# SOME APPROACHES TO THE SYNTHESIS OF PYRROLIDINES

Thesis submitted to the University of Stirling

for the degree of

Doctor of Philosophy

by

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To Ema and Aram and in memory of
Josip and Arshaluis Astvacatrjan

"I have nothing to offer but blood, toil, tears and sweat"

Winston Churchill, speech in the House of Commons,
13 May 1940.

The same comment was made by The Old Mirko to me in Belgrade in September 1972, a few days before I commenced my University courses.

ACKNOWLEDGMENT

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Blairlogie by Stirling.
June 1984

Suren Husinec.

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## ABSTRACT

A general strategy for the synthesis of α-kainic acid has been developed, based on a [3 + 2] cycloaddition reaction between an azomethine ylide and an olefin to furnish the basic pyrrolidine skeleton.

In a first series of experiments, azomethine ylides were generated by a thermal decomposition of $\Delta^2$-1,2,3-triazolines *via* aziridines and were trapped with dipolarophiles yielding pyrrolidine derivatives. The reaction failed with cyclopentenone and thermal decomposition did not take place with triazoline having an S-phenyl substituent. Attempts to prepare triazolines by an intramolecular 1,3-dipolar cycloaddition failed to yield the desired product.

In another series of experiments azomethine ylides were generated by a thermal isomerisation of imines derived from α-amino acid esters and were trapped with dipolarophiles yielding pyrrolidine derivatives. No thermal isomerisation was observed with thioformimidate derivatives of α-amino acid esters.

Azomethine ylides were generated by deprotonation of immonium salts derived from thioformimidate derivative of α-amino acid esters. They were trapped with dipolarophiles yielding pyrrolidine derivatives. No cycloadduct was obtained with cyclopentenone.

A strategy for generating azomethine ylides by desilylation of immonium cations derived from α-amino acid ester derivatives was developed. The basic precursor for the reaction could not be prepared.

Azomethine ylides were also generated by elimination of an S-phenyl group from sarcosine methyl ester derivative; trapping experiment with cyclopentenone failed to produce pyrrolidine derivative.

A strategy for generating azomethine ylides by a base promoted reaction from t-amine-N-oxide derivatives has been investigated.

# REVIEW

Natural phenomena do not present themselves in neatly ordered categories. It is left to us to define and classify them and the result may often seem arbitrary.

## 1. 1,3-DIPOLAR CYCLOADDITIONS

In contrast to the very large number of special methods applicable to synthesis in general, relatively few general methods are available for the synthesis of pyrrolidine derivatives. The 1,3-dipolar cycloaddition offers a remarkably wide range of utility in the synthesis of five-membered heterocycles. These cycloaddition reactions are bimolecular in nature and involve the addition of a "1,3-dipole" to a multiple bond system leading to five-membered heterocyclic rings. (Scheme 1).


Scheme 1.

Although numerous individual examples of this reaction have been known for many years, even in the late nineteenth century, fruitful development of this synthetic principle has been achieved only in recent years and it is mainly due to Huisgen and his school that the concept of 1,3-dipolar cycloaddition and its general application to the synthesis of five-membered heterocycles has been visualised.[1-3]

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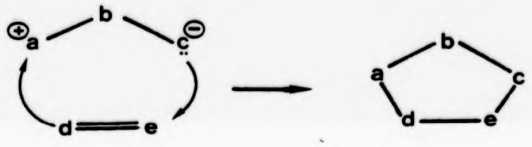
## 1.1 Description and Classification of 1,3-Dipoles

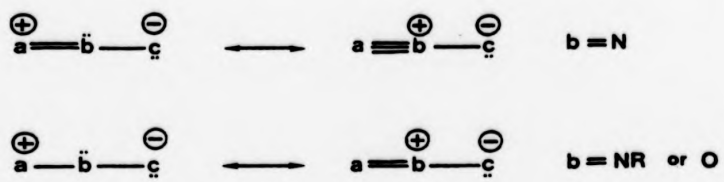
A 1,3-dipole may be defined as a system a-b-c, in which a has an electron sextet, i.e. an incomplete valence shell and carries a formal positive charge, and c is an anionic centre having a free electron pair. In the union of such a 1,3-dipole with a multiple bond system d=e, the so called dipolarophile, a cyclic shift of electrons accompanies and consummates closure of a five-membered ring. (Scheme 2).




Scheme 2

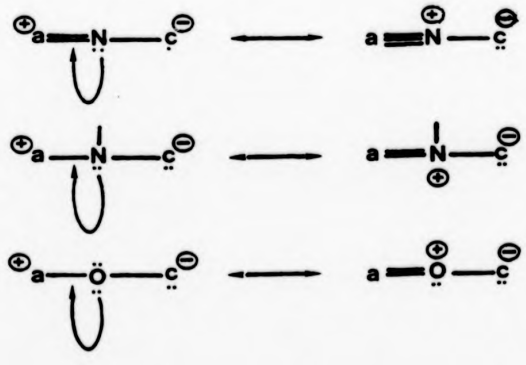
Compounds in which the positive centre a is an electron deficient carbon, nitrogen or oxygen atom are not capable of long lived existence. When the 1,3-dipole is an isolable substance, then the symbolism employed above can only refer to a resonance structure of minor weight. Stabilisation of the reactive system is possible if the lone pair at b fills the electron gap at a by forming an additional bond. In the new mesomeric formula, in which b has now a positive charge, all the centres have completed valence shells. Such a system will be designated as a 1,3-dipole with internal octet stabilisation.

Sextet structures of 1,3-dipoles can be formulated in which a and b are connected by a single bond or by a double bond. Octet stabilised 1,3-dipoles with double bond,



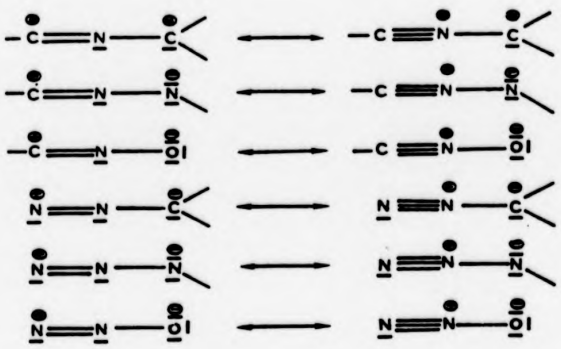

Sextet formula Octet formula

must necessarily have nitrogen as a central atom b, since only this element can supply an unshared electron pair while in the trivalent neutral state. Systems without a double bond may also contain oxygen as the central atom in the 1,3-dipole.



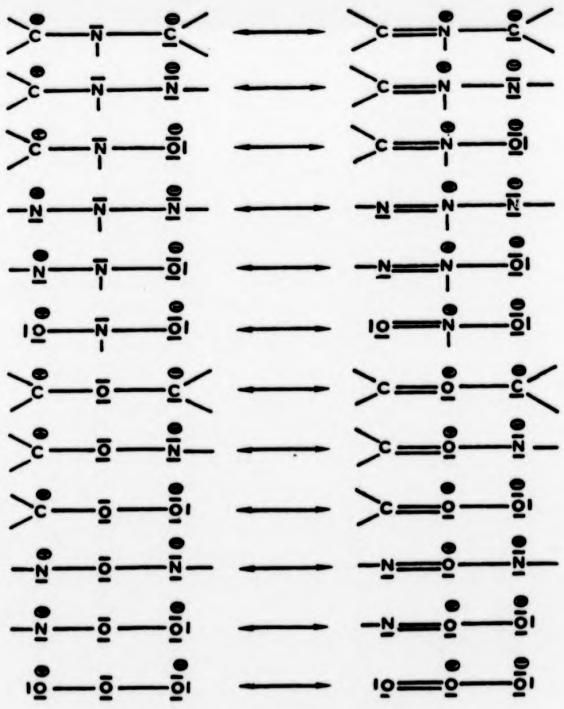
For the sake of classification, 1,3-dipoles may be divided into two main categories: 1,3-dipoles with, and 1,3-dipoles without octet stabilisation.[3] The former dipoles are further divisible into two classes: 1,3-dipoles with and without a double bond orthogonal to the allyl anion system, these two corresponding to the 1,3-dipoles with, and without a double bond in the sextet form, in Huisgen's classification. The geometry of the two classes of dipoles is different since

Octet-stabilized 1,3-dipoles with double bond



Nitrile ylides
Nitrilimines
Nitrile oxides
Diazoalkanes
Azides
Nitrous oxide

Octet-stabilized 1,3-dipoles without double bond



Azomethine ylides
Azomethine imines
Nitrones
Azimines
Azoxy compounds
Nitro compounds
Carbonyl ylides
Carbonyl imines
Carbonyl oxides
Nitroso imines
Nitroso oxides
Ozone

TABLE 1

the orthogonal π bond causes the 1,3-dipoles of the first class to be linear (e.g. diazoalkanes, nitrile oxides), whilst the other dipoles are characterised by being bent, even in the ground state (e.g. azomethine ylides, nitrones, ozone).

Although all of the members of the class of 1,3-dipoles with double bonds are known and have been shown to undergo dipolar additions with multiple bonds, some of the systems without double bonds, such as the azimines, carbonyl imines, nitroso imines and nitroso oxides, have not yet been prepared. All other representatives of this class exhibit pronounced 1,3-dipolar reactivity.

The use of molecular orbital theory, and in particular the knowledge of energy values of the frontier orbitals (highest occupied (HOMO) and lowest unoccupied (LUMO)), their coefficients and symmetry properties, are of great importance for the perturbation approach to reactivity and regiochemistry of 1,3-dipolar cycloaddition. The molecular orbital features of allyl anion and azomethine ylide are shown in Figure 1.[4]

The presence of heteroatoms (more electronegative than carbon) in the 1,3-dipole causes the lowering of the orbital energies which are, in the case of an azomethine ylide, all lower than those of the allyl parent system. However the geometry of the system can reverse this effect.

Although the energy values for HO and LU orbitals and their coefficients can be calculated theoretically by a number of different methods they are not readily obtainable from experimental data.

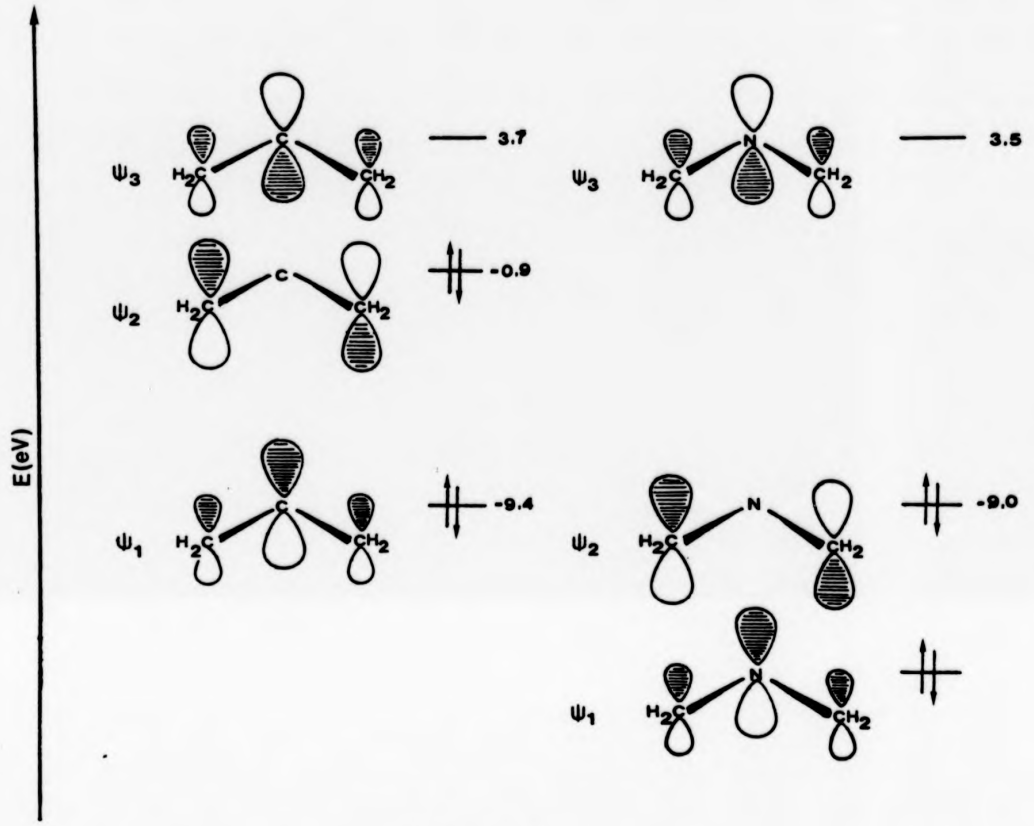



Figure 1

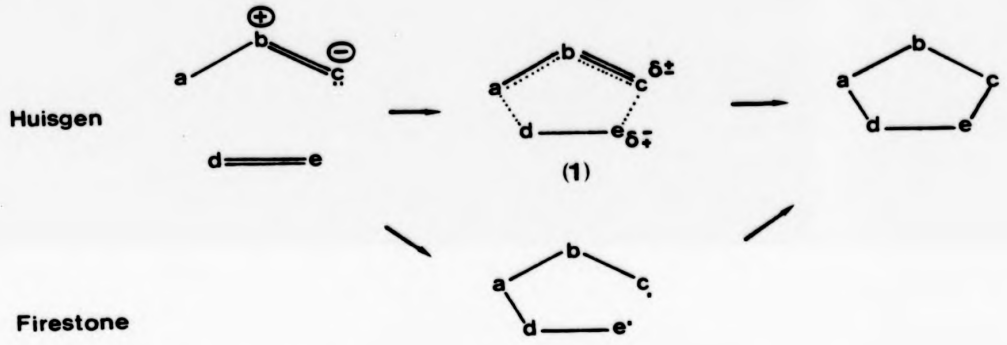
## 1.2 Stereospecificity and Mechanism

The cycloaddition of 1,3-dipoles with alkenes is strictly a stereospecific reaction: cis addition occurs with retention of the stereochemistry of the olefin in the final adduct. Those cases where stereospecificity has not been observed were due to the primary adduct being transformed into the more stable stereoisomer under the reaction conditions.[5]

On the basis of experimental results and theoretical speculations a question of the mechanism of the 1,3-dipolar

cycloaddition has arisen and it is still a subject of a great controversy. At first two extreme theories were proposed for this reaction.

A concerted mechanism proposed by Huisgen[1,2] and a mechanism in two steps proposed and defended by Firestone[6,7]. (Scheme 3).

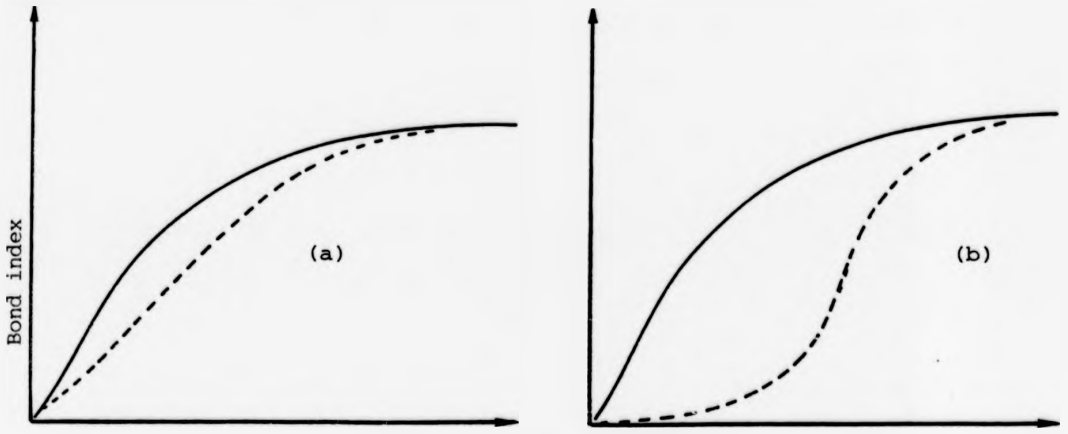



Scheme 3

Huisgen proposed that the two new σ bonds are formed at the same time but not with the same intensity. The unequal progress of bond formation in the transition state together with the fact that one addend acts as electron donor and the other as electron acceptor leads to partial charges, e.g. (1) in the transition state.

The plot of bond indices versus reaction coordinates for synchronous-concerted (a) and simultaneous-concerted (b) cycloaddition are shown in figure 2.

Huisgen suggested that the reaction is also "energetically-concerted" with only one maximum in the reaction profile.[1] (Figure 3).




Plot of bond indices for two new bonds formed for (a) synchronous and (b) simultaneous concerted cyclo-additions.

**Figure 2**


Plot of energies for energetically-concerted (heavy line) and energetically-non-concerted (dashed line) cycloaddition

**Figure 3**

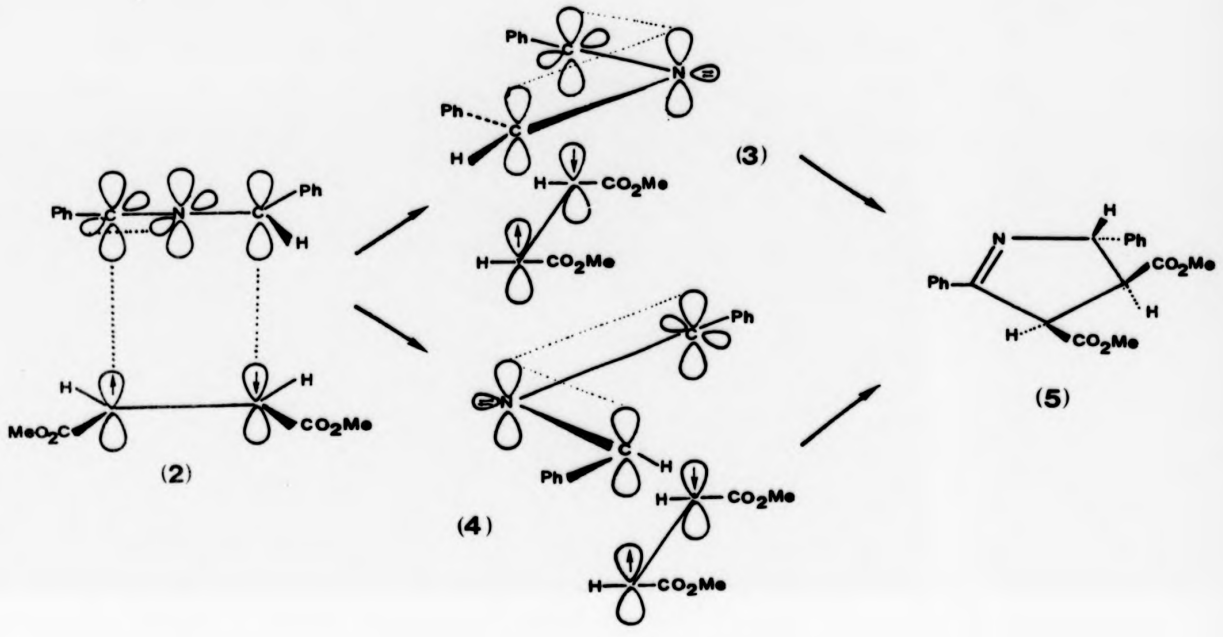
The complete stereospecificity of the reaction is hardly compatible with the diradical mechanism. The small solvent effect on the reaction rate is considered by Firestone to be evidence against zwitterionic intermediate and consistent concerted process. All of the Firestone's arguments have been thoroughly refuted by Huisgen.[2]

## 1.3 The Geometry of the Transition State

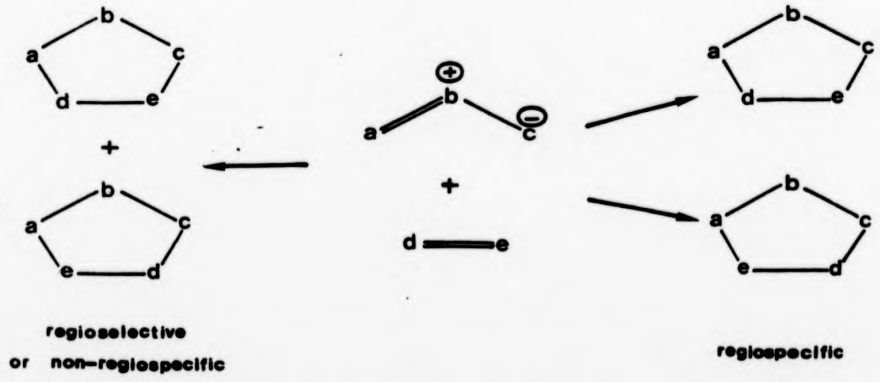
According to Huisgen's proposal 1,3-dipole and dipolarophile approach each other on two parallel planes.[1] The $\pi$ orbitals begin to interact in the $\sigma$ manner when the 1,3-dipole is still linear, e.g. the transoid orientated complex between benzonitrile benzylide and dimethyl maleate (2, Scheme 4). A rehybridisation of the two systems take place successively with bending of the 1,3-dipole to give via endo-3 or exo-4 orientation of the 1,3-dipole with respect to substituents on the dipolarophile adduct (5). However on bending of linear 1,3-dipoles, the allyl anion resonance energy is not lost. The hypothesis was formulated that the bending begins after substantial bonding takes place between 1,3-dipole and dipolarophile.[4] It was observed if one of the two bonds is forming faster than the other, the planes of the two interacting systems are not perfectly parallel.

## 1.4 Regioselectivity

The 1,3-dipolar cycloaddition between two unsymmetrical reagents can be either regiospecific, regioselective or non-regiospecific. (Scheme 5).




Scheme 4




Scheme 5

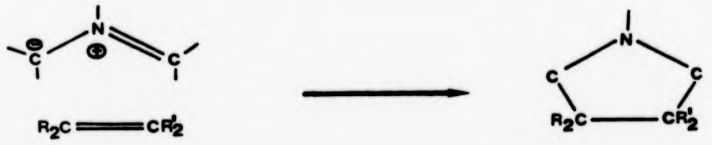
The phenomenon of orientation in 1,3-dipolar cycloadditions has represented an intricate problem for a long time. In recent years, perturbation theory provided a complete rationalisation of regioselectivity of several 1,3-dipolar cycloadditions.[4,8,9]

## 2. AZOMETHINE YLIDES

Azomethine ylides (6), octet stabilised 1,3-dipoles without double bonds, were first predicted and named by Huisgen[1].

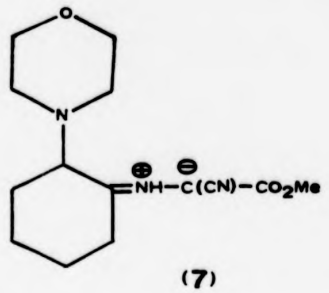
(6) (6)

The azomethine ylide is a very reactive species which is generated "in situ" and readily undergoes 1,3-dipolar cycloaddition with dipolarophiles. Cycloadducts, pyrrolidine derivatives, unambiguously confirm the azomethine ylide existence. This represents the only general method for the synthesis of pyrrolidines. (Scheme 6).

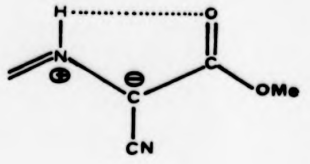


Scheme 6

Some examples of stable azomethine ylides are known in the literature where the 1,3-dipole is a part of an aromatic nucleus. The first stable azomethine ylide that has been isolated and fully characterised,[10] where the 1,3-dipole is not a part of an aromatic nucleus was reported in 1975 (7). X-Ray data confirm unambiguously the ylide structure. It is believed that the ylide is stabilised by intramolecular hydrogen bonding. (Scheme 7).

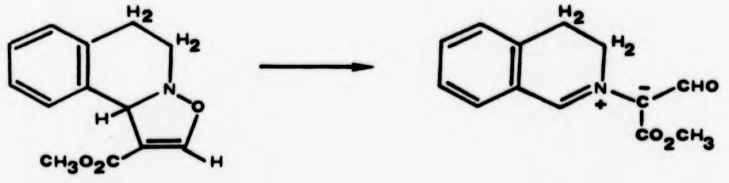


(7)



Scheme 7

Huisgen in his report from 1984, is adamant that compound (9) is the first isolable azomethine ylide in which the 1,3-dipolar system is not part of an aromatic nucleus.[47] The orange crystalline ylide (9) was obtained as a product of rearrangement of 4-isoxazoline (8) at 80°C. (Scheme 8).



(8) (9)

Scheme 8

Since Huisgen's prediction of azomethine ylides several groups have established their existence. Their subsequent 1,3-dipolar cycloaddition has successfully been applied in the synthesis of pyrrolidine derivatives some of them being part of structures of naturally-occurring materials. It is expected that more investigations will be directed toward the development of this general method for the synthesis of specifically substituted pyrrolidines.

## 2.1 Azomethine ylides from aziridines

In 1965, Heine and Peavy[11] submitted the first experimental evidence that many aziridines suffer readily cleavage on heating of carbon-carbon bond. A 3-pyrroline was obtained from 1,2,3-triphenylaziridine and dimethyl acetylene dicarboxylate. (Scheme 9).

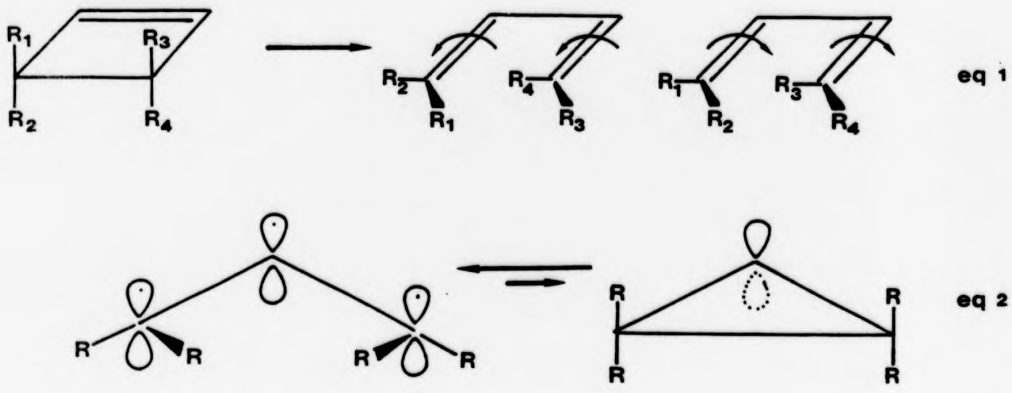

Scheme 9

Several confirmatory examples soon appeared in the literature.[12-15]

In 1965, Woodward and Hoffman[16] made the prediction based on orbital symmetry consideration that the thermal isomerisation of the cyclopropyl anion should proceed via conrotatory ring opening while the photochemical interconversion should proceed by a disrotatory ring opening. These predictions have not received direct experimental verification.

Cyclobutenes were predicted, on thermal activation to open to 1,3-dienes with conrotation of the substituents. The prediction was assumed to apply to all systems containing 4q participating electrons. This prediction was amply verified for 1,3-butadiene-cyclobutene conversion. (Scheme 10, eq. 1).

It was, however, by no means clear whether or not extrapolation was permissible to isoelectronic compounds having more or fewer atoms than butadiene but still the same number of

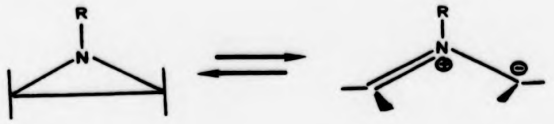



Scheme 10

electrons. The allyl anion, cyclopropyl anion (Scheme 10, eq. 2), which usually lies entirely to the left is a relevant but non-heteroatom containing example. More pertinent however, are the 1,3-dipolar species of general formula (10), recognised by Huisgen as having π electronic system isoelectronic of the allyl anion. Various cases where the three membered ring (11), and 1,3-dipole were in thermal equilibrium were known.

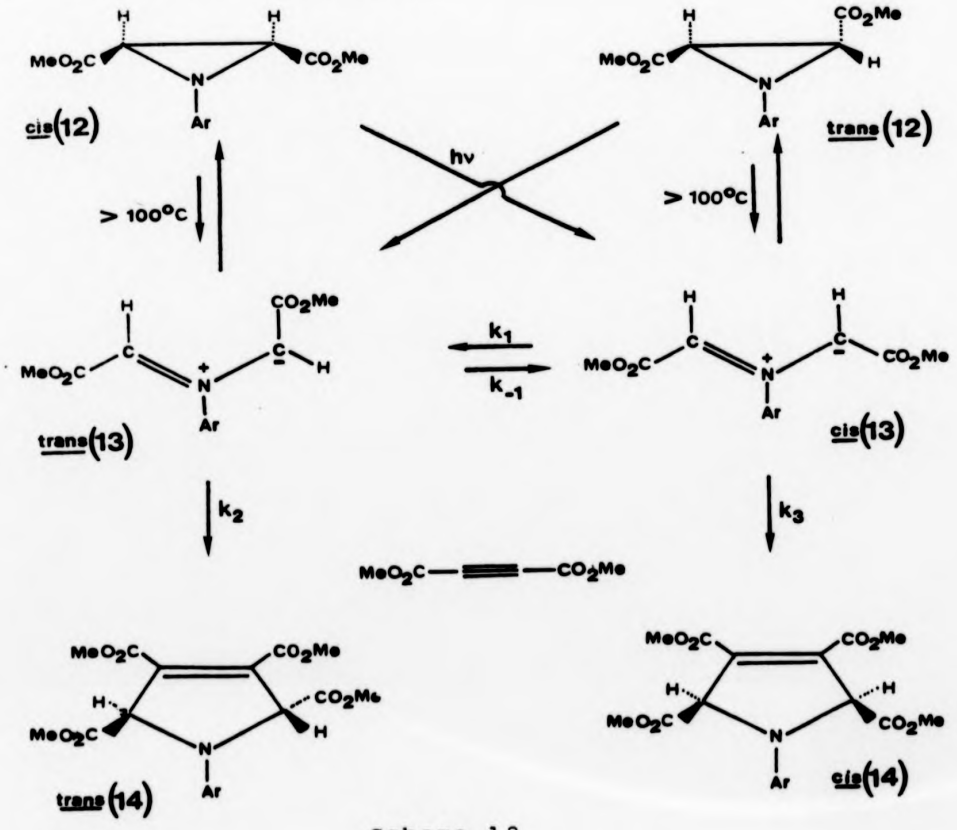

**(10)** **(11)**

The desired reversible ring opening (Scheme 11) had long been known[17,18] with substituted aziridines though only recognised as such at a considerably later date.[12]



Scheme 11

In an elegant exploitation of this observation of reversible valence isomerisation, Huisgen[15] prepared cis-(12) and trans-(12) and demonstrated the stereospecific cycloaddition under thermal conditions, to dimethyl acetylene dicarboxylate. (Scheme 12).




Scheme 12

The stereochemistry of cycloadducts trans-(14) and cis-(14), demonstrate unequivocally that ring opening to azomethine ylides trans-(13) and cis-(13), proceeded stereospecifically in the predicted conrotatory fashion for thermal isomerisation while the photochemical ring cleavage takes a disrotatory course. It may be seen (Scheme 12) that equilibration of the intermediate azomethine ylides competes with the cycloaddition reaction, and it was found only by employing very reactive dipolarophiles could the equilibration process be suppressed completely, and stereoisomerically pure cycloadducts obtained.

The kinetics of aziridine ring cleavage have been investigated by Huisgen and coworkers. From the kinetic data Huisgen constructed a free energy diagram for aziridine ring opening and isomerisation.[19] (Figure 4).

It was found that only one eighth of the molecules of trans-(12) can surmount the energy barrier leading to trans-(13), the remaining revert to trans-(12). For intermediate trans-(13), conversion to cis-(12) is four-fold faster than reversion to cis-(13). The fact that energy profiles show little difference in energy between cis-(13) and trans-(13) lead Huisgen to suspect that the rate constants for the cycloaddition hold the key to the stereospecificity observed (i.e. $k_2 > k_3$) and that only very active dipolarophiles in the Scheme expressed by rate constants $k_3$ react sufficiently rapidly to compete effectively with the isomerisation expressed by $k_{-1}$.[20]

cis-Aziridines cleave thermally in a conrotatory sense to give a structurally unambiguous trans azomethine ylide.

trans-Aziridines under the same conditions, however cleave to cis-azomethine ylides which could exist in two possible forms. (Scheme 13).

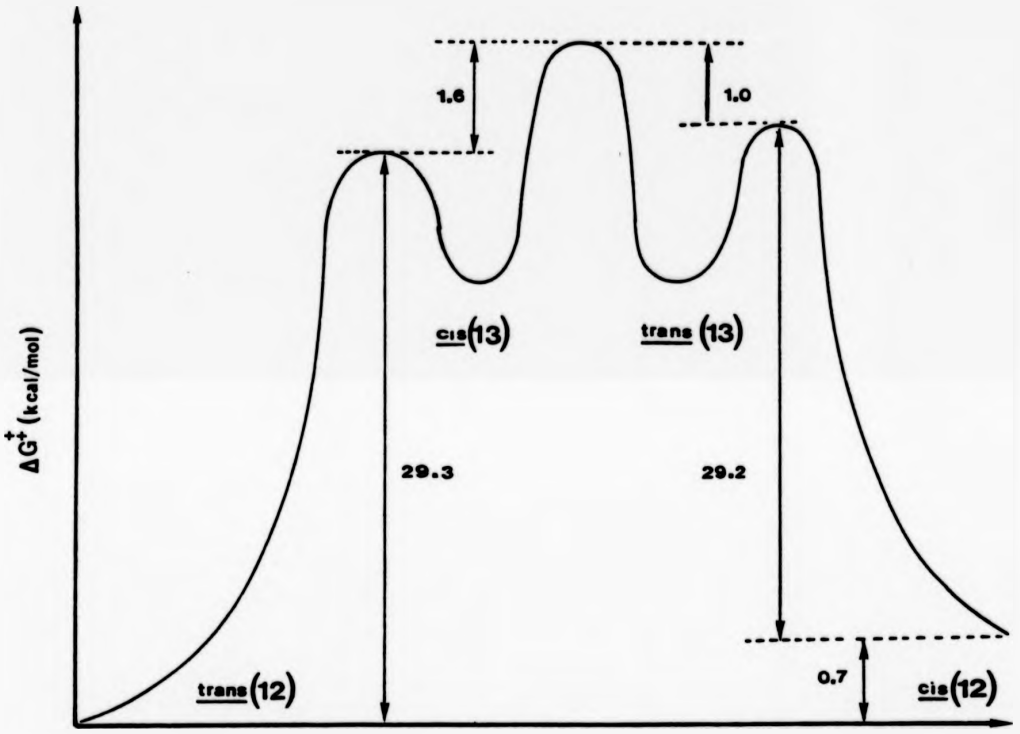
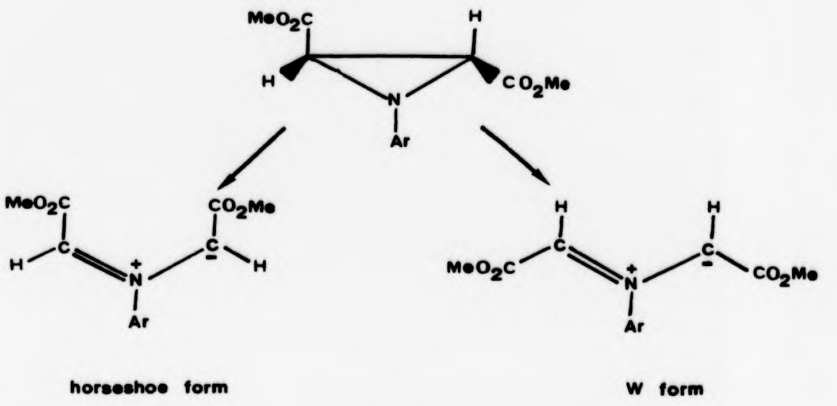


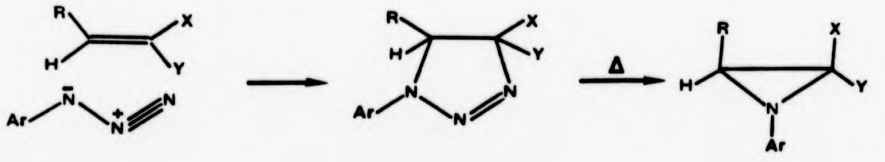

Figure 4

In the "W form" the Van der Waals strain would be expected to be lower than in the "horseshoe" form. It appears from all the examples examined that as predicted, and where two conrotatory opening modes for a trans-aziridine are permitted that the "W" form is preferred.




Scheme 13

Carrié and Texier have made an important contribution to aziridine chemistry and therefore to azomethine ylide chemistry through extensive studies on the addition of phenyl azides to activated olefins. Triazolines were obtained in all these reactions and further converted to aziridines under thermal conditions.[21-23] (Scheme 14).

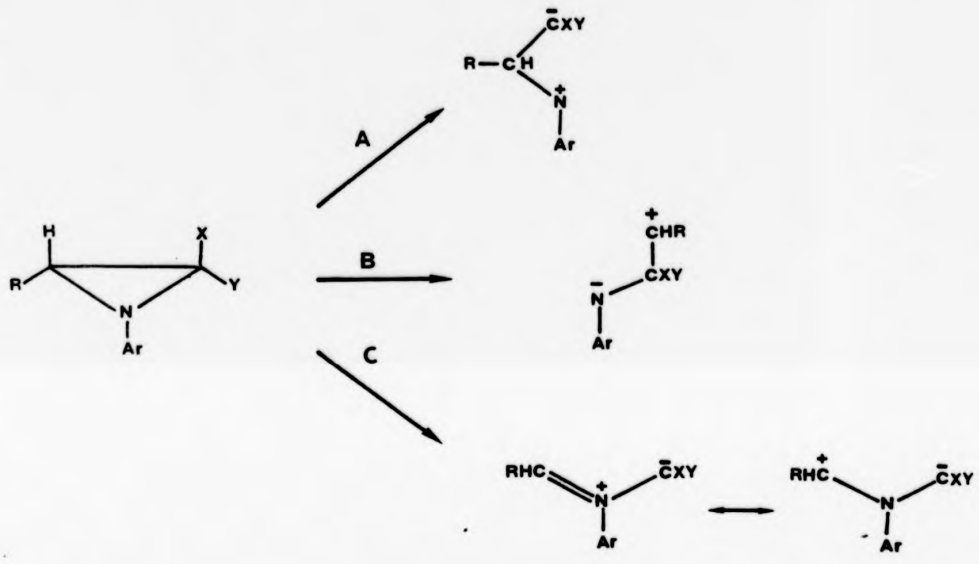



Scheme 14

Carrié and Texier studied both the stereochemistry and the reactivity of aziridines.

Concerning the ring opening path of aziridines, it was necessary to prove the possibility of carbon-carbon bond cleavage since many other examples of carbon nitrogen bond are

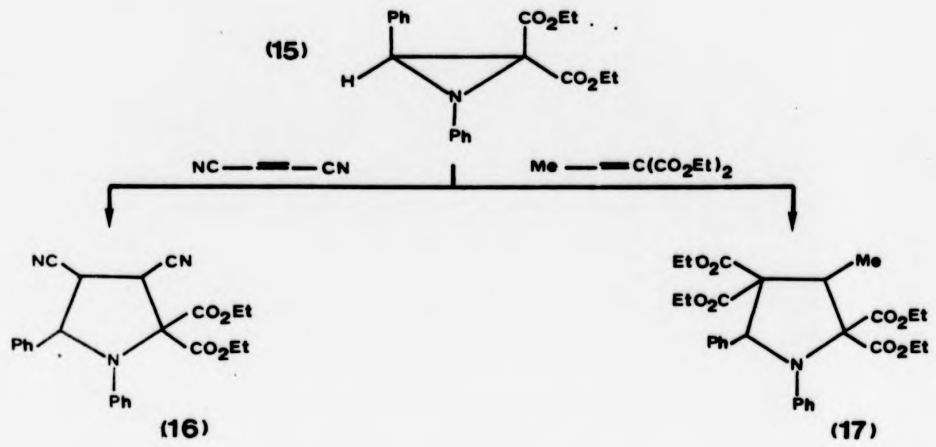
known in aziridine chemistry.[24] Three different ring opening paths of this three-membered ring may be assumed "a priori". (Scheme 15).




Scheme 15

By converting 1,3-diphenyl-2,2-dicarboxyaziridine (15) to pyrrolidine (16) upon heating in the presence of fumaronitrile and to pyrrolidine (17) on heating with diethyl ethylene malonate (Scheme 16) it was proved that the ring opening followed pathway C (Scheme 15), forming the azomethine ylide, the only octet stabilised dipole among the three mentioned.

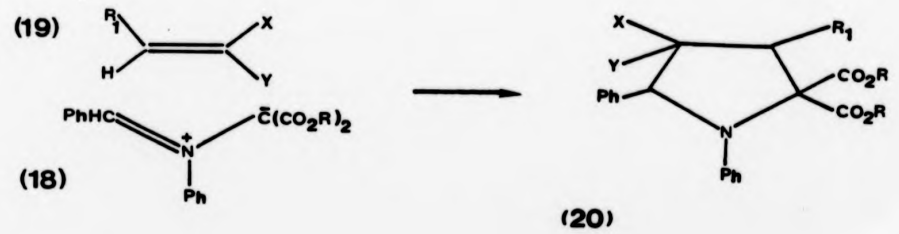
All these addition reactions present striking evidence in favour of the aziridine ring opening, via cleavage of the carbon-carbon bond affording the most stable dipole.[25]




Scheme 16

2.2 Cycloaddition reactions of azomethine ylides

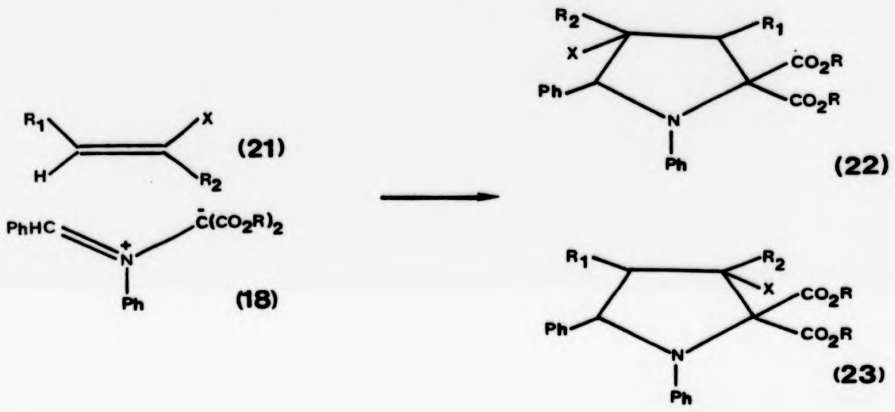
Upon the addition of ylide (18) to olefin (19) only pyrrolidine (20) was formed, in spite of aliphatic or aromatic nature of the $R^1$ group. (Scheme 17).




