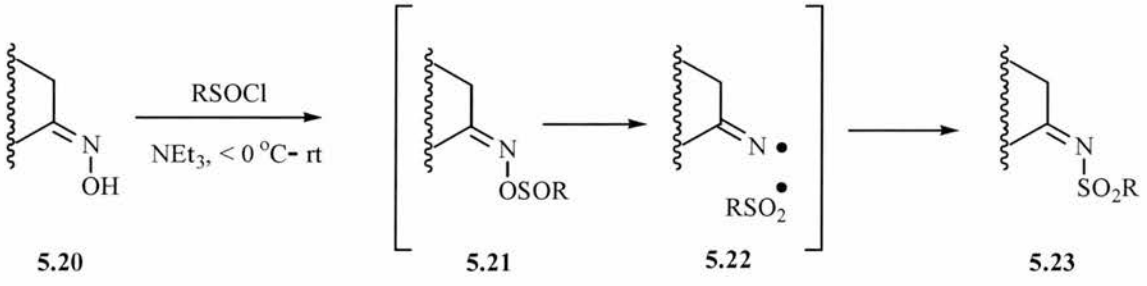
Other research groups have also investigated the generation of iminyl radicals using both tin-based and tin-free chemistry. Meyer and co-workers[8] investigated the generation of iminyl radicals from *N*-benzotriazolylimines on treatment with tributyltin hydride in the presence of AIBN. The chain process was unusual in that the propagation step involved attack on a heterocyclic nitrogen tether, by a stannyl radical (Scheme 6).



5.17 **5.18** **5.19**

Scheme 6

Weinreb and co-workers[9] have developed a new, mild, methodology for the generation of iminyl and amidyl radicals, based on the treatment of oximes with 2,4-dimethylbenzenesulfinyl chloride. Using a series of mechanistic experiments, it was determined that the process involves the initial formation of the sulfinite ester **5.21** which upon warming, undergoes a spontaneous homolysis to an iminyl/sulfinyl 'caged' radical pair **5.22**. Subsequent recombination of this pair was found to afford the product **5.23**.

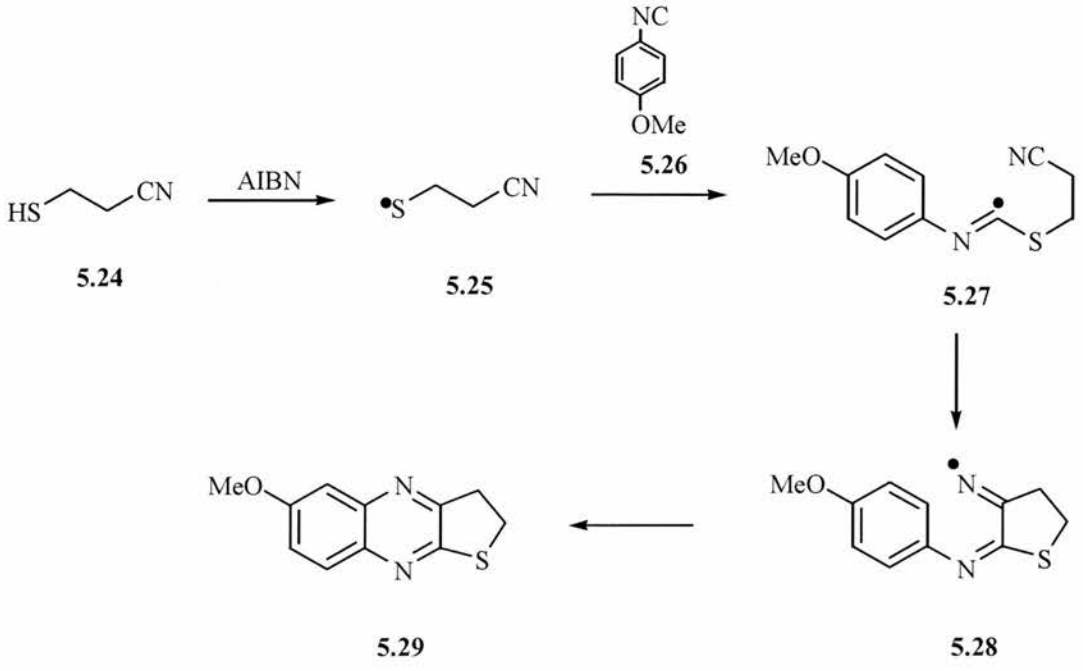


5.20 **5.21** **5.22** **5.23**

Scheme 7

An interesting methodology for the formation of iminyl radicals involves the cyclisation of a carbon-centered radical onto a nitrile. This process has been investigated by various research groups[10-13] and has proved to be an effective source of iminyl radicals.

Nanni and co-workers[14] have investigated the cyclisation of iminyl radicals generated by addition of imidoyl radicals **5.27** onto a nitrile moiety. This has led to the formation of a range of cyclopenta- and thienoquinoxalines (Scheme 8).



Scheme 8

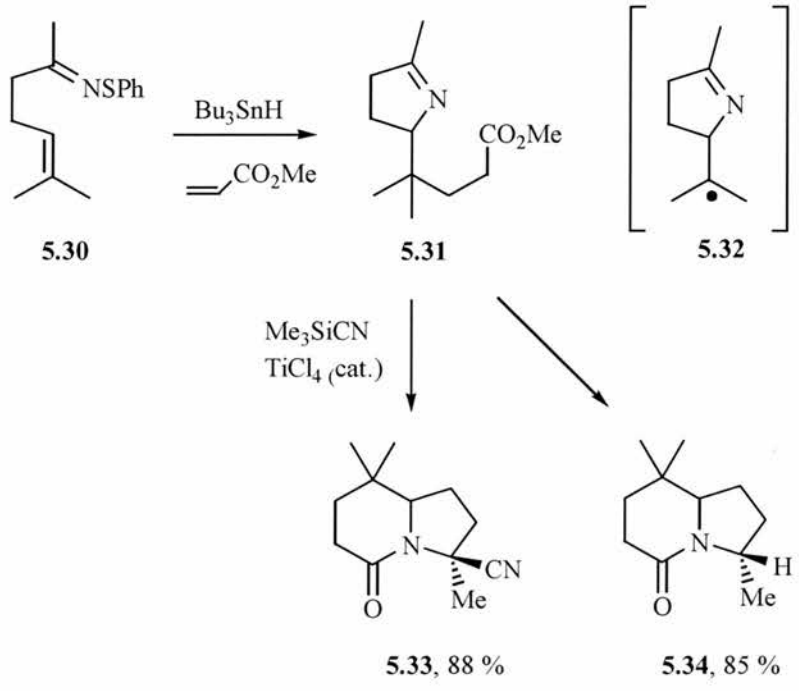
5.1.2 The Use of Iminyl Radicals in Organic Synthesis.

Iminyl radicals are synthetically useful. The addition reactions of iminyl radicals were investigated by Newcomb and co-workers[15] using laser flash photolysis. It was found that radicals cyclise at rates of 2.2×10^6 s^{-1} at 25 °C and addition reactions to thiophenol and *p*-chlorothiophenol took place at 25 °C with rate constants of 0.6 and 1.4×10^7 s^{-1} respectively. These rates are around one order of magnitude less than that of related carbon centered radicals, but this is compensated for by the fact that the rate of hydrogen reduction is also less than that of a related carbon radical. This makes the iminyl radical quite a versatile species for organic synthesis.

The synthetic potential of iminyl radicals has been investigated by Zard.[4] The most useful reactions of iminyl radicals are cyclisation (and addition) reactions to give pyrrolinines and ring-opening reactions of strained rings to give steroids and terpenes.

The cyclisation reactions of iminyl radicals have been applied to the preparation of the skeleton of indolizidine alkaloids **5.33**, **5.34** (Scheme 9). The iminyl radical,

formed on treatment of the sulfinimide with tributyltin hydride could undergo a 5-*exo* cyclisation followed by addition to the electrophilic alkene. Reduction with sodium cyanoborohydride or exposure to trimethylsilyl cyanide was followed by spontaneous cyclisation to give the lactams **5.33** and **5.34** as single isomers.

