REACTIONS OF LACTIM ETHERS, LACTIM THIOETHERS AND CARBONIMIDODITHIOATES: UTILIZATION FOR THE SYNTHESIS OF AMINO ACID DERIVATIVES

A THESIS

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BY

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DECLARATION

I hereby declare that the thesis entitled "**Reactions of Lactim ethers and Lactim thioethers and Carbonimidodithioates: Utilization for the Synthesis of Amino Acid Derivatives**" submitted for Ph. D. degree to the University of Poona has been carried out at National Chemical Laboratory, under the supervision of Dr. S. Rajappa. The work is original and has not been submitted in part or full by me for any degree or diploma to this or any other University.

Date: 2.7.98

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Reactions of Lactim ethers and Lactim thioethers and Carbonimidodithioates: Utilization for the Synthesis of Amino Acid Derivatives"** submitted by M. Anbazhagan was carried out by him under my supervision at the National Chemical Laboratory, Pune. Material that has been obtained from other sources is duly acknowledged in the thesis.

S. Rajappa

Date: 2.7.98

(S. Rajappa)
Research Guide

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M. Anbazhagan

CONTENTS

Abbreviations

Ac	acetyl
aq	aqueous
BOC	*t*-butoxycarbonyl
Bu	butyl
Bz	benzyl
cbz	carbobenzoxy
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess
DBU	1, 8- diazabicyclo[5, 4, 0]Undec-7-ene
Et	ethyl
g	gram
h	hour
HPLC	high performance liquid chromatography
IR	infrared
LAH	lithium aluminium hydride
min	minute
mL	millilitre
mmol	millimole
mp	melting point
MS	mass spectra
Ph	phenyl
Pr	propyl
iPr	isopropyl
rt	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography

...to my beloved Parents

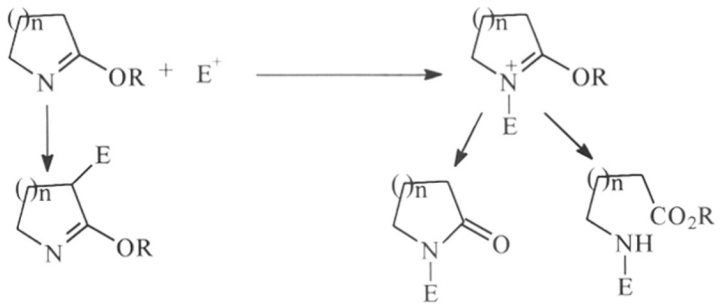
ABSTRACT

The Thesis entitled "**Reactions of Lactim ethers, Lactim Thioethers and Carbonimidodithioates: Utilization for the synthesis of Amino acid Derivatives**" is divided into five chapters.

CHAPTER 1: Introduction to the reactions of lactim ethers with various electrophiles.

This chapter provides a concise account of the reaction of lactim ethers with various elctrophiles. The reaction of lactim ethers with electrophiles can take several routes. In most of these reactions the nitrogen atom of the lactim ether acts as the nucleophile;[1] but this is not always the case. There are examples in the literature where carbon C-3 is the site of electrophilic attack. This obviously results from the reaction of the lactim ether as its enamine tautomer.[2] The initial nucleophilic attack of one molecule of the lactim ether in its enamine form on another molecule of the lactim ether at the electrophilic carbon has been suggested to account for the products of the reaction of the lactim ether with diketene.[3] Reaction at the nitrogen with electrophiles can have at least two other sequels. There are several examples in the literature in which the second step is the attack by the counterion on the alkyl group of the ether leading to N-substituted lactams *via* alkyl-oxygen cleavage (Scheme 1). This is the case with alkylation,[5] acylation[6] and sulfonylation.[7] Most interesting is the reaction of lactim ethers with electrophiles followed by opening of the lactam ring (Scheme 1). Thus ω-isocyanocarboxylic acid esters are reported to result from the reaction of lactim ethers with chloroform in aqueous alkali.[8] Similarly, lactim ether reacts with thiophosgene to form an isothiocyanatocarboxylic ester.[9] There is also a recent report that 1, 4-naphthaquinone reacts with lactim ether in methanol to form 2-(3-methoxycarbonylpropylamino)-1, 4-naphthaquinone.[10]

Scheme 1

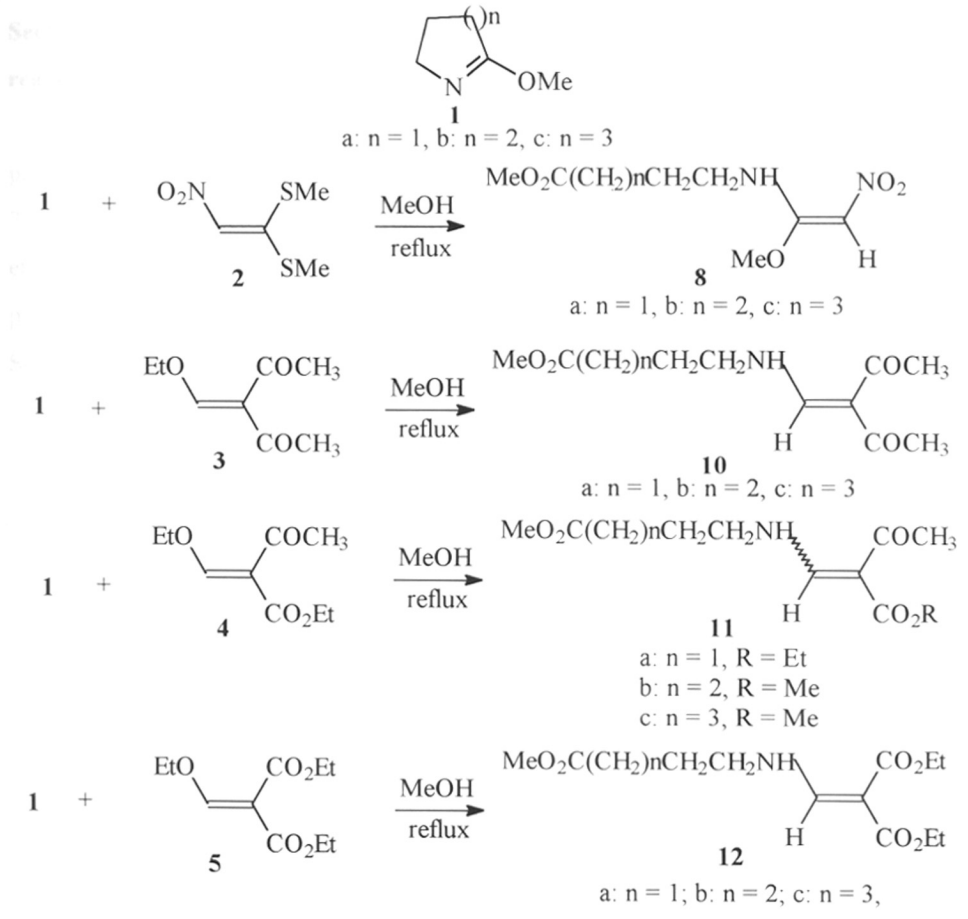


CHAPTER 2: This chapter is divided into five sections

Section A: Reaction of 5, 6 and 7 membered lactim ethers with various push-pull ethylenes and other electrophiles.

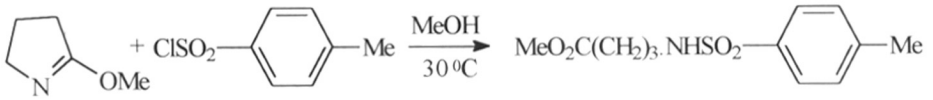
As mentioned earlier the reaction of lactim ethers at nitrogen can lead to atleast two types of products. One type is the N-substituted lactam which is formed *via* alkyl-oxygen cleavage. Most interesting in the context of the present discussion are the reactions of lactim ethers (**1 a-c**) with electrophiles followed by opening of the lactam ring. (Scheme 1). The present study deals with the reaction of lactim ethers with a series of electrophilic push-pull ethylenes (**2-5**) in methanol solution. In all the examples studied, attack took place on the nitrogen atom; this was followed by opening of the ring, leading to the formation of carboxylic esters in 38 to 79% yield (Scheme 2).

Scheme 2

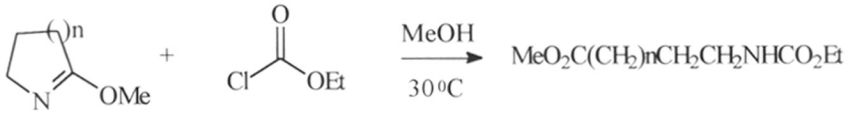


Reaction of 5, 6, and 7 membered lactim ethers **1** (**a, b, c**) with ethyl chloroformate and p- toluenesulfonyl chloride gave ring opened products **10** and **11** (Scheme 3).

Scheme 3



1a **6** **13a**



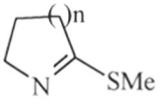
1 **7** **14**

a: n = 1, b: n = 2, c: n = 3

Section B: Reaction of the corresponding lactim thioethers: Camparison of the reactivity of ethers and thioethers.

The reaction of the corresponding lactim thioethers with a series of electrophilic push-pull ethylenes in methanol solution also led to ring opened products (**6 - 9**) in 60 - 79% yield. As expected from the relative nucleophilicity of the nitrogen atom in lactim ethers and lactim thioethers, reaction of lactim thioethers led to the higher yield of the products (Scheme 4).

Scheme 4



12

+ **2** → **8**

3 → **10**

4 → **11**

5 → **12**

6 → **13a**

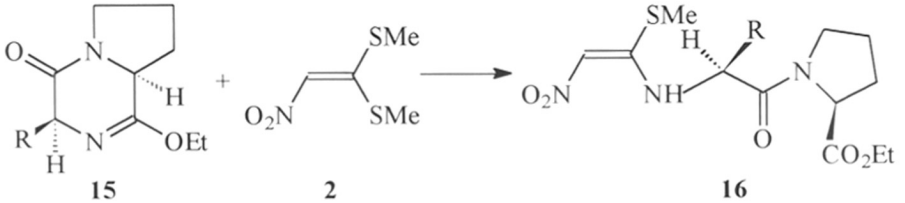
7 → **14**

a: n = 1, b: n = 2, c: n = 3

Section C: Approach to the synthesis of tripeptides *via* diketopiperazine monoimino ether: Use of nitroacetyl group as a peptide synthon

One of the objectives of our group in this area has been to utilise nitroketen O, N- acetals or S,N- acetals for the synthesis of peptides incorporating non- natural α-alkylated amino acids. The route involves hydrolysis to the nitroacetamides and subsequent regiospecific alkylation of the reactive methylene group, followed by reduction of the NO_2 to NH_2.[11] Towards this end, several cyclodipeptide mono iminoethers (**13**)[12] were reacted with 1,1- bismethylmercapto-2- nitroethylene (**2**)(Scheme 5). It was hoped that the resulting nitroketen S,N- acetals (**13**) could be hydrolysed to the corresponding nitroacetamides and then converted in two steps to modified tripeptides.

Scheme 5



15 **2** **16**

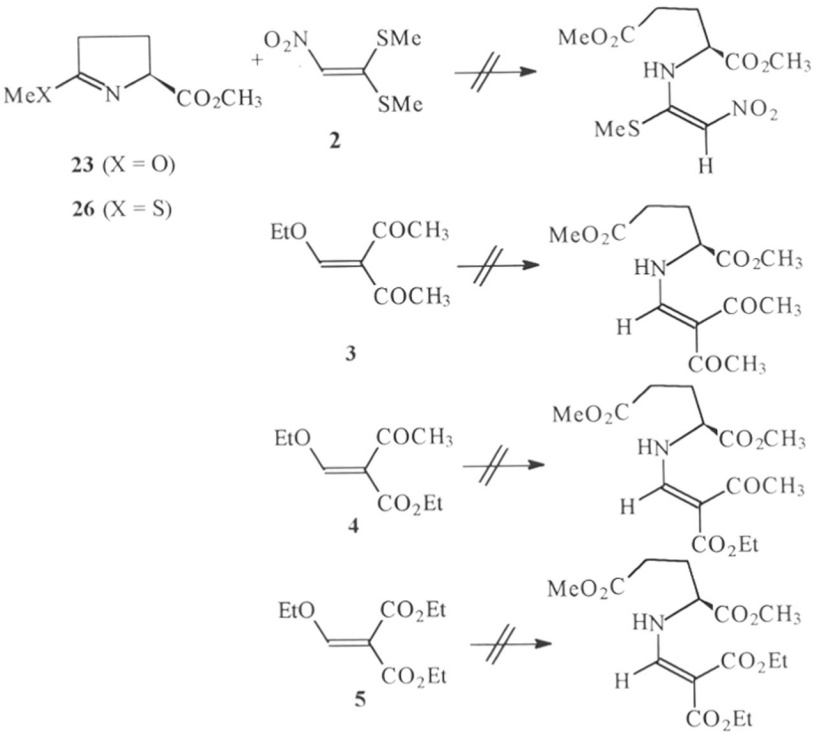
a: R = H; b: = CH_3; c: = $CH(CH_3)_2$; d: = $CH_2CH(CH_3)_2$; e: = CH_2Ph

Unfortunately, the initial condensation was successful only with the cyclo (L-Pro-Gly) monoiminoether (**12;** R= H), leading to **13** (R= H) in 32% yield. The reaction failed with the analogous derivatives of alanine, valine, leucine or phenylalanine. In each case the starting materials were recovered.

Section D: Attempts at ring-opening the lactim ether derived from pyroglutamate

The objective of this study was to make dipeptides incorporating a glutamic acid residue. The reaction of pyroglutamate lactim ether (**14**) with 1, 1′-bismethylthio-2-nitroethylene failed to give the required S, N-acetals. The reaction of pyroglutamate lactim ether with various electrophilic push-pull ethylenes also failed to give ring opened products. All the attempts, such as change of solvent, use of different Lewis acids and change of reaction conditions proved to be futile, starting materials were recovered(Scheme 6).

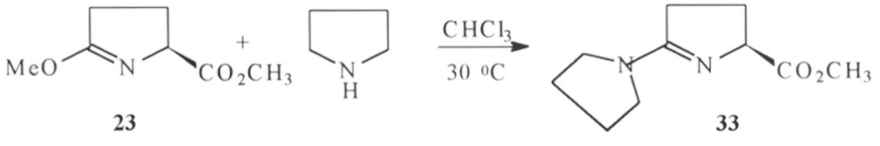
Scheme 6



Section E: Increasing the nucleophilicity of the ring nitrogen in pyroglutamate: Reaction of the derived amidine with acid chlorides and other electrophiles:

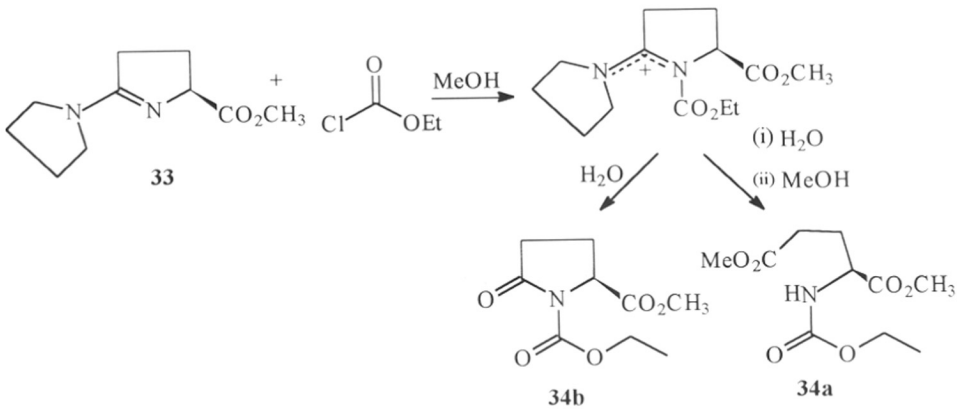
Our objective was to increase the nucleophilicity of the ring nitrogen in pyroglutamate lactim ether by converting it into amidine derivatives. Reaction of the pyroglutamate lactim ether with pyrrolidine in chloroform gave the required amidine (**15**) in 40% yield(Scheme 7).

Scheme 7



This amidine derivative (**15**) also failed to reactt with 1,1'-bismethylthio-2-nitroethylene and all other electrophilic push-pull ethylenes. But it reacted with ethyl chloroformate to give the ring opened product (**16**) (17%) and N-substituted lactam (**17**) (19%)(Scheme 8).

Scheme 8

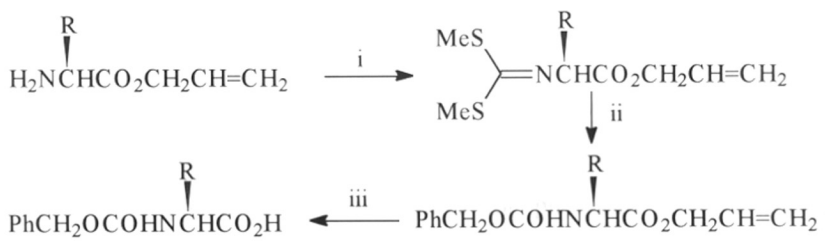


CHAPTER 3:

A Non-Phosgene strategy for the preparation of N-carbobenzoxy amino acids:

Over the past several years, our group has been involved in devising synthetic routes for carbamates that do not require the use of phosgene or methyl isocyanate. The conversion of dithiocarbamates to carbamates in three steps had been reported earlier.[13] This concept has now been extended for the direct conversion of carbonimidodithioates to carbamates in one step. The reaction of amino acid esters with CS_2 followed by methylation with MeI leads to the carbonimidodithioates which was reacted with sodium benzyl alcohoate in THF this was followed by hydrolysis to give benzyl carbamates. The utility of this reaction for the preparation of N- benzyloxycarbonyl-α- amino acids has also been demonstrated. Carbonimidodithioates derived from amino acid allyl esters was reacted with benzyl alcoholate, this was followed by hydrolysis to give benzyl carbamates. Pd(0) catalysed de-allylation resulted the N- carbobenzoxy amino acids.

Scheme 9



R

a: H; b: Me; c: $CHMe_2$
d: CH_2CHMe_2; e: CH_2Ph

Reagents

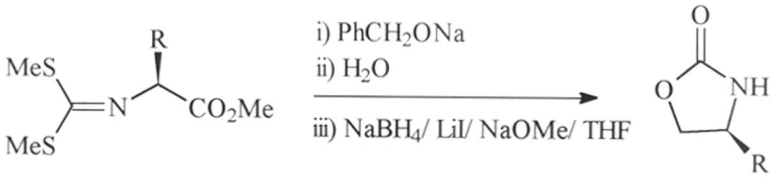
i) CS_2, Et_3N; then MeI ii) $PhCH_2ONa$/ THF; then H_2O, rt
iii) MeCN, DBU, morpholine, $Pd(dba)_2$, PPh_3, rt

CHAPTER 4: Synthesis of chiral oxazolidin-2-ones from α- amino acid esters *via* carbonimidodithioates

"Evans oxazolidinones" are certainly the most successful of the chiral auxiliaries currently available for asymmetric transformations based on acyl group reactivity.[14] The usual procedure employed for the preparation of oxazolidinone is reduction of the appropriate amino acid with BH_3/ BF_3. OEt_2 to amino alcohol and cyclisation by treatment with phosgene or its equivalent, diethyl carbonate. But there are drawbacks: First, the potentially hazardous borane reduction which may result in a violent expulsion of gases and solvents. Secondly, the intermediate water soluble amino alcohol is very difficult to isolate and purify.

It is apparent that in all the synthesis reported so far, the one carbon fragment has been derived from carbonate or a chloroformate. We have developed a simpler, cost effective procedure for the preparation of chiral 2- oxazolidinone from carbonimidodithioates derived from α- amino acid estersin good yields with optical purity. Carbonimidodithioates can be prepared from amino acid esters in a single step in 85-90% yields(Scheme 10).

Scheme 10



CHAPTER 5: Preparation of unsymmetrical di-, and trisubstituted ureas including urea dipeptides from carbonimidodithioates

Unsymmetrically substituted ureas display wide range of biological activities which include HIV-protease inhibitor activity.[15] They are also widely used in pesticides and pharmaceuticals.[16]

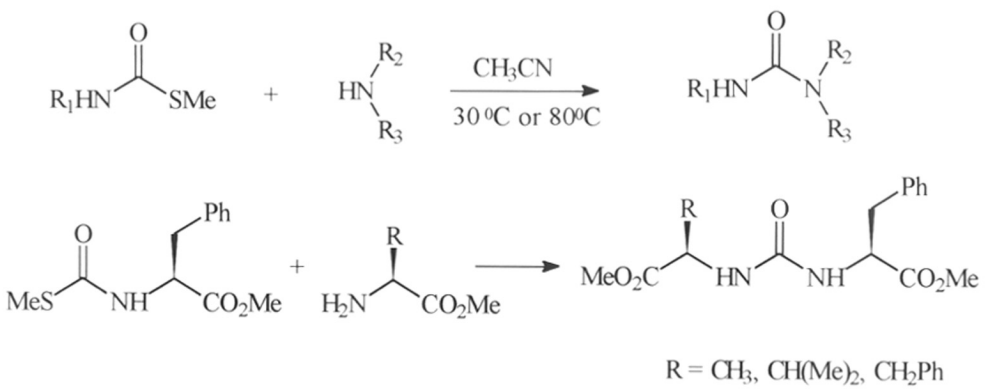
There are numerous methods available for the synthesis of unsymmetrically substituted ureas in good to excellent yields. Most of these methods are unsafe as they involve the use of phosgene. The substitutes for phosgene such as triphosgene, carbonates, isocyanates, carbonyldiimidazole are equally hazardous as they are either prepared from phosgene or generate phosgene during the reaction. The direct reaction of amine with dialkyl carbonates or diphenyl ureas requires drastic conditions.[17] Use of S,S-dimethyl dithiocarbonate involves use of a strong base like LDA which is not suitable for

the synthesis of urea dipeptides as it epimerizes the starting material as well as the product.[18]

We have developed a simple and mild method for the synthesis of unsymmetrically di or tri substituted ureas by the reaction of variuos amines with S-methyl thiocarbamate. Amines or amino acid esters were converted to the corresponding S,S-dimethyl carbonimidodithioates by the procedure involving condensation with CS_2 followed by methylation with methyl iodide in the presence of triethylamine in CH_2Cl_2.[19] These carbonimidodithioates were hydrolysed to the corresponding S-methyl thiocarbamates quantitatively in the presence of $ZnCl_2$ in CH_3CN : H_2O (3:1)

The reaction of various primary, secondary amines with these S- methyl thiocarbamates in CH_3CN at rt or 80 ^{0}C furnished the required urea derivatives in 60 - 89% yield (Scheme 11). S-Methyl thiocarbamate **2** was reacted with amino acid methyl esters to give urea dipeptides in good yields.

Scheme 11



References

1 S. Rajappa, B. G. Advani and R. Sreenivasan, *Ind. J. Chem.*, 1976, **14B**, 391.

2 U. Kraatz, *Tetrahedron*, 1973, **29**, 3991.

3 A. Kato and T. Sakamoto, *Chem. Pharm. Bull.*, 1975, **23**, 2629.

4 U. Kraatz, *Liebigs Ann. Chem.*, 1976, 412.

5 T. Fujii, S. Yoshifuji and K. Yamada, *Chem. Pharm. Bull.*, 1978, **26**, 2071.

6 B. Stoll and W. Griehl, *Helv. Chim. Acta*, 1965, **48**, 1805; H. Kiefer, *Synthesis*, 1972, 81.

7 J. Sheu, M. B. Smith, T. R. Oeschger and J. Satchell, *Org. Prep. Proc. Int.*,

1992, **24**, 147.

8 G. Fengler and A. Boffa, *Ger. Offen.* 1979, 2,808,226; *Chem. Abst.* 1980, **92,** 6085.

9 J. Gonda, P. Kristian and L. Mikler, *Coll. Czech. Chem. Commun.*, 1986, **51**, 112.

10 J.P. Michael, P.F. Cirillo, L. Denner, G.D. Hosken, A.S. Howard and O.S. Tinkler,
Tetrahedron, 1990, **46**, 7923.

11 This is similar to the ring-opening in methanol reported in ref. 10

12 S. Rajappa, *Tetrahedron,* 1981, **37,** 1453.

13 S. K. Tandel, S. Rajappa and S.V. Pansare, *Tetrahedron,* 1993, **49**, 7479.
T. I. Reddy, B.M. Bhawal and S. Rajappa, *Tetrahedron Lett.*, 1992, **33**, 2857.
T.I. Reddy, Ph. D. Thesis, **1992** University of Poona, Pune, India.
G. H. Kulkarni, R. H. Naik, S.K. Tandel and S. Rajappa, *Tetrahedron,* 1991, **47,**1249
S. .R. Deshpande, A. P. Likhite and S. Rajappa, *Tetrahedron,* 1994, **50,** 10367.

14 D. A Evans, Aldrichimia Acta, 1982, **15**, 23; J.R. Gage and D. A. Evans, Org. Synth., 1990, **68**, 83.

15 D. P. Getman,; G. A. DeCrescenzo,; R. M. Heintz,; K. L. Reed,; J. J. Talley,; M. L. Bryant,; M. Clare,; K. A. Houseman,; J. J. Marr,; R. A. Mueller,; M. L. Vazquez,; H. -S. Shieh,; W. C. Stallings,; R. A. Stegeman, *J. Med. Chem.* **1993**, *36*, 288.

16 T. P. Vishnyakova,; I. A. Golubeva,; E. V. Glebova, *Russ. Chem. Rev. (Engl. Transl.)* **1985**, *54*, 249.

17 J. E. Glamkowski,; Y.. Chiang,. *J. Heterocycl. Chem.* **1987**, *24*, 733.

18 M. -K. Leung,; J. -L. Lai,; K. -H. Lau,; H. -H. Yu,; H. -J. Hsiao, *J. Org. Chem.* **1996**, *61*, 4175.

19 M. Anbazhagan,; T. I. Reddy,; S. Rajappa, *J. Chem. Soc., Perkin Trans. 1,* **1997**, 1623.

CHAPTER 1

Introduction to the reactions of lactim ethers with various electrophiles

Introduction

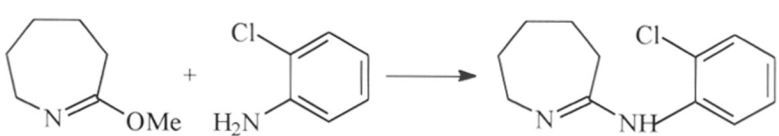
The conversion of lactams into lactim ethers increases the scope for using the former as basic building blocks in organic synthesis. Lactim ethers are capable of undergoing reactions with both electrophiles and nucleophiles. Lactim ethers are highly reactive towards nucleophilic reagents. The reactions of lactim ethers with nitrogen, oxygen and carbon nucleophiles have been exhaustively reviewed.[1] Lactim ethers are used in the synthesis of several important classes of organic compounds.[2] They are also of interest because of their use as accelerators for polymerization.[3] The result of electrophilic attack on lactim ethers however, cannot be predicted easily. This chapter provides a concise account of the reactions of lactim ethers with various electrophiles and nucleophiles.

Nucleophilic attack on lactim ethers

The reaction of lactim ethers with amino derivatives and compounds with active methylene groups, provides promising methods of heterocyclic synthesis.[1]

The formation of amidines from lactim ethers and amines proceeds readily in high yields(Scheme 1).[4]

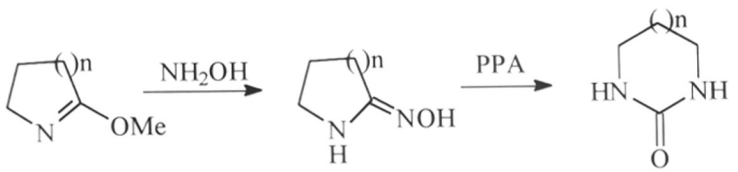
Scheme 1



1c **2**

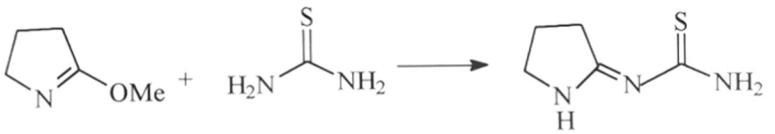
The reaction of lactim ethers with hydroxylamine results in lactamoximes **3** which undergo Beckmann rearrangment with polyphosphoric acid, yielding polymethyleneureas **4**(Scheme 2).[5] Similar reaction of lactim ether **1a** with thiourea leads to the compound **5**.[6]

Scheme 2



1 **3** **4**

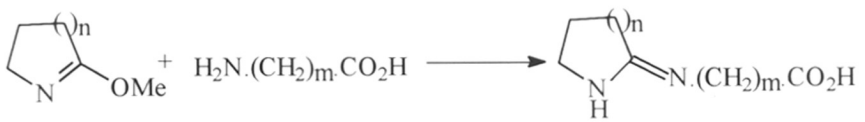
a: n = 1, b: n = 2, c: n = 3



1a **5**

The reaction of lactim ethers with amino acids has been studied in detail.[7] These reactions proceed readily resulting in the substituted amidino acids **6**(Scheme 3).

