A) NITROENAMINES, NITROACETAMIDES AND NITROTHIOACETAMIDES : SYNTHESIS, CONFORMATION AND REACTIVITY

B) RING OPENING REACTION OF LACTAMS AND LACTIM ETHERS

A Thesis
Submitted to the
UNIVERSITY OF BOMBAY

For the Degree of
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

By

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1995

To my
Secondary School Teacher
Mr. Suresh Chincholikar

CERTIFICATE

Certified that the work incorporated in the thesis entitled "(A) Nitroenamines, Nitroacetamides and Nitrothioacetamides, Synthesis, Conformation and Reactivity, (B) Ring opening reaction of Lactams and Lactim Ethers submitted by Mr.Arun N.Dixit was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date

National Chemical Laboratory,
Pune 411 008

S. Rajappa

Dr.S.Rajappa
Research Guide

DECLARATION STATEMENT UNDER 0.771

The work presented in the thesis has been carried out by me under the guidance of Dr.S.Rajappa, Organic Chemistry Division (Synthesis), National Chemical Laboratory, Pune 411 008

The experimental work, observations and interpretations of the data in connection with the studies are entirely my own.

The work reported in this thesis is original and has not been submitted in part or full for any degree or diploma to any other University or Institution.

S. Rajappa

Dr.S.Rajappa
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A.N. Dixit
22/9/95

Arun Dixit
Candidate

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A.N.Dixit

ARUN DIXIT

GENERAL REMARKS

1. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.

2. All the solvent extracts were finally dried over anhydrous sodium sulphate.

3. The compound numbers, scheme numbers and reference numbers etc. given in each chapter refer to that particular chapter only.

4. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.

5. TLC was carried out on silica gel plates prepared by spreading the slurry (chloroform), drying at room temperature.

6. The IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer model 683B.

7. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian FT-80A, Bruker WH-90, Bruker AC-200 spectrometers, using tetramethylsilane as internal standard. The following abbreviations are used : s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

8. The mass spectra were recorded on a Finnigan MAT-1020B-70 ev mass spectrometer.

9. Elemental analysis were performed by Microanalytical Lab, operated by NCL, Pune

10. All optical rotations were measured using sodium D lines on a JASCO-181-digital polarimeter at room temperatures.

Abbreviations

AcOH	Acetic Acid
Ar	Aryl
BOC	*tert*-Butoxycarbonyl
Bz	Benzyl
CBz	Benyloxycarbonyl
DBU	1,8-Diazabicyclo [5,4,0] undec-7-ene
DMF	N,N-Dimethylformamide
Et	Ethyl
eg	Equivalent
g	gram
h	hours
IR	Infrared
M^+	Molecular ion
Me	Methyl
M.P.	Melting Point
MS	Mass Spectrum
Nm	Nanometer
NMR	Nuclear Magnetic Resonance
tlc	Thin Layer Chromatography
THF	Tetrahdrofuran
PTC	Phase Transfer Catalysis
PTSA	P-Toluenesulfonic Acid
Ph	Phenyl
TEA	Triethylamine
rt	Room Temperature

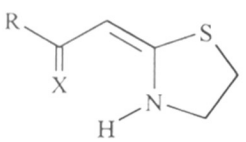
CONTENTS

ABSTRACT

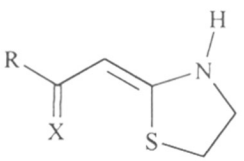
The thesis is divided into five chapters. The abstract discusses the work done chapter-wise

Chapter 1

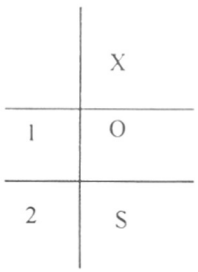
Non-bonded attractive interaction involving a divalent sulfur atom in the solid state has attracted considerable attention in the last few years. All the available evidence is based only on X-ray crystallography. Though there can be difference of opinion about the origin of S...O, S....S, S....Cl non-bonded attractive interactions it is quite clear that such pairs of atoms have contacts closer than the sum of their van der Waals radii. Our group has been interested in furnishing evidence for such non-bonded S...O, S....S interactions in the solution phase. In this chapter we discuss non-covalent interactions between the ring sulfur and the oxygen atom of a suitably located carbonyl moiety, as well as between ring sulfur and the S atom of a suitably located thiocarbonyl group.



E



Z

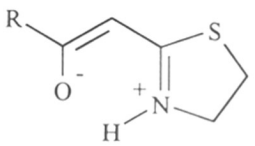


Compound **(1)** can exist in two forms : the E isomer is stabilized by N-H....O intramolecular hydrogen bonding while the Z isomer may be expected to benefit from S...O non-bonded attraction. In non-polar solvents e.g. chloroform compound **(1)** exists in the intramolecularly hydrogen bonded form. This is supported by ^{1}H NMR peak position of NH and also by IR studies. In polar solvents like DMSO, intramolecular hydrogen bonding is weakened. This affects the balance between the two competing forces (N-H...O hydrogen bonding and S...O interactions). As a result the Z isomer makes its appearance in the ^{1}H NMR spectrum of compound **(1)**. Similar ^{1}H NMR studies on the thio-analogue **(2)** also show solvent dependent E,Z isomerisation. the competing forces are N-H....S intramolecular hydrogen bonding and S.....S interaction in case of compound **(2)**.

Possible explanation for E,Z isomerisation

1) Solvent Effect : solvent can affect E,Z isomerisation in two possible ways :

(a) solvation of NH by DMSO molecules, thereby weakening N-H...X intramolecular hydrogen bonding (b) stabilization of resonance structure (**3**) and (**4**) thus lowering the barrier to rotation around C=C in compounds (**1**) and (**2**).



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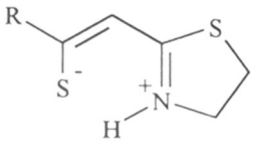

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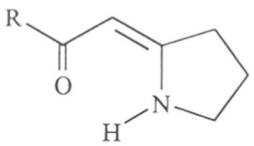
It is to be noted that this explanation assigns no specific role to the sulfur atom. In order to check this hypothesis, compounds (**5**) and (**6**) which lack the ring sulfur were synthesized.



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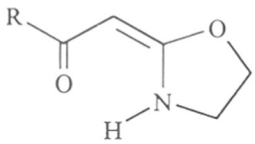

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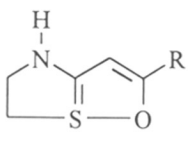
Compound (**5**) has a CH_2 in place of sulfur of the thiazolidine ring whereas in compound (**6**) sulfur has been replaced by an oxygen atom. The ^1H NMR spectra of these compounds (**5**) and (**6**) show only one sharp set of signals both in $CDCl_3$ as well as DMSO-d6. The existence of only E isomer (intramolecularly hydrogen bonded) in DMSO-d6 indicates that the presence of ring sulfur atom in compound (**1**) and (**2**) is a necessary condition to observe the E,Z switch.

(2) Tendency of sulfur to form hypervalent bond :

The ability of sulfur atom to expand its valence and to form hypervalent bonds can lead to structures (7) and (**8**).



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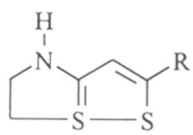

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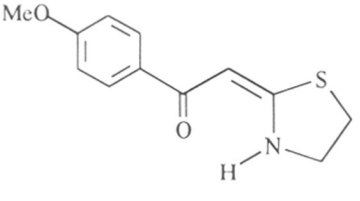
These could be the species responsible for the second set of ^{1}H NMR peaks in DMSO-d_6. This hypothesis has been critically evaluated in the light of experimental facts and literature reports.

(3) S...O and S....S Non-bonded attractive interactions

The idea of non-bonded attractive interactions between a divalent sulfur atom and suitably located oxygen has been used by X-ray crystallographers to explain unusual short contacts. The essential substructure required for S...X non-bonded interaction is S-A=B-Y=X in which A=B is cis. This condition is met in both (**1**) and (**2**). Hence non-bonded attractive interaction is the most convincing explanation for the observed solvent dependent E,Z isomerisation. Non-bonded attractive interaction can be due to electrostatic forces or secondary orbital interactions.

Electronic and Geometric Effects

Our next objective was to determine the effect of electron releasing and electron withdrawing substituents on the phenyl ring on the E,Z equilibrium in DMSO-d_6. This may indirectly help in quantifying the S...X non-bonded attraction. Compounds (**9**) and (**10**) were synthesized for this purpose. Compound (**9**) has an OMe i.e. electron-donating group, whereas compound (**10**) has an NO_2 group which is electron withdrawing in nature. The ^{1}H NMR spectra were recorded in $CDCl_3$ as well as in DMSO-d. The relative ratio of E,Z isomers was found to be practically the same in both cases. It was hence concluded that electronic factors have no significant effect on S...O and S...S non-bonded interactions.



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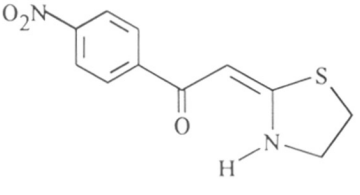

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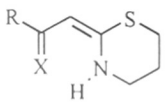
To study the effect of geometry of the molecule on the strength of S...X attraction, the corresponding six-membered ring analogs (**11**) and (**12**) were prepared.

The ^{1}H NMR spectra of these compounds in DMSO-d_6 show only one set of peaks indicating the presence of only the E isomer. This may be due to the stronger intramolecular



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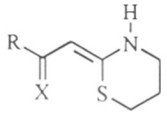

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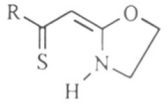


11: X = O

12: X = S

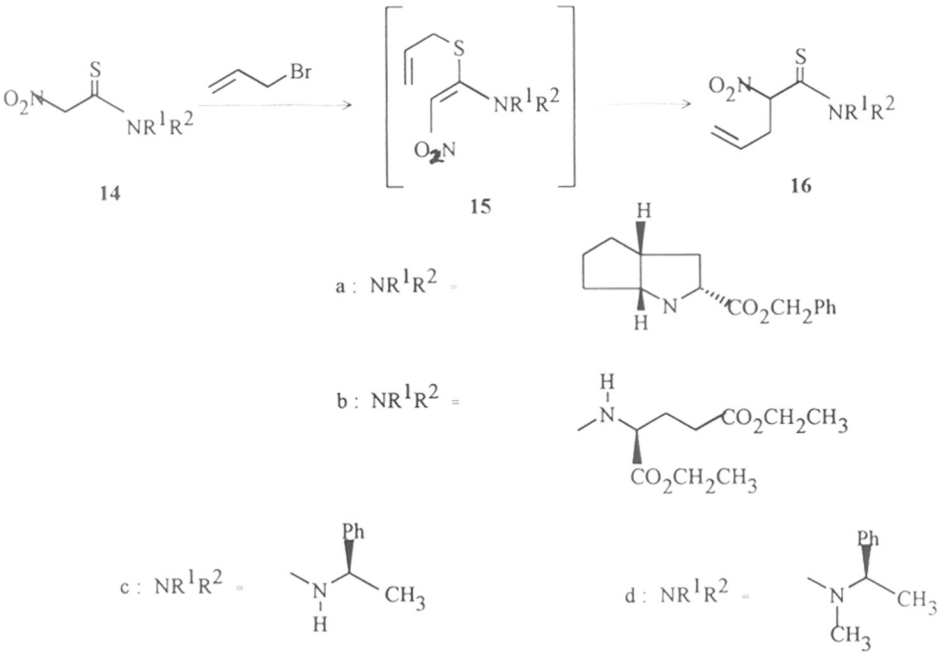
13

hydrogen bonding in compounds (**11**) and (**12**) compared to compounds (**1**) and (**2**). The second probable reason is unfavorable geometry for the necessary n-σ* overlap (HOMO of oxygen or sulfur and LUMO of C-S). Compound (**13**) in which the location of sulfur and oxygen are interchanged, also shows the presence of only the E isomer in $CDCl_3$ as well as in DMSO-d_6. This supports the explanation based on orbital interactions. In compound (**13**) HOMO is the one occupied by non-bonding electrons on sulfur and LUMO is (σ*C-O) which is apparently too high to produce any fruitful interaction.

Chapter 2

This chapter discusses diastereoselectivity in the thio-Claisen rearrangement of nitrothioacetamides. Nitrothioacetamides are very reactive molecules. The allylation or alkylation can be at two possible centers-either at sulfur or at carbon. Generation of the anion by DBU and then treatment with allyl bromide (*Scheme 1*) leads to the S-allylated derivative (**15**). The allylalated compounds (**15a-d**) undergo [3,3] sigmatropic rearrangement to produce C-allylated compounds (**16a-d**). This leads to the generation of a new chiral center. Though [3,3] sigmatropic rearrangement is known to be a powerful technique to generate a new chiral center in fairly predictable stereo chemistry, there are very few reports dealing with chiral induction in thio-Claisen rearrangements. The reason could be the labile nature of such thiocarbonyl compounds. The thio-Claisen rearrangement in which the original chiral center is not a part of the [3,3] sigmatropic framework has been reported by our group. The asymmetric center is three atoms away; thus it is an example of remote stereocontrol. Encouraged by this result particularly with N-nitrothioacetyl-(S)-proline ethyl ester (**de** 66%) we planned to try different chiral auxiliaries in place of (S)-proline ethyl ester. Benzyl N[(prop-2-ene-1-thioacetyl(1R,3R,5R)-2-azabicyclo[3,3,0] octane-3-carboxylate (**16a**) was thus obtained by thio-Claisen rearrangement as a mixture of two

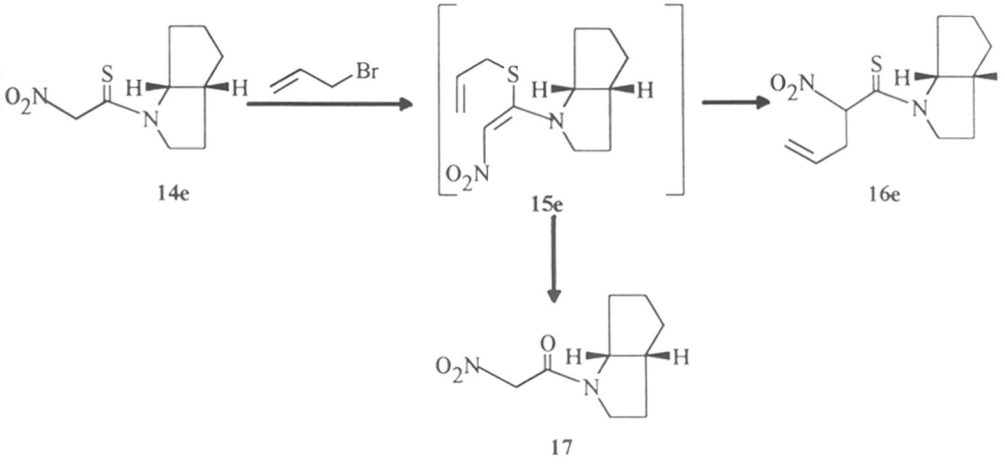
Scheme 1



diastereomers with 69% diastereomeric excess. (S)-Glutamic acid diethyl ester, the open chain aminoacid ester, was tried as a chiral auxiliary. This gave compound (**16b**) with practically zero diastereomeric excess. The rate of rearrangement was extremely slow and it took 20 days to complete the rearrangement at room temperature. The next attempt was to try (S)-α–methylbenzylamine, being a commercially available chiral amine. It proved to be useless as far as controlling the stereochemistry of this rearrangement was concerned. Results with benzyl(1R,3R,5R)-2-azabicyclo [3,3,0] octane-3-carboxylate, (S)-glutamic acid diethyl ester, (S)-methylbenzylamine as well as (S)α-proline ethyl ester and (S)-valine ethyl ester led to the conclusion that secondary amines lead to better stereoselectivity compared to primary amines. The rearrangement of S-allyl-(S)-N-methyl N(nitrothioacetyl) methylbenzyl amine (**15d**) was next attempted. In this molecule the NH has been replaced by N-methyl group. This did not show any improvement in diastereoselectivity. The rate of rearrangement was also not different from that of (**15c**).This leads to the conclusion that only cyclic secondary amines can give good diastereoselectivity. The chiral amine (1R,5R)-2-azabicyclo [3,3,0] octane lacking the carboxylic

ester group at the α-position was next tried as chiral auxiliary. The compound (**15e**) was very prone to hydrolysis and we could not get compound (**16e**). Instead, we got the oxo compound (17)

Scheme 2



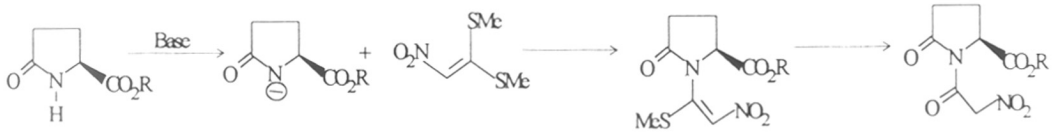
The thio-Claisen rearrangement of S-allylated benzyl N(1-benzoylthioacetyl) (1R,3R,5R) 2-azabicyclo [3,3,O] octane and S-allylated-N(1-prop-2-ene-l-yl)(1R,5R) 2-azabicylco [3,3,0] octane have shown that presence of ester moiety at α-position leads to much better stereoselectivity. Our results thus far show that chiral cyclic amino acid esters show reasonably good asymmetric induction in the thio-Claisen rearrangement of nitrothioacetamides.

Chapter 3

Chapter 3 discusses the attempts to prepare methyl N(nitroacetyl) (S)-2-pyrrolidinone-5-carboxylate (**19**). Our attempts to synthesize (**18**) by condensing (S)-methyl pyroglutamate with 1,1-bismethylthio-2-nitroethene failed when the reaction was carried out in the usual way in acetonitrile at 80°C using PTSA as the catalyst. The failure can be attributed to the low nucleophilicity of nitrogen in pyroglutamate compared with prolinate.

Generation of the anion on the amide nitrogen with different bases and then treatment with 1,1-bismethylthio-2-nitroethene in different solvents either gave very complex product mixtures or led to recovery of the starting material. None of the products formed could be characterised.

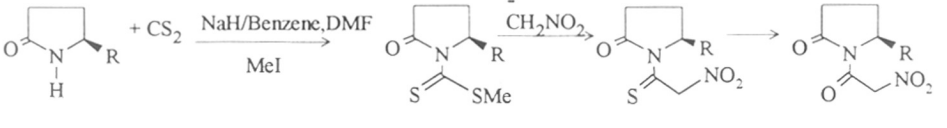
Scheme 3



18 19

Another attempt to synthesize the related thio analog (**21a**) was made by condensing methyl pyroglutamate with CS_2, S-methylating the product, and then replacing the SMe by nitromethane anion in a subsequent step.

Scheme 4



20 21 19

a : R = CO_2 Me, b : R = H

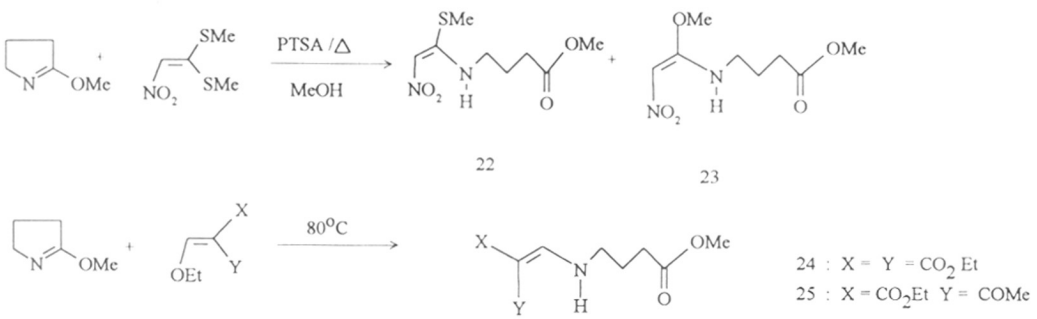
However, the first step in this route gave very poor yield of the product (**20a**). In order to conserve the material the second step was first attempted on the model compound (**20b**) which lacks the carboxylic ester group. This compound was derived from 2-pyrrolidinone by reaction with CS_2 followed by methylation. Different reaction conditions were then tried for substitution of the SMe group in (**20b**) by nitromthane anion. Neither use of different solvents, nor the generation of nitromethane anion by different bases led to the required product (**21b**). Use of catalysts such as zeolite (ReNaY) or KF/Al_2O_3 also failed to yield the desired compound (**21b**). Finally it was decided to try the lactim ether derived from 2-pyrrolidinone as a nucleophile to replace one of the thiomethyl groups of 1,1-bismethylthio-2-nitroethene. The reaction was tried under different conditions. The temperature was varied from 30-80°C. Different catalysts were also tried. The

reaction carried out in methanol at 64°C gave an unexpected ring opened product. These reactions of lactim ethers are discussed in the next chapter.

Chapter 4

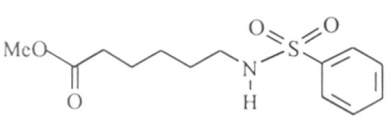
The condesation reaction of (2H)-3,4-dihydro-5-methoxypyrrole (γ-butyrolactim ether) with 1,1-bismethylthio-2-nitroethene gave unexpectedly the ring opened products (**22**) and (**23**) in a total yield of 30%. This chapter discusses similar nucleophilic reactions of lactim ethers with concomitant ring opening.

Scheme 5



Reaction of γ-butyrolactim ether with diethyl ethoxymethylenemalonate and ethyl ethoxymethyleneacetoacetate gave the ring opened products (**24**) and (**25**) respectively. Attempts to condenced caprolactim ether with p-toluenesulfonyl chloride also proceeded with opening of the lactimether ring giving the compound (**26**). Reaction of O-methylcaprolactim with CS_2 in methanol followed by methylation with methyl iodide gave compounds (**27**) . The reaction of (2H)-3,4-dihydro-5-methoxypyrrole with p-toluenesulfonyl chloride took place at room temperature whereas reaction with rest of the electrophiles required elevated temperatures. Reaction of lactim ethers with 1,1-bismethylthio-2-nitroethene was possible only in alcoholic solvents; on the other hand reaction with ethyl ethoxymethyleneacetoacetate and diethyl ethoxymethylenemalonate were carried without solvent. Use of $HgCl_2$ to accelerate the reaction of lactim ether with 1,1-bismethylthio-2-nitroethene was unsuccessful and gave compound (**28**) resulting from the hydrolysis of 1,1-bismethylthio-2-nitroethene in very low yield. Reaction of 2H-3,4-dihydro-5-methoxypyrrole with 1,1-bismethylthio-2-benzoylethene and

Scheme 6



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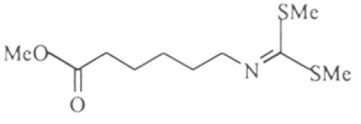

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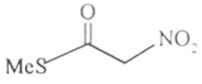


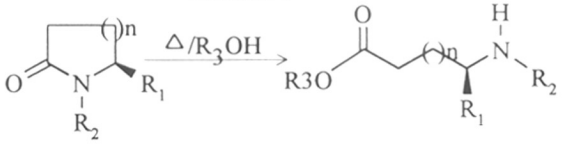
28

1-methylthio-1methylamino-2-nitroethene led to recovery of starting materials. No reaction was observed in methanol or ethanol with or without use of PTSA.

Chapter 5

This chapter reports a versatile acid-catalyzed ring opening of lactams in which the nitrogen atom is linked to CO_2Me, CS_2Me or SO_2Ar. The reaction proceeds under mild condition

Scheme 7



29 **30**

29	R_1	R_2	n	30	R_1	R_2	R_3	n
a	CO_2Me	H	1	**a**	CO_2Me	H	Me	1
b	CO_2Me	H	3	**b**	CO_2Me	H	Et	1
c	CO_2Me	H	1	**c**	CO_2Me	H	Pr^i	1
d	Ts	H	1	**d**	CO_2Me	H	C_6H_{11}	1
e	CO_2Me	CO_2Me	1	**e**	CO_2Me	H	Me	3
				f	CS_2Me	H	Me	1
				g	-Ts	H	Me	1
				h	CO_2Me	CO_2Me	Me	1

leading to ring opened products (**31**). 2-Pyrrolidinone was converted to the carbomethoxy derivative (**29a**) by treatment with NaH and methyl chloroformate. The N-carbomethoxy derivative thus formed on treatment with methanol in presence of PTSA gave ring opened

derivative thus formed on treatment with methanol in presence of PTSA gave ring opened product (**30a**) in 94% yield. There was thus no necessity of introducing the bulky t-BOC group in the first step as has been reported in the literature. It was found that generally N-carbonyl and N-arylsulfonyl lactams were converted to the corresponding acyclic products by acid catalyzed cleavage of the lactam ring in good yield (60-90%) and excellent regioselectivity. Other catalysts such as Amberlite-15 and sodium methoxide were also tried. Reaction was observed to be very slow with Amberlite-15, whereas low yields were obtained for (**31a**) with sodium methoxide as the catalyst. Nitrogen and carbon nucleophiles were also tried for similar reactions. Primary and secondary amines gave rise to opened products in good yield. Our attempts to use carbon nucleophiles for the formation of a C-C bond in such a reaction were futile.

Dr.S. Rajappa
Research Guide

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Candidate

CHAPTER 1

NON-BONDED ATTRACTIVE INTERACTIONS INVOLVING SULFUR

Chapter 1

Non-bonded Attractive Interactions Involving Sulfur

1.1 Summary

This chapter discusses non-bonded attractive interactions involving a sulfur atom. Several examples are known in the literature in which a sulfur and an oxygen atom of the same molecule or different molecules come closer than the sum of their van der Waals radii in the solid state. The evidence is based on X-ray data obtained on the crystals of such molecules.

We have designed several push-pull systems which can fulfill the requirements for such S...O or S...S non-bonded attractive interactions. A series of enaminoketones (**11**) has been synthesized . The ^{1}H NMR spectra of these compounds (**11a-g**) were studied in solvents of different polarity. Very interesting configurational changes involving isomerisation have been observed in such molecules on addition of polar solvents like DMSO-d_6 to the $CDCl_3$ solution.

The effect of substituents on the benzene ring of compounds **11** has also been studied by introducing electron-withdrawing or electron-donating substituents at the *para* position on the benzene ring. Similarly the effect of *ortho* substituents has also been studied by introducing various substituents at the *ortho* position of the benzene ring in compound **11**.

Probable reasons for solvent dependent *E* to *Z* isomerisation have been discussed in detail. To rule out any explanation based solely on solvent effect (which does not assign any role to the ring sulfur atom) the oxazolidine **19** was prepared. It's ^{1}H NMR spectrum was studied in solvents of different polarities. Directionality requirement of non-bonded S...O interaction have been studied by synthesizing the thiazine derivative **24**. The ^{1}H NMR spectra of **24** recorded in solvents of different polarity demonstrated the crucial geometry required for such interaction to occur. The enaminoketones **11** and **24** were converted to the enaminothiones **12** and **27** by treatment with Lawesson's reagent. The study of ^{1}H NMR spectra of enaminothiones in solvents of different polarity shows parallel behavior to that of the enaminoketones **11** and **24**. The possible causes of solvent dependent E/Z isomerisation are also discussed.

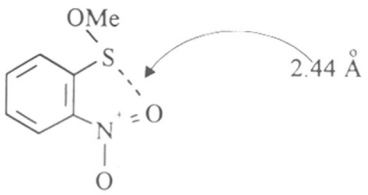
The compound **28** was synthesized by thionation of oxazolidine (**19**). This throws light on the role of HOMO (oxygen lone-pair)-LUMO (S-C antibonding orbital) in non-bonded attractive interactions.

1.2: Introduction

Several types of weak intra and intermolecular attractive forces are known to play a significant role in biological processes as well as in determining the conformation of small molecules. Typically these forces involve energies which are an order of magnitude less than that of covalent bonds. The most important among such weak attractive forces is of course the hydrogen bond between two hetero atoms such as oxygen, nitrogen, sulfur or fluorine. The typical energy involved in such a hydrogen bond is of the order of 4 to 7 k.cal/mole. Recently hydrogen bonds connecting a carbon and oxygen have also been documented in literature[1]. Such C-H...O hydrogen bonds are not as strong as O-H...O or N-H...O hydrogen bonds. The energy of the C-H..O bond is about 1.2 k.cal/mole. However there is a consensus that C-H...O bonds have significant implications in many diverse areas of structural chemistry. Such C-H...O bonds may also be responsible for the tertiary structure in macromolecules.

Another type of weak attractive force is the so-called hydrophobic bonding or van der Waals attraction. This is an extremely weak attraction and can have significant effect only if a large number of such hydrophobic interactions occur at the same time. A third type of weak non-bonded interaction may be specific to compounds containing sulfur or selenium.[2,3] Such attractive forces between two heteroatoms one of which is sulfur or selenium and the other nitrogen or oxygen have been encountered only in the solid state so far. They have been identified by the proximity of the two atoms in the solid state when their structures were determined by X-ray crystallography.[4] These short contacts between two atoms which are not directly linked with each other, but which are spatially proximate may arise through an attractive interaction between sulfur or selenium and the second heteroatom. It must be emphasized that this phenomenon has so far been encountered only in the solid state. The present chapter attempts to provide evidence for the existence of this attractive force even in the solution phase, where it manifests itself by affecting the conformation of the molecule as seen in the NMR spectra.

The first reported example of this non-bonded interaction between sulfur and oxygen was in the structure **1**.[5]



1

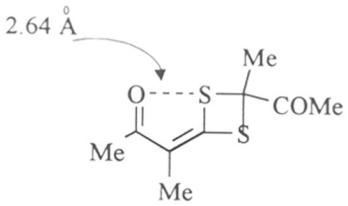
The X-ray crystallographic structure reveals the following interesting facts

i) The molecule is planar .

ii) The distance between sulfur and oxygen of NO_2 is only 2.44 Å whereas the sum of the van der Waals radii of sulfur and oxygen is 3.25Å .

iii) The O....S - O configuration is almost linear.

Subsequently several other examples also came to light in which a sulfur atom was spatially quite close to an oxygen atom to which it was not directly linked in a covalent bond. Compounds (**2**),[6] (**3**)[2] are two examples:



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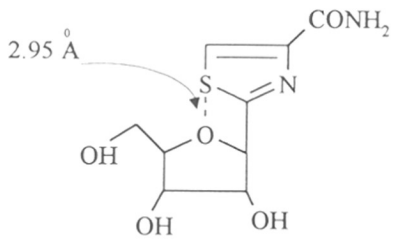

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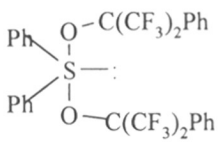
The entire subject has been reviewed by Kucsman and Kapovits.[7] More than 750 divalent sulfur compounds containing intramolecular S...O contacts between 2.00-3.25Å have been identified. Typical interatomic (S...O) distances are given in *Table 1*.

Table 1

Type	S...O Distance Å
S = O covalent bond	1.40 to 1.49
S - O covalent bond	1.56 to 1.65
S....O Hypervalent bond	1.65 to 2.25
S....O Non-bonded	2.03 to 3.25
S/O van der Waal	3.25

It is clear from the table that distances longer than those involved in a S-O single covalent bond can be classified into two types.

i) S... O hypervalent bonds would have a bond length between 1.65 - 2.25 Å. Such hypervalent bonds may involve the classical 3 atom 4 electron bond. Examples are (**4**) and (**5**).



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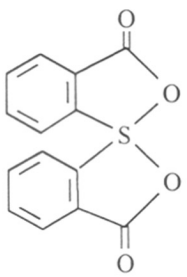

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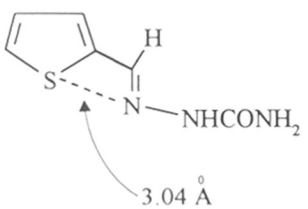
ii) Bond lengths larger than 2.00 Å but less than the sum of the van der Waals radii (3.25Å) are classified as non-bonded interactions.

Other hetroatom pairs, for example S...N[8] or Se...O[9] can also form such non-bonded interactions. Examples are structures **6**, **7**. It must however be mentioned that in the case of **6** the existence of such an interaction has been disputed.[10]

S..N interaction



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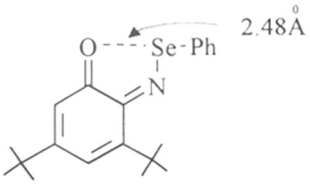
Se..O interaction



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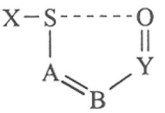
The conclusion drawn from X-ray crystallographic studies are the following [3]



i) S...O interaction is controlled primarily by the size of the quasi-ring, 5-membered rings are the best suited. A 6-membered ring is unable to promote S...O interaction.

ii) Effective interaction requires the part structure S-A = B-Y = O where A = B has the *cis* configuration and B-Y has *s-cis* conformation .

iii) A linear X-S...O sequence .

iv) The more electronegative or polarisable X is (O,N,S) the better for S...O interaction.

Several theoretical approaches have been made to understand the origin of such attractive forces. The factors responsible might be :

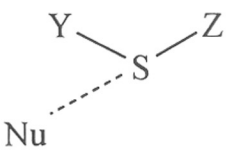
i) Electrostatic (dipole-dipole) forces between X-S, and Y=O moieties

ii) Expansion of sulfur valence shell with sp^3d hybridization

iii) Delocalisation of oxygen lone pair to the S-X anti bonding orbital

iv) Formation of a 6-electron delocalised π-system in the quasi-ring

It has been suggested that this is a case of HOMO (lone pair on heteroatom) LUMO (σ^* of S-Y or S-Z orbital) interaction.[11]



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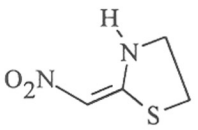
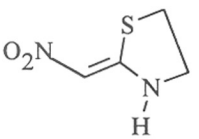
This also corresponds to the attack by nucleophiles on divalent sulfur compounds.[12] Theoretical calculations as well as experimental observations prove that nucleophiles tend to approach divalent sulfur approximately along the extension of one of the covalent bonds to sulfur.

All the available evidence so far for the existence of non-bonded S...X attraction has been based on X-ray crystallographic data in the solid state. In such molecules the two heteroatoms come close to each other in space. Although this evidence is quite convincing, it does not necessarily follow that these two atoms would still be close to each other in solution. Our group

has for the first time presented evidence for a weak attraction between the ring sulfur and the oxygen of the NO_2 in compound **9** in the solution phase.[13]



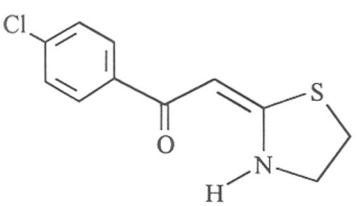
9E



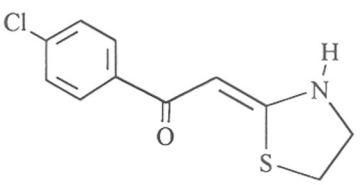
9Z

The evidence is based on the interpretation of ^1H, ^{13}C and ^{15}N NMR data in solvents of different polarities. The evidence is summarized below : The compound exists in the *E* configuration in non-polar solvents like $CDCl_3$. In this configuration the compound derives the benefit from a strong intramolecular hydrogen bond. If this intramolecular H bond is broken by solvation, such as in DMSO-d_6, a change in the configuration occurs and a significant amount of 9*Z* is also observed. In pure DMSO-d_6, the *E:Z* ratio is 1:4. It should be noted that compound **9** is a push-pull system and consequently the central C-C has considerable single bond character. The barrier to rotation is low[14]. The stabilization of the *Z* isomer in polar solvents has been attributed to S..O non-bonded attraction. At the same time X-ray crystal structure determination of compound **9** showed that in the solid state it existed in the *Z* configuration in which the ring sulfur and the oxygen atom of NO_2 are separated only by 2.68Å.

A preliminary NMR analysis showed that compound **10** also showed the same behavior.[15]



10E



10Z

In $CDCl_3$ it existed completely in the intramolecular hydrogen bonded *E* configuration; but in DMSO-d_6 two sets of signals were seen corresponding to *E* and *Z* isomers. The ratio of **10***E* : **10***Z* in DMSO-d_6 was 3 : 2.

1.3: Present work

We have now synthesized a series of enaminones **11** related to **10** and studied their configuration in different solvents by NMR spectroscopy. We have also converted the enaminones **11** to enaminothiones **12** by Lawesson thionation and studied their conformation in solvents of different polarities. Our conclusions are : Quite significant S...O interactions operate in the case of **11***Z* and much weaker S...S interactions in **12***Z*. The attractive forces can be arranged in descending order of strength as : N-H....O > N-H....S > S....O > S....S.

1.4: Results and Discussion

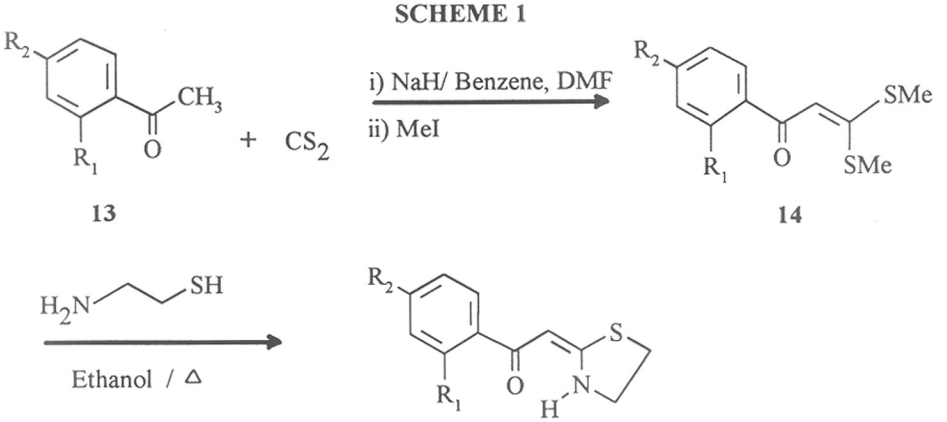
1.4.1: Synthesis of Enaminones (11)

The enaminones were synthesized by two procedures :

1.4.1a: Method (A): Synthesis of keten S,S-acetals and then reaction with 2-aminoethanethiol[16]

Compounds **11b-e** were synthesized by method (a). In the first step substituted acetophenones were condensed with carbon disulfide in presence of NaH in benzene/DMF. The reaction was complete only after addition of DMF to the reaction mixture. Dianion formation was evident from the dark red brown color of the reaction mixture. The dianion was methylated using methyl iodide to give the keten S,S-acetals. The keten S,S-acetals thus formed were then treated with 2-aminoethanethiol in absolute ethanol at 80°C(*Scheme 1)*.

SCHEME 1



13 **14**

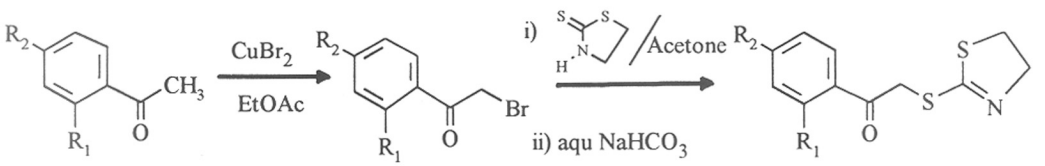
11

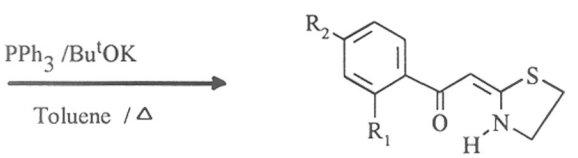
	R_1	R_2
b	H	OMe
c	H	NO_2
d	Cl	H
e	NO_2	H

1.4.1b: Method (b) : Use of Eschenmoser's sulfide contraction method.[17]

Compounds **11f** and **11g** were synthesized by the sulfide contraction method of Eschenmoser. 2-Hydroxyacetophenone and 2-methoxyacetophenone were converted to the corresponding phenacyl bromides by treatment with $CuBr_2$ in boiling ethyl acetate. The 2-hydroxy or 2-methoxy, 2'-bromoacetophenone was then reacted with thiazolidine-2-thione in dry acetone to give a white powdery salt. The salt was neutralized by aqueous sodium bicarbonate to yield **16f** and **16g**. The spectral data are reported in the experimental section. The ^1H NMR spectrum shows a sharp singlet at 3.40δ for SCH_2. The compound was then treated with PPh_3 in presence of a catalytic amount of potassium *t*-butoxide in refluxing toluene to yield **11f** and **11g** in 75-80% yield *(Scheme 2)*.

Scheme 2





11

	R_1	R_2
a[18]	H	H
f	OH	H
g	OMe	H

The enaminones **11a-g** have an electron-withdrawing C=O group at one end and an electron-donating NH at the other end of a double bond. Thus they are typical push-pull ethylenes. In such systems, the central C-C linkage has considerable single bond character. This leads to a lowering of the energy barrier to rotation around the carbon carbon double bond.[13] The lower

barrier to rotation facilitates the *E/Z* conformational change. A strong intramolecular hydrogen bond is possible in the *E* isomer between the oxygen atom of the carbonyl group and N-H.

Initial spectroscopic studies were carried out on the unsubstituted benzoyl derivative **11a**.[18] The IR spectra recorded at different concentrations in $CHCl_3$ do not show any shift of the N-H band at 3210 cm^{-1} or the carbonyl at 1610 cm^{-1}. This concentration independence proves that the compound **11a** exists in the intramolecular hydrogen bonded *E* conformation in non-polar solvents like chloroform. The ^1H NMR spectrum of **11a** in $CDCl_3$ solution exhibits sharp signals characteristic of a single conformation *E*. On addition of DMSO-d_6 to this solution signals corresponding to the *Z* isomer start appearing. The population of *Z* isomer increases with increasing DMSO-d_6 content. Two sets of signals are seen at the same time in solvent of high *polarity*. In a mixture of DMSO-d_6 and $CDCl_3$ (1:4) two signals are seen for NH at 10.44δ and 8.00 δ respectively. The olefinic proton also gives rise to two signals at 6.00δ and 6.30δ. The NH signal at 8.00δ was assigned to the *Z* isomer . This is based on the fact that the NH of the *E* isomer is involved in very strong intramolecular hydrogen bonding and so, it is expected to appear further downfield compared to the NH proton of the *Z* isomer. In the solvent mixture $CDCl_3$: DMSO-d_6 (4 : 1) the *E:Z* ratio was 90 : 10 . In pure DMSO-d_6 the ratio of E:Z isomers is 62 :38. This solvent dependent *E,Z* isomerisation is parallel to that observed earlier in the case of the nitro compound **9**.[15] The ^1H NMR data for compounds **11a-g** are summarized in *Table 2*.

1.4.2: Effect of substituents on the benzene ring of enaminones 11

1.4.2a: Substitution at *para* position

It was then decided to study the effect of electron-donating and electron-withdrawing substituents on the benzene ring on the *E/Z* equilibrium in DMSO-d_6. Compound **11b** has the electron-donating methoxy group *para* to the carbonyl moiety. The ^1H NMR spectrum of **11b** in $CDCl_3$ shows only one sharp set of signals corresponding to the *E* isomer. The NH proton for the *E* isomer appears at 10.6 .δ and the olefinic proton at 6.00δ as a singlet. The ^1H NMR spectrum of **11b** in DMSO-d_6 shows two sets of signals corresponding to the two stereo isomers. Thus there were two singlets for NH; the upfield signal at 8.30δ was due to the *Z* isomer; the downfield one at 10.40δ was assigned to the *E* isomer, since this would be involved in an intramolecular H-bond.

Table 2

1H NMR data of enaninothions (**11**)

Compd.		NH		=CH		NCH_2		SCH_2	
		E	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
11a	$CDCl_3$	10.55	-	5.90	-	3.90	-	3.20	-
	DMSO-d_6	10.40	8.00	6.00	6.30	3.90	3.59	3.30	3.10
11b	$CDCl_3$	10.60	-	6.00	-	3.95	-	3.30	-
	DMSO-d_6	10.40	8.30	6.00	6.35	3.90	3.60	3.10	3.20
11c	$CDCl_3$	10.80	-	5.90	-	4.00	-	3.30	-
	DMSO-d_6	10.50	8.75	6.05	6.30	3.90	3.65	3.65	3.40
11d	$CDCl_3$	10.60	-	5.70	-	4.05	-	3.35	-
	DMSO-d_6	10.25	8.60	**	**	**	**	**	3.10
11e	$CDCl_3$	10.40	-	5.60	-	4.00	-	3.35	-
	DMSO-d_6	10.10	8.70	**	**	**	**	**	**
11f	$CDCl_3$	10.25	-	6.00	-	4.00	-	3.30	-
	DMSO-d_6	10.20	8.95	6.00	6.40	3.80	3.65	3.30	3.15
11g	$CDCl_3$	10.60	-	5.90	-	3.95	-	3.25	-
	DMSO-d_6	10.25	8.30	**	**	**	**	**	**

Similarly, there were two singlets for the olefinic proton at 6.00δ and 6.35δ. The *E:Z* ratio was determined by the integration of these two signals. The *E:Z* ratio in pure DMSO-d_6 was found to be 65:35.

The *p*-nitrobenzoyl analog **11c** was then investigated. This has the strong electron-withdrawing NO_2 group *para* to the carbonyl moiety. The ^1H NMR spectrum of compound **11c** shows only one set of sharp signals in $CDCl_3$ solution. As before, the DMSO-d_6 solution of **11c** shows two sets of signals for all the protons. Two broad singlets for NH were noted at 10.50δ and 8.75δ; the upfield signal at 8.75δ was assigned to the *Z* isomer and the downfield one to the *E* isomer. The olefinic proton was also seen as two singlets at 6.05δ and 6.30δ . The ratio of *E:Z* isomers was determined by the integration of singlets due to the olefinic proton. The *E:Z* ratio was

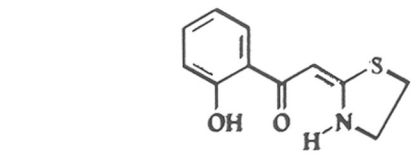
found to be 56 : 44 in this case. Thus there is no significant difference in the *E/Z* equilibrium of **11a** (unsubstituted : E/Z 62:38), **11b** (E:Z, 65:35) and **11c** (E:Z, 56:44) in DMSO-d_6. This leads to the conclusion that the electronic nature of the substituent on the phenyl ring has no significant influence on the relative population of the two isomers. Our original hypothesis was that the relative population of *E,Z* isomers in DMSO-d_6 may indirectly help in quantifying the S...O non-bonded interactions in enaminones **(11)**. In view of the above result, it has to be concluded that the electron-donating or electron-withdrawing substituents on the phenyl ring have no significant effect on the strength of non-bonded S...O interactions in compound **11**.

1.4.2b: Effect of *ortho*-substituents on phenyl ring

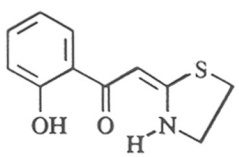
Compound **11d** has a chlorine atom *ortho* to the carbonyl group. The ^{1}H NMR spectrum of compound **11d** in $CDCl_3$ showed only one set of sharp signals. The olefinic proton was seen at 5.70δ as a sharp singlet; the NH proton was noted as a broad singlet at 10.6δ . The ^{1}H NMR spectrum of compound **11d** in DMSO-d_6 showed two signals for the NH proton at 10.25δ and 8.60δ. The downfield signal was assigned to the *E* isomer as usual. The spectrum in DMSO-d_6 solution shows line-broadening and no peak other than NH could be used for determining the E:Z ratio in DMSO-d_6. Taking into account only the NH peaks, the E/Z ratio was found to be 55 : 45

Similar line-broadening in the ^{1}H NMR spectra of other *ortho* substituted phenyl compounds was also observed. Compound **11e** has a nitro group in the *ortho* position to the carbonyl moiety. Two signals for NH were noted at 8.70δ and 10.10δ in DMSO-d_6 solution of **11e**. The downfield signal was assigned to the *E* isomer. The *ortho* methoxy compound **11g** also showed two sets of signals for the NH proton at 10.25δ and 8.30δ.

The *o*-hydroxy compound **11f** behaves differently from the rest of the *ortho* substituted compounds **11d,e,g** Compound **11f** exhibits a set of sharp signals in $CDCl_3$ as well as in DMSO-d_6 solution. The ^{1}H NMR spectrum of **11f** in $CDCl_3$ solution showed the NH at 10.25δ. The olefinic proton appears as a sharp singlet at 6.00δ . The OH proton was also noted as a sharp singlet at 13.55δ . The DMSO-d_6 solution of **11f** shows two sets of signals for all protons. In a 1:1 mixture of $CDCl_3$ and DMSO-d_6 the ratio of *E:Z* was estimated to be 72 : 28. The OH proton showed two singlets at 10.85δ and 10.65δ. The downfield signal was assigned to the *Z* isomer on the basis of relative intensity. On the other hand the NH proton for the *Z* isomer



in DMSO-d6



in $CDCl_3$

appears upfield at 8.95δ, the NH for *E* isomer appears at 10.20δ. The line-broadening of peaks in the ^{1}H NMR spectrum of *ortho* substituted enaminones in DMSO-d_6 solution may be because of slow rotation on the NMR time scale around the Ar-CO bond. In the *o*-hydroxy compound **11f**, one of the conformations has higher stability due to O-H...O hydrogen bonding involving the phenolic OH group and oxygen of carbonyl moiety. This locking of conformation due to the

Table 3.

E / *Z* Ratio in DMSO-d_6

Compound	*E*	*Z*
11a	62	38
11b	65	35
11c	56	44
11d*	55	45
11e*	49	51
11f	48	52
11g*	57	43

* *E* / *Z* ratio calculated from integration NH proton

intramolecular hydrogen bonding leads to sharp signals in the ^{1}H NMR spectrum of **11f** even in solvents of high polarity such as DMSO-d_6. The ratio of *E*:*Z* isomers in pure DMSO-d_6 was determined by the relative integration of olefinic protons corresponding to the two isomers. The *E*:*Z* ratio was found to be 48:52. The relative higher population of the *Z* isomer in **11f** compared to the unsubstituted enaminone **11a** (E:Z, 62:38) can be explained as due to the stabilization of the *Z*-form by an intramolecular O-H...O hydrogen bond. The ratio of *E* :*Z* isomers for compounds (**11a-g**) in different solvent is summarized in *Table 3*

1.4.3: Possible causes of *E* to *Z* isomerisation

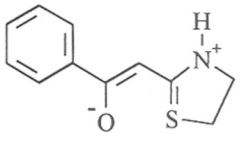
As noted earlier, solvent dependent *E* to *Z* isomerisation has been observed for compound **11a-g**. Two sets of signals were seen in DMSO-d_6 solution indicating the presence of two isomers. As mentioned earlier the enaminones **11a-g** are typical push-pull ethylenes in which the *E* isomer has higher stability due to the intramolecular hydrogen bond. In solvents of high polarity

like DMSO-d_6 these intramolecular hydrogen bonds get weakened due to solvation. Once this happens the *Z* isomers come into existence. Three possible explanations are discussed below for the extra stability of the *Z* isomer in DMSO-d_6.