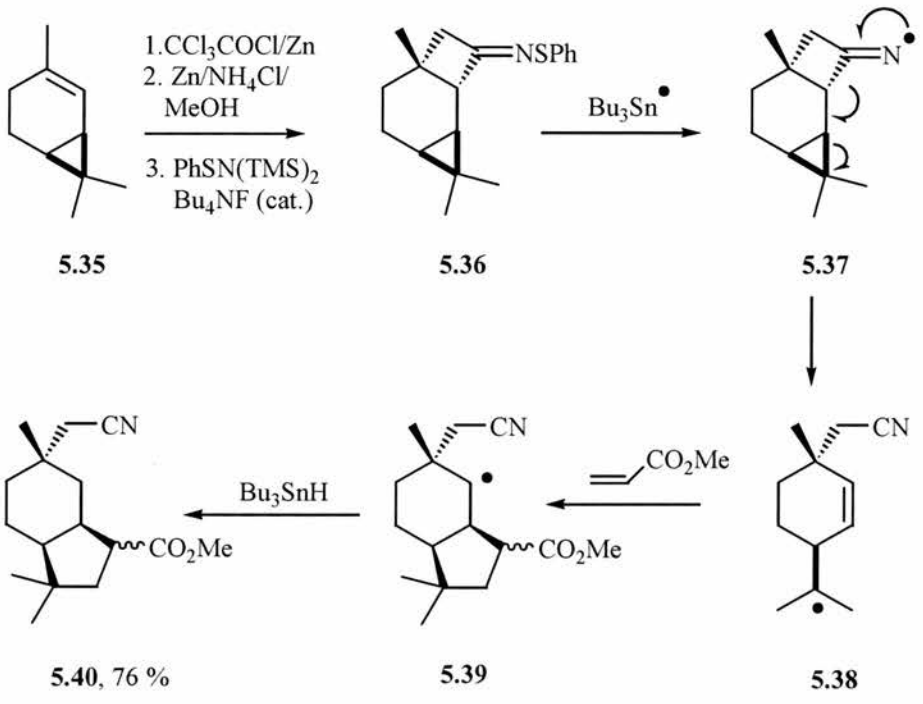


5.30 **5.31** **5.32**

5.33, 88 % **5.34**, 85 %

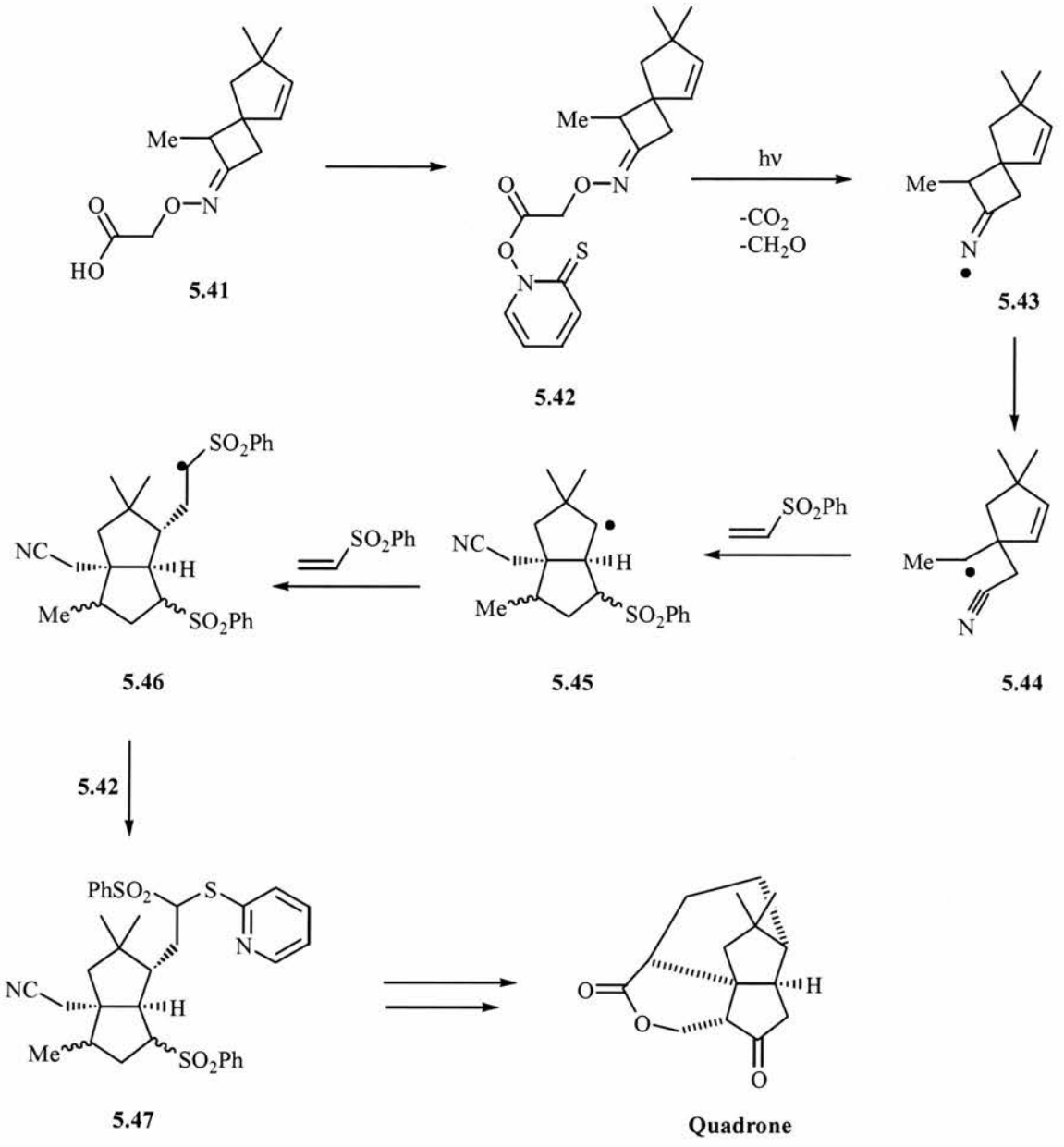
Scheme 9

The ring opening of strained rings such as cyclobutane and some cyclopropane rings by iminyl radicals has been investigated and used in the preparation of steroids.[16] In the absence of a radical trap the process leads to formation of a nitrile through scission of the intermediate cyclobutyliminyl radical to give the more stable iminyl radical. Scheme 10 shows an elegant route to bicyclic compound **5.40** involving a cascade of ring opening reactions followed by a ring closure reaction. The level of stereocontrol is high since the configuration of the carbon bearing the ester group can be corrected (via the enolate) in almost quantitative yield on treatment with base. The starting material was readily prepared from Δ-carene, and its configuration dictates that of the end product.



Scheme 10

The ring-opening tendency of iminyl radicals has also been applied to the preparation of terpenes and alkaloids. In the total synthesis of quadrone, Zard and co-workers demonstrated how the carbon skeleton of quadrone could be assembled in a one pot synthesis starting from the iminyl radical **5.43** derived from a Barton decarboxylation (Scheme 11).

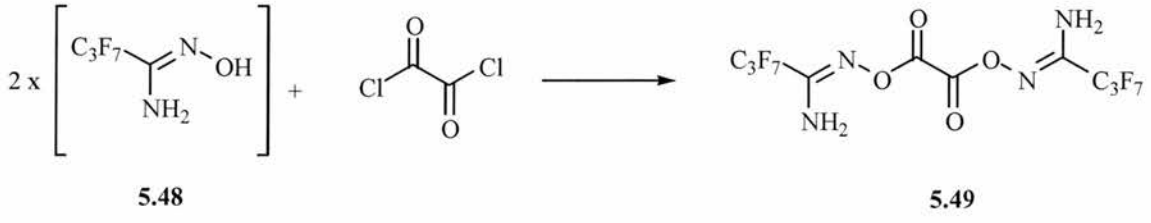


Scheme 11

It can be seen from these examples that iminyl radicals are synthetically useful species and therefore research into the development of new precursors and new applications is ongoing.

5.1.3 Dioxime oxalates

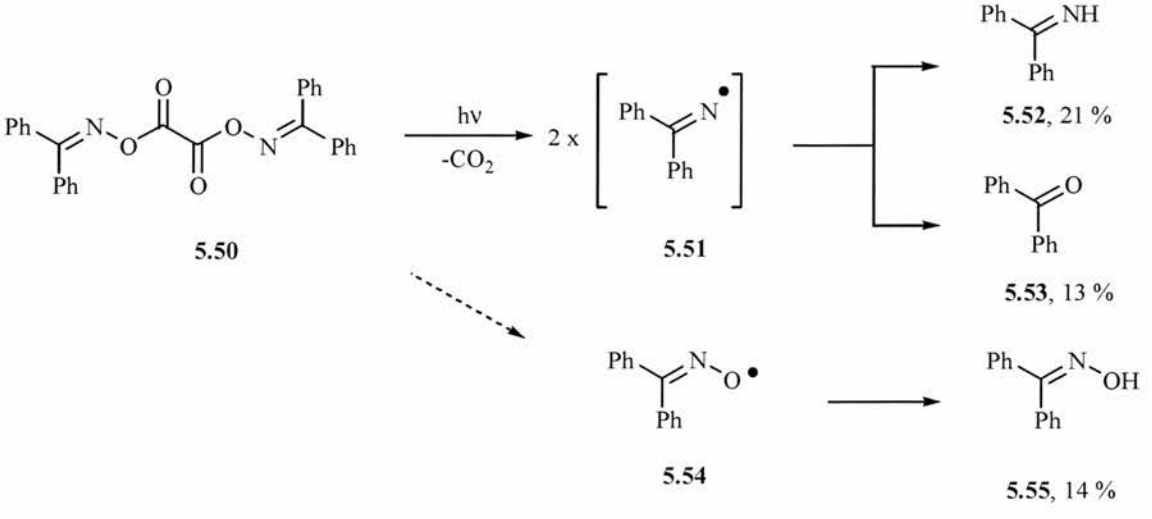
Dioxime oxalates are symmetrical molecules which are readily prepared through the condensation of oxalyl chloride with two moles of an oxime. The first example of a dioxime oxalate was prepared by Brown and co-workers in 1965 and incorporated the highly fluorinated oxime, perfluorobutyramidooxime **5.48** (Scheme 12).



5.48 **5.49**

Scheme 12

Forrester and co-workers[5] investigated dioxime oxalates as photochemical precursors for iminyl radicals. They found that the dioxime oxalate **5.50** derived from benzophenone oxime, on photolysis, underwent homolytic fission of the oxime N-O bond to give two moles of the iminyl radical **5.51** and two moles of CO_2. End product analysis revealed the expected imine **5.52** and benzophenone **5.53** derived from hydrolysis of the imine. The oxime **5.54** was also isolated suggesting that some homolysis of the O-C bond also occurred (Scheme 13).

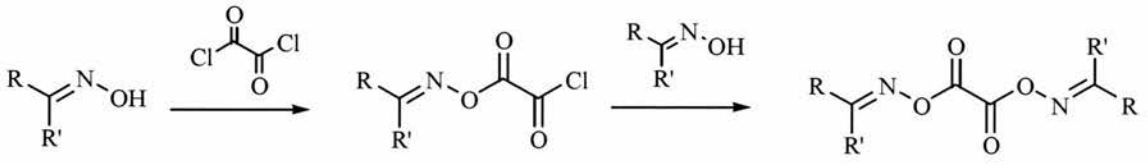


5.50 **5.51**

Scheme 13

The system was examined using ESR spectroscopy and this confirmed the formation of the iminyl radical **5.51**, peaks corresponding to the iminoxyl radical **5.54** were also observed.

Jochims and co-workers[17] have prepared a range of dioxime oxalates as part of their investigation into the Beckmann rearrangement of *O*-(chlorooxalyl)oximes. Their synthetic strategy varied slightly from that of Brown and Forrester in that they first prepared the mono oxime oxalyl chloride and then reacted it with a second mole of the oxime to give the dioxime oxalate in good yield (Scheme 14).



