CYCLOADDITIONS TO 1-AZETINES AND 1-AZETIN-4-ONES

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by

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PhD/8/JJC/SEW

UNIVERSITY OF SALFORD

DEGREE OF DOCTOR OF PHILOSOPHY

This is to certify that the thesis which I have presented for consideration for the degree of PhD embodies the results of my course of further study and research and has been composed by myself.

Signed ..... (Candidate)

NAME IN BLOCK CAPITALS ....ABDUL B.N. LUHESHI.....

DEPARTMENT .....CHEMISTRY AND APPLIED CHEMISTRY.....

Signed ..... (Supervisor)

Date ...9th..Nov...1988

DEDICATION

To my parents

for all their sacrifices and patience

CONTENTS

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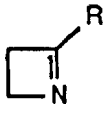
SUMMARY

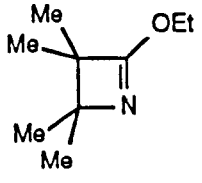
1-Azetines (1) have until recently been unknown. Prepared for the first time in 1967, they since have met with little interest. The azetine system is a thermolabile one, as to be expected from a strained four-membered ring incorporating a C=N bond.



(1)

1,3-Dipolar cycloadditions and [4+2] cycloadditions to the C=N bond of 1-azetines would yield bi-cyclic systems of related structure to the beta-lactam nucleus of beta-lactam antibitics.

Thus, three 1-azetine systems (2-4) were prepared by alkylation of their precursor azetidinones and thioazetidinones.



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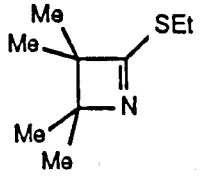

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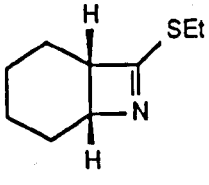
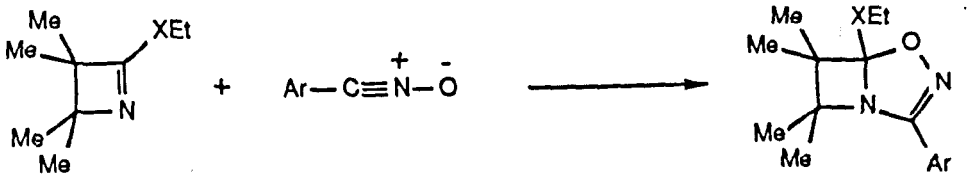


(4)

The ability of these systems to enter into cycloaddition reactions with a variety of 1,3-dipoles and dienes was

investigated.

Nitrile oxides (5) and nitrile ylides (7) were found to add smoothly to the 1-azetine systems to yield the bicyclic adducts (6) and (8) respectively.



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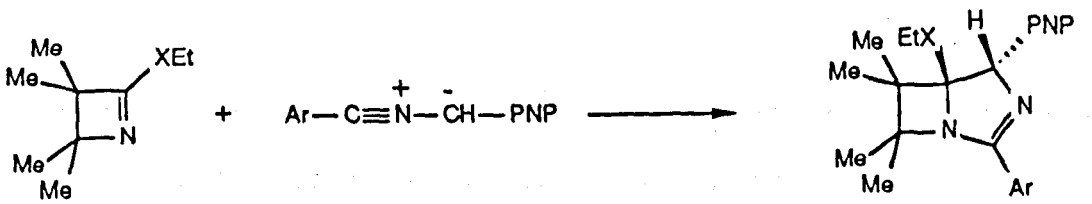
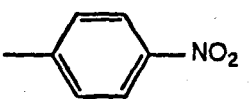
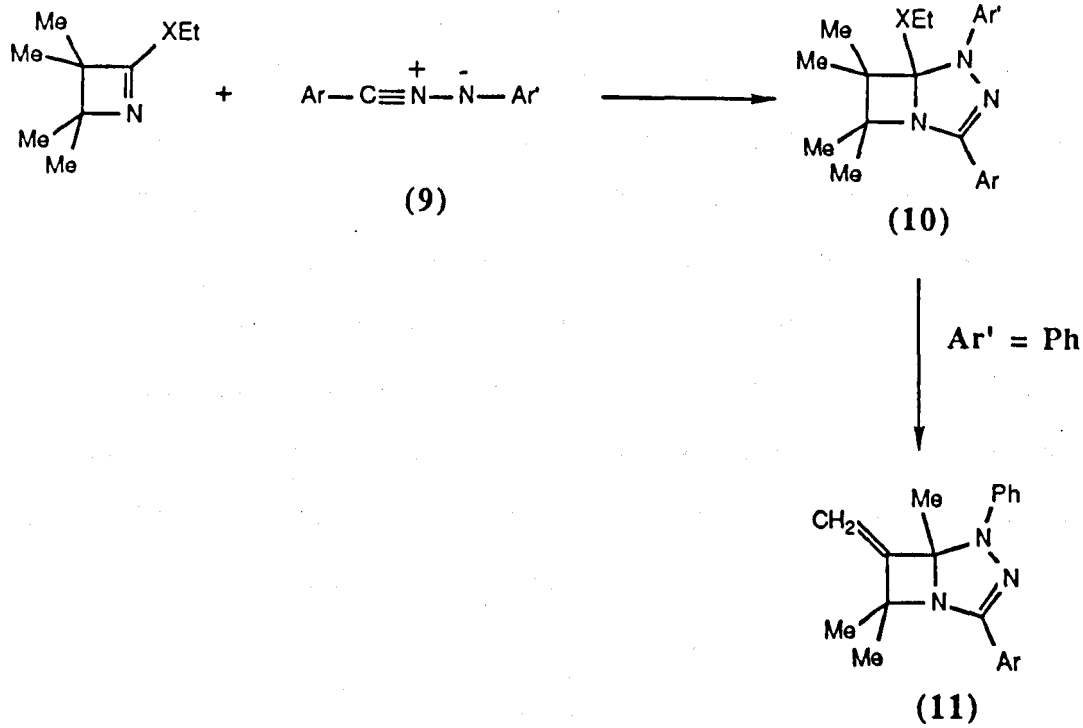


(7) (8)

X = O, S

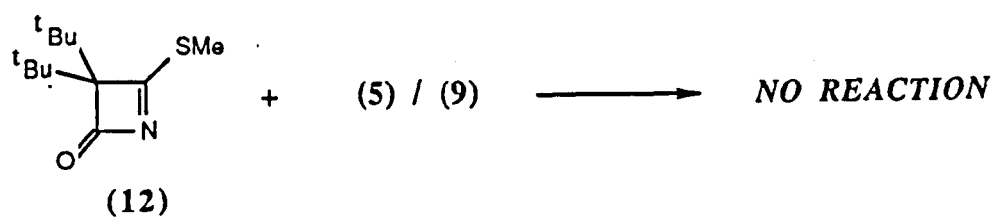
PNP = 

Nitrile imines (9) also add to 1-azetines in a similar fashion to yield the bi-cyclic adduct (10). In some cases, however, these adducts were found to undergo a rearrangement reaction to the bi-cyclic triazoles (11).



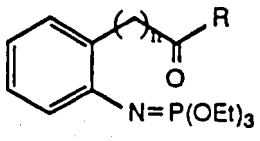
Attempted [4+2] cycloadditions using electron rich and electron deficient dienes to 1-azetines were unsuccesful.

In an extension of this work, addition of 1,3-dipoles to 1-azetin-4-one (12) was also attempted, in a bid to establish a new route to the highly sought after beta-lactam antibiotics. Unfortunately, azetinone (12) was found to be unreactive towards both nitrile oxides and imines.



This lack of reactivity of azetinone (12) is believed to be due to steric hinderance by the geminal t-butyl groups. Hence, several attempts were made to synthesise an azetinone species free of these constraints were made. This work remains incomplete, and is expected to attract further research.

Finally, some work was done to investigate the effectiveness of aryl iminophosphoranes (13) as precursors to a variety of heterocyclic systems, including 1,3-benzoxazoles, 1,4-benzoxazines, and benzodiazepines.



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SECTION A

INTRODUCTION

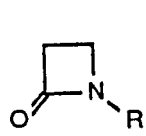
CHAPTER 1

2,4-AZETIDINDIONES, 4-THIOXO-2-AZETIDINONES, AND 1-AZETIN-4-ONES

1.1. INTRODUCTION

Interest in monocyclic β-lactams (1) has been very intense in recent years[1] due to their great versatility as synthetic building blocks for penicillin, cephalosporin, carbapenem and carbacephem antibiotics.

Three closely related systems, however, have been subject to much less scrutiny. These are the 2,4-azetidindiones (2), 4-thioxo-2-azetidinones (3) and the 1-azetin-4-ones (4).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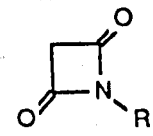
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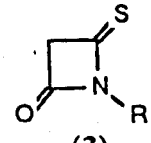
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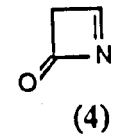
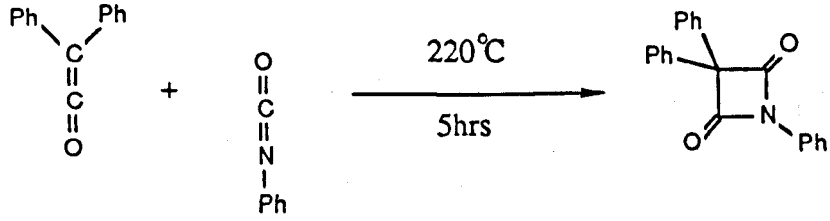

(4)

To our knowledge no reviews have appeared on these systems (2-4). This review will thus attempt to cover their synthesis and chemistry.

1.2. 2,4-AZETIDINDIONES

The first published synthesis of 2,4-azetidindiones (also known as malonimides) was in 1914 by

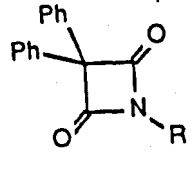
Staudinger.[2] The approach was that of a simple cycloaddition of a ketene to an isocyanate. However, the only success came with the reaction of diphenylketene (5) with phenylisocyanate (6) under vigorous conditions which gave 1,3,3-triphenyl-2,4-azetidindione (7) in 20% yield.



(5) (6) (7)

Reaction of dimethylketene with a variety of aryl isocyanates at -50 °C resulted in only polymeric products. Methyl isocyanate, however, was found to be totally unreactive towards dimethyl ketene, a fact confirmed later by Slotta and Tschesch.[3]

Almost 20 years later, Vogel and his co-workers[4] repeated Staudinger's reactions. Both methyl isocyanate and cyclohexyl isocyanate were reacted with diphenylketene to give diones (8) in 25% yield.

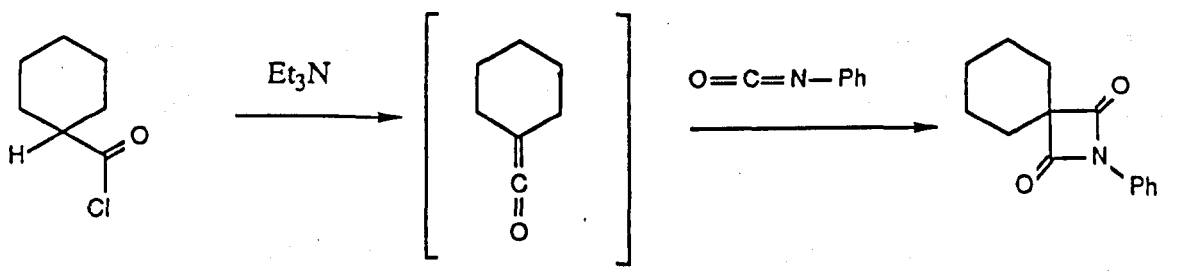


(8)

(8a) R = Me

(8b) R = C_6H_{11}

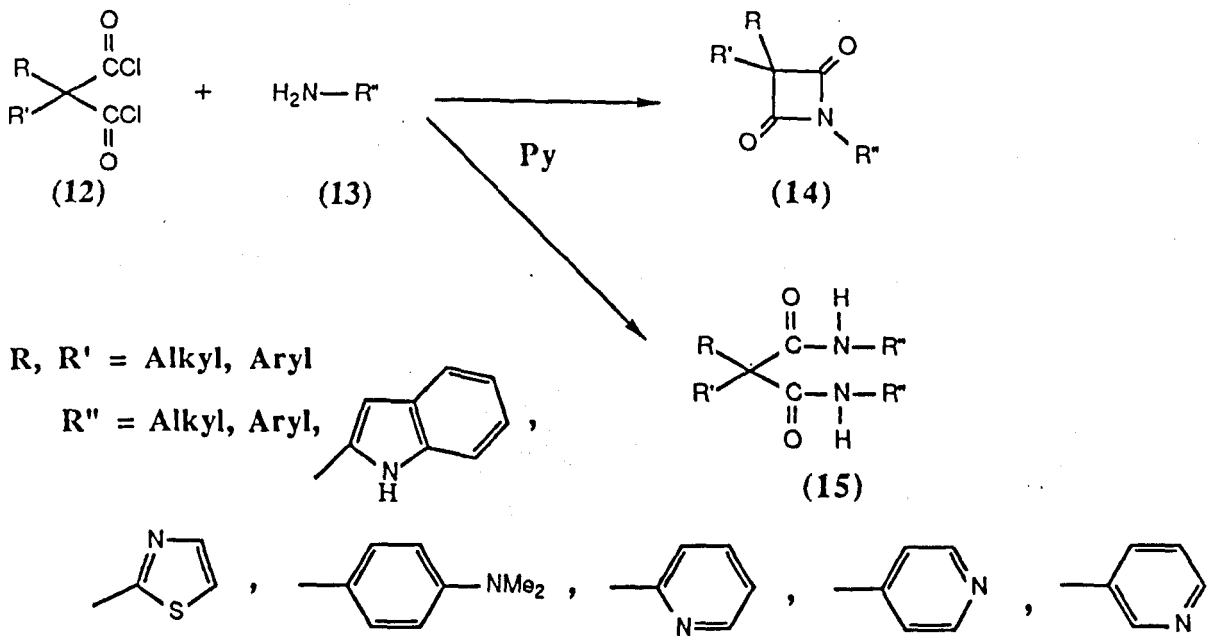
The yield was further improved when the ketene was generated *in situ*. An example of this reaction in which pentamethyleneketene (10) was generated *in situ* by the action of triethylamine on the acid chloride (9) in the presence of phenyl isocyanate (6) has also been reported.[5] The spiro-2, 4-azetidindione (11) was obtained in 50% yield.



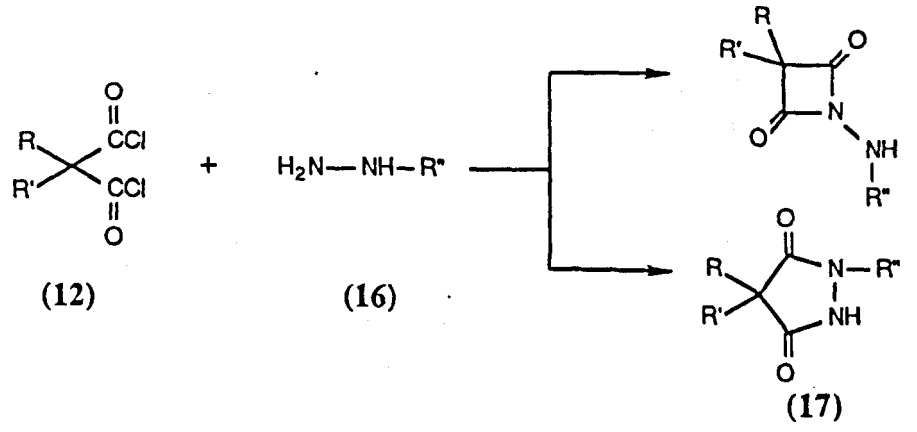
(9) (10) (11)

This method of preparation would appear to be one of the more versatile to date, but no further examples of its use have been reported.

Vogel was able to develop a new synthetic route to the 2,4-azetidindiones.[4] This method was successfully used to prepare 80 new diones, although still in low yield. Reaction of malonyl dichlorides (12) with primary amines (13) under basic conditions was found to yield 2,4-azetidindiones (14). The poor yields were most probably due to the reaction of two moles of amine with one mole of dichloride to give the corresponding diamides (15) and preventing the ring closure step.

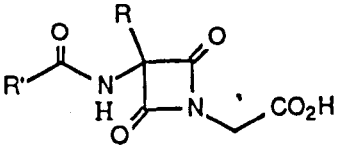


This method was extended to include the reaction of hydrazine derivatives (16) with the malonyl dichlorides to give N-amino-azetidindiones. In this case, however, a competing reaction which yielded pyrazolo-3,5-diones (17) was found to be involved, as shown in Scheme 1.

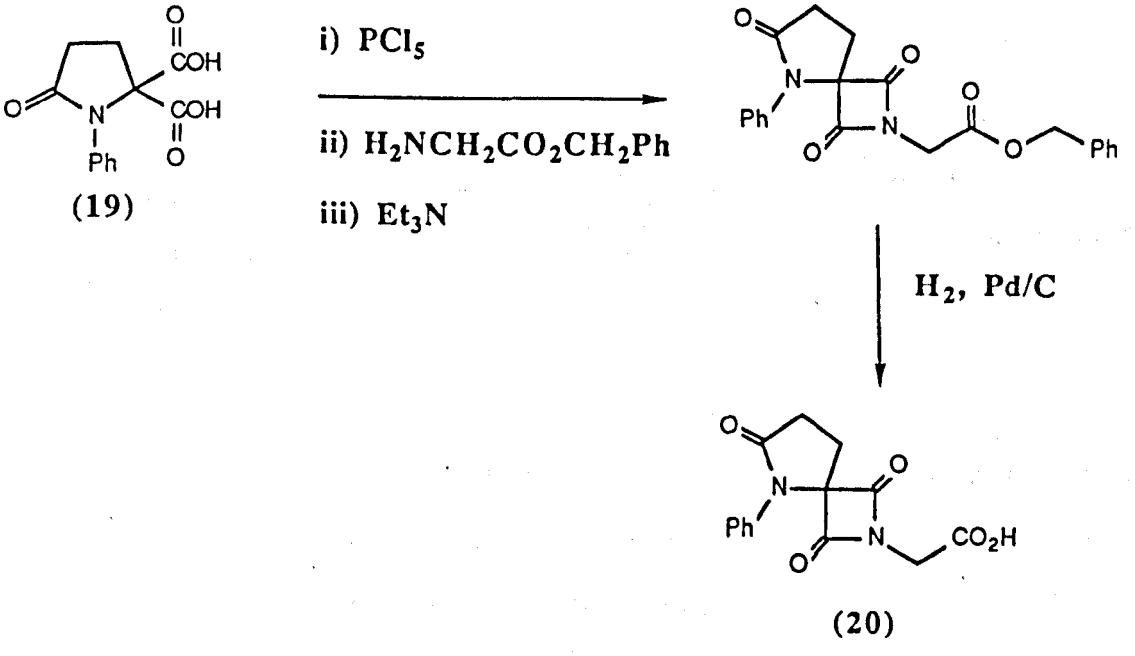


Scheme 1

The dichloride method was later used by Golic[6] in his attempt to synthesise biologically active 2,4-azetidindiones such as (18), and as exemplified in Scheme 2.



(18)

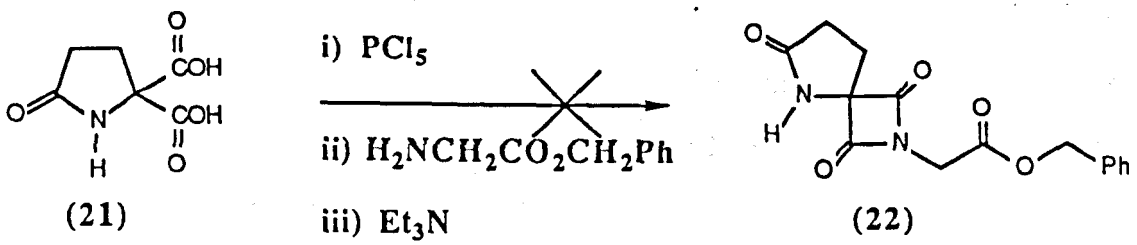


(19)

(20)

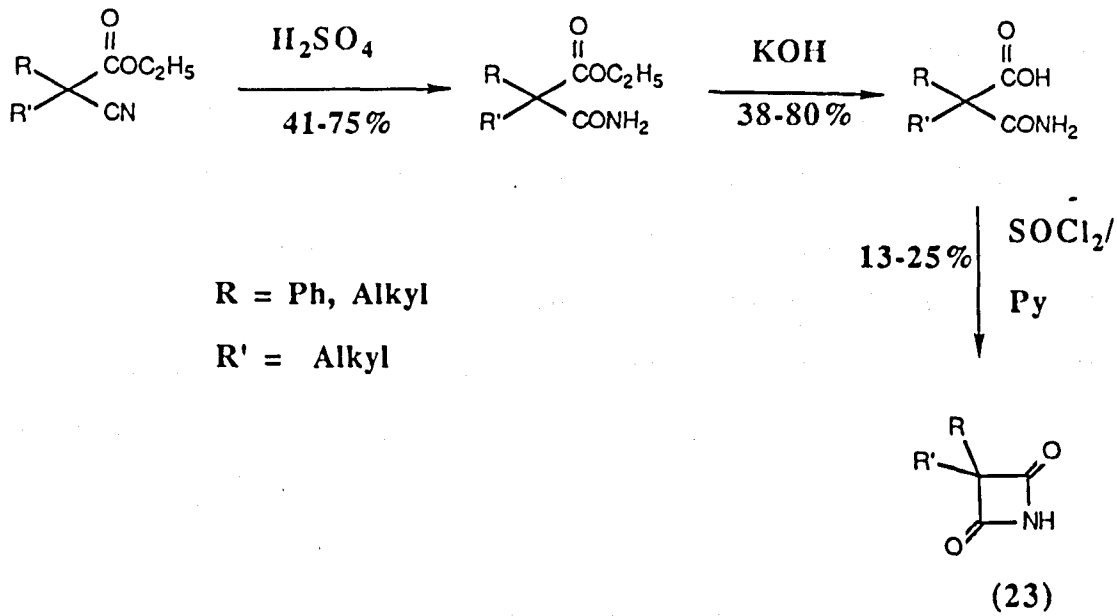
Scheme 2

Spiro-2,4-azetidindione (20) was obtained in low yield and showed no effectiveness against both gram +ve or gram -ve bacteria. In an effort to attain closer structural relationship to penicillin G, Golik attempted the synthesis of azetidindione (22) which contained a secondary rather than a tertiary N-atom in the pyrrolidinone ring, and with the phenyl group displaced to the 3-position. However, treatment of pyrrolidinone (21) with PCl_5 and benzylglycinate in the presence of triethylamine failed to produce azetidinone (22).



(21) (22)

In an attempt to overcome the problems encountered by Staudinger and Vogel, a new method of azetidindione synthesis was published by Testa and Fontanella[7,8] which involved the intramolecular condensation of a carboxylic acid group with an amido group, as shown in Scheme 3.



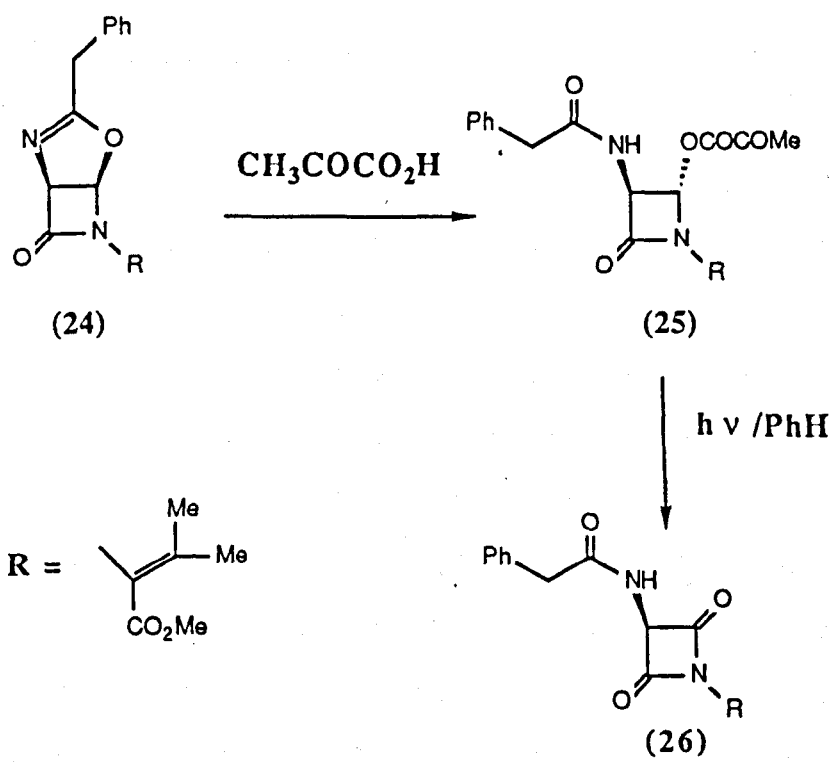
Scheme 3

Although this method had the advantage of providing N-unsubstituted 2,4-azetidindiones (23) it still suffered from poor overall yields.

Work by Stoodley and his co-workers in the late seventies[9] established a novel and high yielding route to 2,4-azetidindiones. The group's aim was to prepare monocyclic ß-lactam derivatives incorporating an electronically activated ß-lactam linkage for testing as antibacterial agents.

The synthesis employed the conversion, described and investigated by Binkley,[10] of pyruvoyl esters of secondary alcohols to ketones, acetaldehyde and carbon monoxide when irradiated in benzene.

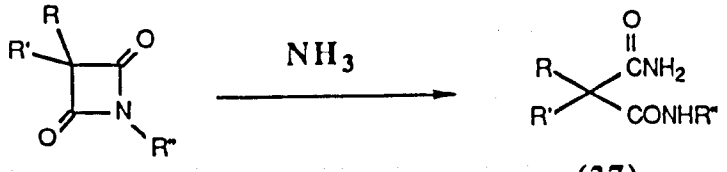
As shown in Scheme 4, treatment of oxazoline-azetidinone (24) with pyruvic acid provided azetidinone (25).[11] Photolysis of (25) in benzene gave 2,4-azetidindione (26) with loss of acetaldehyde and carbon monoxide as predicted. This method has the advantage of providing a 2,4-azetidindione with an acylamine substituent at the 3-position which is usually advantageous when seeking biological activity.



Scheme 4

Finally, 2,4-azetidindiones have been found to have some sedative properties.[7] Surprisingly, their chemistry has not been thoroughly investigated. However, they are known to

be highly susceptible to ammonolysis to malonodiamides (27).



(27)

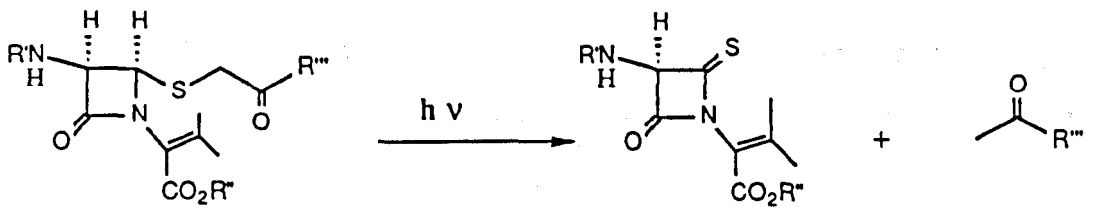
1.3. 4-THIOXO-2-AZETIDINONES

1.3.1. SYNTHESIS

In contrast to the 2,4-azetidindiones, a variety of synthetic methods exist for 4-thioxo-2-azetidinones (also known as thiomalonimides).

Arguably, the first synthesis was published by Re in 1976.[12] He was successful in obtaining 4-thioxo-2-azetidinones (29) by way of a Norrish type II photoelimination reaction of 4-acylmethylthio-2-azetidinones (28) using UV light.

Derivatives of type (28) were prepared from esters of penicillins, penicillin sulphoxides, 6 ß-triphenylmethylaminopenicillanic acid, 4-thia-2,6-diazbicyclo-[3,2,0]hept-2-en-7-one or by total synthesis.[12]



(28) (29)

	R'	R''	R'''
a	$PhOCH_2CO$	CH_3	Ph
b	$PhOCH_2CO$	CH_2Ph	Ph
c	Ph_3C	CH_3	Ph
d	CH_3CO	CH_3	Ph

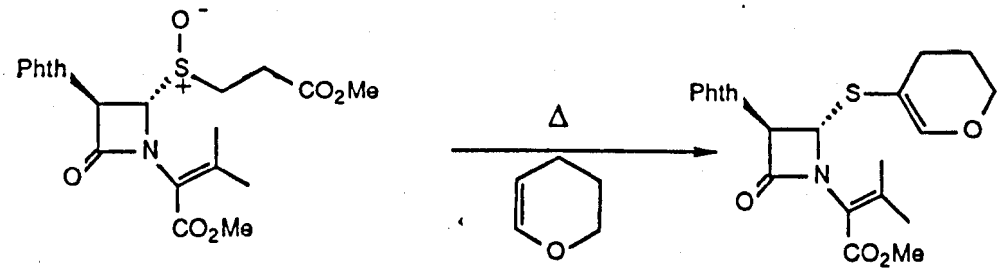
The 4-thioxo-2-azetidinones (29) were obtained in high yield (80%), but proved to be difficult materials to handle, being unrecrystallisable and unstable to chromatography.

A different route to the 4-thioxo-2-azetidinones was published by Bachi in the same year,[13] and came about during an investigation of the thermolysis of β-lactam sulphoxides.

Thermal rearrangement of penicillin sulphoxides into cephalosporin derivatives had been thoroughly studied and now constitutes one of the main ways of synthesis of cephalosporin antibiotics.[14] Sulphoxides bearing an acidic

hydrogen substituent at a β-carbon atom are known to thermolyse to olefins and sulphenic acids, the latter being easily trapped with reagents such as dihydropyran.[15]

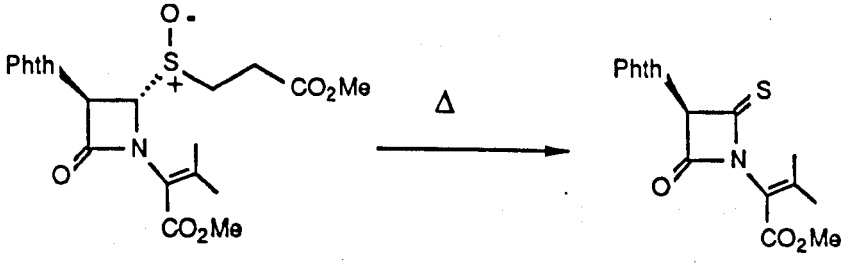
Thus, on thermolysis in dihydropyran with $AlBr_3$ acting as a catalyst, sulphoxide (30) gave the dihydropyranyl derivative (31).



(30) (31)

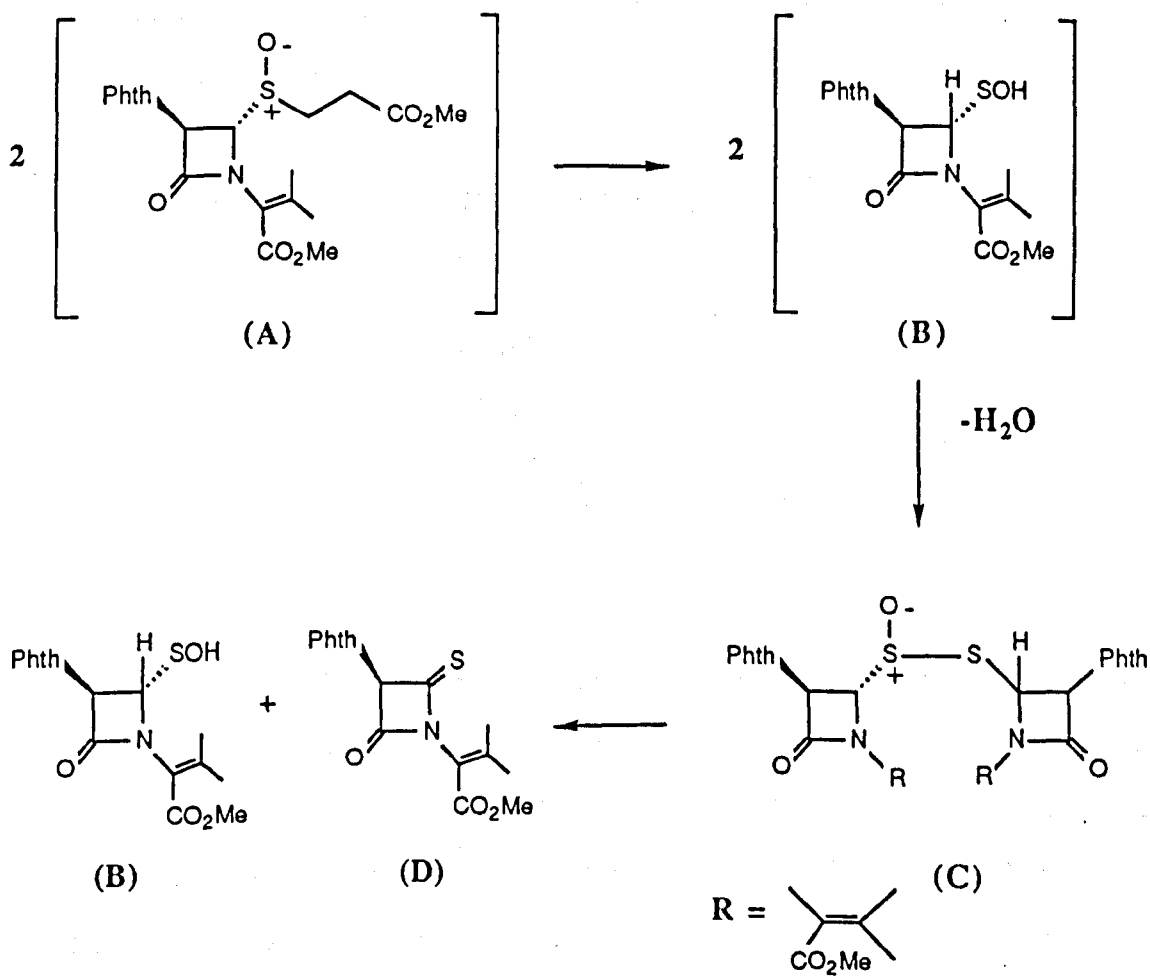
Phth = Phthalimido

However, in the absence of a trapping agent, thermolysis of sulphoxide (30) (sealed tube, 80-100 °C in benzene) was found to yield the 4-thioxo-2-azetidinone (32).



(30) (32)

The production of this novel system was assumed to have occurred by way of a three step process, as shown in Scheme 5.

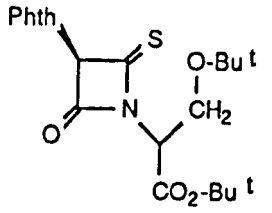


Scheme 5

The sulphenic acid (B) is produced by the thermal elimination of methyl acrylate from the sulphoxide (A). Sulphenic acid (A) is

then believed to undergo a self condensation to the thiosulphenate ester (C); fragmentation of ester (C) then results in the formation of the thioxoazetidinone (D) and the sulphenic acid (B) which is recycled.

This method was extended to include the synthesis of thioxoazetidinones (33) and (34).[16]



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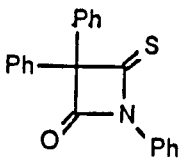
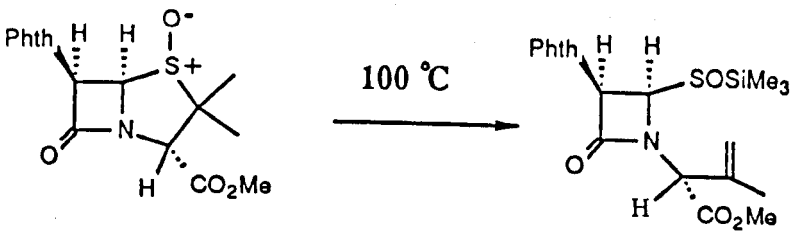


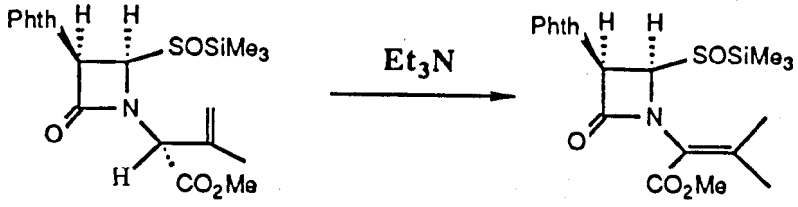
(34)

The mechanism proposed by Bachi[13] was corroborated by Chou and his co-workers.[17] They were able to isolate a protected form of the unstable β-lactam sulphenic acids as the silyl ester (36)[18] by heating the penicillin sulphoxide (35) under reflux in dry benzene with an excess of silylating agent (2:1 molar ratio of trimethylsilyl chloride and hexamethyldisilazane).



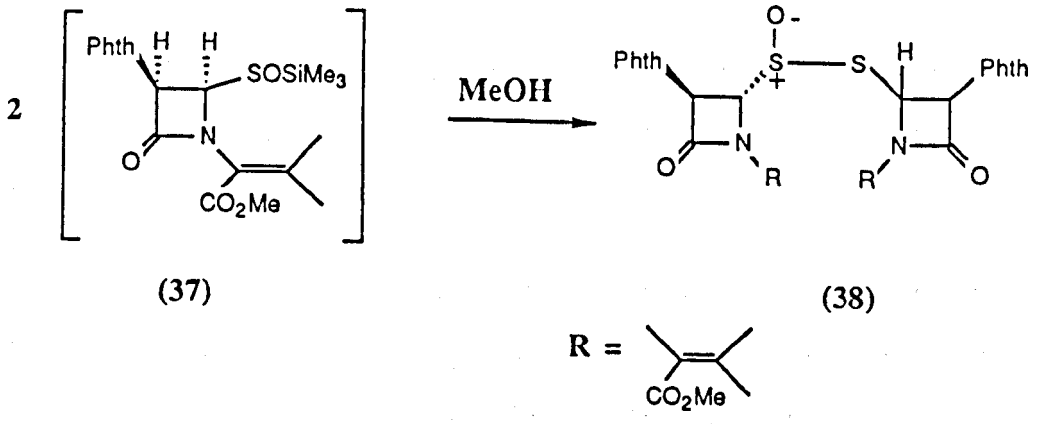
(35) (36)

Treatment of the β,γ-unsaturated ester (36) with a trace of triethylamine resulted in the α,β-unsaturated isomer (37).



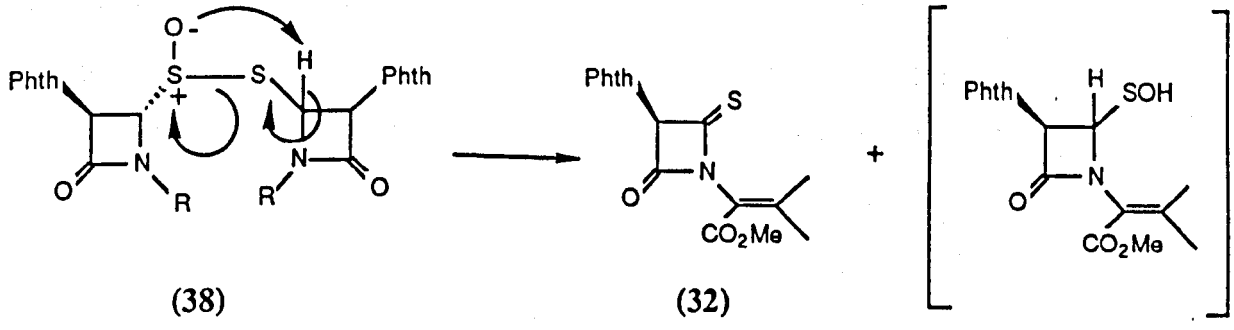
(36) (37)

The corresponding sulphenic acid was easily regenerated by hydrolysis of the silyl ester. In the case of the ester (36), hydrolysis resulted in a nucleophilic addition of the sulphur atom to the vinylic double bond to regenerate the penicillin sulphoxide (35). However, hydrolysis of ester (37) was found to result in an intermolecular condensation reaction of the sulphenic acid moeity to give the thiosulphinate ester (38).



This is believed to occur as a result of the lack of reactivity of the conjugated double bond of the α-β-unsaturated ester to intramolecular 1,4-addition.

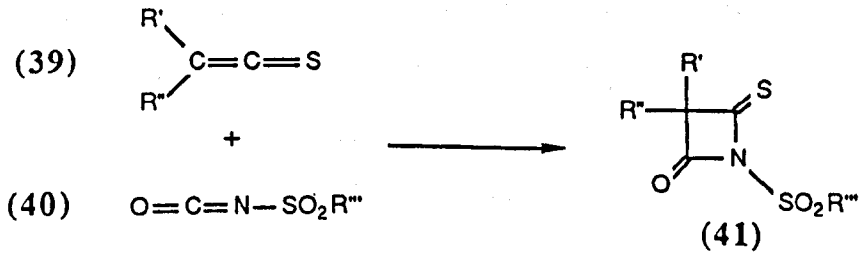
The unusual weakness of the S-S bond of thiosulphinates and the acidity of the β-hydrogen had already been described by Block.[19] Hence, brief heating was all that was required to produce the thioxoazetidinone (32).



The synthesis of 4-thioxo-2-azetidinones proved also to be possible by the reaction of thioketenes with

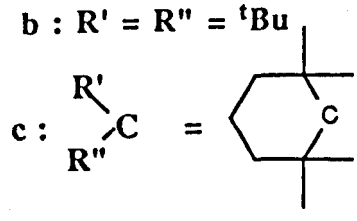
isocyanates. Thioketenes however, are highly unstable species,[20] the only exception being the sterically hindered derivatives e.g. di-t-butylthioketene.

Schaumann[21] was able to prepare and react three such highly hindered thioketenes (39) with a variety of isocyanates (40) to produce the desired 4-thioxo-2-azetidinones (41).



(39) a : R' = ^{i}Pr, R" = ^{t}Bu

b : R' = R" = ^{t}Bu

c : 

(40) a : R''' = OPh

b : R''' = Ph

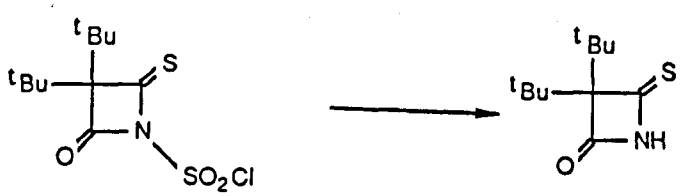
c : R''' = 4-MeC$_6$H$_4$

d : R''' = Me

e : R''' = Cl

This method although straight forward on the surface suffered from several setbacks, the major being the multi-step synthesis needed to produce the stable thioketenes (39a-c). In addition the thioketenes show only low reactivity towards the isocyanates (20 ℃, 3 days) and as a result produce the thioxoazetidinones in variable yield (29-83%).

Schaumann however, was able to isolate the first N-unsubstituted thioxoazetidinone, by the addition of chlorosulphonyl isocyanate (40e) to ketene (39b) which gave the N-chlorosulphonyl-4-thioxo-2-azetidinone (42). Hydrolysis of the chlorosulphonyl group under mild conditions produced the N-unsubstituted 4-thioxo-2-azetidinone (43).

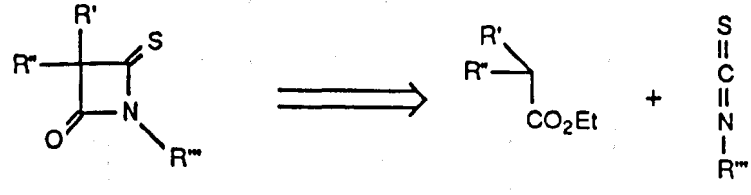


(42) (43)

X-Ray crystallographic structures of the 4-thioxo-2-azetidinone showed that the endocyclic C-N bonds were comparatively long whereas the C=O and C=S bonds were relatively short. This was due possibly to the electron

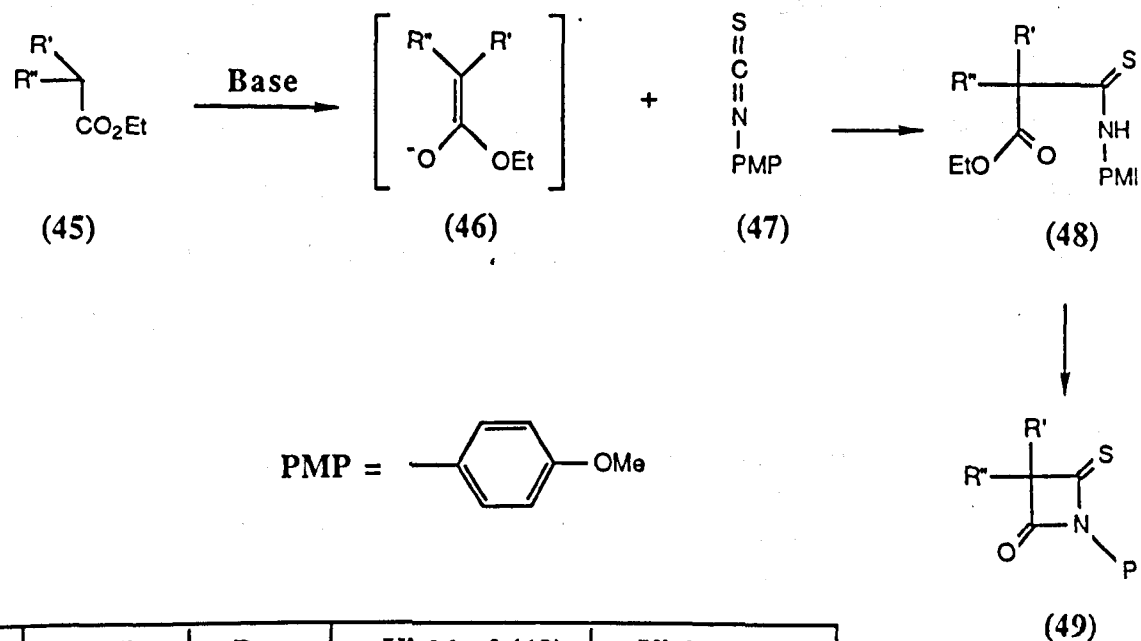
withdrawing effect of the N-sulphonyl residue and the inherent ring strain working together to supress the usual mesomeric interaction in the thio-amide system. In this situation, the difference in the N-C=O/ N-C=S distances (1.441A/ 1.408A) indicated that the thioamide mesomerism is maintained relatively to a larger extent than the interaction with the N-C=O moeity. This is further corroborated by the IR stretching frequencies of the C=O bond which appears at 1820 cm^{-1} showing the lack of the amide resonance stabilisation.

The most recently published synthesis of 4-thioxo-2-azetidinones[22] is probably the most straight forward and arguably the most versatile to date. Retrosynthetic analysis of 4-thioxo-2-azetidinones showed that they could be generated from readily available heterocumulenes (isothiocyanates) and esters as shown in Scheme 6.



Scheme 6

Hence, reaction of the nucleophilic enolate (46) of ester (45) (generated in situ using a base) to the electrophilic isothiocyanate (47) resulted in the production of



(45) (46) (47) (48) (49)

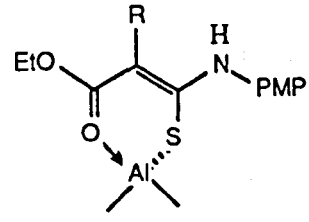
R'	R"	Base	Yield of (48)	Yield of (49)
CH_3	CH_3	LDA	94%	85%
H	CH_3CH_2	LTPM	56%	18%
CH_3	CH_3CH_2	LDA	64%	72%
H	$COOCH_3$	NaH	70%	--

LDA = Lithium Diisopropylamide

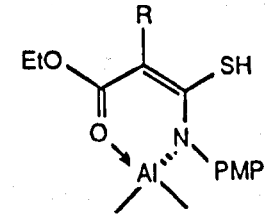
LTPM = Lithium Triphenyl Methane

the acyclic thiomalonic ester (48) in good yield. Cyclisation of these esters was effected by treatment with triethylaluminium in refluxing toluene, to give the 4-thioxo-2-azetidinones (49).

From the results obtained (see Table) it was clear that the nature of the substituents at C2 of the thiomalonic ester, drastically affected the yields of the cyclised product. In the cases where an enolisable proton is present at that position, the cyclic product is either not formed, or formed in a very low yield. The reason for this was thought to be the competitive formation of an inert cyclic aluminium complex such as (50) or (51).

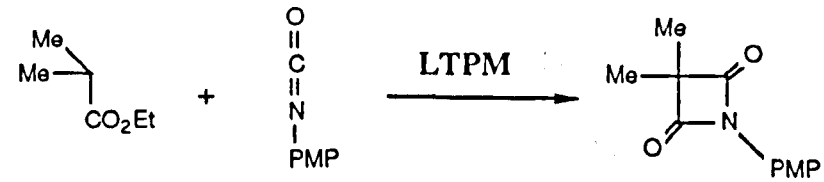


(50)



(51)

This method was further extended to include the synthesis of 1-(p-methoxyphenyl)-3,3-dimethyl-2,4-azetidindione (52) by reaction of ethyl isobutyrate and p-methoxyphenylisocyanate.

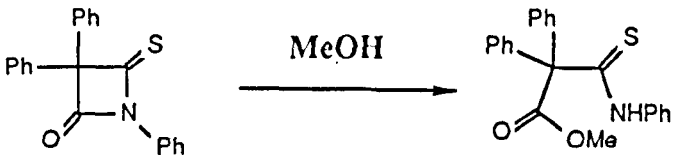


(52)

1.3.2. PROPERTIES AND REACTIONS

The 4-thioxo-2-azetidinones exhibit a strong band in their IR spectra at 1830 cm^{-1}. This frequency is 70-90 cm^{-1} higher than the carbonyl frequency in non-fused b-lactams and 40-60 cm^{-1} higher than the corresponding frequency in the strained bicyclic b-lactam antibiotics. The IR frequency of β-lactams has been taken as an indication of the degree of resonance stabilisation of the amide bond and of its chemical activity. A positive correlation was found between the rate constants of base hydrolysis and IR carbonyl stretching frequencies in various β-lactams. In agreement with this relationship the 4-thioxo-2-azetidinones were found to be highly susceptible to hydrolysis and alcoholysis.[23] They are however stable to trifluoroacetic acid (24 hr at room temperature) and heat (155 °C for 3 hr).[24]

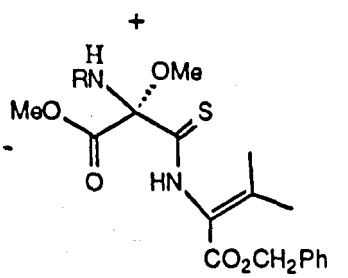
Methanolysis of 3,3-disubstituted 4-thioxo-2-azetidinones, such as (53) was found to occur exclusively at C2 resulting in ring cleavage to give the corresponding thioamide (54).



(53) (54)

In the case of more complex thioxoazetidinones, such as (55) (prepared by Re and co-workers[25]) methanolysis does not stop at the ring cleavage stage, but continues to produce another cyclic product (56) as well as the expected ring opened compound (57).