Scheme 17

The orientation of the addition of dipole (18) to α-substituted olefin (21), having only one activating group (X = ester, acyl, nitrile) was dependent on the dipolarophile stereochemistry: when the ethylenic compound was trans the cycloaddition product always had structure (22). (Scheme 18),

when the dipolarophile was cis (methyl cis-cinnamate) the addition occurred in both directions and mixture of pyrrolidines (22) and (23) resulted. The addition of azomethine ylide (18) was influenced by steric factors and usually did not occur with β-disubstituted dipolarophiles.[26]

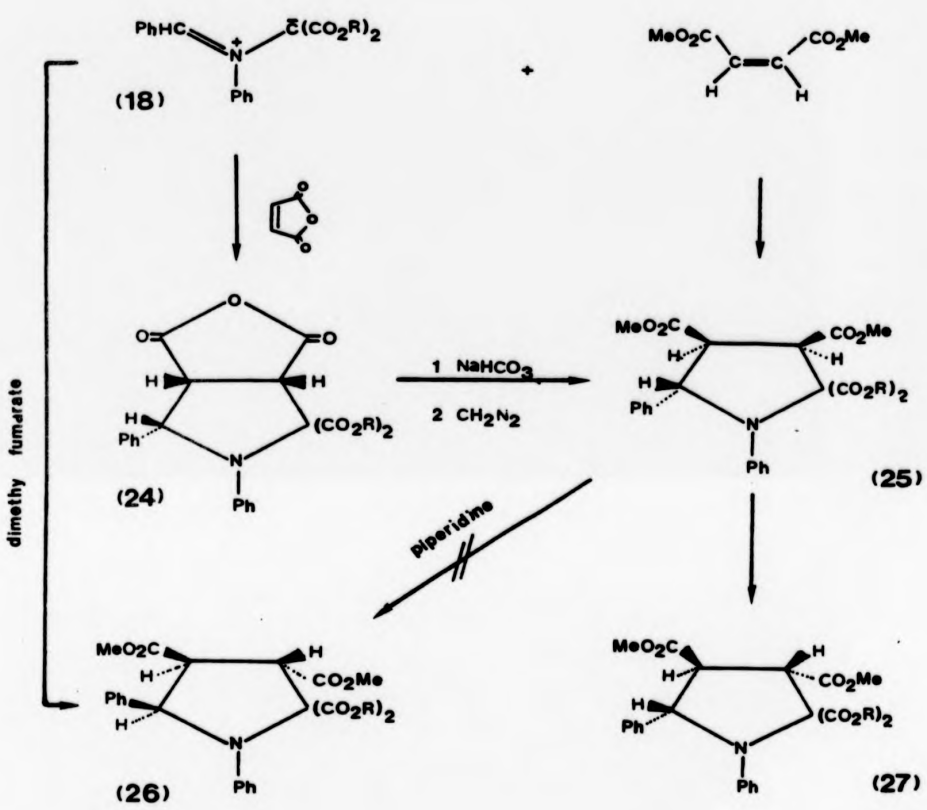



Scheme 18

The azomethine ylide additions are cis as in the case of other 1,3-dipoles, the dipolarophile configuration being maintained. These conclusions were drawn by studying reactions with less complex dipolarophiles allowing a more precise determination of the C-3 and C-4 relative configuration of the pyrrolidine formed in the cycloaddition reaction.[21-23]

Thus the addition of the azomethine ylide (18, R = $CH_3$) on to maleic anhydride, dimethyl maleate and dimethyl fumarate were studied. (Scheme 19).

With maleic anhydride pyrrolidine (24) was formed. The relative configuration on the C-3 and C-4 was determined from spectral data. By treatment with alkalies and further esterification with diazomethane, pyrrolidine (25) was obtained,




Scheme 19

which was identical to the 3+2 dipolar cycloaddition product of the azomethine ylide (18) with dimethyl maleate. When dimethyl fumarate was used two epimeric pyrrolidines (26) and (27) were isolated, differing in configuration at C-5. Pyrrolidine (25) was quantitatively converted to pyrrolidine (27) in the presence of piperidine whilst pyrrolidine (26) which was preferentially formed in the cycloaddition of (18) to dimethyl fumarate, remained unchanged under the same reaction conditions.

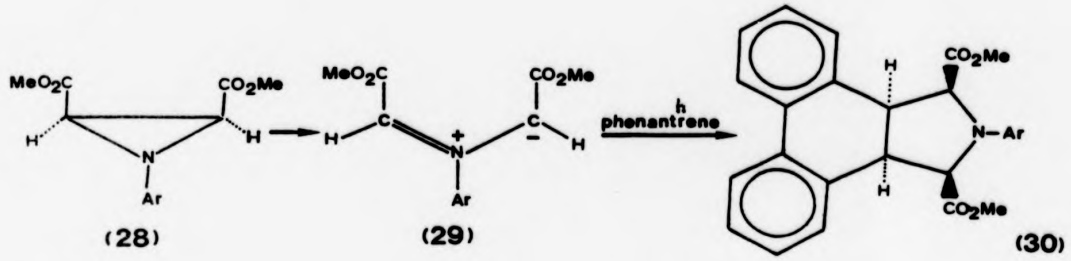
From all these experimental data, the conclusion can be drawn that the addition of the azomethine ylides was as expected a cis addition and that pyrrolidines (26) and (27) were simultaneously formed as a result of different kind of approach of the dipole to the olefin and not because of further epimerization of one of them.

The general rule concerning the addition of azomethine ylide (18) to α-disubstituted olefins $R^1CH=CXY$, (18) was easily determined from nmr analysis. The proton at C-5 of the pyrrolidine (20) always gave a singlet line, independent of aliphatic or aromatic nature of the $R^1$ group. Structure (20) was thus ascertained by the lack of coupling between the two ring protons. Therefore it may be assumed that the carbon atom of the dipole, bearing the two ester groups, usually attacks the carbon with the lowest electron density of the dipolarophile.

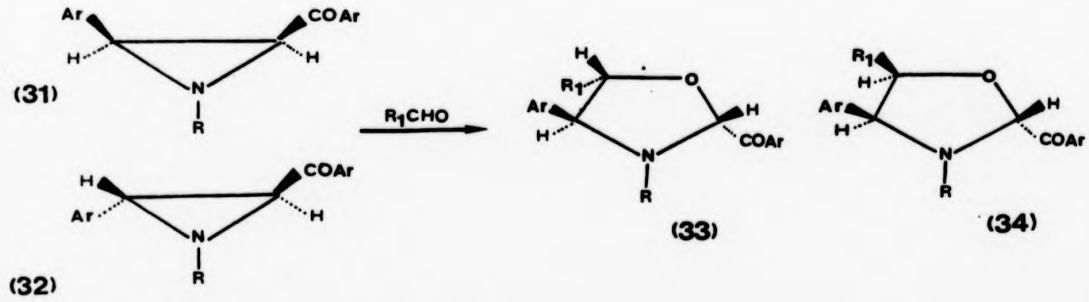
Apart from the azomethine ylide addition to olefins, the reaction of this ylide type with some aromatic systems was also studied.[25]

Thus the azomethine ylide (29) prepared by thermal ring opening of dimethyl aziridine dicarboxylate (28), is sufficiently reactive to disturb the phenanthrene aromatic state affording the cycloaddition product (30). (Scheme 20).

Unsymmetrically substituted aziridines react with aldehydes in a regiospecific fashion. (Scheme 21). Both cis and trans-1-alkyl-2-aryl-3-aroyl-aziridines (31) and (32) react with aliphatic or aromatic aldehydes to give mixtures of oxazolidines (33) and (34) in which the epimer (33) predominates.




Scheme 20

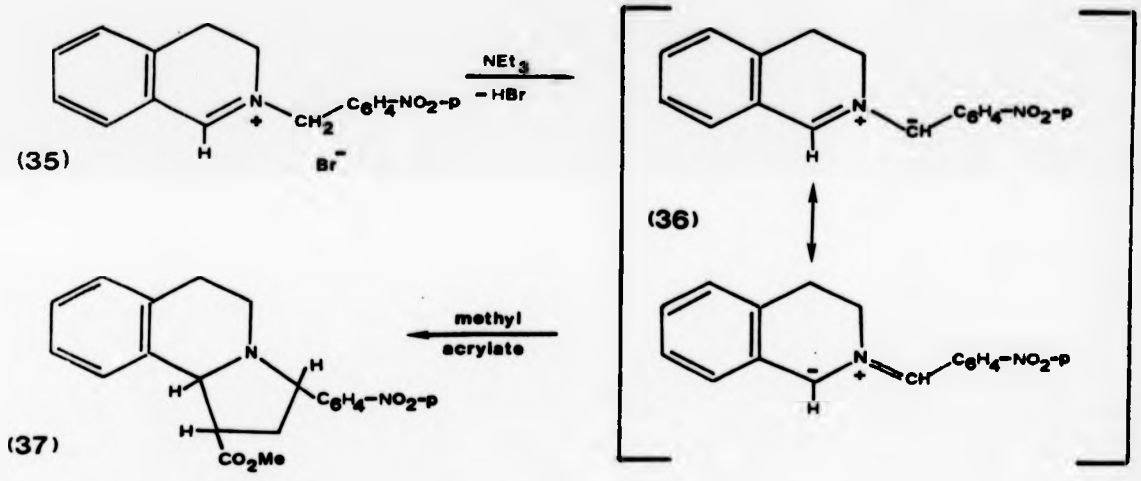



Scheme 21

Several other unsaturated compounds have been reacted with azomethine ylides to give different heterocycles. For azomethine ylides with suitable dipolarophiles the following heterocycles have been synthesised: imidazolines, thiazolines, thiazolidines, oxazolines and oxazolidines and triazolidines.

## 2.3 Azomethine ylides by dehydrohalogenation of immonium salts

Azomethine ylides may be prepared "in situ" by the action of a tertiary base on certain immonium salts. Thus triethylamine liberates an azomethine ylide (36) from N-p-nitrobenzyl-3,4-dihydroisoquinolinium bromide (35), which combines with methyl acrylate to form a 1:1 adduct (37). (Scheme 22).




Scheme 22

Several examples of generation of azomethine ylides by dehydrohalogenation of immonium salts are known from the literature.[3] This method has received little attention in the synthesis of pyrrolidines since it suffers from the limitation that aryl substituents are necessary to stabilise the initially formed azomethine ylide.

## 2.4 X=Y-ZH Systems as potential dipoles

Dehydroamino-acids and their derivatives have attracted interest as synthetic precursors of L-amino acids. Since 1977, Grigg's group from the Queen's University in Belfast have been interested in devising a method for converting L-amino-acid esters into the corresponding dehydroamino acid esters and they commenced their study with the reaction of imines derived from various L-amino-acid esters and aromatic aldehydes.[30] Since then a number of papers has been published by Grigg and his coworkers on a prototropic process involving 1,3-dipole formation by a formal 1,2-hydrogen shift in X=Y-ZH systems.

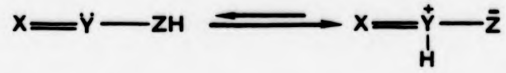
X=Y-ZH systems can be devided into four classes depending on the number of constituent atoms that possess a lone pair of electrons. (Table 2).

| | | | |
|---|---|---|---|
| X=Y—ZH | | | Alkenes |
| $\ddot{X}$=Y—ZH | X=$\ddot{Y}$—ZH | X=Y—$\ddot{Z}$H | Imines, Aldehydes, Ketones, Nitroalkanes |
| $\ddot{X}$=$\ddot{Y}$—ZH | X=$\ddot{Y}$—ZH | $\ddot{X}$=Y—$\ddot{Z}$H | Azo compounds, Hydrazones, Oximes, Amidines |
| $\ddot{X}$=$\ddot{Y}$—$\ddot{Z}$H | | | Triazines |

Table 2

When the central Y atom in an X=Y-ZH system possesses a lone pair of electrons the formal 1,2-hydrogen shift (38⇌39) (Scheme 23) becomes possible. The lone pair of Y is orthogonal to XY π-system and proton transfer from Z to this orthogonal

lone pair on Y would produce a 1,3-dipole. These considerations lead Grigg to suggest that such a formal 1,2-hydrogen shift should occur and would be a general method for generating certain 1,3-dipolar species.[31]



(38) (39)

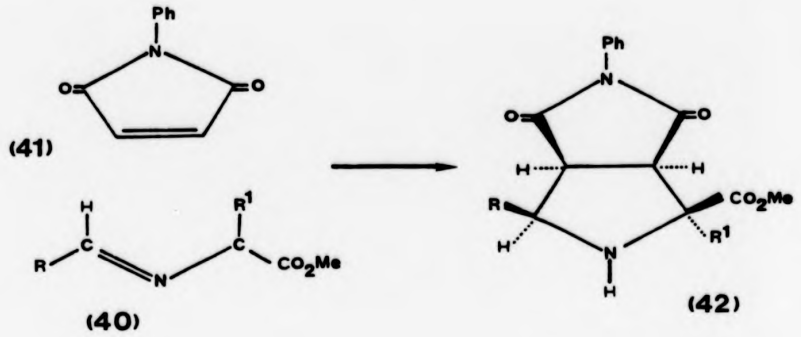
Scheme 23

Species such as (39) would be expected to confirm with the results of the stereospecificity of the 1,3-dipolar cycloaddition reactions. Many examples of imines,[32] hydrazones[33] and oximes[34] have been provided, which illustrate this process by trapping the 1,3-dipoles as their cycloadducts. It has been shown that imines of α-amino-acid esters are good examples of this prototropic process.

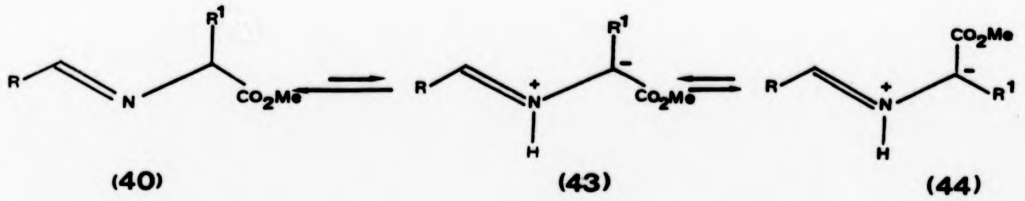
Formation of 1,3-dipoles by thermal tautomeric equilibration (38⇌39) would be expected to be sensitive to the basicity of the ZH proton. Such a dependence is observed when the imine (40) was heated with N-phenylmaleimide (41) in toluene (Scheme 24). Cycloadducts (42) were obtained in good yield as single isomers.[35]

When less reactive dipolarophiles are used as trapping agents a mixture of stereoisomers was obtained which suggested that the stereochemistry of the process is dependent on both 1,3-dipolar species and the dipolarophile.

A dipole generated from (40) could be represented by structures (43) and (44) which are in equilibrium. (Scheme 25).

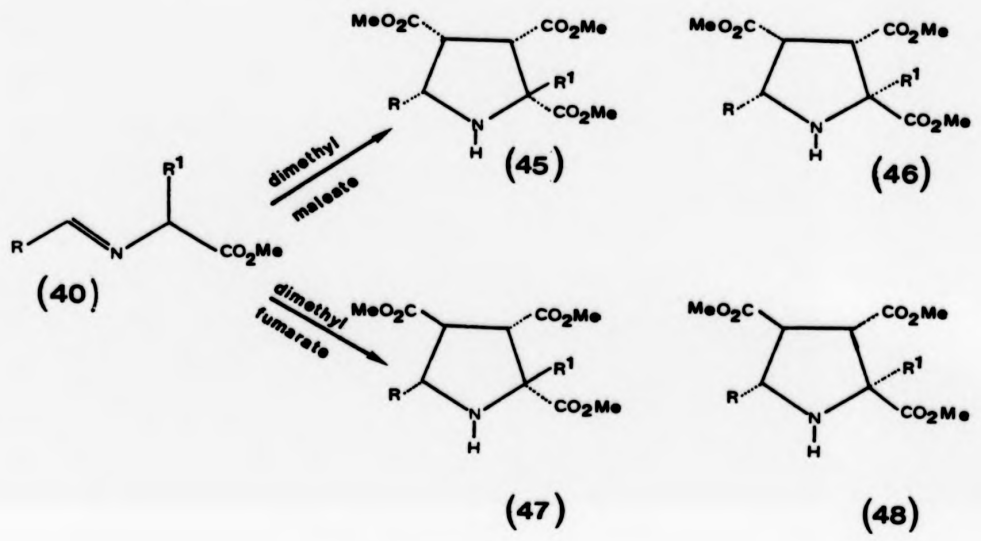



Scheme 24




Scheme 25

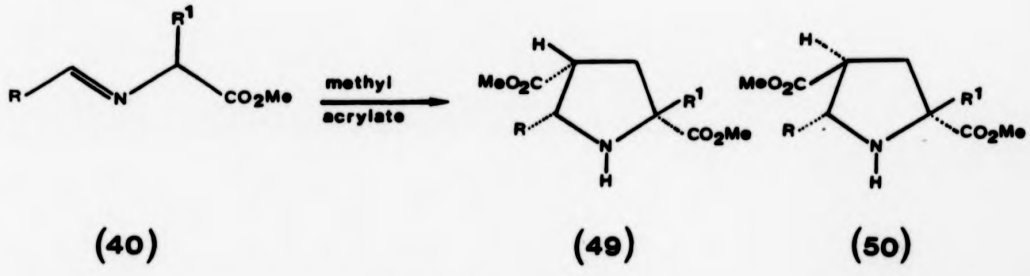
With a reactive dipolarophile, e.g. N-phenylmaleimide, only (43), which is the kinetically generated dipole reacts, while with less reactive dipolarophiles such as dimethyl maleate and dimethyl fumarate, stereomutation (43⇌44) occurs, yielding a mixture of stereoisomers. Thus imines (40, R=2-furyl, p-MeO-$C_6H4$, p-$NO_2$-$C_6H4$, Ph and $R^1$ = Ph) gave pyrrolidines (45) and (46) with dimethyl maleate and pyrrolidines (47) and (48) with dimethyl fumarate in essentially quantitative yield,[33] (relative ratio 3:1) (Scheme 26).




Scheme 26

It is believed that stereomutation (43⇌44) occurs with less reactive dipolarophiles particularly when $R^1$ is phenyl, because the phenyl substituent lowers the barrier of stereomutation.

The regiochemistry of cycloaddition of imine (40) to unsymmetrical dipolarophiles was also studied.[33] Thus the cycloaddition of imine (40) (R=Ph, $R^1$=Me) to methyl acrylate gives a 95:5 mixture of (49) and (50) in quantitative yield. (Scheme 27).




Scheme 27

The isolation of stereospecifically formed pyrrolidine (42) (Scheme 24) is a strong indication that the concerted cycloaddition is involved. Apart from the intervention of the 1,3-dipole (44), other alternative pathways that could lead to (42) include (Scheme 28):

(a) a Michael addition (40) + (41) → (51), followed by a 5-endo-trig cyclisation (51) → (52) → (42);

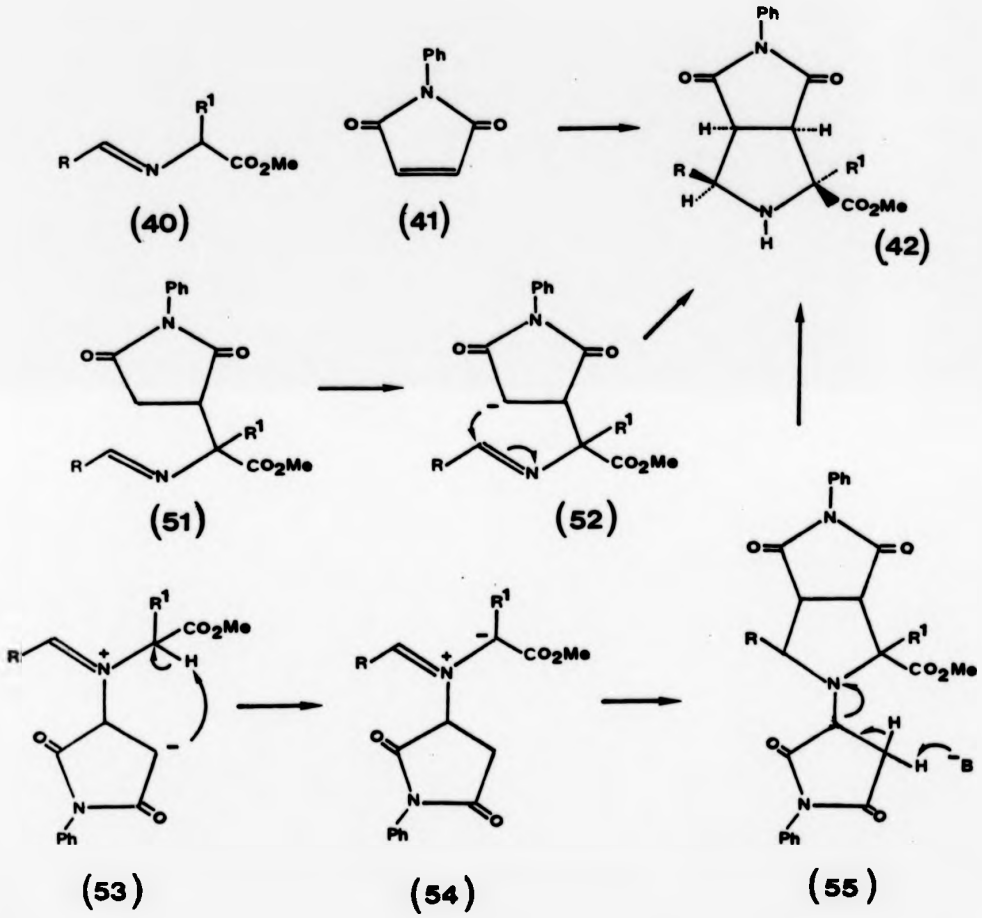
(b) an ene reaction (40) + (41) → (51) followed by a 5-endo-trig cyclisation (51) → (52) → (42);

(c) Michael addition via the nitrogen atom (40) → (41) → (53) and proton transfer to generate a conventional 1,3-dipole (54) followed by a cycloaddition to a further mole of (41) to give the 2:1 adduct (55). Elimination of N-phenylmaleimide would then be necessary to generate (42). (Scheme 28).

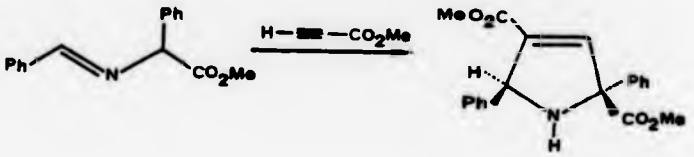
Evidence suggests that the pyrrolidine (42) is not formed by the alternative mechanisms and that the concerted 1,3-dipolar cycloaddition is involved.[35]

Some evidence for the tautomeric equilibrium of the imine (40) with its 1,3-dipolar isomer (43) was given by heating the imine in 50:50 $CDCl_3$-$CD_3OD$ at 70°C. Monitoring of these reactions by nmr spectroscopy showed clean regiospecific deuterium exchange of the proton α- to the carboxylic ester.[32]

The cycloaddition of imines (40) shows a substantial rate enhancement in the presence of Brönsted and Lewis acids.[36] It is believed that acids promote the 1,3-dipole formation from imines. Some of the results are presented in (Table 3).




Scheme 28



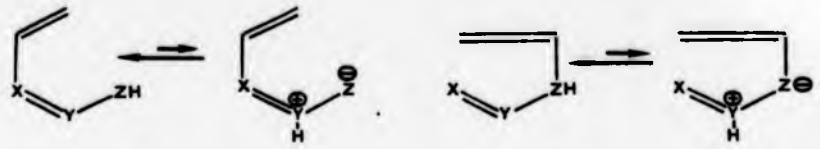

| Brönsted acid | $pK_a$ of the acid | $t_{\frac{1}{2}}$/min |
|---|---|---|
| 2-pyridone | 11.99 | 88 |
| $MeCO_2H$ | 4.75 | 6 |
| Meldrum's acid | 5.1 | 5 |
| 2,4-dinitrophenol | 4.0 | 3 |

| Lewis acid | $t_{\frac{1}{2}}$/h |
|---|---|
| $Zn(OAc)_2.2H_2O$ | 3.0 |
| AgOAc | 3.25 |
| $LiOAc.2H_2O$ | 5.5 |
| $Mg(OAc)_2$ | 8.75 |

Table 3

The effect of substitution on both ends of imine system $RR^1C{=}N{-}CHR^2R^3$ has been studied in detail. The activation of ZH proton is not limited to carboxyl, ester or nitrile. Thus pyridyl, thiazolyl, fluorenyl and dibenzotropyl activate the ZH proton and the corresponding azomethine ylide undergo cyclo-addition to dipolarophiles under thermal activation in good yield.

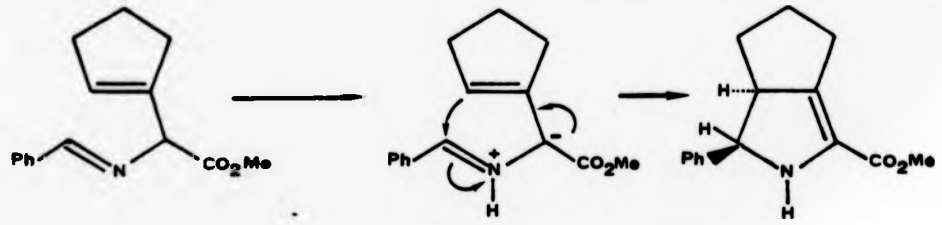
The discovery of a facile thermal equilibration of X=Y-ZH systems with their 1,3-dipolar tautomers suggested the possibility of generating 1,5-dipolar species in this way. The vinylic analogues (56) and (58) are potential precursors of 1,5-dipolar species (57) and (59). (Scheme 29).



(56) (57) (58) (59)

Scheme 29

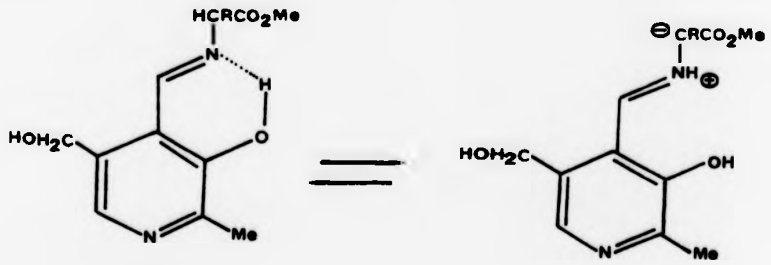
An example of (58⇌59) has been recently reported. Stereospecific 1,5-electrocyclisation to (61) occurred on heating a solution of (60) in various solvents. (Scheme 30).



(60) (61)

Scheme 30

An important biochemical example of the generation of 1,3-dipole from an X=Y-ZH system is provided by pyridoxal enzymes. These enzymes play a central role in connecting carbon and nitrogen metabolism including the formation of biogenetic amines. The suggestion is that there is a thermal tautomeric equilibrium between (62) and a 1,3-dipolar species (63).[31] (Scheme 31).




(62) (63)

Scheme 31

The presence of such reactivity might have biochemical significance in some pyridoxal dependent enzymes.

2.5 Azomethine ylides by desilylation of immonium cations

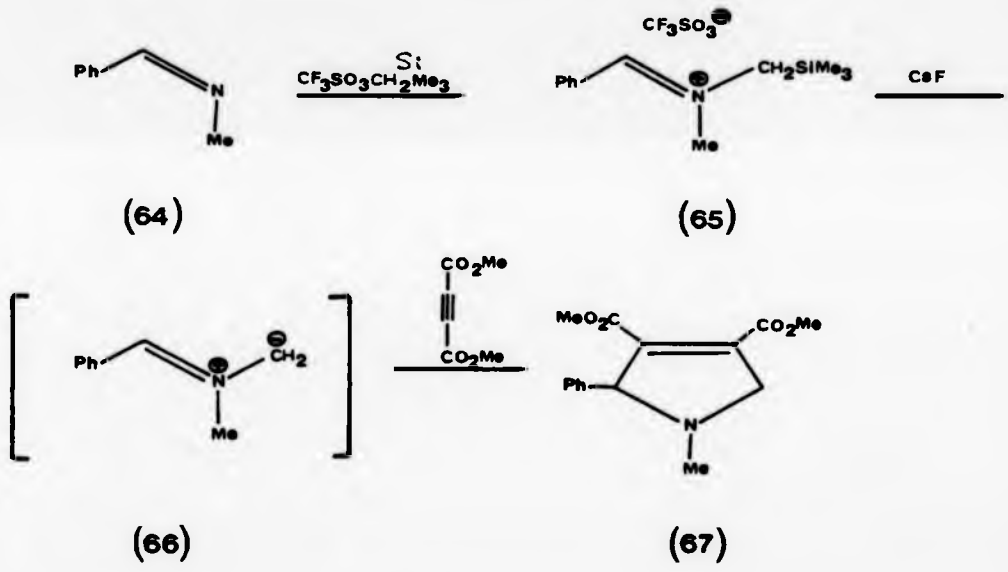
It has been shown in the previous section of this chapter that generation of azomethine ylides, and their subsequent 1,3-dipolar addition to reactive carbon-carbon multiple bond works well when the substituents on the ylide are capable of stabilising the dipole centres. The ring opening of aziridines to azomethine ylides or the thermal isomerisation, imine to azomethine ylide, fails completely when simple alkyl substituents are used.

It is known that fluoride ion induces cleavage of carbon-silicon bond, and this has been widely applied for the generation of nucleophilic carbon species.[38] Even in the presence of electronegative $sp^3$ or $sp^2$ hybridised carbon the attack of fluoride ion occurs preferentially at silicon.

In 1979 Vedejs and Martinez[39] reported that caesium fluoride induced readily desilylation of systems $Me_3SiCH_2X$ where X is positively charged sulphur, nitrogen or phosphorous. The resulting reactive intermediates, undergo 1,3-dipolar

cycloaddition, characteristic of sulphur, nitrogen and phosphorous ylides.

Thus, when the imine (64) was alkylated with trimethylsilyl triflate, the corresponding immonium salt (65) was obtained. (Scheme 32). Desilylation with CsF produced the intermediate azomethine ylide (66) which behaves as 1,3-dipolar species and undergoes 1,3-dipolar cycloaddition with activated olefins producing pyrrolidine (67).



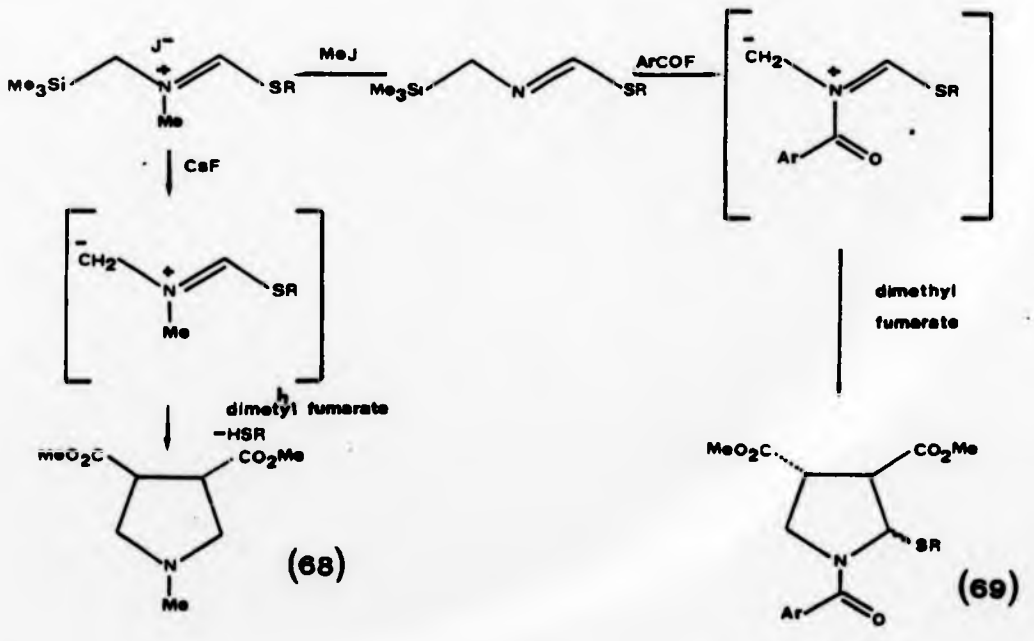

Scheme 32

The discovery of such a non-stabilised azomethine ylide (66) offers many synthetic attractions. It provides a functional group of sufficient flexibility that a diverse range of naturally occurring substances could be synthesised by this route.

Since Vedej's report several groups have been investigating the applicability of non-stabilised azomethine ylides in the synthesis of pyrrolidine derivatives.[40-45]

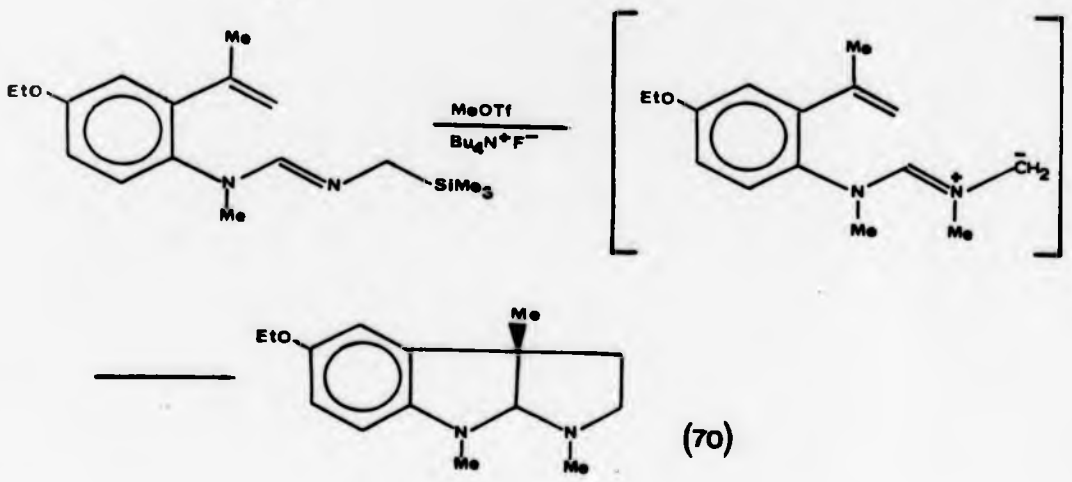
Some interesting applications of this reaction in the domain of natural product synthesis have appeared.

Interest in the synthesis of naturally occurring alkaloids, in particular the neurotoxic physostigmine alkaloid eserethole (70) led Livinghouse to investigate the possibility of an intramolecular 1,3-dipolar cycloaddition of a non-stabilised azomethine ylide to an appropriately situated olefin.[44] He first synthesised pyrrolidines (68) and (69) by desilylation of immonium cations (Scheme 33), using acyl fluorides or caesium fluoride as a source of fluoride ions.[43]




Scheme 33

A similar approach was used in the synthesis of eserethole. (Scheme 34).




(70)

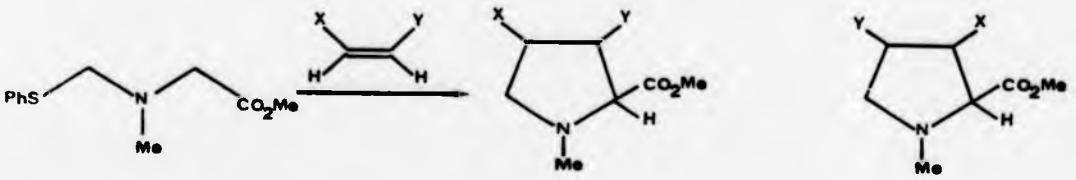
Scheme 34

It is hoped that this general approach to the synthesis of pyrrolidine ring of the physostigmine alkaloids will prove sufficiently flexible for the construction of other naturally occurring ring systems.

Another approach, which has been recently published in the literature and has not yet received full attention is based on the same principle: elimination of a good leaving group.[48]

Thus Imai and coworkers reported in 1984 that the derivative of sarcosine methyl ester (71), with a good leaving group such as SPh β- to the nitrogen atom, with olefinic dipolarophiles undergo a new base promoted cycloaddition to give N-methyl pyrrolidines. (Scheme 35).

With unsymmetrical dipolarophiles two regioisomers are obtained, (72) and (73). On the basis of given experimental results it can be said that the reaction is regioselective or

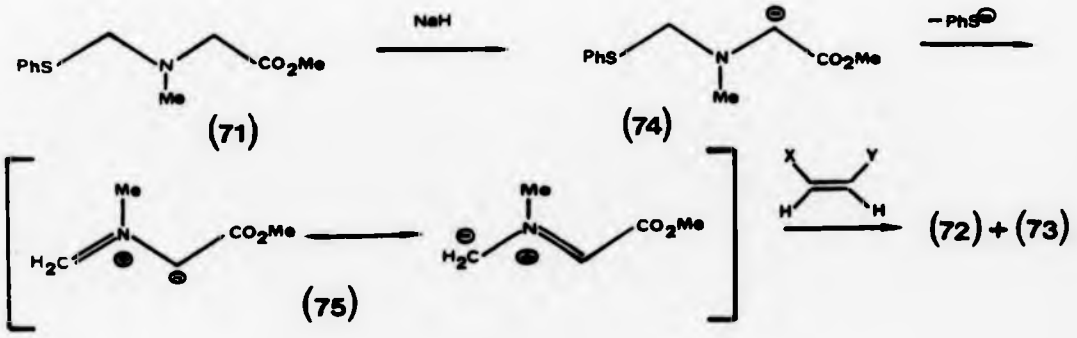


(71) (72) (73)

Scheme 35

non-regiospecific depending on the reactivity of the dipolarophile.

The mechanism was rationalised as follows: the 1,3-dipole (75), formed from the carbanion (74) with the release of phenylthio-carbanion, may be attacked by olefinic dipolarophile to form pyrrolidine ring. (Scheme 36). The two probable extremes in the resonance hybrid of (75) may give the two regioisomers.

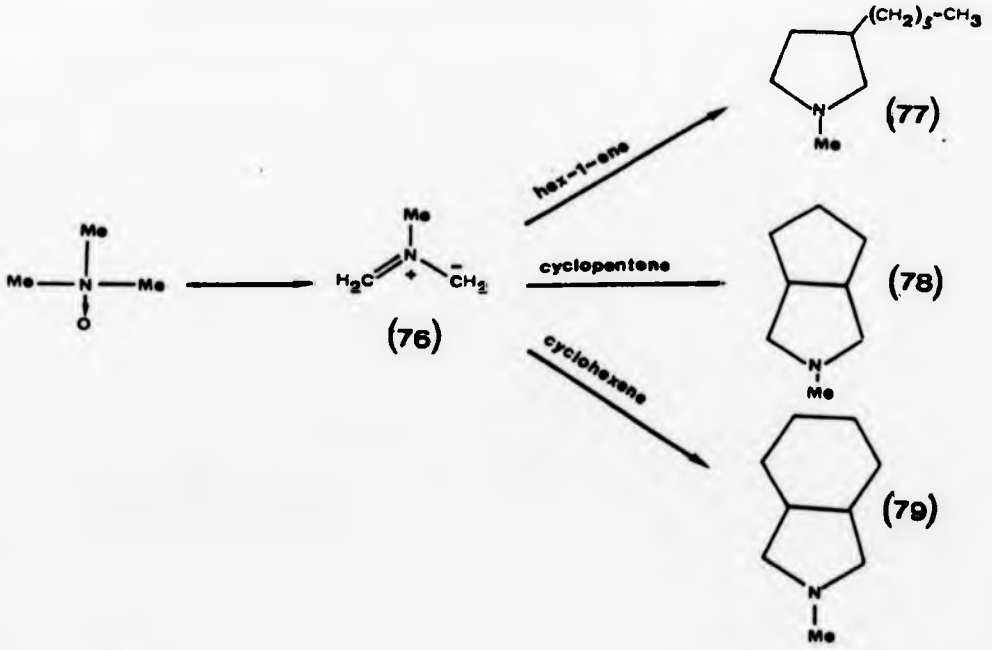


Scheme 36

Further basic and applied investigation of this new 1,3-dipolar cycloaddition which is convenient for the synthesis of functionalised alicyclic amines is under way.

## 2.6 Azomethine ylides from trimethylamine N-oxide

A recent communication reported a novel reaction for the formation of a non-stabilised azomethine ylide.[46] It was reported that when trimethylamine N-oxide was treated with lithium diisopropylamide the azomethine ylide (76) was generated. By virtue of the fact that (76) lacks stabilising substituents it is very reactive and can undergo reactions with non-activated alkenes. Pyrrolidines (77), (78) and (79) were obtained trapping the ylide (76) with hex-1-ene, cyclopentene and cyclohexene respectively. (Scheme 37).



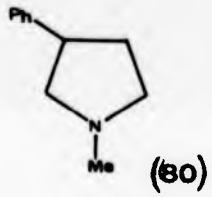

Scheme 37

No mechanistic interpretation is given for such a process but the following suggestions are presented by the authors of the communication in favour of azomethine ylide

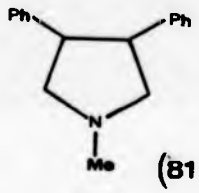
formation:

(a) reaction with styrene takes place easily, yielding 1-methyl-3-phenyl pyrrolidine (80) without polymerisation which might have been induced if a radical species have been present;

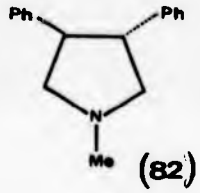
(b) cis or trans stilbene give cis or trans 1-methyl-3,4-diphenyl pyrrolidine (81) and (82) as expected for a 3 + 2 cycloaddition reaction.



(80)



(81)



(82)

It is expected that this reaction may be useful for the synthesis of non-activated pyrrolidine ring compounds.

