APPROACHES TO CHIRAL AZIRIDINATION: FORMATION AND THERMAL REARRANGEMENTS OF N-ETHOXYCARBONYLAZIRIDINES

by

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Thesis presented for the degree of

DOCTOR OF PHILOSOPHY

University of Edinburgh 1988

For Dad

DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. I. Gosney since 1st October 1984, the date of my admission as a research student.

Dian E. Thomson

POST GRADUATE LECTURE COURSES

The following is a statement of the courses attended during the period of research.

Organic Research Seminars (3 years attendance).

Current Topics in Organic Chemistry, various lecturers (10 lectures).

Industrial Chemistry, Drs. A. Nicoll, R. Sinclair and L. Mustoe, Paisley College of Technology, (5 lectures).

Departmental Technical German Lectures and Examination, (1984-85).

Carbohydrate Chemistry, Prof. R. Ramage, (5 lectures).

Modern Synthetic Methods in Organic Chemistry, Prof. R. Ramage, (5 lectures).

Multipulse Methods in n.m.r. Spectroscopy, Dr. I. Sadler, (5 lectures).

The Elements of Cell Biology, Dr. J. Phillips, (5 lectures).

Industrial Topics in Organic Chemistry, ICI Pharmaceutical and Organic Divisions and Beecham Pharmaceuticals, (5 lectures).

Eighth Lakeland Heterocyclic Symposium, Grasmere, May 1987.

ACKNOWLEDGEMENTS

I would like to thank Dr. I. Gosney for his help and guidance throughout the past three years. Thanks is also due to Professor J.I.G. Cadogan and Dr. P. Hodgson for their interest and enthusiasm. Financial assistance from British Petroleum p.l.c. is gratefully acknowledged. The typing of the manuscript is the result of the hard work of Mrs. M. Gibb, to whom I am indebted.

I would also like to extend my gratitude to my colleagues for their help and advice, and to the technical staff of the department of chemistry for their excellent provision of services. Particular thanks is due to Mr. J.R.A. Millar, of the departmental n.m.r. service, for his help and patience.

Finally, I would especially like to express my gratitude to my husband, Graeme, for his patience and encouragement during our university careers, and to my father and brother, for their understanding, help and support.

ABSTRACT

Investigations into the potential synthesis of optically active aziridines *via* asymmetric induction in the addition of alkoxycarbonylnitrenes to alkenes has been carried out. The addition of ethoxycarbonylnitrene, generated by α-elimination from ethyl *p*-nitrobenzenesulphonoxycarbamate, to prochiral alkenes in the presence of an optically active base or phase-transfer catalyst has been studied. No optical activity was recorded in aziridines formed from the reaction of ethoxycarbonylnitrene with styrene or 1-methyl-1-cyclohexene in a two-phase system using the optically active phase-transfer catalyst (-)-*N*-benzylcinchonidinium chloride. Generation of ethoxycarbonylnitrene with the chiral base (*S*,*S*)-2,3-dimethoxy-1,4-bis-(dimethylamino)-butane gave only racemic 1-methyl-7-azabicyclo-[4.1.0]-heptane.

The base induced decomposition of the novel, optically active nitrene precursor [(1*S*)-*endo*]-(-)-bornyl *p*-nitrobenzenesulphonoxycarbamate in the presence of styrene afforded 1-bornoxycarbonyl-2-phenylaziridine as the major product. N.m.r. spectra of the crude product confirmed that no asymmetric induction had taken place during the aziridination.

The above studies brought to light a novel, convenient synthesis of 2-oxazolidinones. Some *N*-ethoxycarbonylaziridines were found to undergo clean,

thermal transformation into 2-oxazolidinones during flash vacuum pyrolysis (FVP) at temperatures in excess of 600°C by a hitherto unreported tandem reaction sequence equivalent to direct insertion of CO_2 into the parent 1H-aziridine. During pyrolysis at 650°C, 1-ethoxycarbonyl-2-phenylaziridine underwent regiospecific ring expansion, following cleavage of the N-C(2) bond to give 5-phenyl-4,5-dihydro-2-ethoxyoxazole. The pyrolysis conditions resulted in subsequent elimination of ethene from the oxazoline, *via* an ene-type mechanism, to give 5-phenyl-2-oxazolidinone in 88% yield. Similar treatment of 1-methoxycarbonyl-2-phenylaziridine afforded only 5-phenyl-4,5-dihydro-2-methoxyoxazole, whereas pyrolysis of 1-*tert*-butoxycarbonyl-2-phenylaziridine resulted in its decomposition to 2-phenylaziridine and gaseous products.

The above synthesis of 5-phenyl-2-oxazolidinone was successfully extended to include the synthesis of other 2-oxazolidinones as well as 2-thiazolidinone and 2-oxazolidinthione from suitable *N*-substituted aziridines. All ring expansions were regiospecific with the exception of that of 1-ethoxycarbonyl-2-*tert*-butylaziridine which was regioselective.

Finally, this tandem reaction sequence was shown to fail when extended to the *N*-ethoxycarbonylazetidine system. Pyrolysis of 1-ethoxycarbonyl-2-phenylazetidine resulted in its decomposition to styrene, methyl isocyanate and acetaldehyde.

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A. INTRODUCTION TO ASYMMETRIC SYNTHESIS

1. General Introduction

The area of asymmetric synthesis is currently receiving much attention, and successful results are having a considerable impact on synthetic chemistry. The synthesis of optically pure organic compounds is a challenging task. Resolution of a racemic synthetic mixture is a useful technique, but it is time consuming and uneconomical if only one enantiomer is required. Reagents that can induce catalytic enantiocontrol of chemical reactions therefore represent an extremely important synthetic method which can provide solutions to long standing problems particularly in the fields of food additives, pesticides and pharmaceuticals.

An asymmetric synthesis can be described as a preferred transformation of a prochiral substrate into one enantiomer of the product, as in the case of epoxides as shown in Scheme 1.

Scheme 1

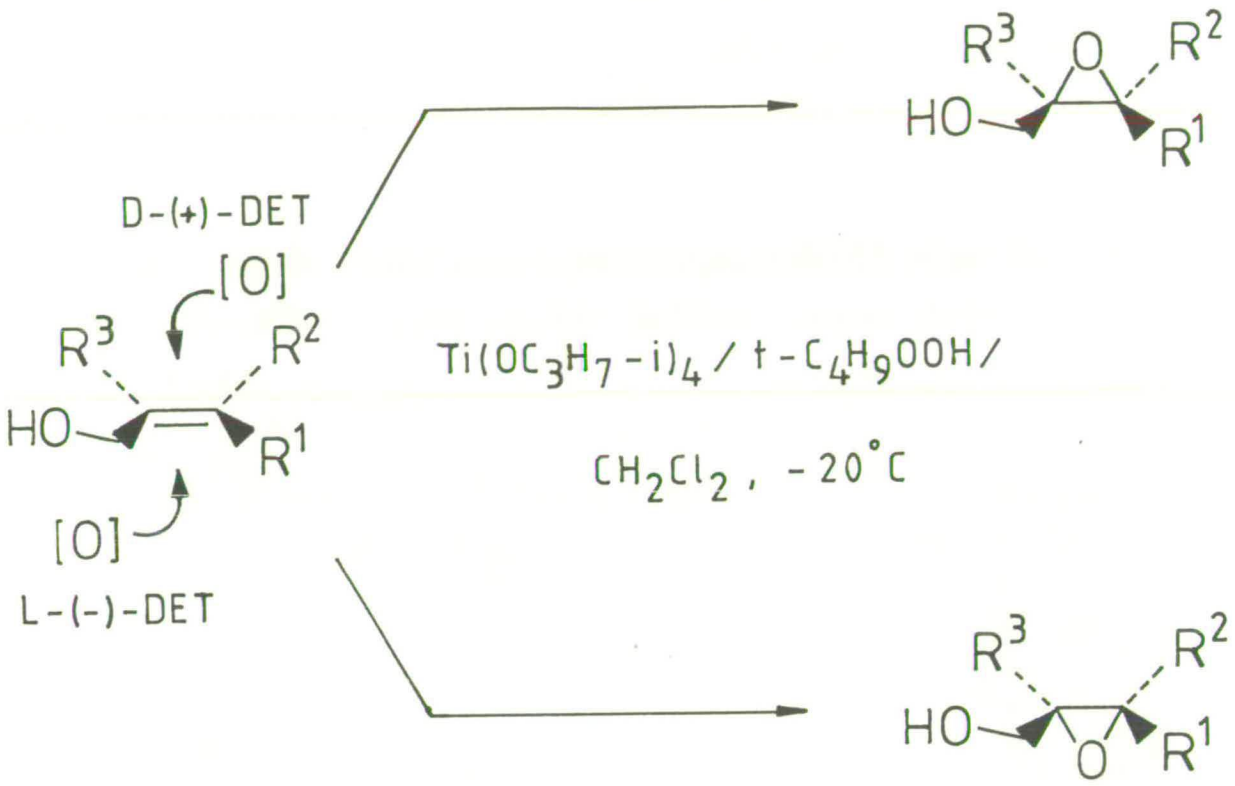
This excludes diastereoselective reactions for which the substrate already contains chiral centres that are preserved in the product as is illustrated in Scheme 2. The former example creates chirality whereas the latter propagates it. In Scheme 1, the alkene possesses enantiotropic faces which are differentiated only by the chirality of the catalyst. The alkene faces in Scheme 2 are already differentiated by the presence of an adjacent chiral centre and are diastereotopic, therefore chirality in the epoxide may be generated by an achiral catalyst.

Scheme 2

The success of asymmetric catalysis lies with the kinetics of the reaction. The enantiomeric excess (ee) is determined by the difference in free energy of activation of the two diastereomeric states formed during the asymmetric reaction. The greater the difference, the better is the enantioselection. There are several important examples of asymmetric catalytic reactions that are mediated by transition metal complexes. These catalysts have been successfully employed to transform achiral substrates into optically pure products. Alkene hydrogenation, carbon-carbon bond formations and alkene oxidations have all been successfully carried out using asymmetric catalysis. These examples are outlined in a review by Bosnich.[1]

2. Asymmetric Epoxidation

Perhaps the best and most important example of asymmetric catalysis is the aforementioned chiral epoxidation of allylic alcohols (Scheme 1). Sharpless discovered that asymmetric epoxidation of primary allylic alcohols using L-(+)- or D-(-)-diethyl tartrate, titanium tetraisopropoxide and dry tert-butyl hydroperoxide gave uniformly high asymmetric induction (95% ee) for a wide range of allylic alcohols.[2-6] The epoxide oxygen is always delivered from the same enantioface of the alkene (given a specific tartrate), as shown in Scheme 3.



Scheme 3

The mechanistic aspects of this asymmetric catalysis centre themselves on several unique properties of the titanium alkoxide system present during the reaction. The mechanism is discussed in a paper by Sharpless.[7]

Epoxides are versatile and important intermediates in organic chemistry and have prompted the publication of reviews of the subject.[3,8,9] Since the Sharpless epoxidation was first reported seven years ago, hundreds of key applications of this reaction have been

reported. Many of these examples are reviewed by Pfenninger.[10] The majority of these examples are taken from the synthesis of naturally occurring, enantiomerically pure compounds such as carbohydrates, terpenes, pheromones and antibiotics, thus emphasising the synthetic importance of asymmetric epoxidation.

B. AZIRIDINES

1. Physical Properties

(1)

Aziridines (1), the nitrogen analogues of epoxides, have also become increasingly important as synthetic intermediates over the past two decades. Aziridines, like epoxides, undergo ring opening reactions with ease. They are perhaps more versatile since, as well as reactivity attributed to the strained ring system, the reactivity of the aziridine nitrogen closely resembles that of other non-aromatic amines.

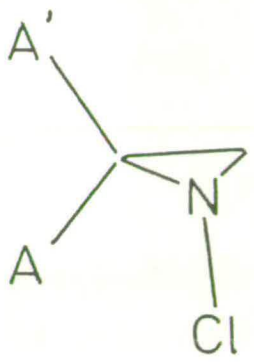
For the purpose of subsequent discussion it is necessary to point out some pertinent properties of aziridines. Lower molecular weight aziridines are colourless oils with an ammonia-like smell. Aziridines require careful handling since they are all highly toxic by inhalation and skin contact, causing severe burns, kidney damage, blindness and respiratory failure. They are also biological alkylating agents, producing symptoms similar to those caused by exposure to high energy radiation, as a result of their attack of DNA. Many aziridines have widespread biological activity[16] and a

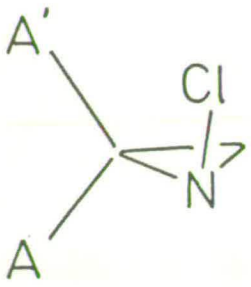
variety of potential industrial uses,[16] but their toxicity to humans has restricted their use.

The structure of the aziridine ring is such that the bond lengths are almost equivalent and the bond angles are all approximately 60°C. The nitrogen atom is pyramidal. Ethylenimine and other aziridines are relatively weak bases due to electron delocalisation in the three membered ring. Measured pKa's fall within the range 7.9-9.4 compared to ammonia (9.5) and dimethylamine (10.7).

In contrast to most amines, bonding constraints of the aziridine ring can depress inversion rates of the nitrogen. This effect can be studied by n.m.r. spectroscopy at low temperatures. In general conjugative effects stabilise the transition state and accelerate inversion. Electron-withdrawing groups on the nitrogen hinder rehybridisation and bulky groups on the nitrogen facilitate inversion.

It was suggested in 1939 that configurational stability at nitrogen might be attainable,[11,12,13] however it was not until 1968 that this was first achieved, when diastereoisomeric pairs of N-chloroaziridines were successfully separated by chromatography.[14]





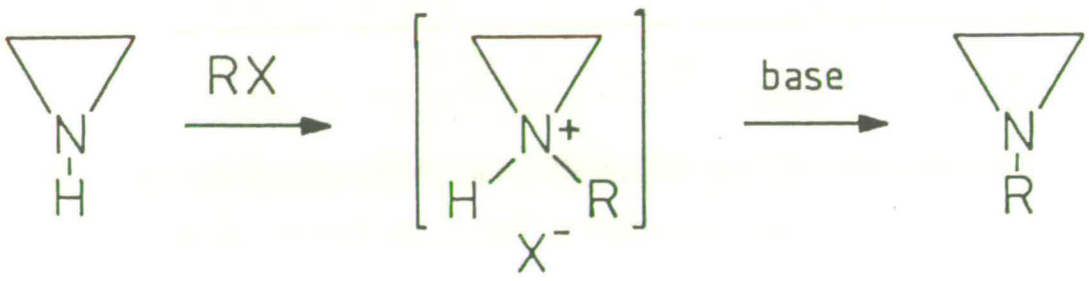
It has also been possible to achieve synthesis of optically active aziridines, in which nitrogen is the only chiral centre, via chlorination with an optically active hypochlorite. This aziridine racemized in 4 days at 0°C.[15]

The aziridine ring is stable to metal hydrides, organometallic reagents, Wittig reagents, ozonolysis and other similar reaction conditions. This allows modification of aziridine side chains to be achieved, thus increasing the value of the product. New synthetic approaches, substituent modifications and ring-opening reactions have resulted in an increase in aziridine utility in synthetic routes, physical studies and biological investigations. The area of aziridine

chemistry has been examined in reviews by Dermer and Ham,[16] Fanta[17] and, more recently, Deyrup.[18]

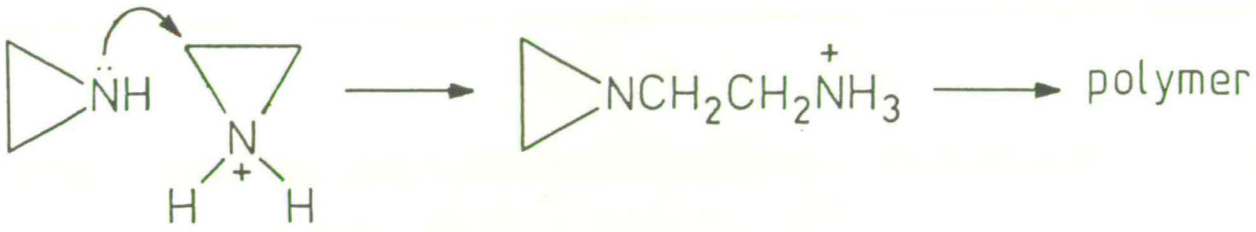
2. General Reactions

For convenience, the reactions of aziridines are generally divided into those in which the ring remains intact and those where the ring is opened or undergoes expansion. The former class of reactions concern themselves mainly with the reactions of the ring nitrogen, although the less common side chain modifications and ring carbon reactions are also included. N-Unsubstituted aziridines will react with alkyl, aryl and acyl halides as well as sulphenyl and sulphonyl halides and phosphorous halides. Precautions must be taken to ensure that the reaction remains under alkaline conditions since the intermediate aziridinium ion is highly susceptible to nucleophilic ring opening, as shown in Scheme 5.



Scheme 4

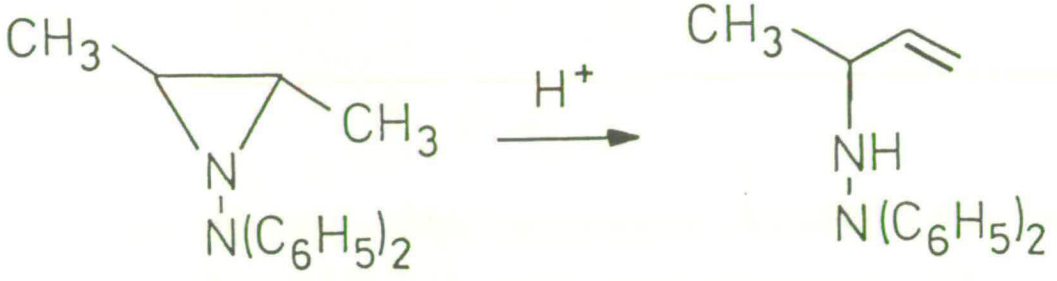
Aziridines will undergo Michael-type additions to a wide variety of alkenes and alkynes. They will also react with epoxides to give β-hydroxyalkylaziridines, but this is successful only if the reactants are very pure. Impurities usually result in the formation of polymeric products. A similar effect is observed on storage of impure aziridines. If the ring becomes protonated it may undergo nucleophilic attack at an aziridine carbon which usually leads to polymerisation by the mechanism outlined in Scheme 5. In contrast to this, highly purified basic aziridines are stable to heat.



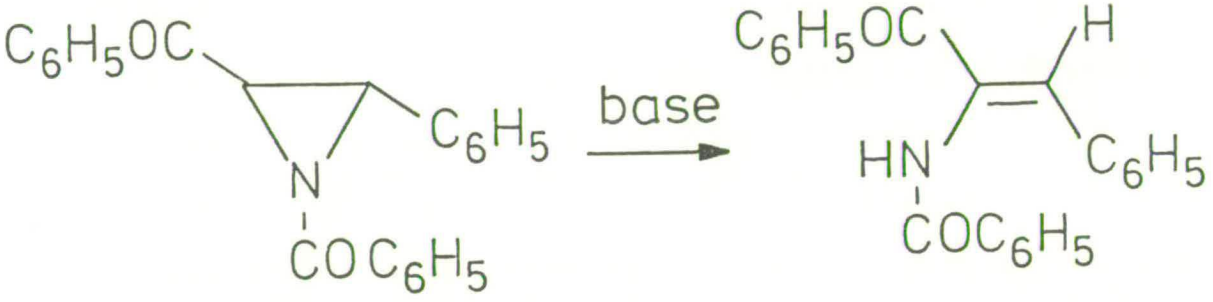
Scheme 5

Reactions in which the ring is opened or enlarged form some of the most useful examples of aziridine chemistry. Acidic and nucleophilic ring opening reactions that occur without resultant isomerisation are generally of little synthetic value. Much more important are the enormous variety of aziridine rearrangements which may occur with acid, base or thermal catalysis. The type of rearrangement which occurs is dictated by the character of the ring substituents as well as reaction conditions. As a result of the many possible types and combinations of substituents, the variety of reported rearrangements are numerous and their nature diverse.

Isomerisations may be simple such as the acid catalysed isomerisation of aziridine (2) to give (3),[19] or the base catalysed rearrangement of (4) to (5).[20]

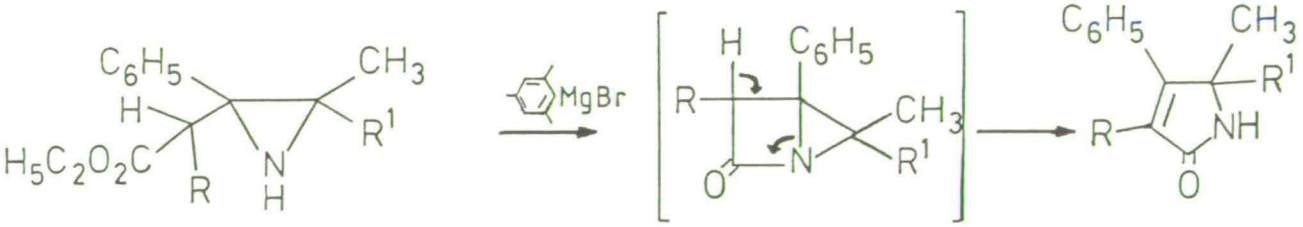


(2) (3)



(4) (5)

Many reactions are mechanistically more complicated such as the rearrangement of aziridine (6) to give (7) <u>via</u> a bicyclic intermediate.[21]

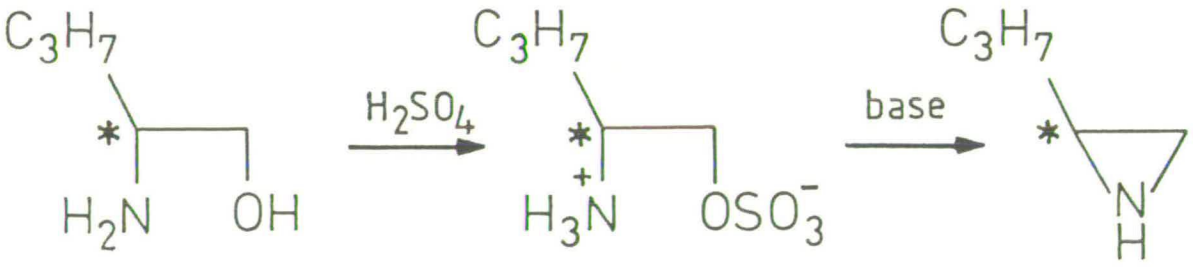


(6) (7)

Aziridine rearrangements have been reviewed in detail by several authors.[22-25]

3. Chiral Aziridines

Despite the wealth of reports concerning chiral epoxidation, there exist few examples of chiral aziridine synthesis. Those which have been reported are adapted from classical synthetic methods for achiral analogues. Several approaches to aziridine synthesis are stereospecific therefore, by using an appropriate optically active reagent, it is possible to produce an optically active product. One such instance is a modification of the Wenker synthesis[26] which starts with an optically active alcohol,[27] as outlined in Scheme 6.

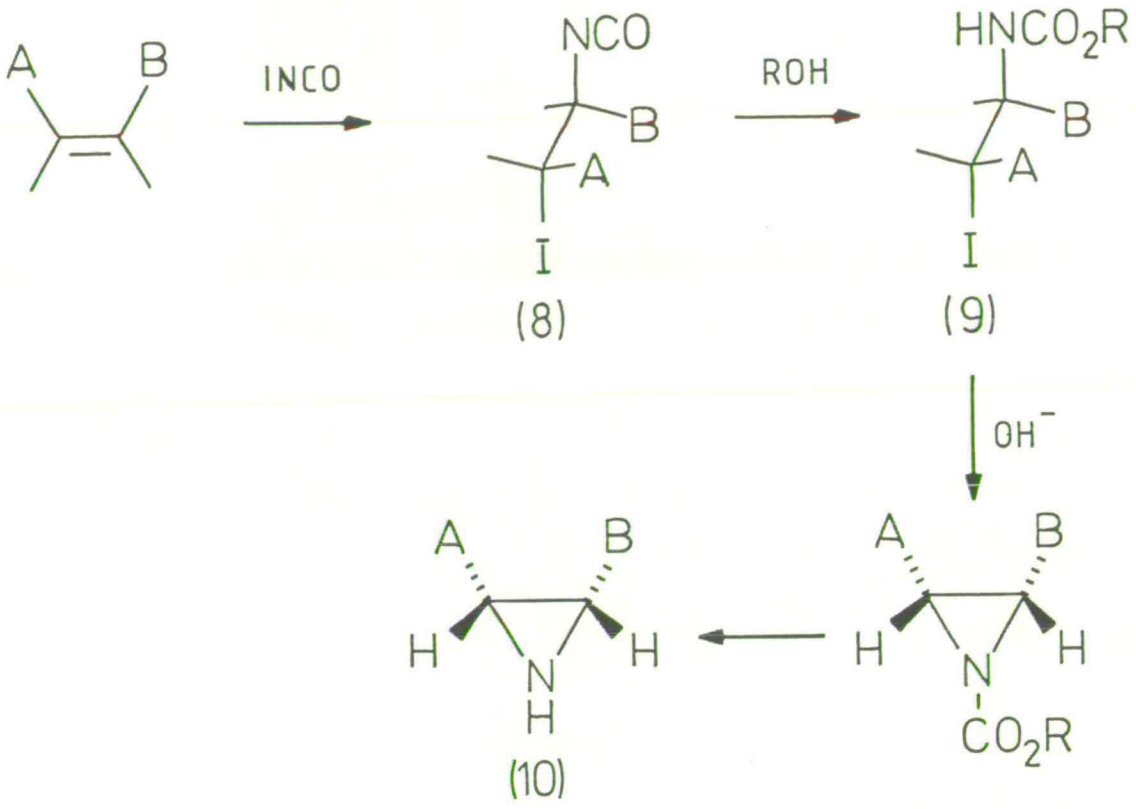


Scheme 6

Since optically active β-aminoalcohols are readily

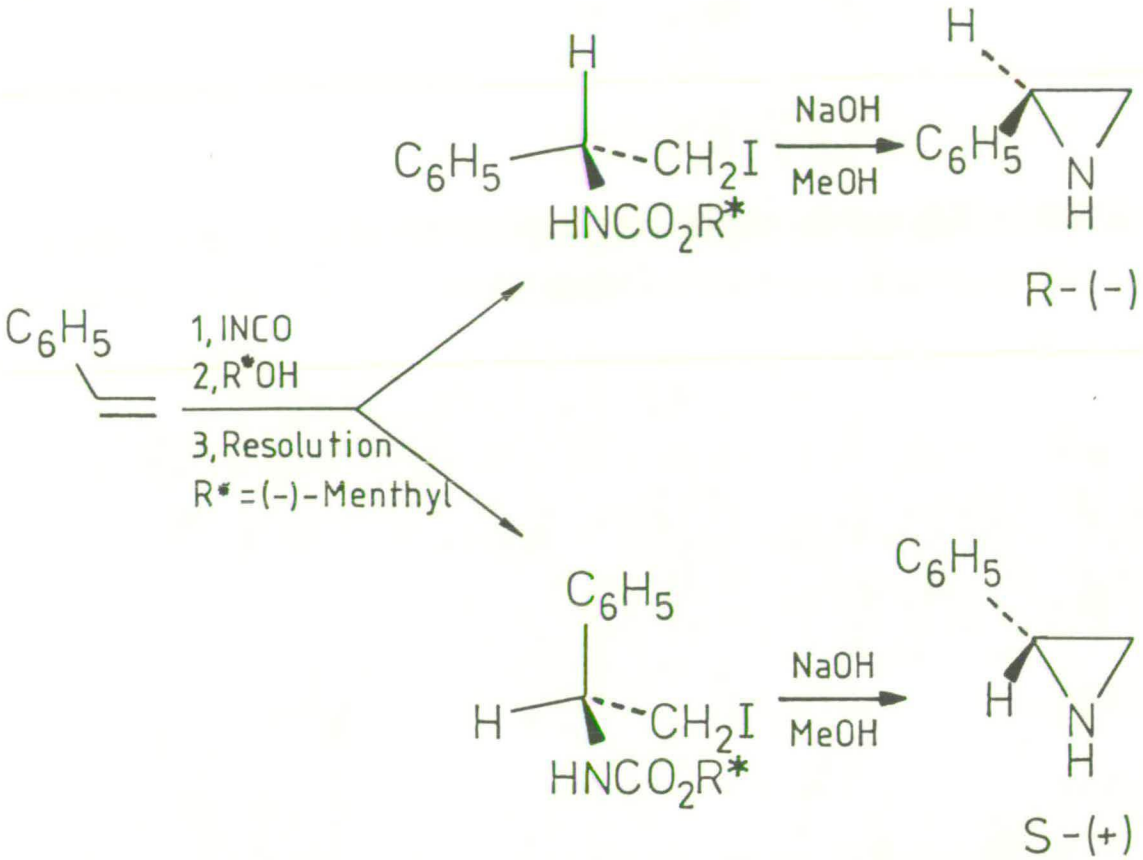
available by reduction of amino acids, it seems surprising that this synthesis has not been exploited.

Fujita *et al*[28] have used a modification of Hassner's β-iodocarbamate cyclisation route to aziridines[29] to prepare optically active 2-phenylaziridines. Iodine isocyanate adds stereospecifically (*trans*), regiospecifically and selectively to alkenes to give high yields of β-iodoisocyanates (8). The conditions are mild and iodine isocyanate can be generated *in situ* from silver cyanate and iodine. Reaction of (8) with an alcohol gives a β-iodocarbamate (9) which is subsequently cyclised and hydrolysed in the presence of base to give the aziridine (10), (Scheme 7)



Scheme 7

The Japanese workers employed a chiral alcohol, (-)-menthol, in their version of Hassner's synthesis. The resulting diastereomeric β-(iodomethyl)benzylcarbamic acid, (-)-menthyl ester was fractionally recrystallised from methanol and the two diastereomers were treated independently with methanolic sodium hydroxide to give (+)- and (-)- 2-phenylaziridine as shown in Scheme 8.



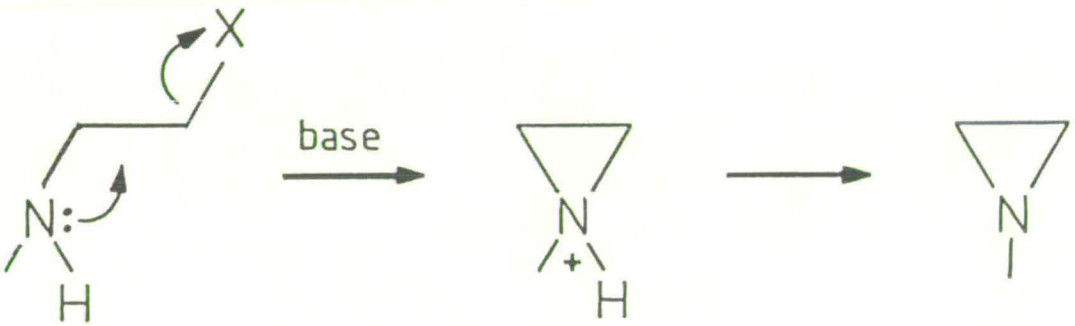
Scheme 8

4. Aziridine Synthesis

In addition to the procedures mentioned above, there are several other general methods of aziridine synthesis which so far have not been adapted to include the synthesis of chiral aziridines. These synthetic methods have been reviewed,[16-18,30] but for the benefit of the reader are briefly summarised here.

(i) Synthetic methods involving internal

cyclisation are the oldest and most straightforward approach to aziridine synthesis. The simplest of these methods are the previously discussed Wenker synthesis[26] and the related Gabriel synthesis.[31] These methods are outlined in Scheme 9.



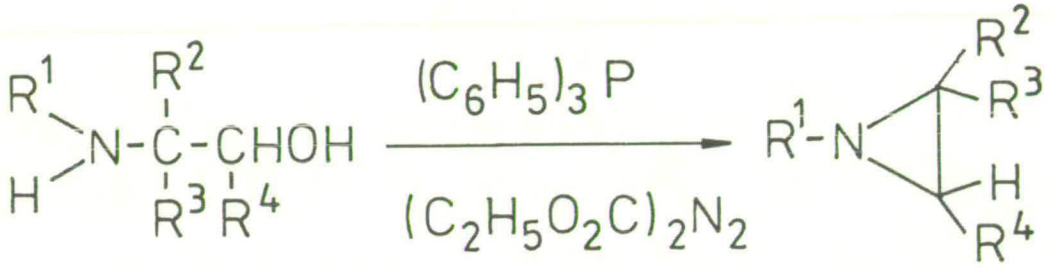
X = Br, Cl, I (Gabriel)

X = OSO_3H (Wenker)

Scheme 9

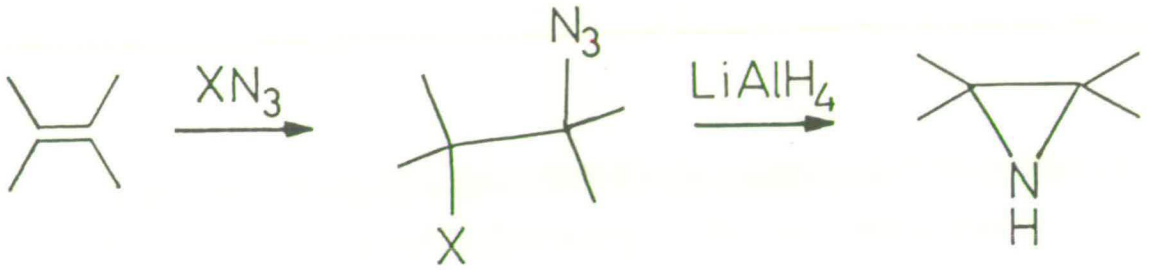
Recent developments in this synthetic approach include new and improved routes to precursors and milder conditions for the cyclisation step. Several publications display superior routes from amino alcohols to aziridines based on the driving force introduced by the strength of the phosphorus-oxygen bond.[32,33] The example outlined in Scheme 10 is a synthesis recently reported by Pfister.[34] The reaction of 2-aminoethanols with triphenylphosphine and diethylazodicarboxylate in

ether or tetrahydrofuran gives good yields of aziridines. These reactions proceed below 0°C and they are stereospecific (ring closure with inversion) making them suitable for the synthesis of chiral aziridines.



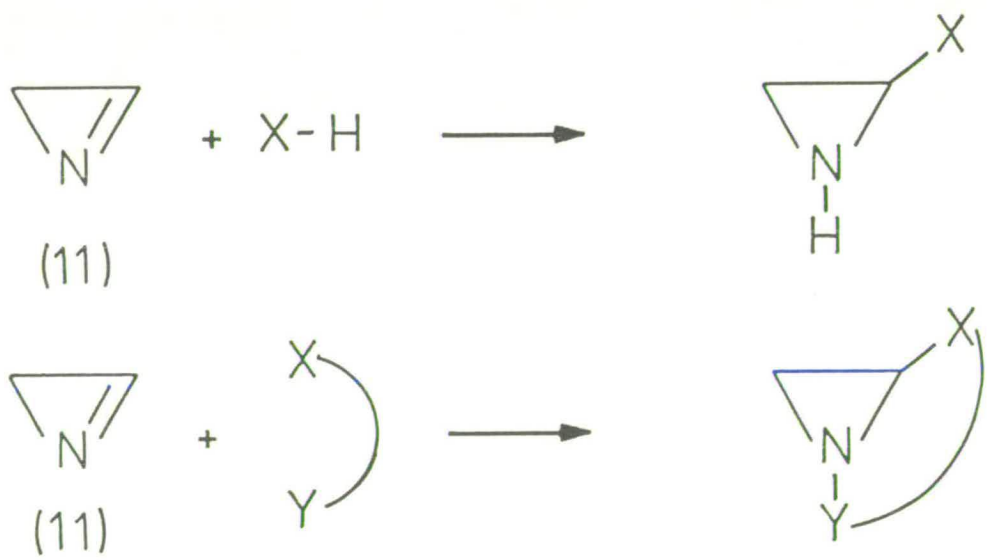
Scheme 10

(ii) The stability of the aziridine ring to many reducing agents allows reductive generation of β-aminohalides and subsequent direct cyclisation to the aziridine. One such approach is the reduction of β-haloazides[35,36] which are accessible through the stereospecific addition of a halogen azide to alkenes. These β-haloazides are reduced by lithium aluminium hydride to give a β-haloamine which will then cyclise to give the corresponding aziridine as outlined in Scheme 11.



Scheme 11

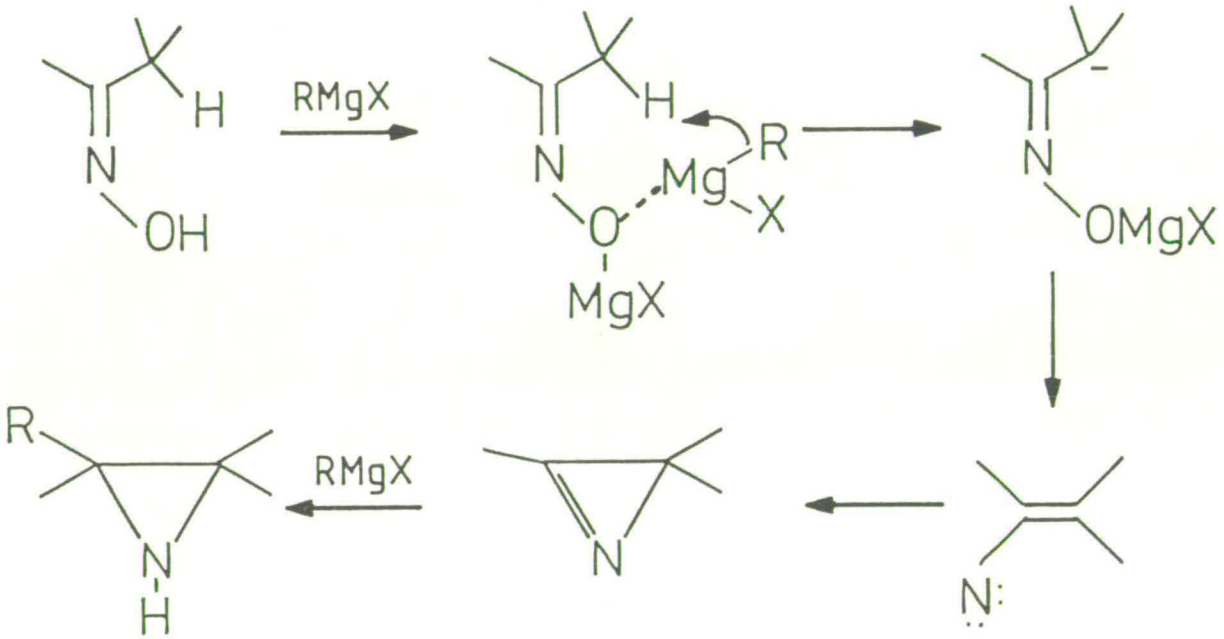
(iii) Synthetic routes to azirines (11) have become more numerous[37] and they can provide a useful precursor in aziridine synthesis. Many types of functionalised aziridines as well as fused ring systems can be obtained via this route.[38]



Related to the conversion of azirines to aziridines is the formation of the latter from oximes. The

reaction between oximes and Grignard reagents (Hoch-Campbell synthesis) and the related lithium aluminium hydride reduction of certain oximes have commanded considerable attention.[39,40,41]

The Hoch-Campbell synthesis involves nitrene formation and cyclisation to an intermediate azirine followed by addition of excess Grignard reagent to produce an aziridine as shown in Scheme 12.

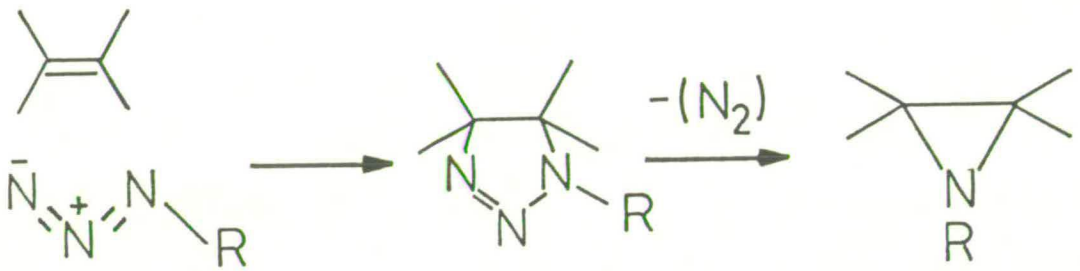


Scheme 12

The reduction of oximes with lithium aluminium hydride in certain cases yields aziridines instead of the expected amine. The reaction is stereoselective (only the cis-aziridine is formed) and ring closure takes place

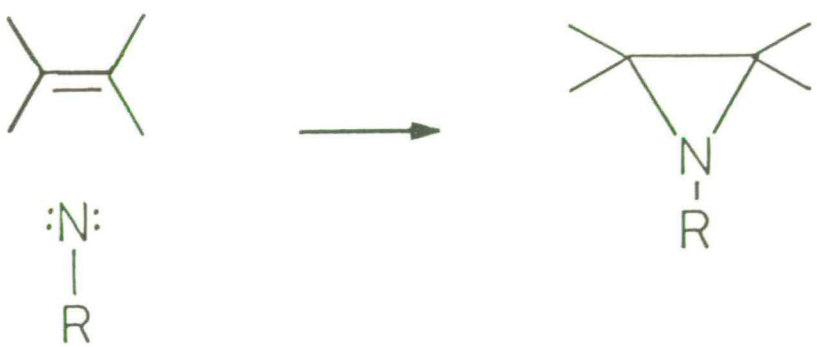
with loss of the α-cis proton. The proposed mechanism is similar to that elucidated for the Hoch-Campbell reaction.

(iv) There exist two major approaches to aziridine synthesis via cycloaddition to alkenes. One approach involves the formation of a triazoline (12) by 1,3-dipolar cycloaddition of an azide to an alkene followed by elimination of nitrogen gas giving an aziridine.[42-45]



(12)

A more direct approach, and one that is important to subsequent discussion in this programme, is the synthesis of aziridines via the addition of nitrenes to alkenes.



Before mentioning some typical examples, the properties and generation of nitrenes will first of all be discussed.

C. NITRENES

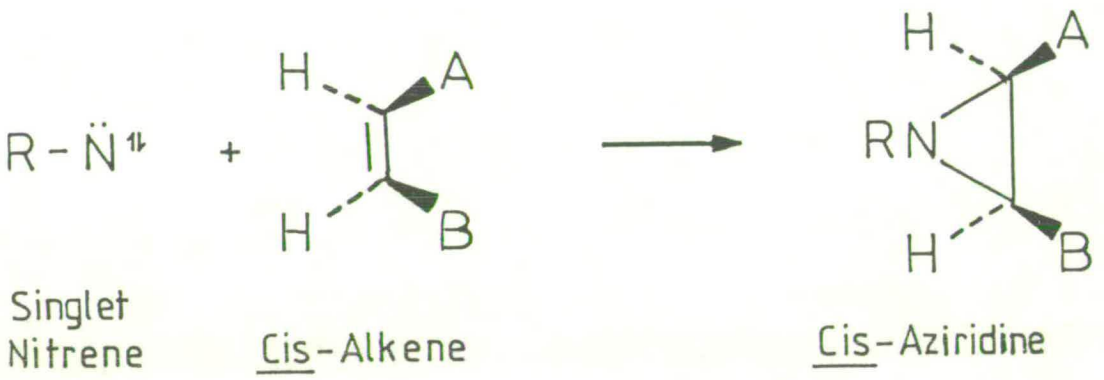
1. Introduction

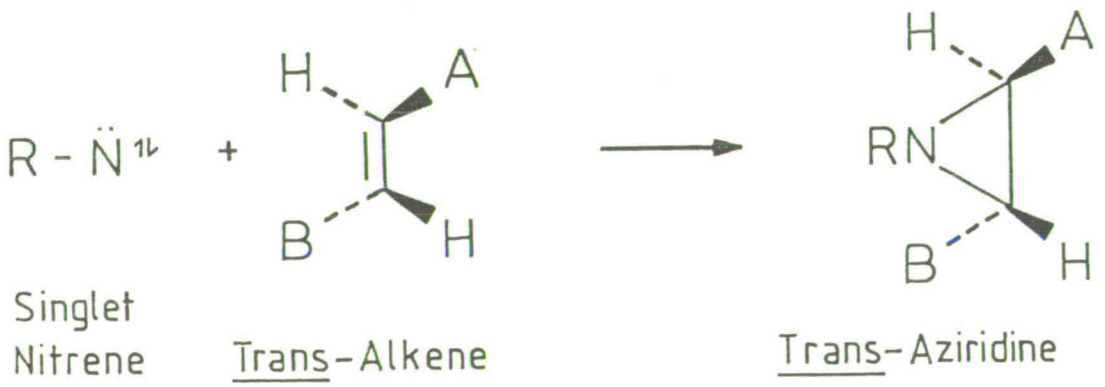
Nitrenes are univalent nitrogen derivatives. They are electron deficient, electroneutral and isoelectronic with carbenes. Lwowski has extensively reviewed the formation, properties and reactions of these reactive intermediates.[30] Nitrenes, like carbenes, can exist in a singlet or a triplet state. Both states have a normal bond to the nitrogen substituent, a set of two spin paired electrons and two electrons that can be arranged in two different ways. The singlet nitrene has these two electrons paired in one orbital, and has an empty bonding orbital. The triplet state has its two electrons in separate orbitals with their spins parallel. On the basis of Hund's rule, the triplet state would be expected to be the ground state. This is generally found to be correct for most nitrenes, one notable exception being aminonitrenes.

2. Nitrene Addition to Alkenes

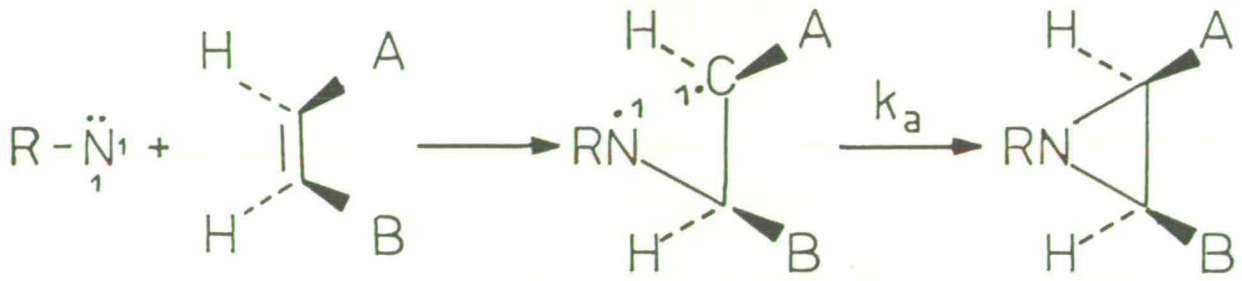
Skell's rules[46] for the addition of triplet and singlet carbenes to alkenes can be adapted for nitrenes. The addition of the singlet species to the carbon-carbon

double bond occurs in a single step, and is stereospecific as shown in Scheme 13. Conversely, Scheme 14 shows that the addition of the triplet species occurs in two discrete steps <u>via</u> a 1,3-diradical intermediate. The rate of ring closure of this intermediate is usually considerably smaller than that for rotation about the carbon-carbon bond, consequently stereospecificity is lost.

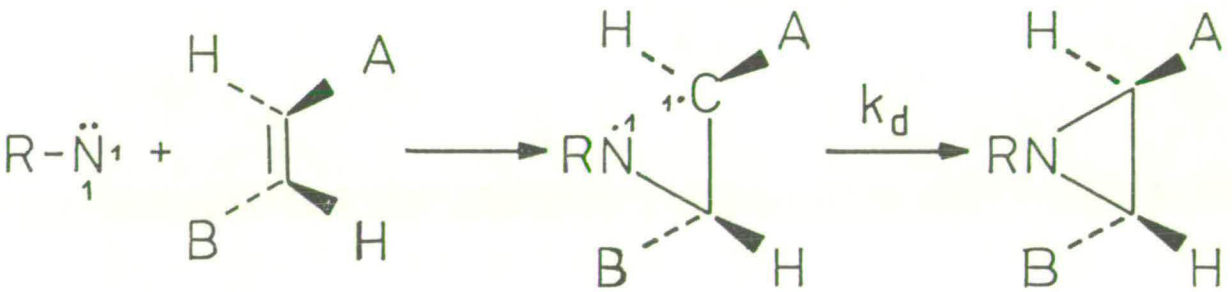




Scheme 13



Triplet Nitrene — Cis-Alkene — Cisoid — Cis-Aziridine



Triplet Nitrene — Trans-Alkene — Transoid — Trans-Aziridine

$$k_d \simeq k_a < k_h \simeq k_c$$

Scheme 14

Thus, to summarise, in the case of a nitrene with a triplet ground state, if it is generated in its ground state then the addition to the double bond will be non-stereospecific. If, however, the nitrene is generated in its singlet state it may undergo intersystem conversion to become a lower energy triplet nitrene. In most cases the reaction of a singlet nitrene is much faster than the intersystem crossing, therefore mainly stereospecific addition will be obtained. The amount of triplet nitrene formed can be controlled by adjusting the concentration of the reactant that consumes the singlet state.

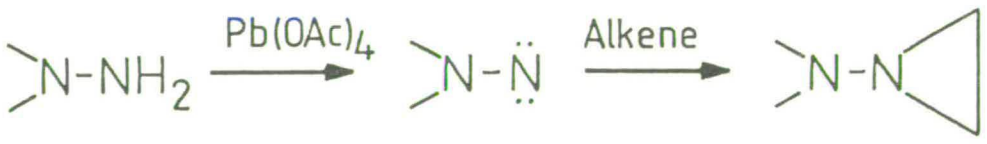
3. Nitrene Generation

Several species of nitrenes are known and approaches to generation include azide decomposition, primary amine oxidation and α-elimination. Despite the variety available, few nitrenes are used in aziridine synthesis. Alkyl nitrenes are very reactive due to lack of delocalization. These nitrenes tend to rearrange and aziridine formation fails. There are few reports of aryl- or sulphonyl-nitrenes forming stable aziridines. Cyanonitrene, formed from cyanogen azide, readily reacts with alkenes, as shown in scheme 15,[47] but this has not been pursued as a general route to aziridines. Many

reports concern themselves with physical aspects of the reaction.[48]

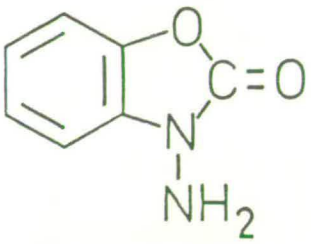
Scheme 15

The most important nitrenes used in the synthesis of aziridines are aminonitrenes and carbonylnitrenes. Lead tetraacetate oxidation of some 1,1-disubstituted hydrazine derivatives (13) in the presence of alkenes forms a useful route to N-aminoaziridines (15) via the aminonitrene (14).[49,50]



(13) (14) (15)

Aminonitrenes have a singlet ground state due to the stabilising power of the substituent. These nitrenes are generated in their singlet ground state, therefore the addition to alkenes is stereospecific.(16) and (17) are typical aminonitrene precursors, whereas structures such as (18) produce rearrangements and the resulting failure of nitrene formation.



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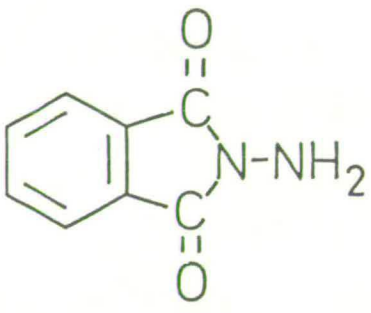

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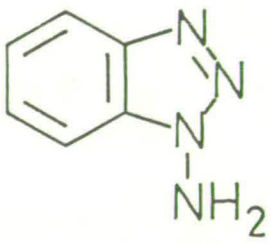
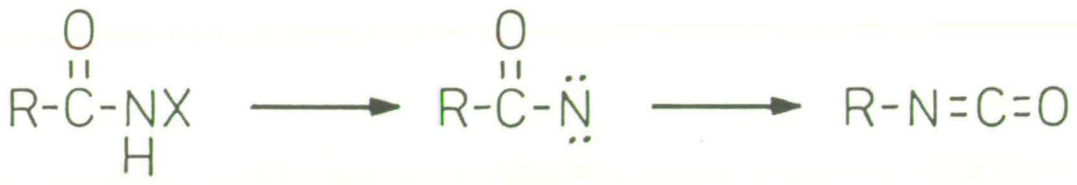


(18)

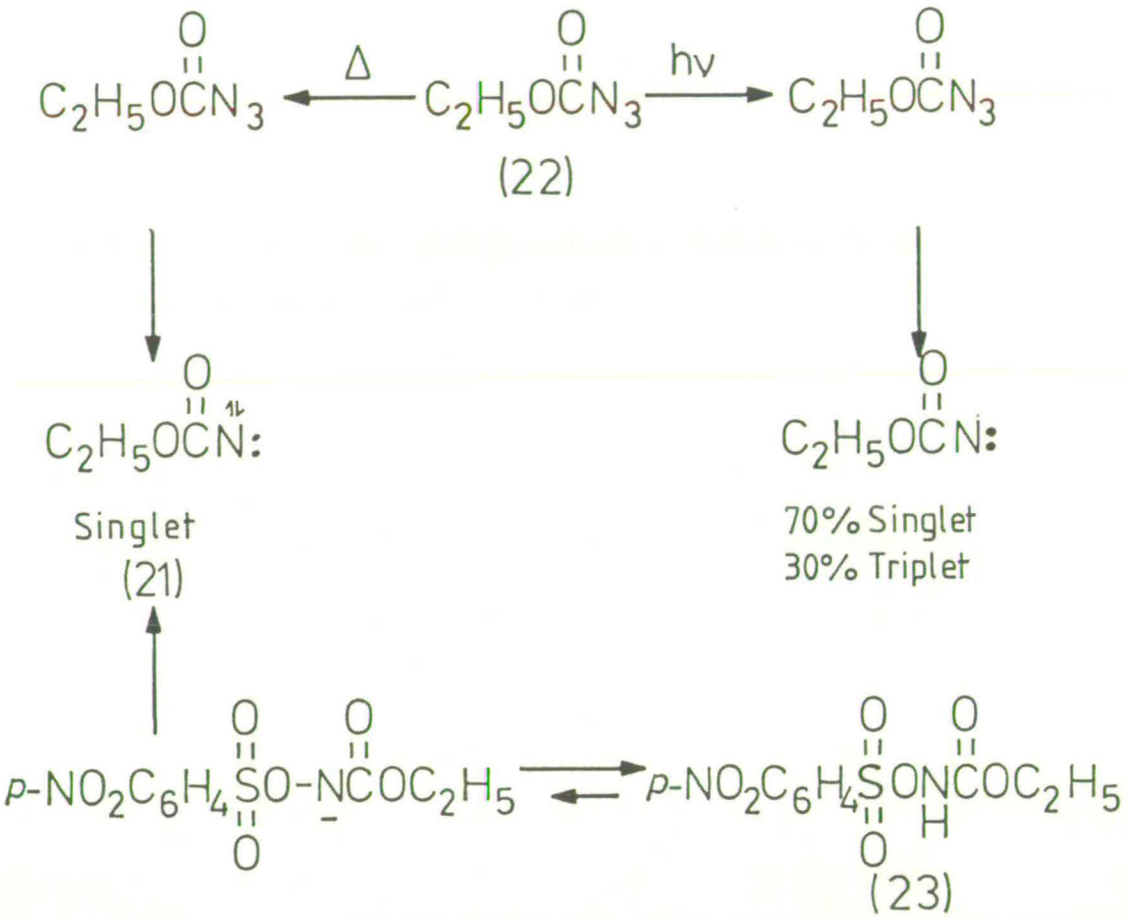
4. Ethoxycarbonylnitrene

Carbonylnitrenes comprise the best known class of nitrenes.[51] The most useful of these in aziridine formation tend to be alkoxycarbonylnitrenes, since alkylcarbonylnitrenes (19) frequently undergo Curtius, Hofmann or Lossen rearrangements to form an isocyanate (20).