(55) (56)

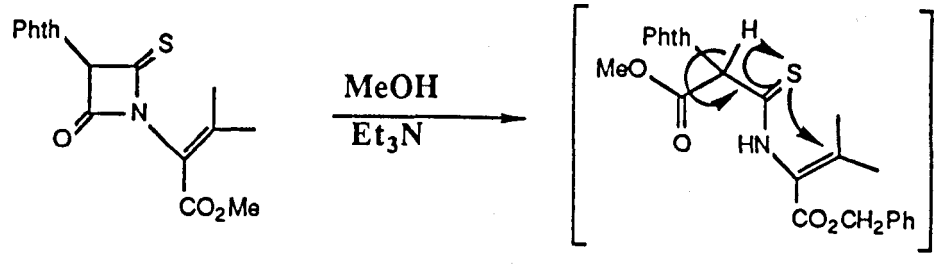


(57)

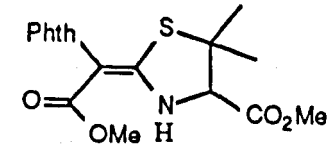
It is probable that initial attack by the methoxide ion at C2, causes ring cleavage to give thioamide (57) which then cyclises to thiazoline (56).

Methanolysis of 4-thioxo-2-azetidinones which have only one substituent at C3 was found to give rise to some extraordinary products.

Bachi[24] claimed that methanolysis of 3-phthalimido-4-thioxo-2-azetidinone (58) in the presence of triethylamine yields two products. The major was assigned as the thiazolidine (60) which is a rearranged product from the primary adduct (59).



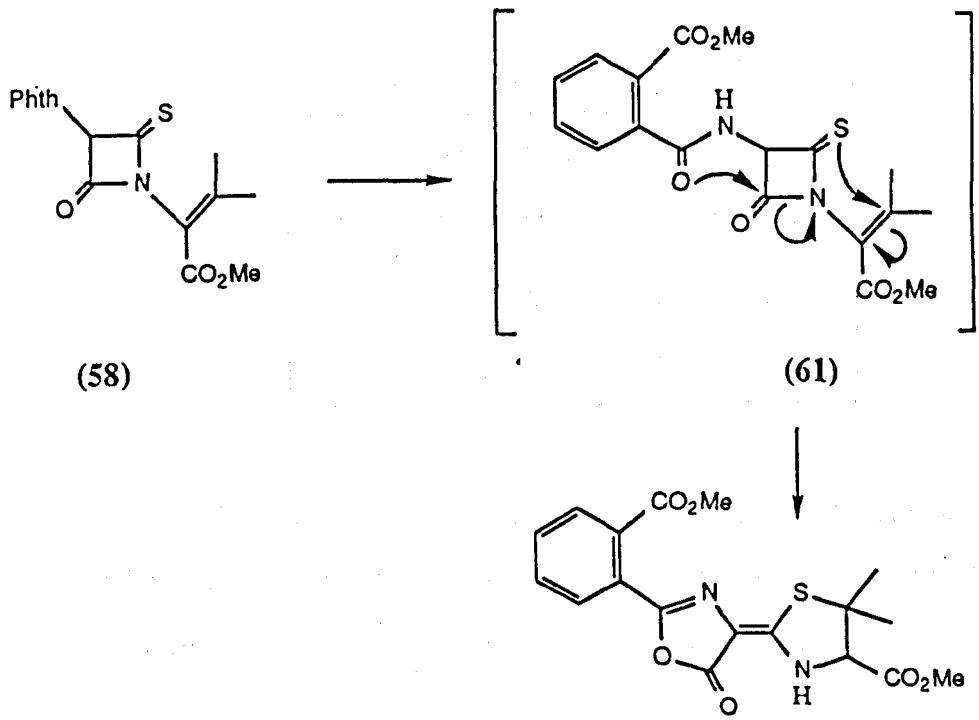
(58) (59)



(60)

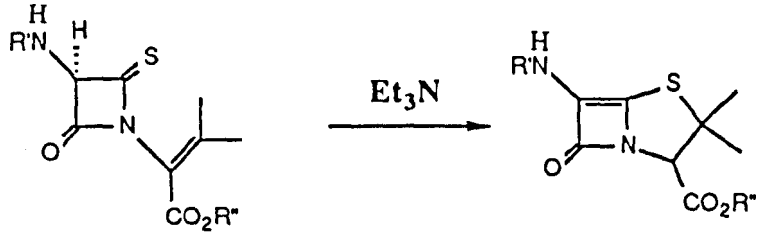
The minor product was suggested to have the oxazolone structure (62). This was thought to be produced by

competitive methanolysis of the phthalimido group in (58) leading to the phthaleamic ester (61), which spontaneously rearranges to oxazolone (62) as shown.



(58) (61) (62)

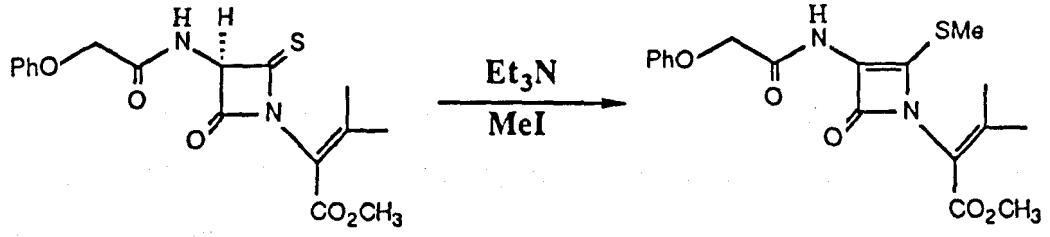
The spectral data of compound (62) was found to be very similar to that shown by a compound which Re had prepared from thioxoazetidinone (63) by treatment with triethylamine, and to which a 5,6-dehydropenicillin (64) structure had been assigned.[26]



(63) (64)

	R'	R"
a	$PhOCH_2CO$	CH_3
b	$PhOCH_2CO$	CH_2Ph
c	Ph_3C	CH_3
d	CH_3CO	CH_3

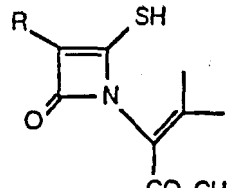
Re[12] also showed that treatment of thioxoazetidinone (63a) with triethylamine in the presence of methyl iodide produced the 1,2-seco-5,6-dehydropenicillin (65).



(63a) (65)

Bachi had disagreed with both of these results on the basis that the formation of a 5,6-dehydropenicillin system would require the intermediacy of a thioenolic system (66) which

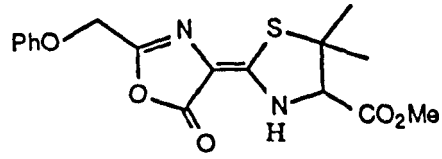
in his opinion was unlikely.



(66)

Furthermore, the formation of oxazolones by an intramolecular attack of an acylamino group on the carbonyl function of 2-azetidinones had been previously experienced in penicillin chemistry.[27]

On these grounds, Bachi proposed structure (67) in place of (64).

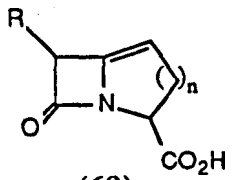


(67)

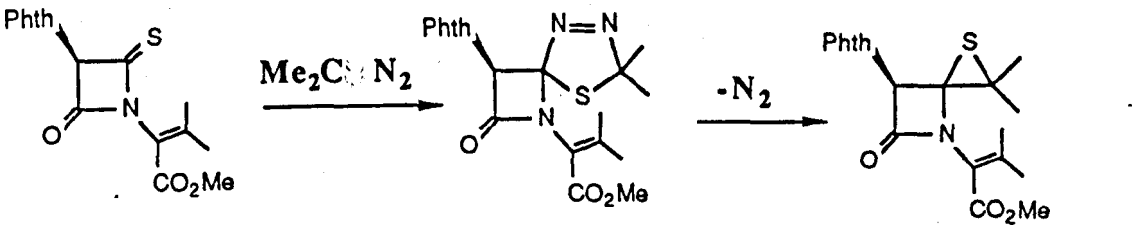
This assignment was corroborated by comparing the UV and IR spectra of the rearranged products (62) with other thiazolidinylidene-oxazolones.

Bachi extended his work on 4-thioxo-2-azetidinones in an attempt to synthesise bicyclic β-lactams of type (68)[24,28] which contain an activating bridge-head double bond. The precursor for such a system would be a 4-alkylidene-2-azetidinone (69).

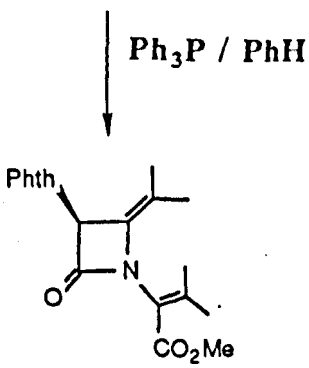
This was conveniently prepared by way of a three step synthesis, the first of which was a 1,3-dipolar cycloaddition of a diazoalkane to the C=S group of thioxoazetidinone (58), as shown in Scheme 7.



(68)



(58)



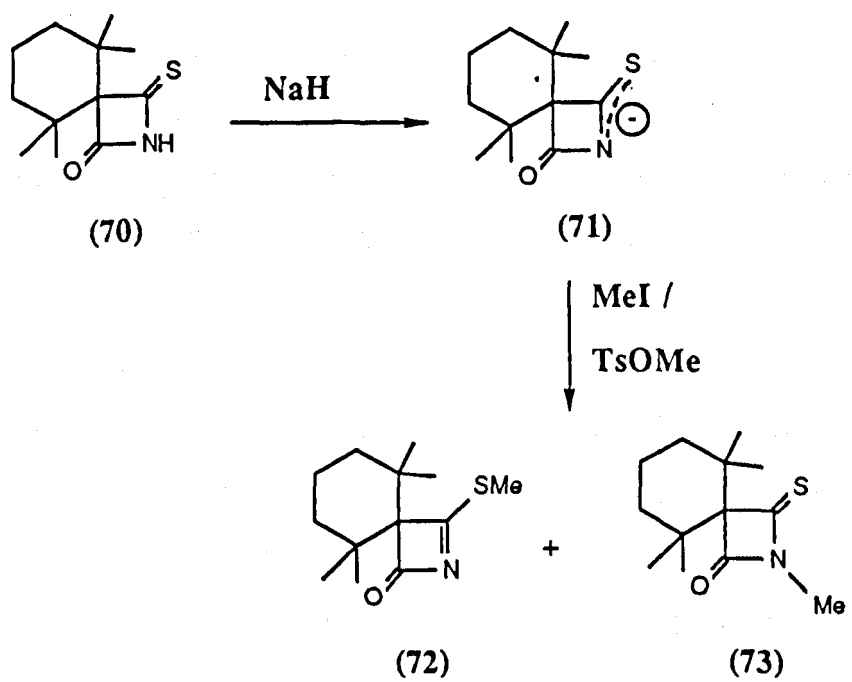
(69)

Scheme 7

Work on N-unsubstituted 4-thioxo-2-azetidinones was done by Schaumann.[21] Treatment of thioxoazetidinone (70)

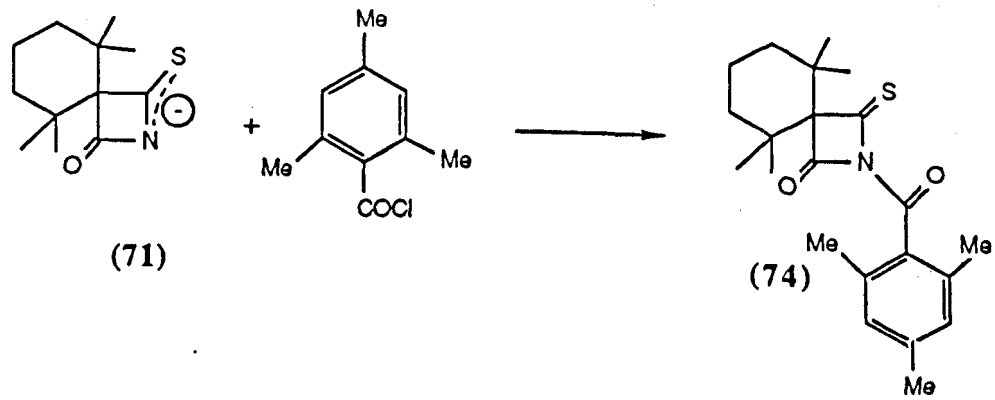
with sodium hydride generated the anion (71). The ambident activity of (71) was verified by different methylation reactions. Methyl Iodide was found to yield exclusively the S-methyl compound (72) as proven by C-13 NMR and UV spectra.

Use of methyl tosylate, however, yielded a mixture of S- (72) and N-methyl (73) derivatives with the former still predominating in spite of the ring strain present in azetinone (72).



(70) (71) (72) (73)

Acylation, on the other hand, was found to occur exclusively on nitrogen.

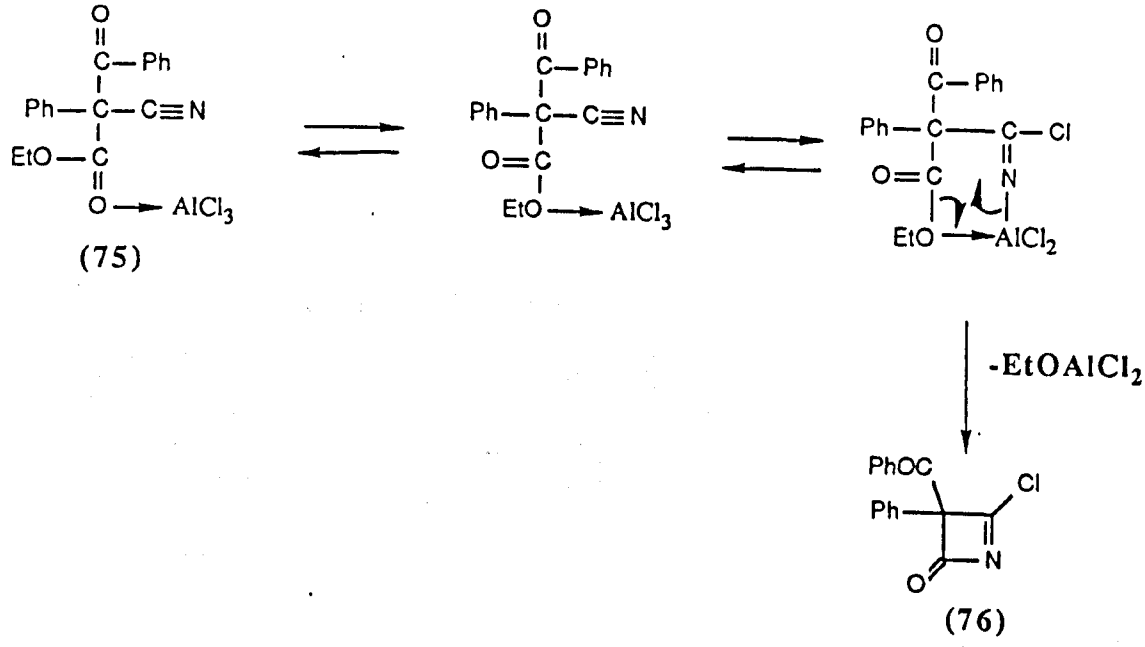


(71) (74)

1.4. 1-AZETIN-4-ONES

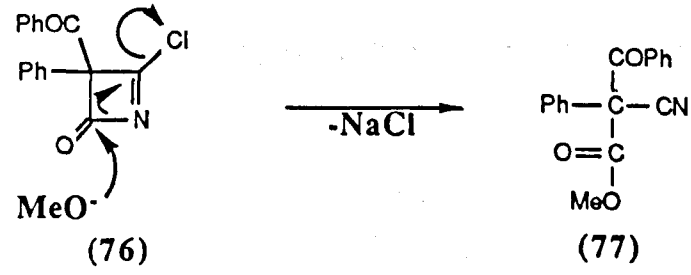
The 1-azetin-4-one (4) system had been postulated as a reactive intermediate by several independent groups. However, only two synthetic methods have been published to date.

The first of these appeared in 1973. Matsui and Motoi,[29] who at the time were involved in aluminium chloride catalysed acylation of active methylene compounds, found that the benzoylation of ethyl-α-cyanophenylacetate (76) afforded a substance whose IR spectrum was devoid of a band due to the cyano peak. Furthermore, the molecular formula was indicative of a loss of the ethoxy group and gain of a chlorine atom. Based on this evidence, the group proposed the cyclic structure (76) for their product. The mechanism offered in explanation of this product was based on the $AlCl_3$ complexing to the oxygen of the ethoxy group followed by transfer of chloride ion to the carbon of the nitrile group and the formation of a six membered ring which loses $C_2H_5OAlCl_2$ to leave the azetinone product (Scheme 8).



Scheme 8

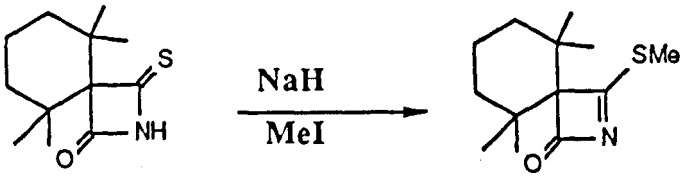
Treatment of compound (76) with sodium methoxide yielded the expected α-benzoyl-α-cyano-ester (77) which is the result of a nucleophilic attack at C4 of the azetinone ring.



Curiously, however, this synthesis has received no further investigation nor has it been exploited by other research groups.

The second synthesis of 1-azetin-4-ones, has already been mentioned (see page 24). Schaumann[21] in his work on 4-thioxo-2-azetidinones showed that treatment of N-unsubstituted thioxoazetidinones such as (70) with NaH and MeI afforded the S-

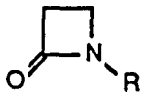
methylated compound (72) as the exclusive product.



(70) (72)

Neither of the methods described above, however offer a general route to 1-azetin-4-ones, although Schaumann has been able to demonstrate that the system may not be as unstable as one might assume.

The fervent interest shown by chemists in new ways to synthesise β-lactam antibiotics has led to a great deal of work being done on monocyclic β-lactams i.e. the azetidin-2-ones (1).

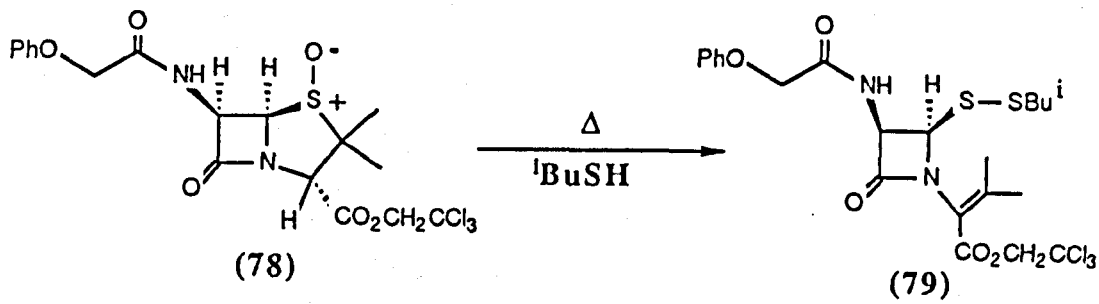


(1)

In particular, reactions which lead to new functionality or to chain extension at position C4 of the azetidinone ring have met with the most interest. In many of these cases the azetinone system has been suggested as a viable intermediate.

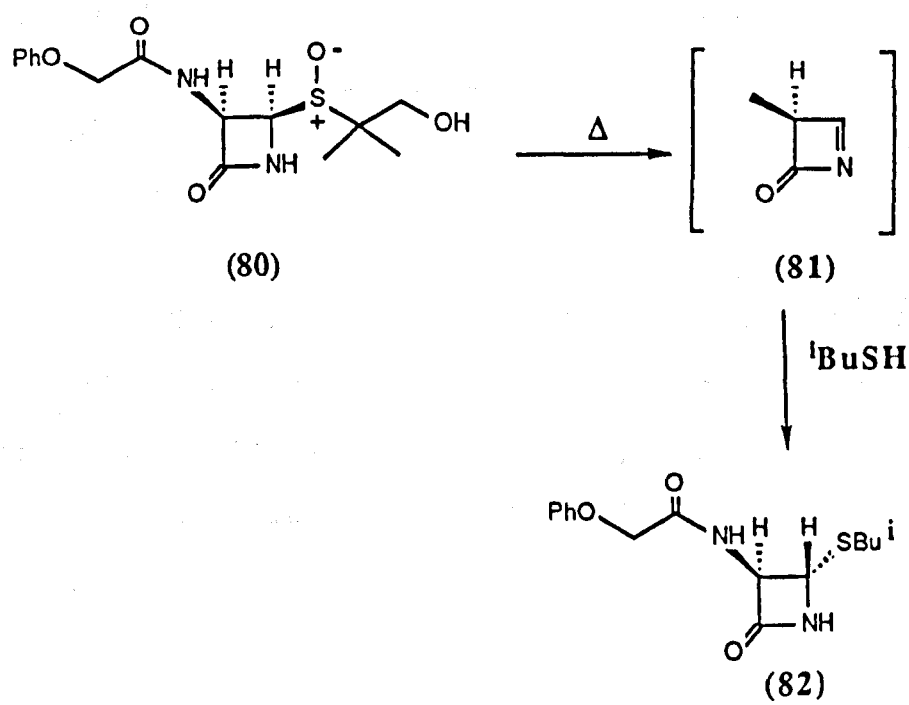
The earliest mention of the azetinone intermediate came from Barton[30] during his work on the trapping of the

sulphenic acid intermediates (generated by thermolysis of sulphoxides e.g. (78)) with thiols to give disulphides e.g. (79).

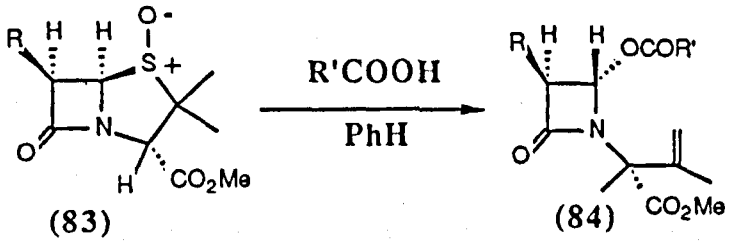


(78) (79)

A similar thermolysis of sulphoxide (80), however, gave a sulphide of <u>trans</u>-geometry between C3 and C4. This was assigned structure (82) and was assumed to be due to an elimination of the sulphoxide side chain to give the intermediate azetinone (81) followed by a nucleophilic attack by the thiol at position C4. This attack being sterically directed to the α-face by the adjacent bulky β-benzamido group.



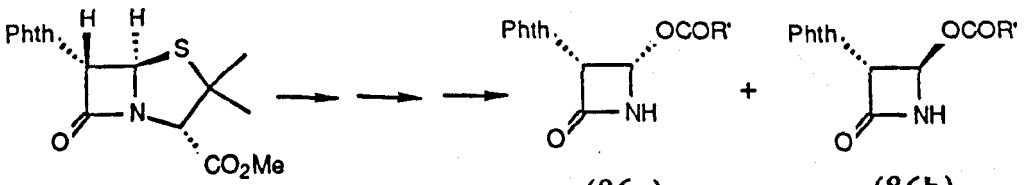
Thermolysis of penicillin sulphoxides, such as (83) in the presence of a carboxylic acid and trimethyl phosphite forms a very useful route to optically active 4-acetoxy-azetidinones (84).[31]



(83) (84)

R = Phthalimido / Phenoxyacetamido

The use of 6-epi-penicillin sulphoxides such as (85), however, gives rise to mixtures of the two possible diastereoisomers (86a & b) i.e. products with both retention and inversion at C4.

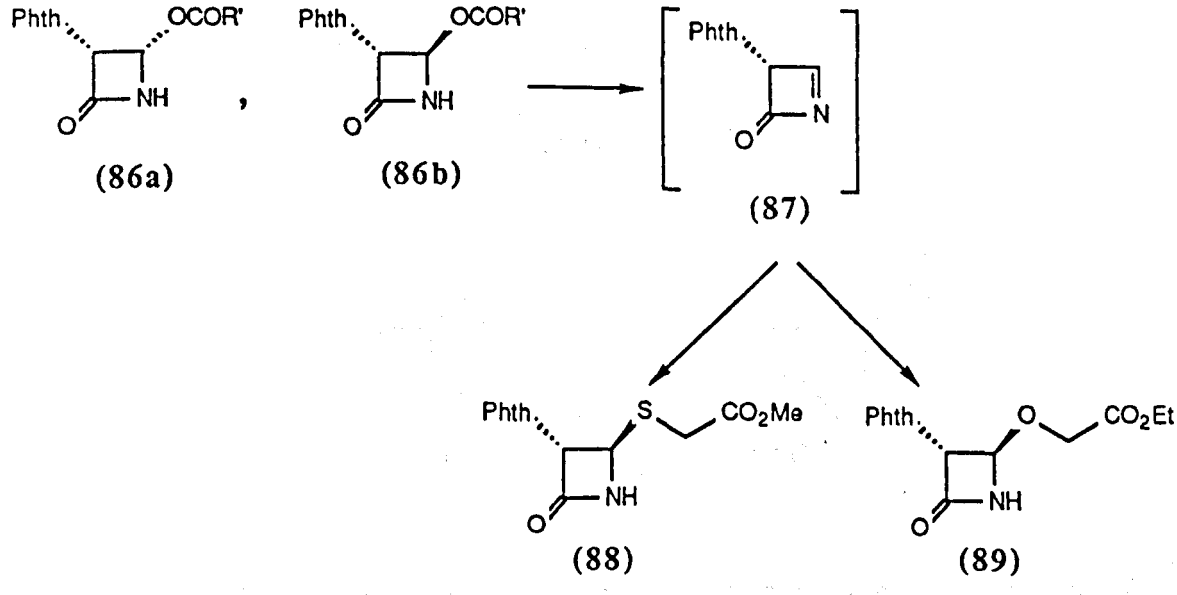


(85) (86a) (86b)

The ratio of cis:trans was dependent on the bulkiness of R' and it increased in favour of the trans isomer with increasing R' size. Furthermore, the catalytic action of a mild Lewis acid transformed (86a) into the more stable (86b).

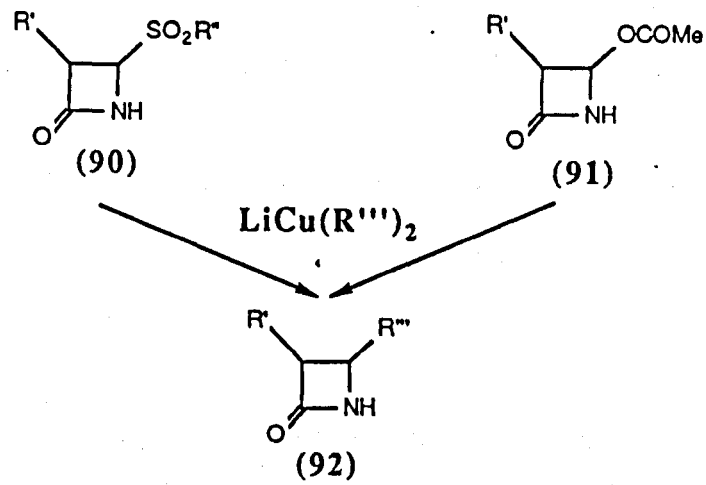
This was believed to occur via the planar azetinone species (87), since the transformation did not occur when N-unsubstituted lactams were used.

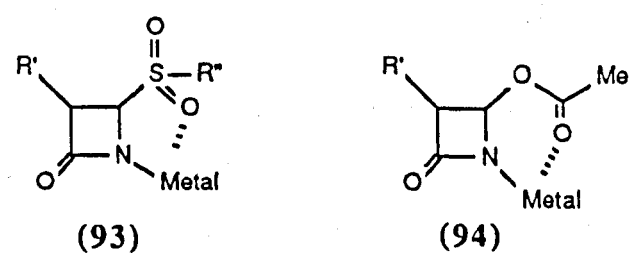
To investigate this possibility, (86a) and (86b) were treated with mercaptans and carbinols. In both cases only optically active trans β-lactams (88) and (89) were obtained. These results support the idea that the displacement reactions occur via 1 planar azetinone (87), in that the nucleophilic species approaches preferentially from the less hindered side, i.e. trans to the phthalimido group, of the four-membered ring.



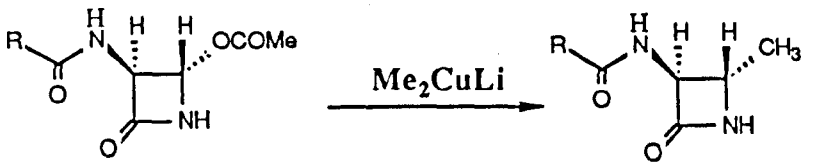
The nucleophilic displacement of acetoxy and sulphonyl groups at C4 position of azetidinones e.g. (90) and (91) by lithium organocuprates, was also postulated to go via an

azetinone species.[32] The azetidinone (92) was believed to be derived from a 5-membered (93) or a 6-membered (94) co-ordination intermediate. However, both cis- and trans- products were produced. When bulky substituents, e.g. tritylamino, were placed at C3, trans- predominated over cis- products.



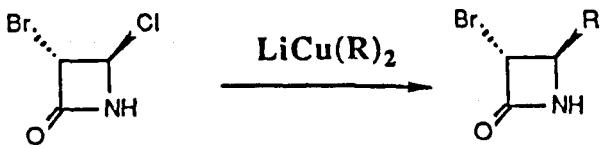


The presence of an acylamino group at position C3 of the azetidinone, however, was reported to yield optically pure products with retention of configuration.[33]



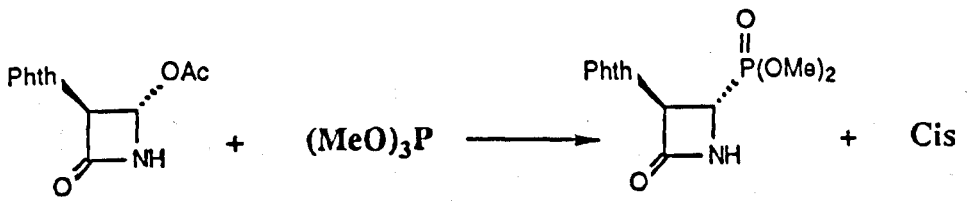
(95) (96)

Organocuprates were further used for the introduction of allylic side chains at C4 of azetidinones.[34] The action of lithium diallyl cuprates on (3S)-bromo-(4R)-chloro-2-azetidinone (97) was found to give exclusively the trans-isomeric product (98). This suggested that the reaction involved the intermediacy of an azetinone and that bromine is bulky enough to sterically direct the approaching nucleophile.



(97) (98)

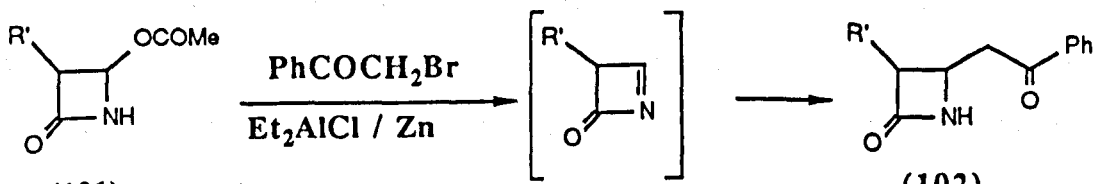
Similarly, organo phosphorous nucleophiles e.g. $(MeO)_3P$ and $(EtO)_3PMe$, were found to displace the acetoxy group of 3β-phthalimido-4α-acetoxy-2-azetidinone (99) with retention of



(99) (100) 69% 10%

configuration.[35] The trans isomer (100), as shown by the coupling constant between C3 and C4, was the major product.

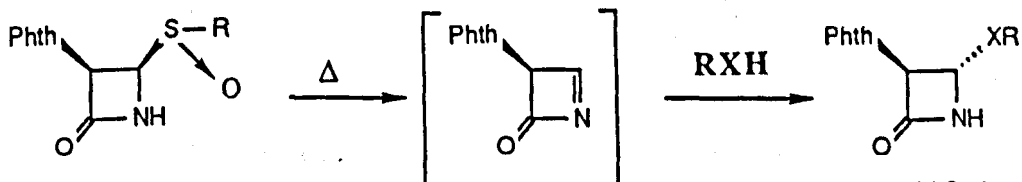
Displacement of the acetoxy group of (101) by aluminium enolates to generate 4-alkylazetidinones, such as (102) is also believed to occur via an azetinone species.[36]



(101) (102)

Bachi and Gross[37] were able to use the directing effect of the C3 substituent on β-lactams to generate pure optically active (4R)-alkoxyazetidinones, which are useful building blocks for clavam and oxacepham derivatives.

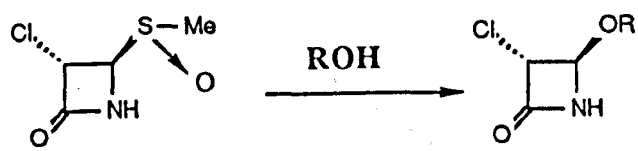
The group had previously established that the thermolysis of (3R,4R)-3-phthalimido-4-alkylsulphinylazetidinones (103) in the presence of nucleophiles RXH, gave rise to trans-substituted β-lactams (104). This was believed to occur by way of a thermal elimination of alkylsulphenic acid to give a highly reactive intermediate, presumed to be an azetinone.



(103) (104)

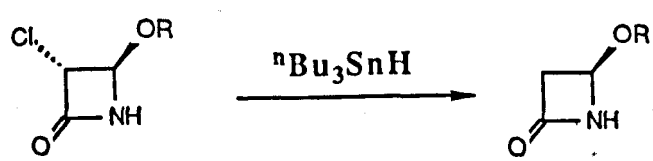
Henceforth, to obtain the 4R-isomer, a 4S-substituted sulphoxide was needed. The compound used was (3S,4R)-3-chloro-4-methylsulphinylazetidinone (105). The chlorine atom was believed to be bulky enough to direct the attacking alcohol to the b-side, and to be readily removable when desired.

Secondary and tertiary alcohols were found to add exclusively to the β-face to give rise to the correct 4R-product (106). However, when an attempt was made to improve the yields by adding a trapping agent for the methane sulphenic acid, a small amount of the 4S-isomer was also isolated.



(105) (106)

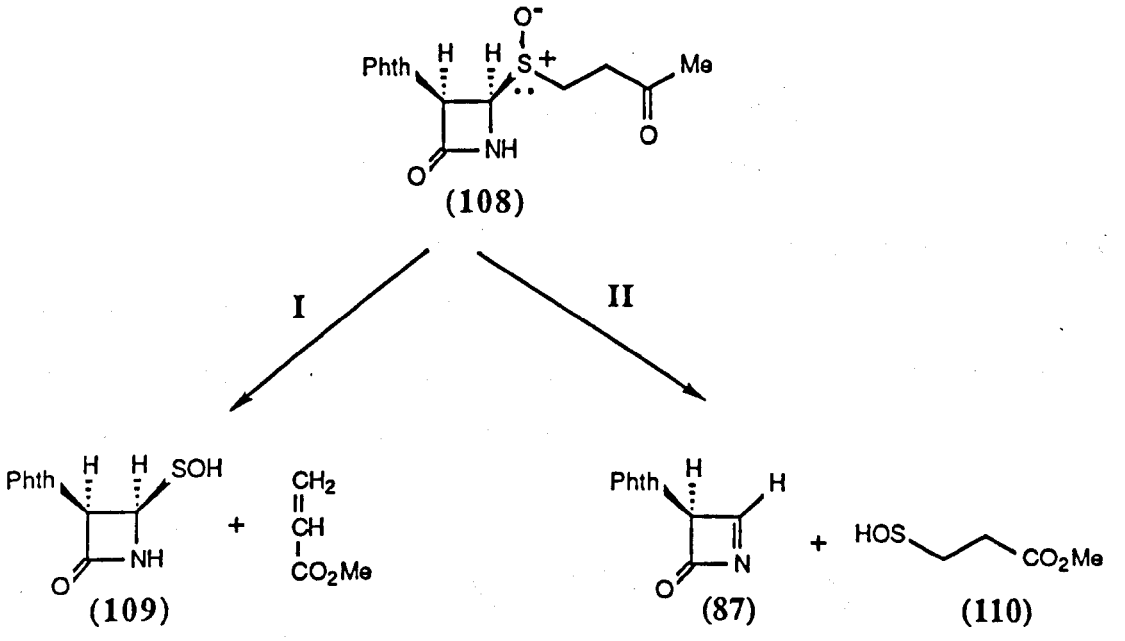
The chlorine atom was effectively removed with tributyl tin hydride to afford the enantiomerically pure (4R)-alkoxyazetidinone (107).



(106) (107)

Bachi and Gross[38] extended their work on β-lactam

sulphoxides to study the mechanism of their thermolysis. They found that the thermolysis of sulphoxides (108) may proceed through <u>syn</u> elimination, either via path I to give the sulphenic acid (109) and methyl acrylate, or via path II to generate the azetinone (87) and the sulphenic acid (110), as shown in Scheme 9.

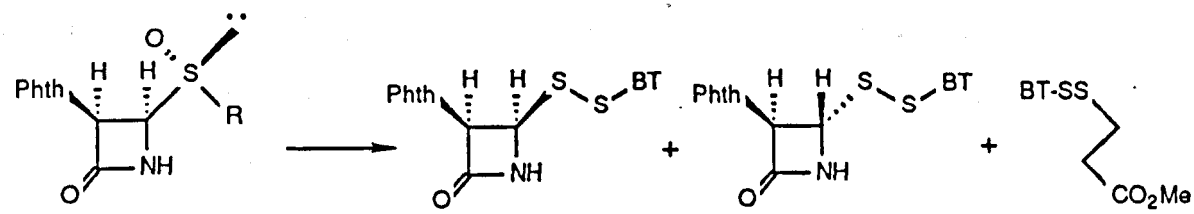


Scheme 9

The path followed was found to be dependent on the stereochemical configuration of the sulphoxide group.

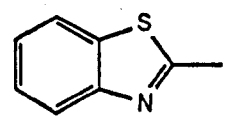
The R-sulphoxide (108a) was heated with 2-mercaptobenzothiazole, a suitable trapping agent for all three

expected products (109, 110 & 87). Three products were isolated; the disulphide (111) (62%), the trans-azetidinone (112) (31%), and the disulphide (113).

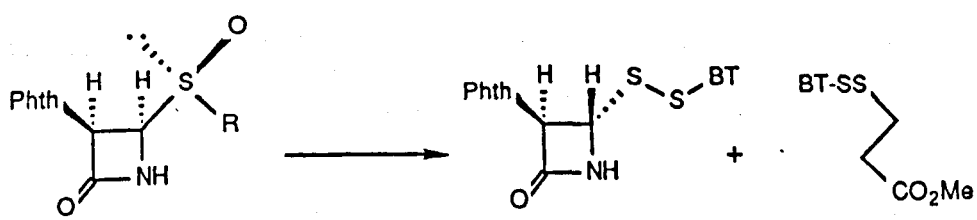


(108a) (111) (112) (113)

BT =



A similar reaction using the S-sulphoxide (108b) gave none of disulphide (111), but the azetidinone (112) as the major product (71%), accompanied by a small amount of the cis-isomer (10%) and the disulphide (113).



(108b) (112) (113)

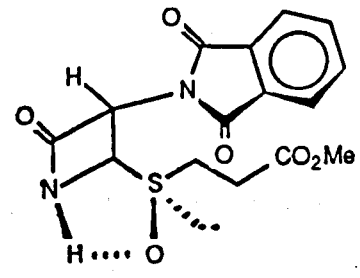
Hence, thermolysis of the R-sulphoxide proceeds via both paths I and II (Scheme 9) with a preference for path I. In contrast, thermolysis of the S-sulphoxide proceeds exclusively

through path II.

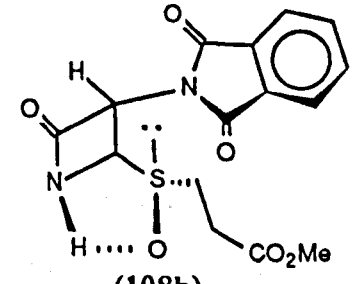
Stoodley et al,[39] had already shown that the syn cycloelimination of a sulphenic acid during thermolysis of sulphoxides bearing one or more hydrogen substituents at a ß-carbon atom, is markedly enhanced as the acidity of the migrating hydrogen is increased.

Taking this into account, Bachi thought that the reaction would proceed exclusively through path II involving the migration of the hydrogen atom linked to the nitrogen, since this is the most acidic. This, however, was true only in the case of the S-sulphoxide. Since the R-isomer (106a) underwent a ß-elimination involving the extraction of a more strongly bonded hydrogen atom.

A possible explanation of these results was offered in terms of the transition state. The elimination of sulphenic acid (110) requires a planar disposition of all the participating atoms, as shown in Fig. 1.



(108a)

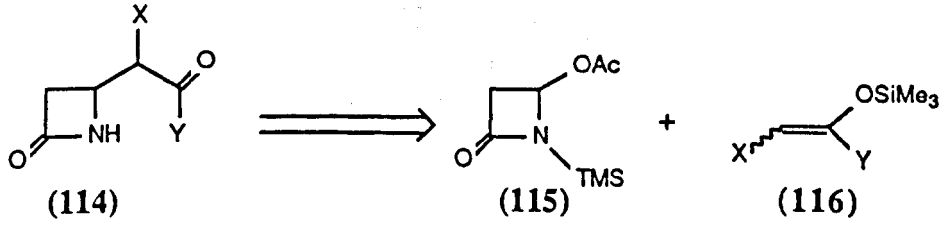


(108b)

Figure 1

It can be easily seen that, in the case of sulphoxide (108b) the transition state is devoid of any non-bonding interactions. In contrast, the isomer (108a), shows a methylene group to be in very close proximity to the phthalimido group. This may increase the energy of this state to a level high enough to force the reaction down path I (Scheme 9), which involves no such interactions. It was thus concluded that the thermolytic dehydrosulphenylation of sulphoxides is regiospecific and determined by the chirality of the sulphoxide.

Barrett and co-workers[40] established a novel route to azetidinones of type (114) by nucleophilic substitution of the acetoxy group at C4 of 1-trimethylsilyl-4-acetoxyazetidinone (115) with trimethylsilyl enol ethers (116).



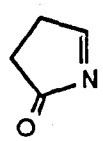
(114) (115) (116)

X = H, Ac, Me, CO_2Me

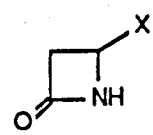
Y = OR, Ar, SAr

Barrett believed these reactions to involve the intermediacy of 1-azetin-4-one. Thus, following a literature precedent[41] which described the trapping of 1-pyrrolin-5-one (117) by Diels-Alder

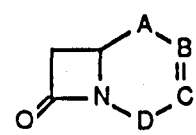
reaction, Barrett made several attempts to capture the 1-azetin-4-one using a variety of 1,3-dipoles, e.g. 2,4,6-trimethylbenzonitrile oxide, and dienes e.g. 4-(dimethylamino)-3-buten-2-one. The generation of azetinone from compounds (118a-f) was studied under acidic, basic, thermal and photochemical conditions. However, in none of these experiments were cyclo-adducts of type (119) detected or isolated.



(117)



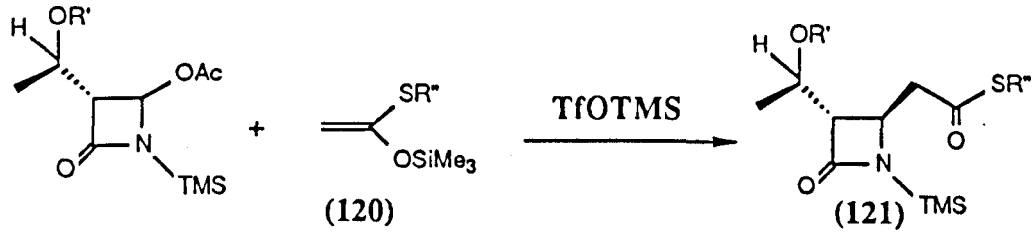
(118)



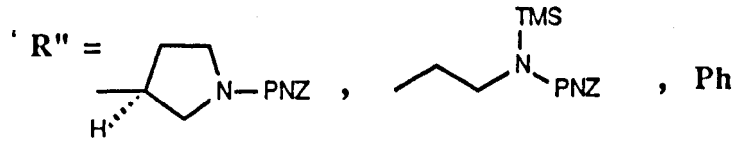
(119)

a X = AcO
b X = OPh
c X = S(CS)OMe
d X = S(CS)Ph
e X = SePh
f X = Se(O)Ph

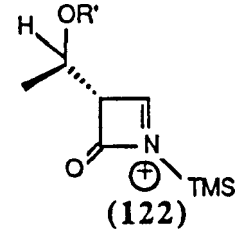
Oida[42] was able to extend Barrett's synthesis[40] of azetidinones of type (114) to include the preparation of azetidinone-thiolesters (121).



R' = TBDMS, p-Nitrobenzyloxycarbonyl (PNZ)

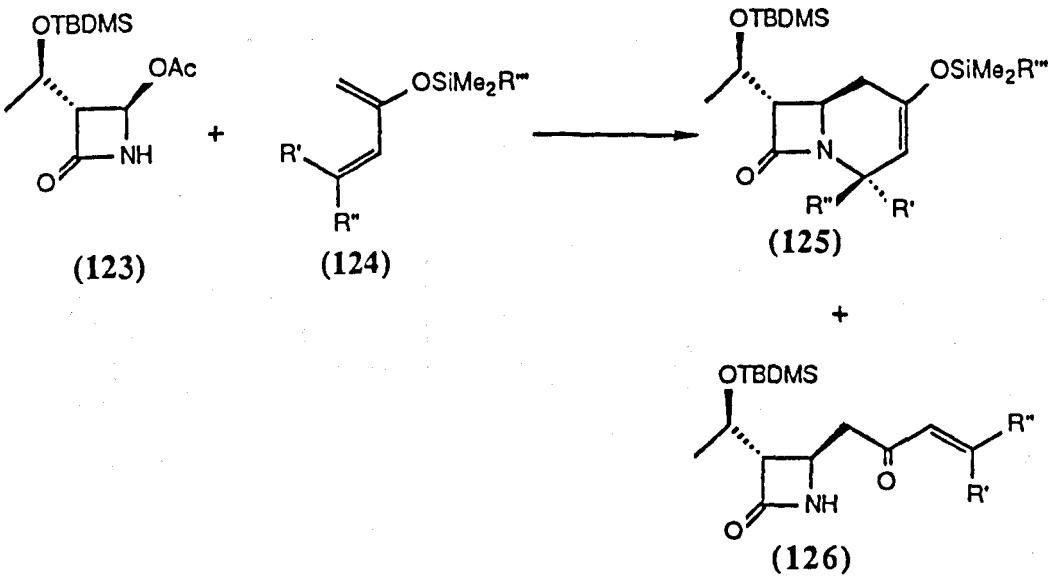
R" = 

This reaction was believed to go by way of an electrophilic attack of the immonium intermediate (122) on the silyl ketene (120). The reaction occurred exclusively at the sterically less hindered ß-face of (122) to afford the trans-azetidinone-thiolesters (121).



Inevitably, the successful trapping of the elusive 1-azetin-4-one intermediate by a Diels-Alder reaction was reported in 1985, during the course of this project. Ueda and Maynard[43] believed that the use of one of the siloxydienes used by Danishefsky[44] to add to unactivated imines, would form a

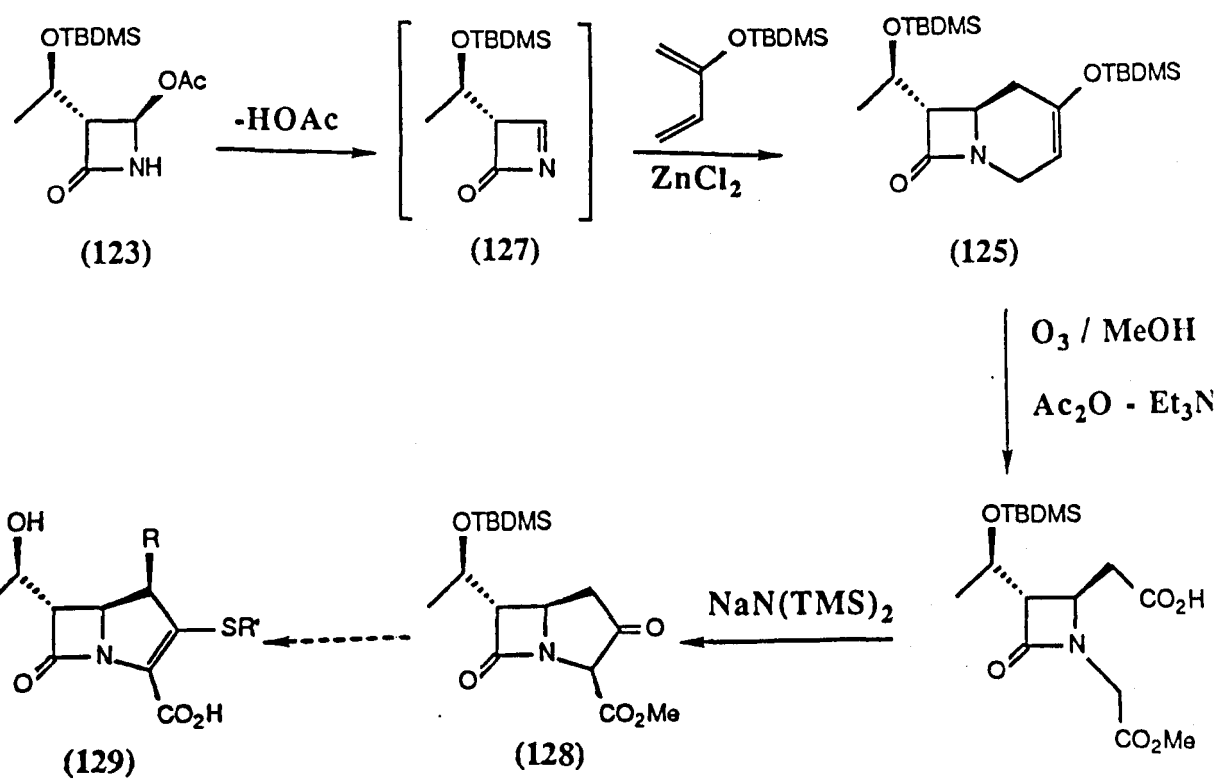
successful trap for the azetinone system. They showed that the treatment of 4-acetoxy-azetidinone (123) with siloxydienes (124a-d) in the presence of fused zinc chloride in dichloromethane afforded the desired cycloadduct (125) albeit in low yield. Not surprisingly the major product was the compound (126) formed by nucleophilic displacement of the acetate by the enolate ester.



(123) (124) (125) (126)

				YIELD / %	
	R^1	R^2	R^3	(125)	(126)
a	H	H	Me	18	75
b	H	Me	Me	20	47
c	H	Ph	t-Bu	0	72
d	Me	Me	Me	0	48

Ueda[45] was able to extend his azetinone trapping reaction to develop a novel four step synthesis of the carbapenem-2-one (128) skeleton, a versatile penultimate precursor of carbapenems (129). The trapping of the azetinone (127) generated <u>in situ</u> from lactam (123) by the siloxydiene (124a) was slightly modified from the initial publication[43] with the effect of increasing the yield of cycloadduct (125) to 54-65%. Ozonolysis of carbacephem (125) and subsequent cyclisation afforded the desired carbapenem system (129) in overall 30% yield.



1.5. CONCLUSION

The work by Ueda et al[43,45] has shown that 1-azetin-4-ones form a viable synthetic intermediate to the bicyclic β-lactam antibiotics. However, to fulfil such a role, the 1-azetin-4-one system must be isolated as a stable compound, similar to one of those prepared by Schaumann,[21] or be generated in practicable yield as a trappable intermediate.

It is therefore important to be able to prepare stable N-unsubstituted 2,4-azetidindiones and N-unsubstituted 4-thioxo-2-azetidinones which appear to be the most practical precursors.