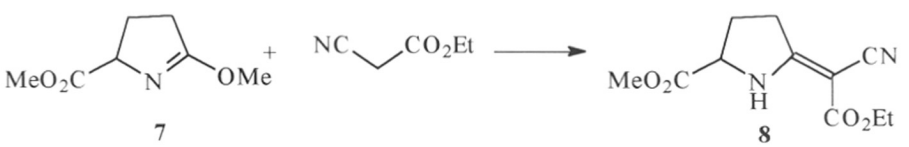
Scheme 3



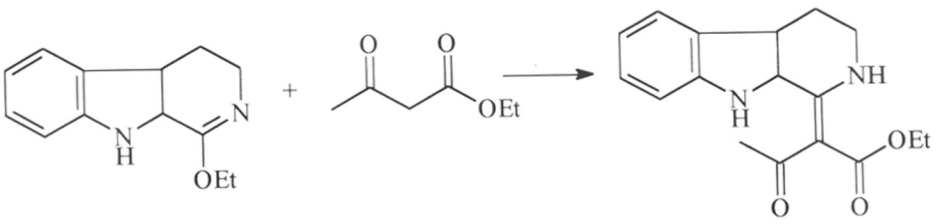
6

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 **7** with ethyl cyanoacetate led to the compound **8**(Scheme 4).[8] Similar condensation of the lactim ether of tetrahydro-β-carbolinone **9** with acetoacetic ester gave compound **10**.[9]

Scheme 4



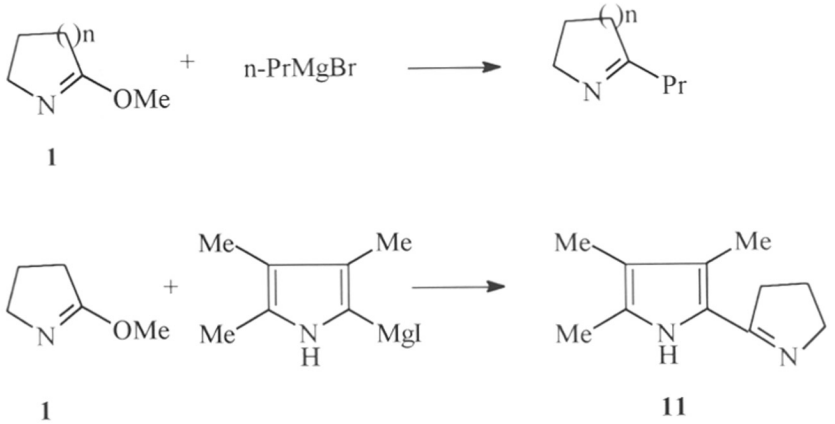
7 **8**



9 **10**

Grignard reagents react with lactim ethers resulting in the substitution of an alkyl or aryl group for the alkoxy group of the lactim ether.[10] An interesting example of this reaction is in the synthesis of 2, 2′-pyrrolylpyrrolines **11**(Scheme 5).

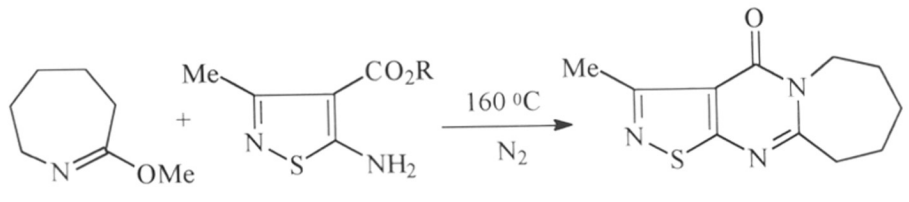
Scheme 5



1 **1** **11**

Initial attack by a nucleophile on the sp^2 carbon can be followed by intramolecular nucleophilic attack by the nitrogen of the lactim ether on a suitably located electrophilic centre. This would lead to cyclisation. For example 5-amino-3-methylisothiazole-4-carboxylic acid and its ester **12** undergo condensation with O-methyl caprolactim **1c** to give 3- methyl-4-oxo-6, 7, 8, 9-tetrahydro-4H, 10H-isothiazolo [5, 4 -d] pyrimidino [1, 2 -a] azepine **13**(Scheme 6).[11]

Scheme 6

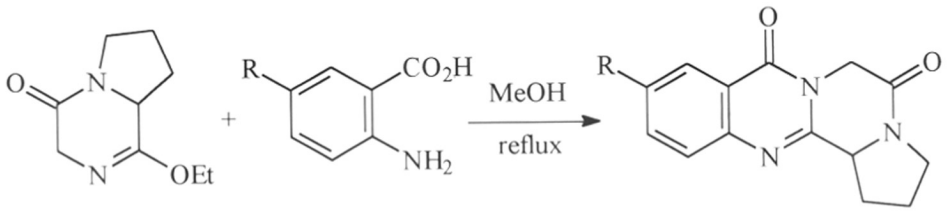


1c **12** **13**

R = H or Et

The reaction of cyclodipeptide monoiminoether **14** with various anthranilic acids produced tetracyclic quinazolones **15**(Scheme 7).[12]

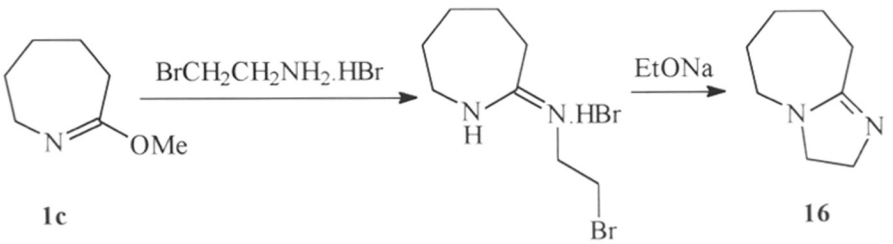
Scheme 7



14 **15**

Similarly in the synthesis of imidazo [1, 2 -a] azepine **16** by Stolle *et al*[13] initial formation of an amidine is followed by cyclisation(Scheme 8).

Scheme 8



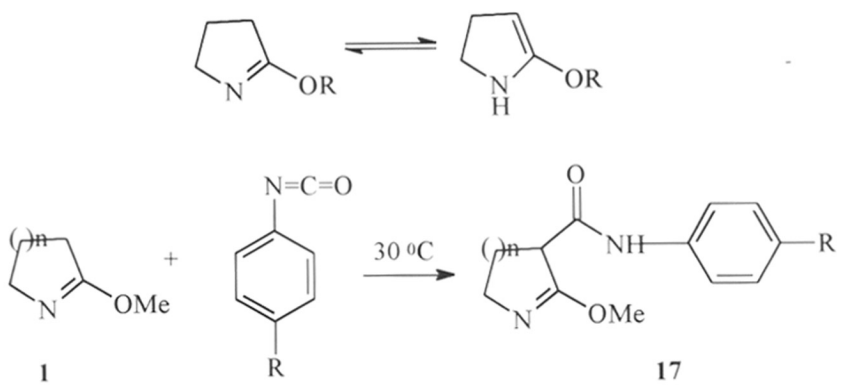
1c **16**

Reaction of lactim ethers with electrophiles

The reaction of lactim ethers with electrophiles can take several routes. In most of the reactions, the nitrogen of the lactim ether acts as the nucleophile. But this is not always the case. There are examples in the literature where C-3 is the site of electrophilic

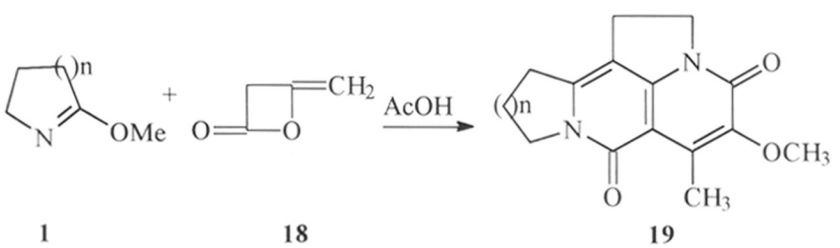
attack. This obviously results from the reaction of the lactim ether as its enamine tautomer. Thus the five membered γ-butyrolactim ether **1a** and its six membered homolog **1b** react with aryl isocyanates at C-3 to form the phenylcarbamoyl derivatives **17**(Scheme 9).[14]

Scheme 9



The initial nucleophilic attack of one molecule of the lactim ether in its enamine form on another molecule of the lactim ether at the electrophilic carbon has been suggested to account for the product **19** of the reaction of lactim ethers with diketene **18**(Scheme 10).[15]

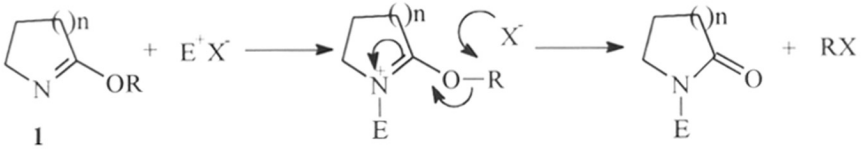
Scheme 10



Electrophilic attack at the nitrogen atom of the lactim ethers can have at least two sequels. There are several examples in the literature in which the second step is the attack by the counterion on the alkyl group of the ether leading to N-substituted lactams

via alkyl-oxygen cleavage(Scheme 11). This is the case with alkylation,[16] acylation[17] and sulfonylation.[18]

Scheme 11

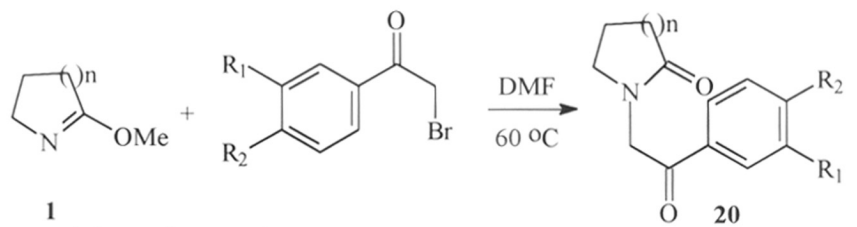


1

a: n = 1 b: n = 2 c: n = 3

Treatment of the lactim ethers **1a-c** with phenacyl bromide or 3, 4-dimethoxyphenacyl bromide in DMF at 60° C furnished the corresponding N-substituted lactams **20** in good yields(Scheme 12).[16]

Scheme 12

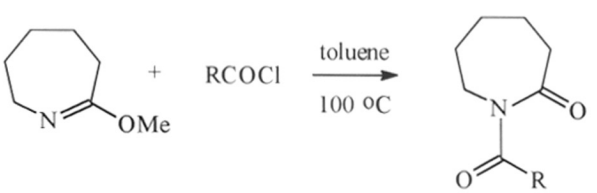


1

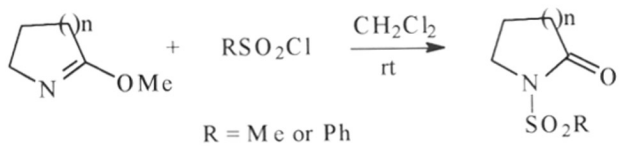
a: n = 1; b: n = 2; c: n = 3

Similarly acylation of caprolactim ether **1c** with acid chlorides in toluene at 100 °C led to the N-acylcaprolactam **21**.[17] N- Sulfonyl lactams **22** were prepared by the reaction of lactim ethers **1a-c** with methanesulfonyl or benzenesulfonyl chloride in CH_2Cl_2 at 30 °C (Scheme 13).[18]

Scheme 13



1c **21**



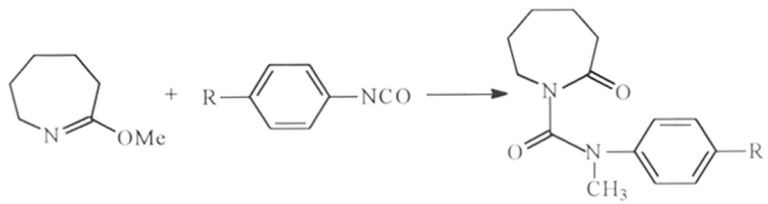
1

a: n = 1; b: n = 2; c: n = 3

22

In the reaction of lactim ether **1c** with aryl isocyanates the counterion is the nitrogen of the original isocyanate; the product therefore, is the N- methylated acyl urea **23**(Scheme 14).[19]

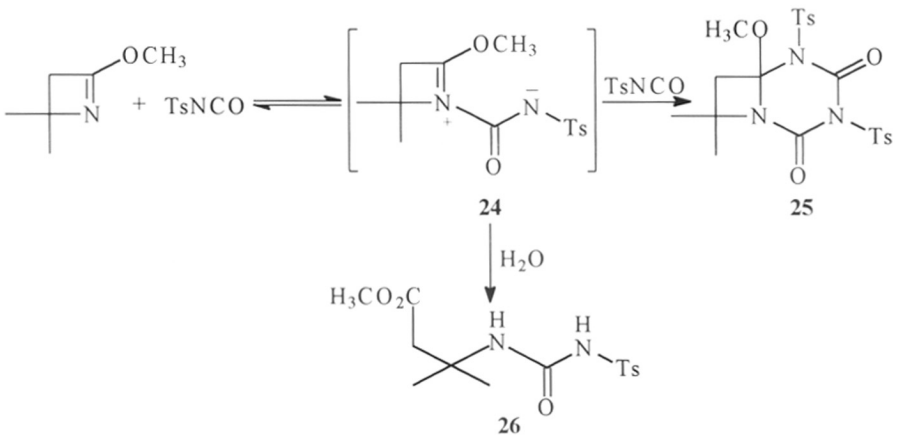
Scheme 14



1c **23**

The intermediate dipolar addition compound **24** has been isolated in the reaction of the four membered lactim ether with p-toluenesulfonyl isocyanate(Scheme15).[20]

Scheme 15

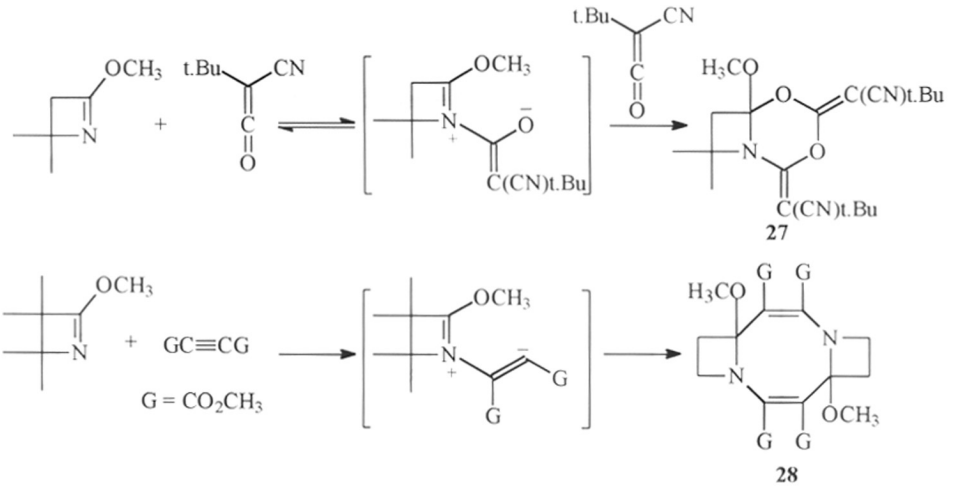


24 **25**

26

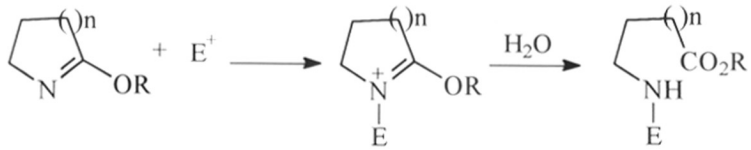
Other alternatives open to such dipolar intermediates is the reaction with a second molecule of the electrophile followed by cyclisation **27** [21] or direct dimerization to form 8-membered ring compound **28**(Scheme 16).[22]

Scheme 16



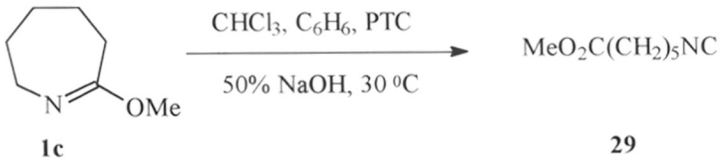
Most interesting is the reaction of lactim ethers with electrophiles followed by opening of the ring(Scheme 17).

Scheme 17



Thus ω-isocyanocarboxylic acid esters **29** are reported to result from the reaction of lactim ethers with chloroform in aqueous alkali or alkaline earth metal hydroxides and a phase transfer catalyst(Scheme 18).[23]

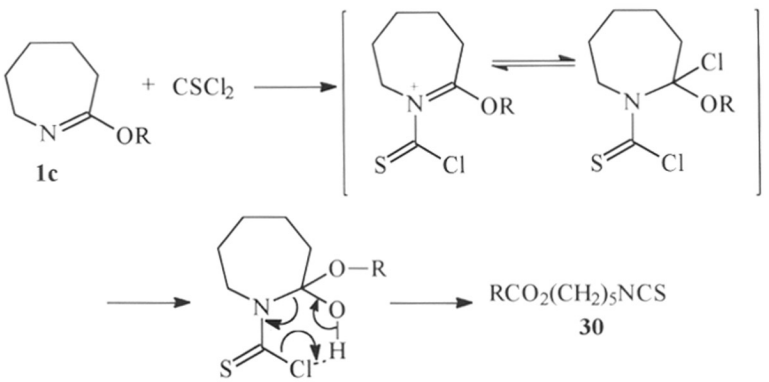
Scheme 18



1c **29**

Similarly lactim ether **1c** reacts with thiophosgene to form the ω-isothiocyanatocarboxylic ester **30**(Scheme 19).[24]

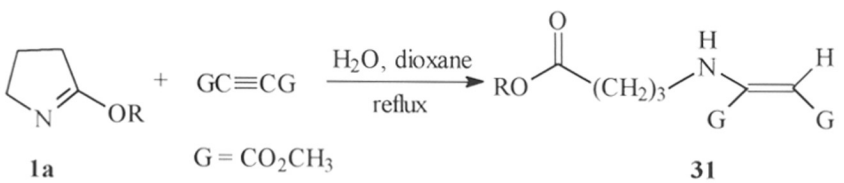
Scheme 19



30

Another example is the reaction of dimethyl acetylenedicarboxylate (DMAD) with γ- butyrolactim ether **1a** in boiling aqueous dioxane yielding the ring-opened compound **31** in 40% yield(Scheme 20).[22]

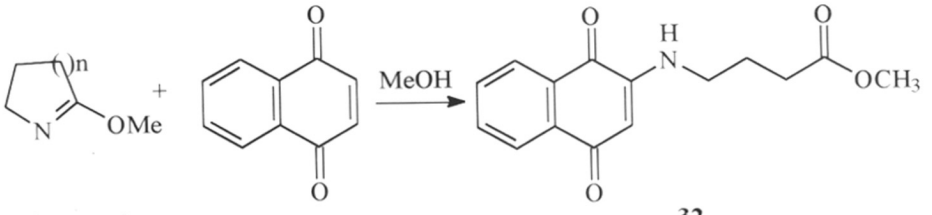
Scheme 20



1a **31**

There is also a recent report that 1,4- naphthaquinone reacts with butyrolactim ether **1a** in methanol to form 2-(3-methoxylcarbonylpropylamino)-1, 4-naphthaquinone **32**(Scheme 21).[25]

Scheme 21



1a : n = 1

32

References

1. R. G. Glushkov and G. Granik, *Adv. Het. Chem.*, **1970**, *12*, 185 edited by A.R Katritzky and A. J. Boulton, Academic press.
2. H. Baumann and D. Leuchs, *Chem. Abstr.*, **1961**, *55*, 27903.
3. R. B. Lund, P. W. Simon, J. R. Pedersen and H. K. Reimschuessel, *Chem. Abstr.*, **1965**, *62*, 10612.
4. R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc*, **1948**, *70*, 2115.
5. A. Etienne and J. Correia, *Compt. Rend*, **1964**, *259c*, 2660.
6. L. Juergen, P. Michael and B. Ute, *Z. Chem*, **1986**, *26*, 289.
7. E. Profft and F. J. Becker, *J. Prakt. Chem*, **1965**, *30*, 18.
8. F. Dominique, R. Benoit, L. Catherine, C. Pascal and D, Daniel, *J. Heterocycl. Chem*, **1992**, *29*, 1285.
9. H. Henecka, R. Lorenz and h. Timmler, *Chem. Abstr*, **1961**, *55*, 3622.
10. V. Dubek and O. Li-kuan, *Coll. Czech. Chem. Commun*, **1965**, *30*,2472.
11. S. Rajappa, B. G. Advani and R. Sreenivasan, *Ind. J. Chem*, **1976**, *14B*, 391.
12. S. Rajappa and B. G. Advani, *Tetrahedron*, **1973**, *29*, 1299.
13. R. Stolle, M. Merkle and F. Hanusch, *J. Prakt. Chem*, **1934**, *140*, 59.
14. U. Kraatz, *Tetrahedron*, **1973**, *29*, 3991
15. T. Kato and T. Sakamoto, *Chem. Pharm. Bull*, **1975**, *23*, 2629.
16. T. Fujii, S. Yoshijuji and K. Yamamoto, *Chem. Pharm. Bull*, **1978**, *26*, 2071.
17. b) B. Stoll and W. Griehl, *Helv. Chim. Acta*, **1965**, *48*, 1805.
    a) H. Kiefer, *Synthesis*, **1972**, 81.
18. J. Sheu, M. B. Smith, T. R. Oeschger and J. Satchell, *Org.Prep. Proc. Int*, **1992**, *24*, 147.
19. U. Kraatz, *Tetrahedron Lett*, **1973**, 1219.

20. D. H. Aue and D. Thomas, *J. Org. Chem*, **1975**, *40*, 2356.

21. D. H. Aue and D. Thomas, *J. Org. Chem*, **1975**, *40*, 2552.

22. D. H. Aue and D. Thomas, *J. Org. Chem*, **1975**, *40*, 2360.

23. G. Fengler and A. Boffa, *Chem. Abstr*, **1980**, *92*, 6085.

24. J. Gonda, P. Kristian and L. Mikler, *Coll. Czech. Chem. Commun*, **1986**, *51*, 112.

25. J. P. Michael, P. F. Cirillo, L. Denner, G. D. Hosken, A. S. Howard and O. S. Tinkler, *Tetrahedron*, **1990**, *46*, 7923.

CHAPTER 2

Chapter 2 has been divided into five sections

Section A: Reaction of 5, 6 and 7 membered lactim ethers with various push-pull ethylenes and other electrophiles.

1. Introduction

This section describes the reaction of lactim ethers with different electrophiles leading to lactam ring opening. There are a few scattered examples known in literature where initial nucleophilic attack by the nitrogen of the lactim ethers has ultimately yielded an acyclic product. Reaction of caprolactim ether with chloroform in presence of alkali or alkaline earth metal hydroxides and a phase transfer catalyst[1], the reaction of lactim ethers with thiophosgene[2], the reaction of dimethyl acetylenedicarboxylate (DMAD) with butyrolactim ether[3] and the reaction of butyrolactim ether with 1,4-naphthaquinone[4] gave ring opened products. Such examples have been catalogued in chapter 1. A detailed study of such reactions has not yet been made. The present section describes several new reactions of lactim ethers with different push-pull ethylenes and other electrophiles which result in lactam ring opening.

2. Objective

The objective was to study the reactions of lactim ethers with different push-pull ethylenes and other electrophiles in detail. This study has potential in synthesis where the lactim ethers (or lactams) are more easily accessible than the corresponding ω-aminoalkyl carboxylic esters.

3. Results and Discussion

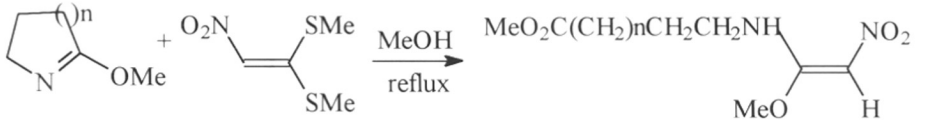
The reactions of γ- butyrolactim ether (**1a**), δ- valerolactim ether (**1b**) and ε-caprolactim ether (**1c**) with different electrophilic push-pull ethylenes namely 1, 1-bismethylthio-2-nitroethene **2**[5], ethoxymethyleneacetylacetone **3**[6], ethyl ethoxymethyleneacetoacetate **4**[6] and diethyl ethoxymethylenemalonate **5**[6] have been studied. For comparison, the reaction of lactim ethers (**1a-c**) with other electrophiles

such as p-toluenesulfonyl chloride (**6**) and ethyl chloroformate (**7**) have also been studied. In all the cases, initial nucleophilic attack by the nitrogen of the lactim ether was followed by ring opening. The yields of the ring opened products, ω- aminoalkyl carboxylic esters ranged from 38 to 68%. The reactions were slow except those of p-toluenesulfonyl chloride and ethyl chloroformate.

3.1 Reaction of lactim ethers (1a-c) with nitroketene dithioacetal (2)

Reaction of the γ- butyrolactim ether **1a** with 1, 1-bismethylthio-2-nitroethene **2** in refluxing methanol for 72h gave methyl N-(1-methoxy-2-nitroethenyl) aminobutanoate **8a** in 43% yield(Scheme 1). The ^{1}H NMR spectrum of the compound **8a** showed a multiplet at 1.90δ due to the central methylene of the $CH_2CH_2CH_2$ chain. The other two methylenes were seen at 2.40δ (t, 2H, J = 8Hz) ($COCH_2$) and 3.45δ (q, 2H, J = 7Hz) (NCH_2). The two methoxy groups appeared as singlets at 3.75δ and 3.90δ. The olefinic proton was seen as a singlet at 6.70δ and NH as a broad singlet at 9.85δ. The mass spectrum of **8a** showed the molecular ion peak (M^+) at m/z 218. From the above data the structure of the compound could be assigned as **8a**(Figure 1).

Scheme 1

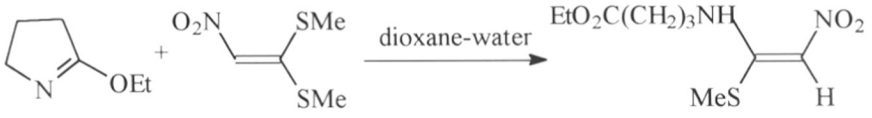


1 a: n = 1, b: n = 2, c: n = 3 **2** **8** a: n = 1, b: n = 2, c: n = 3

By a similar procedure δ-valerolactim ether **1b** and ω- caprolactim ether **1c** were reacted with nitroketene dithioacetal **2** leading to **8b** and **8c** respectively in 50% and 56% yields. As above the structure of **8b** and **8c** were confirmed from their ^{1}H and ^{13}C NMR, mass spectra and elemental analyses.

The intermediacy of the corresponding methylthio compounds in the formation of the methoxy derivatives (**8**) was proved by carrying out the condensation of γ-butyrolactim ethyl ether with nitroketene dithioacetal **2** in dioxane-water (3:1) instead of in methanol; under these conditions, the methylthio substituted nitroenamine **9** was obtained in 65% yield(Scheme 2). The structure of the compound **9** was confirmed from its ^{1}H NMR and other spectral data. The ^{1}H NMR spectrum of a purified sample of **9** showed a triplet at 1.25δ(t, 3H, J = 8.0Hz) due to the CH_3 of the ethoxy group followed by a multiplet at 2.00δ(m, 2H) for the central methylene group of the $CH_2CH_2CH_2$ chain, a triplet at 2.40δ(t, 2H, J = 8.0Hz), due to the CH_2 adjacent to the ester, a sharp singlet at 2.45δ for SCH_3, a quartet at 3.45δ(q, 2H, J = 7.0Hz) due to NCH_2 and another quartet at 4.10δ(q, 2H, J = 8.0Hz) corresponding to OCH_2 of the ethoxy moiety. The olefinic proton was seen as a sharp singlet at 6.55δ and NH proton appears as a broad peak at 10.50δ. The mass spectrum of **9** showed the molecular ion (M^+) peak at m/z 248. From the above data the structure of the compound was proved to be **9**(Figure 2).