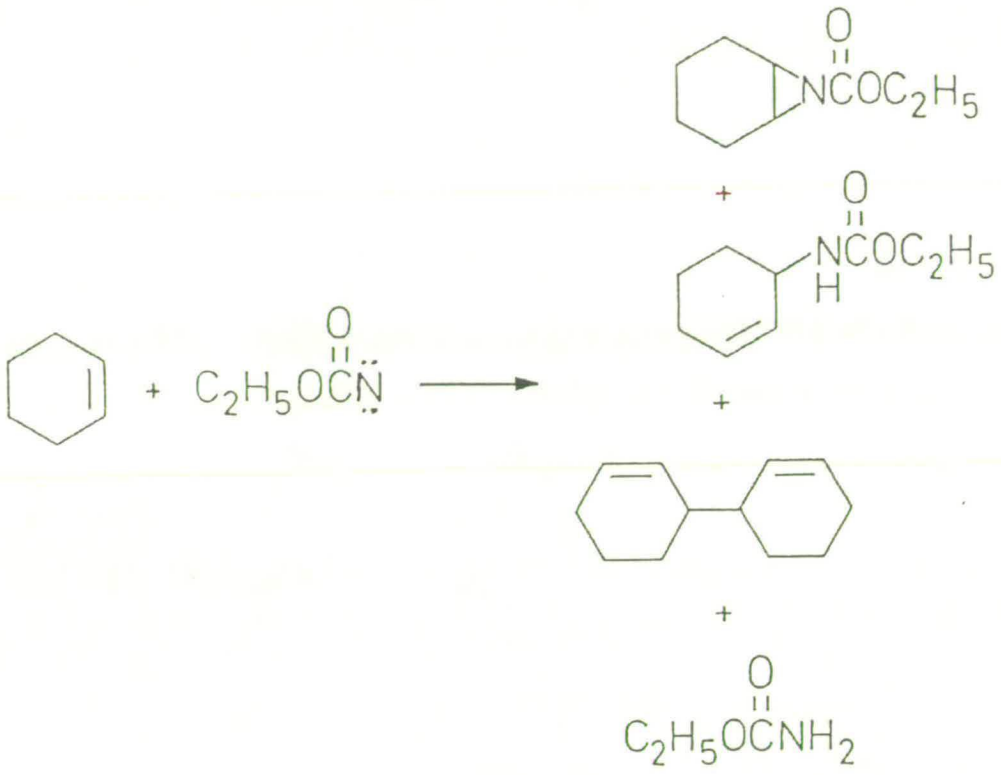
(19) (20)

The most frequently studied alkoxycarbonylnitrene is ethoxycarbonylnitrene (21) which can be generated by thermoloysis or photolysis of ethyl azidoformate (22) or by α-elimination from ethyl p-nitrobenzenesulphonoxy-carbamate (23) (Lwowski's reagent).[52-54] Wasserman showed that carbethoxynitrene has a triplet ground state.[55] Ethoxycarbonylnitrene obtained by α-elimination or by thermolysis of ethyl azidoformate is formed in a singlet state. About 30% of the nitrene obtained by photolysis of ethyl azidoformate is formed in the triplet state.



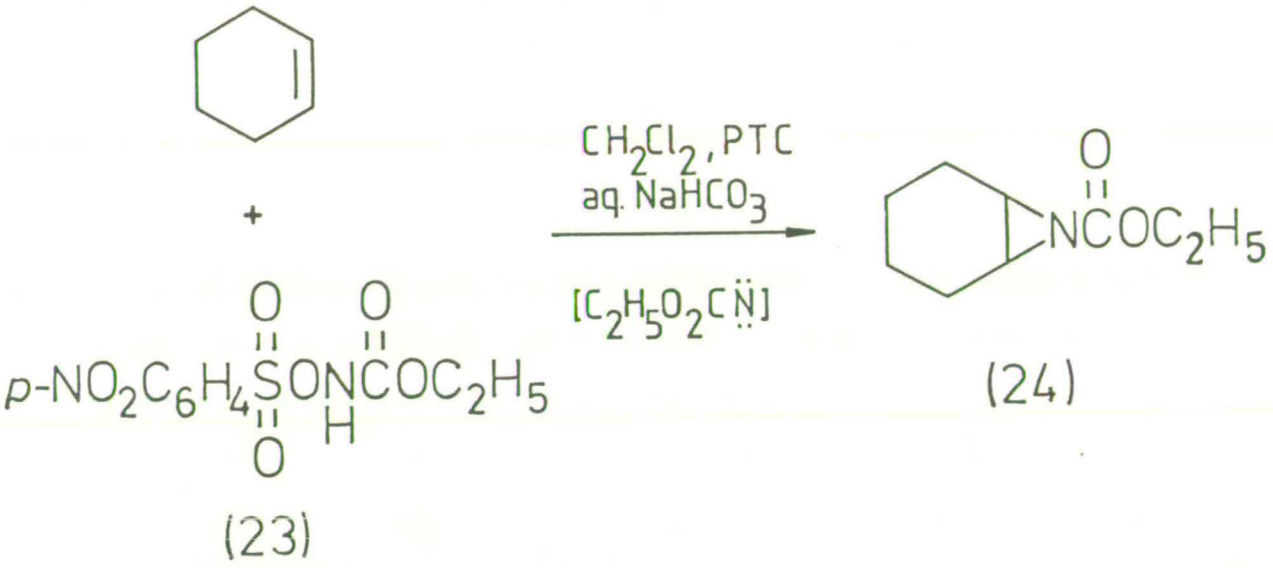
Scheme 16

There are many reported examples of aziridines being formed via the reaction of alkoxycarbonylnitrenes with alkenes. The majority of these reactions are reviewed by Lwowski,[30] Deyrup[18] and Muller and Hamer.[56] These aziridine formations usually result in the formation of by-products from competing bond insertion and proton abstraction reactions. Scheme 17 shows typical products obtained from the reaction of ethoxycarbonylnitrene with cyclohexene.[52-54]



Scheme 17

Seno et al have reported that the base decomposition of Lwowski's reagent in a two-phase system in the presence of cyclohexene and a phase transfer catalyst results in the formation of the 1-ethoxycarbonylaziridine (24).[57] The reactivity and product selectivity are analogous to those reported by Lwowski for the corresponding homogeneous reaction shown in Scheme 17. This indicates that the formation and reaction of ethoxycarbonylnitrene occurs in a two-phase system, despite the fact that nitrenes are considered to be sensitive to water and easily hydrolysed. Triethylbenzylammonium chloride was found to be the most efficient phase-transfer catalyst giving good yields of aziridine and high addition to insertion ratios.



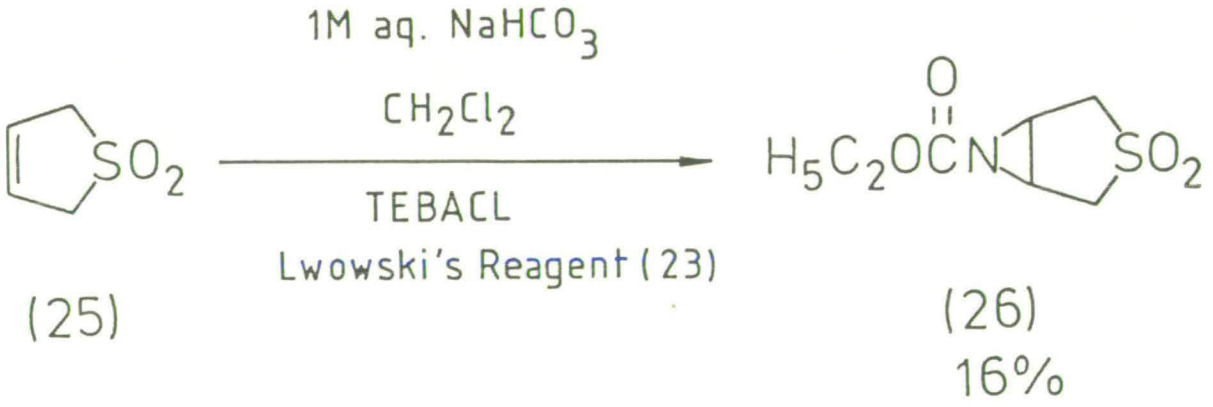
(23) (24)

Phase 18

Phase-transfer catalysed systems have been employed in many types of reactions. They are particularly suited to reactions which proceed *via* unstable intermediates such as carbanions,[58] ylides,[59,60] carbenes[61,62] and the aforementioned nitrenes, since these reactions normally require aprotic solvents and strictly anhydrous conditions. Heterogeneous reactions which employ a phase-transfer catalyst are of great practical value, since the procedure can be carried out using aqueous inorganic base solutions. The principles involved in phase-transfer catalysis are summarised in a review by Weber and Gokel.[63] Dehmlow has reviewed applications of phase-transfer catalysis.[64]

In these laboratories, Gosney *et al*,[65] have reported situations where ethoxycarbonylnitrene generated in a two-phase system is more reactive than its

conventionally generated counterparts. The reaction of (25) with ethoxycarbonylnitrene will not occur in a homogeneous system due to orbital interaction between the sulphone group and the double bond making the alkene electron-deficient. In Scheme 19 (25) afforded the corresponding aziridine (26) only when the nitrene is generated under two-phase conditions. This change in reactivity is thought to be due to the phase-transfer catalyst ensuring an environment at the phase boundary where the only possible nitrene acceptor is the double bond. It is postulated that the sulphone group penetrates the aqueous phase, thereby damping its electronic influence.

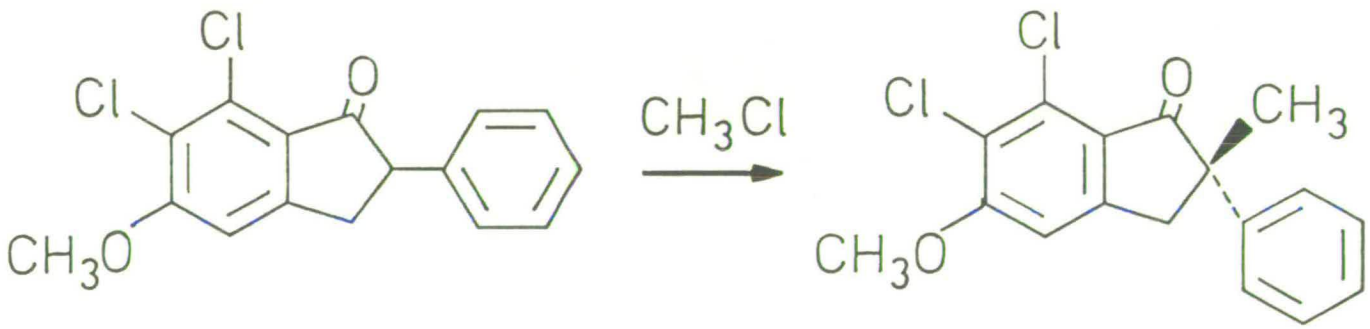


(25) (26) 16%

Scheme 19

D. PROGRAMME OF RESEARCH

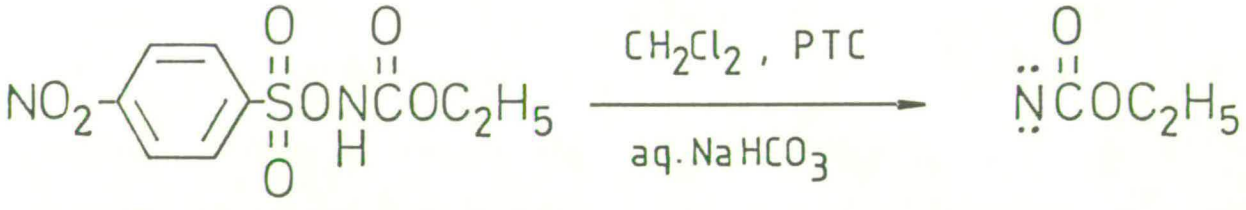
There are several reports of chiral synthesis involving a chiral phase-transfer catalyst in a two phase system. A review of some earlier examples can be found in a discussion of phase-transfer catalysis by Dehmlow.[66] More recent examples of successful asymmetric synthesis include alkylations,[67] Michael additions[68] and the preparation of epoxyketones.[69] The chiral phase-transfer catalyst is generally derived from ephedra or cinchona alkaloids by N-alkylation many of these asymmetric syntheses show enantiomeric excesses in the region of 20-30%. One notable example is Dolling's conversion of (27) to (28) in 95% yield (92% ee) using N-(R)-(trifluoromethyl)benzylcinchoninium bromide as a phase-transfer catalyst.[67]



(27) (28)

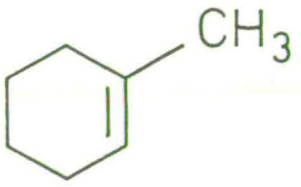
95%, 92% ee

The extension of chiral phase-transfer catalysis to include the addition of nitrenes to alkenes has never been reported. If discovered to be successful, this method might prove to be a facile and economical route to chiral aziridines and, subsequently, other chiral compounds. It has been shown that ethoxycarbonylnitrene (21) can be generated from Lwowski's reagent (23) in a two-phase system using various phase-transfer catalysts.[57,65]



(23) (21)

A study was therefore instigated into the generation and reaction of ethoxycarbonylnitrene in a two-phase system using a chiral phase-transfer catalyst. This concept was to be initially explored by generating ethoxycarbonylnitrene in the presence of 1-methyl-1-cyclohexene (27) using a chiral phase-transfer catalyst, for example (1)-(-)-N-benzylcinchonidinium chloride (29). Optical activity in aziridine (28) would be an indication of successful asymmetric induction.



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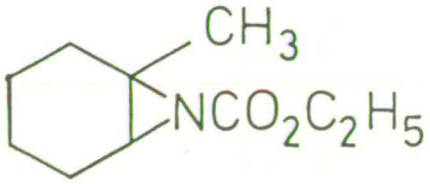

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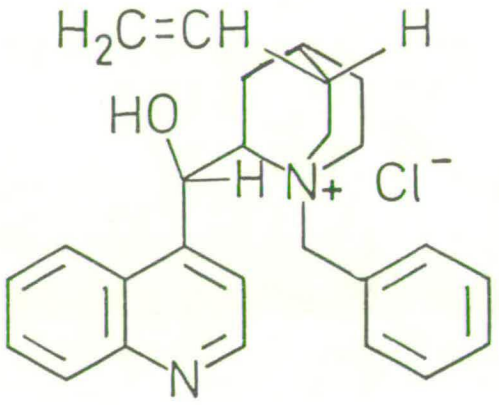
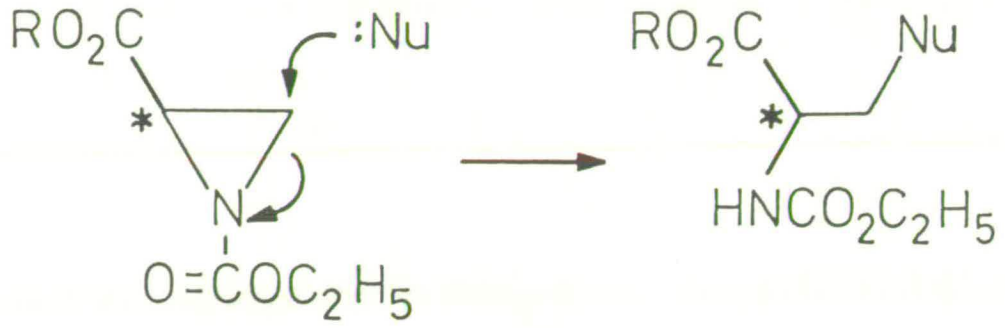


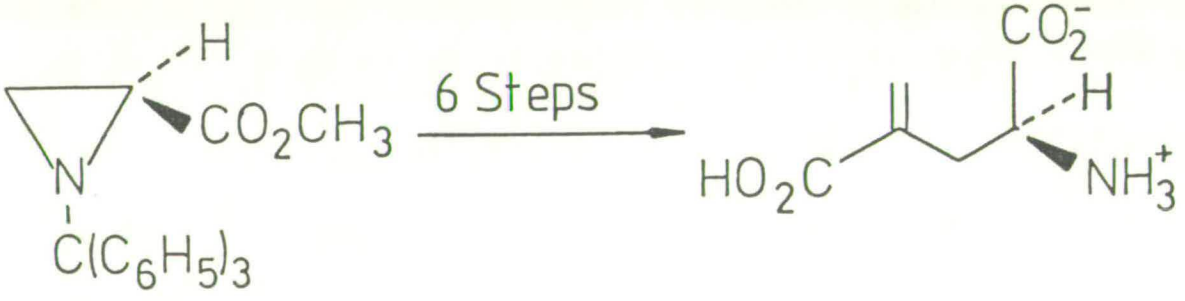
(29)

One interesting possibility for the use of optically active 1-ethoxycarbonylaziridines is a novel amino acid synthesis outlined in Scheme 20.



Scheme 20

As will be detailed later, during the course of this programme, Baldwin et al published the results of a similar idea involving the ring opening of aziridine (30) with Wittig reagents to give unsaturated amino acid (31).[70]



(30) (31)

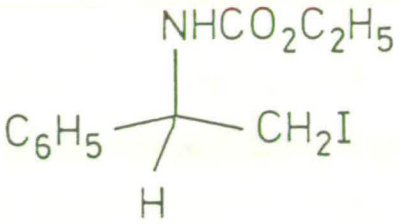
In conjunction with studies of the reaction of ethoxycarbonylnitrene with prochiral alkenes mediated by a chiral phase - transfer catalyst, it was proposed to examine other methods of asymmetric aziridination.

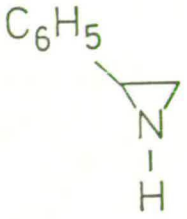
There are several possible techniques for introducing asymmetry in the addition of nitrenes to alkenes. Most obvious methods include the substitution of triethylamine with a chiral base in the homogeneous, base-induced decomposition of Lwowski's reagent in the presence of a prochiral alkene. Asymmetric induction by elaboration of a chiral substrate is an important method of synthesis. Attempts to extend this to the synthesis of aziridines could be effected by the reaction of ethoxycarbonylnitrene with a chiral alkene or, alternatively, through the reaction of an N-alkoxycarbonylnitrene (where the alkyl group is optically active) with a prochiral alkene.

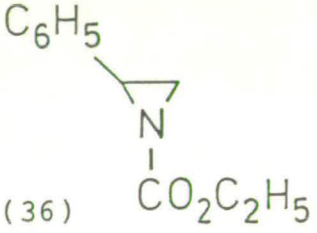
EXPERIMENTAL

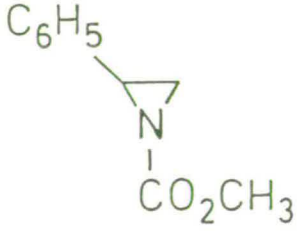
EXPERIMENTAL

CONTENTS









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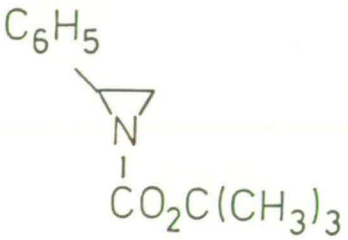

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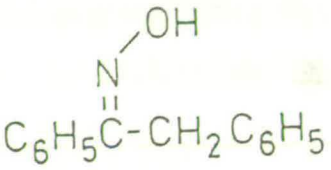

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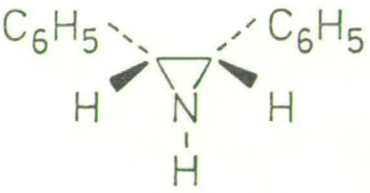

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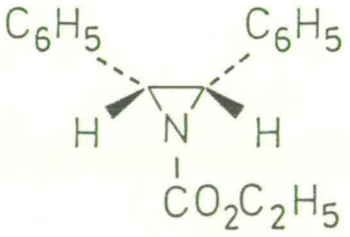

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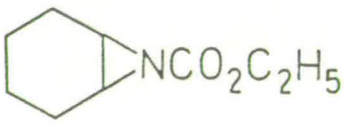

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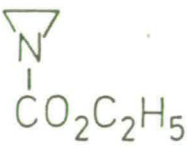

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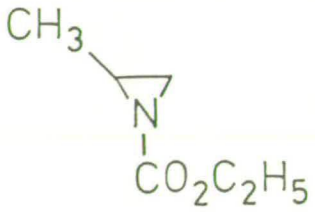

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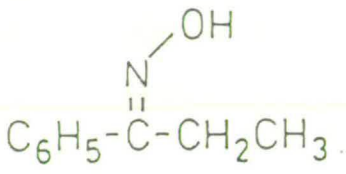

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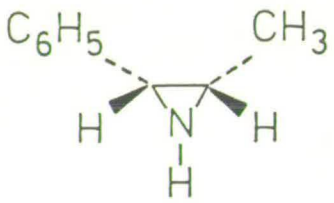

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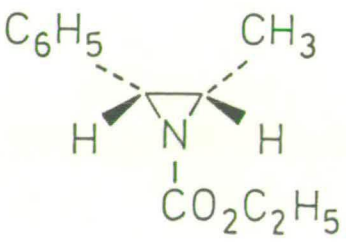

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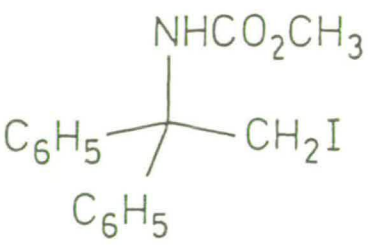

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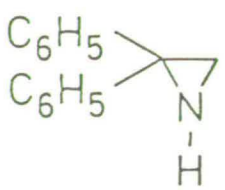

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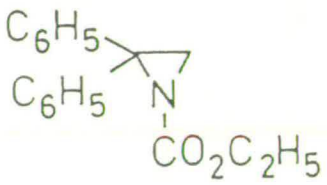

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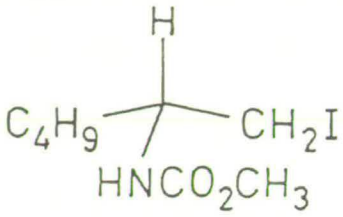

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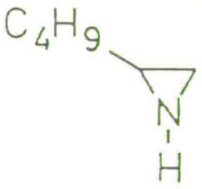

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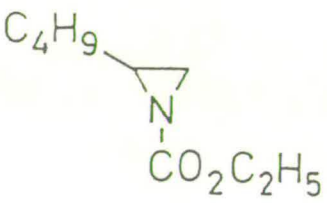

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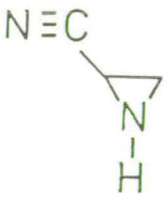

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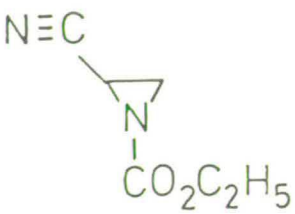

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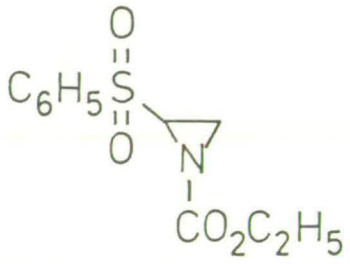

a. via EtO_2CN: addition to phenyl vinyl sulphone

b. via INCO addition to phenyl vinyl sulphone

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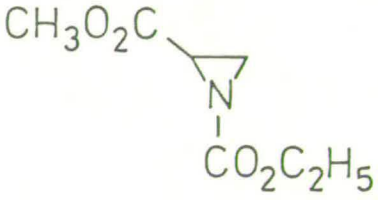
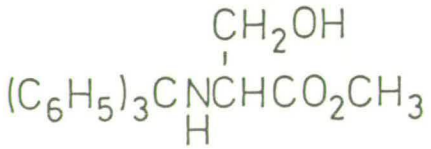


a. via EtO_2CN: addition to methyl acrylate

b. via INCO addition to methyl acrylate

14a. Preparation of



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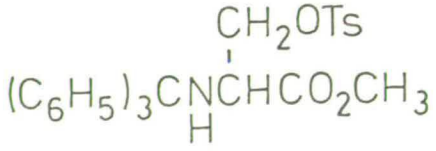

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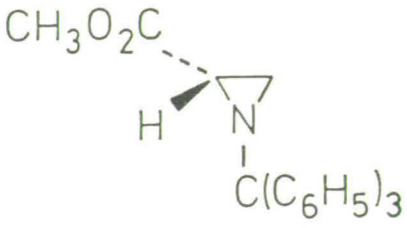

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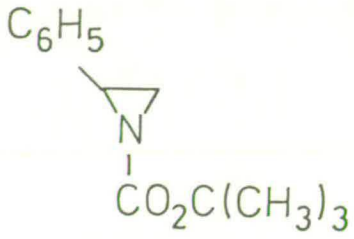

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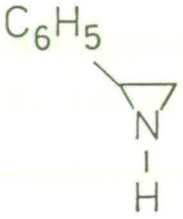

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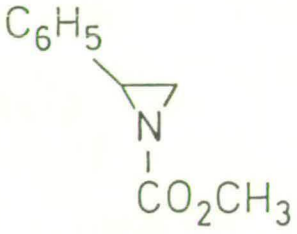
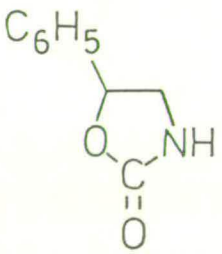


9. Methylation of (86)



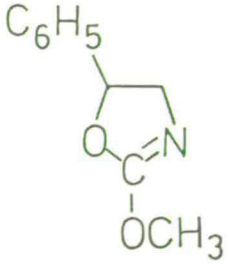
a. Using MeI/K_2CO_3/DMF

b. Using NaH/MeOTs/DMEU

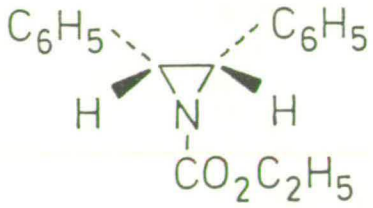
c. Using MeI/Ag_2CO_3/DMSO

d. Using Et_3OBF_4/CH_2Cl_2

10. FVP of (89)



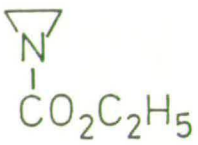
11. FVP of (95)



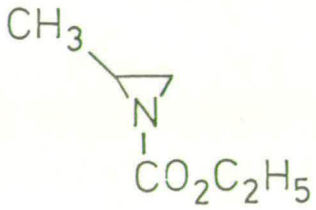
12a. FVP of (76)

b. Thermolysis of "

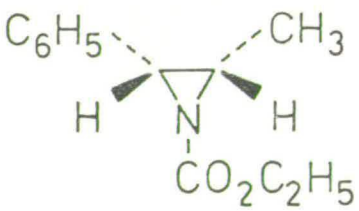
13. FVP of (121)



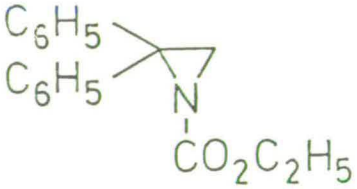
14. FVP of (122)



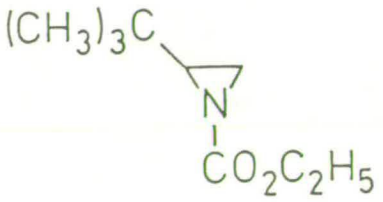
15. FVP of (126)



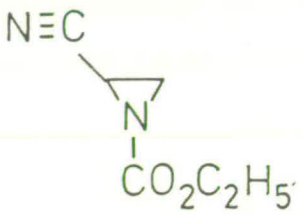
16. FVP of (113)



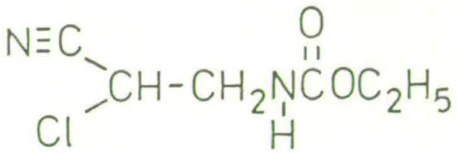
17. FVP of (114)



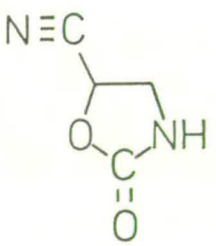
18. FVP of (132)



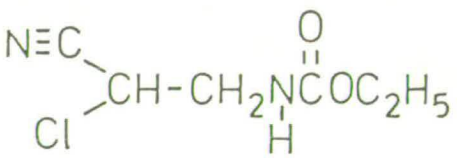
19a. Preparation of



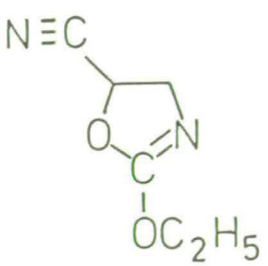
b. Preparation of (133)



20. FVP of



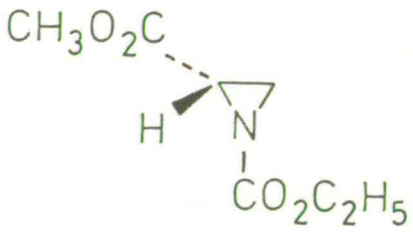
21. Preparation of (134)



22. FVP of "

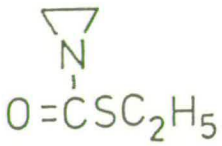
Page

23. FVP of (135)



G. Preparation and FVP of 1-Thioethoxycarbonylaziridines 114

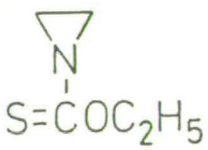
1. Preparation of (140)



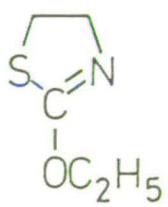
2. FVP of "

3a. Preparation of EtOSCCl (144)

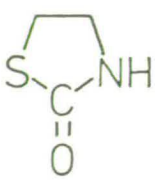
b. Attempted preparation of (141)



4. FVP of (146)



5. Ethylation of (143)



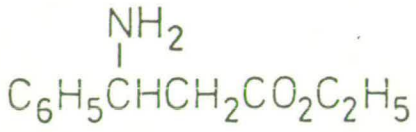
Page

a. using EtO_3BF_4

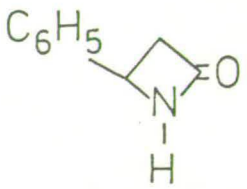
b. using $EtI/K_2CO_3/DMF$

H. Preparation and FVP of 1-Ethoxycarbonyl-2-phenylazetidine 119

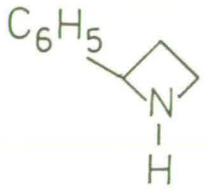
1a. Preparation of (156)



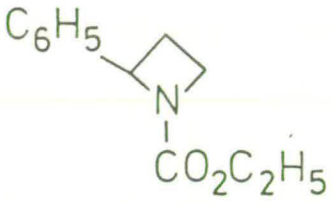
b. Preparation of (157)



c. Preparation of (158)



d. Preparation of (153)



2. FVP of "

A. Symbols and Abbreviations

mol	mole
mmol	millimole
M	mol dm^{-3}
h, min.	hours, minutes
g.l.c.	gas liquid chromatography
t.l.c.	Thin-layer chromatography
i.r.	infrared
ν	wave number
n.m.r.	nuclear magnetic resonance
δ	chemical shift
J	spin-spin coupling constant
s,d,t,q	singlet, doublet, triplet, quartet
m, cm	multiplet, complex multiplet
br	broad
Cq	quarternary carbon
m.s.	mass spectroscopy
m/z	mass to charge ratio
M^+	mass of molecular ion
FVP	flash vacuum pyrolysis
m.p.	melting point
b.p.	boiling point
A.R.	Analytical reagent
Ar	Aromatic

B. INSTRUMENTATION AND GENERAL TECHNIQUES

1. Nuclear Magnetic Resonance Spectroscopy (n.m.r.)

a) ^{1}H n.m.r.

Routine spectra were obtained at 60 MHz on a Varian EM-360 spectrometer or at 80 MHz on a Bruker WP-80 spectrometer. Higher field spectra were obtained at 200 MHz on a Bruker WP-200 spectrometer operated by Mr J.R.A. Millar.

b) ^{13}C n.m.r.

Spectra were obtained at 50.3 MHz on a Bruker WP-200 spectrometer operated by Mr J.R.A. Millar, or at 25 MHz on a Varian CFT-20 spectrometer operated by Miss E. Stevenson. All DEPT spectra were obtained using an angle of $3\pi/4$.

All spectra were obtained from solutions in deuteriochloroform unless otherwise stated and chemical shifts are expressed in parts per million to high frequency of tetramethylsilane.

2. Infrared Spectroscopy

Spectra were obtained on a Perkin Elmer 781

spectrometer. Solids were run as nujol mulls and liquids as thin films, both on sodium chloride discs. Spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

3. Mass Spectroscopy

Mass spectra and accurate mass measurements were obtained on a Kratos MS-50 TS spectrometer operated by Mr. A. Taylor, or on an Associated Electrical Industries MS-902 instrument operated by Miss E. Stevenson.

4. Elemental Analysis

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Carlo Erba Elemental Analyser, Model 1106, operated by Mrs. E. MacDougall.

5. Melting Points

Melting points were determined on a Reichert hot-stage microscope. All melting points are uncorrected.

6. Gas Liquid Chromatography

G.l.c. was performed on a Pye series 204 chromatograph fitted with a flame ionisation detector and employing nitrogen as a carrier gas. The stationary phase was supported on chromosorb W(80-100 mesh) in a 1.5 m x 4.5 mm column.

7. Thin-Layer Chromatography

Analytical t.l.c. was carried out using 0.3 mm layers of alumina (Merck, neutral aluminium oxide 609, Type E) or silica (Merck, Kieselgel 609), containing 0.5% Woelm fluorescent indicator, on glass plates. The components were observed under ultra-violet light or by their reaction with iodine vapour.

8. Preparative Thin-Layer Chromatography

This was carried out using 1.0 mm layers of the supports mentioned above. After locating the components with ultra-violet light, the bands were scraped off and the products removed from the support by soaking in ethyl acetate, chloroform or methanol.

9. Flash Chromatography

This was carried out according to the method of Still *et al*[71] using silica (Merck, Kieselgel 60, 230-400 mesh) as a support and a suitable solvent system under a pressure (7-15 p.s.i.) of compressed air or nitrogen controlled by a Rotaflow tap.

10. Dry-Flash Chromatography

This was carried out according to the method described by Harwood,[72] using Silica (Fluka, Kieselgel G240) and sinters with recommended porosity and diameters. The principle solvent system used was ether / light petroleum (40-60) gradients.

11. Optical rotations

Readings were obtained using a Perkin-Elmer polarimeter, model 141.

12. Drying and Evaporation of Organic Solutions

Organic solutions were dried by standing over anhydrous magnesium sulphate or anhydrous sodium sulphate

prior to evaporation under reduced pressure on a rotary evaporator.

13. Drying and Purification of Solvents

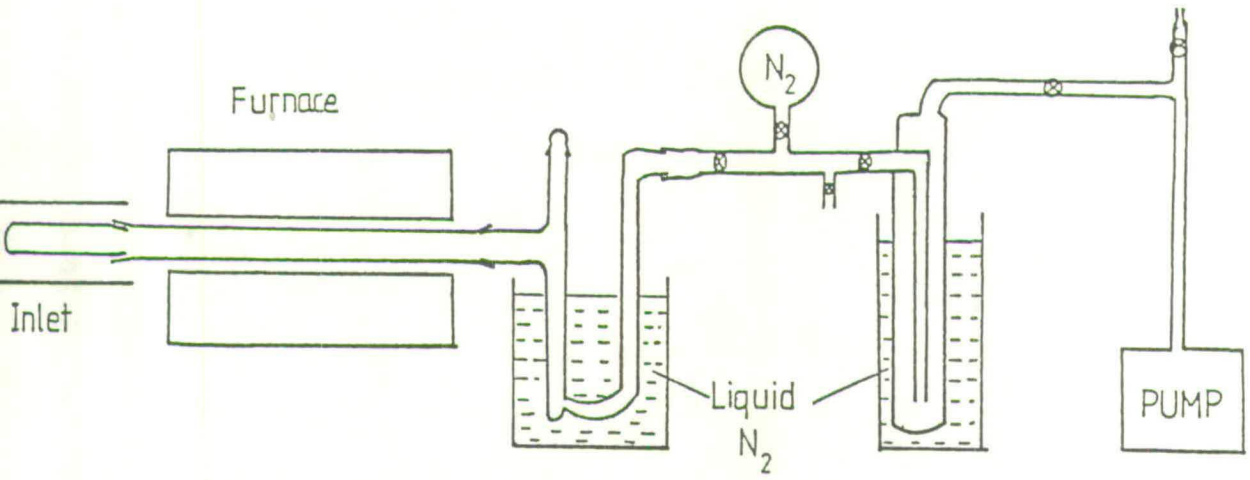
Commercially available solvents were used without further purification unless otherwise indicated. Where pure ether, methanol, chloroform, hexane or pentane were required, the commercial analytical reagent (A.R.) grade solvent was used. Dry ether, benzene and toluene were prepared by addition of sodium wire to the A.R. grade solvent. Dry dichloromethane and chloroform were prepared by washing with 5% aqueous sodium carbonate solution followed by distillation from calcium chloride and storage over 4Å molecular sieve. Dry tetrahydrofuran was prepared by heating the solvent under reflux with calcium hydride in a dry nitrogen atmosphere for 2-3 h followed by distillation and storage over molecular sieve. Acetone was dried by heating under reflux with successive quantities of potassium permanganate until the violet colour persisted. It was then dried over anhydrous calcium sulphate, filtered and distilled onto 4Å molecular sieve.

Commercially available reagents were used without further purification, unless otherwise stated. Products were dried in a vacuum drying pistol using a suitable

desiccant (silica gel, phosphorous pentoxide, anhydrous calcium chloride, etc.).

14. Flash Vacuum Pyrolysis

FVP apparatus based on the design of W.D. Crow[74,75] is depicted in Figure 1.



FVP APPARATUS

Figure 1

The sample (solid or liquid) was volatilised from a horizontal inlet tube, heated in a Buchi Kugelrohr oven, though a silica tube (30 x 2.5 cm). This tube was heated at temperatures between 500-800°C by a Stanton Redcroft laboratory tube furnace LM 8100. The temperature was recorded by placing a Pt/Pt-13% Rh thermocouple in the centre of the furnace. The products were collected in the U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} - 10^{-3} mm Hg by an Edwards model ED 100 high capacity rotary oil pump, the pressure being measured by a Pirani gauge positioned between the trap and the pump, under these conditions the contact time in the hot zone was estimated to be in the range 1-10 milliseconds.

Pyrolysis conditions are quoted as follows: "(Weight of material volatilised, furnace temperature, average pressure during pyrolysis, inlet temperatures)".

Small scale pyrolyses were carried out using about 100 mg of material. After pyrolysis, the system was isolated from the pump and flooded with nitrogen gas. The product could then be dissolved out of the trap in deuteriochloroform and analysed directly by n.m.r. Addition of deuteriochloroform while the trap was still frozen meant that n.m.r. spectra of volatile products could be obtained.

0.5-2.0 g of material was used in large scale pyrolyses. After filling the system with nitrogen and allowing the trap to warm to room temperature, the product was dissolved out with a suitable solvent and was purified by recrystallisation.

C. Preparation of Precursors for Chiral Aziridination

1. Preparation of Ethyl p-nitrobenzenesulphonoxycarbamate (Lwowski's Reagent) (23)

a) Preparation of Ethyl N-hydroxycarbamate

This was prepared according to the method of Lwowski et al.[53] Ethyl chloroformate (15g, 0.14 mol) was added dropwise to a cooled, stirred mixture of hydroxyammonium chloride (9.75 g, 0.14 mol) and potassium carbonate (19g) in ether (75 ml) containing water (1 ml) over a period of 30 min. The mixture was allowed to stir at room temperature for 12 h. The inorganic precipitate was filtered off and the filtrate evaporated to give ethyl N-hydroxycarbamate (15.2 g, 100%) as a colourless oil. νmax (neat) 3000 and 1710 cm^{-1}; δ_H 7.4 (1H, br s), 6.2 (1H, br s), 4.2 (2H, q) and 1.3 (3H, t).

b. Preparation of Ethyl p-nitrobenzenesulphonoxycarbamate (23)

This was prepared according to the method of Lwowski et al[53]. p-Nitrobenzenesulphonyl chloride (32.78g, 0.148 mol) was added slowly to a cooled, stirred solution of ethyl N-hydroxycarbamate (0.138 mol) in anhydrous ether (200 ml). Triethylamine (12.6g) in anhydrous ether (25

ml) was added dropwise at a sufficiently slow rate to ensure that the solution remained acidic at all times. The mixture was allowed to stir at room temperature for 5 h. The precipitate was filtered off and the filtrate evaporated to give ethyl p-nitrobenzenesulphonoxycarbamate as a yellow solid. The product was recrystallised twice from benzene (30.63 g, 77%), m.p. 113-114°C (lit. 116°C). νmax (mull) 3210, 3140, 1790, 1705, 1545, 1360, 1350 and 1200 cm^{-1}; δ_H 8.3 (5H, m), 4.06 (2H, q) and 1.13 (3H, t).

2) Preparation of [(1S)-endo]-(-)-bornyl p-nitrobenzenesulphonoxycarbamate (49)

a) Preparation of [(1S)-endo]-(-)-bornyl chloroformate (50)

[(1S)-endo]-(-)-borneol (9g, 0.058 mol) and dry pyridine (8 ml, 0.1 mol) in anhydrous ether (200 ml) was added dropwise to a cooled, stirred solution of phosgene (12.5% in toluene, 250 ml, 0.3 mol) in dry ether (100 ml). The mixture was allowed to stir at room temperature under a dry nitrogen atmosphere for 95 h. The precipitate was filtered off and the filtrate evaporated to yield [(1S)-endo]-(-)-bornyl chloroformate as a pale yellow oil (97%). (M^+ 216.0913, $C_{11}H_{17}ClO_2$

requires 21.60917); ν max (neat) 1780 cm^{-1}; δ_H 5.0 (1H, ddd), 2.5-1.0 (7H, cm) and 0.9-0.8 (9H, 3s); m/z 218 (M^+), 216 (M^+), 205, 203, 201, 167 (100%).

b) Preparation of [(1S)-endo]-(-)-bornyl N-hydroxycarbamate (51)

[(1S)-endo]-(-)-bornyl chloroformate (7g, 0.032 mol) in ether (10 ml) was added dropwise to a cooled (0°C), stirred mixture of finely ground hydroxyammonium chloride (2.5g, 0.035 mol) and potassium carbonate (4.4g, 0.032 mol) in ether, containing water (0.5 ml). The mixture was stirred at room temperature for 12 h, the precipitate was filtered off and the solvent removed in vacuo to give [(1S)-endo]-(-)-bornyl N-hydroxycarbamate as a colourless crystalline solid (98%), m.p. 85°C. (M^+ 213.1366, $C_{11}M_{19}NO_3$ requires 213.1365); νmax (mull) 3280 and 1690 cm^{-1}; δ_H 7.0 (1H, br s), 4.0 (1H, br s), 4.85 (1H, m), 2.5-0.7 (7H, cm), 0.87 (3H, s), 0.84 (3H, s) and 0.82 (3H, s); m/z 213 (M^+), 154, 143, 136, 121, 108, 95 and 81 (100%).

c) Preparation of [(1S)-endo]-(-)-bornyl p-nitrobenzenesulphonoxycarbamate (49)

p-Nitrobenzenesulphonyl chloride (4.65g, 0.021 mol)

was added gradually to an ice-cooled, stirred solution of [(1S)-endo]-(-)-bornyl N-hydroxycarbamate (0.021 mol) in dry ether (150 ml). Dry triethylamine (0.018 mol) in dry ether (25 ml) was added dropwise, ensuring that the reaction mixture remained acidic at all times. The mixture was stirred at room temperature for 48 h, the precipitate was filtered off and the filtrate evaporated to give [(1S)-endo]-(-)-bornyl p-nitrobenzenesulphonoxy-carbamate as a yellow solid (7.63g, 90%). This was recrystallised from chloroform/hexane to give fine, cream needles, m.p. 138-139°C. (M^+ 398.1155, $C_{17}H_{22}O_7N_2S$ requires 398.1148); ν max (mull) 3240, 3200, 1750, 1705, 1535 and 1195 cm^{-1}; δ_H 9.6 (1H, br s), 8.27 (4H, m), 4.75 (1H, m), 1.4-0.6 (16H, cm)*; δ_C 155.85, 157.17, 139.15, 130.71, 123.98, 83.75, 48.79, 47.74, 44.47, 35.94, 27.65, 26.64, 19.37, 18.47 and 12.97*; m/z 398 (M^+), 383, 340, 292, 264, 217, 203, 196, 188, 154, 136, 121, 107, 97, 79 (100%) and 69.

3) Preparation of (-)-N-Benzylcinchonidinium Chloride (29)

This was prepared according to the method of Colonna and Re.[80] Benzyl chloride (1.29g, 0.01 mol) and (-)-

* Assignments of the ^1H[76,77] and ^{13}C[76,77] n.m.r. spectra of [(1S)-endo]-(-)-borneol have been published.

cinchonidine (3.13g, 0.011 mol) were dissolved in dry acetone (100 ml) and heated at reflux for five days. The mixture was allowed to cool and the crystalline precipitate was filtered off. The crystals were dissolved in hot water and, after hot filtration, the water was removed *in vacuo* to give *(-)-N-benzylcinchonidinium chloride* as colourless crystals (3.05g, 73%), m.p. 199-201°C (lit. 212-213°C); $[\alpha]_D^{20.6}$ -177.3°, (*C* = 0.48, H_2O), (lit. $[\alpha]_D^{20}$ -175.4 (*C* = 0.5, H_2O)).

D. Attempted Chiral Aziridination Reactions

1. General Methods

a) The Reaction of Ethoxycarbonylnitrene with an Alkene in a Two-Phase System

This method is based on that of Seno *et al.*[57] Aqueous sodium hydrogen carbonate solution (1M, 20 ml) and a phase-transfer catalyst (0.5 mmol) were added to a rapidly stirred solution of ethyl *p*-nitrobenzenesulphonoxycarbamate (1.5g, 5 mmol) and an alkene (15 mmol) in dichloromethane (30 ml). The flask was stoppered and stirred or shaken for 4 hours. The reaction mixture was then diluted with dichloromethane (50 ml) and water (50 ml). The organic layer was separated, washed with water, dried and the solvent removed *in vacuo* to give an oily

product. Isolation of the aziridine product was achieved by distillation or chromatography, as appropriate.

b) The Reaction of Ethoxycarbonylnitrene with an Alkene in a Homogeneous System

This approach uses the method of Lwowski et al.[53] Triethylamine (0.8g, 7.8 mmol) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of ethyl p-nitrobenzenesulphonoxycarbamate (2g, 7 mmol) and alkene (21 mmol) in dry dichloromethane (35 ml). The mixture was stirred at room temperature for 4 h, washed with water (3 x 100 ml), dried and the solvent removed to give an oily product. The aziridine was isolated by distillation or chromatography.

2. Attempted Preparation of Chiral 1-Methyl-7-Ethoxy-carbonyl-7-azabicyclo-[4.1.0]-heptane (28)

a) Using a Chiral Phase-Transfer Catalyst

Aqueous sodium hydroxide solution (10%, 20 ml) was added to a rapidly stirred mixture of 1-methyl-1-cyclo-hexene (2g, 21 mmol), (-)-N-benzylcinchonidinium chloride (0.32g, 0.77 mol) and ethyl p-nitrobenzenesulphonoxycar-bamate (1.54g, 5.3 mmol) in dichloromethane (50 ml).

The mixture was stirred for 4 h, diluted with dichloromethane (50 ml), washed with water (3 x 75 ml), dried and the solvent evaporated to give a brown oil (1.07g). A ^{1}H n.m.r. spectrum of the crude oil showed that a considerable proportion of the product was the desired aziridine. The aziridine rearranges fairly rapidly, therefore it must be isolated quickly by flash chromatography (silica, 30% ether in hexane). Under these conditions the aziridine was eluted rapidly, followed closely by its rearrangement product. 1-Methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane[53] was obtained as a colourless oil (0.11g, 12%). νmax 1710, 1510, 1255 and 1070 cm^{-1}; δ_H (200 MHz) 4.1 (2H, q, OCH_2), 2.41 (1H, t, NCH) and 1.9-1.0 (14H, cm); δ_C (DEPT) 61.62 (CH_2), 42.42 (CH), 30.18 (CH_2), 23.39 (CH_2), 22.12 (CH_3), 19.93 (CH_2), 18.08 (CH_2) and 14.33 (CH_3), $[\alpha]_D^{20}$ 0.11(C = 0.9, CH_2Cl_2). Two repeats of this experiment gave the aziridine in similar yields with optical rotations of $[\alpha]_D^{20.6}$ 0.74 (C = 0.27, CH_2Cl_2) and $[\alpha]_D^{20.6}$ 1.28 (C = 0.78, CH_2Cl_2).

An attempt was made to detect optical isomers by ^{1}H n.m.r. spectroscopy using (+)-tris-[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato], europium (III) derivative, as a chiral shift reagent. This spectroscopic experiment was unsuccessful.

1-Methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane rearranges, both in the crude product and during chromatography to give 6-(ethoxycarbonylamino)-1-methyl-cyclohexene as a colourless, crystalline solid, m.p. 44-45°C (lit.[81] 43-46°C). νmax (mull) 3350, 1710, 1670, 1530 and 1250 cm^{-1}; δ_H (200 MHz) 5.5 (1H, m, C(2)H), 4.6 (1H,br s, NH), 4.1 (2H, q, OCH_2), 2.0-1.5 (7H, cm, $C(3)H_2$, $C(4)H_2$, $C(5)H_2$ and C(6)H), 1.61(3H, s, C(1)Me) and 1.2(3H, t, Me); δ_C (DEPT) 135.76((2)CH), 60.40(OCH_2), 48.96 ((6)CH), 29.89 ($(3)CH_2$), 24.93 ($(4)CH_2$), 20.67(C(1)Me), 18.34($(5)CH_2$) and 14.41 (CH_3).

b) Using a Chiral Base

(S,S)-(+)-2,3-Dimethoxy-1,4-bis-(dimethylamino)-butane (1.70g, 8.3 mmol) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of ethyl p-nitrobenzenesulphonoxycarbamate (2.17g, 7.5 mmol) in dry dichlormethane (40 ml). The mixture was stirred at room temperature for 1 h, diluted with dichloromethane (50 ml), washed with water (3 x 100 ml), dried and the solvent removed to give a yellow oil (0.955g). Flash chromatography (silica : 30% ether in hexane) gave 7-ethoxycarbonyl-1-methyl-7-azabicyclo-[4.1.0]-heptane as a pale yellow oil (0.339g, 24%). Spectra were identical to those reported in the literature.[29,53]

$[\alpha]_D^{20}$ = -0.12 (c = 2.5, CH_2Cl_2).