SECTION B

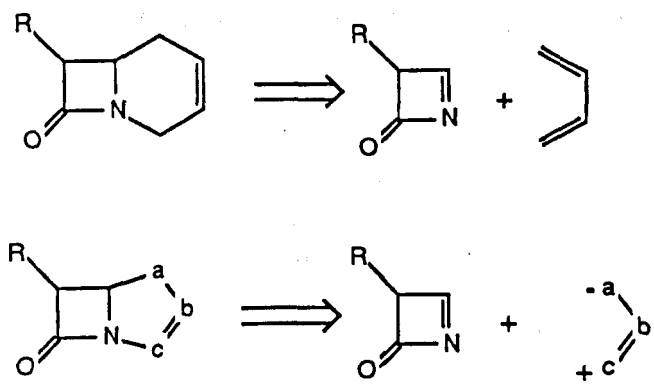
DISCUSSION

CHAPTER 2

1-AZETINES

2.1. INTRODUCTION

Retrosynthetic analysis of bi-cyclic ß-lactam systems (which are common to most of the ß-lactam antibiotics [46]) shows that cycloaddition of either a diene or a 1,3-dipole to an azetinone system would result in these highly sought after systems, as shown in Scheme 10.



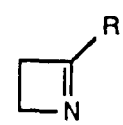
Scheme 10

This project set out to investigate the feasibility of such reactions, which, if successful would describe a versatile one step synthesis of bi-cyclic ß-lactams.

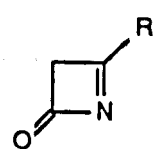
During the early course of this work, Ueda and his co-workers[42] published their successful trapping of the azetinone

system with electron rich siloxy-dienes. These results, although disappointing at the time, did prove the viability of the azetinone system as a potential synthetic precursor to the bicyclic ß-lactam antibiotics.

As has already been shown (see 1.4), the 1-azetin-4-one system has proved very elusive and only one example of its isolation as a stable compound has been described.[19] It was, therefore, decided to first investigate the dienophilic and dipolarophilic character of the more easily obtained 1-azetine system (129), which is closely related to the 1-azetin-4-ones (4).



(129)

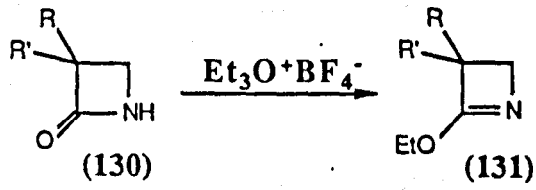


(4)

2.2. HISTORY AND CHEMISTRY OF 1-AZETINES

Testa and Pifferi[47] were responsible for the first synthesis and characterisation of 1-azetines (131) in 1967. However, this synthesis was confined to 3,3-disubstituted 1-azetines e.g. (131a-c), as this pattern of substitution was believed to influence the stability of the ring system.

1-Azetines (131a-c) were prepared from the corresponding 2-azetidinones (130a-c) and triethyloxonium tetrafluoroborate (Meerwein's Reagent).



(130) (131)

a : R = R' = n-C_3H_7

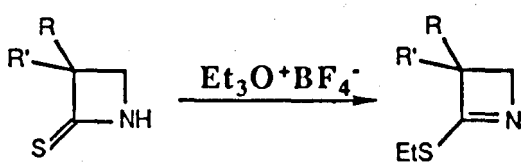
b : R = Ph, R' = C_2H_5

c : R = R' = Ph

2-Ethoxy-3,3-disubstituted-1-azetines (131a-c) were found to be thermolabile substances, as expected in view of the presence of a -CH=N- group in a highly strained ring. Their stability was influenced by the type of substituents at C3 and increased on passing from alkyl to aryl radicals; e.g. compounds (131a) and (131b) were liquids and polymerised at room temperature, while 3,3-diphenyl-2-ethoxy-1-azetine (131c) was a solid which remaind unaltered for long periods of time.

Furthermore, Testa and Pifferi reported that the analogous 3-substituted 2-ethylthio-1-azetines (133a-c), obtained from azetidin-2-thiones (132a-c) and triethyloxonium

tetrafluoroborate, exhibited higher stability to heat and chemical agents than the 2-ethoxy-1-azetines (131).



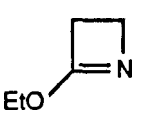
(132) (133)

a : R = Ph, R' = C_2H_5

b : R = R' = Ph

c : R = cyclohexyl, R' = H

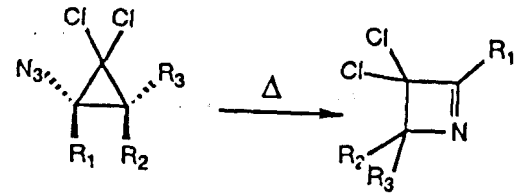
Two years later, in 1969, Bormann[48] was able to extend Testa and Pifferi's synthesis to include 3-monosubstituted, 4-monosubstituted and 4,4-disubstituted-2-ethoxy-1-azetines and, later,[49] the parent compound 1-azetine (134).



(134)

1-Azetines have since been prepared by several other methods. These include the pyrolysis of cyclopropyl

azides[50-52] (135) to azetines (136).



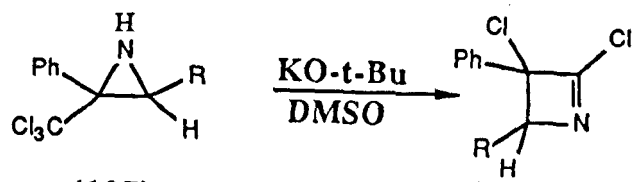
(135) (136)

R_1 = Ph, Me, SMe

R_2 = H, Me

R_3 = H

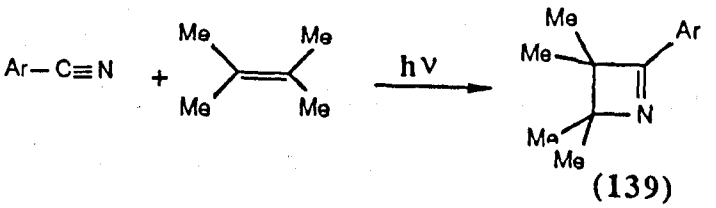
Also the treatment of 2-(trichloromethyl)aziridines (137) with potassium tert-butoxide has been reported[53] to yield 1,2-dichloro-1-azetine derivatives (138).



(137) (138)

R = Me, H, Ph

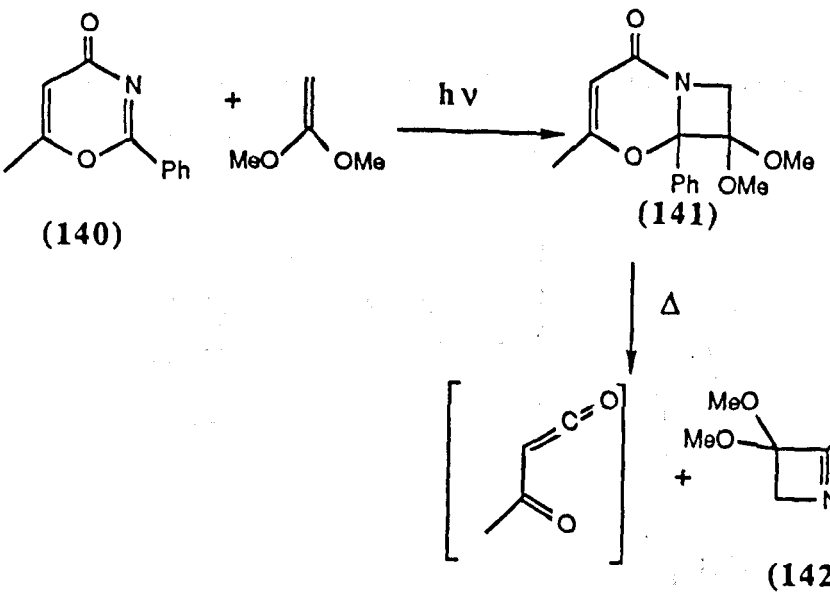
Photochemical cycloaddition of aromatic nitriles to 2,3-dimethylbut-2-ene was found to give stable 2-aryl-1-azetines[54-55] (139).



(139)

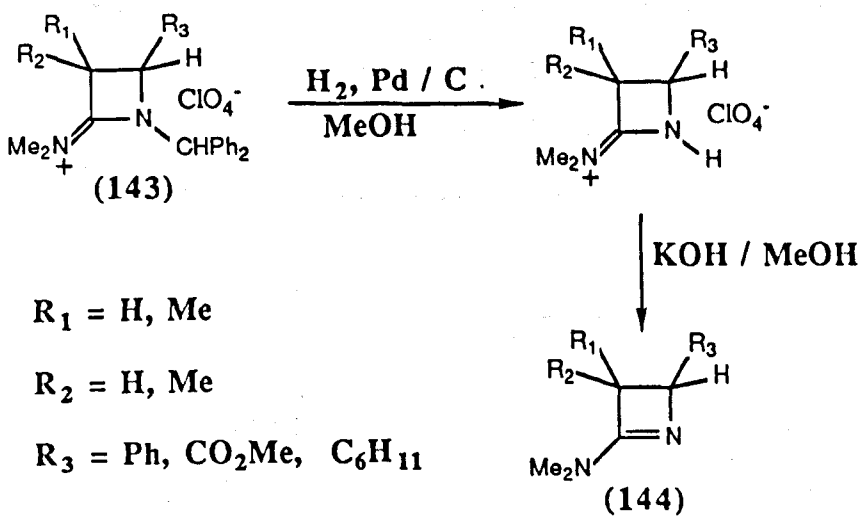
Ar = Ph, 1-naphthyl, 2-naphthyl

2-Phenyl-3,3-dimethoxy-1-azetine (142) was prepared by a novel method involving the [2+2] photocycloaddition of 1,1-dimethoxyethane to the C=N bond of a 1,3-oxazine-4-one (140). This was followed by thermal retro-Diels-Alder fragmentation of the resultant bicyclic azeto-oxazinone (141),[56] as shown below:



(140) (141) (142)

Finally, the novel 2-amino-1-azetines (144) were prepared[57] successfully from azetidin-2-iminium salts (143) by hydrogenolysis followed by treatment with base.

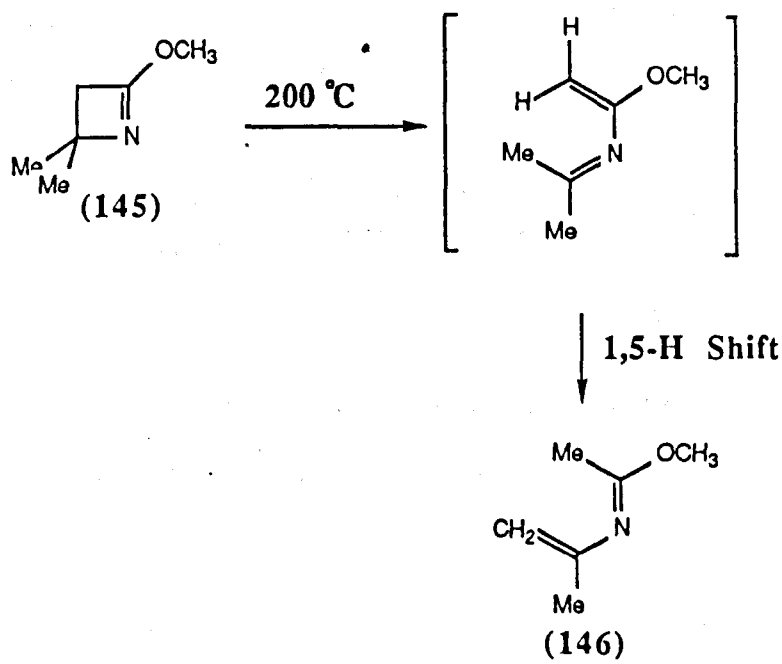


R_1 = H, Me

R_2 = H, Me

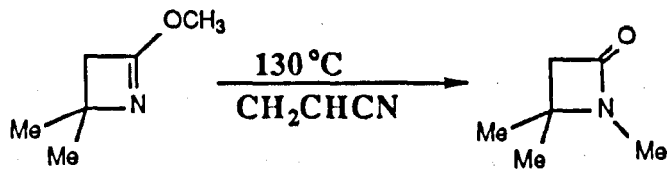
R_3 = Ph, CO_2Me, C_6H_{11}

As has been stated previously, 1-azetines are thermolabile substances. Their decomposition products, however,



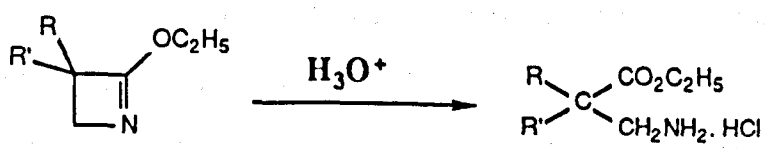
have been found to be dependent on the concentration of the azetine. In the vapour phase, thermolysis of 2-methoxy-1-azetines e.g. (145) at 200 °C for 8 hrs was found to result in complete conversion to the unsaturated imino ether (146).[58]

Thermolysis of azetine (145), as a concentrated solution in acrylonitrile, however, does not cause ring opening, but rearrangement to the N-methyl-β-lactam.



(145) (147)

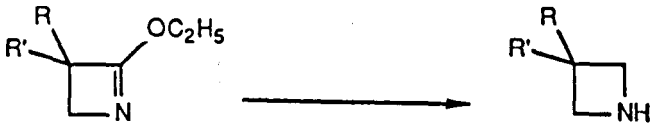
As expected, 1-azetines were found to be acid labile[47]. Treatment with dilute hydrochloric acid causes 2-ethoxy-1-azetines (131) to ring open to the amino esters (148). The 2-ethylthio-1-azetines (133), however, show more stability towards dilute acid, forming water soluble hydrochlorides when treated with dilute HCl.



(131) (148)

Reduction of 1-azetines using lithium aluminium hydride was found to lead to the formation of the corresponding

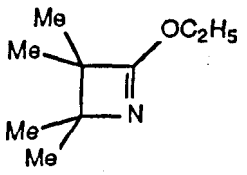
azetidine e.g. (149).



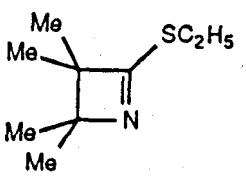
(131) (149)

2.3. PREPARATION OF 1-AZETINES

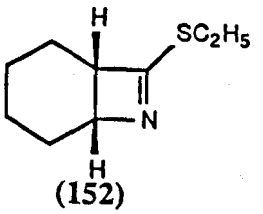
For the purpose of this work, three different azetines were prepared, namely 2-ethoxy-3,3,4,4-tetramethyl-1-azetine (150), 2-ethylthio-3,3,4,4-tetramethyl-1-azetine (151), and 3-ethylthio-2-azabicyclo[4.2.0]oct-2-ene (152).



(150)

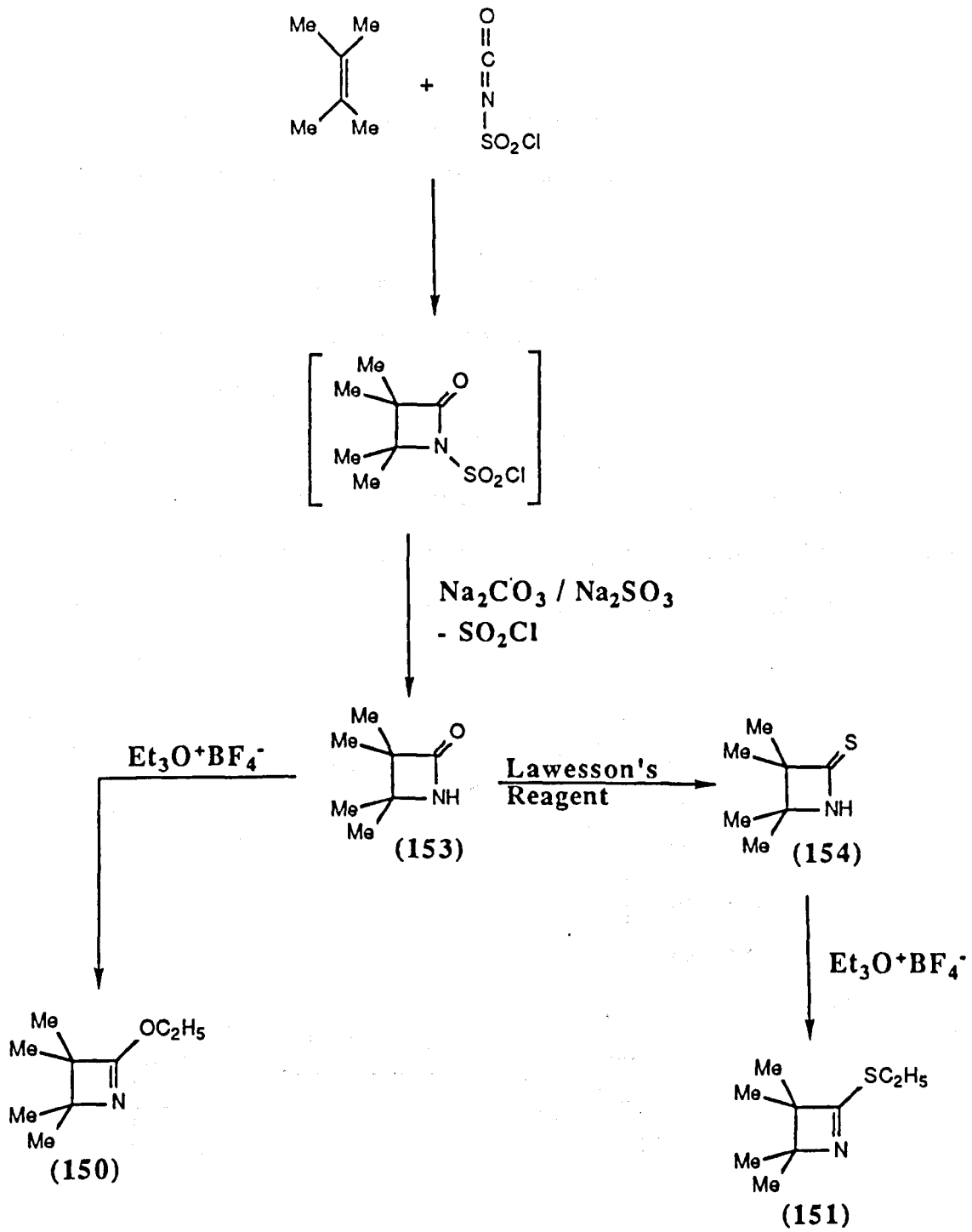


(151)



(152)

Azetines (150 & 151) were both prepared from 3,3,4,4-tetramethylazetidin-2-one (153).[48] Hence, treatment of azetidinone (153) with triethyloxonium tetrafluoroborate in dry dichloromethane produced azetine (150) which was purified by flash silica chromatography. The preparation of azetine (151) required the thionation of azetidinone (153), using Lawesson's reagent[59] in dry THF, to azetidine-2-thione (154). Subsequent

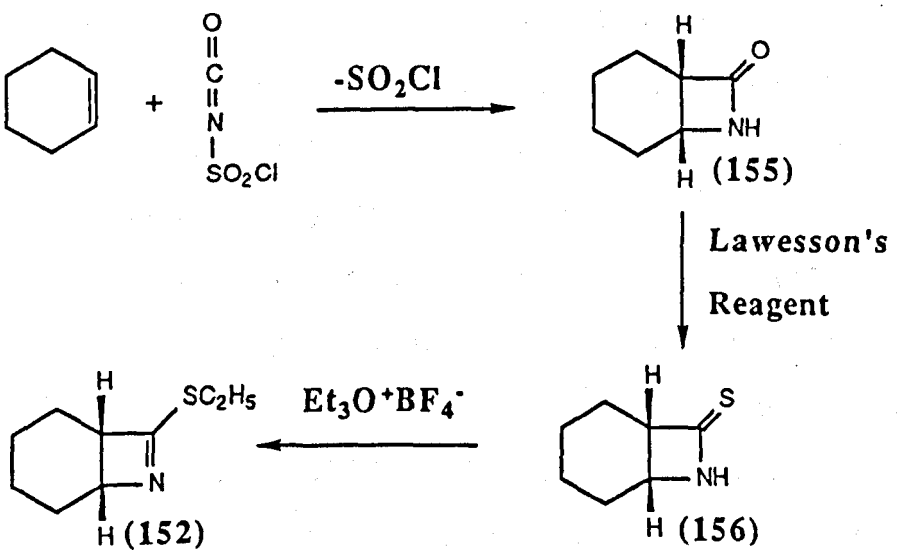

Me
Me
Me
Me
O
C
N
SO2Cl
Me
Me
Me
Me
O
N
SO2Cl
Na2CO3 / Na2SO3
- SO2Cl
Et3O+BF4-
Me
Me
Me
Me
O
NH
(153)
Lawesson's
Reagent
Me
Me
Me
Me
S
NH
(154)
Et3O+BF4-
Me
Me
Me
Me
OC2H5
N
(150)
Me
Me
Me
Me
SC2H5
N
(151)

Scheme 11

treatment of thione (154) with triethyloxonium tetrafluoroborate in dry dichloromethane yielded azetine (151) as a stable oil in good yield.

Azetidin-2-one (153) itself was prepared by the reaction of 2,3-dimethylbut-2-ene with chlorosulphonyl isocyanate in dry ether followed by basic hydrolysis to remove the chlorosulphonyl residue,[59] as shown in Scheme 11.

Similarly, azetine (152) was prepared from thiolactam (156), which in turn was prepared from the bicyclic azetidinone (155)[60] by treatment with Lawesson's reagent, as shown in Scheme 12.



Scheme 12

The 1-azetine structure of azetines (150, 151 &

152) was confirmed by means of IR and NMR spectroscopy. In the case of azetine (150), the IR spectrum showed the loss of the lactam C=O stretching at 1630 cm^{-1} and the appearance of a band at 1630 cm^{-1} indicative of an endocyclic C=N bond.

The NMR spectrum of azetine (150) contained the signals due to the $-CH_3$ and $-CH_2$ groups of the -OEt moiety. The signal due to the methylene group being a quartet at 4.15 ppm. This signal is some 0.7 ppm lower than that expected of a methylene next to oxygen, and about 0.45 ppm lower than that of a methylene in a $-CH_2-O-C=C$ structure. This downfield shift was taken to be an indication of electron density shift from the oxygen towards the nitrogen. This also suggested that the C=N bond of 1-azetines is more highly electron rich than an isolated imine bond. Both the IR and NMR data obtained were in agreement with those published by Testa and Pifferi.[47]

The IR spectra of azetines (151 & 152) were similar, in that they both showed the absence of a band at about 1240 cm^{-1} due to the C=S stretching[61], and the appearance of a band at approximately 1530 cm^{-1} attributed to the C=N stretching.

The NMR spectrum of azetine (151) closely resembles that of azetine (150) with the exception that the methylene (which is now next to sulphur) signal appears at 3.0 ppm. This again is about 0.5 ppm lower than that expected for

a $-CH_2-S-$ structure and is likely to be due to the effect already discussed for azetine (150).

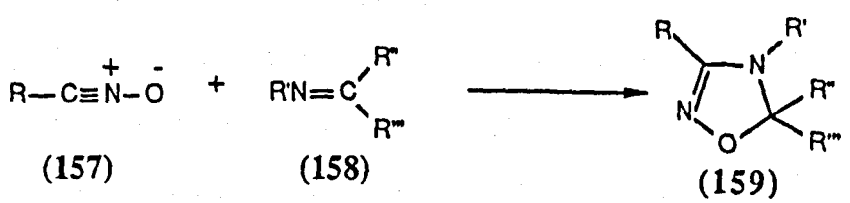
Azetine (152) exhibited a more complex NMR spectrum. The distinctive features of this spectrum were the methylene signal, a doublet of quartets at 2.55 ppm, and a pair of distinctive signals at 3.25 ppm (quartet) and 4.05 ppm (multiplet). These signals were assigned to the two bridge-head methyne protons. The unexpected low field position of these two signals is attributed to strain induced by the bi-cyclic system on the two bridge-head centres.

2.4. 1,3-DIPOLAR CYCLOADDITIONS TO 1-AZETINES

2.4.1. NITRILE OXIDES

a- INTRODUCTION

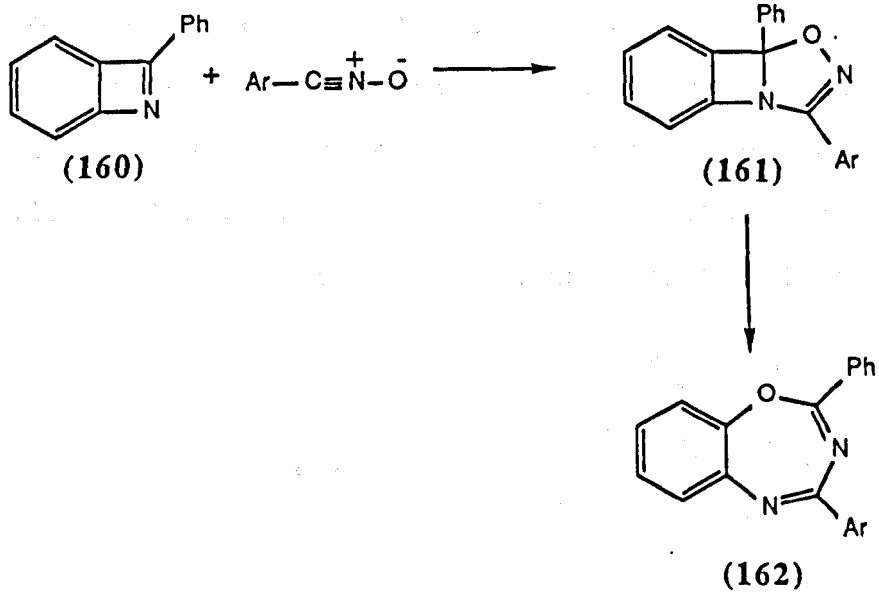
1,3-Dipolar cycloadditions of nitrile oxides (157) to acyclic and cyclic imines (158) to give 1,2,4-oxadiazolines (159) has been well documented.[62a-c]



(157) (158) (159)

R = Alkyl, Aryl

Addition of arylnitrile oxides to 2-phenylbenzazete (160), was found by Rees and co-workers,[63] to yield the unstable primary adducts (161) which spontaneously rearrange to 1,3,5-oxadiazepines (162).

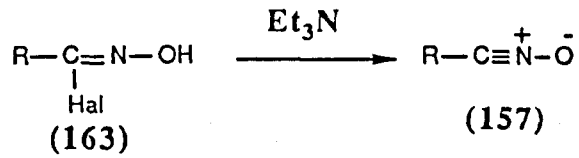


(160) (161) (162)

This rearrangement was believed to occur so as to relieve strain in the 4,5-fused system in adduct (161).

b- GENERATION OF NITRILE OXIDES

By far the most common and straight forward method of generating nitrile oxides, is *in situ*, by treatment of the precursor hydroximoyl halides (163) with triethylamine.[64]



(163) (157)

Hydroximoyl halides undergo an almost immediate dehydrohalogenation with triethylamine. Hence, the amine is usually added slowly to a solution of the hydroximoyl halide and dipolarophile, in order to keep a low stationary concentration of the nitrile oxide. In the absence of a reactive dipolarophile, nitrile oxides are known to dimerise to furoxans (164).

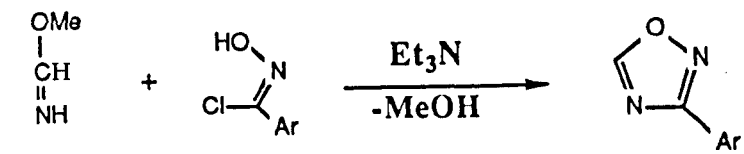
(157) (164)

The hydroximoyl halides (163) are most conveniently prepared from the corresponding aldoximes with halogens,[65] N-chlorosuccinimide[66] or N-bromosuccinimide.[67]

c- REACTION WITH 1-AZETINES

The 1,3-dipolar cycloaddition of nitrile oxides to electron rich olefins (dipolarophiles) is well documented.[66] However, only one publication[69] has appeared concerning the addition of nitrile oxides to electron rich imines. Acyclic imino

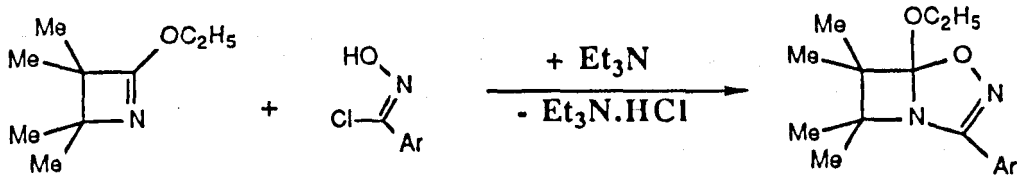
ethers (165) were found to add to nitrile oxides (generated from hydroximoyl chlorides (166) to give 1,2,4-oxadiazoles (167) after loss of methanol.



(165) (166) (167)

The addition of nitrile oxides to 1-azetines - which are cyclic imino ethers - should therefore proceed in a similar manner. Either to give bi-cyclic oxadiazoles or oxadiazapines if ring-opening occurred, as was the case with Rees's benzazetes.

Hence, addition of triethylamine to an equimolar solution of p-methoxybenzohydroximoyl chloride (166a) and 2-ethoxyazetine (150) in dry benzene, resulted in the almost instantaneous precipitation of triethylamine hydrochloride. TLC showed the reaction to be complete after 2 hrs. Filtration followed by solvent removal under vacuum and chromatographic purification of the residue yielded the anticipated 1:1 bicyclic adduct (168a).



(150) (166) (168)

a : Ar = 4-MeO-C_6H_4

b : Ar = C_6H_5

c : Ar = 2-NO_2-C_6H_4

This adduct was characterised by IR and NMR spectroscopy. The latter being the more important. The most prominent features of its spectrum which point to a cycloadduct of the form (168) are as follows; (i) the four methyl groups which appeared as two singlets in azetine (150), each representing two equivalent methyl groups, now appeared as four distinct singlets. This was as expected for a bicyclic system in which the four methyl groups are no longer equivalent, (ii) the signal due to the methylene of the -OEt function had shifted by approximately 0.5 ppm and now appeared as a doublet of quartets. The upfield shift could be accounted for by the loss of the C=N bond (see Section 2.3.) which prevents the electron shift away from the oxygen, thus returning the methylene signal to the expected position for a -CH_2- next to an oxygen. The splitting of the methylene signal to a doublet of quartets is due to the anisotropy induced in the molecule by the presence of the

Fig. 2. 200MHz H^1-NMR SPECTRUM OF 1-AZETINE (150)

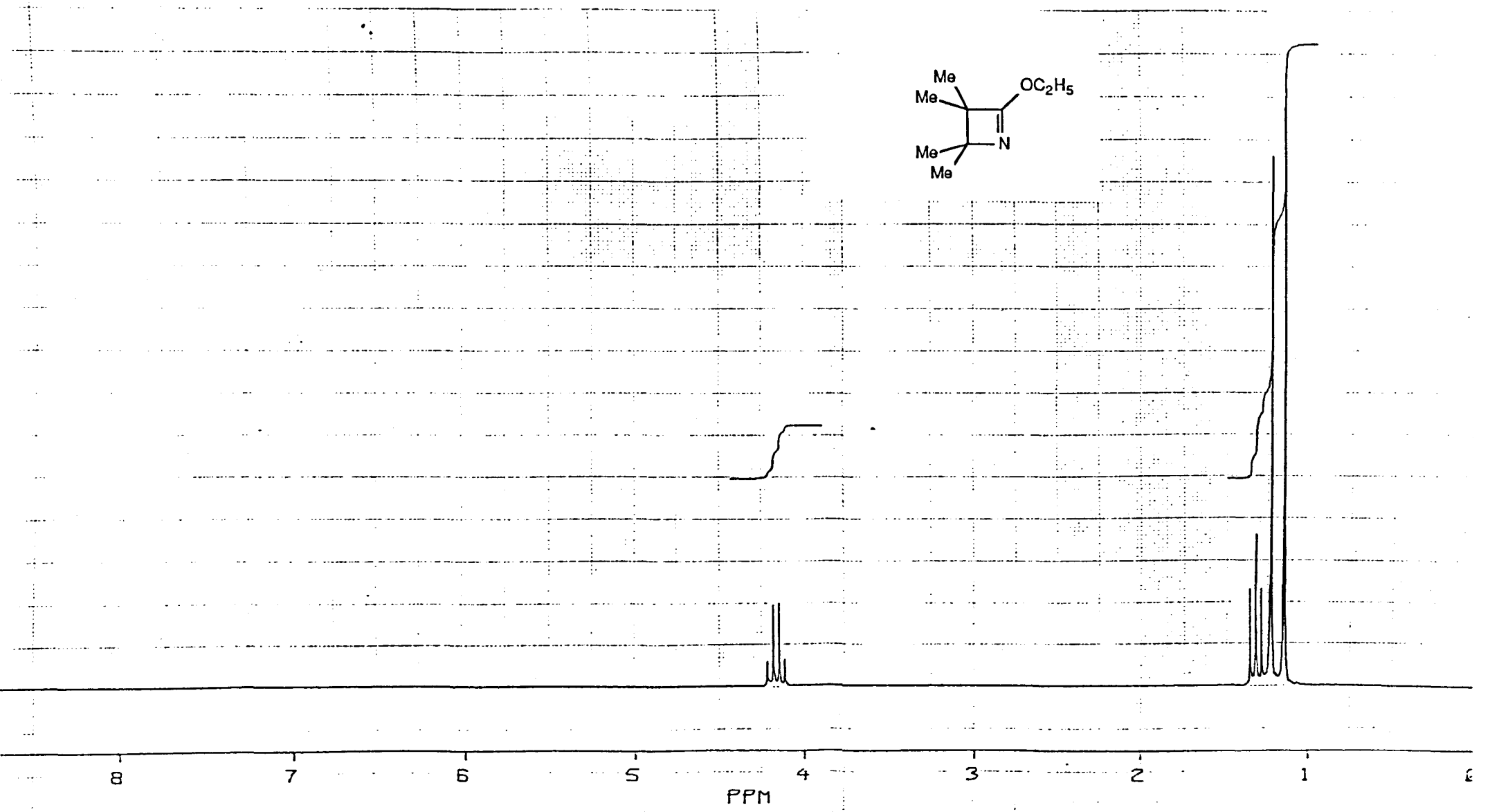
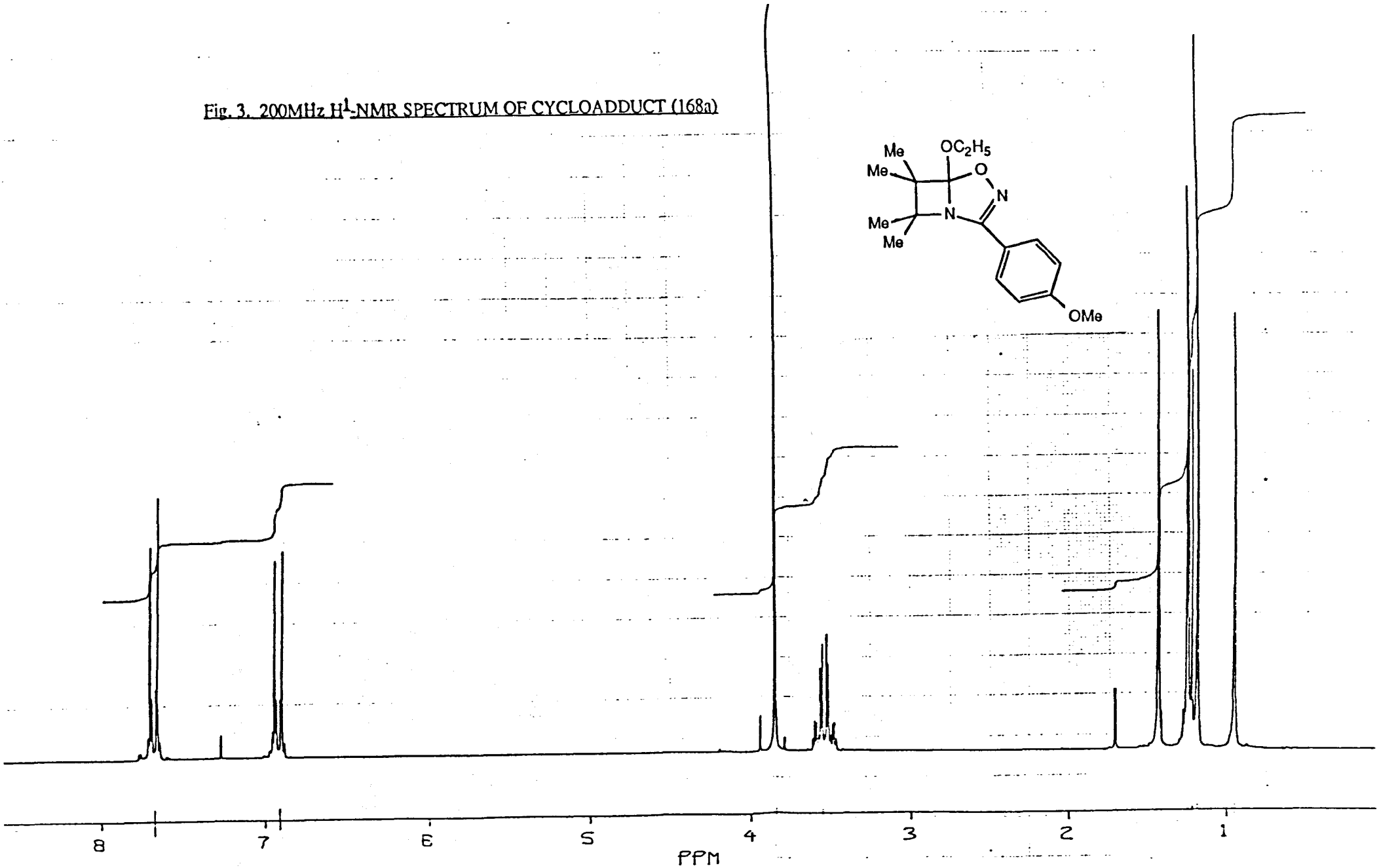
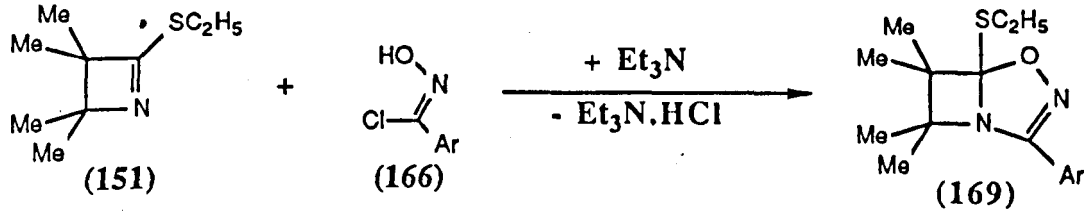


Fig. 3. 200MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (168a)



asymmetric bridge-head centre. Figs 2 and 3 show the 200MHz NMR spectra of azetine (150) and cycloadduct (168) respectively.

Similarly, adduct (169a) was obtained by the treatment of an equimolar solution of 2-ethylthioazetine (151) and p-methoxybenzohydroximoyl chloride (166a) in dry benzene with triethylamine.



a : Ar = 4-MeO-C_6H_4

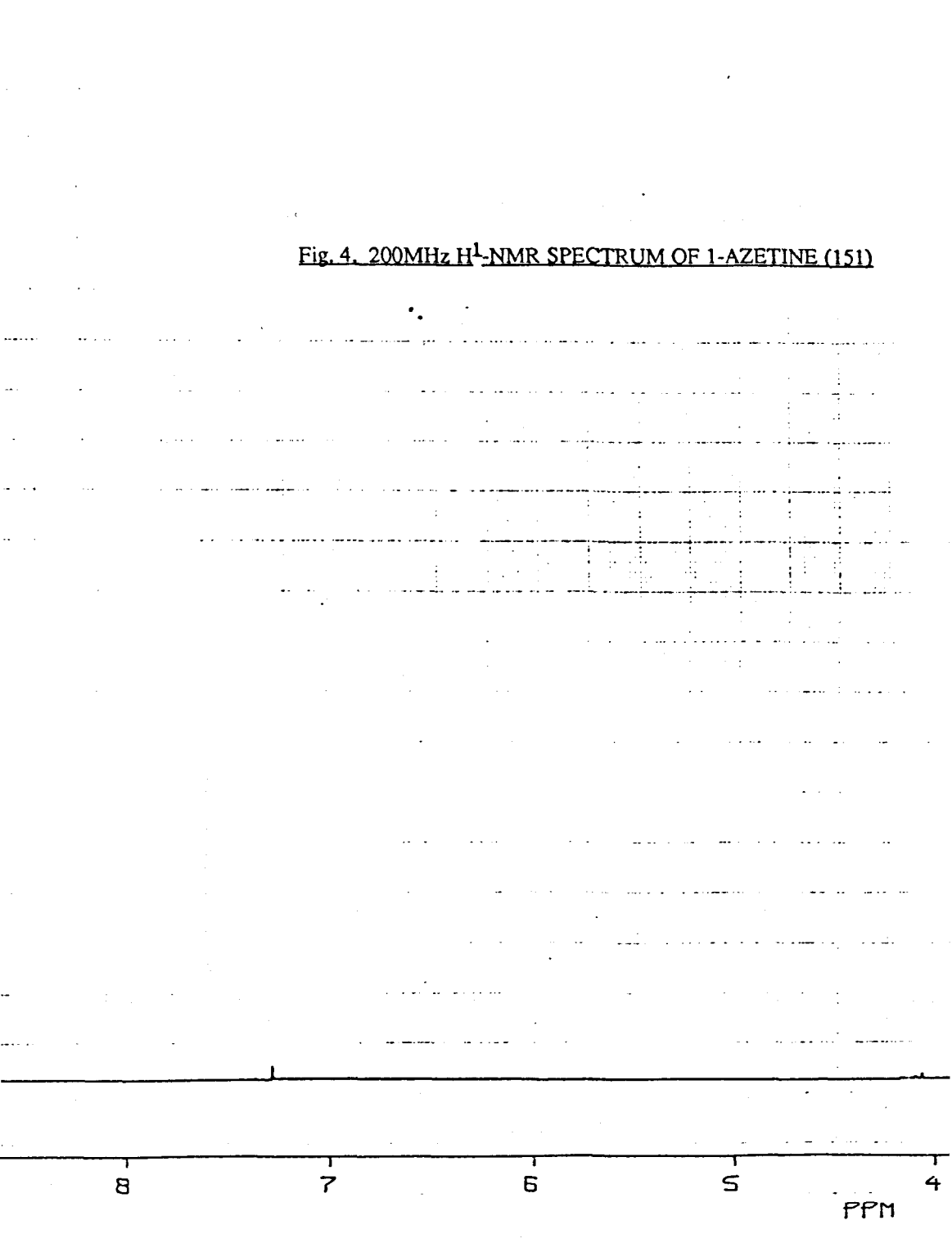
b : Ar = C_6H_5

c : Ar = 2-NO_2-C_6H_4

The NMR spectrum of adduct (169a) followed the same trends shown by adduct (168a) in that there was an upfield shift of the methylene signal by approximatelty 0.25 ppm, accompanied by a splitting to a doublet of quartets. Figs 4 and 5 show the 200MHz NMR spectra of azetine (151) and cycloadduct (169a) respectively.

The addition of p-methoxybenzonitrile oxide to azetine (152) proceeded in a similar manner to those already

Fig. 4. 200MHz H^1-NMR SPECTRUM OF 1-AZETINE (151)



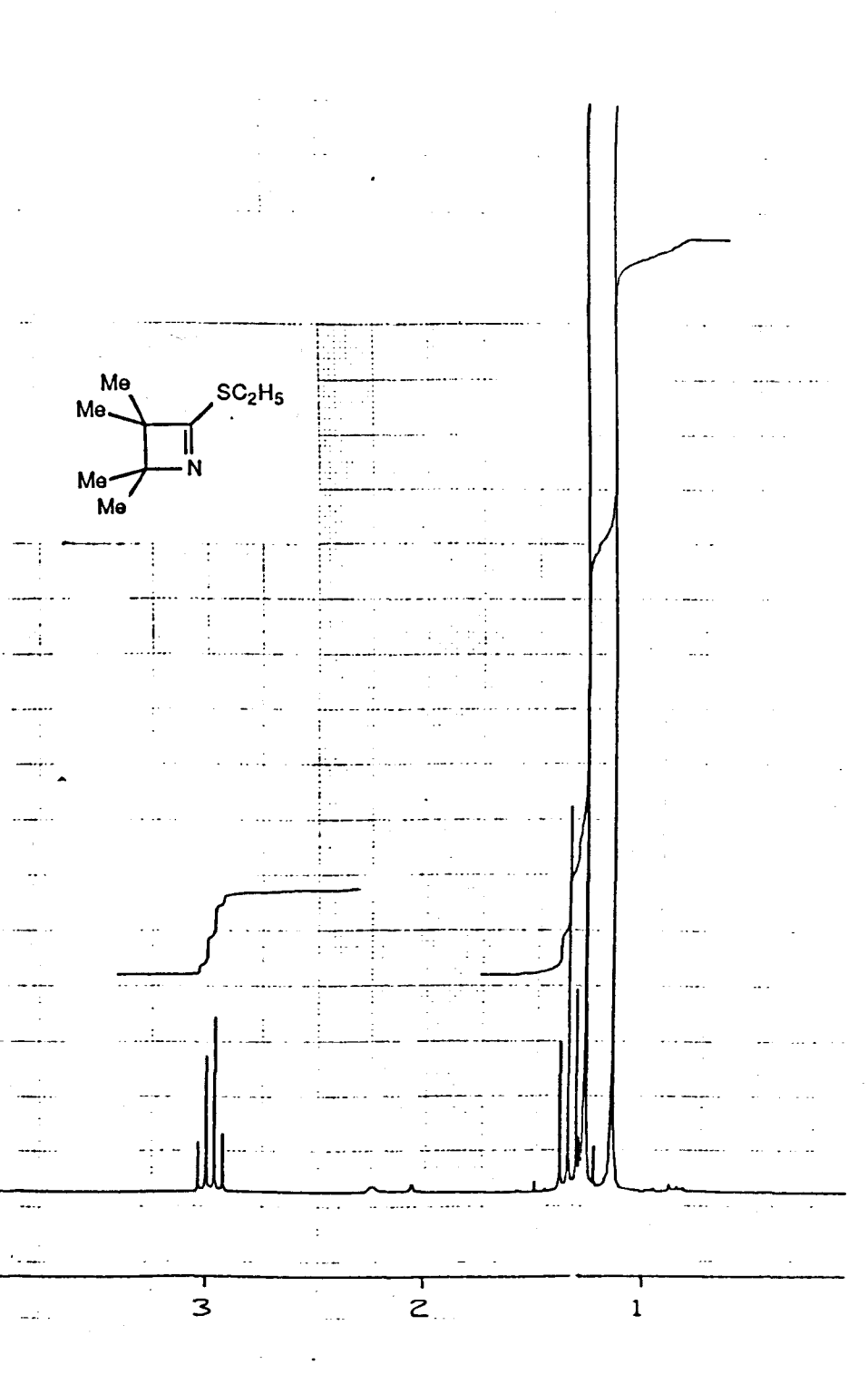
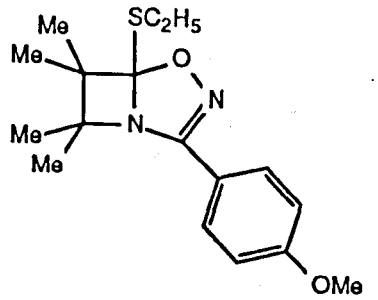
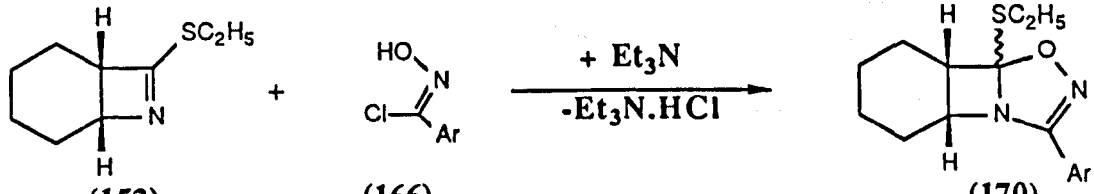

Me
Me
SC2H5
N
Me
Me
3
2
1

Fig. 5. 200MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (169a)



discussed. However, in this case a mixture of the two possible diastereoisomeric adducts (170a) was obtained.



(152) (166) (170)

a : Ar = 4-MeO-C_6H_4

b : Ar = C_6H_5

c : Ar = 2-NO_2-C_6H_4

The presence of the two diastereisomers was evident by TLC. However, attempted separation using HPLC caused the adduct to decompose. High-field NMR also showed evidence for the two diastereoisomers. Most distinctive, was the presence of two sets of triplets closely superimposed. These were assigned to the methyl of the -SEt group. Figs 6 and 7 show the 250MHz spectra of azetine (152) and cycloadduct (170a) respectively.

The use of benzonitrile oxide (generated from hydroximoyl chloride (166b)) and o-nitrobenzonitrile oxide (generated from chloride (166c)) gave similar 1:1 adducts, with all three azetines. The yields for these cycloadditions are given in Table 2.

Fig. 6. 250MHz H^1-NMR SPECTRUM OF BICYCLIC 1-AZETINE (152)

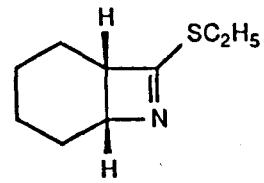


Fig. 7. 250MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (170a)

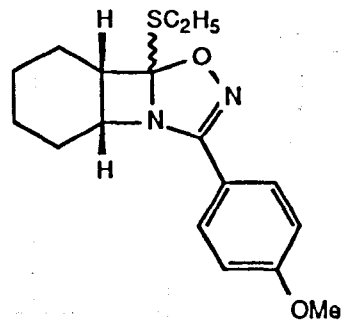
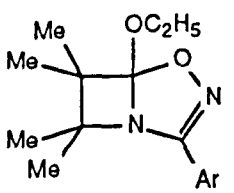
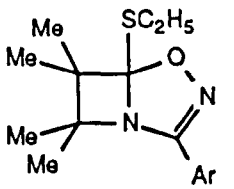


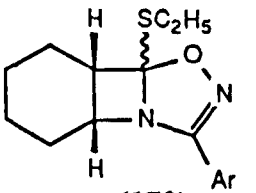
Table 2- Yields of Cycloadducts (168), (169) & (170)



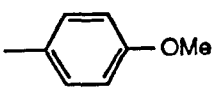
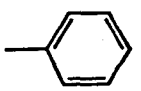
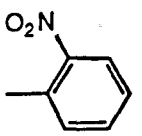
(168)



(169)



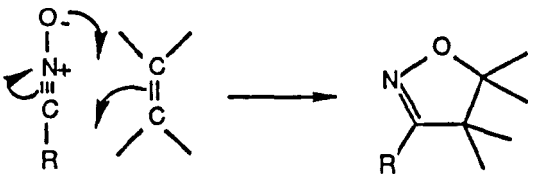
(170)

Ar	YIELD %		
	(168)	(169)	(170)
	72	80	95
	60	62	54
	34	42	43

d- MECHANISM AND REGIOCHEMISTRY OF CYCLOADDITION

The mechanism of 1,3-dipolar cycloadditions has been well investigated, mainly due to work by Huisgen, who has recently reviewed the subject.[70] The cycloadditions are believed to occur in a concerted manner, as shown for example by the independence of their reaction rates from solvent polarities.

The most simplified depiction of 1,3-dipolar cycloadditions is that which employs "curly-arrows" i.e.