1.4.3a: a) Solvent effect

The E/Z equilibrium can be affected in two ways by change of solvent polarity. Highly polar solvents such as DMSO can solvate the NH, thus breaking to a large extent, the intramolecular H-bond in the *E* configuration of **11a**. This solvated molecule in the *E* configuration would have a cluster of solvent molecules around the NH and may therefore be under a steric strain. The net effect of solvation would therefore be to raise the energy of the *E* isomer.

Simultaneously, in solvents of high polarity, the charge separated form of the molecule (**17**) would be favored. In enaminones and other push-pull ethylenes, this would result in lowering the barrier to rotation around the central C=C.

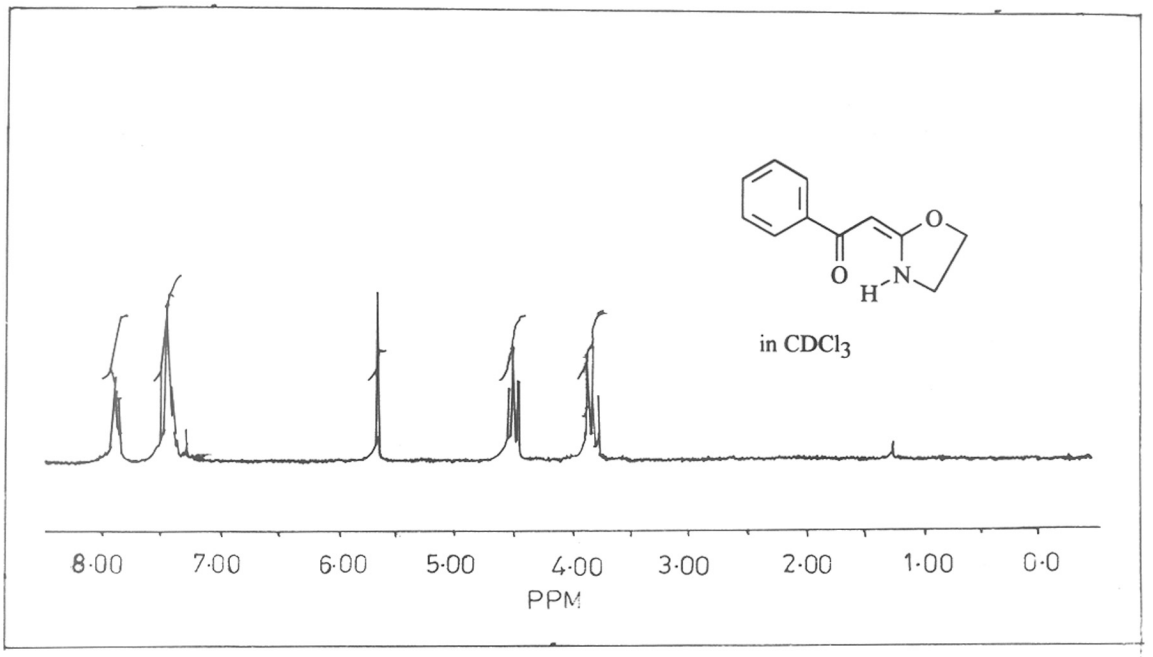


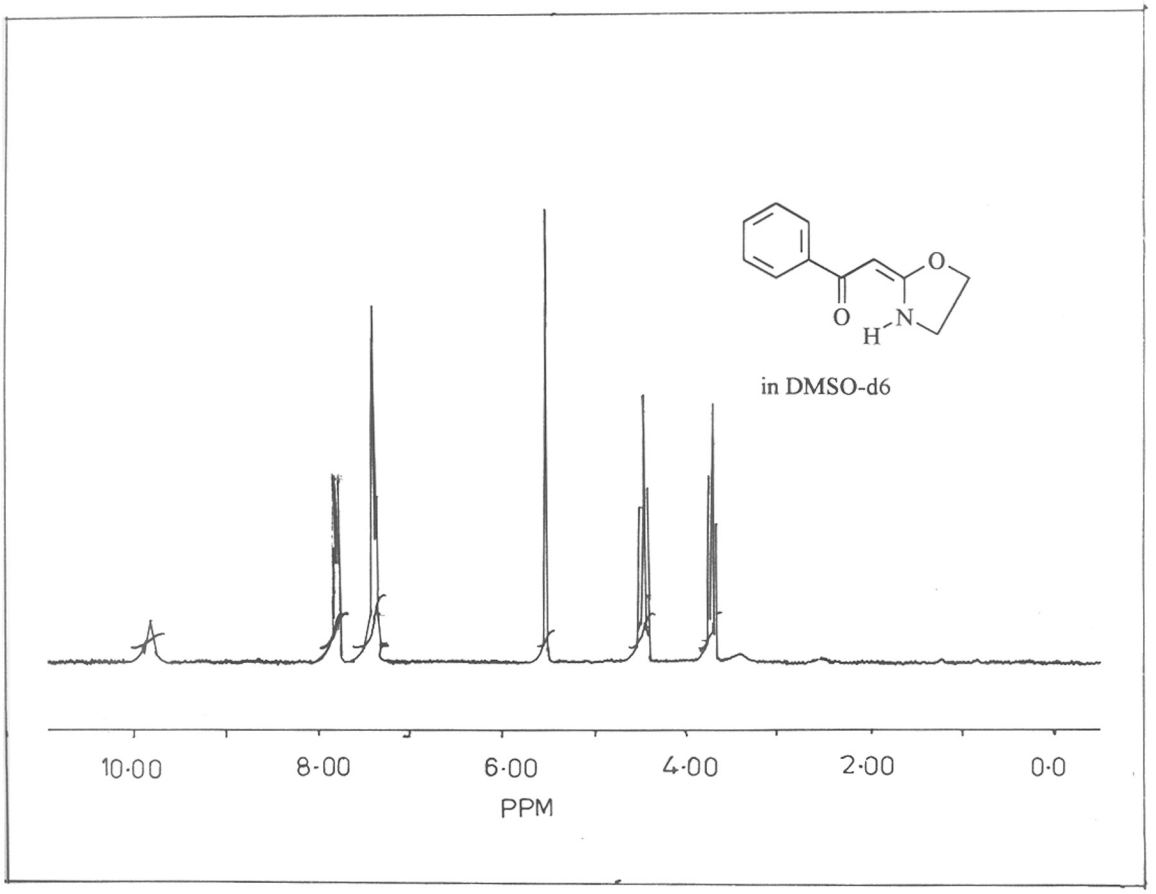
17

This explanation, however, assigns no specific role for the sulfur atom, and should therefore hold good for other similar enaminones lacking the sulfur. In order to check this hypothesis, the oxazolidine **(19)** in which the ring sulfur has been replaced by oxygen was synthesized.

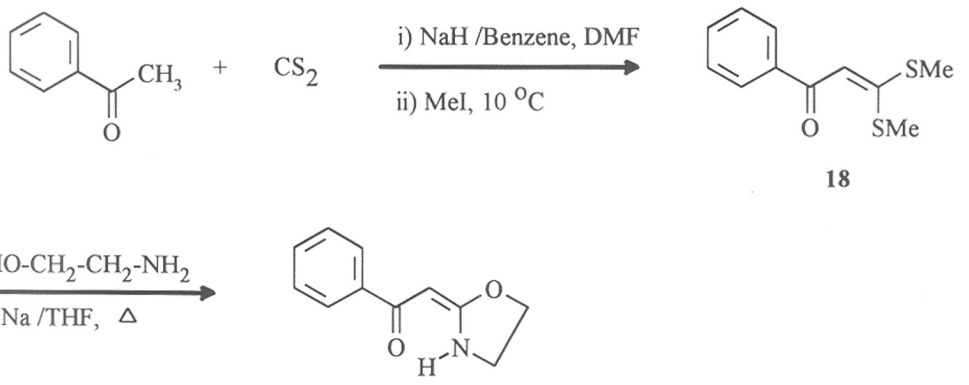
2-Benzoylmethylene oxazolidine **(19)** was prepared in two steps.[19] The first step was the synthesis of the keten S,S-dithioacetal **(18)**. This was prepared by the reaction of acetophenone with carbon disulfide in presence of NaH in benzene-DMF. The dianion formed was methylated using methyl iodide at 10°C. The dithioacetal thus formed was then reacted with 2-aminoethanol in presence of sodium metal in boiling THF to yield compound **19** as shown in *scheme 3*

The ^{1}H NMR spectrum of compound **19** recorded in $CDCl_3$ as well as in DMSO-d_6 shows only one set of sharp signals. The set due to the *Z* isomer was absent. The ^{1}H NMR spectrum in $CDCl_3$ shows two triplets at 3.65δ and 4.50δ due to SCH_2 and OCH_2 groups. The olefinic proton appears as a sharp siglet at 5.60δ whereas a broad singlet due to NH proton is

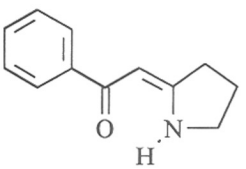

O
O
H
N
in $CDCl_3$
8·00
7·00
6·00
5·00
4·00
3·00
2·00
1·00
0·0
PPM


O
O
H
N
in DMSO-d6
10·00
8·00
6·00
4·00
2·00
0·0
PPM

Scheme 3



at 10.0δ. The aromatic protons were seen between 7.4 - 7.8 as a complex multiplet. The IR spectrum of the compound shows the C=O absorption at 1630 cm^{-1}.



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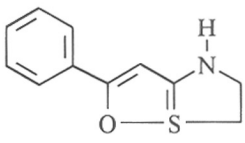
Earlier, the pyrrolidine derivative (**20**) had also been synthesized in our laboratory. Like the oxazolidine (**19**) described above, the pyrrolidine (**20**) also existed only in the intramolecularly H-bonded configuration (in this case, by the rules of nomenclature, (**20*Z***)) in both $CDCl_3$ and DMSO-d_6.[18]

The absence of solvent-dependent isomerisation (NH, CO *cis* to NH, CO *trans*) in these two analogs argues strongly against the explanation based on solvent polarity alone. The ring sulfur atom has to play a crucial role in this process.

1.4.3b: b)Hypervalency of sulfur atom

The ability of sulfur to form hypervalent bonds can be invoked to explain the extra stability of the *Z* form of **11a-g**. Such hypervalent sulfur can give rise to structure **21**.



21

The formation of isomers like **21** is expected to be facilitated in polar solvents like DMSO-d_6. The above proposal may be questioned on a number of grounds :

i) Hypervalent sulfur generally involves a linear arrangement of the X-S-Y unit in which X and Y are highly electronegative atoms or polarisable sulfur (See structures **4** and **5**). Examples of structures with apical C-S-O as in **21** involving a carbon atom have not yet been characterized[20].

ii) Further large electronic changes in **11a-f** should lead to larger effect on chemical shifts in the ^1H NMR spectra of compounds **11a-f** than those observed.

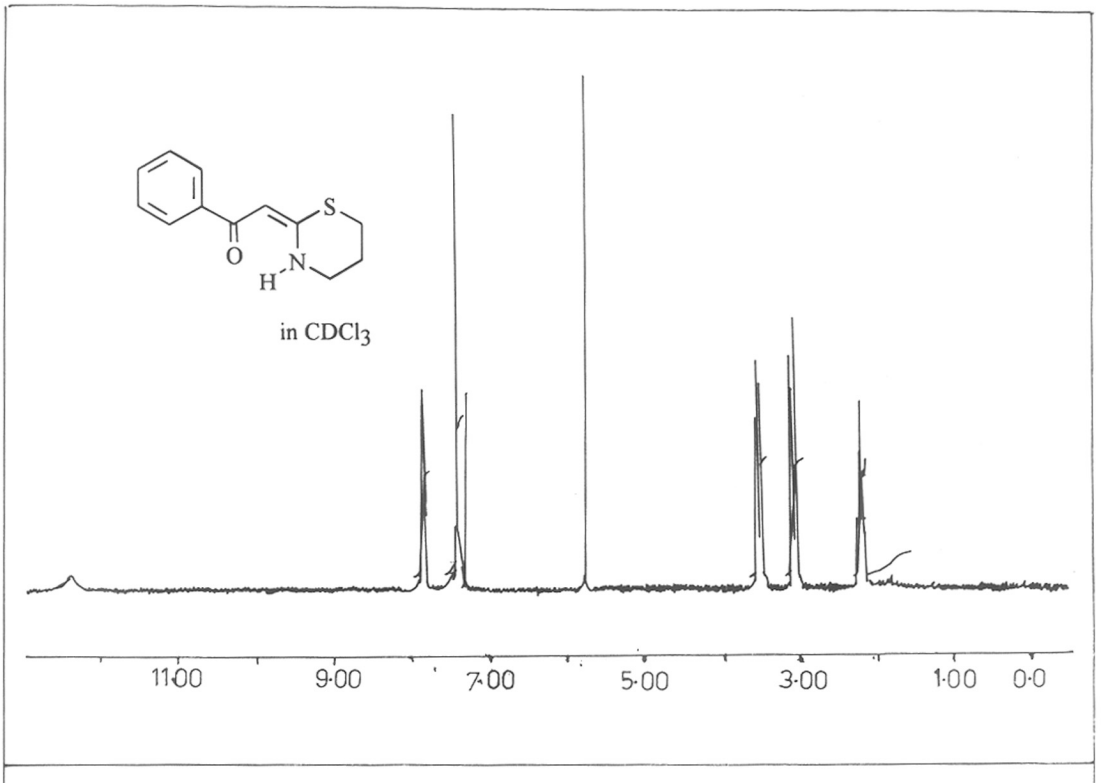
1.4.3c: c) S...O Non-bonded attractive interactions

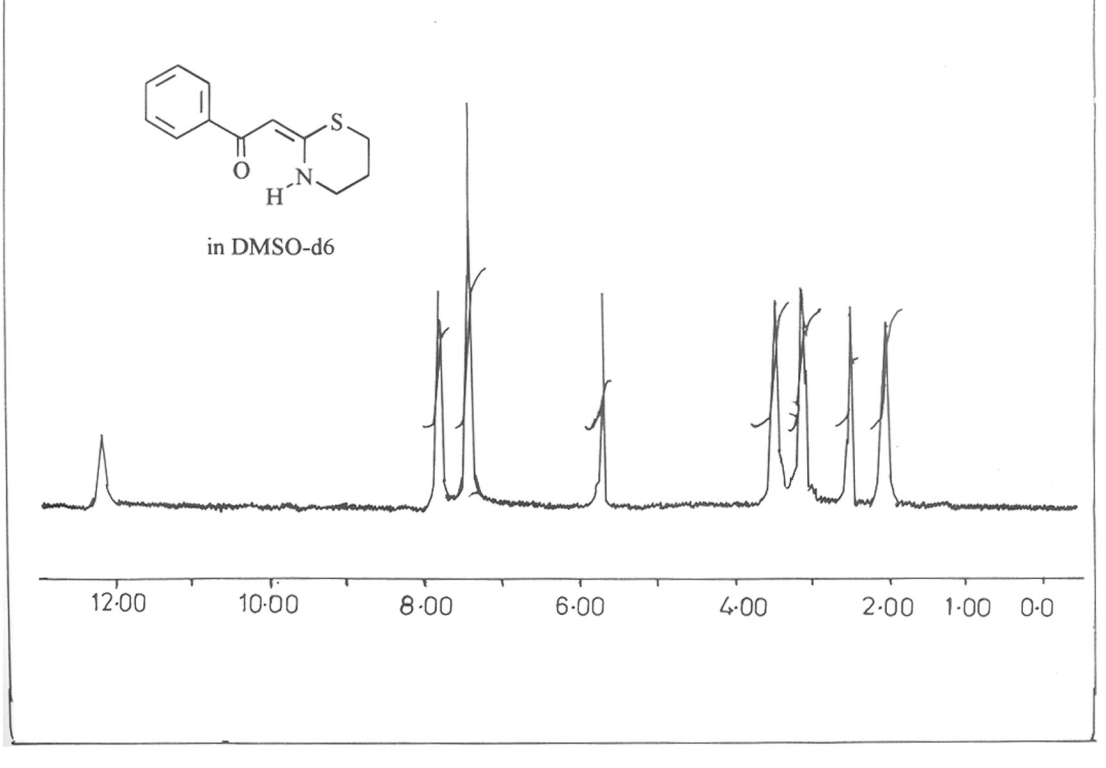
The idea of non-bonded attractive interaction between a divalent sulfur atom and a suitably located oxygen atom has been used by X-ray crystallographers to explain the unusual short S...O contacts[4,7] observed in solid state structures. The essential substructure required is S-A= B-Y =O in which A=B has *cis* configuration and B-Y has the *s-cis* configuration. This condition is met in **11(a-g).** It is therefore most likely that such non-bonded attractive forces might be responsible for the extra stability of the *Z* form of (**11**).

The implication is that once the intramolecular H-bonds in *E* isomer are broken by solvation, the weak attractive (S...O non-bonded) force manifests itself in populating the *Z* configuration.

1.4.4 Directionality Requirement for S...O interactions

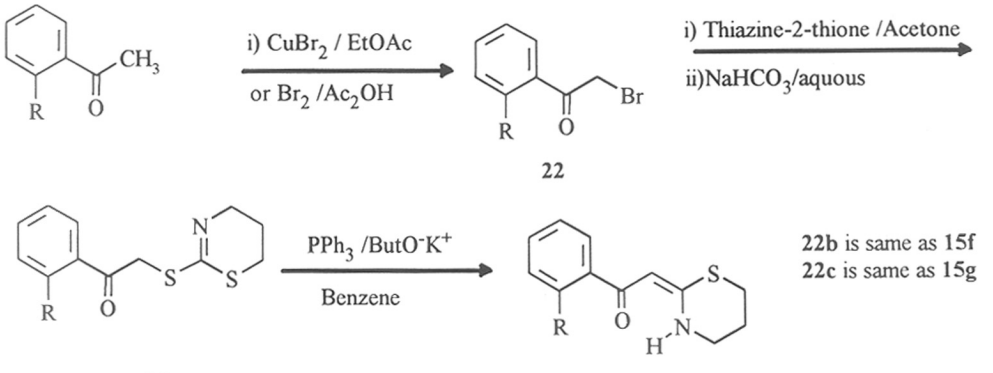
The six membered thiazine analog of enaminone (**11**) was prepared in order to study the effect of molecular geometry particularly at sulfur and oxygen on *E/Z* isomerisation. The thiazine analogs **24a-c** were synthesized by the sulfide contraction method in three steps. The first step was the conversion of acetophenone to the corresponding phenacyl bromide either by Br_2/AcOH or by $CuBr_2$ in ethyl acetate. The phenacyl bromides were then reacted in dry acetone with thiazine-2-thione to give a white insoluble salt. The salt was neutralized with aqueous $NaHCO_3$ to get phenacylthiothiazine (**23a**). The compound (**23a**) was then treated with PPh_3 in presence of a


S
O
N
H
in $CDCl_3$
11·00
9·00
7·00
5·00
3·00
1·00
0·0


S
O
N
H
in DMSO-d6
12·00
10·00
8·00
6·00
4·00
2·00
1·00
0·0

catalytic amount potassium *t*-butoxide in benzene at 80°C to give compound (**24a**). Compounds **24b** and **24c** were synthesized in a similar way as shown in *Scheme 4*. The conformation of the six-membered thiazine analogs (**24a**), (**24b**) and (**24c**) was studied by ^{1}H NMR spectroscopy in solvents of different polarity. The ^{1}H NMR spectrum of compound **24a** havinig no substituents

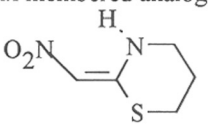
Scheme 4



	R
a	H
b	OH
c	OMe

on the phenyl ring shows only one set of sharp signals in $CDCl_3$ as well as in DMSO-d_6. Signals due to the *Z* isomer were absent. The only isomer present in $CDCl_3$ was assumed to be the *E* isomer by analogy with the enaminones (**11**). Also by comparison of the chemical shift in the ^{1}H NMR spectrum in $CDCl_3$ solution, the only isomer seen in DMSO-d_6 was concluded to be the *E* isomer. The ^{1}H NMR spectrum of (**24a**) in $CDCl_3$ shows a complex multiplet for the ring methylene groups at 2.25δ. Two triplets are seen at 3.20 and 3.55δ corresponding to SCH_2 and NCH_2. A sharp singlet at 5.75δ is assigned to the olefinic proton and the broad singlet at 12.45δ to the NH. Similar study of the ^{1}H NMR spectrum of the *o*-hydroxy thiazine derivative (**24b**) and *o*-methoxy thiazine derivative (**24c**) in $CDCl_3$ and DMSO-d_6 was also carried out. The ^{1}H NMR spectra of (**24b**) and (**24c**) in $CDCl_3$ as well as in DMSO-d_6 show only one sharp set of signals due to the *E* isomer. The NH proton in the case of (**24b**) was noted at 11.70δ and that for (**24c**) at 12.05δ in DMSO-d_6 solution. The ^{1}H NMR spectrum of the thiazine derivatives (**24a**), (**24b**), (**24c**) show only one set of signals in $CDCl_3$ as well as in DMSO d_6. The spectral data are

(**24c**) show only one set of signals in $CDCl_3$ as well as in DMSO-d_6. The spectral data are summarized in *Table 4*. This leads to the conclusion that in the case of the thiazine derivatives, the *Z*-isomer does not derive any extra stability by non-bonded interaction. This means that molecular geometry plays a crucial role in determining the magnitude of this S...O non-bonded attraction. This is obvious from the comparison of compounds (**11a**) and (**24a**). The former has a 5-membered hetero ring as a part of the keten S,N-acetal unit while the latter has a six membered ring. The chemical shift of NH proton in the thiazine derivative is seen further downfield than that of the corresponding thiazolidine derivative. This may indicate the stronger hydrogen bonding in the thiazine. Comparison of the *o*-hydroxyphenyl derivatives of the thiazolidine (**11f**) and thiazine (**24b**) confirms the dramatic effect of changing the size of the hetero ring. The *Z* isomer is populated to the extent of 52% in (**11f**) whereas the thiazine analog (**24b**) exists exclusively as the *E* isomer both in $CDCl_3$ as well as in DMSO-d_6. Similar behavior was also noted for the *o*-methoxy derivatives (**11g**) and (**24c**). Earlier a similar effect had also been reported in the case of the nitro compound (**9**) and its six membered analog (**25**).[15]



25

The explanation suggested for the absence of S...O non-bonded attraction in the *Z*-isomers of (**24**) and the nitro compound (**25**) is based on the geometry requirement for this effect to be manifested. As suggested by the X-ray crystallographic studies, the three atoms involved, namely, O...S-C should lie in a straight line. Such a linear arrangement allows the σ^* of S-C to interact with the lone pair electrons on the oxygen atom. The 5-membered thiazolidine ring apparently permits such a linear arrangement. In contrast, the six membered thiazine derivative does not allow the linear arrangement of C-S...O. Hence solvent dependent *E/Z* isomerisation is not observed in (**24a-c**). The ^1H NMR data in $CDCl_3$ and DMSO-d_6 are summarised in *Table 4*.

Table 4

^1H NMR Data of Thiazines **24**

Sr. No	Solv.	Compd.	NH	=CH	NCH_2	SCH_2
1	$CDCl_3$	**24a**	12.45	5.75	3.55	3.20
2	DMSO-d_6		12.15	5.75	3.45	3.10
3	$CDCl_3$	**24b**	11.90	5.75	3.55	3.15
4	DMSO-d_6		11.75	5.75	3.50	3.10
5	$CDCl_3$	**24c**	12.35	5.70	3.50	3.05
6	DMSO-d_6		12.05	5.50	3.40	3.10

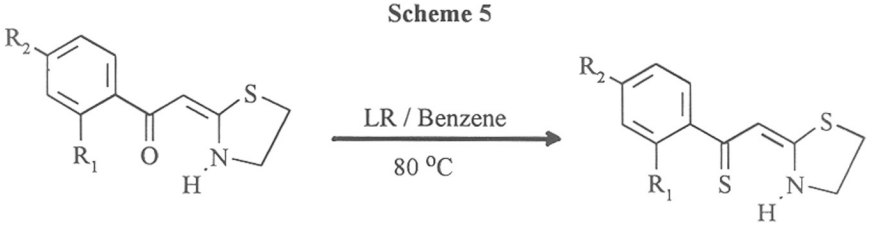
Extension to enaminothiones

The enaminones **(11a-g)** showed solvent dependent *E/Z* isomerisation due to two competing forces, namely N-H...O intramolecular hydrogen bonding in the *E*-isomer and S..O non-bonded interaction in the *Z*-configuration. It was next decided to find out if similar solvent dependent isomerisation could be seen in enaminothiones

1.4.5 : Synthesis of Enaminothiones (12)

The enaminothiones were prepared by the Lawesson thionation of the corresponding enaminones in dry benzene at 80 °C as shown in *scheme 5*.[21] The enaminothiones were obtained

Scheme 5



11 a-g **12 a-g**

	R_1	R_2
a	H	H
b	H	OMe
c	H	NO_2
d	Cl	H
e	NO_2	H
g	OMe	H

in 60-80 % yield. In the IR spectrum, enaminothiones lack the carbonyl stretching absorption around 1600 cm^{-1}. The ^1H NMR spectra show a downfield shift of the olefinic proton as well as of the NH proton due to the higher anisotropic deshielding effect of thiocarbonyl moiety compared to that of the carbonyl moiety.

Attempts to convert the *o*-hydroxyphenyl compound **11f** to the corresponding thio-analog **12f** were unsuccessful. Thionation of **11f** by LR in solvents such as THF, toluene and HMPT at room temperature as well as at elevated temperatures gave uncharacterisable product mixtures. Other thionating agents such as P_2S_5 and Na_2MoS_4 also did not lead to the desired thione.

Enaminothiones such as (**12**) also belong to the class of push-pull ethylenes. They have an electron-withdrawing thiocarbonyl moiety at one end of the carbon carbon double bond and an electron-donating amino group at the other . The energy barrier to rotation around the C=C is low due to the significant single bond character.[14] The *E* isomers of enaminothiones (**12**) also as in the case of enaminones (**11**) have higher stability due to intramolecular N-H...S hydrogen bonding.

The ^1H NMR spectra of the enaminothiones (**12**) were recorded in $CDCl_3$, DMSO-d_6 and mixtures of these two. The enaminothione (**12a**) without any substituent on the benzene ring is discussed below in detail as a representative example.[18] Compound **12a** in $CDCl_3$ shows a sharp set of ^1H NMR signals at room temperature. Addition of DMSO-d_6 leads to the appearance of a second set of signals due to the *Z* isomer. In a mixture of $CDCl_3$ and DMSO-d_6 (4:1) the *E*:*Z* ratio was found to be 9:1. In pure DMSO-d_6 the ratio of *E*:*Z* isomers was 59:41. The DMSO-d_6 solution of **12a** shows two sets of signals for all the protons. The NH proton appears at 13.30 and 9.70δ The downfield signal was assigned to the *E* isomer because it is involved in strong intramolecular hydrogen bonding. The *E*:*Z* ratio was estimated by determining the relative intensities of the two singlets due to the olefinic proton. The signals due to *E* and *Z* isomers were broad at room temperature in pure DMSO-d_6 solution. In a mixture of $CDCl_3$: DMSO (1:4) the signals due to the *E* isomer were sharp at room temperature whereas the signals due to the *Z* isomer were still broad. The study of ^1H NMR spectra at lower probe temperature already carried out in our group, shows that the signals due to the *Z* isomer get sharpened when the temperature of the probe is lowered to -25 °C.[18] The above broadening effect can be attributed to another conformational process *viz* rotation about C-C connecting thiocarbonyl carbon with the olefinic

carbon. The line broadening is observed only in the *Z* isomer of the enaminothione, probably because the S..S non-bonded interaction is too weak to restrict the rotation about S=C-C=C.

In the case of the *E* isomer in the mixed solvent system of intermediate polarity, intramolecular hydrogen bonding is not completely broken. This hydrogen bonding is sufficient to restrict the secondary conformational process of rotation about the carbon carbon single bond. In pure DMSO-d_6 the disruption of the intramolecular hydrogen bond in the *E* isomer leads to broadening of peaks.

1.4.6: Effect of substituents on the benzene ring of enaninothiones(12)on E/Z equilibrium.

1.4.6a: *Para*-Substitution on benzene ring

The next attempt was to study the effect of electron-donating and electron-withdrawing groups on the benzene ring on the *E/Z* equilibrium of enaminothiones (**12**). The ^{1}H NMR spectral study of the *p*-methoxyphenyl derivative (**12b**) and the *p*-nitrophenyl derivative (**12c**) was hence undertaken. The ^{1}H NMR spectrum of methoxyphenyl enaminothione (**12b**) shows line broadening in DMSO-d_6 solution for both the *E* and the *Z* isomers. The SCH_2 and NCH_2 could not be distinguished as two sets of peaks in DMSO-d_6 solution, whereas the olefinic proton was seen at 6.75δ and 7.25δ and the NH proton at 13.30 and 9.70δ respectively. The *E:Z* ratio was found to be 56:44. The ^{1}H NMR spectrum of the *p*-nitrophenyl enaminothione (**12c**) in $CDCl_3$ solution shows one set of sharp peaks. The ^{1}H NMR spectrum in DMSO-d_6 solution shows peak broadening for both the *E* and *Z* isomers. The NH proton appears at 13.20 and 10.50δ as broad singlets. The downfield peak was assigned to the *E* isomer as usual. The E:Z ratio was determined to be 55:45 by the estimation of the relative intensities of these two NH signals.

The *E:Z* ratio of the three compounds, **12a** without any substituent on the benzene ring (*E:Z*, 59:41), (**12b**) *p*-methoxyphenyl derivative (*E:Z*, 56:44) and (**12c**) *p*-nitrophenyl derivative (*E:Z*, 55:45) are not significantly different from each other. It was hence concluded that nature of the substituent on the benzene ring has no significant effect on the *E/Z* equilibrium in enaminothiones (**12**). This observation is similar to that in the case of enaminones (**11**).

Table 5

^{1}H NMR chemical shifts (δ) for enaninothiones (**12**)

Cmopd	Solvent	NH		=CH		NCH_2		SCH_2	
		E	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
12a	$CDCl_3$	13.75	-	6.75	-	4.10	-	3.40	-
	DMSO-d_6	13.30	9.70	6.80	7.15	4.10	3.70	3.45	3.25
12 b	$CDCl_3$	13.75	-	6.70	-	4.15	-	3.30	-
	DMSO-d_6	13.30	9.70	6.75	7.25	**	**	**	**
12 c	$CDCl_3$	13.30	-	6.75	-	4.25	-	3.50	-
	DMSO-d_6	13.20	10.50	**	**	**	**	**	**
12d	$CDCl_3$	13.70	-	6.55	-	4.20	-	3.45	-
	DMSO-d_6	13.70	9.75	6.48	6.70	4.10	**	**	**
12e	$CDCl_3$	13.50	-	6.50	-	4.20	-	3.45	-
	DMSO-d_6	12.90	10.10	**	**	**	**	**	**
12g	$CDCl_3$	13.75	-	6.65	-	4.10	-	3.50	-
	DMSO-d_6	13.15	9.95	6.65	**	**	**	**	**

Table 6

E/Z ratio of enaninothiones in DMSO-d_6

Compd	*E*	*Z*
12a	59	41
12b	56	44
12c	55	45
12d	59	41
12e	60	40
12g	48	52

It was hence concluded that the presence of an electron-donating group or an electron-withdrawing group on the phenyl ring has no significant effect on the non-bonded S...S interactions.

1.4.6b: Effect of *ortho* substituents

The ^{1}H NMR spectra of *o*-chlorothiobenzoyl methylene thiazolidine (**12d**) shows one sharp set of signals in $CDCl_3$ solution. The ^{1}H NMR spectrum in DMSO-d_6 shows line broadening for both *E* and *Z* isomers. Two separate peaks could not be seen for the SCH_2 and NCH_2 protons in this solvent. The NH proton appears as two broad singlets at 13.70 and 9.75δ the downfield peak was assigned to the *E* isomer. Based on the relative intensities of these two NH signals, the *E:Z* ratio was found to be 59:41. Other *ortho*-substituted compounds (**12e**), (**12g**) show similar line broadening in their ^{1}H NMR spectra in DMSO-d_6 solution. In all these cases, only the NH signals had to be used for estimating the E:Z ratio. From then intensities of these two NH signals, the *E:Z* ratio was found to be 60 :40 for compound **12e** and 48 :52 for compound **12g**. In every instance the downfield NH signal was assigned to the *E* isomer.The ^{1}H NMR data and relative population of *E:Z* isomers for enaminothiones (**12**) is summarized in *Table 5* and *Table 6.*

1.4.7: Possible causes for solvent dependent isomerisation in enaminothione (12)

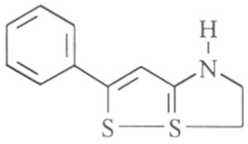
As discussed in the case of enaminones (**11**) the *E* to *Z* isomerisation of enaminothiones (**12**) in polar solvents can be due to any of the following reasons

1.4.7a i) **Solvent effect :**

Increasing solvent polarity can decrease the energy difference between *E* and *Z* isomers and also decrease the barrier to such interconversion. However, as discussed earlier in connection with enaminones, this explanation does not assign any specific role to the nuclear sulfur atom.

1.4.7b ii) Tendency of sulfur to form hypervalent bonds

The tendency of sulfur to form hypervalent bonds might result in a structure such as **26** for the *Z* isomer of compound **12**. However as mentioned in the case of oxo compound (**11**) this



26

explanation cannot be valid since molecules having such apical S-S-C units have not been encountered so far.[20]

1.4.7c: iii) S..S Non-bonded interaction

The S...S non-bonded attractive interaction between ring sulfur and the sulfur of the thiocarbonyl group might be responsible for the increased stability of the **12*Z*** series. The *E* isomer derives its stability from the N-H...S hydrogen bond. In polar solvents like DMSO-d_6, intramolecular hydrogen bonding gets weakened and the weak S..S interaction manifests itself in stabilizing the *Z* isomer.

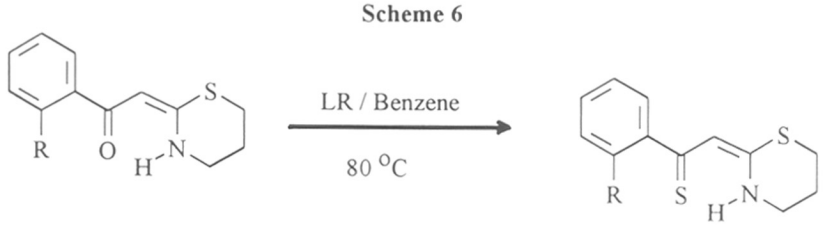
1.4.8: Directionality Requirement for S...S interactions

Changing the size of the sulfur-containing ring in the enaminothione (**12**) from five membered to a six membered one is expected to produce small perturbations in the geometry of the molecule, which might result in disturbing the co-linearity of the three atoms C-S...S. This in turn, would disrupt the S..S non-bonded interaction. In order to test this, the thiazine analog (**27**) was prepared.

1.3.8a: Synthesis of thiobenzoylmethylene thiazine (27a)

Compound (**27a**) was prepared by the Lawesson thionation of the corresponding oxo-compound (**24a**) in dry benzene at 80 °C. Compound (**27c**) was synthesized in the same manner as

Scheme 6



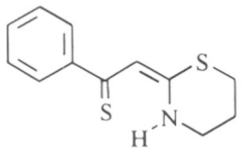
24 **27**

a : R=H

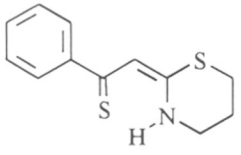
c : R = OMe

shown in *scheme 6*. But, compound **24b** having an *o*-hydroxy group could not be converted to the corresponding thio derivative (**27b**).

The ^{1}H NMR spectrum of compound **27a** shows sharp signals in $CDCl_3$ as well as in DMSO-d_6. Only one set of signals was observed in both the solvents. The ^{1}H NMR spectrum of



in $CDCL_3$



in DMSO-d6

compound **27a** in $CDCl_3$ shows a multiplet at 2.20δ and triplets at 3.15 and 3.65δ due to thiazine ring protons. The olefinic proton is observed at 6.50δ as a sharp singlet. The NH and olefinic protons were shifted downfield compared to the oxo analog (**24a**) due to the stronger anisotropic deshielding effect of the thiocarbonyl group compared to that of the carbonyl group. The only isomer observed in $CDCl_3$ and DMSO-d_6 was the hydrogen bonded *E* isomer. This was also true in the case of the *ortho*-methoxy compound **27c**. The absence of solvent dependent isomerisation in compounds **27a** and **27c** confirmed the critical need for co-linearity of the three atoms C-S...S which apparently is feasible with the thiazolidine, but not with the thiazine. The absence of linearity leads to difficulty in overlap of σ* C-S with the lone pair electrons on sulfur. As a result S....S attractive interaction becomes ineffective and hence solvent dependent *E/Z* isomerisation is not observed for compounds **27a** and **27c**. The ^1H NMR data for thazine derivatives **27** is summarised in *Table 7*.

Table 7

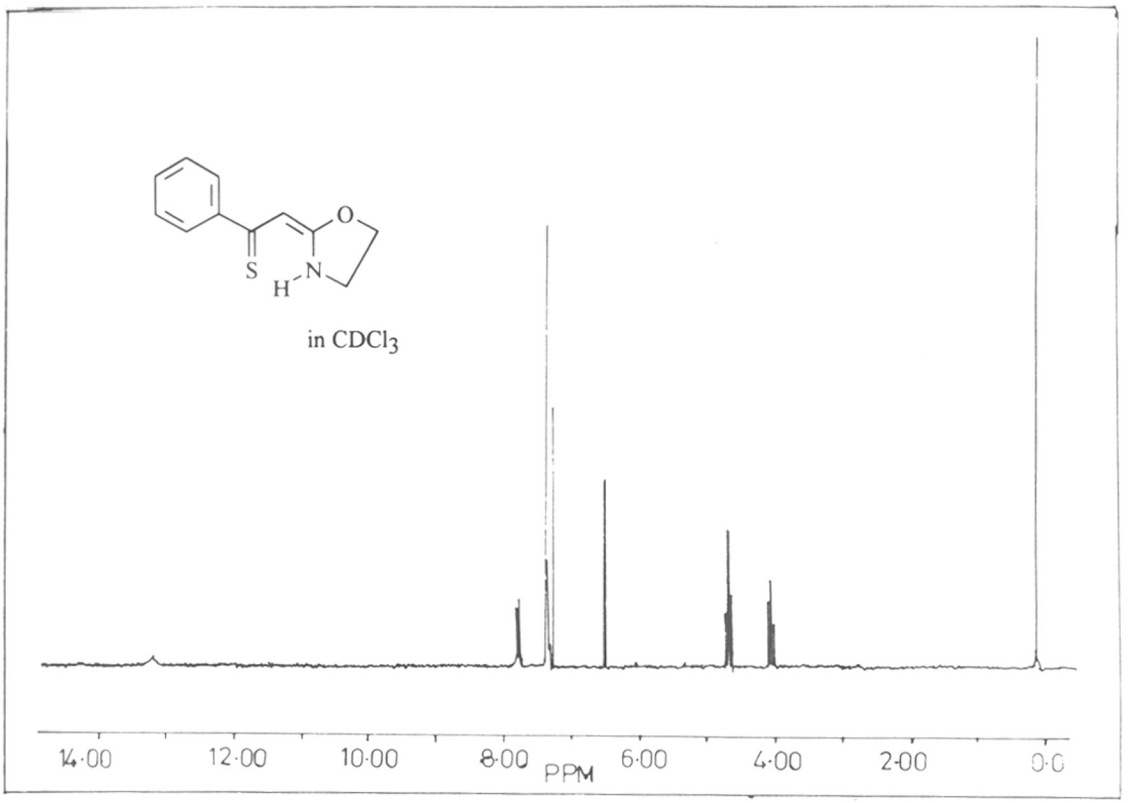
^1H NMR data of thiazine derivative **27**

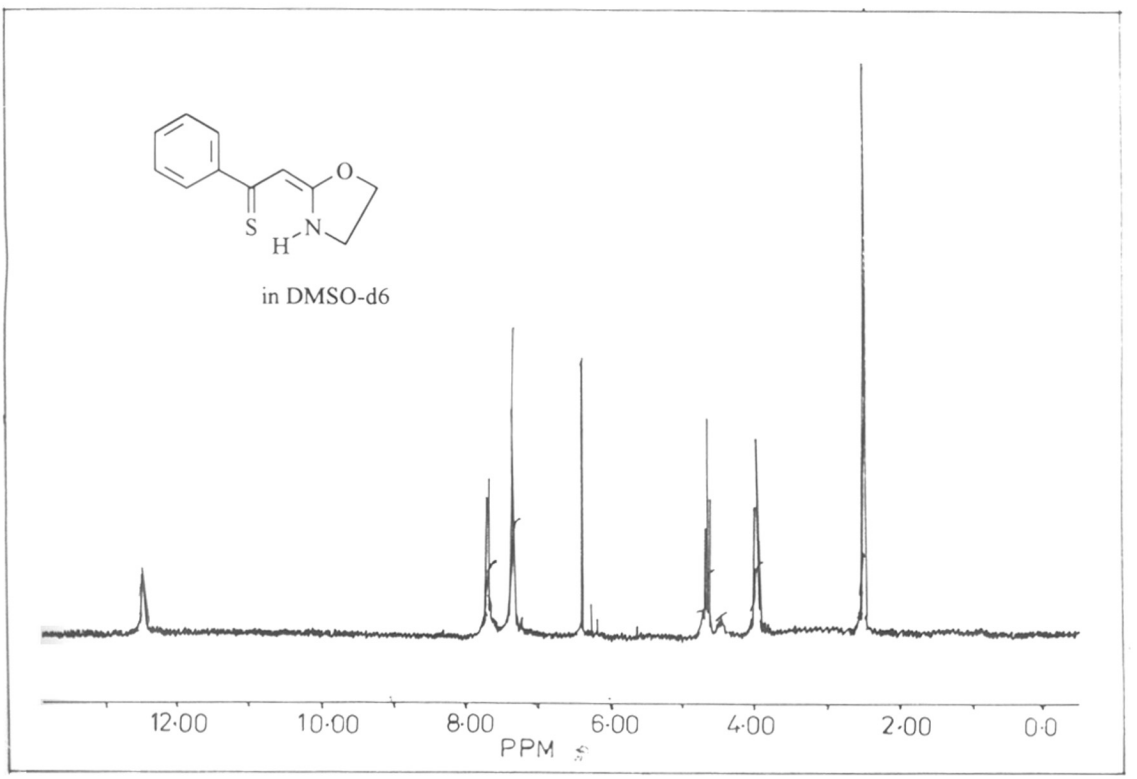
Sr.No	Solvent	Compd.	NH	=CH	NCH_2	SCH_2
1	$CDCl_3$	**27a**	15.00	6.50	3.65	3.15
2	DMSO-d_6	**27a**	15.20	6.45	3.60	3.30
3	$CDCl_3$	**27c**	14.95	6.35	3.60	3.10
4	DMSO-d_6	**27c**	14.65	6.15	3.55	3.15

1.4.9: Effect of HOMO-LUMO energy on S...O interaction

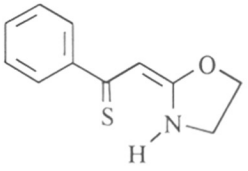
As a further check on our hypothesis, the oxazolidine thione **28** was synthesized by Lawesson thionation of the oxo compound **19**. It is interesting to note that in this thione **28** the location of the oxygen and sulfur atoms is just the reverse as that obtained in the thiazolidine **11a** discussed earlier.

The ^1H NMR spectrum of compound **28** shows sharp signals in $CDCl_3$ as well as in DMSO-d_6 solution. Only one isomer i.e. hydrogen bonded *E* isomer is observed both in $CDCl_3$ and DMSO-d_6 solution. The ^1H NMR spectrum in $CDCl_3$ solution shows two triplets at 4.05δ and


O
S
H
N
in $CDCl_3$
14·00
12·00
10·00
8·00
PPM
6·00
4·00
2·00
0·0


O
S
H
N
in DMSO-d6
12·00
10·00
8·00
PPM
6·00
4·00
2·00
0·0

4.70δ due to NCH_2 and OCH_2 and a sharp singlet at 6.50δ due to the olefinic proton. The aromatic protons appear at 7.4 to 7.80δ as a complex multiplet. The NH proton is seen as a broad singlet at 13.2δ. It is thus obvious that **28*Z*** is not of comparable energy as **28*E*** even in polar solvents when intramoleculr H-bonds are largely broken. This means that (**28*Z***) does not derive any stabilization from S...O non-bonded interaction. The S...O attractive interaction in case of



28

compound (**28**) will arise, if at all, from HOMO (non-bonded electron on thiocarbonyl sulfur) and LUMO (σ*C-O) interaction. In this case, obviously, the LUMO is too high in energy for any fruitful interaction.

1.5 : Conclusions

1. Enaminones **11** are push-pull ethylenes. Hence the energy barrier for rotation about the central C=C is low. The two species observed in DMSO-d_6 solution of **11a-g** are E/Z isomers.
2. Electron-withdrawing or electron-donating groups at the *para* position of the benzene ring in enaminones (**11**) have hardly any effect on the *E:Z* ratio in pure DMSO-d_6 solution. Hence it is concluded that such substitution has no effect on the strength of S..O non-bonded interaction.
3. *Ortho* Substituents on the benzene ring in enaminones **11** lead to line broadening in the ^{1}H NMR spectrum in DMSO-d_6 solution. This is probably because of slow rotation on NMR scale around the Ar-CO bond. The sharp set of peaks in *o*-hydroxy enaminone (**11f**) is due to locking of conformation due to intramolecular hydrogen bonding.
4. The ^{1}H NMR spectral studies on the oxazolidine **19** and pyrrolidine derivative **20** rule out any explanation based solely on solvent effect i.e. solvation of NH and it's steric requirements.
5. S..O non-bonded attractive interaction seems to be the most acceptable explanation for solvent dependent *E/Z* isomerisation in compound **11**.
6. ^{1}H NMR spectral studies on the thiazine derivative **24** demonstrate the crucial geometric requirement necessary for the manifestation of S...O non-bonded interactions. The three atoms C-S...O have to have a linear arrangement.
7. ^{1}H NMR spectral studies on the enaminothiones **12** show behavior parallel to that of enaminones **11**. In this case also, solvent dependent *E/Z* isomerisation is to be attributed to S...S interactions.
8. Electron-donating and electron-withdrawing substituents have no effect on the strength of S...S non-bonded attractive interactions. Directionality requirement of S...S non-bonded interactions is similar to that of S...O non-bonded interactions.
9. The fact that only *E* isomer is observed in $CDCl_3$ as well as in DMSO-d_6 for compound **28** is most probably due to lack of any fruitful HOMO-LUMO interactions as the LUMO (σ*C-O) is too high in energy.

1.6 EXPERIMENTAL

1.6.1: Synthesis of Enaminoketones Method A (11)

1.6.1a: Synthesis of keten-S,S acetals (14 b-e)

General Procedure

Substituted acetophenone (10 mmol) was added to a suspension of NaH (20 mmol) in dry benzene. On addition of CS_2 (10 mmol) to cooled mixture no reaction was evident; but on addition of DMF the solution turned to dark color and remaining NaH was consumed. The contents were cooled to 10°C and methyl iodide (20 mmol) was added. After stirring the reaction mixture overnight water was added to the reaction mixture on next day. Reaction mixture was further diluted with benzene, and DMF was removed by washing benzene layer with several portions of water. Benzene was pumped off at reduced pressure to get keten dithioacetal in 40-65% yield. Product was purified by column chromatography using pet-ether ethyl acetate on 60-120 silica. *(Scheme 1)*

1,1-Bismethylthio-2-(4'-methoxybenzoyl) ethylene (14b)

Nature	Yellow Crystalline solid
M.P.	100 - 102 °C
Yield	65%
I.R. cm^{-1} (nujol)	2900, 1600, 1520
^{1} HNMR	2.44 (s,3H,SMe), 2.48 (s,3H,SMe), 3.8 (s,3H,OMe), 6.6 (s,1H,=CH),
($CDCl_3$)	6.8-7.8 (m,4H,ArH)

1,1 Bis-methylthio-2-(4'-nitrobenzoyl) ethylene (14c)

Nature	Yellow Crystalline solid
M.P.	178 - 180 °C
Yield	52%
I.R. cm^{-1} (nujol)	2940, 1630, 1610, 1530
^{1} HNMR	2.53 (s,3H,SMe), 2.57 (s,3H,SMe), 6.6 (s,1H,=CH),
($CDCl_3$)	6.8-7.8 (m,4H,ArH)

1,1 Bis-methylthio-2-(2'-chlorobenzoyl) ethylene (14d)

Nature	Dark brown solid
M.P.	109-110 °C
Yield	65 %
I.R. cm^{-1} (nujol)	3020, 1630, 1600 ,1440
^{1} HNMR	2.4 (s,6H,SMe), 6.36 (s,1H,=CH),
($CDCl_3$)	7.2 - 7.5 (m,4H,ArH)

1,1 Bis-methylthio-2-(2-nitrobenzoyl) ethylene (14e)

Nature	Dark brown solid
M.P.	155 -156 °C
Yield	52 %
I.R. cm^{-1} (nujol)	2900, 1630, 1610 ,1470
^{1}H NMR	2.44 (s,3H,SMe), 2.50 (s,3H,SMe), 6.10 (s,1H,=CH),
($CDCl_3$)	7.5 - 7.8 (m,4H,ArH)

1.6.1b: Reaction of keten-dithioacetal with 2-amino ethanethiol

In the second step of reaction keten dithioacetal was reacted with 2-amino ethanethiol to yield cyclic S,N-acetals (**11 b-e**). To the suspension of keten-dithioacetal (5 mmol) in absolute ethanol, 2-amino ethanethiol (6 mmol) was added. The reaction mixture was heated to reflux. Reaction was evident due to typical smell of methyl mercaptan. Three to 12h of stirring under reflux condition gave 2-(substituted benzoyl)methylenethiazolidine in 40-70% yield. Product formed was recrystallised from absolute ethanol.