5.56 **5.57** **5.58**

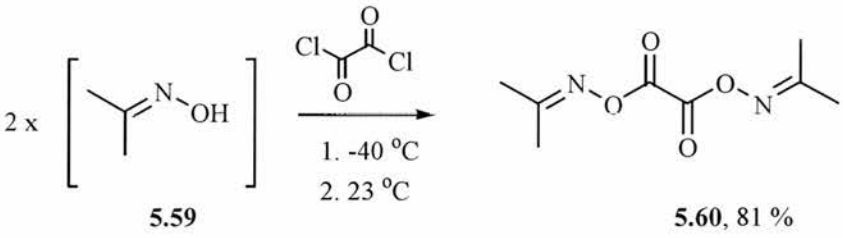
Scheme 14

5.2.0 Results and Discussion

Apart from the work of Forrester[5], no research into the photochemical properties of dioxime oxalates has been conducted. Our research into the oxime oxalate amide system revealed that the oxime N-O bond was a weak bond suitable for homolytic fission. We were interested in investigating the dioxime oxalate system as a photochemical precursor for iminyl radicals and some preliminary investigations were carried out by a senior honours project student.[18] We predicted that the dioxime oxalate system would undergo homolysis to give two moles of the iminyl radical and carbon dioxide.

Acetone *O,O'*-Oxalyldioxime 5.60

The simple dioxime oxalate, acetone *O,O'*-oxalyldioxime was prepared in good yield through the addition of a solution of oxalyl chloride to a cold solution of acetone oxime **5.59**. The mixture was stirred at – 40 °C for 20 min. and then at rt for 1 hr. The solvent was removed and the resulting solid ppt was recrystallised from DCM/pentane at – 20 °C to give the dioxime oxalate as colourless prisims in 81 % yield (Scheme 15).



5.59 **5.60**, 81 %

Scheme 15

Photochemistry of Acetone *O,O'*-Oxalyldioxime 5.60

The photochemistry of the dioxime oxalate was first investigated by ESR spectroscopy. The sample was prepared by taking 20 mg of **5.60** and dissolving it in *tert*-butyl benzene (ca. 500 µl). To this was added 1 Mol eq. of the photosensitizer, *para*-methoxy acetophenone (MAP). The sample was irradiated with light from a 500

W UV lamp and spectra were obtained at a range of temperatures. Fig 1 shows a typical ESR spectrum for the dioxime oxalate **5.60**.

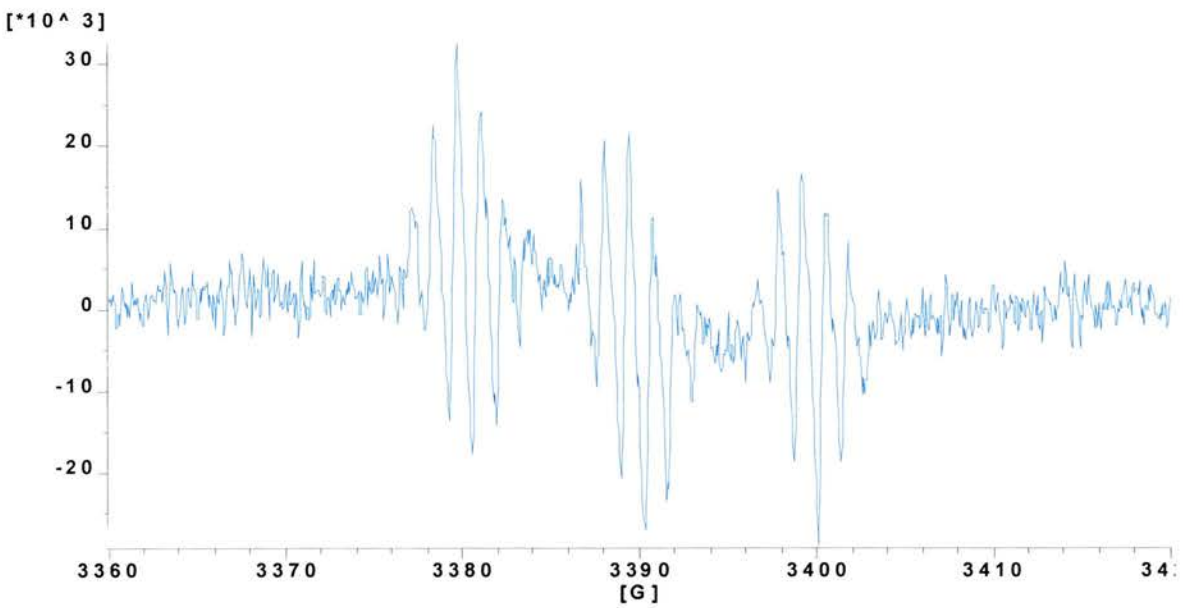
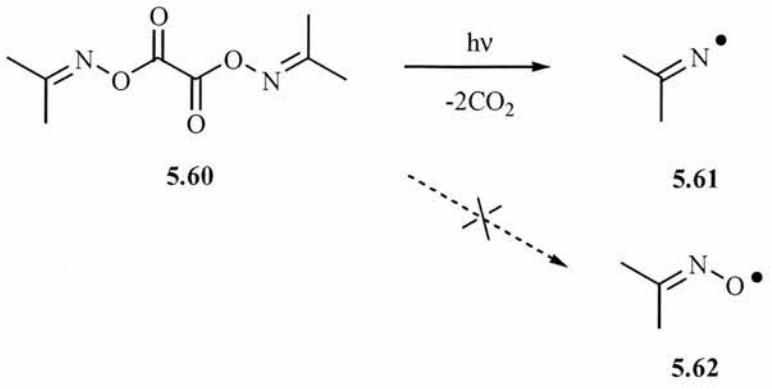


Fig 1. 9.4 GHz ESR spectrum obtained on photolysis of a solution of **60** and MAP in *tert*-butylbenzene at 320 K.

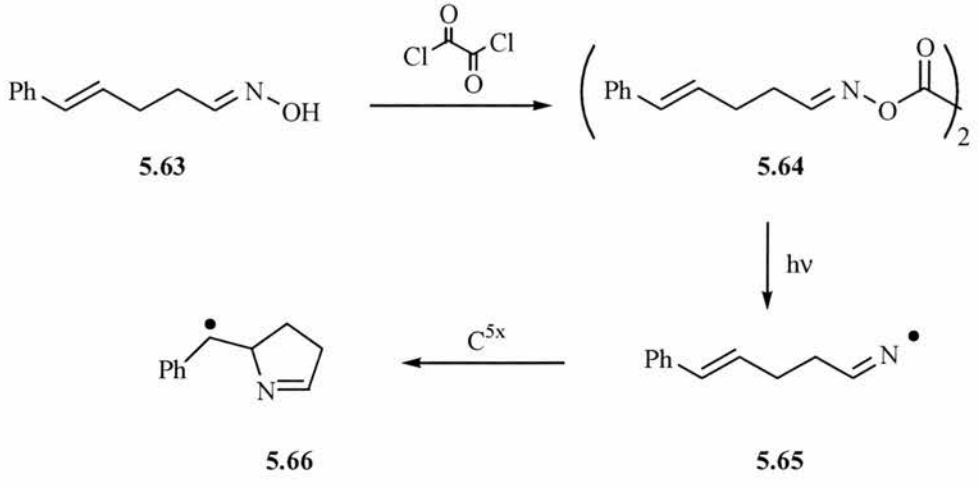
The EPR spectrum consists of a triplet of septets. Each component of the triplet arising from the nitrogen is split into septets by the six equivalent hydrogens. The ESR parameters for the iminyl radical were determined in *tert*-butylbenzene at 320 K, iminyl (I) g = 2.0034, a(N) = 9.8 and a(H) = 1.37 G. As was previously mentioned in chapter 2, the hyperfine splittings (hfs) expected for an iminyl radical of this type are a(N) = 9.6 or 9.7 at 223 K and a(H) = 1.4 or 1.3 at 300 K[19]

The ESR spectrum demonstrates therefore, that scission of the N-O bonds of oxime oxalate amides occurs cleanly and that this is followed by rapid CO_2 loss to afford the iminyl radical **5.61**. No spectrum corresponding to the iminoxyl radical **5.62** was observed and this suggests that homolysis of the N-O oxime bond is preferred (Scheme 16).



Scheme 16

The ESR studies suggested that the dioxime oxalate system could act as a clean photochemical precursor for iminyl radicals. In order to investigate the synthetic potential of this system we designed a dioxime oxalate **5.64** which, on photolysis, would release an iminyl radical **5.65** which could undergo a 5-*exo* cyclisation onto a proximate double bond. The resulting cyclised radical would be 2° benzyl stabilised and would terminate either by abstracting a hydrogen atom directly from solution or else by reacting with dissolved O_2 to give the hydroxylated product (Scheme 17).

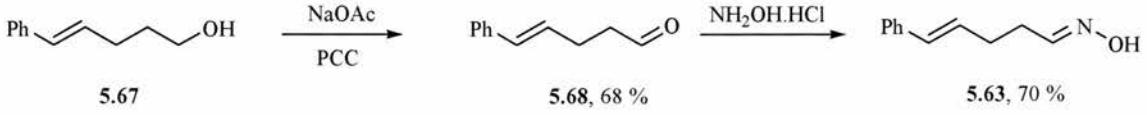


Scheme 17

5-Phenylpent-4-enal Oxime 5.63

In order to prepare the dioxime oxalate **5.64**, it was first necessary to prepare the oxime **5.63**. This was carried out in two steps starting from the alcohol **5.67**. The

alcohol was oxidised to the aldehyde in 68 % yield, using pyridinium chlorochromate. The aldehyde was then converted to the oxime using hydroxylamine hydrochloride. The oxime was isolated as colourless needles in 70 % yield (Scheme 18).



5.67 **5.68**, 68 % **5.63**, 70 %

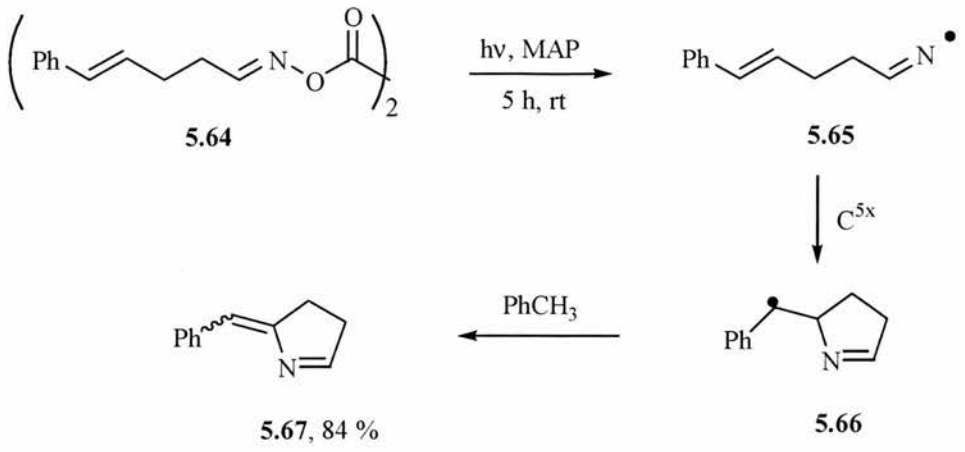
Scheme 18

5-Phenylpent-4-enal *O,O'*-Oxalyldioxime 5.64

The oxime **5.63** was converted to the dioxime oxalate **5.64** by adding two M eq of oxime to a stirred solution of oxalyl chloride at – 40 °C. The solution was stirred at rt for 2 h and after this time the solvent was removed to give the dioxime oxalate **5.64** as a yellow oil. The ^{1}H NMR spectrum of the crude product showed a 100 % conversion and no further purification was carried out.