This treatment, however, is not sufficient in portraying the events of such a reaction. A more adequate treatise is provided by the Frontier Molecular Orbital Theory (FMO).[71]

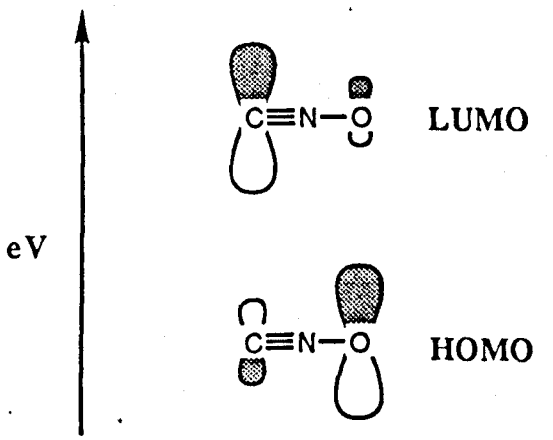


Fig 8 - Schematic representation of the frontier orbitals of nitrile oxides

The frontier orbitals of 1,3-dipoles resemble those of the allyl anion. A schematic representation of the frontier orbitals of nitrile oxides is shown in Fig 8.

The frontier molecular orbitals of the

heterodipolarophiles - such as the C=N bond of interest here - are similar to those of an ordinary olefin, and are depicted in Fig 9.

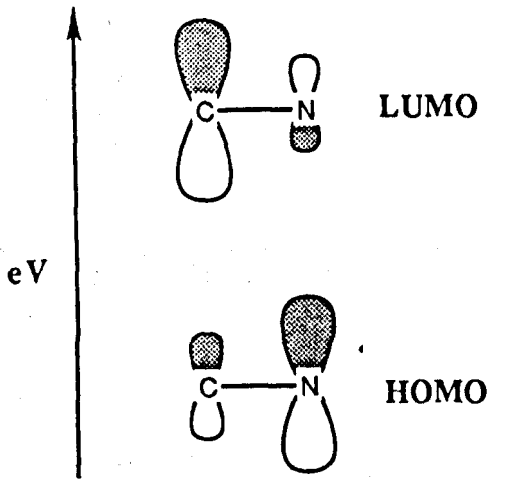


Fig 9 - Schematic representation of the frontier orbitals of a C=N bond

Reaction of 1,3-dipoles with electron deficient dipolarophiles occurs between HOMO (dipole) and LUMO (dipolarophile) i.e. the separation between these two orbitals is smaller than that between LUMO (dipole) and HOMO (dipolarophile) which makes for a stronger interaction. This, however, is reversed in the case of electron-rich dipolarophiles i.e. the interaction is between LUMO (dipole) and HOMO (dipolarophile). Both of these interactions are symmetry-allowed, of course, as can be seen from Fig 10.

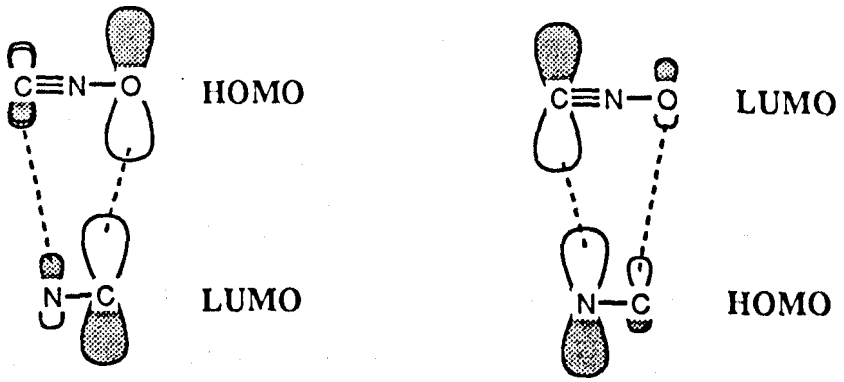


Fig 10 - Frontier orbital interactions in 1,3-dipolar cycloadditions.

The full power of the FMO theory shows itself in predicting the regiochemistry of 1,3-dipolar cycloadditions. Most dipolarophiles are unsymmetrical and will, therefore, be able to add in one of two ways, as shown in Fig 11.

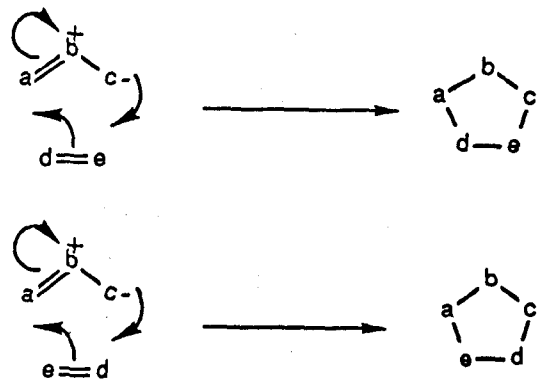


Fig 11 - The two possible regioisomers of a 1,3-dipolar addition to an unsymmetrical dipolarophile.

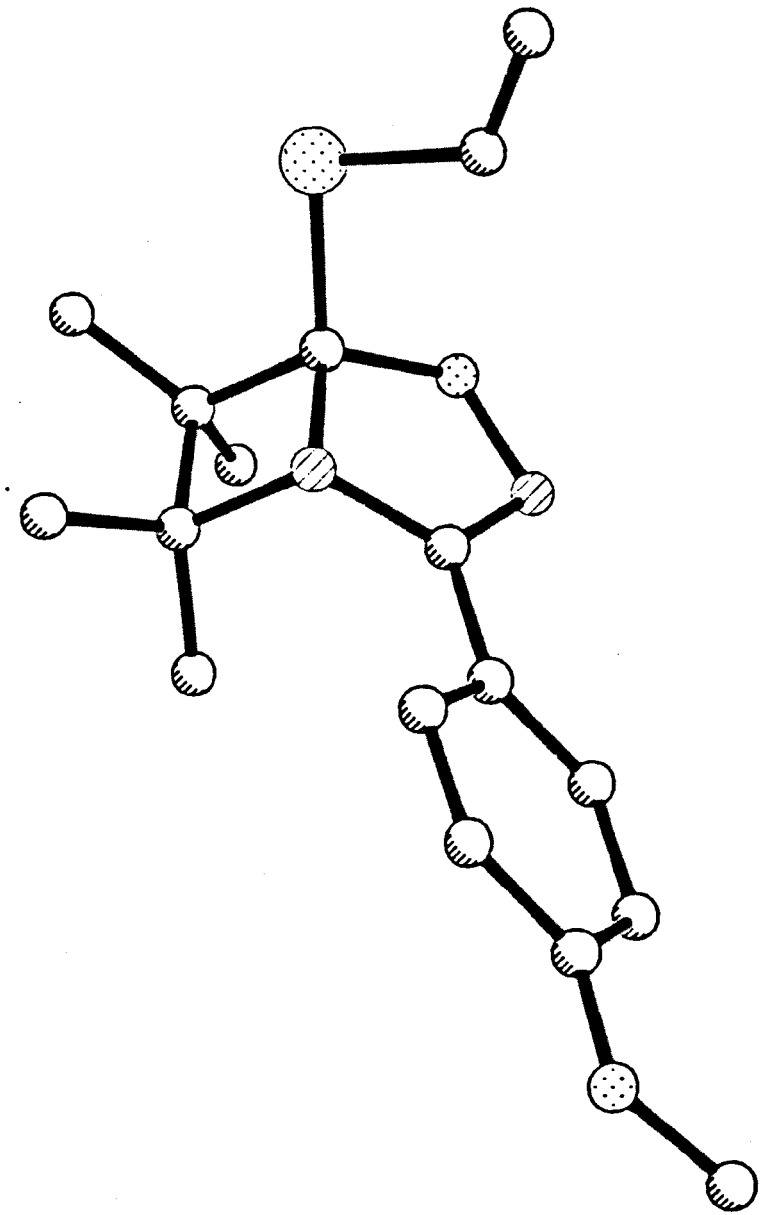
The regiospecificity of these cycloadditions is determined by the size of the coefficients of the relevant orbitals.

In the case of the nitrile oxides the HOMO has the larger coefficient on the oxygen and the smaller coefficient on the carbon terminus of the dipole (the size of the coefficient is related to the size of the orbital "lobes" shown in Fig 8). Conversely, the LUMO has a large coefficient on the carbon and a small coefficient on the oxygen.

The imine bond is polarised as shown in Fig 9, with the HOMO having a larger coefficient on the nitrogen and the smaller one on the carbon. The LUMO of course has the opposite polarisation, with the larger coefficient on the carbon end.

Regioselectivity follows a large-large/small-small coefficient interaction.[71] This is because such an interaction provides stronger bonding than a large-small/small-large interaction.

Applying this to the case of nitrile oxide and 1-azetine, the predicted regiochemistry is that with the oxygen terminus of the dipole bonding to the carbon end of the dipolarophile, and the carbon end of the dipole bonding to the nitrogen end of the dipolarophile, as depicted in Fig 12.



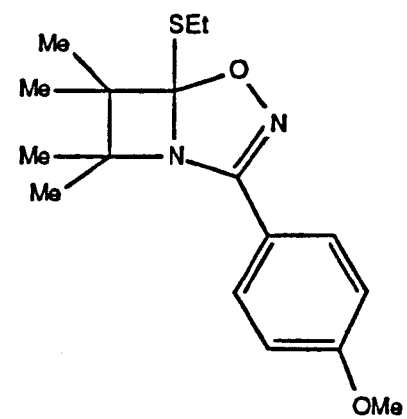


Fig. 13. X-RAY CRYSTALLOGRAPHIC STRUCTURE OF CYCLOADDUCT (169a)

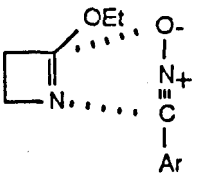


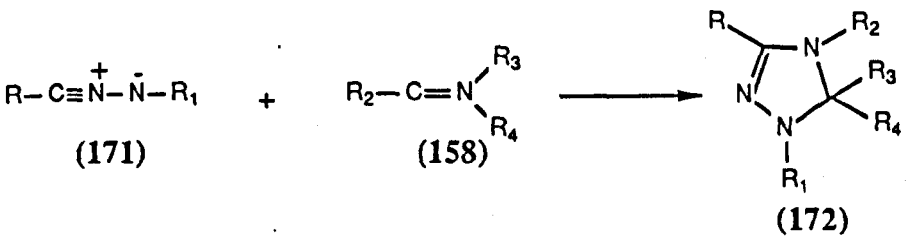
Fig. 12 - Predicted regiochemistry of cycloaddition

To determine whether this predicted regiochemistry is that actually obtained in cycloadducts (168, 169 & 170), a single-crystal X-ray crystallographic study was done on adduct (169a). This is shown in Fig 13 and proves that the predicted regiochemistry is indeed that obtained.

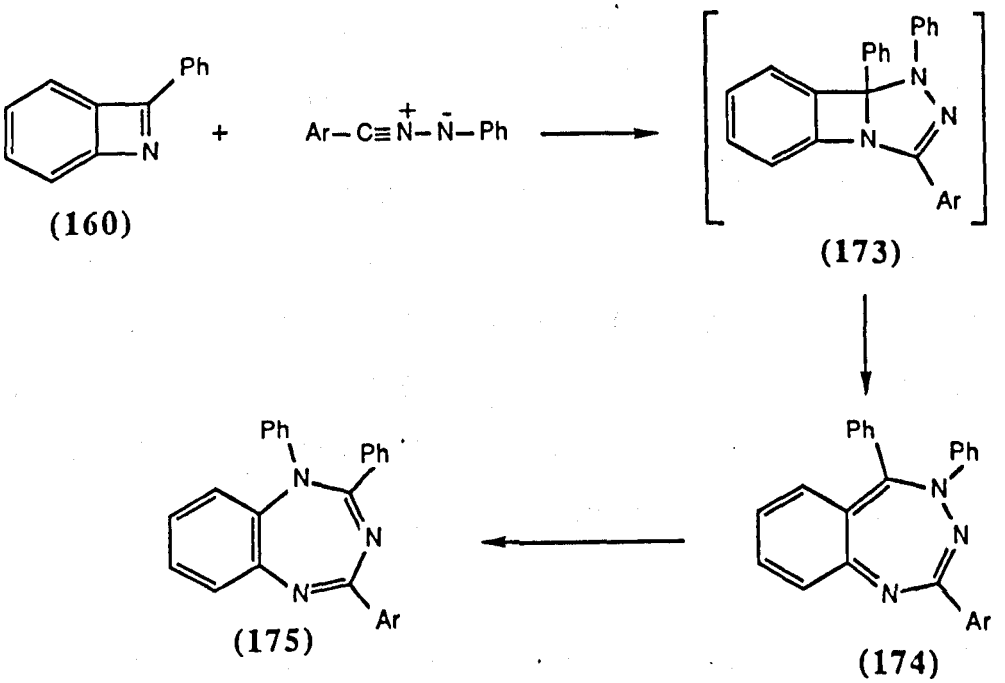
2.4.2. NITRILE IMINES

a- INTRODUCTION

Nitrile imines (171) are very similar in their reactivity to nitrile oxides. Thus with cyclic and acyclic imines (158) they have been found to give 1,2,4-triazoline derivatives (172).[72a-d]

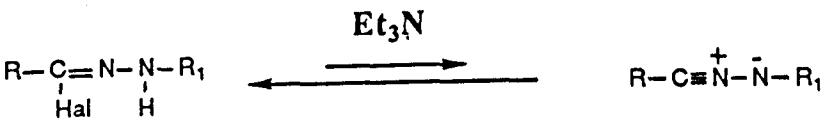


In an extension of the work published by Rees,[63] Storr and co-workers[73] were able to add nitrile imines to 2-phenylbenzazete (160). The products obtained were the expected benzo[f]-1,3,5-triazepines (175) which were believed to be produced by ring opening of the primary adduct (173) followed by rearrangement of the triazepine (174). However, in contrast to the nitrile oxide reaction[63] the primary adducts were not isolable.



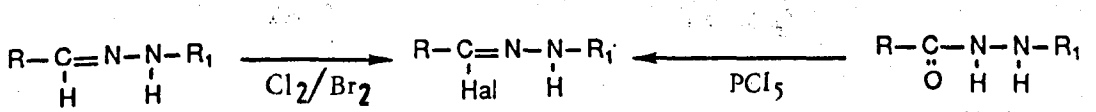
b- GENERATION OF NITRILE IMINES

Nitrile imines are generated *in situ* from their precursor hydrazonoyl halides (176) by treatment with triethylamine. Hydrazonoyl halides undergo an equilibrium reaction with triethylamine in benzene.[74] Hence, in contrast to the generation of nitrile oxides, excess amine (4 equiv.) is added to a benzene solution of the halide and the dipolarophile, and the mixture is heated under reflux.



(176) (171)

The hydrazonoyl halides themselves can be prepared by several means depending on the nature of R and R_1.[68] The two most straight forward ways are (i) by treatment of hydrazides (177) with PCl_5[75] and (ii) by halogenation of aldehyde hydrazones (178).[75] The latter method, however, is only useful in the case of nitro or more heavily substituted N-phenyl rings.

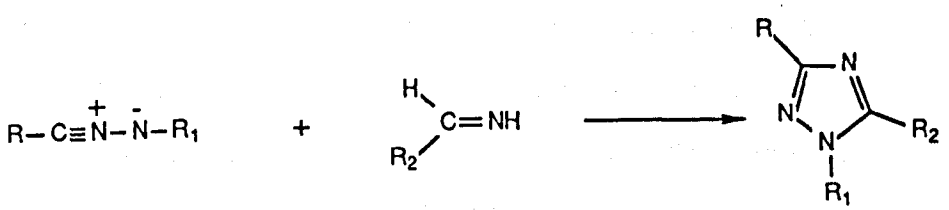


(177) (176) (178)

Hal = Cl, Br

c- REACTION WITH 1-AZETINES

Nitrile imines have been found to add smoothly to the C=N bond of oximes, amidines and imidates to give substituted triazoles (179).[76]



R_2 = OH, NH_2, OR

(179)

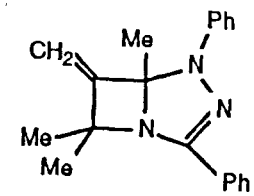
It was expected, therefore, that nitrile imines should add in a similar fashion to the C=N bond of 1-azetines, to give bicyclic triazoles.

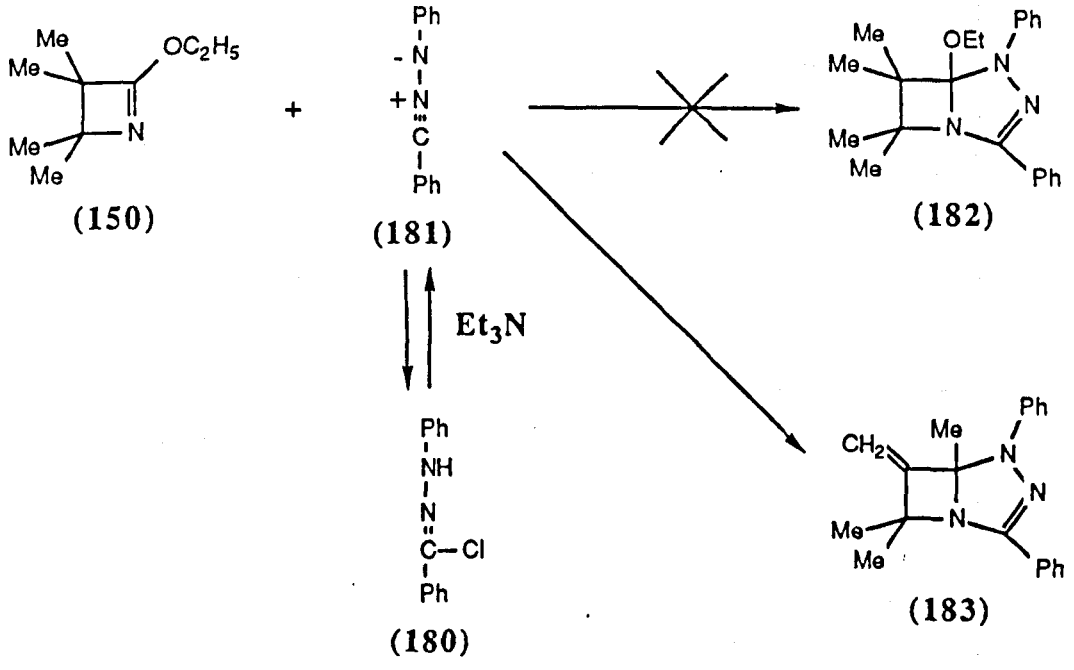
Accordingly, the 1,3-dipolar cycloaddition of diphenyl nitrile imine (181) [generated *in situ* from hydrazonoyl chloride (180) by dehydrohalogenation using triethylamine] to 2-ethoxyazetine (150) was attempted. The reaction was carried out in boiling dry benzene using an equimolar mixture of the azetine and the chloride and an excess of triethylamine. Heating was continued for 2 hrs during which time a precipitate of triethylamine hydrochloride was gradually formed. After work-up and chromatographic purification of the reaction mixture, a crystalline solid was obtained, which was believed to be the cycloadduct (182).

High-field NMR spectroscopy, however, showed that the product did not have the assumed structure (182), in that the proton NMR spectrum showed the total absence of the signals expected for the methyl and methylene of the -OEt function. Furthermore, there were only two signals, in the ratio 1:2, where the four methyl singlets were expected (see Figs 3 & 5). Finally, two singlets, each integrating for one proton appeared at 4.50 ppm and 4.65 ppm. This NMR spectrum is shown in Fig 14.

The product was thus subjected to mass spectroscopic analysis. This showed the molecular ion peak at m/e 303. The molecular weight for the expected adduct (182) was 349. The difference in the two masses corresponded to the loss of EtOH. At this stage the speculative structure (183) was assigned to the product. This fitted both the mass spectrum and more importantly the NMR spectrum. The two signals at 4.5 ppm and 4.65 ppm were in the expected position for an exocyclic methylene group. The geminal methyls were equivalent and appeared as a singlet at 1.45 ppm with the methyl at the bridge-head centre appearing at 1.6 ppm.

Fig. 14. 250MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (183)





In an attempt to confirm this structure, a C-13 NMR spectrum of the product was obtained. The most significant part of this was a singlet at 110 ppm. Which in the proton coupled spectrum appeared as a triplet. Hence, both the position and the coupling of the signal fit an exocyclic $-C=CH_2$ structure. Thess spectra are shown in Figs 15.i. & 15.ii.

The reaction of diphenyl nitrile imine (181) with 2-ethylthioazetine (151) was carried out under the same conditions. As in the previous example, the product obtained was not the primary adduct (184) but once again the rearranged compound (183).

Fig. 15.i. 75MHz C^{13} NMR (UNCOUPLED) SPECTRUM OF CYCLOADDUCT (183)

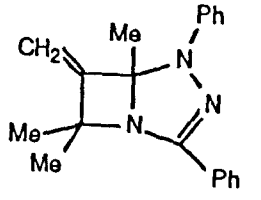
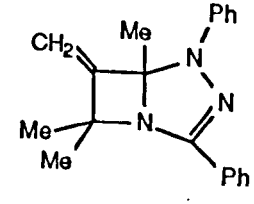
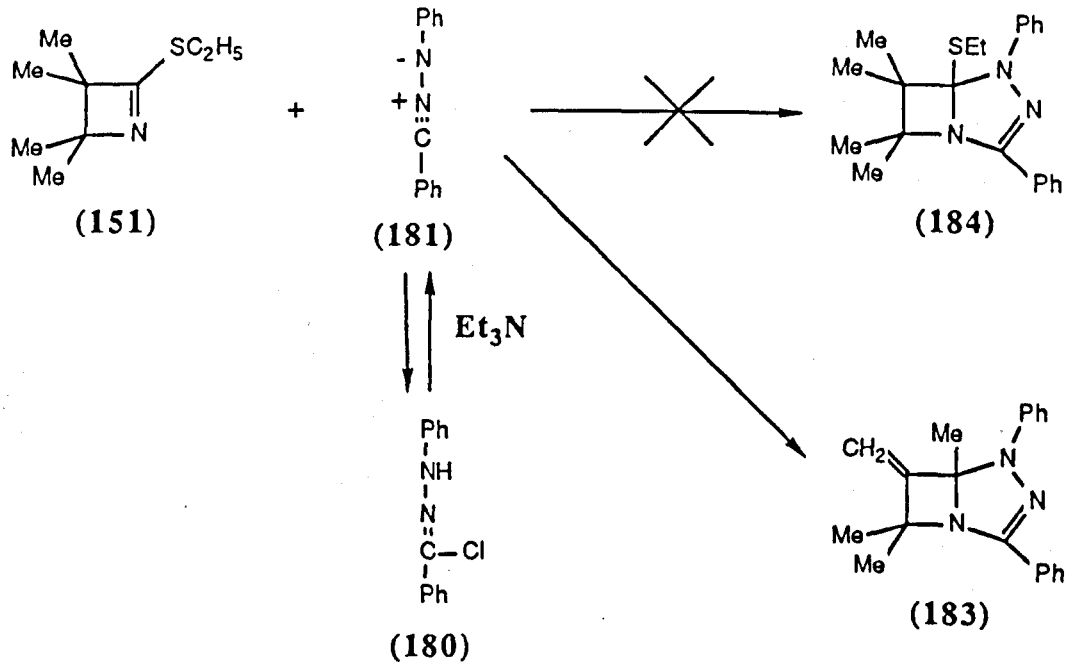


Fig. 15.ii. 75 MHz C^{13}-NMR (PROTON COUPLED) SPECTRUM OF CYCLOADDUCT (183)



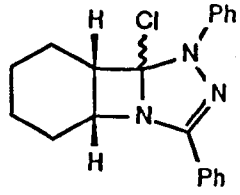


The addition of diphenyl nitrile imine (181) to the bicyclic 2-ethylthioazetine (152) proceeded smoothly under the same conditions, and as with the nitrole oxide cycloadducts (170), an inseparable diastereoisomeric mixture was produced. Also the strong smell of ethanethiol detected during the reaction suggested that the product would not be the expected primary adduct (185).

The NMR spectrum of the isolated product (Fig 16) confirmed this suspicion, and on analysis was found to fit the requirements for a cycloadduct (185) with loss of the -SEt moiety. There was, however, no trace of any alkene protons.

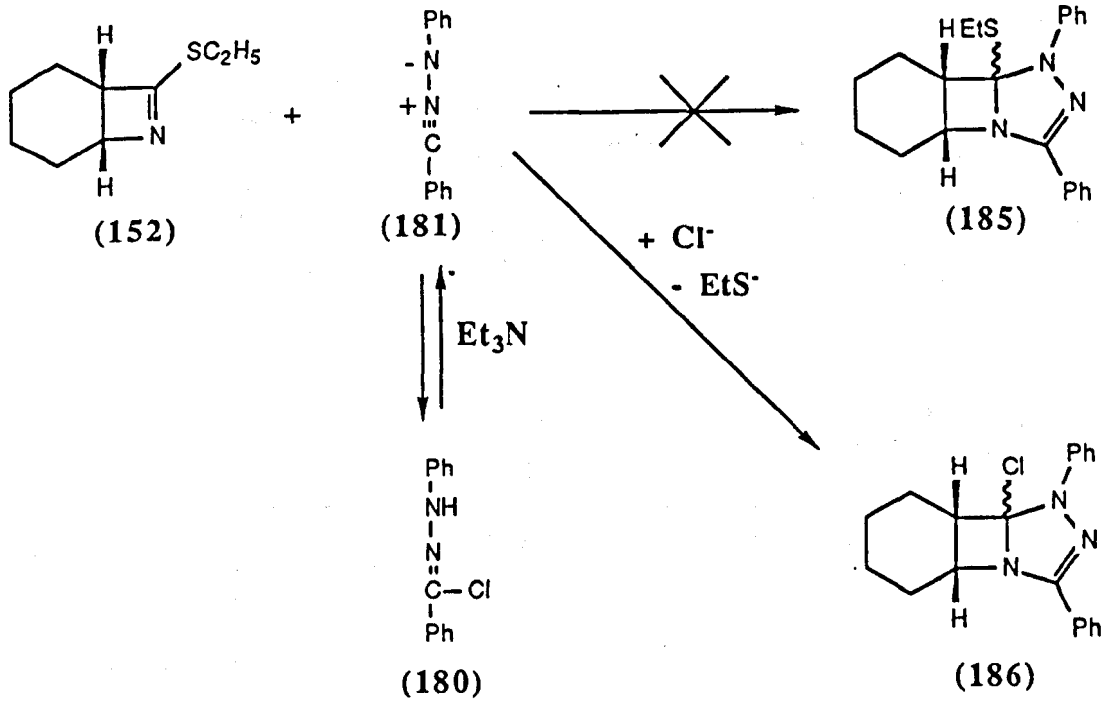
The mass spectrum of this product provided the

Fig. 16. 250MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (186)



crucial piece of evidence in elucidating its structure. The molecular ion peak appeared at m/e 337 (with a smaller peak at m/e 339) rather than the expected m/e 363. Furthermore, the base peak appeared at m/e 302 wich corresponded to loss of Cl.

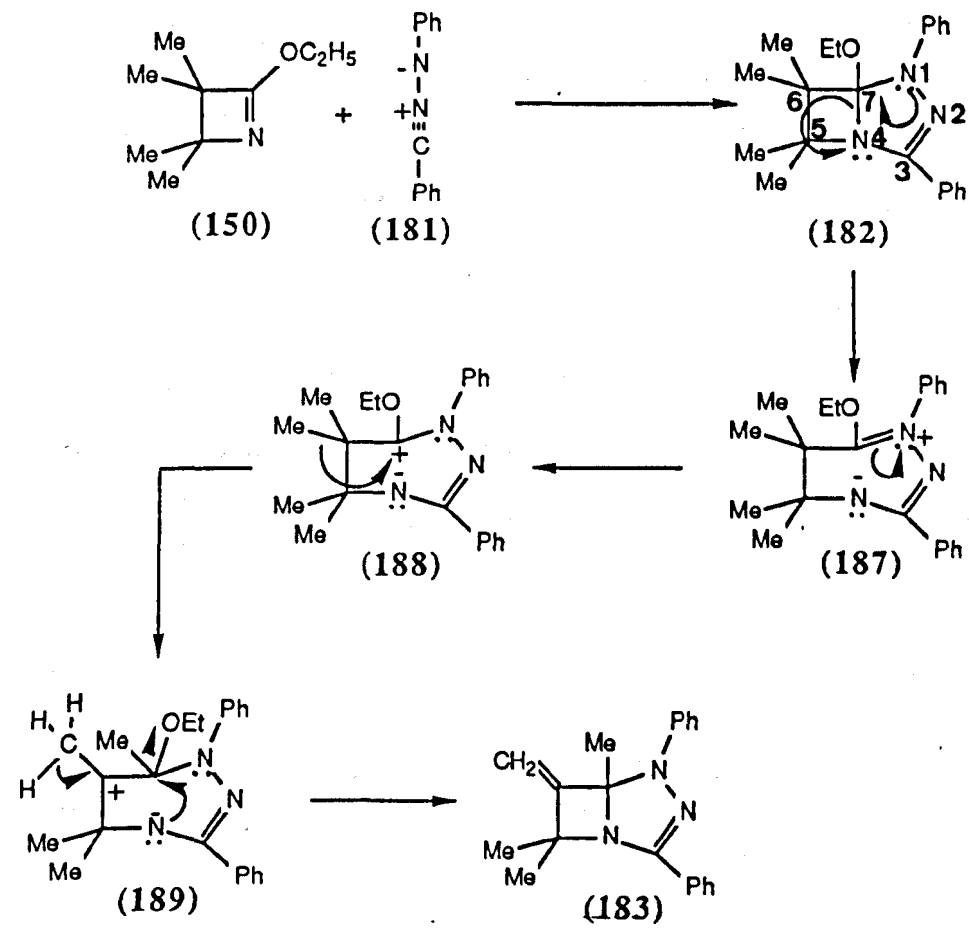
The cycloadduct was thus assigned structure (186) in which the -SEt function had been displaced by Cl^-, the source of the latter being the triethylamine hydrochloride.



In an attempt to account for the production of compounds (183) and (186), two possible mechanisms are put forward. These are shown in Schemes 13 and 14 respectively.

Mechanism A involves the 1,3-dipolar cycloaddition

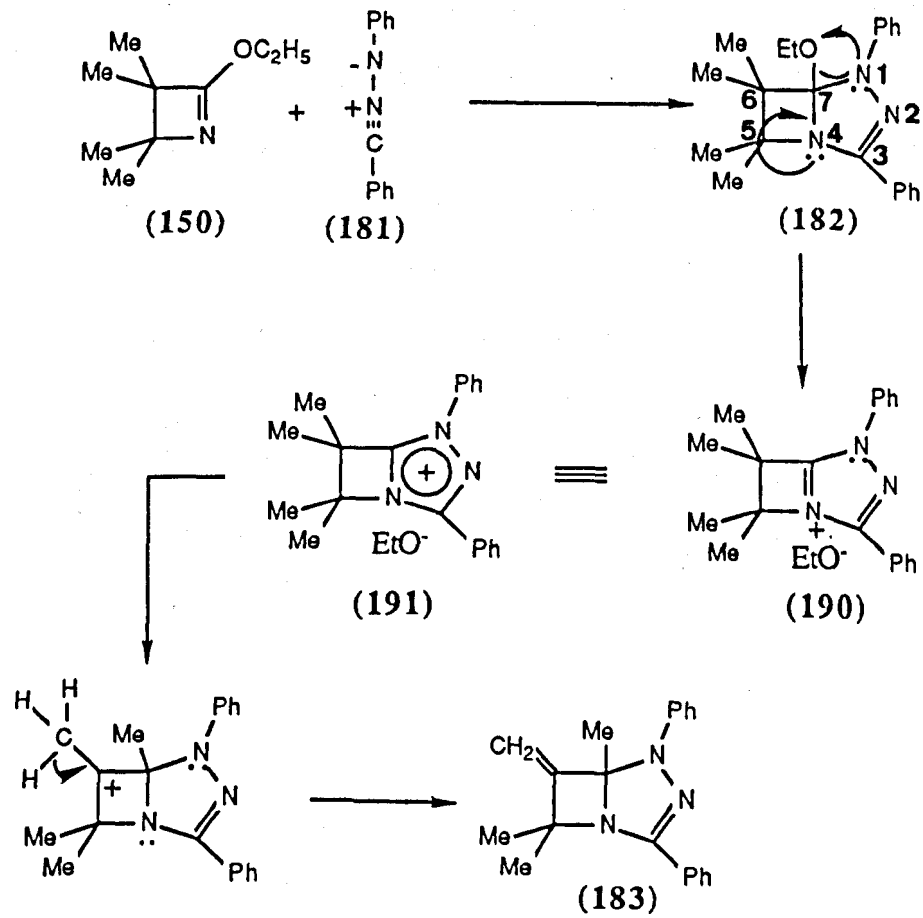
of the nitrile imine to the azetine (e.g. (150)) to produce the primary cycloadduct (182). Electron shift from N-1 causes a ring opening of the bicyclic system to give the zwitterionic imminium species (187) which mesomerises to the stabilised tertiary carbocation (188). Migration of one of the methyl groups from the adjacent position gives carbocation (189) which then ring closes by a transannular nucleophilic displacement of the



Scheme 13

ethoxide by N-4. Loss of a proton from the remaining methyl at C-6 then neutralises the positive charge and yields the isolated product (183).

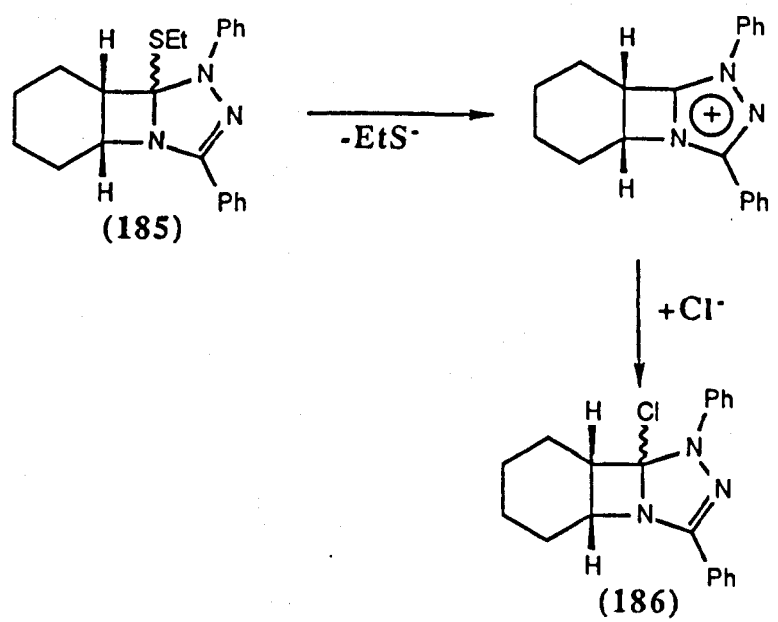
Mechanism B (Scheme 14) again involves the production of the primary adduct (182) as the first step. In this case, however, electron shift occurs from the bridge-head nitrogen N-4, and directly causes the displacement of the ethoxy



Scheme 14

group and the generation of the triazolium species (190), which can be represented as the pseudoaromatic structure (191). Migration of one of the methyl groups from C-6 to C-7 followed by deprotonation again yields the isolated product (183).

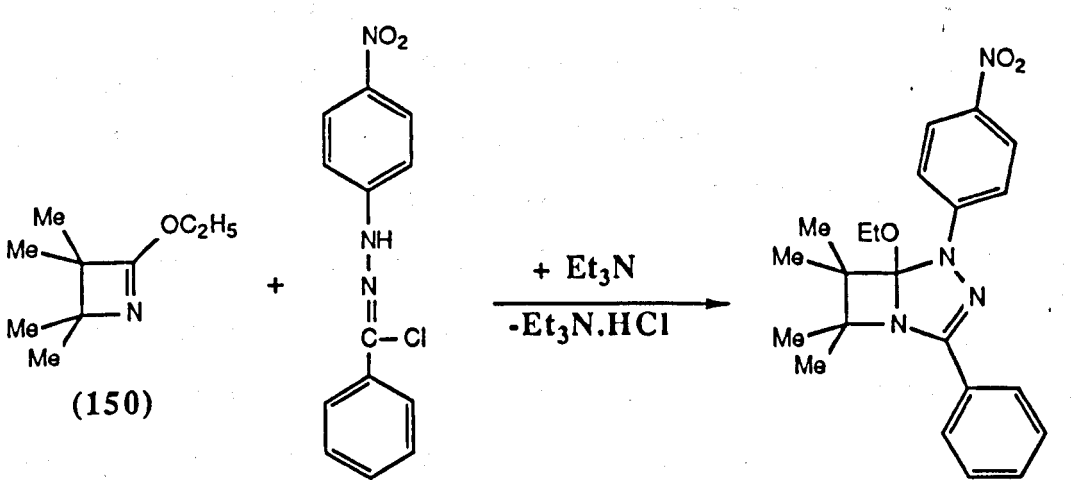
Both mechanisms would apply in the case of monocyclic azetine (151). However, the displacement of -SEt by Cl^- in the production of compound (186) from the bicyclic azetine presumably involves a similar charged intermediate, but yields a different product. It is unlikely that alkyl migration i.e. of a cyclohexyl carbon, would occur in this system, as the product would be a highly strained bridged tricycle. The replacement of -SEt by Cl^- is surprising, however, in view of the poor nucleophilicity of the chloride ion. However, under the reaction



conditions (boiling benzene) -SEt is lost as the volatile ethanethiol and in the absence of an alternative reaction pathway, nucleophilic attack by the chloride takes place.

In both mechanisms A and B, the availability of the lone-pair on N-1, for donation into the system, is a crucial requirement for the process to occur, i.e. either to generate intermediate (187) or the pseudoaromatic species (191). Hence, if this lone pair was to be made "unavailable" then it might be possible to prevent the rearrangement from occurring and allow isolation of the primary adducts.

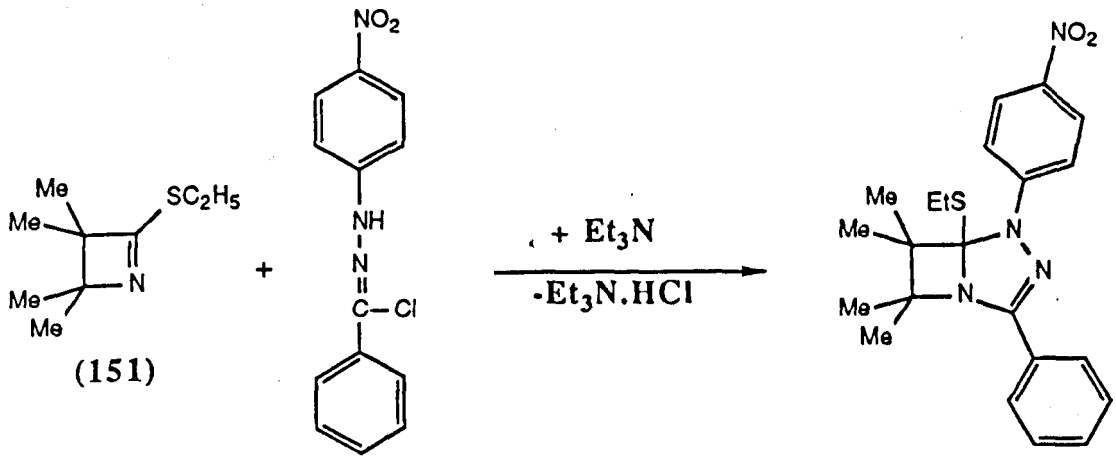
This was done by replacing the N-phenyl group on the nitrile imine with a 4-nitrophenyl group. Thus, treatment of an equimolar solution of hydrazonoyl chloride (192) and azetine (150) in dry benzene, with excess triethylamine followed by



(150) (192) (193)

heating for 2 hrs under reflux gave the desired primary adduct (193) in excellent yield. There was no trace of any rearranged product.

A similar reaction using azetine (151) again gave a good yield of the primary adduct (194).



Surprisingly, when the reaction was carried out with the bicyclic azetine (152), a mixture of the primary adduct (195) and the substituted compound (196) was isolated.

Compounds (193-195) were all identified by high-field NMR spectroscopy. Two examples of which are shown in Figs 17 & 18. The production of these primary adducts, although not distinguishing between the two proposed mechanisms confirms that the rearrangement reaction is dependent on the availability of the lone pair on N-1.

Fig. 17. 250MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (193)

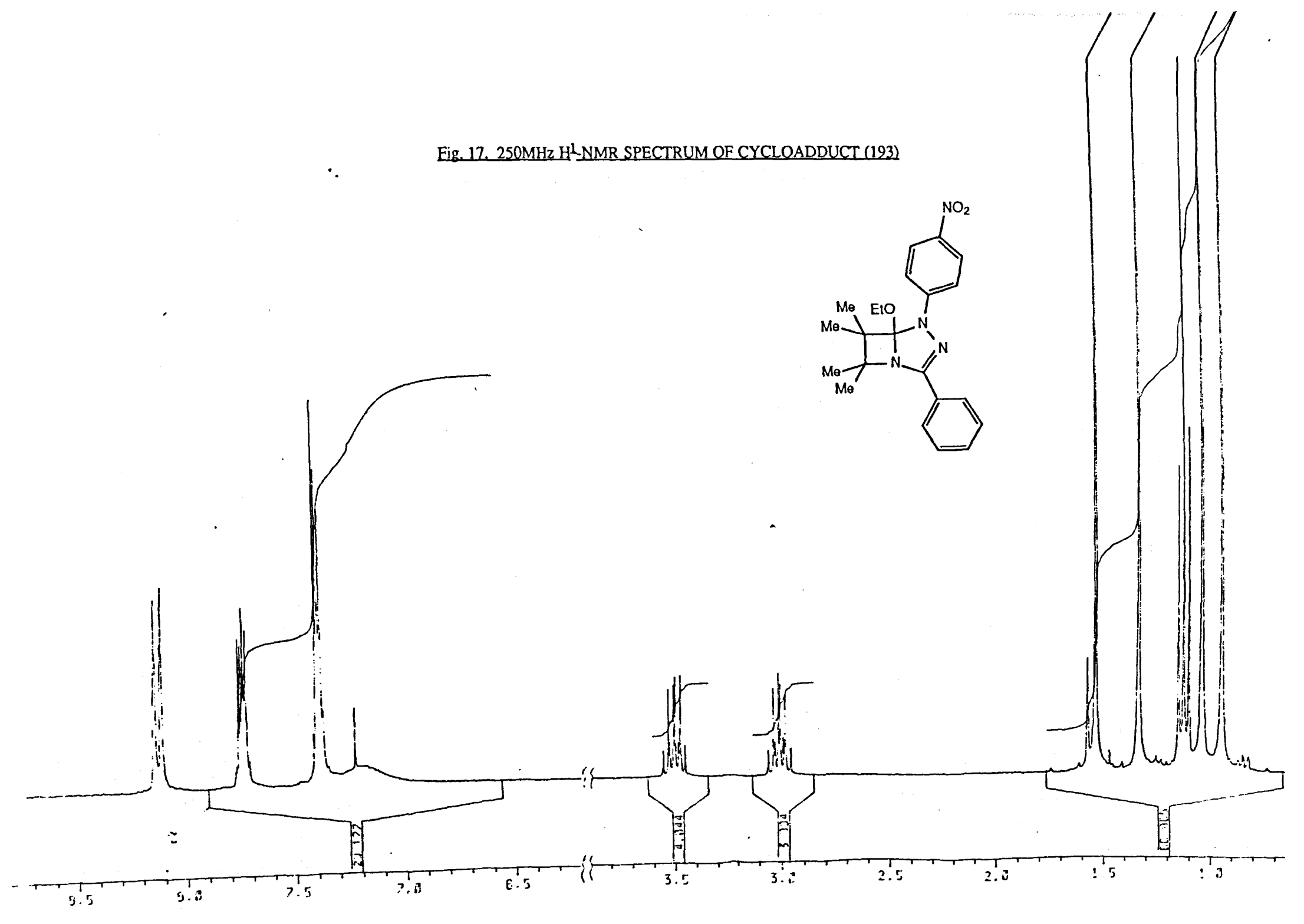
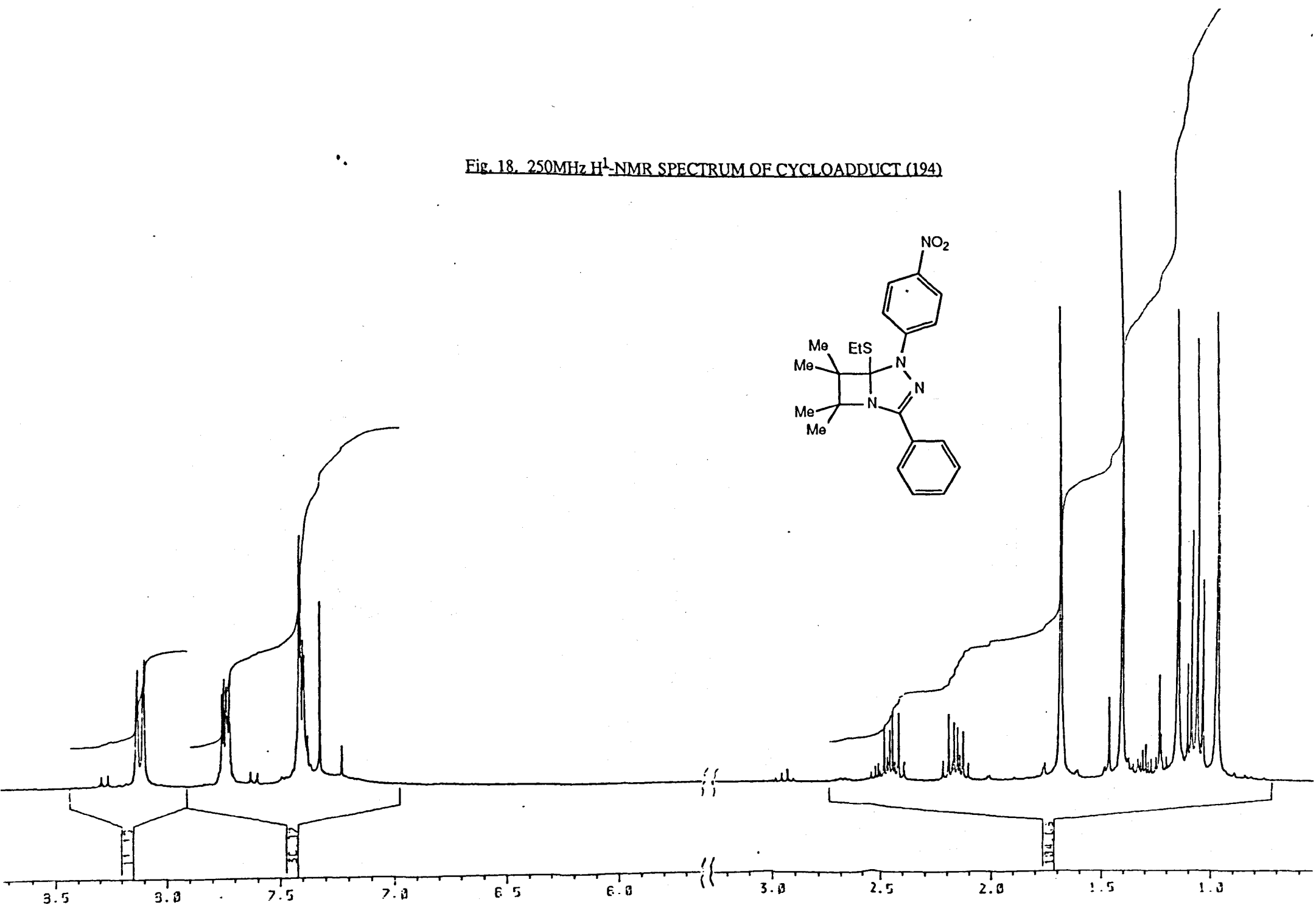
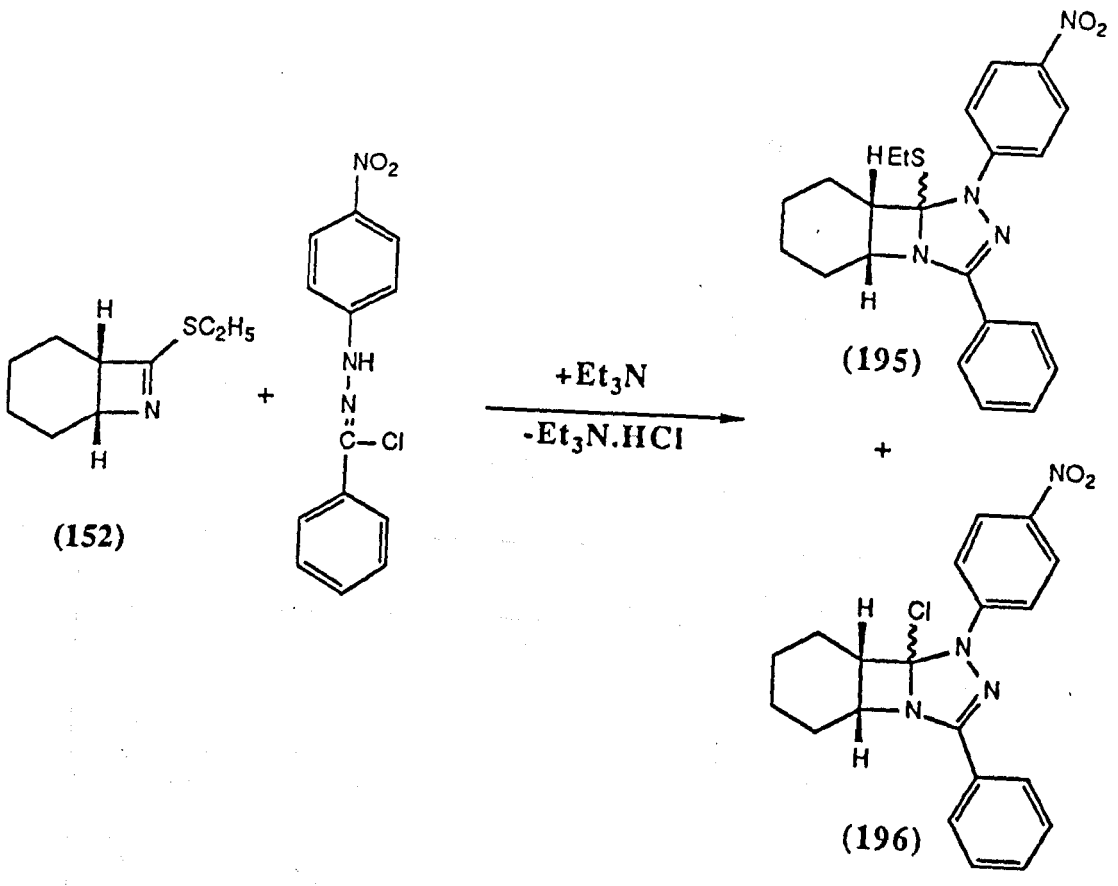
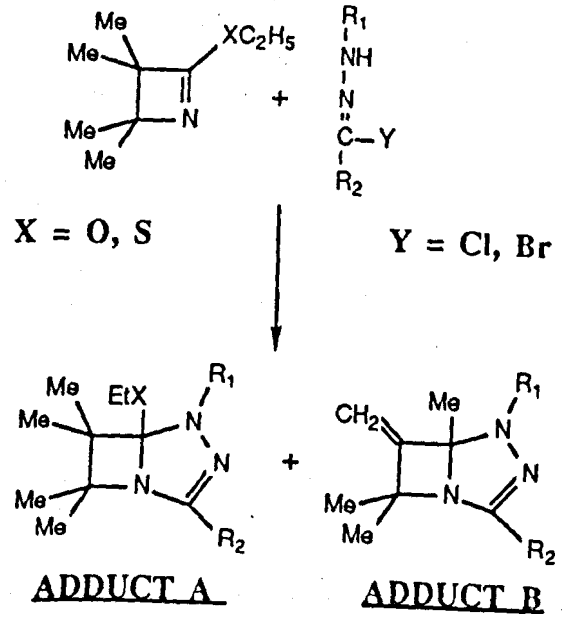


Fig. 18. 250MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (194)

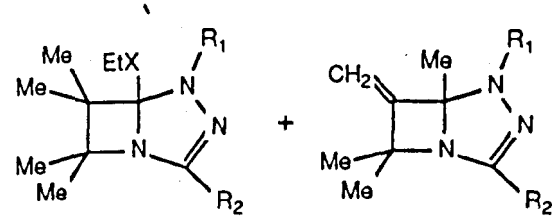




A series of nitrile imines was used in cycloadditions to azetines (150) and (151). The results of these reactions are summarised in Scheme 15 and Tables 3 & 4.