2-(4'-Methoxy benzoyl) methyllenethaizolidine (11b)[16]

Nature	Light Yellow Crystalline Solid
M.P.	154 -156 °C
Yield	52 %
I.R. cm^{-1} (nujol)	3260, 2940, 1610 ,1580
^{1}H NMR	3.30 (t, J=8Hz,2H,SCH_2), 3.75 (s,3H,OMe), 3.95 (t,J=8Hz,2H,NCH_2)
($CDCl_3$)	6.00 (s,1H,=CH), 6.90 -7.80 (m,4H,ArH), 10.60 (bs,1H,NH)

2-(4'-Nitrobenzoyl) methyllenethaizolidine (11c)

Nature	Yellow Crystalline Solid
M.P.	120 -122 °C
Yield	44 %
I.R. cm^{-1} (nujol)	2900, 1600, 1550
^{1} HNMR	3.30 (t, J=8Hz,2H,SCH_2), 4.00 (t,J=8Hz,2H,NCH_2) 5.90 (s,1H,=CH),
($CDCl_3$)	8.00 - 8.30 (m,4H,ArH), 10.80 (bs,1H,NH)
Mass (m/z)	250 (M+, 45%), 128 (100 %)
Anal.calcd.for	C, 52.78; H, 4.02; N, 11.20; S, 12.81
$C_{11}H_{10}N_2O_3S$	
Found	C, 52.80; H, 4.11; N, 11.19; S, 12.67

2-(2'-Chlorobenzoyl) methylenethaizolidine (11d)

Nature	Light yellow Crystalline Solid
M.P.	138 -140 °C
Yield	58 %
I.R. cm^{-1} (nujol)	3250, 3000, 1600
^{1} HNMR	3.35 (t, J=8Hz,2H,SCH_2), 4.05 (t,J=8Hz,2H,NCH_2) 5.70 (s,1H,=CH),
($CDCl_3$)	7.40 - 7.70 (m,4H,ArH), 10.60 (bs,1H,NH)
Mass (m/z)	239 (M+, 45%), 204 (100 %)
Anal.calcd.for	C, 55.12; H, 4.20; N, 5.84
$C_{11}H_{10}ClNOS$	
Found	C, 55.68; H, 4.43; N, 5.77.

2-(2'-Nitrobenzoyl) methyllenethaizolidine (11e)

Nature	Dark brown Solid
M.P.	213-215 °C
Yield	30 %
I.R. cm^{-1} (nujol)	3240, 1610, 1560, 1480.
^{1} HNMR	3.35 (t, J=8Hz,2H,SCH_2), 4.00 (t,J=8Hz,2H,NCH_2) 5.60 (s,1H,=CH),
($CDCl_3$)	7.6 -7.9 (m,4H,ArH), 10.40 (bs,1H,NH)

Mass (m/z)	250 (M+, 12 %), 116 (100 %)
Anal.calcd.for	C, 52.78; H, 4.02.
$C_{11}H_{10}N_2O_3S$	
Found	C,51.70; H, 3.95.

1.6.2 : Synthesis of Enaminoketones Method B (11)

Compound **11f** and **11g** were synthesized by sulfur contraction method in three steps. First step is bromination of side chain of substituted acetophenone. The second step is coupling reaction and the third step is sulfur extrusion ..

1.6.2a: Bromination of *ortho*-substituted acetophenone :

General Procedure

To the suspension of (10 mmol) $CuBr_2$ in 50 ml ethyl acetate, 10.5 mmol of *ortho* substituted acetophenone was added. The reaction mixture was heated to reflux under vigorous stirring. Green $CuBr_2$ turn to white CuBr as reaction proceeds. The course of reaction was monitored by tlc. After completion of reaction 3 to 5 h. Ethyl acetate layer was washed with water to remove traces of unreacted $CuBr_2$. The insoluble inorganic material was filtered out. Ethyl acetate was evaporated under reduced pressure.

2-Bromo (2'-hydroxy)acetophenone 15f

Nature of compd.	Lacrymatic brown liquid
Yield	85 %
IR (neat) cm -1	3060, 1640, 1580, 1580
^1H NMR	4.30 (S, 2H, CH_2), 6.7 - 7.5 (m, 4H, ArH)
($CDCl_3$)	11.60 (S, 1H, OH)

2-Bromo(2'-methoxy) acetophenone 15g

Nature of compd.	Lacrymatic brown liquid
Yield	88 %
IR (neat) cm $^{-1}$	3000, 1690, 1600, 1490
^1H NMR	3.9 (S, 3H, OCH_3), 4.5 (S, 2H, C=CH_2),
($CDCl_3$)	6.8 - 7.8 (m, 4H, ArH)

1.6.2b : Reaction of 2-bromo acetophenones with thiazolidine-2-thione

The 2-bromo acetophenone thus form was used in next reactions without purification. A mixture of thiazolidine-2-thione (8mmol) and 2-bromo-2'-substituted acetophenone or phynacyl bromide (10 mmol) was stirred at 30°C for 1h. The white solid was filtered and dissolved in methanol and neutralized with aqueous $NaHCO_3$. Methanol was evaporated at reduced pressure and organic 2(2'-substituted benzoyl) methylene thiothiazolidine material was extracted in dichloromethane. The dichloromethane layer was dried over Na_2SO_4 and evaporated to give 2-(2'-substituted benzoyl) methylenethiothiazolidine which was further purified by column chromatography using pet-ether ethyl acetate to give compound **16f** and **16g**

2-((2'Hydroxybenzoyl) methyl)thiothiazolidine (16f)

Nature	White solid
Yield	64 %
MP.	115-116 °C
IR cm^{-1} ($CHCl_3$)	3400, 3010, 16540, 1620, 1580
^1H NMR	3.48 (t, 2H, SCH_2), 4.13 (t, 2H, NCH_2), 4.60 (s,2H, SCH_2),
($CDCl_3$)	6.9 - 7.8 (m, 4H, ArH), 11.90 (bs, 1H,NH)

2-((2'Methoxybenzoyl) methyl)thiothiazolidine (16g)

Nature	White solid
Yield	60 %
M.P.	80°C
IR cm^{-1} (nujol)	2940, 2860, 1700, 1600, 1580
^1H NMR	3.31 (t,2H,SCH_2), 4.13 (t,2H,NCH_2), 4.60 (s,2H,SCH_2),
($CDCL_3$)	6.9 -7.8 (m,4H,ArH)

1.6.2c : Desulfurisation

The compound **16f, 16g** 5 mmol was taken in dry toluene 30 ml and PPh_3 (20 mmol) and potassium *t*-butoxide (2 mmol) were added to it and refluxed for 5h under inert atmosphere. Solvent was evaporated and product was purified by column chromatography silica (60 -120) (pet-ether, ethyl acetate)

2-(2'-Hydroxybenzoyl)methylene thiazolidine (11f)

Nature	Yellow crystalline solid
Yield	80 %
M.P.	140 - 141°C
IR cm-1 (nujol)	3260, 3000, 1600, 1580, 1530
^{1}H NMR	3.30 (t, J=8Hz, 2H, SCH_2), 4.00 (t, J = 8Hz, 2H, NCH_2),
($CDCl_3$)	6.00 (S, 1H, =CH), 6.6 - 7.6 (m, 4H, ArH),
	10.25 (bs, 1H, NH), 13.55 (s, 1H, OH)
Mass m/z,	221 (M+, 100%), 121 (60%)
Anal.Calcd.For	C, 59.70; H, 5.00; N, 6.33, S. 14.47
$C_{11}H_{11}NO_2S$	
Found	C, 60.12; H, 5.39, N, 6.33; S, 14.49

2-(2'-Methoxybenzoyl)methylenethiazolidine (11g)

Nature	Light Yellow viscous liquid
Yield	75 %
IR (neat)	3200, 2940, 1600, 1580, 1390
1H NMR	3.25 (t, J = 8Hz, 2H, SCH_2), 3.90 (s, 3H, OCH_3),
($CDCl_3$)	3.95 (t, J=8Hz, 2H, NCH_2), 5.90 (S, 1H, =CH),
	6.95 - 7.6 (m, 4H, ArH), 10.6 (bs, 1H, NH)
Mass m/z,	235 (M+, 21 %), 135 (100 %)

compound was not stable enough for getting microanalysis

1.6.3 : Synthesis of oxazolidene (19)

The oxazolidine (19) was prepared in two steps. The first step was synthesis of 1,1 bis methylthio 2-benzoyl ethylene. The keten dithioacetal thus formed was treated with 2-amino ethanol.

1,1 Bis methylthio-2-benzoyl ethylene (18)

Nature	Yellow solid
Yield	60 %
M.P.	92 °C

I.R	2940, 1610, 1520
^{1}H NMR	2.50 (s,3H,SMe), 2.55 (s,3H,SMe),
($CDCl_3$)	6.5-7.5 (m,5H,ArH)

(*E*)-2-Benzoylmethylene oxazolidine (19)[19]

To the solution of 2-aminoethanol (10 mmol) in THF, sodium metal (10 mmol) was added. The reaction mixture was heated to reflux till all sodium was consumed then (10 mmol) of 1,1-bis methylthio-2-benzoyl ethylene was added reaction mixture was reflux till evolution of methylmercaptan was seized. The THF was evaporated under reduced pressure and product was purified by column chromatography (pet-ether, ethyl acetate).

Nature	Colorless crystalline solid
Yield	62 %
M.P.	110 - 111 °C
IR cm-1 (nujol)	3280, 2920, 1630, 1580.
^{1}H NMR	3.65 (t, J=8Hz, 2H, NCH_2), 4.50 (t, J = 8Hz, 2H, NCH_2),
($CDCl_3$)	5.60 (S, 1H, =CH), 7.4 - 7.6 (m, 4H, ArH), 10.00 (bs, 1H, NH),.
Mass m/z,	189 (M+, 100%), 188 (60%)
Anal.Calcd.For	C, 69.82; H, 5.86; N, 7.40.
$C_{11}H_{11}NO_2$	
Found	C, 69.91; H, 5.78, N, 7.21.

1.6.4: Synthesis of thiozolidine derivative (24)

1.6.4a: Reaction of 2-bromo acetophenones with thiazine-2-thione

The 2-bromo acetophenones (substituted **11g** ,**11h** and phenacyl bromide) were used in next reactions without purification. A mixture of thiazine-2-thione (8mmol) and *ortho* substituted phenacylbromide or phynacyl bromide (10 mmol) was stirred at 30°C for 1h. The white solid was filtered and dissolved in methanol and neutralized with aqueous $NaHCO_3$. Methanol was evaporated at reduced pressure and organic material was extracted in dichloromethane. The dichloromethane layer was dried over Na_2SO_4 and evaporated to give 2-(2'-substituted benzoyl) methylenethiothiazolidine which was further purified by column chromatography using pet-ether ethyl acetate to give compound **23a, 23b** and **23c**

2-(Benzoylmethyl)thiothiazine (23a)

Nature	Low melting colorless solid
Yield	64 %
M.P.	40°C
I.R(neat)cm^{-1}	1700, 1610, 1300
^1H NMR δ	3.62 (t, 2H, NCH_2), 4.37 (s, 2H, $C{=}O\text{-}CH_2$)
($CDCl_3$)	6.4 - 7.9 (m, 5H, ArH)

2-((2'-Hydroxybenzoyl) methyl) thiothiazine 23b'

Nature	Colorless solid powder
Yield	76 %
IR($CHCl_3$)cm^{-1}	2940, 1590, 1370, 3400
^1H NMR δ	2.00 (m, 2H, CCH_2), 2.9 (t, 2H, SCH_2) 3.60 (t, 2H, NCH_2),
($CDCl_3$)	4.50 (s, 2H, $O{=}C\text{-}CH_2$), 6.60 - 7.70 (m, 4H, ArH),
	12.0 (bs, 1H, OH)

2,(2Methoxy benzoyl)methyl thiothiazine 23c

This compound could not be isolated in pure form hence treated as such for next reaction of sulfur extrusion

1.6.4b: Desulfurisation

The compound **23a,** 5 mmol was taken in dry benzene 30 ml and PPh_3 (20 mmol) and potassium *t*-butoxide (2 mmol) were added to it and refluxed for 5h under inert atmosphere. Solvent was evaporated and product was purified by column chromatography silica (60 -120) (pet ether, ethyl acetate). Similarly compounds **24b** and **24c** were prepared.

2-Benzoylmethylenethiazine (24a)

Nature	Colorless crystalline solid
Yield	75 %
M.P.	104-105°C
IR (nujol) cm^{-1}	3000, 1580, 1470 .

^{1}H NMR δ	2.25(m, 2H, CCH_2), 3.20 (t, J=8Hz, 2H, SCH_2),3.55
$CDCl_3$	(t,J=8Hz, 2H, NCH_2), 5.75 (S, 1H, =CH)
	6.40 - 7.9 (m, 5H, ArH), 12.45 (bs, 1H, NH)
Mass m/z	219 (M+, 35 %), 77 (100 %)
Anal.Calcd. for	C, 65.72; H, 5.97; N, 6.38; S, 14.62
$C_{12}H_{13}NOS$	
Found	C, 65.82; H, 6.75; N, 6.64; S, 14.56

2-(2'-Hydroxybenzoyl)methylenethiazine (24b)

Nature	colorless crystalline solid
Yield	50 %
M.P.	125-127 °C
IR($CHCl_3$)	3400, 3020, 1600, 1580 cm-1
^{1}H NMR	2.25 (m, 2H, CCH_2) 3.15 (t, J = 8Hz), 2H, SCH_2),
($CDCl_3$)	3.55 (t, J=8Hz, 2H, NCH_2), 5.75 (S, 1H, =CH), 6.70 - 7.50
	(m, 4H,ArH), 11.75 (bs, 1H, NH), 13.75 (S, 1H, OH)
Mass	m/z 235 (M+, 93%), 188 (100%)
Anal.Calcd. for	C, 61.28; H, 5.57; N, 5.95
$C_{12}H_{13}NO_2S$	
Found	C. 62.00, H, 5.67, N, 6.07

2-(2'-Methoxybenzoyl)methylenethiazine (24c)

Nature	colorless crystalline solid.
Yield	62 %
M.P.	107-108 °C
IR($CHCl_3$)cm-1	3400, 1600, 1610
^{1}H NMR	2.20(m,2H,CCH_2), 3.05 (t,J=8Hz,2H,SCH_2),
($CDCl_3$)	3.50 (t,J=8Hz,2H,NCH_2), 3.75 (s,3H,OCH_3),
	5.70 (s,1H,=CH), 6.90-7.60 (m,4H,ArH), 12.35 (bs,1H,NH)
Mass m/z	249 (M+,9%), 135 (100 %).

Anal.Calcd. for	C, 62.65; H, 6.00; N, 5.60.
$C_{13}H_{15}NO_2S$	
Found	C, 62.60; H, 62.2; N, 5.77.

1.6.5 : Thionation of enaminoketone (11)

General procedure for thionation[21] :

A mixture of, compound **11** (10 mmol) and Lawesson reagent (6 mmol) was stirred and heated in benzene at 80°C under an inert atmosphere for 4h. The solvent was then removed in vacuum and the product purified by chromatography on silica gel column (pet-ether ethyl acetate)

(4'-Methoxythiobenzoyl)methylenethiazolidine (12b)

Nature	Yellow crystalline solid,
M.P	156-157°C
Yield	80 %;
IR cm^{-1} (neat)	2950, 1610, 1560,
^1H NMR	3.30 (t,J=8Hz,2H,SCH_2), 3.85 (s,3H,OCH_3),
($CDCl_3$)	4.15 (t,J=8Hz,2H,NCH_2), 6.70 (s,1H,=CH),
	6.85-7.75 (m,4H,ArH), 13.75 (bs,1H,NH)
Mass m/z,	251 (M+,83 %), 128 (100 %).
Anal.Calcd.For	C, 57.33; H, 5.17
$C_{12}H_{13}NOS_2$	
Found	C, 58.02; H: 5.30

2-(4'-Nitrothiobenzoyl)methylenethiazolidine (12c)

Nature	Dark brown viscous liquid;
Yield	61 %
IR cm^{-1} (neat)	3080, 2920, 1570, 1520
^1H NMR	3.50 (t,J=8Hz,2H,SCH_2), 4.25 (t,J=8Hz,2H,NCH_2), 6.75
($CDCl_3$)	(s,1H,=CH), 7.85- 8.25 (m,4H,ArH), 13.80 (bs,1H,NH);
Mass m/z,	266 (M+,74%), 238 (100 %)
Anal.Calcd.For	C, 49.62; H, 3.75; N, 10.52
$C_{11}H_{10}N_2O_2S_2$	

Found C, 49.80; H, 4.11; N, 11.19

2-(2'-Chlorothiobenzoyl)methylenethiazolidine (12d)

Nature Yellow crystalline solid

M.P. 157-159^{o}C;

Yield 63%

IR cm^{-1} (nujol) 2940, 1560, 1500, 1380

^{1}H NMR 3.45 (t,J=8Hz,2H,SCH_2), 4.20 (t,J=8Hz,2H,NCH_2),

($CDCl_3$) 6.55 (s,1H,=CH), 7.40- 7.80 (m,4H,ArH), 13.70 (bs,1H,NH)

Mass m/z, 255 (M+,45%), 192 (100 %), 220(49%)

Anal.Calcd.For C, 51.65; H,3.94; N, 5.47; S, 25.06.

$C_{11}H_{10}ClNS_2$

Found C, 52.08; H, 3.77 N, 5.62; S, 25.15.

2-(2'-Nitrothiobenzoyl)methylenethiazolidine (12e)

Nature Brown viscous liquid

Yield %

IR cm-1 (nujol) 2970, 1580, 1560, 1480, 1390.

^{1}H NMR 3.45 (t,J=8Hz,2H,SCH_2), 4.20 (t,J=8Hz,2H,NCH_2),

($CDCl_3$) 6.50 (s,1H,=CH), 7.4-7.9 (m,4H,ArH), 13.50 (bs,1H,NH).

Mass m/z, 266 (M+,45%), 61 (100 %).

Compound was not enough stable to obtain satisfactory micro analysis .

2-(2'-Methoxythiobenzoyl)methylenethiazolidine (12g)

Nature Dark brown viscous liquid-

Yield 65 %

IR cm-1 (neat) 3350, 1600, 1500, 1470

^{1}H NMR (δ) 3.30 (t,J=8Hz,2H,SCH_2), 3.85 (s,3H,OCH_3),

($CDCl_3$) 4.10 (t,J=8Hz,2H,NCH_2), 6.65 (s,1H,=CH),

6.90- 7.40 (m,4H,ArH), 13.75 (bs,1H,NH).

Mass m/z, 251 (M+,6%), 234 (100 %), 135(42%)

Anal.Calcd.For C, 57.33; H,5.17.

$C_{12}H_{13}NOS_2$

Found C, 57.63; H, 5.27.

1.6.6: Thionation of thazine derivative (24)

General procedure for thionation

A mixture of compound **24** (10 mmol) and Lawesson reagent (6 mmol) was stirred and heated in benzene at 80°C under an inert atmosphere for 4h. The solvent was then removed in vacuum and the product purified by chromatography on silica gel column (petroleum ether-ethyl acetate).

2-Thiobenzoylmethylenethiazine (27a)

Nature	Yellow crystalline solid
M.P.	157-159°C
Yield	67%
IR cm^{-1} (nujol)	2940, 2860, 1600, 1510.
^1H NMR (δ)	2.20 (m,2H,CCH_2), 3.15 (t,J=7Hz,2H,SCH_2),
($CDCl_3$)	3.65 (t,J=7Hz,2H,NCH_2), 6.50 (s,1H,=CH),
	7.40- 7.80 (m,5H,ArH), 15.00 (bs,1H,NH).
Mass m/z,	235 (M+,70%), 178 (100 %), 202(76 %)
Anal.Calcd.For	C, 61.27; H, 5.53.
$C_{12}H_{13}NS_2$	
Found	C, 61.10; H, 5.56

2-(2-Methoxythiobenzoyl)methylenethiazine (27c)

Nature	Dark brown viscous liquid
M.P.	157-159°C
Yield	59%
IR cm^{-1} (nujol)	3350, 2940, 1620, 1600
^1H NMR (δ)	2.25 (m,2H,CCH_2), 3.10 (t,J=7Hz,2H,SCH_2),
($CDCl_3$)	3.60 (t,J=7Hz,2H,NCH_2), 3.80 (s,1H,OCH_3),
	6.35 (s,1H,=CH), 6.90- 7.40 (m,4H,ArH), 14.95 (bs,1H,NH)
Mass m/z,	265 (M+,1%), 127 (100 %), 129 (43 %)

Compound was not stable enough for getting a good microanalyses

1.6.7: Thionation of oxazolidine (19)

A mixture of, compound **19** (10 mmol) and Lawesson reagent (6 mmol) was stirred in benzene at room temperature under an inert atmosphere for 4h. The solvent was then removed in vacuum and the product purified by chromatography on silica gel column (petroleum ether-ethyl acetate)

(*E*)-2-Thiobenzoylmethylene oxazolidine (28)

Nature	Dark brown viscous liquid
Yield	30 %
IR cm^{-1} (nujol)	3220, 1630, 1600, 1580, 1390, 1220
^1H NMR (δ)	4.05 (t,2H,NCH_2), 4.70 (t,J=7Hz,2H,OCH_2), 6.50 (s,1H,=CH),
($CDCl_3$)	6.90- 7.40 - 7.80 (m,5H,ArH), 13.2 (bs,1H,NH).
Mass m/z,	205 (M+,53 %), 204 (100 %), 129(43)

Compound decomposes on silica hence could not get in pure form to obtain micro analysis. Two dimensional tlc shows tailing which confirms decomposition on silica layer.

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CHAPTER 2

CHIRAL INDUCTION IN THIOCLAISEN REARRANGEMENT OF NITROTHIOACETAMIDES

Chapter 2

Chiral Induction in ThioClaisen Rearrangement of Nitrothioacetamides

2.1 Summary

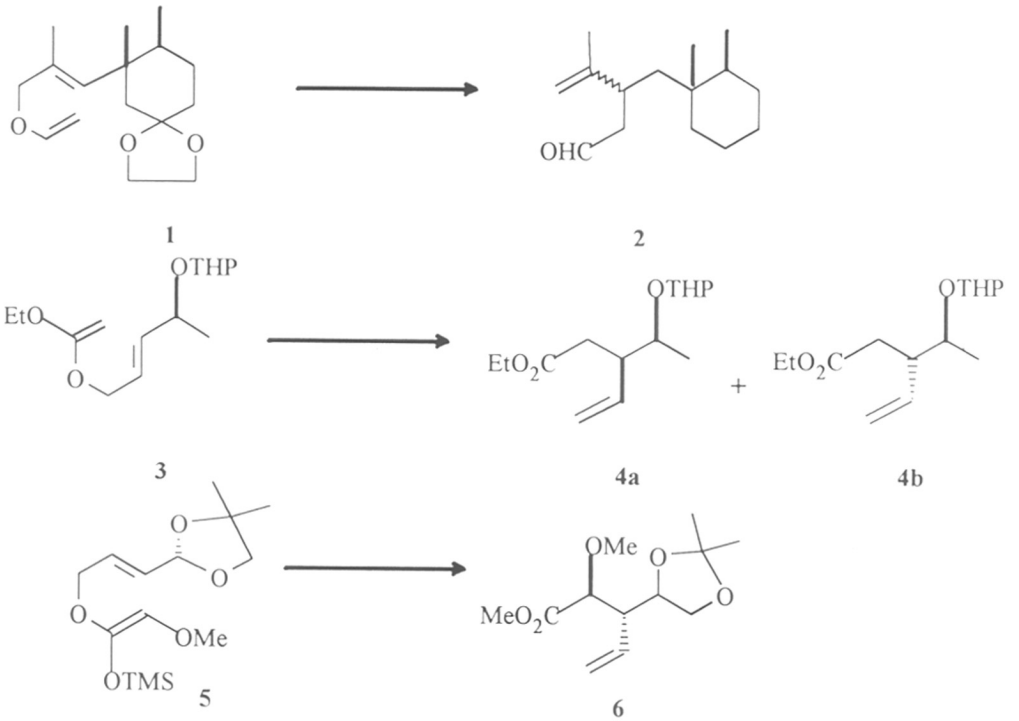
This chapter discusses the chiral induction in thio-Claisen rearrangement of nitrothioacetamides. Different chiral aminoacid esters and amines were tried as chiral auxiliaries to induce diastereoselectivity. Use of (S)-proline ethyl ester and (S)-valine ethyl ester for this purpose has already been reported by our group. [1] The unnatural bicyclic analog of proline, benzyl (1R,3R,5R) 2-azabicyclo [3.3.0]octane-3-carboxylate gave 69% *de* in the thio-Claisen rearrangement. Open chain aminoacid esters such as diethyl glutamate did not give any diastereoselectivity. α-Methylbenzylamine also proved to be of no use as far as diastereoselectivity is concerned. Use of secondary amines such as N-methyl-α-methylbenzylamine gave two diastereomers almost in equal proportions. (1R,5R)-2-Azabicyclo [3.3.0] octane could not be used because the corresponding nitroketen S,N-acetal was very prone to hydrolysis, hence the rearranged C-allyl nitrothioacetamide could not be obtained. All the results so far indicate that cyclic α-aminoacid esters give reasonably high diastereoselectivity in the thio-Claisen rearrangement of nitrothioacetamides. Our attempt to use (S)-prolinol as a chiral auxiliary was futile.

2.2 Introduction

Sigmatropic rearrangement is one of the most efficient techniques to generate a new chiral center with predictable stereochemistry.[1-5] The transition state of the sigmatropic rearrangement is usually highly ordered with the result that specific stereochemical relationships in the starting material are faithfully transferred to the product.[2] In most instances one can derive the correct stereochemical information about the reaction product. [3,3] Sigmatropic rearrangements of acyclic molecules show a preference for a chair like transition state which minimizes 1,3-diaxial interactions.

Claisen rearrangement is probably the best known thermal concerted rearrangement. There are several reports about chirality transfer in Claisen rearrangements. Chiral induction in Claisen rearrangement has been extensively studied. There are also some reports in literature which describe the effect of remote stereocontrol in Claisen rearrangement[6]

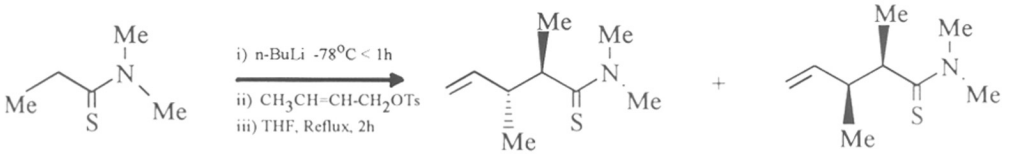
Scheme 1



The rearrangement of the allylvinyl ether (**1**) gives the rearranged product **2** without any diastereoselectivity in the product as shown in *scheme 1*. The keten-acetal **3** derived from (S)-ethyl lactate on Claisen rearrangement produces two diastereomers **4a** and **4b** in the ratio 3:1 i.e. 50% *de*[6]. Similarly the Claisen rearrangement of silylketenacetal of (D) glyceraldehyde acetonide (**5**) gives a mixture of diastereomers **6** with 75% *de*.[6]

Diastereoselectivity in thio-Claisen rearrangement has not received as much attention as the Claisen rearrangement. High diastereoselectivity in α-allylation of secondary and tertiary thioamides has been achieved by making use of thio-Claisen rearrangement[7]. In this example the newly created asymmetric center is located on the allyl chain as shown in the *scheme 2*

Scheme 2



7 **8a** *erythro* (97) **8b** *threo* (3)

Bespin and Perrio reported the thio-Claisen rearrangement of α-hydroxy keten-dithioacetals (**9**) at room temperature. This gave the corresponding α-allylic,β-hydroxydithioester (**10**) with a high level of *syn* selectivity 90/10 (*scheme 3*). The stereochemical outcome is independent of geometry of keten double bond .

Scheme 3

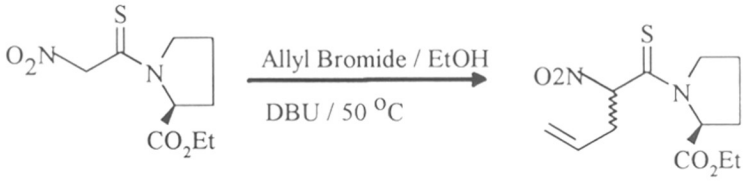
9 **10**

R	*syn* / *anti*	R	*syn* / *anti*
Me	90:10	Et	92 : 8
Pr	94 : 6	Pr^i	96 : 4
Bu^t	97 : 3	Ph	86 : 14

Recently Beslin et.al. have also reported a thio-Claisen rearrangement which generates three asymmetric centers with very high stereoselectivity[9]. In these examples, the original chiral center is vicinal to the newly created center.

Our group has reported reasonably high diastereoselectivity induced by aminoacid esters such as (S)-ethyl prolinate and (S)-ethyl valinate in the thio-Claisen rearrangement of nitrothioacetamides.[10] The chiral carbon of the aminoacid ester is not a part of the rearrangement framework. The asymmetric carbon of the chiral auxiliary is two atoms away from the prochiral carbon of the nitroketen S,N-acetal. A diastereomeric excess of 66% was observed in the case of (S)-proline ethyl ester derivative (**12**) whereas 33% *de* was noted in the case of (S)-valine ethyl ester derivative as shown in the *scheme 4*. These are the **first** examples of remote stereocontrol

Scheme 4.



11 **12**

in thio-Claisen rearrangement[10]. Encouraged by these results it was decided to try different aminoacid esters and chiral amines in place of (S)-proline ethyl ester in thio-Claisen rearrangement of nitrothioacetamides.

2.2: Present work

This chapter describes the effect of a remote chiral center in the thio-Claisen rearrangement of nitrothioacetamides. As reported earlier by our group, use of (S)-proline ethyl ester gave moderate *de* i.e. 66%. Here we report the effect of other aminoacid esters and amines on diastereoselectivity in thio-Claisen rearrangement of nitrothioacetamides.

The unnatural bicyclic analog of proline namely benzyl(1R,3R,5R)-2aza-bicyclo[3,3,0]octane-3-carboxylate in a similar thio-Claisen rearrangement gave 69% *de*. We also have also used diethyl glutamate as a chiral auxiliary which unfortunately gave 0% *de*. The rate of rearrangement was very slow. In this case, intermediate S-allyl nitrothioacetamide was isolated and characterized. This S-allyl nitrothioacetamide **17b** derived from diethyl glutamate rearranged in 20 days to the C-allylnitrothioacetamide **18b**. This undoubtedly proves that the allyl moiety first gets attached to the sulfur and then subsequently gets transferred to the carbon atom *via* a [3,3] sigmatropic rearrangement.

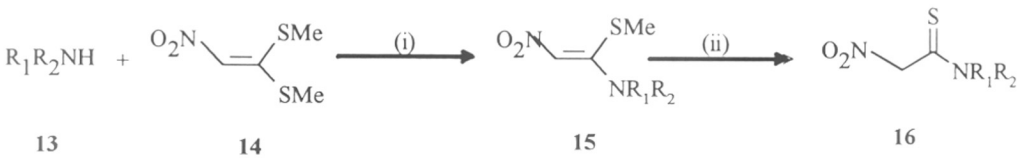
The next attempt was to use α-methylbenzylamine as the chiral auxiliary. The S-allyl keten S,N-acetal **17c** rearranged very slowly, leading to no diastereoselectivity. Relatively low *de* has also been obtained in the case of (S)-valine ethyl ester, which suggests that secondary amines or animoacid esters may lead to better stereocontrol in these reactions. N-Methyl,α-methylbenzylanime was hence employed to achieve better *de*. The keten S,N-acetal **17d** rearranged to the C-allyl nitrothioacetamide **18d** in 12h at 50 ^{o}C. The *de* was not encouraging in this case. Probably good stereocontrol can be achieved only with cyclic aminoacids and amines. In order to check this hypothesis the chiral bicyclic amine (1R,5R)-2azabicyclo[3,3,0]octane was tried as the chiral handle. The keten S,N-acetal was very prone to hydrolysis and the required compound could not be isolated. Likewise our attempts to use (S)-prolinol in the above thio-Claisen rearrangement were also futile.

2.4: Results and Discussion

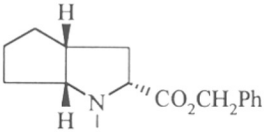
2.4.1: Synthesis of Nitrothioacetamides

Nitrothioacetamides were synthesized in two steps by the procedure standardized by our group. In the first step 1,1-bismethylthio-2-nitroethene was treated with primary or secondary aminoacid esters or amines in a polar solvent like acetonitrile or ethanol.[11] *p*-Toluenesulfonic acid was used as the catalyst to accelerate the reaction. The amine replaces one of the two methylthio group by an addition-elimination sequence to give nitroketen S,N-acetals (**15 a-e**).

Scheme 5



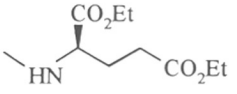
a : R_1R_2N =



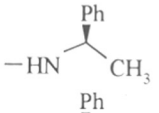
(i) CH_3CN , PTSA or Ethanol

(ii) Na_2S, AcOH / Ethanol

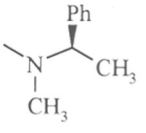
b : R_1R_2N =



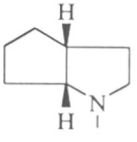
c : R_1R_2N =



d : R_1R_2N =



e : R_1R_2N =



Benzyl (1R,3R,5R)-2-azabicyclo [3.3.0]octane-3-carboxylate (**13a**) was reacted with 1,1-bismethylthio-2-nitroethene (**14**) at 80°C to give benzyl N[(1-methylthio-2-nitroethenyl] (1R,3R,5R)-2-azabicyclo[3,3,0]octane-3-carboxylate (**15a**) in 70% yield. Similarly (1R,5R)-2-

azabicyclo [3.3.0] octane (**13e**) could be condensed with nitroketenedithioacetal (**14**) at room temperature in presence of PTSA in acetonitrile to give N[(1-methylthio-2-nitro)ethenyl](1R,5R)-2-azabicyclo [3.3.0]octane (**15e**) in 75% yield. (S)-α-Methylbenzylamine (**13c**) and (S)-N-methyl-α-methylbenzylamine (**13d**) did not react at room temperature with (**14**); but elevation of temperature to 80°C gave the products (**15c**) and (**15d**) in 85% and 79% yields respectively. The reaction of (S)-diethyl glutamate with 1,1-bismethylthio-2-nitroethene did not proceed under these conditions. The reaction in ethanol with prolonged heating gave diethyl N-[(1-methylthio 2-nitro)ethenyl]-(S)-glutamate (**15b**) in 75% yield. Attempts to condense (S)-N-benzyl-α-methylbenzylamine with nitroketendithioacetal (**14**) were unsuccessful either due to sterric reasons or due to the low nucleophilicity of the amine.

The nitroketen S,N-acetals were characterized by ^{1}H NMR and IR spectroscopy. The structure of (**15a**) was also confirmed by mass spectroscopy and ^{13}C NMR spectrum. The ^{1}H NMR spectra of (**15a-e**) show the olefinic proton in the region 6.7-7.0δ. The thiomethyl protons can be seen as a sharp singlet around 2.4-2.6δ. The IR spectra of (**15a**) and (**15b**) show characteristic ester carbonyl stretching at 1750 and 1740 cm^{-1}. The spectroscopic data are discussed in detail in the experimental section. In the second step, the above nitroketen S,N-acetals (**15a-e**) were converted to nitrothioacetamides by the procedure established by our group[12]. The thiomethyl group was displaced by SH. In a typical experiment (9 mmol) of fused sodium sulfide was added in portions to a solution of the nitroketen S,N-acetal (6mmol) in dry ethanol containing (12 mmol) of acetic acid. The reaction mixture was stirred at room temperature. The reaction was monitored by tlc. Ethanol was removed in vacuum. The organic material was dissolved in dry benzene. The product formed was purified by passage through a short column of silica (60-120) using 20% pet ether ethyl acetate.

Compounds (**15a-d**) were successfully converted to the corresponding nitrothioacetamides (**16a-d**). The ^{1}H NMR spectra of nitrothioacetamides show O_2NCH_2 as two doublets due to geminal coupling around 5.6-5.8δ. The disappearance of the signal at 2.4-2.6δ and at 6.5-6.8δ due to the thiomethyl and olefinic protons in the ^{1}H NMR spectra indicate the conversion to the corresponding thioacetamides. The IR spectra of **16a** and **16b** show ester

carbonyl stretching at 1750 and 1740 cm^{-1}. The signals at 185.22δ in the ^{13}C NMR spectra of compound **16a** were assigned to thio-carbonyl carbon.

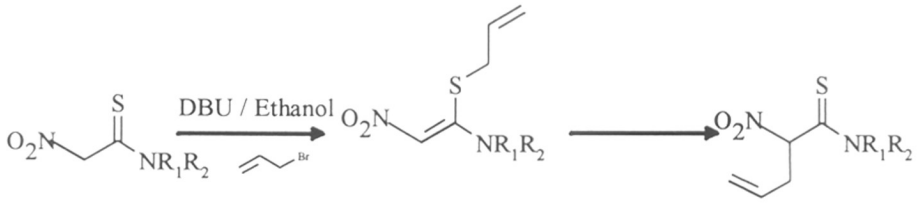
Benzyl N-(nitrothioacetyl)-(1R,3R,5R)-2-azabicyclo [3.3.0]octane-3-carboxylate (**16a**) shows only one set of signals in the ^{1}H NMR as well as ^{13}C NMR spectra. This indicates the presence of only one rotamer (*trans*-amide) this is in contrast to the corresponding (S)-proline derivative (**11**) which shows the presence of *cis* and *trans* rotamers in the ratio 1: 7.[12] Diethyl N-(nitrothioacetyl)-(S)-glutamate (**16b**) was obtained in a similar way in 30 % yield. Only one set of signals was observed in the ^{1}H NMR spectrum of this compound.[12] This is similar to N-nitrothioacetyl (S)-valine ethyl ester which also shows only one set of signals in ^{1}H NMR spectrum. The hydrogen bonding between N-H and NO_2 groups offers extra stability to the isomer; so this is the only rotamer present in these compounds. The synthesis of nitrothioacetamide (**16c**) derived from α-methylbenzylamine was not complete after 12h. Normally in other cases reaction takes 2.5-3.0 h at room temperature. Work up of reaction mixture and removal of inorganic material in the usual way followed by short filtration through a column (silica 60-120) using 10-20 % ethyl acetate in pet-ether gave the product **16c** containing more than 20% starting material (**15c**). The labile nature of the nitrothioacetamide and its decomposition on the silica column imposed a limitation on further purification. An attempt to force the reaction by increasing the temperature gave a non-separable complex mixture. N-Nitrothioacetyl-(S)-α-methylbenzylamine (**16c**) also showed only one set of signals in the ^{1}H NMR spectrum, indicating the presence only one rotamer.

N-Methyl-N-(nitrothioacetyl)-(S)-α-methylbenzylamine (**16d**) was obtained by Na_2S / AcOH treatment on **15d** in 60% yield. Two sets of signals were observed in the ^{1}H NMR spectrum due to the presence of *cis : trans* rotamers. The ratio of *cis : trans* rotamers was estimated to be 1:3. Compound **16e** i.e. N-nitrothioacetyl (1R, 5R)-2-azabicyclo [3.3.0] octane was obtained in 55% yield. This compound being unstable, could not be obtained in very pure form. The ^{1}H NMR spectrum showed two sets of signals due to *cis : trans* isomers. The ratio of *cis : trans* isomers was 1:2.

3.4.2: Allylation of nitrothioacetamides

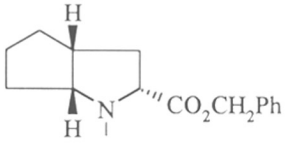
The nitrothioacetamides (**16a-e**) thus prepared were allylated by reaction with allyl bromide in presence of ethanolic DBU at room temperature as shown in *scheme 6*. Use of excess of DBU was avoided in order to suppress the possible epimerisation of the C-allylated compound (**18**).

Scheme 6



16 **17** **18**

a : R_1R_2N =



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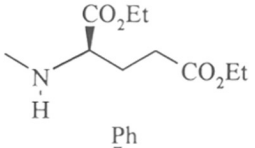
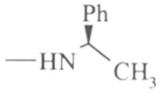
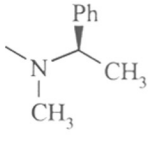


c : R_1R_2N =

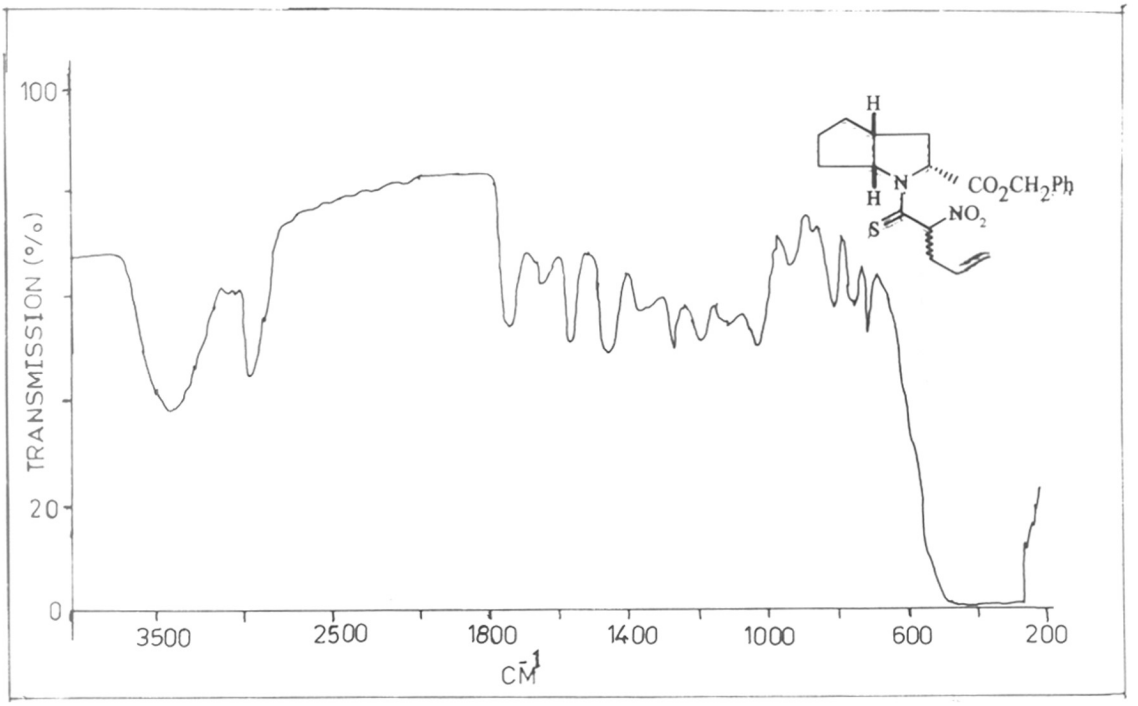


d : R_1R_2N =



2.4.2a: Benzyl N-(α-allyl nitrothioacetyl) (1R,3R,5R)-2-azabicyclo[3.3.0]octane-3-carboxylate (18a)

Nitrothioacetamide (**16a**) on reaction with allyl bromide in presence of DBU in ethanol formed benzyl N[(1-allylthio-2-nitro)ethenyl](1R,3R,5R)-2-azabicyclo-octane-3-carboxylate (**17a**). Compound (**17a**) undergoes sigmatropic rearrangement at room temperature to yield the C-allyl compound (**18a**) in 52 % yield. The IR spectrum of compound (**18a**) shows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20
0
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2500
1800
1400
1000
600
200
CM⁻¹
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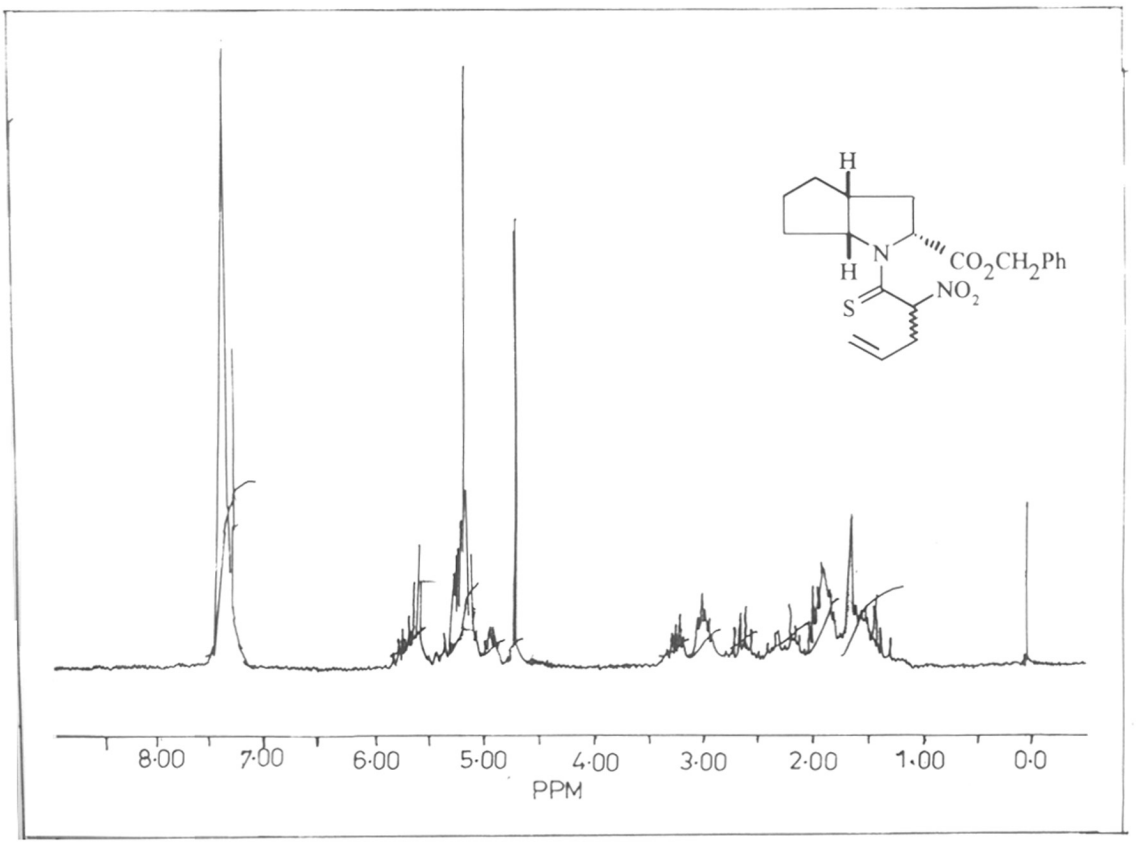
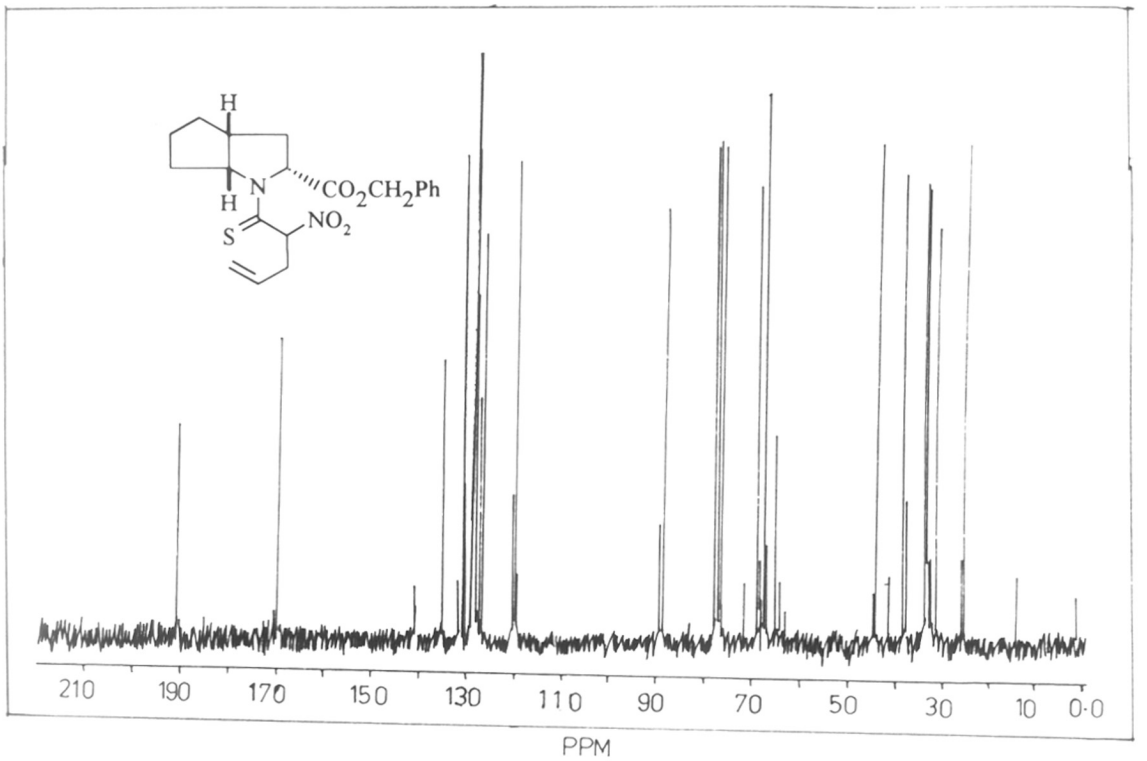
N
H
S
NO₂
CO₂CH₂Ph


8·00
7·00
6·00
5·00
4·00
3·00
2·00
1·00
0·0
PPM
H
N
H
S
NO₂
CO₂CH₂Ph


H
N
H
S
CO_2CH_2Ph
NO_2
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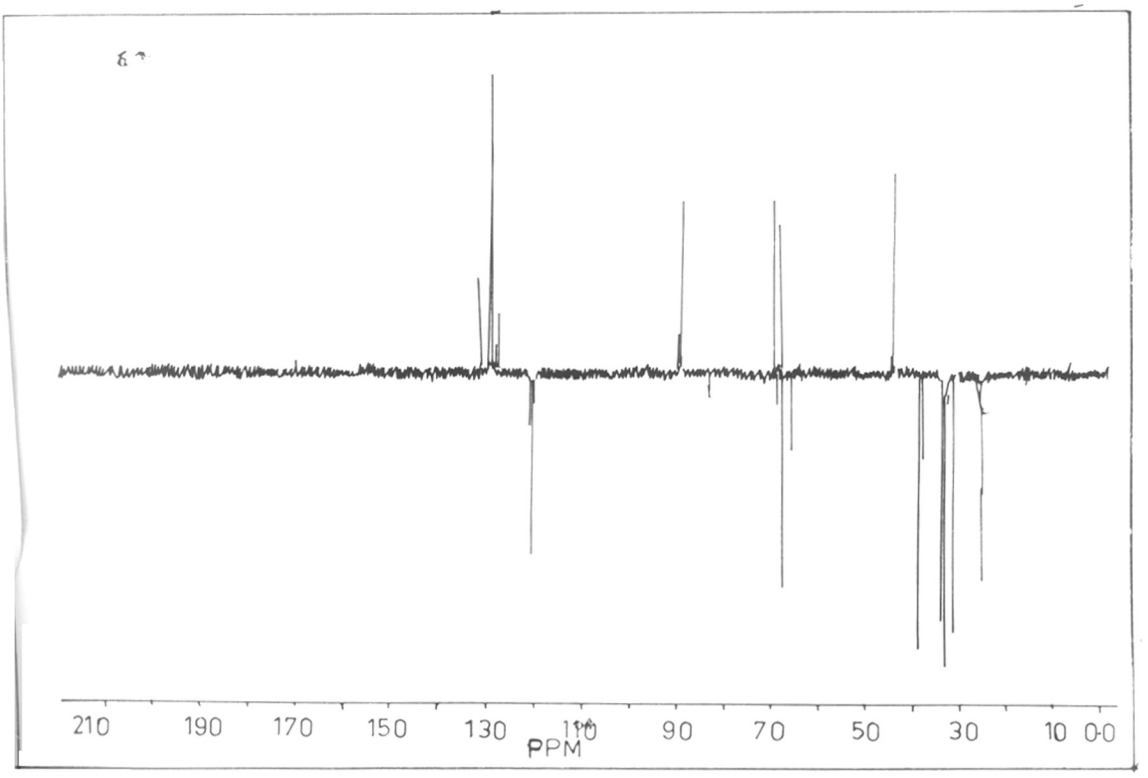
190
170
150
130
110
90
70
50
30
10
0·0
PPM


210
190
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130
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90
70
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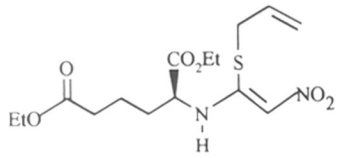
10
0·0
PPM

ester carbonyl stretching at 1750 cm^{-1}. The ^1H NMR spectrum shows a multiplet for 8H at 1.4-2.2 δ; the bridgehead proton appears as a multiplet at 4.9δ. Benzylic CH_2 and olefinic protons of the allylic moiety appear as a complex multiplet for 5H at 5.0-5.38δ NO_2CH and CHNH were observed as a complex multiplet between 5.5 to 5.9δ. Aromatic protons were seen at 7.3 - 7.6δ as expected. This confirms the structure of **18a**. The ^{13}C NMR spectrum shows peaks at 190.64 (191.01)δ due to C=S, and 169.78 (169.62)δ due to C=O of ester moiety. These signals disappear in the DEPT spectrum. The allylic CH_2 appears at 38.57 δand 37.83δ.This represents the maximum chemical shift difference between the two species. The signals due to C=O and allylic CH_2 were used to determine the diastereomeric excess; this was found to be 69% in the case of **18a**. The interpretation was simplified in this case, since only two sets of signals are observed due to the two diastereomers; further doubling of signals due to the presence of *cis* : *trans* rotamer was not seen.