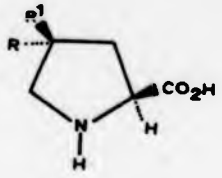
## 3. SYNTHESIS OF NATURALLY OCCURRING PROLINE-BASED AMINO ACIDS

Few materials of natural origin are as versatile in their behaviour and properties as the amino acids, and few have such a variety of biological functions to perform.

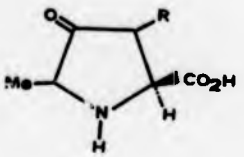
The methods of detection and determination of structure have improved so much that the number of known naturally occurring amino acids has increased rapidly. At the moment 500 are known of which c.a. 240 occur freely in nature, and more are being found each year.

Amongst the heterocyclic amino acids, a number of them are proline derivatives, having a pyrrolidine ring as the basic skeleton. Beside 4-hydroxy-L-proline (83) and the 4-allohydroxy-L-proline (84) with cis L-configuration discovered

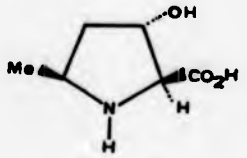
in 1940[49] the D-form (84) has also been noted as a structural unit in the antibiotic etamycin.[50]



| | R | R' |
|---|---|---|
| (83) | OH | H |
| (84) | H | OH |
| (85) | H | $CH_2OH$ |
| (86) | | $=CH_2$ |

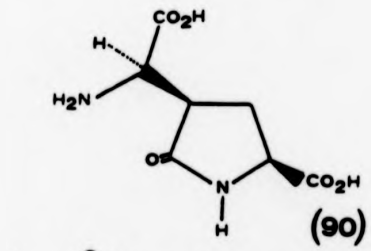


(87) R=H
(88) R=OH

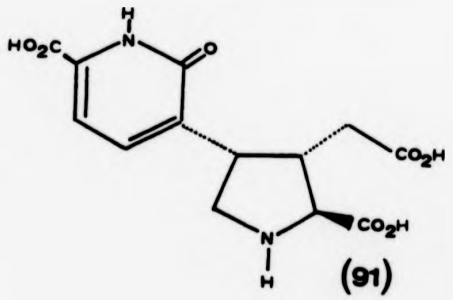


(89)

4-Hydroxymethylproline (85) has been isolated from apples[51] and from Eriobotraya japonica, as has also 4-methylene-D,L-proline (86). Both 5-methyl-4-oxoproline (87) and (88) and 3-hydroxy-5-methylproline (89) were found in the peptide lactone ring of the antibiotic actinomicin Z,[52] N-Methyl-4-hydroxy-proline (83), with $NCH_3$ replacing NH and also known as betonicin, occurs in many plants, one of which is yarrow.[53]



(90)



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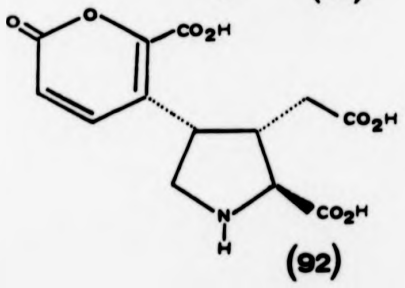

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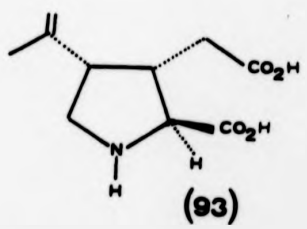
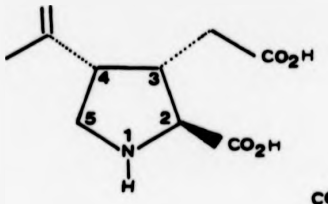


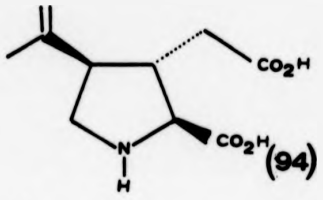
(93)

Other proline derivatives are, a new amino acid (90) from Pentaclethra macrophyllia[54] and acromelic acid A (91) and B (92) which were isolated from the poisonous toadstool Clitocybe acromelelga.[55]

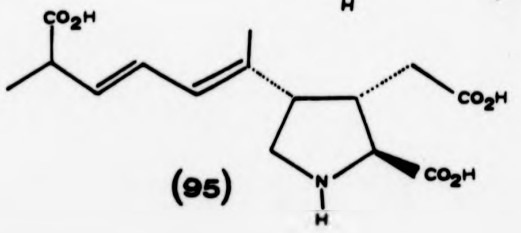
Among mentioned heterocyclic amino acids, α-kainic acid (93) is another example. α-Kainic acid was isolated in 1953 from the marine algae Digenea simplex[56] and more recently from the red algae Centroceras clavulatum[57] found in the Mediterranean. At the time of discovery, α-kainic acid attracted a lot of attention, because of its anthelmintic activity. Initial tests showed α-kainic acid to be three times more powerful than santonin, a drug used for a long time for its anthelmintic properties.[58] In recent years this cyclic amino diacid has attracted considerable medicinal interest owing to its potent neurobiological activity.[59] In a process of purification of α-kainic acid a small amount of an isomer was obtained, α-allokainic acid (94). α-Allokainic acid has very weak anthelmintic properties. Another heterocyclic amino acid with a structure similar to that of α-kainic acid, was isolated from red algae Chondria armata and was called domoic acid (95).[60]




(93)




(94)




(95)

Domoic acid exhibits neurobiological activities similar to the one described for α-kainic acid. The similarity between (93) and (95) is obvious. Apart from the acid and amino functions, it also possesses the unsaturation on the C-4 side chain with the desired stereochemistry. The additional chain attached to the olefinic moiety does not seem to impair the action of domoic acid.

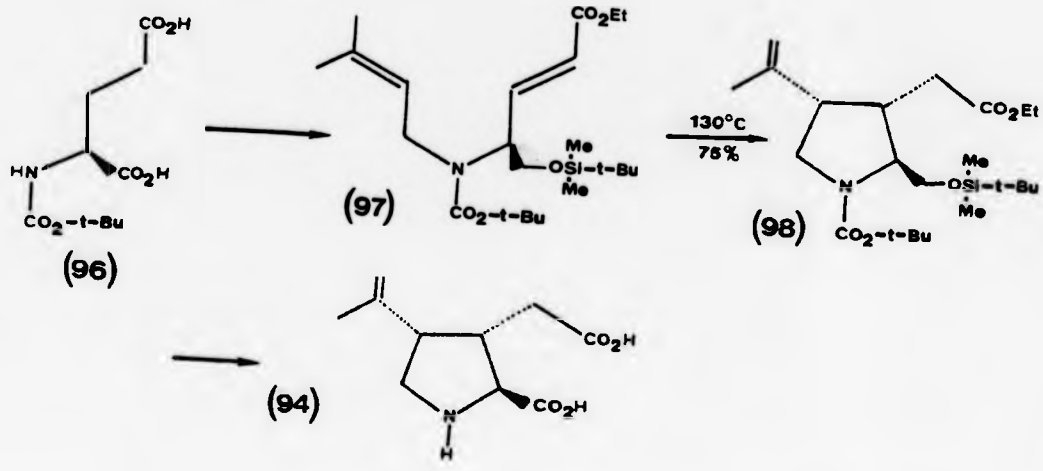
The correct structure of α-kainic acid was elucidated in 1955 from chemical degradation studies,[61] and confirmed later by its X-ray studies.[62]

The first synthesis of kainic acid was developed in 1957 and gave the α-alloisomer.[63] It was a non-stereospecific low yield multistep reaction but served to elucidate the structure.

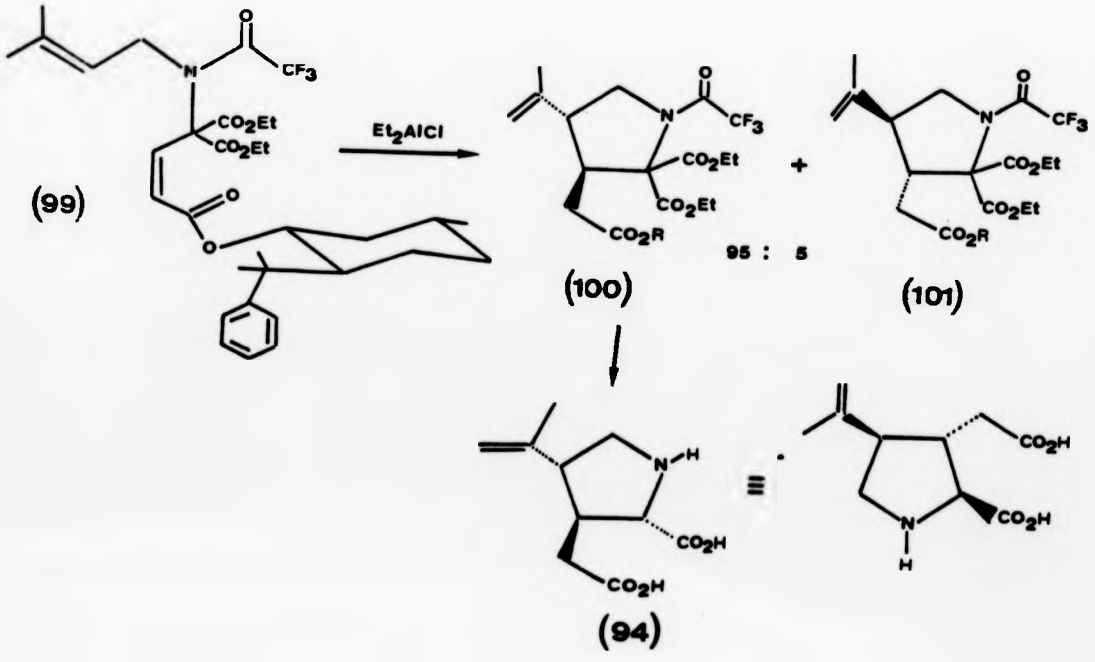
Recently, Oppolzer has communicated an elegant synthesis of α-kainic acid based on an intramolecular ene reaction.[64]

(-)-α-Kainic acid (94) was obtained from glutamic acid derivative (96) by a thermal ene reaction (97 → 98) with the induction of the (S,S)-configuration on the new chiral centres in (98) followed by the removal of the silyl protecting group, oxidation and ester hydrolysis. (Scheme 38).

The epimeric (+)-α-allokainic acid (94) was obtained by analogous ene-reaction of the malonic ester (99), in which the carboxy group attached to the cis double bond has been esterified with an optically active menthol derivative. The ene-reaction of (99) initiated by diethylaluminium chloride gave mainly the compound with the desired configuration (100) (95%) together with 5% of the unwanted stereoisomer (101)[65], (Scheme 39).

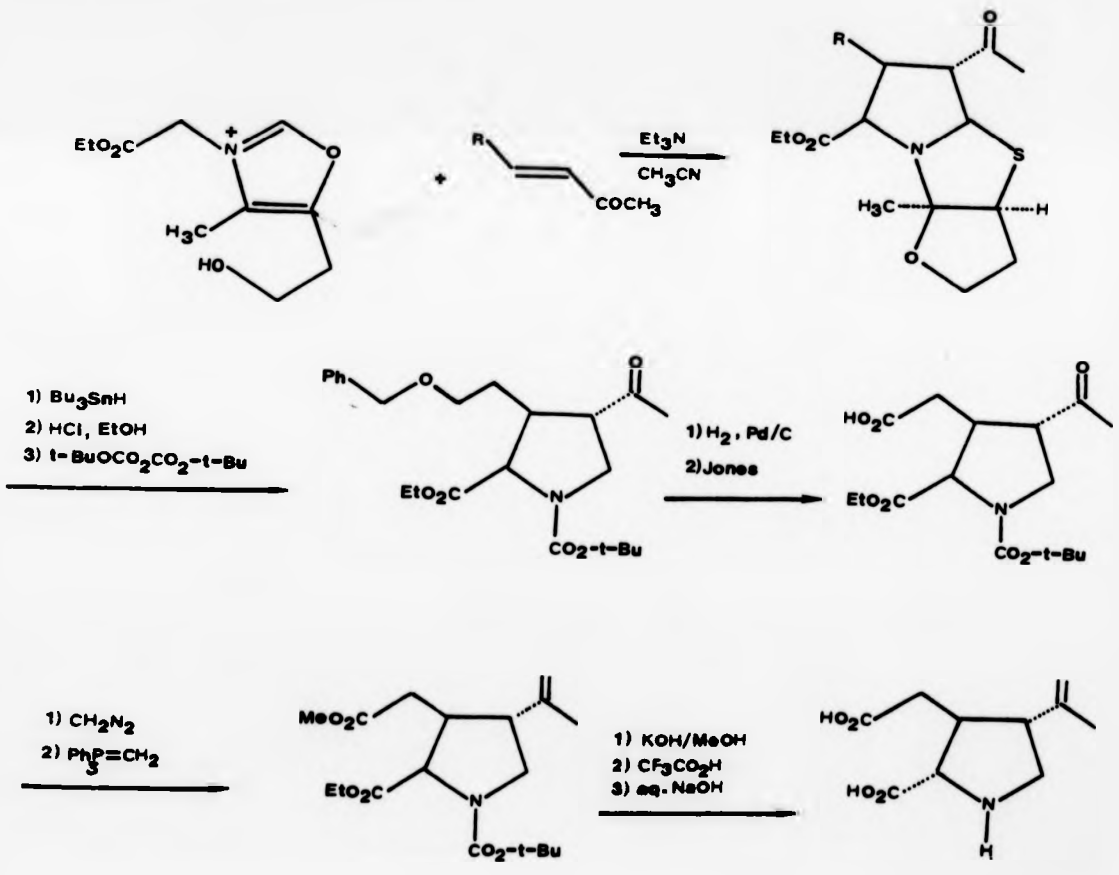



Scheme 38




Scheme 39

In 1981 Kraus and Nagy[66] reported a method of producing functionalised pyrrolidines. Those authors obtained pyrrolidines by a 1,3-dipolar cycloaddition of an azomethine ylide, generated <u>in situ</u>, to a suitable dipolarophile. The stereospecificity of the reaction was also demonstrated. In order to exploit this strategy for the synthesis of pyrrolidine-based natural products the synthesis of α-allokainic acid was achieved.[67] (Scheme 40).




Scheme 40

Oppolzer's strategy for the synthesis of α-kainic acid was a vast improvement on earlier routes due to the use of the symmetry-controlled concerted ene-reaction,[68] to control the stereochemistry of the final product and also to produce the unsaturation in the C-4 side chain. This method provided a much shorter synthetic scheme, and therefore gave a much higher overall yield than the first multistep synthesis. The strategy employed by Kraus, the 1,3-dipolar cycloaddition of azomethine ylide with a suitable olefin in aim to produce pyrrolidine has been known since Huisgen's early investigations of 1,3-dipolar reactions. It has only recently received attention for the synthesis of highly functionalised pyrrolidine derivatives.

REFERENCES

1. R. Huisgen, Angew.Chem.Int.Ed., 1963, 2, 565, 633.

2. R. Huisgen, J.Org.Chem., 1968, 33, 2291.

3. R. Huisgen, R. Grashey and J. Sauer in S. Patai, "The Chemistry of Alkenes", Interscience, New York 1964, p.806.

4. K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strozier and J. K. George, J.Am.Chem.Soc., 1973, 95, 7287.

5. R. Huisgen, M. E. Seidl, G. Wallbillich and H. Knupfer, Tetrahedron, 1962, 17, 3.

6. R. A. Firestone, J.Org.Chem., 1968, 33, 2285.

7. R. A. Firestone, J.Org.Chem., 1972, 37, 2181.

8. J. Bastide and O. Henry-Rousseau, Bull.Soc.Chim.Fr., 1973, 2294.

9. J. Bastide, N. El Ghandour and O. Henry-Rousseau, Tetrahedron Lett., 1972, 4225.

10. J. P. Felury, J. P. Schoeni and D. Clerin, Helv.Chim.Acta., 1975, 58, 2018.

11. H. W. Heine and R. Peavy, Tetrahedron Lett., 1965, 3123.

12(a) A. Padwa and L. Hamilton, Tetrahedron Lett., 1965, 4363.

(b) H. W. Heine, R. Peavy and A. J. Durbetaki, J.Org.Chem., 1966, 31, 3924.

13. R. Huisgen, W. Scheer, G. Szeimies and M. Hubert, Tetrahedron Lett., 1966, 397.

14. P. B. Woller and N. H. Cromwell, J.Heterocyclic Chem., 1968, 5, 579.

15. R. Huisgen, W. Scheer and M. Huber, J.Am.Chem.Soc., 1967, 89, 1753.

16. R. B. Woodward and R. Hoffman, J.Am.Chem.Soc., 1965, 87, 395.

17. T.V.J. Taylor, J. S. Owen and D. Wittacher, J.Chem.Soc., 1938, 206.

18. H. Stravdinger and K. Miescher, Helv.Chim.Acta., 1919, 2, 554.

19. R. Huisgen, W. Scheer and H. Mader, Angew.Chem.Int.Ed., 1969, 8, 602.

20. R. Huisgen, W. Scheer and H. Mader, Angew.Chem.Int.Ed., 1969, 8, 604.

21. R. Carrié and F. Texier, Bull.Soc.Chim.Fr., 1971, 3642.

22. F. Texier and R. Carrié, Bull.Soc.Chim.Fr., 1971, 4119.

23. R. Carrié and F. Texier, Bull.Soc.Chim.Fr., 1972, 258.

24. P. A. Gembitski, M. Loim and D. S. Zhuk, Russ.Chem.Rev., 1966, 2, 104.

25. R. Huisgen, Helv.Chim.Acta., 1967, 50, 2421.

26. R. Huisgen, W. Scheer and H. Mader, Angew.Chem., 1969, 81. 640.

27. G. Dallas, J. W. Lown and P. Moser, J.Chem.Soc., (D), 1970, 278.

28. G. Dallas, J. W. Lown and P. Moser, J.Chem.Soc., (C), 1970, 2383.

29. R. Huisgen, R. Grashey and E. Steingruber, Tetrahedron Lett., 1964, 481.

30. R. Grigg and J. Kemp, J.Chem.Soc.Chem.Comm., 1977, 125.

31. R. Grigg, J. Kemp and N. Thompson, Tetrahedron Lett., 1978, 2827.

32. R. Grigg, J. Kamp, G. Scheldrick and J. Trotter, J.Chem.Soc.Chem.Comm., 1978, 109.

33. R. Grigg and J. Kemp, Tetrahedron Lett., 1980, 2461.

34. R. Grigg, M. Jordan, A. Tangthongkum, F.W.B. Einstein and T. Jones, J.Chem.Soc., Perkin 1, 1984, 47.

35. R. Grigg, H.Q.N. Gunaratne and J. Kemp, J.Chem.Soc., Perkin 1, 1984, 41.

36. R. Grigg and H.Q.N. Gunaratne, J.Chem.Soc.Chem.Comm., 1982, 384.

37. R. Grigg and H.Q.N. Gunaratne, Tetrahedron Lett., 1983, 24, 1201.

38. R. Noyori, K. Yokoyama, J. Sataka, I. Kuwajima, E. Nakamura and M. Shimizu, J.Am.Chem.Soc., 1977, 99, 1265.

39. E. Vedejs and G. R. Martinez, J.Am.Chem.Soc., 1979, 101, 6452.

40. E. Vedejs and G. R. Martinez, J.Am.Chem.Soc., 1980, 102, 7993.

41. K. Ashiva and M. Sekiya, Tetrahedron Lett., 1982, 23, 2589.

42. K. Ashiwa and M. Sekiya, Heterocycles, 1983, 20, 167.

43. T. Livinghouse and R. Smith, J.Chem.Soc.Chem.Comm., 1983, 210.

44. T. Livinghouse and R. Smith, J.Org.Chem., 1983, 48, 1554.

45. A. Padwa, G. Haffmanns and M. Thomas, Tetrahedron Lett., 1983, 24, 4303.

46. R. Beulgemas, G. Negron and G. Roussi, J.Chem.Soc.Chem.Comm., 1983, 31.

47. R. Huisgen and K. Niklas, Heterocycles, 1984, 22, 21.

48. N. Imai, Y. Terao, K. Achiwa and M. Sekiya, Tetrahedron Lett., 1984, 25, 1579.

49. H. Wieland, and B. Witkop, Ann.Chem., 1940, 171, 543.

50. J. C. Sheehan, H. G. Zachav and W. B. Lawson, J.Am.Chem.Soc., 1957, 79, 3933.

51. K. E. Untich, and G. A. Gibbon, Tetrahedron Lett., 1964, 3259.

52. A. B. Maguer, O. A. Stuart, E. Katz and K. T. Mason, J.Org.Chem., 1977, 1000.

53. J.W.W. Morgan, Chem.Ind.(London), 1964, 542.

54. Amino Acids, Peptides and Proteins, Specialist Periodical Reports, Chem.Soc., London, 1976, 8.

55. K. Konno, H. Schirahama and T. Matsumuto, Tetrahedron Lett., 1983, 24, 939.

56. S. Murakami, T. Tahemoto and Z. Shimuzu, J.Pharm.Soc.Japan, 1953, 73, 1026.

57. G. Impellizerri, S. Mangifacio, G. Oriante, M. Piattelli, S. Sciuo6o, E. Fatorusso, S. Magno, C. Santacroce and D. Sica, Phytochemistry, 1975, 14, 1549.

58. Y. Komiya, S. Kando, S. Ohtake and K. Tsukogoshi, Sogo Igaku, 1955, 12, 163; C.A., 54, 13440d.

59. E. G. McGeer, J. W. Olney and P. L. McGeer, "Kainic Acid as Tool in Neurobiology", Raven Press, New York, 1978.

60. K. Daigo, J.Pharm.Soc.Japan, 1959, 79, 350, 365.
T. Takemoto, K. Daigo, Y. Kondo and K. Kondo, J.Pharm.Soc.Japan, 1966, 86, 874.

61. Y. Ueno, H. Nawa, J. Ueyanagi, H. Morimoto, R. Nakamori and T. Matsuoka, J.Pharm.Soc.Japan, 1955, 75, 807, 811, 814.
S. Murakami, T. Takemoto, Z. Tei and K. Diago, J.Pharm.Soc.Japan, 1955, 75, 866, 869.
H. Morimoto, J.Pharm.Soc.Japan, 1955, 75, 901, 941, 943.

62. H. Watase, Y. Tomic and I. Nitta, Bull.Chem.Soc.Japan, 1958, 31, 714.
Nature, 1958, 181, 761.

63. Y. Ueno, R. Nakamori, J. Ueyanagi, H. Nawa, Y. Sana, M. Honjo, R. Nakamori, T. Sugawa, M. Ushibayashi, K. Osugi and S. Tasouka, Proc.Japan Acad., 1957, 33, 53.

64. W. Oppolzer and K. Thirring, J.Am.Chem.Soc., 1982, 104, 4978.

65. W. Oppolzer, C. Robbiani and K. Baatig, Helv.Chim.Acta., 1980, 63, 2015.

66. G. A. Kraus and J. O. Nagy, Tetrahedron Lett., 1981, 22, 2727.

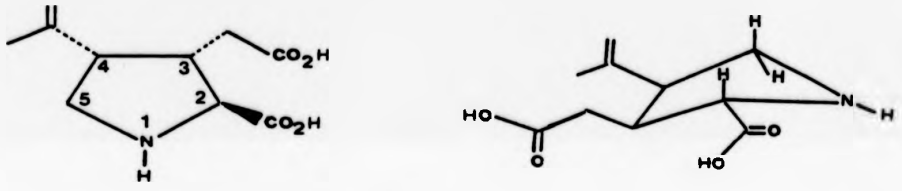
67. G. A. Kraus and J. O. Nagy, Tetrahedron Lett., 1983, 24, 3427.

68. W. Oppolzer and V. Snieckus, Angew.Chem.Int.Ed., 1978, 17, 476.

# DISCUSSION

## 1. GENERAL STRATEGY FOR THE SYNTHESIS OF α-KAINIC ACID BY A 1,3-DIPOLAR CYCLOADDITION REACTION

During the last decade considerable interest has been shown in the anthelmintic and neurochemical properties of the natural product α-kainic acid (kainic acid) (1) and this has culminated in a number of total syntheses of (1) and structurally related molecules as was outlined in Section 3 of the Introduction of this thesis.



(1)

The pharmacological activity of α-kainic acid, depends upon the molecule possessing a free N-H group, two free carboxylic acids, and a side chain containing a double bond at position 4. The stereochemistry of the molecule is critical as only a cis relationship between C-3 and C-4 substituents produces strong anthelmintic responses. Of the known stereoisomers of α-kainic acid, all show considerably reduced biological activity to that of α-kainic acid itself.

The important feature to be considered, when designing a synthesis of α-kainic acid is the cis relationship between the C-3 and C-4 substituents. The chiral centre at position 2 is readily epimerisable and therefore the thermodynamically more favourable trans relationship between the C-2 and C-3 substituents can be easily obtained.

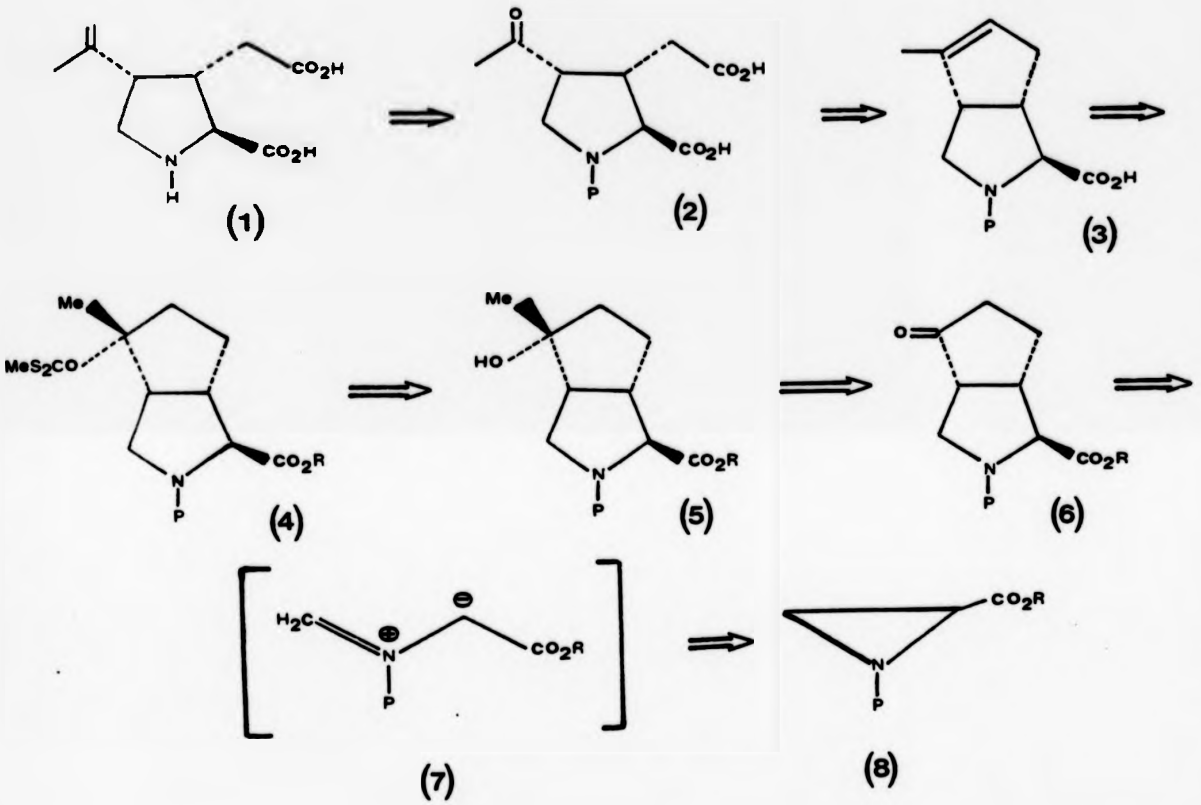
The conformational freedom of the active groups in

α-kainic acid is severely restricted by the pyrrolidine ring, but there is still a fair degree of conformational flexibility associated with the acid group at position 3 and the double bond at position 4 due to rotation of the acetic acid and isopropenyl substituents, respectively about the carbon-carbon single bonds. The simple way of fixing the position of those groups would be to incorporate them into a ring system which could be cleaved at a late stage of the synthesis thus ensuring stereochemical integrity.

An attempt was made by C. H. Strachan[1] to synthesise a conformationally restricted analogue of α-kainic acid by an intramolecular Diels-Alder reaction and a general strategy for the synthesis of α-kainic acid by a 1,3-dipolar cycloaddition was developed.[2]

Retrosynthetic analysis of the problem suggested that the ketone (2) which may be readily transposed into α-kainic acid, should indeed represent our penultimate target, and (2) should in principle be derivable by way of ozonolytic cleavage of the bicyclic pyrrolidine (3) (Scheme 1).

Furthermore the intermediacy of (3) should establish the stereochemical integrity at C-3 and C-4 in the target molecule. The bicyclic pyrrolidine (3) might then be derived by pyrolysis of the acetate or xanthate ester (4) of the tertiary alcohol (5). The pyrolysis of xanthate ester, known as Chugaev reaction proceeds by $E_i$ mechanism. Elimination is <u>syn</u> and requires a coplanar transition state. Only two hydrogens are coplanar and in <u>syn</u> orientation to the xanthate ester group, $H_a$ and $H_b$ (Figure 1).




Scheme 1

Pyrolysis with elimination of $H_b$ would yield (3a), the exomethylene isomer, less favoured compared to the thermodynamically more stable isomer (3).

The tertiary alcohol (5) is the anticipated product from the addition of methyl lithium or methyl magnesium halide

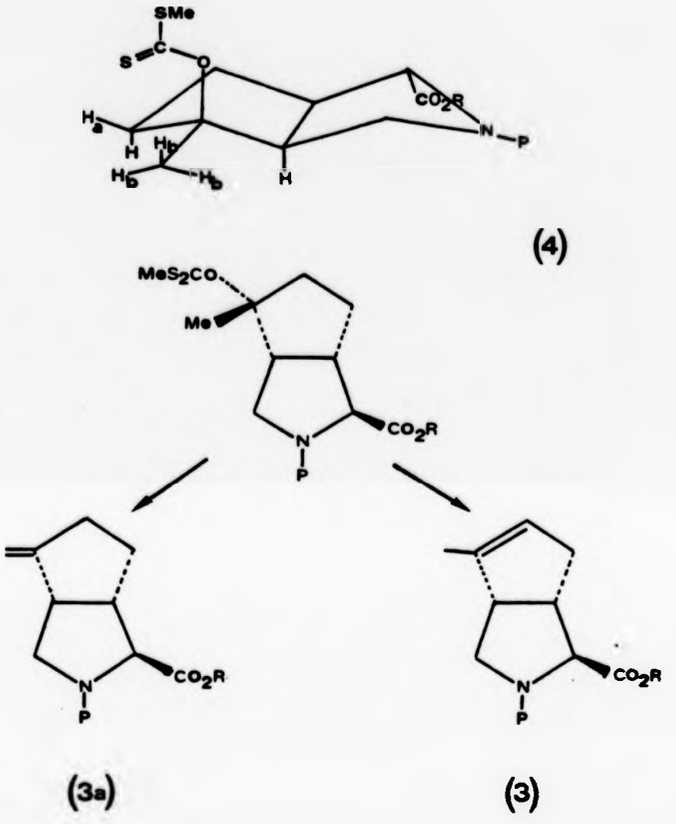



Figure 1

to the bicyclic ketone (6). Thus the addition of an organometallic reagent to (6) would be expected to occur from the least hindered face of the molecule resulting in (5).

A key step is the synthesis of a bicyclic system, with a built in stereochemistry. The only conformational changes possible in this system would be the flexing of the ring.

Synthesis of a bicyclic ketone (6) is not in itself a trivial problem, since the relative stereochemistry at C-2, C-3 and C-4 must be controlled during its formation. However incorrect stereochemistry at C-2 would not present a serious problem, as epimerisation is easily effected. Retrosynthetic analysis of (6) suggests that (6) might be synthesised by way of a [3 + 2] cycloaddition between cyclopentenone and the N-protected aziridine, (8). This conceptually elegant method for construction of five-membered heterocycles proceeds with appropriate stereochemical control. Such a cycloaddition might be expected to result in (6) in a single step, and consistent with the intermediacy of azomethine ylide (7) the regiochemistry of the cycloaddition reaction should be heavily biased toward the formation of (6). The ester substituent apart from being required to produce the acid group at position 2 in the final pyrrolidine, is also important in controlling the regiochemistry of the 1,3-dipolar cycloaddition. The ester does this by stabilising the negative charge on the azomethine ylide, and therefore makes that end of the 1,3-dipole more nucleophilic. The carbonyl of the α,β-unsaturated ketone, cyclopentenone, is also important in controlling the regiochemistry of the cyclo-addition as it polarises the double bond of the 1,3-dipolarophile and stabilises the partial negative charge formed in the transition state due to the unequal rate of bond formation. The protection of nitrogen should also be considered. It is essential to eliminate any interferance of a free amino function in subsequent transformations of (6) into α-kainic acid. P

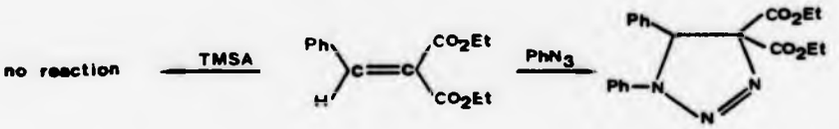
represents any protecting group which can easily be removed at a late stage of the synthesis, but at the same time its electronic features must promote aziridine formation.

## 2. $\Delta^2$-1,2,3-TRIAZOLINES AS PRECURSORS OF AZOMETHINE YLIDES

In the Introduction we explored the observation of different research groups that aziridines suffer ready carbon-carbon bond cleavage yielding azomethine ylides as intermediates. Several methods have been described in the literature for the synthesis of aziridines.[3] Among the methods described, thermal or photochemical decomposition of $\Delta^2$-1,2,3-triazolines (triazolines) presents the most employed one. Triazolines expel nitrogen under rather mild conditions. The synthetic potential of this reaction was recognised in the earliest studies[4] but useful procedures have only recently emerged. Triazolines can be synthesised in several ways[5] but the most common way is the azide olefin addition. Carrié and Texier[6,7] have made an extensive study of the addition of azides to activated olefins leading to triazolines.

Initially, to test the viability of Scheme 1, Strachan examined the synthesis of (8, P = $SiMe_3$, R = Me) since this should furnish the bicyclic ketone (6, P = $SiMe_3$, R = Me) in a single step. Although precedents exist for the addition of trimethylsilyl azide[8] (TMSA) to dipolarophiles, in this laboratory the azide failed to react with methyl acrylate even after protracted reaction times. A further comparison of the reactivity of TMSA toward cycloaddition with diethyl benzal-malonate was made since this compound is known[9] to react with phenyl azide[10] and therefore provided another comparison

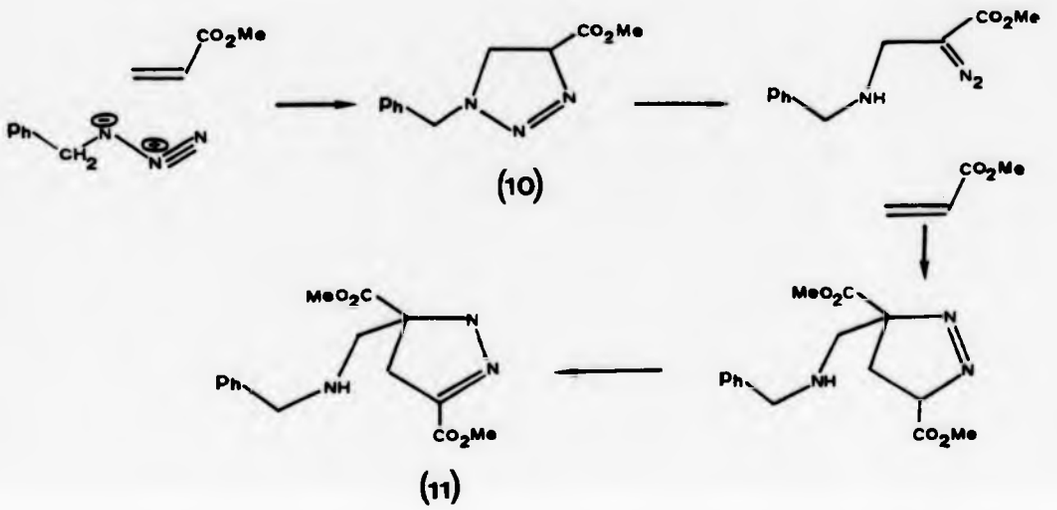
of the effect imposed upon the azide group by trimethylsilyl and phenyl substituents. The phenyl azide had produced the triazoline (9) while the TMSA was found to be unreactive as in a previous case.




(9)

It was considered that 1-benzyl-2-alkoxycarbonyl aziridine (8, P = $CH_2Ph$, R = Me) should serve as a convenient source of the azomethine ylide (7, P = $CH_2Ph$, R = Me) in that the benzyl group should activate the benzyl azide in [3 + 2] cycloaddition reactions and in addition should easily be removed at a late stage of the synthesis.[11] Reaction with benzyl azide with methyl acrylate did not however, yield the expected triazoline (10); instead the $\Delta^2$-pyrazoline (11) was the only isolable product. Huisgen and coworkers[12] have previously noted the formation of $\Delta^2$-pyrazoline during the reaction of phenyl azide with methyl acrylate and it seems probable that $\Delta^2$-pyrazolines arise by the initial ring opening of a triazoline to form a diazo-ester which subsequently reacts with the second molecule of the dipolarophile (Scheme 2).

In view of these problems (8, P = $CH_2Ph$, R = Et) was prepared by an alternative route[13] in order to examine its reactivity in [3 + 2] cycloaddition reaction. On heating the aziridine and cyclopentenone in refluxing xylene, progressive

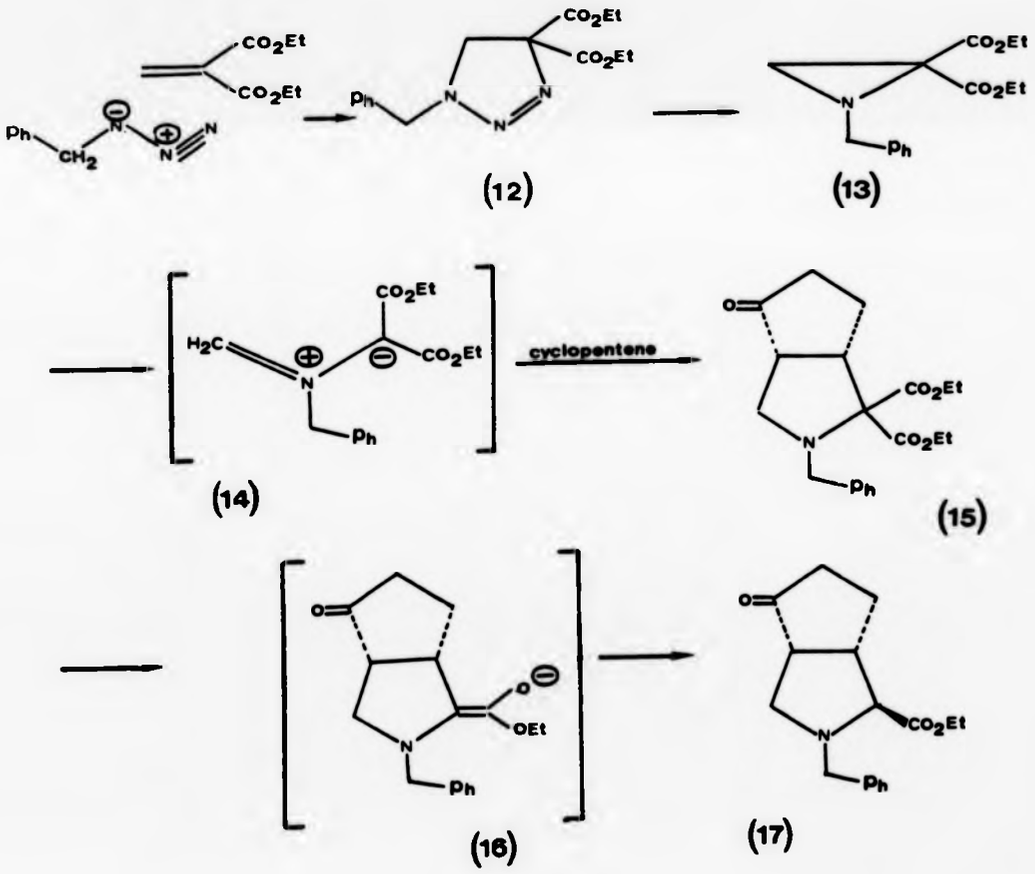



Scheme 2

decomposition of aziridine occurred but no cycloaddition of the azomethine ylide with the cyclopentenone was observed, and only unidentified polymeric products were formed. Similarly no cycloaddition product was obtained with maleic anhydride or diethyl maleate under identical reaction conditions.