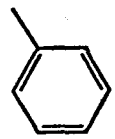
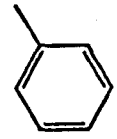
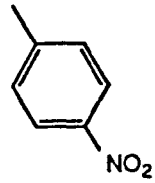
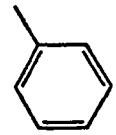
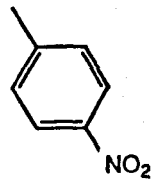
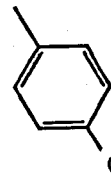
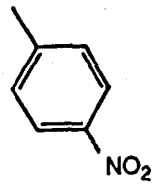
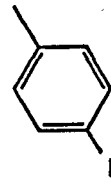
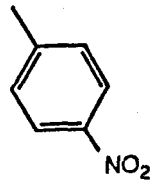


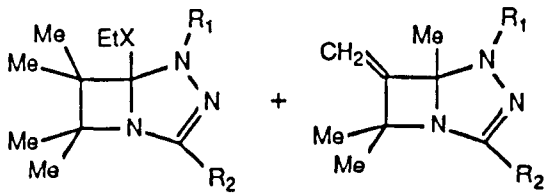
Scheme 15



ADDUCT A ADDUCT B

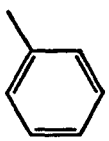
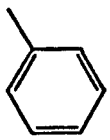
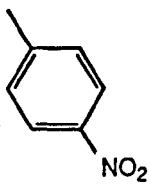
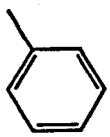
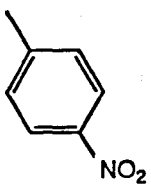
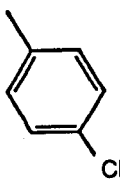
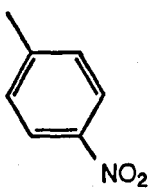
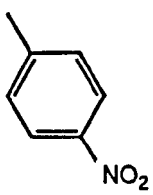
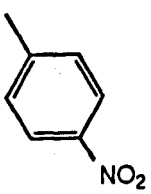
Table 3 - Adduct Yields When X = O

R_1	R_2	Adduct A	Adduct B
		--	57%
		89%	--
		55%	--
		57%	--
	CO_2Me	43%	--

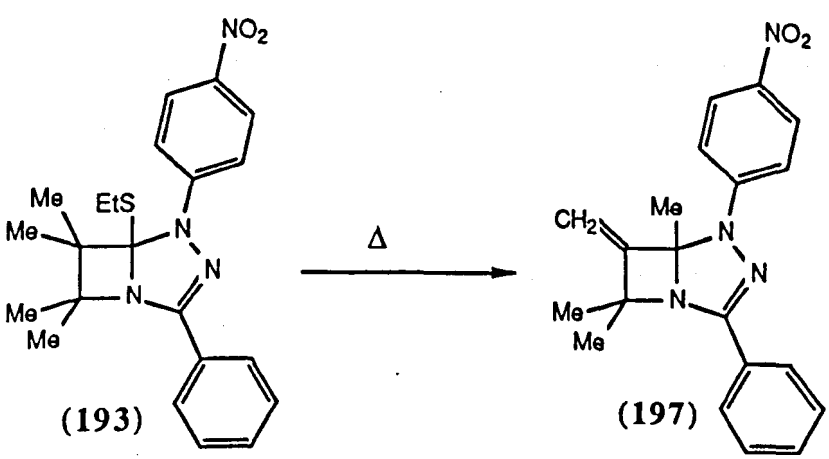


ADDUCT A ADDUCT B

Table 4 - Adduct Yields When X = S

R_1	R_2	Adduct A	Adduct B
		--	60%
		88%	--
		18%	37%
		21%	39%
	CO_2Me	15%	34%

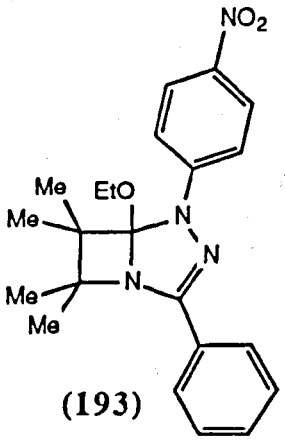
From the results shown in Table 3, it can be clearly seen that the use of N-(p-nitrophenyl)-nitrile imine results in the total prevention of the rearrangement reaction with the ethoxyazetine. Whereas, the results in Table 4 show that only in one case is the primary adduct (entry 2, Table 4) the sole product of the reaction. The -SEt group is known to be a better leaving group than -OEt, thus it may not be too surprising to see that mixtures are produced in most of the additions involving azetine (151) (entries 3-5, Table 4). In order to confirm the intermediacy of the primary adducts (193 & 194) in the formation of the rearranged products, the cycloadduct (193) was heated under reflux in dichlorobenzene (B.pt. 180 °C) for 30 min. Ethanethiol was evolved and an almost quantitaive yield of the rearranged product (197) was obtained; thus demonstrating that the rearrangements go via the initial cycloadducts.



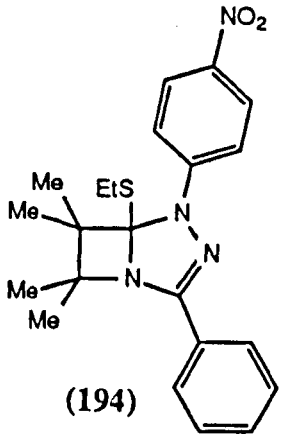
d- MECHANISM OF CYCLOADDITION AND REGIOCHEMISTRY

The mechanism of 1,3-dipolar cycloaddition of nitrile imines to dipolarophiles is very similar to that of the nitrile oxides (see section 2.4.1.d.) and will therefore not be repeated here.

Consequently, the regiochemistry of the cycloaddition should follow the same trends as for nitrile oxides. Hence, the predicted regiochemistry is that depicted in cycloadduct structures (192, 193).



(193)



(194)

A single-crystal X-ray crystallograph of compound (193), shown in Fig 19 confirms that the predicted regiochemistry is indeed the observed one.

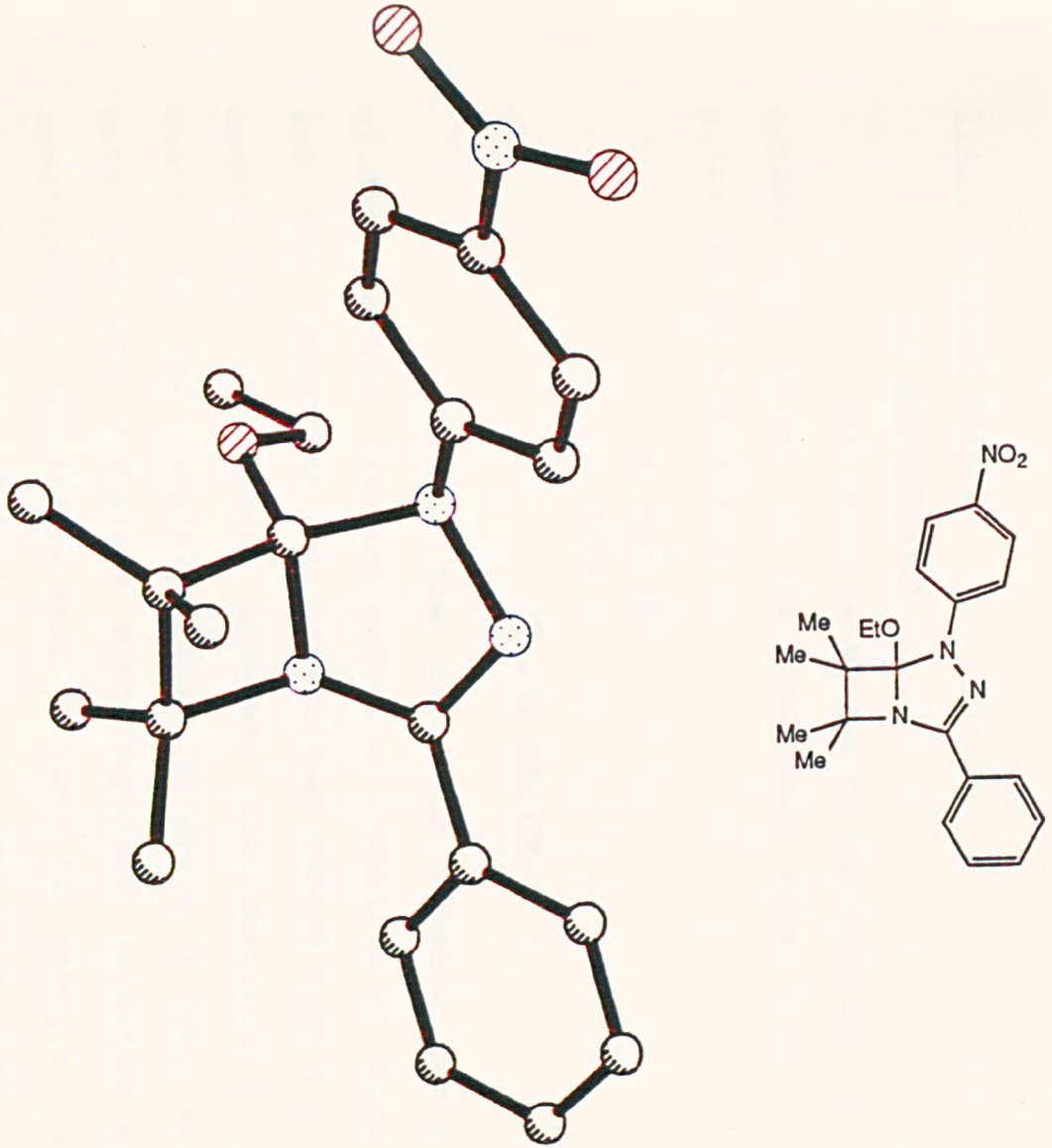
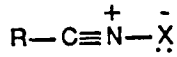


Fig. 19. X-RAY CRYSTALLOGRAPHIC STRUCTURE OF CYCLOADDUCT (193)

2.4.3. NITRILE YLIDES

a- INTRODUCTION

The nitrile ylides belong together with nitrile oxides and imines to the structural type (198), namely the nitrilium betaine family.



(198)

$$X = O, NR, CR_2$$

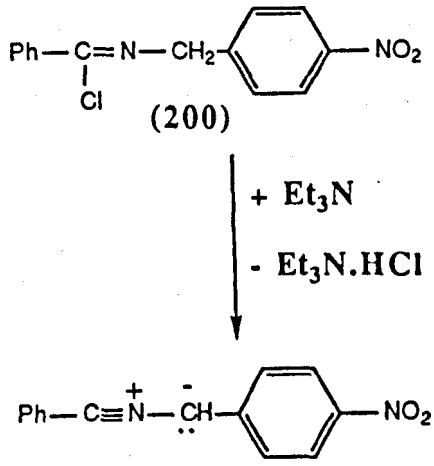
Within the nitrilium betaine series, nitrile ylides have the frontier molecular orbitals of highest energy, and their reactions are, therefore, almost always HOMO (dipole) controlled. This fact, however, also restricts nitrile ylide reactivity. For example, nitrile ylides will react very readily with electron deficient dipolarophiles (electron withdrawing substituents on olefins tend to lower the energies of the HOMO and LUMO of the olefin) such as acrylates and acetylenes. However, no reaction is observed with unactivated olefins and electron rich olefins, such as cyclohexene and ethyl vinyl ether respectively. Nitrile ylides do react with strained olefins such as norbornene (199).

(199)

b- GENERATION OF NITRILE YLIDES

Huisgen[77] was responsible for the generation of the first nitrile ylide and thus establishing a versatile route to these 1,3-dipoles.

This method involves the dehydrohalogenation of imidoyl chlorides e.g. (200) using triethylamine in an inert solvent such as benzene. The production of nitrile ylide (201) is accompanied by the transient appearance of a deep violet colour.[77]



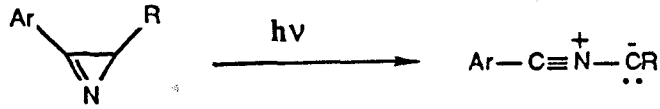
(201)

Huisgen, further reported[78] that the production of nitrile ylide (201) is visibly accelerated (as indicated by the speed of separation of triethylamine hydrochloride) in the presence of reactive dipolarophiles. From this it was concluded that in the

presence of triethylamine hydrochloride, structures (200) and (201) are in equilibrium, with the latter being present only in a low stationary concentration.

The imidoyl chlorides can easily be prepared from N-monoalkylated carboxamides and chlorides such as $SOCl_2$, PCl_5 and $COCl_2$.[79]

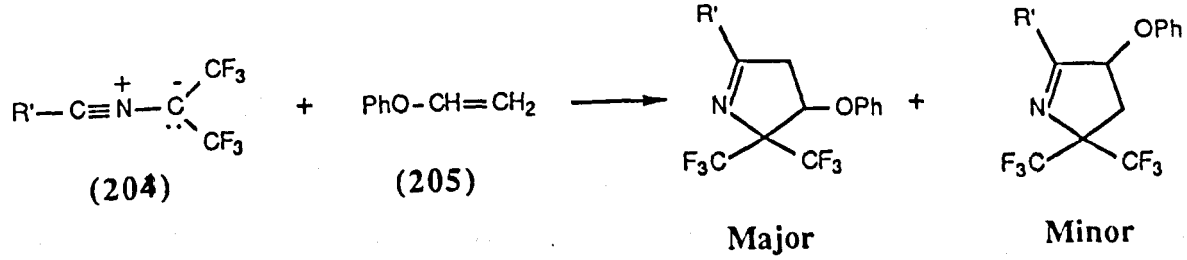
Another important and general access to nitrile ylides is by photochemical ring opening of 3-aryl-2H-azirines (202).[80] A disadvantage of this method, though, lies in the possibility of the generated ylide (203) reacting with its precursor (202). This side-reaction is only totally eradicated in the presence of a reactive dipolarophile.



(202) (203)

c- REACTION WITH 1-AZETINES

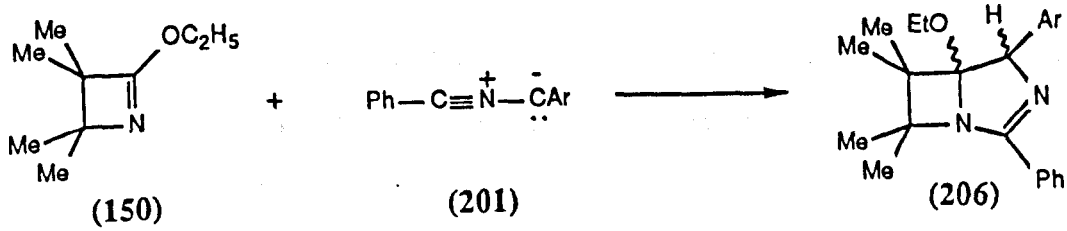
Alkyl- and aryl-substituted nitrile ylides do not react with enol ethers (which are electron rich olefins). One exception is the reaction of nitrilio-hexafluoro-2-propanides (204) which do enter into [2+3] cycloadditions with phenyl vinyl ether (205).[81]



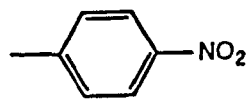
(204) (205) Major Minor

Reaction of nitrile ylides with imino ethers are consequently unknown, and reaction with 2-ethoxy- or 2-ethylthio-azetines is unlikely. On the other hand, 1-azetines are strained molecules, and nitrile ylides are known to add to strained olefins. The out come of these two opposing features in the 1-azetine system may therefore, balance out and allow some reactivity towards nitrile ylides.

Accordingly, benzonitrile p-nitrophenylmethanide (201) was generated from N-(p-nitrobenzyl)benzimidoyl chloride (200) using triethylamine in the presence of 2-ethoxyazetine (150) in dry benzene. The reaction was carried out at room temperature and required 12 hrs to achieve completion as indicated by TLC. Work-up followed by chromatographic purification yielded a crystalline solid, assumed to be the desired cycloadduct (206).

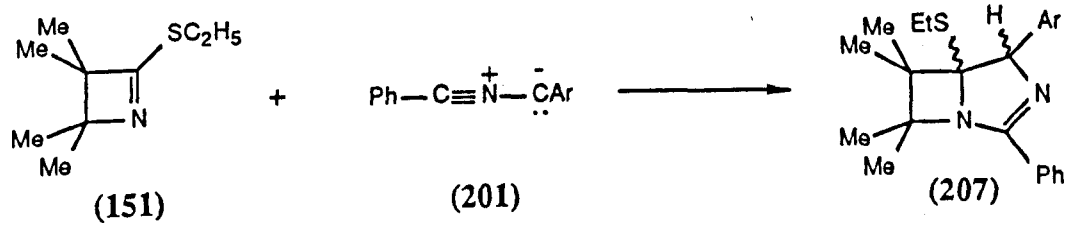


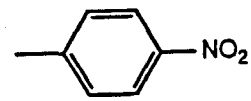
(150) (201) (206)

Ar = 

The structure of the product was confirmed by spectroscopic analysis. The NMR spectrum of compound (206) (as shown in Fig 20) exhibits similar features to the NMR spectra of the nitrile oxide (168) and nitrile imine (193) adducts. Namely, the four non-equivalent methyl groups on the four membered ring, and the anisotropically non-equivalent protons of the methylene of the -OEt function. Unfortunately, the stereochemistry of the cycloadduct could not be determined from this spectroscopic data.

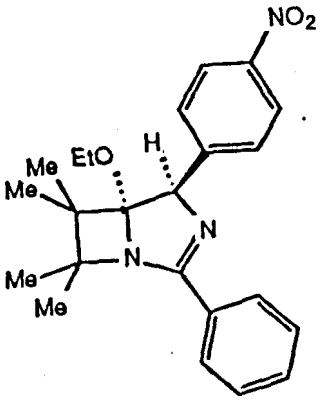
The addition of nitrile ylide (201) to 2-ethylthioazetine (151) proceeded in a similar fashion and yielded the adduct (207) in good yield.

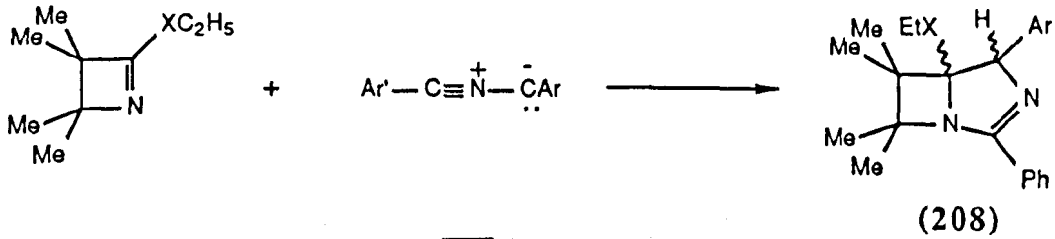


Ar = 

Two other nitrile ylides were successfully added to 1-azetines (150) and (151). The results are summarised in Table 5.

Fig. 20. 250MHz H^1-NMR SPECTRUM OF CYCLOADDUCT (206)





(208)

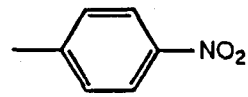
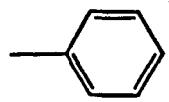
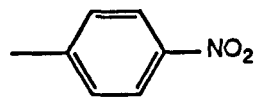
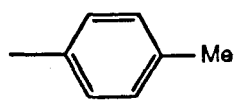
Ar = 

Table 5 - YIELDS OF ADDUCTS (208)

Ar'	YIELD %	
	X = O	X = S
	46	68
	42	45
	53	61

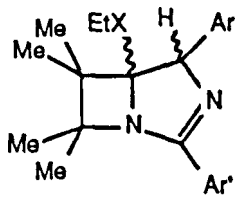
Thus as expected, reaction between nitrile ylides and 1-azetines does occur to give bicyclic products, but only after a relatively long reaction time and in modest to fair yields.

d- MECHANISM, REGIOCHEMISTRY & STEREOCHEMISTRY

The mechanism of the 1,3-dipolar cycloaddition of nitrile ylides to dipolarophiles (1-azetines) follows the same reasoning as that for nitrile oxides and nitrile imines.

It has already been stated that nitrile ylides have the highest frontier orbitals within the nitrilium betaine series, and that their reactions are therefore HOMO (dipole) controlled. As such, their reaction with ethoxy- and ethylthioazetines (which also have high HOMOs and LUMOs) must be almost entirely due to the strain in the four membered ring.

The regiochemistry of the addition will again be similar to that for the nitrile oxides and imines, i.e. with the nitrile carbon bonding to the nitrogen of the C=N bond, and the ylide carbon bonding to the carbon end of the C=N bond, as shown in structure (208).



(208)

An X-ray crystallographic structure (Fig 21) of compound (206) shows this to be the correct regiochemistry. This X-ray structure also serves to show the stereochemistry of the

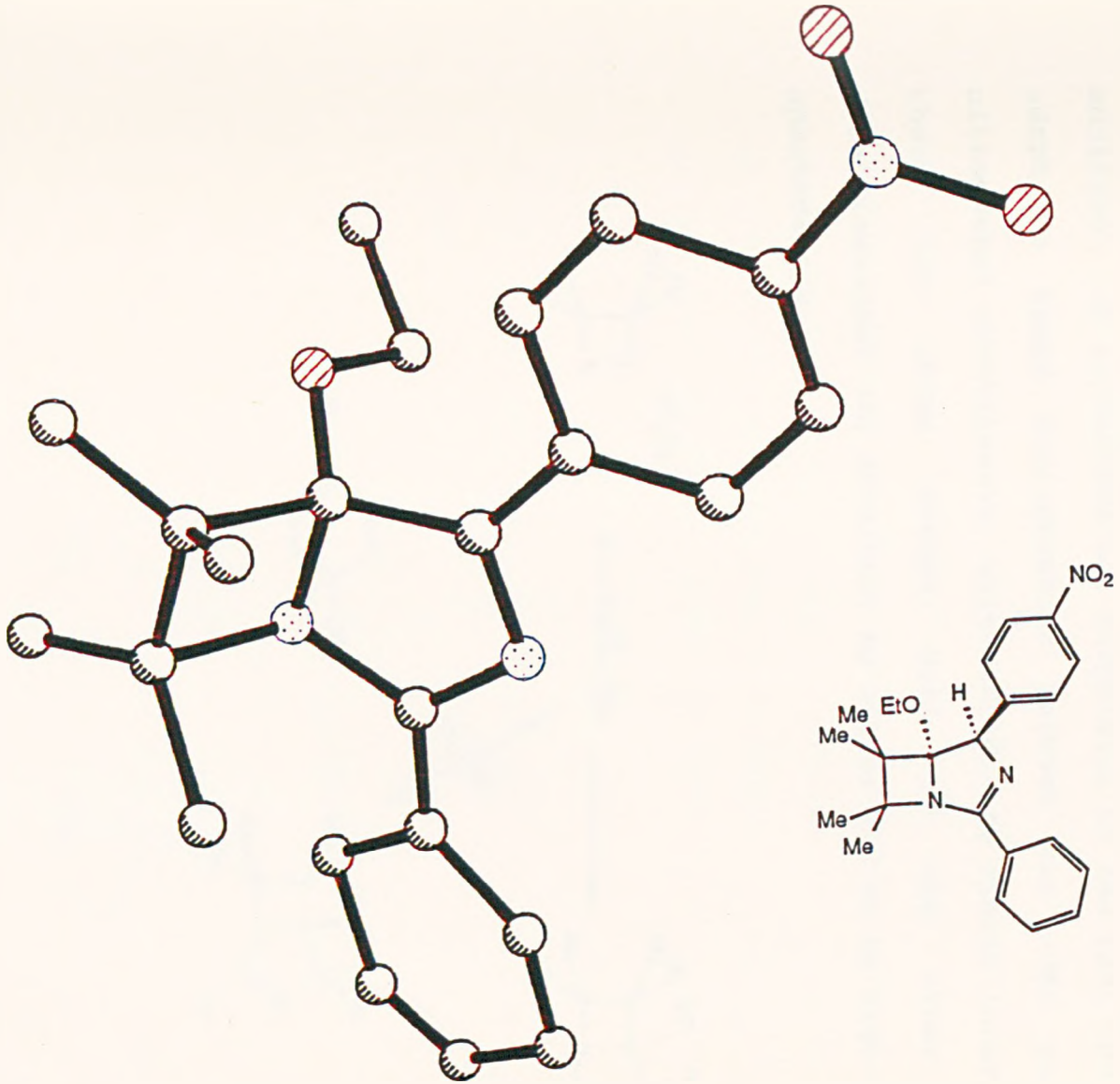
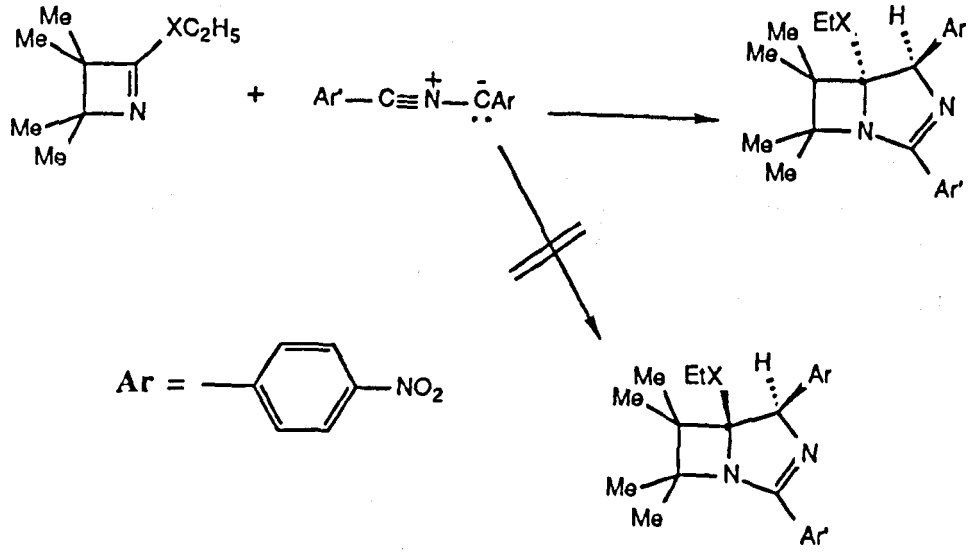


Fig. 21. X-RAY CRYSTALLOGRAPHIC STRUCTURE OF CYCLOADDUCT (206)

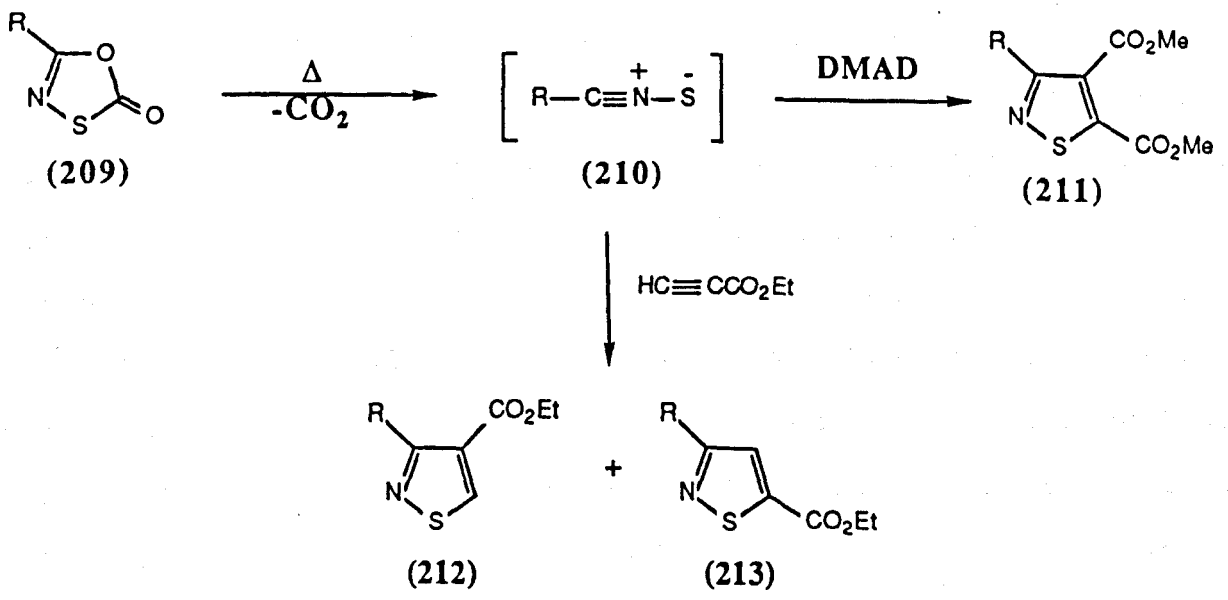
addition. It is perhaps not surprising to see that the molecule adopts a <u>trans</u> configuration between the -OEt and the p-nitrophenyl substituents, which avoids any steric interactions of these two large groups. None of the other possible diastereoisomer was detected, by either TLC or by high-field NMR spectroscopy.



2.4.4. OTHER 1,3-DIPOLES

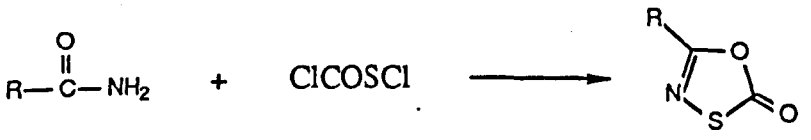
a- NITRILE SULPHIDES

Nitrile sulphides (210) have until very recently been the missing member of the nitrilium betaine series. Pioneering work by Howe[82] resulted in the successful entrapment of both alkyl and aryl nitrile sulphides using dimethyl acetylenedicarboxylate (DMAD) and ethyl propiolate to give isothiazoles (211), (212) and (213).



The nitrile sulphides are generated *in situ* by thermolysis of their precursor 1,3,4-oxathiazol-2-ones (209). The requisite oxathiazoles (209) are readily prepared from amides and

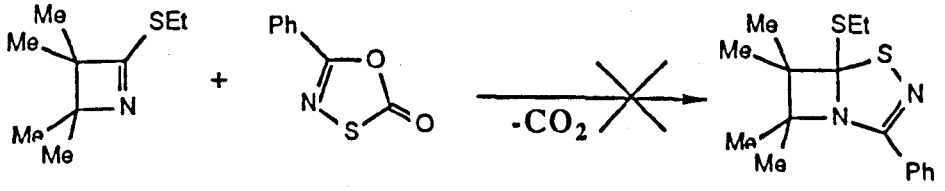
chlorocarbonylsulphenyl chloride.[82]



(209)

Nitrile sulphides have not been used as prolifically as their related nitrile oxides, imines and ylides. Their reported cycloadditions have been restricted to alkyne,[82] alkene,[83] nitriles[84] and carbonyl[85] dipolarophiles.

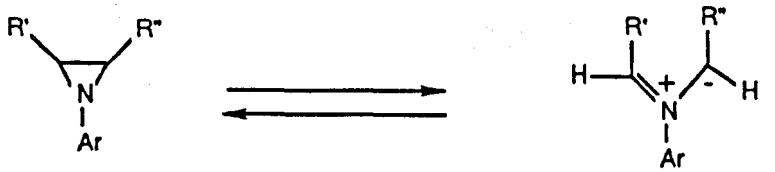
In order to investigate the ability of nitrile sulphides to cycloadd to 1-azetines, 5-phenyl-1,3,4-oxathiazol-2-one (209, R=Ph) was prepared from benzamide and chlorocarbonylsulphenyl chloride. A solution of the oxathiazolone and 2-ethylthioazetine (151) in dry toluene was heated under reflux until all the oxathiazolone was consumed as indicated by TLC. Work-up of the reaction mixture gave an almost quantitative yield of the azetine (151) together with benzonitrile. Disappointingly, this indicates that the nitrile sulphide, although generated, did not undergo cycloaddition with the azetine, but rather decomposed to benzonitrile and sulphur, a known side-reaction.[82]



This lack of reactivity towards azetines was rather surprising, as the nitrile sulphides are believed to have comparable reactivity with nitrile ylides.[82] It is however, possible that the rate of decomposition of the generated nitrile sulphide is higher than the rate of its cycloaddition to the azetine.

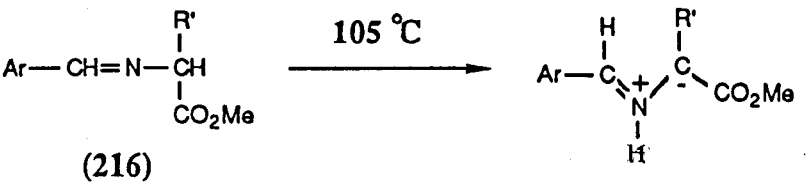
b- AZOMETHINE YLIDES

Azomethine ylides (215) are commonly generated by the electrocyclic ring opening of the readily prepared aziridines (214).[86]



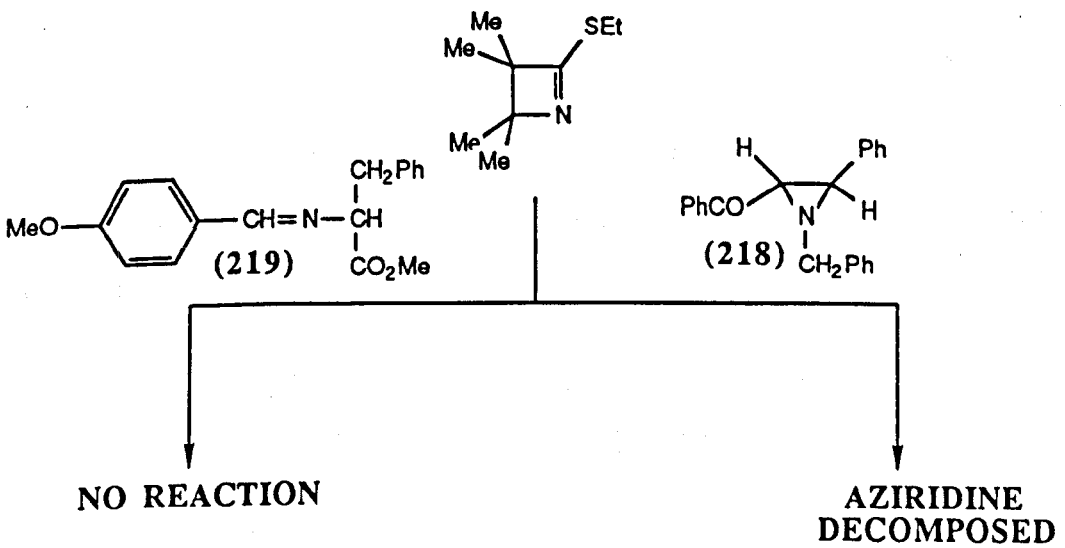
(214) (215)

A unique route to azomethine ylides was recently developed by Grigg,[87] utilising imines of type (216) which on heating undergo a 1,2-proton shift to generate the azomethine species (217).



(216) (217)

It has been observed experimentally[86] that azomethine ylides show low reactivity with simple alkenes, while cycloadditions are accelerated by both electron withdrawing and electron releasing substituents.

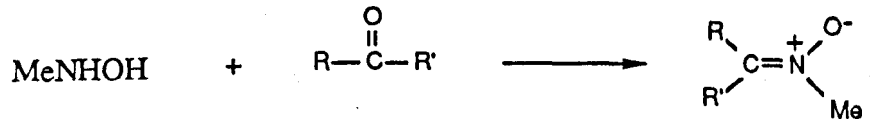


It was, therefore, very disappointing when no reaction was observed between both aziridine (218) and imine (219) and azetine (152). The former resulted in the total decomposition of the aziridine, whilst the latter remained unchanged after heating under reflux for 24 hrs in dry toluene.

c- AZOMETHINE OXIDES (NITRONES)

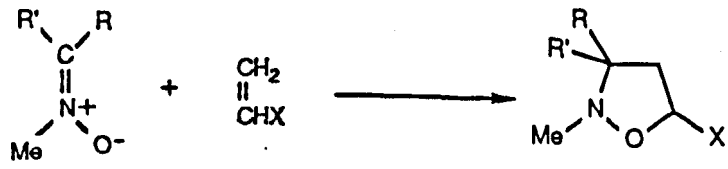
The cycloaddition chemistry of nitrones has recieved a great deal of interest and has recently been reviewed by Tufariello.[88]

Nitrones (220) are frequently prepared by condensation of N-alkylhydroxylamines with aldehydes or ketones.



(220)

Nitrones are known to react with simple alkenes[88] and with electron deficient olefins[88] to give 5-substituted isoxazolidines (221).



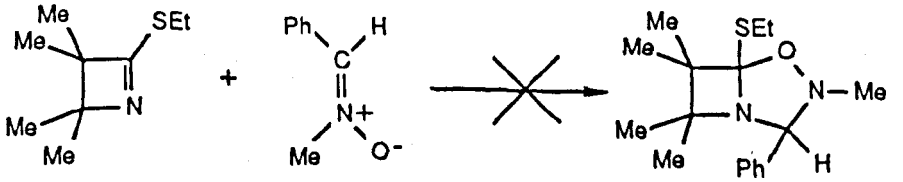
(220) (221)

Fewer instances have been recorded of the cycloaddition of nitrones to electron rich olefins. Butyl vinyl ether[89] and aryl vinyl ethers[90] are notable examples. e.g.

(220) (221)

Mechanistically, the frontier molecular orbital theory has been effectively used to explain both the reactivity and regiochemistry of nitrone additions.[88] Nitrone additions are believed to be HOMO, LUMO (dipole) controlled, depending on the energies of the molecular orbitals of the dipolarophile.

This was encouraging since it meant that there was a good possibility of 1-azetines entering into [3+2] cycloadditions with nitrones. Unfortunately, no reaction was observed between C-phenyl-N-methylnitrone (220, R=H, R'=Ph) and 1-azetine (151) even after heating in dry benzene for 24 hrs under reflux.

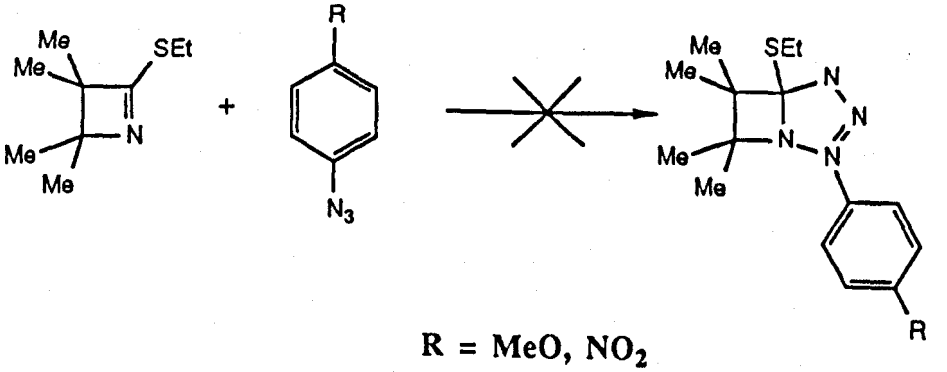


(151)

d- AZIDES

The action of azides as 1,3-dipoles has been known since 1893. They will add to simple alkenes and alkynes as well as to electron rich and electron poor olefins.[91]

It was therefore, puzzling when both p-nitrophenyl azide (electron deficient) and p-methoxyphenyl azide (electron rich) showed no activity towards 2-ethylthioazetine (151) even after heating under reflux in dry benzene for 48hrs.

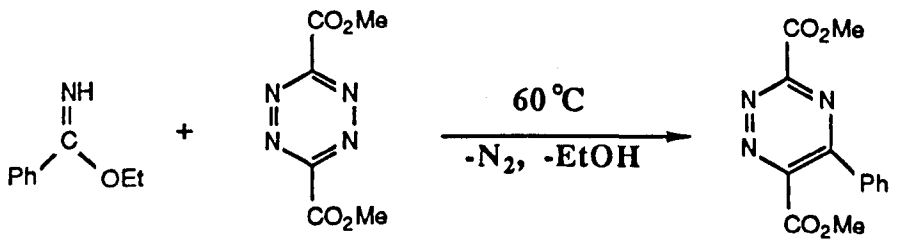


R = MeO, NO_2

2.5. ATTEMPTED [4+2] CYCLOADDITIONS TO 1-AZETINES

2.5.1. INTRODUCTION

The reaction of a wide variety of simple and electron deficient imines with dienes is well known and has been recently reviewed.[92] On the other hand, electron rich imino ethers were found to show reactivity only towards electron deficient dienes.[93] One example is the inverse electron demand Diels-Alder reaction of imino-ether (222) with the sym-tetrazine dicarboxylate (223) to give triazine (224) after loss of nitrogen and ethanol.[93]



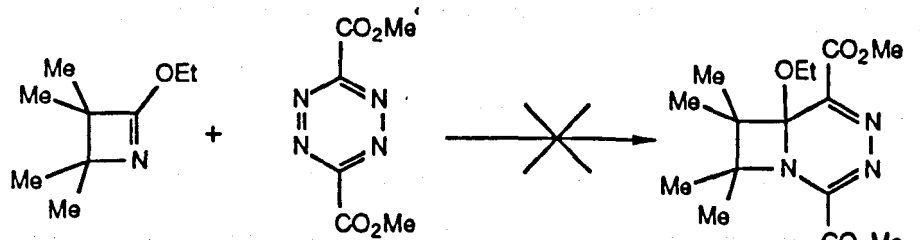
(222) (223) (224)

It was of interest, therefore, to investigate the dienophilic character of 1-azetines towards both electron-rich and electron deficient dienes. As far as we are aware no such reactions have been attempted previously.

2.5.2. ELECTRON-DEFICIENT DIENES

The sym-tetrazine dicarboxylate (223) was prepared by a multi-step procedure from ethyl glycinate as described by Boger and Coleman.[94]

Attempted reaction of tetrazine (223) to 1-azetine (150) in boiling dry benzene for 36 hrs led only to the decomposition of the diene. The azetine was recovered unchanged.



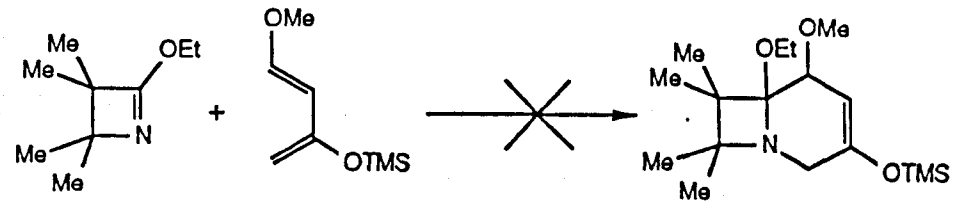
(150) (223)

2.5.3. ELECTRON-RICH DIENES

Having established the lack of reactivity of 1-azetines towards this electron deficient diene, it was necessary, for the sake of completion, to attempt a reaction between 1-azetines and an activated electron-rich diene. The diene of choice was 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (225).

As expected, however, this diene showed no activity towards azetine (150) even after stirring at room

temperature in dry benzene for 48 hrs.



(150) (225)

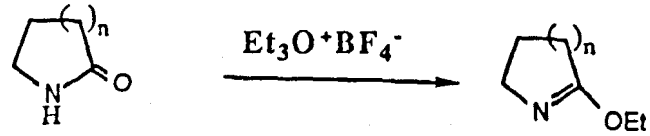
2.6. MISCELLANEOUS

2.6.1. 1,3-DIPOLAR CYCLOADDITIONS TO LARGER RING IMINO ETHERS

The dipolarophilic character of imino ethers has been scarcely investigated. The only work published on the subject is that concerning the addition of nitrile oxides to acyclic imino ethers[69] (see also Section 2.4.1.c.). The 1-azetine work has demonstrated the reactivity of four-membered cyclic imino ethers towards nitrile oxides, imines and ylides.

This prompted the investigation of 1,3-dipolar cycloaddition of nitrile oxides and nitrile imines to larger ring imino ethers.

The 5-, 6-, and 7-membered cyclic imino ethers (229-231) were prepared by alkylation of the respective lactams (226-228) using triethyloxonium tetrafluoroborate.[95]



(226) n = 1

(227) n = 2

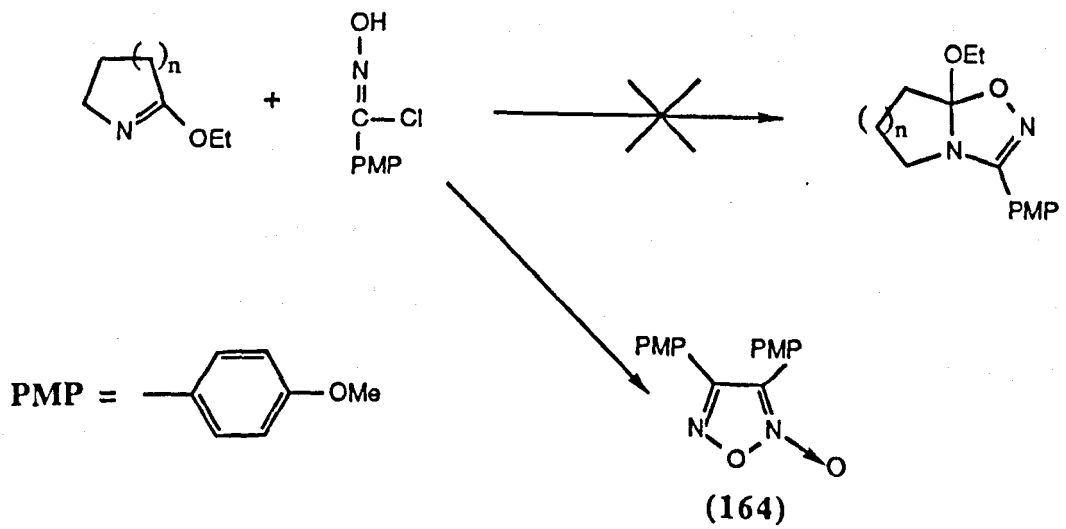
(228) n = 3

(229) n = 1

(230) n = 2

(231) n = 3

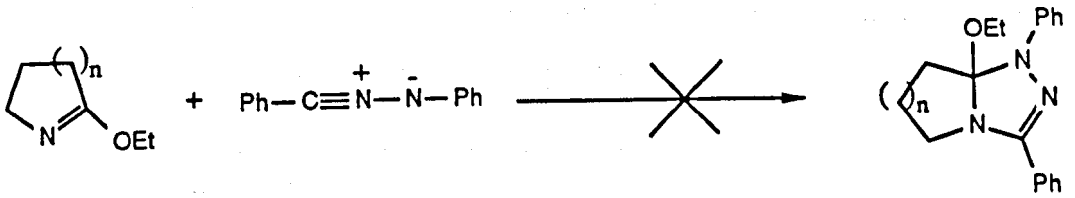
Attempted reaction of these imino ethers with p-methoxybenzonitrile oxide was carried out in a dry benzene solution at room temperature. Surprisingly, no cycloadducts were isolated. The imino ethers were recovered untouched, along with the dimer (164) of the nitrile oxide.



(164)

This lack of reactivity was attributed to the generated nitrile oxide dimerising faster than adding to the imino ether. To avoid this set back, the use of nitrile imines was attempted. As stated earlier, these exist in equilibrium with their precursors in the presence of triethylamine and thus will exist in solution for a longer period of time, effectively increasing the chances of cycloaddition with the imino ethers.

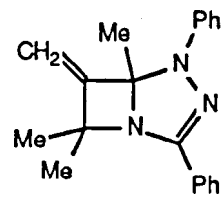
Unfortunately, no reaction was observed between diphenyl nitrile imine and the imino ethers after heating in dry benzene under reflux for 24 hrs.



The one conclusion which can be made from this set of results is that the dipolarophilic character of 1-azetines must owe a great deal to ring strain in the four membered cyclic system.

2.6.2. CHEMISTRY OF 6-METHYLENO AZETOTRIAZOLE (183)

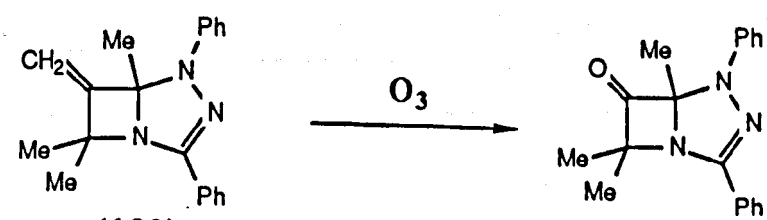
A positive aspect of the rearrangement leading to compound (183) (see Section 2.4.2.c) was that it introduced functionality at the C-6 position of the bicyclic system.



(183)

It was therefore, decided to carry out reactions on the exocyclic double bond in order to lead to some structurally interesting compounds.

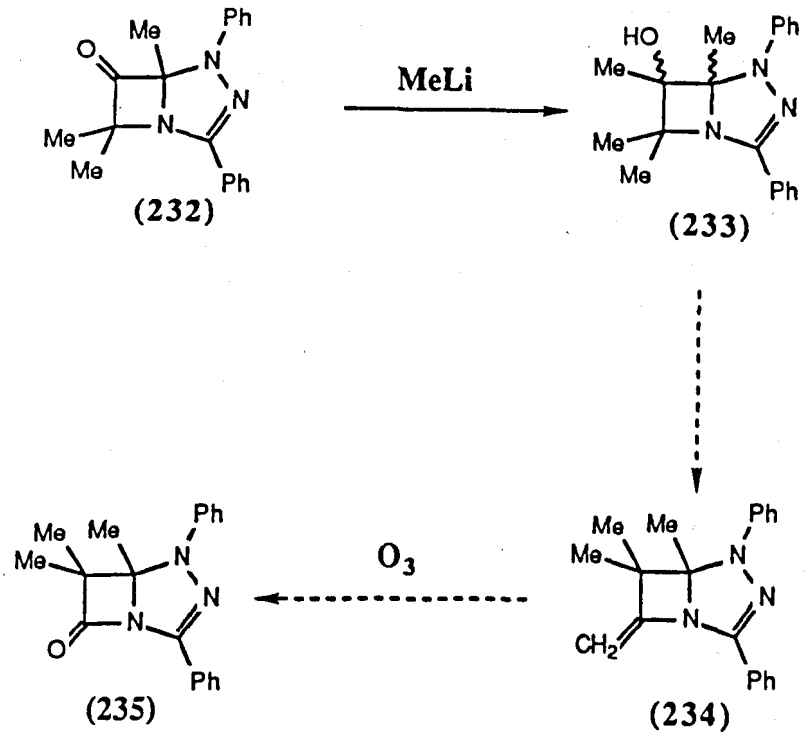
Ozonolysis of compound (183) in dichloromethane at ice temperature led to ketone (232) in fair yield. This was identified by IR and NMR spectroscopy. The former showed a strong peak at 1700 cm^{-1} typical of a ketonic C=O bond stretching. The NMR spectrum, showed the loss of the two singlets at 4.50 ppm and 4.65 ppm (see Fig 14) which were assigned to the exocyclic methylene group.



(183) **(232)**

The production of ketone (232) suggested the possibility of effecting a step-wise rearrangement leading ultimately to the bicyclic ß-lactam (235) as shown in Scheme 16.