2.4.2b: Synthesis of diethyl α-allyl-N-nitrothioacetyl glutamate (18b)

Compound **16b** was converted to the S-allyl derivative (**17b**) in the usual way by treatment with allyl bromide in the presence of ethanolic DBU. The S-allylated compound (**17b**) was first isolated in pure form in 45 % yield which on slow rearrangement at room temperature was converted to the C-allylated nitrothioacetamide (**18b**). The rate of rearrangement was very slow. After 72h the ratio of **17b** : **18b** i.e. S-allyl derivative to C-allyl derivative was 2.5 : 1. The ratio was calculated from the relative intensities of allylic CH_2 signals in the ^1H NMR spectrum. The S-allylated compound shows a doublet at 3.5δ whereas the C-allyl compound (**17b**) shows a complex multiplet at 3.0δ. On the 10th day, rearrangement had occurred to the extent of 40 % and the ratio of **17b** : **18b** was 1.5: 1, on the 15th day, the ratio was 1: 4.6; on the 18th day it was 1:8.2. On the 20th day, only the C-allyl compound (**18b**) was seen in the ^1H NMR spectrum. The rate of rearrangement in $CDCl_3$ and in benzene were observed to be the same. In the ^{13}C NMR spectrum of rearranged product (**18b**) both C=S and O_2NCH gave rise to two peaks 192.47 (191.19) &130.3 (129.2)δ due to the presence of two diastereomers. From the relative hights of the signals of the two sets it was concluded that the two daistereomers were present in equal amounts, i.e., *de* was zero.


O
CO2Et
S
EtO
N
H
NO2

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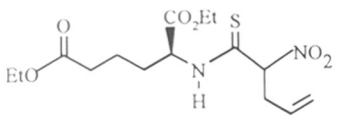
7·00
5·00
3·00
1·0·0
0·0
PPM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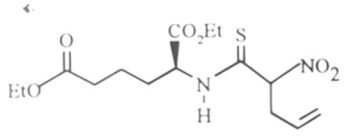
CO2Et
S
EtO
N
H
NO2

7
6
5
4
3
2
1
0·0


CO2Et
S
O
NO2
EtO
N
H

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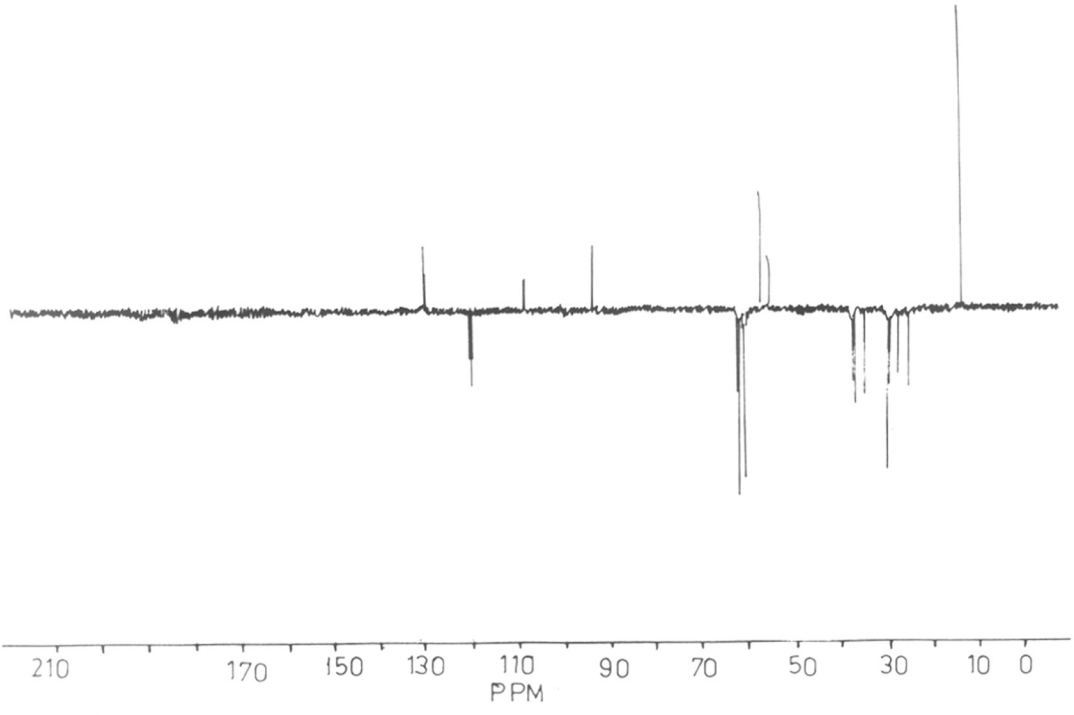
190
170
150
130
110
90
70
50
30
10
0
PPM


210
170
150
130
110
90
70
50
30
10
0
PPM

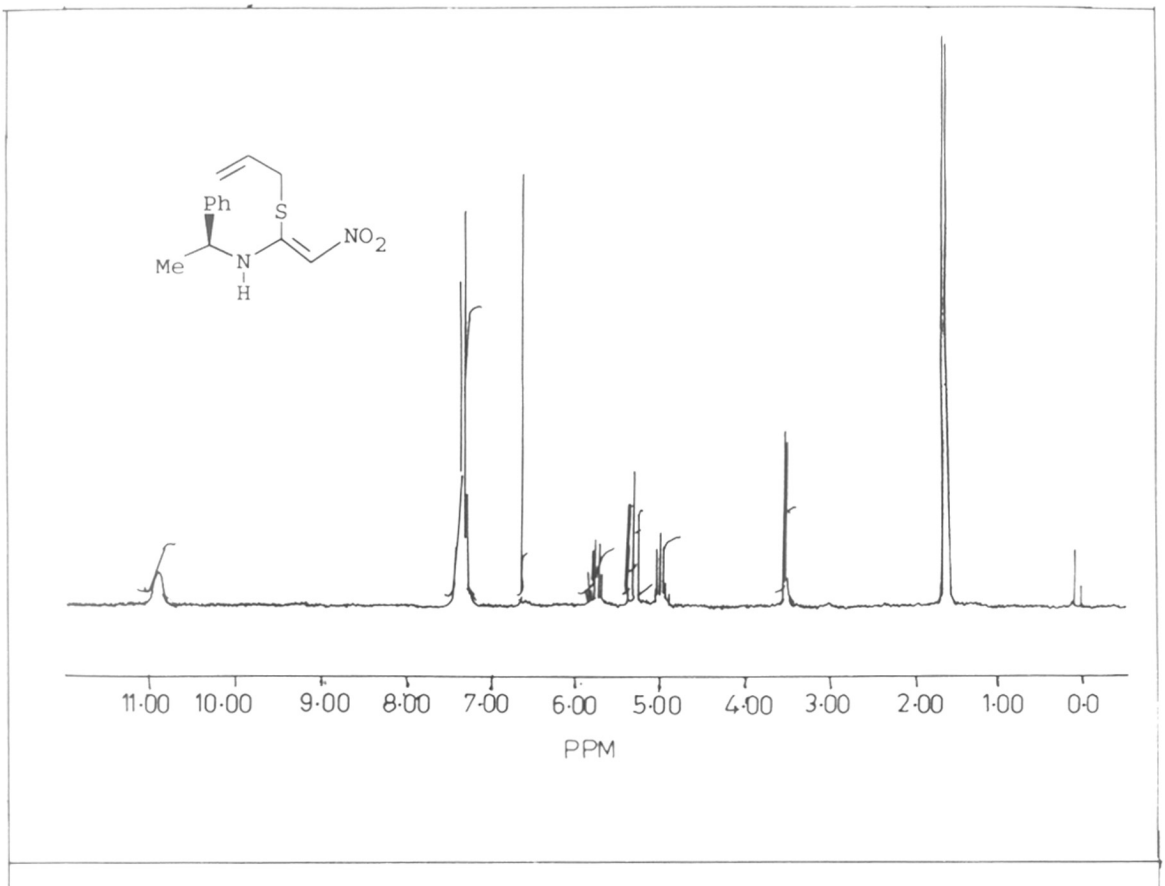
2.4.2c: Synthesis of N-(α-allyl nitrothioacetyl)-α'-methyl benzylamine (18c)

The reaction of nitrothioacetamide (**16c**) with allyl bromide in presence of DBU at room temperature gave the S-allyl compound **17c** in 45% yield. The ^{1}H NMR spectrum of compound **17c** shows a doublet at 1.70δ and a multiplet at 4.90δ due to α-CH_3 and α-CH respectively . The aromatic protons were observed at 7.4δ. The olefinic proton of the nitroethenyl group was noted at 6.70δ whereas the olefinic protons of the allyl moiety appear as doublet at 3.50δ and two multiplets at 5.10δ and 5.30δ.

The [3,3] sigmatropic rearrangement of **17c** was observed to be slow at room temperature. The rearrangement of **17c** took 20 days for completion which is similar to the rearrangement of **17b**. The ^{1}H NMR spectrum of the crude product after 48h shows the presence of a mixture of S-allyl and C-allyl compounds **17c** and **18c.** The rearranged product **18c** shows complex multiplet at 3.0δ; similarly the ^{13}C spectrum of the reaction mixture after 72h. of rearrangement shows both O_2N-C= at 164.0δ and C=S at 190.41δ. Compound **18c** was obtained in 30 % yield after 20 days. The ^{1}H NMR spectrum of the rearranged product **18c** shows a doublet at 1.60δ and a multiplet at 5.15δ due to the Me and CH, the aromatic protons appear at 7.4δ the NH appears at 8.80δ as a broad singlet. The CH_2 of the allyl group was seen at 3.0δ and the olefinic proton at 5.3δ as a multiplet. The ^{13}C NMR spectrum of the C-allyl compound **18c** shows thiocarbonyl as two signals of equal intensity at 190.41 and 190.51δ due to the presence of two diastereomers. The *de* was observed to be 0 % . Similarly two peaks of equal intensity were observed for the α carbon of nitrothioacetyl moiety at 141.5 and 140.9δ. In order to accelerate the thio-Claisen rearrangement, the ethanolic solution of **17c** was heated to 80 °C for three hours. However, this accelerated the hydrolysis leading to the formation of the corresponding nitroacetamide. In order to avoid the hydrolysis the rearrangement was carried out in dry benzene at 80 °C and was complete in 3h.; the *de* was still observed to be zero.

2.4.2d Synthesis of N-methyl-N-(αallyl nitrothioacetyl)-(S)α'methylbenzyl amine (18d)

Nitrothioacetamide **16d** on treatment with allyl bromide in presence of ethanolic DBU gave keten S,N-acetal **17d** in 85% yield. The ^{1}H NMR spectrum of **17d** shows a doublet at 1.7δ (CH_3) and a singlet at 2.75δ(NCH_3) followed by a multiplet at 5.8δ(αCH) due to amine moiety. The aromatic protons appear at 7.4δ. The CH_2 of the allyl moiety appears as a doublet at 3.65δ and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Me
N
H
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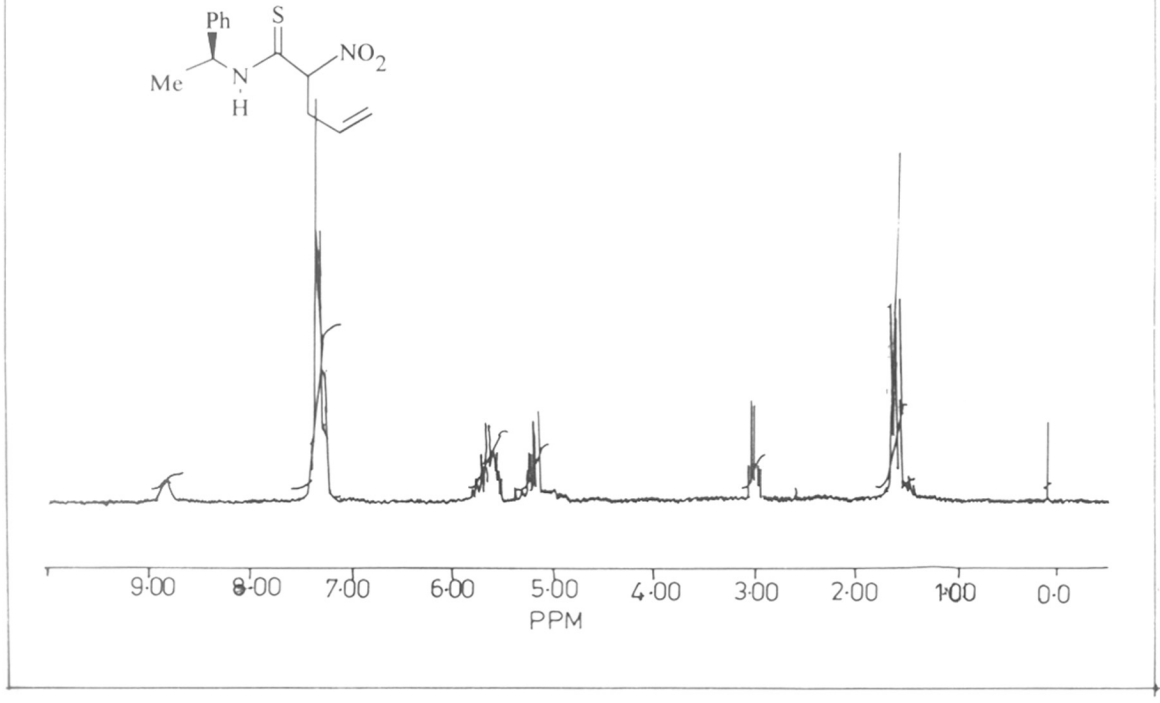
PPM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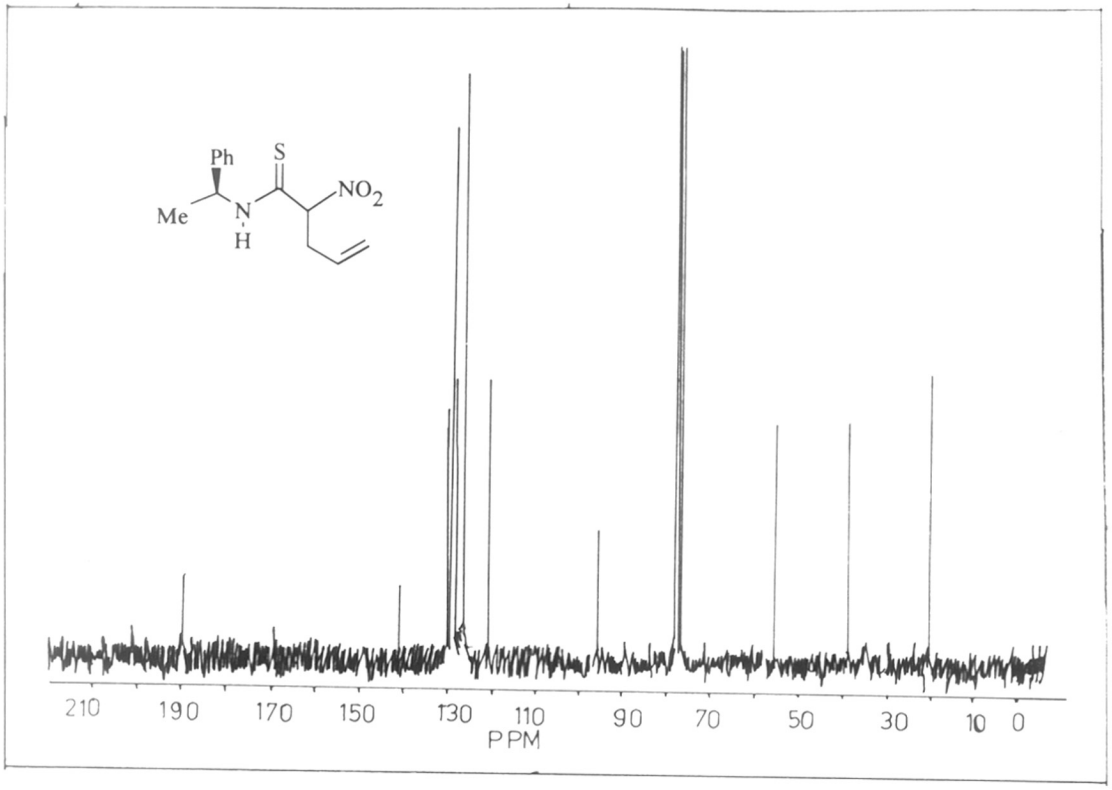
NO2
Me
N
H
9·00 8·00 7·00 6·00 5·00 4·00 3·00 2·00 1·00 0·0
PPM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NO2
Me
N
H
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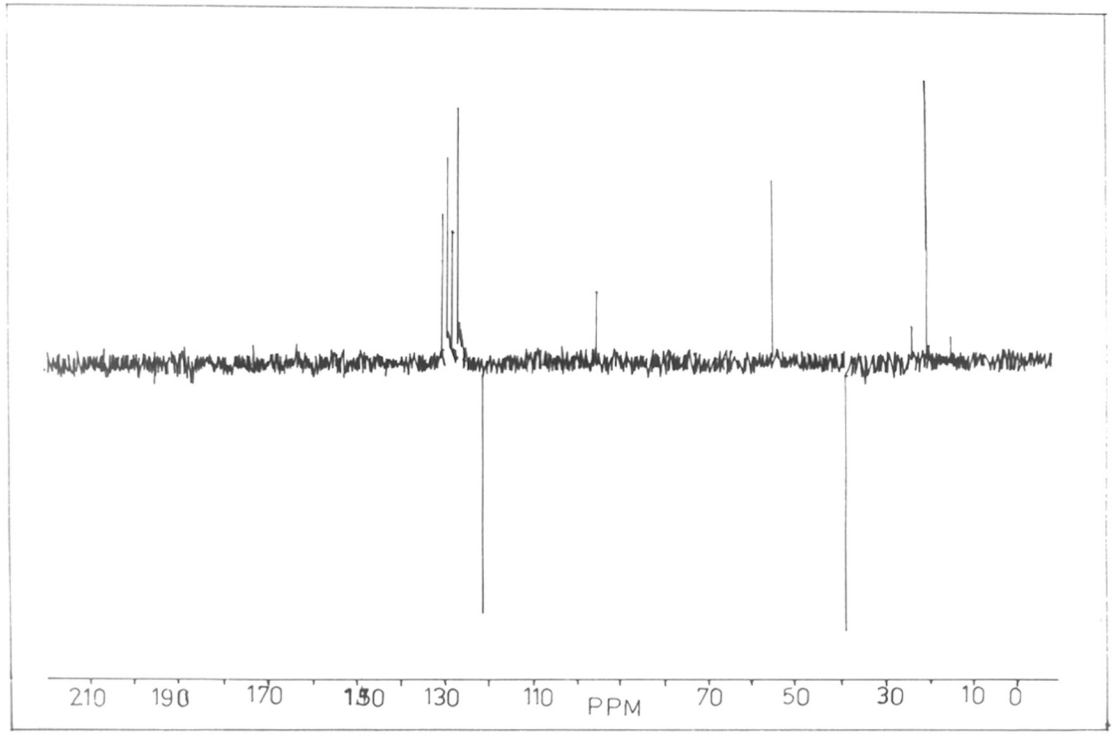
150
130
110
90
70
50
30
10
0
PPM


210
190
170
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130
110
PPM
70
50
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10
0

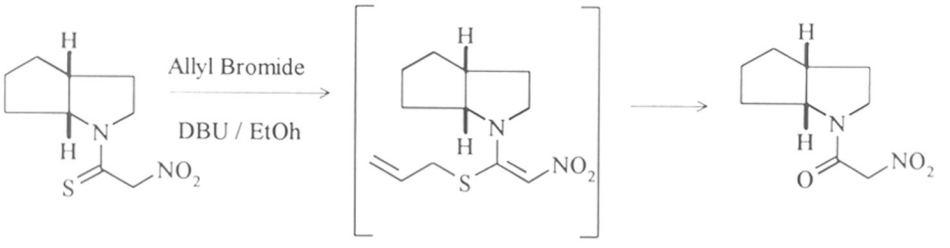
the vinylic protons as a multiplet between 5.1 to 5.95δ. The olefinic proton of the nitroethene appears as a sharp singlet at 6.70δ.

A benzene solution of **17d** on being heated at 50°C for 12h. resulted in the rearrangement of **17d** to the C-allyl nitrothioacetamide **18d** in 85% yield. The ^{1}H NMR spectrum of compound **18d** was complex because of the presence of two sets of peaks due to *cis-trans* isomers for each of the two diastereomers. The ^{1}H NMR spectrum showed a multiplet at 1.5δ (CH_3) followed by a complex multiplet at 2.5-3.6 (5H; NCH_3, and allylc CH_2); another multiplet at 5.0-5.8δ (5H; 3 vinyl protons of allyl and NCH_2) and the aromatic protons at 7.2δ. The ^{13}C NMR spectrum of this compound showed a set of four signals for each carbon except the aromatic ones (*cis/trans* isomer for each diastereomer). Thus, the thiocarbonyl carbon appeared as four signals at 193.14, 192.89, 192.20, 191.82δ. The *de* calculated separately for the *cis* pair and the *trans* pair for different carbons varied from 5-10%. The average value was 6% which hardly has any practical significance. The *cis:trans* ratio was found to be 1:1.5.

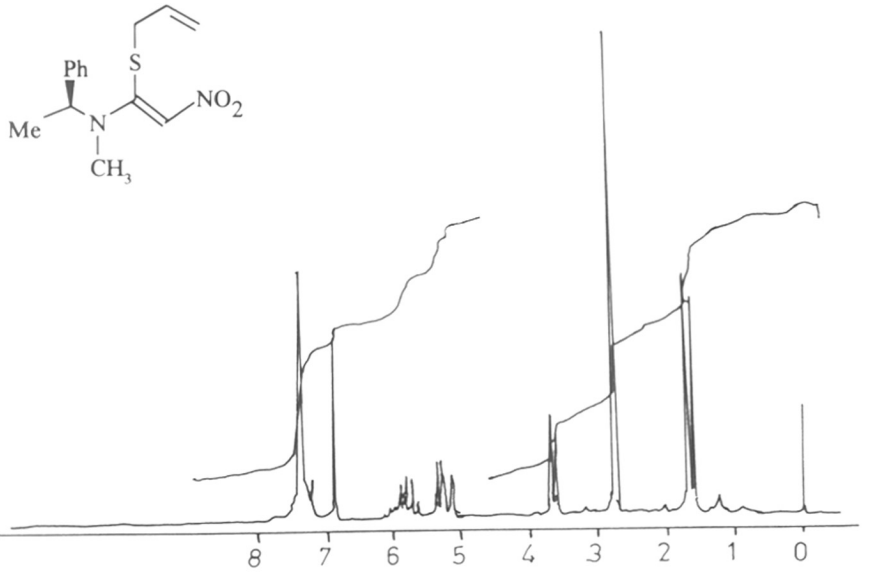
2.4.3: Attempt to synthesise N-(α-allylnitrothioacetyl)-(1R,5R)-2-azabicyclo[3.3.0]octane (18e)

Nitrothioacetamide (**16e**) on treatment with allyl bromide in presence of ethanolic DBU gave compound **17e** which being very prone to hydrolysis gave the nitroacetamide (**19**) as shown in *scheme 7* in 40 % yield. Nitroacetamide (**19**) was characterized by ^{1}H NMR and ^{13}C NMR spectra. Details are given in the experimental section.

Scheme 7



16e **17e** **19**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CH3
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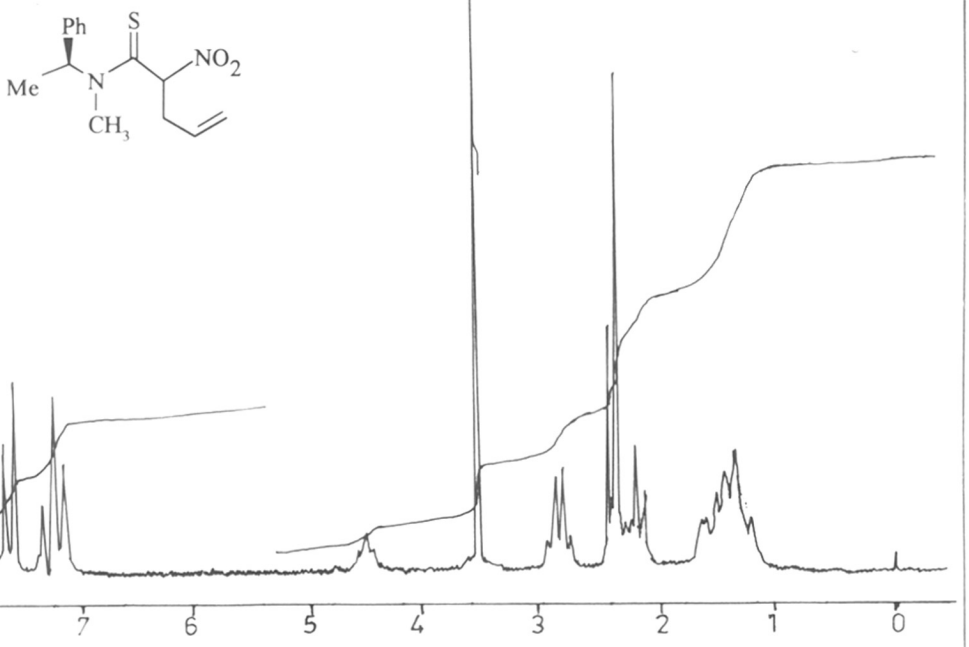
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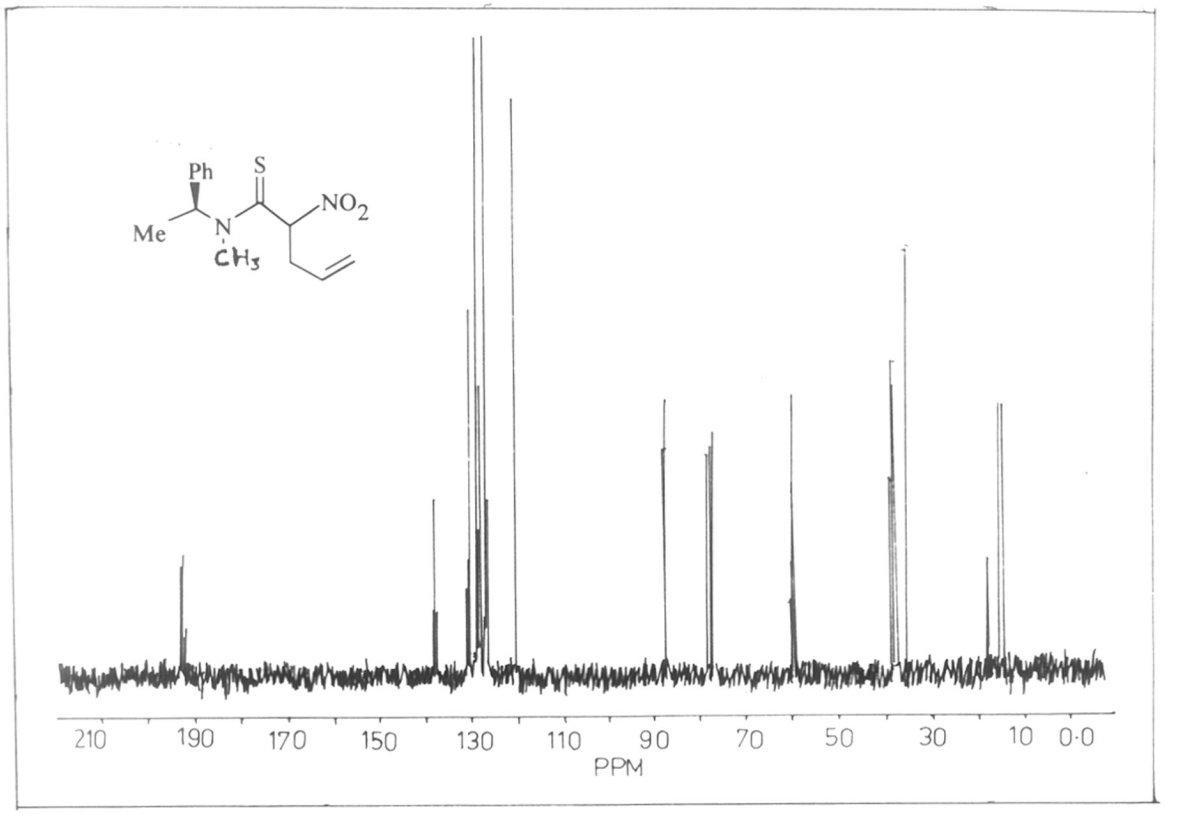
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NO2
Me
N
CH3
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150
130
110
90
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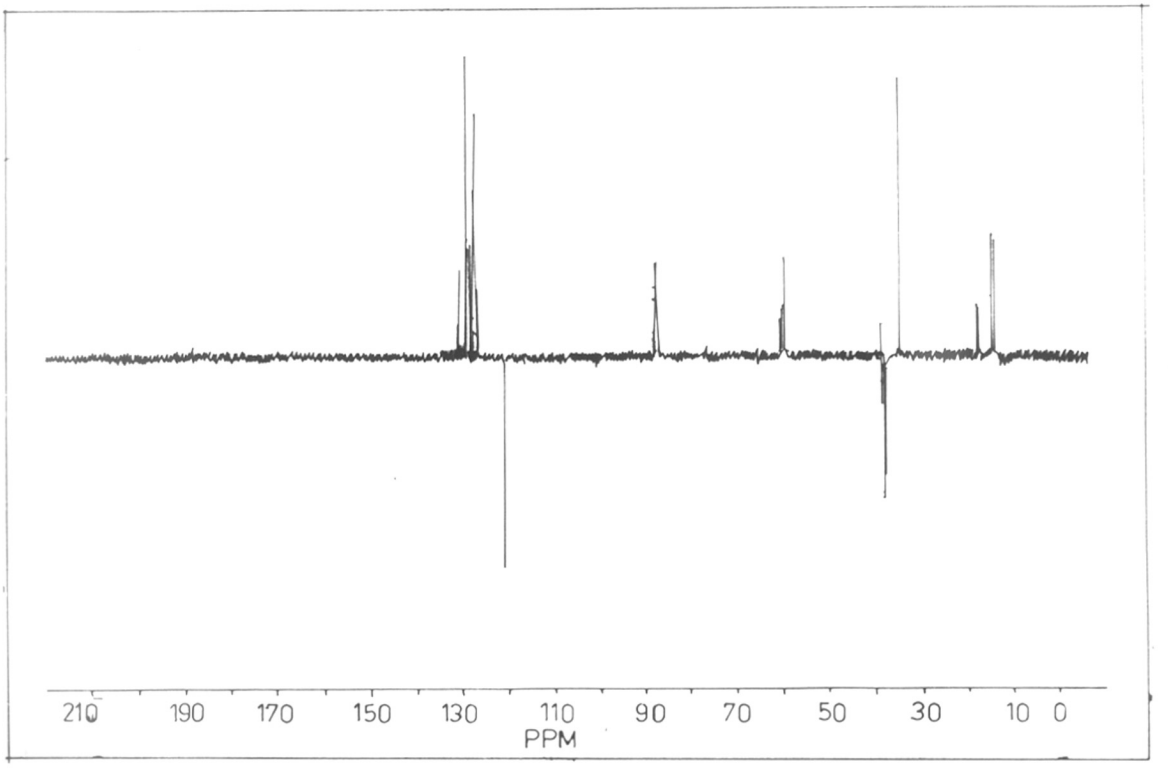
50
30
10
0·0
PPM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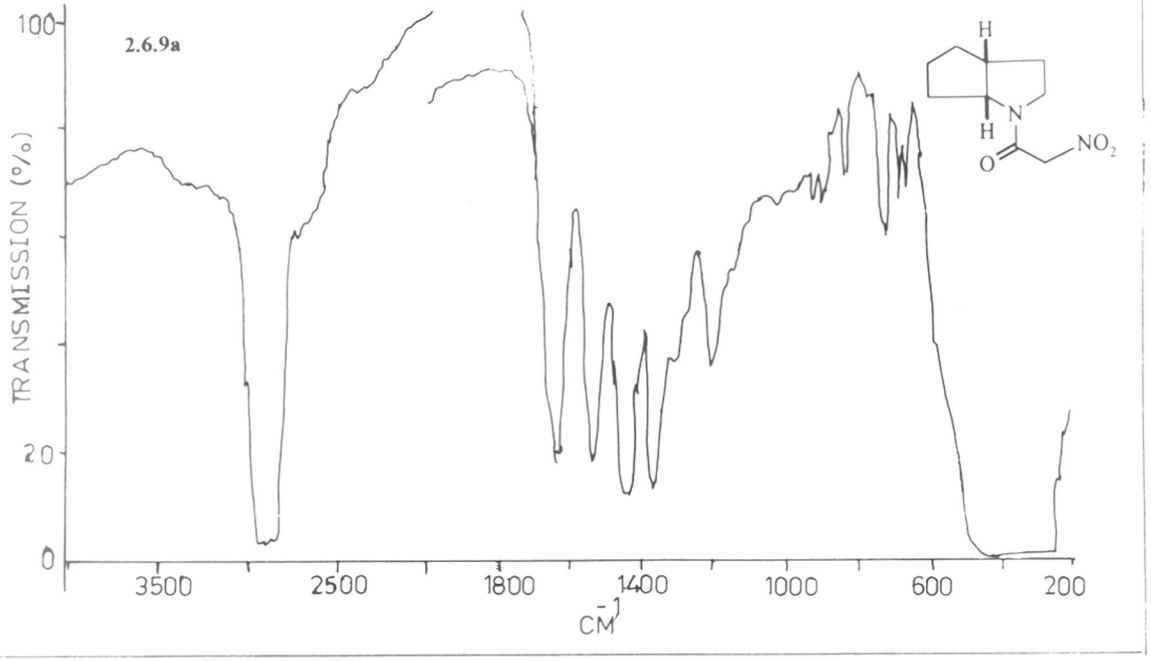
PPM

2.6.9a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TRANSMISSION (%)
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1000
600
200
CM⁻¹
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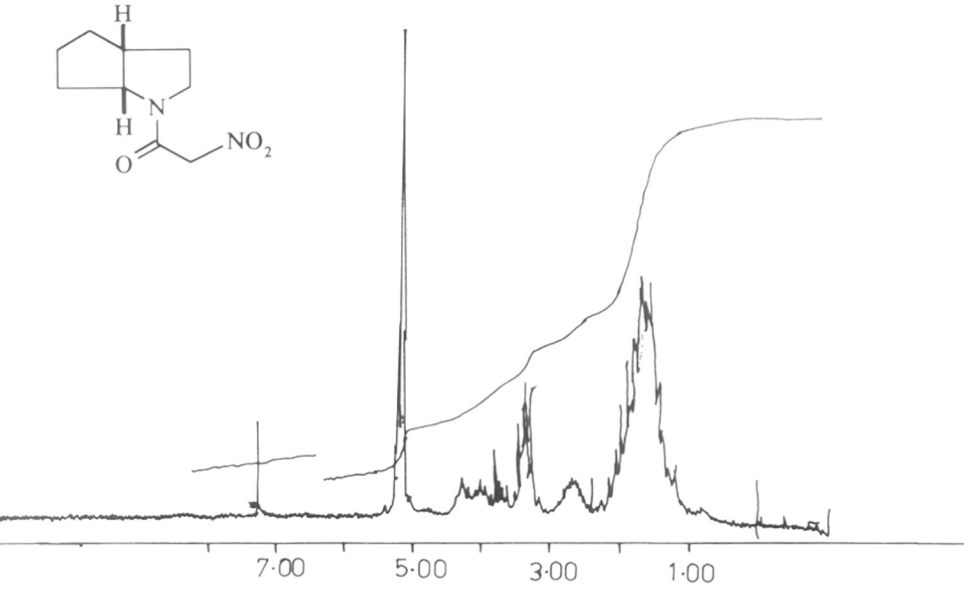
N
H
O
NO2

2.6.9b


H
N
H
O
NO2
7·00
5·00
3·00
1·00

The % *de* and the respective ^{13}C NMR peaks from which it is calculated ,are summarized in *Table 1.*

Table 1

% de and related data for C-allyl nitrothioacetamides

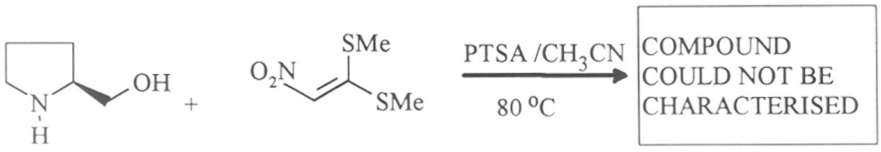
Sr. No.	Compd.No.	% *de*	^{13}C NMR peaks with which de is determined
1	18a	69	169.78 (169.62) **C**=O, 38.57 (37.83) ally CH_2
2	18b	00	192.47 (191.19) **C**=S, 130.3 (129.2) **CH**-NO_2
3	18c	00	190.51 (190.51) **C**=S, 141.5 (140.9) **CH**-NO_2
4	18d	06	193.14 (192.89), 192.20 (191.82) **C**=S.

So far, only cyclic secondary α-aminoacid derivatives have given reasonably good diastereoselectivities in this transformation. The bicyclic secondary amine without the α-carboxylic ester proved very reactive and the rearranged product could not be isolated. The open chain *sec* amine, (S)-α-methylaminoethylbenzene proved disappointing in the reaction. The rate of thio-Claisen rearrangement was observed to vary with different push-pull systems. The rearrangement was complete in 3h at 50°C in the case of the (S)-proline derivative obtained from the thioamide (**11**). Rearrangement was very fast and complete in 3h at room temperature in the case of S-allyl derivative of the nitrothioacetamide of the bicyclic proline analog **16a**. In contrast, the rearrangement was very slow and took 20 days in the case of the glutamic acid derivative (**17b**) and α-methyl benzylamine derivative (**17c**) at room temperature. The rate of rearrangement was increased by heating to 50°C in the case of N-methyl α-methylbenzylamine derivative (**17d**). The rearrangement was complete in 12h at 50°C. Reasonably good diastereoselectivity was observed in those cases where the rate of rearrangement was moderately high. Thus (S)-ethyl prolinate, (S)-ethyl valinate and benzyl (1R,3R,5R)-2-azabicyclo [3.3.0] octane-3-carboxylate gave respectively 66 , 33,[10] and 69 % de. But with similar derivatives of diethyl (S)-glutamate and N-methyl-α-methylbenzylamine the *de* was nearly zero. This is probably because the rate of epimerisation is comparable to the rate of rearrangement.

2.4.4: Extension to cyclic amino alcohol

Results so far indicate that cyclic α-substituted aminoacids induced reasonably high diastereoselectivity in thio-Claisen rearrangement of nitrothioacetamides. Use of (S)-prolinol was hence expected to lead to reasonably good diastereocontrol in the above thio-Claisen rearrangement. The condensation reaction of (S)-prolinol with 1,1-bismethylthio-2-nitroethene was carried out under the usual conditions in acetonitrile in presence of PTSA at 80°C as shown in *scheme 8*. The product from this reaction however could not be characterized due to line broadening in the ^1H NMR spectrum in $CDCl_3$ at room temperature.

Scheme 8



2.5 : Conclusions

1. Isolation of the S-allyl compounds (**17b**) (**17c**) and (**17d**) in pure form proved that the allyl moiety first gets attached to the sulfur atom which subsequently undergoes [3,3] sigmatropic rearrangement to yield the C-allyl nitrothioacetamides **18b**, **18c**, **18d**.
2. Cyclic α-substituted aminoacid esters were proved to be the best for stereocontrol at the new chiral center in thio-Claisen rearrangement of nitrothioacetamides.
3. If the rate of rearrangement is slow, epimerisation at the new chiral center at a comparable rate results in low diastereoselectivity.

2.6: Experimental

2.6.1: Synthesis of 1-methylthio-1-substituted amino-2-nitroethene

General procedure

A solution of amine (10 mmol) in CH_3CN (15ml) was added slowly to the suspension of 1,1-bismethylthio-2-nitroethene (10 mmol) and catalytic amount of PTSA in acetonitrile at room temperature. A clear solution was obtained, evolution of methanethiol was observed by it's characteristic odor. The reaction mixture was stirred at ambient temperature 3-12 h. Reaction temperature was raised in the cases where reaction was not complete. Unreacted starting material (**14**) was precipitated by treating the gum with ice cold ethanol and purified by column chromatography to get (**15**).

Benzyl-N-(1-Methylthio,2-nitroethenyl)(1R,3R,5R)-2-azabicyclo[3.3.3]-octane-3-carboxylate (15a)

Reaction temperature	80°C
Reaction time	6h
Nature of compound	Light yellow viscous liquid
IR(cm^{-1}) (neat)	3420, 3210, 2920, 1720, 1650, 1430, 1510
Yield	70 %
^1H NMR (δ)	1.40-2.40 (m,8H,CH_2), 2.40 (s,3H,SCH_3), 4.25 (m, 1H, NCH),
($CDCl_3$)	4.95 (m, 1H, bridge head), 5.25 (s, 2H,OCH_2), 6.95 (s, 1H, =CH),
	7.40 (s, 5H, ArH)
Mass m/z	362 (M+, 0%), 110 (100%)
$[\alpha]^D$ EtOH	-26.99

Diethyl N-(1-methylthio,2nitroethenyl)glutamate (15b)

Compound (**15b**) was synthesized in similar way as (**15a**) except that the reaction was carried out in ethanol at 80°C for 12h.

Reaction temperature	80°C for
Reaction time	12h
Nature of compound	Brown viscous liquid

Yield	75 %
IR(cm^{-1}) (neat)	3280, 3000, 1750, 1580
^1H NMR (δ)	1.2-1.4 (m, 6H, $2CH_3$), 2.0-2.4,(m, 4H, $2CH_2$), 2.45 (s, 3H, SCH_3),
($CDCl_3$)	4.0-4.2 (m, 4H, $2OCH_2$), 4.5 (m, 1H, NCH), 6.65 (s,1H, =CH),
	10.55 (bs, 1H, NH)

1-(Methylthio-1-(S)(methyl benzylamino))-2-nitroethene (15c)

Reaction temperature	80°C,
Reaction time	12h
Yield	85%
Nature of compound	Brown viscous liquid
IR(cm^{-1}) (neat)	3500, 3020, 1580, 1560
^1H NMR (δ)	1.62 (d, 3H, CCH_3), 2.31 (s, 3H, SCH_3) 47.5 (m, 1H, NCH), 6.45 (s,
($CDCl_3$)	1H, =CH), 7.15 (m, 5H, ArH), 10.60 (bs, 1H, NCH)
$[\alpha]^D$ EtOH	+ 631.87

1-(Methylthio-(S)-(N-methyl, methyl benzylamino))-2-nitroethene (15d)

Reaction temperature	80°C for
Reaction time	12h
Nature of compound	Brown viscous liquid
Yield	79 %
IR(cm^{-1}) (neat)	3020, 1550, 1420, 1450
^1H NMR (δ)	1.68 (d, 2H, CH_3), 2.53 (s, 3H, SCH_3), 2.8 (s, 3H, NCH_3),
($CDCl_3$)	5.8 (m, 1H, NCH), 6.8 (s,1H, =CH), 7.4 (m, 5H, ArH)
^{13}C NMR (δ)	1166.87, 138.24, 128.3, 127.5, 126.72, 126.4, 111.81, 60.20, 36.93,
($CDCl_3$)	17.53, 16.96
$[\alpha]_D$ EtOH	-367.91

1-Methylthio (1R, 5R)-2-azabicyclo [3.3.0] octane-2-nitroethene (15e)

Reaction temperature	30 °C
Reaction time	12h.
Nature of compound	viscous brown liquiod

Yield	75 %
IR (cm^{-1}) (neat)	2950, 1650, 1520, 1450
^1H NMR (δ)	1.5-2.2 (m,8H), 2.45 (s,3H,SCH3), 2.75 (m,1H,bridge head),
($CDCl_3$)	2.40 (m,2H,NCH2), 4.5 (m,1H,NCH), 6.7 (s,1H,=CH)

Compound has corresponding nitroacetamide mixed in it.

2.6.2: Synthesis of Nitrothioacetamide

General procedure

1-Methylthio-1-substituted-2-nitroethene (10 mmol) was dissolved in dry ethanol (deoxygenated) containing acetic acid (20 mmol) and kept under inert atmosphere. Fused Na_2S(15 mmol) was added in many portions through a solid addition funnel. The solid addition funnel was designed in such a way that a close system will be maintained through out the course of the reaction. The solvent was removed and contents were taken in benzene, undisolved salts were filtered off. The filtrate was concentrated to get thick gum which was column chromtographed (silica 60-120) using 10 to 20% ethyl acetate in pet-ether to get pure nitrothioacetamides (**16**).

N-(Nitrothioacetyl) benzyl (1R, 3R, 5R)-2-azabicyclo [3.3.3]octane-3-carboxylate (16a)

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Brown viscous liquid
Yield %	60
IR(cm^{-1}) (neat)	3500, 2950, 1750, 1570
^1H NMR (δ)	1.4-2.2 (m, 8H), 3.00 (m, 1H, bridge head), 4.50 (m, 1H, NCH), 5.2
($CDCl_3$)	(m, 2H, CH_2-C), 5.6 (dd, 2H, CH_2NO_2) 7.4 (m, 5H, ArH),
^{13}C NMR (δ)	25.5, 31.5, 33.1, 33.6, 44.7, 69.04, 65.50, 83.08, 128.60, 128.72,
($CDCl_3$)	129.0, 135.0, 169.84, 185.22
Mass (m/z)	348 (M+, 0%), 154 (100%)
$[\alpha]_D$EtOH	+23.32

(S) Diethyl-N-(nitrothioacetyl)-glutamate (16b)

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Brown viscous liquid
Yield	30 %
IR(cm^{-1}) (neat)	3200, 2200, 1740, 1600, 1450
^{1}HNMR (δ)	1.33 (m, 6H, CH3), 2.4 (m, 4H, NCH_2, OCH_2), 4.22 (m, H,CH_2),
($CDCl_3$)	5.1 (m, 1H, NCH), 5.48 (2H, S, NO_2CH_2), 9.11 (bs, 1H, NH)

N-(Nitrothioacetyl)methylbenzylamine (16c)

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Brown viscous liquid
Yield	60%
IR(cm^{-1}) (neat)	3250, 3040, 1560, 1430
^{1}H NMR (δ)	1.6 (d, 3H,CH_3), 5.45 (s, 2H, CH_2NO_2), 5.65 (m, 1H, NCH), 7.3
($CDCl_3$)	(m, 5H, ArH), 8.80 (bs,1H, NH)
Mass (m/z)	224 (M+, 1%), 178 (100%)

Could not be isolated in pure form hence microanalysis and rotations could not be reported.

N-Methyl-N-(nitrothioacetyl)-(S)-α-methylbenzylamine (16d)

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Brown viscous liquid
Yield	60%
IR(cm^{-1}) (neat)	3000, 1750, 1580, 1510
^{1}H NMR (δ)	1.65 (m,3H,CCH_3), 2.92 and 3.12 (s, 3H, NCH_3),
($CDCl_3$)	5.68 and 5.76 (s, CH_2NO_2, 2H), 4.12 (m, 1H,NCH)
^{13}C NMR (δ)	16.77, 18.45, 50.33, 52.38, 126.29, 126.56, 127.14, 128.40,
($CDCl_3$)	128.62, 128.70, 129.07, 186.96
[α]^{D}EtOH	-367.91

N-(Nitrothioacetyl) (1R,5R)-2-azabicyclo [3.3.0] octane (16e)

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Dark Brown liquid
IR(cm^{-1}) (neat)	3200, 2200, 1600, 1450
^1H NMR (δ)	1.5-2.00 (m, 8H), 2.8-3.0 (m, 1H, bridgehead) 3.65, 3.85
($CDCl_3$)	(m, 2H, NCH_2), 4.45, 4.90 (m, 1H, NCH), 5.50 (dd,2H,O_2NCH_2)

could not be isolated in pure form.