Scheme 2



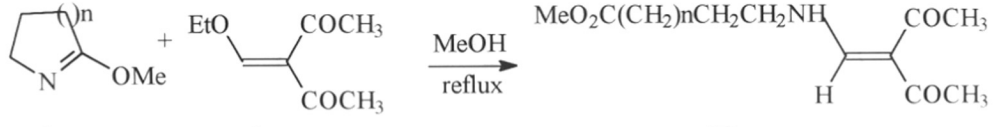
2 **9**

It has been established earlier that nitroenamines possessing an NH group exist almost exclusively in the intramolecularly hydrogen-bonded configuration, especially in non-polar solvents.[7] It is also known that the barrier to rotation around the formal double-bond in such systems is low enough to preclude isolation of the energetically less favoured geometrical isomer.[7] On this basis, the products **8a-c** and **9** have been assigned the (*E*)- configuration (NH and NO_2 *cis* to each other).

3.2 Reaction of lactim ethers (1a-c) with ethoxymethyleneacetylacetone (3)

The reaction of lactim ethers (**1a-c**) took a similar course with other electrophilic push-pull ethylene systems as well. Thus ethoxymethyleneacetylacetone **3** was treated with ω-caprolactim ether **1c** in boiling methanol to give **10c** in 68% yield(Scheme 3). The ^{1}H NMR spectrum of **10c** shows a multiplet at 1.45δ due to the central methylene group of the $CH_2CH_2CH_2CH_2CH_2$ chain followed by another multiplet at 1.65(m, 4H) ($2CH_2$), a singlet at 2.25δ for $COCH_3$, a triplet at 2.35δ(t, 2H, J = 8.0Hz) due to the CH_2 adjacent to the ester, a singlet at 2.50δ corresponding to $COCH_3$ and a quartet at 3.35δ(q, 2H, J = 7.0Hz) due to the NCH_2 protons. The methoxy group appears as a sharp singlet at 3.65δ and the olefinic proton was seen as a doublet at 7.75δ(d, 1H, J = 14Hz). The most downfield signal appears at 11.00δ due to the NH proton. The mass spectrum of the compound showed the molecular ion (M^+) peak at m/z 255. The above data proved the structure of the compound to be **10c**(Figure 3).

Scheme 3



1 **3** **10**

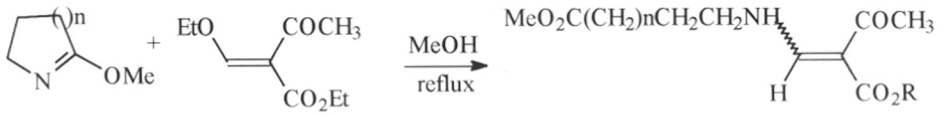
a: n = 1, b: n = 2, c: n = 3 a: n = 1, b: n = 2, c: n = 3

In a similar way γ- butyrolactim ether **1a** and δ-valerolactim ether **1b** underwent reaction with **3** to give **10a** and **10b** in 48% and 53% yields respectively. The structure of both the compounds was established from their IR, ^{1}H NMR and mass spectral data. ^{13}C NMR and microanalytical values provided additional support to the structure **10a**, **10b** and **10c.**

3.3 Reaction of lactim ether (1a-c) with ethyl ethoxymethyleneacetoacetate (4)

The reaction of lactim ethers **1a** with ethyl ethoxymethyleneacetoacetate **4** in refluxing methanol gave compound **11a** in 38% yield(Scheme 4). The ^{1}H NMR spectrum of the compound **11a** showed a triplet at 1.30δ(t, 3H, J = 8Hz) due to the CH_3 of ethyl moiety was closely followed by a multiplet at 2.00δ due to the central methylene group of the $CH_2CH_2CH_2$ chain, a triplet at 2.40δ(t, 2H, J = 7.0Hz) for the $COCH_2$, a singlet at 2.50δ due to the $COCH_3$ protons and a quartet at 3.45δ(q, 2H, J = 7.0Hz) corresponding to NCH_2. The methoxy group appeared as a sharp singlet at 3.75δ followed by a quartet at 4.20δ(q, 2H, J = 8.0Hz) due to the OCH_2 of the ethoxy group. The olefinic proton was seen as a doublet at 8.00δ(d, 1H, J = 14Hz) and the NH proton appeared as a broad peak at 11.00δ. The mass spectrum of **11a** showed the molecular ion (M^+) peak at m/z 257. ^{13}C NMR, IR and analytical data also confirmed the structure of the compound to be **11a**(Figure 4).

Scheme 4



1 **4** **11**

a: n = 1, b: n = 2, c: n = 3

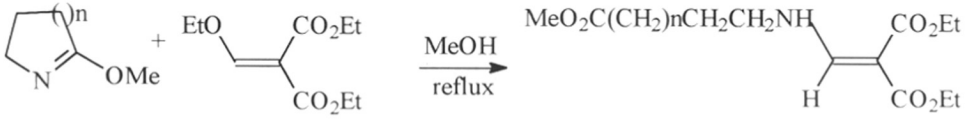
a: n = 1, R = Et
b: n = 2, R = Me
c: n = 3, R = Me

Similarly, lactim ethers **1b** and **1c** on treatment with ethyl ethoxymethyleneacetoacetate (**4**) in refluxing methanol gave **11b** (55%) and **11c** (57%) respectively. As before the structure of **11b** and **11c** was confirmed from their ^{1}H, ^{13}C NMR and other analytical data. Tranesterification had taken place in the two products **11b** and **11c** under the reaction conditions, leading to methyl esters from ethyl ethoxymethyleneacetoacetate (**4**).

3.4 Reaction of lactim ethers (1a-c) with diethyl ethoxymethylenemalonate (5)

Similar reaction of δ- valerolactim ether **1b** with diethyl ethoxymethylenemalonate (**5**) in methanol at 65 °C for 72h gave the ring opened product **12b** in 60% yield(Scheme 5). The structure of the product was confirmed from its spectral data. The ^{1}H NMR spectrum of **12b** showed two overlapping triplets at 1.30δ due to the two CH_3 groups followed by a multiplet at 1.70δ due to the two central methylene groups of the $CH_2CH_2CH_2CH_2$ chain. The other two methylenes were seen at 2.35δ(t, 2H, J = 8.0Hz) for $COCH_2$ and 3.35δ(q, 2H, J = 7.0Hz) for NCH_2. A singlet at 3.70δ was assigned to the methoxy protons; the two OCH_2 groups appeared at 4.20δ. The olefinic proton appeared as a doublet at 7.95δ(d, 1H, J=15Hz) and the NH proton appeared as a broad peak at 9.20δ. The mass spectrum of the compound **12b** showed the molecular ion (M^+) peak at m/z 301. From the above data the structure of the compound was proved to be **12b**(Figure 5).

Scheme 5



1 **5** **12**

a: n = 1, b: n = 2, c: n = 3 a: n = 1; b: n = 2; c: n = 3,

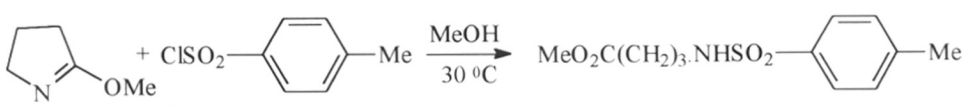
Similarly γ- butyrolactim ether and ω- caprolactim ether reacted with **5** giving the acyclic products **12a** and **12c** in 40% and 55% respectively. As usual the structure of **12a** and **12c** were confirmed from their spectral data and analytical values.

The configuration around the double bond in the aminomethylene acetoacetic ester derivatives **11** is uncertain, although in each case only one species was observed in the NMR spectrum in $CDCl_3$ solution.

3.5 Reaction of γ-butyrolactim ether (1a) with p-toluenesulfonyl chloride (6)

Reaction of γ-butyrolactim ether (**1a**) with p-toluenesulfonyl chloride (**6**) in methanol at 30 °C gave the ring opened product **13a** in 60% yield(Scheme 6). The ^{1}H NMR spectrum of a purified sample of **13a** showed a multiplet at 1.95δ due to the central methylene group of the $CH_2CH_2CH_2$ chain. The other two methylenes were seen at 2.28δ(t, 2H, J = 8.0Hz) ($COCH_2$) and 2.95δ(q, 2H, J = 7.5Hz) (NCH_2). Ar$\underline{CH_3}$ appeared as a sharp singlet at 2.30δ and OCH_3 as another sharp singlet at 3.60δ. The NH proton was seen at 5.00δ as a broad singlet and the aromatic protons appeared as two doublets at 7.30δ and 7.55δ(A_2B_2). The above reaction of p-toluenesulfonyl chloride with butyrolactim ether has also been reported by Sheu *et al*[8]; the spectral values were compared and found to be the same(Figure 6).

Scheme 6



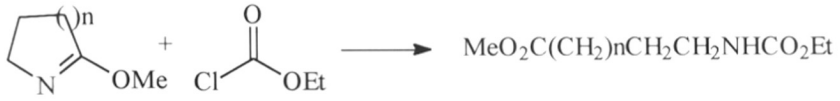
1a **6** **13a**

3.6 Reaction of lactim ethers (1a-c) with ethyl chloroformate (7)

Reaction of ethyl chloroformate (**7**) with lactim ethers (**1a-c**) at 30 °C for 2h in methanol solution gave the acyclic products after an aqueous work-up. Thus δ-valerolactim ether **1b** on treatment with ethyl chloroformate **7** gave the ring opened compound **14b** in 71% yield(Scheme 7). The ^{1}H NMR spectrum of **14b** showed a triplet at 1.20δ(t, 3H, J = 8.0Hz) due to the CH_3 of the ethyl moiety followed by a multiplet at 1.30-1.70δ(m, 2H) for the two central methylene groups of the $CH_2CH_2CH_2CH_2$ chain. The other two methylenes were seen at 2.25δ(t, 2H, J = 8.0Hz) ($COCH_2$) and at 3.10δ(q, 2H, J = 7.5Hz) (NCH_2). The methoxy group appeared as a sharp singlet at 3.60

followed by a quartet at 4.05δ(q, 2H, J = 8.0Hz) corresponding to OCH_2 of the ethoxy moiety. The NH proton was seen at 4.95δ as a broad singlet(Figure 7).

Scheme 7



1 **7** **14**

a: n = 1, b: n = 2, c: n = 3 a: n = 1, b: n = 2, c: n = 3

Similarly, γ- butyrolactim ether **1a** and ω-caprolactim ether **1c** were reacted with ethyl chloroformate **7** to give **14a** and **14c** in 68% and 72% yields respectively. The structure of **14a** and **14c** was proved from their spectral data.

4. Conclusion

- Reaction of lactim ethers with nitroketene dithioacetal led to the N- substituted product with simultaneous lactim ring opening.
- Similar reaction of other electrophiles such as ethoxymethyleneacetylacetone, ethyl ethoxymethyleneacetoaetate, diethyl ethoxymethylenemalonate, p-toluenesulfonyl chloride and ethyl chloroformate also resulted in the formation of acyclic compounds.

Section B: Reaction of lactim thioethers with eletrophiles: Comparison of the reactivity of ethers and thioethers

1. Introduction

In this section the reaction of the lactim thioethers with a series of electrophilic push-pull ethylenes and other electrophiles in methanol is described. This reaction also led to ring opened products. The products were identical with those obtained from lactim ethers as reported in the earlier section.

2. Objective

The objective in this study was to compare the reactivity of the lactim ethers and lactim thioethers with the same set of electrophiles under the same reaction conditions.

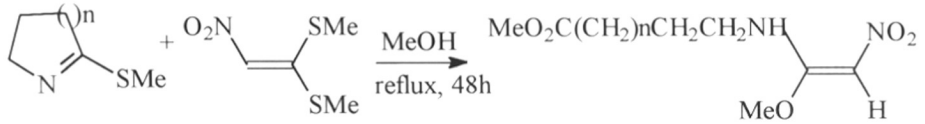
3. Results and Discussion

3.1 Reaction of lactim thioethers with nitroketene dithioacetal (2)

Reaction of lactim thioethers (**15a-c**) with 1, 1-bismethylthio-2-nitroethene **2** in boiling methanol for 48h gave ring-opened products. This reaction of lactim thioether was faster than the reaction of the corresponding lactim ethers (**1a-c**) with **2**. The yield of the products was also higher with the thioethers. Thus γ- butyrolactim thioether **15a** on treatment with **2** in methanol at 65 °C for 48h, gave methyl N-(methoxy-2-nitroethenyl) aminobutanoate **8a** in 64% yield. The methylthio group had been replaced by methoxy under the reaction conditions(Scheme 8). The ^{1}H, ^{13}C NMR and mass spectral data proved the structure of the acyclic compound to be **8a**. Similarly δ-valerolactim thioether **15b** and ω- caprolactim thioether **15c** were reacted with **2** to give the ring-opened products **8b** and **8c** respectively in 65% and 75% yields. As expected from the relative nucleophilicity of the nitrogen atom in lactim ethers and lactim thioethers, reaction of the lactim thioethers with **2** led to the higher yields of the products. Thus lactim thioethers (**15**) gave **8a-c** in 64, 65 and 75% yields respectively on

reaction with **2**, while the corresponding lactim ethers (**1**) gave (**8a-c**) in 43, 50 and 56% yields respectively.

Scheme 8



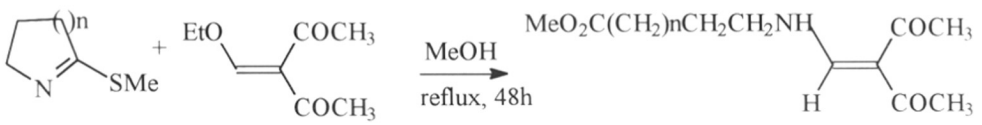
15 **2** **8**

a: n = 1, b: n = 2, c: n = 3 a: n = 1, b: n = 2, c: n = 3

3.2 Reaction of lactim thioethers (15a-c) with ethoxymethyleneacetylacetone (3)

Reaction of the lactim thioether **15a** with ethoxymethyleneacetylacetone **3** in refluxing methanol for 48h gave the ring-opened product **10a** in 71% yield(Scheme 9).

Scheme 9



15 **3** **10**

a: n = 1, b: n = 2, c: n = 3 a: n = 1, b: n = 2, c: n = 3

Similarly the reaction of δ- valerolactim thioether **15b** and ω- caprolactim thioether **15c** led to the ring-opened products **10b** and **10c** in 70% and 79% yields respectively.

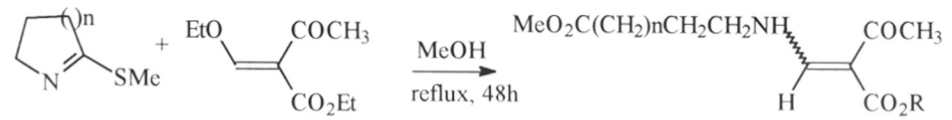
Lactim thioethers invariably gave higher yields of the product as compared to their oxygen counterparts. Thus in the reaction with ethoxymethyleneacetylacetone **3** the yield of **10a** was 48% when lactim ether **1a** was used as the nucleophile, while the lactim thioether **15a** gave the same product in 71% yield. Similarly, in the reaction of ethoxymethyleneacetylacetone **3** with the derivatives of δ- valerolactam, the product **10b** was obtained in 70% yield when lactim thioether **15b** was used as the nucleophile, whereas the lactim ether **1b** gave only a 53% yield of the product **10b**. Likewise, the seven-membered lactim thioether **15c** on reaction with ethoxymethyleneacetylacetone **3**,

gave the product **10c** in 79% yield, whereas the corresponding lactim ether **1c** led to the product **10c** only in 68% yield.

3.3 Reaction of lactim thioethers (15a-c) with ethyl ethoxymethyleneacetoacetate (4)

When lactim thioethers **15a-c** were reacted with ethyl ethoxymethyleneacetoacetate **4** in boiling methanol for 48h the ring-opened products **11a-c** were obtained in 64-70% yield (Scheme 10). The structure of the products were confirmed from their ^{1}H NMR and other spectral data and by comparison with the products obtained earlier (See previous section).

Scheme 10



15 **4**

a: n = 1, b: n = 2, c: n = 3

11

a: n = 1, R = Et
b: n = 2, R = Me
c: n = 3, R = Me

Here also the yield of the ring-opened products **11a-c** were higher compared to the yields from the corresponding lactim ethers. The comparative yields are given in *Table 1*.

Table 1

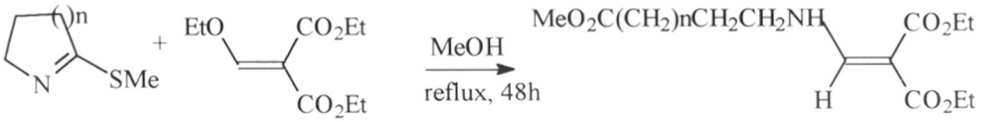
Lactim thioether	Electrophile	Product	Yield* (%)
15a	4	11a	66 (38)
15b	4	11b	64 (55)
15c	4	11c	70 (57)

* values in the parentheses are the yields obtained when the corresponding lactim ethers were used as the nucleophile.

3.4 Reaction of lactim thioethers (15a-c) with diethyl ethoxymethylenemalonate (5)

The lactim thioethers (**15a-c**) on reaction with diethyl ethoxymethylenemalonate **5** in methanol at 65 °C for 48h gave the acyclic products (**12a-c**) in 60-68% yield (Scheme 11). The structure of the products were proved by ^{1}H, ^{13}C NMR and other spectral data.

Scheme 11



15 **5** **12**

a: n = 1, b: n = 2, c: n = 3 a: n = 1; b: n = 2; c: n = 3,

They were identical to the products obtained from the corresponding lactim ethers (See previous section). The lactim thioethers invariably gave higher yields of the products **12a-c**, compared to their oxygen counterparts (*Table 2*).

Table 2

Lactim thioether	Electrophile	Product	Yield* (%)
15a	5	12a	68 (40)
15b	5	12b	60 (60)
15c	5	12c	67 (55)

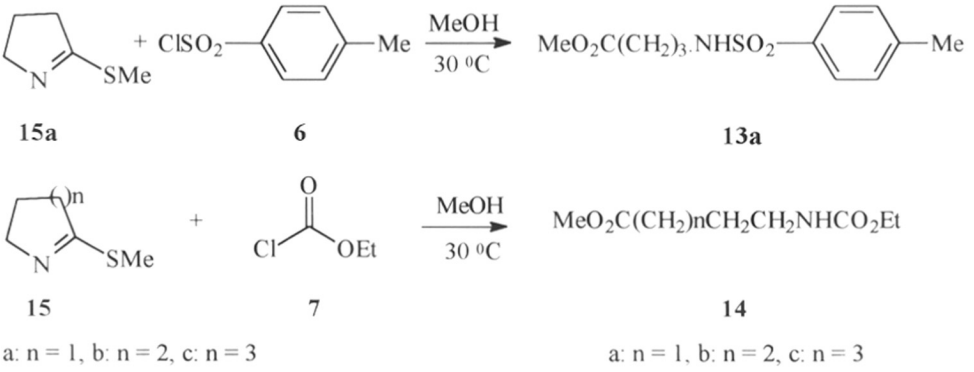
* values in the parentheses are the yields obtained when the corresponding lactim ethers were used as the nucleophile.

3.5 Reaction of lactim thioethers (15a-c) with p-toluenesulfonyl chloride and with ethyl chloroformate

γ- Butyrolactim thioether **15a** on reaction with p-toluenesulfonyl chloride **6** in methanol solution at 30 °C for 6h gave **13a** in 72% yield(Scheme 12). The structure was confirmed from its ^{1}H NMR and other spectral data. The product was identical to the one obtained earlier from the reaction of the lactim ether **1a** with p-toluenesulfonyl

chloride. The lactim thioether gave a higher yield of the product than its oxygen analog under the same reaction conditions.

Scheme 12



Lactim thioethers **15a-c** on treatment with ethyl chloroformate in methanol solution at 30 °C for 2h gave **14a-c** in 71-82% yield(Scheme 12). The corresponding lactim ethers had given slightly lower yields of **14a-c** (68-72%) in the same reaction. The products were characterised by their ^{1}H, ^{13}C NMR and other spectral data.

4. Conclusion

- Reaction of lactim thioethers with nitroketene dithioacetal led to the ring-opened products. The yields of the products were higher compared to the yields from the corresponding lactim ethers.
- Similar reaction of other electrophiles such as ethoxymethyleneacetylacetone, ethyl ethoxymethyleneacetoaetate, diethyl ethoxymethylenemalonate, p-toluenesulfonyl chloride and ethyl chloroformate also resulted in the formation of acyclic compounds with higher yields of the products as compared to their oxygen counterparts.

Section C: Approach to the synthesis of tripeptides *via* diketopiperazine monoiminoethers: Use of nitroacetyl group as a peptide synthon

1. Introduction

Synthesis of non-proteinogenic amino acids and their incorporation into synthetic oligopeptides is one of the main research objectives at present. Especially interesting in this context are the α, α- disubstituted glycine derivatives, in which the α- carbon is quaternary.

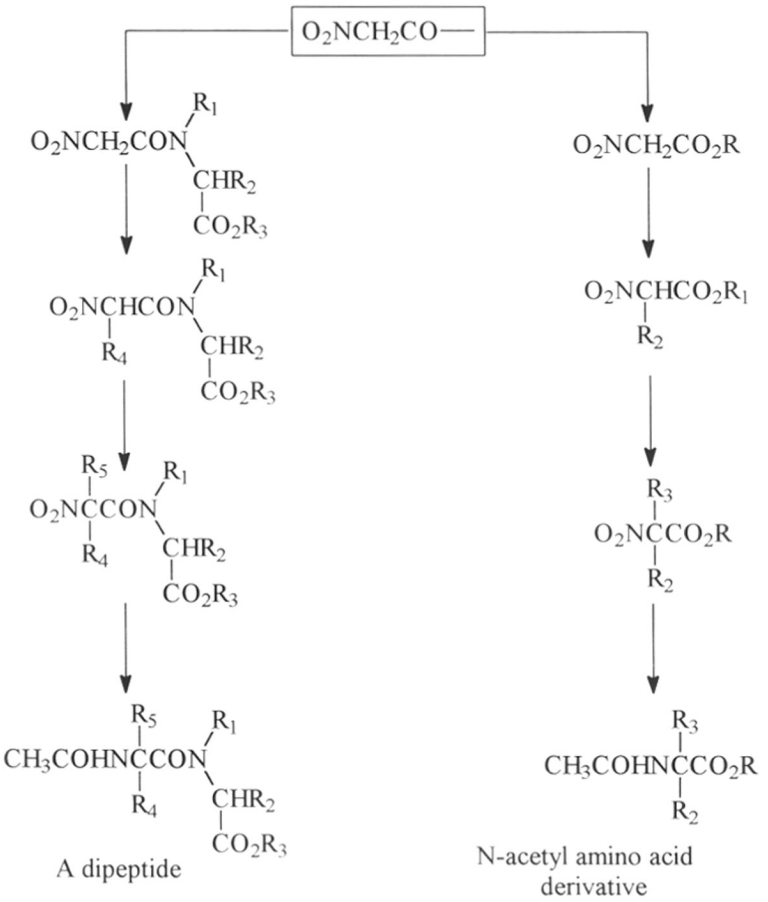
α- Amino isobutyric acid (Aib) is an example of this class. This amino acid is a constituent of Alamethicin and related peptides which are well known for their membrane modifying propeties.[9, 10]

In the recent past many synthetic methods have been developed for the synthesis of such α, α- dialkyl amino acids.[11-13] But the classical methods of incorporation of these amino acids into a peptide chain have been found to be too difficult due to the steric hindrance associated with the quaternary α- carbon atom of the α, α- disubstituted glycine and hence yields of the products are generally poor.[14] If drastic conditions are employed, racemization of other chiral centres in the molecule may occur.[15]

The nitroacetyl group would be an attractive synthon for peptides especially for those involving unnatural α- amino acids and amino acids possessing α, α- dialkyl substituents. Such an approach would have two major advantages, First, the methylene group in the nitroacetyl unit is flanked by a carbonyl and a nitro group, making it highly acidic; reactions with various electrophiles would therefore be feasible at this site. In fact one can expect a regiospecific reaction at this site, even in the presence of other carbonyl activated methylene or methine groups in the substrate. Second, the nitro group is a latent primary amine and can be transformed to an amino group at the end of other

transformations. Thus nitroacetyl derivatives could be converted to unusual peptides or α, α- disubstituted amino acid derivatives as shown below(Scheme 13).

Scheme 13

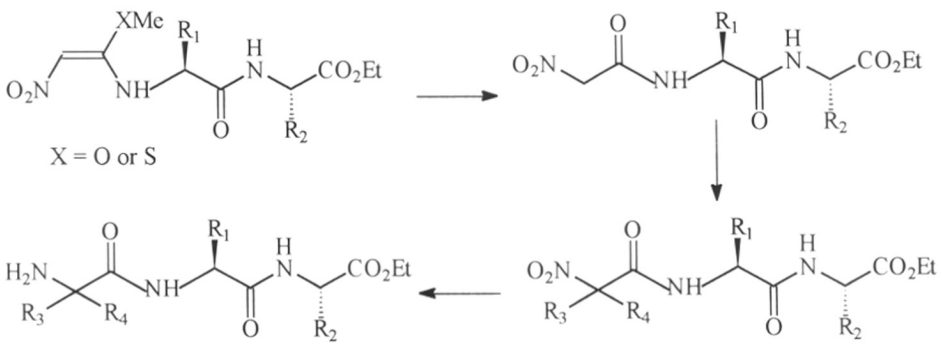


The procedure involves initial synthesis of the nitroacetamide derivative or nitroacetic ester followed by sequential mono or dialkylation at the methylene carbon atom. The last step would be reduction of the nitro group to an amine or acetyl amine. This completes the reaction sequence. Such an approach for the synthesis of tripeptides from the reaction of a diketopiperazine monoiminoether with 1, 1- bismethylthio-2-nitroethene is discussed below.

2. Objective

The objective of this study was to utilise nitroketene O, N- acetal or S, N- acetal for the synthesis of tripeptides incorporating non-natural α- alkylated amino acids at the N- terminus(Scheme 14). The route involves hydrolysis to the nitroacetamides and subsequent regiospecific alkylation of the reactive methylene group, followed by reduction of the NO_2 to NH_2.[16]

Scheme 14

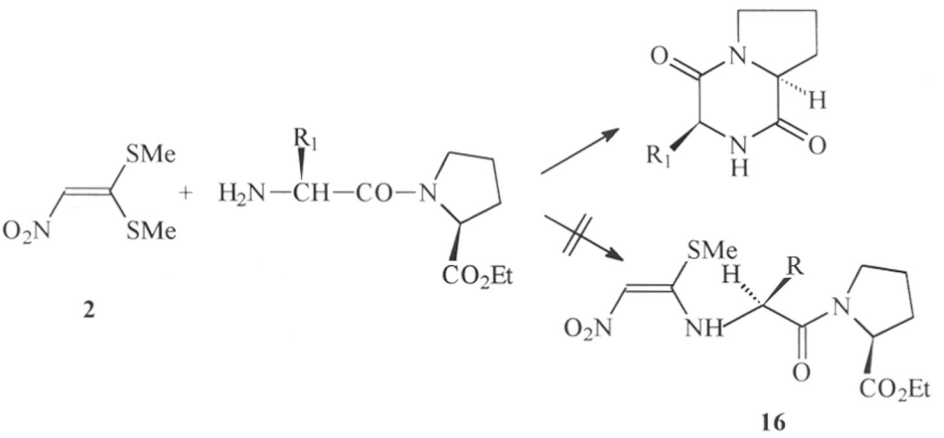


3. Results and Discussion

3.1 Reaction of cyclodipeptide monoiminoether 15[17] with 1,1- bismethylthio-2-nitroethene 2

The initial aim was to synthesise the nitroketene S, N- acetal **16** from 1, 1-bismethylthio-2-nitroethene **2**. One possibility would be to react **2** with the dipeptide having a free NH_2. However, this might result in the formation of the diketopiperazine, rather than the required condensation product **16**(Scheme 15).