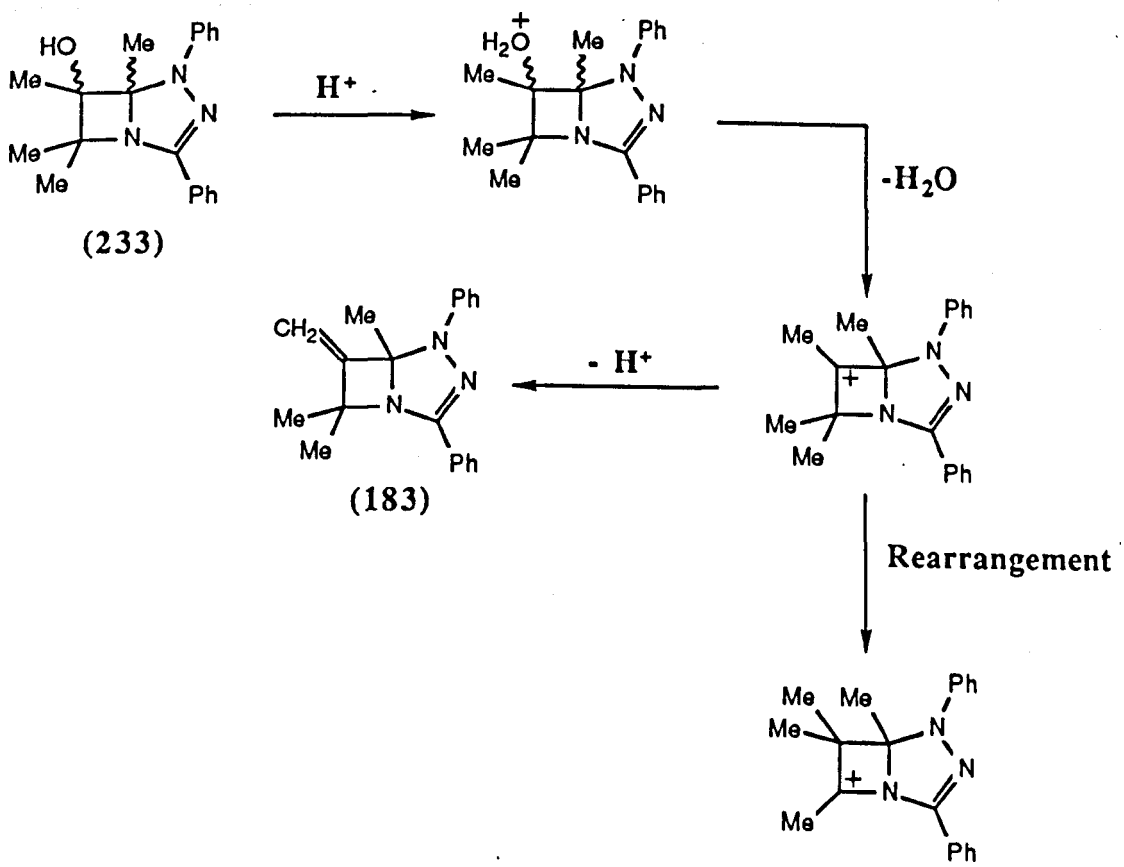
Alkylation of ketone (232) proceeded smoothly using an excess of methyl lithium at -78 °C in dry ether. The tertiary alcohol (233) was obtained in moderate yield after ammonium chloride work-up and chromatographic purification. The IR spectrum of alcohol (233) showed the loss of the peak at 1700 cm^{-1} assigned to the carbonyl group of ketone (232), accompanied by the appearance of a broad band at 3200-3500 cm^{-1}



Scheme 16

assigned to the -OH of the alcohol. The NMR spectrum of compound (233) showed all four methyl groups to be equivalent as a twelve proton singlet at 1.17 ppm. The hydroxyl proton appeared as a broad singlet at 6.28 ppm.

The following step (233-234) was aimed at the generation of a tertiary carbocation at C-6 by acidic protonation of the -OH and subsequent loss of water. This might induce one of the methyl groups at C-5 to migrate to C-6 and consequently



(233)

(183)

give compound (234). There was, however, another possibility and that is loss of a proton from the methyl group at C-6 leading back to compound (183).

Alcohol (233) was not affected by glacial acetic acid or trifluoroacetic acid. However, after stirring in concentrated sulphuric acid for 48 hrs a product was obtained. High-field proton and C-13 NMR spectra were inconsistent with the desired product (234). So far, however, this product has not been characterised and further work on this reaction is planned.

CHAPTER 3

1-AZETIN-4-ONES

3.1. INTRODUCTION

A comprehensive review on the history of the 1-azetin-4-one system (4) has already been given (see Section 1.4.). It can be seen clearly from that review that, although frequently postulated as an intermediate, only two synthetic routes[21,29] have been published for the 1-azetin-4-one system.

As an extension to the work on 1,3-dipolar cycloadditions to 1-azetines (Chapter 2), it was of great interest to attempt similar cycloadditions to 1-azetin-4-ones, since this one step reaction would furnish a direct route to new bicyclic ß-lactam systems.

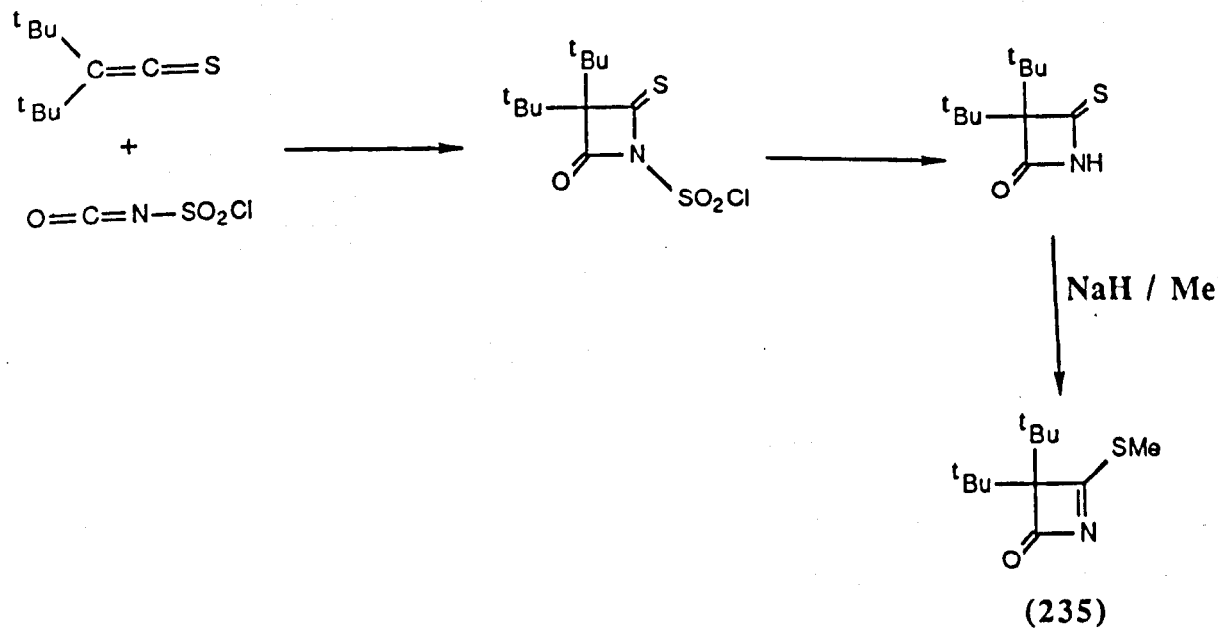
(4)

However, in order to carry out such work, it was necessary either to synthesise a stable 1-azetin-4-one or to be able to generate one *in situ* under conditions compatible with a cycloaddition reaction. The latter has already been shown to be possible by Ueda,[43,45] who isolated cycloadduct (125), albeit in low yield, by addition of an activated diene to a 1-azetin-4-one

species generated *in situ* (see section 1.4.). This work was concentrated, therefore, on attempts to synthesise a stable 1-azetin-4-one system, with a view to studying and hopefully exploiting, its dipolarophilic character.

3.2. PREPARATION OF 3,3-DI-t-BUTYL-1-AZETIN-4-ONE

Initially an effort was made to synthesise 3,3-di-t-butyl-1-azetin-4-one (235) by the route described by Schaumann,[21] as this appears to be one of the only stable 1-azetin-4-ones described so far. This synthesis involved the cycloaddition of chlorosulphonyl isocyanate to di-t-butylthioketene followed by hydrolytic cleavage of the

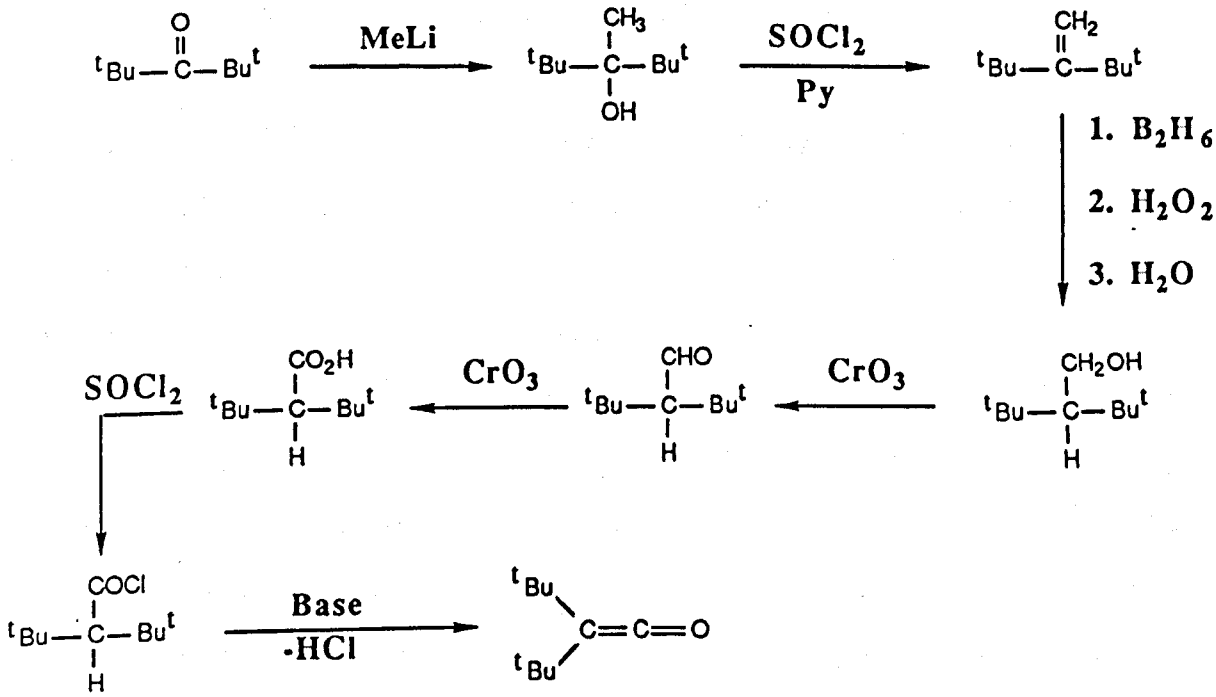


(235)

Scheme 17

chlorosulphonyl residue and alkylation using sodium hydride and methyl iodide, as shown in Scheme 17.

The primary objective was, therefore, to synthesise di-t-butylthioketene. Schaumann[21] was able to obtain this thioketene via the route described by Newman,[96] as outlined in Scheme 18.



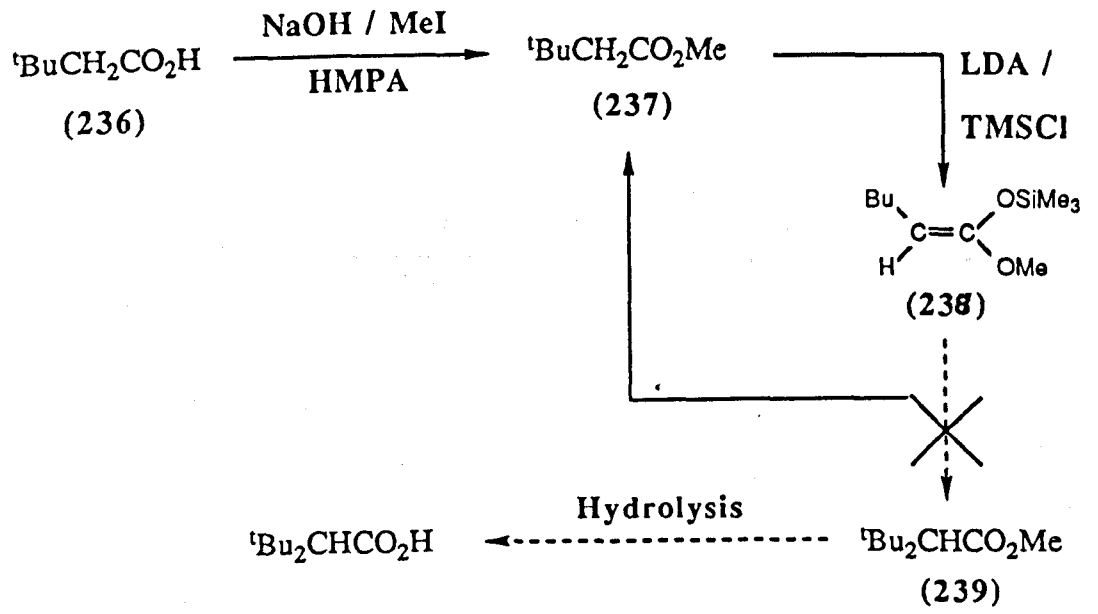
Scheme 18

This synthesis, however, was not considered a viable one, as it involved a tedious eight step route, which utilised hexamethylacetone (a compound not readily available) as starting material.

Hence, a different approach to the thioketene was

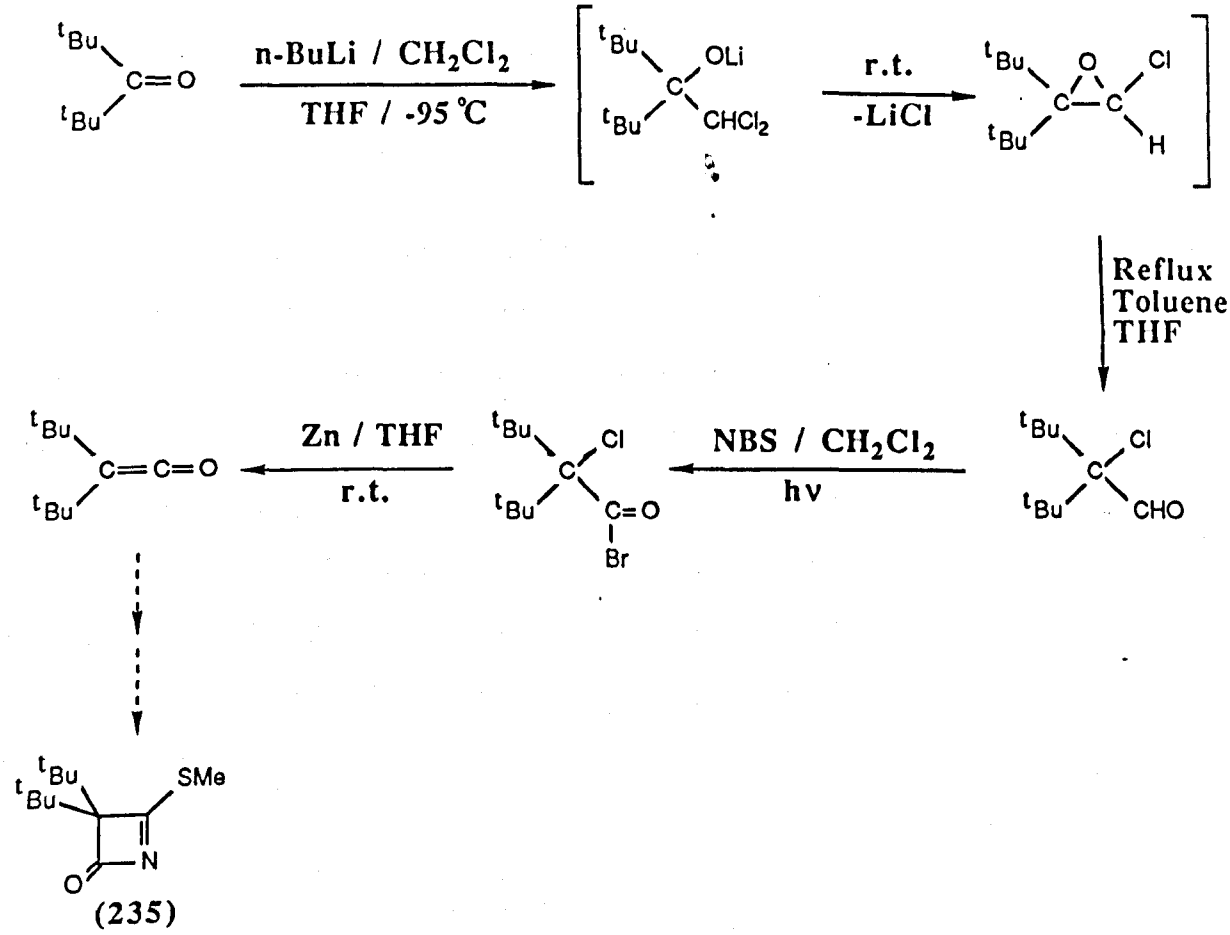
devised. Work published by Dubois[97] had shown a seemingly straight forward four-step procedure for the synthesis of di-t-butylacetic acid (240), the precursor to the thioketene. This route utilised the pungent, but commercially available, t-butylacetic acid as starting material. As shown in Scheme 19, t-butylacetic acid (236) was esterified using methyl iodide in hexamethyl phosphoric triamide (HMPA). The ester (237) was then treated with lithium diisopropylamide (LDA) and trimethylsilyl chloride in dry THF to give the silyl enol ether (238). Enol ether (238) proved to be highly susceptible to hydrolysis and had to be handled under a dry nitrogen atmosphere. According to Dubois's procedure[97] the simple alkylation of enol ether (238) using t-butyl chloride in the presence of zinc chloride as a Lewis catalyst in dichloromethane yields the required methyl di-t-butylacetate (239) as a distillable liquid in fair yield. This step, however, proved to be irreproducible. After countless repetitions the only product obtained was the parent ester (237). This was believed to have arisen from hydrolysis of the enol ether by small quantities of hydrochloric acid present in the t-butyl chloride. Even with the use of strictly dry conditions and freshly distilled t-butyl chloride, the same result was obtained. This result was later substantiated by work done at Roussel Laboratories Ltd. (private communication) where ester

(239) could only be detected as a minor component in the reaction mixture.



Scheme 19

A sample of 3,3-di-t-butyl-1-azetin-4-one was eventually prepared by Dr. S. S. Matharu at Roussel Laboratories Ltd. The route employed was based on a recent publication by Hofmann[98] which utilised hexamethylacetone in a four-step synthesis of di-t-butylketene. This procedure is outlined in Scheme 20. Thionation of the ketene led to di-t-butylthioketene which was then used in the synthesis as described by Schaumann,[21] and illustrated in Scheme 17.



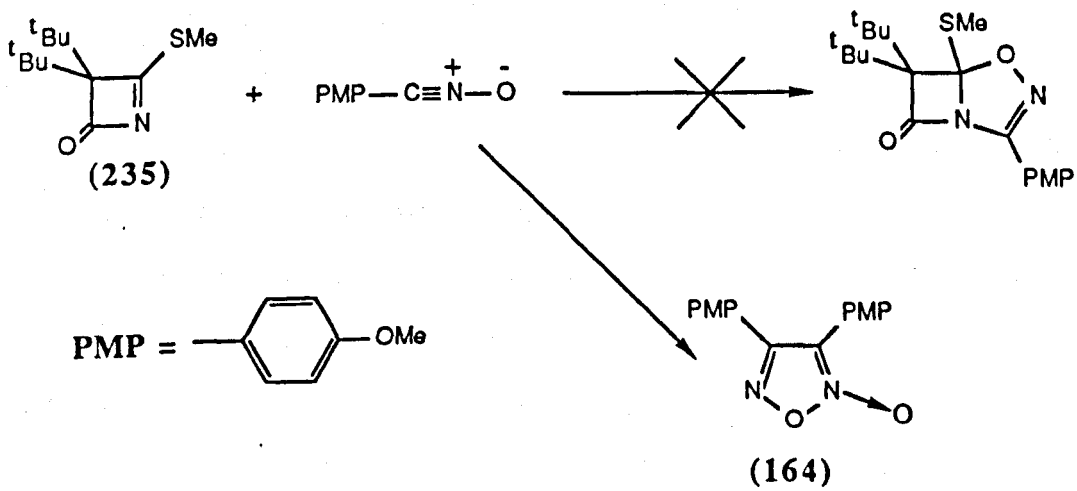
Scheme 20

3.3. 1,3-DIPOLAR CYCLOADDITION TO 3,3-DI-t-BUTYL-1-AZETIN-4-ONE

Compared to the 1-azetine system, 1-azetin-4-ones are more highly strained ring systems due to the extra sp^2 centre of the carbonyl group. Simplistically, then, it was expected that cycloaddition to 1-azetin-4-ones should be more favoured than to 1-azetines, as the reaction would lead to loss of a larger

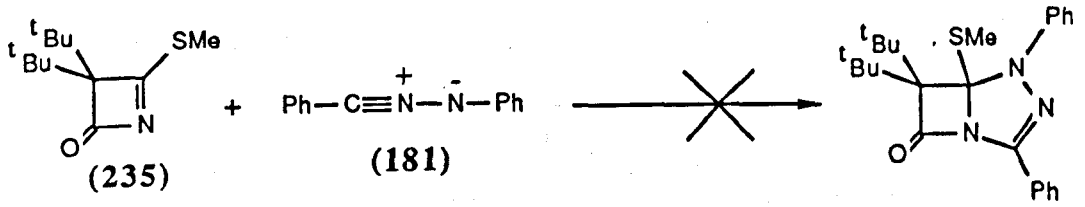
amount of ring strain energy.

The attempted addition of p-methoxybenzonitrile oxide (generated from hydroximoyl chloride (166a) by dehydrochlorination using triethylamine) to 3,3-di-t-butyl-1-azetin-4-one (235) was carried out in dry benzene at room temperature. Care was taken to insure that an excess of the dipolarophile was also present so as to reduce the chances of the dipole dimerising. However, work-up of the reaction mixture followed by chromatographic purification using preparative TLC yielded no cycloadducts. The 1-azetin-4-one (235) was recovered along with furoxan (164), the latter being the product of dipole dimerisation.



Attempted cycloaddition of diphenyl nitrile imine (181) to azetinone (235) was carried out in boiling benzene in

the presence of excess triethylamine. Again, no cycloadducts were isolated. The 1-azetin-4-one was recovered by using preparative TLC.



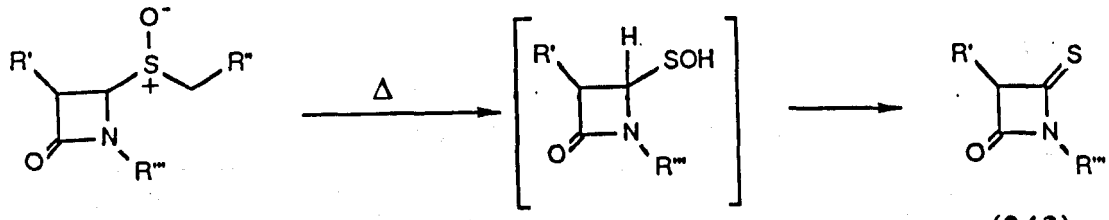
This lack of reactivity of the 1-azetin-4-one was very surprising. Furthermore, the C=N bond in the 1-azetin-4-one system is now part of an acylimine functionality, which are known[92] to be more potent dipolarophiles than ordinary imines. The most likely factor preventing cycloaddition, therefore, must be steric hindrance. This is two fold. First, the t-butyl groups could be preventing approach of the dipole from above or below the plane of the C=N bond. Secondly, in the transition state for cycloaddition, the -SMe would be forced into a position very close to either of the t-butyl groups.

In order to check this idea, it was clearly necessary to synthesise a 1-azetin-4-one system void of bulky substituents at the C-3 position.

3.4. ATTEMPTED NOVEL ROUTES TO THE 1-AZETIN-4-ONE SYSTEM

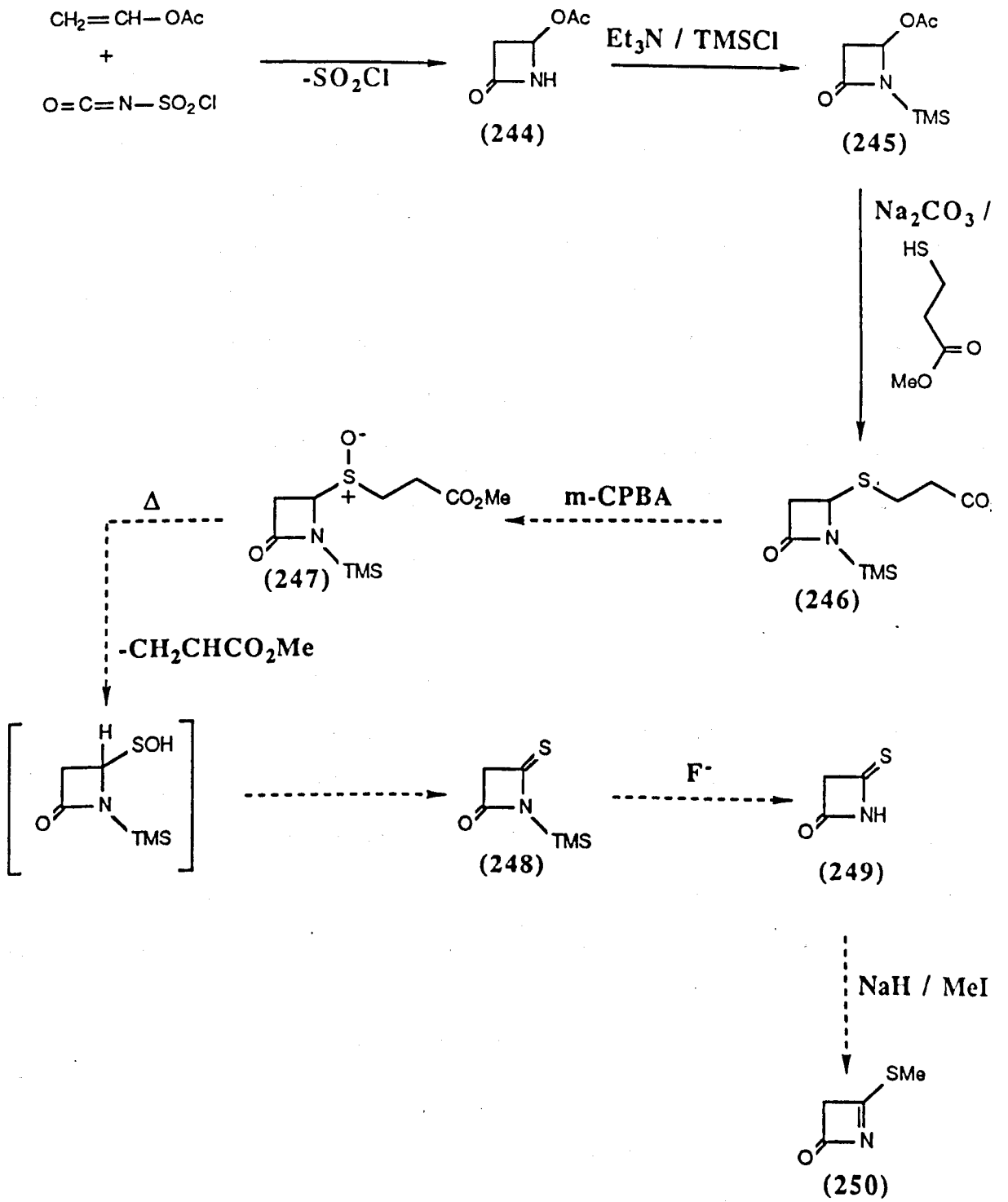
3.4.1. FROM ß-LACTAM SULPHOXIDES

The thermolysis of ß-lactam sulphoxides (241) to 4-thioxo-2-azetidinones (243) has been well documented.[13,15-17]



The reaction has been shown by Chou and his co-workers[17] to go via the intermediate sulphenic acid (242). In all the cases described, however, the product thioxoazetidinones contained N-substituents. For a 4-thioxo-2-azetidinone to be useful as a precursor to the 1-azetin-4-one system, the nitrogen needs to be unsubstituted. This requirement could still be achieved by using a protecting group, such as trimethylsilyl, on the nitrogen which could be easily removed when no longer needed.

Hence, a route was devised to the parent 1-azetin-4-one system (250), as shown in Scheme 21. 4-Acetoxy-2-azetidinone (244) was prepared by the addition of chlorosulphonyl isocyanate to vinyl acetate as described by Clauss.[99] Protection of the nitrogen using trimethylsilyl


CH2=CH—OAc
+
O=C=N—SO2Cl
-SO2Cl
OAc
NH
(244)
Et3N / TMSCl
OAc
N
TMS
(245)
Na2CO3 /
HS
O
MeO
S
CO
N
TMS
(246)
m-CPBA
O-
S
+
CO2Me
N
TMS
(247)
Δ
-CH2CHCO2Me
H
SOH
N
TMS
S
N
TMS
(248)
F-
S
NH
(249)
NaH / MeI
SMe
N
(250)

Scheme 21

chloride and triethylamine proceeded smoothly to give azetidinone (245) as a stable distillable oil. The nucleophilic lability of the acetoxy group is well known,[25,31] and thus, in the presence of sodium carbonate it was displaced by methyl 3-mercaptopropionate to give azetidinone (246) in fair yield. Oxidation of a related sulphide to the corresponding sulphoxide using m-chloroperbenzoic acid has been described by Bachi.[16] Several attempts at this oxidation, however, failed and this route was abandoned at this stage.

3.4.2. FROM ARYL CYANATES AND SULPHONYL CYANIDES

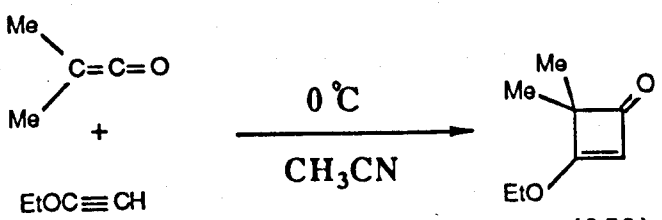
Until 1963, arylcyanates (cyanic esters) (251) were considered unobtainable. A simple synthesis of these compounds was then discovered by Grigat and Putter,[100] which involved the reaction of phenols with cyanogen halides in the presence of base (avoiding an excess of the phenoxide).

$$ArOH + BrCN \xrightarrow{\text{Base}} ArOCN \quad \textbf{(251)}$$

The chemistry of these compounds has been thoroughly investigated and reviewed,[101] and it has been shown that the chemistry of aryl cyanates is mainly dependant on the

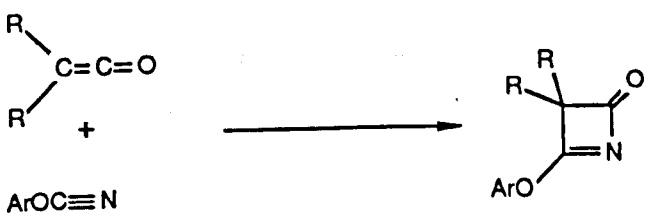
electrophilicity of the carbon atom of the -OCN group. It is this electron deficiency of the carbon atom which was to be the basis of the use of aryl cyanates as precursors to 1-azetin-4-ones.

A recent publication[102] has shown the tendency of ketenes to undergo a step-wise thermal [2+2] cycloaddition with alkoxyacetylenes to give cyclobutenones e.g. (252).

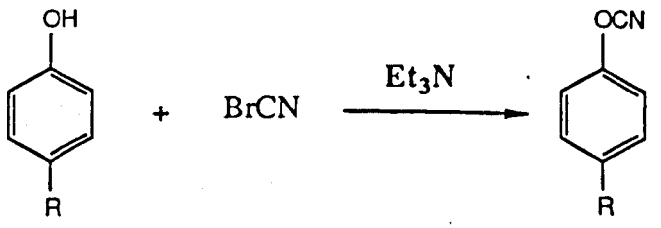


(252)

This suggested the possibility of aryl cyanates undergoing a similar reaction with ketenes to yield 1-azetin-4-ones in one step, i.e.



Thus phenyl cyanate (251 Ar=Ph) and p-nitrophenyl cyanate (251 Ar=p-$NO_2C_6H_4$) were prepared by reaction of phenol and p-nitrophenol, respectively, with cyanogen bromide.

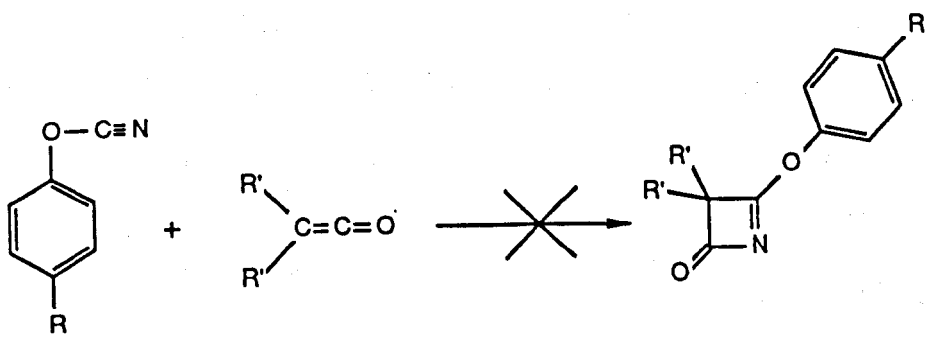


(251)

R = H, NO_2

The use of the 4-nitro group was aimed at increasing the electrophilicity of the cyanate carbon atom, by mesomerically withdrawing electrons away from the cyanate oxygen atom.

Disappointingly, however, neither phenyl cyanate nor p-nitrophenyl cyanate showed any reaction whatsoever, with diphenyl-, dichloro- or dimethyl-ketene even after stirring under a dry atmosphere at room temperature for 3 days. Similarly, photolysis of these reaction mixtures led to none of the desired cyclic products.

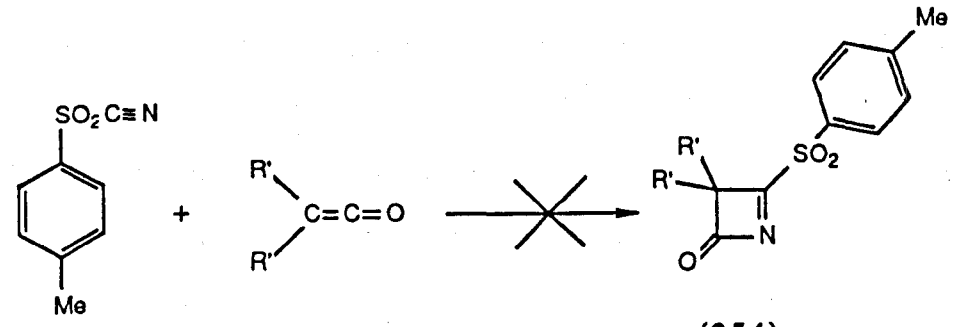


R = H, NO_2

R' = Cl, Me, Ph

p-Toluenesulphonyl cyanide (253) was used instead of the aryl cyanates in a bid to improve the electrophilicity of

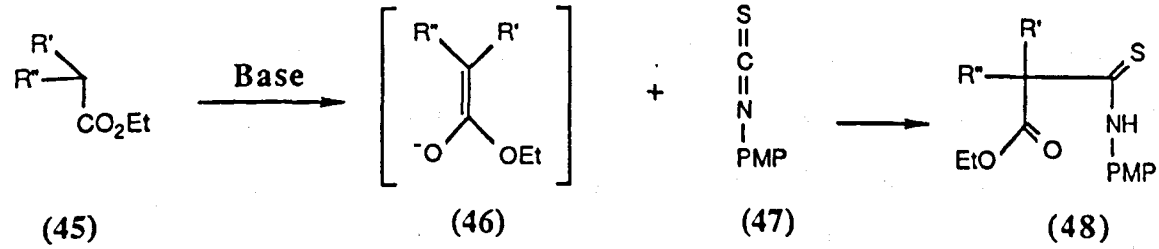
the cyanide carbon atom and thus enhance the chances of reaction with a ketene. Again, however, none of the desired 1-azetin-4-one (254) was obtained after reaction with dimethyl- and diphenyl-ketene for several hours.



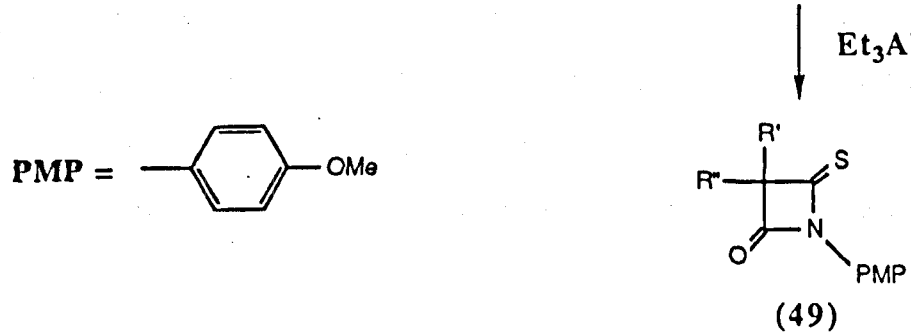
(253) (254)

3.4.3. FROM N-UNSUBSTITUTED-4-THIOXO-2-AZETIDINONES

A unique and versatile route to 4-thioxo-2-azetidinones was published by Cainelli[22] which involved the nucleophilic addition of an enolate (46) (generated in situ) to



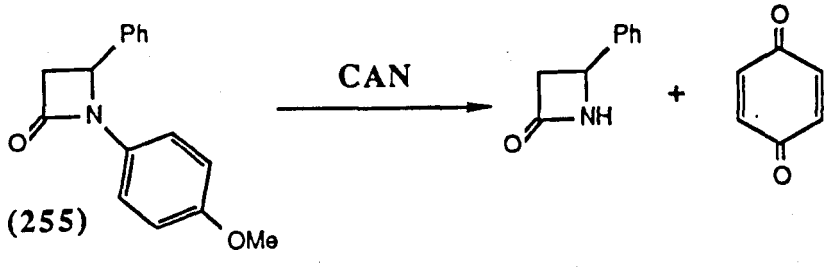
(45) (46) (47) (48)



(49)

p-methoxyphenyl isothiocyanate (47) followed by cyclisation of the resultant thiomalonic ester (48) using triethyl aluminium, to give the required 4-thioxo-2-azetidinone (49).

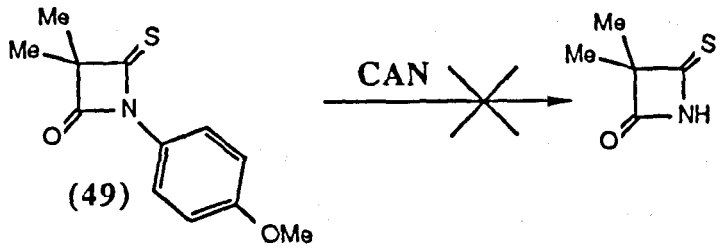
The oxidative cleavage of N-(p-methoxyphenyl) groups in 1-(p-methoxyphenyl)-azetidin-2-ones e.g. (255) has been achieved using ceric ammonium nitrate[103] (CAN) in acetonitrile. Hence, de-blocking of the nitrogen in thioxoazetidinone (49) in this manner would lead to the required N-unsubstituted-4-thioxo-azetidin-2-one.



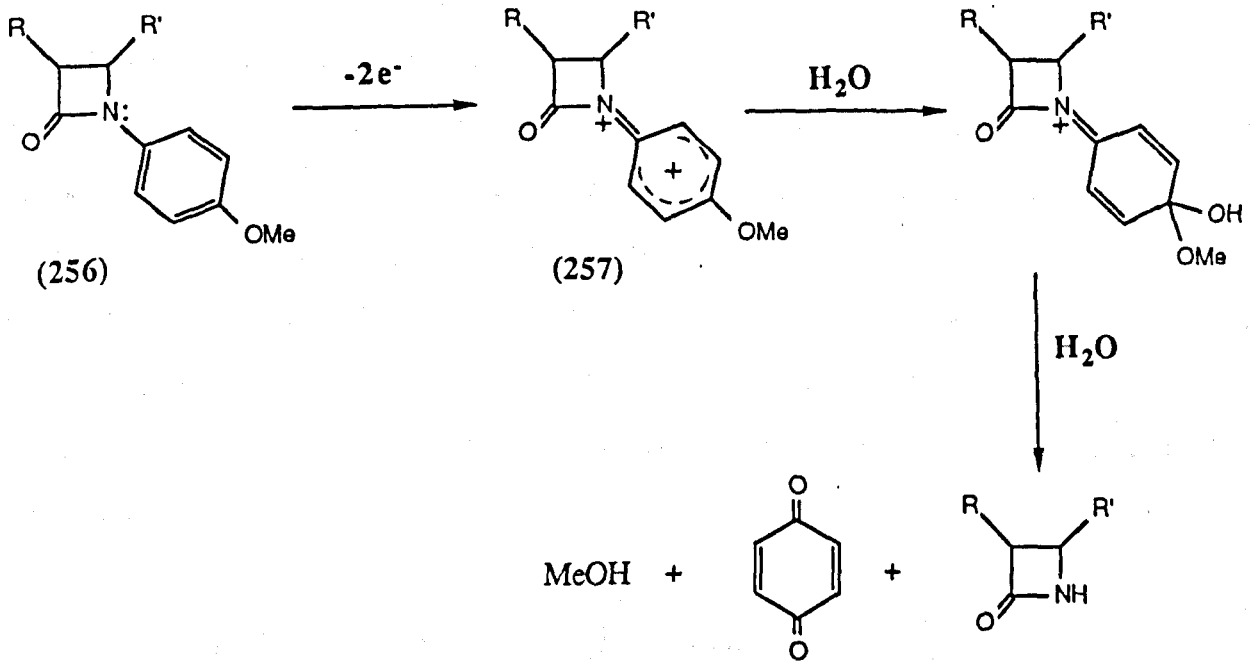
Following the procedure given by Cainelli,[22] the enolate of ethyl isobutyrate (46, R'=R"=Me) was generated at -78 °C in dry THF by treating the ester with LDA. To this was added p-methoxyphenyl isothiocyanate and the solution allowed to warm up to room temperature. Work-up, followed by flash silica chromatography gave the thiomalonic ester (48, R'=R"=Me). This was cyclised by treatment with triethyl aluminium in boiling toluene to give the thioxoazetidinone (49, R'=R"=Me).

To effect the de-blocking of the thioxoazetidinone

nitrogen, a solution of thioxoazetidinone (49) was treated with ceric ammonium nitrate in wet acetonitrile. Unfortunately, even after stirring for 48 hrs work-up of the reaction mixture gave only starting material.



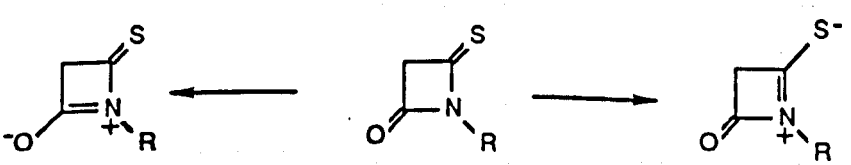
A possible explanation for the failure of this reaction may be found in the proposed mechanism for oxidative dearylations using ceric ammonium nitrate.[104]



Scheme 22

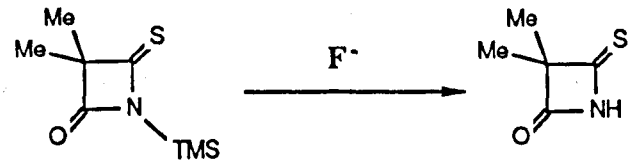
With reference to Scheme 22, the source of the first electron lost from the ring system (256) must be the lone pair of the lactam nitrogen. The generated cation radical is stabilised by resonance into the aromatic ring which supplies the second of the two electrons lost in the oxidation, leading to the dicationic species (257).

Consequently, the availability of the nitrogen lone pair is essential for the oxidation to proceed. One reason that β-lactam bonds are so easily cleaved is the lack of amidic resonance compared to an acyclic amide i.e. in β-lactams the nitrogen lone pair is only involved in bonding to a very small extent. However, the case is different for 4-thioxo-2-azetidinones. The nitrogen lone pair is now involved in thioamidic resonance as well as amidic resonance. The former is known to be predominant as shown by the abnormally high IR stretching frequency of the carbonyl group (1800 cm^{-1}) i.e. resonance form (B) is predominant over resonance form (A). Overall, this probably reduces the availability of the nitrogen lone pair to such an extent that oxidation by the Ce(IV) is prohibited.



(A) (B)

It may be possible to overcome this problem by using an isothiocyanate in the initial step which can be more easily deprotected. For example, use of trimethylsilyl isothiocyanate (a commercially available reagent) may lead to a 4-thioxo-2-azetidinone (258) which could then be desilylated by treatment with fluoride ion. i.e.



(258)

Unfortunately, lack of time prevented looking into the viability of such a reaction.

3.4.4. FROM IMINOPHOSPHORANES

One of the main uses of iminophosphoranes (259) is as analogues of the Wittig P=C ylide. Whereas the Wittig ylide is employed in the generation of new C=C bonds, the iminophosphorane ylide (P=N) generates new N=C bonds. Iminophosphoranes are readily prepared from azides and tertiary phosphines.

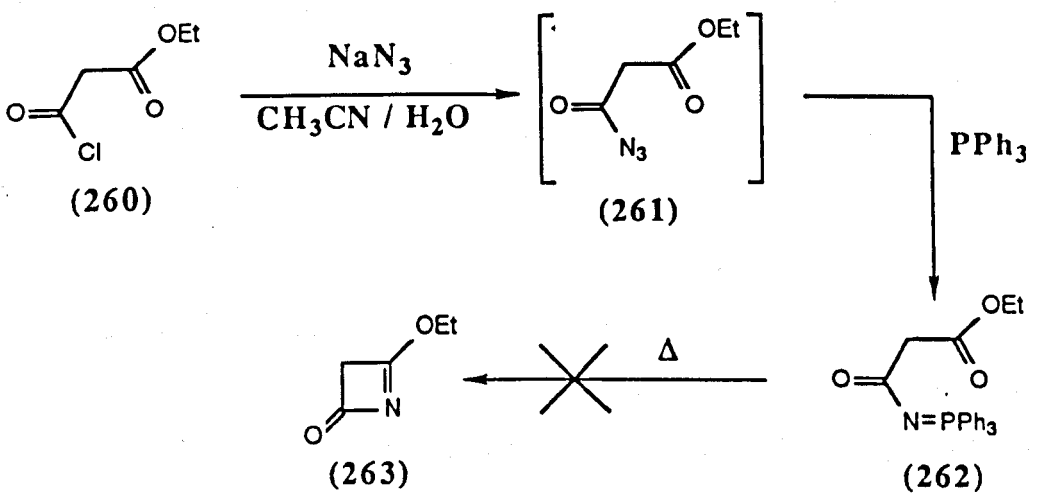
$$R_3P + N_3X \xrightarrow{-N_2} R_3P{=}NX$$

(259)

Iminophosphoranes have found many uses[105-106] not

least as precursors to heterocyclic systems. 5-,[107] 6-,[108] and 7-membered[109] heterocycles have been prepared from iminophosphoranes by intramolecular aza-Wittig reactions usually under very mild conditions. However, no attempts have been reported for making four membered nitrogen heterocycles from iminophosphoranes.

Scheme 23 shows a proposed route to a 1-azetin-4-one system (263) by way of an iminophosphorane intermediate.



Scheme 23

Treatment of ethyl malonyl chloride with sodium azide in acetonitrile/water produced the acyl azide (261). This azide was not isolated but directly treated with an excess of triphenylphosphine. As expected nitrogen gas was

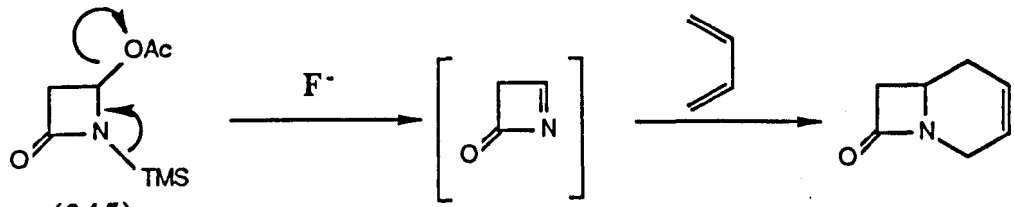
evolved and on work-up iminophosphorane (262) was isolated as a white solid and identified by NMR spectra. It was hoped that on thermolysis, iminophosphorane (262) would undergo an intramolecular aza-Wittig reaction to lose triphenylphosphine oxide and produce 1-azetine-4-one (263). However, thermolysis in toluene lead to a tarry mixture. This may have been due to the thermolability of azetinone (263), which if formed at the high temperatures required for the cyclisation would rapidly decompose. An unsuccessful attempt was made to trap azetinone (263) by Diels-Alder cycloaddition using diphenylisobenzofuran as the diene. Again, a tarry mixture was all that was obtained.

3.4.5. IN-SITU TRAPPING OF 1-AZETIN-4-ONE

Prior to Ueda's trapping of a 1-azetin-4-one system by a Diels-Alder reaction,[43] Barrett[40] had published his unsuccessful attempts to entrap a 1-azetin-4-one system *in-situ* by 1,3-dipolar cycloaddition. Barrett, like Ueda, had concentrated his work on 1-unsubstituted-2-azetidinones, e.g. 4-acetoxy-2-azetidinone, as the source for the 1-azetin-4-one system.

Another possible precursor to an azetinone is 1-trimethylsilyl-4-acetoxy-2-azetidinone (245). It was thought that

treatment of this azetidinone with fluoride ions should promote loss of the trimethysilyl residue, leading to the generation of the intermediate 1-azetin-4-one (264), as shown in Scheme 23, which could then be trapped either by a diene or by a 1,3-dipole.



(245) (264)

Scheme 23

Hence, azetidinone (245) in a solution of dry benzene was treated with tetrabutylammonium fluoride in the presence of several dienes, including cyclopentadiene, 2,3-dimethyl-1,3-butadiene and diphenylisobenzofuran. In all of these cases, however, complex unseparable mixtures of products were obtained. A similar reaction using p-methoxybenzonitrile oxide as the trapping agent gave the same unsuccessful result.

3.5. CONCLUSION

The failure to obtain a stable 1-azetin-4-one derivative has meant that the final objective, i.e. the cycloaddition step, was not possible to achieve. The indications

from the work done so far on 1-azetines still point to the possibility of successful 1,3-dipolar cycloadditions to azetinones void of steric inhibitors. Hence, any future extension of this work must aim at a succesful synthetic route to the elusive 1-azetin-4-ones.

CHAPTER 4

IMINOPHOSPHORANES AS INTERMEDIATES TO HETEROCYCLIC SYSTEMS

4.1. INTRODUCTION

The attempt to prepare an azetinone by ring-closure of an iminophosphorane onto a suitably located carbonyl function has been described in Chapter 3. Synthesis of several heterocycles by this type of intramolecular cyclisation is well documented, but the reaction has not been fully exploited. It was, therefore, of interest to carry out this reaction on several azides that were available in this laboratory, and which if successful would provide a new route to some interesting and in some cases novel heterocycles.