2.6.3: Allylation of nitrothioacetamide (16)

General procedure:

N-nitroacetamide was taken in dry ethanol and kept under inert atmosphere, 1 equivalent of DBU was added to the solution, stirred at room temperature for 5 min., then allyl bromide was added to the solution, and stirred at room temperature to get thick viscous liquid. Ethanol was removed at this stage under reduced pressure. Contents were poured in benzene inorganic material was filtered out. Removal of benzene under reduced pressure gave S-allyl nitrothioacetamide in good yield which were further purified by column chromatography (silica 60-120) using 10 to 20% ethyl acetate in pet-ether.

2.6.3a:BenzylN(1allylthio-2-nitroethenyl)(1R,3R,5R)-2-azabicyclo-octane-3-carboxylate (17a)

This compound could not be isolated. It undergoes very fast [3.3] sigmatropic rearrangement to give c-allylated compound.

2.6.3b: Dietyl N-(1-allylthio-2-nitroethenyl)-(S)-glutamate (17b)

Raction temperature	30°C
Reaction time	5 h.
Nature	Yellow viscous liquid
Yield	45%
IR (cm^{-1}) (neat)	8000, 2940, 1760, 1570, 3300
^1H NMR	1.3 (m, 6H, CH_3), 2.00 (m, 4H, CH_2), 3.5 (d, 2H, SCH_2), 4.2 (m,
($CDCl_3$)	4H, CH_2 ethyl), 4.6 (m, 1H, αCH), 5.0 -6.0 (m, 3H, =CH , $=CH_2$),
	6.6 (S, 1H, =CH-NO_2), 10.5 (bs, 1H, NH)

2.6.3c: N-(1-allylthio,2nitroethenyl)-(S)-methyl benzylamine (17c)

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Yellow viscous liquid
Yield	45 %
IRcm^{-1} (neat)	3400, 2980, 1740, 1470
^1H NMR (δ)	1.6 (d, 3H, CCH_3), 3.5 (d, 2H, SCH_2), 4.9 (m, H, NCH),
($CDCl_3$)	5.3 (t, 2H, $=CH_2$), 6.69 (s, 1H, HC=C)
^{13}C NMR(δ) ($CDCl_3$)	164, 141, 130, 128, 127, 120, 107, 54, 35, 24, 14

2.6.3d: N-(1-allylthio-2-nitroethenyl)-N-methyl,α' methyl benzyl amine (17d)

Reaction temperature	30 °C
Reaction time	5 h.
Nature of compound	Yellow viscous liquid
Yield	85%
IR(cm^{-1}) (neat)	1550, 1620, 1680, 3000
^1H NMR (δ)	1.68 (d, 3H, CH_3), 2.76 (s, 3H, NCH_3), 3.64 (d, 2H, SCH_2), 5.08
($CDCl_3$)	(m, 2H, $=CH_2$), 5.80 (m, 2H, NCHand =CH), 6.88 (s, 1H, $=CHNO_2$),
	7.4 (m, 5H, ArH)
$[\alpha]_D$ EtOH	-367.91

2.6.4: [3,3] Sigmatropic Rearrangement

2.6.4a:

Benzyl N-(α-allyl nitrothioacetyl)(1R,3R,5R)-2-azabicyclo[3.3.0]octane-3-carboxylate (18a)

Compound **17a** could not be isolated. Reaction of allylation cariied out in dry ethanol at room temperature under inert atmosphere gave directly C-allyl compound **(18a).**

Reaction temperature	30 °C
Reaction time	3 h.
Nature of compound	Dark brown viscous liquid
Yield	52 %
IR cm^{-1} (Neat)	3400, 2980, 1750, 1650,. 1460

^{1}H NMR (δ)	1.4 - 2.2 (m,8H), 3.0 (m,2H,CCH_2), 3.20 (m,1H, bridge head),
($CDCl_3$)	4.9 (m,1H,NCH), 5.0-5.3 (m, 5H,=CH_2 ,=CH, $ArCH_2$),
	5.15 (m, 2H, CH, O_2N-CH), 7.3(s, 5H, ArH).
^{13}C NMR (δ)	190.64 (191.01), 169.78 (169.62), 135.34 (134.67), 131.2 (131.9),
($CDCl_3$)	89.37 (88.52), 64.29 (63.17), 44.03 (44.15), 38.57 (37.83),
	25.29 (25.94)
Anal.Cald.for	C, 61.85; H, 6.18, N, 7.21
$C_{20}H_{24}N_2O_4S$	
Found	C, 61.17, H, 5.97, N, 6.90

2.6.4b: Diethyl N-(α-allyl nitrothioacetyl) (S) glutamate (18b)

Compond **17b** was left under inert atmosphere in dry benzene and $CDCl_3$ simultaneously at room temperature. Rate of rearrangement was observed to be same in both cases. The de was observed to be zero.

Reaction temperature	30 °C
Reaction time	20 Days
Nature of compound	Dark brown viscous liquid
Yield	52%
IR(cm^{-1}) (neat)	3200, 1760, 1580, 1430, 1220
^{1}H NMR (δ)	1.3 (m,6H,CH_3), 1.4 (m,4H,CH_2), 3.1 (m, 2H,CH_2,-CH),
($CDCl_3$)	4.2 (m,4H,OCH_2), 5.1 (m,1H,NCH), 5.25 (m,2H,=CH_2),
	5.5 (m,1H, $CHNO_2$), 6.8 (m,1H,=CH), 9.2 (bs,1H,NH).
^{13}C NMR (δ)	192.47 (192.19), 72.93 172.78), 71.86 (19.9.54), 130.46 (130.28),
($CDCl_3$)	130.04 (,128.83, 120.02, 108.92, 94.00, 62.95, 60.92, 60.81,
	57.74, 56.38, 37.78, 37.61, 35.26, 30.12, 26.99, 27.84, 25.75, 25.60
Anal. Calcd. For	C, 46.70; H, 6.58
$C_{14}H_{22}N_2O_6S$	
Found	C, 46.98; H, 5.9

2.6.4c: N(α'-allyl nitrothioacetyl)-(S)-α methyl benzylamine (18c)

Reaction was tried in ethanol at room temperature, rearrangement was very slow and took 20 days for completion. Rearrangement tried in ethanol at elevated temperature 50°C and 80°C gave corresponding nitroacetamide. The reaction done benzene at 80 °C was complete in 3h. The *de* was found to be zero in benzene reflux reaction. The reaction was also done in $CDCl_3$ at room temperature the *de* was observed to zero in this case.

Reaction temperature	30 °C
Reaction time	20 Days
Nature of compound	Dark brown viscous liquid
Yield	40%
IR(cm^{-1}) (neat)	3200, 1750, 1580, 1430
^1H NMR (δ)	1.6 (d, 3H, CCH_3), 3.0 (m, 2H, CCH_2), 5.15 (m, 1H,CH),
($CDCl_3$)	5.3 (m,4H, =CH, $=CH_2$, $CH.NO_2$), 7.35 (m,5H,ArH),
	8.80 (bs, 1H, NH),
^{13}C NMR (δ)	189.8(C=S), 141.5(140.9), 130.3 (129.2), 128, 128.2, 126.6, 125
($CDCl_3$)	(124.24)

Compound could not be obtained in very high purity

2.6.4d: N-Methyl,N-(α'-allyl nitrothioacetyl)-(S)-α methyl benzylamine (18d)

Reaction was done in benzene solution at 50 °C under inert atmospher. The *de* was observed to be 6 %.

Reaction temperature	30 °C
Reaction time	20 Days
Nature of compound	Dark brown viscous liquid
Yield	85 %
IR(cm^{-1}) (neat)	3000, 1750, 1580
^1H NMR (δ)	1.5 (m,8H), 2.5-3.6 (complex m,5H,CH_2,=CH,NCH_3),
($CDCl_3$)	5.0-5.8(m,5H,=CH,$=CH_2$, $CHNO_2$,NCH), 7.2 (m, 5H, ArH)

^{13}CNMR (δ)	193.14 (192.89), 192.20 (191.82), 138.36 (138.18), 138.08, 137.60,
($CDCl_3$)	131.05, 130.84, 130.52, 129.23, 87.53, 87.23, 87.16, 86.48, 60.39,
	60.04, 59.56, 59.35, 38.57, 38.45, 37.85, 37.60, 17.80, 17.50, 14.50,
	13.90
Anal. Calcd. For	C, 60.01; H, 6.35, N: 10.09
$C_{14}H_{18}N_2O_2S$	
Found	C, 60.43, H, 6.47, N, 10.07

2.6.5: The S-allyl compound **(17e)** got hydrolysis to nitroacetamide **(19)** on silica column

N-Nitroacetyl (1R, 5R)-2-azabicyclo [3.3.0]octane (19)

Reaction Temperature	30 °C
Reaction Time	3 h.
Nature	White crystalline
Yield	40%
IR (cm^{-1}) (nujol)	1640, 1550, 1450, 1370
^{1}HMNR (δ)	1.25 - 2.2 (m,8H,4CH_2), 2.75 (m,1H,CH), 3.4 -3.8 (2m,2H,NCH_2),
($CDCl_3$)	4.1- 4.4 (2m,1H, NCH), 5.25 (m,2H, NO_2CH_2)
^{13}C NMR (δ)	159.25, 158.76, 78.17, 77.5, 64.22, 63.87, 47.19, 46.61, 44.64, 41.95,
($CDCl_3$)	35.06, 33.38, 31.96, 31.75, 31.33, 29.58, 25.93, 25.52
Anal.Calcd for	C. 54.54; H, 7.07; N, 14.14,
$C_9H_{14}N_2O_3$	
Found	C, 54.56; H, 7.58, N, 14.13.

2.8: Reference

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CHAPTER 3

ATTEMPTED SYNTHESIS OF N-NITROACETYL PYROGLUTAMATE

Chapter 3

Attempted Synthesis of N-Nitroacetyl pyroglutamate

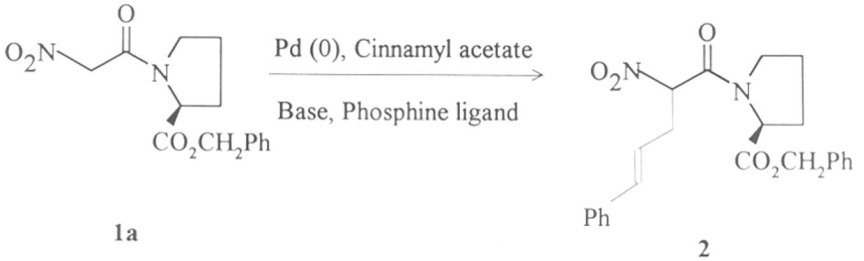
3.1 Summary

This chapter describes the attempts to synthesize N-nitroacetyl pyroglutamate. It was believed that N-nitroacetyl (S)-pyroglutamate might lead to higher stereoselectivity during Pd(0) catalyzed allylation than what was observed with N-nitroacetyl (S)-prolinate. This belief was based on the assumption that compexation of the metal with the exocyclic carbonyl group on one side and the lactam carbonyl on the other would help in fixing the geometry of the amide bond thereby increasing the stereoselectivity of the attack by the incoming electrophile. Condensation of 1,1-bismethylthio-2-nitroethene (**5**) with methyl pyroglutamate to generate the corresponding keten S,N-acetal. would be the first step in the projected sequence. The keten S,N-acetal on hydrolysis would lead to nitroacetyl (S)-pyroglutamate. However, the condensation reaction of pyroglutamate with nitroketen-dithioacetal (**5**) in acetonitirle in presence of PTSA failed to yield the desired product, probably due to the low nucleophilicity of the amide nitrogen compared to the amine nitrogen of prolinate. In order to increase the nucleophilicity of the pyroglutamate, an anion was generated on the amide nitrogen and then treated with the same reagent **5**. The various reaction conditions attempted are described in *Table 1*. As the required product could not be obtained, a different approach was employed (*scheme 4)*. Sodio pyroglutamate was first reacted with CS_2; subsequent methylation gave compound **8a** in very poor yield. The next step in the projected route was the replacement of SMe by CH_2NO_2. This reaction was first tried on the model compound **8b** derived from 2-pyrrolidinone. The reaction of nitromethane with **8b** under various conditions (*Table 2*) did not however give the thiocarbonyl compound. The third attempt was based on the use of S-methyl ester of α-nitrothiolacetic acid (**10**) as the electrophile; however, this could not be induce to react with sodio pyroglutamate. Lastly it was planned to use lactim ethers as the nucleophile. The reaction of butyrolactim ether with **5** in methanol gave the condensation product, which however had at the same time, undergone lactim ring opening.

3.2: Introduction

As a part of the ongoing research in our group, we have been actively involved in demonstrating the use of nitroacetamide as a peptide synthon[1]. There are two distinct advantages in this approach; (i) regioselective alkylation on the active methylene group adjacent to the NO_2 is possible and (ii) the nitro group acts both as an activating group and as a latent primary amino group. Carbon-Carbon bond formation on N-nitroacetyl amino acid derivatives was achieved by Pd(0) catalyzed allylation[2] or Michael addition[3]. Mono-alkylation reactions on these nitroacetamides generate a new chiral center. The conversion of the nitro group to an acetyl amino group resulted in the formation of dipeptides with an α-substituted glycine at the N-terminus. The extent of asymmetric induction, employing different aminoacids, solvents, bases, etc. was examined. In a similar way dialkylation of these nitroacetamides resulted in dipeptides with α,α-disubstituted glycine at the N-terminus .

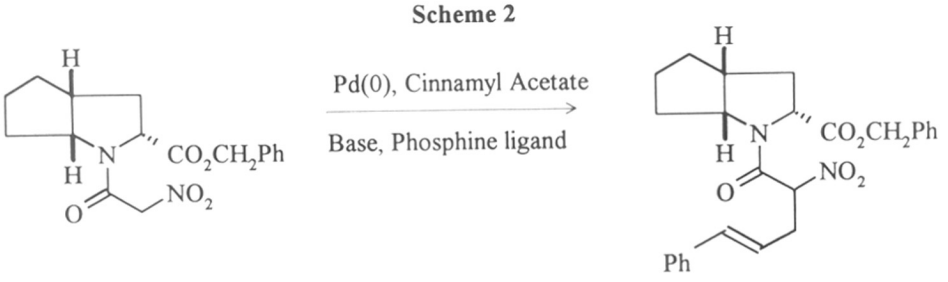
Scheme 1



1a **2**

It was observed that among the naturally occurring aminoacids employed (L)-proline resulted in good diastereoselectivity. A diastereomeric excess of 45% was noted in cinnamylation of benzyl N-nitroacetyl-L-prolinate[2] as shown in *Scheme 1*. Benzyl(1R,3R,5R)-2-azabicyclo[3.3.0]octane-3-carboxylate (a bicyclic analog of proline) on cinnamylation resulted in compound (3) with a diastereomeric excess of 65%.[5]

Scheme 2



1b **3**

The relatively higher diastereomeric excess in the case of compound **(3)** was believed to be due to restricted rotation around the amide bond in the parent nitroacetamide.[5] The bulkier bicyclic amino group in the above nitroacetamide puts additional constraints on rotation around the amide bond.

It was therefore planned to use (S)-methyl pyroglutamate in place of (S)-benzyl prolinate. The lactam carbonyl of the pyroglutamate and the amide carbonyl of the nitroacetamide can complex with metals; such complexation will restrict the rotation around the amide bond and hence it was expected to give high diastereoselectivity in Pd(0) catalyzed allylation reactions. With this aim we decided to try the condensation reaction of 1,1-bis methylthio-2-nitroethene with methyl pyroglutamate in the hope of getting the corresponding keten S,N-acetal. This keten S,N-acetal on hydrolysis would lead to N-nitroacetyl (S)-pyroglutamic acid ester.

3.3: Present work

The present chapter discusses the attempts to synthesise N-nitroacetyl pyroglutamate. The procedure established in our laboratory to condense primary and secondary amines with nitroketen -dithioacetal failed in the case of pyroglutamate. This failure may be ascribed to the low nucleophilicity of the amide nitrogen in pyroglutamate compared to the amine nitrogen. Following this failure, four other routes were attempted to synthesize the required nitroacetyl pyroglutamate :

i. Generation of an anion on the amide nitrogen and then condensing this with nitroketen dithioactal (**5**).

ii. Condensation of sodio pyroglutamate with CS_2 and subsequent methylation followed by displacement of SMe by CH_2NO_2.

iii. Use of S-methyl ester of α-nitrothiolacetic acid as an electrophile instead of nitroketen dithioacetals

iv. Use of the lactim ether as the nucleophile in place of lactam for condensation with nitroketen dithioacetal

The synthesis of S-methyl nitrothiolacetic acid is also described in this chapter.

3.4: Results and Discussion

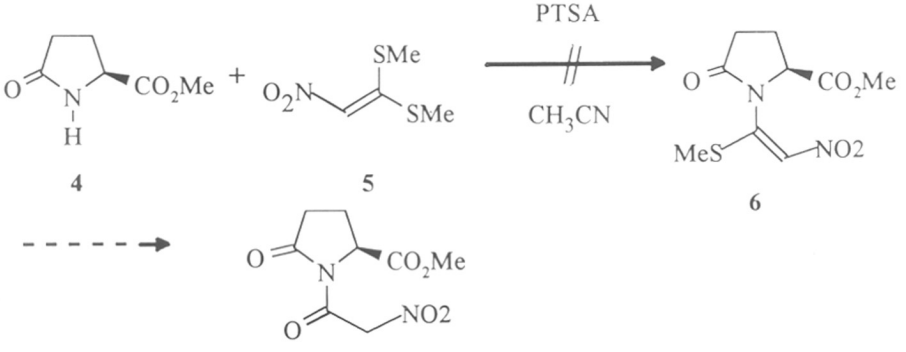
3.4.1 Reaction of methyl pyroglutamate with1,1-bismethylthio-2-nitroethene

The condensation reaction of methyl pyroglutamate with 1,1-bismethylthio-2-nitroethene (5) was first attempted in the usual way, in presence of PTSA in acetonitrile at room temperature[6] (*scheme 3*). However, under these conditions, no reaction was observed. The reaction temperature was hence increased to 80°C. The reaction at higher temperature also led only to recovery of the starting material. Use of ethanol as a solvent at room temperature gave no different result from the reaction in acetonitrile. Use of PTSA in ethanolic solution resulted in transesterification of methyl pyroglutamate to ethyl pyroglutamate. The failure of the condensation reaction under these conditions can be attributed to the low nucleophilicity of the amide nitrogen in methyl pyroglutamate, compared to the nitrogen of ethyl prolinate.

3.4.2: Reaction of anion of methyl pyroglutamate with 1,1-bismethylthio-2-nitroethene

The reaction was then attempted in the presence of weak bases such as sodium bicarbonate and sodium acetate. The attempt, however, failed. Thus reaction of solid 1,1-bismethylthio-2-nitroethene with an aqueous solution of methyl pyroglutamate containing $NaHCO_3$ either at 30°C or at 100°C led only to recovery of the starting materials. Use of sodium acetate in dioxan (homogeneous system) led to a similar result, as also the use of $ZnCl_2$ in the hope of complexing with the sulfur, thereby weakening the C-S bond.

Scheme 3



4 5 6 7

In order to increase the nucleophilicity of the amide nitrogen in methyl pyroglutamate it was decided to generate an anion on the nitrogen and then react it with compound (5). Sodium hydride was used to generate pyroglutamate anion in benzene. The coupling reaction with 1,1-bismethylthio-2-nitroethene was carried out in the same solvent or in a mixture of benzene and DMF to make the sodium salt soluble; however, this was also futile. Further, generation of

Table 1

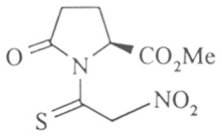
Sr.No	Reagent	Solvent	Temp.	Time
1	$NaHCO_3$	Water	30 °C	24 h.
		Water	100°C	3 h.
2	Na OAc	1-4 Dioxane	30 °C	12h.
		1,4 Dioxane	100 °C	12h.
3	PTSA	CH_3CN	30 °C	12h.
			80 °C	12h.
4	$ZnCl_2$	1-4Dioxane	30 °C	12h.
5	KF/Alunima	CH_3CN	30 °C	12h.
6	NaH	Benzene / DMF	30 °C	3h.
7	NaH /Bezene	DMF	100 °C	3h.
8	NaH / Benzene	1-4Dioxane	100 °C	3h
9	NaH /Benzene	CH_3CN	30 °C	12h.
	$Hg\ Cl_2$			
10	DBU	Benzene	30 °C	12h
11	TEA	Benzene	30 °C	12h.
12	KOH	aq. KOH	30 °C	12h
13	Sodium	THF	64 °C	6h

pyroglutamate anion with sodium hydride in benzene and removal of benzene under reduced pressure gave solid sodio pyroglutamate. The sodio pyroglutamate was treated with 1,1-bismethylthio-2-nitroethene in different solvents such as 1,4-dioxane, acetonitrile and DMF at

room temperature and also at elevated temperature. Neither the starting material nor the product could be isolated from the complex mixture. Use of $HgCl_2$ to modify the leaving group also proved to be unsuccessful. Use of bases such as DBU in benzene, TEA in benzene and KOH in aq-DMSO for the coupling reaction of methyl pyroglutamate with 1,1-bismethylthio-2-nitroethene were unsuccessful. The various conditions employed are summarized in *table 1.*

3.4.3: Reaction of Sodio pyroglutamate with CS_2

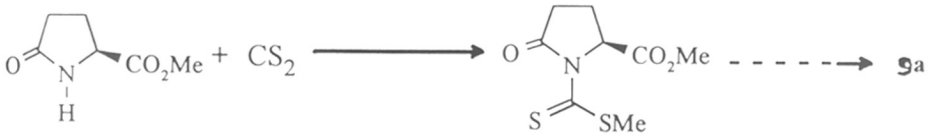
As none of the above conditions employed for condensing methyl pyroglutamate anion with 5 gave the required product, a different approach was resorted to . This involved initial condensation of carbon disulfide with sodio pyroglutamate followed by S-methylation with methyl iodide to give the dithiocarbamate (**8a**) (*scheme 4*). It was hoped that subsequent replacement of the S-methyl group by nitromethane anion would give the nitrothioacetamide (**9a**), the thiocarbonyl analog of the required compound (7).



9a

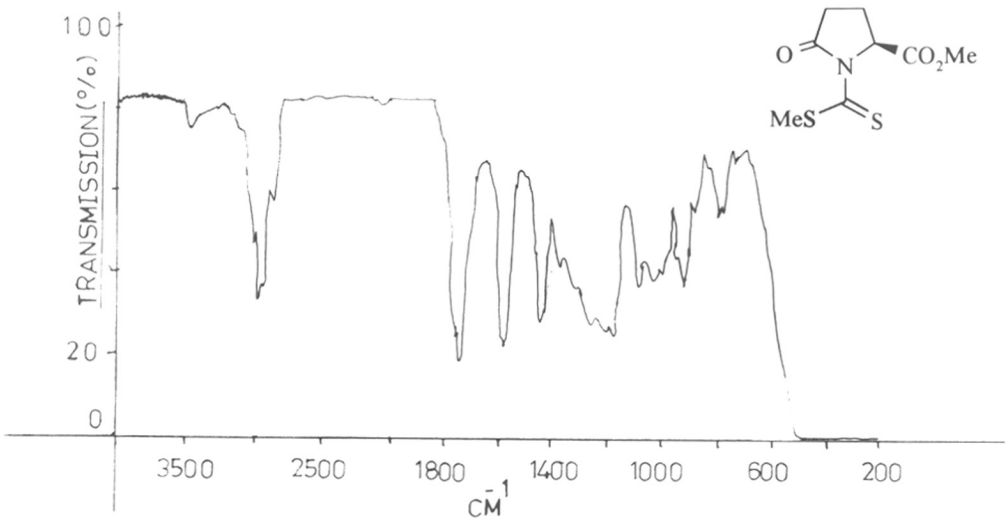
The first step however, gave an extremely poor yield of the required product. Coupling of sodio pyroglutamate with carbon disulfide and subsequent methylation with methyl iodide gave the required dithiocarbamate (**8a**) in 5% yield.

Scheme 4



4 **8a**

The ^1H NMR spectrum of (**8a**) shows thiomethyl protons as two singlets at 2.4 and 2.5δ respectively. The ring protons appear as complex multiplets at 2.4 and 2.6δ , OMe protons are seen as two singlets at 3.6 and 3.7δ. The proton, α-to the carboxylate group is observed as two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1400
1000
600
200
CM-1
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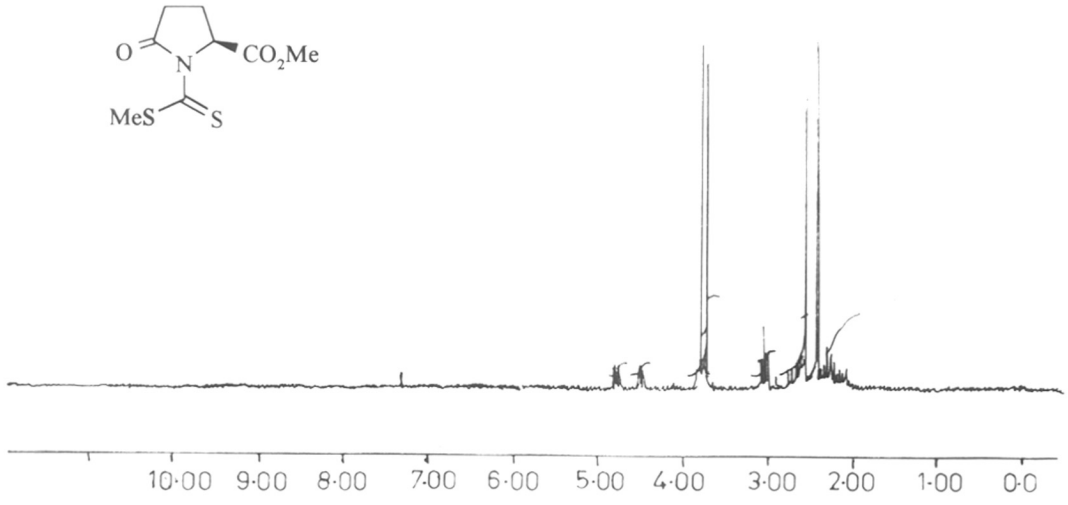
N
CO2Me
MeS
S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CO2Me
MeS
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5·00
4·00
3·00
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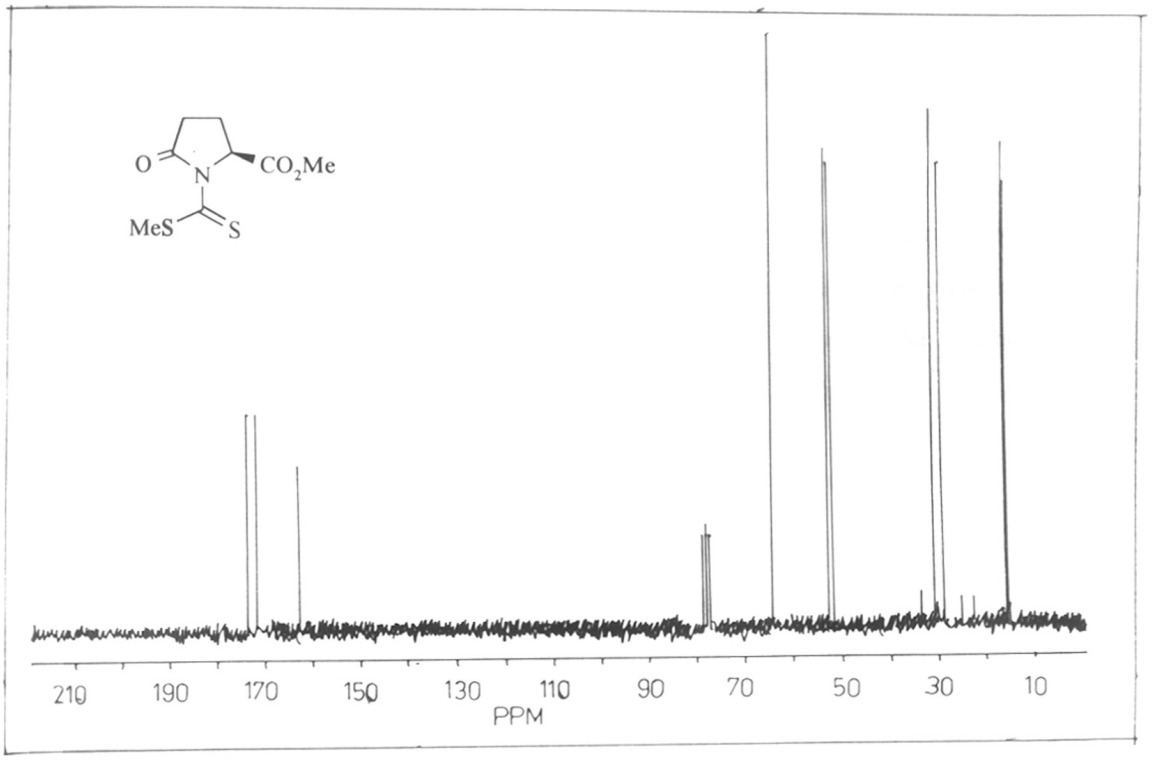
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CO2Me
MeS
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50
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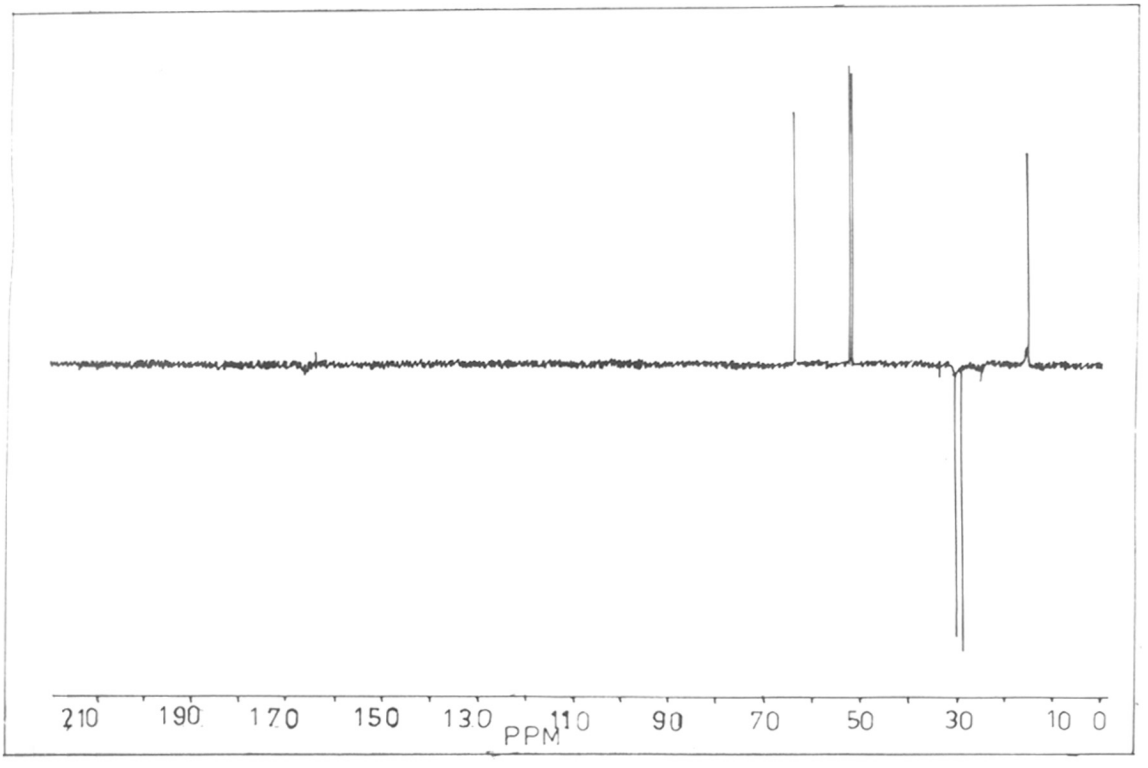
10
PPM


210
190
170
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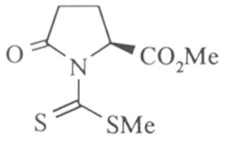
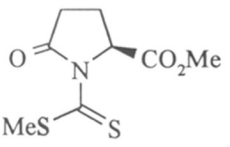
130
110
90
70
50
30
10
0
PPM

multiplets at 4.5 and 4.75δ. The ^{13}C NMR spectrum of the compound (**8a**) similarly shows two sets of signals for some of the carbon atoms : -OCH_3 (51.33, 52.05), -SCH_3 (14.78, 15.09), CON (163.15, 163.15δ) ester carbonyl at 171.53 δ and thioamide carbon at 173.3 δ. The two sets of signals of equal intensity in the ^1H and ^{13}C NMR spectra of this compound indicate the presence of two rotamers in approximate by equal amounts. The rotamers are seen as a consequence of the barrier to rotation around the thioamide bond of (**8a**). Using the N-acylproline terminology, the two rotamers are designated as (**8a*Z***) and (**8a*E***).



8a*Z*



8a*E*

The mass spectrum of (**8a**) shows the molecular ion peak at m/z = 233 $(5\%)_5$ the base peak is observed at m/z = 159. The IR spectrum shows imide carbonyl at 1740 cm^{-1} and ester carbonyl at 1760 cm^{-1}.

3.4.4: Reaction of 2-pyrolidinone with CS_2

The obtention of the dithiocarbamate (**8a**) in only 5% yield was a serious blow to the success of the scheme. In order to conserve the starting material (**8a**) for the next reaction, we have synthesized compound (**8b**) and used it as a model substrate for the nitromethane displacement reaction.

Scheme 5

8b

2-Pyrrolidinone was first reacted with CS_2 in presence of 33 % aqueous KOH in DMSO. The resulting potassium salt of the dithiocarbamic acid was further methylated to give compound (**8b**). Compared to the dithiocarbamate (**8a**) described earlier, compound (**8b**) lacks the

carboxylic ester group at position 5. In both the ^{1}H and ^{13}C NMR spectra of compound (**8b**) only one set of signals is observed, indicating absence of two rotamers (*cisoid* and *transoid*) about the thioamide bond. In the ^{1}H NMR spectrum of (**8b**) the multiplet at 2.15δ was assigned to the -CH_2 group at position 4. The triplet at 2.75δ was due to CH_2-C=O; the triplet at 4.4δ was assigned to -NCH_2 protons; the SMe group appears as a singlet at 2.6δ. The ^{13}C NMR spectrum of (**8b**) shows the thiocarbonyl carbon at 202.2δ and the amide carbonyl at 173.09δ. The signal at 20.36δ was assigned to SCH_3. The assignment was further confirmed by a DEPT spectrum. In the IR spectrum of **8b** imide carbonyl stretching absorption was noted at 1740 cm^{-1}. In the mass spectrum the molecular ion peak was seen at m/z = 175 in 100% intensity.

3.4.5: Attempts towards displacement of SMe with CH_2NO_2 in (8b)

The replacement of -SMe group in (**8b**) by CH_2NO_2 moiety was attempted using different reaction conditions as summarized in *Table 2*

Table 2

Reaction conditions for the reaction of (**8b**) with CH_3NO_2

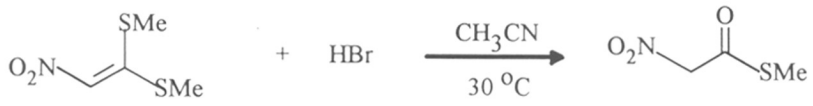
Sr.No.	Reagent	Solvent	Temperature °C	Time h.
1	Zeolite ReNaY	CH_3NO_2	30	12
2	Zeolite ReNaY	CH_3NO_2	100	12
3	Zeolite ReNaY	CH_3NO_2	100	12
4	KF / Alumina	CH_3CN	30	12
5	PTSA	CH_3CN	80	6
6	aq. KOH / TEBA	$CHCl_3$	30	6
7	KOH	EtOH	80	2
8	K_2CO_3	Acetone	30	12

Unfortunately, we were unable to achieve this transformation under any of the above conditions.

3.4.6: Use of S-methyl ester of α-nitrothiolacetic acid for the synthesis of (7)

The third route attempted was the use of S-methyl ester of α-nitrothiolacetic acid (**10**) as an electrophile in place of 1,1-bis-methylthio-2-nitroethene. The required nitrothioacetic acid S-methyl ester was synthesized by selective hydrolysis of 1,1-bismethylthio-2-nitroethene. The reaction of compound (**5**) with aqueous HBr in acetonitrile at room temperature gave compound **10** as shown in *scheme 6* in 92% yield.

Scheme 6

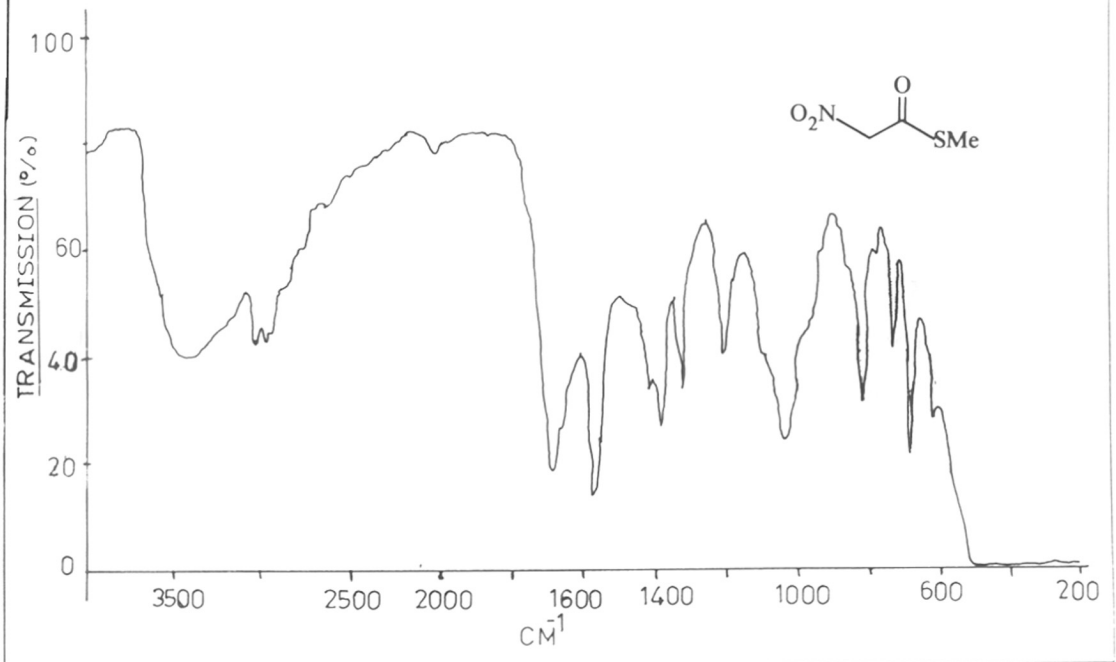


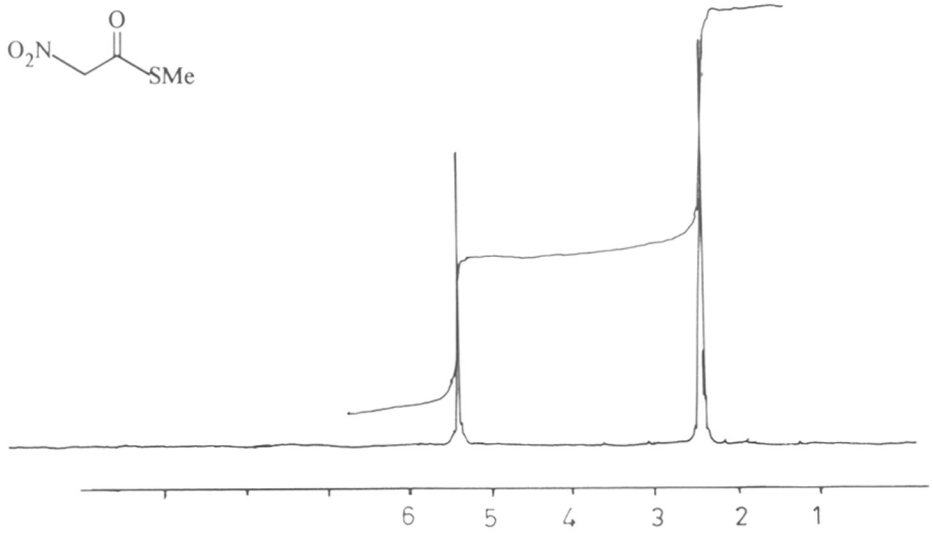
5 **10**

The ^1H NMR spectrum of compound **10** shows singlets at 2.4δ and 5.4δ due to -SMe and NO_2CH_2 protons respectively. IR spectrum shows the carbonyl stretching band at 1680 cm^{-1}. The S-methyl ester of α-nitrothiolacetic acid **10** was treated with the anion of pyroglutamate in benzene and dioxane at room temperature. The reaction was also attempted at elevated temperature. However the reaction did not proceed and the required compound 7 could not be obtained.

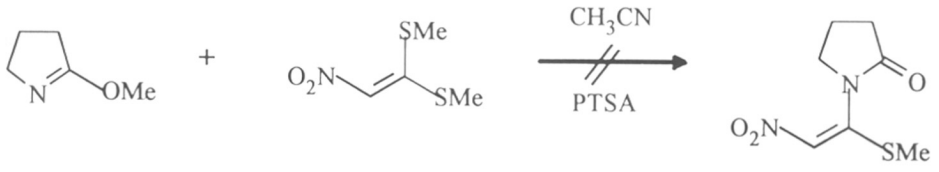
3.4.7: Reaction of lactim ether with nitroketen dithioacetal (5)

It was thought that the lactim ether of pyroglutamate might function as a better nucleophile than the amide or the amide anion of pyroglutamate. In order to test this hypothesis, a model experiment was first carried out with the lactim ether from pyrrolidinone as the nucleophile. Reaction of this achiral lactim ether (**11**) with 1,1-bis-methylthio-2-nitroethene (**5**) was carried out in acetonitrile at room temperature as well as at 80°C. The reaction, however, did not yield the required compound (**12**).


100
60
40
20
0
TRANSMISSION (%)
3500
2500
2000
1600
1400
1000
600
200
CM-1
O2N
O
SMe

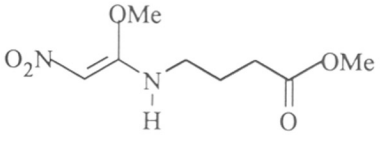

O2N
O
SMe
6
5
4
3
2
1

Scheme 7



11 **5** **12**

instead the starting materials were recovered. On changing the solvent from CH_3CN to methanol the characteristic smell of methyl mercaptan was observed indicating the formation of the condensation product. The reaction in methanol was very slow. After 90h at the reflux temperature, the solvent was evaporated under reduced pressure. The product was purified by column chromatography on silica gel 160-120 using pet-ether ethyl acetate mixture as the eluent. The product from this reaction, unexpectedly proved to have the structure (**13**) in which the lactim ether ring had opened. This ring opening of lactim ethers by reaction with different electrophiles is discussed in the next chapter.



13

3.5: Conclusions :

1. The expected N-nitroacetyl pyroglutamate could not be synthesized by any of the approaches discussed in this chapter.
2. An unexpected reactivity of γ-butyrolactim ether, with ring opening was observed, this is discussed in detail in chapter 4.

3.6: Experimental

Synthesis of Methyl N-(methyl-carbodithioate)-2-pyrrolidinone-5-carboxylate (8a)

Methyl pyroglutamate was dissolved in dry benzene (30 ml), 50% NaH (10 m mol) was slowly added to the stirring solution using a solid addition tube. After evolution of H_2 gas was complete CS_2 was added to the reaction mixture. Reaction mixture was stirred at room temperature for 1h. Reaction mixture was then cooled to 10°C and methyl iodide (10 mmol) was added to it. Benzene was evaporated at reduced pressure and product was purified by column chromatography using pet-ether ethyl acetate.

Nature of compound	Yellow Liquid
Yield	5 %
IR cm^{-1} (neat)	3000, 1740, 1760, 1`580, 1440
^1H NMR (δ)	2.0-2.8 (m,4H,CH_2), 2.4, 2.6 (s,3H,SCH_3), 3.6, 3.7 (s, 3H,OCH_3),
($CDCl_3$)	4.50, 4.75 (m, 1H, NCH)
^{13}C NMR (δ)	15.09(14.78), 28.74, 30.27, 52.05 (51.53), 63.47, 163.15, 171.53,
($CDCl_3$)	173.32
Mass m/z	233 (M+, 62%), 98 (100%)

Satisfactory elemental analysis could not be obtained.

Synthesis of Methyl-2-pyrrolidinone-1-carbodithioate (8b)[7]

This compound was synthesized by the reported procedure with some modifications. To a solution of 2-pyrrolidinone (6g, 071mmol) in dimethylsulfoxide (30 ml) carbon disulfide (6g, 079 mol) was added at room temperature. Aqueous 33% KOH (12 ml) was added below 35°C after stirring for additional 1/2 an hour, methyl iodide (0.08 mol) was added at 10°C. Reaction mixture was allowed to attain room temperature and stirred at room temperature for 1h. Reaction mixture was then poured in ice cold water and solid product was separated by filtration. Further purified by recrystallisation from rectified sprit.

Nature of compound	Light yellow crystalline solid
Yield	15 %
M.P.	96-98 °C
IR cm^{-1} (mujol)	1760, 1470, 1390

^{1}H NMR (δ)	2.15 (m, 2H, CCH_2), 2.60 (s, 3H, SCH_3),
($CDCl_3$)	2.75 (t, 2H, CO-CH_2), 4.4 (t, 2H, NCH_2)
^{13}C NMR ($CDCl_3$)	17.26, 20.35, 33.53, 53.73, 173.09, 202.26
Mass m/z	175 (M+, 100%)

Synthesis of S-methyl nitrothiolacitic acid[8]

To the solution of 1,1bismethylthio-2-nitroethene(10 mmol) in 25 ml acetonitrile, 15 mmol 49 % HBr was added. The reaction mixture was stirred at room temperature for 12 h. Acetonirile was removed at rotary evaporator at reduced pressure. Contents were added to water to remove inorganic material. and organic portion was extracted with dichoromethane. Product was further purified by column chromatography (silica 60-120) using 10 to 20 % ethyl acetate in pet-ether

Nature of compound	viscous liquid
Yield	92 %
IR cm^{-1} (neat)	1680, 1570, 1390
^{1}H NMR (δ)($CDCl_3$)	2.40 (s, 2H, SCH_3), 5.40 (s, 2H, NO_2CH_2),
Mass m/z	135 (M+, 15 %) , 93 (100 %)

3.7: References

1. S.G.Manjunatha, P.Chittari, and S.Rajappa, **Helv. Chem. Acta,** 1991, 74, 1071
2. S.G.Manjunatha, S.Rajappa, **J.Chem.Soc.Chem.Commun.**, 1991, 372
3. A.Thomas, **Ph.D. Thesis** submitted to University of Poona, 1994
4. S.G.Manjunatha, **Ph.D. Thesis** submitted to University of Poona, 1992.
5. P.Chittari, **Ph.D. Thesis** submitted to University of Poona, 1994.
6. S.G.Manjunatha, K.V.Reddy, and S.Rajappa **Teterahedron Lett.**, 1990, **31**, 1327
7. T.Takeshima, M.Ikeda, M.Yokoyama, N.Fukada and M.Muraoka, **J.Chem. Soc.Perkin Trans (I),** 1979, 692
8. T.I.Reddy, **Ph.D. Thesis** submitted to University of Poona, 1992.

CHAPTER 4

NUCLEOPHILIC REACTIONS OF LACTIM ETHERS WITH CONCOMITANT RING OPENING

Chapter 4

Nucleophilic Reactions of Lactim Ether with Concomitant Ring Opening

4.1: Summary

This chapter describes the reaction of lactim ether with different electrophiles leading to lactim ring opening. The reaction of butyrolactim ether with nitroketen-dithioacetal **18** gave compound **20b** in 25% yield. Compound **20b** is formed by the replacement of the SMe group of methyl 4-amino-N-(1-methylthio-2-nitroethenyl)butanoate (**19b**) by OMe of methanol. Compound (**19b**) could not be isolated in pure from, but it's formation could be inferred from, the ^1H NMR spectrum of the reaction mixture without purification. Similar reaction of caprolactim ether with nitroketen-dithioacetal (**18**) gave the ring opened products **19a** in 7% and **20a** in 22% yield respectively. The rate of reaction of lactim ethers with **18** was observed to be very slow. In order to accelerate the reaction different conditions were tried. Use of aqueous methanol improved the rate of reaction but not the yield in the case of butyrolactim ether . Use of catalysts such as $HgCl_2$ or PTSA were of no avail.

Other elecrophiles such as CS_2, ethyl ethoxymethyleneacetoacetate, diethyl ethoxymethylenemalonate and *p*-toluenesulfonyl chloride have also been used in similar ring-opening reactions of lactim ethers. The reaction of caprolactim ether with CS_2 followed by methylation gave compound **22** in 10% yield. Reaction of butyrolactim ether with diethyl (ethoxymethylene) malonate and ethyl (ethoxymethylene)acetoacetate carried out at 100°C without any solvent, gave compounds **24** and **26** in 40% and 30% yields respectively. Reaction of caprolactim ether with *p*-toluenesulfonyl chloride also gave the ring opened compound **28** in 60% yield. Attempted reactions of butyrolactim ether with 1,1-bismethylthio-2-benzoylethylene (**29**) and 1-methylamino-1-methylthio--2-nitroethene (**30**) were unsuccessful and resulted only in recovery of unchanged starting material.