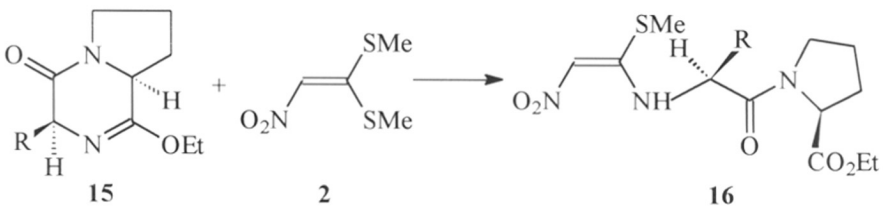
Scheme 15



2 **16**

The lactim ether ring-opening reaction discussed in the earlier sections would therefore be ideally suited in the present case. Towards this objective cyclo (L-Pro-Gly) monoiminoether **15a** was treated with nitroketene dithioacetal **2** in methanol solution at 65 °C for 72h. This gave the condensation product **16a** in 32% as a yellow solid (Scheme 16).

Scheme 16



15 **2** **16**

a: R = H; b: = CH_3; c: = $CH(CH_3)_2$; d: = $CH_2CH(CH_3)_2$; e: = CH_2Ph

The ^1H NMR spectrum of a purified sample of **16a** showed a triplet at 1.30δ(t, 3H, J = 8Hz) for the CH_3 of the ethyl group followed by a multiplet at 1.85-2.40δ(m, 4H) due to the two methylene group protons, a sharp singlet at 2.45δ for SCH_3 and a quartet at 4.20δ(q, 2H, J = 7.1Hz) corresponding to OCH_2 of the ethoxy group. A multiplet was seen at 3.50-4.35δ(m, 5H) due to the $NHCH_2$, NCH_2, NCHCO followed

by a sharp singlet at 6.60δ corresponding to olefinic proton. The NH proton appeared as a broad singlet at 10.70δ(Figure 8). The microanalytiacl data gave further evidence for the structure. Based on the above data, the structure of the compound was confirmed as **16a**.

Likewise several other cyclodipeptide monoiminoethers **15(b to e)** were reacted with **2** in methanol solution, in the hope of obtaining nitroketene S, N-acetal (**16b-e**). Unfortunately, the initial condensation was successful only with the cyclo (L-Pro-Gly) monoiminoether **15a** (R=H), leading to **16a** (R=H). The reaction failed with the analogous derivatives of L- alanine, L- valine, L- leucine and L- phenylalanine; in each case the starting material was recovered.

4. Conclusion

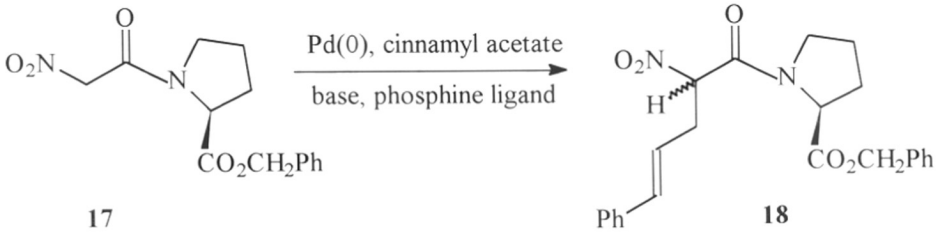
- Cyclodipeptide monoiminoether **15a** (R=H), obtained from cyclo (L-Pro-Gly), gave the ring-opened compound **16a** on reaction with nitroketene dithioacetal.
- The condensation failed when R was an alkyl group in **15**.

Section D: Attempts at ring-opening the lactim ether derived from pyroglutamate

1. Introduction

The concept behind the use of the nitroacetyl group as a synthon for peptide synthesis has been explained in the previous section. Earlier research from this laboratory had shown that in the Pd(0)- catalysed allylation of N- nitroacetyl (S)- prolinate (**17**)[18], the *de* of the product was about 45%(Scheme 17). Other α- amino acids had given lower diastereoselectivity in this allylation.

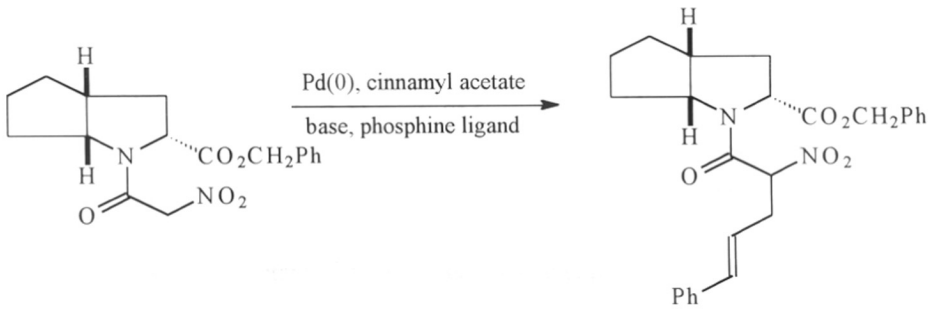
Scheme 17



17 **18**

Benzyl (1R, 3R, 5R)-2-azabicyclo[3.3.0] ocatne-3-carboxylate **19** a bicyclic analog of proline, on cinnamylation resulted in compound **20** with a diastereomeric excess of 65%(Scheme 18).[19]

Scheme 18

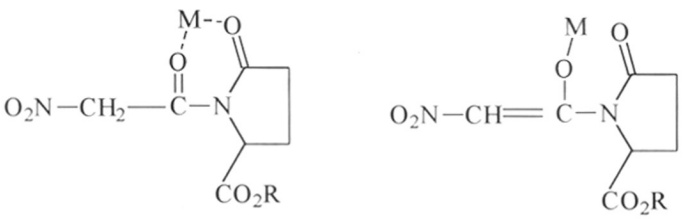


19 **20**

The relatively higher diastereomeric excess in the case of compound **19** was believed to be due to restricted rotation around the amide bond in the parent nitroacetamides. The bulkier bicyclic amino group in the above nitroacetamide puts additional constraints on rotation around the amide bond.

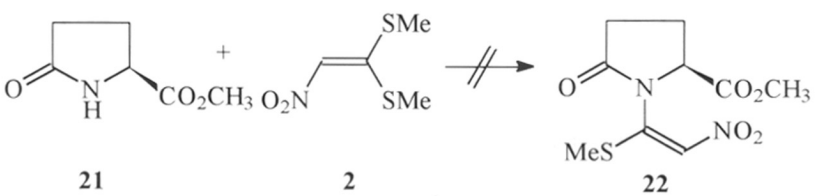
It was felt that the use of (S)- pyroglutamate as the chiral auxiliary in place of (S)- prolinate might lead to enhanced diastereoselectivity, since the configuration around the enolate double bond could be held rigid by utilising the oxygen atoms of the two carbonyl groups for metal-complexation (Structures 1 & 2).

Structures 1 & 2



Unfortunately in earlier work in this laboratory the condensation of 1,1-bismethylthio-2- nitroethene **2** with (S)- methylpyroglutamate **21** had failed to give the nitroketene S, N- acetal **22**(Scheme 19), the putative precursor of the N- nitroacetyl derivative of pyroglutamate.

Scheme 19



21 **2** **22**

Obviously, the lactam nitrogen was not nucleophilic enough to react with **2**. In the earlier section, it has been demonstrated that lactim ethers are better nucleophiles

than lactams; the simple 5-, 6- and 7- membered lactim ethers had been successfully reacted with 1, 1- bismethylthio-2-nitroethene **2** to result in ring-opened products.

2. Objective

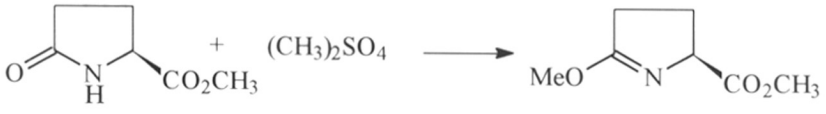
The objective of this study was therefore to increase the nucleophilicity of the nitrogen in pyroglutamate by converting it into the lactim ether, and attempting the condensation of this lactim ether with 1,1- bismethylthio-2-nitroethene **2**.

3. Results and Discussion

3.1 Preparation of pyrogluatamte lactim ether (23)[20]

Pyroglutamate lactim ether was prepared by the reaction of (S)- methyl pyroglutamate[21] **21** with dimethyl sulfate at 30 °C for 48h(Scheme 20). The yield of the lactim ether was 83%. The IR spectrum showed a carbonyl peak at 1730 cm^{-1} and the C=N stretching at 1640 cm^{-1}. The ^1H NMR showed a multiplet at 2.00-2.80δ(m, 4H) ($2CH_2$) followed by two singlets for the two methoxy groups at 3.60δ and 3.80δ, a multiplet at 4.30-4.70δ(m, 1H) due to the =NCHCO.

Scheme 20



21 **23**

3.2 Attempted reaction of pyroglutamate lactim ether (23) with nitroketene dithioacetal (2)

The condensation reaction of pyroglutamate lactim ether **23** with nitroketene dithioacetal **2** in acetonitrile in presence of PTSA at 30 °C failed to give the required compound **24**. The reaction temperature was hence increased to 80 °C. The reaction at the higher temperature also led only to recovery of the starting material(Scheme 21). Attempts to force the reaction by changing the solvent or by using catalysts also were futile. The various reaction conditions attempted are described in *Table 3*.

Scheme 21

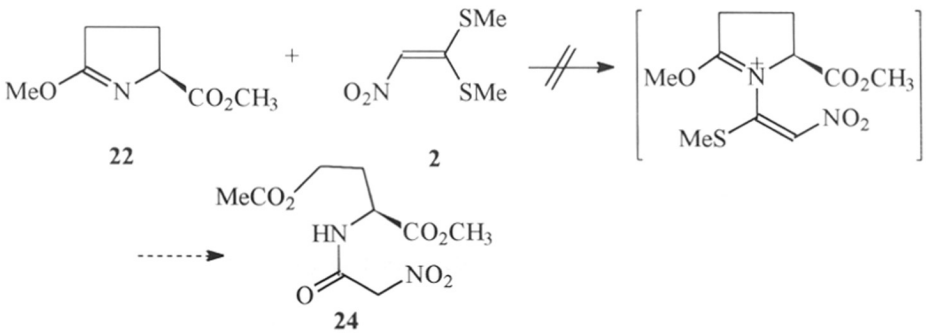


Table 3

No	Catalyst	Solvent	Temperature	Time (h)
1	-	CH_3CN	80 °C	48h
2	-	1,4- Dioxane	100 °C	48h
3	-	CH_3CN: H_2O (3:1)	80 °C	48h
4	-	Dioxane- H_2O (3:1)	100 °C	48h
5	-	Isopropanol	100 °C	48h
6	-	THF	80 °C	48h
7	-	DMF	100 °C	24h
8	-	DMSO	100 °C	24h
9	PTSA	CH_3CN	80 °C	48h
10	PTSA	Dioxane	80 °C	48h
11	PTSA	MeOH	65 °C	48h
12	$ZnCl_2$	MeOH	65 °C	48h
13	$HgCl_2$	MeOH	65 °C	48h
14	$Zn(OAc)_2$	MeOH	65 °C	48h
15	$Hg(OAc)_2$	MeOH	65 °C	48h
16	$Cu(OAc)_2$	MeOH	65 °C	48h
17	$BF_3.OEt_2$	MeOH	65 °C	48h
18	$AlCl_3$	MeOH	65 °C	48h
19	Et_2AlCl	MeOH	65 °C	48h
20	H-mordenite	MeOH	65 °C	48h

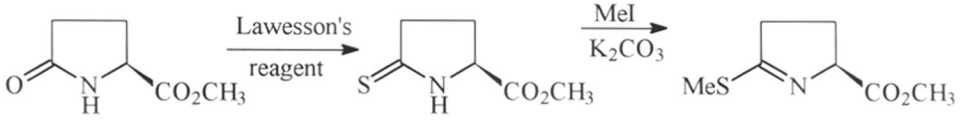
The failure of the condensation reaction can be attributed to the lower nucleophilicity of the imine nitrogen in pyroglutamate lactim ether, compared to the nitrogen of γ- butyrolactim ether.

As discussed in the earlier section, the lactim thioethers lead to higher yields of the products, since they appear to be better nucleophiles than lactim ethers. Therefore it was decided to use the pyroglutamate lactim thioether (**26**) in place of pyroglutamate lactim ether (**23**) in the condensation reaction with nitroketene dithioacetal (**2**).

3.3 Preparation of pyroglutamate lactim thioether (26)

Pyroglutamate lactim thioether **26** was prepared from methyl pyroglutamate **21** in two steps. First **21** was converted to the thiolactam **25** by using Lawessson's reagent.[22] This was then S- methylated by reacting with iodomethane in acetone in the presence of K_2CO_3(Scheme 22). The ^1H NMR spectrum of **26** shows a multiplet at 2.00-2.40δ(m, 2H) due to the ring methylene protons followed by a sharp singlet at 2.50δ for SCH_3, a multiplet at 2.60-2.80δ(m, 2H) corresponding to $=C-CH_2$ protons. The methoxy group appears as a sharp singlet at 3.50δ followed by a multiplet at 4.20δ due to the =NCHCO proton. This data proved the structure to be **26**.

Scheme 22

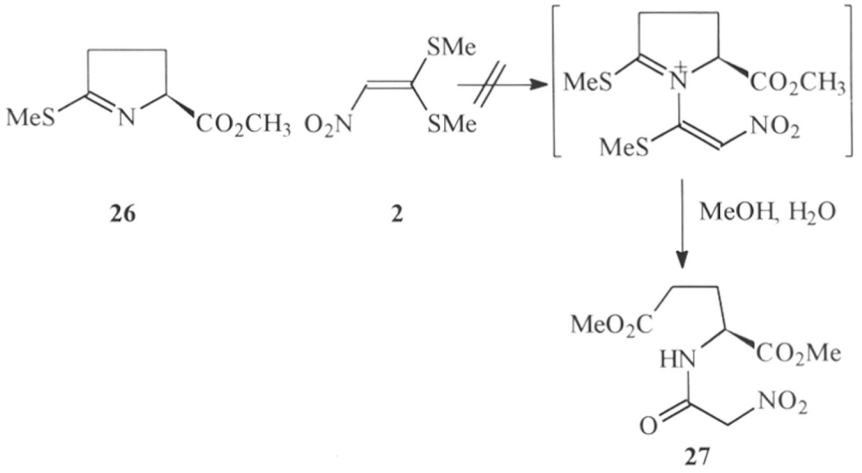


21 **25** **26**

3.4 Attempted reaction of pyroglutamate lactim thioether (26) with 1, 1-bismethylthio-2- nitroethene (2)

In acetonitrile, in the presence of PTSA, the condensation reaction of pyroglutamate lactim thioether **26** with **2** failed to give the required product **27** either at 30 °C or 80 °C(Scheme 23).

Scheme 23

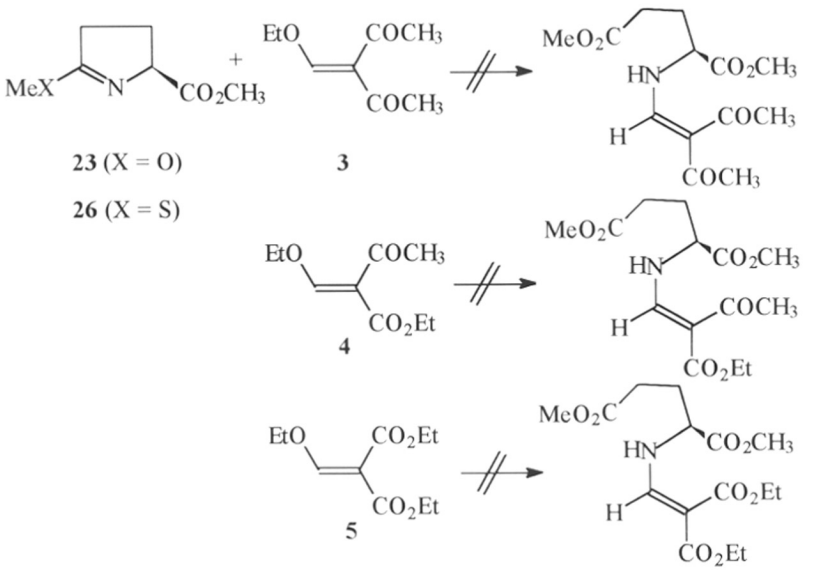


26 **2** **27**

The condensation failed to occur under the following conditions as well: dioxane(100 °C), DMF(100 °C), DMSO(100 °C) or just heating the reactants together in the absence of any solvent at 100 °C. Likewise, the reaction failed in the presence of Lewis acid catalysts ($ZnCl_2$, $HgCl_2$, $BF_3.OEt_2$) or the zeolite H-mordenite (having both Lewis and Bronsted acidity).

Attempts to bring about the reaction of pyroglutamate lactim ether **23** or its sulfur analog **26** with other electrophilic push-pull ethylenes namely ethoxymethyleneacetylacetone **3**, ethyl ethoxymethyleneacetoacetate **4**, and diethyl ethoxymethylenemalonate **5** were also unsuccessful(Scheme 24).

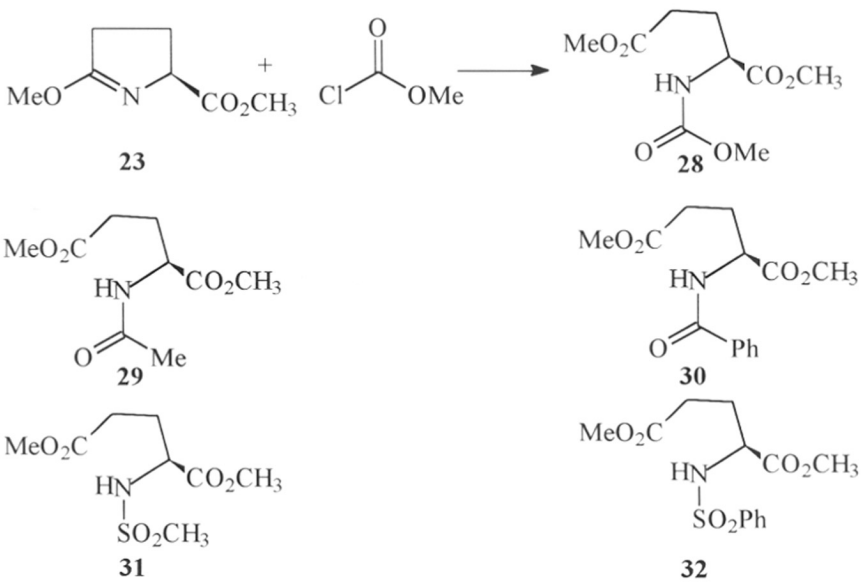
Scheme 24



However the reaction of pyroglutamate lactim ether **23** with more powerful electrophiles such as chloroformates, acid chlorides and sulfonyl chlorides gave good yields of ring-opened products (after aqueous work-up) at 30 °C in the absence of solvent.

Thus methyl chloroformate was reacted with pyroglutamate lactim ether **23** at 30 °C to give the acyclic product **28** in 65% yield(Scheme 25). The structure of the compound was proved from the spectral data. The ^{1}H NMR spectrum of **28** showed a multiplet at 1.85-2.20δ(m, 2H) for the CH_2 protons followed by another multiplet at 2.35-2.40δ(m, 2H) due to the CH_2 adjacent to the ester. Three methoxy groups appeared as two sharp singlets at 3.60δ(s, 6H) and 3.70δ(s, 3H) followed by a multiplet at 4.30-4.40δ(m, 1H) corresponding to NCHCO. The NH proton appeared as a broad peak at 5.45δ. The mass spectrum of the compound exhibited the highest peak at m/z 234, corresponding to (M+1). From the above data the structure of the compound was proved to be **28**(Figure 9).

Scheme 25



Similarly, acetyl chloride, benzoyl chloride, methanesulfonyl chloride and benzenesulfonyl chloride on reaction with pyroglutamate lactim ether at 30 °C without any solvent gave the ring-opened compounds **29**, **30**(Figure 10), **31**(Figure 11) and **32** respectively. The yields of the products ranged from 68 to 77%.

The structure of the compounds were confirmed from their ^{1}H, ^{13}C NMR, IR and mass spectral data. Authentic samples of these compounds were prepared directly from glutamic acid dimethyl ester. The identity was thus confirmed in each case by direct comparison of the respective spectra.

4. Conclusion

- N- Nitroacetyl pyroglutamate could not be synthesized by condensation of pyroglutamate lactim ether with 1, 1- bismthylthio-2-nitroethene, followed by hydrolysis.
- Similarly, pyroglutamate lactim thioether also failed to give the expected product.
- Pyroglutamate lactim ether failed to give the ring-opened product with other electrophilic push-pull ethylenes also.

• In contrast, ring-opened products were obtained by the reaction of pyroglutamate lactim ether with more powerful electrophiles such as methyl chloroformate, acid chlorides and sulfonyl chlorides.

SECTION E: Increasing the nucleophilicity of the ring nitrogen in pyroglutamate: Reaction of the derived amidine with acid chlorides and other electrophiles

1. Introduction

In the previous sections, we had reported that we could not achieve the condensation of pyroglutamate lactim ether or its thio analog with 1, 1-bismethylthio-2-nitroethene. The problem was the extremely poor nucleophilicity of the ring nitrogen in the pyroglutamate derivatives. In order to overcome this, it was decided to convert the lactim ether first into an amidine and then react the latter with electrophiles. It was hoped that the increased nucleophilicity of the amidine would contribute to the success of the scheme.

2. Objective

Our objective in this study was to increase the nucleophilicity of the lactim ether nitrogen, by converting it into an amidine derivative and attempt the reaction with various electrophiles.

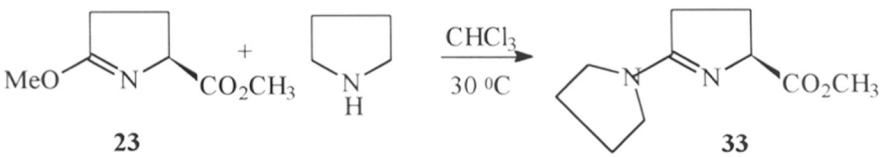
3. Results and Discussion

3.1 Synthesis of the requisite amidine derivative

Pyroglutamate lactim ether **23** was converted into the amidine derivative **33** by the reported procedure.[23] Thus the pyroglutamate lactim ether **23** was treated with pyrrolidine in chloroform at 30 °C to give the amidine **33** in 40% yield(Scheme 26). The structure of the amidine derivative **33** was confirmed from the spectral data. The ^{1}H

NMR spectrum of a purified sample of **33** showed three multiplets, one at 1.85δ(m, 4H) due to two CH_2 groups, the second at 2.10-2.35δ(m, 4H) for two more CH_2 groups and the third at 2.50-2.70(m, 4H) for the two NCH_2 groups, a sharp singlet at 3.70δ for OCH_3 and a doublet of doublet at 4.50δ(dd, 1H, J = 6.0, 7.5Hz) due to the NCHCO. The mass spectrum of **33** showed the molecular ion (M^+) peak at 196. The above data proved the structure of the compound to be **33**(Figure 12).

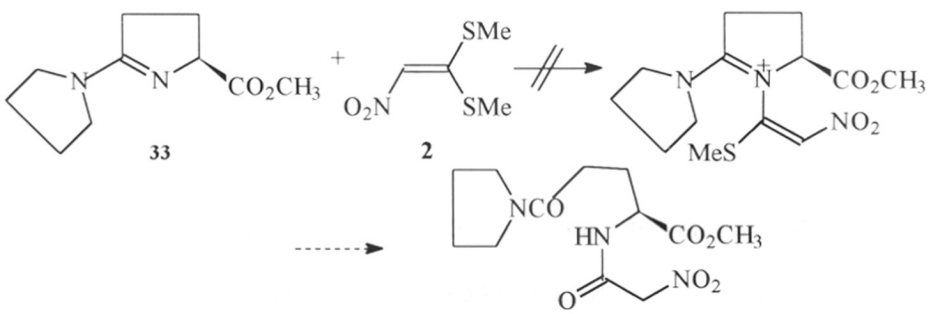
Scheme 26



3.2 Reaction of the amidine (33) with 1, 1-bismethythio-2-nitroethene (2)

The condensation reaction of the derived amidine **33** with nitroketene dithioacetal **2** was first attempted in the usual way[16a] in the presence of PTSA in acetonitrile at 30 °C (Scheme 27). However, under these conditions no reaction was observed. The reaction temperature was then increased to 80 °C, but this also led only to recovery of the starting material.

Scheme 27



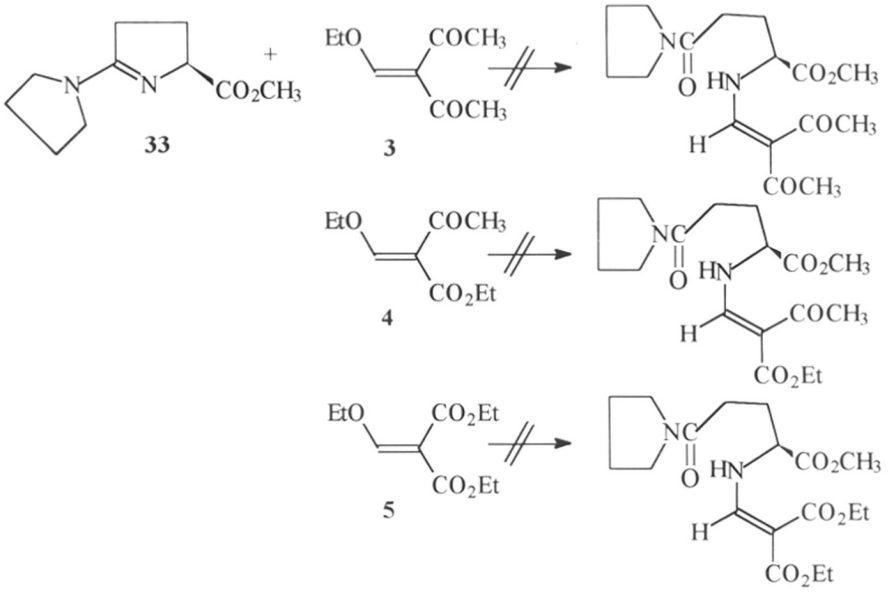
Use of methanol as solvent at 30 °C or 65 °C gave no positive result. Varying the catalyst from PTSA to $ZnCl_2$, $Zn(OAc)_2$, $HgCl_2$, $Hg(OAc)_2$, $Cu(OAc)_2$, Et_2AlCl (in

hexane) and $BF_3.OEt_2$ failed to bring about the reaction. The starting material was recovered in all cases except in the Et_2AlCl catalysed reaction, where the reaction led to a highly polar complex mixture.

3.3 Reaction of the amidine derivative (33) with ethoxymethyleneacetylacetone (3), ethyl ethoxymethyleneacetoacetate (4) and diethyl ethoxymethylenemalonate (5)

The reaction of the amidine **33** with ethoxymethyleneacetylacetone **3** in methanol solution at 65 °C failed to give the condensed product. The starting amidine was recovered even after 48h at reflux temperature(Scheme 28). Similarly, ethyl ethoxymethyleneacetoacetate **4** and diethyl ethoxymethylenemalonate **5** also failed to react with the amidine derivative **33**.