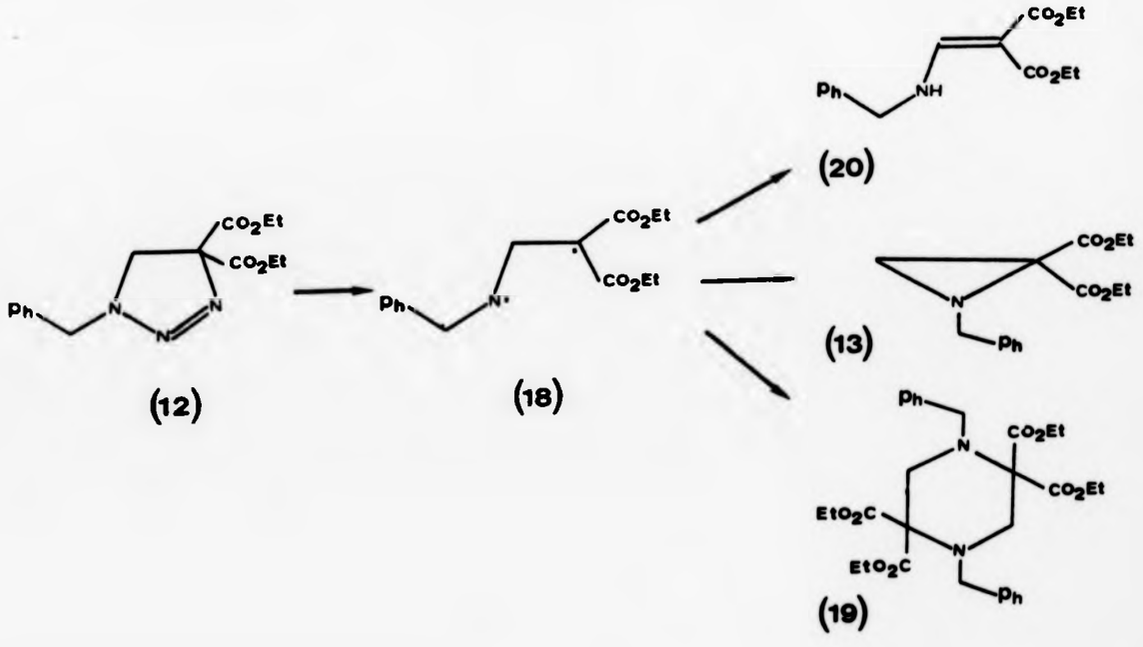
In order to reduce the amount of energy required to bring about aziridine ring fission it was thought that an additional ester group on the aziridine ring might aid in stabilising the azomethine ylide and bring about interconversion at lower temperatures. With this aim in mind aziridine (13) was synthesised as conceptually this molecule has additional advantages. Cycloaddition of the azomethine ylide (14) with cyclopentenone would be expected to furnish (15) with two ethoxy-carbonyl group adjacent to the ring nitrogen atom, and if

selectivity could be achieved in monodecarboxylation, then the correct stereochemistry at C-2, C-3 and C-4 in the target molecule would result. Molecular models of (15) indicate that there is steric congestion of the α-ethoxycarbonyl group and dealkoxycarbonylation using the NaCl/DMSO procedure[14] which proceeds by way of enolate (16) would expect to lead to the preferential formation of (17) (Scheme 3).




Scheme 3

In order to shorten the synthetic sequence it was decided to generate the azomethine ylide (14) *in situ* from the triazoline (12) which was reacted directly with cyclopentenone in refluxing toluene. A mixture of product was obtained, among them a bicyclic ketone (15) in an overall yield of 10%. The low yield and the complexity of the reaction did not offer a practical synthesis of (15) by this route. The low yield of cycloaddition product (15) was thought to be due to the side reactions occurring during the initial decomposition of the triazoline (12) to aziridine (13) and its subsequent ring opening. In addition to the cycloconversion it would appear that (12) is probably undergoing an initial decomposition to yield the diradical (18) which cyclises to aziridine (13), dimerises to piperazine (19) or undergoes hydrogen radical transfer to yield the enamine (20) (Scheme 4).

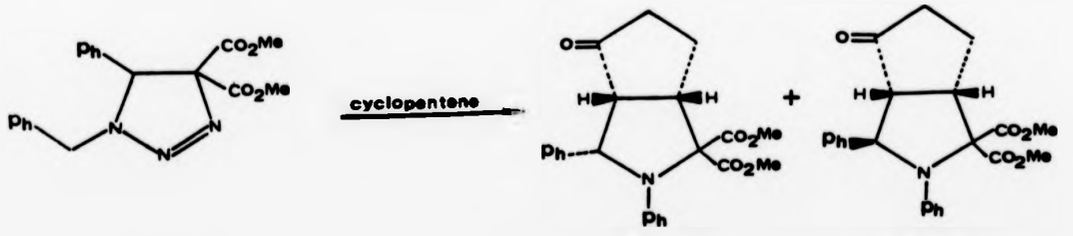



Scheme 4

With these competing pathways in operation, aziridine formation and subsequent ring opening to azomethine ylide would appear to be only a minor reaction pathway. Indeed when attempts were made to carry out cycloaddition reactions with strong dipolarophiles such as diethyl maleate, dimethyl fumarate and maleic anhydride the reaction appeared to follow a similar course with the production of the by-products in all reactions along with minor quantities of the expected cycloaddition product.

The reactivity of the known triazoline (21) has also been examined since the reactivity of this compound is well established.[15-17]

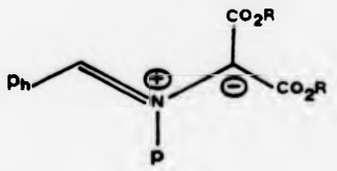
Thus treatment of triazoline (21) with cyclopentenone in refluxing toluene resulted in the formation of the cyclo-addition products (22) and (23) in yield of 13.3% and 1.7%. When the reaction was carried out without solvent in an excess of cyclopentenone, the overall yield was increased to 44%.




(21) (22) (23)

The essential reason for the failure of the cyclo-addition to give significant yields of the bicyclic pyrrolidine is believed to be due to the instability of the azomethine ylide (7). In most of the observed reactions described in the

literature the ylide is stabilised by a phenyl substituent i.e.



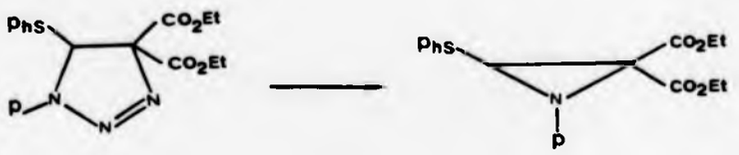

However this inevitably results in the formation of the phenyl substituted pyrrolidines and would necessitate the selective removal of a phenyl group from the reaction product - not an easy task.

Ideally, if we wish to stabilise the ylide, a substituent with some electron donating properties should be used. In addition once it has served its function it should be (a) easily removable, (b) have the possibility of being used as a handle with which to carry out functional manipulations.

The S-phenyl or S-alkyl group should serve all these requirements in that reductive removal with Raney-nickel or nickel boride should generate the pyrrolidine. Oxidative removal will provide the possibility of producing unsaturated pyrrolidines (enamines) derivatives with their attendant reactivity and addition of carbenoids might open up an area of sulphur ylide chemistry.

## 2.1 Triazoline synthesis

Considering the previous work we decided to synthesise a series of triazolines and to investigate their reactivity toward dipolarophiles in [3 + 2] cycloaddition reaction.

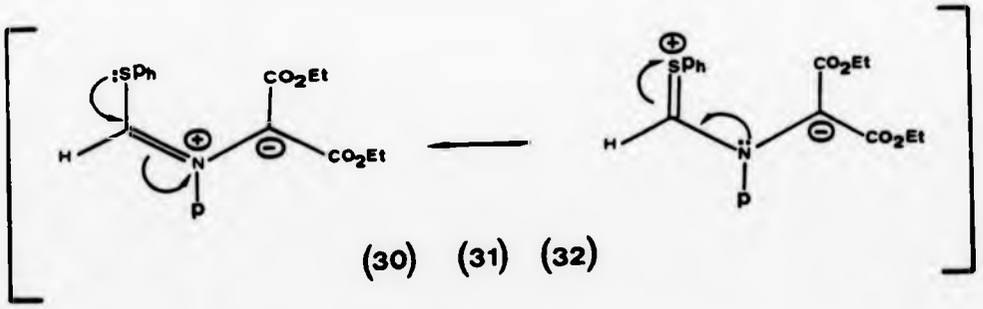


(24) p = $-CH_2-C_6H_4-OCH_3-p$ (27)

(25) p = $-CH_2-C_6H_5$ (28)

(26) p = $-C_6H_5$ (29)

Triazolines (24), (25) and (26) have the SPh substituent at position 5 and therefore are expected to yield aziridines (27), (28) and (29) on heating. Carbon-carbon bond cleavage of aziridines should generate azomethine ylides (30), (31) and (32) respectively (Scheme 5).



(30) (31) (32)

Scheme 5

Those azomethine ylides are stabilised by the "electron push" character of the sulphur atom. In addition the nitrogen atom in triazolines (24) and (25) is protected with p-methoxy benzyl or benzyl group both of them having

a strong activating effect on the corresponding azides during triazoline formation. Their removal at a late stage of the synthesis should not present a problem. p-Methoxy benzyl protecting group is easily cleaved with HCl while the benzyl group could be cleaved by hydrogenolysis liberating the free amine.

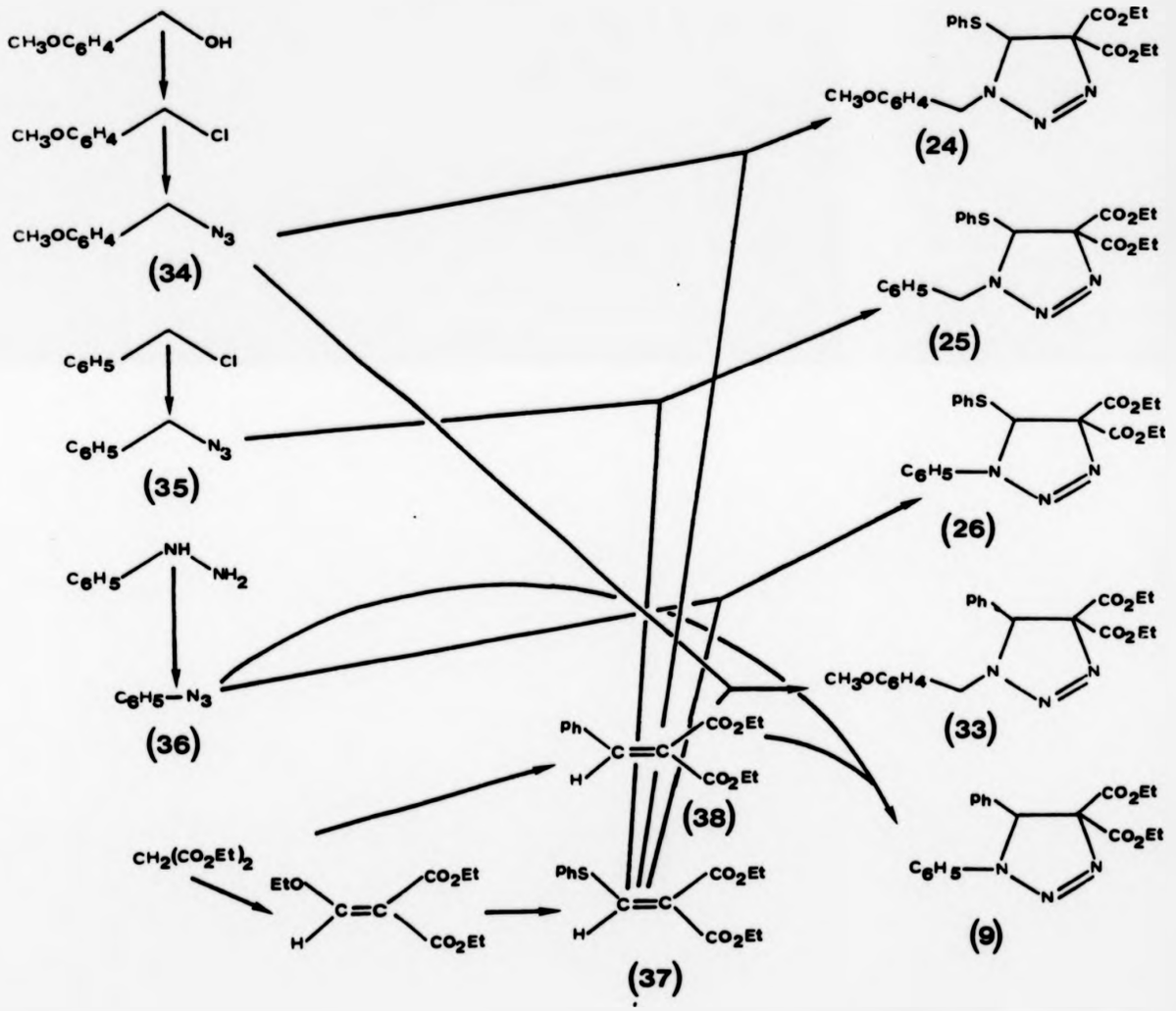
In addition it was decided to synthesise triazolines (9) and (33). Those triazolines do not have suitable substituents at positions 1 and 5 but their reactivity is known, and it is useful to have compounds of known reactivity to compare with new triazolines.

Scheme 6 presents the way how azides (34), (35) and (36) and olefins (37) and (38) were synthesised and the possible combinations of azide and olefin to afford triazolines (9), (24), (25), (26) and (33).

Reaction conditions have been described by Texier and Carrié[6,7] and have been applied in our Scheme. The azide was allowed to react with an equimolar amount of olefin at 60°C for 3 to 4 weeks, without solvent, protected against moisture. The reaction mixture was cooled to room temperature and triazolines crystallised upon the addition of methanol.

In this way, triazolines (33) and (9) were isolated as white crystalline products having a pleasant odour, in a high yield. Triazoline (24) was isolated in poor yield while triazolines (25) and (26) could not be detected in a reaction mixture even after the extended reaction time of eight weeks.

Triazolines (9), (24) and (33) were identified on the


CH3OC6H4OH
CH3OC6H4Cl
CH3OC6H4N3
(34)
C6H5Cl
C6H5N3
(35)
C6H5NHNH2
C6H5N3
(36)
CH2(CO2Et)2
EtO
CO2Et
CO2Et
H
PhS
CO2Et
CO2Et
H
(37)
Ph
CO2Et
CO2Et
H
(38)
PhS
CO2Et
CO2Et
CH3OC6H4
(24)
PhS
CO2Et
CO2Et
C6H5
(25)
PhS
CO2Et
CO2Et
C6H5
(26)
Ph
CO2Et
CO2Et
CH3OC6H4
(33)
Ph
CO2Et
CO2Et
C6H5
(9)

Scheme 6

basis of their spectral (proton n.m.r., i.r. and accurate mass measurement) and microanalytical data. They all show the characteristic $M^+-N_2$ ion in the mass spectrum which is expected for triazolines; ionisation in the mass spectrophotometer occurs at elevated temperature. More informative is the proton n.m.r. spectra of those triazolines. Hydrogen attached to the triazoline ring at position 5 gives a singlet at $\delta$ 5.40, 5.05 and 5.90 for (24), (33) and (9) respectively. The presence of triazoline ring disturbs the magnetic equivalence of benzylic protons in (24) and (33). The result is their mutual coupling and the signal is an AB quartet. The proton n.m.r. spectra of (24) and (33)/(9) differs considerably in the chemical shift of the triplet of the methyl protons belonging to the ethyl ester group. In the spectrum of (24) this group is observed as one triplet, in the spectrum of (33)/(9) two distinct triplets appear. This is probably due to the shielding effect of the phenyl substituent, which is observed in the case of (33)/(9) because of the proximity of this substituent to the two ethyl ester groups.

During the work-up procedure of the reaction mixture of triazoline (24) a small amount of another product was isolated. The structure of this compound was elucidated on a basis of spectral and microanalytical data. From the i.r. spectra we concluded that the secondary amino group was present and that two carbonyl groups are present, one of them being an ethyl ester carbonyl. The proton n.m.r. spectra was the most informative (Figure 2).

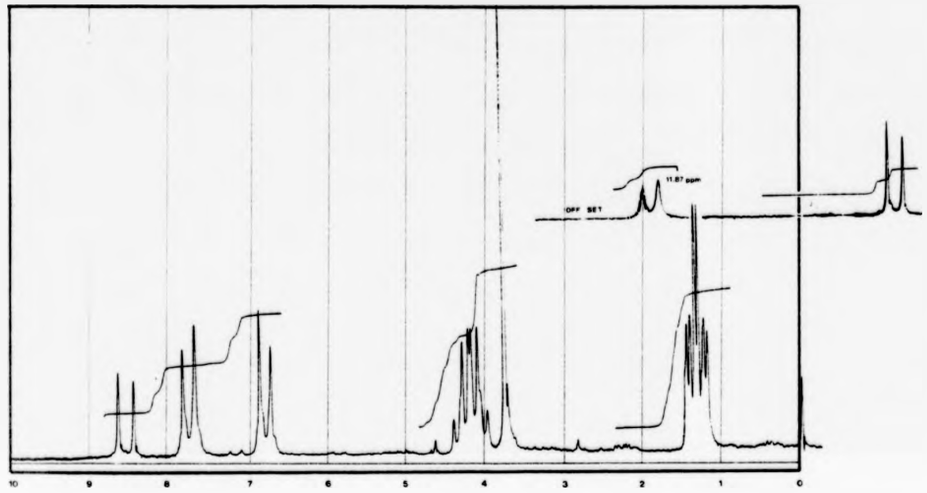
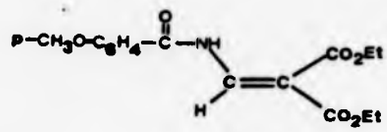
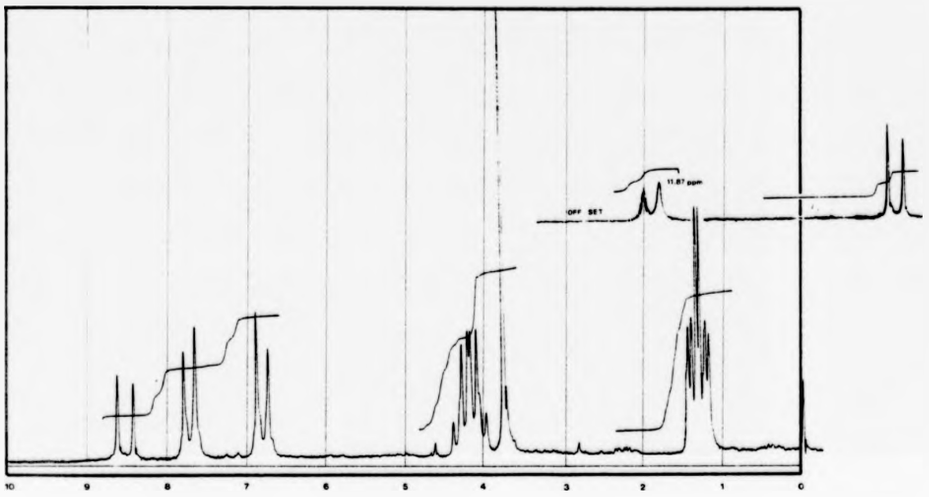


Figure 2

The analysis of this spectrum indicated the presence of a -NH-CH= group, the presence of two ethyl ester groups and the presence of p-methoxy phenyl group. We observed the absence of SPh group as well as the absence of two benzylic protons. Accurate mass measurement gave the molecular ion $M^+$ 321.1218; this along with the microanalysis supports a molecular formula of $C_{16}H_{19}NO_6$. On the basis of these considerations we concluded that the structure of this compound must be (39):



(39)



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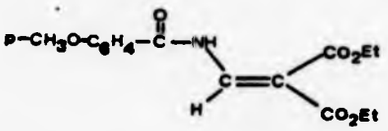
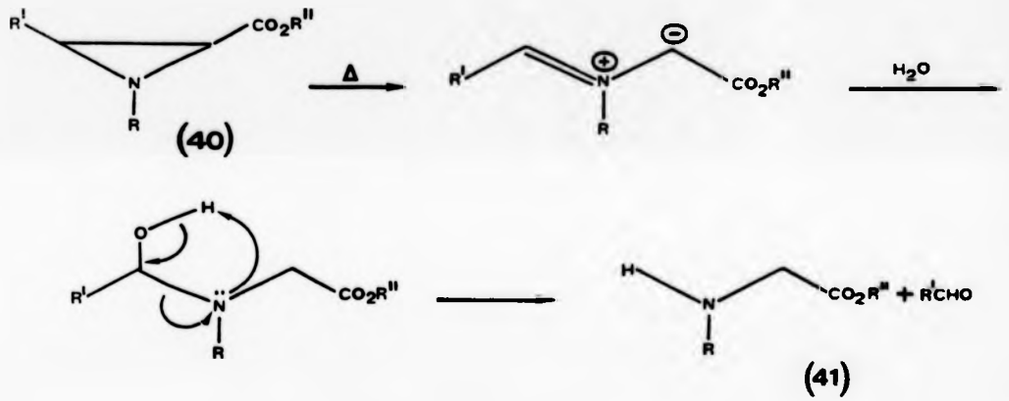


(39)

The following known observations lead us to propose the mechanism for the formation of (39).

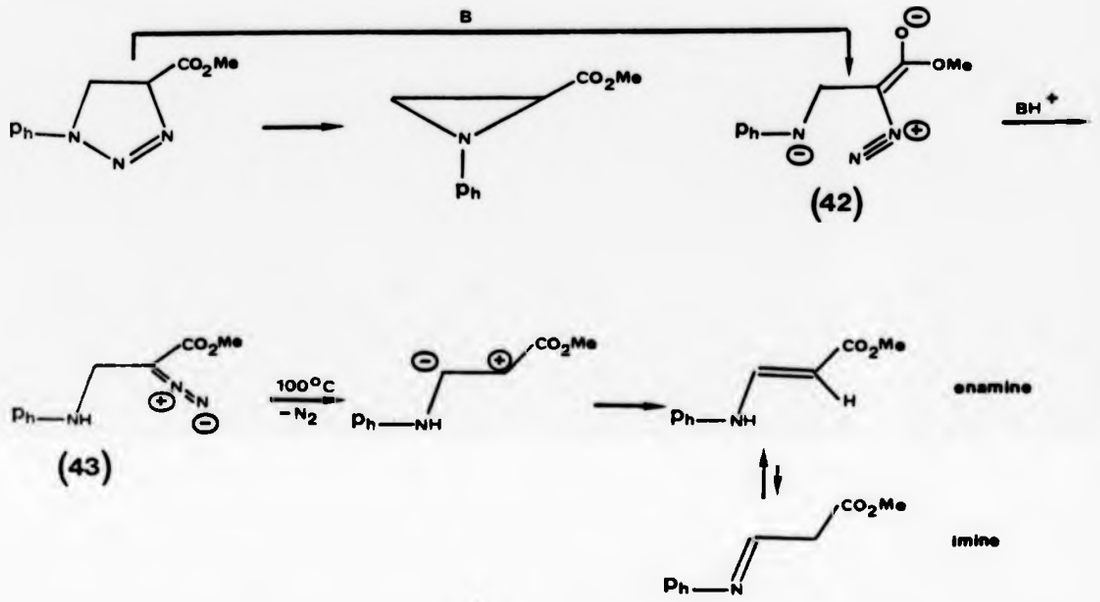
(1) It is known that aziridines (e.g. 40) are hydrolysed to aldehydes and N-substituted amino-esters (41) in the presence of water.[7] The presence of atmospheric moisture is sufficient to hydrolyse aziridines. The proposed mechanism for this transformation is shown in Scheme 7.



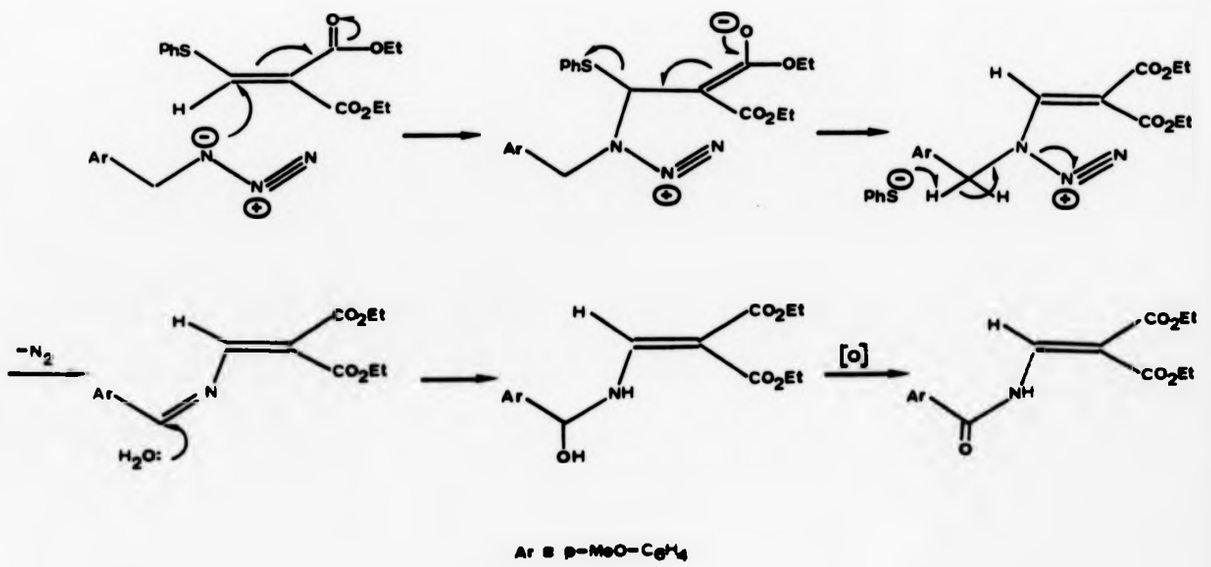

Scheme 7

(2) It has also been observed in a number of cases that during the thermal decomposition of triazolines a mixture of aziridine and imine was obtained.[12] The ratio aziridine:imine was dependent on reaction conditions and substituents of the triazoline at position 1, 4 and 5 (Scheme 8).

On the basis of those observations we propose a mechanism for the formation of (39) (Scheme 9). We cannot support a mechanism analogous to the one outlined in Scheme 8, which proceeds via triazoline formation. In all examples cited




Scheme 8



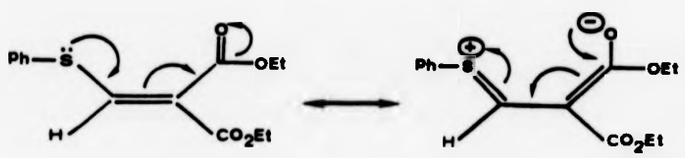

Scheme 9

in the literature where imines or their tautomeric enamines are obtained from thermal decomposition of triazolines, the triazoline has at least one hydrogen atom at position 4. Triazoline (24) has two ethoxycarbonyl groups at position 4, therefore structures (42) and (43) are not possible intermediates.

We can also conclude that aziridine formation did not take place as neither the p-methoxy benzaldehyde nor the substituted amino acid ester were obtained, as a result of aziridine hydrolysis.

The poor yield of triazoline (24) and the absence of reactivity of olefin (37) with azides (35) and (36) forced us to consider an alternative method for the synthesis of triazolines.

In the cycloaddition reaction olefin-azide the olefinic double bond must exhibit high electrophilic character. This might be achieved with electron withdrawing substituents which are able to delocalise the electron density around the double bond. We think that the lack of reactivity of olefin (37) in cycloaddition with azides arose from the fact that the free electron pair on sulphur is in conjugation with the double bond thus increasing the electron density around it (Scheme 10).




Scheme 10

To divert the role of sulphur, and to make it electron attractor instead of being electron donor we thought that oxidising it to the sulphoxide might reduce the electron density at the double bond, making it more electron deficient and therefore more reactive. The sulphide might be regenerated by any of the several possible reductive procedures at a late stage of the synthesis. Sulphides are generally easily oxidised to sulphoxides[19] but in our hands sulphide (37) could not be oxidised. Several oxidants were used: sodium metaperiodate at 0°C, methanol-$H_2O_2$ mixture, m-chloroperbenzoic acid in dichloromethane and $H_2O_2$ in acetone but all those attempts failed to give the desired sulphoxide.

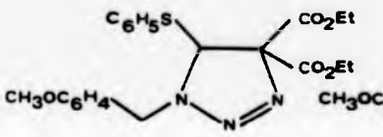
## 2.2 A Study of Triazoline thermolysis

Once the triazolines (9), (24) and (33) were synthesised and fully characterised we decided to investigate their behaviour upon thermal decomposition. In the case where thermal decomposition occurs the intermediate aziridine was not isolated, it was allowed to react in the presence of dipolarophile to produce pyrrolidine. Activated olefins were used in a first series of tests and cyclopentenone and cyclohexenone in a second series.

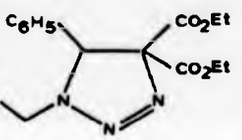
The reaction conditions for thermal decomposition and subsequent 1,3-dipolar cycloaddition were as follows, 0.25M solution of triazoline in a suitable solvent, heated to reflux for 12, 24 and 48 hours in the presence of an equimolar amount of dipolarophile in the atmosphere of an inert gas. A standard work up procedure was employed: evaporation of the solvent, was followed by crystallisation or purification by column

chromatography.

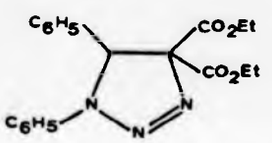
The reaction was carried out at different temperatures: at a temperature of refluxing benzene, toluene and xylene and in the presence of different dipolarophiles: dimethyl acetylene-dicarboxylate, maleic anhydride, dimethyl fumarate, isopropenyl acetate, and methoxy methylenemalonate. All those experiments are summarised in Table 1.




(24)




(33)




(9)

| | Solvent | | |
|---|---|---|---|
| Olefin | Benzene | Toluene | Xylene |
| dimethyl acetylene dicarboxylate | (33) | (24),(33) | (24),(33) |
| maleic anhydride | (33) | (24),(33) | (24),(33) |
| dimethyl fumarate | (33) | (24),(33),(9) | (24),(33) |
| isopropenyl acetate | (33) | (33) | (33) |
| methoxy methylene malonate | (33) | (33) | (33) |

* vertical entry - numbers in the Table 1 correspond to triazolines in a stated solvent.

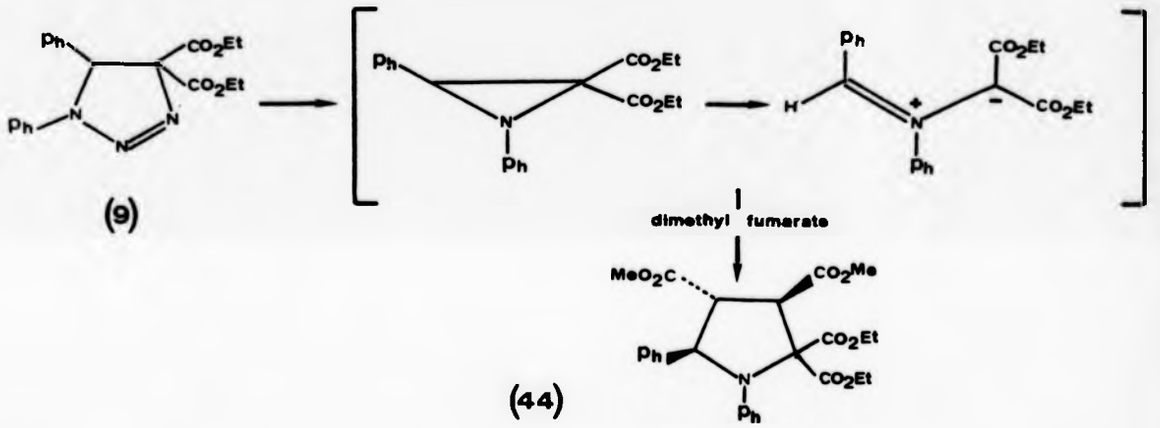
* horizontal entry - suitable dipolarophile

Table 1

Thermolysis of triazolines (24) and (33) under the conditions described above in a combination of different

solvents and dipolarophiles did not give either the cycloadduct nor the aziridine. In all cases triazoline and the dipolarophile were recovered unchanged.

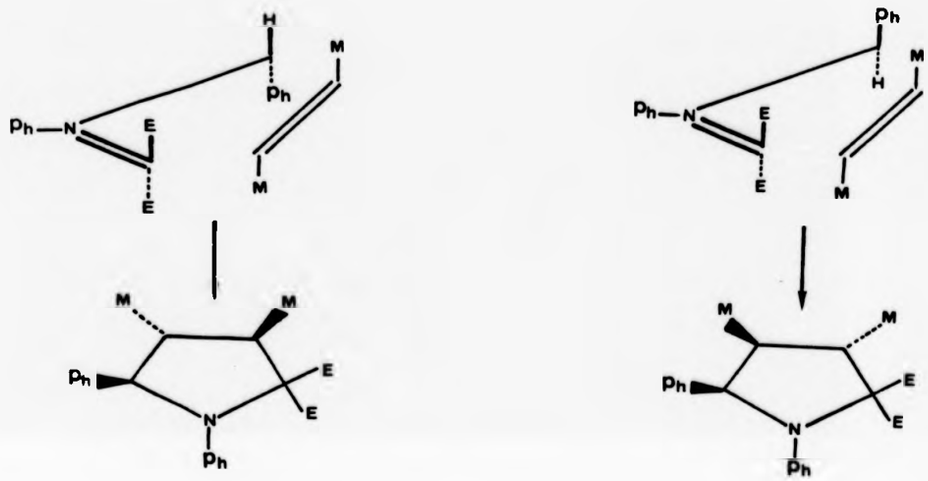
Triazoline (9) gave the expected cycloadduct (44) with dimethyl fumarate:




As a result of two different orientations by which the dipolarophile can approach the ylide a mixture of isomers (44) and (45) could result (Scheme 11).

It is obvious that the isomer (44) should predominate. The methyl ester group and C-4 and the bulky phenyl group at C-5 are <u>trans</u> while in (45) those two groups would be <u>cis</u> which would result in a strong Van der Waals repulsion in the transition state and make this orientation of addition less likely. Those observations have been confirmed by the analysis of proton n.m.r. spectra. Only the presence of one isomer, which we suppose to be (44) was observed.

As we could not achieve the thermal decomposition of




(44) (45)

M = $CO_2Me$

E = $CO_2Et$

Scheme 11

triazolines (24) and (33) we decided to modify the reaction conditions. As nitrogen should be liberated during the thermolysis we thought that if the reaction were to be performed in argon atmosphere instead of nitrogen it might bring the equilibrium to the side of aziridine formation. A series of experiments has been carried out under argon atmosphere. No positive results could be obtained.

Next, we envigased the possibility to use the catalyst able to coordinate with nitrogen.

A first series of tests was carried out using Vaska's catalyst.[20] This homogenous metal-catalyst is used for

hydrogenation of alkenes. Under an atmosphere of hydrogen $IrCl(CO)(PPh_3)_2$ forms a dihydride. Hydrogenation of a substrate S requires coordination with $IrCl(CO)(PPh_3)_2$ as in equations (1-4).

Eq.1. $IrCl(CO)(PPh_3)_2 + S \longrightarrow IrCl(CO)(PPh_3)_2S$

Eq.2. $IrCl(CO)(PPh_3)_2S \longrightarrow IrCl(CO)(PPh_3)S + PPh_3$

Eq.3. $IrCl(CO)(PPh_3)S + H_2 \longrightarrow IrCl(CO)(PPh_3)SH_2$

Eq.4. $IrCl(CO)(PPh_3)SH_2 \longrightarrow IrCl(CO)(PPh_3) + SH_2$

Vaska's catalyst is known to coordinate with dinitrogen ($N_2$) and we thought that on the basis of this principle this catalyst could coordinate with triazoline nitrogen, yielding nitrogen coordinated Vaska's catalyst and the aziridine. An experiment was carried out using a catalytic amount of this catalyst but no aziridine formation was observed.

The next series of experiments was carried out using $RuCl_3.3H_2O$ as catalyst in solvent of different polarity: ethanol, acetonitrile and THF. Ruthenium salts are known to form complexes with nitrogen, but as in the previous case no positive results were obtained.

Such a stability of triazolines (24)/(33) on one side and the reactivity of triazoline (9) on the other could only be explained on the basis of the differences in the inductive effect of the substituent at position 1.

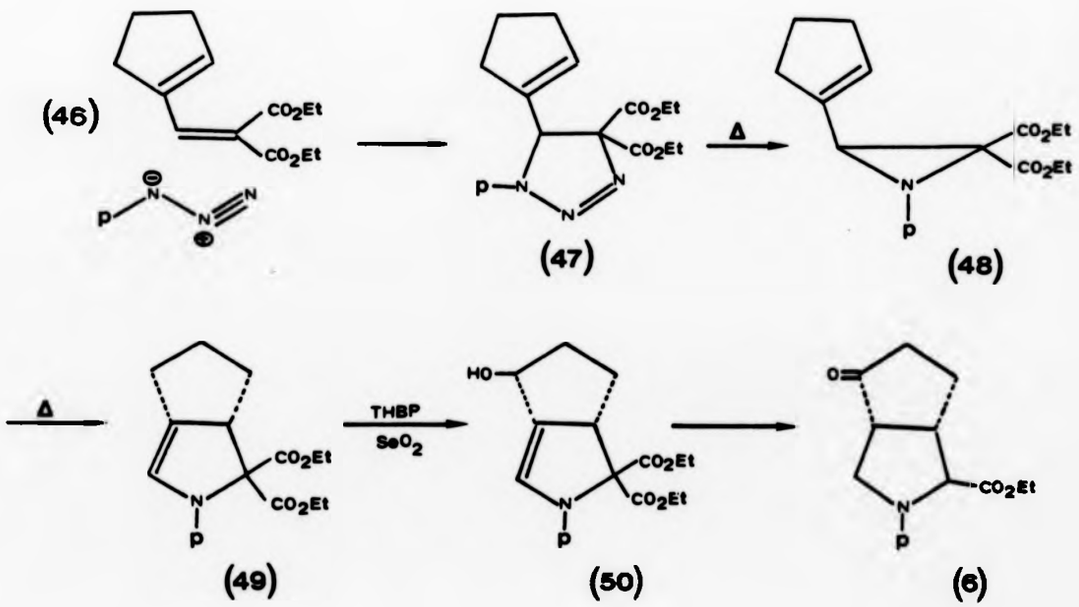
In the case of triazoline (9) the phenyl group with its electron attracting effect induces $N_1$-$N_2$ bond fission. p-Methoxy benzyl group has the opposite effect, it increases

the electron density of triazoline ring making it more stable and resistant to nitrogen elimination.

## 2.3 Pyrrolidines via intramolecular 1,3-dipolar cycloaddition reaction

Recent reviews and publications by Padwa[21,22] and Oppolzer[23] suggested that pyrrolidines may be synthesised by an alternative route. In fact, the intramolecular cycloaddition reaction of a properly functionalised 1,3-dipole represents a general method for the synthesis of fused heterocycles.

The strategy adopted is shown in Scheme 12.



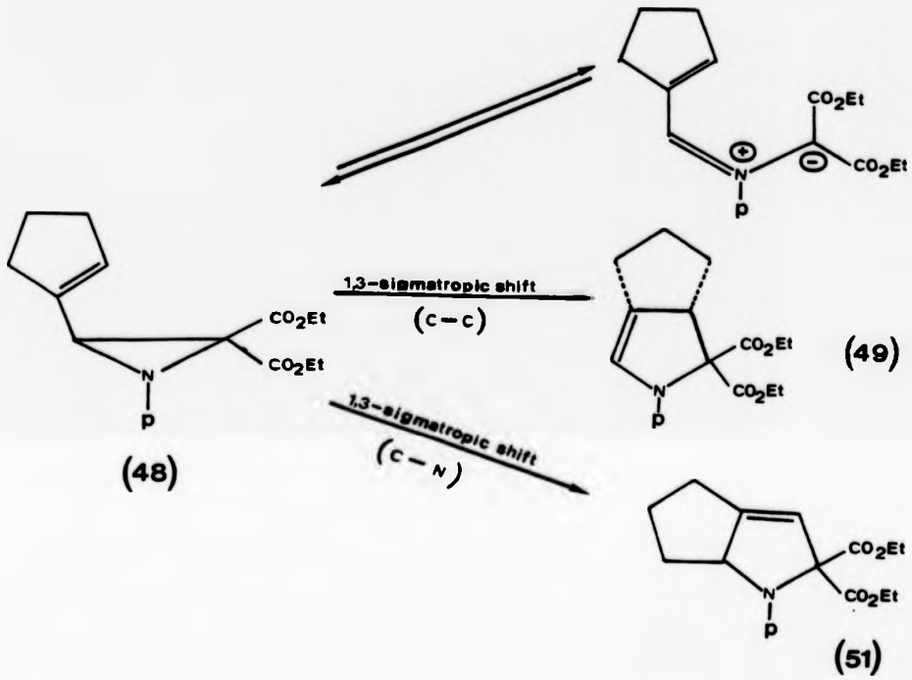

Scheme 12

It was thought that this route might have more chance of success that the intermolecular traizoline formation. The close proximity of cyclopentenyl double bond is in favour of this hypothesis. However compound (48) is also set up for vinyl cyclopropane-cyclopentene conversion. This is a special case of (1,3) sigmatropic migration of carbon, and can also be considered as internal ($\pi^2 + \sigma^2$) cycloaddition reaction. The reaction has been carried out with many vinyl cyclopropanes bearing various substituents on the ring or on the vinyl group.[24] Various heterocyclic analogs are also known.[25,26]

Two 1,3-sigmatropic rearrangements are possible for compound (48) by either the migration of C-C bond to form (49) or C-N bond to give compound (51) (Scheme 13). It is known that 1,3-sigmatropic shifts have high activation energies and therefore require elevated temperatures in order to proceed.[27] It was hoped that gem-diester substituents on (48) would either encourage azomethine ylide formation, or lower the activation energy for C-C bond migration to take place. In either case compound (49) would be formed.

Intramolecular 1,3-dipolar cycloaddition of this type, between an aziridine and an olefin was not been reported in the literature. Compound (46) is in principle derivable by a Knovenagel condensation of cyclopenten-carboxaldehyde and diethyl malonate. A number of unsuccessful attempts were made by Strachan to prepare (46). Using the procedure of Lehnert[28] with $TiCl_4$ as catalyst compound (46) was prepared in high yield.

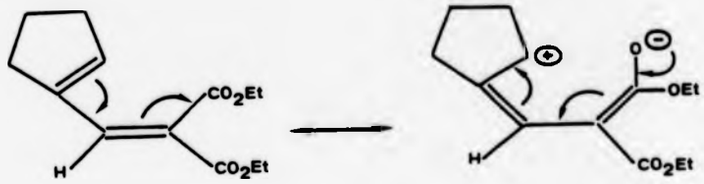
Having had some experience with the stability and the reactivity of triazolines we decided to synthesise (47, P = p-MeO-$C_6H_4$-$CH_2$ and P = $C_6H_5$).