2-Benzylidene-3,4-dihydro-2H-pyrrole 5.65

The dioxime oxalate **5.64** was dissolved in toluene and to this was added 3 M eq of the photosensitizer MAP. The mixture was photolysed with light from a 400 W medium pressure UV lamp using an emersion device for 5h at rt. After this time the solvent was removed to give a yellow oil. The oil was purified by column chromatography and **5.67** was isolated in 84 % yield as a mixture of *E* and *Z* isomers (Scheme 19).



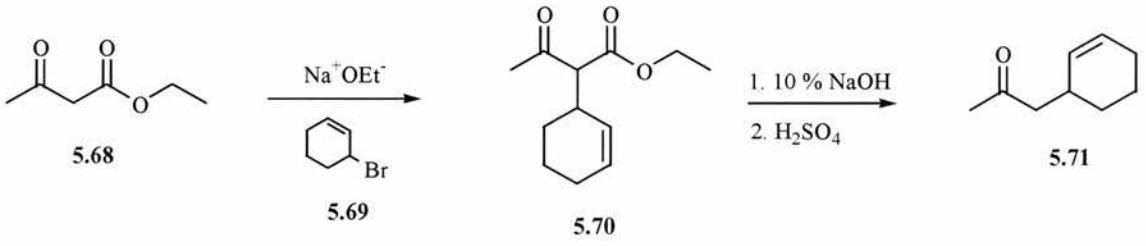
Scheme 19

Interestingly, the cyclised radical **5.66** did not abstract an H-atom from the toluene. Presumably this was because **5.66** is a resonance stabilised benzyl-type radical so H-abstraction would be slightly endothermic. Instead a H-atom was lost giving the extensively conjugated isomer pair **5.67**. It is possible that the H-atom is removed from **5.66** by the excited state of MAP.

Preparation of the dihydropyrrole **5.67** demonstrated that iminyl radicals generated on photolysis of dioxime oxalates could undergo ring closure reactions and were therefore synthetically useful. We were interested in investigating if this source of iminyl radicals could be applied to the preparation of some bicyclic indoles.

Cyclohex-2-enylacetone 5.71

The ketone **5.71** was prepared according to the method of Barltrop and Thomson.[20] Ethyl sodioacetoacetate (formed on treatment of ethyl acetoacetate in ethanol with sodium) was refluxed for 1h with bromocyclohexene **5.69**. The ester **5.70** was distilled and washed with 10 % NaOH and then treated with 50 % H_2SO_4 until slightly acidic. The aqueous solution was extracted with ether, which was dried and evaporated to give the ketone as a colourless oil. The oil was purified by distillation to give the ketone **5.71** in good yield (Scheme 20).

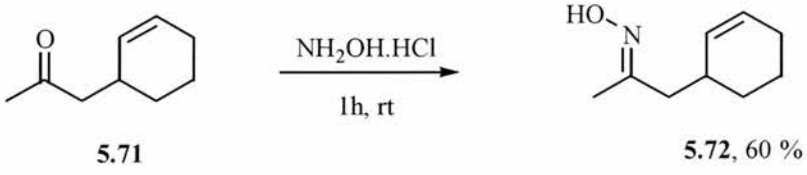


5.68 5.69 5.70 5.71

Scheme 20

Cyclohex-2-enyl Acetone Oxime 5.72

The ketone **5.71** was converted to the corresponding oxime on treatment with hydroxylamine hydrochloride. The oxime was isolated in 60 % yield as a colourless oil via distillation (Scheme 21).

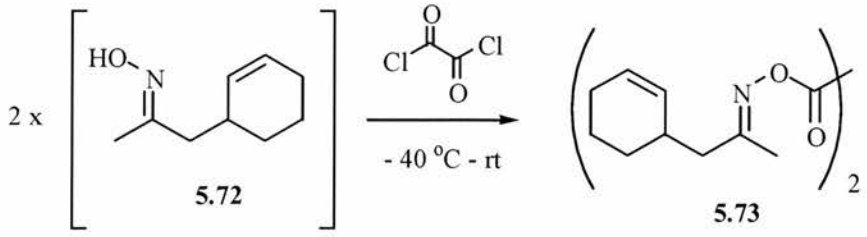


5.71 **5.72**, 60 %

Scheme 21

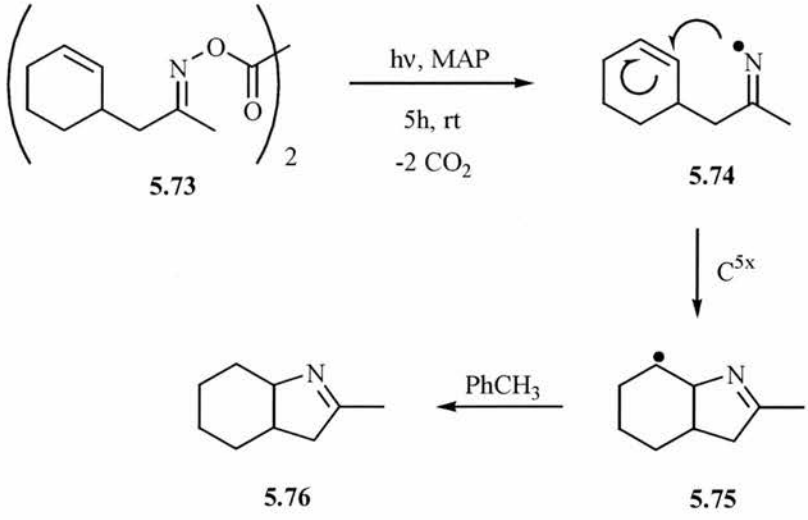
Cyclohex-2-enyl Acetone *O'O*-Oxalyldioxime 5.73

The oxime **5.72** was added to a stirred solution of oxalyl chloride in ether at – 40 °C (Scheme 22). The reaction mixture was stirred at – 40 °C for 20 min and then allowed to reach rt where it was stirred for an additional 1h. A severe colour change was noted as the temperature increased. The colourless solution turned yellow and then dark red. On removal of solvent the dioxime oxalate **5.73** was a deep red colour. Characterisation of the dioxime proved difficult. The ^{1}H NMR showed shifts in the peaks relative to the starting oxime suggesting reaction had taken place. ^{13}C NMR was extremely complicated and suggested that the molecule was unstable. It was not possible to obtain mass spec or elemental analysis data.



Scheme 22

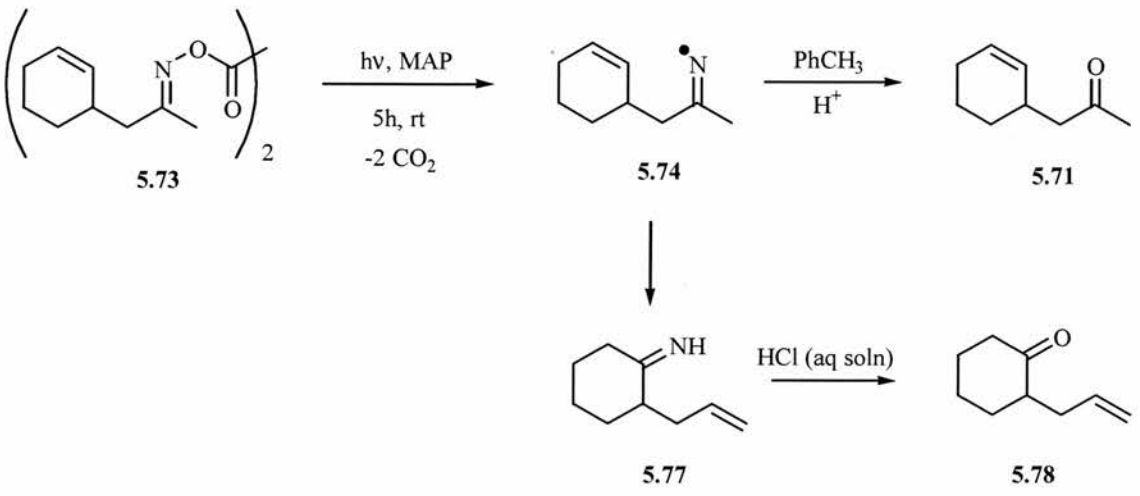
The dioxime was freshly prepared according to the above procedure and then dissolved in toluene. To this was added 1 M eq of photosensetizer and the mixture was photolysed by light from a 400 W UV lamp for 5 h at rt. After this time the solvent was removed and the crude reaction mixture was separated via column chromatography. Scheme 23 illustrates the predicted photochemical route on photolysis of the dioxime oxalate **5.73**.