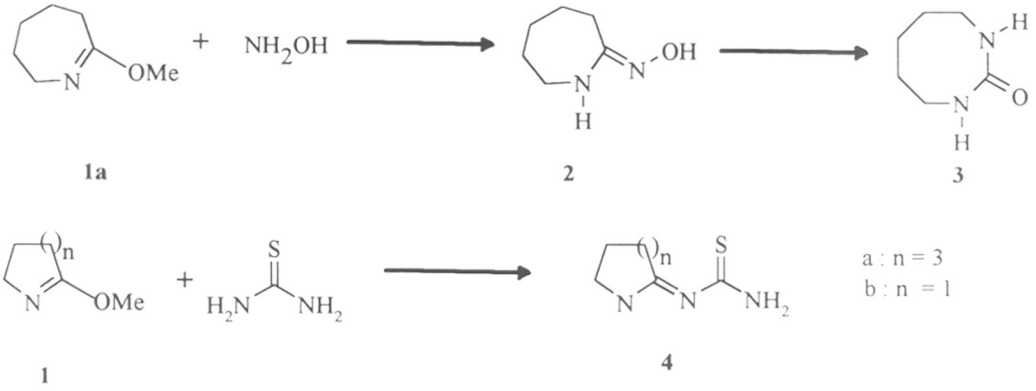
4.2 : Introduction

The conversion of lactams into lactim ethers increases the scope for using these basic building blocks in organic synthesis. Lactim ethers are used in the synthesis of drugs[1] dyes and other important classes of organic compounds. They have also found application as accelerators of polymerization. The chemical properties of lactim ethers are briefly reviewed below.

Lactim ethers are capable of undergoing reactions with both electrophiles and nucleophiles. Nucleophiles attack either the sp^2 hybridized carbon of the imino ether or the carbon attached to the oxygen atom i.e. sp^3 hybridized carbon of the ether linkage, depending on the nature of the attacking nucleophiles. Reaction of lactim ethers with nitrogen, oxygen and carbon nucleophiles have been reviewed exhaustively. Some examples are given below.[2]

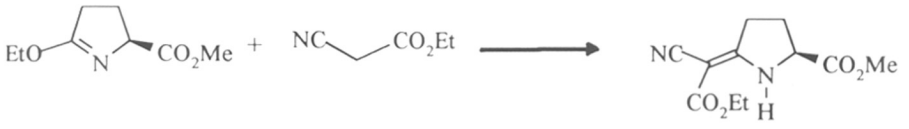
Reaction of caprolactim ether with hydroxyamine followed by Backmann rearrangement leads to the cyclic urea **3.**[3] Similar reaction of lactim ethers with thiourea leads to compound **4**[4] Both these reactions with nitrogen nucleophiles are shown in *scheme 1.*

Scheme 1



A new carbon carbon bond can be formed by the reaction of lactim ethers with active methylene compounds. Condensation of the imino-ether derived from methyl pyroglutamate with ethyl cyanoacetate led to compound **6**[5] (*scheme 2*). Similar reaction of lactim ether **7** with ethyl acetoacetate gave compound **8.**

Scheme 2



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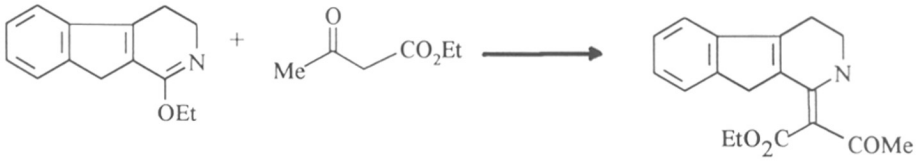
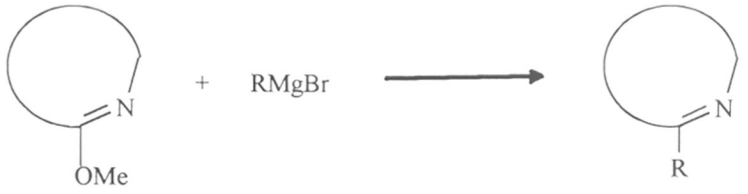


7 8

Grignard reagents are also known to attack lactim ethers to yield the imines **(9)**[7] as shown in *scheme 3.*

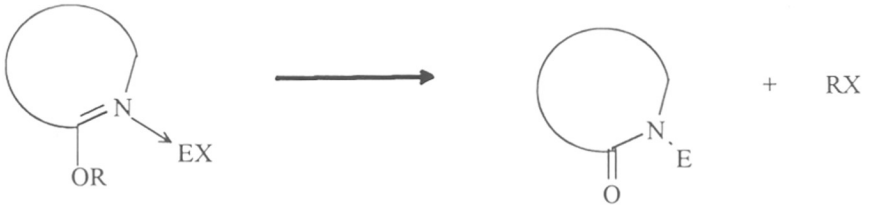
Scheme 3



1 9

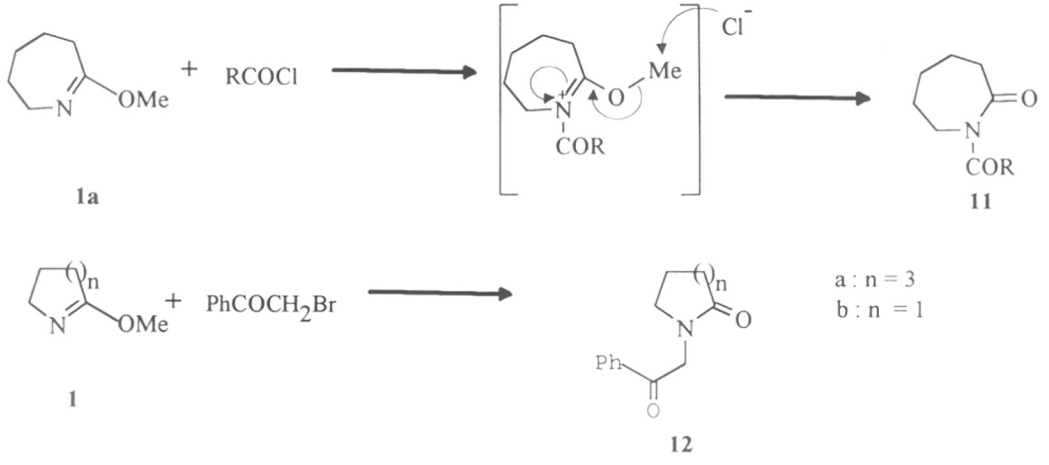
The reaction of lactim ethers with electrophiles : The nitrogen in such lactim ethers is much more nucleophilic than that of lactams. Initial attack of the electrophile on the nitrogen may be followed by cleavage of the alkyl-oxygen bond, perhaps induced by the counter ion. The isomerisation of lactim ethers to N-methyl lactams on treatment with dimethyl sulfate is an example of this process.[8] *(Scheme 4)*

Scheme 4

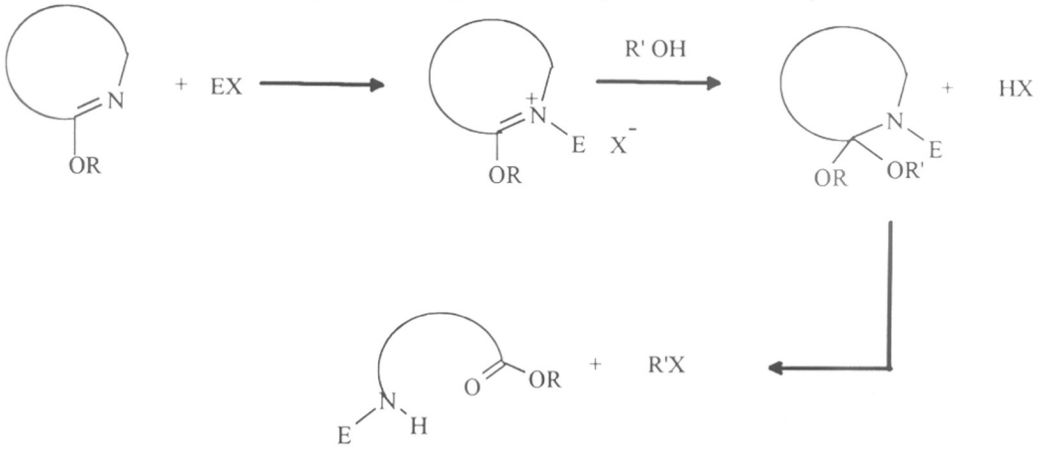


Stolle and Griech also showed that lactim ethers react with acid chlorides[9] to give N-acyl lactams. The reaction of lactim ethers with phenacyl. bromide leads to the N-alkyl compound **12**[10] (*scheme 5*).

Scheme 5



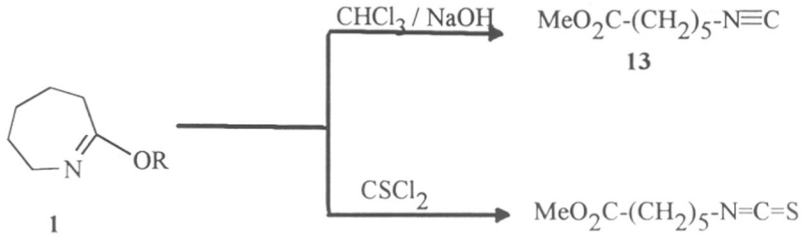
In some cases, initial attack of the electrophile on the nitrogen may be followed by the opening of the lactam ring; this process is usually brought about by the solvent (water or alcohol) acting as the nucleophile. Only a few examples of this sequence have been reported in literature.



i) Reaction of caprolactim ether with chloroform in presence of alkali or alkaline earth metal hydroxides and a phase transfer catalyst gave the ring opened isocyanide **13.**[11] Also the reaction of

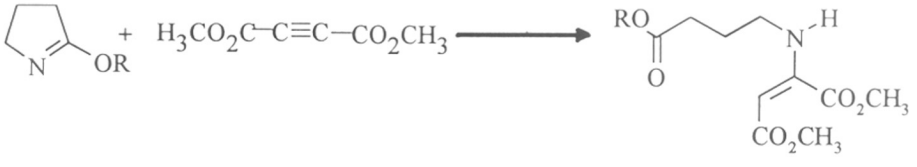
caprolactim ether with thiophosgene gave a 30-70 % yield of the isothiocyanate[12] **14** as shown in *scheme 6.*

Scheme 6



ii) Another example of lactim ether ring cleavage is reported by Aue et.al[13]. Reaction of dimethyl acetylenedicarboxylate (DMAD) with butyrolactim ether in boiling aqueous dioxane yielded compound **15** in around 40% yield.

Scheme 7



15

The lactim ether **16** undergoes oxidative ring opening on treatment with MCPBA[14] (*scheme 8*).

Scheme 8

16 **17**

4.3: Present work

As mentioned briefly in chapter 3, reaction of butyrolactim ether with 1,1-bismethylthio-2-nitroethene (**18**) led to the expected addition-elimination; this was; however, followed by lactim ring opening. There are a few scattered examples known in literature where nucleophilic attack by the nitrogen of the lactim ether has yielded an acyclic product. Such examples have been catalogued in the earlier section of this chapter. A detailed study of such reactions has not yet been made. The present chapter describes several new reactions of lactim ethers with different electrophiles which have resulted in lactim ring opening. The first one is the reaction of 1,1-bismethylthio-2-nitroethene (**18**) with butyrolactim ether as well as with caprolactim ether. Other electrophiles whose reactions with lactim ethers has been studied now are CS_2, ethyl ethoxymethyleneacetoacetate, diethyl ethoxymethylenemalonate and finally *p*-toluenesulfonyl chloride. In all these cases, initial electrophilic attack was followed by ring opening. The yield of the final product in these reactions was found to be low and all the reactions were considerably slow except the reaction of *p*-toluenesulfonyl chloride. An attempt has been made to accelerate the reaction of butyrolactim ether with nitroketen dithioacetal (**18**) by using different catalysts and employing different solvents. The reaction of lactim ether has also been tried with the analogs 1,1-bismethylthio2-bonzoylethene (**29**) and 1-methylthio-1-methylamino-2-nitroethene (**30**). However these attempts led only to the recovery of the starting materials.

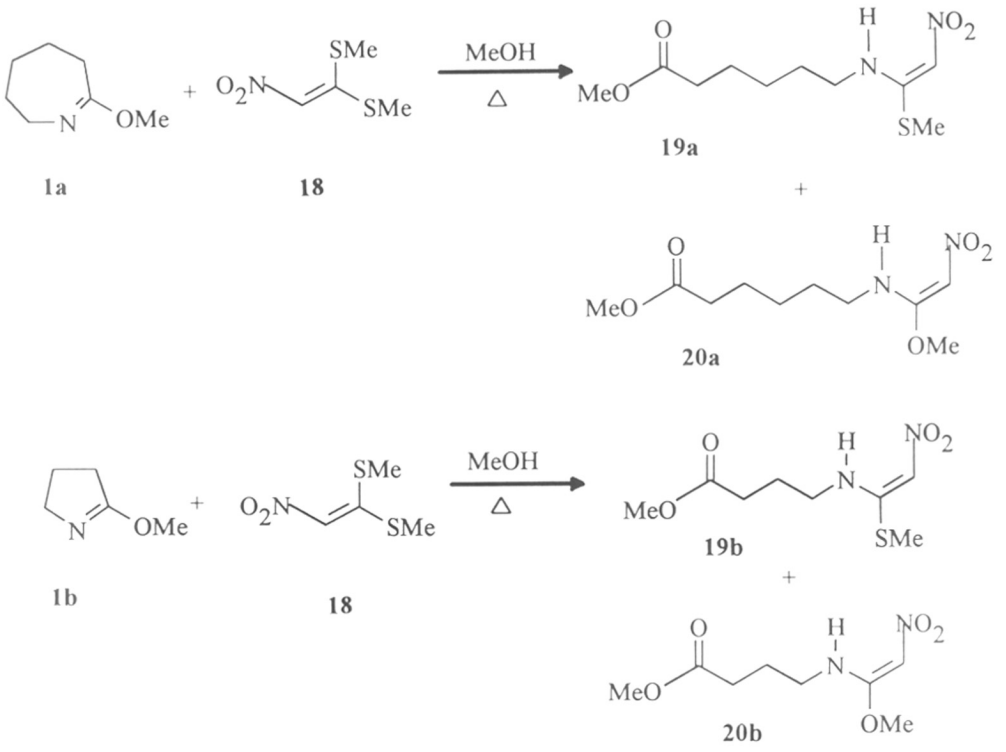
4.4:Results and Discussion

4.4.1: Reaction of lactim ether with nitroketen dithioacetal

Reaction of caprolactim ether (**1a**) with **18** was carried out in boiling methanol for 72h. Purification of the reaction product gave two compounds **19a** and **20a** in 7% and 22% yield respectively. The ^{1}H NMR spectrum of compound **20a** shows two methoxy groups appearing as singlets at 3.60δ and 3.80δ, six methylene protons appear as a multiplet at 1.5δ. The CO-CH_2 and NCH_2 methylenes appear as two triplets at 2.30δ and 3.30δ respectively. The olefinic proton was seen as a sharp singlet at 6.4δ and NH as a broad singlet at 10.50δ. The IR spectrum shows ester carbonyl stretching at 1740 cm^{-1} and NH stretching absorption at 3300 cm^{-1}. The other compound **19a** was obtained only in 7% yield. The ^{1}H NMR spectrum of **19a** shows a multiplet at 1.5δfollowed by two triplets at 2.30δ and 3.30δ due to the methylene protons of $COCH_2$ and NCH_2 respectively. The singlet at 2.48δ was assigned to SCH_3 protons. The olefinic proton was noted at 6.40δ. The NH proton was observed at 9.8δ as a broad singlet.

The reaction of nitroketen-dithioacetal (**18**) with butyrolactim ether (**1b**) was carried out in acetonitrile, benzene or dichloromethane as solvent at room temperature as well as at the boiling point of the respective solvents; but in all these cases the reaction did not proceed. The reaction of butyrolactim ether with **18** in methanol at 65°C gave compound **20b** in 25% yield. The ^{1}H NMR spectrum of compound **20b** shows a multiplet at 1.88δ due to the central methylene group, a triplet at 2.26δ due to $COCH_2$, and the NCH_2 appears as a multiplet at 3.35δ followed by two singlets at 3.55δ and 3.77δ due to the two methoxy groups. The olefinic proton appears as a sharp singlet at 6.51δ; the most downfield signal at 7.66δ was assigned to the NH proton. The IR spectrum of **20b** shows sharp ester carbonyl absorption at 1740 cm^{-1} and NH stretching absorption at 3380 cm^{-1}. The elemental analysis supports the structure of **20b** (*scheme 9*). The formation of **19b** in the above reaction, along with **20b**, was inferred only from the ^{1}H NMR spectrum of the crude reaction mixture. The ^{1}H NMR spectrum of the reaction mixture before purification showed a sharp singlet at 2.4δ(SCH_3) which indicated the formation of **19b.** Compound **19b** could not be obtained in pure form.

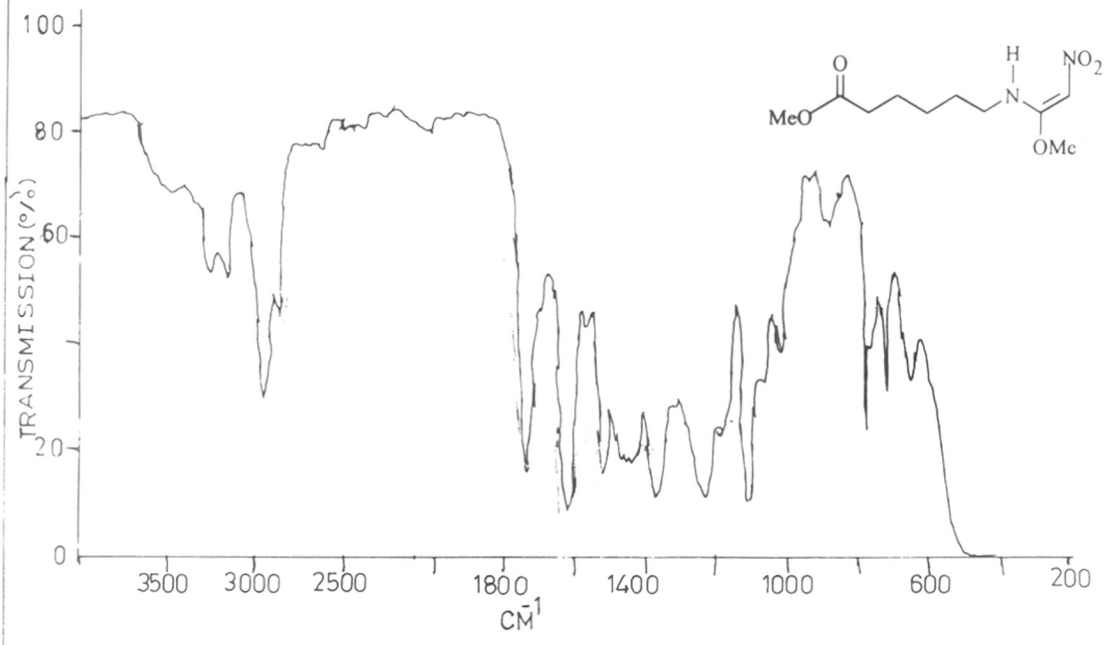
Scheme 9



The reaction of lactim ethers **1a** and **1b** with nitroketen dithioacetal was very slow. Hence the reaction was repeated in solvents other than methanol. The reaction carried out in ethanol as solvent at 80°C gave a complex mixture. The ^1H NMR spectrum of the product mixture without purification indicated the formation of the ring opened compound which had also apparently undergone transesterification.

The use of PTSA as a catalyst in order to accelerate the reaction in methanolic solution was futile. Mercuric chloride was hence used, assuming that the complexation of sulfur with $HgCl_2$ may accelerate the reaction. This did not improve the rate of reaction but gave the methyl ester of α-nitro-thiolacetic acid (**21**) (*scheme 10).*

Use of aqueous methanol (water-methanol 1:3) improved the rate of the reaction of butyrolactim ether (**1b**) with nitroketen dithioacetal (**18**) The reaction was complete in 24h instead of 72h as in methanolic solution. The yield of the reaction was found to be the same in both cases.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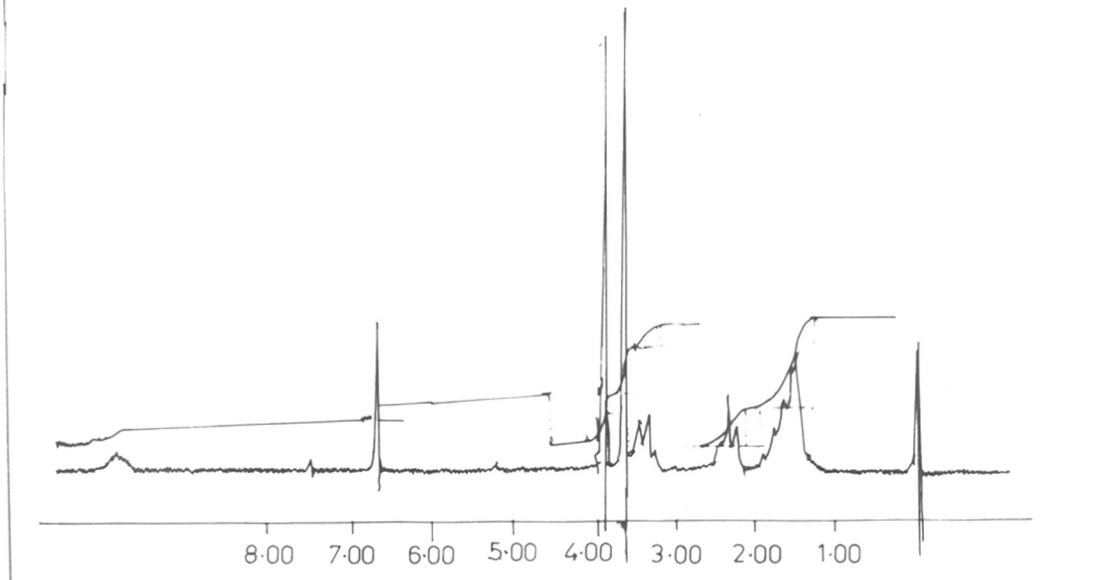
NO2
OMe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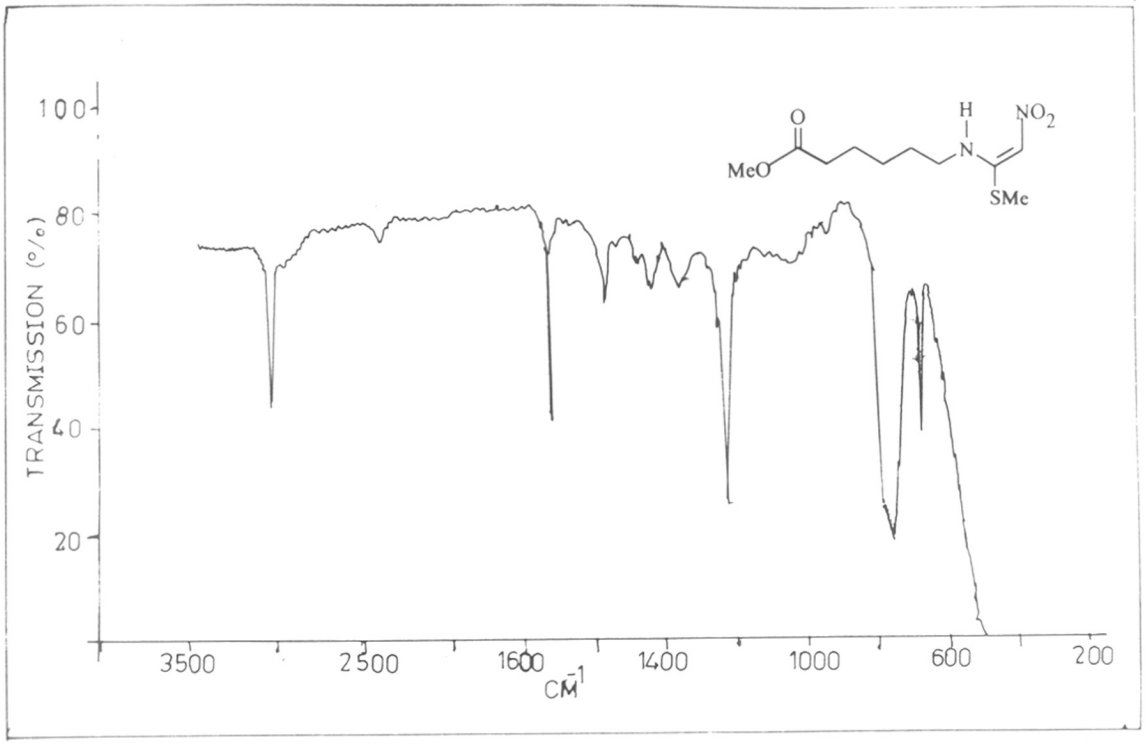
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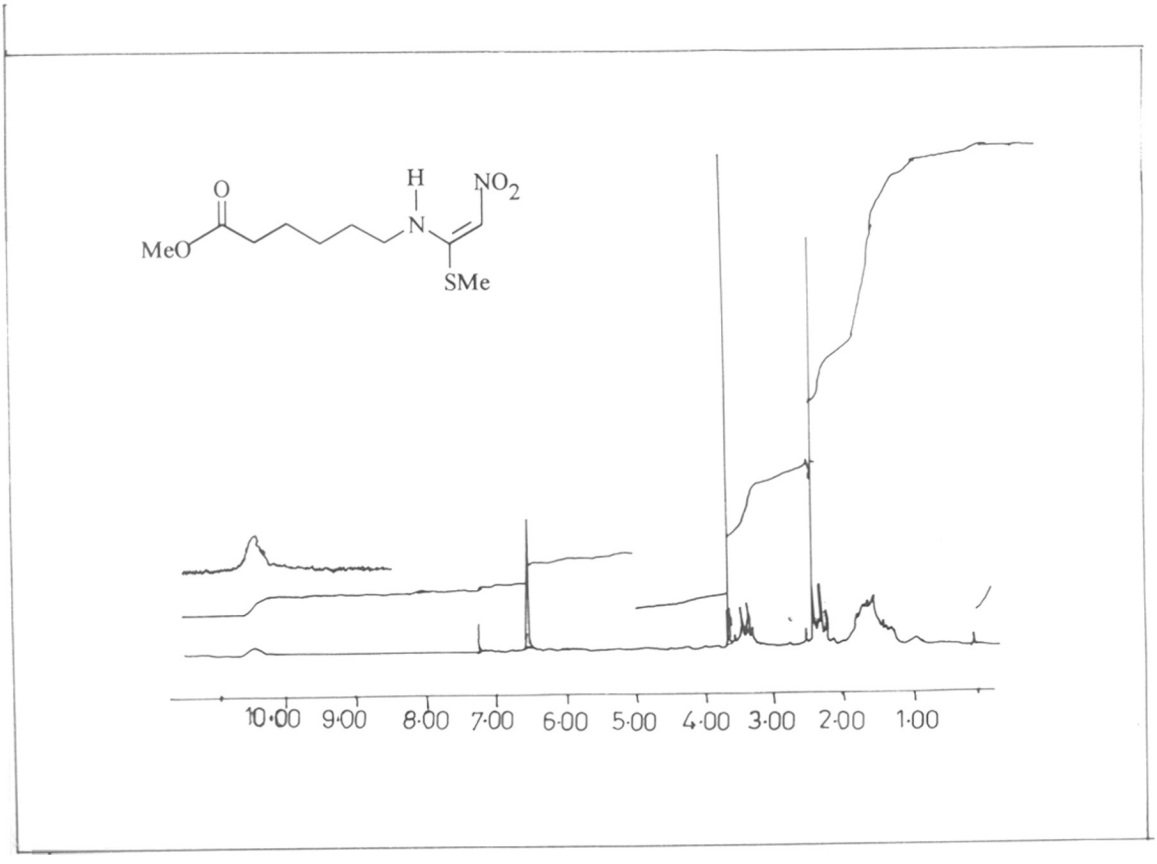
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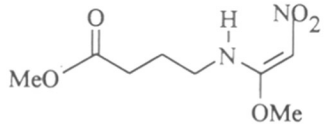
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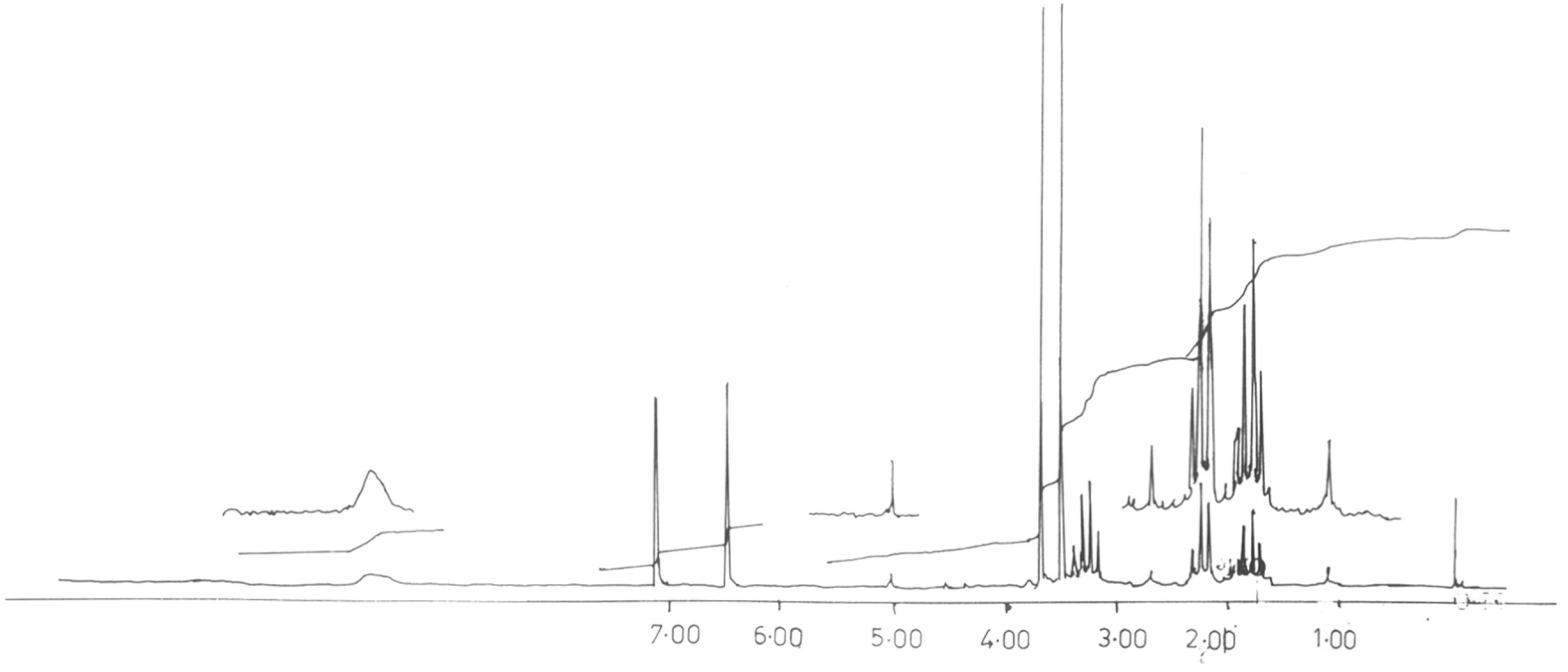
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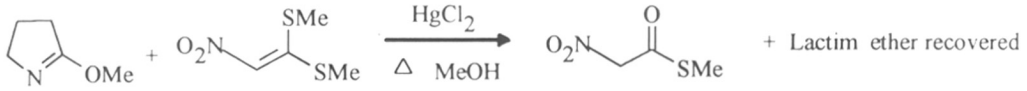
Scheme 10



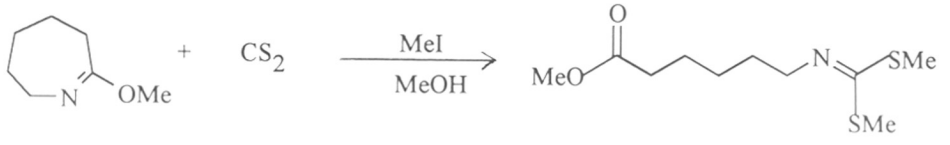
1b **21**

The reaction of caprolactim ether (**1a**) with **18** in aq methanol (1:3) gave a non-separable complex mixture.

4.4.2: Reaction of lactim ether with CS_2

Reaction of caprolactim ether with CS_2 in methanol followed by methylation with methyl iodide gave compound **22** in 10% yield as shown in *scheme 11*. The ^1H NMR spectrum of compound **22** shows a multiplet for 6H at 1.6δ followed by a triplet at 2.15δ due to $COCH_2$; thiomethyl protons appear as two singlets at 2.28δ and 2.75δ . Methylene group attached to nitrogen appears as a multiplet at 3.36δ and the methoxy protons as a sharp singlet at 3.68δ The IR spectrum of compound **22** shows ester carbonyl stretching at 1740 cm^{-1}. The structure of compound **22** was confirmed by elemental analysis.

Scheme 11



1a **22**

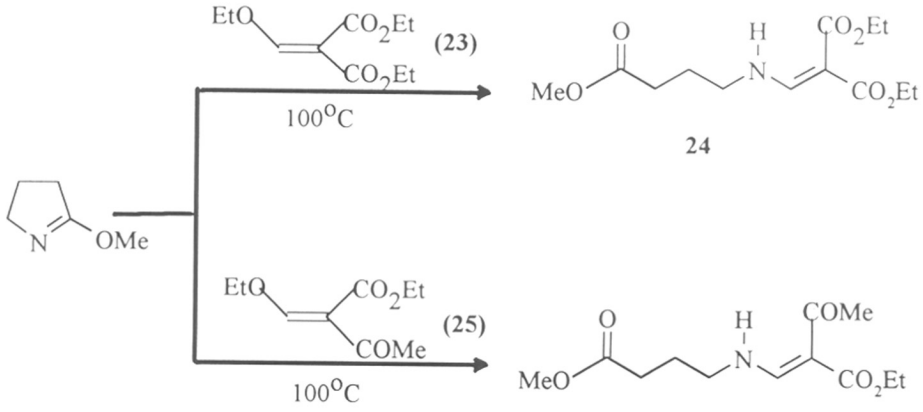
4.4.3: Reaction of lactim ether with ethyl (ethoxymethylene)acetoacetate and diethyl (ethoxymethylene) malonate

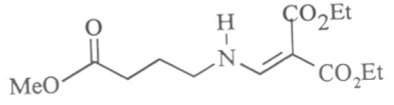
Reaction of butyrolactim ether with diethyl(ethoxymethylene) malonate (**23**) in boiling methanol was found to be extremely slow. Hence both the reactants were mixed and heated to 100°C without solvent for 72h. The progress of the reaction could not be monitored easily by tlc since the tlc pattern was very complex. After 72h, the reaction mixture was filtered through a short pad of silica (60-120) to give compound (**24**) in 40% yield as shown in *scheme 12*.

The ^1H NMR spectrum of compound **24** shows two overlapping triplets at 1.25δ due to the two CH_3 groups followed by a multiplet as 1.95 due to the central methylene, a triplet at 2.35δ due to $COCH_2$ and a multiplet at 3.4δ due to the NCH_2 protons. A singlet at 3.75δ was assigned to the methoxy protons; the two OCH_2 groups appeared at 4.25δ. The olefinic proton was seen as a doublet at 8.00δ. The most downfield signal appears at 9.2δ due to the NH proton. The IR spectrum of compound **24** shows NH stretching absorption at 3290 and ester carbonyl at 1740 cm^{-1} as broad peaks. The structure of compound **24** was also confirmed by ^{13}C NMR spectrum and elemental analysis.

Similar reaction of butyrolactim ether with ethyl (ethoxymethylene) acetoacetate(**25**) at 100°C without use of solvent gave compound **26** in 30% yield. The ^1H NMR spectrum of compound **26** shows triplet at 1.30δ due to CH_3 of ethyl moiety followed by another multiplet due to the central methylene group. The $COCH_2$ protons appear as distorted triplet at 2.0δ and $COCH_3$ as a singlet at 2.4δ; NCH_2 appears at 3.15δ as a multiplet. The methoxy group appears as a sharp singlet at 3.7δ; the quartet at 4.3δ was assigned to OCH_2. A doublet at 8.0δ was assigned to olefinic proton. The NH proton appears at 11.0δ. The IR spectrum shows carbonyl stretching at 1740 and 1680 cm^{-1} and NH absorption at 3490 cm^{-1}. Satisfactory elemental analysis could not be obtained for compound **26**.

Scheme 12

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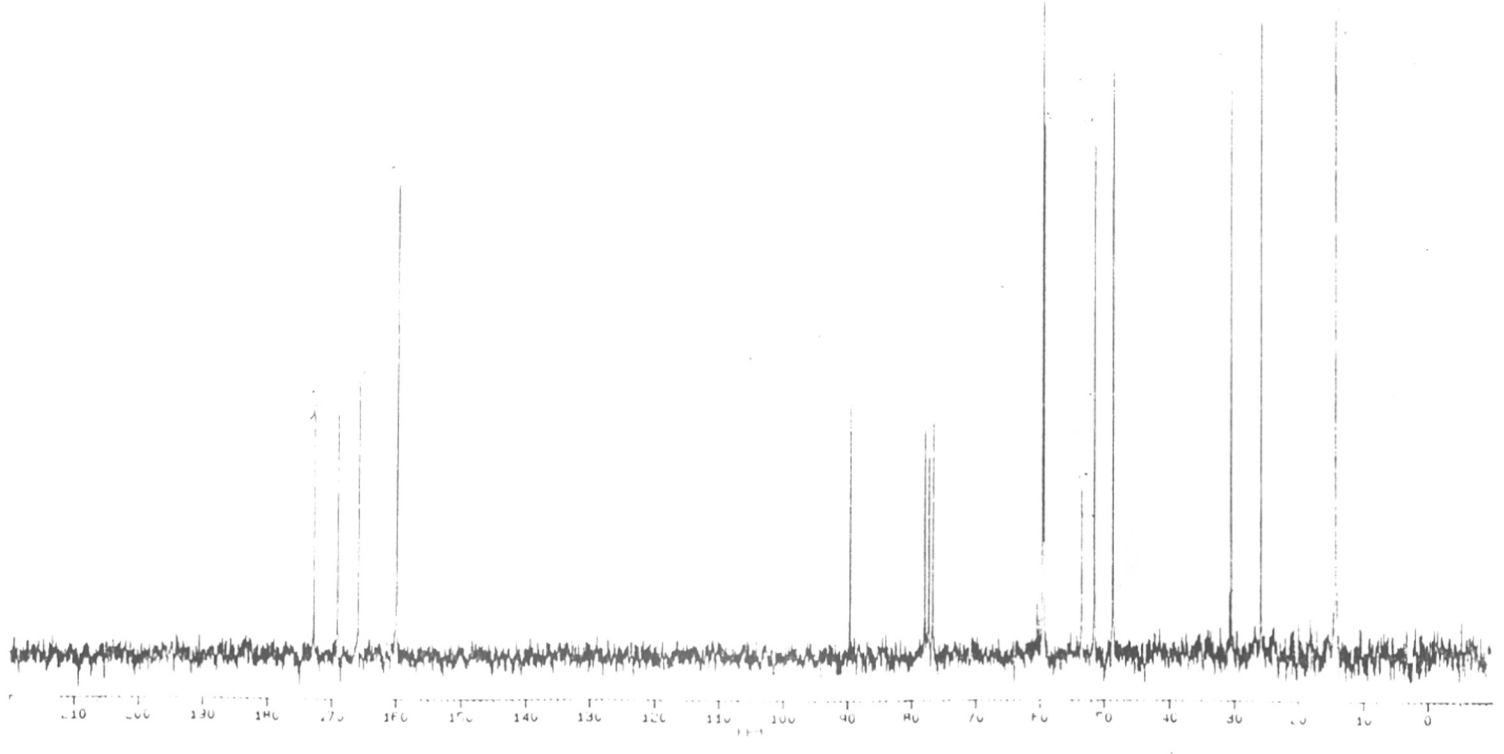

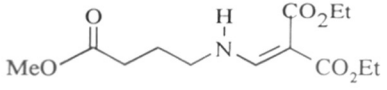
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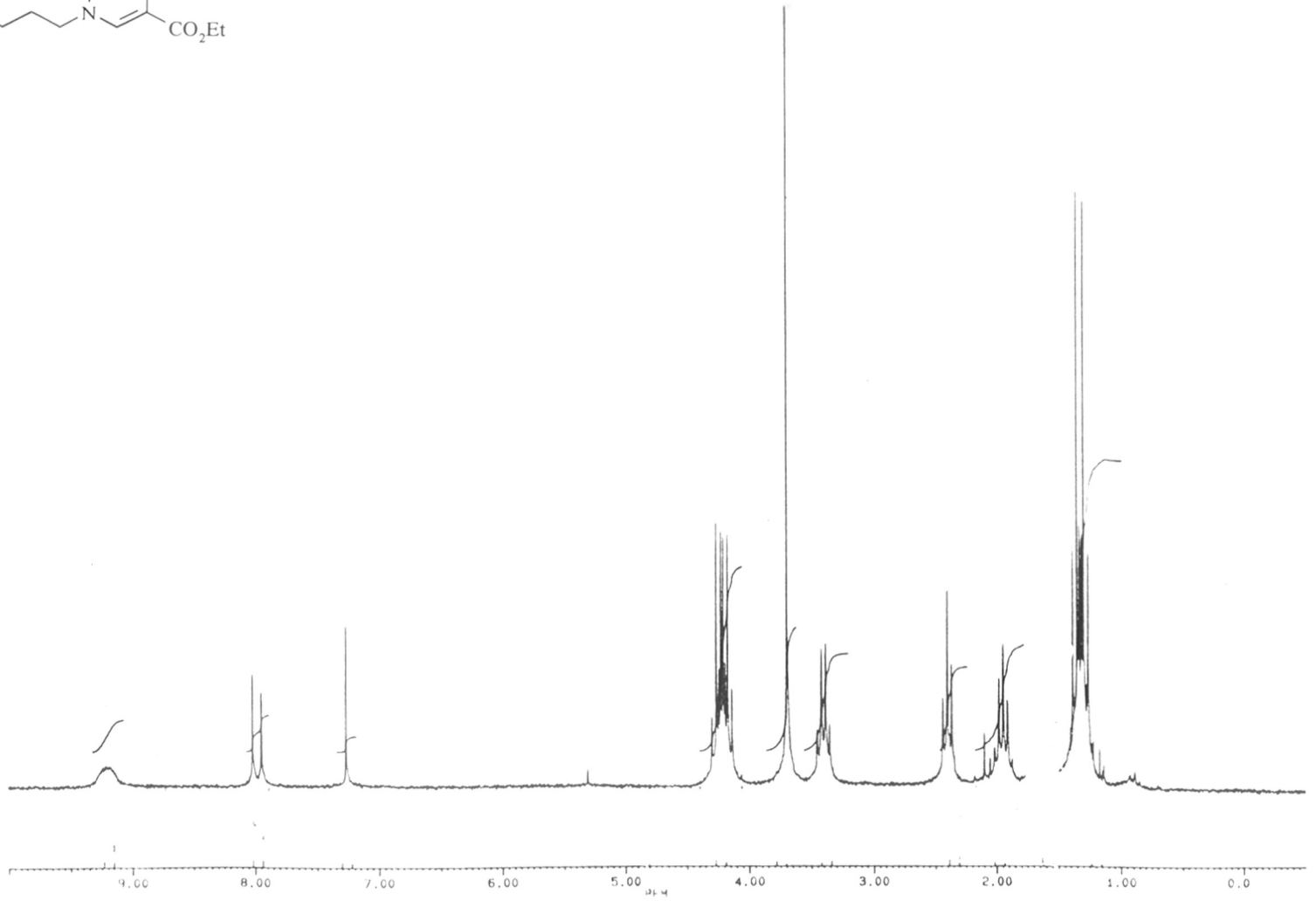
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4.4.4: Reaction of Lactim ether with *p*-toluenesulfonyl chloride

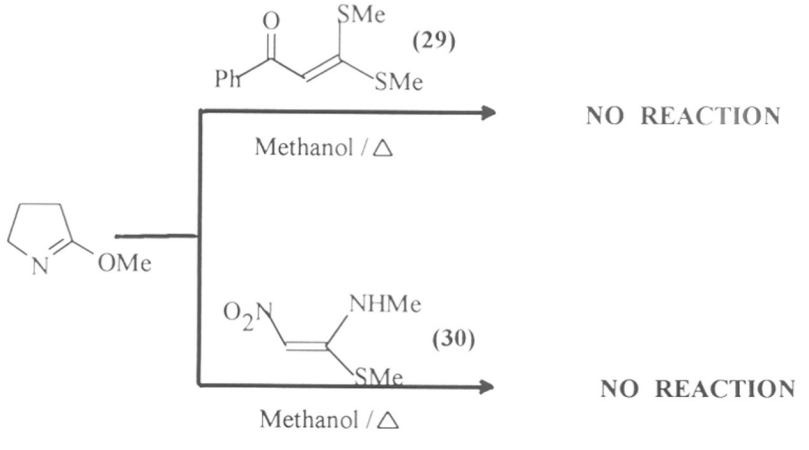
Reaction of caprolactim ether with *p*-toluenesulfonyl chloride in dichloromethane at room temperature followed by normal aqueous work up and purification by column chromatography (silica 60-120) using 10% ethyl acetate in pet-ether gave compound **28** in 60% yield. The ^1H NMR spectrum of compound **28** shows a multiplet at 1.44δ for 6H ($3CH_2$) followed by two triplets at 2.24δ and 2.88δ due to $COCH_2$ and NCH_2 protons respectively. Ar-CH_3 appears as a sharp singlet at 2.37δ and OCH_3 shows another sharp singlet at 3.55δ, NH proton is seen at 4.55δ as a broad singlet. The above reaction of *p*-toluenesulfonyl chloride with caprolactim ether has also been reported by Sheu et al.[15]

Scheme 13

1a **27** **28**

We then planned to extend the scope of the ring opening nucleophilic reactions of lactim ethers by trying some additional electrophiles such as 1-1-bismethylthio-2-benzoylethene (**29**) and

Scheme 14



1-methylamino-1-methylthio-2-nitroethene (**30**) with butyrolactim ether **1b** as shown in *Scheme 14*. Both these reactions were attempted in boiling methanolic solution without any catalyst. In both the cases no reaction was evident either from the tlc or by the expected evolution of methyl mercaptan. Use of a catalyst such as PTSA or change of solvent from methanol to ethanol was futile. Removal of solvent after 72h of reflux gave only the unchanged starting materials.

4.5 : Conclusions

i. Reaction of lactim ethers with nitroketen dithioacetal led to the condensed products with simultaneous lactim ring opening.

ii. Similar reaction with electrophiles such as ethyl ethoxymethyleneacetoacetate, diethyl ethoxymethylenemalonate, CS_2 and *p*-toluenesulfonyl chloride also resulted in the formation of acyclic compounds.

iii. The above reactions proceeded well in alcoholic solvents. Use of non-hydroxylic solvents such as benzene or acetonitrile was found to be unsuccessful.

iv. The reaction of butyrolactim ether with nitroketen dithioacetal could not be accelerated by the use of either PTSA or $HgCl_2$ as catalyst

v. Reaction of lactim ether with 1,1-bismethylthio-2-benzoylethene and 1-methylamino-1-methylthio-2-nitroethene was unsuccessful.

4.6: Experimental

4.6.1: Reaction of lactim ether with 1,1-bismethylthio-2-nitroethene :

To the solution of lactim ether (12 mmol) in methanol, 10 mmols of 1,1, bismethylthio 2-nitroethene was added. Reaction mixture was heated to reflux. The coupling reaction of lactim ether was evident from the smell of methyl mercaptan. Reaction was monitored by tlc. After completion of reaction methanol was evaporated at reduced pressure. Product was separated from 1,1-bismethylthio-2-nitroethene by dissolving in cold ethanol and further purified by column chromatography (silica 60-120) using pet-ether ethyl acetate 75:25.

Reaction with caprolactim ether with 1,1-bis methylthio-2-nitroethene gave two products

Methyl-6-amino-N-(1-methylthio-2-nitroethenyl) hexanoate (19a)

Reaction time	72h
Nature of compound	Thick brown liquid
Yield	7%
IR cm^{-1} (neat)	3300, 3010, 1740, 1580,
^1H NMR (δ)	1.5 (m, 6H, $3CH_2$), 2.36 (t, 2H, $COCH_2$),2.8 (s, 3H, SCH_3)
(CDCl3)	3.3 (t, 2H, NCH_2), 3.60 (s, 3H, OCH_3), 6.48 (s, 1H, =CH),
	10.48 (bs, 1H, NH)

Microanalysis could not be done because of very low yields and separation problems

Methyl-6-amino-N-(1-methoxy-2-nitroethenyl) hexanoate (20a)

Reaction time	72h
Nature	Thick brown liquid
Yield	22 %
IR cm^{-1} (neat)	3360, 3260, 1740, 1620, 1520
^1H NMR (δ)	1.5 ($2t_{mix}$, 6H, $3CH_2$), 2.30 (t, 2H, $COCH_2$), 3.30 (m, 2H, NCH_2), 3.60
($CDCl_3$)	(s, 3H, OCH_3), 3.80(s, 3H, OCH_3), 6.40 (s, 1H, =CH), 9.8 (bs, 1H, NH)
Anal. Calcd For	C,44.03; H, 6.42,
$C_8H_{14}N_2O_5$	
Found	C, 44.52; H, 6.28

Reaction of butyrolactim ether gave compound (**20 b**)

Methyl-4-amino-N(1-methoxy-2-nitroethenyl) butanoate(20 b)

Reaction time	72h
Nature	Thick brown liquid
Yield	25%
^{1}H NMR (δ)	1.82 (m, 2H, CCH_2), 2.26 (t, 2H, $COCH_2$), 3.35 (m, 2H, NCH_2), 3.55 (s,
($CDCl_3$)	3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.51 (s, 1H, =CH), 7.66 (bs, 1H, NH)
IR cm^{-1} (neat)	3380, 1740, 1620, 1430
Anal. Calcd For	C,44.03; H, 6.42,
$C_8H_{14}N_2O_5$	
Found	C, 44.52; H, 6.28

Reaction of was also done in water : MeOH (1:3) where reaction was complete in 24 h

4.6.2 : Reaction of lactim ether with CS_2

To the methanolic solution of caprolactim ether 10 mmol) carbondisulfide (20 mmol) was added and the reaction mixture was stirred at room temperature for 3-5 hrs. Reaction mixture was cooled down to 10°C and then methyl iodide (20 mmol) was added to it. Reaction temperature was maintained 10-20°C for 1/2 h Then allowed to come to room temperature. Solvent was removed under reduced pressure using rotavapour. Product formed was purified by column chromatography silica (60-120) using pet ether ethyl acetate (10:10).