Scheme 13

An equimolar amount of olefin (46) and azide ($p\text{-MeO-}C_6H_4CH_2N_3/C_6H_5N_3$) were allowed to react at 60°C protected against moisture, by a so-called "Christmas Reaction"; this term has been employed for the first time in this laboratory to designate particularly long reactions. They should be set up before Christmas holidays and worked up after holidays (Santa Claus is supposed to bring the reaction products). After several weeks, t.l.c. of the reaction mixture indicated only the presence of starting materials. We believe that the lack of reactivity of (46) toward cycloaddition with azides arose

from the fact that cyclopentenyl double bond is in conjugation with the exocyclic double bond and therefore the addition rate is much slower.




At this stage a conceptually different approach to azomethine ylide synthesis was considered.

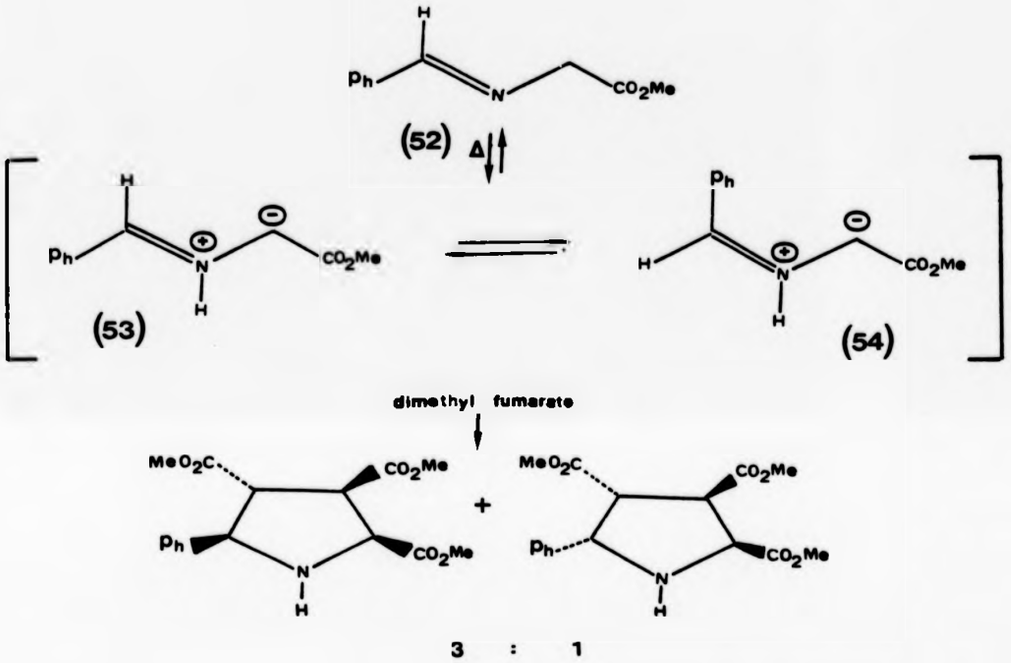
3. AZOMETHINE YLIDES FROM IMIDATES

In the Introduction (Chapter 2.4) was discussed the work of Grigg's research group from the Queen's University of Belfast. Grigg[29] has studied the reactions of imines, particularly those derived from α-aminoacid esters, and he found that they undergo a wide range of 1,3-dipolar cycloaddition reaction on heating in a non-polar solvent in the presence of dipolarophiles, yielding pyrrolidine derivatives (Scheme 14).

The scope of the reaction points to a 1,3-dipolar cycloaddition reaction involving a prototopic equilibrium of the imine (52) with its 1,3-dipolar isomer, the azomethine ylide (53). The regioselectivity of the reaction is explained on the basis of stereomutation (53 ⟹ 54).

On the basis of Grigg's results we considered a novel approach to azomethine ylide.

The parent amino acid derivative of "Grigg's imine"




Scheme 14

(52), which has all necessary substituents for the synthesis of kainic acid is presented in Figure 3.

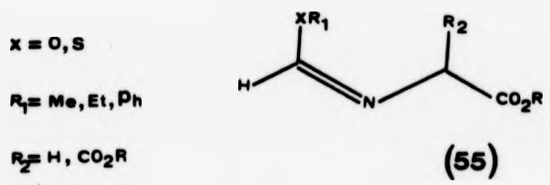
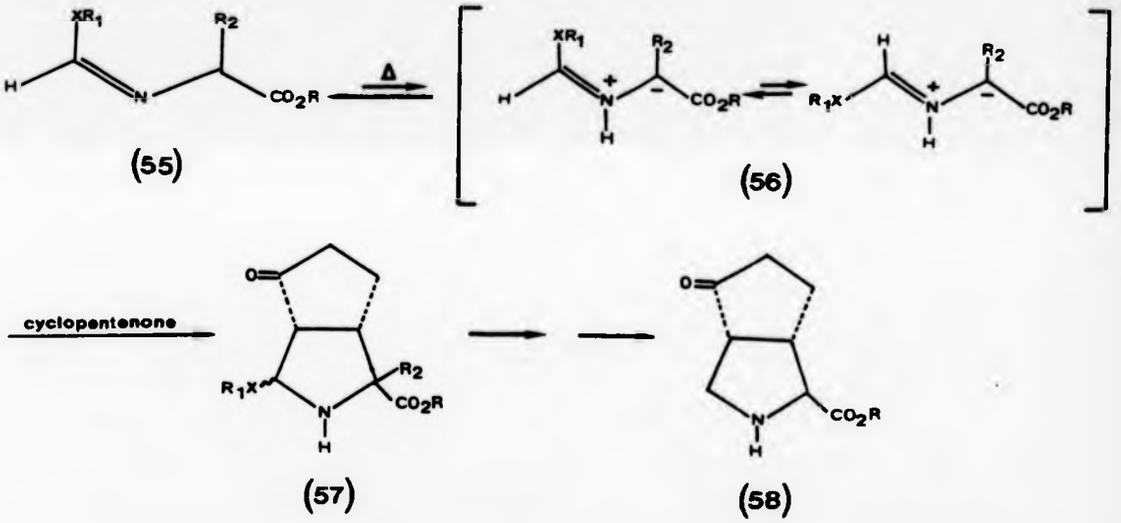



Figure 3

It is believed that such a compound, under the reaction conditions described by Grigg should be in equilibrium with its tautomer, the azomethine ylide (56). In principle such an ylide should undergo a 1,3-dipolar cycloaddition with cyclopentenone, yielding the bicyclic pyrrolidine (57), a key intermediate in our synthesis of kainic acid analogues (Scheme 15).

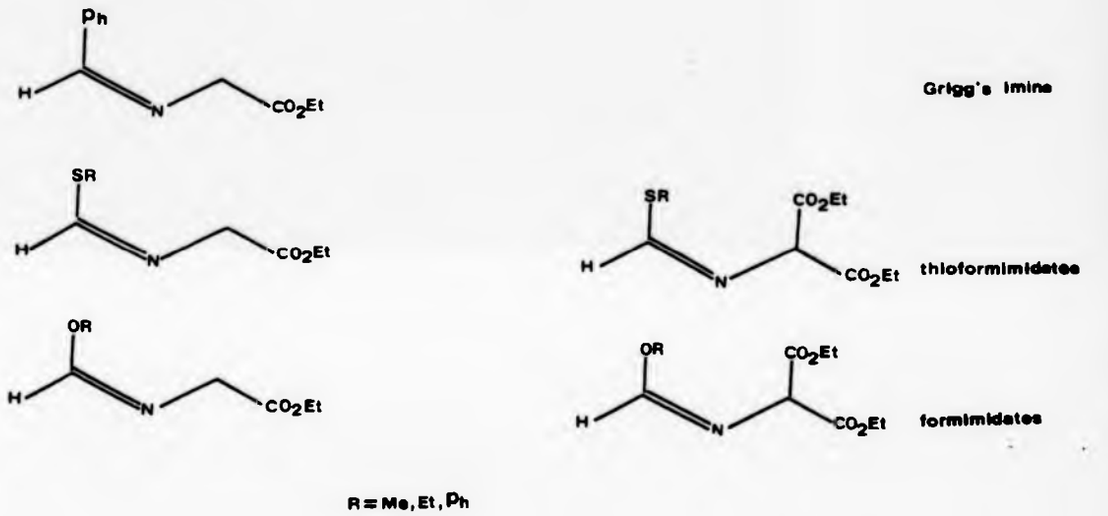



Scheme 15

It was observed by Grigg that the equilibrium (55 ⇌ 56) is dependent on the $pK_a$ of the methine proton. Two geminal ester groups will make such a proton very acidic and therefore induce the ylide formation. $XR_1$ (X being O or S and $R_1$ alkyl or phenyl) should in principle stabilise the ylide.

A synthesis of several thioformimidates and formimidates was undertaken. Benzylidene glycine ethyl ester, the

"Grigg's imine" was also synthesised, because its reactivity is known and it is useful to have compounds of known reactivity for comparison. Two series of imidates were synthesised, one derived from glycine ethyl ester and the other from malonic acid diethyl ester (Scheme 16).



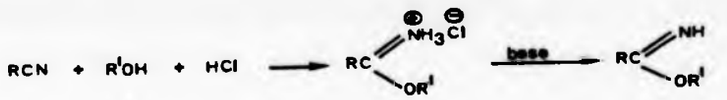

Scheme 16

Thioformimidates are extremely smelly compounds, and their strong unpleasant smell can be described as a mixture of the odour of garlic and sauerkraut and particular safety measures in their handling must be taken; for this reason all the preliminary work was carried out using formimidates. The series of imidates and thioimidates derived from glycine ethyl ester is much easier to handle. Their boiling points are much lower than in the case of imidates derived from diethyl aminomalonate, therefore they could be purified by distillation, thus avoiding column chromatography and the contact with silica

gel which could result in imidate hydrolysis. In addition the proton n.m.r. spectra are simplified thus making their analysis easier.

3.1 Synthesis of imidates

Imidates can be synthesised in several ways. The pioneering work of Pinner in this field is recognised in the naming of the reaction as the Pinner synthesis. It involves a reaction of a nitrile with an alcohol, phenol or thiol under acid conditions[30,31] (Scheme 17).




Scheme 17

The free imidate is liberated by the action of a base. We require formimidates, which would involve the use of hydrogen cyanide. This route was avoided.

Another useful method for the synthesis of imidates is the reaction of nitriles with alcohols under basic conditions[32] (Scheme 18).


Scheme 18

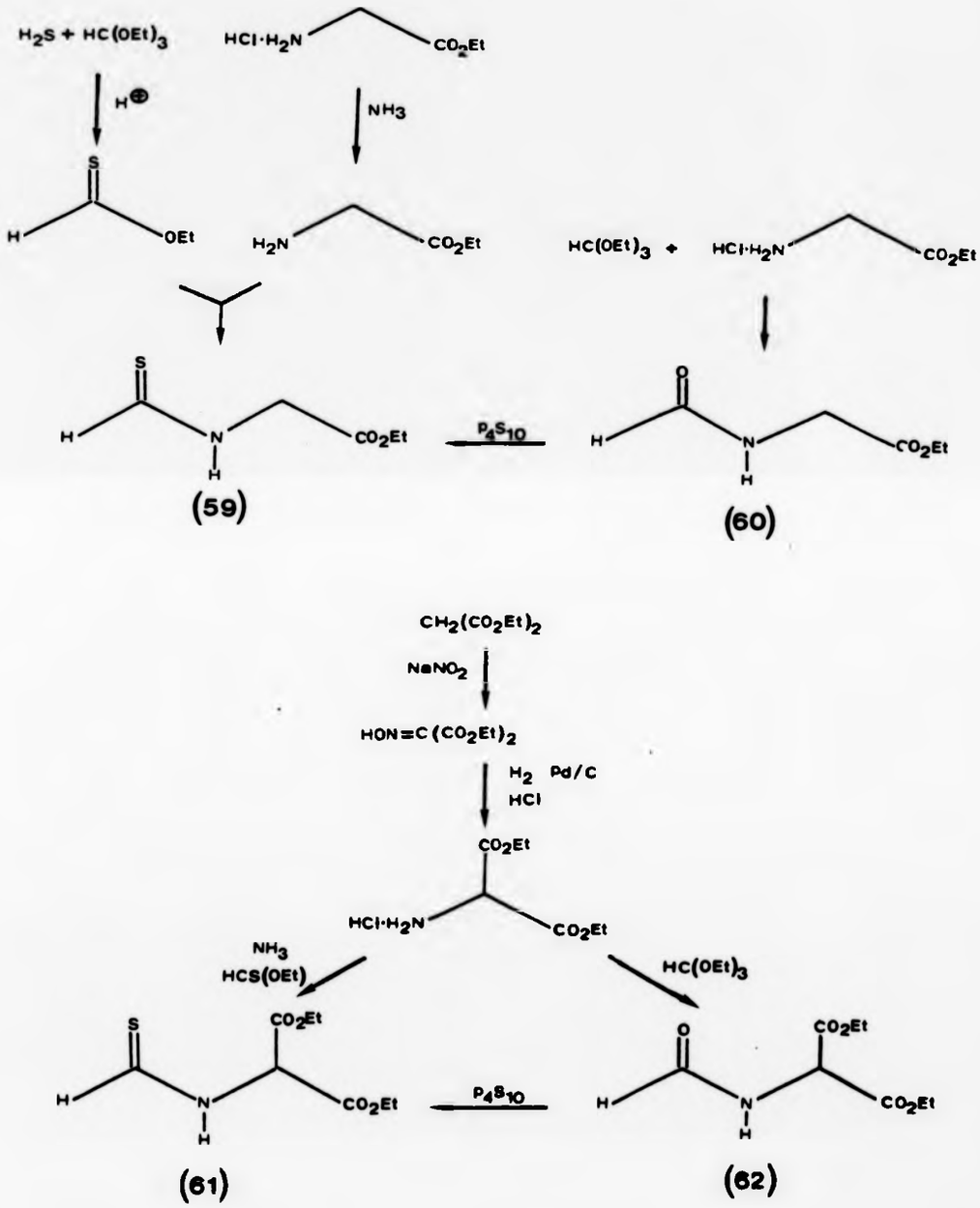
The importance of this base-catalysed reaction lies in the fact that it complements the Pinner acid catalysed synthesis. The presence of moisture is not a great drawback in this reaction as the product is isolated in the form of free imidate which is less sensitive to hydrolysis than the corresponding salt. The reaction suffers from the limitation that the nitrile should have powerful electron withdrawing substituents.

The method that we found the most convenient for the synthesis of imidates is the conversion of amides and thioamides into corresponding imidates.

The synthesis of formamides (60)/(62) and thioformamides (59)/(61) was undertaken (Scheme 19).

Amides, N-formyl glycine ethyl ester (60) and N-formyl methylene malonate diethyl ester (62) were synthesised in high yield when the hydrochloride salt of the amine acid ester was heated (100°C) in the presence of an excess of triethyl orthoformate.

Ethyl thioformate, the reagent needed for the synthesis of thioamides (59) and (61) was synthesised from triethylorthoformate and hydrogen sulphide in the presence of acid, according to the literature procedure.[33] The highest yield obtained in this way (several attempts have been made to improve the yield) was very close to the yield that the authors of the procedure reported which is only 20%. The reason for such a poor yield is probably due to the fact that ethyl thioformate (b.p. 86-88°C) distils as an azeotropic mixture with the solvent (ether) during the work up procedure. Instead of ether as a solvent used for


H2S + HC(OEt)3
HCl·H2N
CO2Et
H⊕
NH3
S
H
OEt
H2N
CO2Et
HC(OEt)3 +
HCl·H2N
CO2Et
S
H
N
H
CO2Et
P4S10
O
H
N
H
CO2Et
(59)
(60)
CH2(CO2Et)2
NaNO2
HON=C(CO2Et)2
H2
Pd/C
HCl
CO2Et
HCl·H2N
CO2Et
NH3
HCS(OEt)
HC(OEt)3
S
CO2Et
H
N
H
CO2Et
P4S10
O
CO2Et
H
N
H
CO2Et
(61)
(62)

Scheme 19

the extraction of ethyl thioformate from the reaction mixture we decided to use chloroform. Ethyl thioformate was used as a chloroform solution in the next step. The yield and the concentration of ethyl thioformate was calculated from the integral ratio of the formate and the chloroform proton in the proton n.m.r. spectrum. Considerable improvement of the yield was observed (70%). Thioamides (59) and (61) were synthesised in a reaction of a free amino acid ester, liberated from the corresponding salt by the action of ammonia and ethyl thioformate in chloroform. An alternative way to thioamides (59) and (61), which was discovered at a later stage of our research, was by heating to reflux in benzene the corresponding amide (60)/(62) with phosphorous pentasulphide. In this way the use of highly toxic hydrogen sulphide was avoided.

Imidates (60)/(62) and thioimidates (59)/(61) were identified on the basis of their spectral analysis (i.r., proton n.m.r. and accurate mass measurement). The most informative was the proton n.m.r. spectrum. The position of the signals of protons for those compounds is summarised in Table 2.

| | Proton Resonances | | | | |
|---|---|---|---|---|---|
| Compound | Formate | NH | Methylene | $CH_2$-$CH_3$ | $CH_2$-$CH_3$ |
| (59) | 9.25 (s) | 8.07 (s,b) | 4.45 (s) | 4.25 (q) | 1.30 (t) |
| (61) | 9.60 (s) | 9.00 (s,b) | 5.65 (d) | 4.35 (q) | 1.35 (t) |
| (60) | 8.20 (s) | 7.45 (s,b) | 4.02 (d) | 4.20 (q) | 1.25 (t) |
| (62) | 8.25 (s) | 7.30 (s,b) | 5.25 (d) | 4.30 (q) | 1.35 (t) |

Table 1

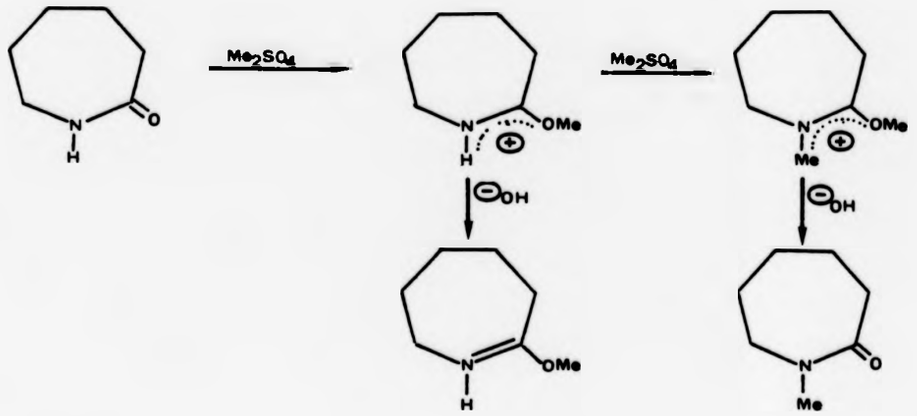
The next step in the synthesis of azomethine ylide precursor is the conversion of amides into the corresponding

imidates. This apparently simple conversion which is well documented and has been reviewed[34] was shown to be extremely difficult in the case of amides (60)/(62) and thioamides (59)/(62). Several methods have been tried to achieve this goal.

(a) Thioamides, in principle, can be alkylated directly at sulphur with alkyl halides; amides do not normally undergo similar attack at oxygen.[30,35,36] An attempt was made to convert thioformamide (59) into the corresponding thioformimidate with methyl iodide in acetone in the presence of anhydrous potassium carbonate as the scavenging agent for the hydroiodic acid liberated during the reaction. The first difficulty that we faced was to separate potassium carbonate from the reaction mixture; its solubility in acetone is considerable. A complex mixture was obtained as a reaction product. The separation of reaction products by column chromatography was found to be extremely difficult and no compounds in satisfactorily pure state could be isolated.

(b) Dimethyl sulphate is known to be a good alkylating reagent and has been used in alkylation of amides and thioamides.[34,37,38] The use of temperatures up to 60°C is required, thus giving exclusively O- or S-alkylating product[39-42] provided equivalent quantities of the reagent are employed, otherwise secondary product result[43,44] (Scheme 20).

In our hands neither N-formyl glycine ethyl ester (60) nor the thioformyl derivative (59) could be alkylated using dimethyl sulphate. After the work up procedure which involved




Scheme 20

treatment of the reaction mixture with aqueous potassium carbonate a polymeric gum was obtained and no compounds could be separated under a variety of chromatographic conditions.

(c) Another reagent which has been used for S- or O-alkylation is diazomethane.[45-47] It was used to obtain imidates from substituted amides, thiamides and N-chloroamides. As in the previous two cases no imidates could be obtained with diazomethane.

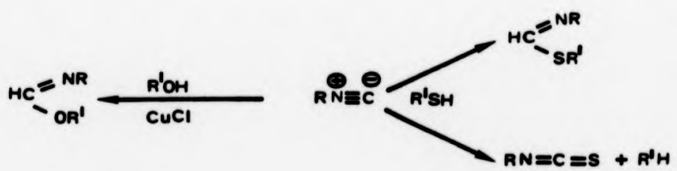
(d) Ohme and Schmitz[48-50] have recently developed a valuable method for the synthesis of formimidates using formamides and benzoyl chloride (Scheme 21).

In our hands, N-formyl glycine ethyl ester (60) and benzoyl chloride in presence of methanol (ethanol) did not give the desired product.

Scheme 21

As we faced these difficulties in conversion of amides and thioamides into imidates we decided to by-pass them and use an alternative method for the synthesis of thioimidates.

Isonitriles have been successfully converted into N-substituted formimidates by their interaction with alcohols in the presence of metal catalyst[51,52] (Scheme 22). Metallic copper or copper oxides were found to be satisfactory for saturated alcohols. When thiols react with isonitriles two competing reactions take place[53,54] (Scheme 22). Thioformimidate formation is favoured if the thiol is primary.

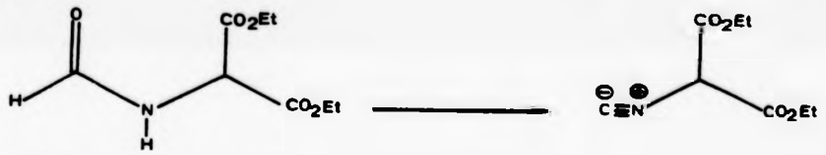


Scheme 22

From these observations we thought that this route may provide the solution to our problem thus avoiding the conversion of amides and thioamides into the corresponding imidates.

The synthesis of isonitriles (63) and (64) was undertaken. Isonitriles can be prepared by elimination of water from formamides.[55] Thus ethylisocyanoacetate (63) was prepared from N-formyl glycine ethyl ester (60) using phosgene and triethylamine according to the described literature procedure.[56]

(60) (63)

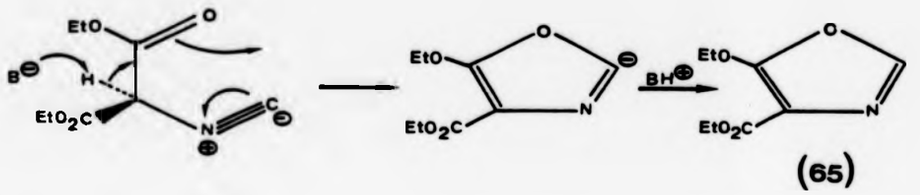


(62) (64)

Using the same experimental procedure (64) could not be isolated. We were confident that the isonitrile was formed; it was detected by its characteristic smell and the i.r. spectrum of the reaction mixture showed the characteristic isonitrile absorption band at 2160 $cm^{-1}$. The same result was obtained in the next experiment when phosphoryl chloride and potassium t-butoxide were used.

We presume that isonitrile (64) was formed but it rearranges to oxazole (65) under basic reaction conditions (Scheme 23). The methine proton of (64) is very acidic and it is presumably abstracted by triethylamine which is present in excess. The 5-endo-dig cyclisation follows yielding oxazole

(65). Precedent exists in the literature for such a reaction. In our case we should be able to confirm this observation by isolating the oxazole (65), although time did not permit further work on this reaction.




(65)

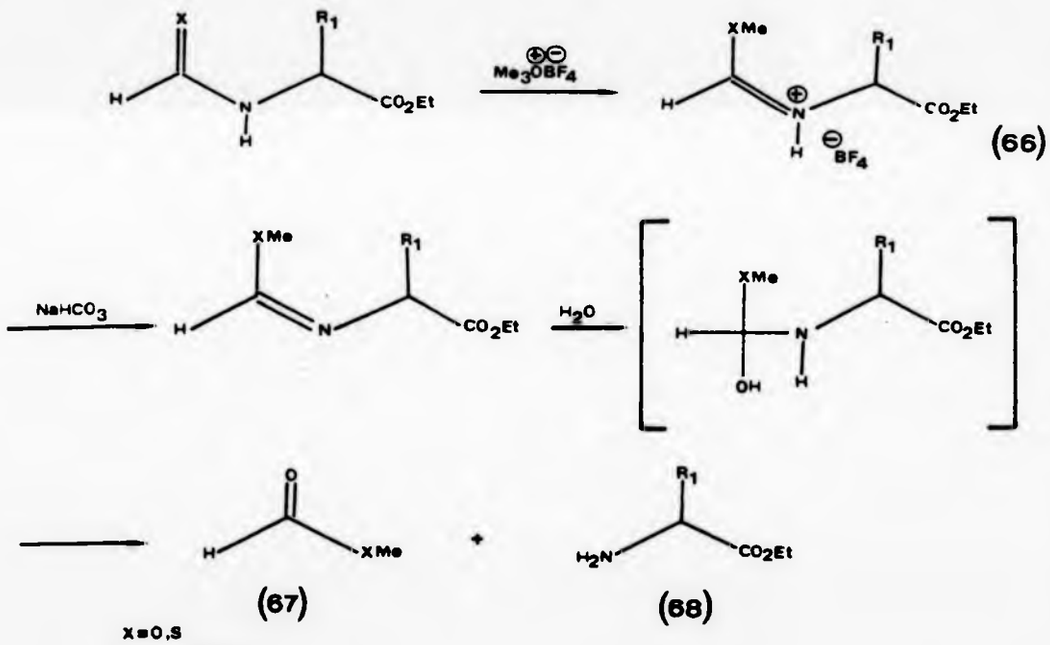
Scheme 23

Ethylisocyanoacetate (63) was allowed to react with an equimolar amount of methanethiol in the presence of a catalytic amount of freshly prepared $Cu(acac)_2$. Thioformimidate was not detected even after extended reaction time. In a second attempt benzene thiol was used instead of methanethiol and the same negative result was obtained.

As these attempts had failed we decided to use trialkyloxonium fluoroborates as reagents for converting amides into the corresponding imidates. Triethyloxonium fluoroborate[57] and trimethyloxonium fluoroborate[58] are powerful alkylating reagents, very toxic, relatively unstable (very hygroscopic). Triethyloxonium fluoroborate is prepared from boron trifluoride etherate and epichlorohydrin in ether under anhydrous reaction conditions. Trimethyloxonium fluoroborate is prepared from triethyloxonium fluoroborate by passing dimethylether through its dichloromethane solution. Their immediate use is recommended.

Those reagents seem to be the reagents of choice in converting amides into the corresponding imidates.[59-63]

Thioamides (59) and (61) and amides (60) and (62) were treated with an excess of trimethyloxonium fluoroborate in dichloromethane at ambient temperature. After 12 hours the t.l.c. of the reaction mixture indicated that the reaction was completed and that the salt (66) was formed (Scheme 24).




Scheme 24

The corresponding imidate should be liberated from its salt by treatment with an excess of base. Treatment of the reaction

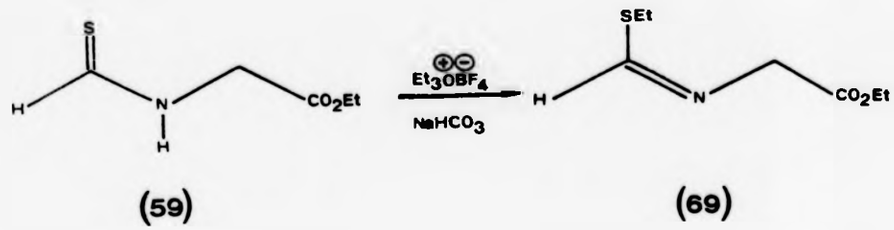
mixture with an excess of aqueous solution of $NaHCO_3$ resulted in the recovery of the amino acid ester (68) and the formate ester (67). Although a number of examples are known from the literature where aqueous work-up procedure is employed it is also well known and documented that imidates are susceptible to hydrolysis.[34] In view of this possibility we decided to avoid aqueous media in the work-up procedure, thus eliminating the possibility of imidate hydrolysis. Once the presence of the salt (66) was established, dichloromethane was evaporated, the residue dissolved in tetrahydrofuran and was added dropwise to a suspension of sodium hydride in tetrahydrofuran. After the work-up procedure a complex mixture was obtained and no pure product could be isolated. Another experiment was performed using n-BuLi as a base at -78°C, no positive results were obtained.

In another experiment triethyloxonium fluoroborate was used for purely practical reasons: dimethylether needed for preparation of trimethyloxonium fluoroborate was not available. When N-thioformylglycine ethyl ester (59) was reacted with an excess of this reagent and the reaction mixture worked-up using the aqueous work-up procedure (excess of an aqueous solution of $NaHCO_3$) followed by the extraction with dichloromethane and by removal of the solvent under reduced pressure yielded an oil which was distilled in vacuo (b.p. 78-80°C/0.1 Tor) and was identified as being S-ethyl formiminoglycinate (69) (Scheme 25).

Attempts to perform this reaction with amides (60), (62) and thioamide (61) failed.

Imidate (69) was identified on the basis of its spectral analysis. The most informative data were obtained from

proton n.m.r. spectrum (Figure 4).




(59) (69)

Scheme 25

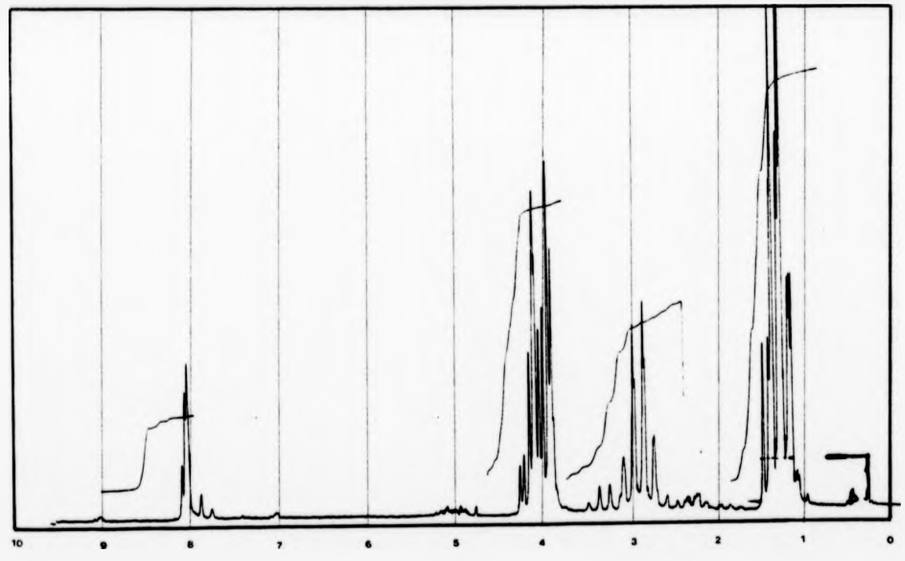
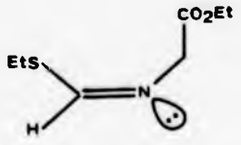


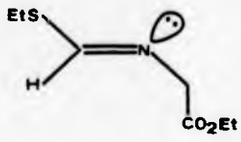

Figure 4

From the proton n.m.r. spectrum we concluded that the imidate (69) exist in two forms: syn (70) and anti (71). The formate proton appears as a multiplet at δ 8.30 and the

methylene protons appear as two distinct singlets at δ 3.98 and 4.01. Protons from the ethyl ester group appear as multiplets at δ 4.15 and 1.30 instead of a distinct quartet and triplet respectively. Those observations lead us to conclude the existence of syn and anti forms of (69).




syn (70)




anti (71)

On the basis of the number of experiments that we performed trying to convert amides and thioamides into the corresponding imidates several questions arose:

(a) why are they so resistant to conversion?

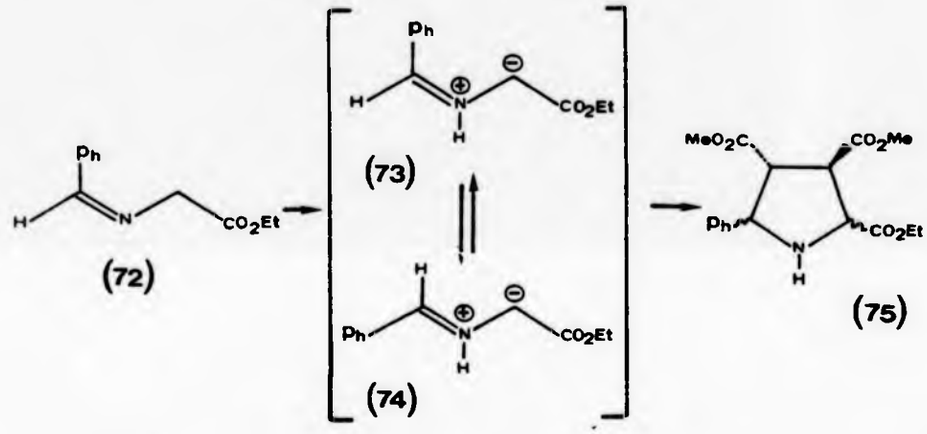
(b) why was the alkylation of (59) successful with triethyloxonium fluoroborate and not with trimethyloxonium fluoroborate?

(c) why was the alkylation of (59) successful while (60), (61) and (62) could not be alkylated?

To those questions we are not able to give a logical answer.

To find the reaction conditions for thermal isomerisation imine (55) $\rightleftharpoons$ azomethine ylide (56) (Scheme 15), we synthesised the "Grigg's imine" benzylidene glycine ethyl ester (72) by a condensation of glycine ethyl ester hydrochloride and benzaldehyde in the presence of triethylamine and magnesium sulphate.

"Grigg's imine" (72) was heated to reflux in toluene in the presence of an equimolar amount of dimethyl fumarate. On cooling and upon addition of methanol, pyrrolidine (75) crystallised from the solution (Scheme 26).




Scheme 26

Theoretically four possible isomers may be obtained (75 a-d) (Scheme 27) depending on the orientation of the ylide and the dipole.

Molecular models indicate that Van der Waals' repulsion between the phenyl and the methyl ester group in (75a) and (75c), which are cis, is considerable. The same observation is true for (75b) where methyl and ethyl ester groups on adjacent carbons are cis. The most stable among the four possible isomers is the isomer (75d) where the sequence of substituents on carbon atoms can be expressed as "trans-trans-trans". The analysis of the proton n.m.r. spectra indicated

(75a)

(75b)

(75c)

(75d)

E = $CO_2Et$

M = $CO_2Me$

Scheme 27

the presence of two isomers with an evident predominence of one; we suppose that (75d) predominates.

Grigg has observed that isomerisation (73 ⇌ 74) occurs. This isomerisation takes place with less active dipolarophiles and when a phenyl substituent is present on the imine. It is believed that such a substituent lowers the barrier of stereomutation. The mixture of isomers that we obtained with a net predominence of (75d) confirms the observation made by Grigg.

As the reaction conditions for the thermal isomerisation imine-azomethine ylide were established we attempted to generate the azomethine ylide (56, X=S, $R_1$=Et, $R_2$=H, R=Et) (Scheme 15) from S-ethylthioformimidate (69) and to trap it with a dipolarophile. Various dipolarophiles were used:

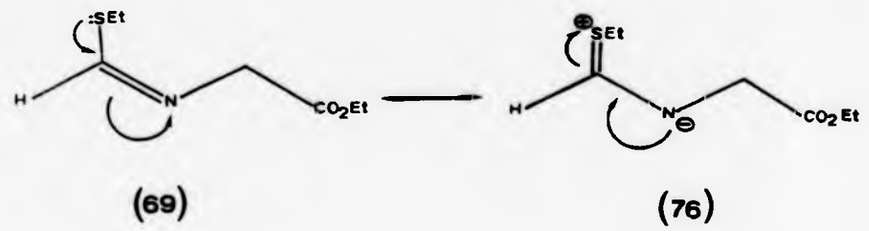
dimethyl acetylene dicarboxylate, dimethyl fumarate, dimethyl maleate and maleic anhydride.

The reaction was performed at the temperature of reflux of different solvents:

benzene, tetrahydrofuran, toluene and xylene.

In all cases starting materials, the dipolarophile and the imidate were recovered unchanged. Several experiments were performed with a catalytic amount of Lewis acid as a catalyst, they are supposed to promote the cycloaddition, no evidence of cycloaddition was observed.

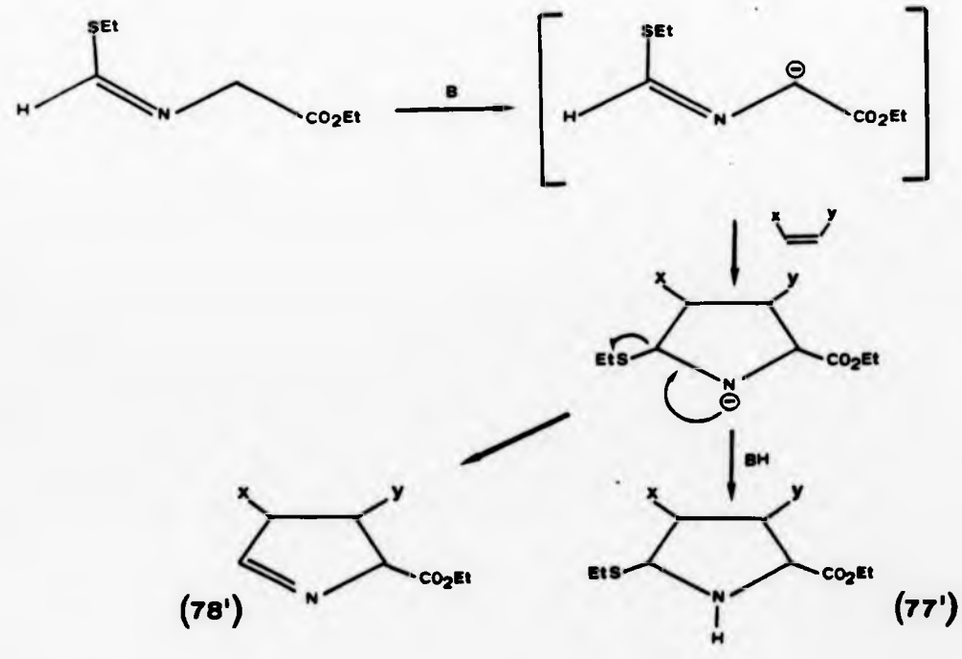
We believe that such a behaviour of thioformimidate (69) could be explained by the presence of sulphur with its "electron push" character (Scheme 28).




(69) (76)

Scheme 28

At this stage we considered the possibility of removing the methylene proton with a suitable base. We believe that (77') could result by the mechanism outlined in Scheme 29. Eventually pyrroline (78') could result by elimination of ethylthiolate anion.




(78') (77')

Scheme 29

Several attempts have been made using different bases: sodium hydride, potassium hydride, n-BuLi in THF at room temperature and at -78°C, with dimethyl acetylenedicarboxylate and dimethyl fumarate as dipolarophiles but no cycloaddition was observed.

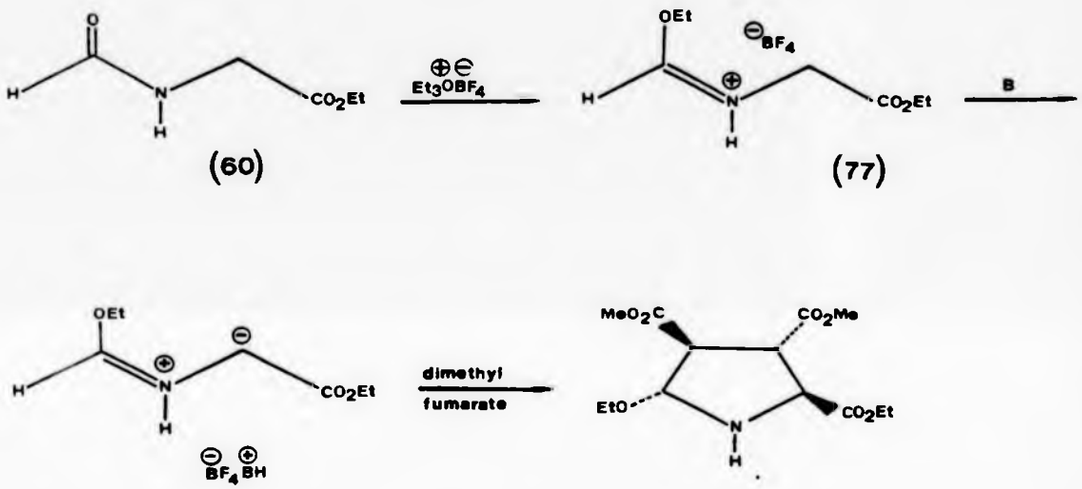
In view of those difficulties we considered alternative approaches to azomethine ylides.

## 4. AZOMETHINE YLIDES BY DEPROTONATION OF IMMONIUM SALTS

We have outlined in the Introduction (Section 2.3) that azomethine ylides can be prepared "in situ" by the action of a base on certain immonium salts. This method for generating azomethine ylides has received little attention. We decided to investigate this novel approach to azomethine ylides thus avoiding imidates, which if synthesised, were obtained with great difficulties.

First, we decided to investigate this route with the material that we already had. We have seen that alkylation of amides/thioamides, with trialkyl oxonium fluoroborate proceeds with the intermediate formation of the fluoroborate salt (77) (Scheme 30). We were confident that the salt was formed; such a reasoning was supported by evidence given by t.l.c. and the proton n.m.r. spectra. When the t.l.c. was carried out (EtOAc:petrol = 3:7) no starting imidate (60) was observed, only one spot visible under the U.V. lamp at the base line, characteristic for salt formation was present. Other evidence was obtained from the proton n.m.r. spectra of the reaction mixture. The signal of the imidate proton (HC(OEt)=), the only signal which is not affected by the solvent appeared at

δ 9.80. The signal of this proton in the starting material appears at δ 8.20 (Table 1). We decided to deprotonate the fluoroborate salt (77) (Scheme 30).