3. Attempted Preparation of Optically Active 1-Ethoxycarbonyl-2-phenylaziridine (36)

a) Using a Chiral Phase-Transfer Catalyst

Aqueous sodium hydroxide solution (10%, 20 ml) was added to a rapidly stirred mixture of styrene (3.3g, 0.03 mol), (-)-N-benzylcinchonidinium chloride (0.46g, 1 mmol) and ethyl p-nitrobenzenesulphonoxycarbamate (3.1g, 10 mmol) in dichloromethane (50 ml), washed with water (3 x 75 ml), dried and the solvent evaporated to give a yellow oil (4.28g). The excess styrene was distilled off and further distillation of the residue gave 1-ethoxy-carbonyl-2-phenylaziridine contaminated with some styrene (total mass = 0.2g, 10% yield of aziridine).

b) (S,S)-(+)-2,3-Dimethoxy-1,4-bis-(dimethylamino)-butane(0.98g, 4.8 mmol) in dry dichloromethane (10 ml) was added dropwise to a stirred solution of ethyl p- nitrobenzenesulphonoxycarbamate (2.42g, 8.3 mmol) and styrene (2.6g, 25 mmol) in dry dichloromethane (30 ml). The mixture was stirred at room temperature for 1 hr, was diluted with dichloromethane (50 ml) washed with water (3 x 100 ml), dried and the solvent removed to give a yellow-brown oil (3.47g). Distillation produced none of the desired 1-ethoxycarbonyl-2-phenylaziridine.

4. The Addition of [(1S)-endo]-(-)-Bornoxycarbonyl-nitrene to styrene

Benzyltriethylammonium chloride (0.07g, 0.3 mmol) was added to a stirred mixture of [(1S)-endo]-(-)-bornyl p-nitrobenzenesulphonoxycarbamate (1g, 2.5 mmol) and styrene (1g, 9.6 mmol) in aqueous sodium hydrogen carbonate solution (1m, 10 ml) and dichloromethane (6 ml). The mixture was stirred vigorously for 5 h. Dichloromethane (100 ml) was added and the mixture was washed with water (3 x 100 ml), dried and the solvent removed to give a yellow oil. Residual styrene was removed under high vacuum at room temperature to give a viscous yellow oil.

A ^{1}H n.m.r. spectrum showed that 1-([(1S)-endo]-(-)-bornoxycarbonyl)-2-phenylaziridine (52) was the major product. δ_H 7.27 (5H, s), 5.8 (1H, m), 3.45 (1H, ddd, J = 6,4 and 1Hz), 2.68 (1H, dd, J = 6 and 1Hz) 2.30 (1H, ddd, J = 4,2 and 1Hz) and 2.2-0.75 (16H, cm).

E. Preparation of 1-Alkoxycarbonylaziridines

1. Preparation of 1-Ethoxycarbonyl-2-phenylaziridine (36)

a) Preparation of 2-Phenylaziridine (81)

i) Preparation of Ethyl (2-Iodo-1-phenylethane) carbamate (82)

This was prepared according to the method of Hassner et al.[29] Iodine (0.1 mol) and freshly prepared, dry silver cyanate (0.13 mol) was added to dry ether (200 ml). The slurry was stirred for 30 min and styrene (0.1 mol) was added in three portions over a 30 min period. The mixture was stirred at room temperature for 5 h after which time the iodine colour had faded. The inorganic salts were filtered off through celite and the filtrate was added to anhydrous ethanol (200 ml) containing a few drops of lithium methoxide solution. This mixture was stoppered and allowed to stand in the dark for 24 h. The ether was removed in vacuo and the remaining solution was poured into ice-water (400 ml) containing a little sodium sulphite. The resulting white solid was filtered off, dried in vacuo over phosphorous pentoxide and recrystallised from ether-pentane to give ethyl (2-iodo-1-phenylethane)-carbamate as a colourless, crystalline solid (25.6g, 80%), m.p. 85.5-86.0°C (lit.,

86.5-87.5°C); νmax (mull) 3325, 1685, 1530, 1260, 1048, 760 and 700 cm^{-1}; δ_H 7.26 (5H, s, Ar), 4.80 (1H, m, CH), 4.13 (2H, q, OCH_2), 3.50 (2H, d, CH_2), and 1.24 (3H, t, CH_3); m/z 319(M^+), 290, 231, 192 (100%), 178, 147, 134, 120, 104, 91, 79 and 77.

ii) Preparation of 2-Phenylaziridine (81)

This was prepared according to the method of Hassner et al.[29] Ethyl (2-iodo-1-phenylethane)-carbamate (10g, 31 mmol) was heated at reflux in potassium hydroxide (10g), methanol (70 ml) and water (30 ml) for 1 h. The solution was cooled to room temperature and poured onto water (250 ml). The aqueous solution was extracted with ether (3 x 250 ml) and the organic solutions were dried and evaporated to give a yellow oil (3.92g). This was distilled to remove traces of acetophenone giving 2-phenylaziridine as a colourless oil (2.9g, 79%), b.p 50°C at 0.4 mm Hg (lit. 94.95°C at 10mm Hg). νmax (neat) 3300 and 3220 cm^{-1}; δ_H 7.23 (5H, s,Ar), 2.94 (1H, dd, J = 6.0 and 3.4 Hz, C(1)H), 2.13 (1H, d, J = 6.Hz, C(2)H (trans)), 1.73 (1H, d, J = 3.4 Hz, C(2)H(cis)) and 0.78 (1H, br s, NH); δ_C (DEPT) 138.24, 126.83, 125.58, 31.88 and 29.01; m/z 119 (M^+), 118, 91, 89, 77 (100%) 65, 63, 57, 41 and 39.

b) Preparation of 2-Phenylaziridine (81)

This was prepared according to the method of Brois.[82] 2-Amino-1-phenylethanol (4.78g, 35 mmol) was dissolved in distilled water and 50% aqueous sulphuric acid was added until neutralised to a methyl red end point. This was followed by addition of an equal volume of acid solution. The water was removed *in vacuo* at ca. 100°C and the product was heated at 130-140°C until a constant weight was reached. The resulting brownish-white crystals were dissolved in 2 M aqueous sodium hydroxide (75 ml) and heated at 100°C for 1 h. A pale brown oil separated out as an upper layer. The mixture was steam distilled until fresh distillate was no longer alkaline. The distillate was extracted with dichloromethane, dried and the solvent removed to give 2-phenylaziridine as a colourless oil.

c) Preparation of 1-Ethoxycarbonyl-2-phenylaziridine (36)

This was prepared by modification of the method of Anastassiou *et al*.[83] 2-Phenylaziridine (0.872g, 7.3 mmol) and triethylamine (3.4 ml) were dissolved in anhydrous ether (75 ml). Ethyl chloroformate (0.9g, 7.3 mmol) was added dropwise to the cooled (0°C), stirred solution and the mixture was stirred at room temperature for 1 h. The mixture was filtered through a celite pad

and the filtrate was evaporated to give 1-ethoxycarbonyl-2-phenylaziridine as a yellow oil (1.4g, 98%). (M^+ 191.0941, $C_{11}H_{13}NO_2$ requires 191.0946); ν max 1725 cm^{-1}; δ_H (200 MHz) 7.3 (5H, s, Ar), 4.15 (2H, q, $C\underline{H}_2$-CH_3), 3.5 (1H, dd, J = 6.3 and 3.6 Hz, C(1)H), 2.67 (1H, d, J = 6.3 Hz, C(2)H trans), 2.26 (1H, d, J = 3.6Hz, C(2)H cis) and 1.25 (3H, t, Me); δ_C 162.87 (Cq), 136.70(Cq), 128.13, 127.48 and 125.87 (all CH), 62.27 (CH_2), 38.94 (CH), 34.61 (CH_2) and 13.93 (CH_3); m/z 191 (M^+), 183, 181, 178 (100%), 167, 165, 162, 155 and 151.

d) Attempted Preparation of 1-Ethoxycarbonyl-2-Phenyl-aziridine (36)

Ethyl (2-iodo-1-phenylethane)carbamate (0.78g, 2.4 mmol) and 1,8-diazabicylo-[5.4.0]-undec-7-ene (DBU) (2.7 mmol, 0.41g) were dissolved in dry tetrahydrofuran (12 ml). The solution was stirred at room temperature for 12 h and the precipitate was filtered off. The filtrate was evaporated to give a pale yellow oil (0.57g). The oil was chromatographed on a short column (5% deactivated alumina, dichloromethane) to remove residual DBU. A ^1H n.m.r. spectrum of the resulting yellow oil was consistent with the product being an equilibrium mixture of ethyl-1-phenyl-2-propenylcarbamate,[84] (84), and ethyl-2-phenyl-2-methyl-N-methylenecarbamate, (85), in a 3:2 ratio. νmax (neat) 3325, 1720, 1510, 1225, 1070, 775

and 695 cm^{-1}; δ_H 7.8 and 7.3 (aromatic, (84) & (85)), 7.3 (br s, NH, (84)) 5.56 and 4.90 (2d, alkene, (84)), 4.25 (q, (85)), 4.12 (q, (84)), 2.36 (s, (85)), 1.31 (t, (85)) and 1.22 (t, (84)); δ_C (DEPT) 131.64, 128.41, 128.26, 127.43, 125.86 (Ar. (84) & (85)), 99.22 (CH_2, (84)) and 14.23 (CH_3, (85)); m/z 191 (M^+, 100%), 162, 146, 132, 119, 104, 91, 77, 64 and 57.

2. Preparation of 1-methoxycarbonyl-2-phenylaziridine (88)

This was prepared via the same method as 1-ethoxycarbonyl-2-phenylaziridine. The reaction of 2-phenylaziridine with methyl chloroformate gave 1-methoxycarbonyl-2-phenylaziridine as a colourless, crystalline solid (94%), m.p. 30-31°C (lit.[85] b.p. 90-93°C at 0.08 mm Hg); (M^+ 177.0784, $C_{10}H_{11}NO_2$ requires 177.0790); ν max 1735 cm^{-1}; δ_H 7.25 (5H,s), 3.67 (3H, s), 3.42 (1H, dd), 2.64 (1H, d), 2.19 (1H, d); δ_C 163.34, 136.63, 128.14, 127.52, 125.80, 53.28, 38.96 and 34.65; m/z 177 (M^+), 176, 146, 128, 118, 104, 91 (100%), 88 and 77.

3) Preparation of 1-tert-butoxycarbonyl-2-phenylaziridine (108)

2-phenylaziridine (0.16g, 1.3 mmol) and

triethylamine (0.14g) were dissolved in dry ether (25 ml) and di-tert-butoxy dicarbonate (0.25g, 1.2 mmol) was added to the stirred solution. The mixture was stirred at room temperature for 24 h and the solvent was removed in vacuo leaving crude 1-tert-butoxycarbonyl-2-phenyl-aziridine as a yellow oil (0.3g, 100%); (M^+ 219.1259, $C_{13}H_{17}NO_2$ requires 219.1259); ν max (neat) 1720 cm^{-1}; δ_H (200 MHz) 7.3 (5H, s), 3.40 (1H, dd, J = 6.5 and 3.6 Hz), 2.6 (1H, d, J = 6.5 Hz), 2.25 (1H, d, J = 3.6 Hz), 1.44 (9H, s). δ_C 161.83, 137.06, 128.16, 127.47, 126.12, 81.01, 39.08, 34.43 and 27.65; m/z 219 (M^+), 208, 174, 163, 146, 128, 118 (100%), 103, 91 and 77.

4. Preparation of Cis-1-ethoxycarbonyl-2,3-diphenyl aziridine (95)

a) Preparation of Deoxybenzoin oxime (93)

This was prepared according to the method of Kotrea et al.[86] Deoxybenzoin (0.957 mol, 10g), hydroxyammonium chloride (10g) and pyridine (10 ml) were heated at reflux in ethanol (100 ml) for 1 h. The ethanol was removed in vacuo and water (100 ml) was added to the residue. The mixture was stirred and cooled to until the product crystallised. The crystals were filtered off, washed with water and vacuum dried. Recrystallisation from aqueous ethanol gave deoxybenzoin oxime as colourless

needles (5.97g, 55%), m.p. 96.5-97.5°C. (lit. 95-96°C).

b) Preparation of cis-2,3-diphenylaziridine (94)

This was prepared according to the method of Kotera et al.[86] Deoxybenzoin oxime (5.97g, 28 mmol) was added to a stirred suspension of lithium aluminium hydride (1g) in dry tetrahydrofuran (100 ml) in a dry nitrogen atmosphere. The mixture was heated, with stirring, at reflux for 3 h, during which time the mixture became cherry red. The mixture was cooled to 0°C and the excess lithium aluminium hydride was destroyed by cautious addition of wet tetrahydrofuran (10% water). The inorganic salts were filtered off and washed with ether and benzene. The filtrate and washings were combined and the solvent evaporated to give a green oil (2.27g). This crude oil was purified by flash chromatography (silica, toluene/ether gradient) to give cis-2,3-diphenylaziridine as a colourless crystalline solid (0.568g, 29%). M.p. 83-84°C (lit. 83-84°C). (Found: C,85.5; H,6.70; N, 7.05% $C_{14}H_{13}N$ requires: C,86.12; H,6.71; N,7.17%.); δ_H 7.15(10H, s), 3.58 (2H, s) and 1.7 (1H, br s).

c) Preparation of cis-1-ethoxycarbonyl-2,3-diphenyl-aziridine (95)

The reaction of cis-2,3-diphenylaziridine (0.2g, 0.7 mmol) with ethyl chloroformate gave cis-1-ethoxycarbonyl-2,3-diphenylaziridine as a pale yellow oil (0.27g, 98%) which crystallised on standing. M.p. 54-55°C; (M^+ 267.1260, $C_{17}H_{17}NO_2$ requires 267.1259); ν max 1725 cm^{-1}; δ_H 7.34 (10H, s), 4.27 (2H, q), 3.96 (2H, s), 1.33 (3H, t); δ_C 163.32, 133.68, 127.59, 127.49, 127.11, 62.55, 46.09 and 14.15, m/z 267 (M^+), 194 (100%) 116, 91 and 77.

5. Preparation of 7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (76)

This was prepared according to the method of Lwowski et al.[53] Dry triethylamine (3.3g, 0.033 mol) in a cyclohexene/dichloromethane solution (50 ml, 20 mol % cyclohexene) was added dropwise to a solution of Lwowski's reagent (0.03 mol, 8.70g) in the same cyclohexene/dichloromethene mixture (250 ml) over a period of 40 minutes. The mixture was stirred at room temperature for 2.5 h and pentane (400 ml) was added to precipitate the triethylammonium p-nitrobenzene-sulphonate. After concentrating the solution in vacuo, the salt was filtered off and the filtrate was evaporated

to give a brown oil (4.71g). The oil was separated into its components by flash chromatography (silica, 25% ether in light petroleum (40-60)) giving 7-ethoxycarbonyl-7-azabi-cyclo-[4.1.0]-heptane (2.233g, 44%). (M^+ 169.1102, $C_9H_{15}NO_2$ requires 169.1103); ν max 1725 cm^{-1}; δ_H 4.05 (2H, q, OCH_2), 2.50 (2H, m, C(1)H and C(6)H), 1.7-1.8 (4H, m, C(2)H and C(5)H), 1.1-1.4 (4H, m, C(3)H and C(4)H) and 1.10(3H, t, CH_3); δ_C 163.40 (C=O), 61.32 (OCH_2), 36.26 (CH, C(1) and C(6)), 23.16 (CH_2, C(2) and C(5)), 19.23 (CH_2, C(3) and C(4)) and 13.72 (CH_3); m/z 169 (M^+), 149, 143, 131, 126, 119, 113, 107, 100, 93, 81, 77 and 69 (100%).

6. Preparation of 1-ethoxycarbonylaziridine (121)

This was prepared by reacting commercially available ethylenimine with ethyl chloroformate. 1-ethoxycarbonyl-aziridine was obtained as a colourless oil (86%). (M^+ 115.0633, $C_5H_9NO_2$ requires 115.0633); ν max 1725 cm^{-1}, δ_H 3.88 (2H, q), 1.93 (4H, s), 1.02 (3H, t); δ_C 163.09, 61.93, 25.14, 13.77; m/z 115 (M^+, 100%), 101, 90, 87, 73 and 69.

7. Preparation of 1-ethoxycarbonyl-2-methylaziridine (122)

This was prepared by reacting commercially available 2-methylaziridine with ethyl chloroformate. 1-ethoxycarbonyl-2-methylaziridine was obtained as a pale yellow oil. ν max 1720 cm^{-1}; δ_H 3.94 (2H, q), 2.27 (1H, m, C(1)H), 2.09 (1H, d, J = 5.6 Hz, C(2)H, trans), 1.72 (1H, d, J = 3.6Hz, C(2) H, cis), 1.08 (3H, d, J = 5.4 Hz, C(1)Me) and 1.07 (3H, t, OCH_3); δ_C 163.42 (C=O), 62.20 (CH_2), 33.56 (CH, C(1)), 32.42 (CH_2, C(2)), 17.24 (C(2)Me) and 14.21(CH_3); m/z 129 (M^+, 100%), 122, 114, 111, 104, 96, 92, 90, 84, 80, 76, 72, 70 and 68.

8. Preparation of Cis 1-ethoxycarbonyl-2-phenyl-3-methylaziridine (126)

a) Preparation of Propiophenone oxime

This was prepared according to the method of Laurent et al.[87] Hydroxyammonium chloride (20g) and sodium acetate (32g) were dissolved in ethanol (100 ml). The mixture was warmed and propiophenone (20g) was added. The mixture was heated at reflux for 5 h, allowed to cool and was poured onto ice/water (500 ml). The crystalline precipitate was filtered off and dried in vacuo over phosphorous pentoxide (22.6g, 98%). The product was

recrystallised from light petroleum (40-60) to give propiophenone oxime. M.p. 53°C (lit. 53°C).

b) Preparation of cis-2-phenyl-3-methylaziridine

This was prepared according to the method of Laurent et al.[87] iso-butyl magnesium bromide was prepared by reacting clean, dry magnesium turnings (4.86g, 0.2 mol) with 1-bromo-2-methylpropane (28g) in dry ether (100ml). Propiophenone oxime (7.45g, 0.05 mol) was added followed by dry toluene (100 ml) and the ether was distilled off. The remaining mixture was heated at reflux for 10 h, allowed to cool and was poured onto a mixture of ice and ammonium chloride. The product was extracted with ether, dried and the solvent removed to give a dark red, viscous oil. This was distilled using bulb-to-bulb distillation to give cis-2-phenyl-3-methyl-aziridine as a pale yellow solid (2.1g, 32%). B.p. 97-98°C at 12 mm Hg, m.p. 44°C (lit. 46°C); (M^+133.0891, $C_9H_{11}N$ requires 133.0891); ν max 3420 cm^{-1}; δ_H 7.28 (5H, s), 3.20 (1H, d, J = 6.5 Hz, C(2)H), 2.36 (1H, m, C(1)H), 0.89 (3H, d, J = 5.7 Hz, C(1)Me) and 0.80 (1H, br s, NH). δ_C 137.39, 127.55, 126.33, 36.90, 31.89 and 13.33; m/z 133 (M^+), 118, 105, 95, 92 and 78 (100%).

c) Preparation of Cis-1-ethoxycarbonyl-2-phenyl-3-methylaziridine (126)

This was prepared by the reaction of cis-2-phenyl-3-methylaziridine (9.95g, 7.1 mmol) with ethyl chloroformate. Cis-1-ethoxycarbonyl-2-phenyl-3-methylaziridine was obtained as a pale yellow oil (1.27g, 87%) (M^+ 205.1103, $C_{12}H_{15}NO_2$ requires 205.1103); νmax 1725 cm^{-1}, δ_H 7.29 (5H, s), 4.16 (2H, q, $OC\underline{H}_2$), 3.61 (1H, d, J = 6.5Hz, C(2)H) 2.79(1H, m, C(3)H, 1.25 (3H, t, CH_3) and 0.98 (3H, d, J=5.6Hz, C(3)Me); δ_C 163.54, 134.59, 127.81, 127.30, 127.11, 62.12, 43.62, 29.56, 14.05 and 12.38; m/z 205 (M^+), 188, 160, 132 (100%), 117, 105, 91 and 77.

9) Preparation of 1-ethoxycarbonyl-2,2-diphenyl-aziridine (113)

a) Preparation of Methyl (2-iodo-1,1-diphenylethane) carbamate

This was prepared according to modification of the method of Hassner et al[29] by Lopez et al.[88,89] Iodine (25.4g, 0.1 mol) and freshly prepared, dry silver cyanate (20g, 0.13 mol) was added to dry ether (200 ml). The slurry was stirred for 30 min and 1,1-diphenylethylene was added in three portions over a 30 min period. The

mixture was stirred for two hours at room temperature by which time the iodine colour had faded. The inorganic salts were filtered off through celite and dry methanol (200 ml) and a few drops of lithium methoxide solution were added to the filtrate. The mixture was stoppered and left to stand in the dark for 24 h. The ether was removed *in vacuo* and the remaining methanol solution was poured onto ice-water (400 ml) containing a little sodium sulphite. A yellow oil formed which was separated from the aqueous solution, dissolved in ether (200 ml), washed with water, dried and the solvent evaporated to give thick, yellow oil. On standing this oil partially crystallised. The crystals were filtered off and washed with a little ether. The product was shown to be crude methyl (2-iodo-1,1-diphenylethane)carbamate (11.3g, 30%). ν_{max} 3360 and 1710 cm^{-1}; δ_H 7.35 (10 H, s), 5.9 (1H, br s), 4.52 (2H, s) and 3.66 (3H, s); δ_C 155.04, 142.33, 128.18, 127.14, 126.21, 63.02, 57.93 and 17.59.

b) Preparation of 2,2-diphenylaziridine

This was prepared by modification of the method of Hassner *et al.*[29] Methyl (2-iodo-1,1-diphenylethane)-carbamate (5.5g, 0.014 mol) was heated at reflux with potassium hydroxide (10g) in methanol (70 ml) and water (30 ml) for 3 h. The mixture was allowed to cool, poured onto water (250 ml) and extracted with ether (3 x 150 ml). The combined ether fractions were washed with

water, dried and the solvent removed in vacuo to give 2,2-diphenylaziridine as a yellow oil (2.49g, 93%) (M^+ 195.1048, $C_{14}H_{13}N$ requires 195.1048); νmax 3290, 758 and 700 cm^{-1}; δ_H 7.36 (10H, s), 2.38 (2H, s), 1.5 (1H, br s). δ_C 142.52, 128.16, 127.58, 126.93, 43.74 and 35.19; m/z 195 (M^+, 100%), 181, 166, 153, 140, 117, 106, 92 and 78.

c) Preparation of 1-ethoxycarbonyl-2,2-diphenyl-aziridine (113)

This was prepared by reacting 2,2-diphenylaziridine (1.9g, 9.7 mmol) with ethyl chloroformate. 1-Ethoxycarbonyl-2,2-diphenylaziridine was obtained as a yellow oil (2.35g, 91%) (M^+ 267.1259, $C_{17}H_{17}NO_2$ requires 267.1259); νmax 1735 cm^{-1}; δ_H 7.34 (10 H, s), 3.87 (2H, q), 2.95 (2H, s) and 0.92 (3H, t); δ_C 161.35, 138.46, 128.36, 127.93, 127.68, 61.98, 52.23, 37.99 and 13.68; m/z 267 (M^+), 223, 195, 179, 166, 92 (100%), 78.

10 Preparation of 1-Ethoxycarbonyl-2-tert-butyl-aziridine (114)

a) Preparation of Methyl (2-Iodo-1-tert-butylethane) carbamate

This was prepared *via* a modification of a method by Hassner *et al*.[29] Iodine (25.4g, 0.1 mol) and dry silver cyanate (20g, 0.13mol) was added to dry ether (200 ml). The slurry was stirred for 30 min and 3,3-dimethylbut-1-ene (8.4g, 0.1 mol) was added in three equal portions over a 30 min period. The slurry was stirred at room temperature until the iodine colour had faded (5 h). The inorganic salts were filtered off through a celite pad and the filtrate was added to dry methanol (200 ml) containing a few drops of lithium methoxide solution. The mixture was placed in the dark for 60 h. The ether was removed *in vacuo* and the remaining methanol solution was poured onto ice-water containing a little sodium sulphite. The white solid was filtered off and was shown to be methyl(2-Iodo-1- tert-butylethane)carbamate (25g, 87%). M.p. 49-50°C; νmax 3340 and 1688 cm^{-1}; δ_H 5.2 (1H, br s), 4.12 (2H, m), 3.60 (3H, s), 3.25 (1H, m), 1.05 (9H, s); m/z 285 (M^+), 284, 269, 253, 241, 227, 221 (100%), 195, 182, 169, 154 and 128.

b) Preparation of 2-tert-butylaziridine

This was prepared *via* a method based on that of Hassner *et al.*[29] A solution of methyl (2-iodo-1-tert-butylethane)carbamate (10g, 0.035 mol) and potassium hydroxide (10g) in methanol (70 ml) and water (30 ml) was heated at reflux for 1.5 h. The solution was cooled and poured onto water (250 ml). The solution was extracted with ether (3 x 100 ml) and the combined organic solutions were washed with water, dried and the solvent removed to give 2-tert-butylaziridine as a yellow oil (2.95g, 85%). (M^+ 99.1048, required for $C_6H_{13}N$ 99.1048); ν_{max} 3300 cm^{-1}; δ_H 1.75 (1H, dd J = 6.1 and 3.8 Hz), 1.54 (1H, d, J = 6.1Hz), 1.35 (1H, d, J = 3.8 Hz) and 0.79 (9H, S); δ_C (DEPT) 39.56, 26.25 and 21.19. m/z 99 (M^+), 85 (100%), 70.

c) Preparation of 1-ethoxycarbonyl-2-tert-butyl-aziridine (114)

This was prepared by reacting 2-tert-butylaziridine (0.95g, 9.6 mmol) with ethyl chloroformate. 1-Ethoxycarbonyl-2-tert-butylaziridine was obtained as a yellow oil (1.53g, 93%). (M^+ 171.1259, $C_9H_{17}NO_2$ requires 171.1259); ν max 1730 cm^{-1}; δ_H 4.05 (2H, q), 2.11 (2H, m), 1.97 (1H, dd), 1.09 (3H, t), 0.85 (9H, s); δ_C 163.83, 61.92, 46.85, 29.97, 29.04, 25.81 and 13.98; m/z

171 (M^+), 156 (100%), 142, 126, 111, 102, 98, 84 and 69.

11. Preparation of 1-Ethoxycarbonyl-2-cyanoaziridine (132)

a) Preparation of 2-cyanoaziridine

This was prepared according to the method of Burzin et al.[90] 2,3-dibromopropionitrile (22.5g, 0.106 mol) was added dropwise, with stirring, to liquid ammonia (200 ml) at -40°C. The solution was stirred at -40°C for 30 min and triethylamine (21.4g, 0.211 mol) was added. The solution was stirred for 3 h and then allowed to warm to room temperature. The residual oil was extracted with anhydrous ether (3 x 100 ml) and the combined organic solutions were evaporated to give a brown oil which rapidly polymerised. The product was washed with dry ether and evaporation of the solution gave 2-cyanoaziridine as a colourless oil, identified by comparison of its characteristics with literature data,[90,91] (0.808g, 11%). ν max (neat) 3300 and 2230 cm^{-1}; δ_H 2.3 (1H, dd), 2.0 (2H, m) and 1.8 (1H, br s).

b) Preparation of 1-Ethoxycarbonyl-2-cyanoaziridine (132)

This was prepared by the reaction of 2-cyanoaziridine (0.808g, 11 mmol) with ethyl chloroformate in the presence of triethylamine, according to the method of Anastassiou et al.[83] 1-ethoxycarbonyl-2-cyanoaziridine was obtained as a contaminated, yellow oil (1.4g). The desired product formed the major fraction. (M^+ 140.0585, $C_6H_8N_2O_2$ requires 140.0586); νmax (neat) 2270 and 1730 cm^{-1}; δ_H 4.15 (2H, q), 3.0 (1H, dd), 2.6 (2H, m) and 1.25 (3H, t); m/z 140 (M^+), 132, 119, 112, 102 (100%), 97, 86, 81, 74, 68, 58, 56 and 52.

The impurity (25% by n.m.r.) displayed a ^1H n.m.r. with δ_H 4.25 (1H, t), 4.23 (2H, q), 3.65 (2H, t) and 1.18 (3H, t).

12. a) Attempted Reaction of Ethyoxycarbonylnitrene with Phenyl vinyl sulphone

Sodium hydrogen carbonate (0.03 mol) in water (30 ml.) was added to a solution of ethyl p-nitrobenzenesulphonoxycarbamate (0.02 mol), phenyl vinyl sulphone (0.021 mol) and tetrabutylammonium bromide (2 mmol) in dichloromethane (40 ml). The mixture was vigorously stirred for 5 h, diluted with water (200 ml) and

extracted with dichloromethane (2 x 150 ml). The combined organic layers were washed with water, dried and the solvent evaporated to give a yellow oil. Analysis by ^{1}H n.m.r. spectra showed that phenyl vinyl sulphone remained and no aziridine was present.

12. b) Attempted Reaction of Phenyl vinyl sulphone with iodine isocyanate

Iodine (0.03 mol) and freshly prepared dry silver cyanate (0.045 mol) in dry ether (80 ml) was stirred for 15 min and phenyl vinyl sulphone (0.03 mol) was added. The mixture was stirred in the dark for 72h. The inorganic salts were filtered off through celite and the filtrate was added to dry methanol (80 ml) containing a few drops of lithium methoxide solution. The mixture was allowed to stand in the dark for 48 h. The ether was removed in vacuo and the remaining methanol solution was poured onto ice-water (150 ml). A yellow precipitate was formed (3.5 g). This was shown to be recovered phenyl vinyl sulphone (70%).

13 a) Attempted Reaction of ethoxycarbonylnitrene with Methyl Acrylate

Sodium hydrogen carbonate (0.03 mol) in water (30

ml) was added to a solution of ethyl p-nitrobenzene-sulphonoxycarbamate (0.01 mol), methyl acrylate (0.02 mol) and tetrabutylammonium bromide (2 mmol) in dichloromethane (40 ml). The reaction mixture was stirred vigorously for 2 h, diluted with water (100 ml) and extracted with dichlormethane (2 x 150 ml). The combined organic layers were washed with water, dried and the solvent removed to give a yellow oil (2.07g) which contained no 1-ethoxycarbonyl-2-methoxycarbonylaziridine.

13. b) Attempted reaction of methyl acrylate with iodine isocyanate

Iodine (0.03 mol) and freshly prepared, dry silver cyanate (0.045 mol) were stirred in dry ether (80 ml) for 15 min, methyl acrylate (0.03 mol) was added and the mixture was stirred for 24 h. The iodine colour had not faded. The silver salts were filtered off through celite and the filtrate was mixed with dry methanol (80 ml) containing a few drops of lithium methoxide solution. After standing in the dark for 24 h, the ether was removed *in vacuo* and the methanol solution was poured onto ice/water (150 ml) containing a little sodium sulphite. No precipitate of the β-iodocarbamate appeared.

14. a) Preparation of N-Trityl-L-Serine, Methyl Ester

The title compound was prepared by modification of the method of Nakajima et al.[92] Trityl chloride (13.4g, 48 mmol) in dry chloroform (40 ml) was added to an ice-cooled, stirred solution of L-serine, methyl ester hydrochloride (7.44g, 48 mmol) and dry triethylamine (9.7g, 96 mmol) in dry chloroform (50 ml). The mixture was stirred for 24 h at 0°C and was washed with 10% aqueous citric acid (250 ml), water (250 ml) and dried. Evaporation gave N-trityl-L-serine, methyl ester as a pale brown, sticky oil (98%) which crystallised on standing. (M^+ 361.1681, $C_{12}H_{23}NO_3$ requires 36.1678); δ_H 7.44 (6H, m, Ar), 7.29 (9H, m, Ar), 3.6 (3H, m, CH and CH_2), 3.30 (3H, s, CH_3) and 2.5 (2H, br s, OH and NH); δ_C 173.82 (C=O), 145.49 (Cq), 128-126 (Ar-CH), 70.79 (Cq), 64.77 (CH_2), 57.76 (CH_3) and 51.62 (CH). m/z 361 (M^+), 330, 320, 302, 288, 260, 243 (100%), 228, 211, 182, 165, 105 and 69.

b. Preparation of O-Tosyl-N-Trityl-L-Serine, Methyl Ester

This was prepared by modification of the method of Nakajima et al.[92] Tosyl chloride (1.84g, 9.63 mmol) in dry pyridine (14 ml) was added to a cooled (-10°C), stirred solution of N-trityl-L-serine, methyl ester

(3.47g, 9.63 mmol) in dry pyridine (20 ml). The mixture was allowed to stir at -10°C for 2 h, and then at 0-4°C for 96 h. The pyridine was removed *in vacuo* at room temperature and the residual oil was partitioned between ethyl acetate and water. The organic layer was washed with 10% citric acid solution and water. The organic solution was dried and the solvent removed to give a brown, sticky material which was identified as *O*-tosyl-*N*-trityl-L-serine, methyl ester (4.54g, 92%), by comparison of it ^1H n.m.r. spectrum with literature data. δ_H 7.75 (2H, d, Ar), 7.25 (17 H, Ar), 3.5 (3H, m, CH_2 and CH), 3.15 (3H, s, OCH_3) and 2.42 (3H, s, Ar - CH_3).

c. *Preparation of 1-Trityl-(2S)-Methoxycarbonyl-aziridine*

This was prepared by the method of Nakajima *et al*.[92] *O*-tosyl-*N*-trityl-L-serine, methyl ester (4.54g, 8.8 mmol) in dry tetrahydrofuran (20 ml) and dry triethylamine (1.77g, 17.6 mmol) was heated at reflux for 20 h and was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with aqueous 10% citric acid, 1M aqueous sodium hydrogen carbonate solution and water. The organic solution was dried and the solvent removed to give a viscous pale brown oil which partially crystallised on standing. This material

was identified as 1-trityl-(2S)-methoxycarbonylaziridine (3.14g) by ^1H n.m.r. and it was used without further purification. δ_H 7.5 (6H, cm, Ar), 7.3 (9H, cm, Ar), 3.75 (3H, s, OCH_3), 2.25 (1H, dd, J = 2.8 and 1.6 Hz, C(2)H), 1.88 (1H, dd, J = 2.8 and 6.2 Hz, C(3)H) and 1.39 (1H, dd, J = 1.6 and 6.2 Hz, C(3)H).

d. Preparation of (2S)-Methoxycarbonylaziridine

This was prepared according to the method of Baldwin et al.[70] Trifluoroacetic acid (15 ml) was added dropwise to a cooled, stirred solution of 1-trityl-(2S)-methoxycarbonylaziridine (2.74g, 8 mmol) in dry dichloromethane (10 ml) and dry methanol (10 ml). The solution was stirred at -5°C for 2 h and the solvent was removed in vacuo. The residual oil was partitioned between ether and water. The aqueous layer was separated, made alkaline with sodium hydrogen carbonate, and extracted with ether. The organic layer was dried and the solvent removed to give (2S)-methoxycarbonyl-aziridine as a colourless oil (95 mg, 11%), identified by comparison of spectra with literature data. δ_H (60 MHz), 3.65 (3H, s), 2.4 (1H, dd), 1.8 (2H, m) and 1.5 (1H, br s).

e. Preparation of 1-Ethoxycarbonyl-(2S)-Methoxycarbonylaziridine (135)

This was prepared from (2S)-methoxycarbonylaziridine (95 mg, 0.9 mmol) by its reaction with ethyl chloroformate. 1-Ethoxycarbonyl-(2S)-methoxycarbonylaziridine was obtained as a pale brown oil (0.135g, 84%). (M^+ 173.0687, $C_7H_{11}NO_4$ requires 173.0688); ν max 1730 cm^{-1}; δ_H 4.13 (2H, q), 3.65 (3H, s), 3.0 (1H, dd), 2.4 (2H, m) and 1.2 (3H, t); m/z 173, 165, 155, 156, 142, 134, 128, 114, 105, 101, 86, 69 (100%), 59 and 55; $[\alpha]_D^{25}$ = -44.3 (c = 1, CH_2Cl_2).

F. FLASH VACUUM PYROLYSIS OF 1-ALKOXYCARBONYL-AZIRIDINES

1a. FVP of 1-Ethoxycarbonyl-2-phenylaziridine (36)

Pyrolysis of the title compound (0.22g, 1.14 mmol, 650°C, 0.01 mm Hg, Inlet 70-80°C) afforded a colourless crystalline solid in the trap head which was identified as 5-phenyl-2-oxazolidinone (86) (0.16g, 88%) by comparison of its characteristics with literature data.[93,94] M.p. 87.8-88.5°C (lit. 88.8-90.2°C). (Found: C, 65.3; H,5.51; N,8.43%; $C_9H_9NO_2$ requires: C,66.3; H,5.50; N,8.6%); (M^+ 163.0634, $C_9H_9NO_2$ requires 163.0633); νmax (mull) 3275 and 1720 cm^{-1}; δ_H 7.37 (5H, s, Ar), 6.13 (1H, br s, NH), 5.61 (1H, t, c(5)H), 3.96 (1H, t, C(4)H, trans) and 3.53 (1H, t, C(4)H, cis); δ_C 159.83, 138.46, 128.75, 125.54, 77.70 and 48.12; m/z 163 (M^+), 118, 107 (100%), 91, 89, 79 and 77.

The yellow oil which collected in the trap well during pyrolysis was identified as starting material (0.02g, 10%).

Pyrolysis of the title compound (0.112g, 0.56 mmol, 500°C. 0.002 mm Hg, Inlet 80-100°C) gave rise to a yellow oil which was identified by ^1H n.m.r. to be mostly starting material containing traces of 5-phenyl-4,5-dihydro-2-ethoxyoxazole (80b) (12%), which was identified by comparison of its spectra with those of an authentic sample. νmax 1670 and 1260 cm^{-1}; δ_H 7.3(5H, m),

5.53(1H, dd), 4.29(2H, q), 4.15 (1H, dd), 3.68(1H, dd) and 1.35 (3H, t).

b. Thermolysis of 1-Ethoxycarbonyl-2-phenylaziridine (36)

A sample of 1-ethoxycarbonyl-2-phenyl-aziridine was placed in an n.m.r. tube and a ^{1}H n.m.r. spectrum of the neat oil was obtained. The sample was heated in an oil bath at 200°C during which time the sample darkened in colour, becoming dark brown. After 4.5 h, a ^{1}H n.m.r. spectrum was recorded which showed that the sample was unchanged.

2) Preparation of 5-Phenyl-4,5-dihydro-2-ethoxyoxazole (80b)

A dichloromethane solution of triethyloxonium tetrafluoroborate[95,96] (0.67M, 1.2 equiv.) was added dropwise to a cooled (0°C), stirred solution of 5-phenyl-2-oxazolidinone (0.24g, 1.4 mmol) in dry dichloromethane (25 ml). The mixture was stirred for 12 h and allowed to stand at room temperature for 24 h. Aqueous potassium carbonate solution (5m, 20 ml) was added, the precipitate was filtered off and the organic layer collected. The aqueous layer was extracted with ether and the combined organic solutions were dried and the

solvent removed to give 5-phenyl-4,5-dihydro-2-ethoxyoxazole as a pale brown oil (0.25g, 94%). (M^+ 191.0940, $C_{11}H_{13}NO_2$ requires 191.0946); νmax (neat) 1670 and 1260 cm^{-1}; δ_H 7.3 (5H, m, Ar), 5.53 (1H, dd, J = 9.5 and 7.6 Hz, C(5)H), 4.29(2H, q, CH_2), 4.15(1H, dd, J=12.6 and 9.5 Hz, C(4)H, trans), 3.58(1H, dd, J = 12.6 and 7.6 Hz, C(4)H, cis) and 1.35(3H, t, CH_3); δ_C 162.34 (C=N), 140.01 (Cq), 128.48, 128.07 and 125.29 (CH, Ar), 81, 51 (C(5)), 66.44 (OCH_2), 59.64 (C(4)) and 14.06(CH_3); m/z 191 (M^+), 176, 163, 135, 118, 107, 91(100%), 85, 79 and 71.

3) FVP of 5-Phenyl-4,5-dihydro-2-ethoxyoxazole (80b)

Pyrolysis of the title compound (54 mg, 0.28 mmol), 600°C, 0.003 mm Hg, Inlet 100-120°C) gave a colourless, crystalline solid in the trap head which was identified by n.m.r. spectroscopy and melting point as 5-phenyl-2-oxazolidinone (86) (45 mg, 97%), m.p. 88-80°C (lit.[93,94] 88.8-90.2°C); νmax (mull) 3275 and 1720 cm^{-1}; δ_H 7.37 (5H, s), 6.13 (1H, br s), 5.61 (1H, t), 3.96 (1H, t) and 3.53 (1H, t).

Pyrolysis of the compound (0.024 g, 0.13 mmol, 500°C, 0.001 mm g, inlet 120°C) gave an oil in the trap well which was identified as starting material (11 mg, 46%), and a colourless solid in the trap head which was identified as 5-phenyl-2-oxazolidinone (86) (11 mg, 54%).

4) Preparation of 4-Phenyl-2-Oxazolidinone (87)

This was prepared according to the method of Hassner *et al*.[29] Ethyl (2-iodo-1-phenylethane)carbamate (3.64g, 11 mmol) was heated in an oil bath (143-146°C) under vacuum (0.6 mm Hg) for 15 min. The ethyl iodide evolved was trapped in a liquid nitrogen cooled trap. The solid, black residue (2.07g) was dissolved in hot chloroform and, on cooling, 4-phenyl-2-oxazolidinone was obtained as small, pale yellow crystals (1.60g, 89%). M.p. 137.5-138°C (lit. 138-139.5°C); (M^+ 163.0636, $C_9H_9NO_2$ requires 163.0633); (Found: C, 65.1; H, 5.44; N, 8.39%; $C_9H_9NO_2$ requires: C, 66.25; H, 5.56; N, 8.58%); ν max 3430 and 1765 cm^{-1}; δ_H 7.3 (5H,s), 6.5(1H, br s), 5.0-4.5 (1H, m), 4.7-4.5 (1H, m) and 4.3-4.0 (1H, m); m/z 163 (M^+), 143, 133, 119, 104(100%), 91, 86 and 78.

5) FVP of 4-phenyl-2-oxazolidinone (87)

The title compound was pyrolysed (0.15g, 1.0 mmol, 700°C, 0.1 mm Hg, inlet 160°C) to give a solid material in the trap head, identified as starting material (0.07g), and a colourless material in the trap well (0.03g). This oil was identified as phenylacetaldehyde by comparison of its spectra with literature spectra.[97,98] ν max 1725 cm^{-1}; δ_H 9.75 (1H, t), 7.3-7.15 (5H, m) and 3.72 (2H, d).

6) FVP of 1-tert-butoxycarbonyl-2-phenylaziridine (108)

Pyrolysis of the title compounds (0.128g, 650°C, 0.005 mm Hg, inlet 60-120°C) produced a red/purple oil (0.077g). This was shown by ^{1}H n.m.r. to consist mainly of 2-phenylaziridine (81) with traces of N-phenyl-methylene methanamine (112). Pyrolysis of the compound (0.123g, 450°C, 0.001 mm Hg, inlet 80°C) gave a yellow oil which was shown by ^{1}H n.m.r. to contain a mixture of 2-phenylaziridine (67%) and 1-tert-butoxycarbonyl-2-phenylaziridine (33%).

7) FVP of 2-phenylaziridine (81)

Pyrolysis of the title compound (0.109g, 0.9 mmol, 700°C, 0.01 mm Hg, inlet 80°C) produced a pale yellow oil which was identified as N-phenylmethylene methanamine (112) (0.13g, 52%) by comparison of its spectra with literature data.[99,100] ν max 3060,3020, 2940, 2880, 2860, 1650, 1600, 1490, 755 and 698cm^{-1}; δ_H 8.25 (1H, q), 7.75-7.13(5H, m), 3.5(3H, d), δ_C 162.32, 130,35, 128.69, 128.44 and 48.01; m/z 119 (M^+) 118(100%), 105, 91, 77, 57 and 42.

8. FVP of 1-methoxycarbonyl-2-phenylaziridine (88)

Pyrolysis of the title compound (0.246g, 1.3 mmol, 600°C, 0.001 mm Hg, inlet 80°C) resulted in the formation of a crystalline solid in the trap head and a yellow oil in the trap well. The trap head material was identified by n.m.r. spectroscopy by comparison with literature data,[101] as trans-methyl-2-phenylethenylcarbamate (90) (0.02g, 10%) m.p. 116-117°C; νmax, 3300, 1703 and 1665 cm^{-1}; δ_H 7.2 (6H, br s), 6.7-6. (1H, br d), 6.0 (1H, d, J = 14.4 Hz) and 3.76 (3H, s); δ_C 128.47, 126.14, 125.12, 123.93, 110.58 and 52.55; m/z 177 (M^+, 100%), 145, 118, 117, 91 and 59. The yellow oil contained an approximately equimolar mixture of 1-methoxycarbonyl-2-phenylaziridine and 5-phenyl-4,5-dihydro-2-methoxyoxazole (89) (0.212g). The latter was identified by comparison of n.m.r. spectra with that of an authentic sample.

9. Methylation of 5-Phenyl-2-Oxazolidonone (86)

a) Using CH_3I/K_2CO_3/DMF

5-Phenyl-2-oxazolidinone (0.101g, 0.62 mmol) was stirred with potassium carbonate (0.044g, 0.32 mmol) and methyl iodide (0.2g, excess) in dry dimethylformamide (3 ml) for 120 h. The reaction mixture was diluted with dichloromethane (50 ml) and repeatedly washed with water

(5 x 50 ml). The organic phase was dried and the solvent removed to give a brown oil (0.064 g).

Analysis by ^{1}H n.m.r. showed this to be a mixture of 3-methyl-5-phenyl-2-oxazolidinone (91), (75%)[102,103] and 5-phenyl-4,5-dihydro-2-methoxyoxazole (89), (25%). δ_H 7.3 (s, (91) and (89)), 5.5 (dd, (89)), 5.4 (t, (91)), 4.1 (dd, (89)), 3.9 (t, (91)), 3.9 (s, (89)), 3.7 (dd, (89)), 3.4 (dd, (91)) and 2.9 (s, (91)).

b) Using NaH/Methyl p-toluenesulphonate/DMEU

This was carried out according to the method of Monahan.[104] 5-Phenyl-2-oxazolidinone (0.093g, 0.57 mmol) was dissolved in dimethylethylene urea (4 ml). Sodium hydride (0.041g, 1.71 mmol) and methyl-p-toluenesulphonate (0.106g, 0.57 mmol) was added and the mixture was stirred at room temperature for 45 min. Methanol (5 ml) was added to decompose any remaining sodium hydride. Water (30 ml) was added and the aqueous solution was extracted with ether (3 x 25 ml). The combined organic layers were washed with water (3 x 25 ml), dried and the solvent removed to give 3-methyl-5-phenyl-2-oxazolidinone (91) as a brown oil (0.06g, 59%). ν max 1750 cm^{-1};[102,103] δ_H 7.3 (5H, s, Ar), 5.4 (1H, t, 5 (C)H), 3.9 (1H, t, 4(C)H, trans), 3.4 (1H, dd, 4(C)H, cis) and 2.9 (3H, s, CH_3).

c) Using $MeI/Ag_2CO_3/DMSO$

This alkylation was carried out according to the method of Chan.[105] 5-Phenyl-2-oxazolidinone (71 mg, 0.43 mmol) was dissolved in dimethylsulphoxide (4 ml), silver carbonate (0.12g) and methyl iodide (0.2 ml, excess) were added and the mixture was stirred at room temperature for 75 h. The reaction mixture was added to water (70 ml) and extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water (3 x 100 ml), dried, and the solvent removed to give a brown solid (67 mg). A ^1H n.m.r. spectrum showed that this solid contained mainly 5-phenyl-2-oxazolidinone (86) with traces of 5-phenyl-4,5-dihydro-2-methoxyoxazole (89) and 3-methyl-5-phenyl-2-oxazolidinone (91).

d) Using Meerwein's Reagent

Trimethyloxonium tetrafluoroborate (0.14g, 0.92 mmol) was added to a stirred, cold (0°C) solution of 5-phenyl-2-oxazolidinone (0.124g, 0.76 mmol) in dry dichloromethane (25 ml). The mixture was stirred for 12 h at room temperature and then allowed to stand for 24 h. Aqueous potassium carbonate solution (5M, 15 ml) was added, the precipitate was filtered off and the organic layer collected. The aqueous layer was extracted with ether, the combined organic layers were dried and the

solvent removed to give 5-phenyl-4,5-dihydro-2-methoxyoxazole (89) as a pale brown oil (0.11g, 82%) (M^+ 177.0970, $C_{10}H_{11}NO_2$ requires 177.0790); ν max 1670, 1450, 1380, 1340, 1265, 733 and 700 cm^{-1}; δ_H 7.32 (5H, s), 5.59 (1H, dd, J=9.4 and 7.8 Hz), 4.19 (1H, dd, J = 12.7 and 9.4 Hz), 3.70 (1H, dd. J = 12.7 and 7.8 Hz) and 3.92 (3H, s); δ_C 163.31, 139.99, 128.56, 128.19, 125.38, 82.09, 59.65 and 57.28; m/z 177 (M^+), 149, 132, 121, 107, 89(100%), 77, 74 and 71.

10) FVP of 5-phenyl-4,5-dihydro-2-methoxyoxazole (89)

Pyrolysis of the title compound (0.02g, 675°C, 0.001 mm Hg, inlet 140°C) yielded a yellow oil. No starting material or 5-phenyl-2-oxazolidinone was present in the product, this being a complex mixture of decomposition products.

11) FVP of cis 1-ethoxycarbonyl-2,3-diphenylaziridine (95)

Pyrolysis of the title compound (0.069g, 0.26 mmol, 650°C, 0.001 mm Hg, inlet 60-100°C) gave a colourless crystalline solid. This was identified as being a mixture of trans-4,5-diphenyl-2-oxazolidinone (97) (75%) and cis- 4,5-diphenyl-2-oxazolidinone (96)

(25%), (Total 0.053g, 86%) by comparison of their spectra with literature data.[94,106,107] Data for product mixture (M^+ 239.0948, $C_{15}H_{13}NO_2$ requires 239.0946); ν max 3220 and 1760 cm^{-1}; δ_H(trans isomer) 7.4-7.0 (10H, m), 6.3 (1H, br s), 5.25 (1H, d, J = 7.3 Hz) and 4.76 (1H, d, J = 7.3Hz); δ_H (cis-isomer) 7.4-7.0 (10H, m), 6.3 (1H, br s), 5.9 (1H, d) and 5.2 (1H, d); δ_C (trans-isomer) 158.69 (C=O), 85.99 (OCH) and 64.71 (NCH); δ_C (cis-isomer) 159.54 (C=O), 82.2 (OCH) and 61.31 (NCH); m/z 239 (M^+), 194(100%), 178, 165, 133, and 122.

12a. FVP of 7-Ethoxycarbonyl-7-Azabicyclo-[4.1.0]-heptane (76)

Pyrolysis of the title compound (0.101g, 1.1 mmol, 650°C, 0.01 mm Hg, inlet 60°C) gave a yellow oil shown to contain ethyl-3-cyclohexenylcarbamate and some starting material. Traces of a colourless insoluble material (considered to be polymeric product) was deposited at the trap head. On standing, the yellow oil precipitated ethyl-3-cyclohexenylcarbamate (129) as colourless needles.[53] ν max 3454, 3348, 3030, 1720, 1497 and 1213 cm^{-1}; δ_H 5.9-5.5 (2H,m) 4.75 (1H, br s), 4.09 (1H, m), 4.07 (2H, q), 1.9-1.6 (6H, cm) and 1.20 (3H, t).

Pyrolysis of the compound at higher temperatures resulted in poorer yields of ethyl-3-cyclohexenyl-carbamate and greater quantities of polymeric residues.

12b. Thermoloysis of 7-Ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (76)

The title compound was placed in a sealed n.m.r. tube and the ^1H n.m.r. spectrum was recorded. The compound was heated in refluxing 1,2-dichlorobenzene (180°C) for 24 h and the n.m.r. spectrum was recorded. Comparison of the spectrum with literature data[53] showed that approximately 20% of the aziridine had been converted to ethyl-3-cyclohexenyl carbamate (129).

13. FVP of 1-ethoxycarbonylaziridine (121)

Pyrolysis of the title compound (0.186g, 1.6 mmol, 750°C, 0.005 mm Hg, inlet 100°C) yielded a gum (0.056g) in the trap well which was identified as a mixture of starting material and polymeric products. The colourless crystalline material in the trap head was identified as 2-oxazolidinone (123) (0.079g, 57%). M.p. 85-86°C (lit.[108] 85-86°C). (M^+ 87.0323, $C_3H_5NO_2$ requires 87.0320); ν max 3260 and 1730 cm^{-1}; δ_H 6.0 (1H, br s), 4.44 (2H, t) and 3.60 (2H, t); δ_C 160.48, 64.83 and 40.57; m/z 87(M^+, 100%), 70. Pyrolysis at 700°C yielded 2-oxazolidinone (16%). The remainder of the product was starting material. Pyrolysis at 800°C yielded 2-oxazolidinone (24%), the majority of the product forming a gummy polymer in the trap well.

14. FVP of 1-Ethoxycarbonyl-2-Methylaziridine (122)

Pyrolysis of the title compound (0.181g, 1.4 mmol, 650°C, 0.05 mm Hg, inlet 150°C) gave a quantitative yield of ethyl-2-propenyl carbamate (124) as a colourless oil.[109] (M^+ 129.0790, $C_6H_{11}NO_2$ requires 129.0790); ν max (neat) 3315, 1700 and 1530 cm^{-1}; δ_H 5.75 (1H, m, C(2)H), 5.0 (3H, m, C(1)H and NH) 4.02 (2H, q, OCH_2), 3.7 (2H, m, $C(3)H_2$) and 1.15 (3H, t, CH_3); δ_C 156.43 (C=O), 134.55 (CH), 115.68, (CH_2), 60.70 (OCH_2), 43.34 (NCH_2) and 14.42 (CH_3); m/z 129 (M^+), 125, 116, 102, 84(100%), 73 and 70.