Methyl6-aza-7,7 dimethylthio heptanoate (20a)

Nature	Yollow liquid
Yield	10 %
^{1}H NMR (δ)	1.60 (m, 2H, $6CH_2$), 2.15 (t, 2H,$COCH_2$), 2.28 (s, 3H, SCH_3),
($CDCl_3$)	2.75 (s, 3H, SCH_3), 3.35 (m, 2H, NCH_2), 3.68 (s, 3H, OCH_3).
IR cm^{-1} (neat)	3380, 1740, 1620, 1430
Anal. Calcd For	C,48.19; H, 7.63
$C_{10}H_{19}NO_2S_2$	
Found	C, 48.42; H, 7.43

4.7.3: Reaction of butyrolactim ether with ethyl (ethoxymethylene) acetoacetate and diethyl (ethoxymethylene) malonate.

To 10 mmol of ethyl (ethoxymethylene) acetoacetate or diethyl (ethoxymethylene) malonate. buterolactim ether (15 mmol) was added. Reaction mixture was heated to 100°C without any solvent. Product form does not show clear tlc. Reaction mixture was passed through short column of silica 60-120 using ethyl acetate. Removal of ethyl acetate at reduced pressure gave coupled product in 35-40% yield which was further purified by column chromatography on silica column (60-120) using 75:25 pet ether ethyl acetate

Methyl4-amino-N(2,2-biscarboethoxy ethenyl) butanoate(24)

Nature	Colourless liquid
Yield	40 %
IR cm^{-1} (neat)	3290, 2950, 1740, 1650, 1600
^1H NMR (δ)	1.25 (2t mix , 3H, CH_3), 1.95 (m, 2H, CH_2), 2.35 (t, 2H, $COCH_2$),
($CDCl_3$)	3.40 (m, 2H, $COCH_2$), 3.75 (s, 3H, OCH_3), 4.25 (m, 2H, OCH_2),
	8.00 (d, 1H, =CH), 9.2 (bs,1H,NH)
^{13}C NMR (δ)	1172.68, 169.01, 165.80, 159.81, 89.55, 59.48,
($CDCl_3$)	51.44, 30.37, 25.74, 14.11
Anal. Calcd For	C,54.35; H, 7.74.
$C_{13}H_{21}NO_6$	
Found	C,55.24; H,7.52

Methyl4-amino-N(2-acyl,2carboethoxy ethynyl) butanoate (26)

Nature	Colourless crystlline solid
Yield	30 %
M.P.	81-83 °C
IR cm^{-1} (neat)	3490, 3280, 1680, 1600
^1H NMR (δ)	1.30 (2t mix, H, $2CH_{3ethyl}$), 2.60 (m, 2H, $COCH_2$), 3.15 (t, 2H, NCH_2),
($CDCl_3$)	3.70 (s, 3H, OCH_3), 4.30 (m, 4H, $2OCH_2$), 8.00 (d, 1H, =CH),
	11.0 (bs, 1H, NH)

Anal. Calcd For	C, 56.03; H, 7.74.
$C_{12}H_{19}NO_5$	
Found	C, 57.00; H, 7.65

Reaction of butrolactim ether with *p*-toluenesulfonyl chloride

To the solution of buterolactime ether (10 mmol) in dichloromethane *p*-toluene sulfonyl chloride (10 mmol) was added. Reaction mixture was stirred at room temperature for 3 h. The dichloromethane was washed with 2 positions 10 ml water. Dichloromthane was pumped off at reduced pressure using rotary evaporator. Product form was purified by column chromatography (silica 60-120) using 12-15% ethyl acetate pet-ether mixture.

Methyl 4-(tosyl amino)butyrate

Nature of compound	Colorless crystalline solid
Yield	70 %
IR(cm^{-1}) (neat)	3400, 3300, 1740, 1610, 1470.
^1H NMR (δ)	1.68 (m, 2H,CH_2), 2.2 (t+s, 5H,$ArCH_3$&$COCH_2$),
($CDCl_3$)	2.80 (m, 2H, NCH_2), 3.52 (s, 3H, OCH_3), 4.5 (bs,1H,NH),
	7.2-7.6 (m,4H,ArH)
Anal. Cacld. For.	C,53.11; H, 6.31
$C_9H_{17}NO_4$	
Found	C, 53.76; H, 6.56.

4.8: References

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CHAPTER 5

FACILE RING-OPENING OF N-ACYL LACTAMS

Chapter 5

Facile Ring Opening of N-Acyl Lactams

5.1: Summary

This chapter discusses a facile acid catalyzed alcoholysis of N-activated lactams which resulted in opening of the lactam ring. N-Carbomethoxy lactams (**9a**) (**9b**) and (**9c**) underwent alcoholysis with complete regioselectivity (*Scheme 6*) giving N-carbomethoxymethylene esters (**10a-f**) in 65 to 95% yields. Similar methanolysis of the dithiocarbamate (**11a**) and N-tosyl-2-pyrrolidinone (**11b**) in presence of PTSA gave the ring opened compounds (**12a**) and (**12b**) in 86% and 76% yield respectively.

Use of nitrogen nucleophiles such as hydroxylamine and hydrazine did not give ring opened products; no reaction was noted. n-Butylamine, a primary amine gave ring opened compound (**13a**) in 90% yield without the use of catalyst. Secondary amines like diethylamine and diisopropylamine did not react with the N-activated lactam (**9a**). 2-Pyrrolidine gave the ring-opened product (**13b**) in good yield.

The above acid-catalyzed ring opening was generally carried out in presence of 1 mol% of PTSA. Ring-opening alcoholysis under the influence of Amberlite-15 (acid catalyst) or of NaOMe or KOH was not as effective as the PTSA-mediated reactions.

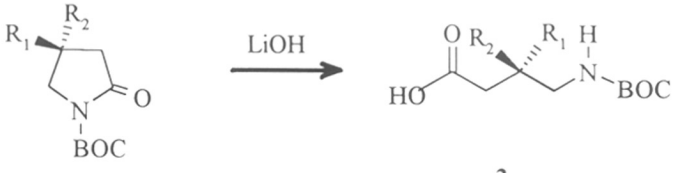
5.2: Introduction

The use of α-aminoacids as starting materials for the synthesis of enantiomerically pure compounds has been well documented. The single chiral center present in naturally occurring α-aminoacids provides a building block for asymmetric synthesis. (D) and (L) Glutamic acids have received much attention in recent times as the source for various chiral synthons.[1,2]

The major problem in the use of dicarboxylic acids such as glutamic acid is selective functionalization of one of the carboxylic acid groups. The differentiation between the two COOH groups could be achieved by established protection-deprotection protocols.[3] One of the most frequently employed techniques is to use pyroglutamate instead of glutamic acid derivatives. The lactam ring in pyroglutamic acid serves as an internal protecting group for the γ-carboxylic group. This permits easy differentiation of the two carboxyl moieties present in glutamic acid.

It is also known that the effective hydrolysis of the secondary amide group poses severe problems and requires special conditions[4].Zell et.al. have reported regioselective hydrolysis of N-*t*-butoxycarbonyl derivatives of lactams and amides by employing lithium hydroxide or sodium methoxide.[5] *(scheme1).*

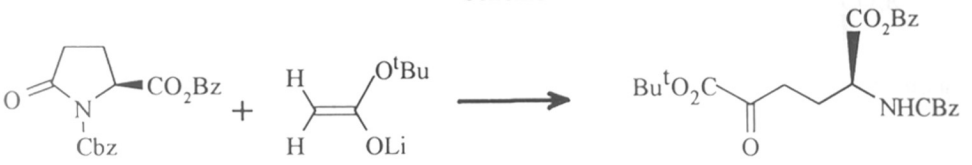
Scheme 1



1 **2**

Regioselective ring opening of the lactam also takes place on reaction with the lithium enolate of *t*-butyl ester to give the product (**4**) in excellent yield as shown in *scheme 2*.[6]

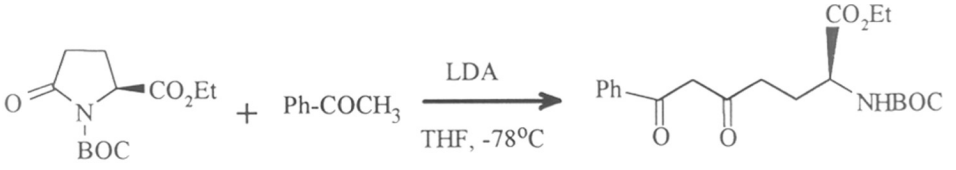
Scheme 2



3 4

N-*t*-Butoxycarbonyl protected ethyl pyroglutamate (**5**) also undergoes regioselective ring opening with various other nucleophiles without racemization of the chiral center as shown in *Scheme 3*.[7] N-Protected ester derivative **5** also undergoes ring opening reactions with Grignard reagents with an excellent regioselectivity.[8]

Scheme 3



5 6

Flynn et.al. have reported that N-*t* butoxycarbonyl-2-pyrrolidinone undergoes methanolysis in presence of sodium methoxide to provide the methyl ester of N-*t*-butoxycarbonyl γ-aminobutanoacid.[9] But it has also been recorded that chemoselectivity is not always maintained and that both the amide as well as the carbamate can be cleaved under these conditions.[10] Alcohols other than methanol have also been used for regioselective ring opening. The method uses KCN as a catalyst with complete regioselectivity and excellent yields.[11](*Scheme* 4)

Scheme 4

5 7

The reaction is slow (around 24h). A modification, using ultrasound to speed up the reaction has been used for the preparation of various mixed ω-diesters, ω-amides and ω-thioesters derived from glutamic acid and α-aminoadipic acid.[12]

5.3: Present work

The present work deals with facile ring opening of N-acylated lactams, using different nucleophiles under mild conditions. The nucleophiles include alcohols such as ethanol, methanol, isopropanol and cyclohexanol. The optimal reaction conditions were established for each of the alcohol tried. The yield was observed to be 85 to 95%. The lactam ring size has been varied to demonstrate the versatility of the procedure.

Different functional groups have been used to activate the lactam carbonyl towards nucleophilic attack. These include carbamate, dithiocarbamate and sulfonamide. Methanolysis of all these compounds was found to be highly regioselective.

These standard set of conditions were then applied to open the N-carbomethoxy pyrogluamate ring. High regioselectivity was observed in this case; but the yield of the acyclic product was found to be slightly low.

Different nitrogen nucleophiles were also tried. Hydroxylamine and hydrazine failed to open the lactam ring under different reaction conditions employed. Primary amines such as n-butyl amine reacted very fast at room temperature without any catalyst to give the acyclic compound in good yield. Open-chain secondary amines such as diethylamine and diisopropylamine did not lead to any reaction, but pyrrolidine reacted to give the ring opened product at 85°C.

Different catalysts such as PTSA, NaOMe Amberlite-15 and KOH were also studied; of these, PTSA gave the best results.

5.4: Results and Discussion

The electrophilicity of the lactam carbonyl is increased by N-acylation: imides are more electrophilic than amides. However, in such N-acyl lactams, the incoming nucleophile can attack either the ring carbonyl or the exocyclic carbonyl. In order to achieve regioselectivity in this reaction, earlier workers have consistently used the bulky N-tert-butoxycarbonyl group for activating the lactam carbonyl. The nucleophile prefers to attack the ring carbonyl for steric reasons. The reaction has been invariably carried out under basic conditions.

Our present results clearly show that under acidic conditions, regiospecific nucleophilic attack takes place on the lactam carbonyl; there is thus no need to employ the bulky t-BOC group on the lactam nitrogen.

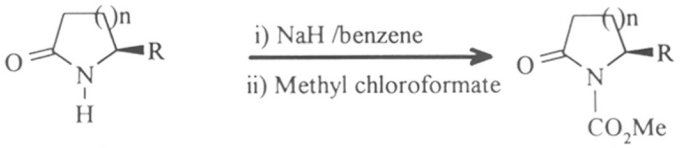
So far all the processes discussed for lactam ring opening employ either strong bases like, LiOH (1.5 eq), NaOMe (1 eq) or very strong nucleophiles such as lithium enolate or Grignard reagent. The only alcoholysis reported with lactam ring opening under neutral conditions uses KCN as the catalyst. The bulky N-BOC group is necessary for good regioselectivity in all these reported alcoholyses

We now report a facile acid catalyzed alcoholysis of 5-membered and 7-membered N-acyl and N-tosyl lactams. The N-carbomethoxy derivatives of 2-pyrrolidinone and methyl pyroglutamate were prepared by reported procedures.[13]

5.4.1: Synthesis of N-carbomethoxy lactams

The amide anion was first generated by means of NaH in benzene. This was then reacted with methyl chloroformate to give the compounds (**9a-c**) in 70-80% yield as shown in *Scheme 5*. The ^{1}H NMR spectra of compounds (**9a-c**) show a sharp singlet due to the methoxy group at 3.5-3.8δ which indicates the formation of the N-carbomethoxy derivative. This is also supported by the absence of the NH proton in the ^{1}H NMR spectra. The IR spectrum of (**9a**)shows carbonyl group absorption 1720 cm^{-1}. Similarly the IR spectrum of (**9b**) shows carbonyl stretching absorption at 1720 cm^{-1} whereas compound (**9c**) shows IR absorption at 1810, and 1720 cm^{-1} due to the presence of ester and carbamate.

Scheme 5



8 **9**

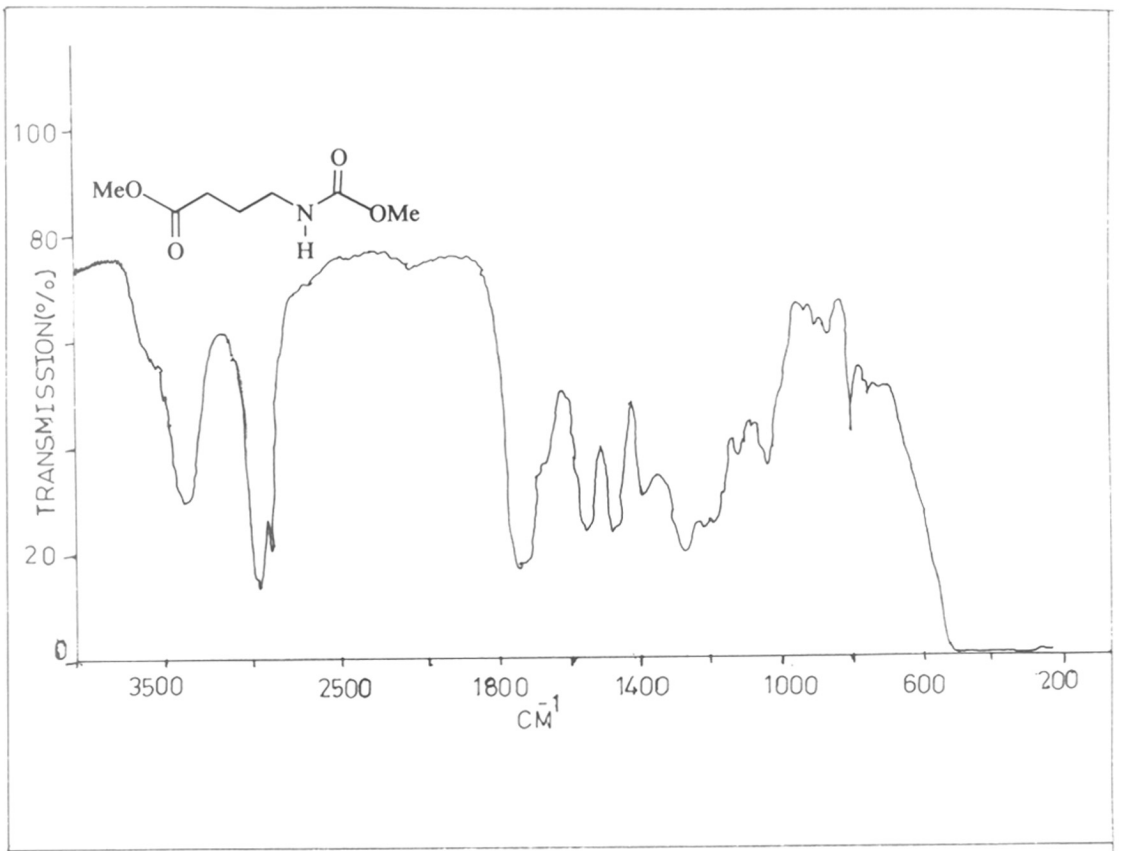
a : R = H n = 1
b : R = H n = 3
c : R = CO_2Me n = 1

5.4.2: Alcoholysis of N-carbomethoxy lactams 9a-c

The N-carbomethoxy-2-pyrrolidinone (**9a**) (1 mmol) was dissolved in methanol containing (0.1 mmol) of PTSA and stirred at room temperature for 36h. The reaction gave the lactam ring opened product (**10a**) in 94% yield. The ^1H NMR spectrum of compound (**10a**) shows two singlets at 3.60 and 3.65δ for two OMe groups. The $CO.CH_2$ protons appear as a triplet at 2.25δ followed by a triplet due to NCH_2 protons at 3.20δ . The central methylene group was observed as a multiplet at 1.85δ. A broad singlet at 4.95δ was assigned to the -NH proton. The IR spectrum shows carbonyl stretching at 1700 and 1740 cm^{-1}. The structure of compound (**10a**) was also confirmed by elemental analysis.

Similar reaction of (**9a**) with ethanol did not occur at room temperature. Heating the ethanolic solution of the N-carbomethoxy derivative (**9a**) with PTSA at 80 °C for 24 h gave the ring opened compound (**10b**) in 90% yield. The ^1H NMR spectrum of compound (**10b**) shows a quartet at 4.0δ and a triplet at 1.12δ due to the ethyl group. Other peaks were observed as in (**10a**).

Similar alcoholysis of (**9a**) with isopropanol at 80°C for 30h gave the ring-opened isopropyl ester (**10c**) in 89% yield. The alcoholysis of (**9a**) with cyclohexanol at 100 °C gave the compound (**10d**) in 88% yield. These are shown in *Scheme 6*. The ^1H NMR spectra of compounds (**10c**) and (**10d**) show NH proton around 5.0δ. Compound (**10c**) shows the isopropyl group as a doublet at 1.2δ (2 Me) and a multiplet at 5.1δ due to the $CH\text{-}Me_2$. The structure of compounds (**10c**) and (**10d**) was also confirmed by elemental analysis.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OMe
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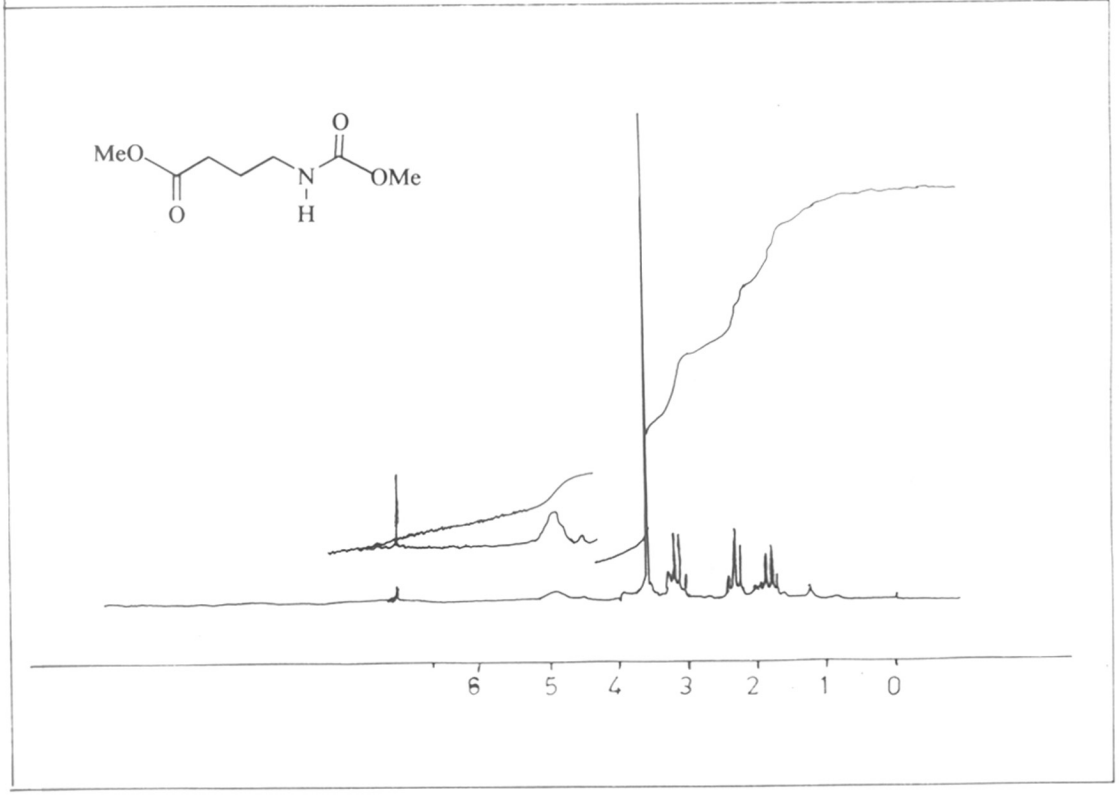
MeO
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The reaction of 1-carbomethoxyhexahydroazepin-2-one (**9b**) with methanol in presence of PTSA gave compound (**10e**) in 86% yield. The ^{1}H NMR spectrum of compound (**10e**) shows NH at 4.8 δ and two methoxy groups at 3.60δ as a single peak..

Scheme 6

9

a : R = H n = 1
b : R = H n = 3
c : R = CO_2Me n = 1

10

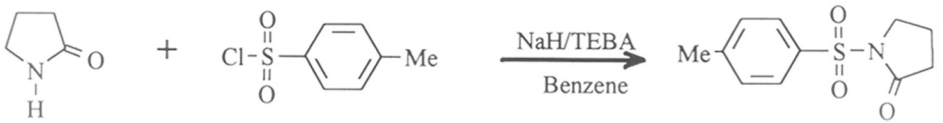
a : R = H R' =Me n = 1
b : R = H R' = Et n = 1
c : R = H R' = Pr^i n = 1
d : R = H R' = C_6H_{11} n = 1
e : R = H R' = Me n = 3
f : R =CO_2Me R' = Me n = 1

The substrate was then changed to methyl N-carbomethoxy pyroglutamate (**9c**). Methanolysis at 65°C gave the ring opened compound (**10f**) in 65% yield. The ^{1}H NMR spectrum of (**10f**) shows three methoxy groups, two at 3.65δ and the third one at 3.70δ. The NH proton was noted at 5.4δas a broad singlet. The IR spectrum shows carbonyl stretching absorption at 1710, 1730 and 1740 cm^{-1}.

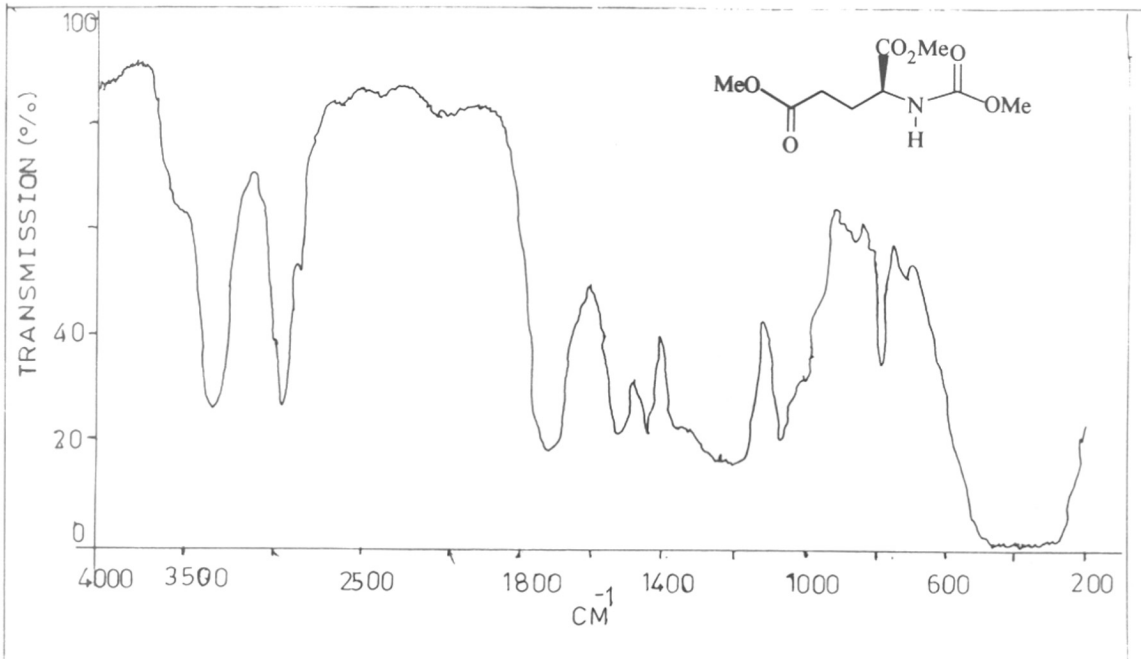
5.4.3: Synthesis of dithiocarbamate 11a and sulfonamide 11b.

Encouraged by the very high regioselecrivity in the alcoholysis of N-carbomethoxy lactams (**9a-c**), we decided to investigate the alcoholysis of lactams in which the nitrogen carries other electron withdrawing groups such as CS_2Me and SO_2Ar in place of the carbomethoxy group.

Scheme 7



11b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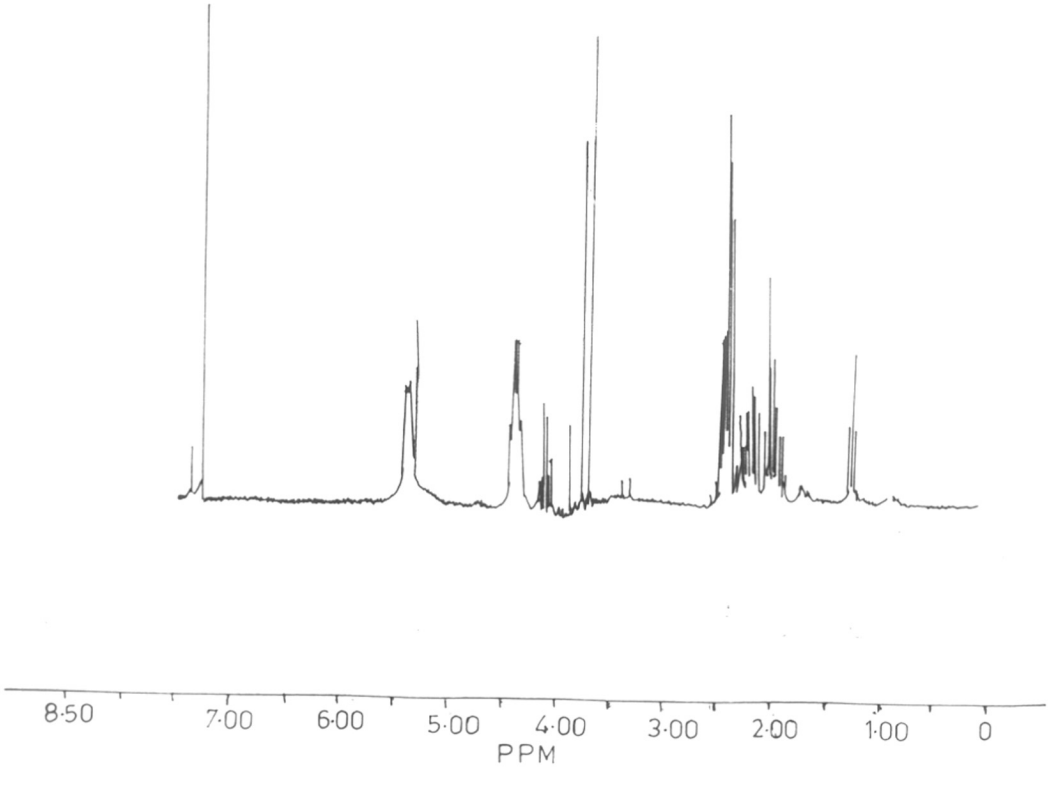
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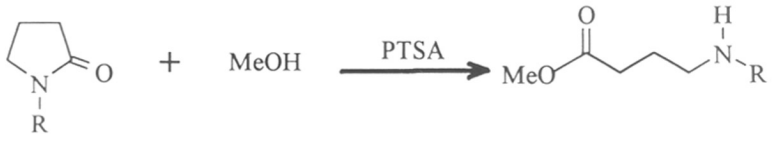
PPM

The dithiocarbamate (**11a**) was prepared by the reported method as discussed in *Chapter 3* (compound No. **9a**). Compound (**11b**) was prepared by reaction of 2-pyrrolidinone with *p*-toluenesulfonyl chloride in presence of tetra butyl ammonium iodide and NaH in 15% yield (*Scheme 7*). The ^{1}H NMR of compound (**11b**) shows the protons of the ring methylene groups at 1.8, 2.2 and 3.8δ δ. The Ar-CH_3 appears as a singlet at 2.25δ .

5.4.4: Alcoholysis of dithiocarbamate(11a) and sulfonamide (11b).

Compound (**11a**) on methanolysis at 65°C for 24 h in presence of PTSA gave the ring opened product **12a** in 86% yield. The ^{1}H NMR spectrum of compound **12a** shows $COCH_2$ at 2.2δ, and the central methylene at 1.88δ. The -SCH_3 protons appear at 2.25δ as a sharp singlet, whereas -NCH_2 appears as a multiplet merged with the singlet due to methoxy protons between 3.5δ and 3.8δ. The NH proton is seen at 7.8δ as a broad singlet. This is considerably downfield compared to the NH signal of the oxo compound (**10a**). The IR spectrum of compound (**12a**) shows the NH stretching at 3550 cm^{-1} and the ester carbonyl absorption at 1740 cm^{-1}. The structure of compound (**12a**) is also confirmed by elemental analysis.

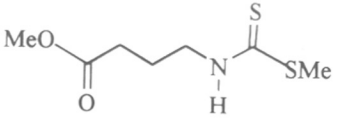
Scheme 8



11 **12**

a : R = CS_2Me
b : R = $SO_2C_6H_4$-Me

The N-tosyl lactam (**11b**) on methanolysis at 65°C for 24h gave the ring opened product (**12b**) in 70% yield (Shown in *Scheme 8*). The ^{1}H NMR spectrum of (**12b**) shows the central methylene at 1.68δ as a multiplet, Ar-CH_3 as a sharp singlet with a triplet for $COCH_2$ between 2.2 and 2.58δ. A multiplet at 2.8δ was assigned to the NCH_2 protons; NH appears as a broad singlet at 4.5δ whereas the most downfield ABquartet at 7.2-7.6δ are due to the aromatic protons of the tosyl group. The IR spectrum shows N-H stretching at 3400 cm^{-1} , The ester carbonyl absorption is observed at 1740 cm^{-1}. The structure of compound (**12b**) was also confirmed by elemental analysis.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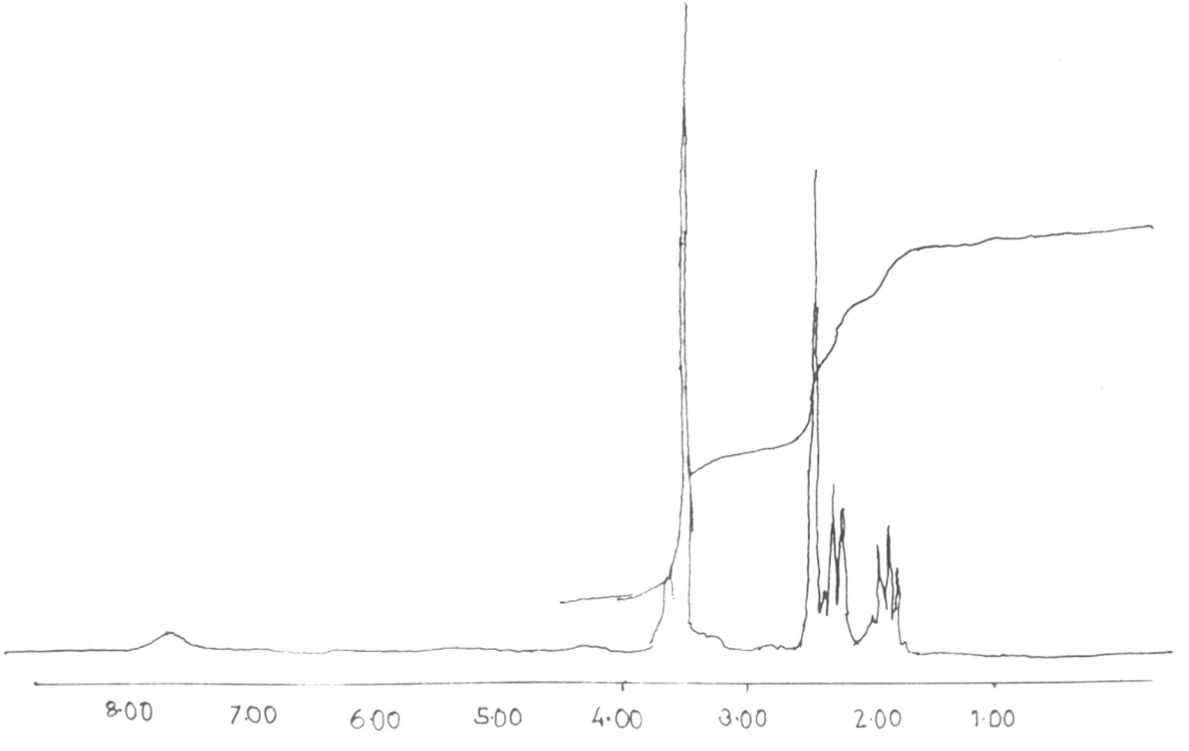
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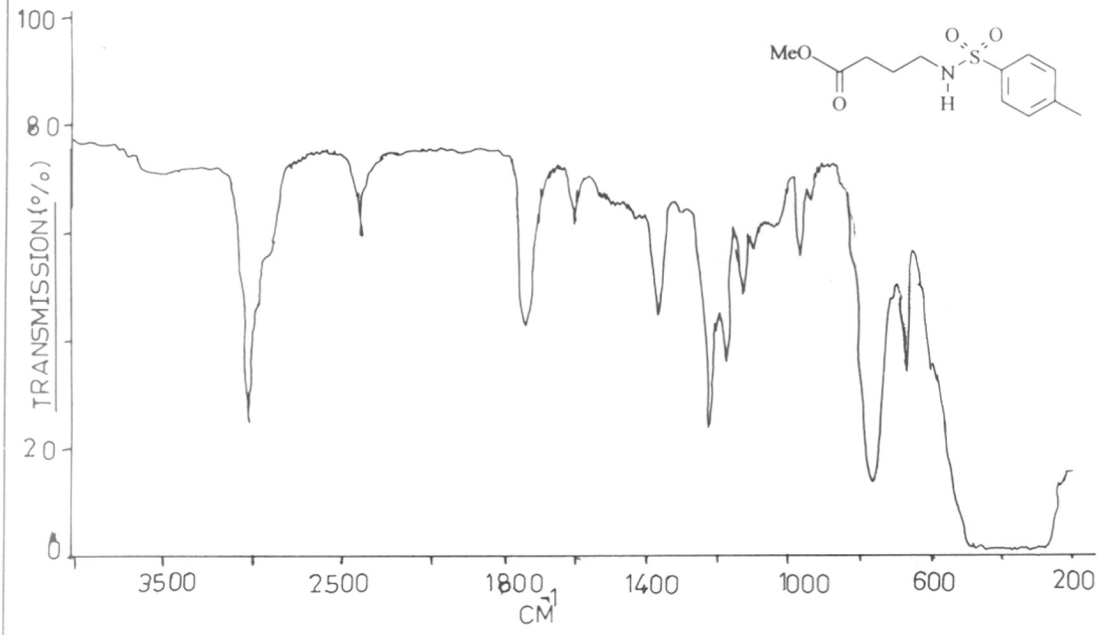
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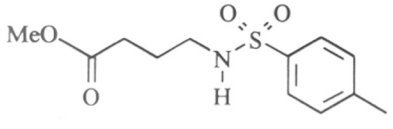
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5.4.5: Extension to other nucleophiles

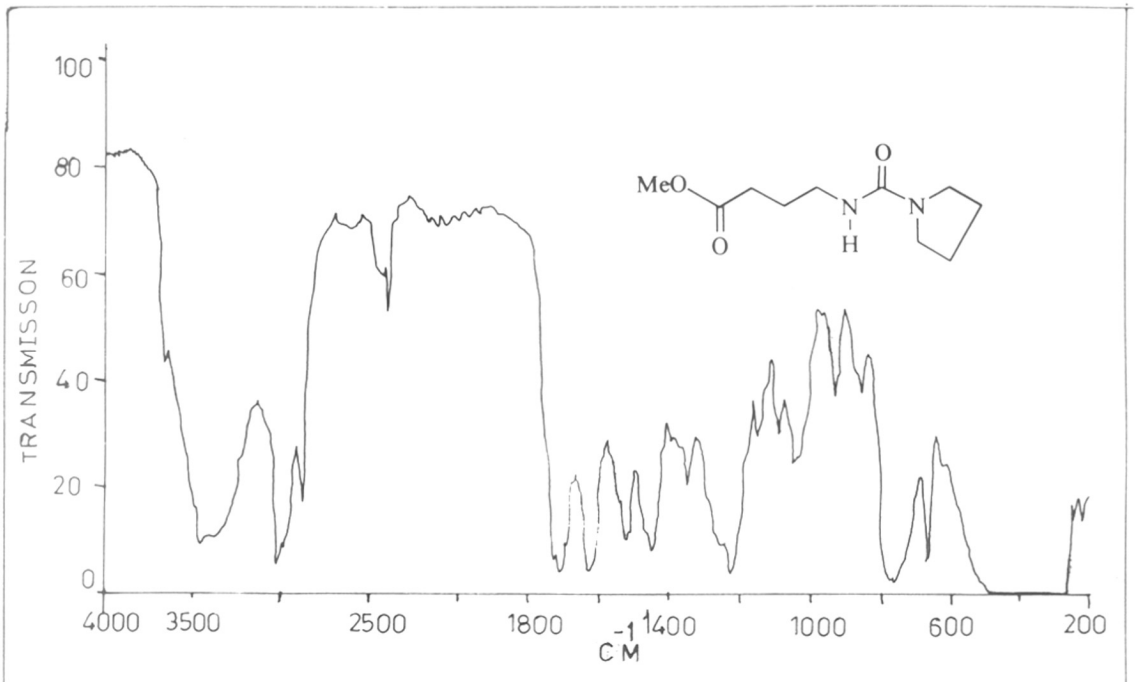
The next objective was to use nucleophiles other than alcohols under similar reaction conditions. Nitrogen nucleophiles such as hydroxylamine and hydrazine hydrate gave non-separable complex mixtures as products. n-Butylamine did not react with (**9a**) in acetonitrile under the usual PTSA catalysis conditions. Hence N-carbomethoxy-2-pyrrolidinone was treated with n-butylamine without any solvent. The reaction was complete in 30 min and gave the ring-opened product **13a** in 95% yield (*Scheme 9*).

Scheme 9

9a **13**

a : R_1 = $CH_3(CH_2)_3$- , R_2 = H
b : R_1 = R2 = -$(CH_2)_4$-

The excess n-butylamine was removed under reduced pressure and the product was purified by column chromatography on neutral alumina grade II with an 80:20 mixture of pet-ether, ethyl acetate as the eluent. The ^{1}H NMR spectrum of compound (**13a**) shows the methyl group at 0.9δ as a triplet followed by a multiplet for 6H due to three methylene groups, two from the butyl and one from pyrrolidinone moieties. The two NCH_2 protons appear as a complex multiplet at 3.2-3.4δ for 4H, methoxy protons appear as a clean singlet at 3.8δ and the two NH protons as broad singlets at 5.5δ and 6.3δ. The IR spectrum shows amide stretching at 1650 cm^{-1}. The structure of compound (**13a**) was also confirmed by elemental analysis. Secondary amines such as diisopropylamine and diethylamine did not react with the lacam **9a** in presence of PTSA at room temperature or at 80°C. The failure could possibly be due to the steric bulk of the nucleophiles. In contrast, pyrrolidine, a cyclic *sec* amine which is less bulky than diethylamine, reacted with (**9a**) to give the ring-opened compound (**13b**) in 76% yield. The^{1}H NMR spectrum of (**13b**) shows a multiplet for 8H at 1.6 -2.0δ followed by a triplet due to CH_2CO at 2.17 δ, two NCH_2 at 3.22δ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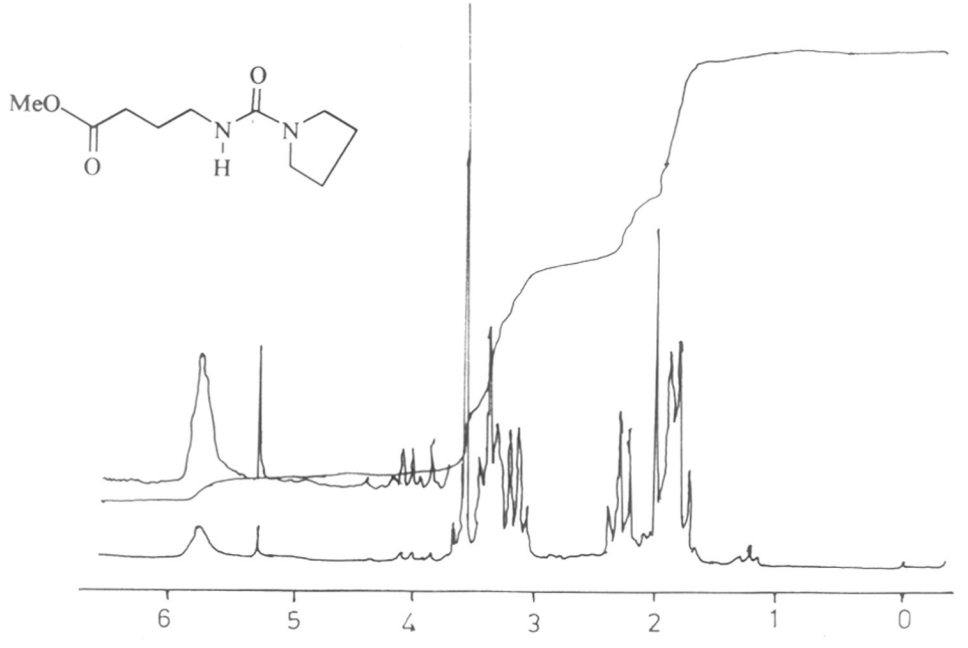
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OCH_3 at 3.55δ and NH as a broad singlet at 5.65δ. The IR spectrum shows amide stretching at 1620 and N-carbomethoxy carbonyl at 1710 cm^{-1}. The structure was further confirmed by elemental analysis.

Table 1

Conversion of Lactams to acyclic products : Summary of reaction conditions

Substrate	Nucliophile	Temp.°C	Time h	Product	Catalyst	Yield %
9a	MeOH	25	36	**10a**	PTSA	94
9a	EtOH	80	24	**10b**	PTSA	90
9a	Pr^iOH	80	30	**10c**	PTSA	89
9a	$C_6H_{11}OH$	100	24	**10d**	PTSA	88
9b	MeOH	65	22	**10e**	PTSA	86
9c	MeOH	65	24	**10f**	PTSA	65
11a	MeOH	65	24	**12a**	PTSA	86
11b	MeOH	65	24	**12b**	PTSA	70
9a	n-$BuNH_2$	25	0.5	**13a**	-	95
9a	2-pyrrolidine			**13b**	-	76
9a	MeOH	65	72	**10a**	Amberlite-15	20
9a	MeOH	25	3	**10a**	NaOMe	60
9a	EtOH	25	5	**10b**	KOH[a]	25

a : KOH was used in stiochiometric quantities

Our attempts to open N-acyl-2-pyrrolidinone with active methylene compounds such as nitromethane and ethyl acetoacetate in presence of bases like TEA or DBU were futile. We could not achieve C-C bond formation with concomitant lactam ring-opening. Use of ethanolic KOH in the attempted reaction with CH_3NO_2 led to compound **11a** in 30 % yield . The reaction conditions, Products and yield, are summarized in *Table 1*.

5.4.5: Use of different catalysts

P-Toluenesulfonic acid was found to be an effective catalyst for the alcoholysis of N-acyllactams. The use of an acidic ion exchange resin such as Amberlite-15 in place of PTSA can have two distinct advantages i) easy separation of the catalyst ii) reusability of catalyst. Attempted

methanolysis of N-carbomethoxy-2-pyrrolidinone (**9a**) using this resin, was unsuccessful at room temperature. At 65°C the reaction did occur but was extremely slow. The conversion was only 12-15% after 72h. Sodium methoxide was also found to be an effective catalyst for the methanolysis of (**9a**). The reaction was complete in 12h at room temperature. However, the yield of product (**10a**) in this base catalyzed reaction was only 60%. This may be due to partial cleavage of the N-acyl group. The treatment of (**9a**) with ethanolic KOH also gave the product (**10b**) of alcoholysis, but in very poor yield (25-30%) Moreover, stoichiometric quantities of KOH had to be used in this case.

5.5: Conclusions

i. *p*-Toluenesulfonic acid has been demonstrated to be an effective catalyst for the alcoholysis of N-acylated lactams. The optimised conditions have been employed for ring opening of N-acyl-pyroglutamate giving the corresponding acyclic product in 65% yield.

ii. Other N-acyl groups such as *p*-tosyl and $-CS_2Me$ have also been shown to be equally effective in giving rise to ring cleavage under acid-catalysed alcoholysis.

iii. Nitrogen nucleophiles such as primary and cyclic secondary amines are found to open the lactam ring with high regioselectivity.

iv. Amberlie-15 was found to be much less effective than PTSA for the ring-opening reaction. NaOMe and alcoholic KOH were found to be less selective; resulting thereby in poor yields of the product.

v. Our attempts to react acive methylene compounds with N-acyl lactams in order to create a new C-C bond with concomitant ring opening were futile.

5.6: Experimental

5.6.1: Synthesis of N-carbomethoxy-2-pyrrolidinone (9a)

2-Pyrrolidinone (1 mmol) was added slowly to the suspension of sodium hydride (50%) (1 m mol) in benzene at room temperature. The reaction mixture was stirred continuously. After completion of addition of 2-pyrrolidinon. Methyl chloroformate (1.2 mmol) was added to the reaction mixture. Reaction mixture was stirred at room temperature for 2 h. Normal aqueous workup and extraction in dichloromethane gave compound **9a**. It was further purified by column chromatography on 60-120 silica using pet-ether ethyl acetate (90:10).

Nature	Colorless viscous liquid
Yield	55 %
I.R. cm^{-1} (nujol)	3460, 2970, 1790, 1720
^{1} HNMR ($CDCl_3$)	2.1 - 2.8(m, 4H, CH_2), 3.66 (m, 2H, NCH_2) 3.83 (S, 3H, OCH_3)

N-Carbomethoxy caprolactam (9b)

Compound (**9b**) was synthesized in the similar way as compound (**9a**) except caprolactam was used in place of 2-pyrrolidinone.

Nature	Yellow Crystalline Solid
M.P.	120 -122 °C
Yield	44 %
I.R. cm^{-1} (nujol)	3470, 2970, 1790, 1720
^{1}H NMR ($CDCl_3$)	1.68 (m, 8H), 2.70 (m, 4H, NCH_2, $C{=}OCH_2$), 3.92 (s, OCH_3, 3H)

Methyl N-Carboxymethyl pyroglutamate (9c)

compound (**9c**) was prepared in the same way as (**9a**) using methyl pyroglutamate.

Nature	Yellow Crystalline Solid
Yield	33%
I.R. cm^{-1} (CCl_4)	2980, 1810, 1770, 1720, 1550

^{1}H NMR	1.96 - 2.75 (m, 4, CH_2), 3.70 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3),
($CDCl_3$)	4.64 (m,1H, NCH)

5.6.2: Alcoholysis of N-acylated Lactams

General Procedure

The solution of N-acyl lactam (1 mmol) in appropriate alcohol containing (0.1 m mol) of *p*-toluene sulfonic acid, was stirred at the given temperature(varies from 30°C-100°C) for 12 to 36h. The course of reaction was monitored by tlc. After completion of reaction the solvent was removed at reduced pressure at rotary evaporator. The ring cleaved product **11 (a-g)** was purified by column chromatography on alumina grade II with pet ether ethyl acetate 90:10

Methyl 4-(carbomethoxy amino) butyrate (10a)

Reaction temperature	25 °C
Reaction time	36 h.
Nature of compound	viscous liquid
Yield	94 %
IR(cm^{-1}) (neat)	2940, 1700, 1740, 1630.
^{1}H NMR (δ)	1.8 (m, 2H,CCH_2), 2.25 (t, 2H, CO CH_2), 3.20(t, 2H, N CH_2),
($CDCl_3$)	3.60 (s, 3H, OCH_3), 3.65 (s, 3H, CH_3), 4.95 (bs, 1H, NH),
Anal. Cacld. For.	C,48.0; H,7.40; N,8.0
$C_7H_{13}NO_4$	
Found	C,48.30; H,7.57; N,7.73.

Ethyl 4-(carbomethoxy amino) butyrate (10b)

Reaction temperature	80 °C
Reaction time	24 h.
Nature of compound	viscous liquid
Yield	90 %
IR(cm^{-1}) (neat)	3490, 3380, 3000, 2980, 1750, 1730, 1530 .
^{1}H NMR (δ)	1.12 (t, 3H,CH_3), 1.68 (m 2H, CCH_2), 2.15(m, 4H, CCH_2&$COCH_2$),
($CDCl_3$)	3.10 (m, 2H, NCH_2), 3.48 (s, 3H, OCH_3), 4.00 (q, 2H, OCH_2),
	5.05 (bs,1H, NH)

Anal. Cacld. For.	C,50.79; H, 7.93
$C_8H_{15}NO_4$	
Found	C, 50.80; H, 8.30.

Isopropyl 4-(carbomethoxy amino) butyrate (10c)

Reaction temperature	80 °C
Reaction time	30 h.
Nature of compound	Colorless viscous liquid
Yield	89 %
IR(cm^{-1}) (neat)	3400, 3300, 1750, 1740.
^1H NMR (δ)	1.20 (d, 6H,$2CH_3$), 1.8 (m 2H, CCH_2), 2.20(t, 2H, $COCH_2$),
($CDCl_3$)	3.20 (m, 2H, NCH_2), 3.60 (s, 3H, OCH_3),
	5.00 (m+bs, 2H, $OCH_{,\&}NH$).
Anal. Cacld. For.	C,53.20; H, 8.37
$C_9H_{17}NO_4$	
Found	C, 53.31; H, 8.75.