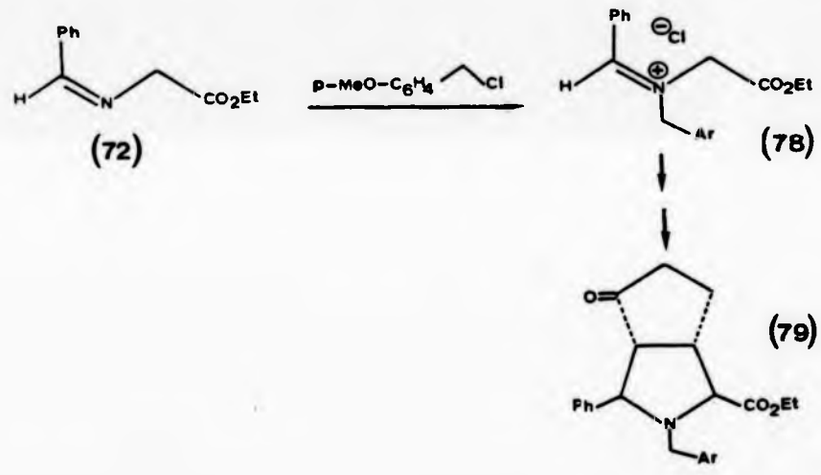



Scheme 30

N-formyl glycine ethyl ester was allowed to react with an excess of triethyloxonium fluoroborate. Once that the formation of the salt (77) was established, triethyl amine and dimethyl fumarate were added. After the work-up procedure, only dimethyl fumarate and imide (60) were recovered. No cyclo-addition product was obtained.

It has been described that azomethine ylides can be obtained "in situ" by dehydrohalogenation of immonium salts.[64] As deprotonation of fluoroborate salt was not successful we decided to synthesise the hydrochloride of the imidate and to try to dehydrohalogenate it.

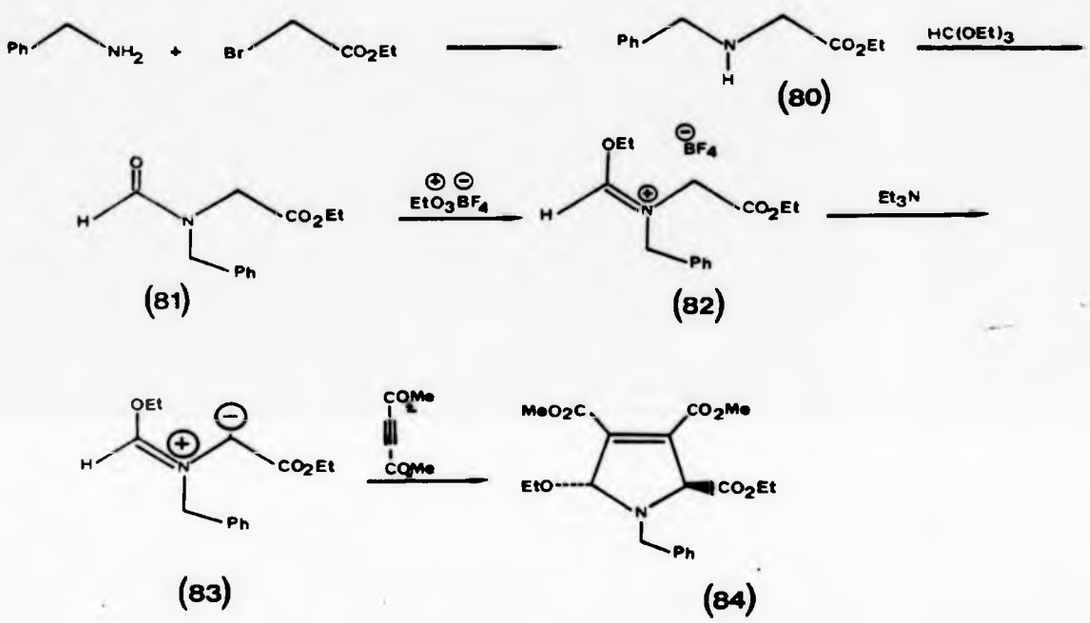
It was decided to examine the reaction of already available "Grigg's imine" (72). Imines are in principle easily converted into their salts by treatment with an equimolar amount of alkyl halide.[65] p-Methoxy benzyl chloride was used, in principle it should yield the salt (78) which on dehydrohalogenation and subsequent cycloaddition should be converted into the N-protected pyrrolidine (79) (Scheme 31).




Scheme 31

Unfortunately the salt (78) could not be obtained. We presume that the phenyl substituent on (72) lowers the basicity of the nitrogen atom. We considered that the salt analogues to (78) might be synthesised by an alternative route (Scheme 32).

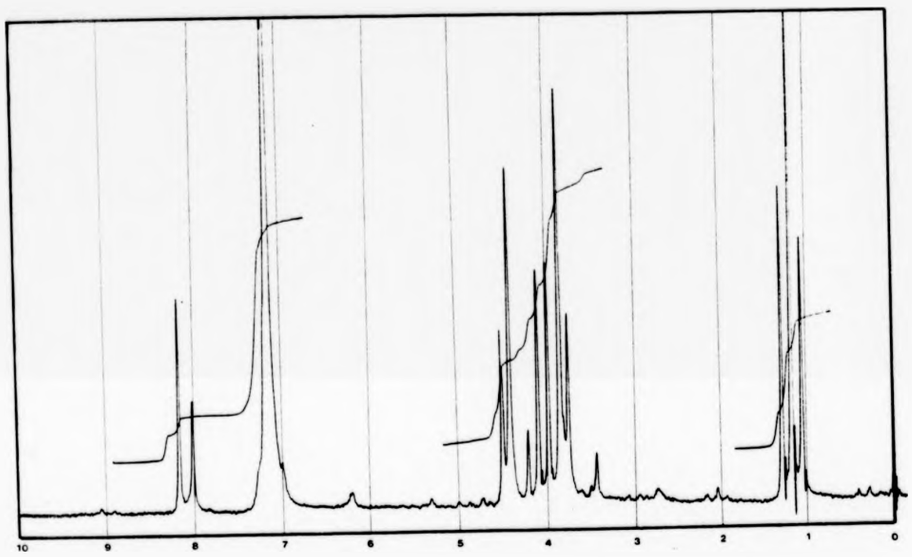
N-benzyl glycine ethyl ester (80) was prepared by a literature procedure[66] in a reaction of ethyl bromoacetate

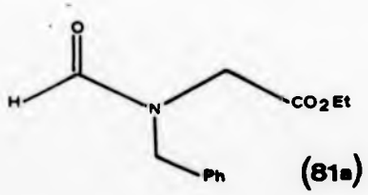



Scheme 32

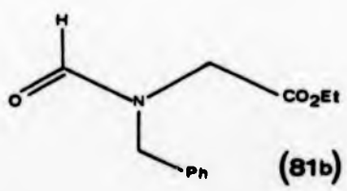
with an excess of benzyl amine. Treating the hydrochloride salt of (80) with an excess of triethylorthoformate, (81) was obtained. N-benzyl-N-formyl glycine ethyl ester (81) was identified on the basis of its spectral analysis. On the basis of the proton n.m.r. spectra analysis we concluded the existence of two conformers (81a) and (81b) depending on the orientation of the benzyl group with respect to the amide carbonyl (Figure 5).

N-benzyl-N-formyl glycine ethyl ester (81) was treated with an excess of triethyl oxonium fluoroborate. Once that the formation of the salt (82) was established an equimolar




(81a)

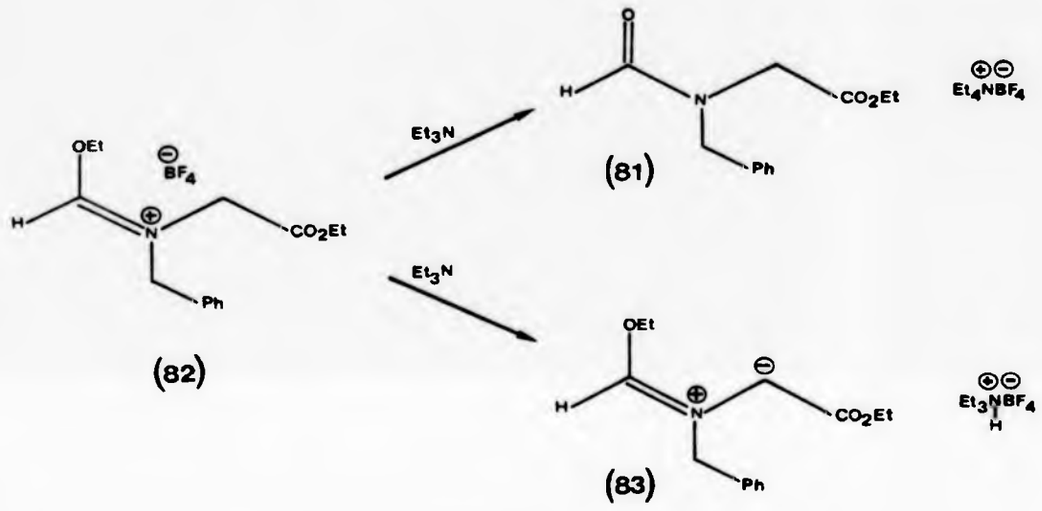



(81b)

Figure 5

amount of dimethyl acetylene dicarboxylate and triethyl amine was added. The t.l.c. of the reaction mixture indicated the presence of two major components, one of them corresponding by its $R_f$ value to (81). We presume that upon the addition of a

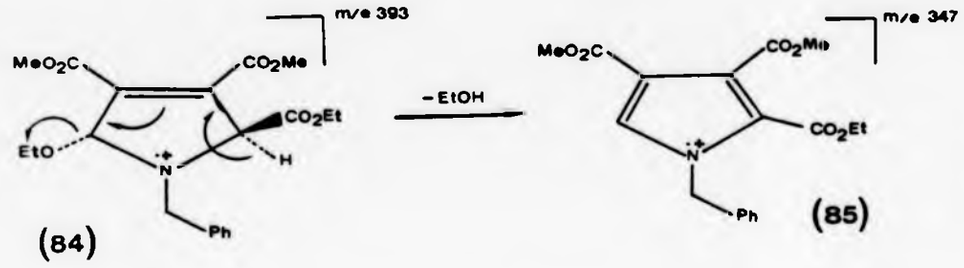
base, two competing reactions take place (Scheme 33), the formation of the ylide (83) being the favoured one.




Scheme 33

The second compound eluted from the column was identified on the basis of its spectral analysis as pyrrolidine (84) (Scheme 32). Proton n.m.r. spectra of (84) unambiguously demonstrated the structure of (84). The triplet at δ 1.15, the quartet at 3.15 and the multiplet at 3.30 - 4.15 indicated the presence of two ethyl groups one of them being the ethyl ester and the other belonging to the ethoxy substituent at C-5. Signals corresponding to methyl ester protons appear as two distinct singlets at δ 3.35 and 3.85. Benzylic protons appear at δ 4.45 and five aromatic protons appear as multiplet at δ 7.25. Accurate mass measurement did not give the molecular ion corresponding to $C_{20}H_{25}NO_7$ at m/e 393; another ion was

present at m/e 347 which corresponds to $C_{18}H_{19}NO_6$. As ionisation in the mass spectrophotometer occurs at elevated temperatures the elimination of ethanol from (84) is likely to occur, thus yielding the ion (85) at m/e 347 (Scheme 34).




Scheme 34

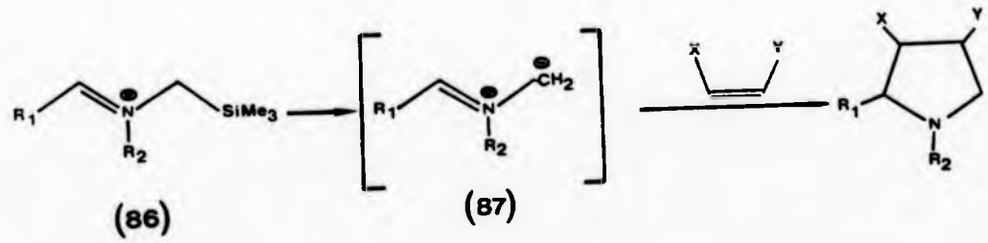
In our next experiment cyclopentenone was used as a trapping reagent. Unfortunately, by varying the reaction conditions (concentration, solvent and temperature) no cycloaddition product could be obtained.

Cyclopentenone is not a strong dipolarophile; its double bond is activated only by an adjacent carbonyl and a ring strain, therefore the azomethine ylide must compensate this weak dipolarophilic character of cyclopentenone which means that this ylide must be very reactive.

Although we have clearly demonstrated that this reaction has potential for the synthesis of pyrrolidine ring, it would not be applicable for the synthesis of bicyclic pyrrolidine, the key intermediate in our synthesis of kainic acid and as such, alternative strategies must be considered.

## 5. AZOMETHINE YLIDES BY DESILYLATION OF IMMONIUM CATIONS

Recently, interest has been shown in synthetic methods for generating azomethine ylides by desilylation of appropriately substituted immonium cations.[67-70] Such ylides are intercepted with various dipolarophiles and pyrrolidine derivatives are obtained (Scheme 35). This general scheme has been applied to the synthesis of a number of pyrrolidines, some of them being part of naturally-occurring materials. It has great potential in the synthesis of five-membered heterocycles since non-stabilised azomethine ylides of type (87) are very difficult to obtain.



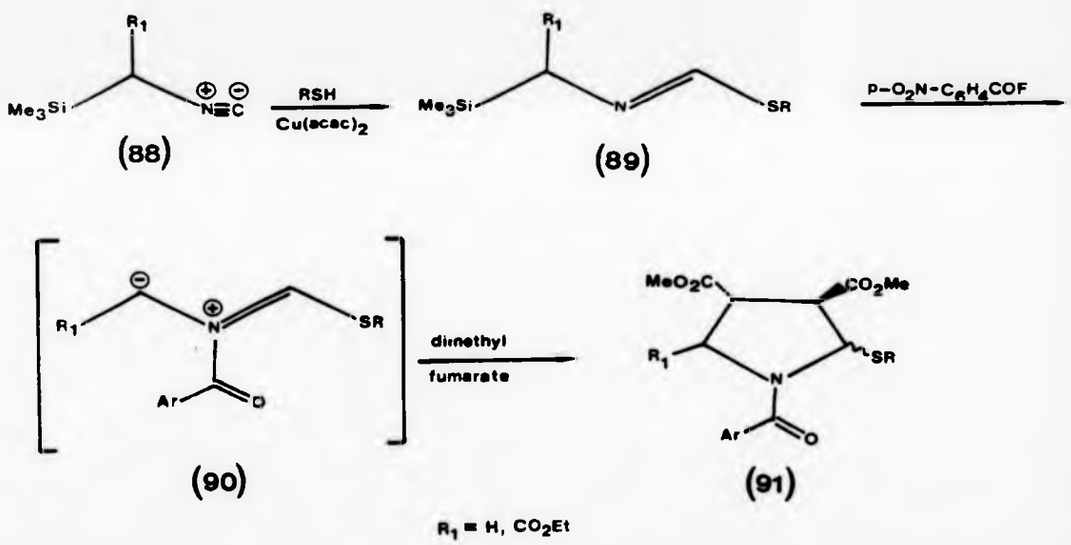

(86) (87)

Scheme 35

Silicon is more electropositive than carbon, thus resulting in a strong polarisation of the C-Si bond with a tendency for nucleophilic attack to occur at silicon. This bond is readily cleaved by ionic reagents particularly if the attacking nucleophile is oxygen or halogen. Fluoride ion from caesium fluoride or from acyl fluorides, seems to be the ionic reagent of choice for C-Si bond fission.[71]

We decided to investigate this route toward azomethine ylides and to apply the strategy developed by Livinghouse[67]

(Scheme 36). Livinghouse converted the isonitrile (88 $R_1$=H) into the corresponding thioimidate (89 $R_1$=H) with the alkyl thiol in the presence of $Cu(acac)_2$. We have already described that this conversion in the case of ethylisocyanoacetate (63) was not possible. At the time when this synthesis was planned this fact was not known, these two syntheses were carried out in parallel.




Scheme 36

Livinghouse desilylated the thioimidate (89 $R_1$=H) with p-nitroacyl fluoride, the intermediate azomethine ylide (90 $R_1$=H) was trapped with dimethyl fumarate yielding pyrrolidine (91 $R_1$=H). We decided to carry out the synthesis outlined in Scheme 36 with (88 $R_1$=$CO_2Et$). The synthesis of (88 $R_1$=$CO_2Et$)

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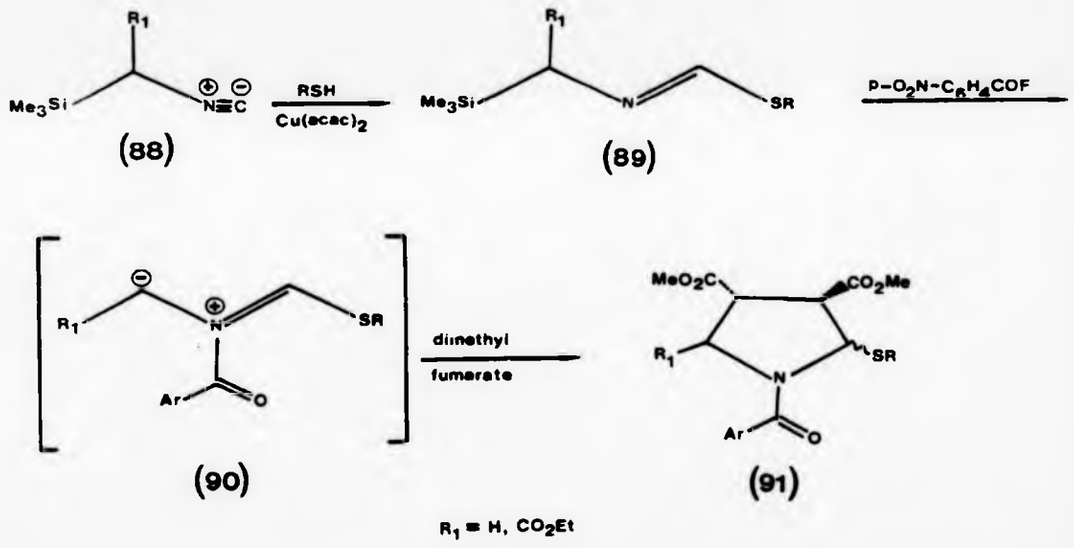


Scheme 36

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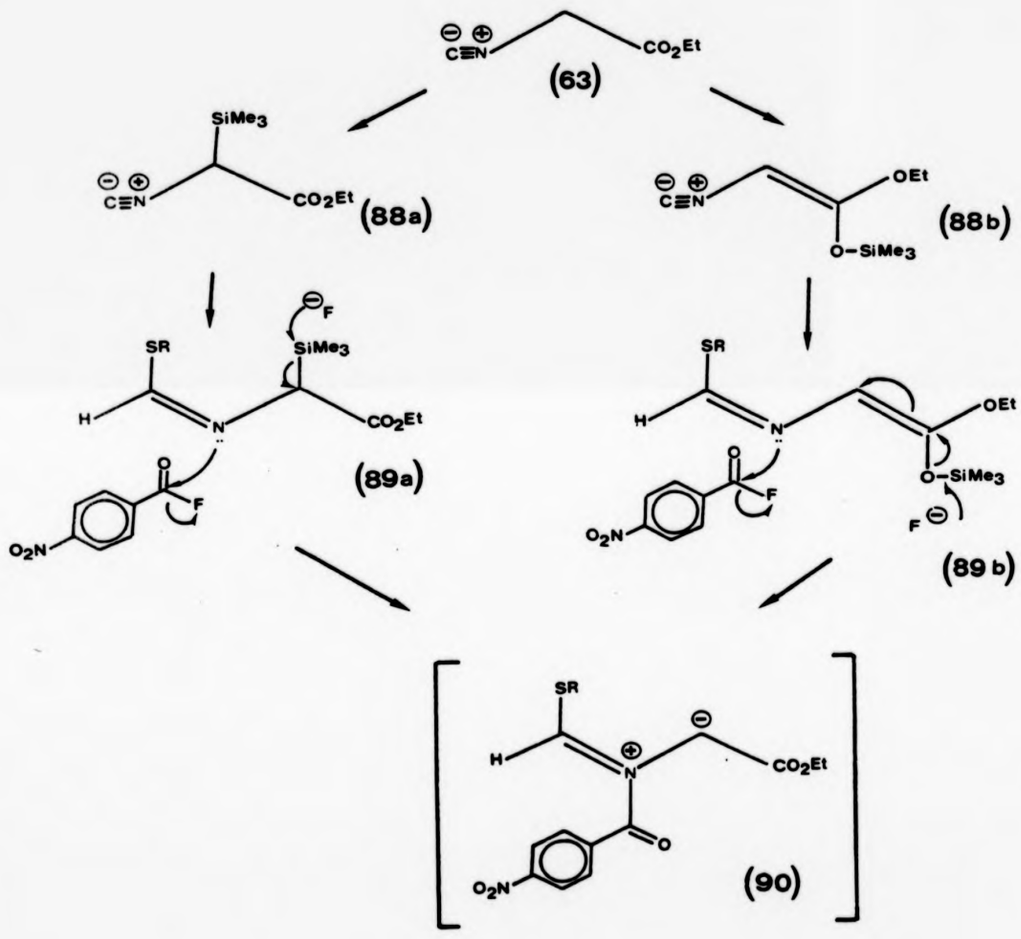
was undertaken (Scheme 37).




Scheme 37

Ethyl isocyanoacetate was already available. Silylation of (63) should in principle give the mixture of C and O-silylated product, (88a) and (88b) with the predominence

of O-silylated product because of the favourable conjugation. The mixture of silylated products can be used in the next step; it can be seen from (Scheme 37) that desilylation of (89a) and (89b) gives the azomethine ylide (90).

Silylation of carboxylic acid derivatives is a well documented reaction.[71] In diethyl malonate the methylene group is activated in a similar way to the methylene group in the isonitrile (63), therefore we decided to use diethyl malonate as a model to find the appropriate reaction conditions for silylation. With trimethylsilyl chloride and sodium hydride diethyl malonate was silylated smoothly and the corresponding silylketene acetal was obtained in excellent yield.

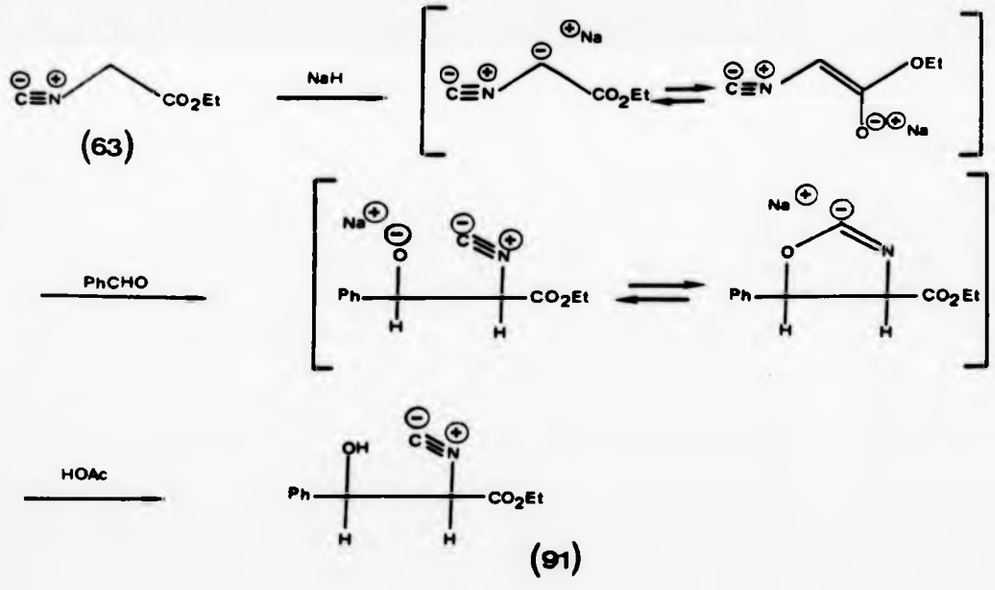
Thus the isonitrile (63) was treated with sodium hydride and the enolate was quenched with trimethylsilyl chloride. At the end of the reaction the reaction mixture was centrifuged to separate the sodium chloride formed during the reaction, the solvent was evaporated and the residue distilled under reduced pressure. No product in satisfactorily pure state could be obtained. The proton n.m.r. spectrum indicated only the small amount of silylated product (5%).

Hoppe reviewed methods for the synthesis of α-metalated isocyanides.[72] Isocyanides having powerful electron withdrawing substituents in the α position can be completely ionised with n-BuLi, potassium-t-butoxide, sodium hydride, sodium ethoxide or even triethylamine.

As our first attempt with trimethylsilyl chloride and sodium hydride failed, we decided to carry out the same reaction using n-BuLi in THF at -78°C.[73,74] This attempt also

failed to give the desired product; therefore we decided to increase the solvent polarity and we used the mixture of THF and HMPA with n-BuLi as a base. No silylation was observed.

To be sure that during all those attempts the anion of (63) was formed and that we had correct reaction conditions we decided to treat ethylisocyanoacetate with sodium hydride in the presence of benzaldehyde, compound (91) was obtained, as it was described in the literature[73] (Scheme 38).

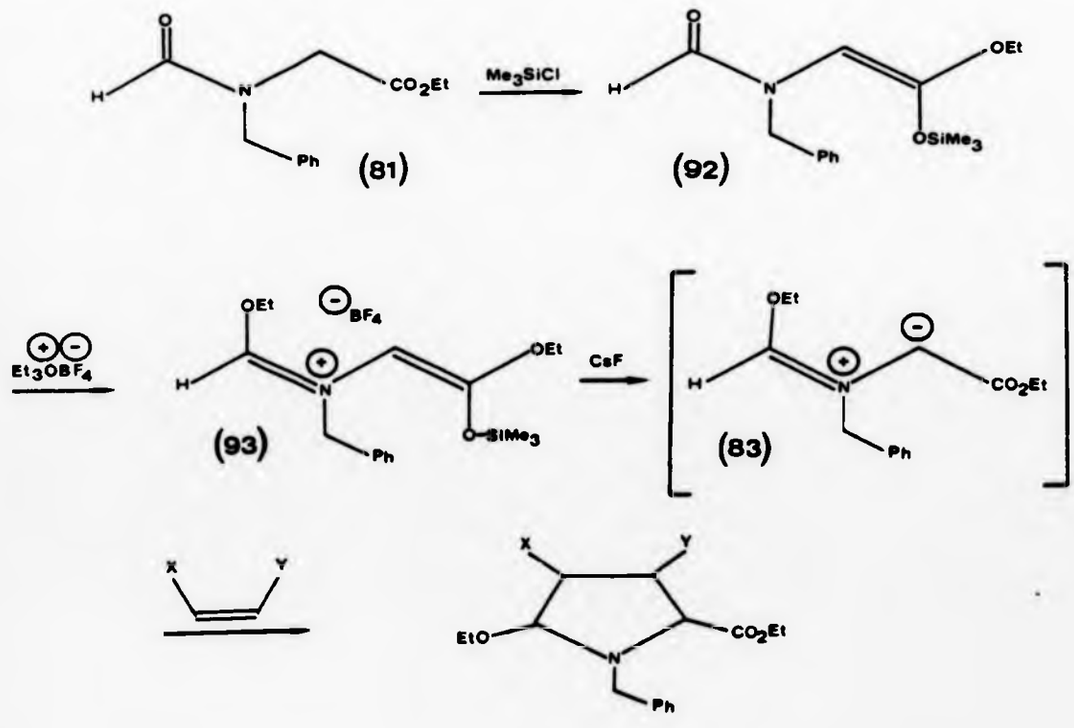



Scheme 38

At this stage we discovered that the transformation isonitrile (63) → imidate with alkyl thiol and $Cu(acac)_2$ was not feasible; as this problem was added to the problem of

silylation we decided to abandon this route and to consider alternative methods.

We have already seen that N-formyl-N-benzyl glycine ethyl ester (81) can be converted into the corresponding imidate salt and that such a salt can be deprotonated yielding the ylide (83) (Scheme 32) which was trapped with a suitable dipolarophile; we therefore decided to combine the path outlined in Scheme 32 with the one outlined in Scheme 37 thus avoiding the isonitrile imidate transformation and the silylation of isonitrile (63), reactions which are shown not to be feasible. This alternative route is outlined in Scheme 39.

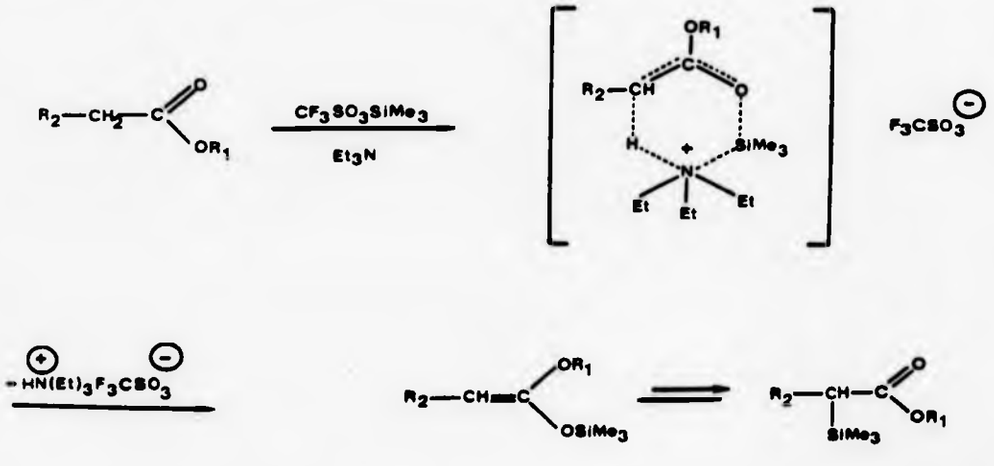



Scheme 39

This path includes silylation of (81). Compound (92) should in principle yield the corresponding imidate (93). Desilylation of (93) with cesium fluoride, reagent used by Padwa[69], should yield the azomethine ylide (83) the same ylide obtained by deprotonation of (82) (Scheme 33). In this case the reaction should proceed only toward the ylide formation which was not observed in the previous case, where the competing reaction was taking place (Scheme 33).

The synthesis of (92) was undertaken. As several attempts have been made using trimethylsilyl chloride as silylating reagent we decided to use trimethylsilyl iodide.[71] This reagent seemed to be more reactive than the trimethylsilyl chloride. Several attempts have been made but without success.

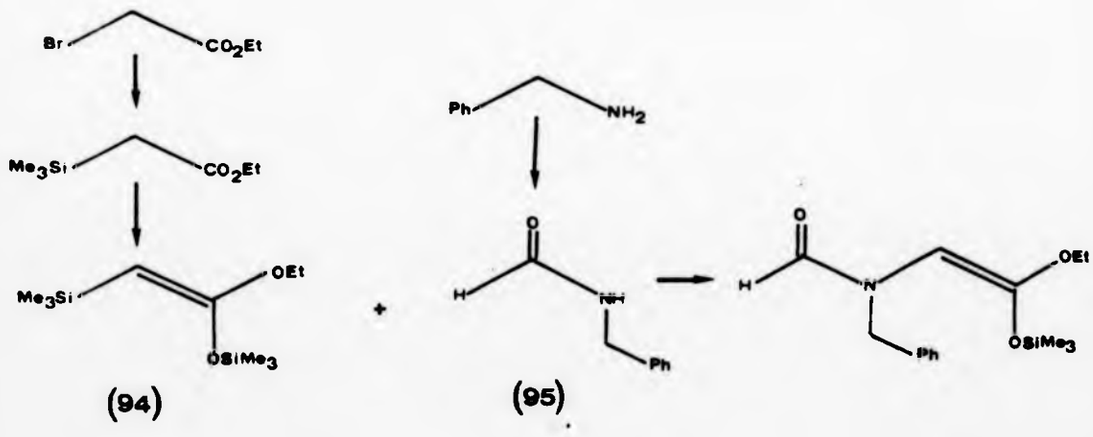
In the next series of experiments, trimethylsilyl triflate was used as silylating reagent. Triflate, being a good leaving group, allows the reaction to proceed smoothly under very mild reaction conditions. Triethylamine seems to be the best auxiliary base, triethylammonium triflate being insoluble in organic solvents precipitates in liquid form thus indicating the end of the reaction (Scheme 40).




Scheme 40

This reagent also failed to give the desired silyl ketene acetal.

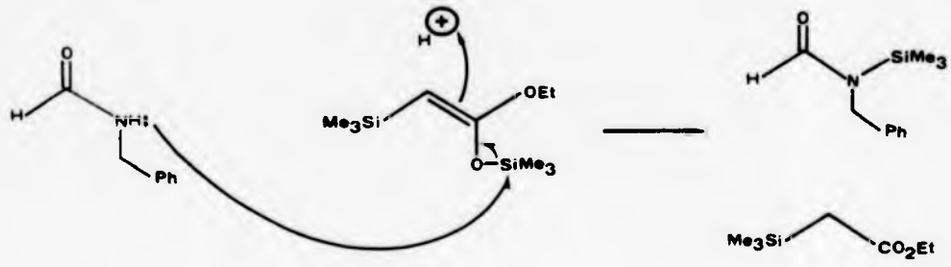
We have seen that in all our numerous attempts of silylation, this reaction was found to be extremely difficult to perform whenever the compound that we wanted to silylate had a nitrogen atom α to the methylene ethyl ester group when the nitrogen is part of an imidate, imide or isonitrile. We have not found similar examples of silylation in the literature and time did not permit us to carry on further investigations to find the reasons for such a behaviour of those compounds toward silylation. We therefore considered the alternative possibility: first to incorporate the trimethylsilyl group and then to condensate it with a suitable amine (Scheme 41).




Scheme 41

It was expected that the nucleophilic attack of the nitrogen from N-formyl-N-benzyl amine[75] will be at the $sp^2$ C of the silyl ketene acetal (94)[76] rather than at silicon.

Unfortunately the reaction proceeded by the attack of the nitrogen at silicon yielding the N-protected amine and the ethyl trimethylsilyl acetate[77] (Scheme 42).



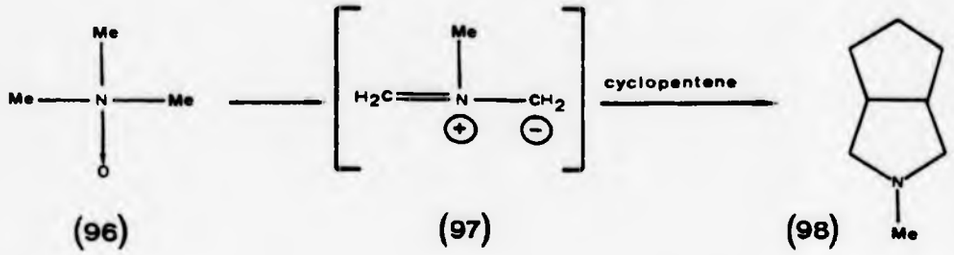

Scheme 42

In view of the difficulties encountered this approach was abandoned in favour of an alternative approach.

## 6. NON-STABILISED AZOMETHINE YLIDES FROM AMINE N-OXIDES

A recent communication reported a novel approach to non-stabilised azomethine ylides.[78] It was reported that when triethylamine-N-oxide (96) was treated with a strong base, such as LDA, at -78°C the ylide (97) was generated; this ylide being very reactive undergoes a subsequent 1,3-dipolar cycloaddition with a variety of weak dipolarophiles (even alkenes) yielding N-methyl-pyrrolidine derivatives (98) (Scheme 43).

The authors of the communication gave some evidence in favour of the ylide formation, but no mechanistic interpretation for the formation of the ylide (97) was given. Although only one example is given (triethylamine-N-oxide) and another research group reported that they failed to isolate pyrrolidine derivatives from the reaction of tribenzylamine-N-



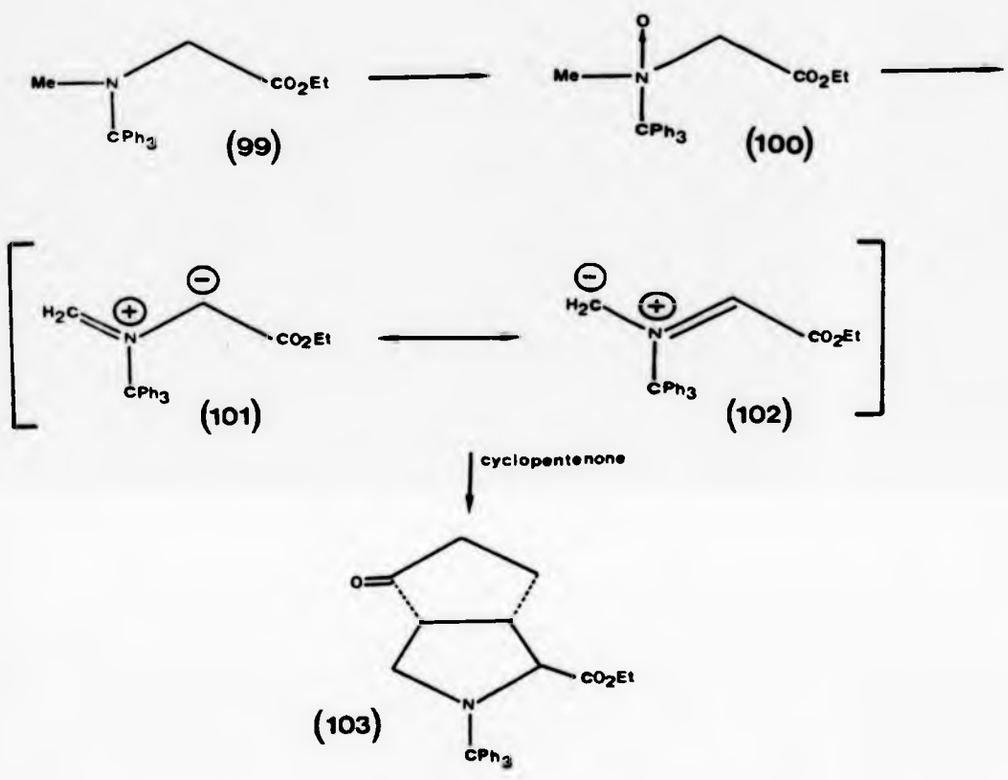

(96) (97) (98)

Scheme 43

oxide with n-BuLi in the presence of an excess of dipolarophile (unspecified)[79] we decided to investigate this novel approach to non-stabilised azomethine ylides and eventually to apply it in our synthesis of kainic acid precursors.

It is evident that the N-oxide (100) derived from the N-protected sarcosine methyl ester (99) should be a suitable model for the investigation of this novel approach (Scheme 44).

Sarcosine methyl ester hydrochloride was easily obtained in a high yield by a literature procedure[80] by the action of methanol in the presence of thionyl chloride on sarcosine. Alternatively the hydrochloride salt of methyl sarcosine can be obtained by refluxing the methanol solution of the acid saturated with gaseous HCl. Methyl sarcosinate was protected and derivative (99) was obtained under mild reaction conditions using trityl chloride.[81] The trityl group as N-protecting group has several advantages. This group is easily introduced under very mild reaction conditions on one hand and on the other hand mild reaction conditions are required for its removal. The other advantage of this group, in our




Scheme 44

particular case, is that there is no α-hydrogens attached to the tertiary carbon, therefore the number of resonance structures of the ylide is reduced to minimum.

We expect that two extreme resonance structures of the ylide are possible, (101) and (102) (Scheme 44), although we believe that structure (101) should predominate because of the presence of the adjacent carboxylic ester group which should stabilise the negative charge. This ylide is expected to undergo a 1,3-dipolar cycloaddition reaction with cyclopentenone to

yield the bicyclic ketone (103), the key intermediate in our synthesis of kainic acid.

Oxidation of tertiary amines to N-oxides is a well documented reaction and the synthetic utility of various reagents has been reviewed.[82-84] Several attempts have been made in this laboratory to oxidise (99), but all failed to yield the desired N-oxide.

(a) Our first attempt was carried out using hydrogen peroxide. The reaction failed to give the N-oxide, the deprotected methyl sarcosine was obtained.

(b) m-Chloro perbenzoic acid was the reagent that we used in our next attempt to oxidise (99) to (100). This reagent is generally used under rather mild reaction conditions and high yields of N-oxides are reported. As in the previous case we obtained the deprotected methyl sarcosine.

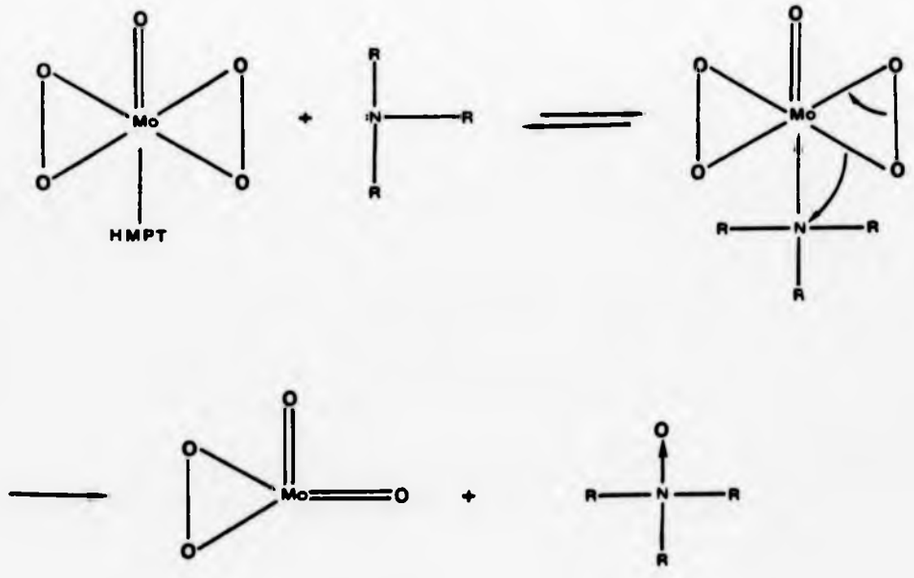
(c) In our third experiment an alternative method to the standard m-chloroperbenzoic acid oxidation was carried out. This preparation of N-oxides proceeds below room temperature with entirely non-aqueous solvents[85] with pure m-chloroperbenzoic acid.[86] The intermediate, N-oxide m-chlorobenzoate was passed through a column of alumina and in principle the N-oxide should be obtained. Unfortunately no N-oxide formation was observed in our case.