4.2. IMINOPHOSPHORANES

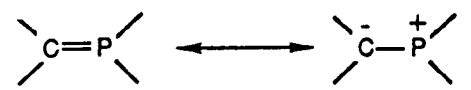
The reaction of azides with tertiary phosphines yields iminophosphoranes (259) via the unstable intermediate phosphazides (265).

$$R_3P + N_3X \longrightarrow \underset{(265)}{\left[R_3P{=}N{-}N{=}NX\right]} \longrightarrow \underset{(259)}{R_3P{=}NX}$$

This reaction was discovered in 1919 by Staudinger and Meyer and thus given the name The Staudinger Reaction. Further work by Kebachnik demonstrated that, besides the tertiary phosphines, the esters of phosphoric acids may also be used for the preparation of phosphazo compounds.

Although the reaction with organic azides is typical for all trialkyl and triaryl phosphines, mixed phosphines, etc., triphenyl phosphine, which is easily accessible and convenient in operation, is generally used. A variety of aliphatic and aromatic azides can be employed for the imination of phosphines.

One of the main uses of iminophosphoranes (259) is as analogues of the Wittig P=C ylide. Whereas the Wittig ylide is employed in the generation of new C=C bonds, the iminophosphorane ylide (266) generates new N=C bonds.



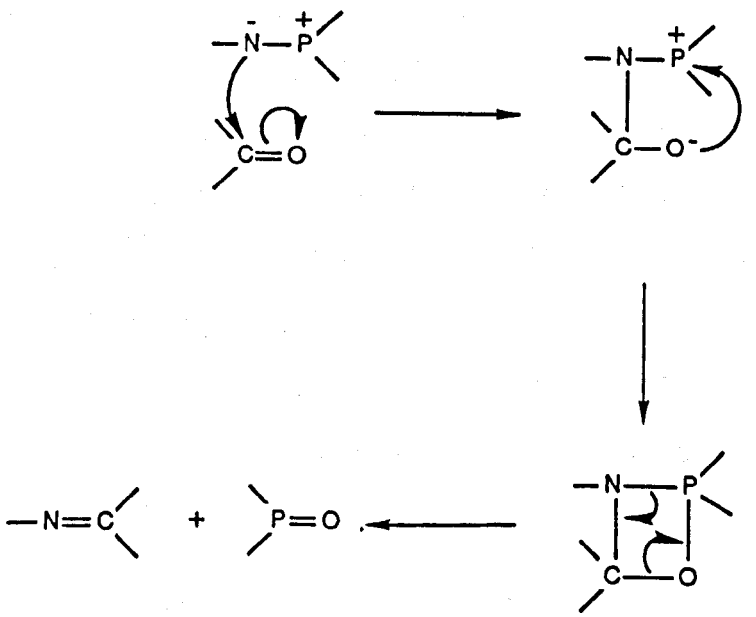
The Wittig Ylide

The Iminophosphorane Ylide

(266)

The mechanism is believed to follow that involved in the Wittig reaction. Hence, initial attack by the nucleophilic nitrogen of the ylide on the carbon of the carbonyl group generates the

zwitterionic species (267) which undergoes ring closure to generate the unstable betaine species (268). The betaine (268) then decomposes into the phosphine oxide (269) and the newly formed -N=C- group.



Reactions involving oxygen abstraction by the iminophosphorane ylide are dubbed aza-Wittig reactions. These reactions can be both inter- or intra-molecular in nature. In general, they usually occur under very mild conditions and thus offer a versatile route to both common and less accessible heterocyclic systems. However, little use appears to have been made of iminophosphoranes derived from aryl azides as intermediates to heterocycles. In this section some examples of

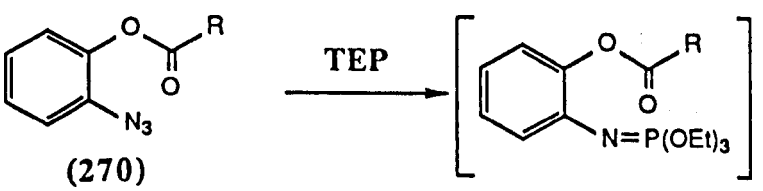
the use of a variety of aryl azides to generate a series of heterocyclic systems of differing ring size are described.

4.3. INTRAMOLECULAR AZA-WITTIG REACTIONS

4.3.1. 5-MEMBERED HETEROCYCLIC SYSTEMS

A wide variety of 5-membered heterocyclic systems have been prepared using aza-Wittig chemistry. These included 1,2,4-oxadiazoles,[107] tetrazoles,[110] 1,3-oxazoles,[111] benzoxazoles,[112] and cyclic imines.[113]

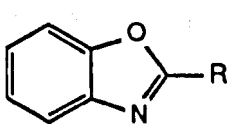
Of these, however, only 2-phenylbenzoxazole (271a) and 2-methylbenzoxazole (271b) were prepared by treatment of an aryl azide (270) with triethylphosphite (TEP).[112]



(270)

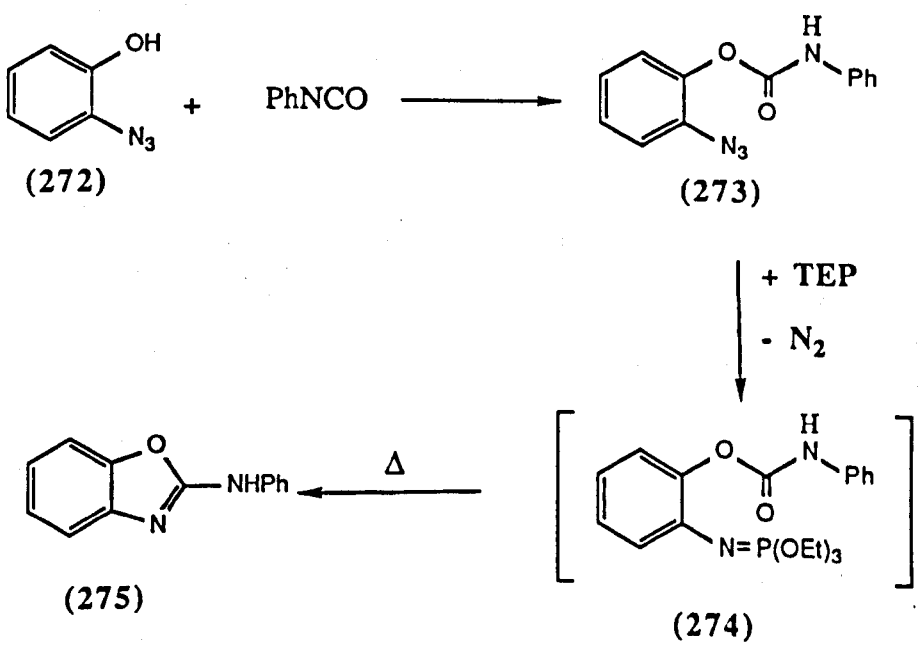
a : R = Ph

b : R = Me



(271)

It has been shown that 2-anilino-benzoxazole (275) can be prepared in a similar manner by treatment of azide (273) with TEP in boiling benzene. Hence, reaction of o-azidophenol (272) with phenyl isocyanate gave the azido carbamate (273) in good yield. Treatment of a benzene solution of azide (273) with TEP under an inert atmosphere caused the evolution of nitrogen gas by the reaction mixture as the iminophosphorane (274) was generated. Subsequent heating was required to furnish the aza-Wittig cyclisation to benzoxazole (275).

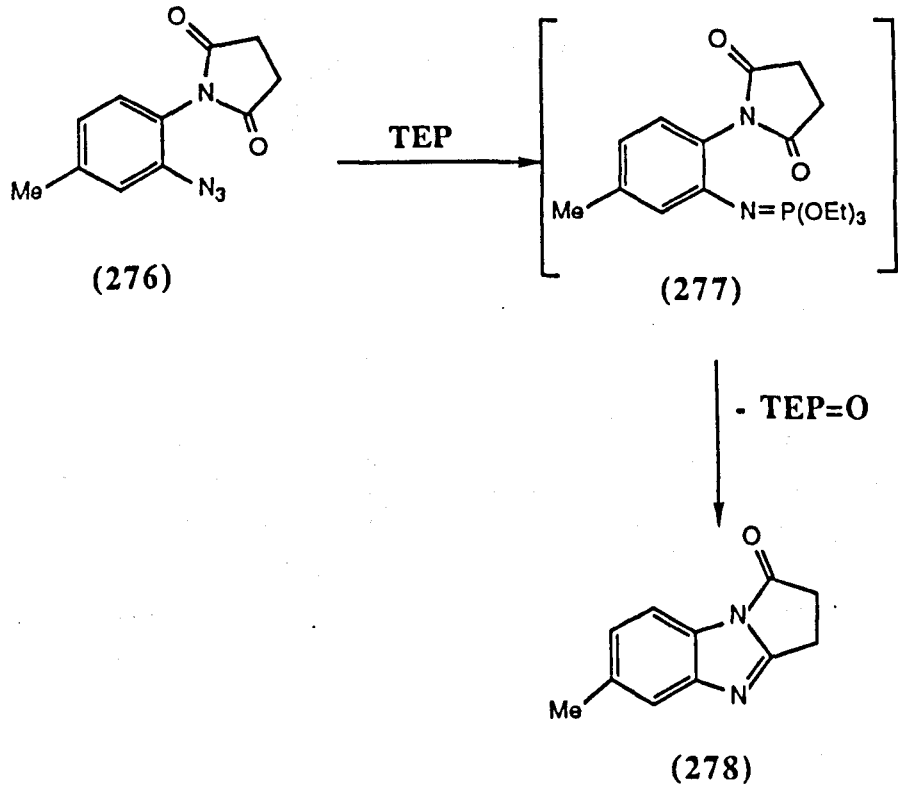


(272) (273) (274) (275)

The availability of azide (276) in this laboratory, prompted a similar aza-Wittig reaction. Iminophosphorane (277) was readily prepared by treatment of a dry

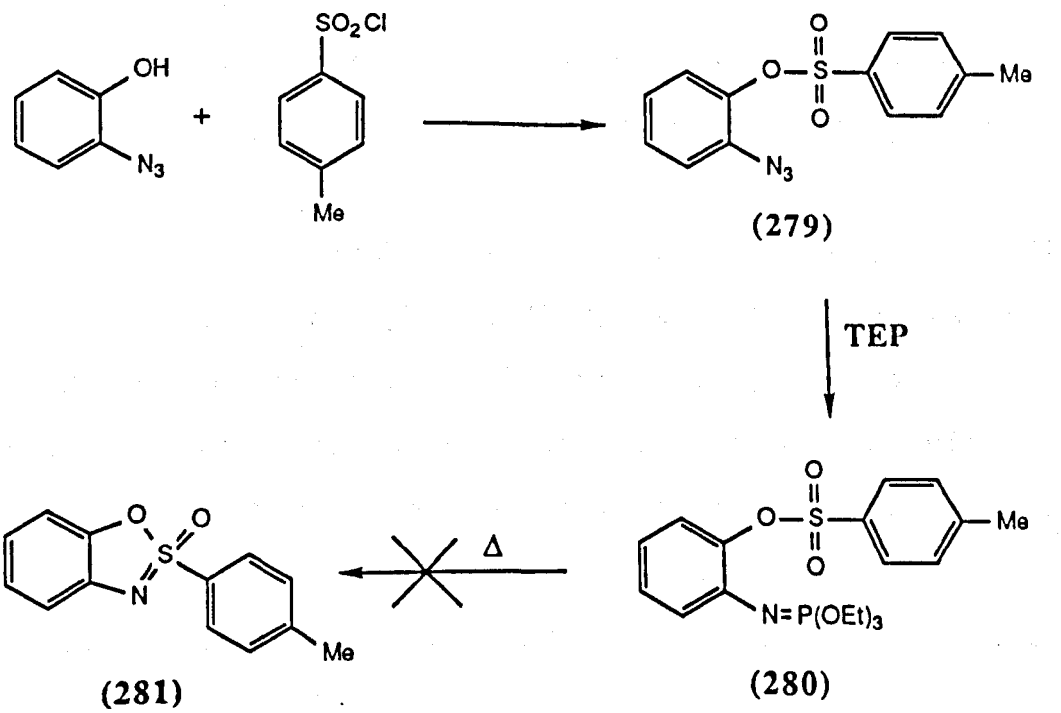
benzene solution of azide (276) with TEP. Subsequent heating of this reaction mixture failed to cause ring closure, as was shown by TLC. It was, therefore, necessary to remove the solvent under vacuum and redissolve the unpurified iminophosphorane in o-dichlorobenzene. Further heating for several hours was sufficient to effect ring closure and yield the pyrrolo benzimidazole (278) as a crystalline solid.

IR spectroscopic studies of benzimidazole (278) showed the loss of the azide band (2200 cm^{-1} in azide (276)) and one of the imide crbonyl bands (1740 cm^{-1} in azide (276)). A band at 1665 cm^{-1} was assigned to the remaining amide carbonyl group of the benzimidazole.



Finally, an attempt was made to prepare the heterocyclic system (281) via an iminophosphorane intermediate. This reaction was of interest not only because only one example of this ring system has been reported,[114] but also because as far as we are aware no intramolecular aza-Wittig reactions onto an S=O group have been reported. In fact, formation of sulphoximides by this route has met with little interest.[115]

Tosylate (279) was readily obtained from o-azidophenol (272) and p-toluenesulphonyl chloride. Treatment of the tosylate with TEP in benzene gave the iminophosphorane



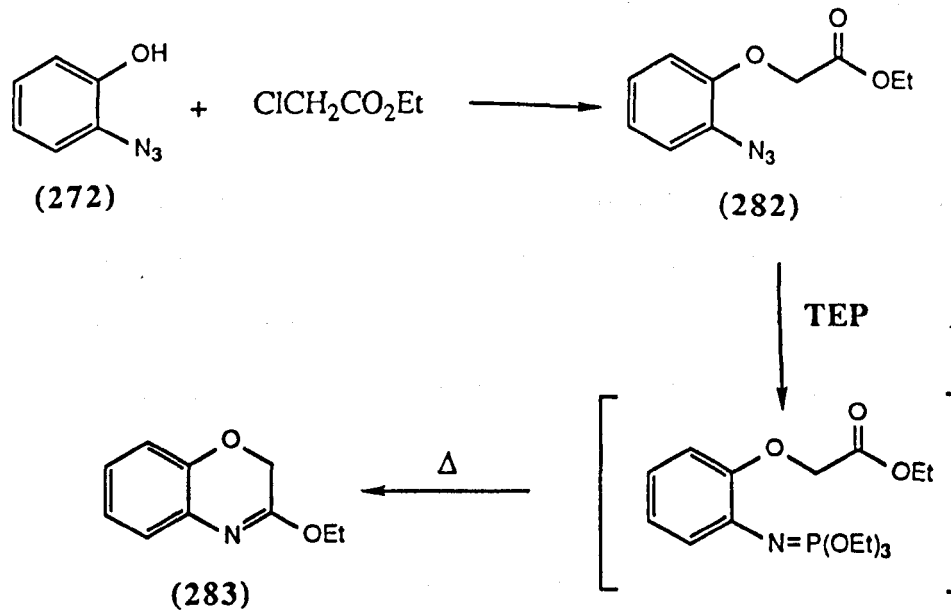
(280) in quantitative yield. Thermolysis of intermediate (280) for several days in dichlorobenzene, however, failed to effect cyclisation. This lack of reactivity cannot be explained so far. However, further investigation on this cyclisation are being carried out.

4.3.2. 6-MEMBERED HETEROCYCLIC SYSTEMS

Isoquinolines,[108], quinolines,[116] and 1,3-benzoxazin-4-ones[117] represent a few examples in which aza-Wittig chemistry has been used in the synthesis of 6-membered heterocyclic compounds.

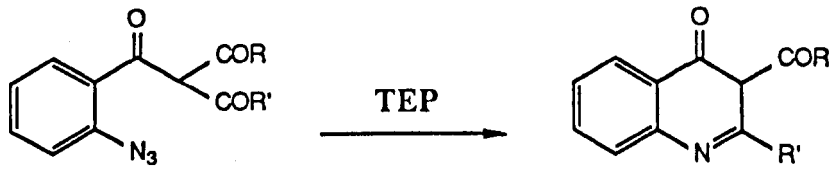
As an extension of these examples, the use of aza-Wittig chemistry to prepare 1,4-benzoxazines and quinolones was attempted.

The 2H-3-ethoxy-1,4-benzoxazine was readily prepared utilising o-azidophenol (272) as starting material. Reaction of ethyl chloroacetate with the azidophenol gave azide (282) in high yield. Subsequent treatment of the azide with TEP in a dry benzene solution gave the intermediate iminophosphorane, which was not isolated, but directly heated under reflux for 2 hrs to yield the benzoxazine (283) as a white crystalline solid.



(272) (282) (283)

A series of four quinolones (285) were similarly prepared utilising aryl azides (284a-d). However, in all four cases no heating was required for the reaction to proceed to completion. Treatment of a vigorously stirred solution of the



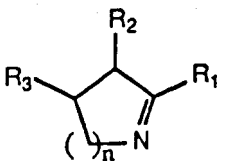
(284) (285)

	R	R'
a	OEt	OEt
b	Ph	Ph
c	OEt	Ph
d	OEt	Me

respective azide in dry toluene caused the precipitation of the cyclised product in very high yield. Crystallisation from methanol provided the pure products which were identified by IR and NMR spectroscopy and comparison of melting points with literature values.

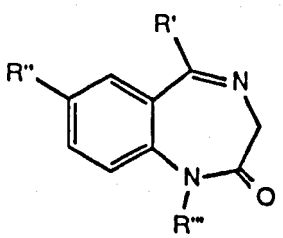
4.3.3. 7-MEMBERED HETEROCYCLIC SYSTEMS

Only two examples are known of the use of aza-Wittig reactions in the production of 7-membered heterocycles. These concerned the preparation of cyclic imines[113] (286) and benzo-1,4-diazepines,[109] (287) respectively.



(286)

R_1, R_2, R_3 = Alkyl, Aryl



R' = H, Ph

R'' = H, NO_2, C

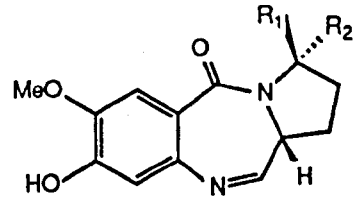
R''' = H, Me

(287)

The application of the intramolecular aza-Wittig cyclisation to the synthesis of the highly sought after pyrrolo[1,4]benzodiazepines antitumour antibiotics, however, has not been reported.[118]

A great deal of interest has been shown in the synthesis of the carbinolamine-containing

pyrrolo[1,4]benzodiazepine group of antibiotics,[119] which include among others neothramycin A & B (288).



(288)

NEOTHRAMYCIN

A : $R_1 = H$, $R_2 = OH$

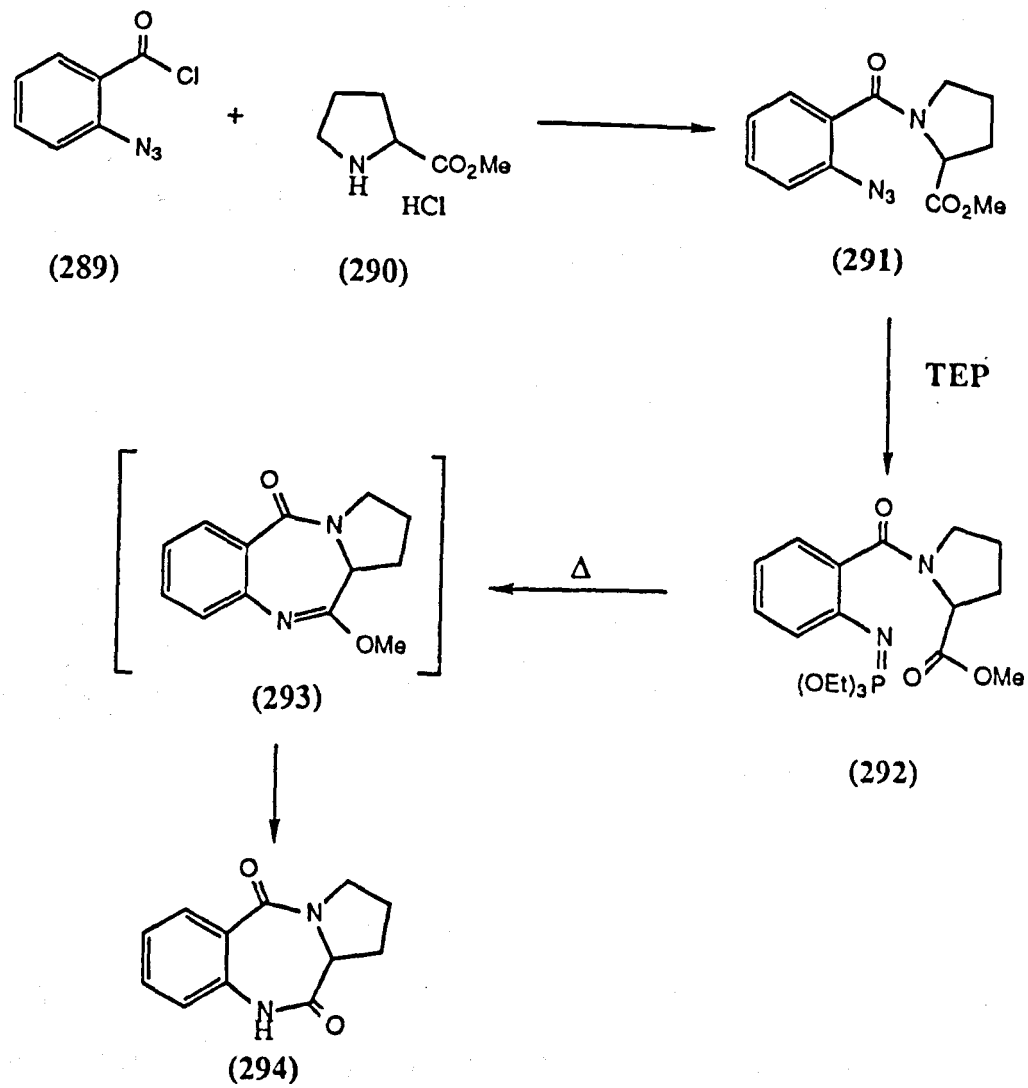
B : $R_1 = OH$, $R_2 = H$

However, until recently,[120] a variety of synthetic problems were encountered. Namely, low yields, loss of unsaturation in the product (due to the reductive conditions needed for the synthesis) and loss of stereochemistry.

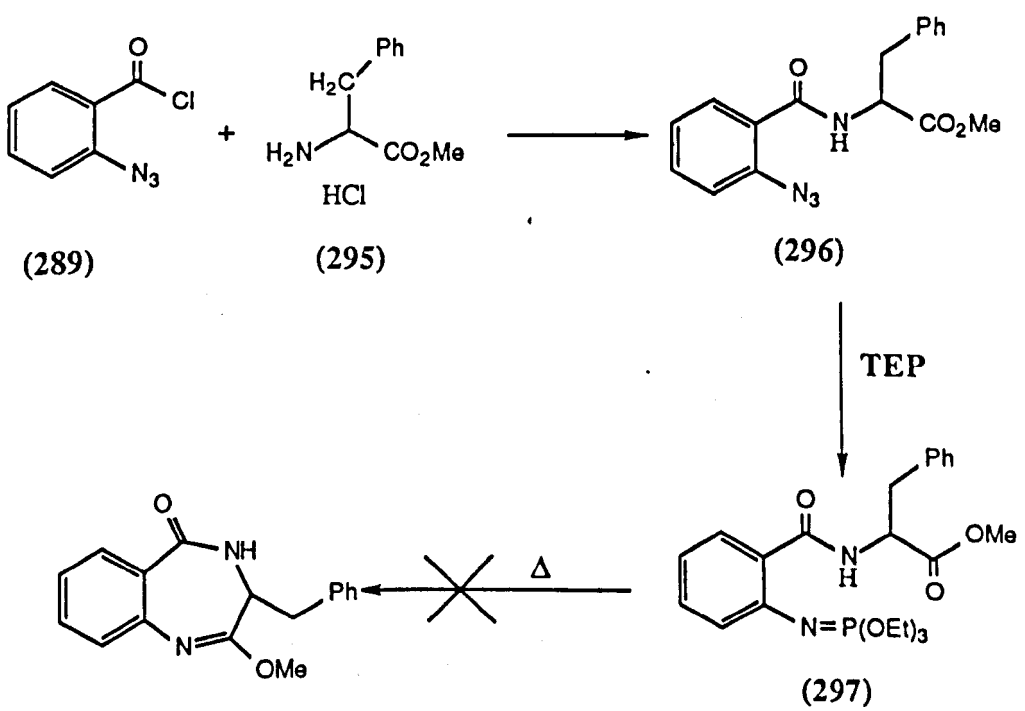
A successful application of the aza-Wittig cyclisation would overcome these problems. Since, typically, neutral mild conditions are employed.

Hence, the azido benzamide (291) was readily prepared from o-azidobenzoyl chloride (289) and proline methyl ester (290). Treatment of azide (291) with TEP in a solution of toluene resulted in the evolution of nitrogen gas and gave iminophosphorane (292) on chromatographic work-up. Thermolysis of the iminophosphorane in toluene for 6 hrs gave a benzodiazepine in practicable yield. However, spectroscopic investigation showed the absence of the expected imino ether functionality. Further investigation showed the product to be the well known di-lactam

(294). This is believed to have arisen from hydrolysis of the desired imino ether (293). Further work is expected to investigate the isolation of benzodiazepine (293) without having to resort to hydrolytic work-up procedures.



Interestingly, when a similar cyclisation was attempted on the azido amide (296), prepared from o-azidobenzoyl chloride and phenylalanine methyl ester (295), the acyclic iminophosphorane (297) proved resistant to ring closure, even after heating at high temperatures for long periods of time.



4.4. CONCLUSION

From the work illustrated here as well as that already published, it can be clearly seen that the aza-Wittig reaction provides a highly useful and versatile route to a variety of heterocyclic products. In general, though, it appears

that iminophosphoranes derived from alkyl and acyl azides are more potent as aza-Wittig ylides. The size of the generated ring also appears to influence the rate and yield of the reaction. As has been shown, 6-membered hetetocycles were by far the most readily obtained.

SECTION C

EXPERIMENTAL

EXPERIMENTAL

PREPARATION OF 3,3,4,4-TETRAMETHYLAZETIDIN-2-ONE (153)

To a stirred solution of chlorosulphonyl isocyanate (8.4g/ 0.06mol) in dry ether (10-15ml) under an atmosphere of dry nitrogen, was added 2,3-dimethylbut-2-ene (5g/ 0.06mol) dropwise maintaining the temperature between 30-35 °C. The reaction mixture was then stirred for a further hour whilst it cooled to room temperature. The solution was then cooled in a salt-ice bath. The product, 1-chlorosulphonyl-3,3,4,4-tetramthylazetidin-2-one crystallised out as a white solid. This was filtered off and then redissolved in fresh ether. This solution was then added dropwise to a vigourosly stirred mixture of water (30ml), ice (25g), sodium bicarbonate (12g) and hydrated sodium sulphite (8g). The mixture was stirred for a further 30mins at ice temperature. The inorganic solids were filtered off and the organic phase separated out. The aqueous phase was further extracted with dichloromethane (2 x 25ml). The combined organic extracts were dried over $MgSO_4$. Filtration followed by removal of solvent under vacuum gave the product as a white solid. This was recrystallised from ether to give pure 3,3,4,4-tetramethylazetidin-2-one (6.7g/ 0.05mol), 88% yield, m.pt. 103-105 °C [lit[121] 104 °C].

PREPARATION OF 3,3,4,4-TETRAMETHYLAZETIDIN-2-THIONE (154)

To a stirred solution of 3,3,4,4-tetramethylazetidinone (1g/ 7.9mmol) in dry THF (15ml) was added Lawesson's Reagent (1.59g/ 3.9mmol). The mixture was stirred under nitrogen for 20mins. Then heated at 60°C for a further 20mins. After cooling, the solvent was removed under vacuum and the residue chromatographed on flash silica, eluent 7:3 pet. ether: ethyl acetate. The product was isolated as a white solid, this was recrystallised from pet. ether 60/80 to give white needles of 3,3,4,4-tetramethylazetidin-2-thione (1g/ 7.03mmol) 89% yield.

M.pt. 123-124°C.

NMR: 1.25ppm(s, 6H); 1.40ppm(s, 6H); 8.40ppm(bs, 1H).

IR: 1240cm^{-1} (C=S).

Micro Analysis: Required for $C_7H_{13}NS$: C,58.69; H,9.14; N,9.78; S,22.38; Found: C,58.72; H,9.04; N,9.79; S,22.7

PREPARATION OF 3,3,4,4-TETRAMETHYL-1-AZETINE (150)

To a stirred solution of triethyloxunium tetrafluoroborate (1M, 60ml) in dichloromethane was added 3,3,4,4-tetramethylazetidinone (5g/ 0.039mol), under an

atmosphere of dry nitrogen. The reaction mixture was stirred for 1hr at room temperature, and then heated under reflux for a further 1hr. It was then cooled and added dropwise to a stirred 50% potassium carbonate solution (20ml) at -10 °C. The two phase mixture was further diluted by adding dichloromethane (20ml) and then filtered through celite. The organic phase was immediately separated off and dried over magnesium sulphate. After removal of the solvent under vacuum the residue was chromatographed on flash silica, eluent 8:2 pet. ether:ethyl acetate. 3,3,4,4-tetramethyl-1-azetine (3.26g/ 0.02mol), yield 54%, was isolated as a liquid B.pt. 78-80 °C/50mmHg.[47]

PREPARATION OF 2-ETHYLTHIO-3,3,4,4-TETRAMETHYL-1-AZETINE (151)

To a solution of triethyloxonium tetrafluoroborate (10.5ml of 1M solution in CH_2Cl_2) was added tetramethylazetidinthione (1g/ 7mmol) under an inert atmosphere. The mixture was stirred at room temperature for 1hr and then heate under reflux for a further 1hr. After cooling, the solution was added dropwise to 50% potassium carbonate solution (10ml) at -10 °C. After filtration, the organic phase was sparated out and immediately dried over magnesium sulphate. Filtration was followed by removal of the solvent under vacuum. The oily residue was then purified by flash silica chromatography (pet. ether:

EtOAc; 8:2). 2-Ethylthio-3,3,4,4-tetramethyl-1-azetine (1g/ 6.8mmol), yield 89%, was obtained as a colourless oil.

NMR: 1.12ppm(s, 6H); 1.22ppm(s, 6H); 1.28ppm(t, 3H); 2.99ppm(q, 2H)

IR: 1640cm^{-1} (C=N)

Micro Analysis: Required for $C_9H_{17}NS$: C,63.10; H,10.01; N,8.18; Found: C,63.14; H,9.88; N,8.24

PREPARARION OF 7-AZABICYCLO[4.2.0]OCTAN-8-ONE (155)

A neat mixture of cyclohexene (13g/ 0.16mol) and chlorosulphonyl isocyanate (22.6g/ 0.16mol) was stirred under an inert atmosphere at room temperature for 36hrs. The mixture was then dissolved in diethyl ether (100ml) and this was added dropwise to a vigorously stirred mixture of water (30ml), ice (60g), sodium bicarbonate (30g) and sodium sulphite (20g). The stirring was continued for 30mins. After filtration, the organic phase was separated out and the aqueous phase extracted with ether (3 x 50ml). The combined organic phases were dried over magnesium sulphate. After filtration, the solvent was stripped off leaving a light orange solid. This was recrystallised from cyclohexane to give 7-azabicyclo[4.2.0]octan-8-one (9.8g/ 0.08mol), yield 49%, as a yellow solid. M.pt. 53-55 °C. (Lit.[60] m.pt. 57-58 °C).

PREPARATION OF 7-AZABICYCLO[4.2.0]OCTAN-8-THIONE (156)

To a solution of 7-azabicyclo[4.2.0]octan-8-one (2g/ 0.016mol) in dry THF (30ml) was added Lawesson's Reagent (3.24g/ 8mmol). The mixture was stirred under dry nitrogen for 1hr. The solvent was then removed under vacuum and the residue purified by flash silica chromatography (pet. ether: EtOAc; 7:3). 7-Azabicyclo[4.2.0]octan-8-thione (1.4g/ 0.01mol), yield 62%, was obtained as a white solid which was recrystallised from pet. ether 60/80 to give white needles.

M.pt.: 85-87 °C.

NMR: 1.35-1.95ppm(m, 8H), 3.15ppm(bm, 1H), 4.32ppm(q, 1H), 8.15ppm(bs, 1H).

IR: 1240cm^{-1} (C=S).

Micro Analysis: Required for $C_7H_{11}NS$: C,59.53; H,7.85; N,9.92; S,22.70; Found: C,59.57; H,7.82; N,10.00; S,22.75

PREPARATION OF 3-ETHYLTHIO-2-AZABICYCLO[4.2.0]OCT-2-ENE (151)

To a solution of triethyloxonium tetrafluoroborate (9.4ml/ of 1M solution in CH_2Cl_2) was added 7-azabicyclo[4.2.0]octane-8-thione (1.2g/ 8.5mmol) under dry nitrogen. The mixture was stirred at room temperature for 1hr and

then under reflux for a further 1hr. After cooling it was added dropwise to a 50% potassium carbonate solution (10ml) at -20 °C. The precipitate is filtered off through celite and the organic phase was separated off. After drying over magnesium sulphate and filtration the solvent was stripped off to leave an oily residue. This was purified by flash silica chromatography (pet. ether:EtOAc, 8:2). 3-Ethylthio-2-azabicyclo[4.2.0]octene (1.1g/ 6.5mmol), yield 77%, was isolated as a colourless oil.

NMR: 1.30ppm(t, 3H), 1.20-1.80ppm(m, 8H), 2.95ppm(dq, 2H), 3.25ppm(q, 1H), 4.05ppm(m, 1H).

IR: 1635cm^{-1} (C=N).

Micro Analysis: Required for $C_9H_{15}NS$: C,63.85; H,8.93; N,8.27: Found: C,63.89; H,8.90; N,8.23

GENERAL PROCEDURE FOR THE PREPARATION OF ALDOXIMES

To a stirred solution of the aldehyde (0.037mol) in water (10ml), ethanol (10ml) and ice (17ml) was added hydroxylamine hydrochloride (0.04mol). A 40% NaOH solution (7ml, 0.1mol) was then added, keeping the temperature between 25-30 °C. The mixture was stirred for 1hr, extracted with ether (40ml) to remove any neutral impurities. The aqueous phase was acidified to pH6 with conc. HCl keeping the temperature between 20-30 °C and

then extracted with ether again (2 x 40ml). The combined organic extracts were dried over magnesium sulphate followed by filtration and removal of the solvent under vacuum. The solid oximes were not purified any further and taken on to the next step.

The oximes prepared were benzaldehyde oxime (yield 100%, m.pt. 33-35 °C [lit[122] 35 °C]); 4-methoxybenzaldehyde oxime (yield 80%, m.pt. 133-135 °C [lit[123] 133 °C]); and 2-nitrobenzaldehyde oxime (yield 97%, m.pt. 103-105 °C [lit[124] 102-103 °C]).

GENERAL PROCEDURE FOR THE PREPARATION OF HYDROXIMOYL CHLORIDES

To a stirred solution of the benzaldoxime (0.03mol) in DMF (25ml) at 25-30 °C was added about 1/5th of the solid N-chlorosuccinimide (0.03mol in total). If the reaction was not seen to initiate within 5mins (as shown by a slight rise in temperature), 20ml of gas from the head space of a concentrated HCl reagent bottle was collected in a syringe and then bubbled into the DMF solution. Reaction was seen to initiate within another 5-10mins (except for nitro substituted benzaldoxime, which required heating to 45-60 °C to initiate). Once the reaction began, the temperature was kept below 35 °C (below 50 °C for nitro substituted benzaldoxime) by the rate of the addition of the remaining NCS. After 30-60mins exothermicity ceased and TLC showed the reaction to be complete. The solution was poured onto

four volumes of water and extracted with ether (2 x 40ml). The combined ether extracts were dryed over magnesium sulphate. After filtration the solvent was removed under vacuum to give the solid hydroximoyl chloride.

The hydroximoyl chlorides prepared were: benzohydroximoyl chlorid (yield 55%, m.pt.43-45 °C [lit[125] 45 °C]); 4-methoxybenzohydroximoyl chloride (yield 95%, m.pt. 88-90 °C [Lit[126] 88-89 °C]) and 2-nitrobenzohydroximoyl chloride (yield 77% m.pt. 92-94 °C [lit[125] 90-93 °C]).

GENERAL PROCEDURE FOR THE ADDITION OF NITRILE OXIDES TO 1-AZETINES

To a stirred solution of the 1-azetine (1.17mmol) and the hydroximoyl chloride (1.17mmol) in dry benzene (20ml) under an atmosphere of dry nitrogen, was added triethylamine (1.3mmol) dropwise. The mixture was stirred at room temperature for 2hrs. The precipitated triethylamine hydrochloride was filtered off and washed with dichloromethane. The washings and filtrate were combined and the solvent removed under vacuum. The residue was purified by flash silica chromatography to give the pure product.

DATA FOR CYCLOADDUCTS (168a-c), (169a-c) & (170a-c)

3-(p-Methoxyphenyl)-5,5,6,6-tetramethyl-7-ethoxy-1-oxa-2,4-diaza-bicyclo[3.2.0]hept-2-ene (168a):

Purification: Flash silica chromatography (pet. ether:EtOAc 8:2)

Yield: 72%

M.pt.: 107-109 °C (recrystallised from hexane)

NMR: 0.95ppm(s, 3H), 1.20ppm(s,3H), 1.225ppm(t, 3H), 1.25ppm(s, 3H), 1.43ppm(s, 3H), 3.55ppm(dq, 2H), 3.83ppm(s, 3H), 6.90ppm(dd, 2H), 7.68ppm(dd, 2H).

Micro Analysis: Required for $C_{17}H_{24}N_2O_3$: C,67.08; H,7.95; N,9.20; Found: C,66.80; H,7.93; N,9.12

3-Phenyl-5,5,6,6-tetramethyl-7-ethoxy-1-oxa-2,4-diazabicyclo[3.2.0]hept-2-ene (168b)

Purification: Flash silica chromatography (pet.ether: dichloro-methane 8:2).

Yield: 60%

M.pt.: 106-108 °C (recrystallised from pet. ether 60/80)

NMR: 0.9ppm(s, 3H), 1.18ppm(s, 3H), 1.20ppm(t, 3H), 1.22ppm(s, 3H), 1.41ppm(s, 3H), 3.49ppm(dq, 2H), 7.35-7.58ppm(m, 3H), 7.67-7.70ppm(m, 2H).

Micro Analysis: Required for $C_{16}H_{22}N_2O_2$: C,70.04; H,8.08; N,10.21; Found: C,70.20; H,7.95; N,10.29

3-(o-Nitrophenyl)-5,5,6,6-tetramethyl-7-ethoxy-1-oxa-2,4-diazabicyclo[3.2.0]hept-2-ene (168c)

Purification: Flash silica chromatography (pet. ether: EtOAc 8:2)

Yield: 34%

M.pt.: 103-104 °C (recrystallised from hexane)

NMR: 0.88ppm(s, 3H), 1.11ppm(s, 3H), 1.16ppm(s, 3H), 1.23ppm(t, 3H), 1.25ppm(s, 3H), 3.55ppm(m, 1H), 3.65ppm(m, 1H), 7.5-7.63ppm(m, 3H), 7.73ppm(dd, 1H)

Micro Analysis: Required for $C_{16}H_{21}N_3O_4$: C,60.17; H,6.63; N,13.16; Found: C,59.96; H,6.55; N,12.87

3-(p-Methoxyphenyl)-5,5,6,6-tetramethyl-7-ethylyhio-1-oxa-2,4-diazabicyclo[3.2.0]hept-2-ene (169a)

Purification: Flash silica chromatography (pet. ether: EtOAc 8:2)

Yield: 80%

M.pt.: 106-108 °C (recrystallised from hexane)

NMR: 1.0ppm(s,3 H), 1.27ppm(m, 9H), 1.55ppm(s, 3H), 2.68ppm(dq, 2H), 3.85ppm(s, 3H), 6.93ppm(dd, 2H), 7.65ppm(dd, 2H)

Micro Analysis: Required for $C_{17}H_{24}N_2O_2S$: C,63.75; H,7.50; N,8.75; S,10.00; Found: C,63.56; H,7.52; N,8.69; S,9.94

3-Phenyl-5,5,6,6-tetramethyl-7-ethylthio-1-oxa-2,4-diazabicyclo[3.2.0]hept-2-ene (169b)

Purification: Flash silica chromatography (pet. ether: EtOAc 8.5:1.5)

Yield: 62%

M.pt.: 132-134 °C (recrystallised from hexane)

NMR: 0.95ppm(s, 3H), 1.20-1.25ppm(m, 9H), 1.52ppm(s, 3H), 2.64ppm(m, 2H), 7.38ppm(m, 3H), 7.69ppm(dd, 2H)

Micro Analysis: Required for $C_{16}H_{22}N_2OS$: C,66.17; H,7.64; N,9.65; Found: C,66.26; H,7.43; N,9.42

3-(o-Nitrophenyl)-5,5,6,6-tetramethyl-7-ethylthio-1-oxa-2,4-diazabicyclo[3.2.0]hept-2-ene (169c)

Purification: Flash silica chromatography (pet. ether: dichloromethane 3:1)

Yield: 42%

M.pt.: 90-91 °C (recrystallised from hexane)

NMR: 0.96ppm(s, 3H), 1.15ppm(s, 3H), 1.27ppm(s, 3H), 1.27ppm(t, 3H), 1.42ppm(s, 3H), 2.70ppm(m, 2H), 7.50-7.65ppm(m, 3H), 7.73ppm(dd, 1H)

Micro Analysis: Required for $C_{16}H_{21}N_3O_3S$: C,57.29; H,6.31; N,12.53; Found: C,57.32; H,6.05; N,12.23

3-(p-Methoxyphenyl)-11-ethythio-1,2,4-oxadiazotricyclo[5.4.0^{5,10}.0^{4,11}]undec-2-ene (170a)

Purification: Flash silica chromatography (pet. ether: EtOAc 8:2)

Yield: 95%

M.pt.: 69-71 °C (recrystallised from pet. ether 60/80)

NMR: 1.28ppm(t, 3H), 1.1-2.1ppm(bm, 8H), 2.69ppm(dq, 2H), 3.45ppm(dt, 1H), 3.80ppm(s, 3H), 3.85ppm(m, 1H), 6.89ppm(dd, 2H), 7.62ppm(dd, 2H)

Micro Analysis: Required for $C_{17}H_{22}N_2O_2S$: C,64.12; H,6.97; N,8.80; S,10.07; Found: C,63.62; H,6.86; N,8.84; S,10.11

3-Phenyl-11-ethylthio-1,2,4-oxadiazotricyclo[5.4.0^{5,10}.0^{4,11}]undec-2-ene (170b)

Purification: Flash silica chromatography (pet. ether: EtOAc 9.5:0.5)

Yield: 54%

M.pt.: Semi-liquid (mixture of two diastereoisomers)

NMR: 1.25ppm(t, 3H), 1.1-2.1ppm(bm, 8H), 2.68ppm(m, 2H), 3.50ppm(dt, 1H), 3.90ppm(q, 1H), 7.40ppm(m, 3H), 7.69ppm(dd, 2H)

Micro Analysis: Required for $C_{16}H_{20}N_2OS$: C,66.63; H,6.99; N,9.72; Found: C,66.41; H,7.13; N,9.69

3-(o-Nitrophenyl)-11-ethylthio-1,2,4-oxadiazotricyclo[5.4.0^{5,10}.0^{4,11}]undec-2-ene (170c)

Purification: Flash silica chromatography (pet. ether: EtOAc 9.5:0.5)

Yield: 43%

M.pt.: Semi-liquid (mixture of two diastereoisomers)

NMR: 1.32ppm(t, 3H), 1.1-2.0ppm(bm, 8H), 2.75ppm(m, 2H), 3.56ppm(dt, 1H), 3.90ppm(bq, 1H), 7.30ppm(s, 1H), 7.55ppm (m, 2H), 7.69ppm(dd, 1H)

Micro Analysis: Required for $C_{16}H_{19}N_3O_3S$: C,57.64; H,5.74; N,12.60; Found: C,57.72; H,5.68; N,12.54

PREPARATION OF α-CHLORO-HYDRAZIDES (180) & (192)

To a stirred solution of the hydrazine (1.54g/ 0.014mol) in pyridine (10ml) was added benzoyl chloride (2g/ 0.014mol) dropwise. The mixture was stirred for a further 20mins and then poured on to ice cold water and stirred until a solid precipitated out. The solid was filtered, washed with water and then dried at 100 °C. The hydrazide was recrystallised from ethanol.

N-Benzoyl-N'-phenylhydrazide was obtained in 96% yield, m.pt. 167-169 °C (lit.[127] 168 °C).

N-Benzoyl-N'-(p-nitrophenyl)hydrazide was obtained in 83%, m.pt. 190-192 °C (lit.[128] m.pt. 193-194 °C).

An intimately ground mixture of dry hydrazide (0.07mol) and phosphoruos pentachloride (0.07mol) was dissolved in dry ether (50ml). The mixture was heated under reflux over night. After cooling, a solution of phenol (30g) in dry ether (50ml) was added to the reaction mixture followed by methanol (40ml). When the exthormic reaction subsided, the solvent was reduced to half bulk, and the remainder was allowed to cool over several days in the refrigirator. The α-chlorohydrazide crystallised out as dark needles.

α-Chlorobenzaldehyde phenylhydrazone was obtained in 59% yield; m.pt. 129-131 °C (lit.[127] 130 °C).

α-Chlorobenzaldehyde (p-nitrophenyl)hydrazone was obtained in 79% yield; m.pt. 188-190 (lit.[128] 189-191 °C).

GENERAL PROCEDURE FOR THE PREPARATION OF N-ARYLHYDRAZIDOYL BROMIDES

To a suspension of the appropriate hydrazone (0.04mol) in glacial acetic acid (100ml) was added a solution of bromine (0.08mol) in glacial acetic acid (20ml) with vigorous stirring. The solid reaction products were collected by filtration and dried by suction.

The hydrazidoyl bromides prepared were: N-(p-

chlorobenzyl)-N'-(p-nitrophenl)hydrazidoyl bromide [yield 55%, m.pt. 222-224 °C (lit.[129] 222-223 °C)]; N-(p-nitrobenzyl)-N'-(p-nitrophenyl)hydrazidoyl bromide [yield 49%, m.pt. 280-282 °C].

PREPARATION OF METHYL α-BROMOGLYOXYLATE-p-NITROPHENYLHYDRAZONE

p-Nitroaniline (2g/ 0.015mol) was dissolved by heating in water (8ml) containing conc. hydrochloric acid (4ml). The resulting hot solution was poured onto ice and the amine hydrochloride precipitated. A solution of sodium nitrite (1.12g/ 0.015mol) in water (4ml) was added to this mixture and the resulting diazonium solution was added rapidly to a solution of methyl acetoacetate (1.6ml/ 0.015mol) in ethanol (12ml) and ice water (20ml) containing sodium acetate (4g/ 0.05mol). The reaction mixture immediately thickened as the product precipitated out of solution. After stirring for 4hrs the yellow solid was removed by filtration, washed thoroughly, and dried at 60 °C. Methyl a-acetoxyglyoxylate-p-nitophenylhydrazone (3.5g/ 0.013mol) was obtained as an amorphous solid, yield 88%. This was used directly in the next step without further purification.

Methyl α-acetoxyglyoxylate-p-nitrophenylhydrazone (2g/ 7.6mmol) was added to a mixture of glacial acetic acid (11ml) and acetic anhydride (6ml) containing sodium acetate

(1.5g) and the temperature was lowered to 0 °C by means of an ice-salt bath. To this was added, over a one hour period, bromine (1.2g/ 7.6mmol) dissolved in glacial actic acid (2ml). The product was precipitated by pouring the reaction mixture into water (50ml). After filtration and thorough washing, methyl α-bromoglyoxylate-p-nitrophenylhydrazone (1.8g/ 6mmol) was obtained in 79% yield; m.pt. 164-167 °C.

GENERAL PROCEDURE FOR THE ADDITION OF NITRILE IMINES TO 1-AZETINES

To a stirred solution of the azetine (1.46mmol) and the hydrazidoyl halide (1.75mmol) in dry benzene (20ml) under an atmosphere of dry nitrogen, was added triethylamine (4 eqv.) dropwise. The mixture was heated under reflux and followed by TLC. When the reaction was completed, the precipitated triethyamine hydrochloride was filtered off and the solvent removed under vacuum. The residue was then purified by column chromatography.

DATA FOR NITRILE IMINE CYCLOADDUCTS

1,3-Diphenyl-5,5,7-trimethyl-6-methyleno-1,2,4-triazabicyclo[3.2.0]hept-2-ene (183)

Purification: Flash silica chromatography (pet. ether: EtOAc 9.5:0.5)

Yield: 60%

M.pt.: 94-95 °C (recrystallised from pet. ether/EtOAc)

IR: 1620cm^{-1} (C=N), 1600cm^{-1} (C=C)

NMR: 1.40ppm(s, 6H), 1.63ppm(s, 3H), 4.54ppm(s, 1H), 4.68ppm(s, 1H), 7.38ppm(m, 8H), 8.15ppm(dd, 2H).

Micro Analysis: Required for $C_{20}H_{21}N_3$: C,79.17; H,6.98; N,13.85;
Found: C,78.88; H,6.86; N,13.65

1,3-Bis(phenyl)-11-chloro-1,2,4-triazatricyclo[5.4.0.^{5,10}.0^{4,11}]undec-2-ene (186)

Purification: Flash silica chromatography (pet. ether:EtOAc 6:1)

Yield: 73%

M.pt.: Semi-liquid (mixture of diastereoisomers)

NMR: 1.2-2.0ppm(bm, 8H), 3.0ppm(dt, 1H), 4.43ppm(dt, 1H), 7.37ppm(m, 3H), 7.52ppm(m, 5H), 8.14ppm(dd, 2H).

Mass Spectrum: m/e 339 (M^++2), m/e 337 (M^+), m/e 302 (-Cl^-).

Micro Analysis: (Compound too unstable to analyse).

1-(p-Nitrophenyl)-3-phenyl-5,5,6,6-tetramethyl-7-ethoxy-1,2,4-triazabicyclo[3.2.0]hept-2-ene (193)

Purification: Trituration with pet. ether 60/80 of the crude residue.

Yield: 89%

M.pt.: 141-143 °C (recrystallised from pet. ether 40/60)

IR: 1620cm^{-1} (C=N), 1490cm^{-1} (NO_2)

NMR: 0.94ppm(s, 3H), 1.05ppm(s, 3H), 1.22ppm(t, 3H), 1.34ppm(s, 3H), 1.55ppm(s, 3H), 3.0ppm(dq, 1H), 3.50ppm(dq, 1H), 7.20ppm(d, 2H), 7.40ppm(m, 3H), 7.75ppm(dd, 2H), 8.15ppm(dd, 2H).

Micro Analysis: Required for $C_{22}H_{26}N_4O_3$: C,66.99; H,6.64; N,14.20; Found: C,67.05; H,6.68; N,14.34

1-(p-Nitrophenyl)-3-phenyl-5,5,6,6-tetramethyl-7-ethylthio-1,2,4-triazabicyclo[3.2.0]hept-2-ene (194)

Purification: Trituration of the crude product with pet. ether 60/80.

Yield: 88%

M.pt.: 153-154 °C (recrystallised from pet. ether/ EtOAc)

IR: 1620cm^{-1} (C=N), 1490cm^{-1} (NO_2)

NMR: 0.98ppm(s, 3H), 1.05ppm(t, 3H), 1.13ppm(s, 3H), 1.40ppm(s, 3H), 1.69ppm(s, 3H), 2.15ppm(dq, 1H), 2.45ppm(dq, 1H), 7.30ppm(dd, 2H), 7.42ppm(m, 3H), 7.75ppm(dd, 2H), 8.12ppm(d, 2H).