Scheme 28



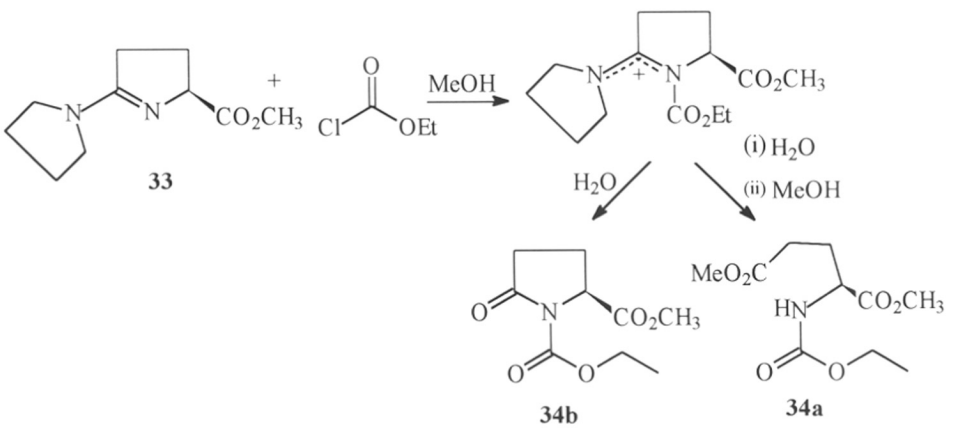
3.4 Reaction of the amidine derivative (33) with ethyl chloroformate (7)

Reaction of the amidine derivative **33** with ethyl chloroformate **7** in methanol at 30 °C gave two products **34a** and **34b** in 14% and 19% yields respectively(Scheme 29). The structure of the two products was confirmed from their ^1H NMR spectra. The ^1H

NMR spectrum of **34a** shows a triplet at 1.20δ(t, 3H, J = 8.0Hz) for the CH_3 of the ethyl moiety, followed by two multiplets at 1.90-2.20δ(m, 2H) and at 2.30-2.40δ(m, 2H) corresponding respectively to CH_2 and $COCH_2$. Two methoxy groups appeared at 3.60δ and 3.70δ as singlets, followed by a quartet at 4.10δ(q, 2H, J = 7.0Hz) due to the OCH_2 of the ethyl group and a multiplet at 4.30δ(m, 1H) corresponding to NCHCO. The NH proton appeared as a broad peak at 5.40δ. The mass spectrum of **34a** showed the molecular ion (M^+) peak at m/z 248. From the above data it was inferred that compound had resulted by initial attack at the ring nitrogen, followed by hydrolytic ring-opening to give **34a**(Figure 13).

The ^1H NMR spectrum of **34b** showed a triplet at 1.20δ(t, 3H, J = 8.2Hz) due to the CH_3 group of the ethyl group, followed by two multiplets at 2.00-2.40δ(m, 2H) and 2.45-2.60(m, 2H) corresponding to CH_2 and $COCH_2$ respectively. A sharp singlet at 3.75δ was assigned to OCH_3, followed by a quartet at 4.15δ(q, 2H, J = 7.4Hz) due to the OCH_2 protons of the ethyl group and a multiplet at 4.60δ(m, 1H) for the NCHCO. The mass spectrum showed the molecular ion(M^+) peak at m/z 215. These data proved the structure of the compound to be **34b**(Figure 14); obviously this had resulted by initial attack of the acid chloride at the ring nitrogen, followed by hydrolysis.

Scheme 4



In view of the earlier results from this laboratory, it is likely that **34a** results from the methanolysis of **34b**.

4. Conclusion

- The amidine derivative did not give the expected product on reaction with 1,1-bismethylthio-2-nitroethene.
- The condensation reaction of the amidine with other electrophilic push-pull ethylenes also failed.
- Ethyl chloroformate gave two products on treatment with the amidine; one is the ring-opened product **34a** and the other is an N-substituted lactam **34b**.

5. Experimental

General

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (125 °C) which was cooled under argon. All organic layers obtained from extractions were dried over anhydrous Na_2SO_4. The term *in vacuo* refers to the removal of solvent on a rotary evaporator followed by evacuation (<5 mm Hg) to constant sample weight. Solvents for anhydrous reactions were dried according to Perrin *et al.*[24] THF, benzene and diethyl ether were distilled from sodium and benzophenone. Acetonitrile, CH_2Cl_2, triethyl amine were distilled from CaH_2. Solvents for chromatography were distilled at the respective constant boiling point. Petroleum ether refers to the fraction boiling in the range 60-80 °C.

All commercial α- amino acids, reducing agents used were obtained from Aldrich Chemical Co. Progress of the reaction was monitored by TLC and visualized by UV absorption by flourescence quenching or I_2 or both. Commercial precoated silica gel(Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 60-120 mesh obtained from S. D. Fine Chemical Co. India or SRL, India. Flash chromatography[25] was performed according to Still *et al* using 230-400 mesh silica gel from SRL, India. A Buchi GKR-51 Kugelrohr distillation apparatus was used for distilling liquid samples.

All melting points are uncorrected in degrees Celsius and were recorded on a Thermolink melting point apparatus or Tanaco micro melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B, model 1620 FT-IR and AIT Mattson, UK, model RS-1 FT-IR. IR bands were expressed in cm^{-1}. ^1H NMR spectra were recorded using TMS as internal reference on Bruker MSL-300, Bruker AC-200 or Bruker WH-90 instruments using $CDCl_3$ as solvent. Chemical shifts are reported

in δ. Abbreviations used are as follows; s : singlet, d : doublet, t : triplet, dd : doublet of doublet, q : quartet, br : broad, m : multiplet. ^{13}C NMR spectra were recorded on Bruker MSL-300 or Bruker AC-200 instruments operating at 75MHz and 50 MHz respectively. Mass spectra were recorded on a Finnigan-Mat 1020C mass spectrometer and are obtained in an ionization potential of 70eV. Optical rotations were measured at the sodium D line on a JASCO-181 digital polarimeter at ambient temperature. HPLC analysis was carried out using a chiral column (DAICEL CHIRALCEL OD) employing gradient elution. Elemental analysis were performed on a Carlo Erba CHN-S EA 1108 Elemental Analyser or by conventional combustion techniques by the Microanalysis facilities at NCL, Pune.

5.1 Preparation of lactim ethers and lactim thioethers

The lactim ethers were prepared according to the literature method[26]; thio lactams were obtained from their oxygen counterparts using Lawesson's reagent[22] and etherified by iodomethane in acetone in the presence of K_2CO_3.

5.2 Reaction of lactim ethers with 1,1- bismethylthio-2-nitroethene

To a solution of lactim ether **1a** (2mmol) in methanol (10 ml) 1, 1-bismthylthio-2-niroethene **2** (2mmol) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC. The coupling reaction of lactim ether was evident from the smell of methyl mercaptan. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample (**8a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70). Similarly lactim ether **1b** and **1c** reacted with 1, 1-bismthylthio-2- nitroethene **2** gave **8b** and **8c** respectively.

Methyl 4-[N-(1-methoxy-2-nitroethenyl)] aminobutanoate (8a)

Yield (%)	43
IR(Neat)/cm^{-1}	3360, 3260, 2960, 1740, 1520
^1H NMR ($CDCl_3$) (200 MHz)	1.9(m, 2H, CH_2), 2.35(t, 2H, $COCH_2$, J = 8Hz), 3.45(q, 2H, NCH_2, J = 7Hz), 3.75(s, 3H, OCH_3), 3.9(s, 3H, OCH_3), 6.70(s, 1H, =CH), 9.85(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	24.22, 30.42, 39.43, 51.06, 56.57, 97.32, 164.26, 172.44
MS (m/z)	218(M^+), 187, 172, 140, 112 (100%) 98
Analysis	Found: C, 43.99; H, 6.24; N, 12.60. $C_8H_{14}N_2O_5$ requires C, 44.03; H, 6.42; N, 12.84%.

Methyl 5-[N-(1-methoxy-2-nitroethenyl)] aminopentanoate (8b)

Yield (%)	50
IR(Neat)/cm^{-1}	3144, 2954, 1729, 1642, 1510, 1380
^1H NMR ($CDCl_3$) (200 MHz)	1.55-1.70 (m, 4H, $2CH_2$), 2.35(t, 2H, $COCH_2$, J = 5Hz), 3.35(q, 2H, NCH_2, J = 7Hz), 3.65(s, 3H, OMe), 3.85(s, 3H, OMe), 6.65(s, 1H, =CH), 9.85(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	21.80, 28.71, 33.11, 40.14, 51.22, 56.89, 97.57, 164.54, 173.23;
MS (m/z)	232(M^+), 201, 186, 176, 154, 140, 112, 98, 55(100%)
Analysis	Found: C, 46.52; H, 6.62; N, 12.08. $C_9H_{16}N_2O_5$ requires C, 46.55; H, 6.89; N, 12.06%.

Methyl 6-[N-(1-methoxy-2-nitroethenyl) aminohexanoate (8c)

Yield (%)	56
IR(Neat)/cm^{-1}	3250, 2960, 1745, 1630, 1520, 1450
^1H NMR ($CDCl_3$) (200 MHz)	1.40(m, 2H, CH_2), 1.50-1.70(m, 4H, $2CH_2$), 2.30(t, 2H, $COCH_2$, J = 8Hz), 3.35(q, 2H, NCH_2, J = 7Hz), 3.65(s, 3H, OCH_3), 3.85(s, 3H, OCH_3), 6.65(s, 1H, =CH), 9.85(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	23.48, 25.26, 28.24, 32.79, 39.63, 50.47, 56.26, 96.85, 163.85 172.83
MS (m/z)	246(M^+), 229, 215, 200, 173, 168, 154, 131, 126, 112, 85(100%)
Analysis	Found: C, 48.73; H, 7.48; N, 11.23. $C_{10}H_{18}N_2O_5$ requires C, 48.78; H, 7.31; N, 11.38%.

Reaction of γ- butyrolactim ethyl ether with 1,1- bismethylthio-2-nitroethene (2)

To a solution of γ- butyrolactim ethyl ether (2mmol) in dioxane-water (3:1) (10 ml) 1, 1-bismthylthio-2-niroethene **2** (2mmol) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC. The coupling reaction of lactim ether was evident from the smell of methyl mercaptan. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample (**9a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70).

Ethyl 4-[N-(1-methylmercapto-2-nitroethenyl)] aminobutanoate. (9a)

Yield (%)	65
IR(Neat)/cm^{-1}	3280, 2980, 2920, 1730, 1580, 1460, 1420
^1H NMR ($CDCl_3$)	1.25(t, 3H, CH_3, J = 8Hz), 2.00(m, 2H, CH_2), 2.40(t, 2H, $COCH_2$, J =

(200 MHz)	8Hz), 2.45(s, 3H, SCH_3), 3.45(q, 2H, NCH_2, J = 7Hz), 4.10(q, 2H, OCH_2, J = 8Hz), 6.55(s, 1H, =CH), 10.50(br, 1H, NH)
^{13}C NMR($CDCl_3$)	13.72, 13.87, 24.00, 30.64, 43.34, 60.21, 105.86, 164.67, 171.97
(50 MHz)	
MS (m/z)	248(M^+), 231, 215, 202, 157, 147, 119, 115, 101, 87(100%), 73
Analysis	Found: C, 43.72; H, 6.79; N, 11.17. $C_9H_{16}N_2O_4S$ requires C, 43.54; H, 6.45; N, 11.29%.

Reaction of lactim ethers (1a-c) with ethoxymethyleneacetylacetone (3)

To a solution of lactim ether **1a** (2mmol) in methanol (10 ml) ethoxymethyleneacetylacetone (2mmol) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample (**10a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70). Similarly lactim ether **1b** and **1c** reacted with ethoxymethyleneacetylacetone **3** gave **10b** and **10c** respectively.

Methyl 4-[N-(2, 2-bisacetyl)ethenyl] aminobutanoate. (10a)

Yield (%)	48
IR(Neat)/cm^{-1}	3200, 2920, 1730, 1640, 1600, 1460
^1H NMR ($CDCl_3$)	1.95(m, 2H, CH_2), 2.25(s, 3H, $COCH_3$), 2.40(t, 2H, $COCH_2$, J =
(200 MHz)	8Hz), 2.45(s, 3H, $COCH_3$), 3.45(q, 2H, NCH_2, J = 7Hz), 3.70(s, 3H, OCH_3), 7.70(d, 1H, =CH, J = 14Hz), 11.00(br, 1H, NH)
^{13}C NMR($CDCl_3$)	24.91, 26.02, 29.59, 30.51, 48.15, 50.53, 110.22, 159.54, 171.82,
(50 MHz)	193.22, 198.50

MS (m/z)	227(M^+), 212, 196, 180, 154, 138, 126(100%), 112, 101
Analysis	Found: C, 58.15; H, 7.32; N, 6.05. $C_{11}H_{17}NO_4$ requires C, 58.14; H, 7.48; N, 6.16%.

Methyl 5-[N-(2, 2-bisacetyl)ethenyl] aminopentanoate. (10b)

Yield (%)	53
IR(Neat)/cm^{-1}	3200, 2951, 2360, 1740, 1633, 1390
^1H NMR ($CDCl_3$) (200 MHz)	1.65(m, 4H, $2CH_2$), 2.25(s, 3H, $COCH_3$), 2.35(t, 2H, $COCH_2$, J = 6Hz), 2.45(s, 3H, $COCH_3$), 3.35(q, 2H, $NHCH_2$, J = 7Hz), 3.65(s, 3H, OCH_3), 7.70(d, 1H. =CH, J = 13Hz), 11.05(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	20.95, 26.30, 29.30, 30.80, 32.45, 48.89, 50.60, 110.30, 156.64, 172.48, 193.37, 198.66
MS (m/z)	241(M^+), 226, 210, 194, 152, 126(100%), 112, 98, 83
Analysis	Found: C, 59.95; H, 7.91; N, 5.72. $C_{12}H_{19}NO_4$ requires C, 59.75; H, 7.88; N, 5.80%

Methyl 6-[N-(2,2-bisacetyl)ethenyl] aminohexanoate. (10c)

Yield (%)	68
IR(Neat)/cm^{-1}	3210, 2980, 1745, 1630, 1600, 1405, 1320
^1H NMR ($CDCl_3$) (200 MHz)	1.45(m, 2H, CH_2), 1.65(m, 4H, $2CH_2$), 2.25(s, 3H, $COCH_3$), 2.35(t, 2H, $COCH_2$, J = 8Hz), 2.50(s, 3H, $COCH_3$), 3.35(q, 2H, NCH_2, J = 7Hz), 3.65(s, 3H, OCH_3), 7.75(d, 1H, =CH, J = 15Hz), 11.00(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	23.20, 24.75, 25.92, 29.19, 30.46, 32.45, 48.73, 50.17, 109.87, 159.38, 172.42, 193.08, 198.31

MS (m/z)	255(M^+), 240, 224, 198, 166, 154, 140, 126(100%), 112, 96, 69
Analysis	Found: C, 61.00; H, 8.59; N, 5.43. $C_{13}H_{21}NO_4$ requires C, 61.17; H, 8.23; N, 5.49%.

Reaction of lactim ethers (1a-c) with ethyl ethoxymethyleneacetoacetate (4)

To a solution of lactim ether **1a** (2mmol) in methanol (10 ml) ethyl ethoxymethyleneacetoacetate (**4**) (2mmol) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample (**11a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70). Similarly lactim ether **1b** and **1c** reacted with ethyl ethoxymethyleneacetoacetate **4** gave **11b** and **11c** respectively.

Methyl 4-[N-(2-acetyl-2-carboethoxy)ethenyl] aminobutanoate. (11a)

Yield (%)	38
IR(Neat)/cm^{-1}	3490, 3280, 2940, 1730, 1720, 1680, 1590, 1540
^1H NMR ($CDCl_3$) (200 MHz)	1.25-1.45(m, 5H, CH_2, CH_3), 2.40(t, 2H, $COCH_2$, J = 8Hz), 2,50(s, 3H, $COCH_3$), 3.45(q, 2H, NCH_2, J = 7Hz), 3.75(s, 3H, OCH_3), 4.20(q, 2H, OCH_2, J=8Hz), 8.00(d, 1H, =CH, J = 14Hz), 11.00(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	25.29, 26.43, 30.04, 30.93, 48.64, 49.41, 51.09, 110.87, 159.88, 172.36, 194.10, 199.48
MS (m/z)	257(M^+), 243, 212, 196, 180, 164, 138(100%), 124, 110
Analysis	Found: C, 55.96; H, 7.15; N, 5.25. $C_{12}H_{19}NO_5$ requires C, 56.03; H, 7.39; N, 5.44%.

Methyl 5-[N-(2-acetyl-2-carbomethoxy)ethenyl] aminopentanoate. (11b)

Yield (%)	55
IR(Neat)/cm^{-1}	3390, 2950, 1740, 1700, 1605, 1430
^1H NMR ($CDCl_3$) (200 MHz)	1.25-1.75(m, 4H, $2CH_2$), 1.95(s, 3H, $COCH_3$), 2.30(t, 2H, $COCH_2$, J = 6.5Hz), 3.27(q, 2H, NCH_2, J = 5Hz), 3.60(s, 3H, OCH_3), 3.65(s, 3H, OCH_3), 8.10(d, 1H, =CH, J = 12Hz), 11.10(br, 1H, NH)
MS (m/z)	257(M^+), 242, 211, 196, 182, 166, 137(100%), 124, 89
Analysis	Found: C, 56.18; H, 7.01; N, 5.62. $C_{12}H_{19}NO_5$ requires C, 56.03; H, 7.39; N, 5.44%.

Methyl 6-[N-(2-acetyl-2-carbomethoxy)ethenyl] aminohexanoate. (11c)

Yield (%)	57
IR(Neat)/cm^{-1}	3300, 2960, 1740, 1650, 1615, 1450, 1370
^1H NMR ($CDCl_3$) (200 MHz)	1.30(t, 3H, CH_3, J = 8Hz), 1.55-1.85(m, 6H, $3CH_2$), 2.20(s, 3H, $COCH_3$), 2.30(t, 2H, $COCH_2$, J = 8Hz), 3.35(q, 2H, NCH_2, J = 7Hz), 3.70(s, 3H, OCH_3), 4.20(q, 2H, OCH_2, J = 8Hz), 8.00(d, 1H, =CH, J = 14Hz), 8.55(br, 1H, NH)
MS (m/z)	271(M^+), 257, 243, 228, 212, 18, 170, 156, 142, 96(100%)
Analysis	Found: C, 57.27; H, 7.46; N, 5.50. $C_{13}H_{21}NO_5$ requires C, 57.56; H, 7.74; N, 5.16%.

Reaction of lactim ethers (1a-c) with diethyl ethoxymethylenemalonate (5)

To a solution of lactim ether **1a** (2mmol) in methanol (10 ml) diethyl ethoxymethylenemalonate (**5**) (2mmol) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC. After completion of the reaction, the

solvent was removed under reduced pressure. The crude sample (**12a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70). Similarly lactim ether **1b** and **1c** reacted with diethyl ethoxymethylenemalonate **5** gave **12b** and **12c** respectively

Methyl 4-[N-(2,2-biscarboethoxy)ethenyl] aminobutanoate. (12a)

Yield (%)	40
IR(Neat)/cm^{-1}	3290, 2950, 1740, 1650, 1620, 1540
^{1}H NMR ($CDCl_3$) (200 MHz)	1.15(m, 6H, $2CH_3$), 1.90(m, 2H, CH_2), 2.35(t, 2H, $COCH_2$, J = 8Hz), 3.35(q, 2H, NCH_2, J = 7Hz), 3.60(s, 3H, OCH_3), 4.20(m, 4H, $2OCH_2$), 7.50(d, 1H, =CH, J = 15Hz), 9.2(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.11, 25.74, 30.37, 50.44, 52.20, 54.70, 59.48, 60.31, 89.55, 159.81, 165.80, 169.01, 172.68
MS (m/z)	287(M^+), 261, 218, 203, 189, 175, 161, 145, 131, 115, 89, 75(100%)
Analysis	Found: C, 54.13; H, 7.60. $C_{13}H_{21}NO_6$ requires C, 54.35; H, 7.31%.

Methyl 5-[N-(2,2-biscarboethoxy)ethenyl] aminopentanoate. (12b)

Yield (%)	60
IR(Neat)/cm^{-1}	3287, 2952, 1736, 1656, 1430, 1220
^{1}H NMR ($CDCl_3$) (200 MHz)	1.30(t, 6H, $2CH_3$, J = 10Hz), 1.70(m, 4H, $2CH_2$), 2.35(t, 2H, $COCH_2$, J = 8Hz), 3.35(q, 2H, NCH_2, J = 8Hz), 3.70(s, 3H, OCH_3), 4.20(q, 4H, $2CH_2$, J = 10Hz), 7.95(d, 1H, =CH, J = 15Hz), 9.20(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	13.70, 13.74, 21.16, 29.67, 32.63, 48.62, 50.67, 58.63, 58.78, 88.84, 159.29, 165.28, 168.41, 172.59
MS (m/z)	301(M^+), 256, 224, 209, 154, 128, 96, 82, 55(100%)

Analysis	Found: C, 56.08; H, 7.62; N, 4.44. $C_{14}H_{23}NO_6$ requires C, 55.81; H, 7.64; N, 4.65%.

Methyl 6-[N-(2,2-biscarboethoxy)ethenyl] aminohexanoate. (12c)

Yield (%)	55
IR(Neat)/cm^{-1}	3300, 2980, 1730, 1630, 1570, 1450
^1H NMR ($CDCl_3$) (200 MHz)	1.14-1.40(m, 8H, CH_2, $2CH_3$), 1.60(m, 4H, $2CH_2$), 2.35(t, 2H, $COCH_2$, J = 8Hz), 3.30(q, 2H, $NHCH_2$, J = 7Hz), 3.60(s, 3H, OCH_3), 4.25(q, 4H, $2OCH_2$, J = 8Hz), 7.95(d, 1H, =CH, J = 16Hz), 9.15(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.06, 14.15, 24.12, 25.66, 30.14, 33.42, 49.21, 51.13, 59.21, 59.40, 89.28, 159.65, 165.88, 169.08, 173.41
MS (m/z)	315(M^+), 309, 296, 270, 238, 223, 195, 167, 154(100%), 128
Analysis	Found: C, 56.85; H, 7.72; N, 4.21. $C_{15}H_{25}NO_6$ requires C, 57.14; H, 7.93; N, 4.44%.

Reaction of lactim ethers (1a) with p- toluenesulfonyl chloride (6)

To a solution of lactim ether **1a** (2mmol) in methanol (10 ml) p- toluenesulfonyl chloride (**6**) (2mmol) was added. The mixture was stirred at 30 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was taken in EtOAc (25 ml) and washed twice with water. The crude sample (**13a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70).

Methyl 4-(4-toluenesulfonylamino) butanoate (13a)

Yield (%)	60
IR(nujol)/cm^{-1}	3300, 2990, 2820, 1735, 1610, 1520, 1450, 1340, 1280
^1H NMR ($CDCl_3$) (200 MHz)	1.82(m, 2H, CH_2), 2.28(t, 2H, $COCH_2$, J = 8.0Hz), 2.95(q, 2H, NCH_2, J = 7.0Hz), 3.65(s, 3H, OCH_3), 4.95(br, 1H, NH), 7.30(d, 2H, Ar), 7.75(d, 2H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	21.44, 24.71, 30.92, 42.46, 51.65, 127.04, 129.71, 173.02, 143.32, 173.67
Analysis	Found: C, 51.01; H, 6.290. $C_{12}H_{19}N_3O_5S$ requires C, 50.97; H, 5.17%.

Reaction of lactim ethers (1a-c) with ethyl chloroformate (7)

To a solution of lactim ether **1a-c** (2mmol) in methanol (10 ml) ethyl chloroformate (7) (2mmol) was added. The mixture was stirred at 30 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was taken in EtOAc (25 ml) and washed twice with water. The organic layer was dried over anhydrous Na_2SO_4. The crude sample (**14a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70). Similarly lactim ether **1b** and **1c** reacted with ethyl chloroformate **7** gave **14b** and **14c** respectively.

Methyl 4-(carethoxyamino) butanoate (14a)

Yield (%)	68
IR(Neat)/cm^{-1}	3300, 2980, 1730, 1690, 1530, 1450, 1370, 1250, 1180
^1H NMR ($CDCl_3$) (200 MHz)	1.15(t, 3H, CH_3, J = 8.0Hz), 1.75(m, 2H, CH_2), 2.30(t, 2H, $COCH_2$, J = 8.0Hz), 3.15(q, 2H, NCH_2, J = 7.0Hz), 3.60(s, 3H, OCH_3), 4.00(q, 2H, OCH2), J = 7.0Hz), 5.10(br, 1H, NH)

^{13}C NMR($CDCl_3$) (50 MHz)	13.83, 24.50, 30.47, 39.48, 50.77, 59.80, 156.39, 173.15
MS (m/z)	189(M^+), 158, 144, 129, 116(100%), 112, 102, 86, 74
Analysis	Found: C, 50.35; H, 7.48; N, 7.67. $C_{15}H_{25}NO_6$ requires C, 50.70; H, 7.40; N, 7.90%.

Methyl 5-(carbethoxyamnio) pentanoate (14b)

Yield (%)	71
IR(Neat)/cm^{-1}	3354, 2952, 1734, 1718, 1637, 1560, 1525, 1490
^1H NMR ($CDCl_3$) (200 MHz)	1.20(t, 3H, CH_3 J = 8.0Hz), 1.35-170(m, 4H, $2CH_2$), 2.25(t, 2H, $COCH_2$, J = 8.0Hz), 3.10(q, 2H, NCH_2, J = 7.0Hz), 3.60(s, 3H, OCH_3), 4.05(q, 2H, OCH_2, J = 8.0Hz), 4.95(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.13, 21.62, 28.95, 33.02, 39.94, 50.80, 59.84, 156.52, 173.30
MS (m/z)	203(M^+), 171, 158, 143, 130(100%), 115, 102, 87, 74
Analysis	Found: C, 53.20; H, 8.50; N, 6.73. $C_{15}H_{25}NO_6$ requires C, 53.20; H, 8.77; N, 6.73%.

Methyl 6-(carbethoxyamino)hexanoate (14c)

Yield (%)	72
IR(Neat)/cm^{-1}	3390, 3050, 2980, 1730, 1718, 1650, 1530, 1450, 1420
^1H NMR ($CDCl_3$) (200 MHz)	1.15(t, 3H, CH_3, J = 8.0Hz), 1.25-1.60(m, 6H, $3CH_2$), 2.30(t, 2H, $COCH_2$, J = 8.0Hz), 3.25(q, 2H, OCH_2, NCH_2, J = 7.0Hz), 3.65(s, 3H, OCH_3), 4.05(q, 2H, OCH_2, J = 7Hz), 4.80(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.13, 24.06, 25.74, 29.16, 33.36, 40.24, 50.85, 59.97, 156.41, 173.48

MS (m/z)	217(M^+), 196, 180, 167, 152, 138, 128(100%), 110, 96, 83
Analysis	Found: C, 55.10; H, 8.72; N, 6.53. $C_{15}H_{25}NO_6$ requires C, 55.29; H, 8.72; N, 6.53%.

5.2 Reaction of cyclo (L-Pro-Gly) monoimino ether (15) with 1,1- bismethylthio-2-nitroethene (2)

To a solution of cyclo (L-Pro-Gly) monoimino ether **15** (2mmol) in methanol (10 ml) 1, 1-bismthylthio-2-niroethene **2** (2mmol) was added. The mixture was refluxed and the progress of the reaction was monitored by TLC. The coupling reaction of lactim ether was evident from the smell of methyl mercaptan. After completion of the reaction, the solvent was removed under reduced pressure. The crude sample (**16a**) was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (35:65).

Nitroenamine (16a) (R =H) yellow solid, mp 85-87 ^{0}C (EtOH.

Yield (%)	32
IR(Neat)/cm^{-1}	3210, 2950, 1745, 1630, 1505, 1410, 1380
^{1}H NMR ($CDCl_3$) (200 MHz)	1.30(t, 3H, CH_3, J = 10.0Hz), 1.85-2.30(m, 4H, $2CH_2$), 2.45(s, 3H, SMe), 3.60(q, 2H, OCH_2, J = 9.0Hz), 4.10-4.35(m, 5H, $NHCH_2$, NCH_2, NCHCO), 6.60(s, 1H, =CH), 10.70(br, 1H, NH)
MS (m/z)	299, 271, 223, 199, 125, 98, 83, 70(100%)
Analysis	Found: C, 45.38; H, 5.59. $C_{12}H_{19}N_3O_5S$ requires C, 45.42; H, 5.99%.