(d) In our next experiment we decided to perform this reaction with t-butyl-hydroperoxide in the presence of $VO(acac)_2$. Tertiary amine have been found to react with organic hydroperoxides in the presence of group VB and VIB

transition metal, and to give excellent yields of amine oxides.[87] We obtained only the deprotected methyl sarcosine.

(e) In the last experiment diperoxo-oxohexamethylphosphoramidomolybdenum (VI), $MoO_5$.HMPT was used as oxidising agent. This reagent was prepared by the procedure described by Mimoun et al.[88] by dissolving $MoO_3$ in hydrogen peroxide (30%) at 40°C followed upon cooling by the addition of HMPT. A yellow precipitate was formed immediately and it was recrystallised from methanol. This reagent was handled with care and it was stored at low temperature.

There are no reports in the literature for the use of this reagent in the preparation of N-oxides but we decided to use it by analogy with the literature procedure for the formation of epoxides.[89] We presume that the mechanism should be as follows:



Unfortunately the reaction failed to yield the desired N-oxide.

(f) Another reagent which should be considered is ozone. Tertiary amines are readily converted to the corresponding amine oxides. This reaction is of synthetic value and has been reviewed[83,90] although that time did not permit to carry out this experiment.

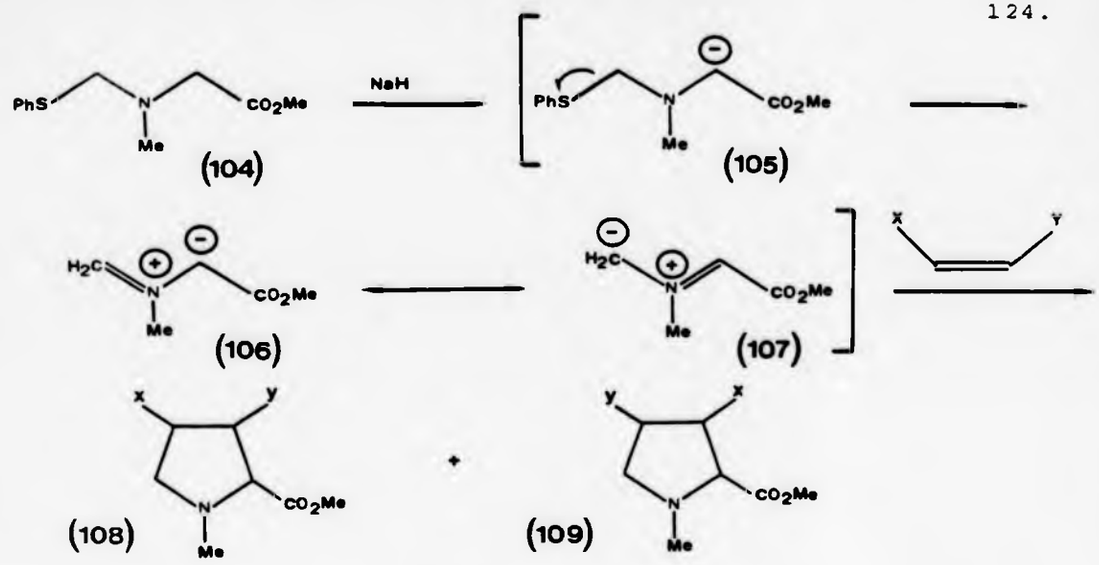
In all our experiments methyl sarcosine was obtained. We presume that the free radical reaction took place, the free radical being generated thermally. It is known that compounds containing peroxide, O-O bonds have bond energies of 25-35 kcal/mol and as such should be useful radical initiator at 50-150°C. On the other hand, trityl radical is known to be a very stable one although its formation could not be explained on the basis of rather mild reaction conditions employed in our experiments. An example of coupling of trityl and t-butoxy radical has been reported.[91]

We believe that this route has synthetic value and needs more investigation, but as we were running out of time this project could not be examined in more detail.

## 7. AZOMETHINE YLIDES FROM METHYL SARCOSINATE DERIVATIVES

Esters of N-phenylthiomethyl sarcosine (104) have been found to undergo a new base promoted 1,3-dipolar cycloaddition with olefinic dipolarophiles yielding pyrrolidine derivatives[92] (Scheme 45).

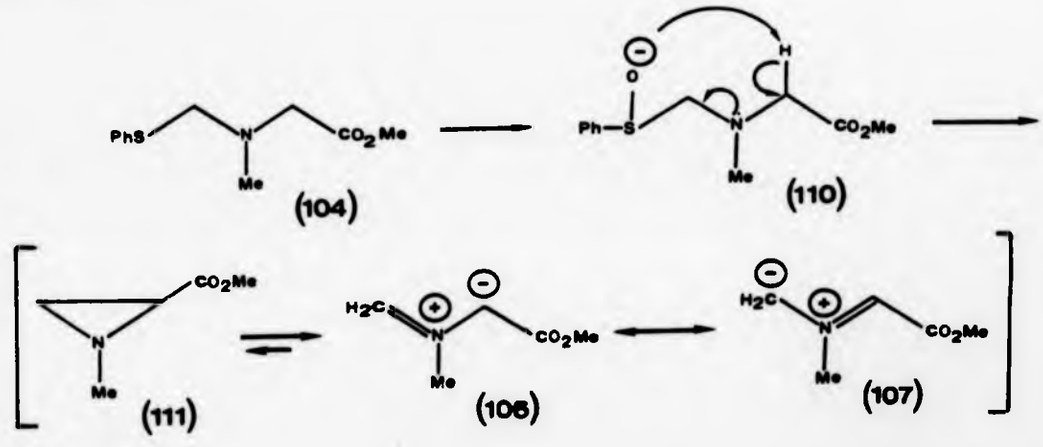
With unsymmetrical dipolarophiles two regioisomers are obtained, (108) and (109). The authors of the communication




Scheme 45

suggest the mechanism, outlined in Scheme 46, although we believe that the intermediacy of aziridines (111) is more probable.

Support for such a view might be obtained by synthesising the S-oxide of (104); such a compound should in principle yield the aziridine (111) under thermal reaction conditions (the presence of the base should not be needed) which would undergo a subsequent ring opening yielding ylides (106) or (107).




Scheme 46

Initially to test the viability of (Scheme 46) we decided to synthesise N-phenylthiomethyl sarcosine methyl ester (104) and to carry out the 1,3-dipolar cycloaddition reaction under the reaction conditions described by the authors of the communication.

Sarcosine methyl ester hydrochloride was already available, and the free amino acid ester was generated from the salt by passing ammonia through a chloroform solution of the salt. Refluxing the amino acid ester with an equimolar amount of thiophenol and an excess of paraformaldehyde with a catalytic amount of p-toluene sulphonic acid in methanol yielded (104) with the spectral and physical characteristics identical to the ones described in the literature.[92]

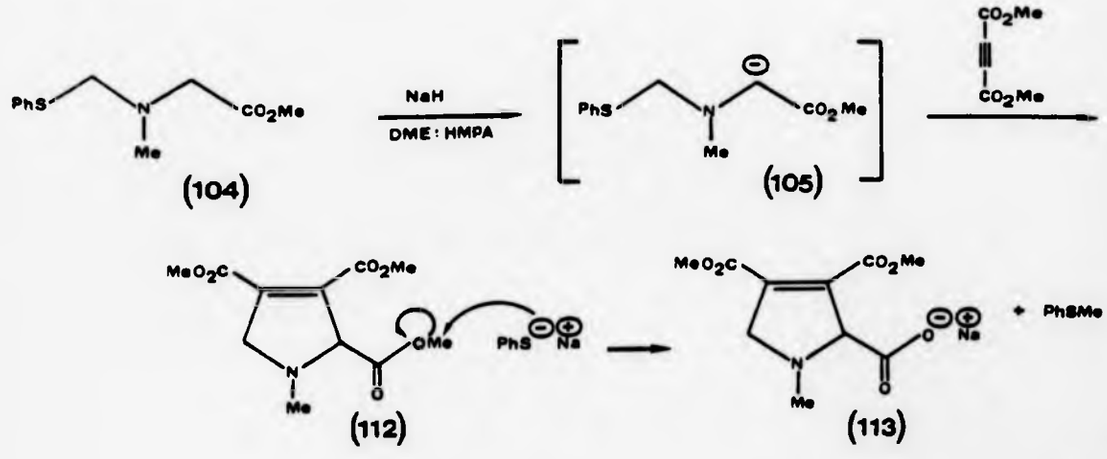
We decided also to synthesise N-phenylthiomethyl-N-benzyl glycine ethyl ester (112). This compound upon 1,3-dipolar cycloaddition reaction with dipolarophiles should yield the N-benzyl protected pyrrolidine, thus making the deprotection of the nitrogen much easier. This compound was synthesised by analogy to the described synthesis of (104) starting from the N-benzyl glycine ethyl ester (80), which was already available (Scheme 47).


(80) (112)

Scheme 47

Compound (112) was identified on the basis of its spectral characteristics. In the mass spectrum the molecular ion $M^+$ 315 did not appear but the ion resulting by the loss of PhS group was present (m/e 206, 76.3%).

We first decided to carry out the cycloaddition of the ylide formed from (104) with dimethyl acetylene dicarboxylate as dipolarophile, which should in principle yield (112) (Scheme 48). The reaction was carried out under the following reaction conditions: the amino acid ester derivative with a slight excess of dimethyl acetylene dicarboxylate with an excess of sodium hydride was refluxed in a mixture of dimethoxyethane and HMPA (10:0.9). The insoluble material was filtered off and the residue worked up as it was described in the literature. The proton n.m.r. spectrum of the filtrate indicated the presence of HMPA (b.p. 232°C) and phenyl methyl sulphide (b.p. 189-190°C). The insoluble material which was believed to be $PhS^-Na^+$ was taken up in $D_2O$, as it was not soluble in organic solvents, and the proton n.m.r. spectrum was recorded. On the basis of its analysis the presence of the salt (113) was established (Scheme 48).




Scheme 48

We believe that the thiophenolate anion, initially formed, act as a good nucleophile in the presence of HMPA and attacks the methyl group of one of the methyl ester groups. A similar example was reported in the literature where the iodide ion in the presence of HMPA acts as a nucleophile.[93] As those results were obtained we decided to perform the same reaction, under the same experimental conditions, without HMPA. The reaction mixture was worked up as described above and the analysis of the proton n.m.r. spectrum of the crude reaction product indicated the presence of the cycloadduct (112). Time did not permit us to purify and fully characterise (112). An attempt was made using cyclopentenone as dipolarophile but no cycloadduct could be detected.

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# EXPERIMENTAL

Proton n.m.r. spectra were recorded as dilute solutions in the stated solvent with tetramethylsilane as internal standard on a Perkin Elmer R24 at 60 MHz or Perkin Elmer R32 at 90 MHz. Infra-red spectra were recorded on a Perkin Elmer 577 Grating infra-red spectrophotometer. Accurate mass measurement was recorded on a Joel JMS D100. Melting points were determined on a Kofler block and are uncorrected.

Analytical t.l.c. was carried out using plastic plates coated with Merck Kieselgel $GF_{254}$ (Type 60) and column chromatography was carried out using Merck Kieselgel $HF_{254}$ in an adaption of the pressure method of Still.[94]

Solvents were purified and pre-dried according to the procedures described in "Purification of Laboratory Chemicals".[95]

Preparation of p-methoxy benzyl chloride

p-Methoxy benzyl alcohol (20g 0.14 mol) and conc.HCl (58g) were stirred at room temperature for 2 hrs. The organic layer was separated, dried ($MgSO_4$) and used in the next step without further purification. 20.1g (89%) of the title compound was obtained. $\nu_{max}$ 2820, 1610 and 1590 $cm^{-1}$.[96]

Preparation of p-methoxy benzyl azide (34)

p-Methoxy benzyl chloride (4.2g 0.027 mol) and sodium azide (1.74g 0.027 mol) were dissolved in anhydrous dimethylformamide (40 mL) and the reaction mixture was stirred at room temperature for 24 hrs. The reaction mixture was poured into water (400 mL), extracted with ether (3 x 50 mL), dried ($Na_2SO_4$) and the solvent removed under reduced pressure

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(T° < 20°C) yielding 3.8g (87%) of the title compound. $\nu_{max}$ 2980, 2080, 1600 and 1580 $cm^{-1}$.[96]

Preparation of phenyl azide (36)

A mixture of conc.HCl (55.5 mL) and water (300 mL) was stirred in an ice salt bath. Phenyl hydrazine (35.5g 0.38 mol) was added dropwise over a period of 30 mins. The reaction mixture was cooled at 0°C, ether (100 mL) was added and a solution of sodium nitrite (25g 0.36 mol) in water (30 mL) was added dropwise at such a rate that the temperature never rose above 5°C. The reaction mixture was stirred at room temperature for 2 hrs. The etheral layer was separated and the water layer extracted with ether (2 x 100 mL). Combined etheral layers were dried ($MgSO_4$) and the solvent removed under reduced pressure at room temperature. Distillation of the residue in vacuo gave the title compound 29.7g (76%), b.p. 32°C/2 Tor (lit.[10] 41-43°C/5 Tor). $\nu_{max}$ 3000, 2100, 1600, 1500, 1280, 810 and 760 $cm^{-1}$.

Preparation of benzyl azide (35)

To a solution of benzyl chloride (54g 0.38 mol) in acetone (300 mL) a solution of sodium azide (25g 0.38 mol) in water was added. The reaction mixture was stirred at room temperature for 2 hrs. then poured into water (1000 mL). The organic layer was separated and dried ($MgSO_4$). 41g (73%) of the title compound was obtained.[97] $\nu_{max}$ 3000, 2100, 1600 and 1500 $cm^{-1}$.

Preparation of diethyl ethoxy methylene malonate

Triethyl ortho-formate (100g 0.675 mol), acetic anhydride (126g, 1.23 mol), diethyl malonate (96g 0.60 mol) and a catalytic amount of zinc chloride were placed in a three necked flask fitted with a gas inlet tube, a thermometer and a Vigreux column fitted with a still head and a condenser. The contents of the flask were agitated with an air stream during five minutes and heated as follows: 102-115°C for 2.5 hrs., 115-127°C for 7 hrs. (after eight hours of heating, additional (20g 0.135 mol) of triethylortho formate and (25g 0.41 mol) of acetic anhydride was added), and heating was continued at 127-145°C for 2 hrs. and 145-155°C for 2 hrs. The contents of the flask were filtered and distilled under reduced pressure. 19.4g of diethyl malonate was recovered (b.p. 80°C/3 Tor) and 32g (30.8%) of the title compound was obtained, b.p. 106-107°C/0.3 Tor (lit.[98] 108-110°C/0.25 Tor). $\nu_{max}$ 2980, 1715, 1625 and 1090 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.60 (1H,s), 4.20 (6H,m), 1.35 (9H,m).

Preparation of diethyl S-phenyl methylene malonate (37)

Ethoxymethylene malonate (5g 0.023 mol), thiophenol (5.09g 0.046 mol) and a catalytic amount of p-toluene sulphonic acid were dissolved in toluene (20 mL) and heated so that the ethanol formed during the reaction was distilled off. The reaction mixture was heated to reflux for an additional 20 mins. The reaction mixture was washed with sodium hydroxide (10 mL of 1M solution) and water (50 mL). The organic layer was separated and dried ($Na_2SO_4$). Concentration of the resultant solution and

distillation in vacuo gave the title compound 4.2g (65%)., b.p. 172-175°C/0.5 Tor. $\nu_{max}$ 3000, 1720, 1630, 1300 and 840 $cm^{-1}$. $\delta$ ($CDCl_3$): 8.32 (1H,s), 7.40 5H,m), 4.30 (4H,m), 1.35 (6H,m). Found: $M^+$ 280.0777, $C_{14}H_{16}O_4S$ requires 280.0770.

Preparation of diethyl benzalmalonate (38)

Diethyl malonate (50g 0.312 mol), benzaldehyde (38g 0.358 mol) and piperidine (4 mL) were dissolved in benzene (100 mL) and heated to reflux for 18 hrs. Water formed during the reaction was collected in a Dean and Stark assembly. The reaction mixture was washed with water (50 mL), hydrochloric acid (50 mL of 1M solution) and saturated sodium bicarbonate (50 mL). Combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled in vacuo yielding the title compound 64.3g (83%), b.p. 125°C/0.1 Tor (lit.[9] 144-142/2 Tor). $\nu_{max}$ 2980, 1715, 1630 and 1060 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.70 (1H,s), 7.40 (5H,m), 4.30 (4H,q), 1.32 (6H,m).

Preparation of 1-(4-methoxybenzyl)-4,4-di(ethoxycarbonyl)-5-phenylthio-$\Delta^2$-1,2,3-triazoline (24)

S-phenyl methylene malonate (5g 0.018 mol) and p-methoxy benzyl azide (2.4g 0.018 mol) were left for three weeks at 65°C protected against moisture. Methanol was added and the reaction mixture was left in a deep freeze for two days. 2.4g (30%) of the title compound which crystallised as white crystals were collected by filtration, m.p. 79-80°C. $\nu_{max}$ 2950, 1730, 1600 and 1110 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.35 (5H,s), 6.95 (4H, AA'BB'q), 5.40 (1H,s), 5.00 (2H,ABq), 4.20 (4H,m), 3.70 (3H,s), 1.30 (6H,6). Found: C, 59.37: H, 5.55; N, 9.37%.

$C_{22}H_{25}N_3O_5S$ requires C, 59.59; H, 5.64; N, 9.48%.

The filtrate was left in a deep freeze for another week. 0.4g (7.2%) of white feathery crystals, m.p. 166°C were isolated by filtration. This compound was identified as p-methoxybenzoyl aminomethylenemalonate diethyl ester (39). $\nu_{max}$ 2980, 1700, 1680 and 1600 $cm^{-1}$. δ ($CDCl_3$): 11.87 (1H, broad d), 8.82 (1H,d), 7.50 (4H,AA'BB'q), 4.30 (4H,m), 3.93 (3H,s), 1.35 (6H,m). M/e 135 (base peak). Found: $M^+$ 321.1218, $C_{16}H_{19}NO_6$ requires 321.1213. Found: C, 60.20; H, 5.84; N, 4.37%. $C_{16}H_{19}NO_6$ requires C, 59.85; H, 5.96; N, 4.36.

Preparation of 1-(4-methoxybenzyl)-4,4-di(ethoxycarbonyl-5-phenyl-$\Delta^2$-1,2,3-triazoline (33).

Diethyl benzal malonate (5g 0.020 mol) and p-methoxy benzyl azide (3.3g 0.020 mol) were left for three weeks at 65°C protected against moisture. Methanol was added and the reaction mixture was left in a deep freeze for two days. 4.2g (50%) of white crystals of (33) were collected by filtration, m.p. 68°C. $\nu_{max}$ 2980, 1730, 1600 and 1120 $cm^{-1}$. δ ($CDCl_3$): 7.25 (5H,m), 6.80 (4H,AA'BB'q), 5.05 (1H,s), 4.70 (2H,AB,q), 4.30 (2H,m), 3.80 (3H,s), 3.70 (2H,m), 1.30 (3H,t), 0.80 (3H,t). M/e 121 (base peak). Found: $M^+$ 411.1754, $C_{22}H_{25}N_3O_5$ requires 411.1794. Found: C, 64.15; H, 6.16; N, 10.22%. $C_{22}H_{25}N_3O_5$ requires C, 64.23; H, 6.08; N, 10.22%.

Preparation of 1,5-diphenyl-4,4-di(ethoxycarbonyl)-$\Delta^2$-1,2,3-triazoline (9)

Diethyl benzal malonate (45g 0.18 mol) and phenyl azide (21.5g 0.18 mol) were left for three weeks at 65°C

protected against moisture. Methanol was added and the reaction mixture was left in a deep freeze for two days. 32g (48%) of white crystals identified as the title compound were collected by filtration, m.p. 94-96°C (lit.[6] m.p. 98°C). $\nu_{max}$ 2990, 1740, 1600 and 1150 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.30 (1H,m), 5.90 (1H,s), 4.40 (2H,m), 3.70 (2H,m), 1.32 (3H,t), 0.85 (3H,t). M/e 180 (base peak), 339 ($M^+ - N_2$). Found: $M^+ - N_2$ 339.1473, $C_{20}H_{21}NO_4$ requires 339.1471.

Preparation of 1,5-diphenyl-2,2-di(ethoxycarbonyl)-3,4-di(methoxycarbonyl)-pyrrolidine (44)

1,5-diphenyl-4,4-di(ethoxycarbonyl)-$\Delta^2$-1,2,3-triazoline (9), (2g 5.4 mmol) and dimethyl fumarate (0.78g 5.4 mmol) were dissolved in toluene (15 mL) and heated to reflux for 12 hrs. under nitrogen. The solvent was removed under reduced pressure and the title compound, 1.7g (56%) crystallised upon addition of ether, m.p. 119-121°C. $\nu_{max}$ 3000, 1740 and 1600 $cm^{-1}$. $\delta$ ($CDCl_3$): 6.50-760 (10H,m), 5.30 (1H,d), 4.00-4.60 (6H,m), 3.80 (3H,s), 3.40 (3H,s), 1.40 (3H,t), 1.20 (3H,t). M/e 378 (base peak), Found: $M^+$ 483.1917, $C_{26}H_{29}NO_8$ requires 483.1894.

Attempts of pyrrolidine preparation by thermal decomposition of 1-(4-methoxybenzyl)-4,4-di(ethoxycarbonyl)-5-phenyl-$\Delta^2$-1,2,3-triazoline (33) and 1-(4-methoxybenzyl)-4,4-di(ethoxycarbonyl)-5-phenylthio-$\Delta^2$-1,2,3-triazoline (24)

Triazolines (33) or (24) with an equimolar amount of activated olefin were dissolved in a suitable solvent (0.25M solution) and heated to reflux for 12 hrs. under nitrogen. The progress of the reaction was monitored by t.l.c. (petrol:EtOAc = 7:3). Heating was continued for 24 and 48 hrs.

Where appropriate the reaction mixture was separated using flash column chromatography (25g $SiO_2$).

Those experiments are summarised in the Table below:

| Entry | Activated Olefin | Solvent (triazoline) Benzene | Toluene | Xylene |
|---|---|---|---|---|
| 1 | dimethylacetylene dicarboxylate | (33) | (24),(33) | (24),(33) |
| 2 | maleic anhydride | (33) | (24),(33) | (24),(33) |
| 3 | dimethyl fumarate | (33) | (24),(33) | (24),(33) |
| 4 | isopropenyl acetate | (33) | (33) | (33) |
| 5 | methoxy methylene malonate | (33) | (33) | (33) |

* A set of experiments (entry 1) was carried out in argon atmosphere.

* A set of experiments (entry 1 and 2) was carried out under nitrogen with a catalytic amount of Vaska's salt.

* Triazolines (24) and (33) with an equimolar amount of dimethyl acetylene-dicarboxylate in ethanol, acetonitrile and tetrahydrofuran (0.25M solution) with a catalytic amount of $RuCl_3.3H_2O$ under nitrogen were heated to reflux for 12, 24 and 48 hrs.

In all the above described experiments the starting materials were recovered unchanged.

Attempts of preparation of 1-benzyl-4,4-di(ethoxycarbonyl)-5-phenylthio-$\Delta^2$-1,2,3-triazoline (24) and 1-phenyl-4,4-di(ethoxycarbonyl)-5-phenylthio-$\Delta^2$-1,2,3-triazoline (26)

S-phenyl methylene malonate and an equimolar amount of benzyl azide (or phenyl azide) were left at 65°C protected against moisture. The progress of the reaction was monitored by t.l.c. (petrol:EtOAc = 7:3). The usual reaction time of three weeks was extended to eight weeks. The t.l.c. and the proton n.m.r. spectra of the reaction mixture indicated only the presence of starting materials.

Preparation of cyclohexane-1,2-diol (mixture of *cis* and *trans*)

Cyclohexene (132g 1.6 mol) was added to formic acid (528g) and the reaction mixture was warmed to 45°C. Hydrogen peroxide (208g 100 volumes) was added dropwise over a period of 2 hrs. not allowing the temperature to rise above 60°C. The reaction mixture was stirred for an additional hour. Most of the acid was removed under reduced pressure. Upon addition of acetone and standing in a deep freeze for few hours 46g (26%) of the title compound crystallised, m.p. 79°C (lit.[99] *trans* isomer m.p. 103.5°C).

Preparation of cyclopentencarboxaldehyde

Sodium periodate (26g 0.12 mol) was suspended in water (300 mL), acidified with conc.$HNO_3$ (6.2 mL) and stirred at room temperature until the salt dissolved. The pH of the solution was adjusted to 4 by a dropwise addition of NaOH solution. Cyclohexane-1,2-diol (mixture of *cis* and *trans*) (11.8g 0.1 mol) was added at once and the mixture stirred at room temperature for 2 hrs. Ether (100 mL) and a solution of NaOH (37 mL of 20% solution) was added and the reaction mixture stirred for an additional 30 mins. The etheral layer was separated and the aqueous phase extracted with ether (3 x 100 mL). Combined etheral layers were dried ($MgSO_4$). Concentration of the solution and distillation *in vacuo* gave 5.07g (52%) of the title compound, b.p. 48°C/20 Tor (lit.[99] b.p. 52°C/20 Tor).

Preparation of ethyl-2-ethoxycarbonyl-3-(cyclopentenyl)-prop-2-enoate (46)

A solution of titaniumtetrachloride (12 mL) in $CCl_4$ (27 mL) was added dropwise to THF (216 mL) cooled at 0°C (ice salt bath). Diethyl malonate (8.6g 0.053 mol) and cyclopentencarboxaldehyde (5.2g 0.054 mol) were added at once. A solution of pyridine (17.3 mL) in THF (38 mL) was added dropwise over a period of 30 mins. with the temperature of the reaction mixture being maintained at 0°C. The reaction mixture was stirred at 0°C for 30 mins. and then at room temperature for an additional 30 mins. Water (50 mL) was added cautiously and then ether (50 mL) and the reaction mixture was stirred for an additional 15 mins. The etheral layer was separated and the aqueous phase extracted with ether (3 x 30 mL). Combined etheral layers were dried ($MgSO_4$). Concentration and distillation of the residue in vacuo yielded 9g (70%) of the title compound, b.p. 110°/0.5 Tor. $\nu_{max}$ 2980, 1780, 1740 and 1620 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.35 (1H,s), 6.35 (1H,broad,s), 4.22 (4H,q), 2.42 (4H,m), 2.00 (2H,q), 1.30 (6H,t). M/e 136 (base peak). Found: $M^+$ 238.1208, $C_{13}H_{18}O_4$ requires 238.1206.

Attempts of preparation of 1-benzyl-3,3-di-(ethoxycarbonyl)-4-cyclopentyl-$\Delta^2$-1,2,3-triazoline (47)

Ethyl-2-ethoxycarbonyl-3-(cyclopropenyl)-prop-2-enoate (46) and an equimolar amount of benzyl azide (or phenyl azide) were left at 65°C protected against moisture. The progress of the reaction was monitored by t.l.c. (petrol:EtOAc = 7:3). The usual reaction time of three weeks was extended to eight weeks. The t.l.c. and the proton n.m.r. spectra of the reaction mixture indicated only the presence of starting materials.

Preparation of ethyl thionformate

Hydrogen sulphide was introduced by means of a gas inlet tube into the solution of triethyl orthoformate (41.6g 0.30 mol), acetic acid (81.5g) hydroquinone (0.5g) and three drops of conc.$H_2SO_4$ until the theoretical amount was absorbed (10.2g 0.30 mol). The reaction mixture was then poured into water (400 mL) and extracted with ether (3 x 100 mL). The etheral layer was separated, washed with saturated $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed by distillation at atmospheric pressure. Distillation of the residue gave 5g (20%) of the title compound, b.p. 86-88°C (lit.[33] 86.5-87°C).
$\delta$ ($CDCl_3$): 9.70 (1H,s), 4.55 (2H,q), 1.40 (3H,t).

In another attempt ethyl thionformate was extracted with chloroform instead of ether and was used as a chloroform solution in the next step. The amount of ethyl thionformate was calculated from the integral of the proton n.m.r. spectra. The yield obtained using this work-up procedure was 70%.

Preparation of N-thioformyl glycine ethyl ester (59)

Glycine ethyl ester hydrochloride (3g 0.022 mol) was suspended in chloroform (50 mL) and ammonia was introduced by means of a gas inlet tube. The salt was separated by filtration. To the remaining solution of glycine ethyl ester in chloroform a solution of ethyl thioformate (1.8g 0.020 mol) in chloroform (10 mL) was added dropwise over a period of 15 mins. The reaction mixture was stirred at room temperature for 12 hrs. Concentration and distillation in vacuo gave 2.7g (72%) of the title compound, b.p. 127-130°C/0.1 Tor.

$\nu_{max}$ 3000, 1740 and 1350 $cm^{-1}$. $\delta$ ($CDCl_3$): 9.52 (1H,s), 8.07 (1H,broad,s), 4.45 (2H,s), 4.25 (2H,q), 1.30 (3H,t). $M^+$ (base peak) 147.0354, $C_5H_9NO_2S$ requires 147.0348.

Preparation of isonitrosomalonate

Diethyl malonate (50g 0.312 mol) was placed in a flask fitted with a stirrer and a thermometer and the flask was cooled in an ice salt bath. A mixture of glacial acetic acid (57 mL) and water (81 mL) was added with stirring. With a temperature at about 5°C sodium nitrite (65g 0.955 mol) was added in portions over a period of 1.5 hrs. the temperature being maintained around 5°C during the addition. After all of the sodium nitrite was added the ice bath was removed and the stirring was continued for 4 hrs. During this time the temperature reaches a maximum of 34-38°C within 2 hrs. and falls to about 29°C by the end of the stirring period. The reaction mixture was transferred into the separatory funnel and extracted with ether (3 x 100 mL). The combined etheral layers were used in the next step immediately.

Preparation of diethyl amino malonate hydrochloride

The etheral solution of diethyl isonitrosomalonate was washed with 80 mL portions of $NaHCO_3$ (1% solution) until the final wash had a distinct yellow colour. The etheral solution was dried ($Na_2SO_4$) in a refrigerator overnight and then filtered into a tared round bottomed flask. Ether was removed under reduced pressure (T° < 30°C). The residue was dissolved in absolute ethanol (250 mL) and palladium on charcoal (7g 10%) was added and hydrogenation was carried out at

atmospheric pressure. When the theoretical amount of hydrogen was absorbed the catalyst was removed by filtration and the solvent removed under reduced pressure (T° < 50°C).

The crude diethyl amino malonate was diluted with ether (200 mL), the flask was cooled in an ice bath and hydrogen chloride was introduced into the system by means of a gas inlet tube. White crystals of the title compound, 40.9g (62% based on diethyl malonate) were collected by filtration, m.p. 163°C (lit.[100] m.p. 164-165°C). $\nu_{max}$ 3300 and 1740 $cm^{-1}$. $\delta$ ($CDCl_3$): 4.15 (5H,q), 2.02 (2H,s), 1.25 (6H,t).

Preparation of N-thioformylmalonate diethyl ester (61)

Diethyl aminomalonate hydrochloride (10.2g 0.049 mol) was suspended in dry chloroform (75 mL) and ammonia was introduced by means of a gas inlet tube. The salt was separated by filtration. To the remaining solution of diethyl aminomalonate in chloroform a solution of ethyl thioformate (4.40g 0.049 mol) in chloroform (20 mL) was added dropwise over a period of 15 mins. The reaction mixture was stirred at room temperature for 12 hrs. Concentration of the solution and distillation in vacuo gave 6.5g (61%) of the title compound, b.p. 145-147°C/0.1 Tor. $\nu_{max}$ 3350 and 1750 $cm^{-1}$. $\delta$ ($CHCl_3$): 9.60 (1H,d), 9.00 (1H,broad,s), 5.65 (1H,d), 4.35 (4H,q), 1.35 (3H,t). M/e 102 (base peak), $M^+$ 219.0572, $C_8H_{13}NO_4S$ requires 219.0566.

Preparation of N-formyl glycine ethyl ester (60)

Glycine ethyl ester hydrochloride (92.5g 0.66 mol) and triethylorthoformate (99g 0.66 mol) were stirred (mechanical

stirrer) and heated till the temperature of the oil bath reached 110°C. At that temperature the salt goes into the solution. The reaction mixture was heated at that temperature for 3 hrs. On cooling a saturated solution of $NaHCO_3$ was added (100 mL) with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). Combined dichloromethane layers were dried ($MgSO_4$). The solvent was removed and the residue was distilled under reduced pressure yielding 71.3g (82%) of the title compound, b.p. 105°C/0.1 Tor. (lit.[33] b.p. 94-97°C/0.05 Tor). $\nu_{max}$ 3350, 3000, 1745 and 1680 $cm^{-1}$. $\delta$ ($CDCl_3$): 8.22 (1H,s), 7.50 (1H,broad,s), 4.20 (2H,q), 4.05 (2H,d), 1.27 (3H,t).

Preparation of N-formyl aminomalonate diethyl ester (62)

Diethylaminomalonate hydrochloride (20g 0.094 mol) and triethyl orthoformate (14g 0.094 mol) were allowed to react by the above described procedure. 17.8g (93%) of the title compound was obtained, b.p. 124-126°C/0.5 Tor. $\nu_{max}$ 3500, 3000, 1750 and 1720 $cm^{-1}$. $\delta$ ($CDCl_3$): 8.25 (1H,s), 7.30 (1H,d), 5.25 (1H,d), 4.30 (4H,q), 1.35 (6H,t). $M^+$ 204.0873, $C_8H_{14}NO_5$ requires 204.0873.

Preparation of N-thioformyl glycine ethyl ester (59) - (alternative method)

N-formyl glycine ethyl ester (2g 9 mmol) and phosphorous pentasulphide (1g 2.2 mmol) were dissolved in benzene (20 mL) and heated to reflux for 12 hrs. The reaction mixture was filtered and the solvent was removed under reduced pressure, distillation *in vacuo* gave 1.8g (82%) of the title compound, b.p. 128°C/0.1 Tor.

Preparation of N-thioformyl malonate diethyl ester (61) - (alternative method)

N-formyl amino malonate diethyl ester (2g 9.8 mmol) and phosphorous pentasulphide (1g 2.2 mmol) were dissolved in benzene (20 mL) and heated to reflux overnight. The reaction mixture was filtered and the solvent removed under reduced pressure. Distillation in vacuo gave 1.5g (72%) of the title compound.

Preparation of triethyloxonium fluoroborate

Epichlorohydrin (70g 0.755 mol) was added dropwise to a a stirred solution of freshly distilled boron trifluoride etherate (182g 1 mol) in ether (250 mL). Epichlorohydrin was added at such a rate to maintain a vigorous boiling (about 1 hour was needed). The reaction mixture was heated to reflux for an additional hour and then allowed to stand at room temperature overnight. White crystals were collected by filtration. They were either used immediately in the next step or were kept under ether in a deep freeze. Yield, 102g (71%).[57]

Preparation of trimethyloxonium fluoroborate

Freshly prepared triethyloxonium fluoroborate (85g 0.45 mol) was dissolved in anhydrous methylene chloride (250 mL) and the flask was cooled in an ice bath. Dry dimethyl ether was introduced by means of a gas inlet tube over a period of 12 hrs. The reaction mixture was allowed to stand at room temperature for an additional 12 hrs. White crystals 53g (81%) were collected by quick filtration, m.p. 139°C (lit.[58] m.p. 141-143°C). This reagent was either used immediately or was kept under dichloromethane in a deep freeze.

Attempts of conversion of N-formylamides and N-thioformyl amides into the corresponding imidates

(a) Methyl iodide as alkylating agent: N-thioformyl glycine ethyl ester (2g 13 mmol), methyl iodide (1.93g 13 mmol) and potassium carbonate (5g) were suspended in acetone (50 mL) and stirred at room temperature for 12 hrs. The reaction mixture was filtered then centrifuged (2500 rpm) and the solvent was carefully decanted (this operation was repeated three times). The solvent was removed under reduced pressure and the residue was chromatographed on a 25g silica-gel column. No pure product could be isolated.

(b) Dimethyl sulphate as alkylating agent: N-formyl glycine ethyl ester (2g 15 mmol) was dissolved in benzene (50 mL) and dimethyl sulphate (1.92g 15 mmol) was added dropwise. The reaction mixture was heated to reflux for 12 hrs. Potassium carbonate (50 mL of 50% solution) was added dropwise. The reaction mixture was extracted with ether (3 x 50 mL), combined etheral layer were dried ($MgSO_4$) and the solvent removed under reduced pressure. Polymeric gum was obtained and no components could be separated.

(c) Diazomethane as alkylating reagent: N-formyl glycine ethyl ester (2g 15 mmol) was dissolved in ether (50 mL) and an etheral solution of diazomethane (freshly prepared from 22g of Diazald[10]) was added dropwise. The reaction mixture was stirred for 12 hrs. and the solvent was removed under reduced pressure. The proton n.m.r. spectra indicated only the presence of N-formyl glycine ethyl ester.

(d) Methanol (Ethanol) and benzoyl chloride as alkylating reagents: N-formyl glycine ethyl ester (2g 15 mmol) and methanol (0.48g 15 mmol) in ether (10 mL) were added dropwise to a solution of benzoyl chloride (2.1g 15 mmol) in ether (20 mL) at 10°C. The reaction mixture was stirred at that temperature for 30 mins. and the solid which precipitated filtered. The crystals were identified as benzoic acid. The solvent from the filtrate was removed under reduced pressure and the residue was identified as N-formyl glycine ethyl ester.

The same reaction was performed with ethanol instead of methanol and the same results were obtained.

(e) Trimethyloxoniumfluoroborate as alkylating reagent - aqueous work up: N-formyl glycine ethyl ester (2g 15 mmol) was dissolved in nitromethane (20 mL), and a solution of freshly prepared trimethyloxonium fluoroborate (3.3g 22.5 mmol) in nitromethane (20 mL) was added dropwise over a period of 20 mins. The reaction mixture was stirred at room temperature for 12 hrs. The reaction mixture was poured onto a saturated solution of $NaHCO_3$ (200 mL) with vigorous stirring. The organic layer was separated and the aqueous phase was washed with dichloromethane (2 x 100 mL). Combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The proton n.m.r. spectra indicated only the presence of glycine ethyl ester.

The same reaction was carried out with N-thioformyl glycine ethyl ester, N-formyl aminomalonate diethyl ester

and N-thioformyl amino malonate diethyl ester - the analysis of proton n.m.r. spectra indicated the presence of amino acid ester derivatives only.

(f) Trimethyloxonium fluoroborate as alkylating reagent - non-aqueous work up: N-formyl glycine ethyl ester (2g 15 mmol) was dissolved in nitromethane (20 mL) and a solution of freshly prepared trimethyl oxonium fluoroborate (3.3g 22.5 mmol) in nitromethane (20 mL) was added over a period of 20 mins. The reaction mixture was stirred at room temperature for 12 hrs. Proton n.m.r. spectra of the reaction mixture was recorded, a singlet at 8.30 indicated that the alkylation had taken place. This was confirmed by t.l.c. (petrol:EtOAc = 7:3), one spot at a base line was visible under the UV lamp. The solvent was removed under reduced pressure and the residue was dissolved in THF (30 mL). This solution was added dropwise to a suspension of sodium hydride (97% 0.58g 25 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 1 hr. then it was centrifuged (2500 rpm) and the solvent decanted (this operation was repeated three times). The solvent was evaporated. The proton n.m.r. spectra of the residual polymeric gum indicated the presence of a complex mixture and no product could have been isolated.
The same complex mixture was obtained when the salt was neutralised with n-BuLi in THF at -78°C.

Preparation of ethylisocyanoacetate (63)

Phosgene (15g 0.12 mol) was absorbed in dichloromethane (80 mL) and this solution was added dropwise to a cooled mixture of N-formyl glycine ethyl ester (18.6g 0.12 mol) and triethylamine (42.5 mL) in dichloromethane (80 mL). The reaction mixture was stirred in an ice salt bath for 2 hrs. The precipitate formed during the reaction was separated by filtration. It was washed with dichloromethane and the filtrate was concentrated. Benzene (30 mL) was added and the precipitate formed was separated by filtration. The filtrate was concentrated and the residue distilled *in vacuo* yielding 16g (72%) of the title compound, b.p. 25-28°C/0.1 Tor (lit.[56] b.p. 89-91°C/11 Tor). $\nu_{max}$ 2990, 2160, 1755, 1210 and 1035 $cm^{-1}$.
$\delta$ ($CDCl_3$): 4.30 (4H,m), 1.35 (3H,t).

Attempts of preparation of isocyano diethyl malonate (64)

(a) Phosgene as dehydrating reagent: the reaction was performed as it was described above. No isocyano diethyl malonate was isolated.

(b) Phosphoryl chloride as dehydrating reagent: potassium (2.5g 0.06 mol) was allowed to react with t-butanol (40 mL). When potassium was completely dissolved N-formyl malonate diethyl ester (5g 0.02 mol) was added. Phosphoryl chloride (14g 0.091 mol) was added dropwise with vigorous stirring under nitrogen. The reaction mixture was stirred at room temperature for 1 hr. and then poured onto ice-cold saturated solution of $NaHCO_3$ (500 mL). The organic phase was extracted with dichloromethane (2 x 100 mL), combined organic layers were dried ($MgSO_4$) and the solvent was

removed under reduced pressure. Although during the work up procedure the characteristic odour of isocyanides was detected and that the infra-red spectra showed the characteristic isocyanide absorption at $\nu_{max}$ 2160 $cm^{-1}$, the title compound could not be isolated.

Attempts of conversion of ethylisocyanoacetate (63) to the imidate

(a) with methane thiol: ethylisocyanoacetate (2g 18 mmol) was dissolved in dichloromethane (20 mL) and a catalytic amount of $Cu(acac)_2$ was added. Methanethiol was introduced by means of a gas inlet tube until a theoretical amount was absorbed (1.2g 25 mmol). The reaction mixture was heated to reflux for 12 hrs. The solvent was removed under reduced pressure. The analysis of the proton n.m.r. spectra indicated only the presence of ethylisocyanoacetate.