Scheme 23

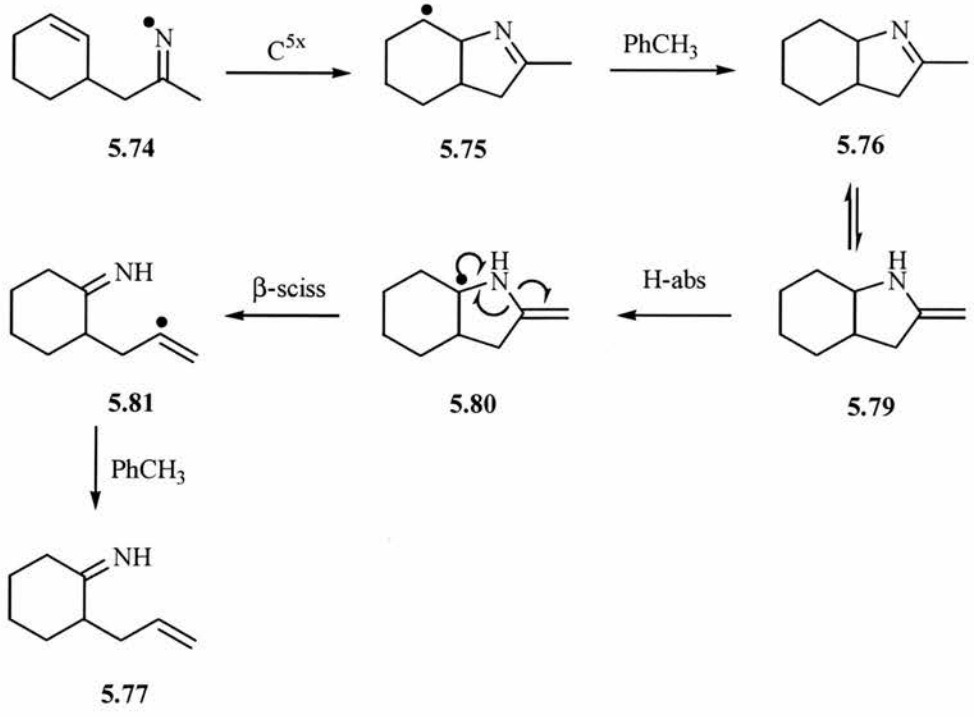
It was expected that the dioxime oxalate would follow the same photochemical route as the previous dioxime oxalates. In this instance however, none of the cyclised product **5.76** was observed. The products isolated by column chromatography were the ketone **5.71** which results from hydrolysis of the reduced iminyl radical and the imine

5.77. The imine was converted into the known ketone **5.78** as further proof of its structure (Scheme 24).



Scheme 24

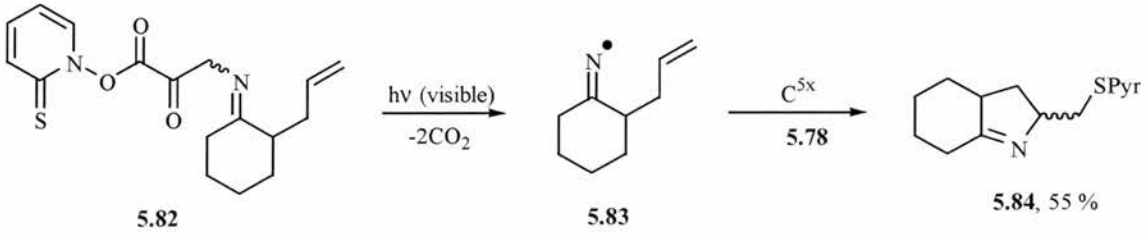
The imine **5.77** was an unexpected product from the photolysis of **5.73** and Scheme 25 shows a possible mechanism for its formation.



Scheme 25

The mechanism explains the final product but the β-scission step going from **5.80** to **5.81** is considered unlikely since it relies on the breaking of the strong N-C bond. The location of the nitrogen atom in the final product suggests that cyclisation does occur and that **5.77** is derived from the cyclised radical **5.75**.

After the failure of dioxime oxalate **5.73** to furnish the cyclised product **5.76**, it was decided to look at some known iminyl radical cyclisations and to see if they could be applied to the dioxime oxalate system. Zard and c-workers[21] had previously prepared the Barton ester **5.82** and the resulting iminyl radical **5.83** underwent 5-*exo* cyclisation to give the cyclised derivative **5.84** in a yield of 55 % (Scheme 26).

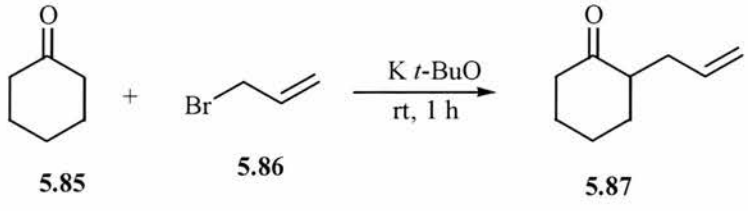


Scheme 26

The same iminyl radical **5.83** could be generated using dioxime oxalates as the precursor and this known iminyl radical would cyclise to give the target indole.

Allyl-2-Cyclohexanone 5.87

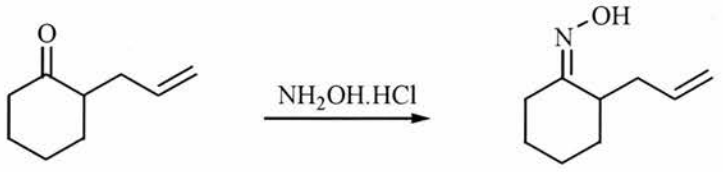
The starting ketone was prepared in 100 % yield through the reaction of cyclohexanone with allyl bromide in the presence of base, according to the literature procedure of Mousseron and co-workers[22] (Scheme 27).



Scheme 27

Allyl-2-Cyclohexanone Oxime 5.88

The ketone **5.87** was converted into the corresponding oxime **5.88** through the reaction with hydroxylamine hydrochloride. The oxime was isolated as a colourless oil in 58 % yield (Scheme 28).

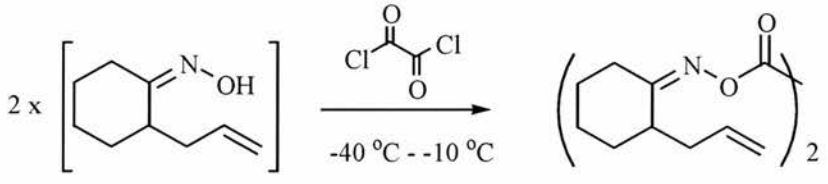


5.87 **5.88**

Scheme 28

Allyl-2-Cyclohexanone *O'O*-Oxalyldioxime 5.89

The oxime was converted to the dioxime oxalate through reaction with oxalyl chloride (Scheme 29). The original methodology employed for the formation of the dioxime gave a red solution which was difficult to characterise so the reaction was repeated at a lower temperature. Addition of the oxime was carried out at – 40 °C and then the mixture was stirred at – 20 °C for 3 h and then at – 10 °C for 15 min. After this time the solvent was removed at -10 °C to give the dioxime oxalate as a colourless oil which turned yellow on contact with air and a deep red on standing. The dioxime **5.89** was again extremely unstable and difficult to characterise.

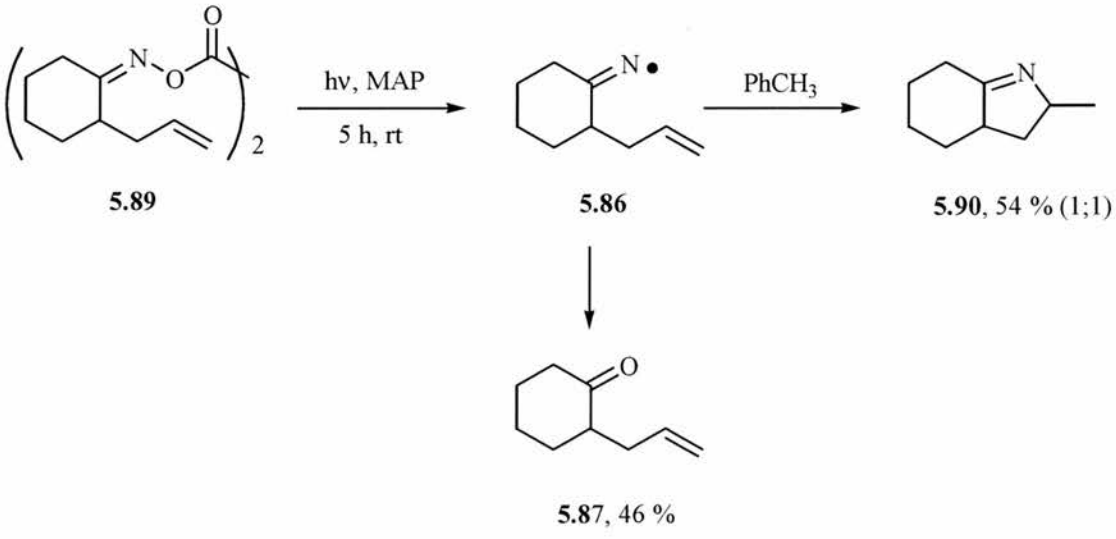


5.88 **5.89**

Scheme 29

The dioxime oxalate **5.89** was freshly prepared according to the method described above and immediately photolysed by light from a 400 W UV lamp in

toluene and in the presence of MAP. The solvent was removed and the crude NMR revealed two products. The cyclised indole had been formed in 46 % (1:1; *cis:trans*) and the remaining product was the starting ketone. Yields were determined by ^{1}H NMR by direct comparison with the photosensitizer. The yield of 46 % for the cyclised species compared quite favourably to the yield obtained for Zard's Barton ester.



5.89 **5.86** **5.90**, 54 % (1;1)

5.87, 46 %

Scheme 30

5.3.0 Conclusions

It is clear form the above work that dioxime oxalates function well as a clean, photochemical source of iminyl radicals. By varying the nature of the starting oxime, it was possible to prepare several interesting, nitrogen containing heterocycles.

ESR spectroscopy was used to identify and characterise the iminyl radicals derived from the simple dioxime oxalates.

The chemistry of the iminyl radicals was not always predictable and in some cases, significant quantities of the direct reduction products were isolated.

The chemistry surrounding the preparation of complex dioxime oxalates requires further investigation and the stability of the dioxime oxalate system should be investigated.

It was found that dioxime oxalates incorporating more complex oximes were more difficult to prepare and to isolate. This may limit the synthetic potential of the dioxime oxalate system.

5.4.0 Experimental.

Acetone *O,O'*-oxalyldioxime[17] 5.60

To a stirred solution of oxalyl chloride (1.27 g; 10 mmol) in ether (10 cm^3) at – 40°C was added a solution of acetone oxime (1.46 g; 20 mmol). The mixture was stirred at – 40 °C for 20 min and then at rt for 1 hr. After this time the solvent was removed to give the dioxime oxalate as a colourless solid (1.62 g; 81 %). The product was recrystallised from DCM/pentane at – 20 °C to give the dioxime oxalate as colourless prisims, mp = 58 – 62 °C (lit[17] = 66 -67 °C); ν_{max}(NaCl)/cm^{-1} 1716 (C=O); ^{1}H NMR, (300 MHz, $CDCl_3$) δ_H 2.10, 2.09 (2 x CH_3); δ_C ($CDCl_3$) 17.4, 21.3 (CH_3), 156.6, 166.5 (C=O, C=N).