15. FVP of cis-1-ethoxycarbonyl-2-phenyl-3-methyl-aziridine (126)

Pyrolysis of the title compound (0.195g, 0.95 mmol, 600°C, 0.005mm Hg, inlet 150°C) gave complete conversion to Ethyl-1-phenyl-2-propenylcarbamate (128) as a colourless oil.[84] (M^+ 205.1106, $C_{12}H_{15}NO_2$ requires 205.1103); νmax 3320 and 1700 cm^{-1}; δ_H 7.25 (5H, br s), 6.2-5.7 and 5.4-5.0 (5H, m), 4.14 (2H, q) and 1.22 (3H, t); δ_C 137.67, 120.49, 127.39, 126.87, 115.46, 60.83, 56.92 and 14.43; m/z 205 (M^+), 176, 157, 143, 132, 116(100%), 105, 91 and 77.

16. FVP of 1-ethoxycarbonyl-2,2-diphenylaziridine (113)

Pyrolysis of the title compound (0.109g, 0.4 mmol, 675°C, 0.01 mm Hg, inlet 150°C) gave a yellow-green solid. This was dissolved in dichloromethane and a colourless insoluble precipitate was filtered off (8 mg). This material was insoluble in common organic solvents and was thought to be polymeric material. The filtrate yielded a green solid on evaporation (0.071g). ^1H n.m.r. spectra of this material showed that it consisted of predominantly 5,5'-diphenyl-2-oxazolidinone (116) with traces of 5,5'-diphenyl-4,5-dihydro-2-ethoxyoxazole (115) (δ_H 7.25 (10H, s), 4.18(2H, q), 4.12 (2H, s) and 1.25 (3H, t)). The material was purified by flash chromatography (Silica, ether/petroleum (40-60) gradient) to give 5,5'- diphenyl-2-oxazolidinone (116) (0.07g, 73%). M.p. 200°C (lit.[110,111] 200°C). (M^+ 2.39.0957, $C_{15}H_{13}NO_2$ requires 239.0946); (Found: C, 75.8; H, 5.56; N, 5.83%; $C_{15}H_{14}NO_2$ requires: C, 75.3; H, 5.48; N,5.85%; νmax (mull) 3275 and 1735 cm^{-1}; δ_H 7.34 (10H, s), 5.85 (1H, br s), 4.18 (2H, s); δ_C (d_6-dmso) 157.55, 143.16, 128.43, 127.73, 125.06, 85.04 and 52.49; m/z 239(M^+), 194, 183(100%), 165, 143, 131, 119, 111, 105, 91, 81, 77 and 69. Pyrolysis of the title compound (0.139g, 0.52 mmol, 600°C 0.005 mm Hg, inlet 200°C) yielded a yellow solid (0.093g) shown by ^1H m.m.r. spectra to be predominantly 5,5'- diphenyl-4,5-dihydro-

2-ethoxyoxazole (115) with some insoluble colourless material and 5,5'-diphenyl-2-oxazolidinone (116). Attempts to isolate the 5,5-diphenyl-4,5-dihydro-2-ethoxyoxazole by column chromatography on silica failed, since the material decomposed on the column.

17. FVP of 1-ethoxycarbonyl-2-tert-butylaziridine (114)

Pyrolysis of the title compound (0.45g, 2.6 mmol, 700°C, 0.2 mmHg, inlet 180°C) gave a yellow, crystalline material which was identified as a mixture of 5-tert-butyl-2-oxazolidinone (117) and 4-tert-butyl-2-oxazolidinone (118)[106] in the ratio 37:10 (0.17g, 46%). Attempts were made to separate the isomers by flash chromatography and thin layer chromatography, but this failed since their Rf values are almost identical. (M^+ 143.0945, $C_7H_{13}NO_2$ requires 143.0946); ν max (5-isomer) 3310 and 1730 cm^{-1}, (4-isomer) 3260 and 1730 cm^{-1}; δ_H (5-isomer) 6.49 (1H, br s), 4.29 (1H, dd, J = 8.8 and 7.9 Hz), 3.48 (1H, t, J = 8.9 Hz), 3.35 (1H, t, J = 8.4Hz), and 0.92 (9H, s), (4- isomer) 7.25 (1H, br s), 4.16 (2H, m), 3.60 (1H, dd) and 0.87 (9H, s); δ_C (5-isomer) 160.74, 84.12, 41.66, 33.60 and 24.31, (4-isomer) 160.86, 66.57, 61.57, 33.27 and 24.70; m/z (mixture) 143 (M^+), 128, 114, 107, 100, 95, 87(100%), 79 and 69.

18. FVP of 1-ethoxycarbonyl-2-cyanoaziridine (132)

Pyrolysis of the contaminated title compound (77 mg, 0.55 mmol, 650°C, 0.01 mm Hg, inlet 120°C) yielded a yellow glass which was virtually insoluble in $CDCl_3$ or d_6-acetone.

Pyrolysis at 550°C afforded a colourless oil in the trap head. A ^1H n.m.r. spectrum (d_6-acetone) showed the presence of the contaminant from the starting material to be the major component, along with traces of 1-ethoxycarbonyl-2-cyanoaziridine and unidentified minor components. No 5-cyano-2-oxazolidinone or 5-cyano-4,5-dihydro-2-ethoxyoxazole were present. Following the removal of this n.m.r. sample from the trap, there remained a yellow, glass like material which was insoluble in acetone.

19. Preparation of 5-cyano-2-oxazolidinone (134)

a) Preparation of Ethyl N-(2-chloro-2-cyanoethyl)-carbamate

This was prepared according to the method of Swern et al.[112] A solution of N,N-dichlorourethane (8g, 0.05 mol) in dry benzene (25 ml) was kept under a dry nitrogen atmosphere in a 100 ml round bottomed flask. Acrylonitrile (inhibitor free, 0.05 mol) was added

dropwise and the mixture was heated at 85°C for 6 h. Aqueous sodium bisulphite solution (20%, 50 ml) was added to the ice-cooled solution and the organic layer was separated. The aqueous phase was extracted with ether (2 x 25 ml) and the combined organic layers were washed with water (2 x 25 ml), dried and the solvent removed to give a colourless oil. Distillation gave urethane, and ethyl N-(2-chloro-2-cyanoethyl)-carbamate (4.37g, 49%) as a colourless oil. B.p. 140-145 at 1 mm Hg (lit. 101-102 at 0.3 mm Hg). ν max 3360, 2250, 1720, 1530 and 780 cm^{-1}; δ_H 5.7 (1H, br s), 4.63 (1H, t), 4.12 (2H, q), 3.63 (2H, t) and 1.20 (3H, t).

b) Preparation of 5-cyano-2-oxazolidinone (133)

The title compound was prepared by modification of the method of Swern et al.[112,113,114] Thermolysis of ethyl N-(2-Chloro-2-cyanoethyl)-carbamate (4.37 g, 0.025 mol), as a neat liquid at 160-165°C under a stream of dry nitrogen, gave a black, solid product. Dry acetone (50 ml) was added, the black precipitate (1.3 g) was filtered off and the filtrate was evaporated to give a brown oil (1.82 g). The oil was shown by ^1H n.m.r. to contain the desired product.

A portion of the oil (0.74 g) was placed on a florisil column (100-200 mesh, 20 g). Elution was carried out with ether (120 ml) and methanol (100 ml).

Evaporation of the methanol eluate gave 5-cyano-2-oxazolidinone as a pale brown solid (0.25g, projected yield from thermolysis : 22%). M.p. 92-93°C (lit. 94.5-95.5°C). ν max (mull) 3320, 2255 and 1760 cm^{-1}; δ_H (d_6-acetone) 7.0 (1H, br s), 5.58 (1H, dd, J = 4.9 and 8.5 Hz) and 3.9 (2H, m); δ_C (d_6-acetone) 156.75 (Cq), 115.90 (Cq), 62.09 (CH) and 44.34 (CH_2).

20. FVP of Ethyl N-(2-Chloro-2-cyanoethyl)-carbamate

Pyrolysis of the title compound (0.31 g, 1.7 mmol, 550°C, 0.01 mm Hg, inlet 100°C) gave a colourless polymeric solid in the trap head and oil in the trap well which was identified as starting material.

Pyrolysis at 630°C gave only the colourless polymeric material. No evidence of the presence of 5-cyano-2-oxazolidinone was detected.

21. Preparation of 5-cyano-4,5-dihydro-2-ethoxyoxazole (134)

Triethyloxonium tetrafluoroborate in dichloromethane (0.67 M, 5 ml) was added dropwise to an ice-cooled, stirred solution of 5-cyano-2-oxazolidinone (0.25 g, 2.2 mmol) in dry dichloromethane (20 ml). The mixture was stirred at room temperature for 12 h and then

was allowed to stand for 24 h. The solution was stirred and aqueous potassium carbonate solution (5M, 20 ml) was added dropwise. The precipitate was filtered off and the organic layer collected. The aqueous layer was extracted with ether (3 x 50 ml) and the combined organic solutions were dried and the solvent evaporated to give a brown oil (0.19 g) which was identified as 5-cyano-4,5-dihydro-2-ethoxyoxazole. ν max (neat) 2255, 1680, 1255 and 1030 cm^{-1}; δ_H (d_6-acetone) 5.5 (1H, dd), 4.25 (4 H, m) and 1.32 (3H, t); δ_C 161.13 (Cq), 116.66 (Cq), 67.85 (CH_2), 65.23 (CH), 56.79 (CH_2) and 13.81 (CH_3).

22. FVP of 5-Cyano-4,5-dihydro-2-ethoxyoxazole (134)

Pyrolysis of the title compound (66mg, 0.47 mmol, 650°C, .0001 mm Hg, inlet 150°C) afforded 5-cyano-2-oxazolinone (133), (39mg, 75%) as a pale brown solid whose characteristics were identical to literature data.[112-114]

23. FVP of 1-Ethoxycarbonyl-(2S)-Methoxycarbonyl-aziridine (135)

Pyrolysis of the title compound (27 mg, 0.15 mmol, 600°C, 0.01 mm Hg, inlet, 100-120°C) gave a yellow oil. A ^1H n.m.r. spectrum of this product showed that it was a

complex mixture of components. Comparison of this spectrum with literature data for 5-methoxycarbonyl-2-oxazolidinone[114] showed that this material was absent.

G. Preparation and FVP of 1-Thioethoxycarbonyl-aziridines

1. Preparation of 1-Thioethoxycarbonylaziridine (140)

S-Ethyl chlorothiolformate (1.4 g, 0.012 mol) in dry ether (5 ml) was added dropwise to a cooled (0°C), stirred solution of ethylenimine (0.5 g 0.012 mol) and triethylamine (1.37 g, 0.013 mol) in dry ether (70 ml). The mixture was allowed to stir at room temperature for 2 h, the precipitate was filtered off and the filtrate evaporated to give 1-thioethoxycarbonylaziridine as a foul-smelling, pale yellow oil (1.55 g, 100%) (M^+ 131.0401, C_5H_9NOS requires 131.0405); ν max (neat) 1680 cm^{-1}; δ_H 2.78 (2H, q), 2.21 (4H, s) and 1.19 (3H, t); δ_C 181.58, 26.55, 24.38 and 14.66; m/z, 131(M^+), 113, 100, 93, 88, 79 and 69(100%).

2. FVP of 1-thioethoxycarbonylaziridine (140)

Pyrolysis of the title compound (0.16 g, 0.48 mmol, 650°C, 0.005 mm Hg, inlet 160°C) gave a solid

product (0.092 g) which was shown by ^1H n.m.r. to be a mixture of polymeric material and 2-oxazolidinthione.[115,116] The 2-oxazolidinthione was dissolved in dichloromethane and the less soluble polymeric material was filtered off. Evaporation of the filtrate gave a pale yellow solid. This was recrystallised from ether/hexane to give 2-oxazolidinthione (142) as pale yellow, needle crystals (0.068 g, 54%), m.p. 95-96°C. (M^+ 103.0090, C_3H_5NOS requires 103.0092); νmax (mull) 3220, 1170 and 1530 cm^{-1}; δ_H 8.2(1H, br s, NH), 4.66(2H, t, C(5)H_2) and 3.78 (2H,t,C(4)H_2); δ_C 189.94, 70.17 and 43.99; m/z 103 (M^+, 100%), 88, 73, 70, 62, 59, 56, 50 45, 42 and 32; Found: C, 34.98; H, 4.86; N, 13.6%, C_3H_5NOS requires C, 34.96; H, 4.89; N, 13.59%.

3. Preparation and FVP of 1-Ethoxythiocarbonyl-aziridine (141)

a) Preparation of O-Ethyl chlorothioformate (144)

This was prepared according to the method of Bogemann et al.[117] Sodium (2.3 g, 0.1 mol) in dry ethanol (45 ml) was added dropwise to an ice-cooled, stirred solution of thiophosgene (11.5g, 0.1 mol) in dry chloroform (100 ml). The mixture was allowed to stir at room temperature for 3 h and was then washed with water (100 ml). The chloroform layer was dried and the

solvent removed to give a yellow oil. This was distilled (48°C at 0.1 mm g) to give a pale yellow oil (8.91 g) shown to contain O,O-diethyl thiocarbonate (145) δ_H 4.44 (2H, q) and 1.33 (3H,t) and O-ethylchlorothioformate (144) (60% by n.m.r., 5.3 g), δ_H 4.56 (2H, q) and 1.42 (3H, t).

b) Attempted Preparation of 1-Ethoxythiocarbonyl-aziridine (141)

O-Ethyl chlorothioformate (contaminated with O,O-diethyl thiocarbonate. 5.3 g, 0.04 mol) was added dropwise to a cooled (-5°C), stirred solution of ethylenimine (1.73g, 0.04 mol) and triethylamine (0.044 mol, 4.5 g) in dry ether (400 ml). The mixture was allowed to stir for 2 h at 0°C, the precipitate was filtered off and the filtrate washed with water, dried and the solvent removed to give a brown oil (6.98 g). On evaporation of the solvent, an exothermic reaction took place resulting in the product becoming extremely hot. The oil was shown to be a mixture of 4,5-dihydro-2-ethoxythiazole and O,O-diethyl thiocarbonate. The residual impurity was removed by bulb-to-bulb distillation leaving 4,5-dihydro-2-ethoxythiazole (146) as a brown oil (5.1 g, 97%). (M^+ 131.0404, C_5H_9NOS requires 131.0404); ν max 1630 cm^{-1}; δ_H 4.16 (2H, q), 3.41 (2H, m, $C(5)H_2$), 3.13 (2H, m, $C(4)H_2$) and 1.17

(3H,t); δ_C 156.66, 63.43, 49.43, 31.45 and 13.97; m/z 131 (M^+), 103, 78, 65, 47, 45 and 32(100%).

4. FVP of 4,5-dihydro-2-ethoxythiazole (146)

Pyrolysis of the title compound (0.23 g, 1.7 mmol, 65°C, 0.001 mm Hg, inlet 200°C) gave a colourless crystalline solid (0.092 g) and a negligible trace of yellow oil in the trap well. Careful recrystallisation of the solid in warm ether/pentane gave 2-thiazolidinone (143) (0.09 g, 54%),[118,119] m.p. 51.5-52°C (lit. 54°C); (M^+ 103.0092, C_3H_5NOS requires 103.0094); ν max 3190, 3080 and 1720cm^{-1}; δ_H 6.8 (1H, br s) and 3.52 (4H, m); δ_C 176.28, 43.12 and 29.71; m/z 103 (M^+, 100%), 60, 45 and 31.

5. Ethylation of 2-Thiazolidinone (143)

a. Using Triethyloxonium tetrafluoroborate

Triethyloxonium tetrafluoroborate in dichloromethane (0.67 M, 4 ml) was added dropwise to a cooled (0°C), stirred solution of 2-thiazolidinone (0.208 g, 1.6 mmol) in dry dichlormethane (40 ml). The mixture was stirred at room temperature for 12 h and then allowed to stand for 24 h. The solution was stirred and aqueous

potassium carbonate solution (5 m, 15 ml) was added dropwise. The precipitate was filtered off and the organic layer collected. The aqueous layer was extracted with ether (3 x 50 ml) and the combined organic solutions were dried and the solvent evaporated to give a pale yellow oil (151) (0.25 g); ν max 1630 cm^{-1}; δ_H 4.14 (2H, q), 3.83 (2H, t), 3.26 (2H, t) and 1.08 (3H, t); δ_C 167.27, 66.12, 57.78, 34.92 and 13.77; m/z 131(M^+), 103(100%), 88, 75, 60, 56, 45, 42 and 27.

b. Using $EtI/K_2CO_3/DMF$

2-Thiazolidinone (0.05 g, 0.49 mmol), potassium carbonate (0.04 g, 0.25 mmol), ethyl iodide (3 ml) and dimethyl formamide (10 ml) were heated at reflux for 36 h. The mixture was diluted with dichloromethane (50 ml), washed with water (5 x 50 ml) dried and the solvent removed to give a yellow oil. Purification by dry-flash chromatography (silica, hexane/ether gradient) gave 3-Ethyl-2-thiazolidinone (152) as a pale yellow oil (0.042 g, 66%). (M^+ 131.0405, $C_5H_9NO_2$ requires 131.040); ν max 1670 cm^{-1}; δ_H 3.6 (2H, m), 3.3 (2H, q) 3.2 (2H, m) and 1.09 (3H, t); δ_C 158.61, 47.84, 39.41, 25.39 and 12.37; m/z 131(M^+), 116, 103, 88, 69(100%), 60, 59, 56 and 57.

H. Preparation and FVP of 1-Ethoxycarbonyl-2-phenylazetidine

1. Preparation of 1-Ethoxycarbonyl-2-Phenylazetidine (153)

a) Preparation of Ethyl-3-Amino-3-Phenylpropionate (156)

This was prepared by modification of the method of Bodanszky.[120] 3-Amino-3-phenylpropionic acid (5.45g, 33 mmol) and toluene-4-sulphonic acid (12.54 g, 66 mmol) were heated at reflux in dry ethanol (100 ml) for 24 h. The solvent was removed under vacuum and the remaining oil was triturated with dry ether (100 ml) to give Ethyl-3-amino-3-phenylpropionate hydrotosylate (11.52 g, 91%). This was added to aqueous sodium bicarbonate solution (1M, 100 ml) and was extracted with ether (4 x 100 ml). The combined organic solutions were washed with water, dried and the solvent removed to give ethyl-3-amino-3-phenylpropionate as a colourless oil (3.60 g, 57%); (M^+ 193.1105, $C_{11}N_{15}NO_2$ requires 193.1103); ν max 3380, 3300 and 1730 cm^{-1}; δ_H 7.28 (5H, s), 4.2 (1H, m), 4.09, (2H, q), 2.61 (2H, d), 2.2-1.8 (2H, br s) and 1.18 (3H, t); δ_C 171.44, 144.45, 128.14, 126.89, 125.80, 49.96, 52.31, 43.88 and 13.76; m/z 193 (M^+, 100%), 186, 181, 177, 169, 163, 156 and 157.

b) Preparation of 4-phenyl-2-azetidinone (157)

This was prepared according to the method of Testa et al.[122] Methyl magnesium iodide was prepared from dry magnesium turnings (1.81 g) and methyl iodide (11.3 g) in dry ether (50 ml). The Grignard reagent was cooled to 0°C and ethyl-3-amino-3-phenylpropionate (3.603 g, 19 mmol) in dry ether (25 ml) was added dropwise with stirring. The solution was stirred at room temperature for 4 h and allowed to stand for 16 h. The mixture was cooled to 0°C and was treated dropwise with 20% aqueous ammonium chloride solution. The mixture was adjusted to pH 5 using dilute hydrochloric acid and the ether layer was separated. The aqueous layer was repeatedly extracted with ether and the combined organic solutions were washed with dilute hydrochloric acid and then with water until the washings were neutral. The ether solution was dried and the solvent evaporated to give 4-phenyl-2-azetidinone as a yellow, crystalline solid (0.85g, 31%). M.p. 106-107°C (lit. 107-108°C); (M^+ 147.0689, C_9H_9NO requires 147.068); νmax 3200 and 1710 cm^{-1}; δ_H 7.35 (5H, s, Ar), 6.5 (1H, br s, NH), 4.7 (1H, dd, J = 5.3 and 2.5 Hz, C(4)H), 3.42 (1H, ddd, J = 14.8, 5.3 and 2.4 Hz, C(3)H), 2.84 (1H, ddd, J = 14.8, 2.5 and 0.9 Hz, C(3)H); δ_C 167.87 (C=O), 140.20 (Cq), 128.73, 128.08 and 125.57 (CH, Ar) 50.25 (CH) and 47.84 (CH_2); m/z 147 (M^+), 131, 122, 104 (100%), 91 and 77.

c) Preparation of 2-Phenylazetidine (158)

This was prepared according to the methods of Testa et al[122] and Wells et al.[123] 4-Phenyl-2-azetidinone (0.5 g, 3.4 mmol) was added gradually, under a dry nitrogen atmosphere, to an ice-cooled, stirred suspension of lithium aluminium hydride (0.45 g) in dry ether (30 ml). The mixture was boiled, with stirring for 4 h, cooled to 0°C and treated dropwise with 20% aqueous ammonium chloride (4 ml). The precipitate was filtered off and washed with ether. The combined organic solutions were dried and the solvent removed to give 2-phenylazetidine as a yellow oil (0.29 g, 64%), (M^+ 133.0891, $C_9H_{11}N$ requires 133.0887); νmax (neat) 3320, 2490, 1450, 733 and 700 cm^{-1}; δ_H (200 MHz) 7.3 (5H, m, Ar), 4.92 (1H, t, C(2)H), 3.7 (1H, m, C(4)H), 3.4 (1H, m, C(4)H), 2.83 (1H, br s, NH) and 2.3-2.6 (2H, m, $C(3)H_2$); δ_C 144.86 (Cq), 128.07, 126.88 and 125.54 (all CH, Ar), 61.35 ((2)CH), 43.20($(4)CH_2$) and 30.06 ($(3)CH_2$); m/z 133 (M^+), 132, 120, 106, 91(100%), 77 and 70.

d) Preparation of 1-Ethoxycarbonyl-2-Phenylazetidine (153)

Ethyl chloroformate (0.23 g) was added dropwise to a cooled, stirred solution of 2-phenylazetidine (0.28 g,

2.1 mmol) and triethylamine (0.25 g) in dry ether (40 ml). The mixture was stirred at room temperature for 2 h and the precipitate was filtered off through a celite pad. Evaporation of the filtrate in vacuo gave 1-ethoxycarbonyl-2-phenylazetidine as a yellow oil (0.37 g, 86%) which distilled with some decomposition. Purification was accomplished by flash chromatography (silica, ether/petroleum (40/60). B.p. 220 at 0.05 mm Hg, (M^+ 205.1097, $C_{12}H_{15}NO_2$ requires 205.1103); νmax (neat) 1695 cm^{-1}; δ_H 7.32 (5H, s, Ar), 5.24 (1H, dd, J = 8.7 and 6.3 Hz, C(2)H), 4.05 (2H, q, J = 7.1 Hz, OCH_2), 4.03 (2H, t, J = 7.8 Hz, C(4)H_2), 2.8-2.4 (1H, m, C(3)H), 2.3-2.0 (1H, m, C(3)H), and 1.13 (3H, t, J = 1.7 Hz, CH_3); δ_C 157.13 (C=O), 142.21 (Cq), 128.33, 127.24 and 125.56 (all CH, Ar), 64.20 ((2)CH), 60.67 (OCH_2), 46.67 ((4)CH_2), 25.63 ((3)CH_2) and 14.46 (CH_3); m/z 205 (M^+), 176, 160, 132, 114, 104 (100%), 91 and 77.

2. FVP of 1-ethoxycarbonyl-2-phenylazetidine (153)

Pyrolysis of the title compound (54 mg 0.26 mmol, 680°C, 0.01 mm Hg, inlet 200°C) gave a pale yellow oil (36 mg). ^1H n.m.r. spectra of the oil showed that it was a mixture of styrene with some starting material. Pyrolysis of the azetidine was repeated (73 mg, 0.35 mmol, 680°C, 0.005 mm Hg, inlet 200°C). After pyrolysis was complete, the trap was flooded with dry nitrogen

whilst being kept cold in a dry ice/acetone bath. The trap was removed from the apparatus under a stream of nitrogen, stoppered and maintained at -78°C while $CDCl_3$ was introduced *via* a septum and syringe and was allowed to run down the trap stem to dissolve any volatile products. The trap was then allowed to warm to room temperature and a ^1H n.m.r. spectrum was recorded. This spectrum was consistent with the presence of *Styrene* and starting material. A singlet at 3.0 δ and a quartet at 9.75 and doublet at 2.2 δ were assigned to *methyl isocyanate* and *acetaldehyde* respectively by comparison with literature n.m.r. spectra.[97]

DISCUSSION

DISCUSSION

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DISCUSSION

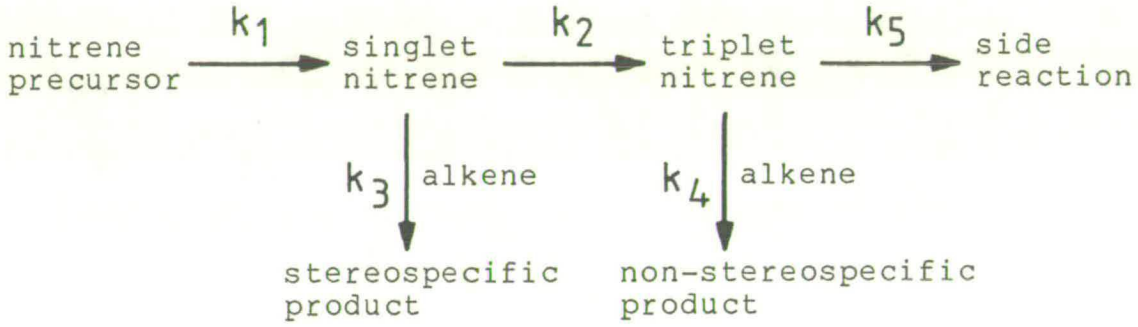
A. ATTEMPTED CHIRAL AZIRIDINATION

1. Introduction

Initial work in the field of chiral aziridination centred on the use of chiral phase-transfer catalysts. As mentioned previously, Seno *et al*[57] have studied in detail the generation of ethoxycarbonylnitrene by α-elimination and its reaction with alkenes under two-phase conditions. They showed, using the reaction of cyclohexene with ethoxycarbonylnitrene, that the products obtained from this type of two-phase reaction were similar in type and ratio to products obtained from the decomposition of ethyl azidoformate and from the homogeneous α-elimination of ethoxycarbonylnitrene by triethylamine, indicating that ethoxycarbonylnitrene is the intermediate present in the two-phase system (Schemes 17 and 18). They also studied the effect of type and concentration of phase-transfer catalyst. No reaction occurred without a catalyst. Product yields increased rapidly on addition of up to 10 mol % quantities of catalyst. Larger proportions of catalyst failed to improve aziridine yields significantly. The ratio of aziridine to nitrene-insertion products was shown to be independent of the catalyst concentration. The variation of catalytic ability of several quaternary

ammonium and phosphonium halides were tested by Seno et al. Longer and more hydrophobic groups on nitrogen appear to increase the catalytic ability. No significant differences were observed between ammonium chlorides and bromides. The most successful catalyst for the production of the aziridine was identified as triethylbenzylammonium chloride (TEBACL).

The singlet nitrenes generated in the two-phase system and in the homogeneous system have similar reactivity and the addition reaction of the singlet nitrene has been shown to be about 30 times faster than the decay to the triplet (ground) state ($k_3/k_2 = 30$) (Scheme 21).



Scheme 21

There is a difference in the reactivity of the triplet nitrene in a two-phase system. In the case of ammonium chlorides and bromides, the ratio of side reactions such as hydrogen abstraction to form ethyl carbamate is low compared to the case of a homogeneous

system. Contrary to this, the ratio of side reactions (k_5/k_4) is very high in the case of ammonium iodides. Iodide ions are considered to enter into the organic phase more easily than chloride or bromide ions and the results imply that triplet nitrene is consumed by iodide ions in some unknown process.

In certain circumstances the two-phase reaction of ethoxycarbonylnitrene may be more reactive than its conventionally generated counterpart. This situation is exemplified in the aforementioned studies of the reaction of ethoxycarbonylnitrene with unsaturated cyclic sulphones by Gosney *et al.*[65] The nitrene, when generated from Lwowski's reagent by α-elimination, will only add to the alkene in a two-phase system as is indicated for the aziridination of sulphone (32) in Scheme 22. The failure of the homogeneous reaction is attributed to the presence of orbital interactions between the SO_2 group and the double bond.

(32)

phase-transfer 43%

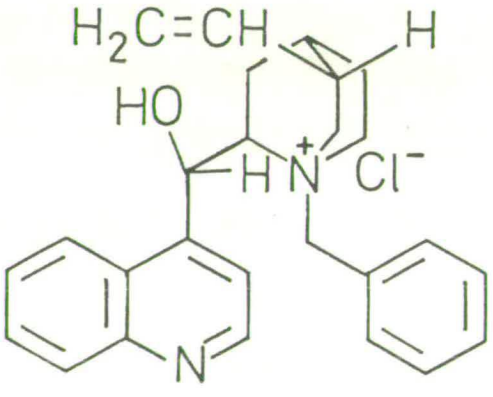
homogeneous 0%

Scheme 22

2. Attempted Preparation of Optically Active 1-Ethoxycarbonylaziridines

The system chosen to be studied initially, involved the addition of ethoxycarbonylnitrene to 1-methyl-1-cyclohexene to generate 1-methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (28) with a chiral centre at C-(1). (-)-N-Benzylcinchonidinium chloride (29), readily available from the reaction of benzyl chloride with commercially available (-)-cinchonidine, was chosen as the chiral phase-transfer catalyst.

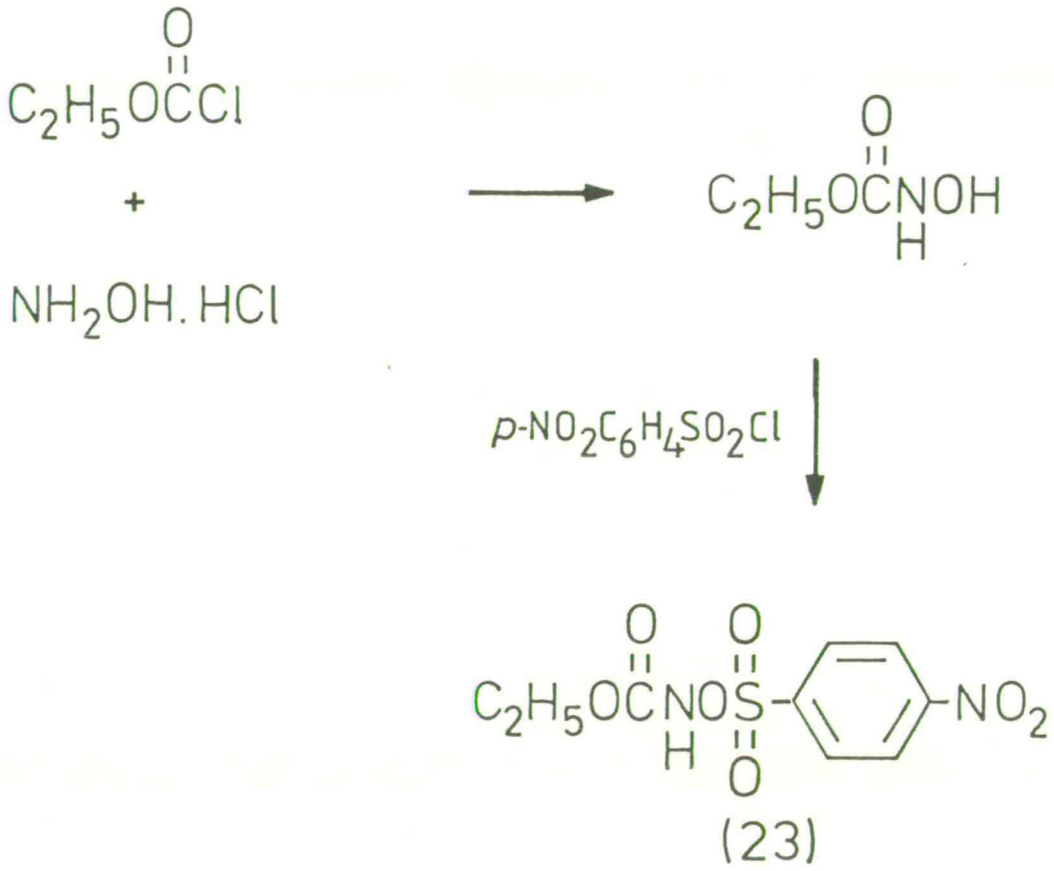
(28)



(29)

The most convenient source of ethoxycarbonylnitrene is ethyl p-nitrobenzenesulphonoxycarbamate (Lwowski's Reagent), (23). Lwowski's reagent was prepared from the reaction of ethyl N-hydroxycarbamate,

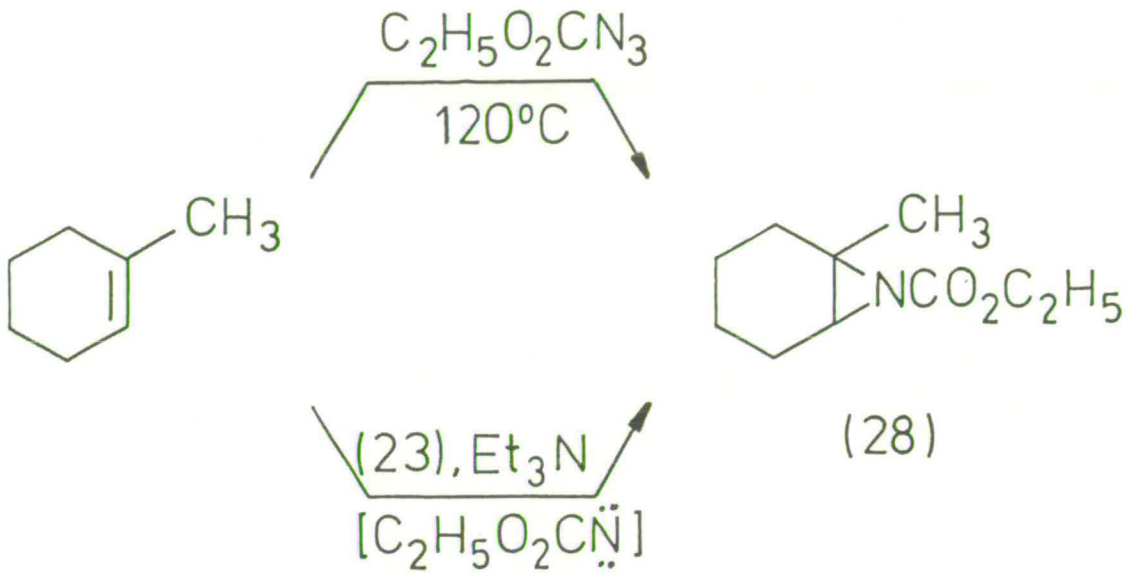
obtained from the reaction of ethyl chloroformate with hydroxyammonium chloride, with p-nitrobenzenesulphonyl chloride (Scheme 23).



(23)

Scheme 23

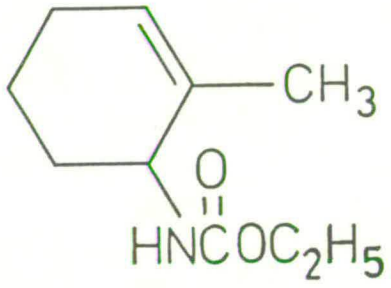
1-Methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (28) had previously been prepared by Takeuchi et al[81] by the reaction of ethyl azidoformate with 1-methyl-cyclohexene (Scheme 24).



Scheme 24

An authenic sample of (28) was prepared by modification of the method of Lwowski et al[53] where ethoxycarbonylnitrene was generated by triethylamine-induced α-elimination from Lwowski's reagent in a dichloromethane solution of 1-methyl-1-cyclohexene. The yield of aziridine (28) was calculated by ^1H n.m.r. spectroscopy to be 32%. This value was obtained by addition of a known weight of benzene to a known weight of the crude product. Comparison of the integral sizes of the aziridine signals with that of the benzene standard allowed the weight of the aziridine, and thus

the yield, to be calculated. Attempts to purify the crude product by flash chromatography afforded a 23% yield of (28) which was contaminated with an impurity. This was identified as the isomeric 6-(ethoxycarbonylamino)-1-methyl-1-cyclohexene (33). Further fractions obtained from the chromatographic separation were shown by ^1H n.m.r. to be pure (33), (15%).

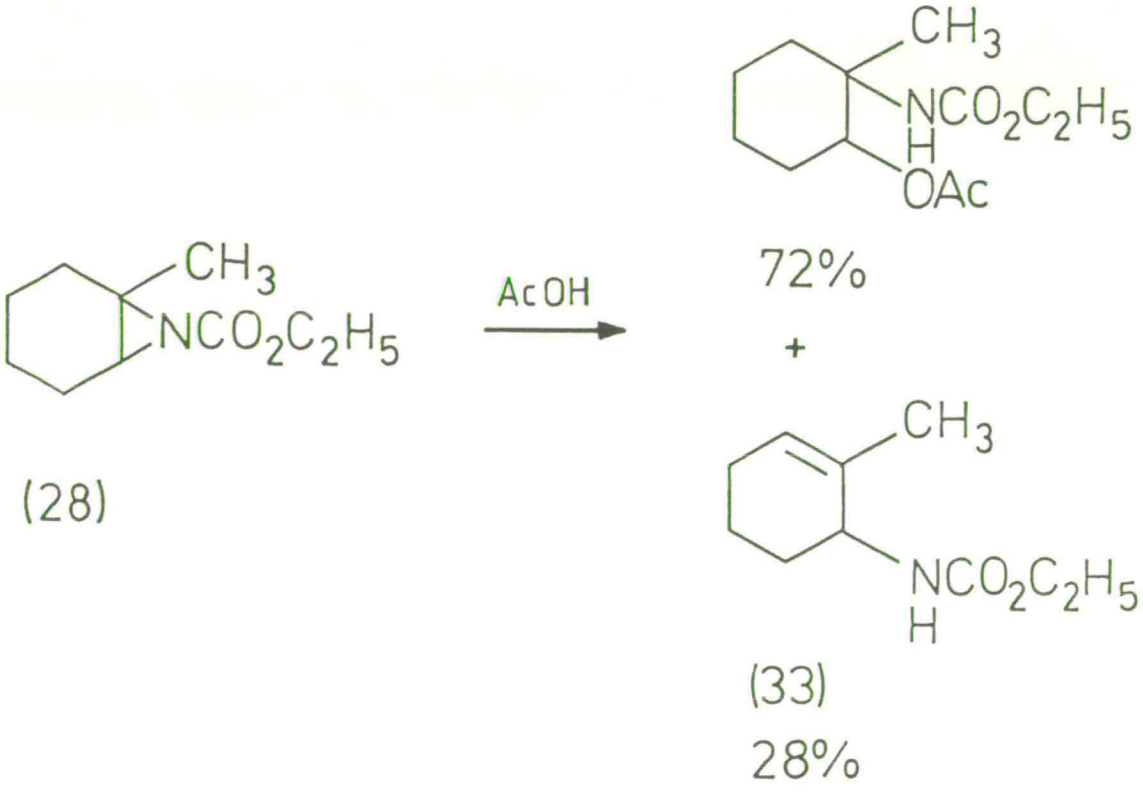


(33)

The formation of the by-product (33) can be accounted for by nitrene insertion into the allylic C-H bond. A portion of the compound may have been formed in this way, but only a very small amount was evident in the ^1H n.m.r. spectrum of the crude product. The presence of (33) is more adequately explained by the rearrangement of aziridine (28) during chromatography. A series of spectra of a sample of aziridine (28) in $CDCl_3$ was recorded over a period of days. Total isomerisation of the aziridine to (33) occurred within five days. A neat

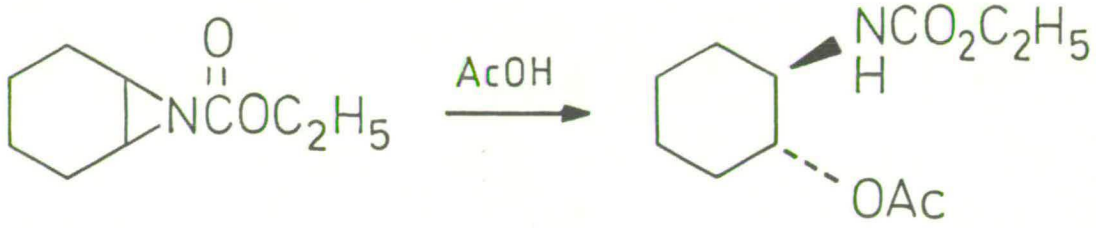
sample of the aziridine also rearranged totally over a similar time period. Elevated temperatures accelerated the transformation. Considering the quantity of (33) which was obtained during the purification of (28), it seems likely that chromatography conditions also accelerate the isomerisation.

These observations are in agreement with reports by Takeuchi et al[81] that 1-methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (28) readily isomerised to 6-(ethoxycarbonylamino)-1-methyl-1-cyclohexene (33) in the presence of acetic acid at room temperature (Scheme 25).



Scheme 25

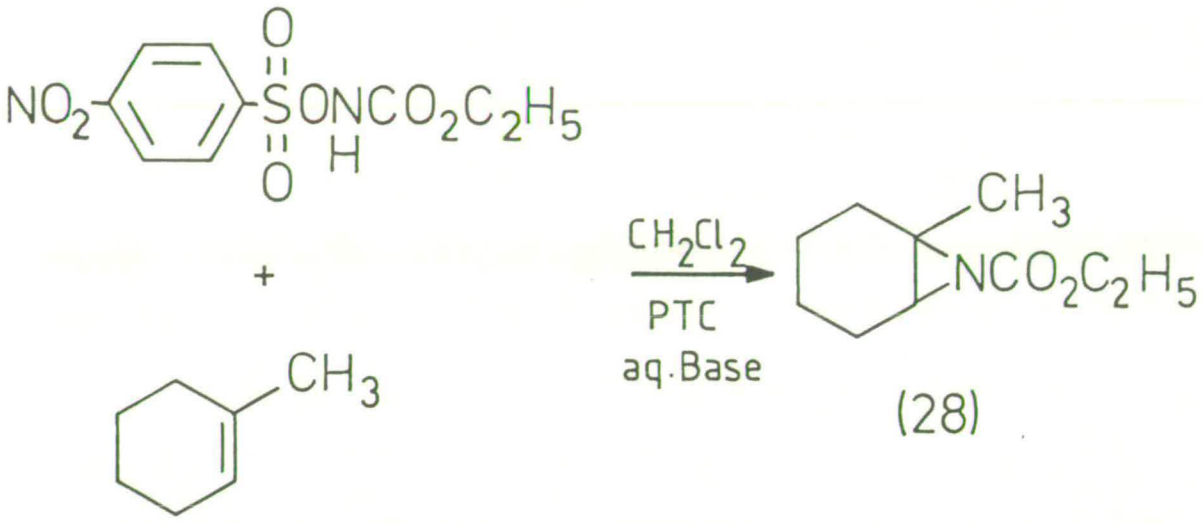
Similar treatment of 7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane gave only (34) (Scheme 26). The Japanese workers reported that the formation of (33) in Scheme 25 can be attributed to the existence of a greater degree of ring strain in aziridine (28) compared to aziridine (24).



(24) (34)

Scheme 26

Attempts were made to synthesise aziridine (28) using the phase-transfer method of Seno et al[57] as outlined in Scheme 27.



Scheme 27

The use of aqueous sodium hydrogen carbonate as a base together with triethylbenzylammonium chloride (TEBACL) as a phase-transfer catalyst provided only small amounts of aziridine (28), regardless of the reaction time. Repetition of the procedure using 50% aqueous sodium hydroxide solution as a base resulted in the formation of a tarry product. 10% Aqueous sodium hydroxide solution proved to be a suitable base for the reaction of ethoxycarbonylnitrene with 1-methyl-1-cyclohexene. 1-Methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (28) was produced in yields of up to 22% (by n.m.r.) using these reaction conditions. Mechanical shaking or vigorous magnetic stirring proved to be adequate methods of agitation, ensuring large organic/aqueous phase boundaries. Placing the reaction vessel in an ultrasonic bath proved relatively inefficient and gave only low yields of aziridine.

Optimum yields of pure (28) were obtained after the reaction had been allowed to proceed for 2-3 hours. The work-up procedure was rapidly executed and this was followed directly by flash chromatography. Care was taken during the chromatographic separation in order to optimise the yield of pure aziridine, since the Rf values for (28) and (33) were found to be similar in various solvent systems tested. Attempts to separate the isomers by distillation under reduced pressure failed due to the low thermal stability of (28).

Once this procedure for the preparation and purification of 1-methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0] heptane (28) had been optimised, the experiment was repeated using the chiral phase-transfer catalyst (29). The aziridine obtained was purified and its optical rotation was recorded immediately. The results of several experiments are summarised in Table 1.

Table 1

Recorded Optical Rotations for Aziridine (28)

Reaction Time (hours)	Aziridine Yield %	Specific Optical Rotation $[\alpha]_D^{20}$
1.5	2.9	-
1.5	2.7	-
2.5	11.1	+ 0.11(c=0.9, CH_2Cl_2)
4	6.0	+ 0.74(c=0.27, CH_2Cl_2)
4	4.5	+ 1.28(c=0.79, CH_2Cl_2)

Repetition of the reaction depicted in Scheme 27 using the chiral catalyst (29) with aqueous sodium hydrogen carbonate as a base afforded (33) in approximately 20% yield. No aziridine was present in the crude product.

The results summarised in Table 1 show that some optical rotation is displayed by the aziridine product. Optical activity in (28) ought to be an indication of successful asymmetric induction, but a recent paper by Dehmlow *et al*[66] cautions that degradation products from chiral quaternary ammonium compounds (free amines and epoxides) have high specific rotations. These have been shown to be responsible for a number of false claims of asymmetric induction in the literature.

Many successful chiral phase-transfer catalysts have a β-hydroxy group in the quaternary ammonium cation. This provides an inflexible arrangement which is a prerequisite for optical induction. Under basic conditions, these catalysts may decompose to form epoxides which have a very high specific rotation. Alternatively, small amounts of tertiary amine hydrohalide may be formed during the process of quaternization. The free, optically active, amine may be regenerated on work-up after a phase-transfer catalysed reaction. Impurities from either process can give rise to apparent activity in the reaction product. As a result of this issue, several claims of optical induction have been disproved.

Dehmlow *et al* showed that the percentage

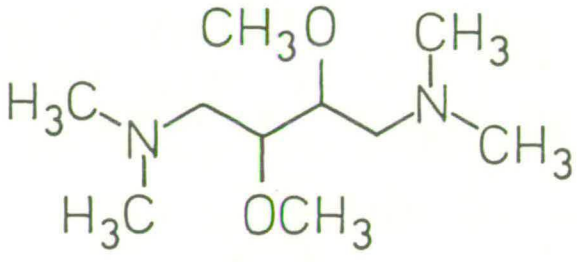
decomposition of (-)-N-benzylcinchonidinium chloride (29) caused by exposure to 10% aqueous sodium hydroxide was likely to be small[66] and, with regard to present work, chromatography is likely to separate from the expected product (28) any amine or epoxide which may form.

The specific optical rotations recorded for aziridine (28) in Table 1 are too small for a definite deduction to be made, but the results are not indicative of efficient chiral induction.

The system under study proved to have several drawbacks including poor yields of aziridine (28) as well as formation of a product which is thermally labile. A new system was clearly needed in order to continue these studies into chiral aziridination. Before terminating present investigations into the preparation of optically active 1-methyl-7-ethoxycarbonyl-7-azabicyclo-[4.1.0]-heptane (28) an attempt was made to synthesise chiral (28) in a homogeneous system using a chiral base in place of triethylamine. Chiral solvents have been used in organic chemistry as a means of producing non-racemic products in synthesis. This approach to asymmetric synthesis has been reviewed by Morrison.[124,125]

(S,S)-(+)-2,3-dimethoxy-1,4-bis-(dimethylamino)-butane (35) is a commercially available base and solvent which has been used for the purpose of producing optically active products. For example, Seebach et al have shown that (35) can be used in the asymmetric

synthesis of alcohols from aldehydes and organometallic reagents. The addition of butyllithium to benzaldehyde in the presence of (35) can produce 1-phenyl-1-pentanol in up to 40% enantiomeric excess, with the yields being raised appreciably when the asymmetric base is also the solvent.[126,127]

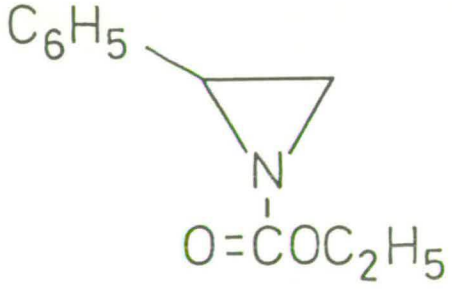


(35)

The reaction of 1-methyl-1-cyclohexene with ethoxycarbonylnitrene generated by α-elimination with one molar equivalent of (S,S)-(+)-2,3-dimethoxy-1,4-bis-(dimethylamino)-butane gave only an 8.36% yield of (28). Use of a two molar equivalent of the base gave a 25% yield of pure (28), ($[\alpha]_D^{20}$ = -0.12° (c = 2.5, CH_2Cl_2)). This result shows that the amount of asymmetric induction which occurs in the formation of (28) using the chiral base (35), is negligible. The chemical yield of aziridine (28) was high compared to the yields of the aziridine isolated from the two-phase

system. Earlier it was shown that the preparation of aziridine (28) in a homogeneous system using triethylamine as a base afforded yields in the region of 32% (by n.m.r. spectroscopy). It would appear that the preparation of the aziridine *via* a two-phase reaction gave consistently lower yields, with a maximum of only 11% of the aziridine being isolated. This effect may be due to the aziridine being sensitive to the conditions of the two-phase system.

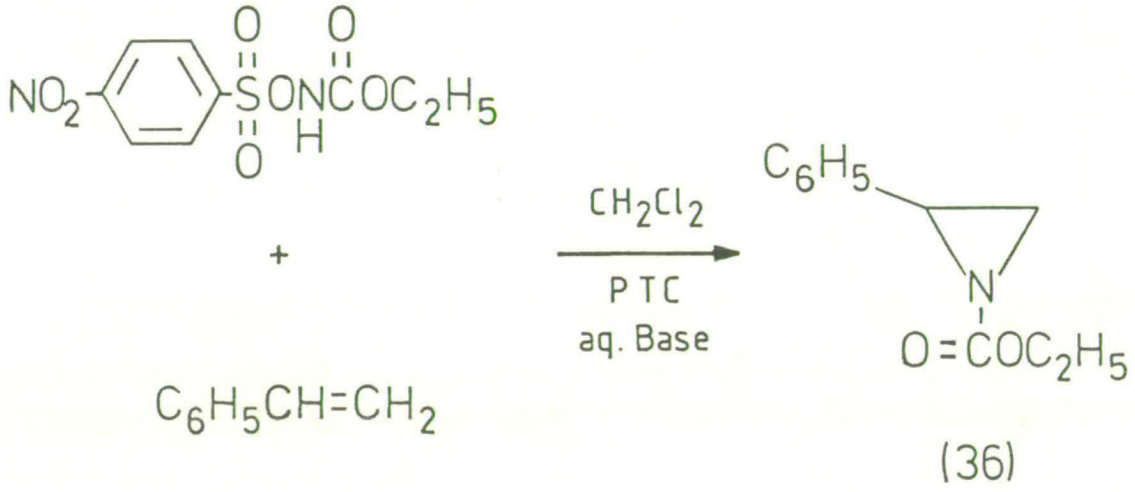
It was envisaged that fewer problems would be encountered in the study of chiral aziridination by selecting 1-ethoxycarbonyl-2-phenylaziridine (36) as the target molecule since (36) is known to be more stable than aziridine (28).[81]



(36)

1-Ethoxycarbonyl-2-phenylaziridine has a simple and very distinct ^{1}H n.m.r. spectrum. As such, optical resolution work using chiral shift reagents should be straightforward. A further benefit is that optically pure 2-phenylaziridines have been prepared by Fujita *et al*,[28]

by the aforementioned method outlined in Scheme 7. Optical rotation measurements have also been recorded for (S)-(+)- and (R)-(-)-2-phenylaziridines as well as for optically pure 1-substituted-2-phenylaziridines. These values can obviously be used directly to quantify the success of chiral aziridination attempts by the procedure shown in Scheme 28.