5.2 Reaction of pyroglutamate lactim ethers (23) with methyl chloroformate

Pyroglutamate lactim ether **23** (2mmol) and methyl chloroformate (2mmol) was stirred at 30 °C and the progress of the reaction was monitored by TLC. After

completion of the reaction, the mixture was taken in EtOAc (25 ml) and washed twice with water. The organic layer was dried over anhydrous Na_2SO_4. The crude sample **(28)** was purified by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70). Similarly pyroglutamate lactim ether **(23)** was reacted with acetyl chloride, benzoyl chloride, methanesulfonyl chloride and benzenesulfonyl chloride gave **29**, **30**, **31** and **32** respectively.

N- Carbomethoxydimethyl glutamate (28)

Yield (%)	65
IR(Neat)/cm^{-1}	3290, 3010, 2975, 1740, 1728, 1675, 1510, 1455, 1327
^{1}H NMR ($CDCl_3$)	1.95-2.20(m, 2H, CH_2), 2.30-2.50(m, 2H, CH_2), 3.60(s, 6H, $2OCH_3$),
(200 MHz)	3.70(s, 3H, OCH_3), 4.30(m, 1H, NCHCO), 5.60(br, 1H, NH)
^{13}C NMR($CDCl_3$)	27.16, 29.91, 51.55, 53.31, 156.82, 172.51, 173.11
(50 MHz)	
MS (m/z)	234(M+1), 216, 202, 188, 174, 142, 127, 114(100%), 98
Analysis	Found: C, 46.43; H, 6.73; N, 6.26. $C_9H_{15}NO_6$ requires C, 46.35; H, 6.43; N, 6.00%.

N- Acetyldimethyl glutamate (29)

Yield (%)	72
IR(Neat)/cm^{-1}	3370, 2970, 2890, 1732, 1715, 1670, 1515, 1430, 1370
^{1}H NMR ($CDCl_3$)	2.05(s, 3H, CH_3), 2.10-2.25(m, 2H, CH_2), 2.35-2.50(m, 2H, CH_2),
(200 MHz)	3.65(s, 3H, OCH_3), 3.76(s, 3H, OCH_3), 4.60(m, 1H, NCHCO), 6.5(br,
	1H, NH)
^{13}C NMR($CDCl_3$)	22.16, 26.54, 29.74, 51.33, 51.90, 170.59, 172.13, 172.87

(50 MHz)	
MS (m/z)	218(M+1), 186, 174, 158, 144, 126, 116, 98, 84(100%)
Analysis	Found: C, 49.00; H, 7.07; N, 6.09. $C_9H_{15}NO_5$ requires C, 49.70; H, 6.90; N, 6.40%.

N- Benzoyldimethyl glutamate (30)

Yield (%)	68
IR(Neat)/cm^{-1}	3282, 2957, 1738, 1726, 1648, 1439, 1327, 1266, 1215
^1H NMR ($CDCl_3$)	2.15-2.35(m, 2H, CH_2), 2.45-2.55(m, 2H, CH_2), 3.65(s, 3H, OCH_3),
(200 MHz)	3.80(s, 3H, OCH_3), 4.80(m, 1H, NCHCO), 7.05(br, 1H, NH), 7.50-7.70(m, 5H, Ar)
^{13}C NMR($CDCl_3$)	26.73, 30.12, 51.57, 52.13, 52.22, 127.07, 128.26, 131.52, 133.46,
(50 MHz)	167.24, 172.23, 173.31
MS (m/z)	279(M^+), 264, 247, 220, 188, 174, 161, 130, 114, 105(100%), 91, 77
Analysis	Found: C, 60.54; H, 6.34; N, 5.12. $C_{14}H_{17}NO_5$ requires C, 60.21; H, 6.09; N, 5.01%.

N- Methanesulfonyldimethyl glutamate (31)

Yield (%)	77
IR(Neat)/cm^{-1}	3281, 3010, 2960, 1738, 1729, 1439, 1329, 1299, 1213
^1H NMR ($CDCl_3$)	2.15-2.30(m, 2H, CH_2), 2.50-2.60(m, 2H, CH_2), 2.95(s, 3H, SO_2CH_3),
(200 MHz)	3.80(s, 3H, OCH_3), 3.80(s, 3H, OCH_3), 4.15(m, 1H, NH, NCHCO), 5.35(br, 1H, NH)
MS (m/z)	236, 222, 212, 194, 162, 134, 114, 98, 84(100%), 79
Analysis	Found: C, 37.64; H, 5.80; N, 5.64. $C_8H_{15}NO_6S$ requires C, 37.94; H, 5.92; N, 5.53%.

N- Benzenesulfonyldimethyl glutamate (32)

Yield (%)	70
IR(Neat)/cm^{-1}	3273, 3005, 2955, 1738, 1726, 1447, 1342, 1220, 1165
^1H NMR ($CDCl_3$) (200 MHz)	1.85-2.20(m, 2H, CH_2), 2.40-2.50(m, 2H, CH_2), 3.50(s, 3H, OCH_3), 3.65(s, 3H, OCH_3), 4.00(m, 1H, NCHCO), 5.50(br, 1H, NH), 7.40-7.75(m, 5H, Ar)
MS (m/z)	316(M+1), 298, 284, 256, 224, 196, 174, 160, 141, 125, 114, 98, 77(100%)
Analysis	Found: C, 50.21; H, 5.59; N, 4.66. $C_{13}H_{17}NO_6S$ requires C, 49.52; H, 5.39; N, 4.44%.

Preparation of the amidine derivative (33)

Pyroglutamate lactimether (**23**) (10 mmol) was taken in $CHCl_3$ (25 ml). To that pyrrolidine (10 mmol) was added slowly and the nixture was stirred at 30 °C for 6h. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure and the crude product were purified over basic alumina using methanol- $CHCl_3$ (2:98) gave the amidine (**33**) in 40% yield.

Amidine derivative (33)

Yield (%)	40
IR(Neat)/cm^{-1}	3020, 2881, 1735, 1678, 1604. 1468, 1396, 1355
^1H NMR ($CDCl_3$) (200 MHz)	1.90(m, 4H, $2CH_2$), 2.05-2.40(m, 2H, CH_2), 2.50-2.70(m, 2H, CH_2), 3.20-3.40(m, 4H, $2CH_2$), 3.70(s, 3H, OCH_3), 4.50(dd, 1H, =NCHCO, J = 6.0, 8.0Hz)
^{13}C NMR($CDCl_3$) (50 MHz)	25.17, 27.32, 32.18, 47.39, 51.46, 69.34, 167.63, 175.29
MS (m/z)	196(M^+), 181, 168, 158, 144, 137(100%), 119, 108, 95, 80

Reaction of the amidine derivative (33) with ethyl chloroformate (7)

To a solution of amidine **33** (2mmol) in methanol (10 ml) ethyl chloroformate (**7**) (2mmol) was added. The mixture was stirred at 30 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was taken in EtOAc (25 ml) and washed twice with water. The organic layer was dried over anhydrous Na_2SO_4. TLC showed two products and the products were separated by flash column chromatography over silica gel (230-400 mesh) using acetone : pet ether (30:70) gave **34a** and **34b** in 14% and 19% yields respectively.

N-Carbethoxy dimethyl glutamate (34a)

Yield (%)	14
IR(Neat)/cm^{-1}	3280, 3015, 2980, 1738, 1724, 1690, 1520, 1462, 1415, 1327
^1H NMR ($CDCl_3$) (200 MHz)	1.20(t, 3H, CH_3, J = 8.2Hz), 1.95-2.25(m, 2H, CH_2), 2.45(m, 2H, CH2), 3.65(s, 3H, OCH_3), 3.75(s, 3H, OCH_3), 4.10(q, 2H, OCH_2, J = 7.5Hz), 4.35(m, 1H, NCHCO), 5.40(br, 1H, NH)
MS (m/z)	248(M+1), 215, 202, 188, 156, 142, 128, 112, 98, 84(100%), 70
Analysis	Found: C, 48.31; H, 6.93; N, 5.88. $C_{10}H_{17}NO_6$ requires C, 48.58; H, 6.88; N, 5.66%.

N-Carbethoxy methyl pyroglutamate (34b)

Yield (%)	19
IR(Neat)/cm^{-1}	3028, 2915, 2887, 1735, 1698, 1670, 1525, 1461, 1375
^1H NMR ($CDCl_3$) (200 MHz)	1.15(t, 3H, CH_3, J = 8.0Hz), 1.95-2.10(m, 2H, CH_2), 2.35-2.65(m, 2H, CH_2), 3.70(s, 3H, OCH_3), 4.15(q, 2H, OCH_2, J = 7.0Hz), 4.60(dd, 1H, NCHCO, J = 6.0, 8.0Hz)

MS (m/z)	215(M^+), 202, 183, 156, 142, 128, 110, 98, 84(100%), 70
Analysis	Found: C, 50.65; H, 6.40; N, 6.88. $C_9H_{13}NO_5$ requires C, 50.23; H, 6.04; N, 6.51%.

References

1. F. Gerd and B. Artuz, Chem. Abstr., **1980**, *92*, 6085c .
2. J. Gonda, P. Kristian and L. Mikler, *Coll. Czech. Chem. Commun*, **1986**, *51*, 112.
3. D. H. Aue and D. Thomas, *J. Org. Chem*, **1975**, *40*, 2360.
4. J. P. Michael, P. F. Cirillo, L. Denner, G. D. Hosken, A. S. Howard and O. S. Tinkler, *Tetrahedron*, **1990**, *46*, 7923.
5. R. Gompper and H. Schafter, Chem. Ber., **1967**, *100*, 591.
6. W. E. Parham and L. J. Reed, Org. Synth Coll. Vol. **1955**, *3*, 395.
7. S. Rajappa, *Tetrahedron,* **1981**, *37*, 1453..
8. J. Sheu, M. B. Smith, T. R. Oeschger and J. Satchell, *Org. Prep. Proc. Int*, **1992**, *24*, 147.
9. R. W. Roeske and S. J. Kennedy, Chemistry and Biochemistry of Amino acids, Peptides and Proteins, Ed. by B. Weinstein, Vol. *7*, p 205.
10. R. Nagaraj, N. Shamala and P. Balaram, J. Am. Chem. Soc., **1979**, *101*, 16.
11. R. Fitzi and D. Seebach., Tetrahedron., **1988**, *44*, 5292.
12. I. Ojima, H. C. Chen and X. Qui., Tetrahedron., **1988**, *44*, 5302.
13. P. J. Sinchair, D. Zhai, R. reibenspies and R. M. Williams, J. Am. Chem. Soc., **1986**, *108*, 1103.
14. M. T. Leplawy, D. S. Jones, G. W. Kermer and R. C. Shepard, Tetrahedron., **1960**, *11*, 39.
15. a) H. Schmilt and G. Jung, Liebigs Ann. Chem., **1985**, 321.
    b) R. Nagaraj and P. Balaram, Tetrahedron., **1981**, *37*, 2001.
16. a) S. G. Manjunatha, K. V. Reddy and S. Rajappa, *Tetrahedron Lett.,* **1990**, *31*, 1327.
    b) S. G. Manjunatha, P. Chittari and S. Rajappa, *Helv. Chim. Acta,* **1991**, *74*, 1071. c) A. Thomas, S. G. Manjunatha and S. Rajappa, *Helv. Chim. Acta,* **1992**, *75*, 715.

17. S. Rajappa and B. G. Advani, *Tetrahedron,* **1973**, *29*, 1299.

18. S. G. Manjunatha and S. Rajappa, J Chem Soc., Chem. Commun., **1991**, 372.

19. S. G. Manjunatha, Ph. D Thesis, University of Poona, Pune, India, **1992.**

20. T. Nagasaka, A. Tsukada and F. Hamaguchi, Heterocycles., **1986**, *24*, 2015.

21. R. B. Silverman and M. A. Levy, J. Org. Chem., **1980**, *45*, 815.

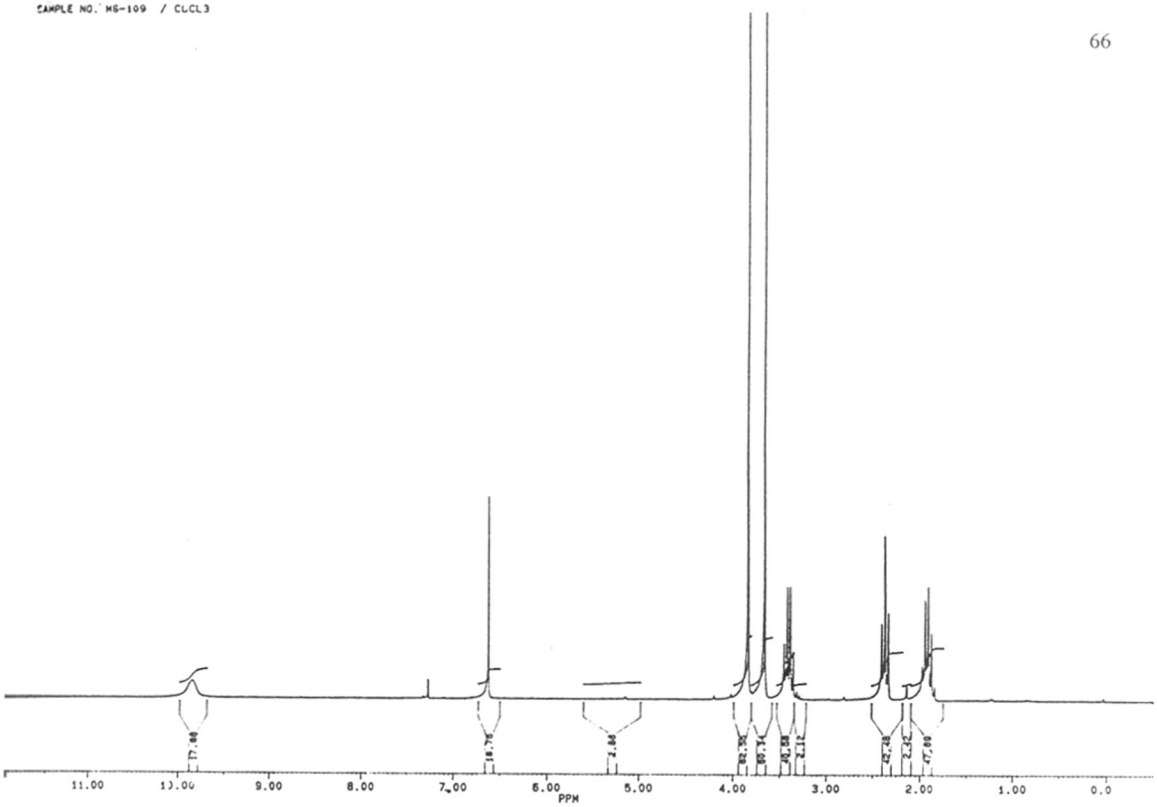
22. I. Thomson, K. Clausen, S. Scheibye and S. O. Lawesson, *Org. Synth.* **1984**, *62*, 158.

23. R. Gompper and W. Beitschaft, *Angew. Che, Int. Ed. Engl.,* **1983**, *22*, 717.

24. D. D. Perrin and W. L. F. Armarego, "Purification of Laboratory Chemicals", Third Ed., Pergamon press, **1988.**

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

26. R. E. Benson and T. L. Cairns, *Org. Synth. Coll. Vol.,***1963**, *4*, 588.



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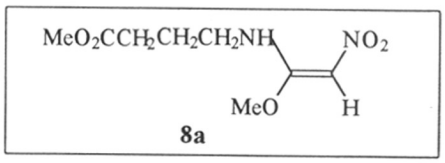
MA – I -109



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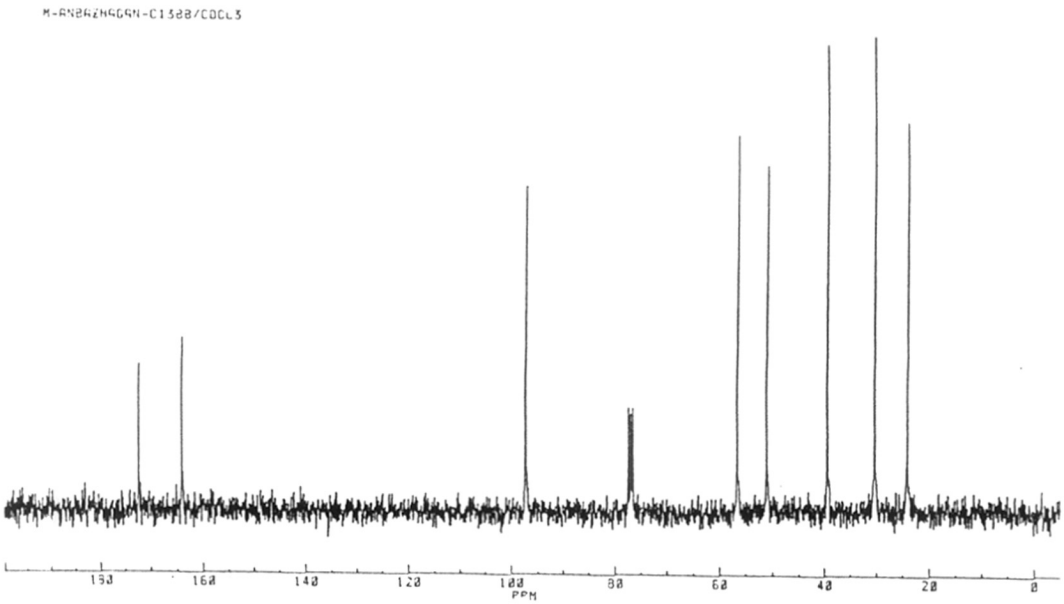

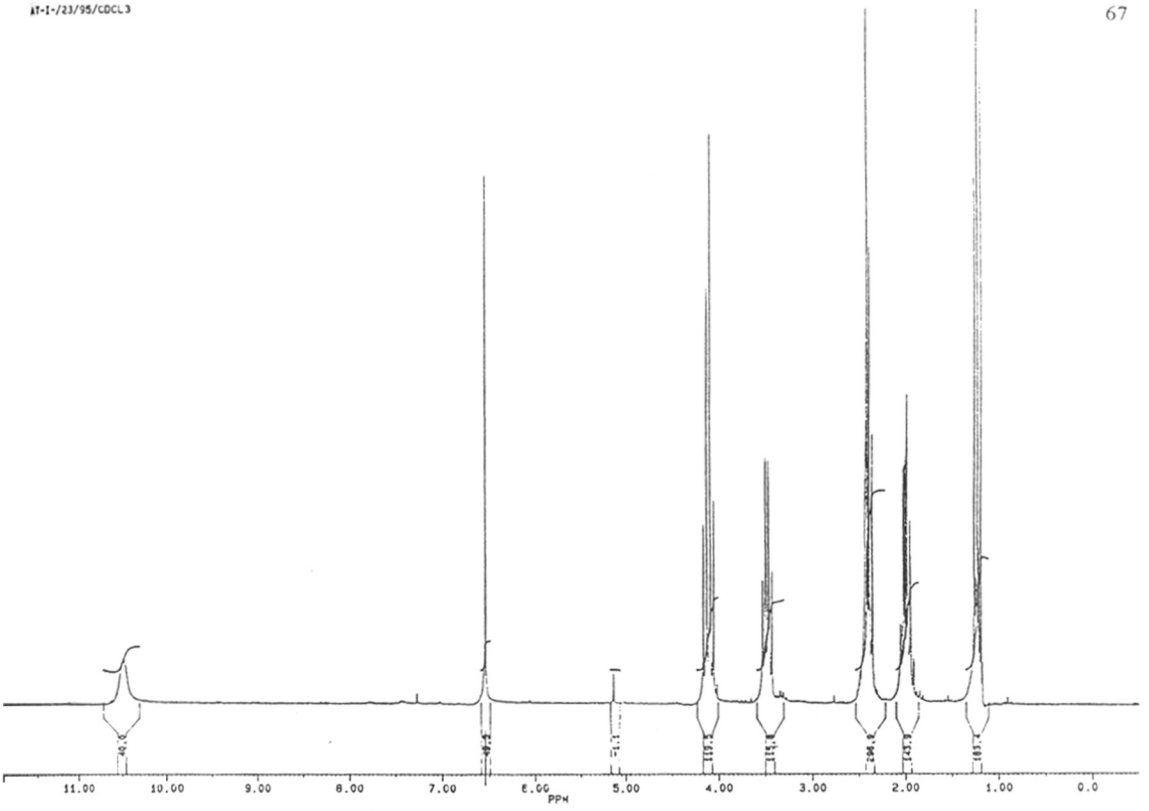
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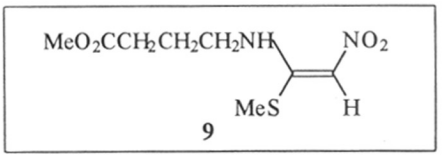
Figure 2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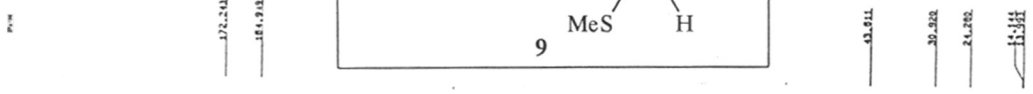
NO2
MeS
H

9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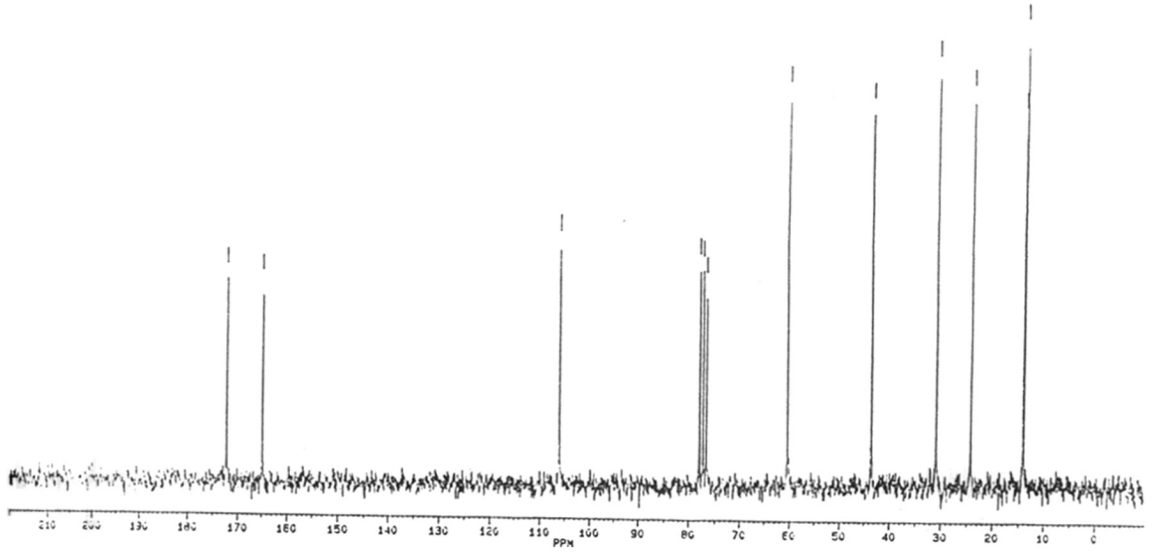
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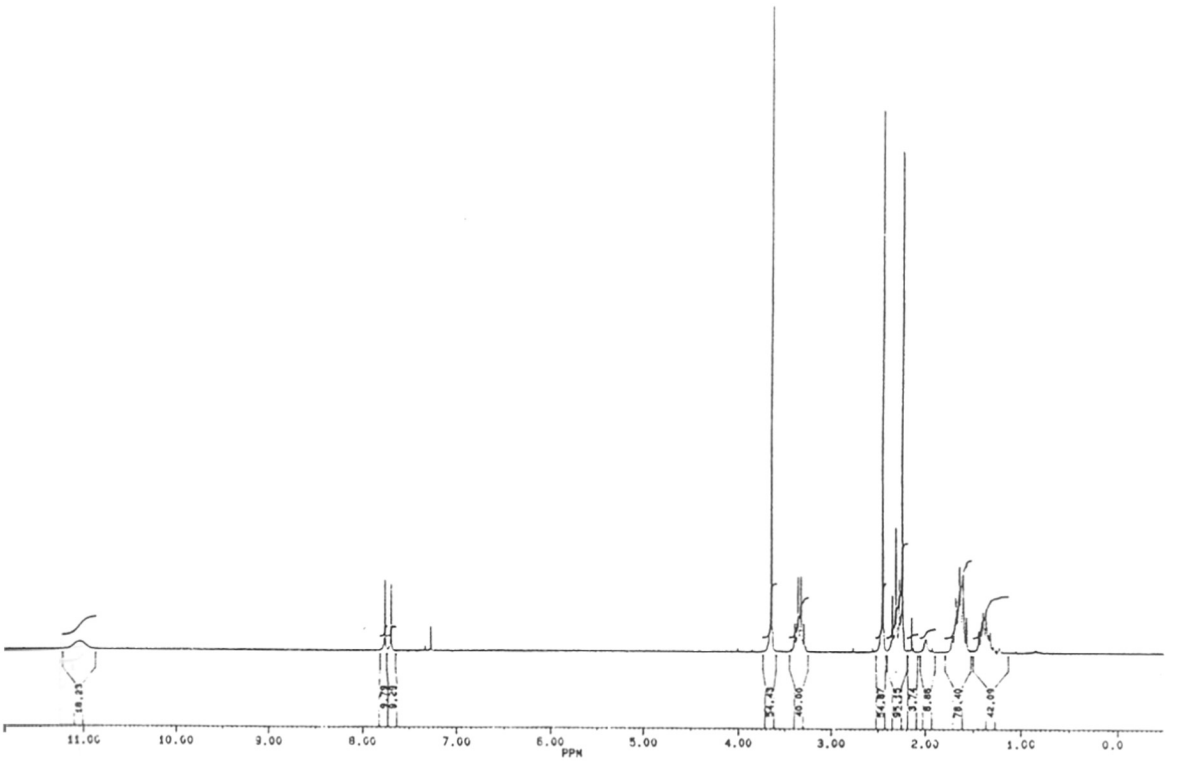
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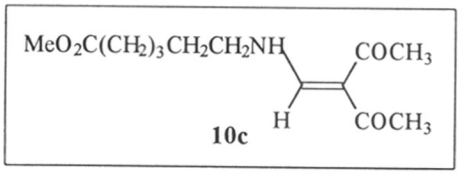
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COCH3