Cyclohexyl 4(carbomethoxy amino)butyrate (10d)

Reaction temperature	100 °C
Reaction time	24 h.
Nature of compound	Colorless viscous liquid
Yield	88 %
IR(cm^{-1}) (neat)	3300, 2890, 1750, 1730.
^1H NMR (δ)	1.20-2.0 (m, 8H), 3.40(m, 2H, NCH_2), 3.6 (s 3H, OCH_3),
($CDCl_3$)	3.20 (m, 2H, NCH_2), 3.60 (s, 3H, OCH_3), (bs, 1H, NH).
Anal. Cacld. For.	C,59.25; H, 8.64
$C_{12}H_{21}NO_4$	
Found	C, 60.10; H, 8.72.

Methyl 4(carbomethoxy amino)hexanoate (10e)

Reaction temperature	100 °C
Reaction time	24 h.

Nature of compound	Colorless viscous liquid
Yield	88 %
IR(cm^{-1}) (neat)	3300, 2890, 1750, 1730.
^1H NMR (δ)	1.20-2.0 (m, 8H), 3.40(m, 2H, NCH_2), 3.6 (s 3H, OCH_3),
($CDCl_3$)	3.20 (m, 2H, NCH_2), 3.60 (s, 3H, OCH_3), (bs, 1H, NH).
Anal. Cacld. For.	C,59.25; H, 8.64
$C_{12}H_{21}NO_4$	
Found	C, 60.10; H, 8.72.

Methyl N-Carbomethoxy -(S)-glutamate (10f)

Reaction temperature	65 °C
Reaction time	22 h.
Nature of compound	Colorless viscous liquid
Yield	86 %
IR(cm^{-1}) (neat)	3340, 2780, 1740, 1730, 1710.
^1H NMR (δ)	2.45 (m, 4H,$COCH_2$&CCH_2,), 3.65(2s, 6H, $2OCH_3$),
($CDCl_3$)	3.70 (s 3H,OCH_3), 4.40 (m,1H,αCH), 5.4 (bs,1H,NH).

5.6.3a: Synthesis of Methyl-2-pyrrolidinone-1-carbodithioate (11a)

This compound was synthesized by the reported procedure with some modifications. To a solution of 2-pyrrolidinone (6g, 071mmol) in dimethylsulfoxide (30 ml) carbon disulfide (6g, 079 mol) was added at room temperature. Aqueous 33% KOH (12 ml) was added below 35°C after stirring for additional 1/2 an hour, methyl iodide (0.08 mol) was added at 10°C. Reaction mixture was allowed to attain room temperature and stirred at room temperature for 1h. Reaction mixture was then poured in ice cold water and solid product was separated by filtration. Further purified by recrystallisation from rectified sprit.

Nature of compound	Light yellow crystalline solid
Yield	15 %
M.P.	96-98 °C
IR cm^{-1} (mujol)	1760, 1470, 1390

^{1}H NMR (δ)	2.15 (m, 2H, CCH_2), 2.60 (s, 3H, SCH_3),
($CDCl_3$)	2.75 (t, 2H, CO-CH_2), 4.4 (t, 2H, NCH_2)
^{13}C NMR ($CDCl_3$)	17.26, 20.35, 33.53, 53.73, 173.09, 202.26
Mass m/z	175 (M+, 100%)

5.6.3b: N-tosyl-2-pyrrilidinone (11b)

To the supention of NaH (50%,1 mmol) in benzene 2-pyrrolidinone (1 mmol) was added slowly. *p*-Toluenesulfonyl chloride (1 mmol) was then added to the reaction mixture. Tetrabututyl ammonium iodide was also added in catalytic quantity. Reaction mixture was stirred for 3 h at room temperature solvent was removed at rotavapour under reduced pressure. Product was purified by column chromatography on (10-120) silica column using pet-ether ethyl acetate 90:10 to give compound **11b.**

Nature	Yellow Crystalline Solid
M.P.	120 -122 °C
Yield	15 %
I.R. cm^{-1} (nujol)	3280, 3000, 1750, 1620, 1480.
^{1}H NMR (δ)	2.00 (m,2H,CH_2), 2.36-2.50 (t+s, 5H,$ArCH_3$&C=OCH_2),
($CDCl_3$)	3.88 (t,2H,NCH_2), 7.2 (ABq,4H, ArH)

5.6.4a: Methyl 4-(methyl carbodithioate amino) heptanoate (12a)

The solution of N-thioacyl lactams (1 mmol) in methanol containing (0.1 m mol) of *p*-toluene sulfonic acid, was stirred at the 65°C for 24 h. The course of reaction was monitored by tlc. After completion of reaction the solvent was removed at reduced pressure at rotary evaporator. The ring cleaved product **12a,** which was further purified by column chromatography on alumina grade II with pet ether ethyl acetate 90:10

Nature of compound	Yellow viscous liquid
Yield	86 %
IR(cm^{-1}) (neat)	3550, 1740, 1530, 1510, 1450.
^{1}H NMR (δ)	1.80 (m, 2H,CH_2), 2.2 (t, 2H,$COCH_2$), 2.24 (s 3H, SCH_3),
($CDCl_3$)	3.5-3.8 (m+s, 5H, OCH_3&NCH_2), 7.8 (bs,1H,NH).

Anal. Cacld. For.	C,40.55; H, 6.35
$C_9H_{17}NO_4$	
Found	C,40.90; H, 6.55.

5.6.4b: Methyl 4 (tosyl amino) butyrate (12b)

The solution of N-tosyl2-pyrilidinone (1 mmol) in methanol containing (0.1 m mol) of *p*-toluene sulfonic acid, was stirred at the room temperature for 24 h. The course of reaction was monitored by tlc. After completion of reaction the solvent was removed at reduced pressure at rotary evaporator. The ring cleaved product **12a,** which was further purified by column chromatography on alumina grade II with pet ether ethyl acetate 90:10

Nature of compound	Colorless crystalline solid
Yield	70 %
IR(cm^{-1}) (neat)	3400, 3300, 1740, 1610, 1470.
^1H NMR (δ)	1.68 (m, 2H,CH_2), 2.2 (t+s, 5H,$ArCH_3$&$COCH_2$),
($CDCl_3$)	2.80 (m, 2H, NCH_2), 3.52 (s, 3H, OCH_3), 4.5 (bs,1H,NH),
	7.2-7.6 (m,4H,ArH)
Anal. Cacld. For.	C,53.11; H, 6.31
$C_9H_{17}NO_4$	
Found	C, 53.76; H, 6.56.

5.7.5a: N-Butyl(4-carbomethoxyamino) butyramide (13a)

N-carbomethoxy-2-pyrrolidinone (1 mmol) was mixed with 2 (mmol) of butylamine and stirred for 30 min. After completion of reaction excess of butyl amine was pumped off . The product obtained was further purified by column chromatography using alumina grade II, pet ether ethyl acetate (80:20).

Nature of compound	Colorless viscous liquid.
Yield	95 %
IR(cm^{-1}) (neat)	3280, 3340, 1710, 1650.
^1H NMR (δ)	0.9 (t, 3H,CH_3), 1.2 -1.8 (m,6H,3CCH_2), 2.0-2.3 (t,2H,NCH_2), 3.25
($CDCl_3$)	(m, 4H,$COCH_2$), 3.8 (s, 3H, OCH_3), 5.5 (bs,1H,NH), 6.3(bs,1H,NH)

Anal. Cacld. For.	C,55.55; H, 9.25; N,12.95
$C_{10}H_{20}N_2O_3$	
Found	C, 55.34; H, 9.26; N, 12.63.

5.6.5b: Pyrrolidine (4-carbomethoxy amine)butyramide (13b)

N-Carbomethoxy-2-pyrrolidone (1 mmol) was mixed with (2 mmol) of pyrrolidine and heated to 85°C for 10h. After completion of reaction produt was purified by column chromatography on neutral alumina grade II column by pet-ether ethyl acetate (80:20).

Nature of compound	Colorless viscous liquid.
Yield	70 %
IR(cm^{-1}) (neat)	3300, 2970, 1710, 1620.
^1H NMR (δ)	1.65-2.00 (m, 8H,4CH_2), 2.17 (t,2H,$COCH_2$), 3.25 (m,6H,3NCH_2),
($CDCl_3$)	3.55 (s, 3H, OCH_3), 5.65 (bs,1H,NH)
Anal. Cacld. For.	C,56.07; H,8.41
$C_{10}H_{18}N_2O_3$	
Found	C,55.85; H,8.46.

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PUBLICATIONS

1. Facile Acid Catalyzed Ring Cleavage of N-Acylated Lactams

   Arun.N.Dixit, Sagun K.Tandel and Srinivasachari.Rajappa, **Tetrahedron Lett.**, 1994, **35**, 6133

2. Conformational Preferences of α-Functionalised Keten-S,N-acetals: Potential role of S..O and S..S Interactions in Solution

   Arun N.Dixit, K.Venodhar Reddy, Abdul Rakeeb A.S.Deshmukh, Srinivasachari Rajappa, Biswajit Ganguly, and Jayaraman Chandrasekhar, **Tetrahedron,** 1995**, 51,** 1437

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Facile Acid Catalyzed Ring Cleavage of N-Acylated Lactams#

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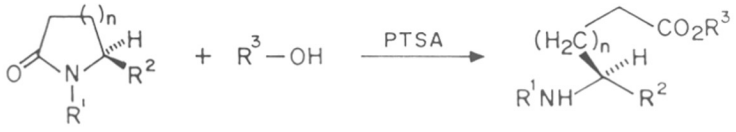
*Abstract : N-Alkoxycarbonyl and N-arylsulfonyl lactams (**1a - e**) were prepared and converted to the corresponding acyclic products (**2a - h**) by acid catalyzed cleavage of the lactam ring in good yields and excellent regioselectivity.*

The designing of a method for the hydrolysis of lactams under mild conditions has been an objective of several investigations in the last few years.[1-5] Most of the solutions to this problem have depended on the preliminary activation of the carbonyl (rendered more electrophilic) by N-alkoxycarbonylation of the lactam. In the resulting -CO-N-CO-O-R unit, attack by HO^- or MeO^- takes place preferentially at the lactam carbonyl (more electrophilic than the urethane carbonyl). However, the regioselectivity also depends to some extent on the bulk of the R group; the *tert*-butoxycarbonyl group gives the best results.[1] The scope of the reaction is therefore rather restricted. N-Tosyl derivatives of pyrrolidones (including pyroglutamic acid tert-butyl ester[6]) have been successfully cleaved by NaOH or LiOH.[6,7] We now report a versatile *acid catalyzed* ring opening of lactams in which the nitrogen atom is linked to -COOMe, -CSSMe or $-SO_2Ar$; the reaction proceeds under mild conditions and acyclic products are obtained in good to excellent yields. 2-Pyrrolidone was converted to the N-carbomethoxy derivative (**1a**) by treatment with sodium hydride followed by methyl chloroformate.[8] A solution of this (1 mmole) in methanol containing p-toluenesulfonic acid (PTSA) (0.1 mmole) was stirred at 25°C for 36 h. Evaporation of the solvent, followed by chromatographic purification (alumina, grade II; pet.ether - ethyl acetate) gave the ring opened product **2a** in 94% yield. There was thus no necessity of introducing the bulky *t*-Boc group in the first step.



	R^1	R^2	n
a :	-COOMe	H	1
b :	-COOMe	H	3
c :	-CSSMe	H	1
d :	-Ts	H	1
e :	-COOMe	-COOMe	1

	R^1	R^2	R^3	n
a :	-COOMe	H	Me	1
b :	-COOMe	H	Et	1
c :	-COOMe	H	^{i}Pr	1
d :	-COOMe	H	C_6H_{11}	1
e :	-COOMe	H	Me	3
f :	-CSSMe	H	Me	1
g :	-Ts	H	Me	1
h :	-COOMe	-COOMe	Me	1

Acyclic compounds (**2b, c, d**) were generated in equally good yields by the use of the appropriate alcohol in the ring opening reaction. The N-acylated lactams (**1b** to **1e**) were prepared similarly and converted to the corresponding acyclic products (**2e** to **2h**) in good yields and excellent regioselectivity (***Table 1***). No cleavage of carbamate or dithiocarbamate was observed under these acid catalyzed conditions.[9]

Table 1

Conversion of Lactams (**1**) to acyclic products (**2**)

Substrate	R^3OH	Temp °C	Time (h)	Product[a]	Yield(%)
1a	MeOH	25	36	**2a**[11]	94
1a	EtOH	80	24	**2b**[10]	90
1a	i-PrOH	80	30	**2c**[10]	89
1a	$C_6H_{11}OH$	100	24	**2d**[10]	88
1b	MeOH	65	22	**2e**[11]	86
1c	MeOH	65	24	**2f**[12]	86
1d	MeOH	65	24	**2g**[13]	70
1e	MeOH	65	24	**2h**[14]	65[b]

a : All the products, except **2g** (m.p.89°C) were liquids or gums. b : $[\alpha]_D$: + 7.65 (Partial recemisation might have occurred during the preparation of **1e**.)

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NCL communication No. 5988

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9. We have found that the reaction could also be carried out using sodium methoxide as the catalyst (1 mole %); however, the yield of the product in the base-catalysed reaction was only 60 %, perhaps due to partial cleavage of the N-acyl group.
10. Satisfactory analytical values were obtained for all new compounds.
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Conformational Preferences of α-Functionalised Keten-S,N-acetals: Potential role of S..O and S..S Interactions in Solution

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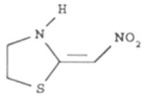
Abstract: PMR spectra of carbonyl compounds **2a-k** reveal significant variations in the population of *E* and *Z* isomers on changing the solvent from $CDCl_3$ to DMSO-d_6. In non-polar media, the intramolecular N-H....O hydrogen bonded form is exclusively observed. In DMSO-d_6, the alternative *Z* form is also populated. A similar conformational switch is also noted in the corresponding thiones. Different interpretations are critically analysed. The most consistent explanation is suggested to involve an interplay of N-H....X hydrogen bonding and S...X attractive interaction (X = O,S) in these systems. Ab initio calculations support this interpretation.

In earlier papers [1,2] we had reported an intriguing solvent-dependent conformational equilibrium in the nitro derivative **1**. In non-polar solvents, **1** was shown to exist exclusively in the intramolecular H-bonded *E*-conformation. However, on increasing the solvent polarity, the *Z*-form was also populated, with two sets of peaks being seen simultaneously in ^1H, ^{13}C and ^{15}N NMR spectra. The *Z*:*E* ratio in DMSO-d6, the solvent of maximum polarity studied, was 4:1. The solid state structure of **1** as determined by X-ray diffraction corresponds to **1**-*Z*. Interestingly, the structure revealed a short S..O contact of 2.68Å (sum of the van der Waals radii: 3.2 Å), suggesting a possible role for an attractive interaction between the atoms in determining the conformational equilibrium changes. In a preliminary study, we had shown that a similar solvent-dependent *E*/*Z* change occurs in the carbonyl derivative **2b** as well[2].

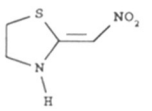
In the present article we establish the generality of the conformational behaviour for a number of carbonyl derivatives, **2a-k**. Various explanations for the observed population differences are discussed and evaluated using data obtained for the related models **9-12**. The conformational study has also been extended to the thione derivatives **7**. A consistent interpretation for all the observed results is provided with supportive ab initio calculations on model systems.

Synthesis

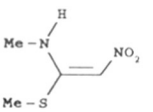
The enaminoketones **2** were prepared by using either one of the two known routes :(a) Condensation of an α-haloketone with a cyclic dithiocarbamate, followed by sulfur extrusion[3] or (b) condensation of an acylketen dithioacetal with the appropriate amimoalcohol or aminothiol[4]. The methyl ketone **2h** was prepared by the second method, using acetylacetone as the starting material; final mono deacetylation yielded **2h**[4]. Lawesson thionation of the enaminoketones led to the thioacylketen S,N-acetals[23].



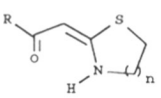
1 (E)



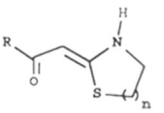
1 (Z)



(3)



2 (E)



2 (Z)

	R	n
a:	Ph	1
b:	4-Cl-C_6H_4	1
c:	4-MeO-C_6H_4	1
d:	4-NO_2-C_6H_4	1
e:	2-HO-C_6H_4	1
f:	2-MeO-C_6H_4	1
g:	2-Cl-C_6H_4	1
h:	Me	1
i:	Ph	2
j:	2-HO-C_6H_4	2
k:	2-MeO-C_6H_4	2

Results and Discussion.

E/Z equilibria in carbonyl compounds 2.

The IR spectrum of **2a** in $CHCl_3$ exhibits concentration-independent bands at 3210 and 1610 cm^{-1} for the NH and CO stretching modes respectively. This proves that in $CHCl_3$, **2a** exists in the intramolecularly H-bonded *E* configuration. The ^1H NMR spectrum of this compound in $CDCl_3$ at 20°C exhibits sharp signals characteristic of a single conformer (*E*). On addition of DMSO-d6 to this solution, signals corresponding to the (*Z*) isomer appear. The population of the (*Z*) isomer increases with increasing DMSO-d6 content, reaching nearly 40% in pure DMSO-d6. This behaviour is reminiscent of that of **1**, although in that case, the proportion of the *Z* conformer in DMSO-d6 reached 80%. The assignment of the peaks in pure $CDCl_3$ and DMSO-d6 to the *E* and *Z* isomers of **2** is shown in Table 1. The large chemical shift difference for **NH** between the intramolecular H-bonded *E* configuration and the *Z* form is noteworthy. The *para* substituted compounds **2b, 2c** and **2d** as well as the *ortho*-hydroxy derivative **2e** and the methyl ketone **2h** behave in a similar manner. However, in the case of *o*-methoxyphenyl **2f** and *o*-chlorophenyl **2g** derivatives, there is considerable line-broadening in DMSO-d6 solution, although the peaks are sharp in $CDCl_3$. The *E/Z* ratios of **2a-2e** and **2h** in DMSO-d6 are shown in Table 2. The ratio varies over a narrow margin.

Table 1

^{1}H NMR Chemical shifts (δ) for Compound **2**

Compd		NH		=CH		NCH_2		SCH_2	
		E	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
2a	$CDCl_3$	10.55	-	5.90	-	3.90	-	3.20	-
	DMSO-d6	10.40	8.00	6.00	6.30	3.90	3.59	3.30	3.10
2b	$CDCl_3$	10.55	-	5.90	-	3.90	-	3.20	-
	DMSO-d6	10.50	8.40	5.90	6.20	4.00	3.85	3.30	3.05
2c	$CDCl_3$	10.60	-	6.00		3.95		3.30	-
	DMSO-d6	10.33	8.30	6.00	6.33	3.90	3.60	3.10	3.20
2d	$CDCl_3$	10.80	-	5.90	-	4.00	-	3.30	-
	DMSO-d6	10.50	8.75	6.30	6.05	3.90	3.65	3.65	3.40
2e	$CDCl_3$	10.25	-	6.00	-	4.00	-	3.30	-
	DMSO-d6	10.20	8.95	6.00	6.40	3.80	3.65	3.30	3.15
2f	$CDCl_3$	10.60	-	5.90	-	3.95	-	3.25	-
	DMSO-d6	10.25	8.30	**	**	**	**	**	**
2g	$CDCl_3$	10.60	-	5.70	-	4.05	-	3.35	-
	DMSO-d6	10.25	8.60	**	**	**	**	**	3.10
2h	$CDCl_3$	10.90	-	5.30	-	3.85	-	3.20	-
	DMSO-d6	9.90	8.10	5.20	5.60	3.80	3.50	3.20	3.00
2i	$CDCl_3$	12.45	-	5.75	-	3.55	-	3.20	-
	DMSO-d6	12.15	-	5.75	-	3.45	-	3.10	-
2j	$CDCl_3$	11.75	-	5.75	-	3.55	-	3.15	-
	DMSO-d6	11.90	-	5.75	-	3.50	-	3.10	-
2k	$CDCl_3$	12.35	-	5.70	-	3.50	-	3.05	-
	DMSO-d6	12.05	-	5.50	-	3.40	-	3.10	-

** :- Line broadening

There is no significant difference in the behaviour of **2c** (*E*:*Z* = 65:35) and **2d** (*E*:*Z* = 56:44). Thus, the electronic nature of the substituents on the phenyl ring has no influence on the relative population of the two isomers. The higher population of (*Z*) isomer in the case of **2e** is to be expected, since it can still avail itself of an intramolecular H-bond with the phenolic OH being the donor.

Molecular geometry seems to play a crucial role in determining the magnitude of solvent induced shift of conformational equilibrium. This is obvious from a comparison of the two benzoyl derivatives **2a** and **2i**. The former has a 5-membered hetero ring as part of the keten-S,N-acetal, while the latter has a 6-membered ring. The thiazolidine derivative **2a**, as mentioned above, exhibits solvent dependent conformational change. In contrast, the thiazine derivative **2i** shows only one sharp set of peaks in both $CDCl_3$ and DMSO-d6. In all these cases, the *E*-configuration is assigned, based on IR spectral data and the chemical shift of the NH in the ^{1}H NMR spectrum. The NH signal in the thiazine is seen further downfield than in the thiazolidine derivatives; this may indicate a stronger intramolecular H-bond in the former. The comparison of the *ortho*-hydroxyphenyl derivatives **2e** and **2j** brings out the dramatic effect of changing the hetero-ring size. While in the former, in DMSO-d6 solution, the *Z*-conformer is populated to the extent of 52%, with the thiazine analog **2j**, the *Z*-isomer is not observable at all.

Table 2

E/Z ratio in DMSO-d6

Compound	*E*	*Z*
2a	62	38
2b	65	35
2c	65	35
2d	56	44
2e	48	52
2h	59	41
2i	<95	>5
2j	100	-
2k	100	-

The important conclusion therefore emerges that the relative energy of the *E* and *Z* isomers in **2** is critically dependent on the geometry of the molecule and especially on the local alignment at S and O. A similar observation had been made earlier with the nitro compounds.[2] An entropic price apparently has to be paid for orienting the molecule in the proper geometry. The open-chain analog **3**[5] which has freedom of rotation around the N-CH_3 and S-CH_3 bonds, also prefers to remain in the *E* form in polar and nonpolar solvents.

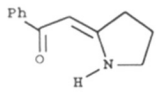
Factors influencing E/Z ratios

In push-pull ethylene systems, such as those present in **1**, **2** and **3**, the barrier to rotation around the formal C-C double bond is considerably reduced[6]; typically, this could be of the order of 10-15 kcal. $mole^{-1}$. Interconversion of *E* and *Z* isomers should occur readily under the conditions studied experimentally. Hence the relative populations of conformers directly reflect their stabilities. As noted above, both **1a** and **2a** exist exclusively in the intramolecular hydrogen-bonded *E* form in non-polar solvents, while in polar solvents there is a significant population of the *Z*- conformer.

Three possible explanations can be considered for the increased stability of the Z-isomers in polar solvents.

i) Solvent effect

It is known that the barrier to rotation around the C-C double bond in push-pull systems decreases in solvents of high dielectric constant. Along with this, the difference in energy between *E* and *Z* forms also decreases with increasing solvent polarity.[6,8] There may therefore be an increase in the population of the isomer with greater charge separation, viz.,the one in which NH and C=O are *trans* to each other. This explanation assigns no role for the sulfur atom in the ring, and should therefore be valid for the isosters **4** and **5** of **2a**. To assess this proposal, the pyrrolidine **4** and oxazolidine derivative **5** were synthesized[3,9] and their ^1H NMR spectra in $CDCl_3$ and DMSO-d6 recorded. It was clear that in both cases, there was no change in configuration in going from non-polar to polar solvents. (Table 3). This



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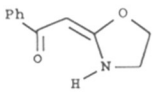

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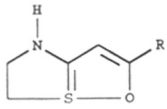
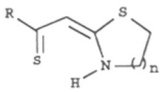
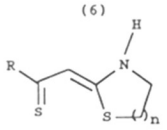


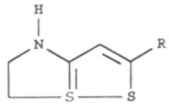
(6)



7 (E)



7 (Z)



(8)

Table 3

^{1}H NMR Data for the Pyrrolidine (**4**) and Oxazolidine (**5**) analogs of **2a**

Compound		NH	=CH	XCH_2	NCH_2
4	$CDCl_3$	13.30	5.80	1.90[a]	3.60
	DMSO-d6	10.20	5.80	1.90	3.55
5	$CDCl_3$	10.00	5.60	4.50[b]	3.65
	DMSO-d6	9.85	5.55	4.50	3.75

a: X = CH_2; b: X = O

renders any explanation based exclusively on solvent polarity extremely unlikely. The same holds true for any presumed steric effect due to solvation of NH in DMSO-d6. The solvent induced conformational change in **1** and **2** must therefore involve an active role for sulfur.

ii) Hypervalent Sulfur.

The ability of sulfur to form hypervalent structures can be invoked to suggest that the Z-isomer of **2a-h** is in fact a structure as shown in **6**. This represents an extreme description of the S..O attractive interaction. Since the structure is expected to be highly polarized, it may be stabilized in DMSO. The geometric criteria for the proposed structure with T-shape at the hypervalent sulfur are likely to be quite stringent. Hence, the observed differences in the behaviour of thiazolidine **2a** and thiazine **2i** can be readily understood. The proposal can also be extended to thiones (**7**), as shown in (**8**) which would explain the intriguing results discussed below.

The above proposal may be questioned on a number of grounds. Hypervalent sulfur structures generally involve linear arrangements of X-S-Y units in which X and Y are highly electronegative atoms or polarizable sulfur[7]. Examples of structures with apical C-S-O units, as in **6**, have not yet been characterized. Further, large electronic structural changes as in **6** should lead to larger effects on the chemical shifts than those observed for **2Z**.

A proposal involving a mild attractive S..O interaction would best explain the observed results.

iii) Non-bonded S..O interaction.

The idea of non-bonded attractive interaction between a divalent sulfur atom and a suitably located oxygen has been used by X-ray crystallographers to explain the unusual short contact observed in several solid state structures[10]. The essential sub-structure required for the interaction is S-A=B-Y=O in which A=B has the *cis*-configuration and B-Y has *s-cis* configuration. This condition is met in both **1***Z* and **2***Z*. It is therefore likely that such a non-bonded attractive force might be responsible for the observed behaviour of these compounds. The implication is that once the intramolecular H-bonds of the *E* isomers are broken by solvation, the weak attractive force manifests itself in populating the *Z* configuration. Obviously this also explains the absence of such behaviour in the case of the pyrrolidine **4** and the oxazolidine **5** analogs.

Another important aspect which has come to light from an X-ray crystallographic analysis is the co-linearity of the three atoms C-S..O; this arrangement might be essential for the interaction of the lone pair on oxygen with the σ^* antibonding orbital of the C-S bond. This in turn might explain the difference in behaviour between the thiazolidine **2a** and the thiazine **2i**.

Although (S,O) and a number of other atom pairs have been shown to exhibit such non-bonded attraction[11,12], all the evidence observed so far refer only to the solid state. To our knowledge, there has been no confirmed instance in which this has been observed in solution.

E/Z equilibria in thiones (**7**)

Table 4

^{1}H NMR Data and *E/Z* ratios for the Enaminothiones[c] **7**

Compound	Solvent	NH		=CH		NCH_2		SCH_2		*E/Z*
	-	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	
7a	$CDCl_3$	13.75	-	6.75	-	4.15	-	3.40	-	100/0
	DMSO-d6	13.31	9.71	6.20	7.15	4.10	3.75	3.40	3.25	59/41
7c	$CDCl_3$	13.70	-	6.70	-	4.15	-	3.30	-	100/0
	DMSO-d6	13.20	9.60	6.75	7.25	**	**	**	**	56/44[b]
7d	$CDCl_3$	13.30	-	6.75	-	4.25	-	3.50	-	100/0
	DMSO-d6	13.20	10.50	**	**	**	**	**	**	**
7f	$CDCl_3$	13.75	-	6.65	-	4.10	-	3.30	-	100/0
	DMSO-d6	13.15	9.55	6.45	**	**	**	**	**	**
7g	$CDCl_3$	13.70	-	6.55	-	4.20	-	3.45	-	100/0
	DMSO-d6	13.10	9.75	6.70	6.48	4.10	**	**	**	**
7h	$CDCl_3$	13.50	-	6.30	-	4.05	-	3.35	-	100/0
	DMSO-d6	13.10	9.43	5.80	6.60	4.05	3.65	3.40	3.20	67/33
7i	$CDCl_3$	15.00	-	6.50	-	3.55	-	3.20	-	100/0
	DMSO-d6	15.20	-	6.45	-	3.60	-	3.20	-	100/0
7k	$CDCl_3$	14.95	-	6.35	-	3.60	-	3.10	-	100/0
	DMSO-d6	14.65	-	6.15	-	3.55	-	3.15	-	100/0

** :- Line broadening; b: Ratio calculated from NH integration c:'a' to 'k' same as **2** except 'b' 'c' and 'j'

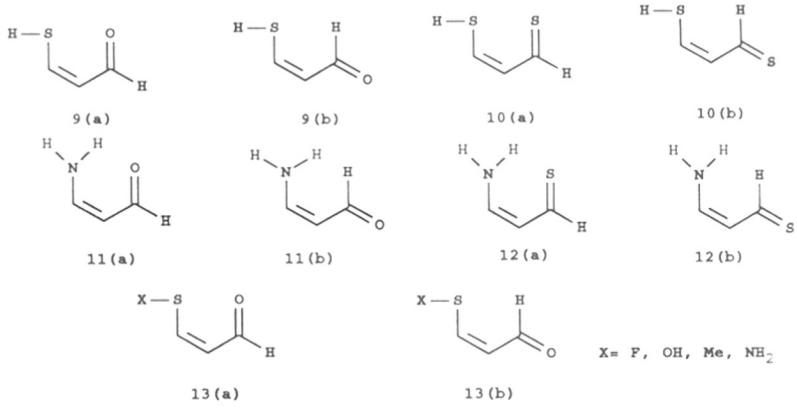
In a further extrapolation of this study, we have included the thiones **7** generated by Lawesson thionation[23] of the acylketen-S,N-acetals **2**. The phenolic compound **2e** and **2j** did not yield any product in this reaction. The relevant ^{1}H NMR data and *E/Z* ratios are given in Table 4. Interestingly the behaviour of the thiones more or less parallels that of the oxo compounds **2**. Thus **7a** exists in the *E* form in $CDCl_3$; but in DMSO-d6, the *E/Z* ratio is 60:40. The same is true of **7c** and the methyl compound **7h**. As with the oxo compounds **2i** and **2k**, the thiobenzoyl derivatives **7i** and **7k** of the thiazine series exist only in the *E*-form even in pure DMSO-d6. The *ortho*-substituted derivatives **7f** and **7g** as well as the *p*-nitrophenyl compound **7d** show considerable line broadening in DMSO-d6; the *E/Z* ratio could not therefore be determined in these cases.

The surprising similarity in the *E/Z* ratio of **2a** and **7a** in DMSO-d6 may appear to throw some doubt on the validity of the non-bonded S...O attractive forces as being operative in the former. One explanation could be that while the conformational equilibrium in **2a** measures the strength of the S..O interaction relative to an intramolecular N-H...O hydrogen bond, the corresponding equilibrium with **7a** compares the weak S..S interaction with the N-H..S hydrogen bond (which is definitely known to be weaker than N-H..O hydrogen bond)[13].

Theoretical studies -

To confirm the above interpretation, ab initio calculations[14-16] were carried out on model systems. The magnitudes of S..O and S..S interactions were probed using **9** and **10**. In order to obtain a direct comparison with N-H..O and N-H..S hydrogen bond strengths, the amino derivatives **11** and **12** were examined. Two conformations were considered in each case, of which only one has a potentially stabilizing intramolecular interaction. Geometry optimization was carried out with the 3-21G and 3-21G* (augmented with d orbitals on sulfur) basis sets. Additional calculations were carried out with the 6-31G* basis set (d functions on all non-hydrogen atoms) and also including electron correlation at the second order Moller-Plesset level using the 3-21G* geometries

On the basis of the computed conformational energy differences (Table 5), the strongest intramolecular interaction among the systems studied is the N-H..O hydrogen bond in **11**. A value of 6.5 k.cal. mol^{-1} is obtained at the 6-31G* level. The N-H..S interaction is weaker (5.0 k.cal. mol^{-1}). These values as well as their basis set dependence are comparable to earlier results on related hydrogen bonded systems.[16,17] Compared to the hydrogen bonds, the S..O interaction in **9** is quite weak. Even after inclusion of sulfur d orbitals, **9a** is computed to be more stable than **9b** by 3.1 k.cal. mol^{-1}. At the highest level employed, MP2/6-31G*, the magnitude of S..O interaction in **9** is estimated to be 2.4 k.cal. mol^{-1}. Although this represents a relatively modest attractive interaction, it can prove to be significant in determining conformations.



Among the systems considered, intramolecular interaction between divalent sulfur and the thiocarbonyl unit is the weakest. At uncorrelated level of theory, S..S interaction is computed to be mildly repulsive. However, at the MP2/6-31G* level, a small stabilization is indicated.

The optimized geometries of **9-12** provided additional insights into the nature of interactions in these systems. The S..O distance in **9a** is 2.90 Å at the 6-31G* level. It becomes shorter (2.84Å) with the inclusion of d orbitals on sulfur. This value is larger than that observed for **1** (2.68 Å)[1], consistent with the stronger S..O interaction expected for the nitro compound. A key structural feature in **9a** is that the carbonyl oxygen is nearly collinear with the H-S bond (168°). Further, the computed O=C..S angle is around 93°. The p-type oxygen lone pair is ideally placed for interaction with the H-S σ^* orbital. These results are similar to those computed earlier[18] for model system **13** and to the preferred direction of nucleophilic approach towards sulfur noted on the basis of an analysis of a large number of crystal structures[19]. Chemical evidence also points to the preference for backside approach of nucleophiles towards sulfur[20].

The nonbonded S..S distance is quite large in **10a** (3-21G : 3.34Å; 3-21G* : 3.21Å). While the H-S..S unit is computed to be fairly collinear (171°), the relatively acute C=S..S angle (79°) suggests that the thiocarbonyl in-plane lone pair is not ideally aligned for interaction with the H-S σ^* orbital. The magnitude of S..S interaction may therefore be larger in unencumbered systems.

The computed geometries of **11a** and **12a** reveal the presence of hydrogen bonding. The H..O (2.01 A°) and H..S (2.38 A°) contacts are fairly short, but shorter distances have been noted in unconstrained systems[16,17]. The favored collinear arrangement[21] of N-H..O (126°) and N-H..S (131°) units are not achieved. The carbonyl group is better aligned than the thione for interaction on the basis of the computed C=O..H (100°) and C=S..H (84°) angles.

Interestingly, the presence of a hydrogen bond or S..O interaction does not produce significant reduction in the bond angles involving the heavy atoms. The largest reduction on removing potential intramolecular attraction is around 4° for **12a** relative to **12b**. In general, the angles are all greater than 120°. Angle distortions are not prerequisites or indicators of intramolecular interactions in these systems[22].

Table 5.

Calculated Total Energies (Hartree) and Relative energies (k.cal mole^{-1}) of **9-12**[a].

Molecule	3-21G*		6-31G*		MP2/6-31G*	
	E	Rel *E*	*E*	Rel *E*	*E*	Rel *E*
9a	-585.35840	0.0	-588.26818	0.0	-588.94231	0.0
9b	-585.35349	3.1	-588.26786	0.2	-588.93844	2.4
10a	-906.57509	1.1	910.90502	2.3	-911.56642	0.0
10b	-906.57686	0.0	-910.90874	0.0	-911.56572	0.4
11a	-244.43617	0.0	-245.80350	0.0		
11b	-244.42077	9.6	-245.79311	6.5		
12a	565.65498	0.0	568.44449	0.0		
12b	-565.64633	5.4	-568.43637	5.0a		

a: Using 3-21G* optimized geometries

Conclusions

The present study of conformational equilibria in different solvent systems using NMR provides convincing evidence for the presence of an attractive intramolecular S...O interaction in the enaminoketones **2**(**a** to **h**). The related S....S interaction in the enaminothiones **7** is weak. Greater attraction may be possible in conformationally less constrained systems. Ab initio calculations on models yield quantitative estimates of these interactions relative to intramolecular hydrogen bond strengths in related geometries.

Acknowledgement

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EXPERIMENTAL

General : Melting points are uncorrected. IR spectra were recorded in $CHCl_3$ solution or as nujol mulls on a Perkin-Elmer model 599B infrared spectrometer, using NaCl optics. PMR spectra were recorded on a Bruker WH90 or a Bruker AC-200 instrument; chemical shifts are expressed in ppm. downfield from Me_4Si used as internal standard.

Synthesis of enaminoketones 2. Method A Compounds 2a[4], 2e[4], 2f, 2i, 2j and 2k were prepared in two steps by the sulfide contraction route. The first step was S-alkylation of thiazolidine-2-thione or 1,3-thiazine-2-thione by the α-haloketone. This was followed by sulfur extrusion[3] in the second step to give the enaminoketones **2**.

2-Benzoylmethylenethiazolidine (2a[4]): Yield 69%; Light yellow crystalline solid, m.p. 168°C; ^{1}**H NMR** ($CDCl_3$): δ 3.20 (t,J=8Hz,2H,SCH_2), 3.90 (t,J=8Hz,2H,NCH_2), 5.90 (s,1H,=CH), 7.2-7.8 (m,5H,ArH), 10.55 (bs,1H,NH); **IR** (nujol): 3200, 1600, 1580cm^{-1}; **MS:** m/z 205 (M^+,10%); 204 (100).

2-(2-Hydroxybenzoyl)methylenethiazolidine (2e): Yield 80%; Yellow crystalline solid, m.p. 140°C; ^{1}H NMR ($CDCl_3$): δ 3.30 (t,J=8Hz,2H,SCH_2), 4.00 (t,J=8Hz,2H,NCH_2), 6.00 (s,1H,=CH), 6.6-7.6 (m,4H,ArH), 10.25 (bs,1H,NH), 13.55(s,1H,OH); **IR**(nujol): 3260, 3000, 1600, 1580, 1530 cm^{-1}; **MS:** m/z 221 (M^+, 100%), 121 (60), 204 (45), 101 (30); Anal. Calcd. for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.00; N, 6.33; S, 14.47. Found: C, 60.12; H, 5.39; N, 6.33; S, 14.49.

2-(2-Methoxybenzoyl)methylenethiazolidine (2f): Yield 75%; Light yellow viscous liquid; ^{1}H NMR($CDCl_3$): δ 3.25 (t,J=8Hz,2H,SCH_2), 3.90 (s,3H,OCH_3), 3.95 (t,J=8Hz,2H,NCH_2), 5.9 (s,1H,=CH), 6.95-7.6(m,4H,ArH), 10.6 (bs,1H,NH); **IR**(neat): 1390, 1580,1600, 2940, 3200 cm^{-1}; **MS:** m/z 235 (M^+ 21%), 135 (100), 204 (86). Compound was not stable enough for getting a good microanalysis.

2-Benzoylmethylenethiazine (2i): Yield 75%; Colourless crystalline solid, m.p. 104-105°C; ^{1}H NMR ($CDCl_3$): δ 2.25 (m,2H,CCH_2), 3.20 (t,J=8Hz,2H,SCH_2), 3.55 (t,J=8Hz,2H,NCH_2), 5.75 (s,1H,=CH), 6.40-7.9(m,5H,ArH), 12.45(bs,1H,NH); **IR**(nujol): 3000, 1580, 1470 cm^{-1}; **MS:** m/z 219 (M^+,35%), 77 (100); Anal. Calcd. for $C_{12}H_{13}NOS$ C, 65.72; H, 5.97; N, 6.38; S, 14.62. Found: C, 65.82; H, 6.75; N, 6.64; S, 14.56.

2-(2-Hydroxybenzoyl)methylenethiazine (2j): Yield 50%; Colourless crystlline solid, m.p. 125-127°C; ^{1}H NMR ($CDCl_3$): δ2.25(m,2H,CCH_2), 3.15(t,J=8Hz,2H,SCH_2), 3.55(t,J=8Hz,2H,NCH_2), 5.75 (s,1H,=CH), 6.70-7.50(m,4H,ArH), 11.75 (bs,1H,NH), 13.75 (s,1H,OH); **IR**($CHCl_3$) 3400, 3020, 1600, 1580 cm^{-1}; **MS:** m/z 235 (M^+,93%), 188 (100); Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.28; H, 5.57; N, 5.95. Found: C, 62.00; H, 5.67; N, 6.07.

2-(2-Methoxybenzoyl)methylenethiazine (2k): Yield 62%; Colourless crystalline solid, m.p. 107-108°C; ^{1}H NMR ($CDCl_3$): δ2.20(m,2H,CCH_2), 3.05(t,J=8Hz,2H,SCH_2), 3.50(t,J=8Hz,2H,NCH_2), 3.75(s,3H,OCH_3), 5.70(s,1H,=CH), 6.90-7.60(m,4H,ArH), 12.35(bs,1H,NH); **IR**(nujol+$CHCl_3$): 3400, 1600, 1610 cm^{-1}; **MS:** m/z 249 (M^+,9%), 135 (100); Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.65; H, 6.00; N, 5.60. Found: C, 62.60; H, 62.2; N, 5.77.

Method B Compounds **2b**[2]**,2c**[4]**,2d,2g** were prepared by condensation of an acylketene dithioacetal with 2-aminoethanethiol in ethanol at reflux temperature[4].

2-(4-Chlorobenzoyl)methylenethiazolidine (2b[2]**):** Yield 80%; Light yellow crystalline solid, m.p. 137-139°C; ^{1}H NMR ($CDCl_3$): δ3.20(t,J=8Hz,2H,SCH_2), 3.90(t,J=8Hz,2H,NCH_2), 5.90(s,1H,=CH), 7.30 (d,J=9Hz,2H,ArH), 7.70 (d,J=9Hz,2H,ArH), 10.55 (bs,1H,NH); **IR**(nujol): 3200, 1590 cm^{-1}; **MS:** m/z 239 (M^+,79%).

2-(4-Methoxybenzoyl)methylenethiazolidine (2c[4]**):** Yield 73%; Light yellow crystlline solid, m.p. 154-156$_0$C; ^{1}H NMR ($CDCl_3$): δ3.30(t,J=8Hz,2H,SCH_2), 3.75(s,3H,OCH_3), 3.95(t,J=8Hz,2H,NCH_2), 6.00(s,1H,=CH), 6.90-7.80(m,4H,ArH), 10.60(bs,1H,NH); **IR**($CHCl_3$) 3260,2940,1610, 1580 cm^{-1}; **MS:** m/z 235 (M^+,64%).

2-(4-Nitrobenzoyl)methylenethiazolidine (2d): Yield 44%; Yellow crystalline solid, m.p. 120-122°C; ^{1}H NMR ($CDCl_3$): δ3.30(t,J=8Hz,2H,SCH_2), 4.00(t,J=8Hz,2H,NCH_2), 5.90(s,1H,=CH), 8.00-8.30(m,4H,ArH), 10.80(bs,1H,NH); **IR**(nujol): 2900, 1600, 1550 cm^{-1}; **MS:** m/z 250 (M^+,45%),128 (100); Anal. Calcd. for $C_{11}H_{10}N_2O_3S$: C, 52.78; H, 4.02; N, 11.20; S, 12.81. Found: C, 52.80; H, 4.11; N, 11.19; S, 12.67.

2-(2-Chlorobenzoyl)methylenethiazolidine (2g): Yield 58%; Light yellow crystalline solid, m.p. 138-140°C; ^{1}H NMR ($CDCl_3$): δ3.35(t,J=8Hz,2H,SCH_2), 4.05(t,J=8Hz,2H,NCH_2), 5.70(s,1H,=CH), 7.40-7.70(m,4H,ArH), 10.60 (bs,1H,NH); **IR**(nujol): 3250, 3000, 1600 cm^{-1}; **MS:** m/z 239 (M^+,45%), 204 (100); Anal. Calcd. for $C_{11}H_{10}ClNOS$: C, 55.12; H, 4.20; N, 5.84. Found: C, 55.68; H, 4.43; N, 5.77.

1-Phenyl-2-(2-pyrrolidinylidene)ethanone (4): This compound was prepared by a reported procedure for 1-4'-bromophenyl2-(2-pyrrolidinylidine)-ethanone[3]; m.p 110°C; Anal. Calcd. for $C_{12}H_{13}NO$: C, 77.01; H, 6.95. Found: C, 77.52; H, 7.01.

(E)-2-(Benzoylmethylene)oxazolidine (5)[9]**:** was prepared by the reported method[9] m.p. 103-104; Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.91; H, 5.78; N, 7.21.

General procedure for thionation

A mixture of, compound **2** (10 mmol) and Lawesson reagent[23] (6 mmol) was stirred and heated in benzene at 80°C under an inert atmosphere for 4h. The solvent was then removed in vacuo and the product purified by chromatography on silica gel column (petroleum ether-ethyl acetate)

2-Thiobenzoylmethylenethiazolidine (7a): Yield 75%; Yellow crystalline solid, m.p. 94-95°C; **^{1}H NMR** ($CDCl_3$)**:** δ 3.35 (t,J=8Hz,2H,SCH_2), 4.15 (t,J=8Hz,2H,NCH_2), 6.70 (s,1H,=CH), 7.30-7.80 (m,5H,ArH), 13.75 (bs,1H,NH); **MS:** m/z 221 (M^+,83%), 128 (100); **IR**(nujol)**:** 3000, 2800, 1570, 1550 cm^{-1}; Anal. Calcd. for $C_{11}H_{11}NS_2$: C, 59.72; H, 4.97. Found: C, 59.52; H: 4.89.

2-(4-Methoxythiobenzoyl)methylenethiazolidine (7c): Yield 80%; Yellow crystalline solid, m.p. 156-157°C; **^{1}H NMR** ($CDCl_3$)**:** δ 3.30(t,J=8Hz,2H,SCH_2), 3.85(s,3H,OCH_3), 4.15(t,J=8Hz,2H,NCH_2), 6.70(s,1H,=CH), 6.85-7.75(m,4H,ArH), 13.75 (bs,1H,NH); **IR**(nujol)**:** 2950, 1610, 1560, cm^{-1}; **MS:** m/z 251 (M^+,83%), 128 (100); Anal. Calcd. for $C_{12}H_{13}NOS_2$: C, 57.33; H, Found: C, 58.02; H: 5.30.

2-(4-Nitrothiobenzoyl)methylenethiazolidine (7d): Yield 61%; Dark brown viscous liquid; **^{1}H NMR** ($CDCl_3$)**:** δ 3.50 (t,J=8Hz,2H,SCH_2), 4.25 (t,J=8Hz,2H,NCH_2), 6.75 (s,1H,=CH), 7.85- 8.25 (m,4H,ArH), 13.80 (bs,1H,NH); **IR**(neat)**:** 3080, 2920, 1570, 1520 cm^{-1}; **MS:** m/z 266 (M^+,74%), 238 (100); Anal. Calcd. for $C_{11}H_{10}N_2O_2S_2$: C, 49.62; H, 3.75; N, 10.52. Found: C, 49.80; H, 4.11; N, 11.19.

2-(2-Methoxythiobenzoyl)methylenethiazolidine (7f): Yield 65%; Dark brown viscous liquid; **^{1}H NMR** ($CDCl_3$)**:** δ 3.30 (t,J=8Hz,2H,SCH_2), 3.85 (s,3H,OCH_3), 4.10 (t,J=8Hz,2H,NCH_2), 6.65 (s,1H,=CH), 6.90-7.40 (m,4H,ArH), 13.75 (bs,1H,NH); **IR**(neat)**:** 3350, 1600, 1500, 1470 cm^{-1}; **MS:** m/z 251 (M^+,6%), 234 (100), 135(42); Anal. Calcd. for $C_{12}H_{13}NOS_2$: C, 57.33; H, 5.17. Found: C, 57.63; H, 5.27.

2-(2-Chlorothiobenzoyl)methylenethiazolidine (7g): Yield 63%; Yellow crystalline solid, m.p. 157-159°C; **^{1}H NMR** ($CDCl_3$)**:** δ3.45 (t,J=8Hz,2H,SCH_2), 4.20 (t,J=8Hz,2H,NCH_2), 6.55 (s,1H,=CH), 7.40- 7.80 (m,4H,ArH), 13.70 (bs,1H,NH); **IR**$^{-1}$(nujol): 2940, 1560, 1500, 1380 cm^{-1}; **MS:** m/z 255 (M^+,45%), 192 (100), 220(49); Anal. Calcd. for $C_{11}H_{10}ClNS_2$: C, 51.65; H, 3.94; N, 5.47; S, 25.06. Found: C, 52.08; H, 3.77 N, 5.62; S, 25.15.

2-Thioacetylmethylenethiazolidine (7h): Yield 85%; Yellow crystalline solid, m.p. 100°C; **^{1}H NMR** ($CDCl_3$)**:** δ2.54(s,3H,CH_3), 3.34(t,J=8Hz,2H,SCH_2), 4.10(t,J=8Hz,2H,NCH_2), 6.30(s,1H,=CH), 13.50 (bs,1H,NH); **IR**(nujol)**:** 3400, 1570, 1470, 1390, 1280cm^{-1}; **MS:** m/z 159 (M^+,80%), 131 (100). Compound was not stable enough for getting a good microanalysis.

2-Thiobenzoylmethylenethiazine (7i): Yield 67%; Yellow crystlline solid, m.p. 157-159°C; **^{1}H NMR** ($CDCl_3$)**:** δ 2.20 (m,2H,CCH_2), 3.15 (t,J=7Hz,2H,SCH_2), 3.65 (t,J=7Hz,2H,NCH_2), 6.50 (s,1H,=CH), 7.40-7.80(m,5H,ArH), 15.00(bs,1H,NH), **IR**(nujol)**:** 2940,2860,1600,1510cm^{-1}; **MS:** m/z 235 (M^+,70%), 178 (100), 202(76); Anal. Calcd. for $C_{12}H_{13}NS_2$: C, 61.27; H, 5.53. Found: C, 61.10; H, 5.56.

2-(2-Methoxythiobenzoyl)methylenethiazine (7k): Yield 59%; Dark brown viscous liquid; **^{1}H NMR** ($CDCl_3$)**:** δ2.25 (m,2H,CCH_2), 3.10 (t,J=7Hz,2H,SCH_2), 3.60 (t,J=7Hz,2H,NCH_2), 3.80 (s,1H,OCH_3), 6.35 (s,1H,=CH), 6.90-7.40 (m,4H,ArH), 14.95 (bs,1H,NH); **IR**(neat)**:** 3350, 2940, 1620, 1600 cm^{-1}; **MS:** m/z 265 (M^+,1%), 127 (100), 129(43). Compound was not stable enough for getting a good microanalysis.

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