Scheme 28

The expected aziridine (36) was obtained as the major product from the reaction of ethoxycarbonylnitrene with styrene using TEBACL as a catalyst. Purification of the aziridine was best achieved by reduced pressure distillation. Yields of up to 23% were obtained using

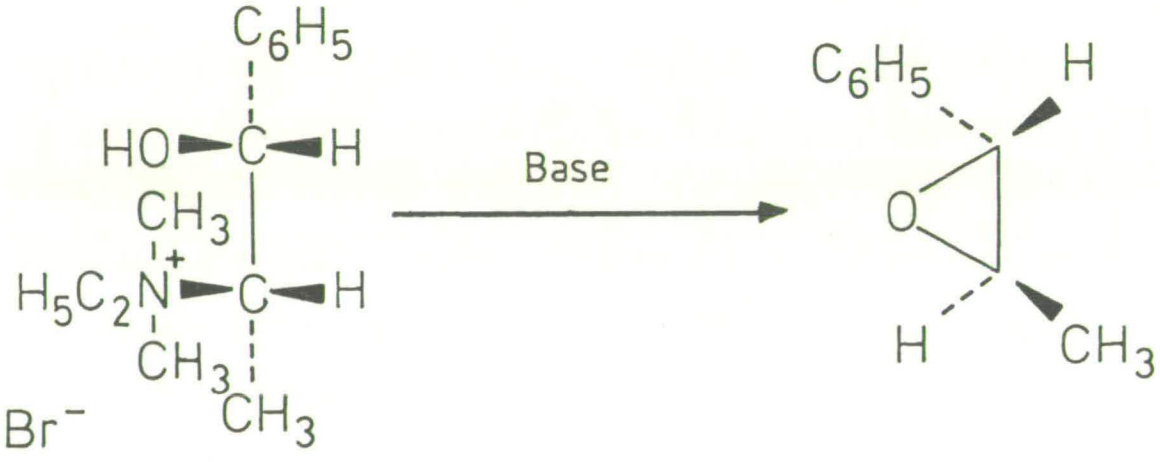
this method. Caution had to be shown during the purification by distillation, since the temperature involved may be sufficient to destroy the aziridine. A good vacuum and a low distillation temperature ensured a maximum yield of 1-ethoxycarbonyl-2-phenylaziridine. Flash chromatography on silica (Merck, Kieselgel 60) was of limited success. Partial or total destruction of the aziridine ring occurred if the substance remained in contact with the silica for a period of time. Rapid elution using a more polar system resulted in (36) being obtained, but it was generally contaminated with residual styrene together with other minor products. Chromatography on alumina also proved to be unsatisfactory, since the aziridine (or its decompositon products) tended to adhere to the column.

The two-phase reaction of ethoxycarbonylnitrene with styrene using (-)-N-benzylcinchonidinium chloride as a catalyst produced 1-ethoxycarbonyl-2-phenylaziridine in a 10% yield after purification. No significant optical rotation was obtained from this sample.

Attempts were made to produce optically active (36) in a homogeneous system using the chiral base (S,S)-(+)-2,3-dimethoxy-1,4-bis-(dimethylamino)-butane (35). Very little aziridine was formed during this reaction and none could be isolated.

The results obtained from attempted chiral aziridination of both 1-methyl-1-cyclohexene and styrene lead to the conclusion that no appreciable chiral

induction takes place, either in the presence of a chiral base or a chiral phase-transfer catalyst. These results may be compared with those obtained by Japanese workers for chiral cyclopropanation of alkenes with carbenes. Hiyama et al have reported that small optical rotations were measured in cyclopropanes produced from the reaction of base- generated dichlorocarbene with styrene and trans- propenylbenzene in the presence of ephedrine derivative (37) thus indicating that chiral cyclopropanation had occurred.[128]



(37) (38)

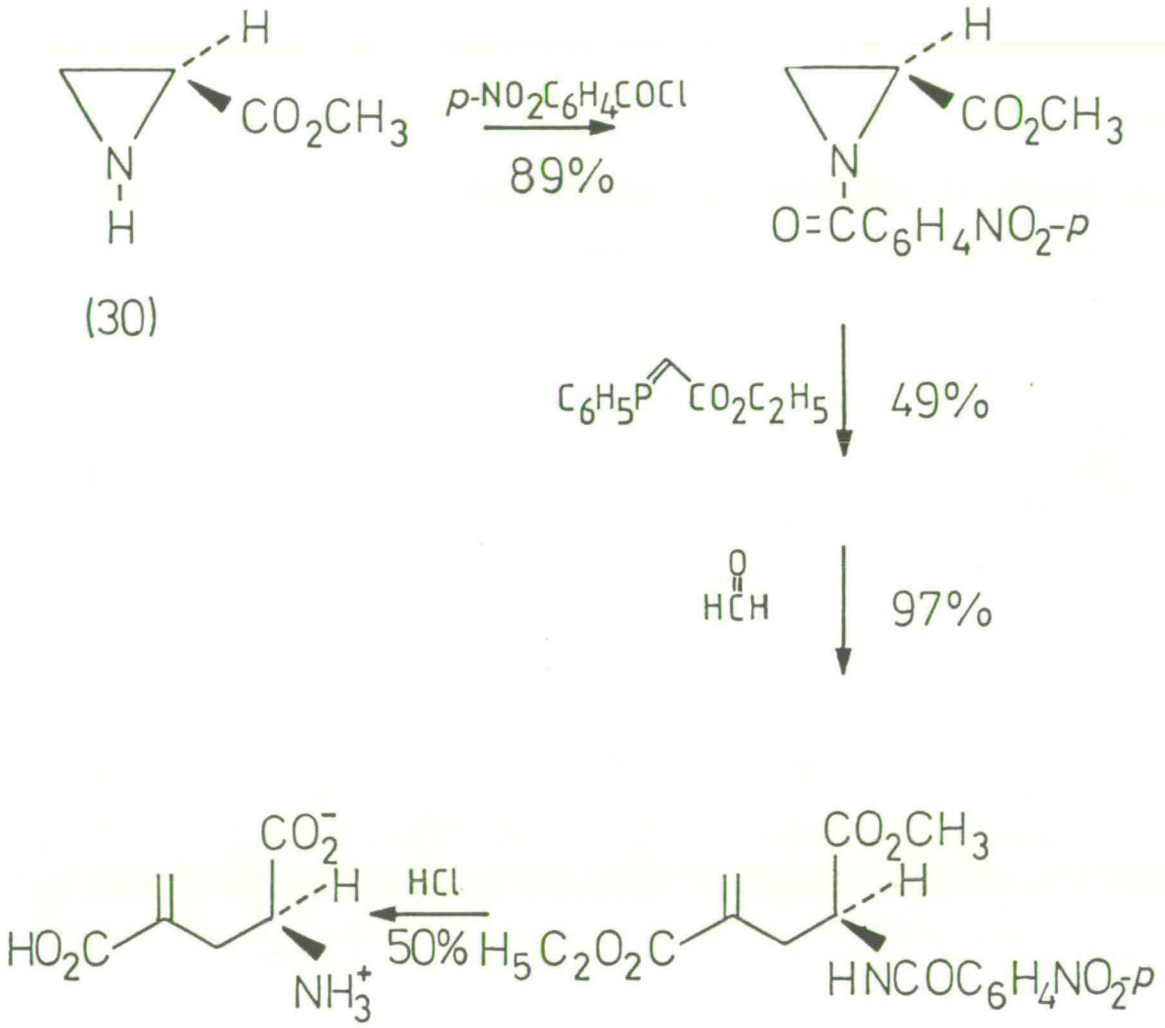
Scheme 29

Dehmlow et al[66] showed that these small rotations were not genuine, but due to the formation of epoxide (38)

from the catalyst as shown in Scheme 29. Claims by Kimura *et al* that chiral tertiary amines have successfully catalysed enantioselective addition of dichlorocarbene to alkenes[129] have been similarly disproved.[66] Dehmlow and co-workers consider these results to be evidence for the formation of free dichlorocarbene during phase-transfer catalysis.

3. Other Approaches to the Preparation of Optically Active Aziridines

On the basis of these results it seemed futile to continue the study of chiral aziridination *via* nitrene addition in the presence of a chiral phase-transfer catalyst or a chiral base since it appeared unlikely that ethoxycarbonylnitrene would associate in any way with the chiral moiety. It was felt that the study of chiral aziridine synthesis ought to be pursued further, since it has obvious potential in organic synthesis. The afore-mentioned novel amino acid synthesis of Baldwin *et al*[70] goes some way to emphasise this point. This recent report shows that the reaction of carbonyl-stabilised Wittig reagents with activated aziridine-(2*S*)-carboxylates have been used to provide a synthesis of optically pure unsaturated amino acids. This is exemplified by the enantioefficient synthesis of naturally occurring 4-alkylidine-(2*S*)-glutamic acids as shown in Scheme 30.

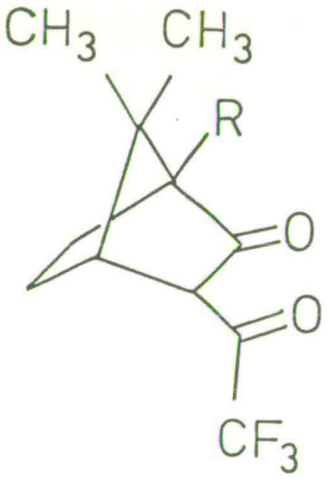


Scheme 30

A drawback of this approach is that (2S)-methoxycarbonyl-aziridine (30) is obtained via a four-step synthesis starting from optically active L-serine.[70,92] An efficient general method of chiral aziridination may provide starting materials for the synthesis of other

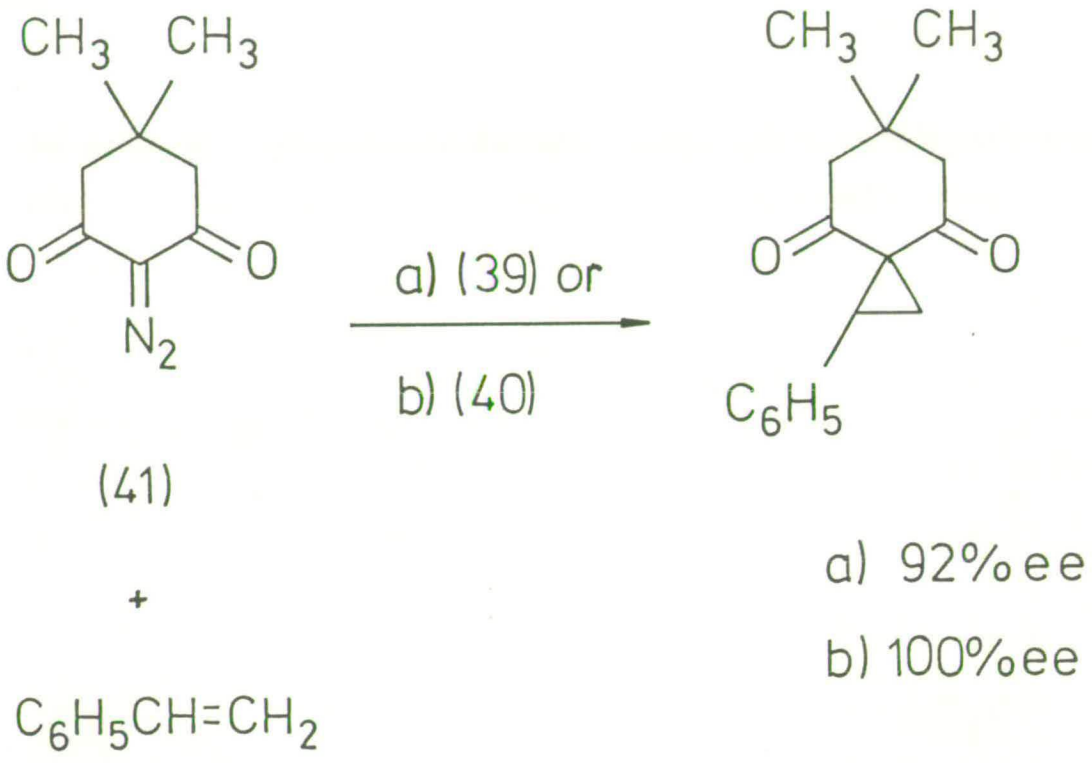
types of natural products as well as opening the way to the efficient preparation of chirally pure non-natural amino acids.

Although it seems unlikely that catalytic chiral induction of carbene or nitrene addition to an alkene can be realised, Matlin et al[130] have reported that asymmetric cyclopropanations via carbenoid intermediates have been induced with chiral metal complexes. Thus, copper complexes of 3-trifluoroacetyl-(+)-camphors (39) and (40) gave high optical yields when used in the cyclopropanation of styrene with 2-diazodimedone (41) (Scheme 31).



(39) R = CH_3

(40) R = $HC{=}CH_2$



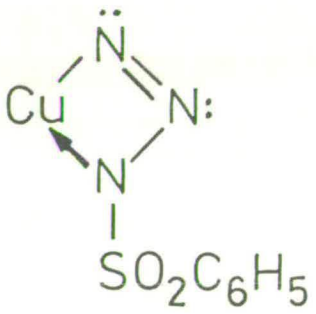
Scheme 31

Attempts could be made to extend this approach to the nitrene series. In 1967 Kwart et al[131,132] reported that the cuprous chloride catalysed decomposition of benzenesulphonyl azide in cyclohexene gave a variety of products including aziridine (42) in a 15% yield (Scheme 32).

(42)

Scheme 32

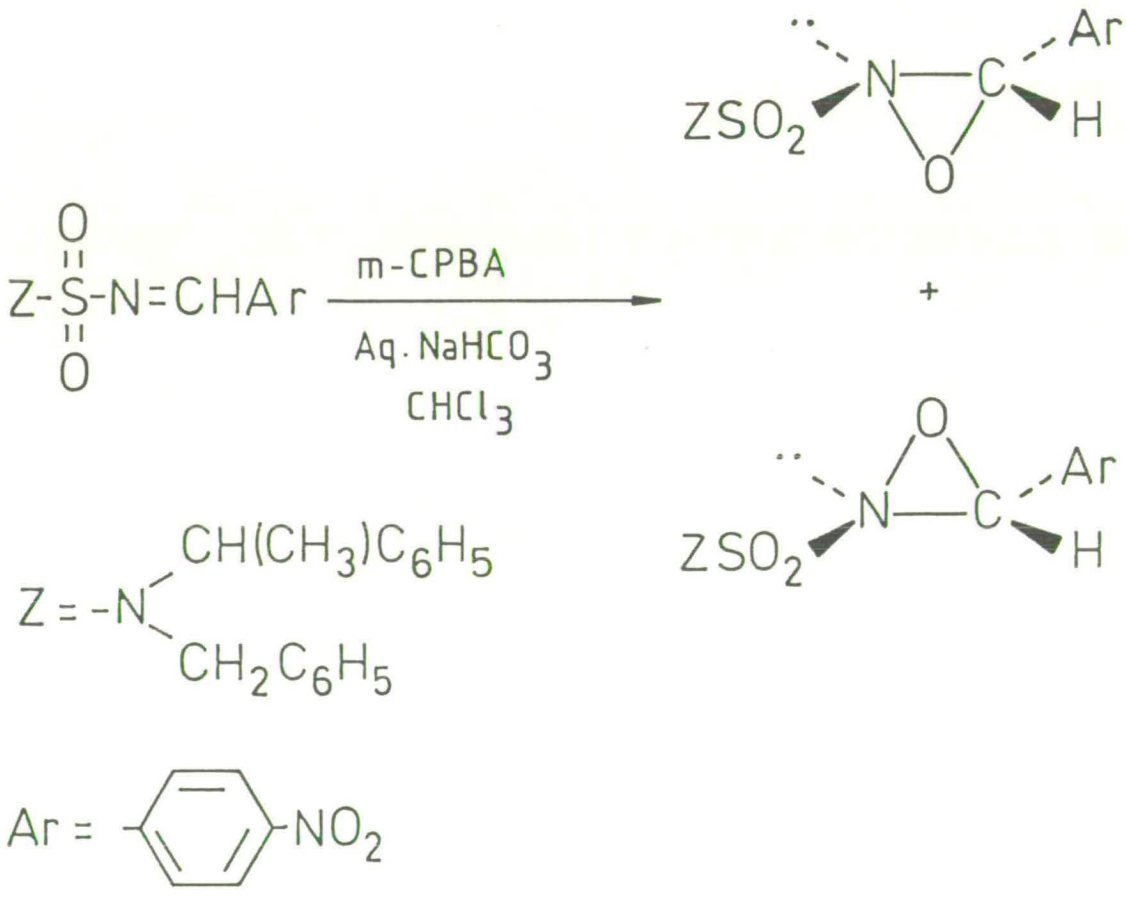
To account for the induced decomposition of the azide, the authors invoked the formation of a copper-azide complex (a nitrenoid), (43).



(43)

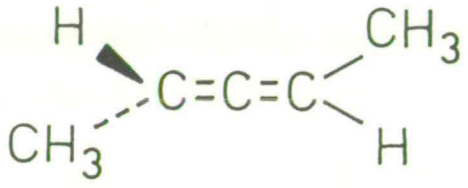
Substitution of cuprous chloride by, for example, chiral copper complex (39) or (40) may lead to chiral induction in the product. However, as mentioned previously in the introduction, sulphonylnitrenes are not particularly useful in the synthesis of aziridines and few examples of 1-sulphonylaziridines are known.

An alternative approach to these systems where a chiral catalyst is used to induce asymmetry in the product, is a process whereby asymmetry is induced by elaboration of a chiral substrate. A recently reported example, related to the present discussion, is the epoxidation of chiral sulphamides to give optically active 2-sulphamyloxaziridines.[133] Scheme 33 illustrates the synthesis of diastereoisomeric 2-sulphamyloxaziridines which are separable by fractional recrystallisation.

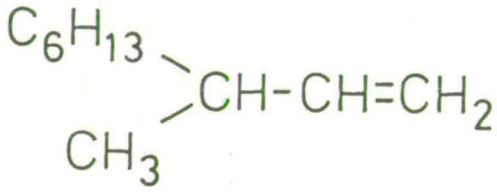


Scheme 33

Investigation of the addition of ethoxycarbonylnitrene to a chiral allene or alkene such as (44) and (45) may provide a route to optically active aziridines.

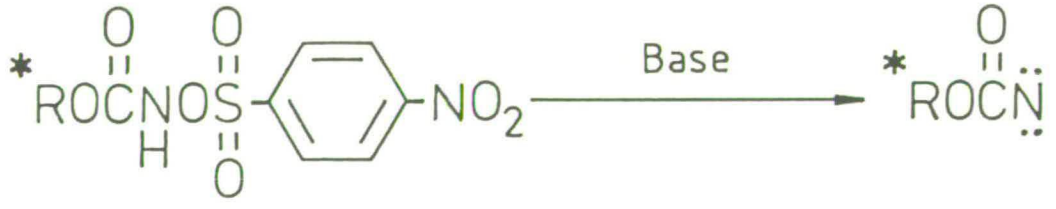


(44)



(45)

A further option for the realisation of asymmetric aziridination is provided by the reaction of a chiral nitrene with a prochiral alkene. In essence, the chiral nitrene (46) could be generated by base-induced α-elimination from a "Lwowski-type" reagent (47) where R is an optically active moiety (Scheme 34).

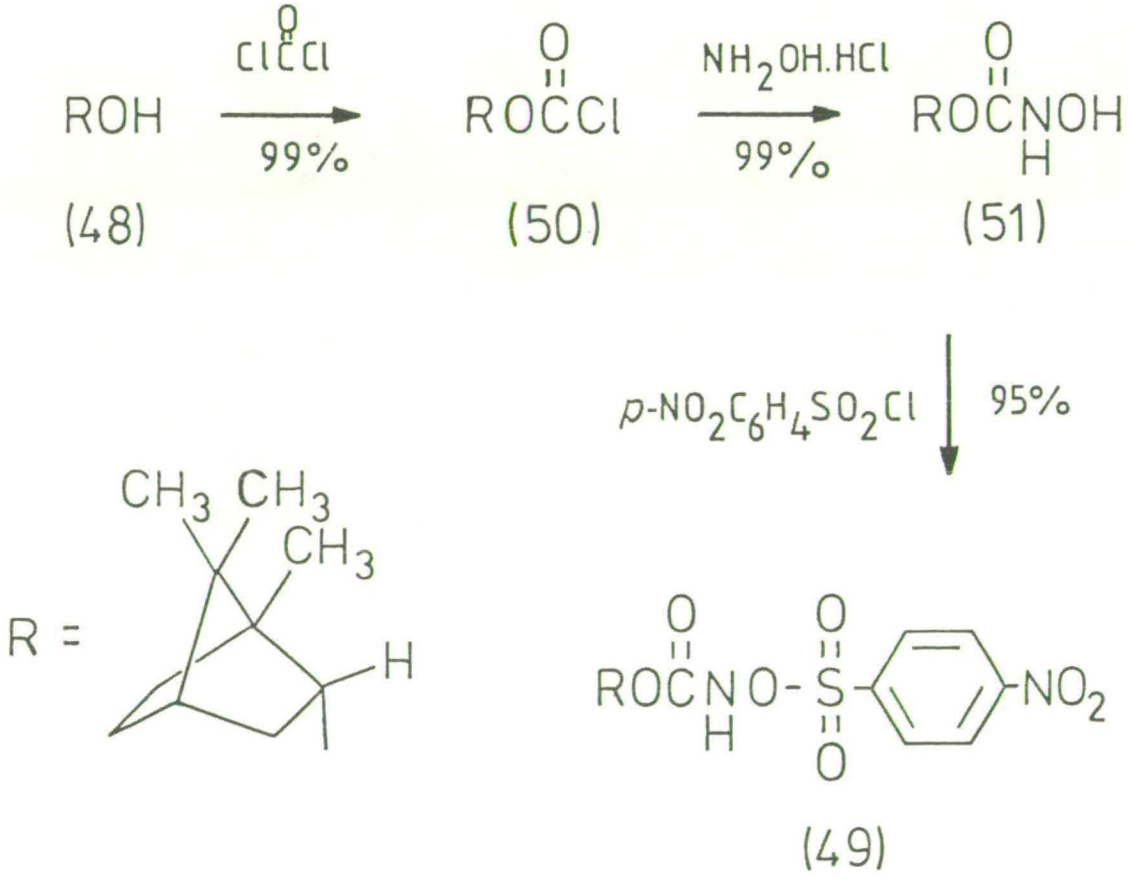


(47) (46)

Scheme 34

Naturally-occurring optically active alcohols, such as readily available [(1S)-endo]-(-)-borneol (48), would form a suitable source of a chiral alkyl group in (47).

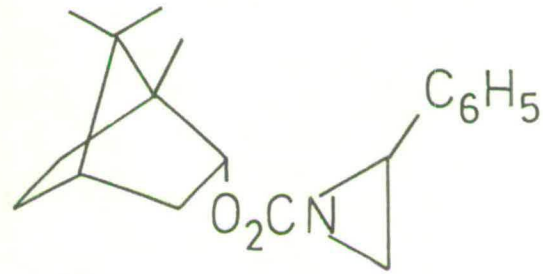
Adopting this approach, [(1S)-endo]-(-)-bornyl p-nitrobenzenesulphonoxycarbamate (49) was synthesised in good yield by conversion of the chiral alcohol into [1S)-endo]-(-)-bornyl chloroformate (50) followed by the synthesis of the corresponding N-hydroxycarbamate (51). The subsequent reaction of (51) with p-nitrobenzene-sulphonyl chloride gave (49) in yields of over 90% (Scheme 35).



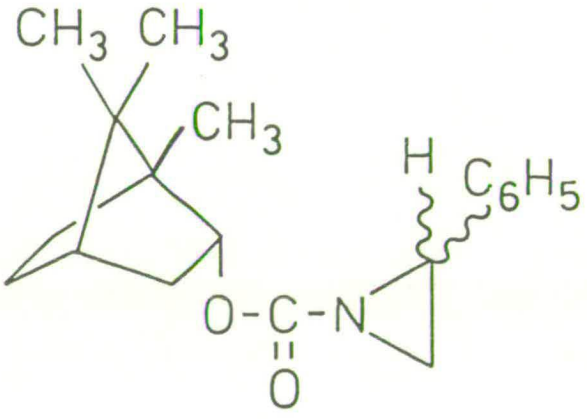
Scheme 35

Figure 2

^1H n.m.r.
80 MHz , $CDCl_3$



Preliminary experimental work involved the heterogeneous generation of [1S)-endo]-(-)-bornoxy-carbonylnitrene by aqueous sodium hydrogen carbonate - induced α-elimination from (49) in the presence of styrene. Work-up of the reaction in the usual manner[57,53] followed by removal of excess styrene by reduced pressure distillation at room temperature gave a sticky yellow oil which was shown by ^1H n.m.r. spectroscopy to contain aziridine (52) as the major component.

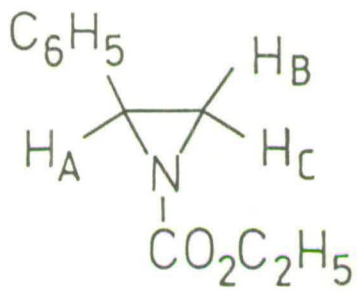


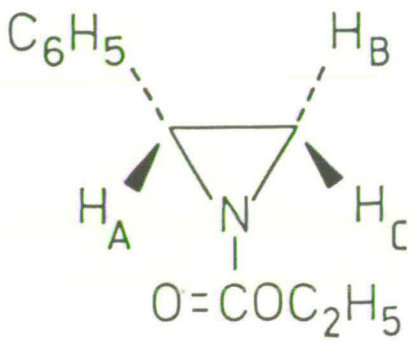
(52)

Removal of the residual styrene at temperatures in excess of 20-30°C resulted in rearrangement of the aziridine. With regard to this observation, no attempt was made to purify the aziridine at this stage. Examination of the 80 MHz ^1H n.m.r. spectrum of the crude aziridine showed that the signals produced by the ring protons in aziridine (52) (Figure 2) differed from the signals produced by the ring protons in, for example, 1-ethoxy-carbonyl-2-phenylaziridine (36), as shown in Figure 3.

Figure 3

^{1}H n.m.r.
200 MHz
$CDCl_3$



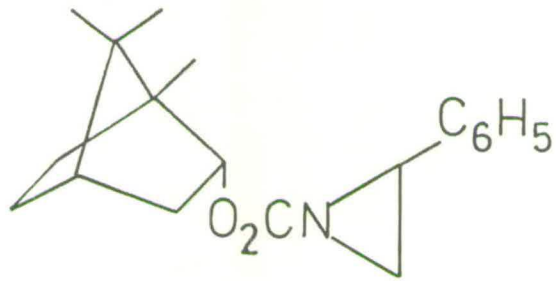


(36)

The three ring protons of aziridine (36) produce three distinct multiplets (Figure 3). H_A appears as a doublet of doublets at 3.50 δ with $^3J_{cis}$ = 6.3 Hz due to coupling with H_C and $^3J_{trans}$ = 3.6 Hz due to coupling with H_B. H_B gives rise to a doublet at 2.67 δ with $^3J_{cis}$ = 6.3 Hz and H_C appears as a fine-split doublet with $^3J_{trans}$ = 3.6 Hz. The gem spin-spin coupling constant between H_B and H_C in aziridine (36) is zero. This phenomenon is conveniently explained in terms of the molecular orbital theory of spin-spin coupling.[134]

The 80MHz ^1H n.m.r. spectrum of crude aziridine (52) is shown in Figure 2, and the pattern of signals due to its three aziridine ring protons are shown as an expansion in Figure 4. The chemical shifts of these three protons are similar to those for the ring protons of aziridine (36). The main difference between the spectra of these two compounds is the multiplicity of the signals. In Figure 4 the signals at 3.5 δ and 2.7 δ are

^1H n.m.r.
80 MHz , $CDCl_3$
Expansion



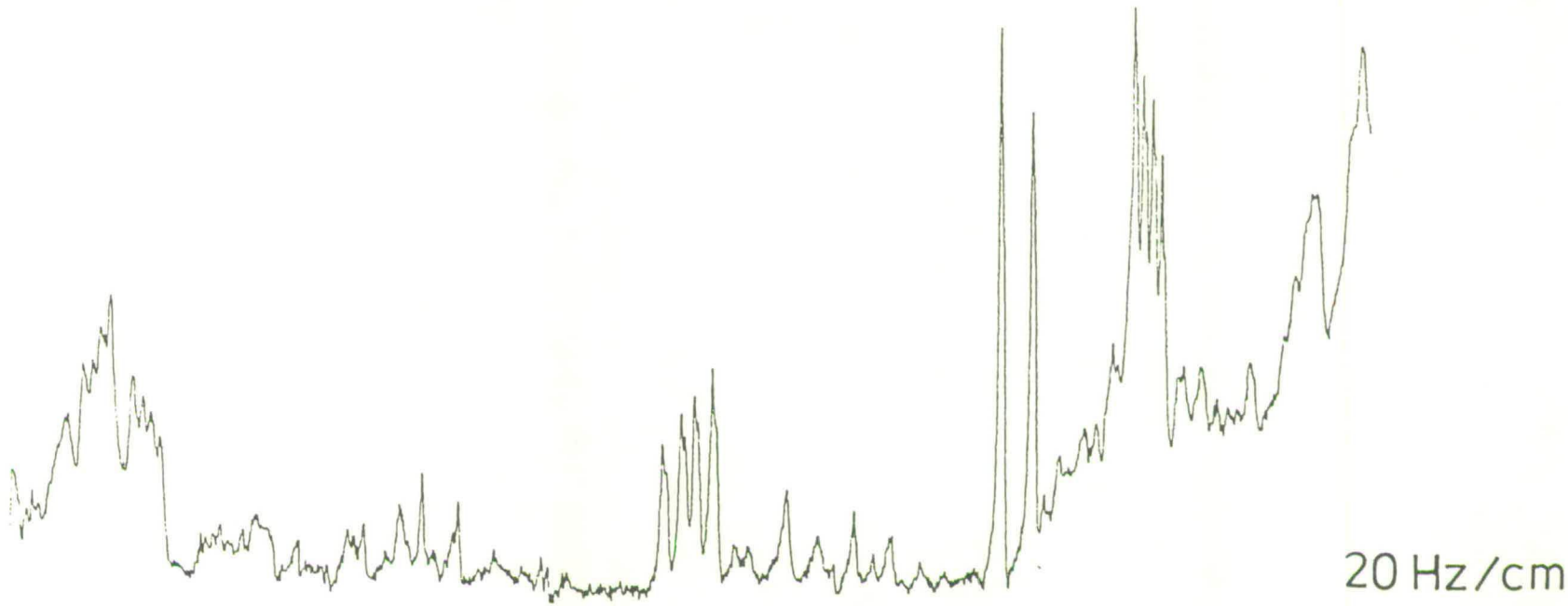


Figure 4

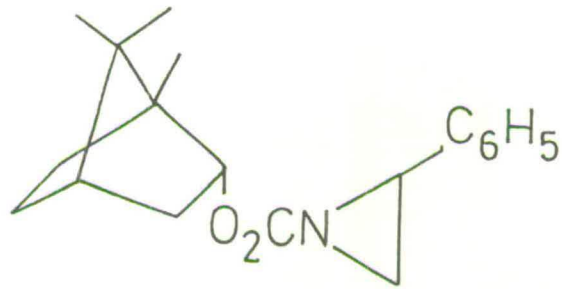
similar to the signals produced by H_A and H_B in Figure 3, but the signal at 2.3 δ appears as a four-peak multiplet instead of the fine-split doublet which is produced by H_C in 1-ethoxycarbonyl-2-phenylaziridine (36).

High field ^1H n.m.r. spectroscopy with decoupling and/or nuclear Overhauser enhancement studies would be helpful in discovering the significance of the aziridine spectrum shown in Figures 2 and 4. Unfortunately, shortage of time prevented these investigations from being carried out.

Studies carried out in conjunction with Dr. I. Dawson showed that the homogeneous reaction of [(1S)-endo]-(-)-bornoxycarbonylnitrene with styrene also gave aziridine (52) as the major product. The stereoselectivity of both the homogeneous and heterogeneous aziridination reactions was determined by proton-decoupled ^{13}C n.m.r. spectroscopy of the crude products. No difference in the relative proportions of the two diastereomeric aziridines could be detected. In both cases, two pairs of resonances of equal intensity were observed for the aziridine ring protons at 39.2 and 38.9 ppm (C(1)) and 34.3 and 33.9 ppm (C(2)) (Figure 5). These ^{13}C n.m.r. spectra were also identical to that for an authentic 1:1 mixture of both diastereomers, prepared from the reaction of racemic 2-phenylaziridine

Figure 5

^{13}C n.m.r.
50 MHz , $CDCl_3$



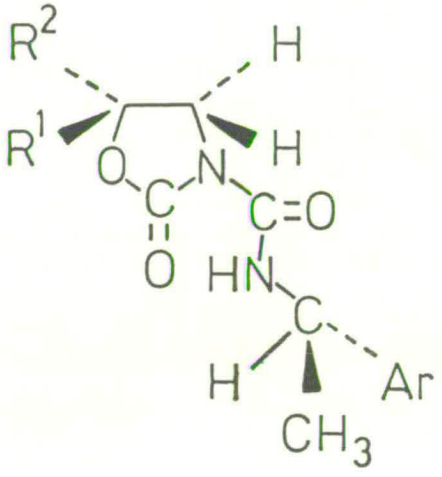
with [(1S)-endo]-(-)-bornyl chloroformate.*

Attempts to promote some degree of selectivity by lowering the reaction temperature were prevented by the failure of the nitrene precursor (49) to react with the base (triethylamine) at temperatures below -5°C.*

In conclusion, the use of the [(1S)-endo]-(-)-bornyl moiety as the chiral auxillary in an alkoxycarbonyl nitrene does not lead to any discernible enantiomeric excess in aziridine formation under the conditions employed. This can probably be attributed to the fact that the bornyl moiety is too remote from the bond-making nitrene centre to allow for any discrimination in the activation energies of the different transition states leading to the two possible diastereomeric aziridines (52).

* This work was carried out by Dr. Ian Dawson, University of Edinburgh.

An interesting observation by Pirkle and co-workers[94] which is relevant to this discussion, is that signals due to the ring protons in diastereoisomers of 2-oxazolidinone (53) have very similar chemical shifts.



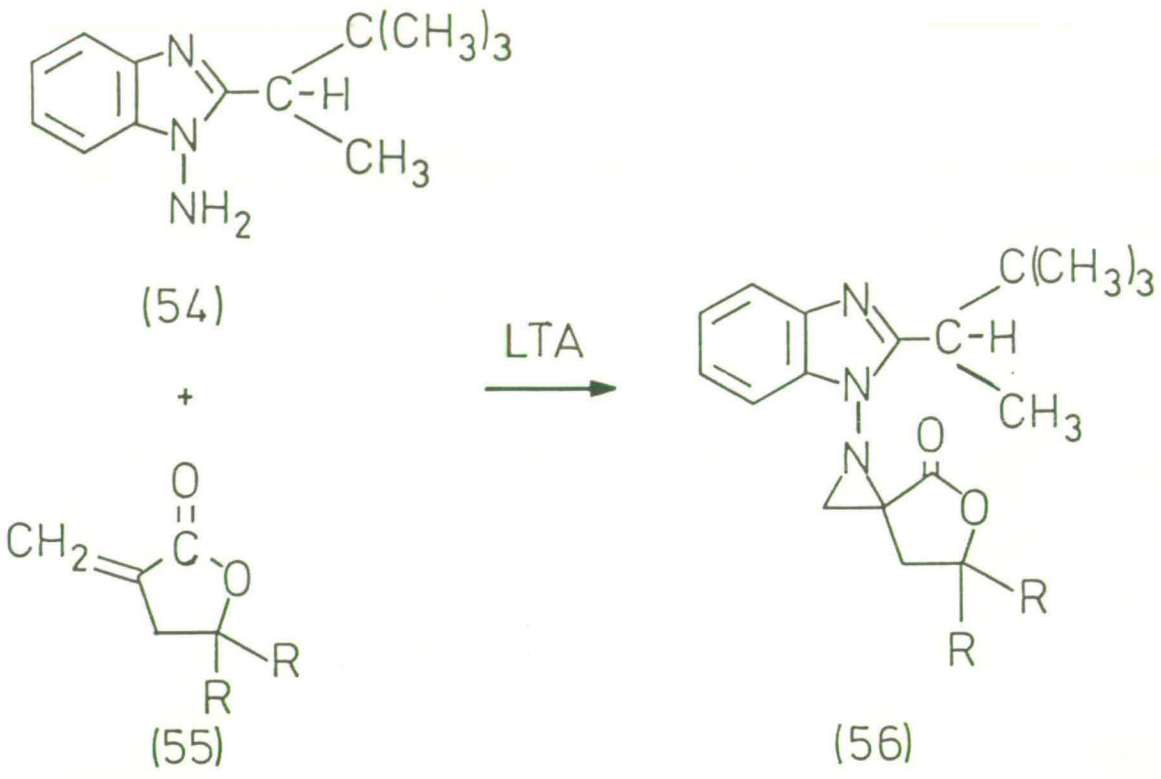
(53a) $R^1 = C_6H_5$, $R^2 = H$

(53b) $R^1 = H$, $R^2 = C_6H_5$

Scheme 36

Pirkle and co-workers reported that the non-equivalence of proton shifts of diasteroisomers (53 a) and (53 b) is in the region of 0.03-0.07 ppm. This system bears a strong similarity to the aziridine (52) since the two optical centres are a comparable distance apart. As such, the diastereoisomers of aziridine (52) might be expected to have extremely close proton resonances. I. Dawson showed that the ^{1}H chemical shifts of the aziridine ring protons were unresolvable even at 360 MHz.

During the progress of this research, Atkinson *et al*[135-138] have published some experimental details which imply that chiral aziridination is possible *via* the reaction of *N*-aminonitrenes with prochiral alkenes. Their work involved the oxidation of racemic *N*-aminobenzimidazole (54) with lead tetraacetate (LTA) to give the corresponding *N*-aminonitrene. The generation of this *N*-aminonitrene in the presence of α-methylene-γ-butyrolactone (55 a) afforded a 5.3:1 ratio of stereoisomeric aziridines (56 a). This ratio was obtained from high field n.m.r. spectroscopy of the crude product. In contrast, the corresponding reaction with butyrolactone (55 b) resulted in the formation of aziridine (56 b) in a 69% yield as a single pair of enantiomers, the other pair being absent according to n.m.r. spectroscopy (Scheme 37).



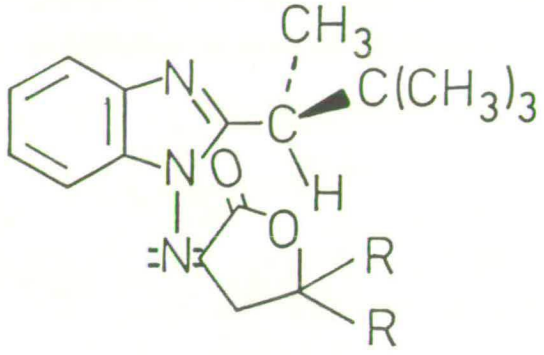
(56 a) R = H, Stereoselective

(56 b) R = Me, Stereospecific

Scheme 37

Atkinson and co-workers accounted for this stereo-specificity by formulating the transition state geometry shown in (57), in which the benzimidazole and butyrolactone are contained in parallel planes. The nitrogen-nitrogen bond is depicted as being orthogonal to the plane containing the alkene π-electrons, and there is an attractive secondary interaction between the

carbonyl group of the butyrolactone and the 2-position of the heterocycle.



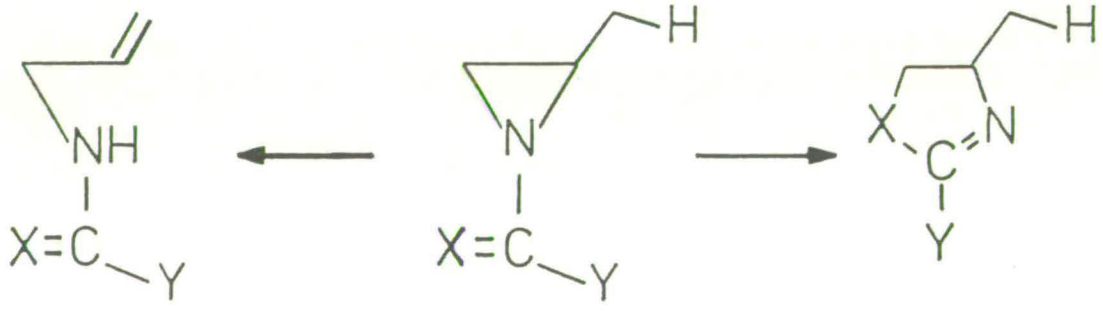
(57)

So far Atkinson et al have not used an optically active nitrene, the consequence of this being that, even in the situation of total stereospecificity, the best that can be achieved is the formation of a pair of enantiomers rather than a single diastereoisomer. If the optically pure nitrene can be prepared then chiral aziridination is a definite possibility.

B. PREPARATION AND PYROLYSIS OF 1-ALKOXYCARBONYLAZIRIDINES

1. Introduction

The rearrangement of aziridines bearing unsaturation on the ring nitrogen atom is a well documented aspect of aziridine chemistry. This type of aziridine (58) has been reported to undergo two major types of rearrangement under a variety of conditions (Scheme 38).



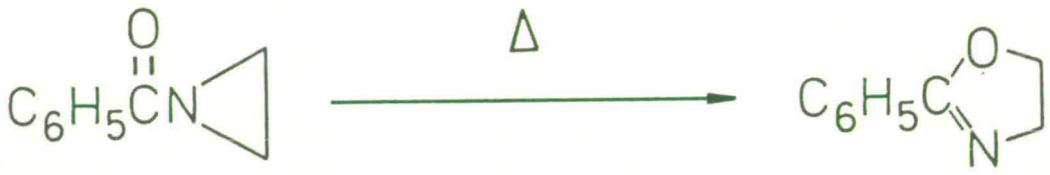
(60) (58) (59)

X = O, S, NR

Y = R, OR, NR_2, RNH, SR etc.

Scheme 38

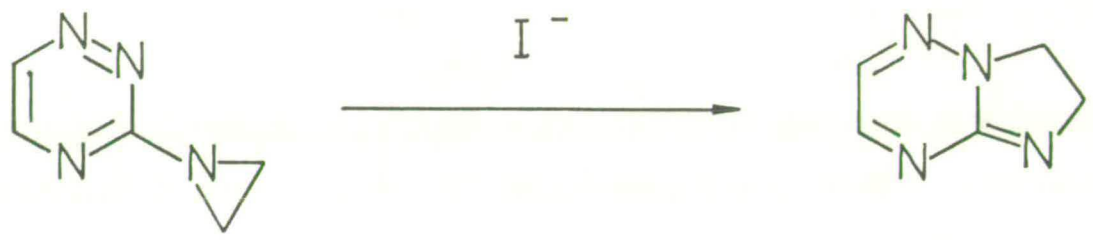
The first isomerisation of this type of aziridine was recorded by Gabriel and Stelzner in 1895. They discovered that distillation of crude 1-benzoylaziridine gave 2-phenyl- 2-oxazoline[139] (Scheme 39).



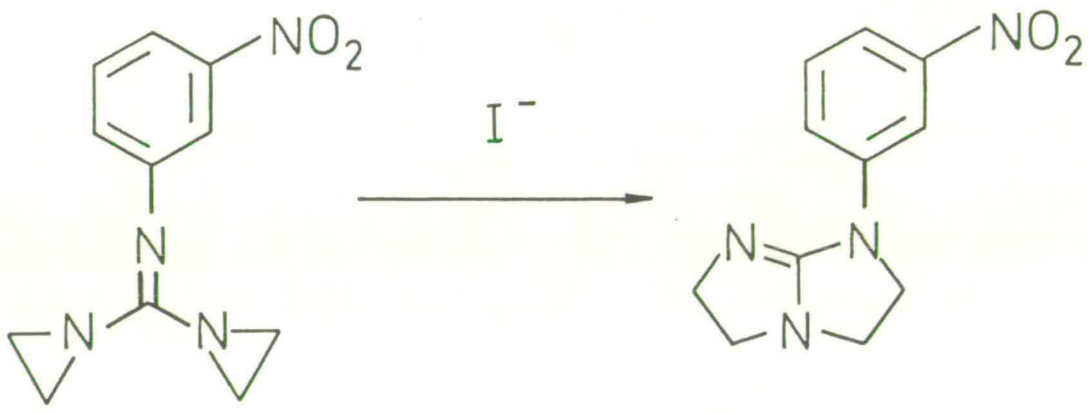
Scheme 39

Since there are numerous possibilities for the nature of X and Y in Scheme 38, this infers the existence of a large family of aziridines of the general structure (58). As a result of this, over the past ninety years there have been many reports of rearrangements of the types depicted in Scheme 38. The various acidic, nucleophilic and thermolytic rearrangements, as well as mechanistic and kinetic aspects of the transformations, have been reviewed.[140-146]

These rearrangements of aziridines of general structure (58) to give five-membered heterocycles are synthetically useful. The importance is displayed, for example, in the synthesis of complex or fused heterocyclic compounds such as those described in Schemes 40 and 41.[142]



Scheme 40

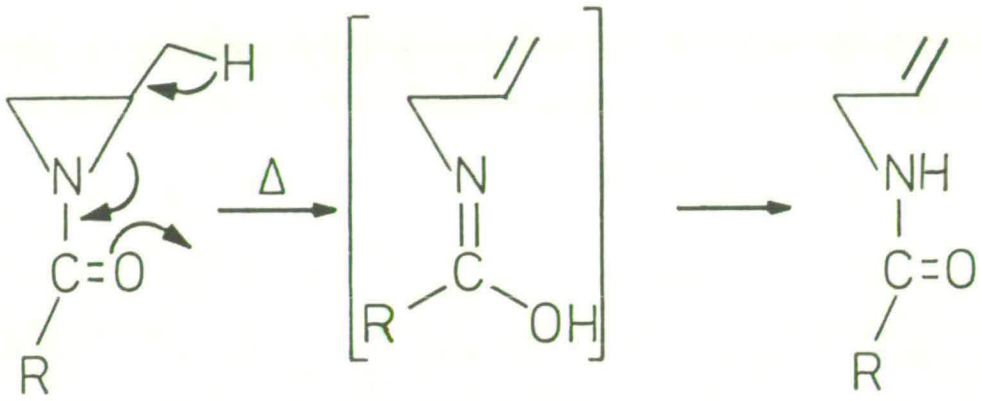


Scheme 41

The rearrangement of aziridine (58) to give ring-expanded product (59) is known to occur <u>via</u> nucleophilic, acidic or thermal conditions, whereas the rearrangement of (58) to give ring-opened product (60) usually occurs thermally.

The thermal isomerisation of 1-acyl-2-

alkylaziridines (61) usually results in the formation of N-allyl amides (62) (Scheme 42).



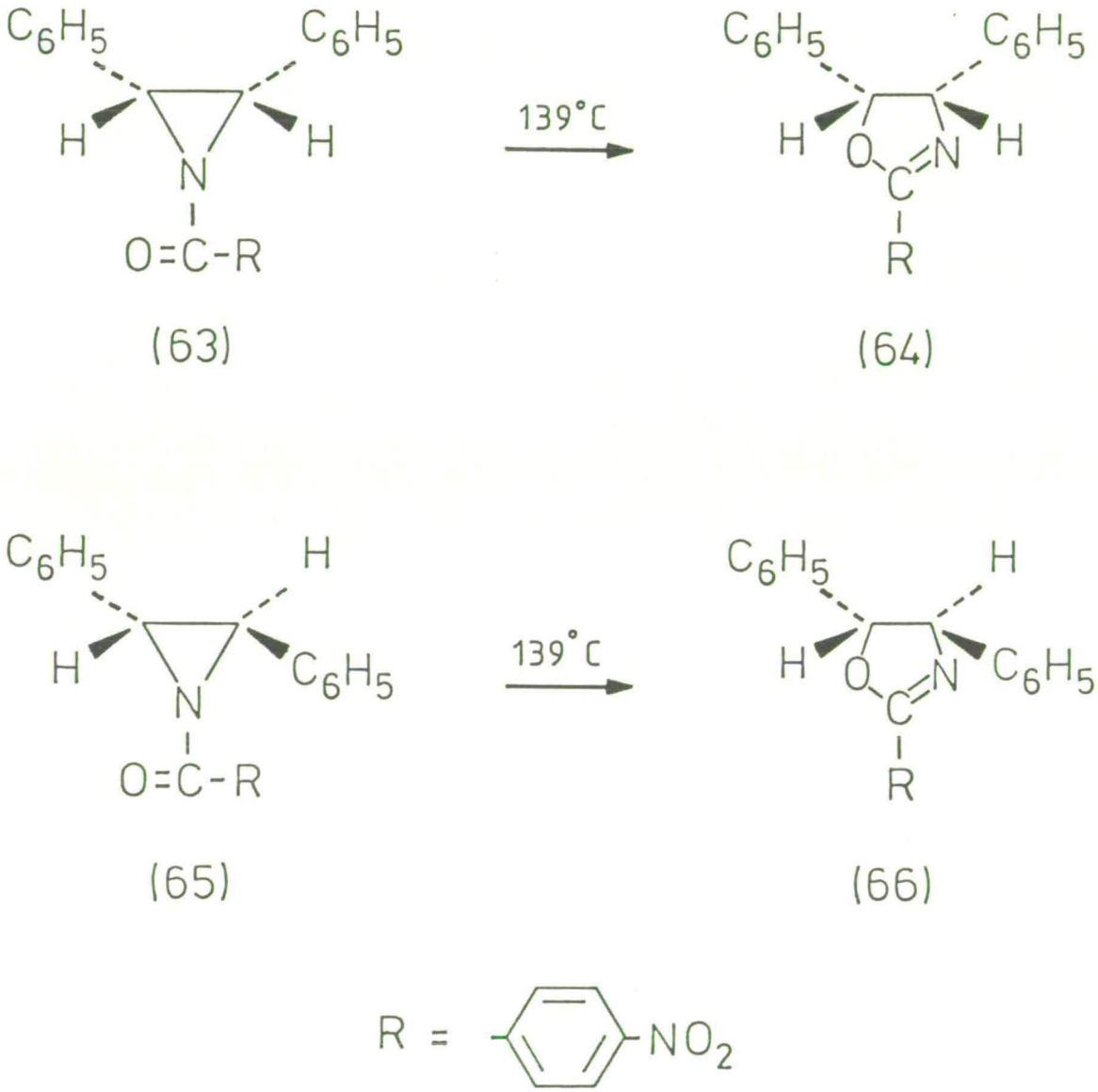
(61) (62)

Scheme 42

First-order kinetics, a high entropy of activation and a lack of solvent effect, along with a Hammett equation indicative of a negative charge accumulation on the nitrogen, all go to support the presence of a concerted, six-centre transition state.[147-149]

Thermal isomerisation of (61) to (62) is not possible in the absence of C-alkyl substituents which bear protons at the α- position to the aziridine ring. The isomerisation is also difficult for aziridines in which steric factors prevent bond formation between the amido-oxygen and the α-proton of the alkyl group. In these situations, usually an oxazoline is obtained. The former situation is illustrated in Scheme 43 by the conversion of 1-acylaziridines (63) and (65) to give

oxazolines (64) and (66).[150] The stereochemistry of these isomerisations will be discussed in a later section. The latter case is demonstrated by the isomerisation of bicyclic aziridine (67) to give the fused oxazoline (68)[151] (Scheme 44).

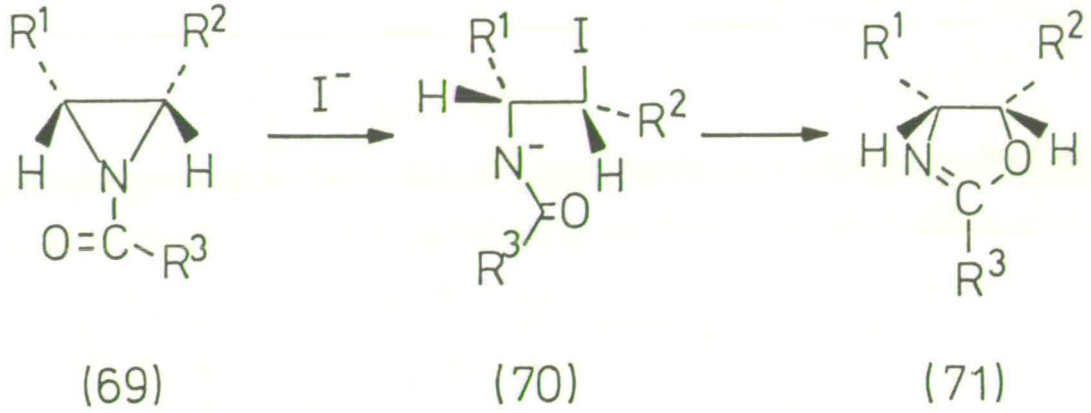


Scheme 43

(67) (68)

Scheme 44

Many examples have been reported concerning the isomerisation of 1-acylaziridines to 2-substituted-oxazolines by nucleophilic catalysis with, for example, iodide and thiocyanate ions. Similar acid and base catalysed rearrangements have been reported, but these have not yet been studied in detail.[152] The nucleophilic isomerisation of 1-acylaziridines has been reviewed.[153] The isomerisation has been explained in terms of a two-step mechanism involving attack by the nucleophile on the aziridinyl carbon to form ion (70) which cyclises to give the oxazoline (Scheme 45).