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MA-I-121
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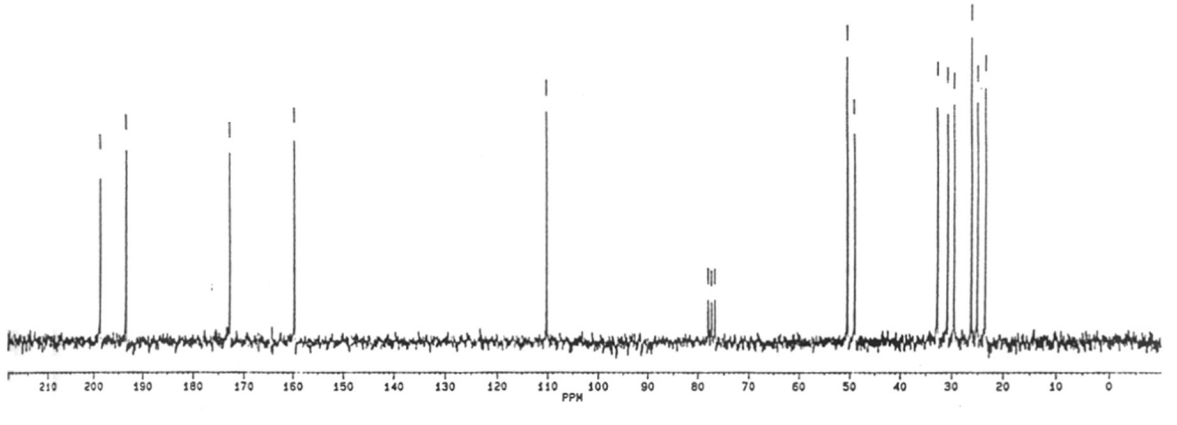
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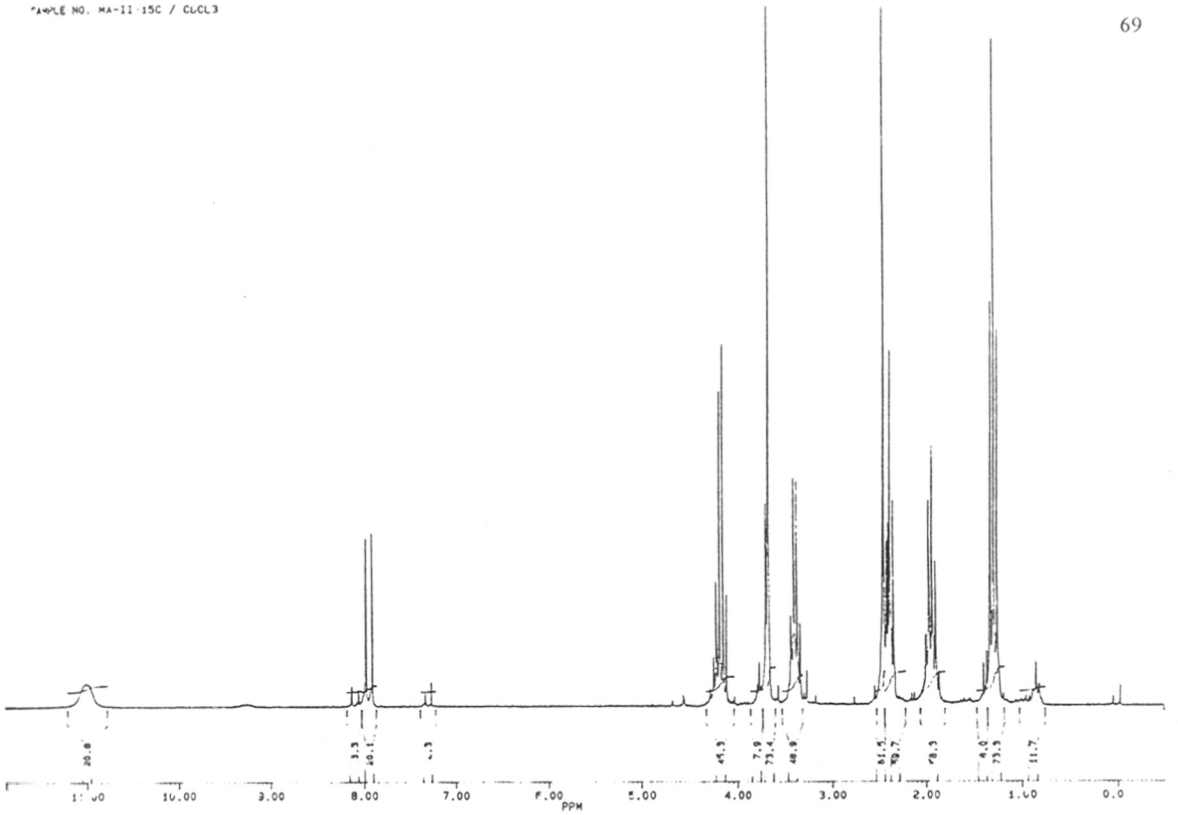

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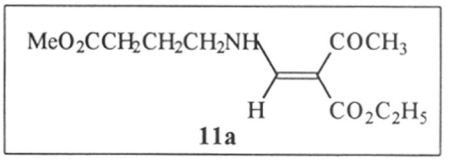

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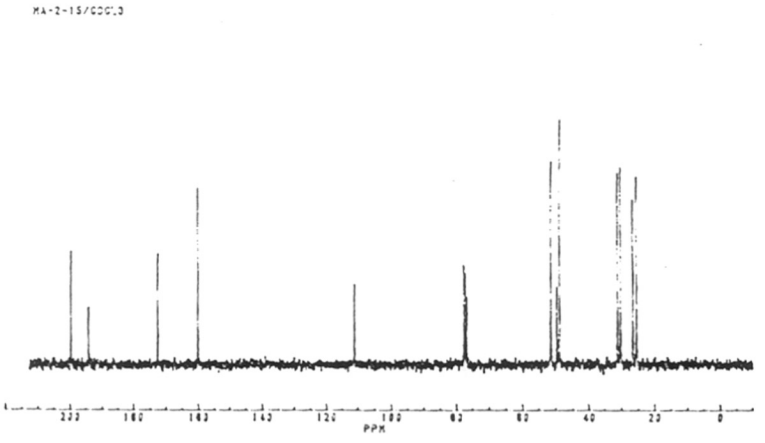

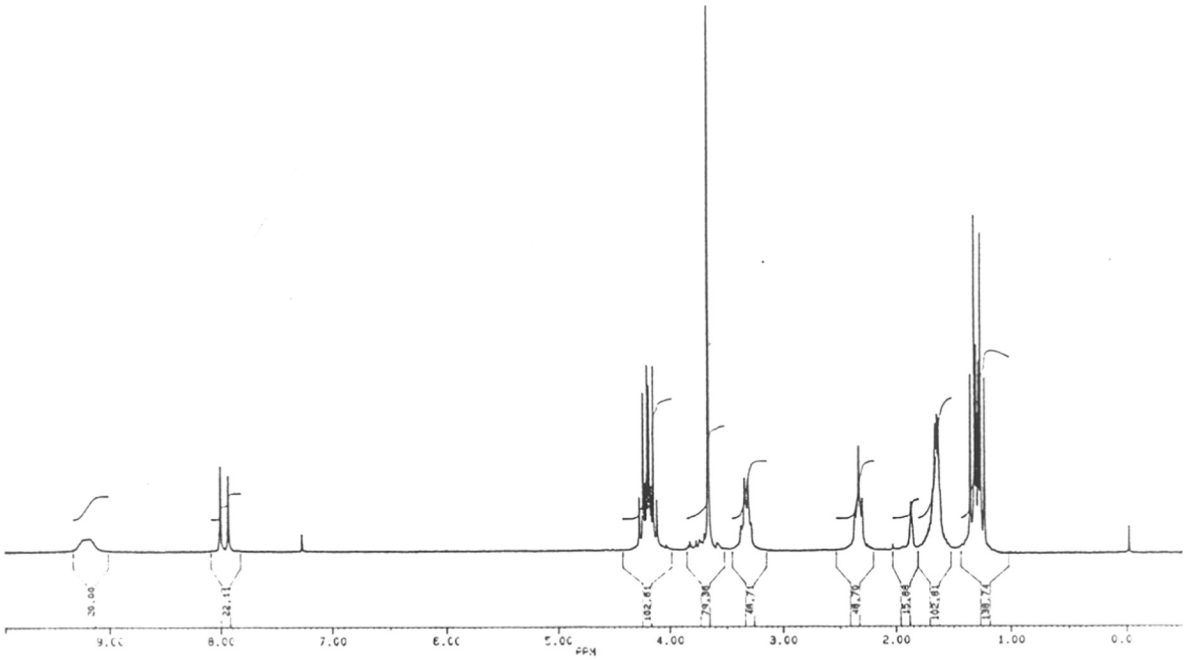
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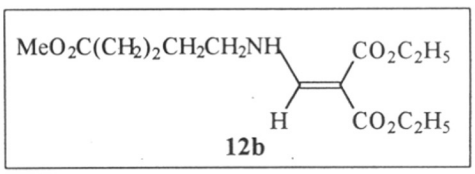
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12b

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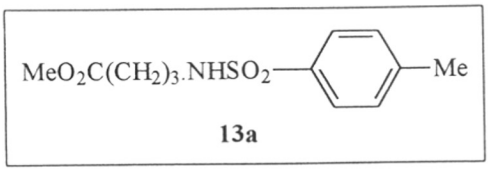

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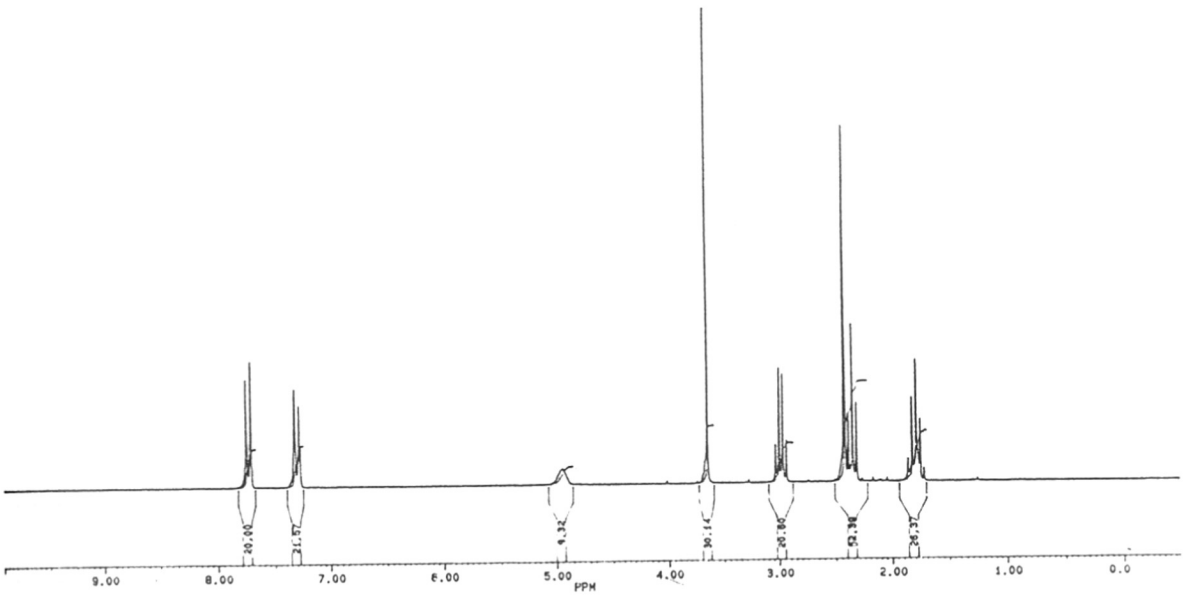

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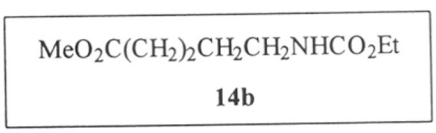

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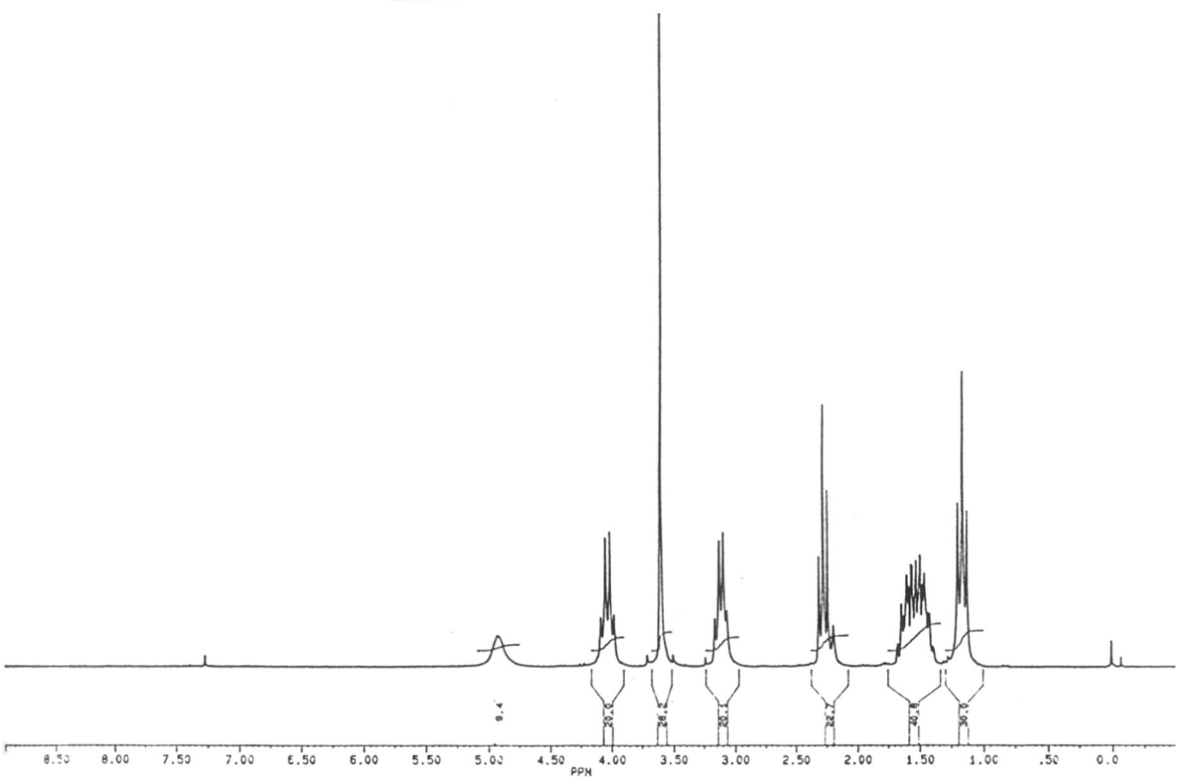

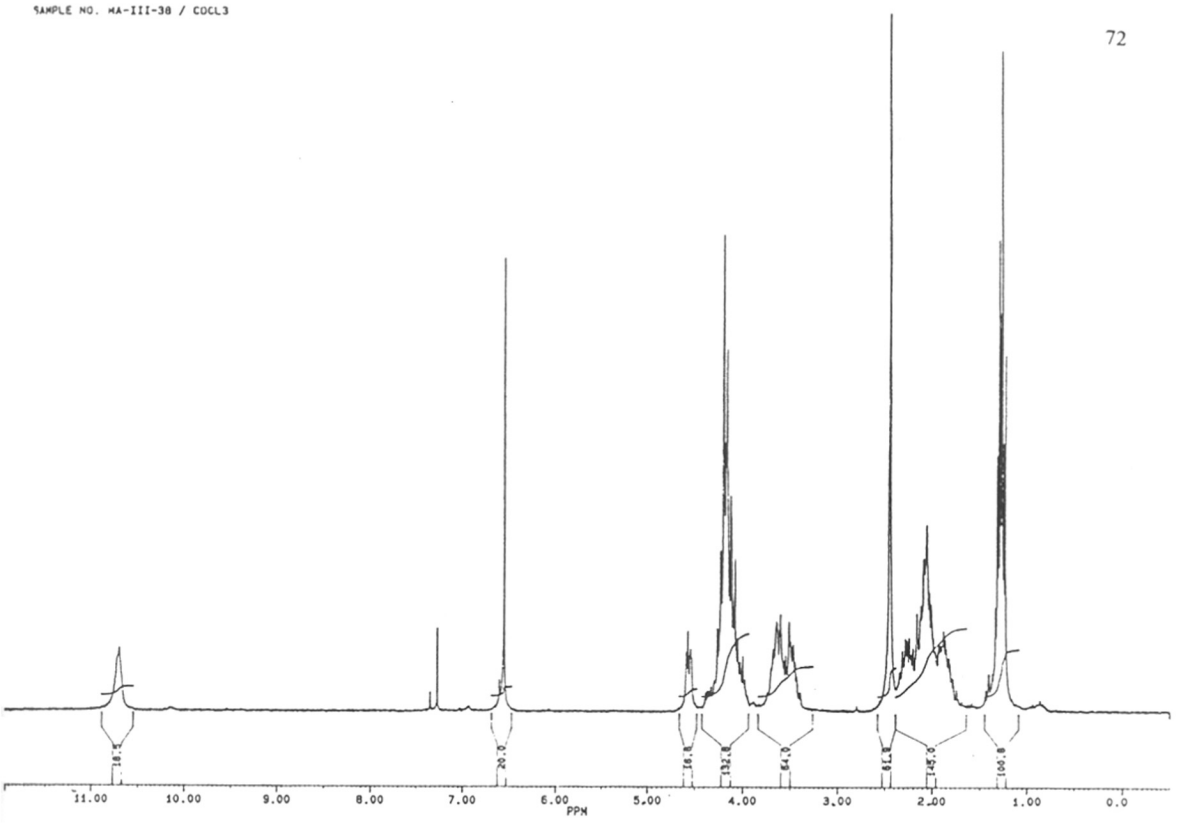
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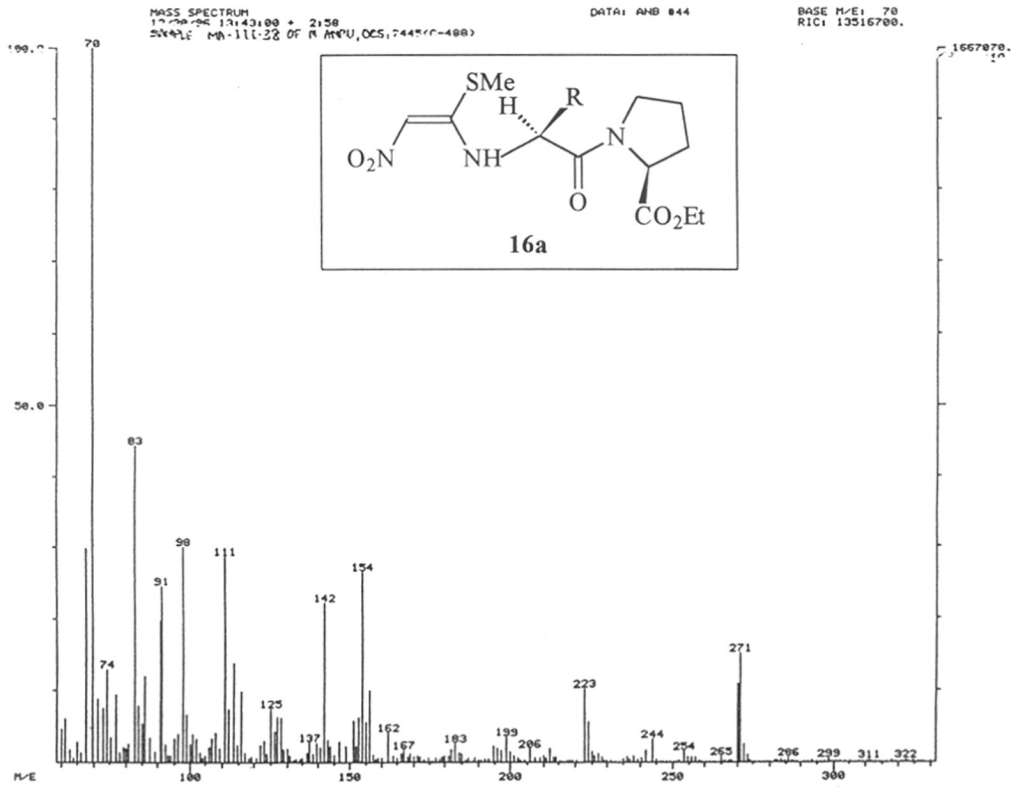
Figure 8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NH
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M/E
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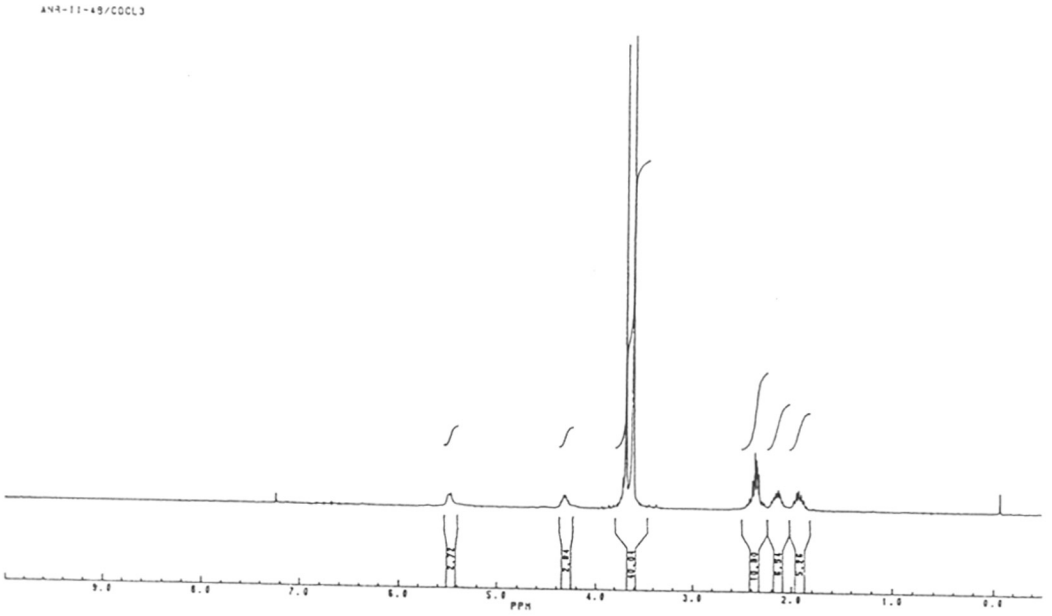

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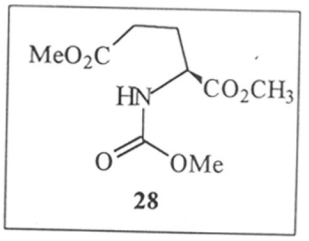

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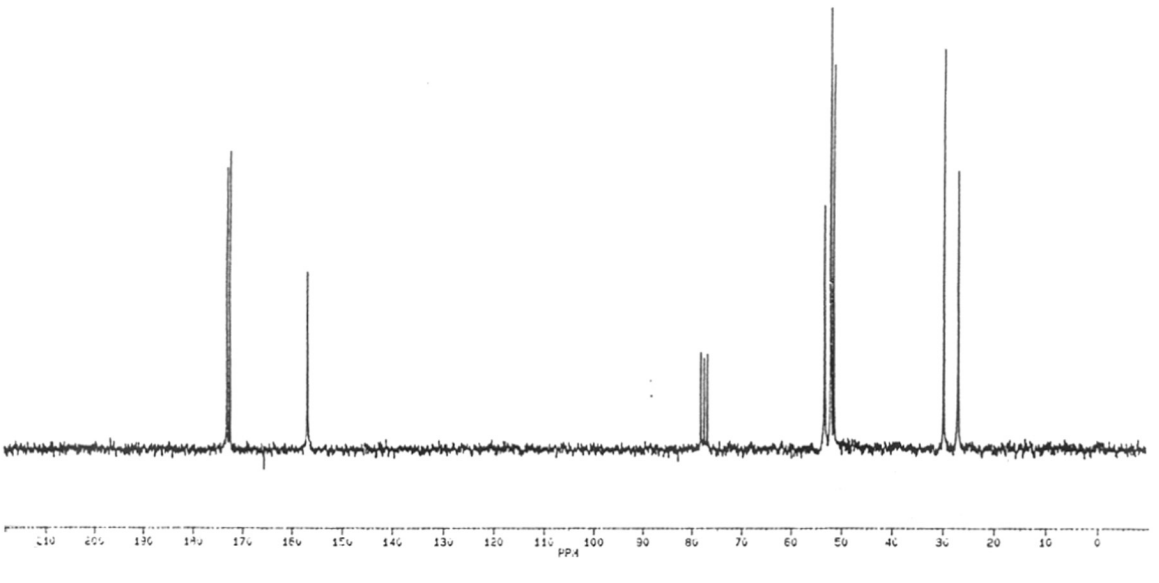
AM-7-48



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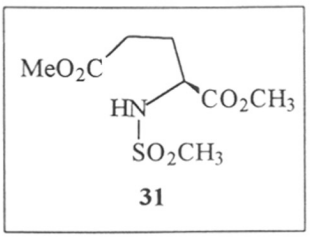

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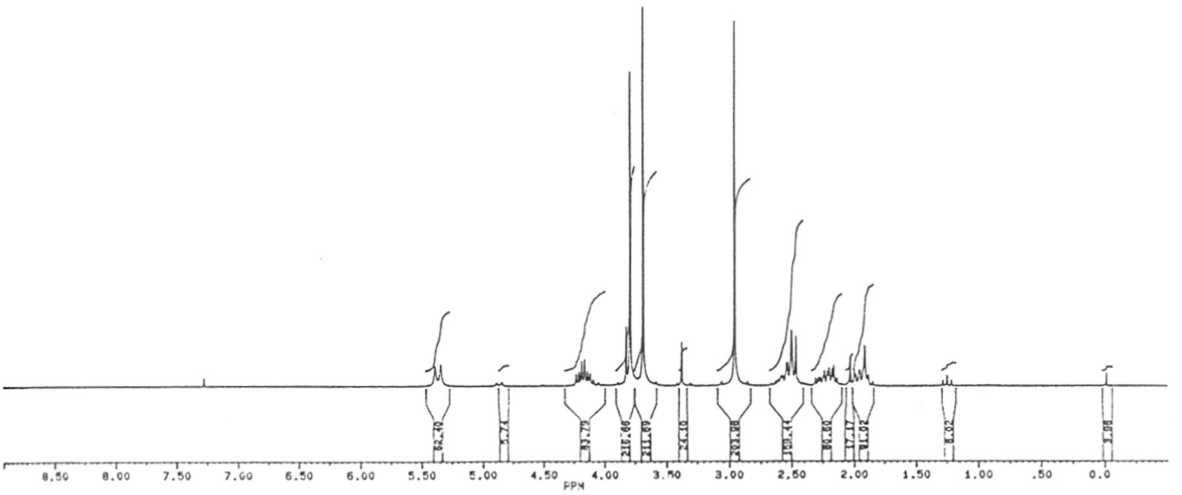

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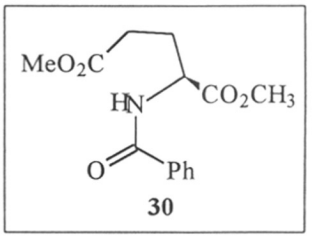

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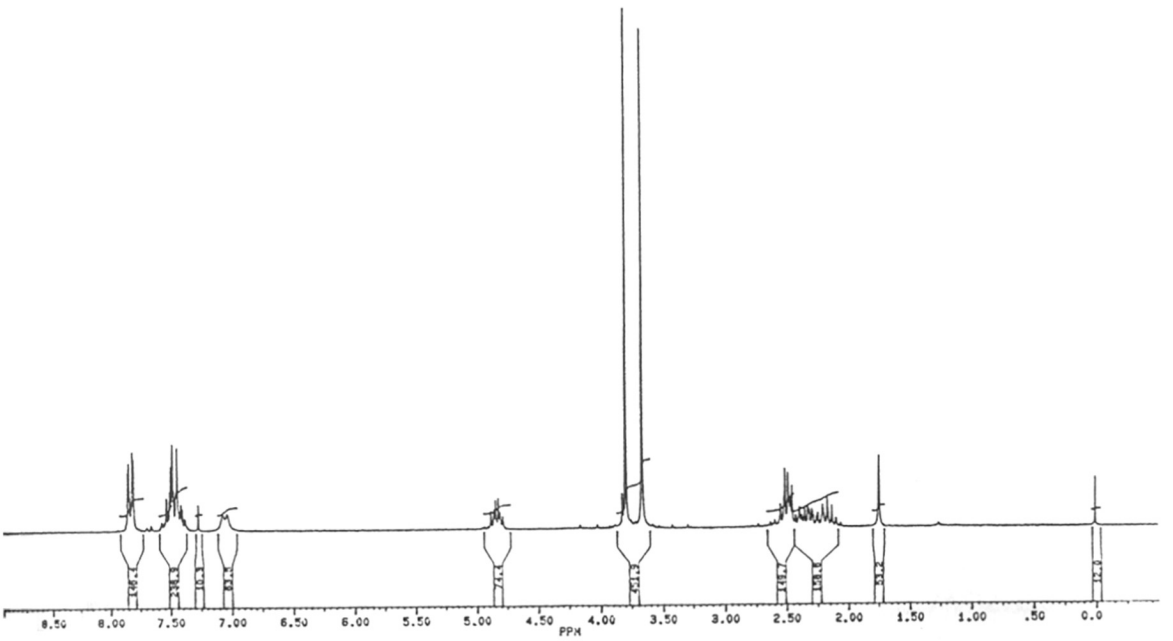