5-Phenylpent-4-enal oxime[18] 5.63

To a solution of NaOH (1.0 g; 24 mmol) in H_2O (10 cm^3) was added 5-phenyl-pent-4-enal (1.3 g; 8 mmol) followed by hydroxylamine hydrochloride (0.7 g; 10 mmol) and the mixture was stirred vigorously. After leaving overnight, the colourless crystalline mass of the sodium derivative of the oxime separated out. Water was added until a clear solution was obtained and CO_2 was bubbled through until a thick white emulsion appeared. The oxime was extracted with ether (4 x 25 cm^3), dried over $MgSO_4$ and evaporated to dryness to give the crude oxime. This was recrystallised from ether/hexane to give the pure oxime as colourless needles (1.0 g; 70 %); m p = 88-90 °C, δ_H (300 MHz, $CDCl_3$) 2.50 (4H, m, 2 x CH_2), 6.19 (1H, dt, J 16 and 7, =CH), 6.53 (1H, d, J 16, =CH), 7.25-7.40 (6H, m, ArH, HCN).

5-Phenylpent-4-enal dioxime oxalate[18] 5.64

5-Phenylpent-4-enal oxime (0.42 g; 2.4 mmol) was dissolved in dry ether (5 cm^3) and added dropwise to a stirred solution of oxalyl chloride (0.15 g; 1.2 mmol) in ether (5 cm^3) at –40 °C. The mixture was stirred at – 40 °C for 20 min and then allowed to stir at rt for 2 h. After this time the solvent was removed to give the dioxime as a yellow oil (0.49 g; 100 %). δ_H (300 MHz, $CDCl_3$) 2.50 (8H, m, 4 x CH_2), 6.19 (2H, dt, J 16 and 7, 2 x =CH), 6.53 (2H, d, J 16, 2 x =CH), 7.25-7.40 (12H, m, PhH, 2 x CHN).

Attempts to obtain ^{13}C and mass spec data were unsuccessful due to rapid degradation of the compound.

5-Phenylpent-4-enal[18] 5.68

To a stirred solution of sodium acetate (2 g; 12 mmol) and sodium bicarbonate (2 g; 12 mmol) in DCM (250 cm^3) was added an excess of pyridinium chlorochromate (8 g; 36 mmol) followed by 5-phenylpent-4-en-1-ol (2 g; 12 mmol) and the resultant suspension was stirred at rt for 1h. After this time, diethyl ether (400 cm^3) was added and the mixture stirred for an additional 15 min. The reaction mixture was filtered through a pad of silica, and the solvent removed under vacuum to give a brown oil. The oil was distilled on a Kugelrohr at 115 °C/12 mm Hg to give the product as a clear oil (1.40 g, 68 %); δ_H (300 MHz, $CDCl_3$) 2.50-2.65 (4H, m, 2 x CH_2), 6.17 (1H, dt, J 16 and 7, CH), 6.40 (1H, d, J 16, CH), 7.20-7.40 (5H, m, PhH), 9.80 (1H, s, CHO).

Preparative scale photolysis of 5-phenylpent-4-enal dioxime oxalate[18]

5-Phenylpent-4-enal dioxime oxalate (500 mg; 3.6 mmol) and MAP (540 mg; 3.6 mmol) were dissolved in toluene (400 cm^3) and placed in a quartz reaction vessel. The mixture was photolysed at ambient temperature by light from a 400 W medium pressure Hg lamp for 5 h. After this time the solvent was evaporated to give a yellow oil. The oil was columned over silica (EtOAc; hexane) 60:40 to give the product as a yellow oil (86 % by NMR), isolated yield (320 mg; 84 %); δ_H (300 MHz, $CDCl_3$) 2.45-2.75 (4H, m, 2 x CH_2), 5.57 (1/2 H, dt, J 13 and 7, =CHPh), 6.11 (1/2 H, dt, J 16 and 5, =CHPh), 6.44 (1/ 2 H, d, J 16), 6.52 (1/2 H, d, J 13, HC=N), 7.25-7.40 (5H, m, PhH);δ_C (75MHz; $CDCl_3$) 18.0 (CH_2), 24.8 (CH_2), 29.2 (CH_2), 125.9, 126.7, 127.6, 127.9, 128.1, 128.8, 128.8, 129.0 (ArCH), 132.6 (HC=N), 133.4 (HC=C).

The product was placed in $CDCl_3$, and analysed by GC/MS; peak no. 423, 5-phenylpent-4-enal (2 %), *m/z* (relative intensity) 160 (M^+,18), 128 (11), 117 (37), 115 (54), 91 (61), 77 (21), 77 (21), 65 (12); peak no. 471, *E*- or *Z*-2-benzylidiene-3,4-dihydro-(2H)-pyrrole **5.67** (54 %), *m/z* (relative intensity) 157 (M^+,22), 117 (100), 102 (6), 91 (27); peak no. 502, *E*- or *Z*-2-benzylidiene-3,4-dihydro-(2H)-pyrrole **67** (42 %), *m/z* (relative intensity) 157 (M^+,100), 129 (7), 117 (73); (Found M^+ 158.0975, $C_{11}H_{12}N$ requires M^+ 158.0970).

Cyclohex-2-enylacetone[20] 5.71

Ethyl sodioacetate [from sodium (3.0 g) and ethyl acetoacetate (18.6 g)] in ethanol (45 cm^3) was refluxed for 1 h with 3-bromocyclohexene (20.6 g; 0.13 M). The product was filtered to remove NaBr and the filtrate evaporated to dryness and then distilled to give an ester (18 g) bp = 140-145 °C/12mmHg. The ester was washed with 10 % NaOH (150 cm^3) for 4 h and then treated with 50 % H_2SO_4 until slightly acidic. The product was extracted with ether (100 cm^3) and dried ($MgSO_4$). Evaporation to dryness yielded the product as a colourless oil which was further purified by Kugelrohr bulb to bulb distillation (78-80 °C/12 mmHg), (8.0 g; 45 %), δ_H (300 MHz, $CDCl_3$) 1.21 (1H, m), 1.58 (1H, m), 1.67 (1H, m), 1.78 (1H, m), 1.93-1.98 (2H, m), 2.19 (3H, s, Me), 2.41 (2H, m), 2.63 (1H, m), 5.50 (1H, m, =CH), 5.69 (1H, m, =CH).

Cyclohex-2-enyl acetone oxime 5.72

A mixture of the cyclohexen-2-enyl acetone (1.38 g; 0.01 M), hydroxylamine hydrochloride (0.71 g; 0.01 M) and sodium carbonate (0.54 g; 5 mmol) in H_2O (10 cm^3) were stirred at rt for 1 h under nitrogen. The reaction mixture was extracted with DCM (3 x 30 cm^3) and the combined extracts washed with water and dried ($MgSO_4$). Evaporation to dryness gave the crude oxime as a pale yellow oil (which turned dark yellow on standing). The oxime was further purified by Kugelrohr bulb to bulb distillation (120-125 °C/12 mmHg) to give the oxime as a colourless oil which solidified on cooling (0.92 g; 60 %); δ_H (300 MHz, $CDCl_3$) 1.24 (1H, m), 1.55 (1H, m), 1.74 (2H, m), 1.90 (3H, s, Me), 1.94-2.01 (2H, m), 2.15 (2H, m), 2.40 (1H, m), 5.54 (1H, m, =CH), 5.70 (1H, m, =CH); δ_C($CDCl_3$) 21.4, 25.5, 29.3, 30.9, 35.3, 42.5, 128.3, 130.8, 167.3.

Cyclohex-2-enyl acetone *O'O*-oxalyldioxime 5.73

To a stirred solution of oxalyl chloride (420 mg; 3.25 mmol) in diethylether (10 cm^3) was added to a solution of cyclohex-2-enyl acetone oxime (1.0 g; 6.5 mmol) in ether (5 cm^3) at – 40 °C. The solution was stirred at – 40 °C for 20 min and then at rt for 3 h. After this time the solvent was removed to give the dioxime oxalate as a yellow oil. ν_{max}(NaCl)/cm^{-1} 1787, 1758 (C=O), 1639 (C=N); δ_H (300MHz, $CDCl_3$) 1.26 (2H, m),

1.54 (2H, m), 1.75 (4H, m), 1.88-2.03 (4H, m), 2.07 (6H, s, 2 x Me), 2.23-2.52 (6H, m), 5.50 (2H, m, =CH), 5.74 (2H, m, =CH).

Preparative scale photolysis of cyclohex-2-enyl dioximeoxalate

Cyclohex-2-enyl dioxime oxalate (1.17 g; 3.25mmol) and MAP (1.5 g; 9.75 mmol) were dissolved in toluene (400 cm^3) and placed in a quartz reaction vessel. The mixture was photolysed at ambient temperature by light from a 400 W medium pressure Hg lamp for 5 h. After this time the solvent was evaporated to give a yellow oil. The oil was columned over silica (DCM- DCM/MeOH; 10:1) to give the pure products 2-allyl-cyclohexideneamine and cyclohex-2-enylacetone. The sample was also submitted for analysis by GC/MS; peak no. 566, 2-allyl-cyclohexideneamine, *m/z* (relative intensity) 138 (MH^+,100), 95 (15); peak no. 572, *E*- or *Z*-2-allyl-cyclohexideneamine, *m/z* (relative intensity) 138 (MH^+,100), 95 (16); peak no. 575, cyclohex-2-enyl acetone, *m/z* (relative intensity) 139 (MH^+,33), 81 (100), 59 (8).

Hydrolysis of 2-allyl-cyclohexideneamine[22]

2-Allyl-cyclohexideneamine (50 mg; 0.36 mmol) was dissolved in water (10 cm^3). To this was added dilute HCl (ca.10 cm^3), and the solution was heated at 80 °C for 20 min. After this time the solution was extracted into diethyl ether, dried and concentrated to give allyl-2-cyclohexanone as the only product. δ_H (300MHz, $CDCl_3$) 1.24-1.43 (1H, m), 1.50-2.16 (6H, m), 2.22-2.38 (1H, m), 2.43 -2.55 (1H, m), 5.02 (2H, m, $=CH_2$) 5.73 (1H, m, =CH).