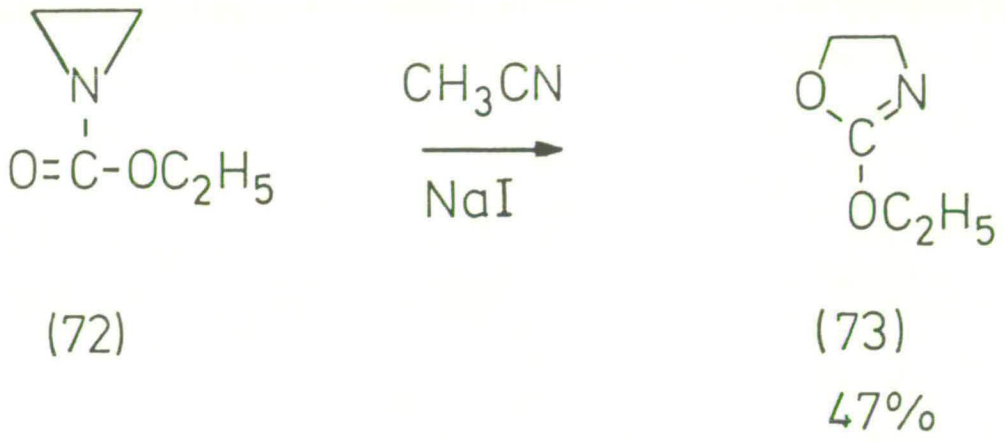
(69) (70) (71)

Scheme 45

Stereochemical studies are consistent with the proposed mechanism, the isomerisation being shown to proceed with retention of configuration. Thus, in a boiling solution of sodium iodide in butanone, trans- or cis-2,3-disubstituted aziridines (69) will rearrange to give trans- or cis-4,5-disubstituted-4,5-dihydro-oxazoles (71) respectively. These transformations are the result of a double inversion at the aziridine carbon.[153] Another observation which favours the proposed mechanism is that results show that the nucleophile will attack the more positive carbon of the aziridine ring, thus giving selectivity.[150]

Few reports exist concerning the rearrangements of 1-ethoxycarbonylaziridines and other 1-alkoxy- and 1-aryloxy-carbonylaziridines. Ham[154,155] reported that 1-ethoxycarbonylaziridine (72), when heated in boiling

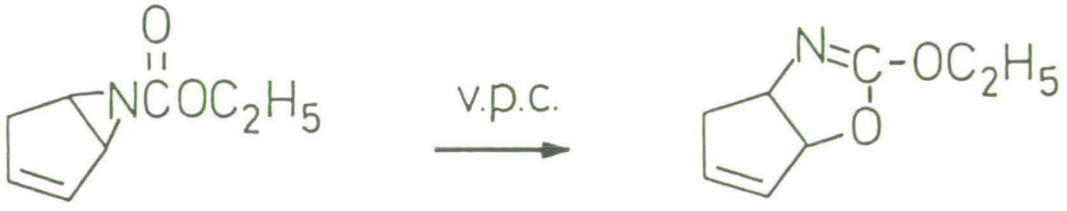
acetonitrile with sodium iodide for four days, afforded 4,5-dihydro-2-ethoxyoxazole (73) (Scheme 46).



(72) (73) 47%

Scheme 46

Lwowski et al have reported the thermal conversion of aziridine (74) to (75) during vapour-phase chromatography,[156] and the related conversion of (76) to (77) during gas-liquid chromatography[53] (Scheme 47 and 48).



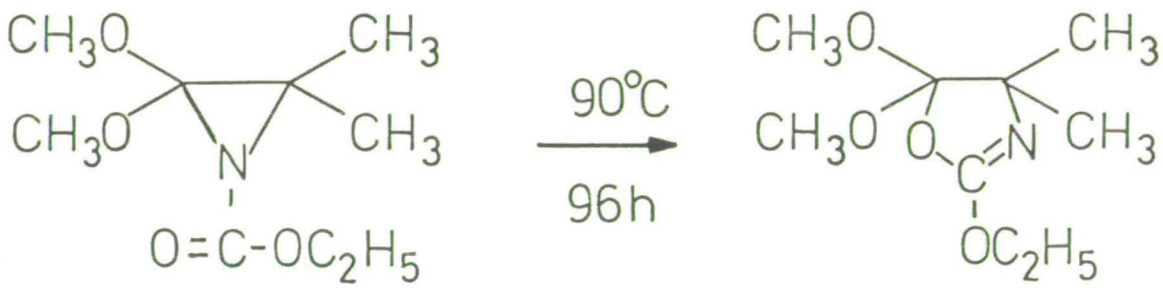
(74) (75)

Scheme 47

(76) (77)

Scheme 48

It has been reported by Graziano and Scarpati[157] that the conversion of tetra-substituted 1-ethoxycarbonylaziridine (78) to oxazoline (79) requires heating at 90°C for four days (Scheme 49).

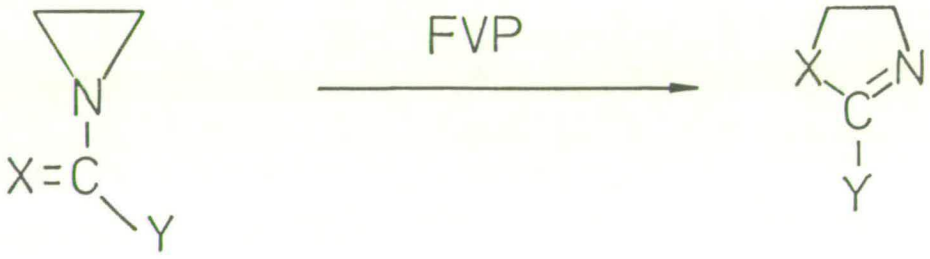


(78) (79)

Scheme 49

The above examples which demonstrate thermal oxazoline formation exemplify the fact that present routes to the five-membered heterocycles from suitable aziridines are not necessarily convenient.

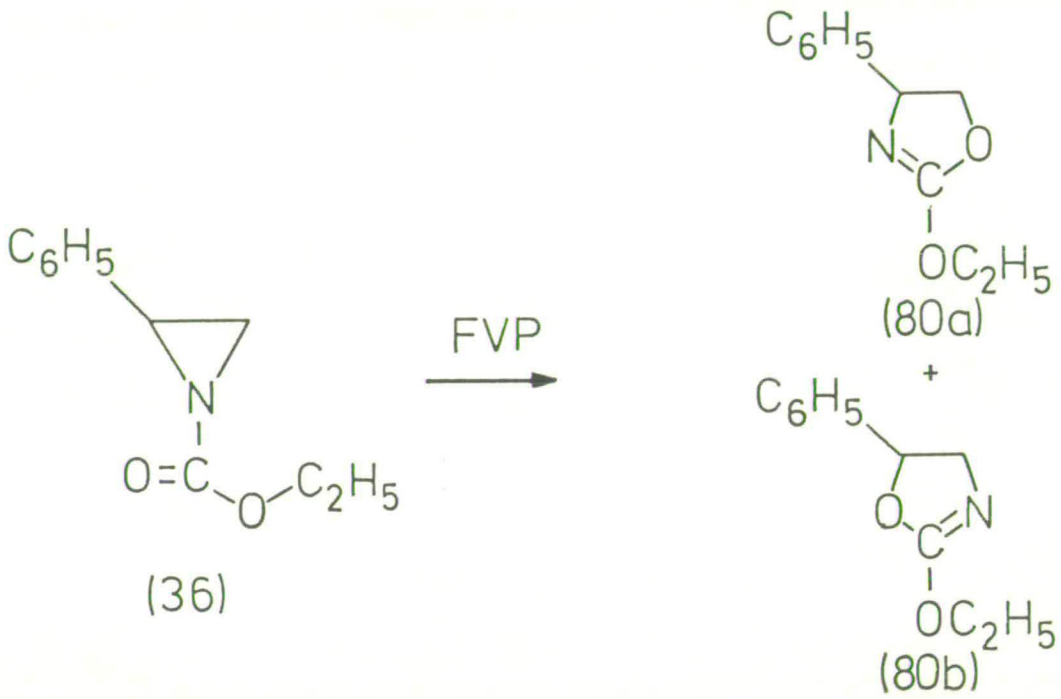
Despite the number and variety of aziridine rearrangements which have been recorded, no flash vacuum pyrolysis (FVP) studies have been reported. The technique of FVP may provide a convenient, fast approach to the synthesis of five-membered heterocycles from aziridines which bear unsaturation on the ring nitrogen (Scheme 50).



Scheme 50

In parallel to the work concerning the synthesis of chiral 1-ethoxycarbonylaziridines, an ongoing investigation was initiated to study the pyrolysis of these compounds. The study of the rearrangement of aziridines was to commence with the pyrolysis 1-ethoxycarbonyl-2-phenylaziridine (36). This compound cannot form an allyl carbamate, as illustrated in Scheme

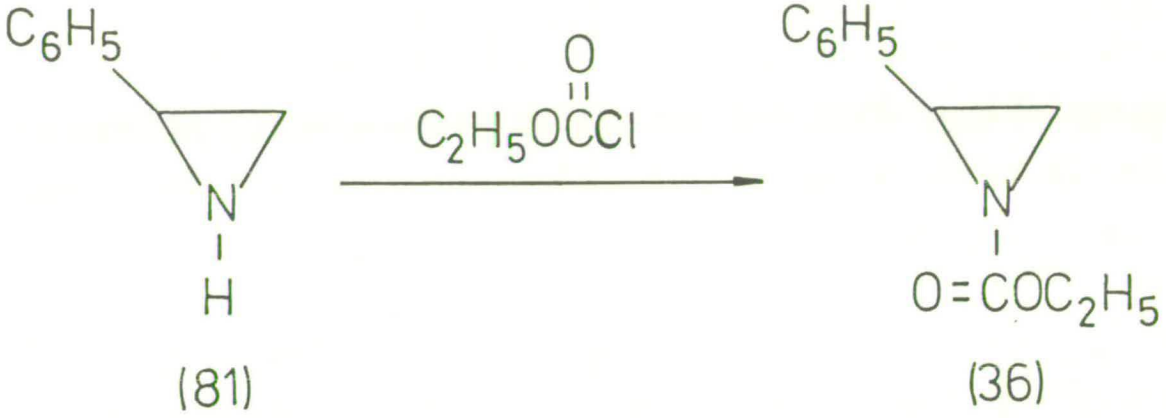
42, due to the absence of an α-proton on the ring-carbon substituent, therefore 4- and/or 5-phenyl-4,5-dihydro-2-ethoxyoxazole (80a), (80b) might be expected to form as a result of pyrolysis (Scheme 51).



Scheme 51

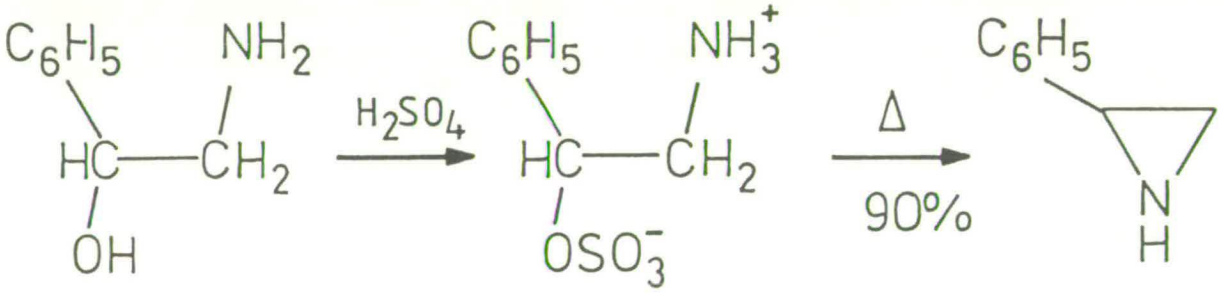
2. FVP of 1-Ethoxycarbonyl-2-phenylaziridine

1-Ethoxycarbonyl-2-phenylaziridine (36) was prepared from the reaction of ethyl chloroformate and 2-phenylaziridine (81) (Scheme 52), which was obtained from the cyclisation of 2-amino-1-phenylethanol *via* a Wenker synthesis as shown in Scheme 53.



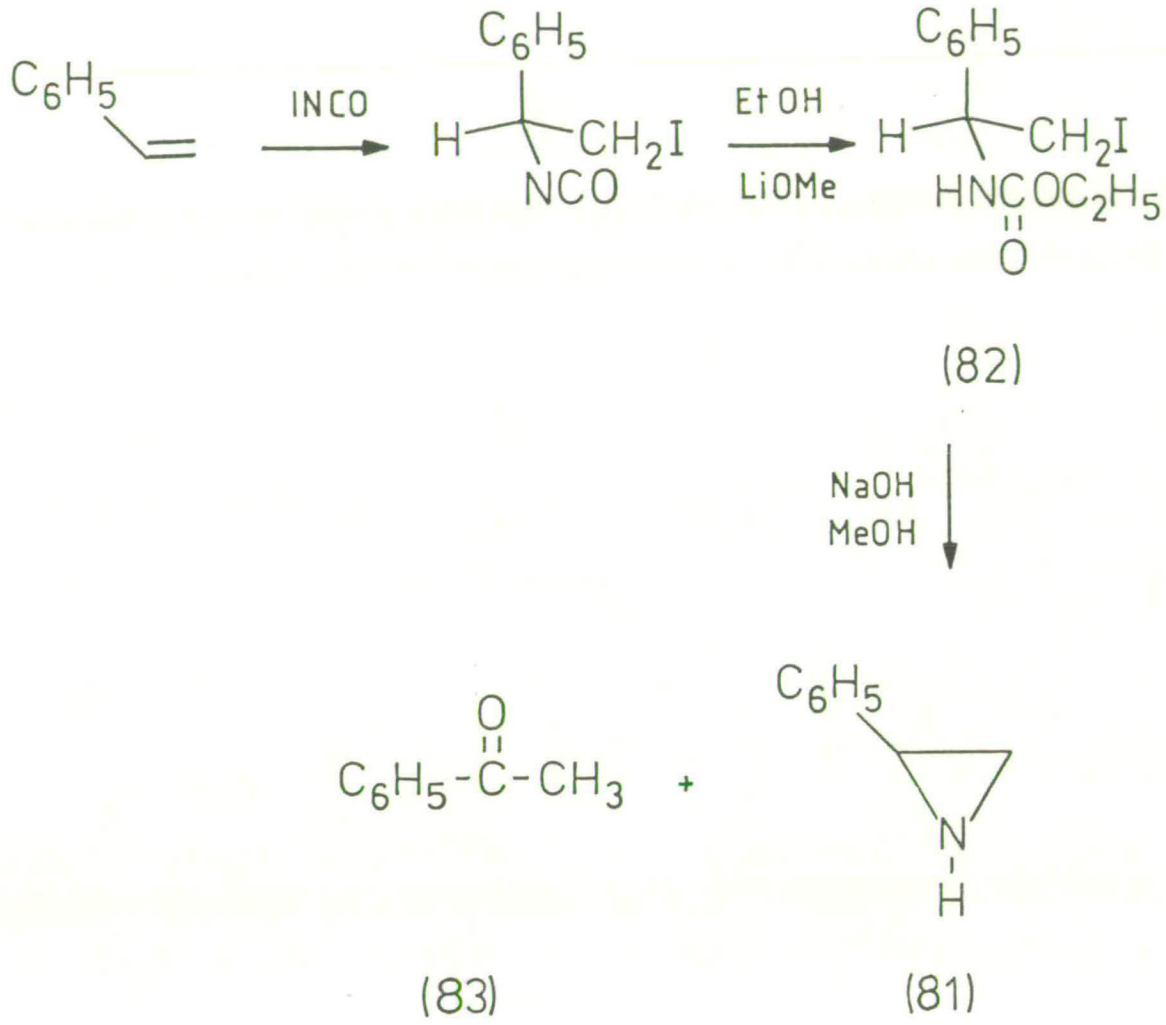
(81) (36)

Scheme 52



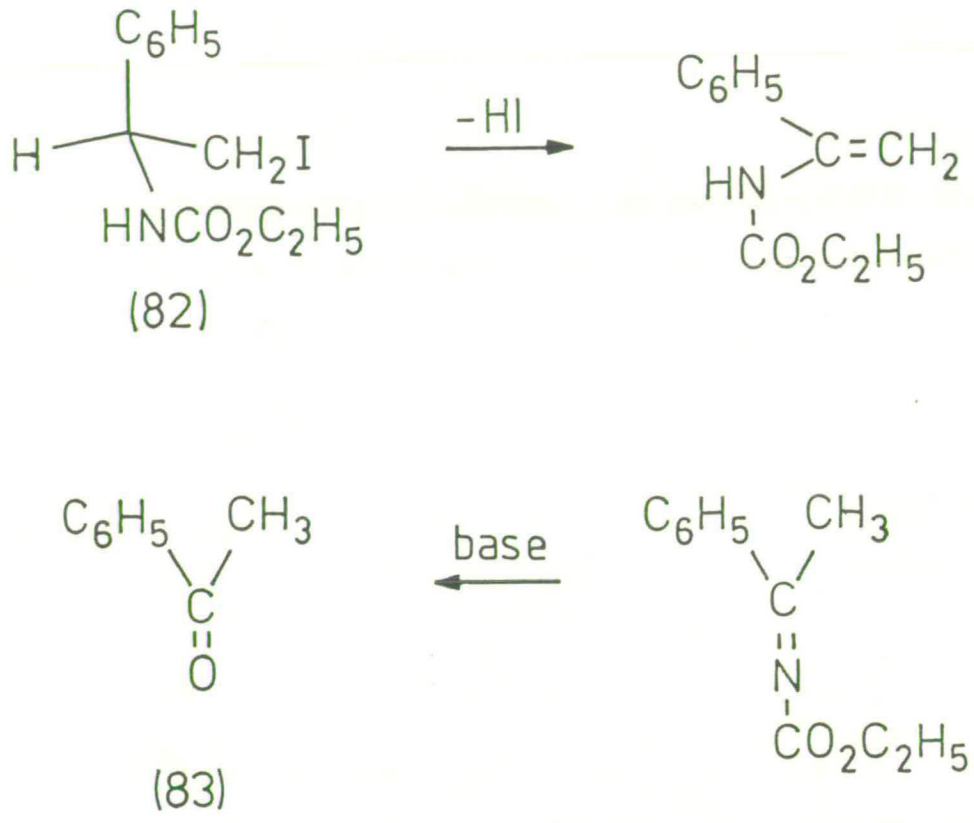
(81)

Scheme 53



Scheme 54

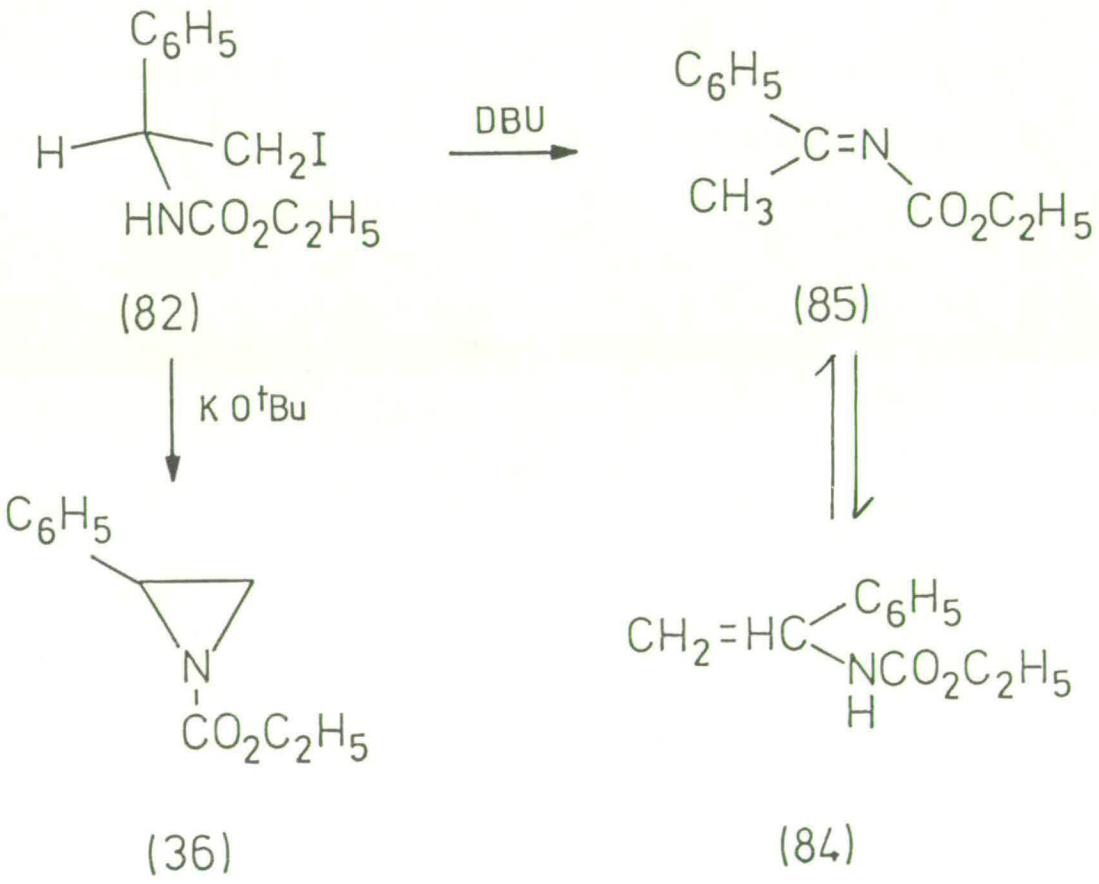
(81) was also prepared <u>via</u> the basic hydrolysis of ethyl (2-iodo-1-phenylethane)carbamate (82) (Scheme 54). This method, however, has the drawback of producing acetophenone as a by-product. Acetophenone (83) is produced from (82) due to elimination of hydrogen iodide with concomitant ketone production which competes with the cyclisation reaction as shown in Scheme 55.



Scheme 55

It was proposed that treatment of the β-iodocarbamate (82) with a suitable hindered base would give 1-ethoxycarbonyl-2-phenylaziridine (36). The use of sodium hydroxide as a base promotes the formation of 2-phenylaziridine due to hydrolysis of (36). A hindered base should be unable to hydrolyse the N-subsituent, allowing 1-ethoxycarbonyl-2-phenylaziridine to be obtained directly from the β-iodocarbamate. Treatment of (82) with 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), however, resulted in formation of an equilibrium mixture

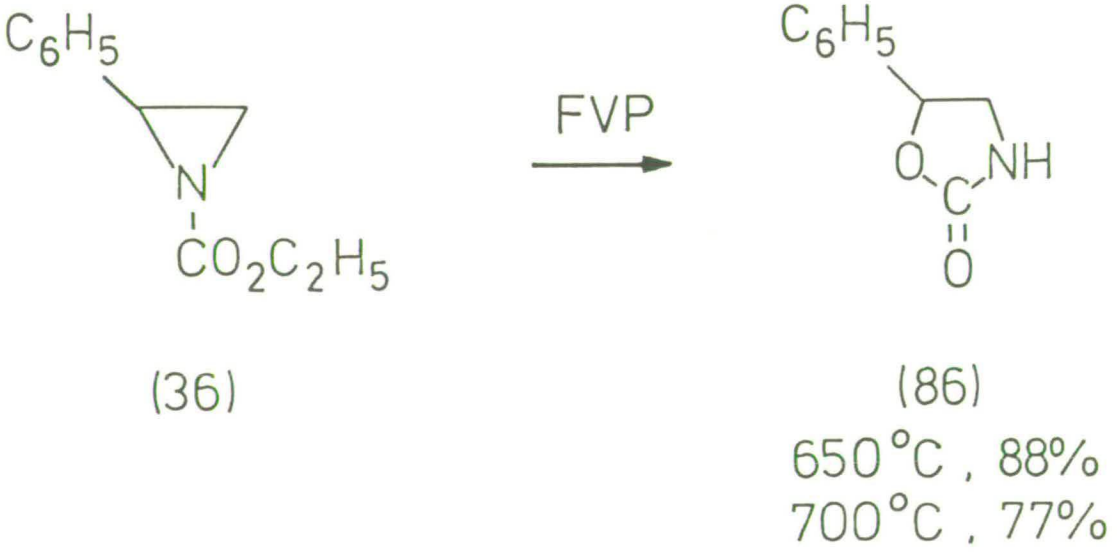
of ethyl-1-phenyl-2-propenylcarbamate (84) and ethyl-2-phenyl-2- methyl-N-methylenecarbamate (85) in a ratio of 3:2. Hassner et al[29] have reported that potassium tert- butoxide is a suitable base, the use of which results only in the formation of 1-ethoxycarbonyl-2-phenylaziridine (36) From (82) (Scheme 56).



Scheme 56

Thermolysis of neat (36) at 200°C resulted in the sample colour changing from yellow to dark brown. Despite this colour change, an n.m.r. spectrum of the sample was still unchanged after 4.5 hours.

Samples of 1-ethoxycarbonyl-2-phenylaziridine were subjected to flash vacuum pyrolysis conditions. Pyrolysis of (36) through a furnace at 650°C gave two distinct compounds in the trap. The main portion of the product formed as a colourless crystalline solid in the trap head. This material was identified, by comparison of its characteristics with literature data, as 5-phenyl-2-oxazolidinone (86) (88% yield). The small amount of oily material which gathered in the bottom of the trap was identified as residual starting material.



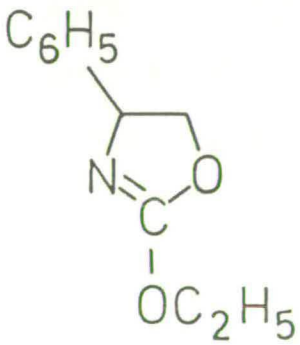
(36) (86)

650°C, 88%
700°C, 77%

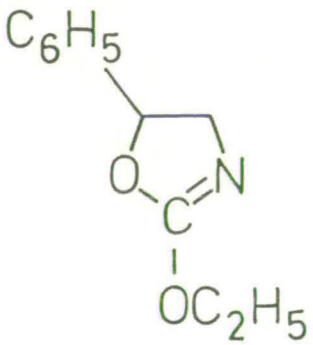
Scheme 57

The pyrolysis was repeated with a furnace temperature of 700°C. This resulted in the production of (86) in a 77% yield. No trace of starting material was evident at this higher pyrolysis temperature. The lower yield of (86) can be explained by the presence in the trap of some colourless insoluble material which was thought to be a polymer. The formation of this polymer may be attributed to decomposition of some of the 2-oxazolidinone, due to extrusion of carbon dioxide, to give 2-phenylaziridine. This aziridine may then form a polymer on its own, or it may co-polymerise with the 5-phenyl-2-oxazolidinone.

No trace of the expected 4- and/or 5-phenyl-4,5-dihydro-2-ethoxyoxazole (80a,b) was found in the product at 650 and 700°C

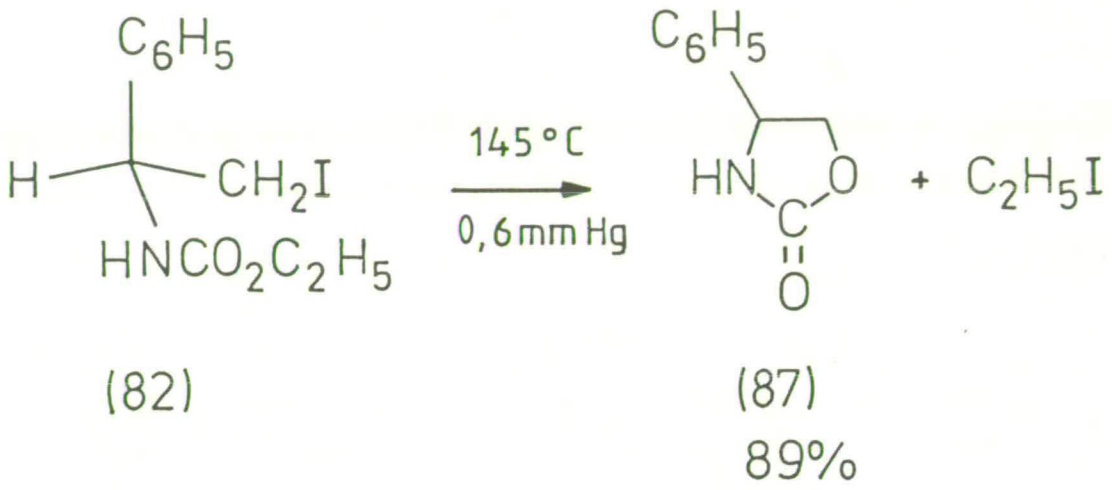


(80a)



(80b)

An authentic sample of 4-phenyl-2-oxazolidinone (87) was prepared by thermolysis of ethyl (2-iodo-1-phenylethane) carbamate (82) (Scheme 58)[29].



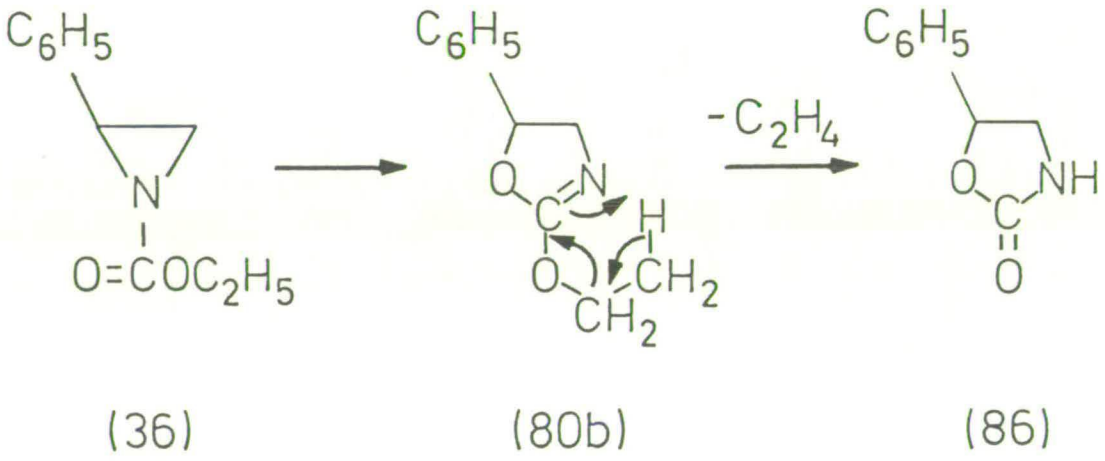
(82) (87) 89%

Scheme 58

Comparison of the ^{1}H n.m.r. spectrum of (87) with spectra of the pyrolysis product ensured that only 5-phenyl-2-oxazolidinone (86), and none of the isomeric 4-phenyl-2-oxazolidinone (87), was formed during pyrolysis of 1-ethoxycarbonyl-2-phenylaziridine (36). 4-Phenyl-2-oxazolidinone (87) was recovered unchanged after its pyrolysis at 700°C, no isomerisation to 5-phenyl-2-oxazolidinone occurred.

3. Elucidation of the Mechanism

The pyrolysis of 1-ethoxycarbonyl-2-phenyl-aziridine (36) was expected to produce a phenyl-substituted-4,5-dihydro-2-ethoxyoxazole. The formation of 5-phenyl-2-oxazolidinone (86) may have occurred due to the elimination of ethene from initially produced 5-phenyl-4,5-dihydro-2-ethoxyoxazole (80b) (Scheme 59).

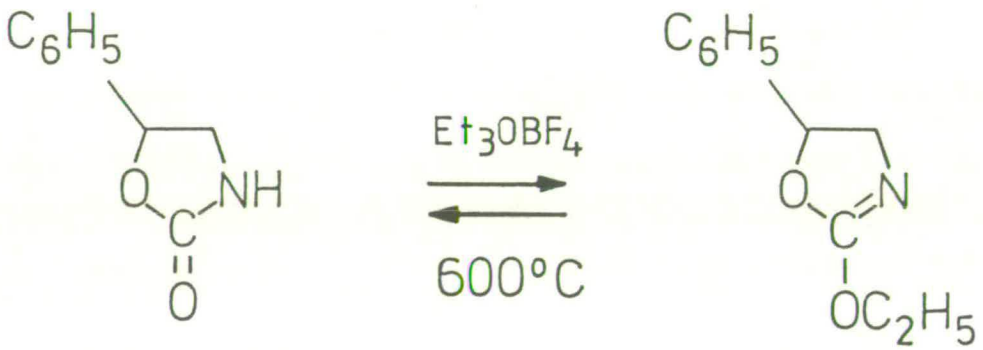


(36) (80b) (86)

Scheme 59

If (80b) is an intermediate during the pyrolysis of 1-ethoxycarbonyl-2-phenylaziridine, then independent

synthesis of (80b) followed by pyrolysis under similar conditions to that of aziridine (36) should give only 5-phenyl-2-oxazolidinone. 5-Phenyl-4,5-dihydro-2-ethoxy-oxazole (80b) was prepared in a 94% yield from the reaction of 5-phenyl-2-oxazolidinone (86) with Meerwein's reagent. Flash vacuum pyrolysis of (80b) at 600°C afforded a 98% yield of (86), thus proving that (80b) could be an intermediate during the pyrolysis of 1-ethoxycarbonyl-2-phenylaziridine (Scheme 60).



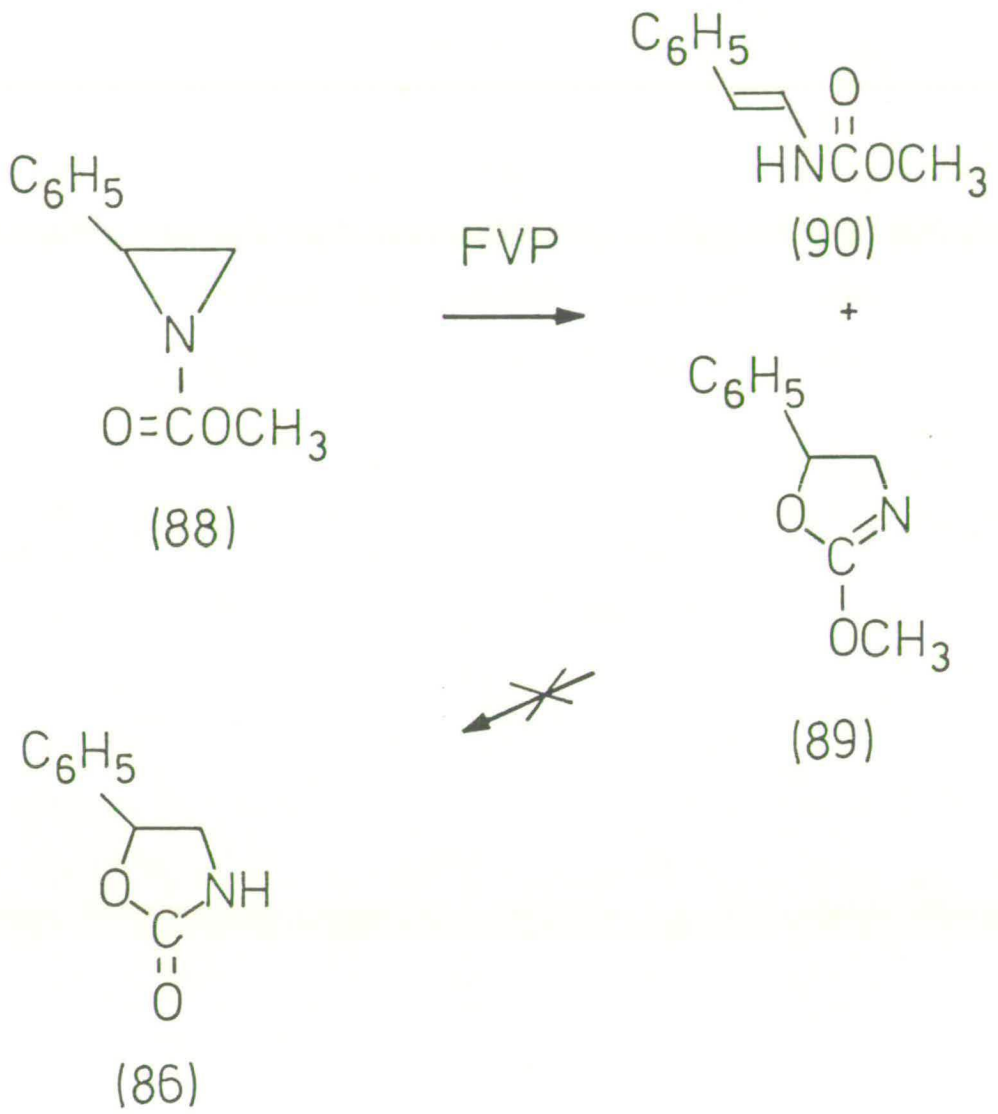
(86) (80b)

Scheme 60

Pyrolysis of (80b) at 500°C resulted in the production of a mixture of the starting material (46%) and 5-phenyl-2-oxazolidinone (86) (54%), showing that the oxazoline will partially survive this pyrolysis temperature.

Pyrolysis of 1-ethoxycarbonyl-2-phenylaziridine was carried out at 500°C in an attempt to isolate 5-phenyl-4,5-dihydro-2-ethoxyoxazole. This pyrolysis resulted in the production of a yellow oil which was shown to contain starting material, 5-phenyl-2-oxazolidinone and 5-phenyl-4,5-dihydro-2-ethoxyoxazole (12%, by n.m.r.), thus confirming the postulated reaction mechanism outlined in Scheme 59.

A further test to confirm this pathway was achieved by investigation of the pyrolysis of 1-methoxycarbonyl-2-phenylaziridine (88). It was expected that, if the pyrolysis of 1-ethoxycarbonyl-2-phenylaziridine to give 5-phenyl-2-oxazolidinone and ethene proceeds <u>via</u> a 5-phenyl-4,5-dihydro-2-ethoxy-oxazole intermediate, then the pyrolysis of (88) under similar conditions should produce only 5-phenyl-4,5-dihydro-2-methoxyoxazole (89) since the system would be unable to eliminate an alkene to form the 2-oxazolidinone (86) (Scheme 61).

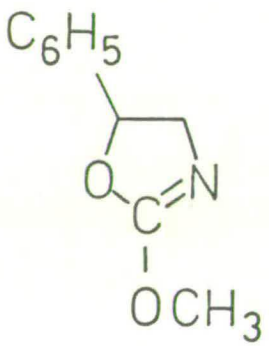


Scheme 61

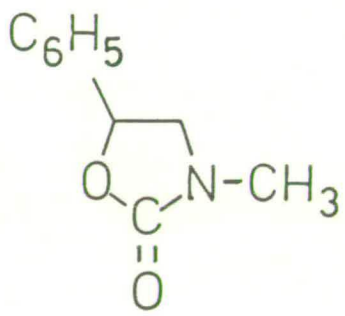
1-Methoxycarbonyl-2-phenylaziridine (88) was prepared from the reaction of 2-phenylaziridine (81) with methyl chloroformate. Pyrolysis of (88) at 600°C afforded an approximately equimolar mixture of starting material (88) and 5-phenyl-4,5-dihydro-2-methoxyoxazole (89). Traces of trans-methyl-2-phenylethenylcarbamate (90) were deposited at the trap head during pyrolysis.

A similar mixture of products was obtained from pyrolysis of (88) at 650°C. No trace of 5-phenyl-2-oxazolidinone was formed during the pyrolysis.

(89) was prepared by alkylation of (86) with trimethyloxonium tetrafluoroborate. The results of methylation of (86) with various reagents to give 5-phenyl-4,5-dihydro-2-methoxyoxazole (89) and 3-methyl-5-phenyl-2-oxazolidinone (91) are displayed in Table 2.



(89)



(91)

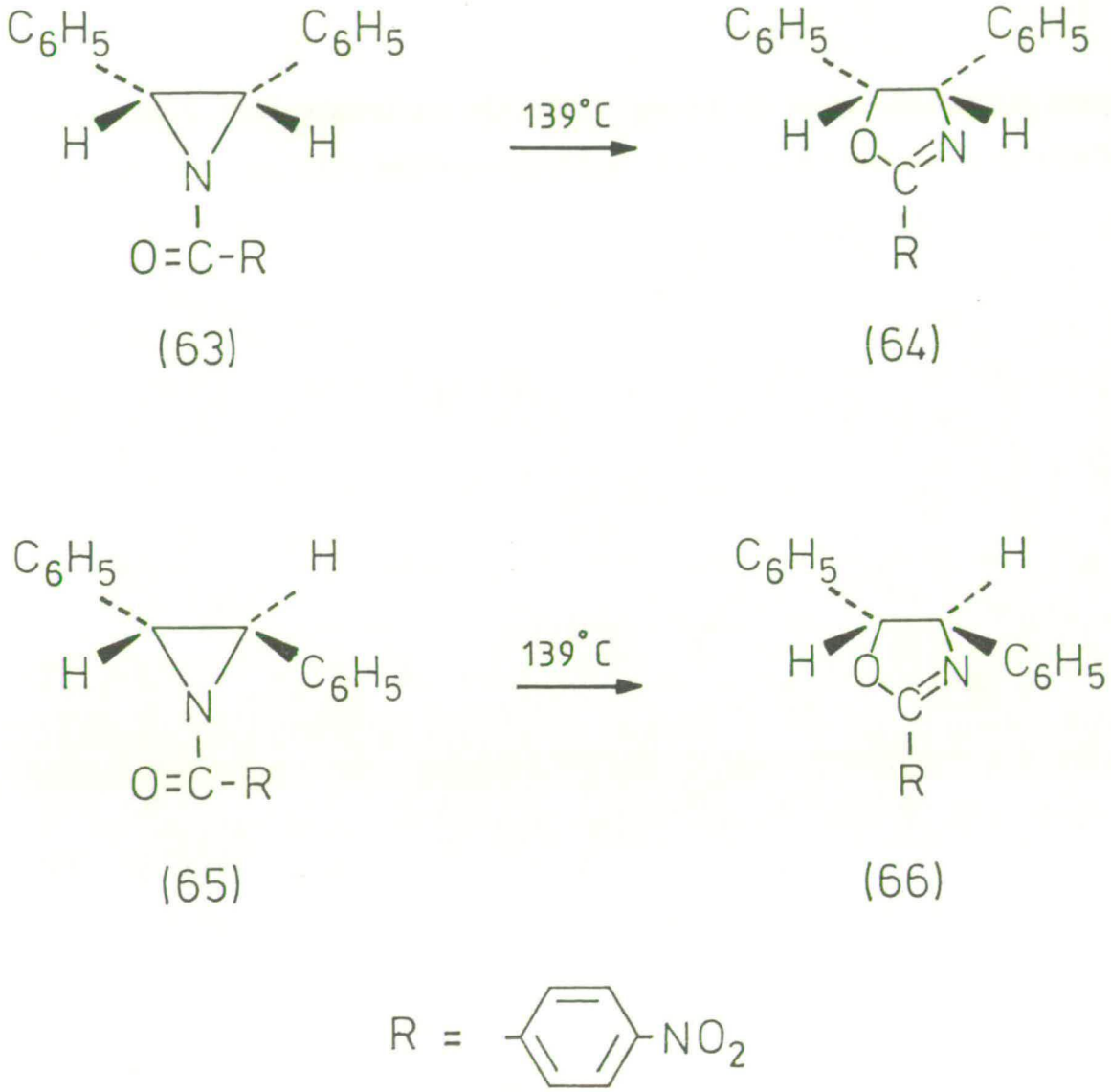
Table 2

Methylation of (86)

Reaction Conditions	(89)	(91)
$MeI/K_2CO_3/DMF$	25%	75%
$MeI/Ag_2CO_3/DMF$	trace	trace
MeOTs/NaH/DMEU	-	59%
Me_3OBF_4/CH_2Cl_2	82%	-

Pyrolysis of (89) at 600°C afforded a yellow oil which consisted mainly of starting material. Pyrolysis of the oxazoline through a furnace at 675°C afforded a mixture of decomposition products and starting material.

A stereochemical study of the thermolytic conversion of 1-acylaziridines to oxazolines by Heine *et al*[150] has shown that the isomerisation occurs with clear-cut retention of configuration. Scheme 62 shows that *cis*- and *trans*-1-*p*-nitrobenzoyl-2,3-diphenyl-aziridines (63) and (65) rearrange to *cis*- and *trans*-4,5-diphenyl-4,5-dihydro-2-*p*-nitrophenyloxazoles (64) and (66) respectively.



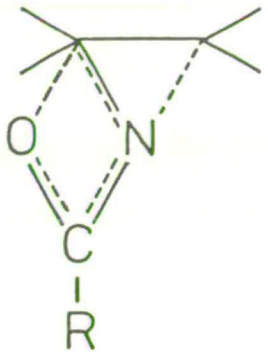
(63) (64)

(65) (66)

R =

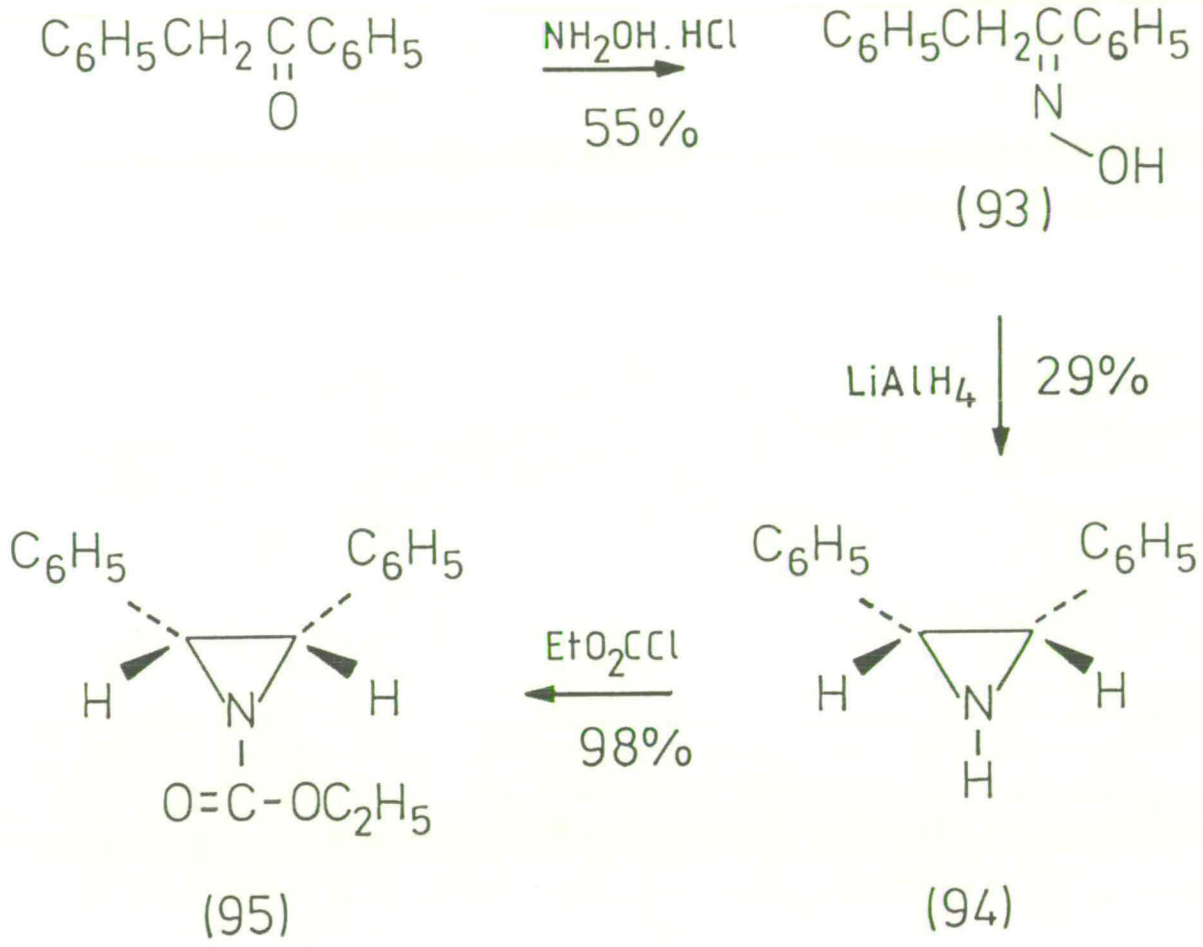
Scheme 62

To account for the observed stereospecificity, the four-centred transition state (92) has been proposed.[143,150]



(92)

Evidence for the mechanism of the pyrolytic ring expansion of a 1-ethoxycarbonylaziridine to an oxazoline may be gained through study of the stereochemistry of the reaction. The stereochemistry was investigated by examining the flash vacuum pyrolysis of cis-1-ethoxycarbonyl-2,3-diphenylaziridine (95) which was prepared via the synthesis outlined in Scheme 63.

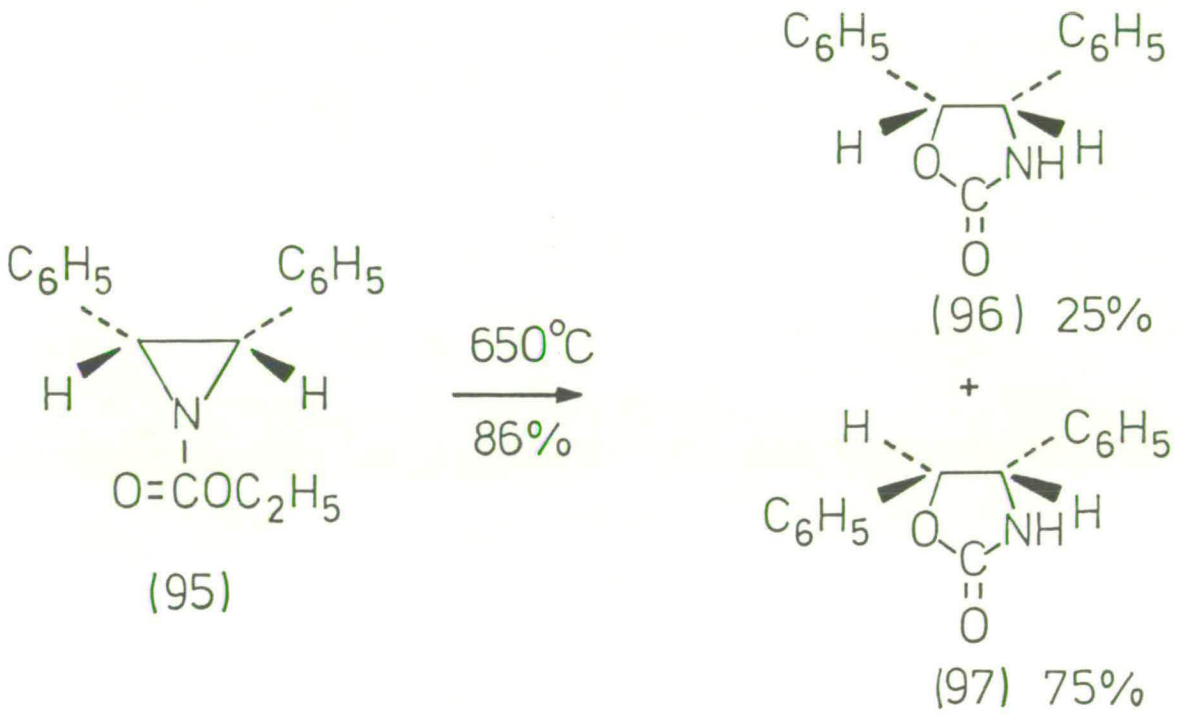


Scheme 63

The reduction of oximes with lithium aluminium hydride generally produces the corresponding amine. In the above example the reduction of oxime (93) leads to the formation of aziridine (94) *via* the generation of a nitrene followed by its intramolecular reaction to form an azirine. The azirine is then reduced to give (94).

FVP of *cis*-1-ethoxycarbonyl-2,3-diphenylaziridine

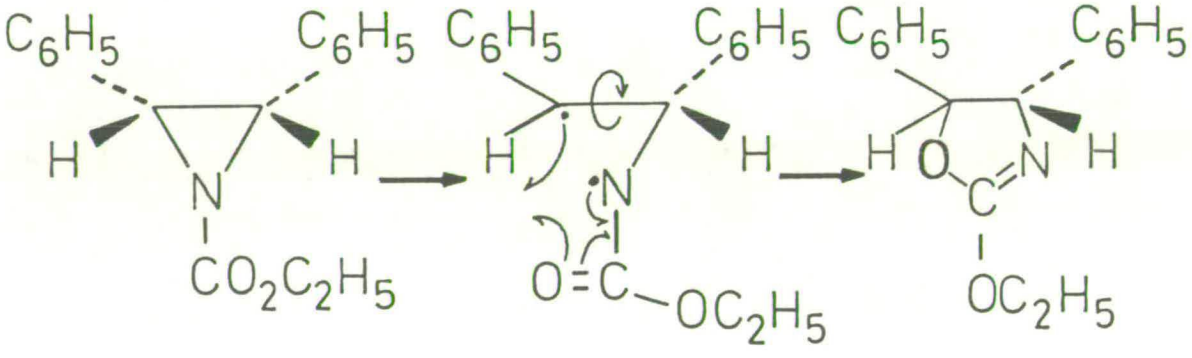
through a furnace at 600°C provided a mixture of starting material and cis- and trans-4,5-diphenyl-2-oxazolidinones (96) and (97). Pyrolysis of (95) at 650°C afforded (96) and (97) as a mixture (86% yield). The relative amounts of the isomers, estimated by ^{1}H n.m.r. spectroscopy, was shown to be 75% trans and 25% cis (Scheme 64).



Scheme 64

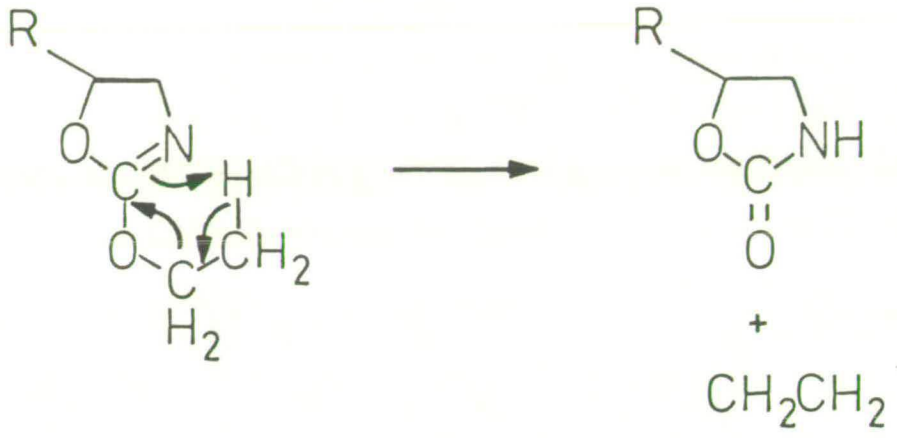
This result shows that the pyrolysis of (95) is not stereospecific. The transition state proposed by Heine for the stereospecific thermolytic rearrangement of cis- and trans-1-p-nitrobenzoyl-2,3-diphenylaziridines (Scheme 62) cannot be implicated during the pyrolytic

rearrangement of (95). A likely explanation for this outcome lies with the probable formation of a diradical which is not tightly bound in the gas phase. Cleavage of the aziridine N-C(2) bond to give a diradical may be followed by free rotation about the C(2)-C(3) bond. This rotation is in competition with the formation of the oxazoline (Scheme 65). Delocalisation within the diradical will stabilise the intermediate, allowing bond rotation to occur and the thermodynamically favoured trans-isomer to form as the major product.