Micro Analysis: Required for $C_{22}H_{26}N_4O_2S$: C,64.36; H,6.38; N,13.65; S,7.81; Found: C,64.59; H,6.33, N,13.96; S,7.08

1-(p-Nitrophenyl)-3-phenyl-11-ethylthio-1,2,4-triazatricyclo[5.4.0.^{5,10}.0^{4,11}]undec-2-ene (195)

Purification: Flash silica chromatography (pet. ether: EtOAc 8:2)

Yield: 42%

M.pt.: Semi-solid (mixture of two diastereoisomers)

NMR: 0.9-2.1ppm(bm, 8H), 1.05ppm(t, 3H), 2.28ppm(dq, 1H), 2.53ppm(dq, 1H), 3.40ppm(q, 1H), 3.92ppm(bq, 1H), 7.21ppm(d, 2H), 7.39ppm(m, 3H), 7.78ppm(m, 2H), 8.15ppm(dd, 2H).

Micro Analysis: Required for $C_{22}H_{24}N_4O_2S$: C,64.68; H,5.92; N,13.72; Found: C,64.81; H,5.88; N,13.67

1-(p-Nitrophenyl)-3-phenyl-11-chloro-1,2,4-triazatricyclo[5.4.0^{5,10}.0^{4,11}]undec-2-ene (196)

Purification: Flash silica chromatography (pet. ether: EtOAc 7:3)

Yield: 54%

M.pt.: Semi-solid (mixture of two diastereisomers)

NMR: 0.9-2.0ppm(bm, 8H), 3.02ppm(bq, 1H), 4.42ppm(dt, 1H), 7.41ppm(m, 3H), 7.78ppm(d, 2H), 8.13ppm(dd, 2H), 8.40ppm(d, 2H).

Micro Analysis: Required for $C_{20}H_{19}N_4O_2Cl$: C,62.74; H,5.00; N,14.64; Found: C,62.55; H,4.98; N,14.49

1-(p-Nitrophenyl)-3-(p-chlorophenyl)-5,5,6,6-tetramethyl-7-ethoxy-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (hexane:EtOAc 9:1)

Yield: 55%

M.pt.: 189-191 °C (recrystallisation from hexane/EtOAc)

NMR: 0.93ppm(s, 3H), 1.02ppm(s, 3H), 1.11ppm(t, 3H), 1.32ppm(s, 3H), 1.51ppm(s, 3H), 3.00ppm(dq, 1H), 3.98ppm(dq, 1H), 7.18ppm(dd, 2H), 7.35ppm(dd, 2H), 7.67ppm(dd, 2H), 8.11ppm(dd, 2H).

Micro Analysis: Required for $C_{22}H_{25}N_4O_3Cl$: C,61.60; H,5.88; N,13.06; Found: C,61.58; H,5.76; N,13.25

1,3-Bis(p-nitrophenyl)-5,5,6,6-tetramethyl-7-ethoxy-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (Hexane:EtOAc 9:1)

Yield: 57%

M.pt.: 211-213 °C (recrystallisable from hexane/EtOAc)

NMR: 0.95ppm(s, 3H), 1.05ppm(s, 3H), 1.15ppm(t, 3H), 1.36ppm(s, 3H), 1.58ppm(s, 3H), 3.00ppm(dq, 1H), 3.49ppm(dq, 1H), 7.22ppm(dd, 2H), 7.88ppm(dd, 2H), 8.13ppm(dd, 2H), 8.25ppm(d, 2H).

Micro Analysis: Required for $C_{22}H_{25}N_5O_5$: C,60.12; H,5.73; N,15.94; Found: C,60.33; H,5.67; N,16.18

1-(p-Nitrophenyl)-3-carbomethoxy-5,5,6,6-tetramethyl-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (pet. ether:EtOAc 9:1)

Yield: 43%

M.pt.: 124-126 ℃

NMR: 1.00ppm(s, 3H), 1.10ppm(t, 3H), 1.18ppm(s, 3H), 1.30ppm(s, 3H), 1.50ppm(s, 3H), 2.96ppm(dq, 1H), 3.50ppm(dq, 1H), 3.89ppm(s, 3H), 7.22ppm(dd, 2H), 8.12ppm(dd, 2H).

Micro Analysis: Required for $C_{18}H_{24}N_4O_5$: C,57.43; H,6.43; N,14.89; Found: C,57.25; H,6.39; N,14.98

1-(p-Nitrophenyl)-3-(p-chlorophenyl)-5,5,6,6-tetramethyl-7-ethylthio1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (hexane:EtOAc 9:1)

Yield: 18%

M.pt.: Oil (the compound could not be separated from the rearranged product)

NMR: 0.98ppm(s, 3H), 1.05ppm(t, 3H), 1.14ppm(s, 3H), 1.40ppm(s, 3H), 1.69ppm(s, 3H), 2.15ppm(dq, 1H), 2.43ppm(dq, 1H), 7.68ppm(dd, 2H), 7.90ppm(dd, 2H), 8.11ppm(dd, 2H), 8.33ppm(dd, 2H).

Micro Analysis: (Could not be obtained due to inseparable mixture)

1,3-Bis(p-nitrophenyl)-5,5,6,6-tetramethyl-7-ethylthio-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (hexane:EtOAc 9:1)

Yield: 21%

M.pt.: Oil (mixture with rearranged product)

NMR: 0.99ppm(s, 3H), 1.05ppm(t, 3H), 1.16ppm(s, 3H), 1.56ppm(s, 3H), 1.70ppm(s, 3H), 2.14ppm(m, 1H), 2.41ppm(m, 1H), 7.25ppm(dd, 2H), 7.91ppm(dd, 2H), 8.12ppm(dd, 2H), 8.23ppm(dd, 2H).

Micro Analysis: (Could not be obtained due to inseparable mixture).

1-(p-Nitrophenyl)-3-carbomethoxy-5,5,6,6-tetramethyl-7-ethylthio-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (pet. ether:EtOAc 8:2)

Yield: 34%

M.pt.: Oil (mixture with rearranged product)

NMR: 1.05ppm(t, 3H), 1.18ppm(s, 3H), 1.37ppm(s, 3H), 1.62ppm(s, 3H), 2.00ppm(s, 3H), 2.11ppm(dq, 1H), 2.49ppm(dq, 1H), 3.88ppm(s, 3H), 7.30ppm(d, 2H), 8.10ppm(d, 2H).

Micro Analysis: (Could not be obtained due to inseparable mixture).

1-(p-Nitrophenyl)-3-(p-chlorophenyl)-5,5,7-trimethyl-6-methyleno-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (hexane:EtOAc 9:1)

Yield: 37%

M.pt.: Oil (mixture with primary adduct)

NMR: 1.45ppm(s, 6H), 1.67ppm(s, 3H), 4.61ppm(s, 1H), 4.79ppm(s, 3H), 7.38ppm(dd, 2H), 7.61ppm(dd, 2H), 8.05ppm(dd, 2H), 8.29ppm(dd, 2H).

Micro Analysis: (Could not be obtained due to mixture with primary adduct).

1,3-Bis(p-nitrophenyl)-5,5,7-trimethyl-6-methyleno-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (hexane:EtOAc 9:1)

Yield: 39%

M.Pt.: Oil (mixture with primary adduct)

NMR: 1.455ppm(s, 6H), 1.67ppm(s, 3H), 4.61ppm(s, 1H), 4.80ppm(s, 1H), 7.22ppm(d, 2H), 7.88ppm(d, 2H), 8.13ppm(d, 2H), 8.25ppm(d, 2H).

Micro Analysis: (Could not be obtained due to mixture with primary adduct)

1-(p-nitrophenyl)-3-carbomethoxy-5,5,7-trimethyl-6-methyleno-1,2,4-triazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (Pet. ether:EtOAc 8:2)

Yield: 15%

M.pt.: Oil (mixture with primary adduct)

NMR: 1.43ppm(s, 6H), 1.62ppm(s, 3H), 3.98(s, 3H), 4.55ppm(s, 1H), 4.74ppm(s, 1H), 7.54ppm(d, 2H), 8.28ppm(d, 2H).

Micro Analysis: (Could not be obtained due to mixture with primary adduct).

PREPARATION OF 1-(p-NITROPHENYL)-3-PHENYL-5,5,7-TRIMETHYL-6-METHYLENO-1,2,4-TRIAZABICYCLO[3.2.0]HEPT-2-ENE (197)

A solution of primary adduct (193) (0.2g/ 0.5mmol) in dichlorobenzene (5ml) was heated under reflux for 30mins. The solvent was distilled off at atmospheric pressure to leave a dark oily residue. This residue was purified by flash silica chromatography (pet. ether: EtOac 9:1). The product (0.17g/ 0.49mmol) was obtained as a crystalline solid.

Yield: 98%

M.pt.: 131-133°C. (crystallisable from pet. ether 60/80)

NMR: 1.46ppm(s, 6H), 1.68ppm(s, 3H), 4.62ppm(s, 1H), 4.78ppm(s, 1H), 7.40ppm(m, 3H), 7.62ppm(dd, 2H), 8.11ppm(dd, 2H), 8.28ppm(dd, 2H).

Micro Analysis: Required for $C_{20}H_{20}N_4O_2$: C,68.95; H,5.79; N,16.08; Found: C,68.85; H,5.88; N,15.86

GENERAL PROCEDURE FOR THE PREPARATION OF IMIDOYL CHLORIDES

A solution of the amide (3.7mmol) in thionyl chloride was heated under reflux under an inert atmosphere for 30mins. After cooling, the excess thionyl chloride was removed under vacuum to leave a solid residue. This residue was then recrystallised from dry cyclohexane under dry nitrogen (Note: the subsequent filtration had to be done under dry nitrogen also). The purified imidoyl chloride was then used directly in the next step.

The imidoyl chlorides prepared were: N-(p-nitrobenzyl)-benzimidoyl chloride, yield 85%; m.pt. 71-73 °C [lit.[130] 73-74 °C]; N-(p-nitrobenzyl)-p-toluimidoyl chloride, yield 64%; m.pt. 86-87 °C [lit[131] 89 °C]; N-(p-nitrobenzyl)-p-nitrobenzimidoyl chloride, yield 59%; m.pt. 93-95 °C.

GENERAL PROCEDURE FOR THE ADDITION OF NITRILE YLIDES TO 1-AZETINES

To a solution of the azetine (2.18mmol) and the imidoyl chloride (2.18mmol) in dry benzene (20ml) under an atmosphere of dry nitrogen was added triethylamine (1.5eqv).

After stirring for several hours at room temperature, a precipitate was gradually formed. When the reaction was seen to be complete, the precipitate was filtered off and the solvent removed under vacuum, to leave an oily residue. This was purified by flash silica chromatography to give the expected primary adduct as a crytalline solid.

DATA FOR NITRILE YLIDE CYCLOADDUCTS

1-(p-Nitrophenyl)-3-phenyl-5,5,6,6-tetramethyl-7-ethoxy-2,4-diazabicyclo[3.2.0]hept-2-ene (206)

Purification: Flash silica chromatography (pet. ether:EtOAc 8.5:1.5)

Yield: 46%

M.pt.: 165-167 °C (recrystallisable from pet. ether 60/80)

NMR: 0.38ppm(s, 3H), 0.70ppm(s, 3H), 0.95ppm(s, 3H), 1.38ppm(t, 3H), 1.49ppm(s, 3H), 3.59(dq, 1H), 3.84ppm(dq, 1H), 5.48ppm(s, 1H), 7.40ppm(m, 3H), 7.76ppm(bd, 2H), 7.83ppm(dd, 2H), 8.19ppm(dd, 2H).

Micro Analysis: Required for $C_{23}H_{27}N_3O_3$: C,70.21; H,6.92; N,10.68; Found: C,70.24; H,6.97; N,10.72

1-(p-Nitrophenyl)-3-phenyl-5,5,6,6-tetramethyl-7-ethylthio-2,4-diazabicyclo[3.2.0]hept-2-ene (207)

Purification: Flash silica chromatography (pet. ether:EtOAc 8.5:1.5)

Yield: 68%

M.pt.: 148-149°C (recrystallisable from pet ether 60/80)

NMR: 0.46ppm(s, 3H), 0.72ppm(s, 3H), 1.08ppm(s, 3H), 1.36ppm(t, 3H), 1.74ppm(s, 3H), 2.60ppm(dq, 1H), 2.74ppm(dq, 1H), 5.71ppm(s, 1H), 7.41ppm(m, 3H), 7.85ppm(dd, 2H), 8.00ppm(d, 2H), 8.19ppm(d, 2H).

Micro Analysis: Required for $C_{23}H_{27}N_3O_2S$: C,67.45; H,6.65; N,10.26, S,7.83; Found: C,67.52; H,6.65; N,10.30, S,7.89

1,3-Bis(p-nitrophenyl)-5,5,6,6-tetramethyl-7-ethoxy-2,4-diazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (pet. ether:EtOAc 8:2)

Yield: 42%

M.pt.: 173-175°C (recrystallisable from pet. ether 60/80)

NMR: 0.43ppm(s, 3H), 0.62ppm(s, 3H), 0.97ppm(s, 3H), 1.31ppm(t, 3H), 1.49ppm(s, 3H), 3.58ppm(dq, 1H), 3.84ppm(dq, 1H), 5.53ppm(s, 1H), 7.85ppm(dd, 2H), 8.11ppm(dd, 2H),

8.19ppm(dd, 2H), 8.27ppm(dd, 2H).

Micro Analysis: Required for $C_{23}H_{29}N_3O_3$: C,69.85; H,7.39; N,10.63; Found: C,69.65; H,7.46; N,10.71

1-(p-Nitrophenyl)-3-(p-toluoyl)-5,5,6,6-tetramethyl-7-ethoxy-2,4-diazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (pet. ether:EtOAc 9:1)

Yield: 53%

M.pt.: 166-168 °C (recrystallisable from pet. ether 60/80)

NMR: 0.43ppm(s, 3H), 0.76ppm(s, 3H), 0.94ppm(s, 3H), 1.36ppm(t, 3H), 1.51ppm(s, 3H), 2.26ppm(s, 3H), 3.54ppm(dq, 1H), 3.79ppm(dq, 1H), 5.41ppm(s, 1H), 6.98ppm(dd, 2H), 7.14ppm(dd, 2H), 7.82ppm(dd, 2H), 8.18ppm(dd, 2H).

Micro Analysis: Required for $C_{22}N_{26}N_4O_5$: C,61.96; H,6.15; N,13.14; Found: C,62.08; H,6.34; N,13.27

1,3-Bis(p-nitrophenyl)-5,5,6,6-tetramethyl-7-ethylthio-2,4-diazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (pet. ether:EtOAc 9:1)

Yield: 45%

M.pt.: 164-166 °C (recrystallisable from pet. ether 60/80)

NMR: 0.45ppm(s, 3H), 0.73ppm(s, 3H), 1.05ppm(s, 3H), 1.21ppm(t, 3H), 1.77ppm(s, 3H), 2.61ppm(dq, 1H), 2.73ppm(dq, 1H),

5.78ppm(s, 1H), 7.90ppm(dd, 2H), 8.00ppm(dd, 2H), 8.18ppm(dd, 2H), 8.29ppm(dd, 2H).

Micro Analysis: Required for $C_{23}H_{29}N_3O_2S$: C,67.12; H,7.10; N,10.21; Found: C,67.25; H,7.02; N,10.35

1-(p-Nitrophenyl)-3-(p-toluoyl)-5,5,6,6-tetramethyl-7-ethylthio-2,4-diazabicyclo[3.2.0]hept-2-ene

Purification: Flash silica chromatography (pet. ether:EtOAc 8:2)

Yield: 61%

M.pt.: 182-184 °C (recrystallisable from pet. ether 60/80)

NMR: 0.44ppm(s, 3H), 0.69ppm(s, 3H), 1.14ppm(s, 3H), 1.34ppm(t, 3H), 1.76ppm(s, 3H), 2.25ppm(s, 3H), 2.59ppm(dq, 1H), 2.73(dq, 1H), 5.60ppm(s, 1H), 7.03ppm(dd, 2H), 7.18ppm(dd, 2H), 8.12ppm(dd, 2H), 8.26ppm(dd, 2H).

Micro Analysis: Required for $C_{22}H_{26}N_4O_4S$: C,61.96; H,6.15; N,13.14; Found: C,62.10; H,5.99; N,13.16

PREPARATION OF 5-PHENYL-1,3,4-OXATHIAZOL-2-ONE (209)

To a stirred solution of benzamide (2g/ 0.017mol) in toluene was added chlorocarbonylsulphenyl chloride (3.27g/ 0.025mol). The mixture was stirred at 100 °C for 2hrs. The solvent was removed under vacuum leaving a white solid. The product (1.6g/ 8.9mmol), yield 53%, was recrystallised from ethyl acetate. M.pt. 69-71 °C [lit.[82] 69-71 °C].

ATTEMPTED CYCLOADDITION OF BENZONITRILE SULPHIDE TO 1-AZETINE (151)

A solution of azetine (151) (0.2g/ 1.17mmol) and 5-phenyl-oxathiazolone (209) (0.26g/ 1.46mmol) in dry toluene (20ml) was heated at reflux under dry nitrogen and the reaction followed by TLC. After several hours the oxathiazolone was seen to have been consumed, however, on chromatographic work-up a quantiative yield of the azetine (151) was returned unchanged.

ATTEMPTED CYCLOADDITION OF AZIRIDINE (218) TO 1-AZETINE (151)

A solution of the azetine (0.11g/ 0.67mmol) and the aziridine (0.2g/ 0.67mmol) in dry benzene (15ml) was stirred and heated under reflux under an inert atmosphere for 12hrs. Chromatographic work-up yielded an almost quantitative yield of the unchanged aziridine (151). None of the starting aziridine (218) could be isolated and was assumed to have decomposed under the reaction conditions.

PREPARATION OF METHYL N-p-METHOXYBENZYLIDENEPHENYLALINATE (219)

To a stirred solution of phenylalanine methyl ester hydrochloride (5g/ 0.023mol) and sodium carbonate (2.4g/ 0.023mol) in water (77ml) was added p-anisaldehyde (3.13g/ 0.023mol). The mixture was stirred at 40 °C for 45mins and then at

room temperature for a further 16hrs. The mixture was then extracted with chloroform (3 x 25ml) and the combined organic extracts back washed with water (2 x 25ml). After drying over magnesium sulphate the organic solvent was removed under vacuum to give the crude imine as a solid. The product (6g/ 0.02mol), yield 88%, was purified by crystallisation from pet. ether 60/80. M.pt. 70-72 °C [lit.[87] 71-73 °C].

ATTEMPTED CYCLOADDITION OF AZOMETHINE YLIDE (219) TO 1-AZETINE (151)

A stirred solution of the azetine (0.2g/ 1.17mmol) and imine (219) (0.35g/ 1.17mmol) in dry toluene (20ml) under dry nitrogen was heated under reflux for 24hrs. Chromatographic work-up of the reaction mixture returned both starting materials back unchanged.

ATTEMPTED CYCLOADDITION OF N-METHYLBENZYLNITRONE (220) TO 1-AZETINE (151)

A stirred solution of azetine (151) (0.2g/ 1.17mmol) and the nitrone (220) (0.16g/ 1.17mmol) in dry benzene, was heated under reflux under an atmosphere of dry nitrogen. The reaction was monitored by TLC. Heating was continued for 24hrs, after which no reaction was detected.

ATTEMPTED CYCLOADDITION OF p-METHOXY- AND p-NITRO-PHENYLAZIDE TO 1-AZETINE (150)

A stirred solution of azetine (150) (0.1g/ 0.65mmol) and the azide (1 eqv.) in dry benzene (15ml) was heated under reflux under an inert atmosphere for up to 3 days. No reaction was detected by TLC.

PREPARATION OF DIMETHYL 1,2,4,5-TETRAZINE-3,6-DICARBOXYLATE (223)

A solution of ethyl glycinate hydrochloride (125g) in water (162ml) was mixed with dichloromethane (385ml) in a 2L, 3-necked flask and cooled to -5°C. A solution of ice-cold sodium nitrite (75g) in water (162ml) was added with stirring. The temperature was lowered to -9°C, and 5% sulphuric acid (61ml) was added from a dropping funnel, during a period of about 3mins. After approx. 15mins the reaction mixture was transferred to an ice cold 2L separating funnel, and the yellow green dichloromethane layer was run off into 5% sodium bicarbonate solution (644ml). The aqueous layer was extracted once with dichloromethane. The combined organic layers were returned to the separating funnel along with the bicarbonate solution. The mixture was shaken until no trace of acid remained as was shown by indicator paper. The organic layer was separated off and dried over magnesium sulphate. After filtration, the solvent was

removed under vacuum to give a yellow green oil. Ethyl diazoacetate (85g), yield 80% was directly used in the next step.

To a solution of sodium hydroxide (180g) in water (265ml), was added ethyl diazoacetate (85g) dropwise over 1hr. The temperature was maintained at 90 °C during the addition. After cooling, the product was poured into 95% ethanol (1l) and the mixture stirred. The alcohol was decanted and the washing procedure was repeated five times. The precipitate was filtered, washed with absolute alcohol and dry ether, and air dried. Sodium dihydro-1,2,4,5-tetrazine-3,5-dicarboxylate (66g), yield 84%, was obtained as a yellow-brown solid, and was directly used in the next step without further purification.

A slurry of the sodium salt (66g) in water (80ml) containing crushed ice (80g) was cooled with an ice/salt bath, and conc. hydrochloric acid (150ml) was added dropwise over 40-50mins. The product was immediately collected by filtration. It was then suspended in water (200ml), stirred at 0 °C for 30min and then filtered off. The product was washed with ice/water (20ml), dried in air for a short time and then under vacuum for several hours. Dihydro-1,2,4,5-tetrazine-3,5-dicarboxylic acid (4g), yield 7%, was obtained as a light brown solid, m.pt. 141-144 °C [lit[94] 144-148 °C]. This product was directly used in the next step without further purification.

Absolute methanol (25ml) was cooled to -30 °C and freshly distilled thionyl chloride (5ml) was added dropwise. A suspension of the dicarboxylic acid (4g) in absolute methanol (30ml) was added in four portions over approx. 30mins, whilst maintaining the temperature at -30 °C. The reaction mixture was then allowed to warm up to room temperature and subsequently was warmed to 35-40 °C for 2hrs. The mixture was cooled to 0 °C with an ice bath and the precipitate collected by filtration. The precipitate was washed dry methanol and dry ether and then dried under vacuum. Dimethyl dihydro-1,2,4,5-tetrazine-3,6-dicarboxylate (1g), yield 25%, was obtained as a yellow solid, m.pt. 166-169 °C [lit[94] 171-172 °C]. The product was directly used in the next step without further purification.

A slurry of the dihydro ester (1g) in dichloromethane (40ml) was cooled with an ice/water bath. Nitrous gases were generated in a separate vessel by the disproportionation of nitrous acid (HONO):10ml of 6M sodium nitrite was added dropwise with stirring to conc. hydrochloric acid (6.25ml). The brown gases were bubbled directly into the stirred reaction mixture for 15min. The colour of the reaction mixture changed from orange to bright red during the addition. The solvent and excess gases were removed under vacuum to afford the product, after stirring for 1.5hrs. Dimethyl 1,2,4,5-

tetrazine3,6-dicarboxylate (0.9g), yield 90%, was obtained as a bright red crystalline solid, m.pt. 173-175 °C [lit[94] 173-175 °C].

ATTEMPTED CYCLOADDITION OF TETRAZINE (223) TO 1-AZETINE (150)

A solution of azetine (150) (0.2g/ 1.29mmol) and tetrazine (223) (0.25g/ 1.26mmol) in dry benzene was stirred under nitrogen. The reaction was followed by TLC. After 24hrs at room temperature the mixture was heated under reflux for 5hrs. Removal of the solvent and chromatography of the residue showed that the tetrazine had decomposed without cycloaddition to the azetine.

PREPARATION OF O-ETHYLBUTYROLACTIM (229)

Pyrrolidinone (226) (2.5g/ 0.03mol) was treated with a solution of triethyloxonium tetrafluoroborate in dichloromethane (30ml of 1M soln.) under an atmosphere of dry nitrogen. The mixture was stirred at room temperature for 2hrs and then under reflux for a further 2hrs. After cooling, the mixture was added, dropwise, to a cold 50% solution of potassium carbonate. The mixture was then filtered rapidly through celite and the organic phase separated off and dried over magnesium sulphate. The solvent was removed and the residue chromatographed

on flash silica (pet. ether: EtOAc 8:2). O-Ethylbutyrolactim (1.1g/ 9.7mmol), yield 32%, was obtained as a colourless oil. B.pt. 50-60 °C/15mmHg [lit[132] 50-60 °C/15mmHg]. NMR and IR spectroscopic values were in agreement with those in the literature.[132]

PREPARATION OF O-ETHYLVALEROLACTIM (230)

The procedure used here was the same as that described for imino ether (229). 2-Ethoxy valerolactim was obtained in 43% yield as a colourless oil after distillation, b.pt. 85-90 °C/60mmHg [lit[132] 87 °C/64mmHg]. NMR and IR spectroscopic values were in agreement with those in the literature.[132]

PREPARATION OF O-ETHYLCAPROLACTIM (231)

The method employed here followed the procedure given for imino ether (229). 3,4,5,6-tetrahydro-7-ethoxy-2H-azepine was obtained in 63% yield as a colourless oil after distillation, b.pt. 80-85 °C/ 26mmHg [lit[133] 81-82 °C/26mmHg. IR and NMR spectroscopic values were in agreement with those given in the literature.[133]

ATTEMPTED CYCLOADDITION OF p-METHOXYBENZONITRILE OXIDE TO IMINO ETHERS (229-231)

To a stirred solution of the imino ether (1.57mmol) and p-methoxyphenylhydroximoyl chloride (1.57mmol) in dry benzene under dry nitrogen was added triethylamine (1.2 eqv.) dropwise. The reaction was monitored by TLC. After several hours stirring, the triethylamine hydrochloride precipitate was filtered off and the residue purified by flash silica chromatography. In all three cases the imino ethers were isolated unreacted along with furoxan (164), which was the dimerisation product of the nitrile oxide.

ATTEMPTED CYCLOADDITION OF NITRILE IMINE (181) TO IMINO ETHERS (229-231)

To a stirred equimolar solution of the imino ether and hydrazidoyl chloride (180) in dry benzene under an atmosphere of dry nitrogen was added triethylamine (4 eqv.). The mixture was heated under reflux for upto 24hrs and monitored by TLC. Chromatographic work-up gave the unreacted imino ethers.

OZONOLYSIS OF 1,3-BISPHENYL-5,5,7-TRIMETHYL-6-METHYLENO-1,2,4-TRIAZABICYCLO[3.2.0]HEPT-2-ENE (183)

Ozone gas was bubbled at a gentle rate through a solution of compound (183) in dichloromethane at ice temperature

for 40mins. Excess dimethyl sulphide was then added and the mixture stirred for 1hr at room temperature. The solvent was removed under vacuum and the residue purified by flash silica chromatography (pet. ether: EtOAc 9:1). The product 1,3-bisphenyl-5,5,7-trimethyl-1,2,4-triazabicyclo[3.2.0]heptene-6-one (232) was isolated as a white solid.

Yield: 60%

M.pt.: 91-93 °C (recrystallisable from pet. ether 60/80)

IR: 1720cm^{-1} (C=O)

NMR: 1.46ppm(s, 6H), 2.09ppm(s, 3H), 7.45ppm(m, 8H), 8.13ppm(dd, 2H).

Micro Analysis: Required for $C_{19}H_{19}N_3O$: C,74.73; H,6.27; N,13.76;
Found: C,74.50; H,6.25; N,13.70

PREPARATION OF 1,3-BISPHENYL-5,5,6,7-TETRAMETHYL-6-HYDROXY-1,2,4-TRIAZABICYCLO[3.2.0]HEPT-2-ENE (233)

To a stirred solution of ketone (232) (0.2g/ 0.66mmol) in dry ether (10ml) under an atmosphere of dry nitrogen, was added a solution of methyl lithium in diethyl ether (0.5ml of 1.55M soln.) at -78 °C. The mixture was stirred as it warmed up to room temperature. After stirring for 3hrs at room temperature the reaction mixture was quenched by the addition of an ammonium chloride solution (10ml). The organic layer was

separated off and the aqueous layer was further extracted using diethyl ether (2 x 10ml). The combined organic extracts were dried over magnesium sulphate. The solvent was removed under vacuum after filtration, to leave an oily residue. The residue was purified by flash silica chromatography (pet. ether: EtOAc 9:1). The product 1,3-bisphenyl-5,5,6,7-tetramethyl-6-hydroxy-1,2,4-triazabicyclo[3.2.0]heptene (0.11g/ 0.34mmol), was obtained as an oil, because of the diastereoisomeric mixture.

Yield: 52%

IR: 3400cm^{-1} (-OH), 1600cm^{-1} (C=C)

NMR: 1.16ppm(s, 12H), 6.30ppm(bs, 1H), 7.40ppm(m, 5H), 7.51ppm(m, 3H), 8.06ppm(dd, 2H).

Micro Analysis: Required for $C_{20}H_{23}N_3O$: C,74.74; H,7.21; N,13.07;
Found: C,74.66; H,7.30, N,13.15

PREPARATION OF METHYL t-BUTYLACETATE (237)

To a solution of t-butylacetic acid (5g/ 0.04mol) in HMPA (50ml) was added 25% sodium hydroxide solution (7ml). The mixture was stirred at room temperature for 1hr, after which methyl iodide (10ml/ 0.16mol) was added, and the solution was stirred for a further 1hr. The solution was then poured onto 5% hydrochloric acid solution (200ml) and then extracted with ether (3 x 50ml). The combined organic ectracts were washed with water

and then dried over magnesium sulphate. After filtration, the solvent was removed under vacuum and the residue distilled at 120-122 °C [lit.[97] 120-122 °C]. Methyl t-butylacetate (4g/ 0.03mol), yield 75%, was obtained as a colourless liquid.

ENOLISATION OF METHYL t-BUTYLACETATE

To a stirred solution of di-isopropylamine (7.54ml/ 0.04mol) in dry THF (30ml) under a dry atmosphere, was added n-BuLi (0.04mol) at 0 °C. The mixture was stirred for 30mins before being cooled down to -78 °C. Methyl t-butylacetate (5.5g/ 0.04mol) was added to the solution, which was then stirred at -78 °C for a further 1hr. Freshly distilled trimethylsilyl chloride (14.4ml/ 0.12mol) was slowly added to the cold reaction mixture over 30mins. The stirred mixture was then allowed to slowly warm up to room temperature, upon which a precipitate was formed. The precipitate was filtered off and the filtrate distilled at atmospheric pressure to remove the THF. The product was then distilled off at 80-85 °C/100mmHg [lit[97] 80-85 °C/ 100mmHg]. The trimethylsilyl enol ether (238) (5.4g/ 0.027mol), yield 67%, was obtained as a colourless liquid which rapidly decomposed on standing and therefore, had to be stored under dry nitrogen and used as rapidly as possible for the next step.

ATTEMPTED PREPARATION OF METHYL DI-t-BUTYLACETATE (239)

To a solution of the enol ether (5g/ 0.025mol) in dry dichloromethane was added freshly distilled t-butlychloride (6.9g/ 0.074mol) and a catalytic amount of dry zinc chloride. The mixture was stirred for 24hrs under dry nitrogen. It was then poured onto a cold 5% solution of sodium bicarbonate (150ml) and extracted with dichloromethane (3 x 50ml). The combined organic extracts were dried over magnesium sulphate. The solvent was then removed under vacuum and the residue distilled. The product obtained was identified as methyl t-butylacetate (237) rather than the desired methyl di-t-butylacetate (239).

ATTEMPTED CYCLOADDITION OF p-METHOXYBENZONITRILE OXIDE TO 2-METHLTHIO-3,3-DI-t-BUTYL-1-AZETIN-4-ONE

A solution of azetinone (235) (10mg/ 0.04mmol) and p-methoxyphenylhydorximoyl chloride (8.2mg/ 0.04mmol) in dry benzene (2ml) was stirred under dry nitrogen at room temperature. Triethtylamine (0.2ml/ excess) was added dropwise. After stirring for 2.5hrs, the reaction mixture was filtered and the solvent removed under vacuum. The high-field NMR spectrum of the crude residue showed that the azetinone (235) was still intact, indicative of the lack of cycloaddition.

PREPARATION OF 4-ACETOXYAZETIDIN-2-ONE (244)

Chlorosulphonyl isocyanate (18ml/ 0.207mol) was added, dropwise, to vinyl acetate (100ml) with stirring under an atmosphere of dry nitrogen. The temperature during the addition was controlled at 20-25 °C with the aid of an acetone/ dry ice bath. Stirring was continued for a further 20mins after the completion of the isocyanate addition. The temperature of the reaction mixture was then lowered to -20 °C. The cold solution was then syringed into a vigorously stirred mixture of water (20ml), ice (100g), sodium bicarbonate (47g), hydrated sodium sulphite (33g) and dichloromethane (100ml). The heterogenous mixture was stirred for a further 30mins at ice temperature. The mixture was then filtered through celite and the filtrate transferred to a separating funnel. The organic layer was run off and the aqueous layer extracted with dichloromethane (2 x 40ml). The combined organic extracts were then dried over magnesium sulphate. After filtration, the solvent was removed under vacuum to leave an orange residue. This residue was then distilled at 80-82 °C/ 10^{-3}mmHg [lit[99] b.pt. 80-82 °C/10^{-3}mmHg]. 4-Acetoxyazetidin-2-one (8g/ 0.06mol), yield 30%, was obtained as a pale yellow solid m.pt. 33-35 °C [lit[99] m.pt. 33-35 °C].

PREPARATION OF 1-TRIMETHYLSILYL-4-ACETOXYAZETIDIN-2-ONE (245)

To a stirred solution of 4-acetoxyazetidin-2-one (4.3g/ 0.03mol) in dry ether (100ml), at 0 °C, under an atmosphere of dry nitrogen, was added triethylamine (6ml/ 0.04moKl) followed by freshly distilled trimethylsilyl chloride (5ml/ 0.04mol). The mixture was stirred for a further 2hrs at ice temperature. The solvent was then removed under vacuum to leave a white solid which was extracted with dry hexane (3 x 50ml). The combined organic extracts were filtered and then concentrated under vacuum. The residue was distilled at 80-82 °C/ 0.5mmHg [lit[40] b.pt. 80-81 °C/ 0.5mmHg]. 1-Trimethylsilyl-4-acetoxyazetidin-2-one (5.2g/ 0.026mol), yield 86%, was obtained as a stable colourless oil.

PREPARATION OF 1-TRIMETHYLSILYL-4-(2-METHOXYCARBONYL)ETHYLTHIO-AZETIDIN-2-ONE (246)

To a stirred solution of azetidinone (245) (9g/ 0.07mol) in absolute ethanol (100ml) was added methyl 3-mercaptopropionate (9ml/ 0.07mol) followed by a solution of sodium carbonate (0.07mol) in water (10ml). The reaction mixture was stirred for 5hrs at room temperature. The mixture was then diluted with water (20ml) and extracted with ethyl acetate (3 x

30ml). The combined organic extracts were dried over magnesium sulphate. After filtration, the solvent was removed under vacuum to leave the crude product as an oil. Attempted chromatographic purification of the residue reulted in the hydrolysis of the N-trimethylsilyl group. The crude product was therefore used directly in the following step. The product (10.27g/ 0.05mol), yield 78% (crude) was identified by its NMR spectrum: 0.23ppm(s, 9H), 2.4ppm(m, 4H), 2.8ppm(d, 2H), 3.3ppm(dd, 1H), 4.1ppm(s, 3H).

ATTEMPTED OXIDATION OF SULPHIDE (246)

To a solution of azetidinone (246) (1g/ 5.3mmol) in chloroform (150ml) was added m-CPBA (0.9g/ 5.3mmol). The mixture was stirred at -35 °C, under dry nitrogen for 3hrs. The mixture was then warmed up to room temperature, washed with 5% sodium bicarbonate solution and water, dried over magnesium sulphate and the solvent removed under vacuum. Spectroscopic analysis showed that the oxidation had failed.

PREPARATION OF PHENYL CYANATE (251)

To a stirred solution of cyanogen bromide (15g/ 0.14mol) in acetonitrile (50ml) was added a solution of phenol (13.2g/ 0.14mol) in dry ether (50ml). Triethylamine (20.2ml/ 0.14mol) was added dropwise whilst the temperature was maintained

at 5-10 °C over 30-40mins. Stirring was continuoed for a further 15mins. The solvent was removed under a vacuum and a few drops of polyphosphate ester were added to the residue, which was then distilled at 75-77 °C/ 10mmHg [lit[100] 82-83 °C/ 10mmHg]. Phenylcyanate (251) (13g/ 0.11mol), yield 78%, was obtained as a colourless oil.

p-Nitrophenyl cyanate was prepared in a similar manner. Yield, 45%, m.pt. 63-65 °C [lit[100] 66 °C].

ATTEMPTED CYCLOADDITION OF A KETENE TO PHENYL CYANATE

To a stirred mixture of phenyl cycanate and the ketene precursor (dichloroacetyl chloride to generatre dichloroketene; chlorodiphenylacetyl chloride to generate diphenylketene; dimethylketene was prepared previously as a solution in ethyl acetate) in dry toluene was added triethylamine. The reaction mixture was heated under reflux for several hours and the reaction monitored by TLC. In all three cases tarry mixtures were produced with no isolable products.

PREPARATION OF THIOMALONIC ESTER (48)

To a stirred solution of diisopropylamine (0.72ml/ 5.16mmol) in dry THF (5ml) under an atmosphere of dry nitrogen, was added n-BuLi (4.3mmol) at 0 °C. This mixture was stirred for 30min at ice temperature, and then the temperature was

lowered to -78 °C. Ethyl isobutyrate (0.5g/ 4.3mmol) was slowly syringed in and the mixture stirred for a further 1hr at -78 °C. p-Methoxyphenylisothiocyanate (0.71g/ 4.3mmol) was added dropwise to the cold mixture which was then stirred whilst it slowly warmed up to room temperature. The reaction mixture was quenched with a saturated ammonium chloride solution, and then extracted with diethyl ether (3 x 10ml). The combined organic extracts were washed with cold water and saturated sodium chloride solution. After drying over magnesium sulphate and filtration, the solvent was removed under vacuum. The oily residue was purified by flash silica chromatography (pet. ether: EtOAc 9:1). The product was isolated as a yellow green solid (0.9g/ 3.2mmol), yield 74%, m.pt. 53-55 °C. The NMR spectroscopic values were in agreement with those in the literature.[22]

PREPARATION OF 1-(p-METHOXYPHENYL)-3,3-DIMETHYL-4-THIOXOAZETIDIN-2-ONE (49)

To a stirred solution of thiomalonic ester (48) (0.5g/ 1.8mmol) in dry toluene (10ml) under a dry atmosphere, was added a solution of triethyl aluminium in hexane (0.55ml of 1.9M soln.). The mixture was heated under reflux for 2hrs. After cooling, methanol (1ml) was added dropwise to remove any excess triethyl aluminium. The mixture was then quenched with water and

then extracted with diethyl ether (3 x 10ml). The combined organic extracts were washed with cold water and then saturated sodium chloride solution. After drying over magnesium sulphate and filtration, the solvent was removed under vacuum. The oily residue was then purified by flash silica chrmoatography (pet. ether: EtOAc 9.5:0.5). The product (0.3g/ 1.3mmol), yield 72%, was obtained as an oil. IR and NMR spectroscopic values were in agreement with those in the literature.[22]

ATTEMPTED OXIDATIVE DE-ARYLATION OF 4-THIOXO-2-AZETIDINONE (49)

A solution of thioxoazetidinone (49) (0.6g/ 2.6mmol) in acetonitrile was cooled to 0 °C. To this was added a solution of ceric ammonium nitrate (5.12g/ 9.4mmol) in methanol (10ml) over 10mins. The mixture was allowed to warm up to room temperature with stirring and the rection monitored by TLC. After stirring for 24hrs, the reaction mixture was quenched with water and then extracted with ethyl acetate (3 x 15ml). The combined organic extracts were dried over magnesium sulphate, filtered, and the solvent removed under vacuum. A quantitative yield of the starting material was isolated.

PREPARATION OF ETHYL MALONYLTRIPHENYLIMINOPHOSPHORANE (262)

To a stirred solution of sodium azide (0.33g/ 5.4mmol) in water (0.5ml) was added with ice-cooling a solution

of ethyl malonyl chloride (0.5g/ 3.3mmol) in acetonitrile (2ml). The mixture was stirred for 1hr at room temperature. Water (1ml) was added and the mixture was stirred for a further 1hr. The organic layer was separated off and the aqueous layer extracted with acetonitrile (2 x 5ml). The combined organic extracts were dried over magnesium sulphate.

To the solution of ethyl azidomalonate was added an excess of triphenylphosphine in acetonitrile with stirring. Nitrogen gas was seen to be evolved. The mixture was stirred for a further 30mins. The solvent was removed under vacuum and the residue purified by flash silica chromatography (pet. ether: EtOAc 7:3). The product (0.7g/ 1.9mmol), yield 60%, was obtained as a white solid, m.pt. 146-149 °C.

IR: 3050cm^{-1}, 3000cm^{-1}, 1720cm^{-1}, 1600cm^{-1}

NMR: 1.21ppm(t, 3H), 3.49ppm(d, 2H), 4.15ppm(quintet, 2H), 7.3-7.8ppm(m, 15H).

ATTEMPTED CYCLISATION OF IMINOPHOSPHORANE (262)

A solution of iminophosphorane (262) (0.2g/ 0.51mmol) in toluene (10ml) was heated under reflux for several hours. The reaction was monitored by TLC. A tarry mixture of inseparable products was produced.

PREPARATION OF o-AZIDOPHENOL (272)

In a 3-necked flask fitted with a mechanical stirrer and a dropping funnel and cooled in a dry ice/acetone bath was placed o-aminophenol (5g/ 0.05mol) in water (50ml) and hydrochloric acid (17ml). The aminophenol was diazotised with sodium nitrite (3.4g/ 0.05mol) in water (17ml). To the cold liquid was added sodium azide (8g/ 0.12mol) in water (a sodium hydroxide trap was fitted to the apparatus to guard against any hydrazoic acid given off under the acidic conditions). The solution was stirred for 1hr at 0 °C. It was then extracted with diethyl ether (3 x 50ml). The combined organic extracts were washed with 8% sodium carbonate solution (3 x 25ml) and then dried over magnesium sulphate. After filtration, the organic solvent was removed. o-Azidophenol (4g/ 0.03mol), yield 60%, was obtained as a yellow solid.

PREPARATION OF N-(o-AZIDOPHENYL) PHENYLCARBAMATE

A solution of o-azidophenol (0.5g/ 3.7mmol) and phenylisocyanate (0.44g/ 3.7mmol) in dry acetonitrile (10ml) was heated under reflux for 2hrs. After cooling, the solvent was removed under vacuum and the residue purified by flash silica

chromatography (pet. ether: EtOAc 7:3). N-Phenyl-(o-azidophenyl)carbamate (0.81g/ 3.2mmol), yield 86%, was obtained as a crystalline solid. M.pt. 124-126 °C.

IR: 3380cm^{-1} (N-H), 2150cm^{-1} (N_3), 1740cm^{-1} (C=O).

NMR: 5.8ppm(bs, 1H), 7.2-7.4ppm(m, 9H).

PREPARATION OF 2-ANILINO-1,3-BENZOXAZOLE (275)

To a stirred solution of azide (273) in benzene (10ml) was added triethyl phosphite (0.3ml/ 1.1 eqv.). Gas bubbles were given off, and when these ceased the mixture was heated under reflux for 24hrs. After cooling, the solvent was removed and the residue purified by flash silica chromatography (pet. ether: EtOAc 8:2). 2-Anilino-1,3-benzoxazole (0.21g/ 1mmol), yield 63%, was obtained as a crystalline solid. M.pt. 172-174 °C [lit[134] 172-173 °C].

PREPARATION OF PYRROLO BENZIMIDAZOLE (278)

To a stirred solution of 3-azido-4-succinimidotoluene (276) (0.5g/ 2.17mmol) in dry benzene (10ml) was added triethyl phosphite (0.41ml/ 1.1 eqv.). Gas bubbles were given off. The solution was heated under reflux over-night and the reaction monitored by TLC. At the end of this period the acyclic iminophosphorane (277) was seen to be still present. The solvent was, therefore, removed under vacuum and the residue

redissolved in o-dichlorobenzene. This solution was heated under reflux for 1hr. After cooling, the solvent was distilled off at atmospheric pressure and the residue purified by flash silica chromatography (pet. ether: EtOAc 9:1). 6-Methylpyrrolobenzimidazol-2-one (0.29g/ 1.56mmol), yield 72%, was obtained as a crystalline solid. M.pt. 163-165°C.

IR: 1665cm^{-1} (C=O)

NMR: 2.4ppm(s, 3H), 3.2ppm(s, 4H), 7.2ppm(d, 1H); 7.5ppm(s, 1H), 7.8ppm(d, 1H).

PREPARATION OF o-AZIDOPHENYLTOSYLATE (279)

To a stirred solution of o-azidophenol (0.5g/ 3.7mmol) in pyridine (5ml) was added p-toluenesulphonyl chloride (0.78g/ 4.07mmol). The mixture was heated on a water bath for 30mins. After cooling, the mixture was poured onto cold water (10ml) with vigorous stirring until a solid precipitated out. o-Azidophenyltosylate (0.7g/ 2.4mmol), yield 65%, was obtained as a crystalline solid, m.pt. 189-191°C.

IR: 2190cm^{-1} (N_3)

NMR: 2.3ppm(s, 3H), 7.3ppm(d, 2H), 7.5ppm(m, 4H), 7.8ppm(d, 2H).

ATTEMPTED PREPARATION OF SULPHOXIMIDE (281)

To a stirred solution of o-azidophenyltosylate (0.2g/ 0.7mmol) in benzene (10ml) was added triethyl phosphite (0.13ml/ 1.1 eqv.). Gas bubbles were given off and TLC showed that all the azide had been consumed to generate iminophosphorane (280). The mixture was heated under reflux for 48hrs, with no observable change. The solvent was, therefore, removed and the residue redisolved in o-dichlorobenzene. Constant heating under reflux for a further 3 days proved ineffective in ring closing the iminophosphorane.

PREPARATION OF ETHYL (o-AZIDOPHENOXY)ACETATE (282)

To a stirred solution of the phenol (0.5g/ 3.7mmol) in acetone (15ml) was added anhydrous potassium carbonate (0.77g/ excess) followed by a solution of ethyl chloroacetate (0.4ml/ 3.7mmol) in acetone (5ml). The mixture was heated under reflux overnight. After cooling, the inorganic material was filtered off. The solvent was removed under vacuum and the residue redisolved in diethyl ether (20ml). The ethereal solution was washed with 2M sodium hydroxide solution (2 x 10ml) and cold water (2 x 20ml). The organic layer was dried over

magnesium sulphate. After filtration, the solvent was removed under vacuum to give the product. Ethyl (o-azidophenoxy)acetate (0.72g/ 3.2mmol), yield 88%, was obtained as a crystalline solid, m.pt. 142-144 °C.

IR: 2200cm^{-1} (N_3), 1740cm^{-1} (C=O).

NMR: 1.2ppm(t, 3H), 4.1ppm(q, 2H), 4.3ppm(s, 2H), 7.4-76ppm(m, 4H).

PREPARATION OF 2H-3-ETHOXY-1,4-BENZOXAZINE (283)

To a solution of the ethyl (o-azidophenoxy)acetate (282) (0.5g/ 2.26mmol) in benzene (10ml) was added triethyl phosphite (0.43ml/ 1.1 eqv.) and the mixture heated under reflux with stirring for 2hrs. After cooling, the solvent was removed under vacuum and the residue purified by flash silica chromatography (pet. ether: EtOAc 8:2). 2H-3-Ethoxy-1,4-benzoxazine (0.37g/ 2.3mmol), yield 94%, was isolated as a white solid m.pt. 167-169 [lit[135] 168 °C].

PREPARATION OF QUINOLINES (285)

To a stirred solution of the respective o-azidobenzoylmalonate (284a-d) (0.27mmol) in toluene (10ml) was added triethyl phosphite (0.05ml/ 1.1 eqv.), dropwise. After several minutes a precipitate was formed. The suspension was

stirred for a further 30mins. The precipitate was filtered and air dried. After crystallisation from methanol the pure cyclised product was obtained as a crystalline solid.

The following quinolones were prepared: 3H-2-Ethoxy-3-carbethoxyquinolin-4-one (285a), yield 94%, m.pt. 96-97 °C [lit[136] 101 °C]; 3H-2-phenyl-3-benzoylquinolin-4-one (285b), yield 92%, m.pt. 286-288 °C [lit[137] 287-289 °C]; 3H-2-phenyl-3-carbethoxyquinolin-4-one (285c), yield 72%, m.pt. 234-236 °C [lit[138] 232 °C]; & 3H-2-methyl-3-carbethoxyquinolin-4-one (285d), yield 81%, m.pt. 231-233 °C [lit[139] 231-232 °C].

PREPARATION OF METHYL N-(o-AZIDOBENZOYL)PROLINATE (291)

To a stirred solution of proline methyl ester hydrochloride (1g/ 6mmol) in triethylamine (15ml) at ice temperature, was added, dropwise, a solution of o-azidobenzoylchloride (1.1g/ 6mmol) in THF (10ml). The mixture was stirred for 2hrs. It was then poured onto ice cold water and extracted with diethyl ether (3 x 30ml). The combined organic extracts were washed with cold water and then dried over magnesium sulphate. After filtration, the solvent was removed under vacuum and the residue purified by flash silica chromatography (pet. ether: EtOAc 8:2). The product (1.4g/ 5mmol), was obtained as a light yellow solid, yield 84%, m.pt. 103-105 °C.

IR: 2150cm^{-1} (N_3), 1740cm^{-1} (C=O), 1640cm^{-1} (C=O).

NMR: 1.6ppm(m, 4H), 2.7ppm(m, 2H), 2.8ppm(t, 1H), 3.9ppm(s, 3H), 7.4-7.7ppm(bm, 4H).

PREPARATION OF 2,3-DIHYDRO-1H-PYRROLO[2,1-c][1,4]BENZODIAZEPINE-5,11(10H,11aH)-DIONE (294)

To a stirred solution of azido benzamide (291) (1g/ 3.6mmol) in toluene (15ml) was added triethyl phosphite (1.1 eqv.). Gas bubbles were given off. The mixture was stirred at room temperature for a further 1hr. The solvent was stripped off under vacuum and the residue purified by flash silica chromatography (pet. ether: EtOAc 7:3). The isolated iminophosphorane (292) was redisolved in toluene (10ml) and the solution heated under reflux for 6hrs. After cooling, the solvent was removed under vacuum, and the residue purified by flash silica chromatography (pet. ether: EtOAc 8:2). The product (0.54g/ 2.5mmol), yield 69%, was isolated as a crystalline solid, m.pt. 219-221 °c (recrystallised from ethanol) [lit[140] 220-222 °C].

PREPARATION OF METHYL N-(o-AZIDOBENZOYL)PHENYLALANINATE (296)

The procedure used followed that described for azido benzamide (291).

The product (296) was obtained in 73% yield, m.pt. 64-66 ℃.

IR: 3400cm^{-1} (N-H), 2150cm^{-1} (N_3), 1750cm^{-1} (C=O), 1660cm^{-1} (C=O), 1600cm^{-1} (C=C).

NMR: 3.2ppm(d, 1H), 3.8ppm(s, 3H), 5.1ppm(dd, 2H), 7.3ppm(m, 7H), 7.9-8.1ppm(m, 2H).

SECTION D

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