Allyl-2-cyclohexanone[22] 5.84

To a stirred solution of potassium *tert*-butoxide (13.4 g; 0.12 M) in dry ether (100 cm^3) was added cyclohexanone. The mixture was stirred at rt for 1 h after which time bromocyclohexene (12 g; 0.1 mmol) was added over 20 min. The mixture was left stirring at ambient temperature overnight. Water was added, dropwise at first, and then portionwise until the mixture went clear. The organic layer was separated and then the aqueous layer was extracted with ether (4 x 25 cm^3). The combined organic layers were dried ($MgSO_4$) and then evaporated to dryness to give the title ketone as a colourless oil

(13.8 g; 100 %), δ_H (300 MHz, $CDCl_3$) 1.24-1.43 (1H, m), 1.50-2.16 (6H, m), 2.22-2.38 (1H, m), 2.43-2.55 (1H, m), 5.02 (2H, m, $=CH_2$) 5.73 (1H, m, =CH).

Allyl-2-cyclohexanone oxime 5.85

To a stirred solution of the ketone (5.52 g; 40 mmol) in EtOH (80 cm^3) was added NaOAc (6.0 g; 44 mmol) and hydroxylamine hydrochloride (3.0 g; 44 mmol). The mixture was stirred at rt for 3 h. After this time, water was added until the solution became clear. The EtOH was removed by distillation and the remaining water was extracted with DCM (4 x 25 cm^3). The combined organic extracts were dried ($MgSO_4$) and then evaporated to dryness to give the crude oxime. The oxime was purified via Kugelrohr bulb to bulb distillation to give the pure oxime as a colourless oil (3.20 g: 58 %) bp = 125-128 °C δ_H (300 MHz, $CDCl_3$) 1.39-1.81 (6H, m), 1.83-1.92 (1H, m), 2.06-2.38 (3H, m), 2.45-2.53 (1/2H, m), 2.75-2.83 (1/2H, m), 4.99-5.09 (2H, m, $=CH_2$), 5.70-5.86 (1H, m, =CH).

Allyl-2-cyclohexanone dioxime oxalate 5.86

To a stirred solution of oxalyl chloride (0.5 g; 3.9 mmol) in diethyl ether (10 cm^3) at –40 °C was added to a solution of allyl-2-cyclohexanone oxime (1.2 g; 7.8 mmol) in ether (5 cm^3). The solution was stirred at –40 °C for 20 min and then at at –20 °C for 3 h and finally at at –10 °C for 20 min. After this time the solvent was removed at –10 °C to give the dioxime oxalate as a colourless oil (1.4 g; 100 %) which turned yellow on contact with air and then a deep red on standing δ_H (300 MHz, $CDCl_3$) 1.42-1.78 (12H, m), 1.86 (2H, m), 2.08-2.45 (6H, m), 2.54 (1H, m), 2.72 (1H, m), 4.97 (4H, m, $=CH_2$), 5.66 (2H, m, =CH).

Preparative scale photolysis of allyl-2-cyclohexanone dioxime oxalate[23]

Allyl-2-cyclohexanone dioxime oxalate (1.4 g; 3.9 mmol) and MAP (1.75 g; 11.7 mmol) were dissolved in toluene (400 cm^3) and placed in a quartz reaction vessel. The mixture was photolysed at ambient temperature by light from a 400 W medium pressure Hg lamp for 5 h. After this time the solvent was evaporated to give a yellow oil. NMR analysis revealed the composition of the oil to be 46 % cyclised product, 2-methyl-3,3a,4,5,6,7-hexahydro-2H-indole (21 % *cis*, 25 % *trans*) and 54 % of the allyl-

2-cyclohexanone δ_H (300 MHz, $CDCl_3$) mixture of two isomers, major isomer: 1.42 (3H, d, J 7, CH_3),0.89 2.28 (9H, m), 2.35 (1H, dd, J 7 and 13, CH), 3.90 (1H, m, NCH) minor isomer 1.27 (3H, d, J 7, CH_3),0.89 2.28 (9H, m), 2.31 (1H, dd, J 7 and 13, CH), 4.15 (1H, m, NCH).

5.5.0 References

(1) W. R. Bowman, D. R. Coghlan and H. Shah, *C. R. Acad. Sci., Ser: IIc: Chim.*, 2001, **4**, 625.

(2) D. Gennet and S. Z. Zard, *Chem. Comm.*, 2003, 1870-1871.

(3) W. R. Bowman, M. J. Broadhurst, D. R. Coghlan and K. A. Lewis, *Tetrahedron Lett.*, 1997, **38**, 6301-6304.

(4) S. Z. Zard, *Synlett.*, 1996, 1148.

(5) A. R. Forrester, M. Gill, C. J. Meyer, J. S. Sadd and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 1979, 606.

(6) J. Boivin, E. Fouquet and S. Z. Zard, *Tetrahedron Lett.*, 1991, **32**, 4299.

(7) J. Boivin, A.-M. Schiano and S. Z. Zard, *Tetrahedron Lett.*, 1992, **33**, 7849.

(8) L. E. Kaim and C. Meyer, *J. Org. Chem.*, 1996, **61**, 1556-1557.

(9) X. Lin, G. D. Artman, D. Stien and S. M. Weinreb, *Tetrahedron*, 2001, **57**, 8779-8791.

(10) D. L. J. Clive, P. L. Beaulieu and L. Set, *J. Org. Chem.*, 1984, **49**, 1313.

(11) B. Chenera, C. P. Chuang, D. J. Hart and L. Y. Hsu, *J. Org. Chem.*, 1985, **50**, 5409.

(12) A. L. J. Beckwith, D. M. O'Shea, S. Gerba and S. W. Westwood, *J. Chem. Soc., Chem. Commun.*, 1987, 666.

(13) B. W. Yeung, J. L. M. Contelles and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1989.

(14) C. M. Camaggi, R. Leardini, D. Nanni and G. Zanardi, *Tetrahedron*, 1998, **54**, 5587-5598.

(15) M.-H. Tadic-Biadatti, A.-C. Callier-Dublanchet, J. H. Horner, B. Quiclet-Sire, S. Z. Zard and M. Newcomb, *J. Org. Chem.*, 1997, **62**, 559-563.

(16) J. Boivin, E. Fouquet and S. Z. Zard, *J. Am. Chem. Soc.*, 1991, **113**, 1055.

(17) J. C. Jochims, S. Hehl and S. Herzberger, *Synthesis*, 1990, 1128-1133.

(18) R. Mitchell, *University of St. Andrews, Senior Honours Project*, 1999.

(19) Landolt-Bornstein: *Magnetic Properties of Free Radicals*; Springer-Verlag: Berlin, 1979 and 1987.

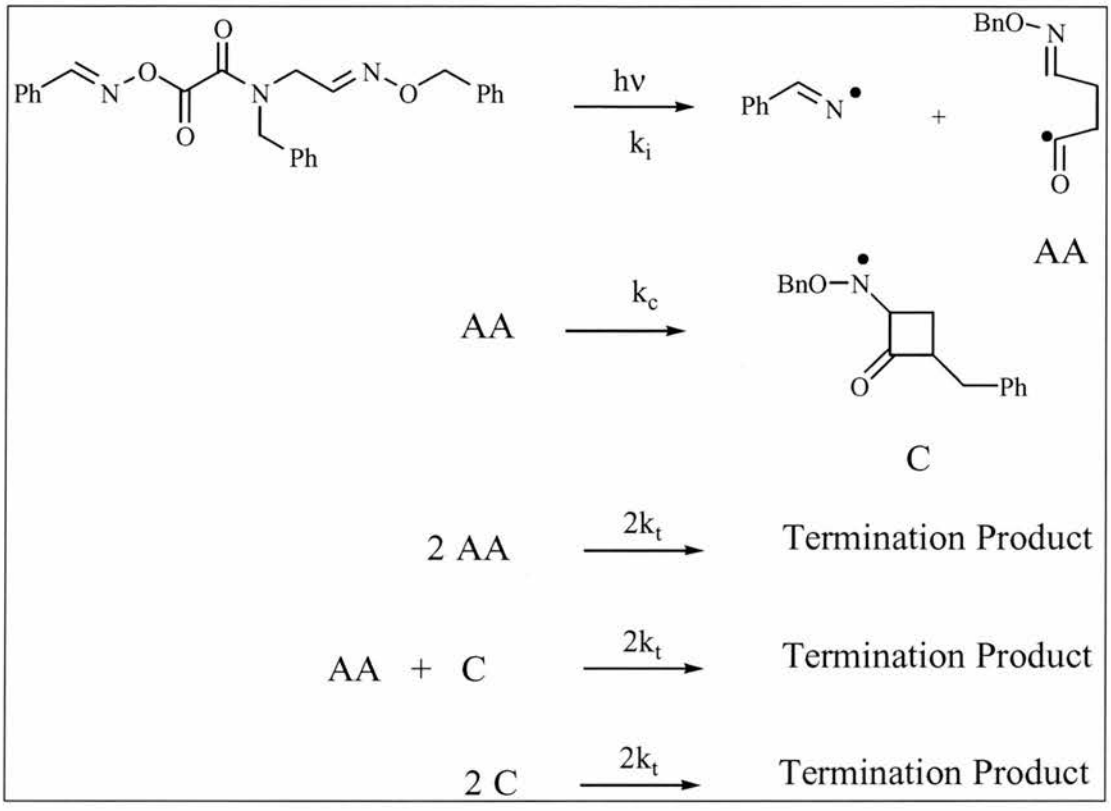
(20) J. A. Barltrop and A. Thomson, *J. Chem. Soc. (c)*, 1968, 155.

(21) J. Boivin, E. Fouquet, A.-M. Schiano and S. Z. Zard, *Tetrahedron,* 1994, **50**, 1769-1776.

(22) M. Mousseron, R. Jacquier and H. Christol, *Bull. Soc. Chem. Fr.,* 1957, 346-352.

(23) J. Boivin, E. Fouquet and S. Z. Zard, *Tetrahedron,* 1994, 1745-1756.