Scheme 65

The second of the two steps involved during the pyrolysis of a 1-ethoxycarbonylaziridine involves the elimination of ethene from the oxazoline, probably via the pericyclic route illustrated in Scheme 66.



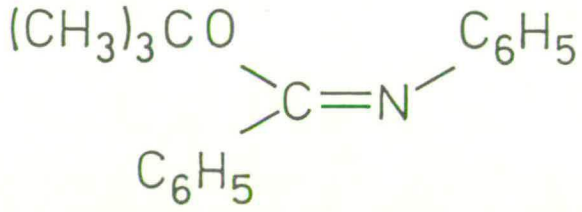
Scheme 66

This aza-ene type reaction is rare. Taylor[158] has reported that 2-ethoxypyridine (98) undergoes thermal elimination of ethene to give 2-pyridone *via* a six-centred cyclic process which is a rare nitrogen analogue of ester pyrolysis[159] (Scheme 67).

(98)

Scheme 67

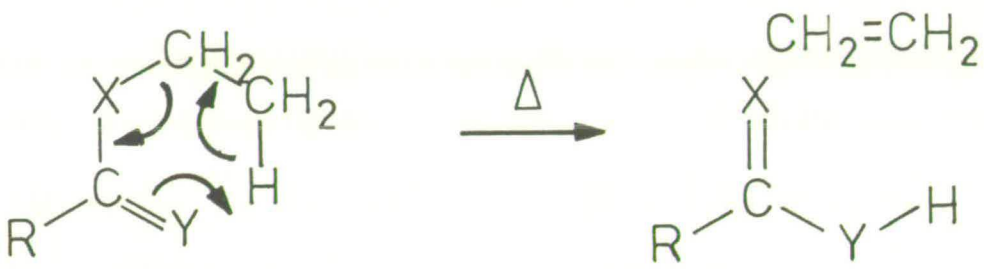
The reaction is reported to be first-order and unimolecular. Kinetic data obtained over a 50°C range gives a good Arrhenius plot and a log A factor which is typical for a reaction having a semi-concerted 6-centred cyclic transition state. Taylor states that this is the first report of this type of rearrangement, except for an observation by Wiberg et al[160] that (99) is unstable.



(99)

In a more recent paper, Sukenik et al[161] similarly reported that the pyrolysis of octyl pyridyl ethers in an atmospheric pressure flow system at 400-500°C gives a mixture of isomeric octenes and 2-pyridone.

Taylor states that the interchange of X and Y in Scheme 68 should produce a considerable change in the alkene elimination rate.

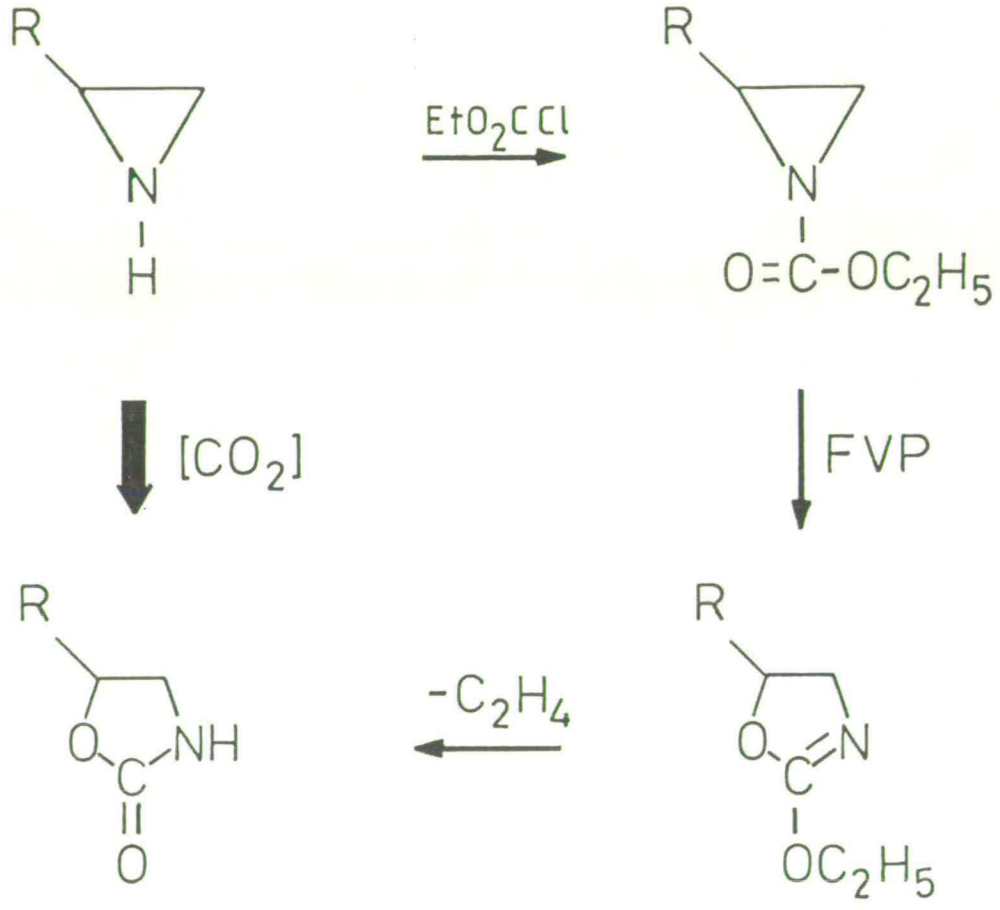


Scheme 68

This change in rate may be attributable to the energy change accompanying the change from -X-C=Y to X=C-Y- on going from reagents to products. Alternatively, electron withdrawal by X (which favours polarisation of the C_α-X bond, the primary step of the elimination) makes this group less able to form a Y-H bond when substituted at the position Y.[158,162,163] On the basis of this, Taylor predicts that the pyrolysis of amides (X = NH, Y = O, R = alkyl) would proceed slowly due to the low polarity of the C_α-NH bond. Thus, the pyrolysis of iminoethers (X = O, Y = NH, R = alkyl) could be expected to be rapid.

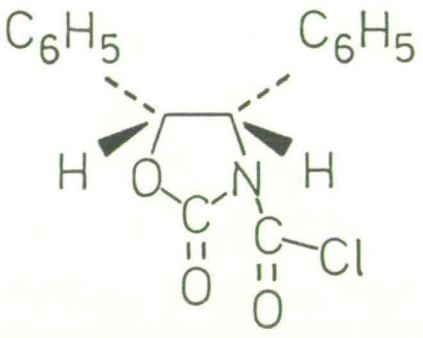
4. Introduction to 2-Oxazolidinones

The novel transformation discussed in previous sections and illustrated in Scheme 69 is notable for its unique sequence of reactions. The combined effect of these rearrangements mimics the normally difficult process of CO_2 insertion into a 1H-aziridine to give a 2-oxazolidinone, without recourse to CO_2.

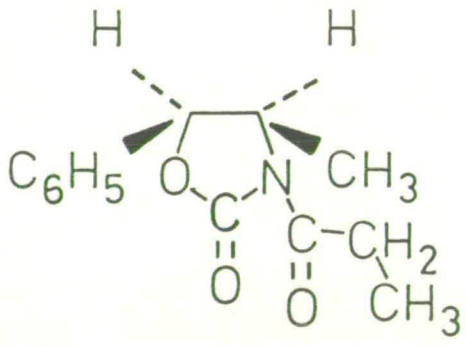


Scheme 69

2-Oxazolidinones are industrially and pharmaceutically important materials. They are implicated in polymer manufacture, and many types of biologically active compounds are based on the 2-oxazolidinone ring system. Recently, Pirkle *et al*[94] have used simple chiral 2-oxazolidinones such as (100), obtained *via* a multistage synthesis, as auxiliaries in the optical resolution of chiral amines.



(100)



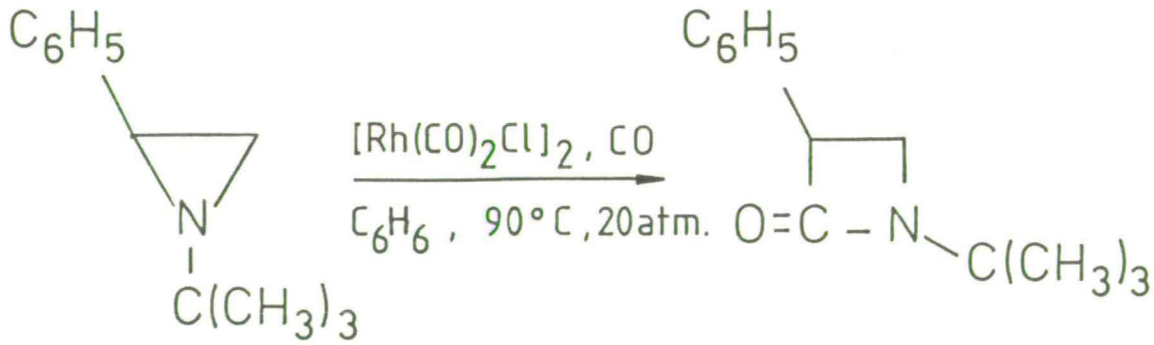
(101)

Evans *et al*[164] have successfully used 2-oxazolidinones, such as (101), as recyclable chiral auxiliaries which allow access to, for example, β-hydroxyacids or esters with excellent enantio- and diastereo-selectivity.

A review by Dyen and Swern covers the many syntheses, properties and applications of 2-oxazolidinones.[165] Traditional routes to these heterocyclic compounds involve the reactions of epoxides or β-haloalcohols with urea, or the reaction of β-amino-

alcohols with phosgene, urea, dialkylcarbonates or isocyanates. Disadvantages of this approach include inaccessibility of starting materials or the lack of regio- and stereo-specificity.

There exist few reports concerning the preparation of 2-oxazolidinones *via* the direct insertion of CO_2 into aziridines. Those methods which have been employed have limitations and 2-oxazolidinones are produced with varying degrees of success, unlike the successful β-lactam syntheses which result from the related insertion of CO into aziridines. Alper *et al*[166], for example, have reported that the treatment of 1-*tert*-butyl-2-phenylaziridine (102) with carbon monoxide in benzene, using a rhodium catalyst at 90°C and 20 atmospheres, affords the β-lactam (103) in quantitative yield (Scheme 70).



(102) (103)

Scheme 70

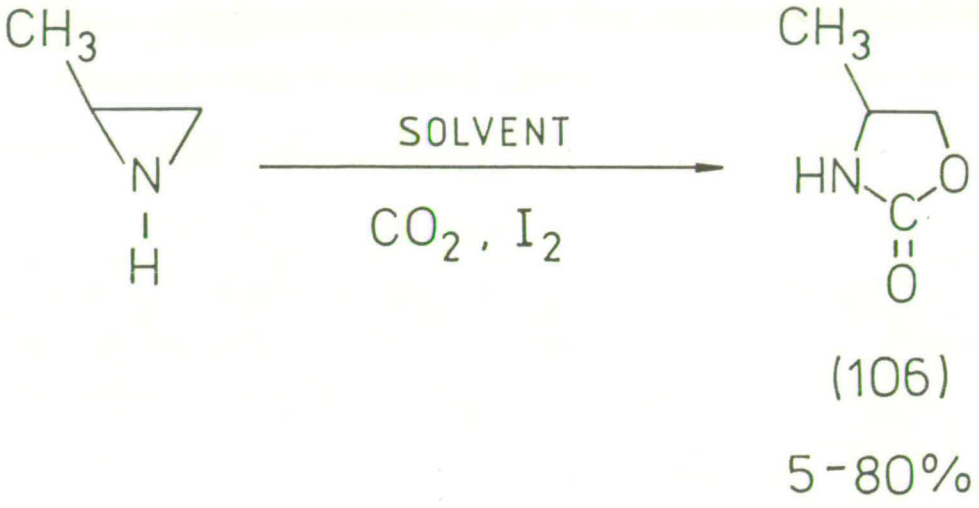
In 1970, Sineokov et al[167] reported that the conversion of aziridine (104) to 2-oxazolidinone (105) could be achieved in yields ranging from 40-80% by the reaction of (104) with CO_2, using a tetra-substituted ammonium halide catalyst (Scheme 71).

(104) (105)

Scheme 71

More recently, Ninagawa et al[168] discovered that the CO_2 insertion outlined in Scheme 71 can be accomplished in yields of 0 - 86% using an aprotic solvent such as HMPA with an organo-tin or organo-antimony catalyst at high pressure. Soga et al[169] have reported that 4-methyl-2-oxazolidinone (106) may be prepared through the reaction of propylenimine with CO_2 under pressure in the presence of iodine. Oxazolidinone yields are variable and are dictated by reactant

concentrations as well as the nature of the solvent[169] (Scheme 72).



(106)

5-80%

Scheme 72

The above CO_2-insertion techniques are blighted not only by the requirement for high temperatures and pressures, but by the formation of variable amounts of polyurethane copolymers. A further disadvantage which is encountered in the first two examples, is the competing formation of diarylpiperazines (107).

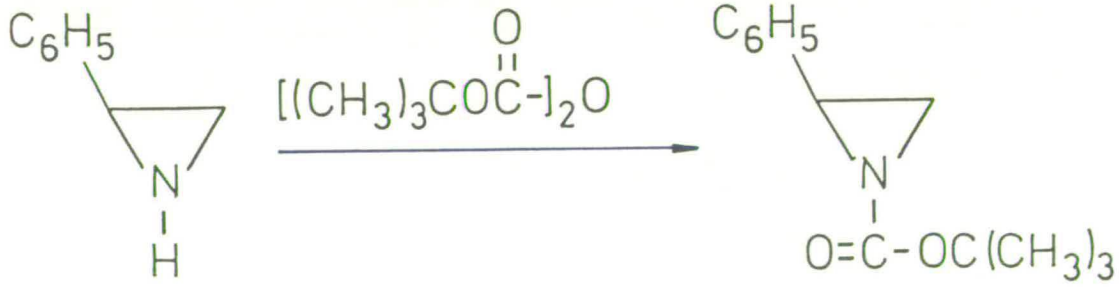
(107)

5 FVP of Other 1-Alkoxycarbonylaziridines

a. FVP of 1-tert-Butoxycarbonyl-2-phenylaziridine

Following the success of the pyrolytic conversion of 1-ethoxycarbonyl-2,3-diphenylaziridine to afford 5-phenyl-2-oxazolidinone and 4,5-diphenyl-2-oxazolidinones respectively, it was endeavoured to extend this process of "CO_2 insertion" to encompass other 1-alkoxycarbonylaziridines.

1-tert-butoxycarbonyl-2-phenylaziridine (108) was obtained through the reaction of 2-phenylaziridine with di-tert-butyl dicarbonate (Scheme 73).



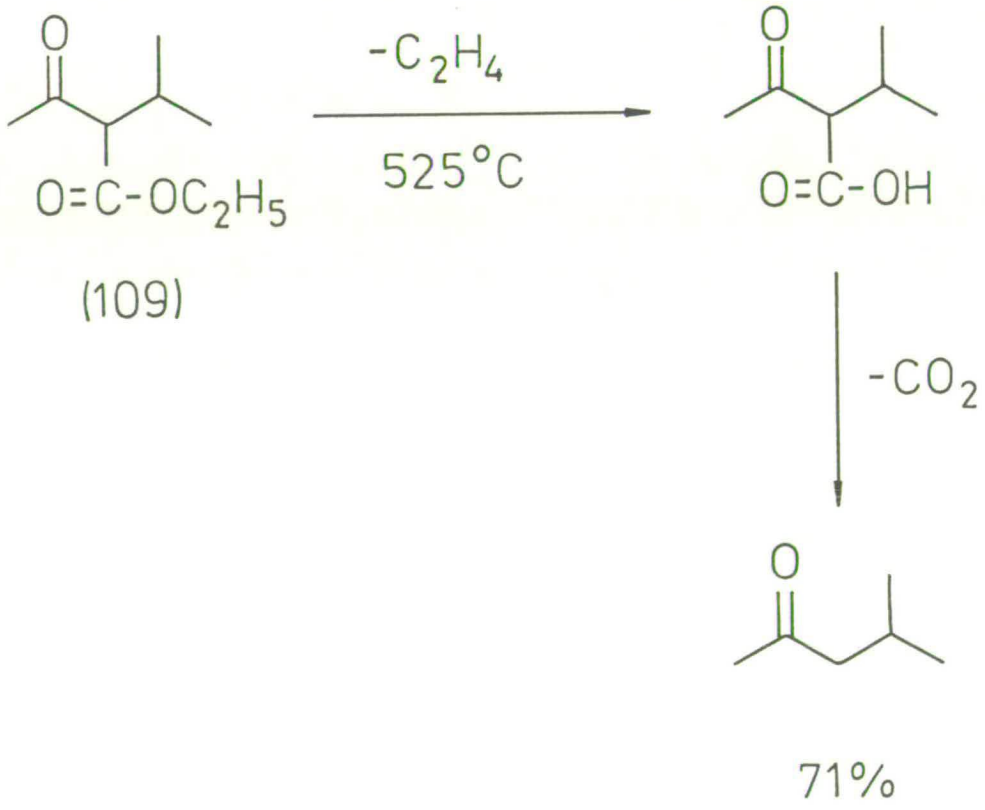
(108)

Scheme 73

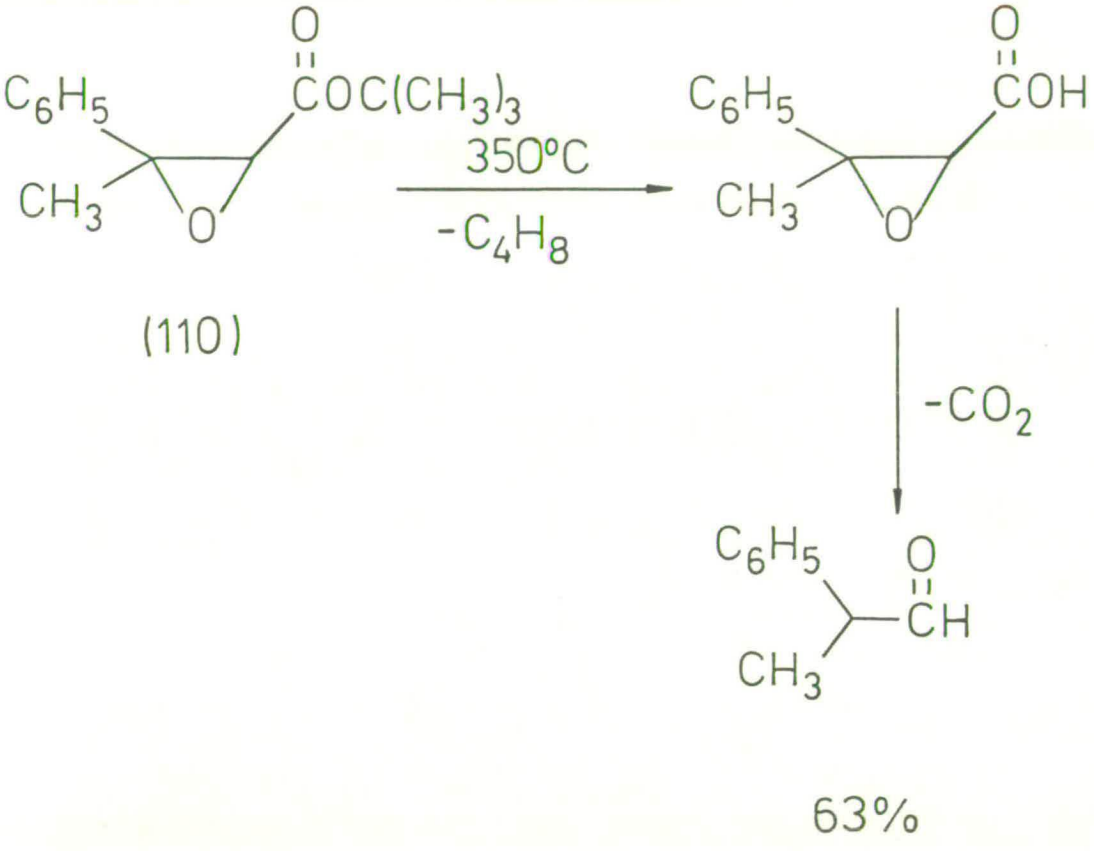
It was presumed that (108) would undergo pyrolytic conversion to give 5-phenyl-2-oxazolidinone (86) and

iso-butene in a similar manner to the transformation of 1-ethoxycarbonyl-2-phenylaziridine (36) to give (86) with elimination of ethene. Buchi et al[170] reported that a pyrolysis temperature of 525°C is required to induce the elimination of ethene from ethyl ester (109) (Scheme 74).

In comparison to this Bailey and co-workers[159,171] showed that elimination of iso-butene from the tert-butyl ester (110) requires pyrolysis at only 350°C under otherwise similar conditions (Scheme 75).



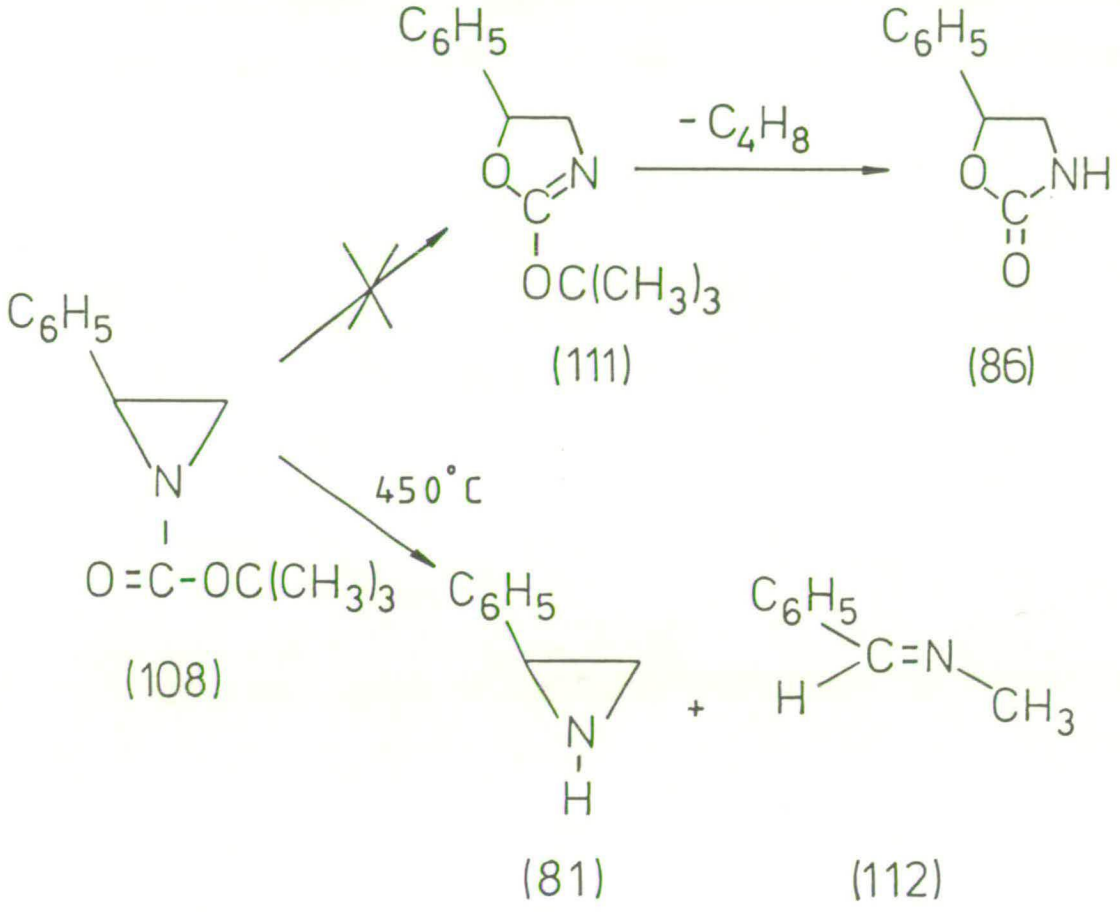
Scheme 74



Scheme 75

On the basis of the above information, it was assumed that the formation of oxazoline (111) followed by the elimination of iso-butene would occur at a relatively low temperature. Pyrolysis of (108) at 450°C afforded only a mixture of starting material (33%) and 2-phenylaziridine (67%), but pyrolysis at 500 and 650°C produced mixtures of 2-phenylaziridine (81) and N-phenylmethylene methanamine (112). None of the anticipated oxazoline

(111) or 5-phenyl-2-oxazolidinone (86) was obtained (Scheme 76).



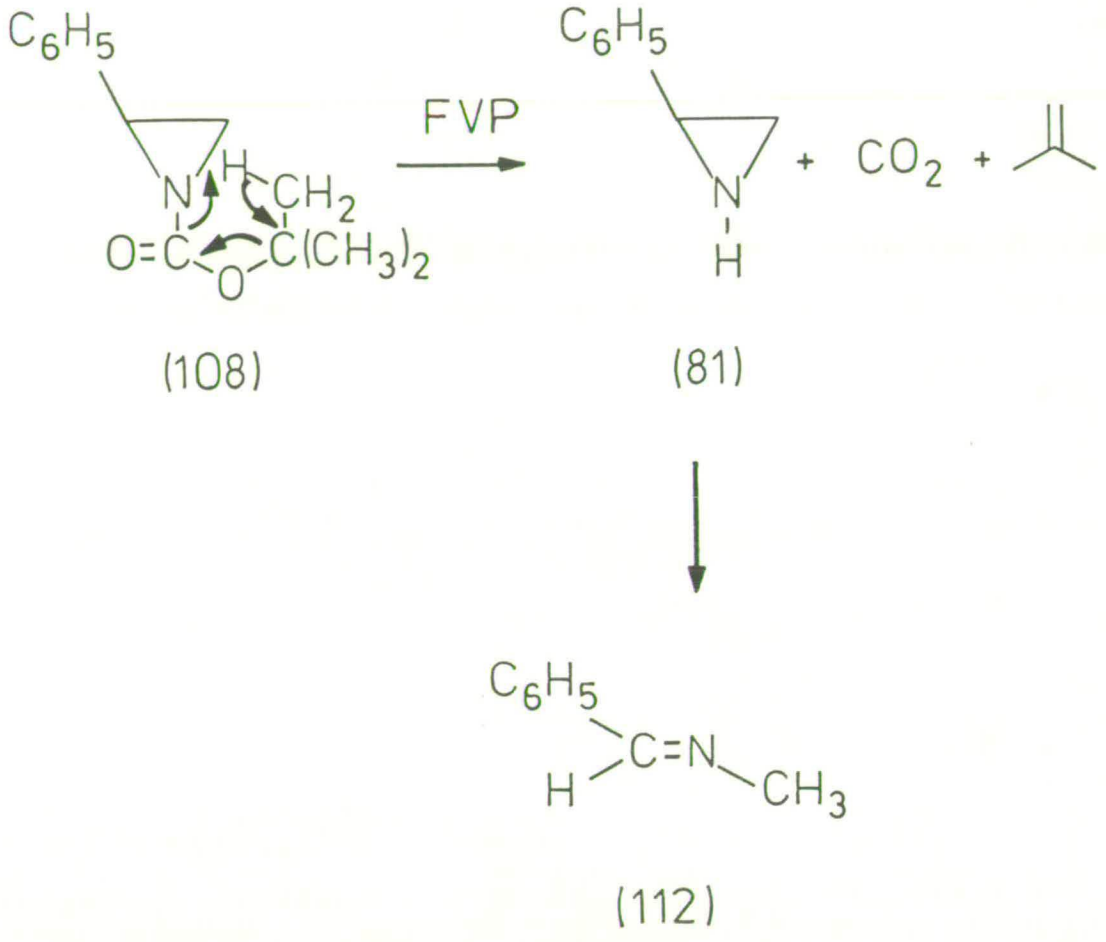
Scheme 76

Pyrolysis of 2-phenylaziridine (81) through a furnace at 650°C resulted in its partial isomerisation to N-phenylmethylene methanamine (112) (Scheme 77).

(81) (112)

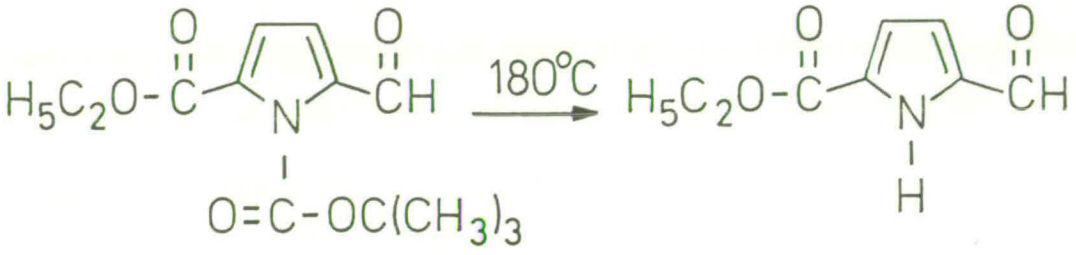
Scheme 77

The formation of (112) during pyrolysis of 1-tert-butoxycarbonyl-2-phenylaziridine (108) can thus be explained by loss of the nitrogen-substituent to give (81) followed by the partial rearrangement of the latter to give N-phenylmethylene methanamine (112). Since 2-phenylaziridine and N-phenylmethylene methanamine were the only products isolated from the pyrolysis, it is assumed that the loss of the tert-butoxycarbonyl group is due to its thermal decomposition to gaseous compounds. The mechanism outlined in Scheme 78 indicates that these gaseous products are likely to be iso-butene and carbon dioxide.



Scheme 78

Cava et al[172] have shown that the N-tert-butoxycarbonyl (BOC) group on indoles and pyrroles can be removed cleanly and in high yield by simple, neat thermolysis at 180°C (Scheme 79). Acid and base hydrolysis of the substituent was found to be inadequate and inconsistent.



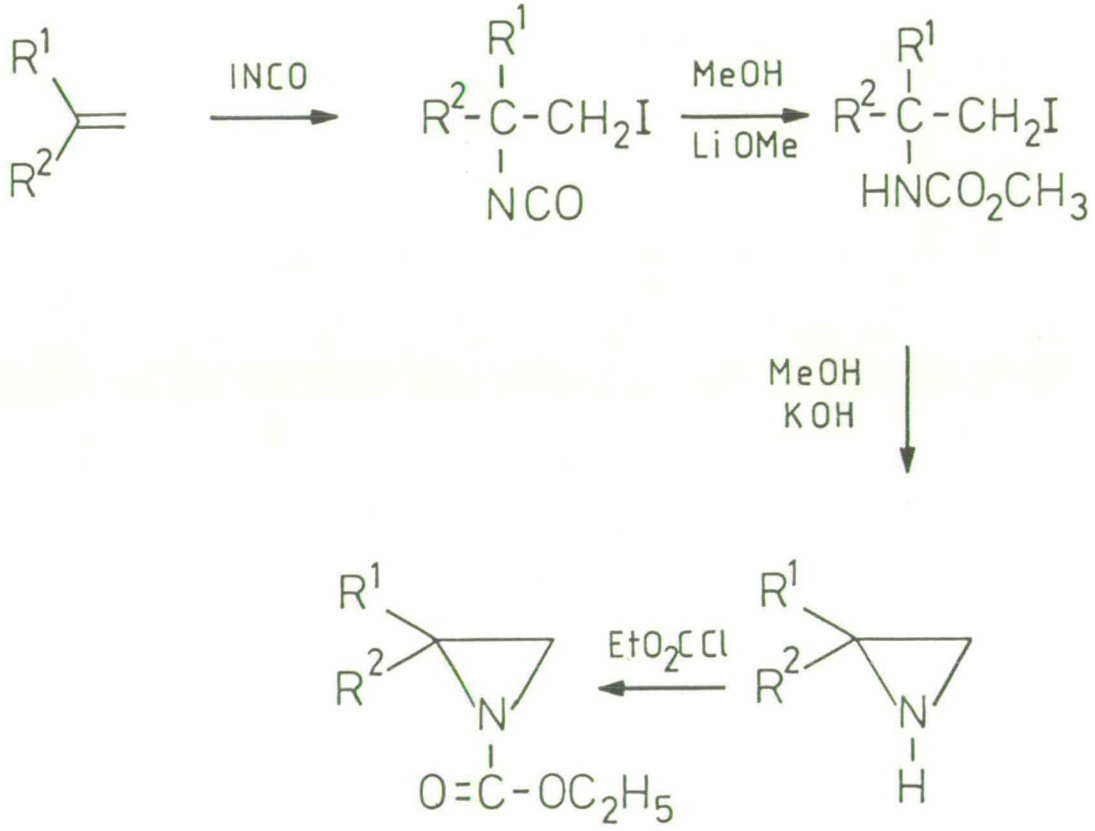
Scheme 79

Wasserman *et al*[173,174] have reported the similar thermolytic removal of the *N*-*tert*-butoxycarbonyl group from secondary aliphatic amines in boiling diphenyl ether.

The BOC group is commonly used as a protecting species in amino acid chemistry. Its removal is usually effected with trifluoroacetic acid or sodium ethoxide which may endanger other functional groups that are present in the system. It follows from this that the thermolytic removal of the BOC group may prove useful in amino acid chemistry. In addition to this, the present work has shown that the BOC group provides a convenient protecting group for aziridines. The group is easily introduced and can be removed thermally, eliminating the requirement for acid or basic conditions which may destroy the aziridine ring.

b. FVP of 1-Ethoxycarbonyl-2,2-diphenylaziridine and 1-Ethoxycarbonyl-2-tert-butylaziridine

1-Ethoxycarbonyl-2,2-diphenylaziridine (113) and 1-ethoxycarbonyl-2-tert-butylaziridine (114) were prepared from 1,1-diphenylethene and 3,3-dimethylbut-1-ene respectively via the route outlined in Scheme 80.

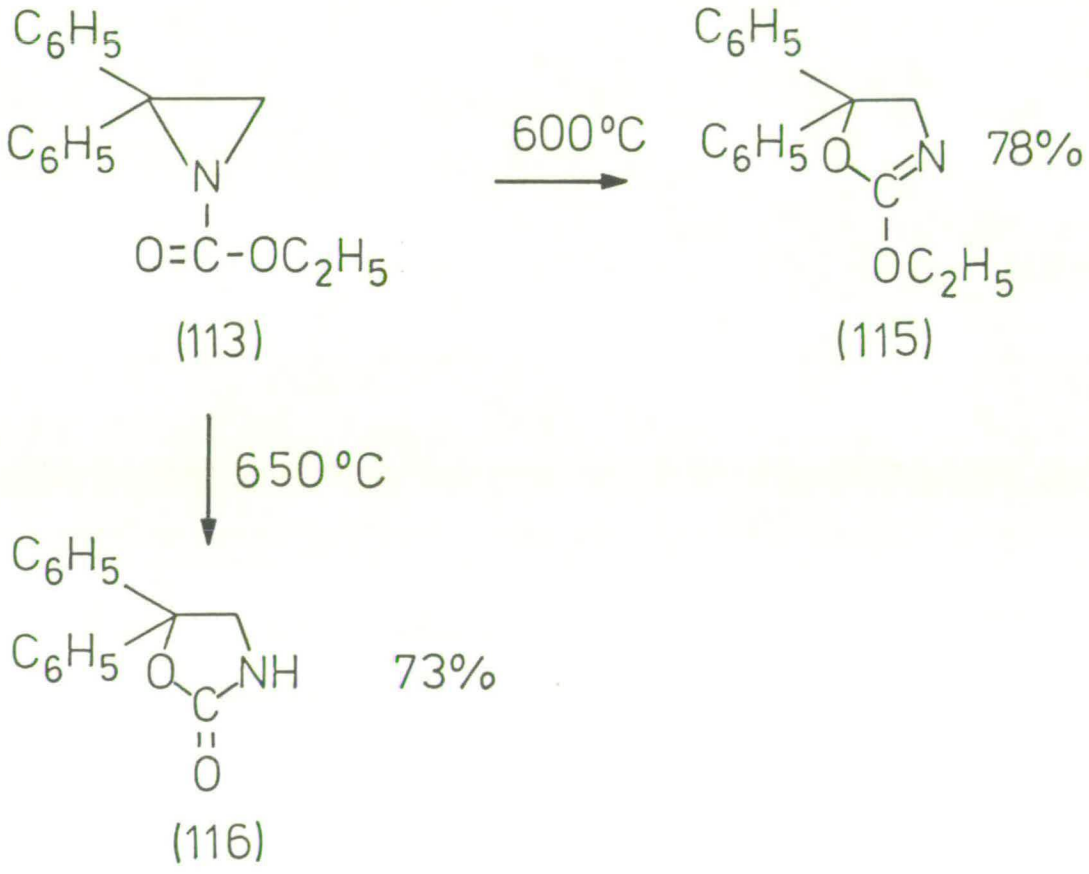


$R^1 = R^2 = C_6H_5$ (113)

$R^1 = H, R^2 = C(CH_3)_3$ (114)

Scheme 80

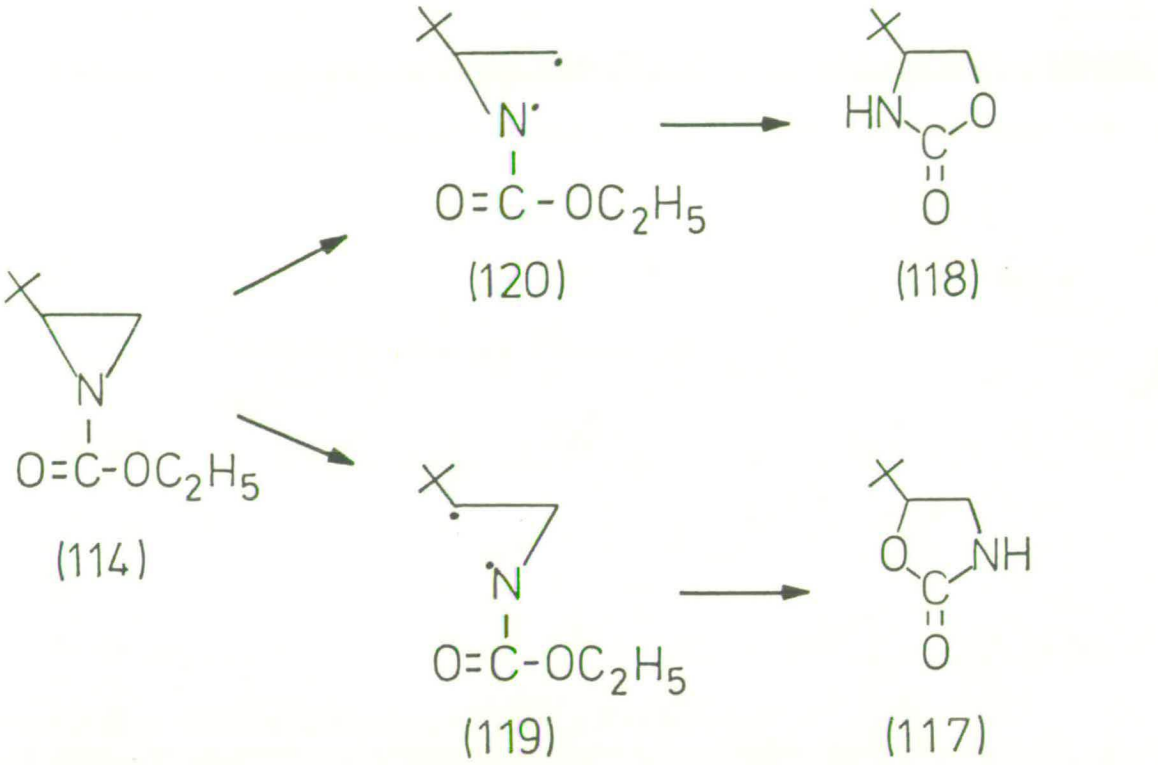
Pyrolysis of (113) through a furnace at 600°C afforded a 78% yield of 5,5-diphenyl-4,5-dihydro-2-ethoxyoxazole (115) which was contaminated with some polymeric material and traces of 5,5'-diphenyl-2-oxazolidinone (116). Pyrolysis at 650°C produced (116) (73%) the remainder of the product being an insoluble, colourless polymer (Scheme 81).



Scheme 81

Pyrolysis of (114) at 650°C afforded a 46% chemical yield of 5-tert-butyl-2-oxazolidinone (117) and 4-tert-butyl-2-oxazolidinone (118) in a ratio 37:10 (by n.m.r.). Attempts to separate the two isomers by column chromatography and thin-layer chromatography failed due

to the similarity of the R_f values.



(118):(117) = 10:37

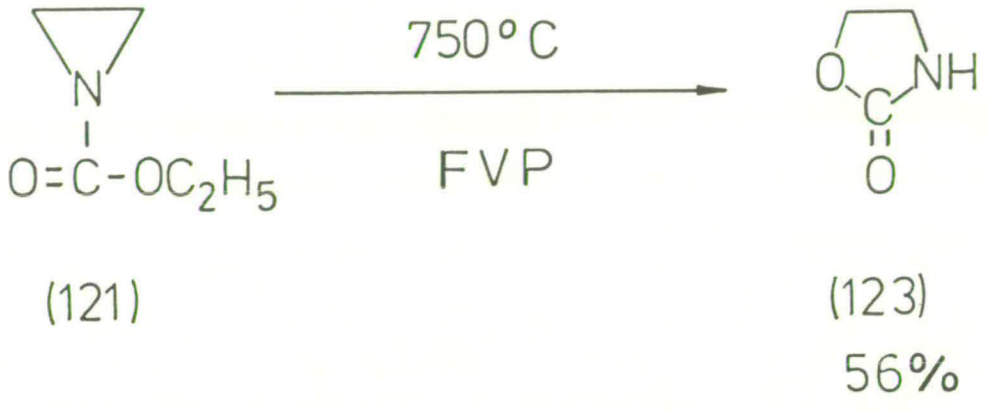
Scheme 82

Unlike previous examples, pyrolysis of 1-ethoxycarbonyl-2-tert-butylaziridine proceeds with regioselectivity rather than regiospecificity, showing that competition exists between the breaking of the N-C(2) bond and the N-C(3) bond. The composition of this mixture of 2-oxazolidinones shown in Scheme 82 can be explained by the stabilising effect of the tert-butyl substituent making intermediate (119) predominant. However, the stabilising effect of the 2-tert-butyl

substituent is not as marked as the stabilising power of the 2-phenyl substituent during the pyrolysis of 1-ethoxycarbonyl-2-phenylaziridine, where only 5-phenyl-2-oxazolidinone (86) is formed.

C. FVP of 1-Ethoxycarbonylaziridine and 1-Ethoxycarbonyl-2-methylazirdine

1-Ethoxycarbonylaziridine (121) and 1-ethoxycarbonyl-2-methylaziridine (122) were prepared, in quantitative yields, through the respective reactions of commercially available ethylenimine and propylenimine with ethyl chloroformate. Pyrolysis of (121) at temperatures below 750°C resulted in small yields (16%) of 2-oxazolidinone (123) with good recovery of starting material. Pyrolysis at 750°C afforded (123) in a 56% yield as a colourless, crystalline solid in the trap head. The oily substance which formed in the trap well was identified as residual starting material (Scheme 83).

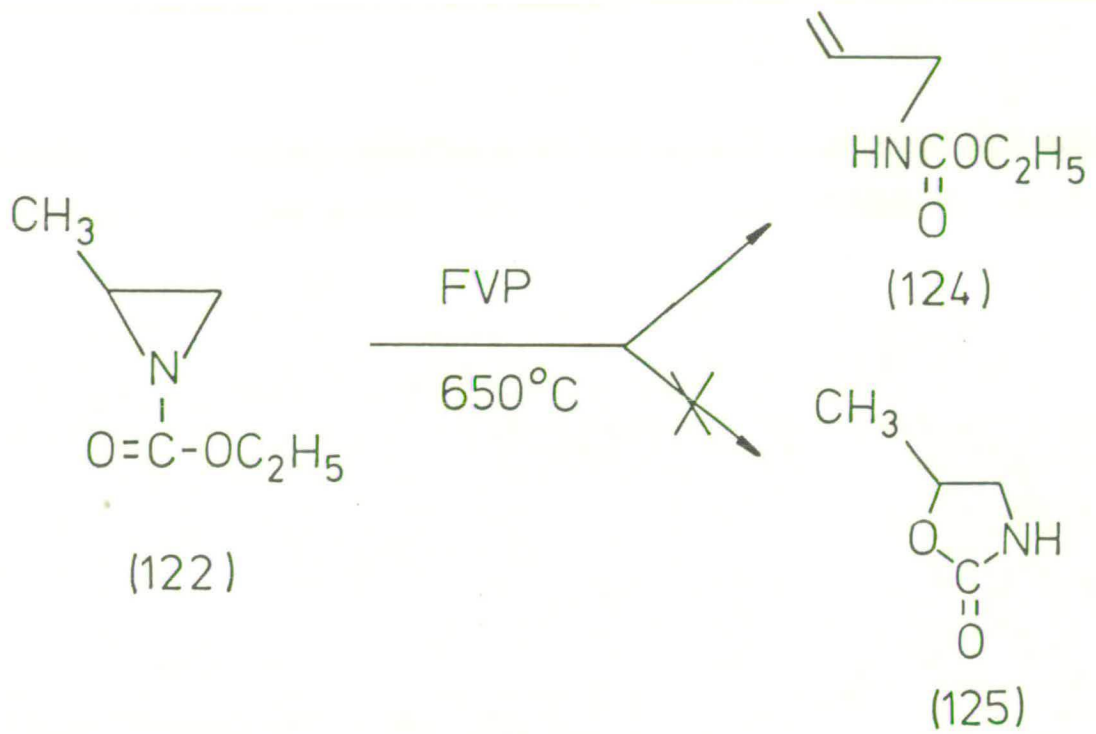


(121) (123) 56%

Scheme 83

Repetition of the pyrolysis using a furnace temperature of 800°C resulted in a yield of only 24% (123). The remainder of the product was obtained as a gummy, polymeric residue which probably resulted from decomposition of 2-oxazolidinone to give ethylenimine and CO_2, followed by polymerisation of the aziridine.

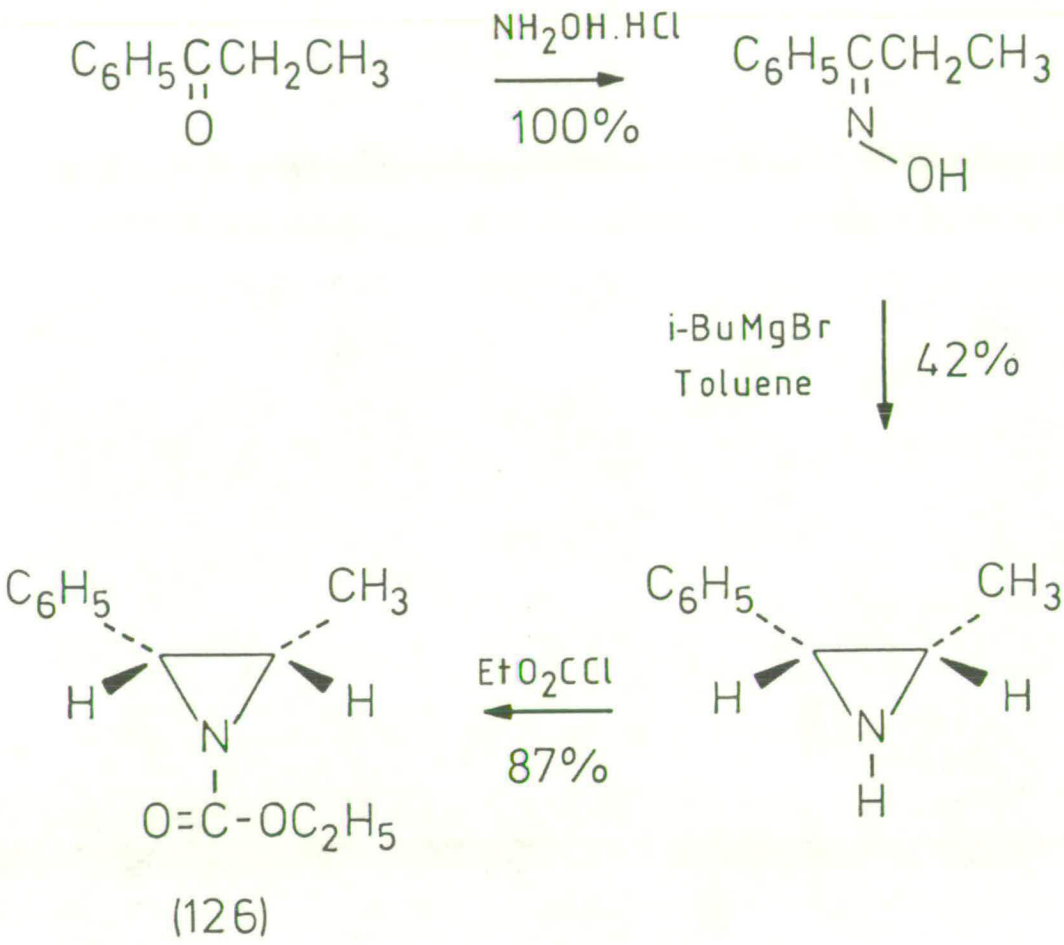
1-Ethoxycarbonyl-2-methylaziridine (122) bears protons at the α-position of the 2-alkyl group. Scheme 84 shows that thermal isomerism of this aziridine is likely to provide ethyl-2-propenylcarbamate (124). It was proposed that pyrolytic conditions may furnish 5-methyl-2-oxazolidinone (125). However, pyrolysis of (122) afforded a quantitative yield of (124) at 650°C (Scheme 84).



Scheme 84

d) FVP of 1-Ethoxycarbonyl-2-phenyl-3-methylaziridine

In order to study the competition of 2-oxazolidinone and allyl carbamate formation in more detail, cis-1-ethoxycarbonyl-2-phenyl-3-methylaziridine (126) was prepared from propiophenone via the Hoch-Campbell synthesis outlined in Scheme 85.

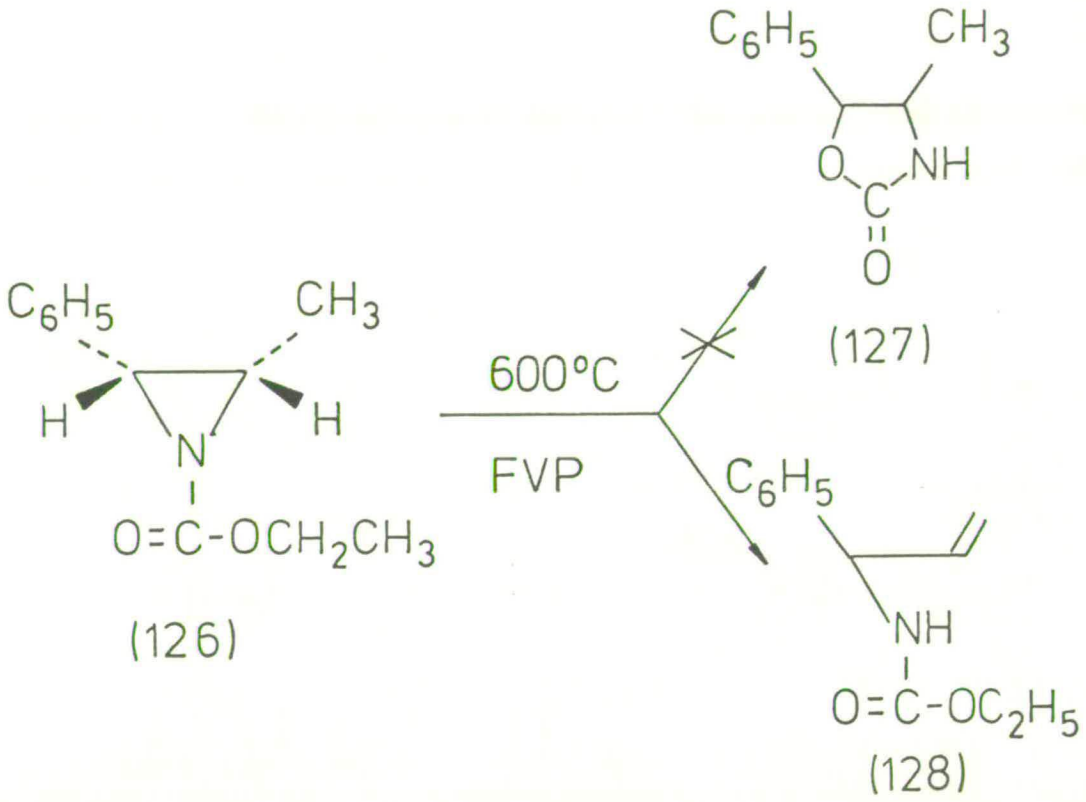


(126)

Scheme 85

It was postulated that pyrolysis of (126) might lead to a mixture of 4-methyl-5-phenyl-2-oxazolidinone (127) and ethyl-1-phenyl-2-propenylcarbamate (128). Pyrolysis of aziridine (126) at 600°C produced total conversion to allyl carbamate (128). This particular rearrangement has already been reported by Laurent et al[84], where the transformation was brought about by thermolysis at

200°C (Scheme 86).