(b) with thiophenyl: ethylisocyanoacetate (2g 18 mmol), thiophenol (1.94g 18 mmol) and a catalytic amount of $Cu(acac)_2$ were heated at 50°C for 12 hrs. The t.l.c. (petrol:EtOAc = 7.3) of the reaction mixture indicated the presence of two compounds. The separation of those two compounds was performed on a 25g silica-gel column (petrol:EtOAc = 95:5). The less polar compound was isolated as white crystals, m.p. 59°C and was identified as diphenyldisulphide (lit.[101] m.p. 61.5°C), the second compound was identified as ethylisocyanoacetate.

Preparation of Ethyl-S-ethyl formiminoglycinate (69)

N-thioformyl glycine ethyl ester (3g 20 mmol) was dissolved in dichloromethane (30 mL) and freshly prepared

triethyloxonium fluoroborate (8g 42 mmol) in dichloromethane (30 mL) was added dropwise. The reaction mixture was stirred at room temperature for 12 hrs, then with vigorous stirring (mechanical stirrer) was added dropwise to a saturated solution of $NaHCO_3$ (250 mL). The organic phase was separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined dichloromethane layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled in vacuo yielding 2.8g (78%) of the title compound, b.p. 78-80°/0.1 Tor. $\nu_{max}$ 3000, 1740, 1600 and 1200 $cm^{-1}$. $\delta$ ($CDCl_3$): 8.30 (1H,m), 4.15 (4H,m), 3.98 and 4.01 (1H,s,s), 3.05 (2H,q), 1.30 (6H,m). $M^+$ 175.0667, $C_7H_{13}NO_2S$ requires 175.0667.

The same procedure was employed in an attempt to ethylate N-formyl glycine ethyl ester, N-thioformyl amino malonate and N-formyl amino malonate. Only the amino acid ester was detected.

Preparation of benzylideneglycine ethyl ester (72)

Glycine ethyl ester hydrochloride (10.1g 0.072 mol), benzaldehyde (7.67g 0.072 mol), triethylamine (20 mL) and magnesium sulphate (6g) were suspended in dichloromethane (150 mL) and stirred at room temperature for 8 hrs. The reaction mixture was filtered and the solvent was removed under reduced pressure at room temperature. The residue was partitioned between water and ether, the etheral layer was separated, it was washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure yielding 11g (79%) of the title compound.[102] $\delta$ ($CDCl_3$): 8.10 (1H,s), 7.45 (5H,m), 4.20 (2H,s), 4.10 (2H,q), 1.22 (3H,t).

Preparation of 2-ethoxycarbonyl-3,4-dimethoxycarbonyl-5-phenyl-pyrrolidine (75)

Benzylidene glycine ethyl ester (1g 5.2 mmol) and dimethyl fumarate (0.75g 5.2 mmol) were dissolved in toluene (20 mL) and heated to reflux for 12 hrs. On cooling the solvent was removed under reduced pressure and the title compound, 0.92g (52%) crystallised upon addition of methanol, m.p. 79-81°C. $\nu_{max}$ 3300, 2980, 1740 and 1600 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.40 (5H,m), 3.30-4.50 (12H,m), 2.50 (1H,broad,s), 1.30 (3H,t). $M^+$ 335.1363, $C_{17}H_{21}NO_6$ requires 335.1369.

Attempts of generating the azomethine ylide from ethyl-S-ethyl formimino glycinate and its subsequent cycloaddition with various dipolarophiles

(a) Ethyl-S-ethyl formiminoglycinate (1g 5.2 mmol) with an equimolar amount of an activated olefin in a suitable solvent (0.25M solution) was heated to reflux for 12 (24) hrs. The progress of the reaction was monitored by t.l.c. (petrol:EtOAc = 7:3). Where appropriate the reaction components were separated by column chromatography. Those experiments are summarised in the Table below:

| Entry | Activated Olefin | Solvent | | |
|---|---|---|---|---|
| | | Benzene | THF | Toluene |
| 1 | dimethylacetylene dicarboxylate | x | x | x |
| 2 | dimethyl fumarate | x | x | x |
| 3 | dimethyl maleate | | | x |
| 4 | maleic anhydride | | | x |

* A set of experiments (entry 1 and 2) were carried out using a catalytic amount of $ZnCl_2$.

* In all above described experiments starting materials were recovered unchanged.

(b) Ethyl-S-ethyl formimino glycinate (1g 5.2 mmol) in THF (5 mL) was added dropwise to a suspension of sodium hydride (97%, 0.12g 5.2 mmol) in THF (5 mL) and dimethyl fumarate (0.75g 5.2 mmol). The reaction mixture was stirred at room temperature for 12 hrs. then it was centrifuged (2500 rpm) and the solvent was decanted (this operation was repeated three times). The solvent was removed under reduced pressure. The proton n.m.r. spectra indicated the presence of a complex mixture and no compound in satisfactorily pure state could be isolated.

(c) The same experiment described under (b) was carried out using hexane solution of n-BuLi as a base. No positive results were obtained.

Attempts of generating the azomethine ylide from the fluoroborate salt of Ethyl-S-ethyl formimino glycinate and its subsequent cycloaddition

N-thioformyl glycine ethyl ester (1g 6.6 mmol) was dissolved in dichloromethane (10 mL) and freshly prepared triethyloxonium fluoroborate (2.6g 14 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was monitored by t.l.c. (petrol:EtOAc = 7:3) and the proton n.m.r. The reaction mixture was stirred at room temperature for 12 hrs. Triethyl amine (5 mL) and dimethyl fumarate (0.82g 6.6 mmol) were added. The reaction mixture was stirred at room temperature for 12 hrs. The solvent was removed under reduced pressure and the residue was purified by column chromatography (25g silica gel). No pure component in satisfactory yield could be obtained.

Attempts of alkylation of benzylidene glycine ethyl ester with p-methoxy benzyl chloride (78)

Benzylidene glycine ethyl ester (0.5g 2.6 mmol) and p-methoxy benzyl chloride (0.4g 2.6 mmol) were dissolved in toluene (5 mL) and the reaction mixture was stirred at room temperature for 12 hrs. The reaction was monitored by t.l.c. (petrol:EtOAc = 7:3). As no reaction occurred the reaction mixture was heated to reflux for 12 (24) hrs. The salt could not be detected.

The same reaction was performed in nitromethane with the same negative result.

Preparation of N-benzyl glycine ethyl ester (80)

A solution of ethyl bromoacetate (7.4g 0.044 mol) in ether (45 mL) was added dropwise to a solution of benzylamine (10g 0.093 mol) in ether (45 mL). The reaction mixture was stirred at room temperature for 1 hr. The precipitate formed during the reaction was separated by filtration and the solvent removed from the filtrate under reduced pressure. The residue was taken up in $CCl_4$ (100 mL) and filtered through a column of $Al_2O_3$ (75g Grade II). The solvent was removed under reduced pressure and the residue distilled *in vacuo* yielding 6.4g (75%) of the title compound, b.p. 90°C/0.1 Tor (lit.[66] b.p. 139-140°C/11 Tor). $\nu_{max}$ 3315, 2990, 1735 and 1030 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.20 (5H,s), 4.20 (2H,q), 3.80 (2H,s), 3.30 (2H,s), 1.85 (1H,broad,s), 1.20 (3H,t). $M^+$ 193.1103, $C_{11}H_{15}NO_2$ requires 193.1098.

N-benzyl glycine ethyl ester was dissolved in ether (50 mL) and HCl was introduced by means of a gas inlet tube. White crystals were collected by filtration.

Preparation of N-benzyl-N-formyl glycine ethyl ester (81)

N-benzyl glycine ethyl ester hydrochloride (7.6g 0.033 mol) and triethyl orthoformate (10g 0.076 mol) were heated at 110°C for 12 hrs. The ethanol formed during the reaction and the excess of triethyl orthoformate were removed under reduced pressure. The residue was washed with a saturated solution of $NaHCO_3$ and extracted with dichloromethane (3 x 50 mL). Combined dichloromethane layers were dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue was distilled *in vacuo* yielding 4.9g (67%) of the title compound, b.p. 120°C/0.1 Tor (lit.[103] b.p. 150-152°C/12 Tor). $\nu_{max}$ 2980, 1740 and 1670 $cm^{-1}$. $\delta$ ($CDCl_3$): 8.20 (1H,d), 7.20 (5H,m), 4.60 (2H,d), 3.80-4.30 (4H,m), 1.20 (3H,t). $M^+$ 221.1057, $C_{12}H_{15}NO_3$ requires 221.1053.

Preparation of N-benzyl-N-thioformyl glycine ethyl ester

N-benzyl-N-formyl glycine ethyl ester (2g 9 mmol) and phosphorous pentasulphide (1g 2.2 mmol) were dissolved in benzene (20 mL) and heated to reflux for 12 hrs. The reaction mixture was filtered and the solvent was removed under reduced pressure yielding 1.9g (88%) of the title compound. $\nu_{max}$ 2990, 1740 and 1590 $cm^{-1}$. $\delta$ ($CDCl_3$): 9.40 (1H,d), 7.30 (5H,s), 4.75 (2H,s), 4.40 (2H,s), 4.15 (2H,q), 1.25 (3H,t). $M^+$ 237.0824, $C_{12}H_{15}NO_2S$ requires 237.0824.

Preparation of ethyl bromomalonate

Diethyl malonate (80g 0.5 mol) was dissolved in $CCl_4$ (75 mL), and a few drops of bromine were added. The reaction was initiated by means of a spot light (500W) and bromine

(79g 0.5 mol) was added dropwise over a period of 1 hr. The reaction mixture was heated to reflux for 2 hrs. On cooling the reaction mixture was washed with a solution of $Na_2CO_3$ (4 x 100 mL of 5% solution). The organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled *in vacuo* yielding 85g (72%) of the title compound, b.p. 64°C/0.1 Tor (lit.[104] b.p. 121-125°C/16 Tor).

Attempt of preparation of N-benzyl aminomalonate diethyl ester

The synthesis of the title compound was attempted by analogy with the described procedure for the preparation of N-benzyl glycine ethyl ester. The reaction failed to yield the desired product.

Preparation of 1-benzyl-2-ethoxycarbonyl-3,4-dimethoxycarbonyl-5-phenyl-$\Delta^3$-pyrroline (84)

N-benzyl-N-formyl glycine ethyl ester (2.3g 10 mmol) and freshly prepared triethyl oxonium fluoroborate (3.1g 16 mmol) were dissolved in dichloromethane (50 mL) and stirred at room temperature for 12 hrs. The progress of the reaction was monitored by t.l.c. (petrol:EtOAc = 7:3) and by proton n.m.r. After 12 hrs. of stirring, dimethylacetylene dicarboxylate (1.5g 10 mmol) was added by means of a syringe through a septum cap. Triethyl amine (5 mL) was added dropwise over a period of 10 mins and the reaction mixture stirred at room temperature for 12 hrs. The solvent was removed under reduced pressure. The t.l.c. of the crude product indicated the presence of two components. The separation was performed on a 30g silica gel (petrol:EtOAc = 95:5). 0.75g of the first component were

isolated and it was identified as N-benzyl-N-formyl glycine ethyl ester. The second component, 0.7g (17%) was isolated as a yellow viscous oil and was identified as (84). $\nu_{max}$ 3000, 1750, 1700 and 1570 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.25 (5H,m), 4.55 (2H,s), 3.30-4.15 (4H,m), 3.85 (3H,s), 3.55 (3H,s), 3.15 (2H,q), 1.15 (6H,m). $M^+$ 345.1218, $C_{18}H_{19}NO_6$ requires 345.1213.

Preparation of 2-ethoxy-3-benzyl-4-ethoxycarbonyl-6,8-dioxo-7-phenyl-3,7-diazabicyclo-[3,3,0]-octane

N-benzyl-N-formyl glycine ethyl ester (5g 22 mmol) and freshly prepared triethyl oxonium fluoroborate (6.8g 35 mmol) were dissolved in dichloromethane (100 mL) and stirred at room temperature for 12 hrs. N-Phenyl maleimide (3.9g 22 mmol) was added. Triethyl amine (7.5 mL) was added dropwise over a period of 10 mins, and the reaction mixture was stirred at room temperature for 12 hrs. The solvent was removed under reduced pressure. The t.l.c. of the reaction mixture indicated the presence of three products. The separation was performed on a 50g silica gel column (petrol:EtOAc = 95:5). 1.42g of the first component was isolated and it was identified as being N-benzyl-N-formyl glycine ethyl ester, 1.1g of the second component was isolated and it was identified as N-phenylmaleimide. The title component was isolated and recrystallised from methanol yielding pale yellow crystals (0.85g 9%) m.p. 54°C. $\nu_{max}$: 3000, 1750, 1720, 1600, 790 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.05 (10H,m), 4.85 (2H,AB,q), 4.10 (6H,m), 3.45 (2H,q), 1.20 (6H,m).

Molecular ion was not present in the mass spectrum and time did not permit to carry out the microanalysis.

Preparation of ethyl 3-ethoxy-3-trimethylsilyloxy-propenoate

Diethyl malonate (5g 30 mmol) in THF (30 mL) was added dropwise over a period of 30 mins. to a suspension of sodium hydride (50% dispersion in oil, 1.6g 33 mmol) in THF (30 mL). The reaction was stirred at room temperature for 2 hrs. Trimethylsilyl chloride (8.47g 78 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 hrs. The solvent was removed under reduced pressure and the residue distilled *in vacuo* yielding 5.5g (80%) of the title compound, b.p. 62°C/0.01 Tor (lit.[105] b.p. 61°C/0.1 Tor).

Preparation of ethyl-2-isocyano-3-hydroxy-3-phenyl propionate (91)

To a suspension of sodium hydride (97%, 0.21g 8.8 mmol) in THF (30 mL) a solution of ethylisocyanoacetate (1g 8.8 mmol) in THF (30 mL) and benzaldehyde (0.93g 8.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 hrs. then poured into water (100 mL) acidified with HCl (pH 3-4) and extracted with ether (2 x 100 mL). Combined etheral layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled *in vacuo* yielding 1.2g (62%) of the title compound, b.p. 155-156°C/0.1 Tor (lit.[73] b.p. 156-158°C/0.1 Tor).

Attempts of silylation of ethylisocyanoacetate

(a) Ethyl isocyanoacetate (1g 8.8 mmol) in THF (20 mL) was added dropwise over a period of 30 mins. to a suspension of sodium hydride (50% dispersion in oil, 0.44g 8.8 mmol). The reaction mixture was stirred at room temperature for

Preparation of ethyl 3-ethoxy-3-trimethylsilyloxy-propenoate

Diethyl malonate (5g 30 mmol) in THF (30 mL) was added dropwise over a period of 30 mins. to a suspension of sodium hydride (50% dispersion in oil, 1.6g 33 mmol) in THF (30 mL). The reaction was stirred at room temperature for 2 hrs. Trimethylsilyl chloride (8.47g 78 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 3 hrs. The solvent was removed under reduced pressure and the residue distilled *in vacuo* yielding 5.5g (80%) of the title compound, b.p. 62°C/0.01 Tor (lit.[105] b.p. 61°C/0.1 Tor).

Preparation of ethyl-2-isocyano-3-hydroxy-3-phenyl propionate (91)

To a suspension of sodium hydride (97%, 0.21g 8.8 mmol) in THF (30 mL) a solution of ethylisocyanoacetate (1g 8.8 mmol) in THF (30 mL) and benzaldehyde (0.93g 8.8 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 3 hrs. then poured into water (100 mL) acidified with HCl (pH 3-4) and extracted with ether (2 x 100 mL). Combined etheral layers were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue distilled *in vacuo* yielding 1.2g (62%) of the title compound, b.p. 155-156°C/0.1 Tor (lit.[73] b.p. 156-158°C/0.1 Tor).

Attempts of silylation of ethylisocyanoacetate

(a) Ethyl isocyanoacetate (1g 8.8 mmol) in THF (20 mL) was added dropwise over a period of 30 mins. to a suspension of sodium hydride (50% dispersion in oil, 0.44g 8.8 mmol). The reaction mixture was stirred at room temperature for

3 hrs. Trimethyl silylchloride (2.4g 22 mmol) was added dropwise and the reaction mixture was stirred at room temperature for an additional 3 hrs. It was then filtered and centrifuged (2500 rpm). The solvent was decanted and it was removed under reduced pressure. The proton n.m.r. spectra of the crude reaction product was recorded in $CCl_4$ (no internal standard). No trimethylsilyl group could be detected in the n.m.r. spectrum.

(b) The same experiment was repeated using dry sodium hydride (97%, 0.22g 8.8 mmol). No positive result was obtained.

(c) Another experiment was carried out using dry NaH suspended in a mixture THF:HMPA = 1:1. No positive results were obtained.

(d) An experiment was carried out using a hexane solution of n-BuLi at -78°C. Trimethyl silylchloride was added at the same temperature and the reaction mixture was allowed slowly to warm to room temperature. No positive results were obtained.

(e) Two experiments were carried out (as described under (c) and (d)) using trimethylsilyl iodide. No positive results were obtained.

Attempts of silylation of N-benzyl-N-formyl glycine ethyl ester

A set of experiments was performed in an attempt to silylate N-benzyl-N-formyl glycine ethyl ester; the experimental conditions are outlined below:

(a) N-benzyl-N-formyl glycine ethyl ester, NaH (97%), $Me_3SiCl$ (molar ratio 1:1.1:2.5) in THF at RT.

(b) N-benzyl-N-formyl glycine ethyl ester, NaH (97%), $Me_3SiCl$ (molar ratio 1:1.1:2.5) in THF:HMPA (1:1) at RT.

(c) N-benzyl-N-glycine ethyl ester, n-BuLi (1.6M solution in hexane), $Me_3SiCl$, (molar ratio 1:1.1:2.5) in THF at -78°C.

(d) N-benzyl-N-formyl glycine ethyl ester, n-BuLi (1.6M solution in hexane), $Me_3SiCl$ (molar ratio 1:1.1:2.5) in THF:HMPA (1:1) at -78°C.

(e) Experiments a, b, c, d instead of $Me_3SiCl$, $Me_3SiI$ was used.

(f) N-benzyl-N-formyl glycine ethyl ester, $Et_3N$, trimethylsilyl triflate (molar ratio 1:1.1:1.2) in ether at 0-10°C.

In all the above described experiments no silylated product was observed.

Preparation of ethyl trimethylsilylacetate

Freshly sand-papered zinc strips (7.28g 0.11g atom) were suspended in ether (115 mL). A solution of ethyl bromo-acetate (9.2g 0.115 mol) and trimethylsilylchloride (10g 0.092 mol) in ether (50 mL) were added dropwise with a vigorous stirring. During the addition the reaction mixture was heated to reflux gently. The reaction mixture was stirred for an additional 4 hrs., then cooled and HCl (92 mL of 1M solution) was carefully added. Stirring was continued for another 15 mins. The organic layer was separated, washed with water (100 mL), saturated $NaHCO_3$ (100 mL). The etheral layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure at room temperature. The residue was distilled *in vacuo* yielding 8.9g (61%) of the title compound, b.p. 40°C/20 Tor (lit.[77] b.p. 76-77°C/40 Tor). $\delta$ ($CCl_4$): 4.05 (2H,q), 1.85 (2H,s), 1.25 (3H,t), 0.20 (9H,s).

Preparation of O-ethyl-C,O-bis-(trimethylsilyl)-ketene-acetal (94)

To a solution of diisopropylamine (24g 0.23 mol) in THF (250 mL) cooled at -78°C a solution of n-BuLi (155 mL of a 1.5M solution in hexane 0.23 mol) was added and the reaction mixture was stirred at -78°C for 30 mins. Ethyl trimethylsilyl-acetate (25g 0.156 mol) was added dropwise over a period of 30 mins. and the reaction mixture was stirred at -78°C for 3.5 hrs. Trimethylsilylchloride (31g 0.285 mol) was added dropwise and the reaction mixture was stirred at room temperature for 1.5 hrs. The solvent was removed under reduced pressure and the residue was distilled *in vacuo* yielding 26g (72%) of the title compound, b.p. 39-40°C/0.5 Tor (lit.[76] b.p. 40-41°C/0.5 Tor). $\nu_{max}$ 2960, 1610 and 1160 $cm^{-1}$. $\delta$ ($CCl_4$): 4.00 (2H,q), 3.00 (1H,s), 1.25 (3H,t), 0.30 (9H,s), 0.05 (9H,s).

Preparation of N-benzyl-N-formyl amine (95)

Benzylamine (30g 0.28 mol) and ethyl formate (20.7g 0.28 mol) were heated to reflux for 12 hrs. The reaction mixture was allowed to cool and petrol (40-60) was added. 34g (89%) of white crystals which were separated by filtration were obtained, m.p. 60°C (lit.[106] m.p. 59-60°C).

Attempt of condensation of N-benzyl-N-formyl amine with O-ethyl-C,O-bis-(trimethylsilyl)-ketene-acetal

To a solution of O-ethyl-C,O-bis-(trimethylsilyl)-ketene-acetal (5g 0.012 mol) in ether (25 mL) a solution of N-benzyl-N-formyl amine (2.9g 0.021 mol) in ether (25 mL) was added dropwise. The reaction mixture was stirred at room temperature for 6 hrs. The solvent was removed under reduced

Preparation of O-ethyl-C,O-bis-(trimethylsilyl)-ketene-acetal (94)

To a solution of diisopropylamine (24g 0.23 mol) in THF (250 mL) cooled at -78°C a solution of n-BuLi (155 mL of a 1.5M solution in hexane 0.23 mol) was added and the reaction mixture was stirred at -78°C for 30 mins. Ethyl trimethylsilyl-acetate (25g 0.156 mol) was added dropwise over a period of 30 mins. and the reaction mixture was stirred at -78°C for 3.5 hrs. Trimethylsilylchloride (31g 0.285 mol) was added dropwise and the reaction mixture was stirred at room temperature for 1.5 hrs. The solvent was removed under reduced pressure and the residue was distilled in vacuo yielding 26g (72%) of the title compound, b.p. 39-40°C/0.5 Tor (lit.[76] b.p. 40-41°C/0.5 Tor). $\nu_{max}$ 2960, 1610 and 1160 $cm^{-1}$. $\delta$ ($CCl_4$): 4.00 (2H,q), 3.00 (1H,s), 1.25 (3H,t), 0.30 (9H,s), 0.05 (9H,s).

Preparation of N-benzyl-N-formyl amine (95)

Benzylamine (30g 0.28 mol) and ethyl formate (20.7g 0.28 mol) were heated to reflux for 12 hrs. The reaction mixture was allowed to cool and petrol (40-60) was added. 34g (89%) of white crystals which were separated by filtration were obtained, m.p. 60°C (lit.[106] m.p. 59-60°C).

Attempt of condensation of N-benzyl-N-formyl amine with O-ethyl-C,O-bis-(trimethylsilyl)-ketene-acetal

To a solution of O-ethyl-C,O-bis-(trimethylsilyl)-ketene-acetal (5g 0.012 mol) in ether (25 mL) a solution of N-benzyl-N-formyl amine (2.9g 0.021 mol) in ether (25 mL) was added dropwise. The reaction mixture was stirred at room temperature for 6 hrs. The solvent was removed under reduced

pressure. The proton n.m.r. spectra of the residue indicated the presence of ethyltrimethylsilyl acetate and N-benzyl-N-formyl-N-(trimethylsilyl)-amine.

Preparation of sarcosine methyl ester hydrochloride

Sarcosine (20g 0.22 mol) was dissolved in methanol (840 mL) and thionyl chloride (101 mL) was added dropwise over a period of 2 hrs. The reaction mixture was heated to reflux for 3 hrs, then cooled and the solvent removed under reduced pressure; traces of thionyl chloride were removed by diluting the solution with benzene and reconcentrating. The white solid (27g, 87%) was washed with dry ether and dried overnight in a vacuum oven. $\delta$ ($H_2O$): 4.10 (2H,s), 3.85 (3H,s), 2.80 (3H,s).[80]

Preparation of N-trityl sarcosine methyl ester (99)

To a suspension of sarcosine methyl ester hydrochloride (10g 0.071 mol) in chloroform (165 mL) and triethylamine (18.3 mL), trityl chloride (18.2g 0.065 mol) was added. The reaction mixture was stirred at room temperature for 8 hrs., it was then washed with water (100 mL), diluted acetic acid (100 mL of 1M solution) and water (100 mL) again. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The remaining slurry was dissolved in petrol (40-60) and filtered through a column of silica gel (40g) with petrol. Removal of the solvent under reduced pressure yielded 18g (72%) of the title compound. M.p. 86°C. $\nu_{max}$: 3000, 1745 and 1450 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.20 (15H,m), 3.65 (3H,s), 2.95 (2H,s), 2.10 (3H,s). Found: $M^+$ 345.1702, $C_{23}H_{23}NO_2$ requires 345.1729.

Attempts of oxidising N-trityl sarcosine methyl ester

(a) hydrogen peroxide: N-trityl sarcosine methyl ester (2g 5 mmol) was dissolved in glacial acetic acid (20 mL) and hydrogen peroxide (5 mL, 30%) was added and the reaction mixture was stirred at 70-80°C for 3 hrs. An additional portion of hydrogen peroxide (5 mL 30%) was added and the reaction mixture was maintained for an additional nine hours at that temperature. Upon cooling the solution was concentrated under reduced pressure, diluted with water (100 mL) and concentrated again. The residue was made strongly alkaline with sodium carbonate and extracted with chloroform. Evaporation of the solvent yielded an oil which was identified as sarcosine methyl ester.

(b) m-chloroperbenzoic acid: To a solution of sarcosine methyl ester (2g 5 mmol) in glacial acetic acid (20 mL) a suspension of m-chloroperbenzoic acid (1.29g 7.5 mmol) in glacial acetic acid (10 mL) was added. The reaction mixture was heated at 50-60°C for 1.5 hrs. then poured into water (150 mL). The insoluble material was filtered off and the filtrate evaporated to dryness. No N-oxide could be detected.

(c) m-chloro perbenzoic acid; alternative method:
m-Chloroperbenzoic acid of 99% assay was obtained by washing the commercial 85% material with a phosphate buffer at pH 7.5 and drying the residue under the reduced pressure.[86]
To a solution of m-chlorobenzoic acid (0.8g 5 mmol) in chloroform (10 mL) a solution of N-trityl sarcosine methyl

ester (2g 5 mmol) in chloroform (5 mL) was added dropwise. The temperature of the reaction mixture was maintained below 5°C. The reaction mixture was stirred for 3 hrs. during which time the mixture was allowed to come to room temperature. The solution was passed through a column of alkaline alumina (40g). Evaporation of the solvent yielded an oil which was identified as sarcosine methyl ester.

(d) t-butylhydroperoxide: A solution of N-trityl methyl sarcosine (2g 5 mmol), t-butylhydroperoxide (0.46g 5 mmol) and a catalytic amount of $VO(acac)_2$ in t-butyl alcohol (30 mL) were heated to reflux for 3 hrs. Upon cooling the reaction mixture was concentrated but no N-oxide could be detected.

(e) $MoO_5$.HMPT: Diperoxo oxohexamethyl phosphoramido molybdenum (VI) was prepared by dissolving molybdenum trioxide (50g) at 40°C in hydrogen peroxide (250 mL 30%). The yellow solution so obtained was cooled to 10°C and HMPT (62.3g) was added with efficient stirring. A yellow precipitate was collected by filtration and it was washed several times with ether. The dried material was crystallised from methanol and it was stored in a deep freeze.[88]
N-trityl methyl sarcosine (2g 5 mmol) was dissolved in dichloromethane (50 mL) and $MoO_5$.HMPT (5g) was added. The reaction mixture was stirred for 3 hrs. at room temperature. No N-oxide could be detected.

Preparation of N-phenylthiomethyl sarcosine methyl ester (104)

A solution of sarcosine methyl ester (16.2g 0.157 mol), thiophenol (15.3g 0.157 mol), paraformaldehyde (6.75g 0.225 mol) and a catalytic amount of p-toluene sulphonic acid in methanol (100 mL) were heated to reflux for 24 hrs. The excess of paraformaldehyde was filtered off and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (100 mL) and it was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Distillation of the residue *in vacuo* yielded 25.4g (72%) of the title compound.
B.p. 120-124°C/0.5 Tor (lit.[92] b.p. 119-120°C/0.05 Tor).
$\nu_{max}$: 2970, 1750, 1440, 1060 and 740 $cm^{-1}$. $\delta$ ($CDCl_3$): 7.30 (5H,m), 4.60 (2H,s), 3.65 (3H,s), 3.40 (2H,s), 2.50 (3H,s).
Found: $M^+$ 225.0839, $C_{11}H_{15}NO_2S$ requires 225.0824.

Preparation of N-phenylthiomethyl-N-benzyl glycine ethyl ester (111)

The title compound was prepared by analogy to the preparation of N-phenylthiomethyl sarcosine methyl ester described above with the following reagents: N-benzyl glycine ethyl ester (5g 0.025 mol), thiophenol (2.75g 0.025 mol), paraformaldehyde (1.08g 0.036 mol) and a catalytic amount of p-toluene sulphonic acid in methanol (75 mL).
Yield 6.3g (74%). $\nu_{max}$: 2980, 1745 and 1190 $cm^{-1}$.
$\delta$ ($CDCl_3$): 7.08 (5H,s), 4.45 (2H,s), 3.95 (2H,q), 3.70 (2H,s), 3.35 (2H,s), 1.18 (3H,s). M/e (base peak) 91, m/e 206 ($M^+$-PhS) (76.3%). Found: ($M^+$-PhS) 206.1189, $C_{12}H_{16}NO_2$ requires 206.1182.

Preparation of N-methyl-$\Delta^3$-tricarboxymethoxy pyrrolidine (112)

N-phenyl thiomethyl sarcosine methyl ester (1g 4.4 mmol) and dimethyl acetylene dicarboxylate (0.75g 5.2 mmol) were added to a suspension of sodium hydride (0.21g 9 mmol) in dimethoxy ethane (10 mL) and HMPA (0.9 mL). The reaction mixture was heated to reflux for 8 hrs. Upon cooling the precipitate was filtered off and the filtrate was washed with sodium carbonate (30 mL of 30% solution). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed under reduced pressure. The analysis of the proton n.m.r. spectrum indicated the presence of HMPA. $\delta$ ($CDCl_3$): 2.70 and 2.55 (two singlets of equal intensity) and phenyl methyl sulphide $\delta$ ($CDCl_3$): 5.15 (5H,s), 2.45 (3H,s).

The insoluble material was dissolved in $D_2O$ and the proton n.m.r. spectra was recorded. $\delta$ ($D_2O$): 3.70 (3H,s), 3.30-3.00 (3H,m), 3.05 (3H,s), 2.90 (3H,s), 2.70 (3H,s).

The same experiment was performed without HMPA and the reaction mixture worked up as it is described above. The proton n.m.r. spectrum of the crude product was recorded. $\delta$ ($CDCl_3$): 3.75 (6H,s), 3.65 (3H,s), 3.60 (3H,s).

The same experiment was performed with cyclopentenone as dipolarophile; no cycloadduct was detected.

## REFERENCES


1. C. H. Strachan, PhD Thesis, University of Stirling, 1982.
2. S. Husinec, A.E.A. Porter, J. S. Roberts and C. H. Strachan, submitted for publication in J.Chem.Soc.Perkin 1.
3. P. A. Gambetski, N. M. Loim and D. S. Zhuk, Russ.Chem.Rev., 1966, 2, 105.
4. L. Wolff, Ann., 1912, 394, 30, 60.
5. P. Scheiner, Selected Organic Transformations, 1970, 1, 327.
6. R. Carrié and F. Texier, Bull.Soc.Chim.Fr., 1971, 3642.
7. F. Texier and R. Carrié, Bull.Soc.Chim.Fr., 1971, 4119.
8. S. S. Washburne, W. R. Peterson and D. A. Berman, J.Org.Chem., 1972, 37, 1738.
9. C. F. Allen and F. W. Sprangler, Org.Synth.Col., 3, 1955, 377.
10. L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, 1, Wiley, 1967.
11. H. King and T. S. Work, J.Chem.Soc., 1940, 1307.
12. R. Huisgen, G. Szeimies and L. Mobius, Chem.Ber., 1966, 99, 475.
13. M. A. Stolberg, J. J. O'Neill and T. Wagner-Javregg, J.Am.Chem.Soc., 1953, 75, 5045.
14. J. H. Makgraf, M. S. Ibsen, J. B. Kinney, J. W. Kuper, J. B. Luric, D. R. Mars, C. A. McCarthey, J. M. Pile and T. J. Pritchard, J.Org.Chem., 1977, 42, 2631.
15. F. Texier and R. Carrié, Bull.Soc.Chim.Fr., 1972, 258.
16. F. Texier and R. Carrié, Bull.Soc.Chim.Fr., 1972, 2373.
17. F. Texier and R. Carrié, Bull.Soc.Chim.Fr., 1974, 310.

18. Y. Gelas-Mialhe, R. Hierle and R. Vessiere, Bull.Soc.Chim.Fr., 1974, 709.

19. T. Durst in "Comprehensive Organic Chemistry, 3, pt.11.6, Pergamon Press, 1979.

20. R. G. Salmon, Tetrahedron, 1983, 39, 485.

21. A. Padwa and H. Ku, J.Org.Chem., 1979, 44, 255.

22. A. Padwa, Angew.Chem.Int.Ed., 1977, 15, 123.

23. W. Oppolzer, Angew.Chem.Int.Ed., 1977, 16, 10.

24. R. Frey, Adv.Phys.Org.Chem., 1966, 4, 147.

25. H. Heine, Mech.Mol.Migr., 1971, 3, 145.

26. Dermer and Ham in "Ethylene amine and Other Aziridines", p.282, Academic Press, 1969.

27. R. B. Woodward and R. Hoffmann, in "The Conservation of Orbital Symmetry", Academic Press, 1970.

28. W. Lehnert, Tetrahedron, 1973, 29, 635.

29. R. Grigg, H.Q.N. Gunaratne and J. Kemp, J.Chem.Soc.Perkin 1, 1984, 41.

30. R. Roger and D. G. Neilson, Chem.Rev., 1961, 61, 179.

31. S. R. Sandler and W. Karo, "Organic Functional Group Preparation", 3, Academic Press, 1972.

32. F. C. Schaefer and G. A. Peters, J.Org.Chem., 1961, 26, 142.

33. G. D. Hartman and L. M. Weinstock, Organic Synthesis, 1980, 59, 184.

34. D. G. Neilson in "The Chemistry of Amides and Imidates", Wiley, 1975.

35. W. Wolter and K. B. Reubke in "The Chemistry of Amides", Interscience Publishers, 1970.

36. K. A. Petrov and L. N. Andrev, Russ.Chem.Rev., 1971, 40, 505.

37. R. G. Glushkov and V. G. Granik, Adv.Heterocyclic Chem., 1970, 12, 185.

38. B. C. Challis and J. A. Challis in "The Chemistry of Amides", Interscience Publishers, 1970.

39. H. Berdereck, F. Efferenberger and E. Henseleit, Chem.Ber., 1965, 98, 2754.

40. J. Yates and E. Haddock, Brit.Pat., 1966, 1,039,459; Chem.Abs., 1966, 65, 14357.

41. P. Reynaud, R. C. Moreau and N. H. Thu, Compt.Rend., 1961, 253, 1968.

42. H. Berdereck, G. Simshen and W. Kanthlerner, Chem.Ber., 1971, 104, 924.

43. H. Berdereck, R. Gompper, H. Rempfer, K. Kelm and H. Keck, Chem.Ber., 1959, 92, 329.

44. H. Berdereck, F. Efferenberger and S. Simchen, Chem.Ber., 1963, 96, 1350.

45. N. Stojanic and V. Han, Bul.Sci.Conseil.Acad.RSF Yugoslavia, 1966, 11, 98; Chem.Abs., 1966, 65, 20084.

46. O. O. Orazi, R. A. Corral and H. Schuttenberg, Tetrahedron Lett., 1969, 2639.

47. R. Blaser, P. Imfeld and O. Schindler, Helv.Chim.Acta., 1969, 52, 569.

48. R. Ohme and E. Schmitz, Ann.Chem., 1968, 716, 207.

49. R. Ohme and E. Schmitz, Angew.Chem.Int.Ed., 1967, 6, 566.

50. R. Ohme and E. Schmitz, German (East) Pat., 1967, 57,119; Chem.Abs., 1968, 68, 114092r.

51. T. Sageusa, Y. Ito, S. Kobayashi and K. Hirota, Tetrahedron Lett., 1967, 521.

52. T. Sageusa, Y. Ito, S. Kobayashi, N. Takeda and K. Hirota, Tetrahedron Lett., 1967, 1273.

53. T. Sageusa, Y. Ito, S. Kobayashi, K. Hirota and N. Takeda, Can.J.Chem., 1969, 47, 1217.

54. T. Sageusa, S. Kobayashi, K. Hirota, Y. Okumura and Y. Ito, Bull.Chem.Soc.Japan, 1968, 41, 1638.

55. K. Hoffman, Gokel Marquarding and Ugi in "Isonitrile Chemistry", Academic Press, 1971.

56. I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer and K. Offermann, Angew.Chem.Int.Ed., 1965, 4, 472.

57. H. Merween, Organic Synthesis, 1966, 46, 113.

58. H. Merween, Organic Synthesis, 1966, 46, 120.

59. W. Ried and E. Schmidt, Ann.Chem., 1966, 695, 217.

60. W. Ried, D. Piechaczek and E. Vollberg, Ann.Chem., 1970, 734, 13.

61. R. F. Borch, Tetrahedron Lett., 1968, 61.

62. R. R. Fraser and R. B. Swingle, Can.J.Chem., 1970, 48, 2065.

63. S. Petersen and E. Tietze, Ann.Chem., 1959, 623, 166.

64. R. Huisgen, R. Grashey and J. Sauer in "The Chemistry of Alkenes", Interscience Publishers, 1964.

65. G. Tennant in "Comprehensive Organic Chemistry", 2, Pergamon Press, 1979.

66. E. Hardegger, F. Szabo, P. Liechti, Ch. Rostetter and W. Zankowska-Jasinska, Helv.Chim.Acta., 1968, 51, 78.

67. T. Livinghouse and R. Smith, J.Chem.Soc.Chem.Comm., 1968, 210.

68. R. Smith and T. Livinghouse, J.Org.Chem., 1983, 48, 4773.

69. A. Padwa, G. Haffmann and M. Thomas, Tetrahedron Lett., 24, 4303.

70. E. Vedejs and F. G. West, J.Org.Chem., 1983, 48, 4773.

71. E. Colvin in "Silicon in Organic Synthesis", Butterworths, 1981.

72. D. Hoppe, Angew.Chem.Int.Ed., 1974, 13, 789.

73. U. Scholkopf, F. Gerhart and R. Schorder, Angew.Chem. Int.Ed., 1969, 8, 672.

74. U. Scholkopf, F. Gerhart, R. Schorder and D. Hoppe, Ann.Chem., 1972, 766, 116.

75. C. A. Buehler and C. A. MacKenzie, J.Am.Chem.Soc., 1937, 421.

76. I. Matsuda, S. Murata and Y. Izumi, J.Org.Chem., 1980, 45, 237.

77. R. J. Fessenden and J. S. Fessenden, J.Org.Chem., 1967, 32, 3535.

78. R. Beaugelmas, G. Negron and G. Roussi, J.Chem.Soc.Chem.Comm., 1983, 31.

79. H. Takayama and T. Nomoto, J.Chem.Soc.Chem.Comm., 1982, 408.

80. M. A. Wuoanela and R. B. Woodward, Tetrahedron, 1976, 32, 1085.

81. L. Zevras, D. Borouas and E. Gazis, J.Am.Chem.Soc., 1963, 85, 3660.

82. B. C. Challis and A. R. Butler in "The Chemistry of Amino Group", Wiley, 1968.

83. H. Freytag in "Methoden der Organischen Chemie" (Houben-Weyl) 11 pt.2 (Ed. E. Müller) George Thieme, Stuttgart, 1958, p.190.

84. D. Swern, Chem.Rev., 1946, 68, 1484.

85. J. Cymerman Craig and K. K. Purshothman, J.Org.Chem., 1970, 35, 1721.

86. N. N. Scwartz and J. H. Blumbergs, J.Org.Chem., 1964, 29, 1976.

87. M. N. Sheng and J. G. Zajacek, J.Org.Chem., 1968, 33, 588.

88. H. Mimoun, I. S. de Roch and L. Sajus, Bull.Soc.Chim.Fr., 1969, 1481.

89. H. Mimoun, I. S. de Roch and L. Sajus, Tetrahedron, 1970, 26, 37.

90. P. S. Bailey, Chem.Rev., 1958, 58, 925.

91. J. P. Lorand and P. D. Bartelett, J.Am.Chem.Soc., 1966, 88, 3294.

92. N. Imai, Y. Terao, K. Achiwa and M. Sekiya, Tetrahedron Lett., 1984, 25, 1579.

93. M. Asaoka, K. Miyake and H. Takei, Chem.Lett., 1975, 1149.

94. W. C. Still, M. Khan and A. Mitra, J.Org.Chem., 1978, 43, 2923.

95. D. D. Perrin, W.L.F. Armarego and D. R. Perrin in "Purification of Laboratory Chemicals", Pergamon Press, 1966.

96. D. R. Buckle and C.J.M. Rockell, J.Chem.Soc.Perkin 1, 1982, 627.

97. R. Curtius and G. Eherhart, Chem.Ber., 55, 1565.

98. W. E. Parham and L. J. Reed, Org.Synth.Col., 3, 1955, 395.

99. J. R. Brown, H. B. Henbert and E.R.H. Jones, J.Chem.Soc., 1950, 3634.

100. W. H. Hartung, J.R.H. Beaujon and G. Cocolas, Org.Synth.Col., 5, 1973, 376.

101. I. Gutmann, Chem.Ber., 56, 2366.

102. G. Stork, A.Y.W. Long and A. M. Touzin, J.Org.Chem., 1976, 41, 3491.

103. J. A. King and F. H. McMillan, J.Am.Chem.Soc., 1950, 72, 1236.

104. C. S. Palmer and P. W. McWherter, Org.Synth.Col., 1, 1964, 245.

105. H. Emde et al., Synthesis, 1982, 1.

106. J.P.E. Human and J. A. Mills, J.Chem.Soc., 1948, 1457.