Appendix 1



Derivation of Steady State Equation

$$\frac{d[AA]}{d_t} = 0 = \Phi I_a [P] - k_c [AA] - 2k_t [AA]^2 - 2k_t [AA][C]$$

$$\frac{d[C]}{d_t} = 0 = k_c[AA] - 2k_t [AA][C] - 2k_t [C]^2$$

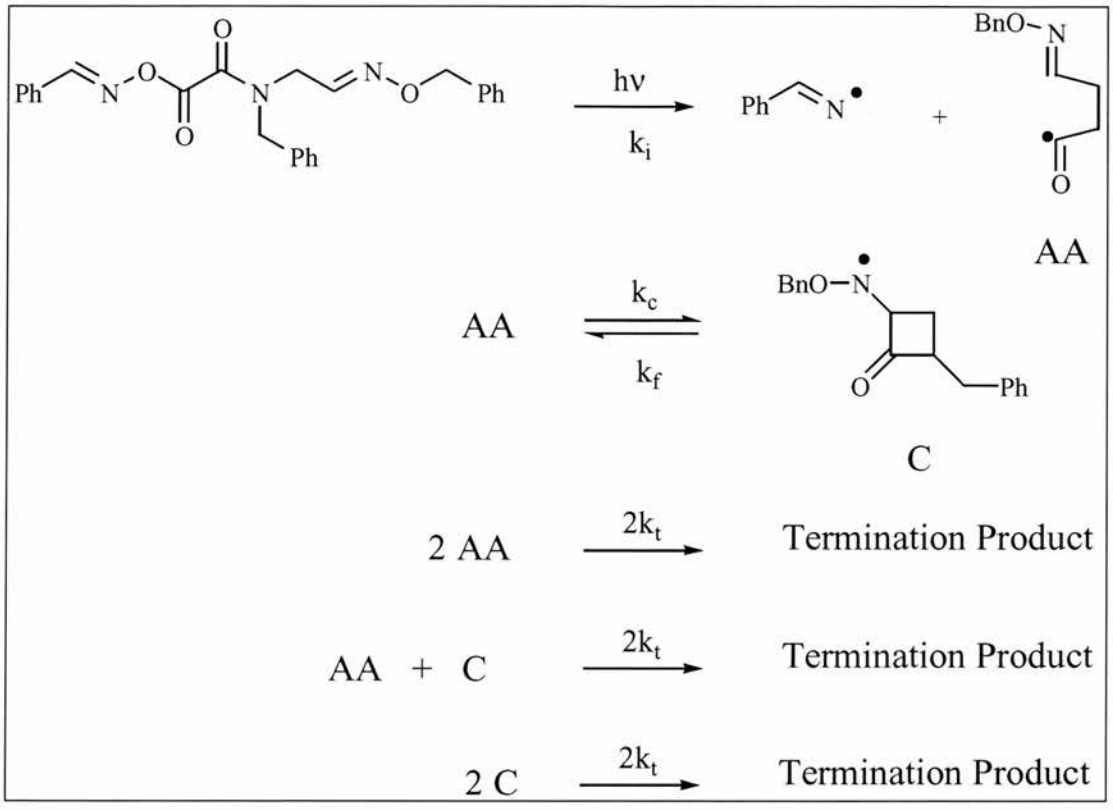
Dividing by $2k_t$ [AA] [C]:

$$0 = \frac{k_c [AA]}{2k_t [AA][C]} - 1 - \frac{2k_t [C]}{2k_t [AA][C]}$$

Rearranges to:

$$\boxed{\frac{k_c}{2k_t} = [C] + \frac{[C]^2}{[AA]}}$$

Appendix 2



Derivation of Steady State Equation:

$$\frac{d[AA]}{d_t} = 0 = \Phi I_a [P] - k_c [AA] + k_f [C] - 2k_t [AA]^2 - 2k_t [AA][C]$$

$$\frac{d[C]}{d_t} = 0 = k_c[AA] - k_f [C] - 2k_t [AA][C] - 2k_t [C]^2$$

Devide by $2k_t[AA][C]$:

$$0 = \frac{k_c [AA]}{2k_t [AA][C]} - \frac{k_f [C]}{2k_t [AA][C]} - 1 - \frac{2k_t [C]}{2k_t [AA][C]}$$

Rearranges to:

$$\frac{k_c}{2k_t} = \frac{k_f[C]}{2k_t[AA]} + [C] + \frac{[C]^2}{[AA]}$$

or :

$$[C] + \frac{[C]^2}{[AA]} = -\frac{k_f[C]}{2k_t[AA]} + \frac{k_c}{2k_t}$$

$$\mathbf{y} = \mathbf{mx} + \mathbf{c}$$

If k_f is small, this simplifies to:

$$\frac{k_c}{2k_t} = [C] + \frac{[C]^2}{[AA]}$$

Appendix 3

Table 1 Atomic coordinates and U(eq) for **93** (Chapter 4)

Atom	x	y	z	U(eq)
N(1)	3203(2)	3614(1)	5024(1)	21(1)
C(2)	4768(2)	3566(1)	4708(1)	22(1)
S(3)	4584(1)	2954(1)	3595(1)	26(1)
C(4)	2637(2)	3247(1)	3235(1)	26(1)
C(5)	1982(2)	3347(1)	4295(1)	22(1)
C(6)	2835(2)	3891(1)	5928(1)	21(1)
O(6)	1546(1)	3902(1)	6190(1)	29(1)
C(7)	4089(2)	4264(1)	6623(1)	21(1)
O(7)	4714(1)	4811(1)	6377(1)	26(1)
O(8)	4231(1)	3926(1)	7546(1)	25(1)
N(9)	5386(2)	4264(1)	8251(1)	25(1)
C(10)	5207(2)	4026(1)	9153(1)	23(1)
C(11)	6240(2)	4265(1)	10035(1)	22(1)
C(12)	6073(2)	3964(1)	11003(1)	27(1)
C(13)	7007(2)	4186(1)	11862(2)	33(1)
C(14)	8105(2)	4711(1)	11753(2)	36(1)
C(15)	8280(2)	5010(1)	10790(2)	35(1)
C(16)	7360(2)	4791(1)	9934(1)	29(1)
C(17)	5835(2)	3249(1)	5548(1)	25(1)
C(18)	7155(2)	3540(1)	5895(1)	27(1)
C(19)	8098(2)	3189(1)	6775(2)	43(1)
C(20)	7813(2)	4230(1)	5479(2)	38(1)
C(21)	2591(2)	3979(1)	2650(2)	30(1)
C(22)	1834(2)	2650(1)	2574(1)	33(1)
C(23)	1329(2)	2632(1)	4673(1)	26(1)
O(23)	2045(2)	2135(1)	5085(1)	34(1)
O(24)	-165(1)	2626(1)	4439(1)	33(1)
C(25)	-936(2)	1957(1)	4684(2)	44(1)

Table 2 Bond lengths (Å) for **93** (Chapter 4).

Atom	Atom	Distance	Atom	Atom	Distance
N(1)	C(6)	1.344(2)	N(9)	C(10)	1.272(2)
N(1)	C(5)	1.462(2)	C(10)	C(11)	1.472(2)
N(1)	C(2)	1.489(2)	C(11)	C(12)	1.391(3)
C(2)	C(17)	1.498(2)	C(11)	C(16)	1.395(3)
C(2)	S(3)	1.820(17)	C(12)	C(13)	1.393(3)
S(3)	C(4)	1.835(18)	C(13)	C(14)	1.380(3)
C(4)	C(22)	1.523(2)	C(14)	C(15)	1.385(3)
C(4)	C(21)	1.529(3)	C(15)	C(16)	1.382(3)
C(4)	C(5)	1.552(3)	C(17)	C(18)	1.332(2)
C(5)	C(23)	1.521(2)	C(18)	C(19)	1.501(3)
C(6)	O(6)	1.225(2)	C(18)	C(20)	1.503(3)
C(6)	C(7)	1.531(2)	C(23)	O(23)	1.203(2)
C(7)	O(7)	1.196(2)	C(23)	O(24)	1.339(2)
C(7)	O(8)	1.343(2)	O(24)	C(25)	1.444(2)
O(8)	N(9)	1.453(18)			

Table 3 Bond angles (°) for **93** (Chapter 4).

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C(6)	N(1)	C(5)	117.79(14)	O(8)	C(7)	C(6)	109.41(14)
C(6)	N(1)	C(2)	124.63(13)	C(7)	O(8)	N(9)	112.20(12)
C(5)	N(1)	C(2)	117.58(13)	C(10)	N(9)	O(8)	107.47(14)
N(1)	C(2)	C(17)	111.85(14)	N(9)	C(10)	C(11)	119.88(16)
N(1)	C(2)	S(3)	103.51(10)	C(12)	C(11)	C(16)	119.15(16)
C(17)	C(2)	S(3)	110.71(12)	C(12)	C(11)	C(10)	118.69(16)
C(2)	S(3)	C(4)	92.51(8)	C(16)	C(11)	C(10)	122.15(16)
C(22)	C(4)	C(21)	110.24(15)	C(11)	C(12)	C(13)	120.50(18)
C(22)	C(4)	C(5)	112.94(15)	C(14)	C(13)	C(12)	119.80(18)
C(21)	C(4)	C(5)	110.09(15)	C(13)	C(14)	C(15)	119.93(17)
C(22)	C(4)	S(3)	108.96(13)	C(16)	C(15)	C(14)	120.62(18)
C(21)	C(4)	S(3)	111.28(12)	C(15)	C(16)	C(11)	119.98(17)
C(5)	C(4)	S(3)	103.15(11)	C(18)	C(17)	C(2)	125.53(16)
N(1)	C(5)	C(23)	110.93(14)	C(17)	C(18)	C(20)	124.69(16)
N(1)	C(5)	C(4)	107.34(13)	C(19)	C(18)	C(20)	114.70(16)
C(23)	C(5)	C(4)	111.73(14)	O(23)	C(23)	O(24)	125.02(16)
O(6)	C(6)	N(1)	123.63(15)	O(23)	C(23)	C(5)	125.49(16)
O(6)	C(6)	C(7)	118.85(15)	O(24)	C(23)	C(5)	109.44(15)
N(1)	C(6)	C(7)	117.34(14)	C(23)	O(24)	C(25)	116.00(15)
O(7)	C(7)	O(8)	127.41(15)	O(7)	C(7)	C(6)	122.84(15)