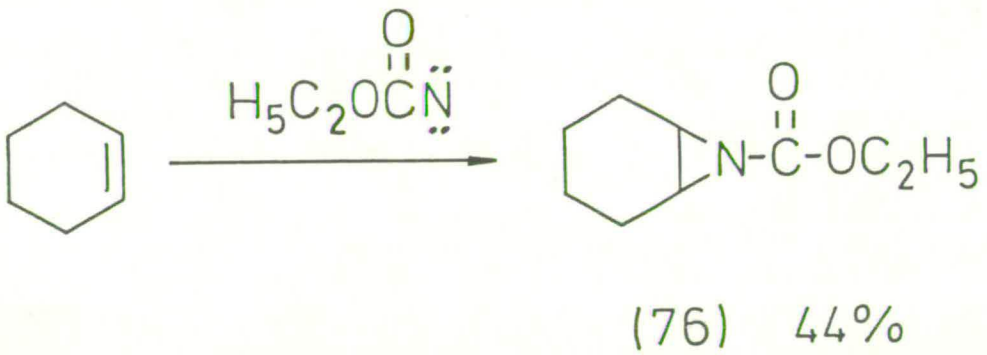
Scheme 86

e. FVP of 7-Ethoxycarbonyl-7-azabicyclo[4.1.0]heptane

Lwowski et al have already demonstrated that the thermal isomerisation of certain 1-ethoxycarbonyl-aziridines to the corresponding allyl carbamate may be difficult in situations where steric factors prevent bond formation between the carbonyl oxygen and the proton of the alkyl group.[53,156] Such an occurrence is exhibited in the thermal rearrangement of 7-ethoxycarbonyl-7-

azabicyclo-[4.1.0]-heptane (76). Lwowski et al reported that g.l.c. conditions partially converted aziridine (76) to the isomeric cis-4,5-cyclohexano-4,5-dihydro-2-ethoxyoxazole (77) as shown in Scheme 48.

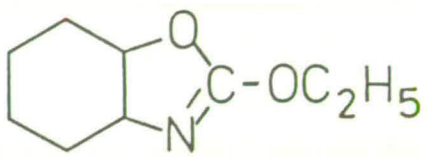
Aziridine (76) was prepared through the reaction of ethoxycarbonylnitrene with cyclohexene, as indicated in Scheme 87.



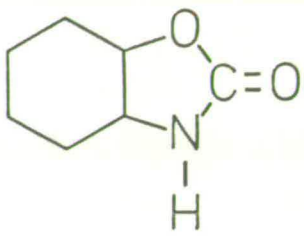
(76) 44%

Scheme 87

Pyrolysis of aziridine (76) through a furnace at 550°C afforded only ethyl-3-cyclohexenylcarbamate (129), (25% yield) and starting material. Pyrolysis at 650°C afforded a small yield of a colourless, polymeric solid in the trap head and (129) as a pale yellow oil in the trap well. There was no evidence for the formation of oxazoline (77) or 2-oxazolidinone (130) in n.m.r. spectra of the product.

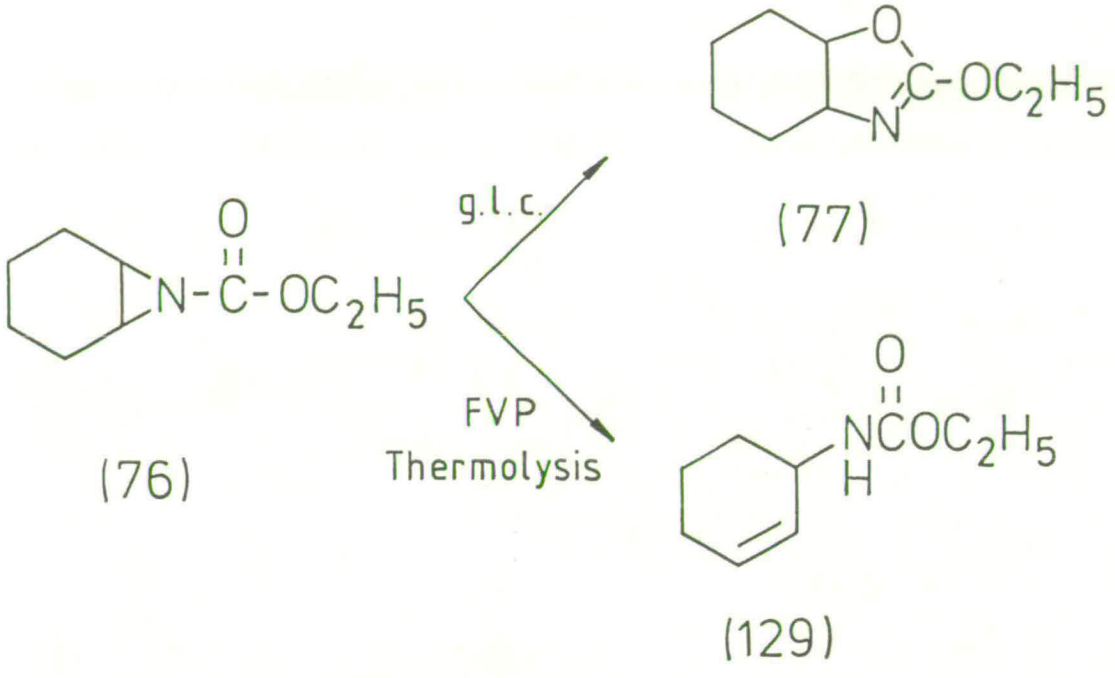


(77)



(130)

Thermolysis of neat (76) in a sealed tube at 180°C resulted in a 20% conversion to (129) after 24 hours. This result is in agreement with Lwowski's observation that neat thermolysis of (76) in a tube containing nichrome helices at 230°C resulted in a 16% conversion to (129) after two hours[175] (Scheme 88).

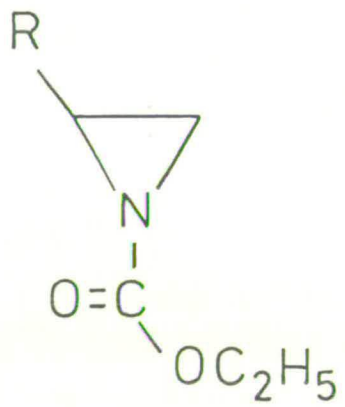


Scheme 88

It would appear, from the above results, that the pyrolytic conversion of 1-ethoxycarbonylaziridines to 2-oxazolidinones is only possible if the substituents on the aziridine ring carbon atoms are free of α-protons.

f. Preparation of Aziridines from Electrophilic Alkenes

Attempts were made to synthesise and pyrolyse 1-ethoxycarbonyl-2-phenylsulphonylaziridine (130) and 1-ethoxycarbonyl-2-methoxycarbonylaziridine (131) from phenyl vinyl sulphone and methyl acrylate respectively.



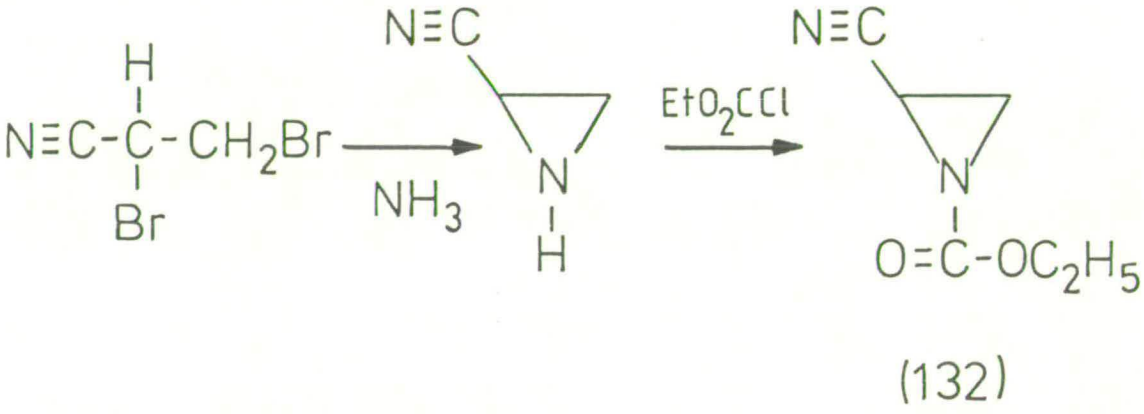
R = $PhSO_2$- (130)

R = MeO_2C- (131)

Unfortunately, most available aziridine syntheses involve, as a first step, the addition of an electrophile such as iodine isocyanate or ethoxycarbonylnitrene to the alkene. In the case of both phenyl vinyl sulphone and methyl acrylate, the alkenes themselves are electrophiles and all attempts to synthesise (130) and (131) failed.

g. FVP of 1-Ethoxycarbonyl-2-cyanoaziridine

Crude 1-ethoxycarbonyl-2-cyanoaziridine (132) was prepared, in poor yield, from 2,3-dibromopropionitrile *via* the route outlined in Scheme 89.



(132)

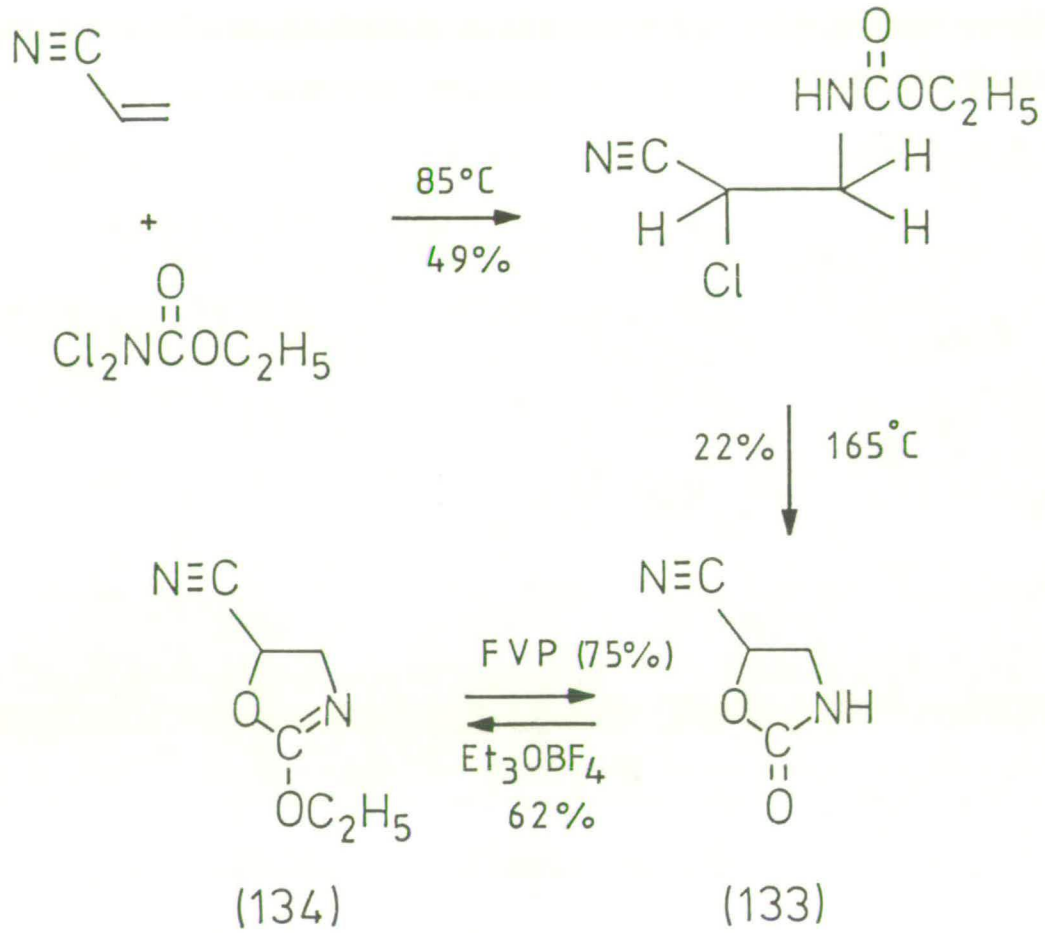
Scheme 89

Successful pyrolytic conversion into 5-cyano-2-oxazolidinone would provide a compound in which the substituent could be successfully modified.

Pyrolysis of 1-ethoxycarbonyl-2-cyanoaziridine at 650°C afforded only a yellow insoluble glass. Pyrolysis at 550°C produced a mixture of an insoluble glass and a colourless oil at the trap head. The oil was shown to consist mainly of the impurity which was originally contained in the starting material together with traces of (132). No 5-cyano-2-oxazolidinone (133) or 5-cyano-4,5-dihydro-2-ethoxyoxazole (134) were present.

An authentic sample of (133) was obtained by the

method of Swern et al[112-114], outlined in Scheme 90.



Scheme 90

5-Cyano-4,5-dihydro-2-ethoxyoxazole (134) was prepared by reacting (133) with Meerwein's reagent. Subsequent pyrolysis of (133) at 650°C gave (134) in 75% yield indicating that, in the case of the pyrolysis of 1-ethoxycarbonyl-2-cyanoaziridine, the ring expansion

step appears to have failed. This may be due to the fact that the aziridine was impure, causing polymerisation to occur.

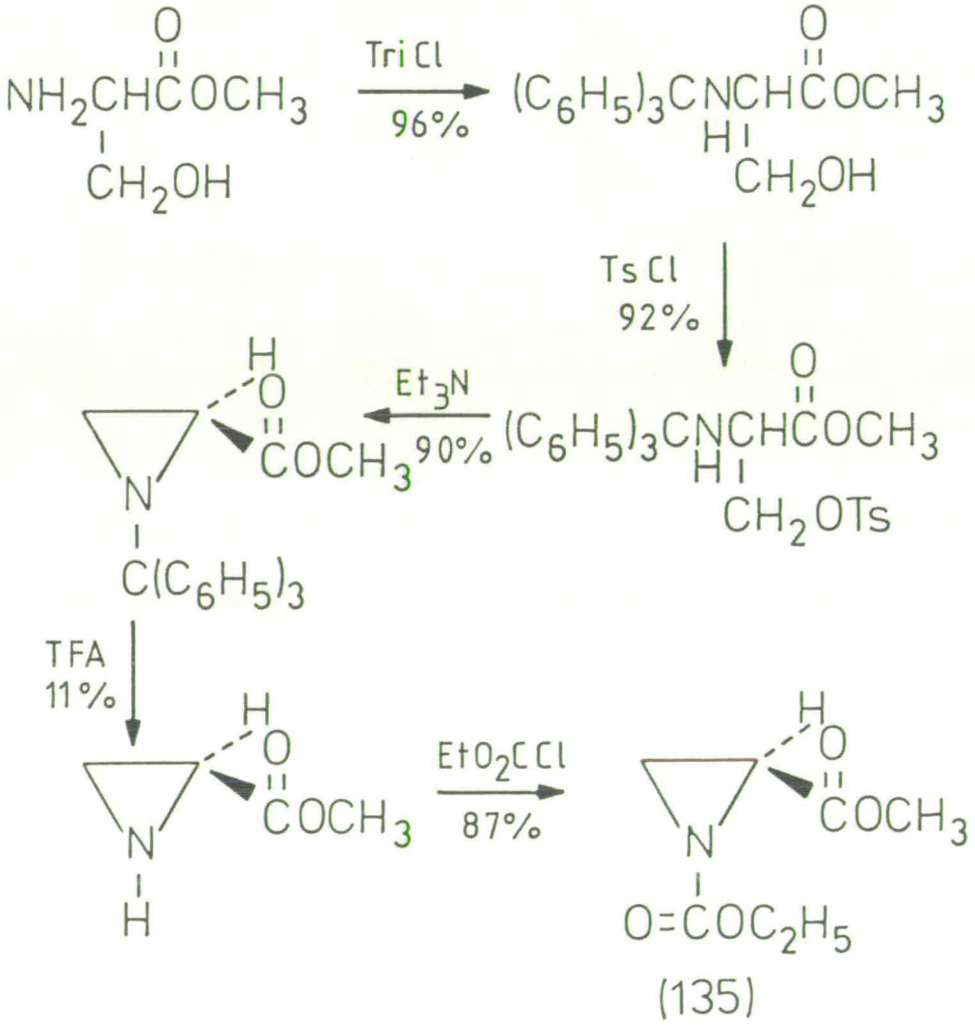
Limitation of time prevented further research into this topic. There is obviously a need to synthesise pure 1-ethoxycarbonyl-2-cyanoaziridine in order to study the possibility of it undergoing pyrolytic ring expansion to give 5-cyano-4,5-dihydro-2-ethoxyoxazole.

H. FVP of 1-Ethoxycarbonyl-(2S)-methoxycarbonyl aziridine

The importance of asymmetric synthesis has been discussed in earlier chapters. In view of the importance of optically active compounds, it would seem worthwhile to attempt the synthesis of optically active 2-oxazolidinones by pyrolysis of optically active 1-ethoxycarbonylaziridines. The previously mentioned preparation of both *cis*- and *trans*-4,5-diphenyl-2-oxazolidinone from *cis*-1-ethoxycarbonyl-2,3-diphenyl-aziridine suggests a ring-expansion mechanism whereby racemisation of a chiral aziridine will occur (see Scheme 65). Few examples of chirally pure aziridines have been prepared, the most recent being 1-ethoxycarbonyl-(2S)-methoxycarbonylaziridine. This aziridine bears a C-substituent which is devoid of a proton in the

α-position to the ring carbon atom, thus ring expansion to give an oxazoline will be favoured during pyrolysis since an allyl carbamate cannot be formed (see Scheme 42).

1-Ethoxycarbonyl-(2S)-methoxycarbonylaziridine (135) was successfully obtained by the method of Baldwin et al[70] from the methyl ester of L-serine via the synthetic route outlined in Scheme 91.

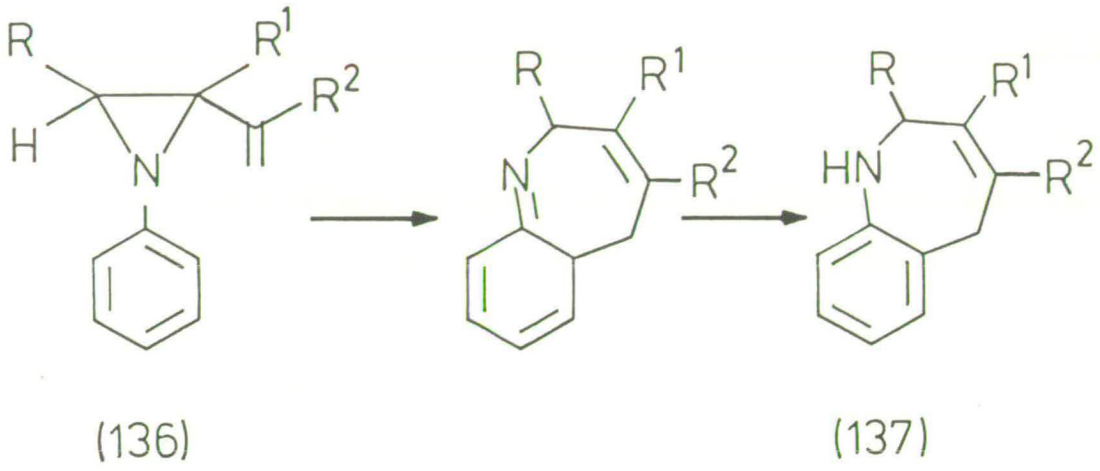


Scheme 91

An interesting detail within the above reaction scheme is the successful utilisation of trifluoroacetic acid (TFA) to effect the removal of the trityl protecting group. This is a solitary instance where an aziridine ring remains intact in the presence of an acid.

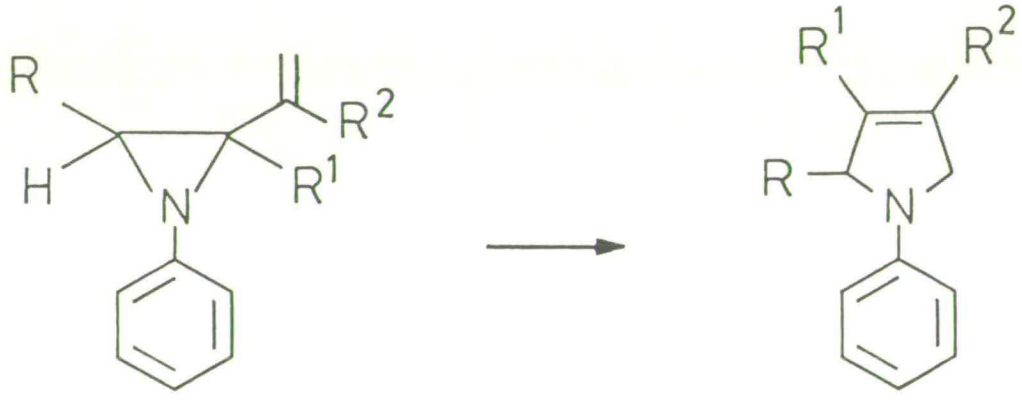
The pyrolytic rearrangement of optically active (135) promises to be of great interest. Should pyrolysis of the aziridine result in the formation of 5-methoxycarbonyl-2-oxazolidinone then, based on the result of pyrolysis of cis-1-ethoxycarbonyl-2,3-diphenyl-aziridine, optical activity is likely to be lost in the product.

In addition to this point of interest, the ring-carbon bears an unsaturated substituent. Rearrangement of this type of aziridine is known to occur, the reaction course depending on the geometry of the aziridine as well as its type. For example, thermolysis of aziridine (136) gives (137) (Scheme 92) in contrast to thermolysis of the isomeric aziridine (138) which gives 3-pyrroline (139)[142] (Scheme 93).



(136) (137)

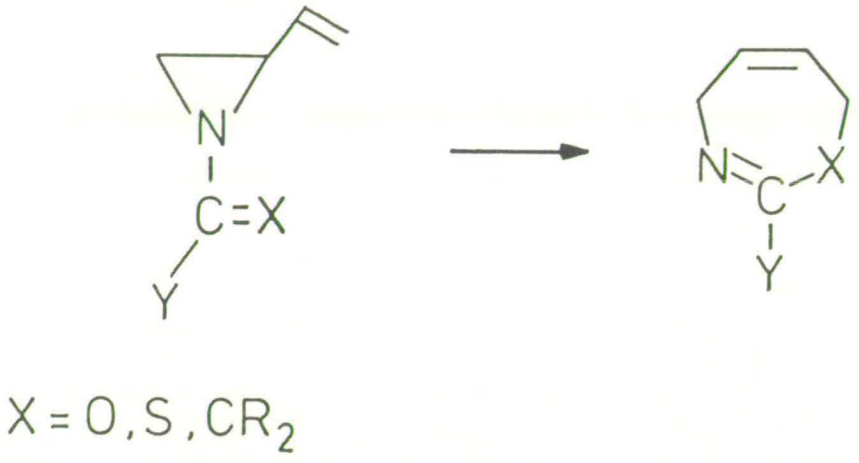
Scheme 92



(138) (139)

Scheme 93

Thermal Cope-type rearrangements between C-vinyl and unsaturated N-substituents are also known[176] (Scheme 94).



X = O, S, CR_2

Scheme 94

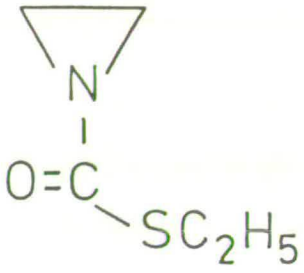
Early investigations into the pyrolysis of 1-ethoxycarbonyl-(2S)-methoxycarbonylaziridine indicate that a mixture of products is created. Further investigation into the rearrangement of this interesting system is required but limitation of time prevented this topic from being pursued further.

The stereochemistry of the 1-ethoxycarbonyl aziridine expansion to an oxazoline could be more conveniently studied using optically pure 1-ethoxycarbonyl-2-phenylaziridine. The formation of optically pure 2-phenylaziridines by Fujita *et al*[28] has already been discussed (see page 14). The reaction of optically active 2-phenylaziridine with ethyl chloroformate would provide a suitable aziridine with which to conduct stereochemical studies.

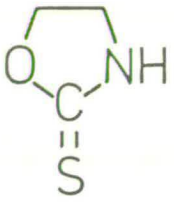
C. PREPARATION AND PYROLYSIS OF 1-THIOETHOXYCARBONYL-AZIRIDINE AND RELATED SYSTEMS

1. Introduction

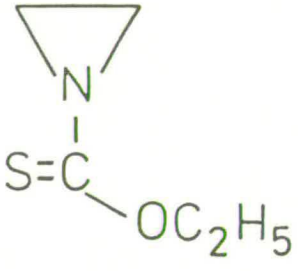
This section concerns itself with the synthesis and pyrolysis of two novel aziridines, namely 1-thioethoxycarbonylaziridine (140) and 1-ethoxythiocarbonylaziridine (141), for the purpose of determining if the pyrolytic conversion of 1-ethoxycarbonylaziridines to 2-oxazolidinones will hold for thio-analogues. This investigation should also serve to confirm the mechanistic theories postulated for the novel 2-oxazolidinone synthesis. The results obtained and the mechanism elucidated in the previous chapter would imply that only 2-oxazolidinthione (142) would be obtained from pyrolysis of aziridine (140), and pyrolysis of aziridine (141) should afford only 2-thiazolidinone (143). Mixtures of (142) and (143) from the pyrolysis of either aziridine would indicate a different reaction mechanism for the ring expansion than that indicated previously.



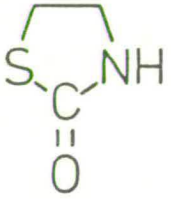
(140)



(142)



(141)

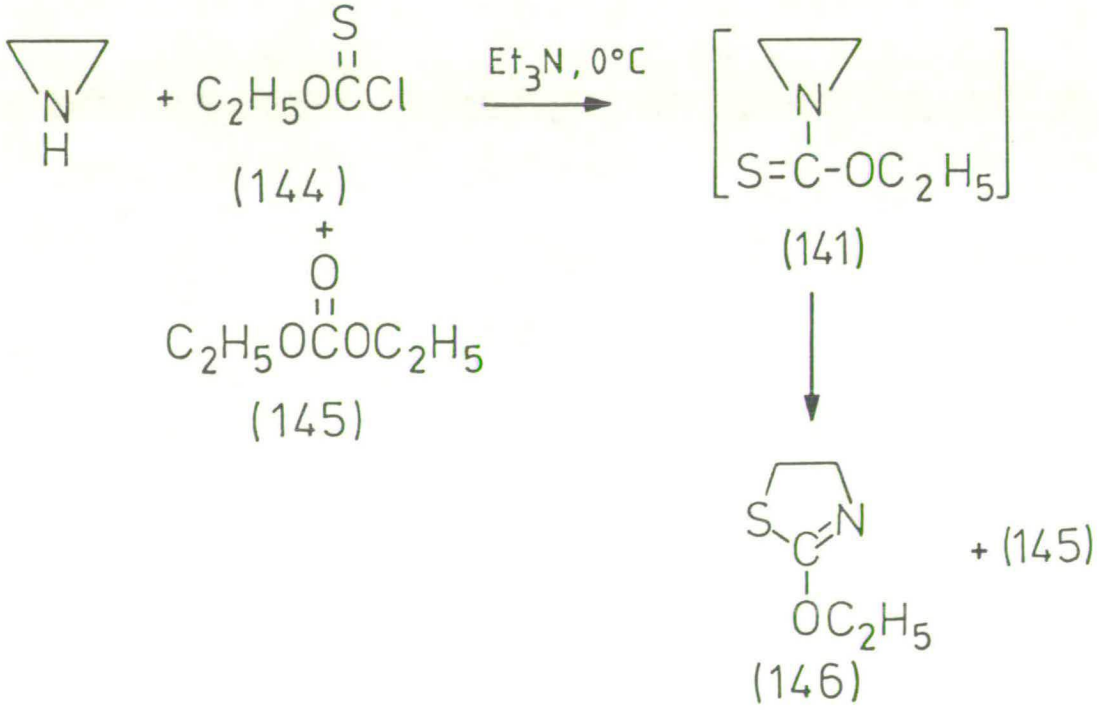


(143)

2. Preparation of 1-Thioethoxycarbonylaziridine and related compounds

(140) was readily available, in excellent yield, through the reaction of ethylenimine with commercially available S-ethylchlorothiolformate. Unfortunately, the preparation of (141) proved to be more difficult. The reaction of thiophosgene with sodium ethoxide gave a mixture of the desired O-ethylchlorothioformate (144) and O,O-diethylthiocarbonate (145). Due to the physical similarities of the two compounds, it was difficult to

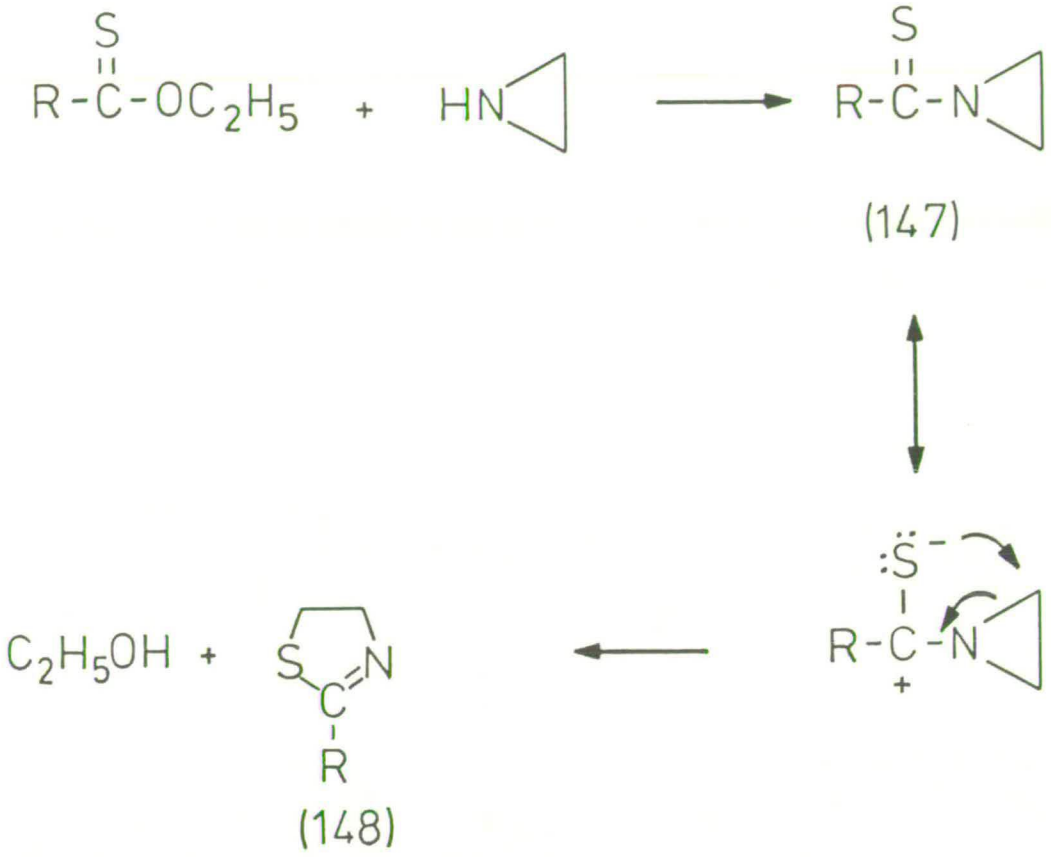
purify (144) completely by distillation.[177] The reaction of the crude O-ethylchlorothioformate with ethylenimine did not produce the expected 1-ethoxythiocarbonylaziridine. The ^1H n.m.r. spectrum of the resulting oil indicated the presence of residual O,O-diethylthiocarbonate and a single product which displayed the following spectrum : 4.16 (2H, q), 3.41 (2H, t), 3.13 (2H, t) and 1.17δ(3H, t). The ir spectrum revealed the absence of NH, OH, C=O and C=S, but a band at 1630 cm^{-1} was present which is typical of a C=N group. The above evidence together with other spectroscopic corroboration identified the product as 4,5-dihydro-2-ethoxythiazole (146) (Scheme 95).



Scheme 95

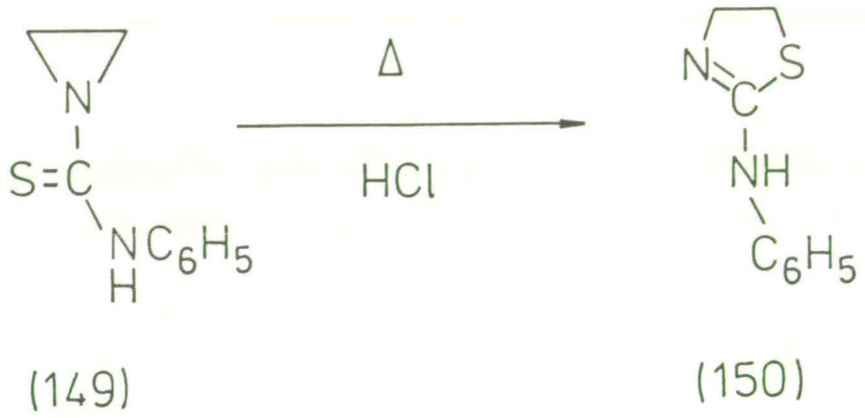
It is likely that the desired aziridine (141) was initially formed and immediate ring expansion occurred to give (146) even at room temperatures in the region of 0°C. These conditions are vastly different to the pyrolytic conditions required to accomplish the analogous conversion of 1-ethoxycarbonylaziridine to 2-oxazolidinone. This effect is most conveniently attributed to the greater nucleophilicity of the sulphur atom in (141) compared to the corresponding oxygen atom in 1-ethoxycarbonylaziridine.

Reynaud *et al*[178] have reported that the reaction of ethyl thio-esters with ethylenimine and propylenimine produces thiazoline (148) and ethanol instead of the expected aziridine (147). They state that, without doubt, the origin of this spontaneous rearrangement lies with the nucleophilicity of the sulphur (Scheme 96).



Scheme 96

In contast to this, Heine et al have reported that the conversion of aziridine (149) into ring-expanded product (150) requires concentrated acid and heat[179] (Scheme 97).

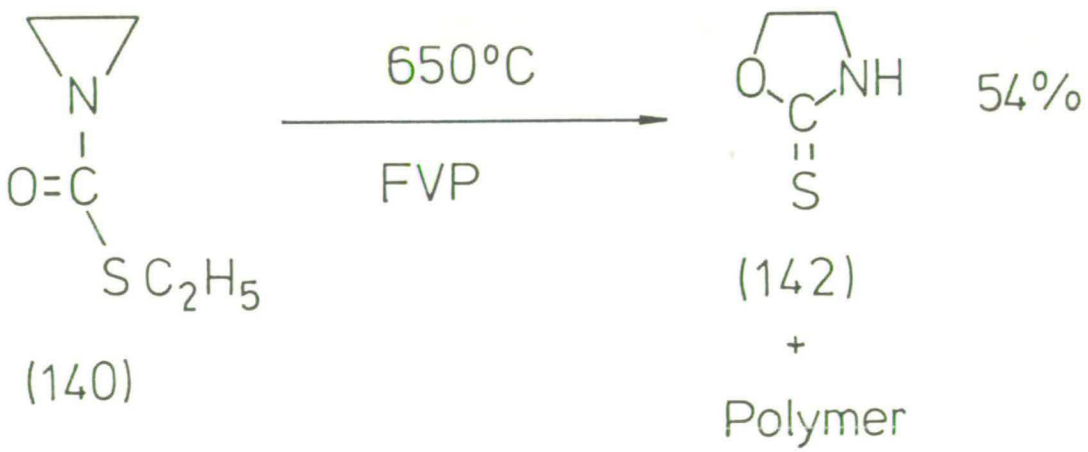


(149) (150)

Scheme 97

3. Pyrolysis of 1-Thioethoxycarbonylaziridine and 4,5-dihydro-2-ethoxythiazole

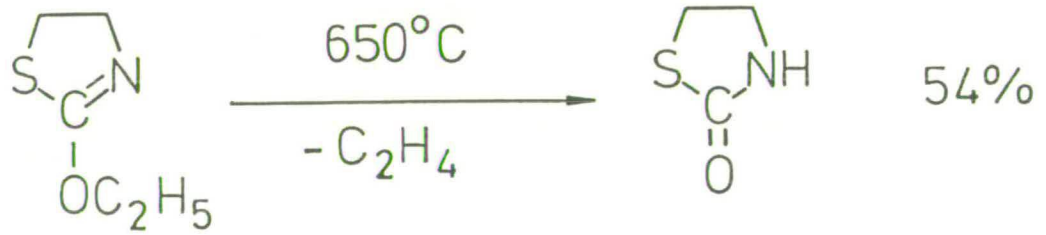
Pyrolysis of 1-thioethoxycarbonylaziridine (140) at 650°C gave 2-oxazolidinthione (142) contaminated with polymeric material (Scheme 98).



Scheme 98

The polymeric contaminant was easily removed from the main product by virtue of its relative insolubility, leaving pure 2-oxazolidinthione (54% yield). None of the isomeric 2-thiazolidinone (143) was produced, strengthening the case for the mechanism of the ring expansion reaction shown in Scheme 59.

Pyrolysis of 4,5-dihydro-2-ethoxythiazole (146) required a high inlet temperature, since the oil appeared to form a surface which prevents distillation of the reactant. The most favourable reaction conditions were obtained by heating the inlet to a temperature of 200°C with a good vacuum and a furnace temperature of 650°C. Under these conditions, 2-thiazolidinone (143) was obtained in a 54% yield after recrystallisation (Scheme 99).

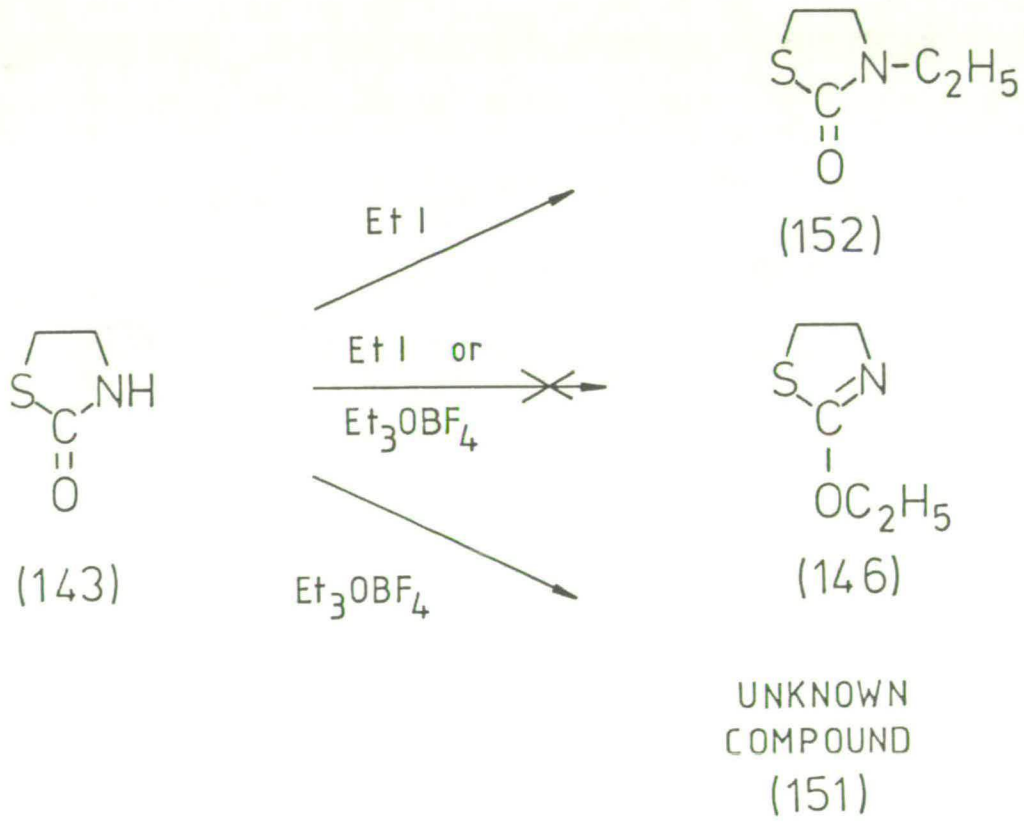


(146) (143)

Scheme 99

4. Alkylation of 2-Thiazolidinone

An attempt was made to synthesise a sample of 4,5-dihydro-2-ethoxythiazole (146) through the ethylation of 2-thiazolidinone (143) with Meerwein's reagent. The reaction gave an unidentified compound (151) which did not exhibit the spectroscopic characteristics displayed by (146). Ethylation of 2-thiazolidinone with ethyl iodide in the presence of potassium carbonate in dimethyl formamide (DMF) resulted in a 66% yield of 3-ethyl-2-thiazolidinone (152) (Scheme 100). The spectroscopic characteristics of (151), (152) and (146) are summarised in Table 3.



Scheme 100

Table 3

Spectroscopic Characteristics of Some

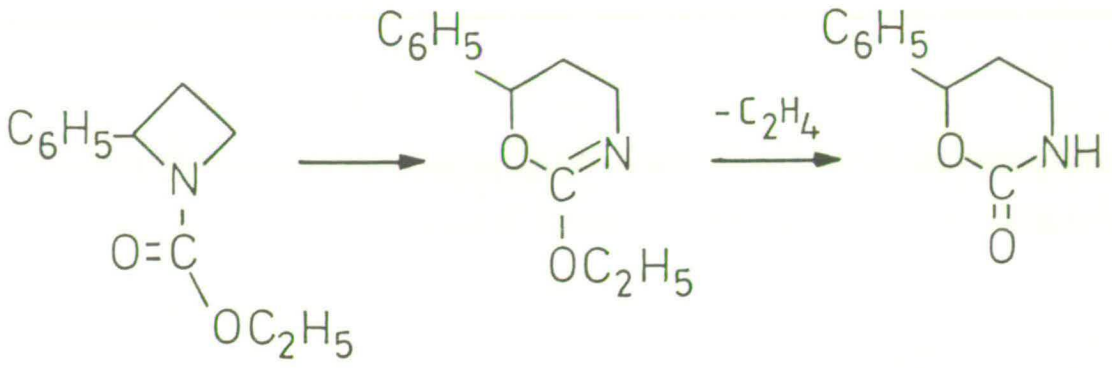
Ethylated 2-Thiazolidinones

	νmax (cm^{-1})	^{1}H (δ)	^{13}C (δ)
(146)	1630	4.16 (2H, q) 3.41 (2H, t) 3.13 (2H, t) 1.17 (3H, t)	156.66 (Cq) 63.43 (CH_2) 49.43 (CH_2) 31.45 (CH_2) 13.97 (CH_3)
(152)	1670	3.6 (2H, m) 3.3 (2H, q) 3.2 (2H, m) 1.09 (3H, t)	158.61 (Cq) 47.84 (CH_2) 39.41 (CH_2) 25.39 (CH_2) 12.37 (CH_3)
(151)	1630	4.14 (2H, q) 3.83 (2H, t) 3.26 (2H, t) 1.08 (3H, t)	167.27 (Cq) 66.12 (CH_2) 57.78 (CH_2) 34.92 (CH_2) 13.77 (CH_3)

D. PREPARATION AND PYROLYSIS OF 1-ETHOXYCARBONYL-2-PHENYLAZETIDINE

1. Introduction

This final chapter deals with the synthesis and pyrolysis of a 1-ethoxycarbonylazetidine. The purpose of this study being to see if the mimic reaction for the CO_2 insertion into aziridines, discussed in previous chapters, could be extended to the preparation of six-membered rings. No report exists in the field of azetidine chemistry of a ring expansion to a six-membered heterocycle which corresponds to the already described isomerisation of suitably substituted aziridines to give five-membered heterocycles. Should this ring expansion of azetidines be possible, then this would prove to be a useful route to various six-membered heterocyclic rings. The feasibility of this novel rearrangement was to be explored by studying the pyrolysis of 1-ethoxycarbonyl-2-phenylazetidine (153). Successful ring expansion of (153) should give oxazine (154) which should provide 1,3-oxazin-2-one (155) after elimination of ethene (Scheme 101).

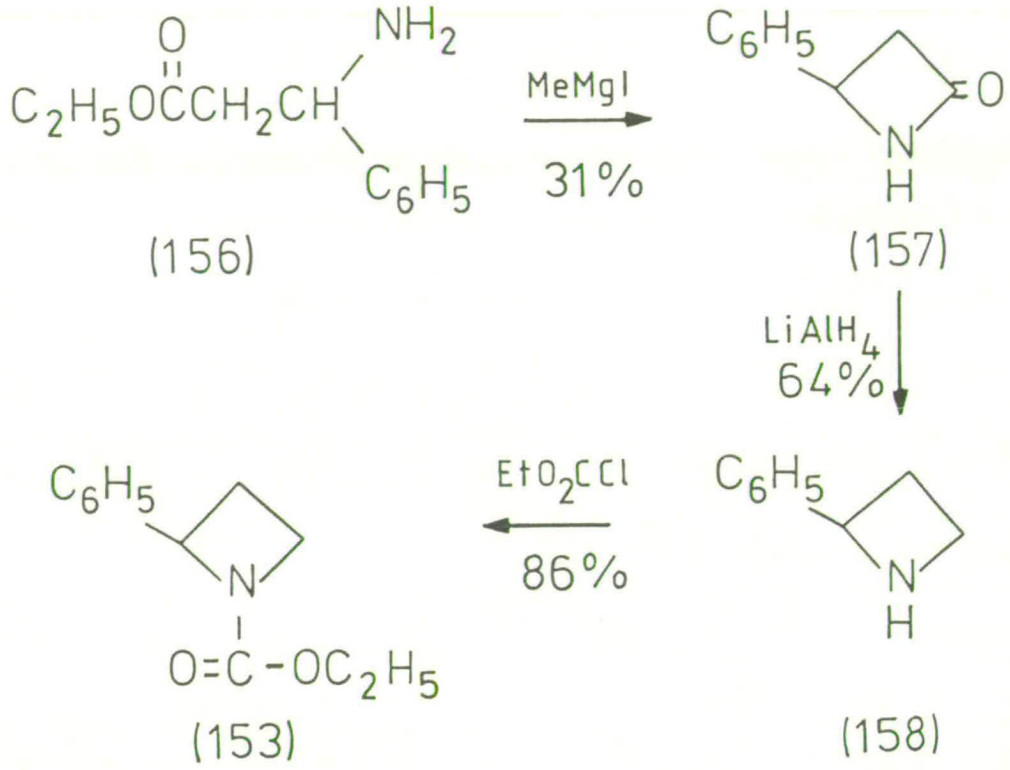


(153) (154) (155)

Scheme 101

2. Preparation of 1-Ethoxycarbonyl-2-phenylazetidine

The synthesis of (153) was achieved by the method outlined in Scheme 102. Ethyl-3-amino-3-phenylpropionate (156) was obtained in 57% yield by esterification of the commercially available acid. (156) was cyclised in the presence of excess methyl magnesium iodide to give 4-phenyl-2-azetidinone (157) in 31% yield. Reduction of this β-lactam afforded 2-phenylazetidine (158) (64%). This azetidine must be handled quickly and carefully under a nitrogen atmosphere since it is a strong base and rapidly reacts with atmospheric CO_2. Reaction of (158) with ethyl chloroformate provided 1-ethoxycarbonyl-2-phenylazetidine.(153)

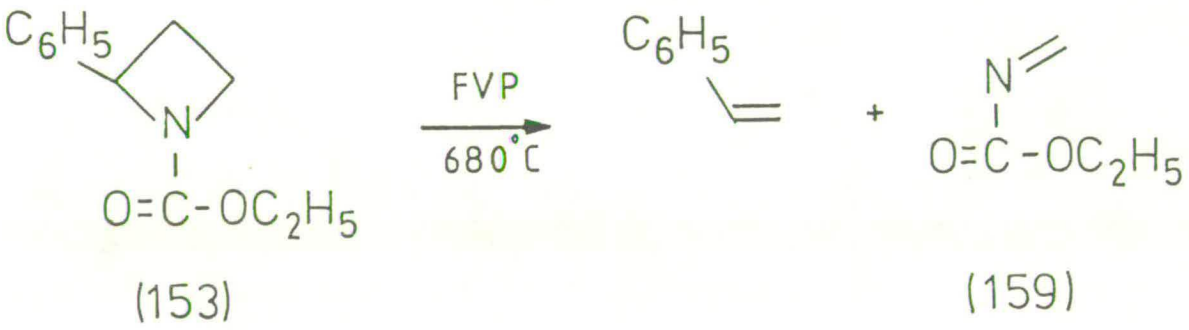


Scheme 102

3. Pyrolysis of 1-Ethoxycarbonyl-2-phenylazetidine

Pyrolysis of (153) at 680°C followed by analysis of the products by ^{1}H n.m.r. in the usual manner indicated the presence of styrene with traces of starting material. Clearly the speculated ring expansion followed by elimination of ethene depicted in Scheme 101 had not been realised. The pyrolysis was repeated with the modification that deuteriochloroform was added to the

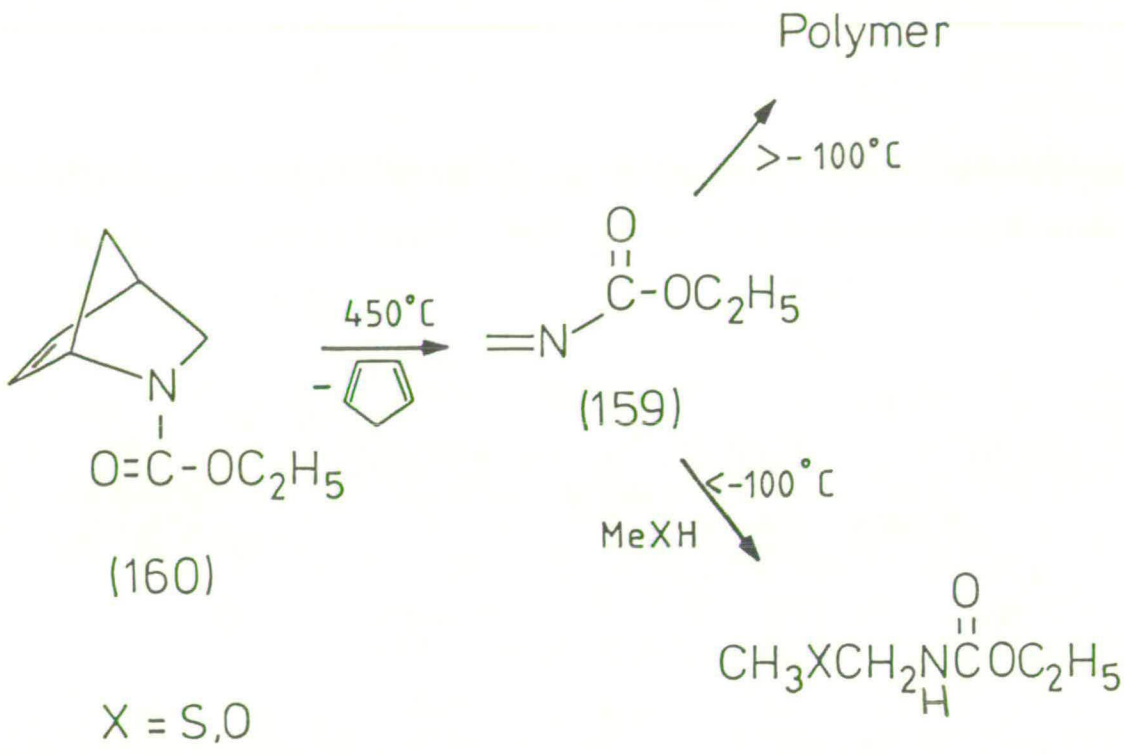
cold trap before it was allowed to warm to room temperature. A ^{1}H n.m.r. spectrum of this solution showed that the solution contained styrene and traces of starting material as well as a singlet at 3.9 δ and a doublet (2.2 δ, 3H) and quartet (9.75 δ, 1H), indicating the presence of methyl isocyanate and acetaldehyde respectively. Extrusion of styrene from (153) would leave ethyl N-methylenecarbamate (159) (Scheme 103).



(153) (159)

Scheme 103

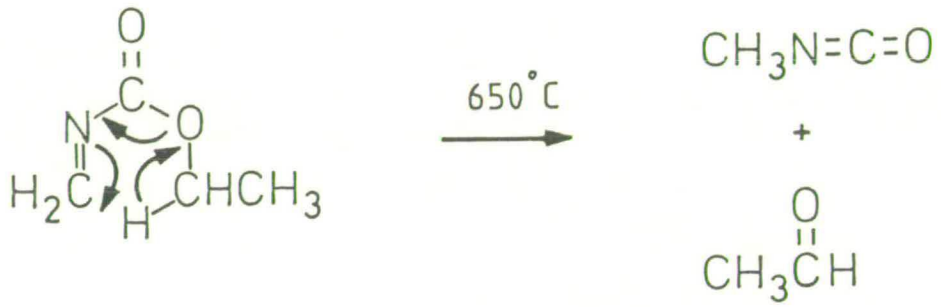
Ripoll et al have shown that (159) is formed during the pyrolysis of N-acyl-2-azabicyclo[2.2.1]hept-5-enes (160)[180] (Scheme 104).



Scheme 104

N-acylimines are highly unstable due to their strong polarisability and rapid tautomerisation. The French workers confirmed the structure of ethyl N-methylenecarbamate and other N-acylimines by the formation at low temperature of adducts with methanol and methanethiol followed by comparison of their spectral properties with those of independently synthesised compounds. Polymerisation of these N-acylimines occurs even at temperatures as low as -100°C, but Ripoll et al[181] discovered that when pyrolysis of (160) was carried out at 650°C, the

resulting ethyl N-methylenecarbamate undergoes a quantitative retroene cleavage to form methyl isocyanate and acetaldehyde (Scheme 105).



Scheme 105

It seems unlikely that any 1-ethoxycarbonyl-azetidine will give a 1,3-oxazin-2-one on pyrolysis, since substituents which will encourage the cleavage of the N-C(1) bond followed by ring expansion will also encourage the extrusion of the alkene.

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