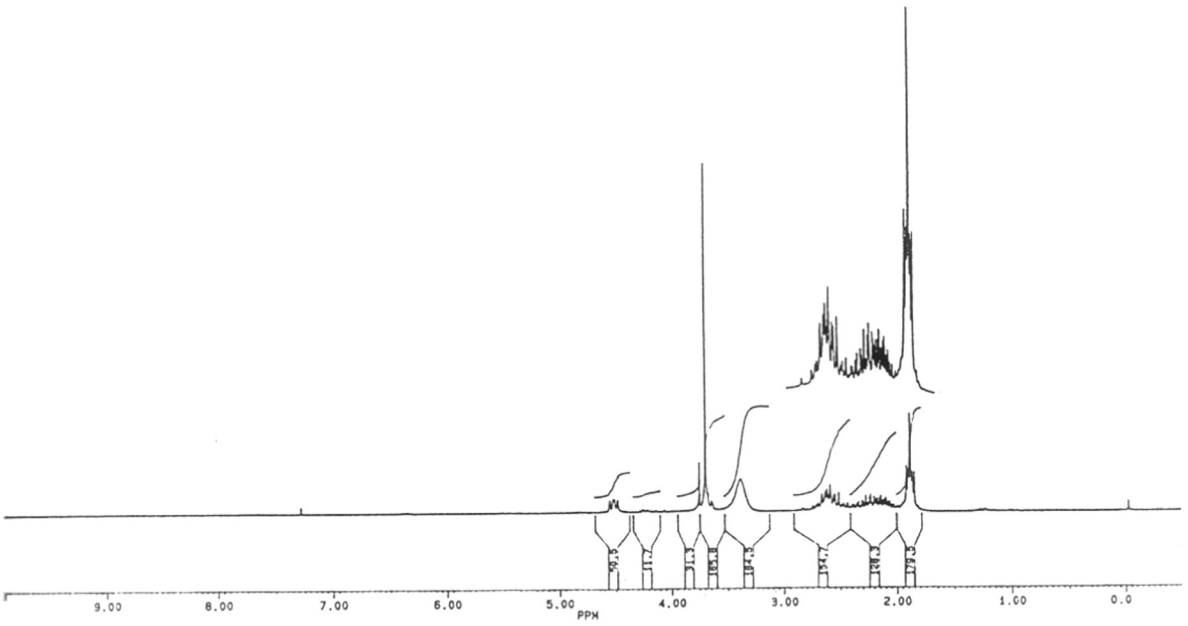

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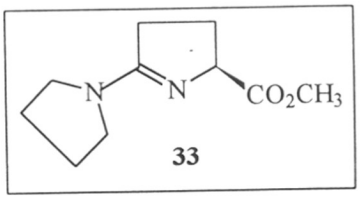

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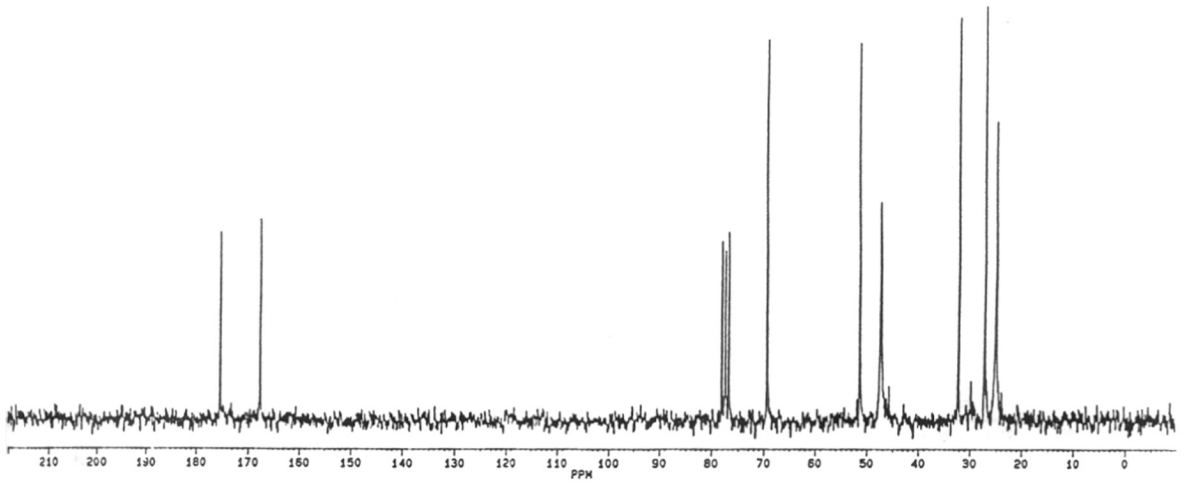
MA-VII-45C



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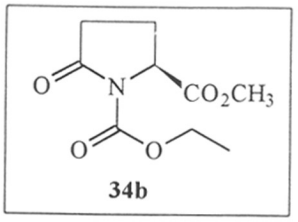

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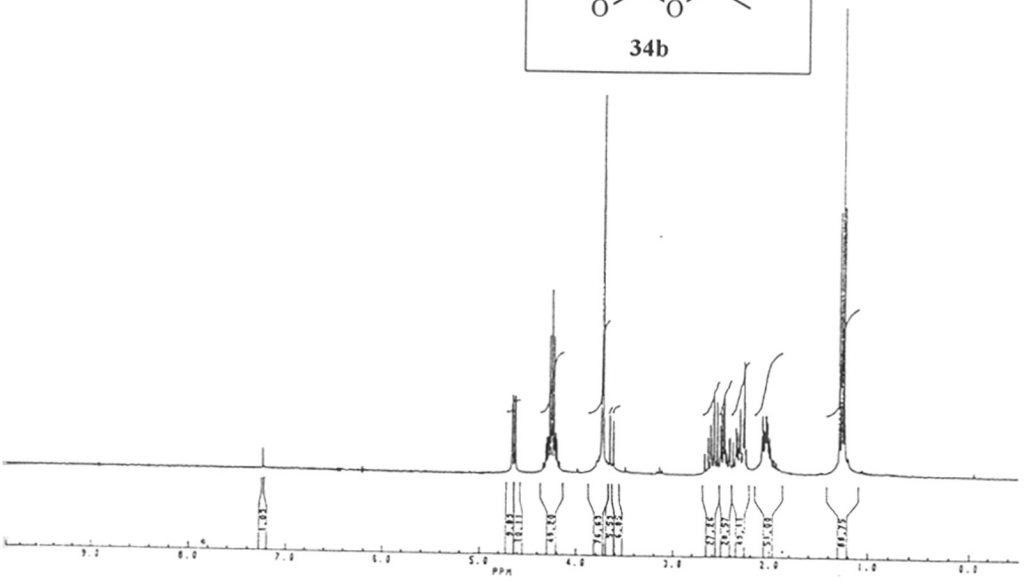
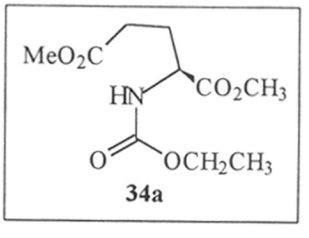


Figure 13



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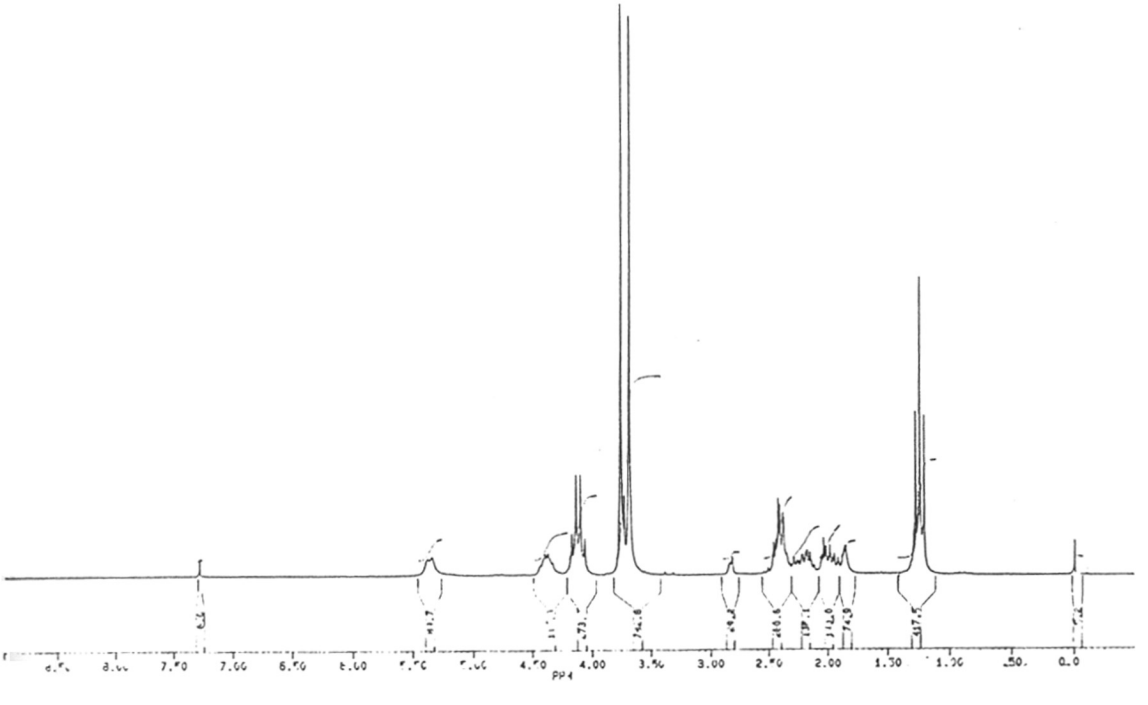


CHAPTER 3

A Non-Phosgene strategy for the preparation of

N-carbobenzoxy -α- amino acids

A. Synthesis of Carbamates: Survey of literature

1. Introduction

Alkyl and aryl esters of carbamic acids are known as carbamates. Some of these are widely used as chemical agents for plant protection. The aryl esters of N-methylcarbamic acids are used to control harmful insects. The alkyl esters of N- aryl carbamic acids are powerful herbicides for the control of weeds. The phenyl carbamates are especially useful as insecticides; an important member of the group is Sevin or Carbaryl (1-naphthyl) N- methylcarbamate which is very effective against many insect pests of fruit, vegetable, cotton and for control of earthworms and other insects in turf. Carbamates may sometimes be used as substitutes for DDT in order to reduce environmental pollution since they do biodegrade and consequently do not accumulate in the ecosystem. Other interesting N- methylcarbamates include Propoxur or Baygon and Carbofuran. A brief summary of the methods known for the preparation of carbamates is given below.

2.General methods for the synthesis of aryl esters of carbamates

2.1 From alkyl isocyanates

The most important method for producing the aryl esters of N-alkylcarbamic acid is the reaction of alkyl isocyanates with phenols in the presence of a base(Scheme 1).[1]

Scheme 1

$$PhOH + RNCO \xrightarrow{base} PhOCONHR$$

This reaction takes place easily producing quantitative yields at a relatively low temperature.

2.2 From aryl chloroformates and diaryl carbonates

Aryl chloroformates can be converted to aryl N- alkylcarbamates on treatment with an alkyl amine(Scheme 2). This reaction goes quite easily in the presence of HCl acceptors such as alkali hydroxides, carbonates or organic bases.[2]

Scheme 2

$$ArOCOCl + RNH_2 \longrightarrow ArOCONHR + HCl$$

The action of methyl amine on diaryl carbonates also generates the aryl esters of N- methylcarbamic acid(Scheme 3).

Scheme 3

$$(ArO)_2CO + CH_3NH_2 \longrightarrow ArOCONHCH_3 + ArOH$$

2.3 From Urea

N- Unsubstituted aryl carbamates could also be prepared by treating phenols with 0.5 equivalent of urea in an organic solvent containing no active hydrogen at reflux temperature(Scheme 4).[3]

Scheme 4

$$PhOH + H_2NCONH_2 \xrightarrow[\text{reflux}]{\text{toluene}} H_2NCOOPh + NH_3$$

2.4 From Nitroarenes

Reductive carbonylation of aromatic nitro compounds with carbon monoxide in the presence of phenol and a catalyst containing Pd, V or Fe, tertiary amine and halogen, furnished aryl carbamates(Scheme 5).[4]

Scheme 5

$$ArNO_2 + PhOH + CO \xrightarrow{\text{catalyst}} ArNHCOOPh$$

2.5 From carboxylic acids

Another method of synthesis of carbamates from carboxylic acids has been described by Yamada.[5] In this method an equimolar mixture of carboxylic acid, triethyl amine and diphenylphosphorazide (DPPA) was refluxed in the presence of the hydroxyl component for 5-25 h. Both aromatic and aliphatic carboxylic acids afforded urethanes in satisfactory yields(Scheme 6). Obviously the reaction proceeds *via* the aryl isocyanate.

Scheme 6

$$ArCOOH + N_3P(O)(OPh)_2 \xrightarrow{R'OH} ArNHCOOR'$$

$R' = alkyl$

3. General methods for the synthesis of alkyl esters of carbamates

3.1 From Urea

Alkyl carbamates have been prepared by heating alcohols with urea under pressure at 150 °C(Scheme 7).[6] For example butyl carbamate was obtained in 75% yield when urea and 4 moles of butanol were refluxed at 120 °C for 40h.

Paquin[7] in 1946 found that the use of metal salts as catalysts in the reaction not only increases the yield but also reduces the reaction time.

Scheme 7

$$ROH + H_2NCONH_2 \xrightarrow{\Delta} H_2NCOOR + NH_3$$

3.2 Ammonolysis of alkyl chloroformates

The ammonolysis of alkyl chloroformate is an excellent general method for the preparation of carbamate esters(Scheme 8).[8]

Scheme 8

$$ROCOCl + 2\,NH_3 \longrightarrow ROCONH_2 + NH_4Cl$$

3.3 Transesterification

Prior to 1948, there were isolated examples in the literature which described the formation of novel carbamates by heating together ethyl chloroformate with higher boiling alcohols with or without a base.[9] In 1948 Kraft[10] found that aluminium isopropoxide catalysed the interchange reaction between ethyl carbamate and benzyl alcohol to give benzyl carbamate in good yield(Scheme 9).

Scheme 9

$$RNHCOOEt + PhCH_2OH \xrightarrow[\text{isopropoxide}]{\text{aluminium}} RNHCOOCH_2Ph$$

N- Alkyl carbamates as well as unsubstituted carbamates (R = H) can be used as the interchange component.[11]

3.4 Oxidative alkoxycarbonylation of amines

Carbamates are usually prepared by the reaction of alcohols with isocyanates, manufactured by phosgenation of corresponding amines. To avoid the use of the toxic phosgene, a few catalytic methods for the preparation of carbamates directly from amines and carbon monoxide by oxidative alkoxycarbonylation have been reported. One such method uses selenium and bases.[12] Another uses $PdCl_2$ as the catalyst in the presence of a Lewis acid.[13]

Fukuoka *et al* have described another method of synthesis of carbamates from amines using metallic Pd/ I^- catalyst system(Scheme 10).[14]

Scheme 10

$$R'NH_2 + CO + R''OH + 1/2\,O_2 \xrightarrow{Pd/\,I^-} R'NHCOOR''$$

A homogeneously catalysed reaction has been reported for the synthesis of alkyl carbamates from amines and carbon monoxide by Alper *et al*(Scheme 11).[15] This method uses $PdCl_2$ as the catalyst and $CuCl_2$ as re-oxidant. Other platinum group metals have also been used as catalysts for the reaction.[16]

Scheme 11

$$ArNH_2 + CO + ROH \xrightarrow[O_2,\ HCl]{PdCl_2,\ CuCl_2} ArNHCOOR$$

3.5 From carbon dioxide

An efficient Cu- promoted carbamate formation from carbon dioxide, amines and alkyl halides has been described(Scheme 12).[17] A stable metal-complex intermediate of the type $R_2NCOOCu(CN\ t\text{-}Bu)_n$ has been isolated, which on further treatment with methyl iodide gives the carbamate.

Scheme 12

$$CuOBu.^t + R'R''NH + CO_2 \xrightarrow{-\,t.BuOH} R'R''NCO_2Cu$$

$$R'R''NCO_2Cu \xrightarrow{Bu.^tNC} R'R''NCO_2Cu(CNBu.^t)n$$

$$R'R''NCO_2Cu(CNBu.^t)n \xrightarrow{MeI} R'R''NCO_2Me$$

Recently Aresta and Quaranta have synthesised alkyl carbamates from amines, carbon dioxide and alkyl halides in the presence of crown ethers(Scheme 13).[18]

Scheme 13

$$R'NH_2 + CO_2 + R''Cl \xrightarrow{\text{crown ether}} R'NHCO_2R''$$

During the reaction a "host-guest" adduct is formed between the crown ether and monoalkylammonium cation RNH_3^+ to give $[RNH_3CE]^+ [O_2CNHR]^-$. The crown ether increases the solubility of the carbamate ion and enhances the nucleophilicity of carbamate anion towards alkyl halide resulting in the formation of the desired alkyl carbamates.

Recently, Rossi *et al*[19] have reported a safe methodology for the synthesis of linear and cyclic alkyl and aryl carbamates by reaction of amines with tetraalkylammonium hydrogen carbonate in the presence of an alkyl halide(Scheme 14).

Scheme 14

$$R'R''NH \xrightarrow[2)\ RX]{1)\ Et_4NHCO_3} R'R''NCO_2R + Et_4NX + H_2O$$

3.6 Electrochemical oxidation

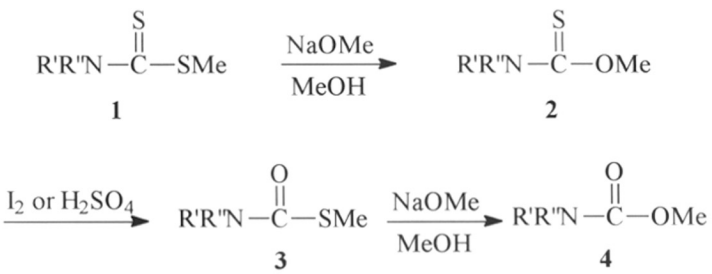
Electrochemical oxidation of formamide to carbamic acid esters in 57-88% yield has been reported by Degner *et al*.[20] The electro-oxidation is carried out in an undivided electrochemical cell with graphite anodes and cathodes at 20-25 °C with an electrolyte containing NaBr as the conductive salt.

3.7 From thiocarbamates

It may be noted that almost all the methods described above use either hazardous starting materials like phosgene or isocyanates or vigorous reaction conditions. Inspite of these drawbacks, there is ever increasing demand for the carbamate pesticides and hence there is a need to develop a new and safe route for the synthesis of carbamates.

Over the past several years our group has been involved in devising synthetic routes for N- methylcarbamates that do not require the use of either phosgene or methyl isocyanate. Earlier, our group had reported the conversion of dithiocarbamate **1** into carbamate **4** in three steps(Scheme 15).[21] In that sequence, a dithiocarbamate **1** was converted first into a O- methyl thiocarbamate **2**, which was isomerised in excellent yield to the corresponding S- methyl thiocarbamate **3**; the latter could be easily transformed by sodium methoxide in methanol into the methyl carbamate **4**.

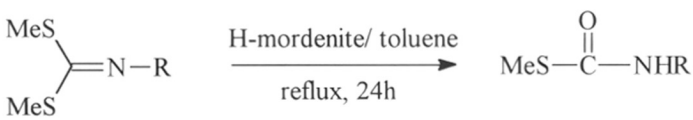
Scheme 15



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

In a related piece of research, it has also been shown in our laboratory that S-methyl thiocarbamate **6** could be directly prepared from carbonimidodithioates[22, 23] **5** by zeolite catalysed partial hydrolysis(Scheme 16). This, therefore provides an alternative route to methyl carbamates **4**; ($R'' = H$)

Scheme 16



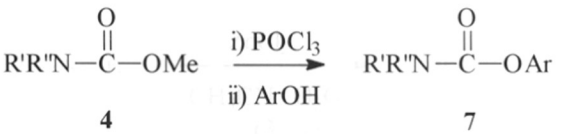
5 **6**

4. Conversion of alkyl carbamates to aryl carbamates

The industrial importance of easy access to alkyl carbamates such as compound **4** stems from the fact that these can be subjected to transesterification with substituted

phenols, leading to commercially important aryl carbamate pesticides **7** (R′ = Me; R″ = H)(Scheme 17).

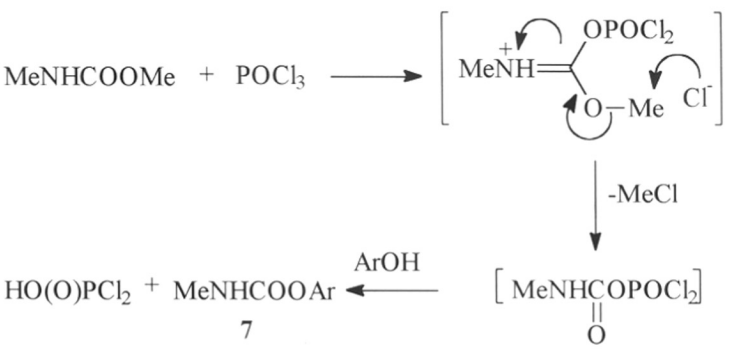
Scheme 17



4 **7**

This contrathermodynamic transesterification was achieved through a modified Vilsmeier reaction(Scheme 18).[24, 25]

Scheme 18



7

B. Present work

1. Objective

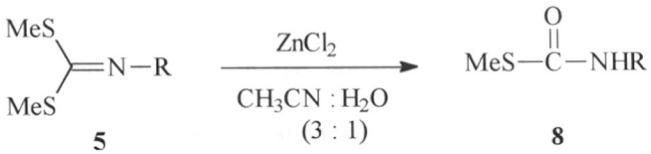
The objective of the present study was to devise a new route for the preparation of carbamates that does not require phosgene or isocyanate, and to demonstrate the utility of this reaction for the preparation of N- benzyloxycarbonyl -α- amino acids.

2. Results and Discussion

The initial success in this reaction was based on the earlier discovery in our group[25] that $ZnCl_2$ is an efficient catalyst for the hydrolysis of carbonimidodithioates **5**. The product obtained was dependent on the solvent used for the reaction. In acetonitrile-

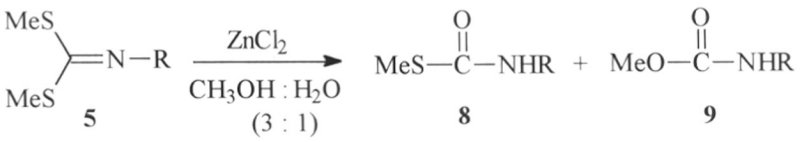
water (3:1) the $ZnCl_2$- catalysed hydrolysis of the imino-sulfide in substrate **5** at 80 °C for 6-10h led to the S- methyl N- alkylthiocarbamate **8**(Scheme 19).

Scheme 19



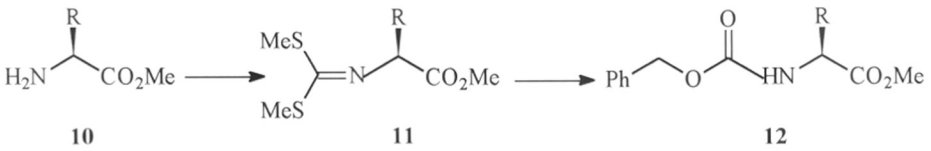
However if the reaction was carried out in MeOH-H_2O (3:1) at 60 °C for 10-12h, further methanolysis tookplace, giving the carbamates **9** in good yields along with small amounts of the thiocarbamate **8**(Scheme 20). The intermediate S- methylthiocarbamates **8** were identical with those obtained earlier by zeolite - catalysed hydrolysis.[22]

Scheme 20



The next logical step was to extend this sequence for the conversion of carbonimidodithioates **11** derived from α- amino acid esters **10** to benzyl carbamates **12** (Scheme 21).

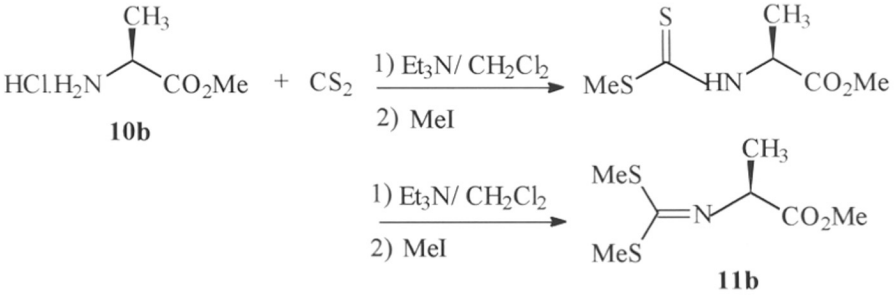
Scheme 21

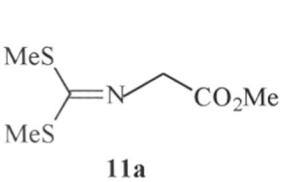


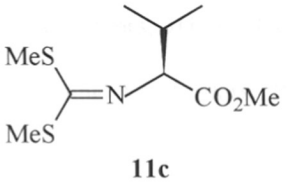
2.1 Synthesis of carbonimidodithioic acid dimethyl esters (11 a-d) from α- amino acid esters.

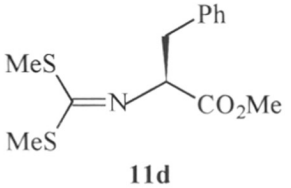
These carbonimidodithioates were prepared by the usual procedure[23] with appropriate modifications. Thus (L)- alanine methyl ester hydrochloride **10b** was condensed with carbon disulfide in the presence of triethylamine as the base in dichloromethane. Subsequent bismethylation with methyl iodide gave the product **11b** as a liquid in 69% yield(Scheme 22). The ^{1}H NMR spectrum of a purified sample of **11b** showed a doublet at1.40δ (d, 3H, J = 10.0Hz), singlets at 2.40, 2.55δ (2 SMe), 3.76δ (OMe) and a quartet at 4.50δ (q, 1H, J = 8.0Hz) corresponding to NCH. Further support to the structure was provided by the mass spectrum which showed the molecular ion (M^+) peak at m/z 207. The above data proved the structure of the product to be **11b**(Figure 15). By a similar procedure the bismethylthio methylene derivatives of glycine, (L)- valine and (L)- phenylalanine methyl esters(**11 a, c, d**) were prepared in more than 80% yields. All these compounds were characterised by their ^{1}H NMR spectra and other analytical data(**11c** - Figure 16). The reactions are generally clean and fast.

Scheme 22









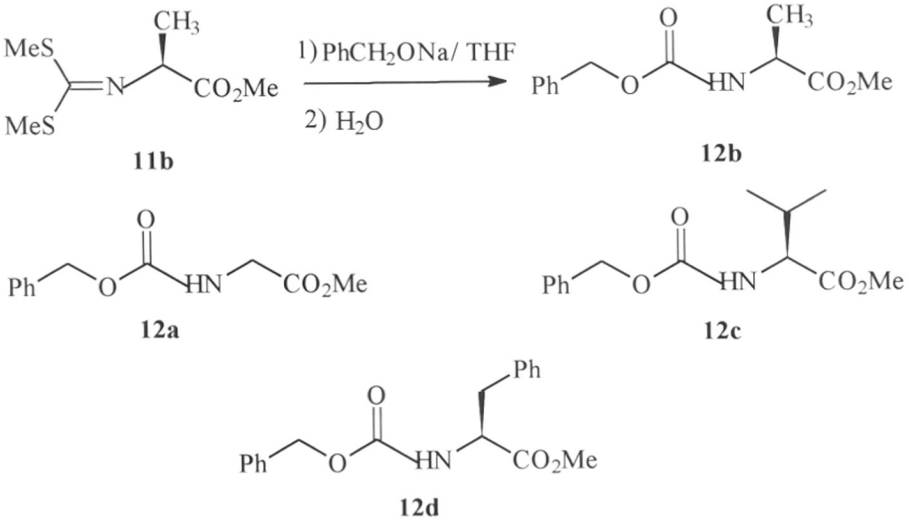
2.2 Conversion of carbonimidodithioates (11 a-d) into benzyl carbamates

Our first attempt in this direction by replacing methanol with benzyl alcohol in the $ZnCl_2$- catalysed alcoholysis of the (L)- alanine derivative **11b** proved to be futile. The reaction of carbonimidodithioate **11b** with benzyl alcohol-water (3:1) in the presence of $ZnCl_2$ and a phase transfer catalyst ($n\text{-}Bu_4N^+Br^-$) also failed to give the desired product. Applying anhydrous reaction conditions using anhydrous $ZnCl_2$ and dry benzyl alcohol at 30 °C or 100 °C was also in vain. Replacement of the Lewis acid catalyst $ZnCl_2$ with other Lewis or Bronsted acids such as $HgCl_2$, p-toluenesulfonic acid, BF_3-etherate, aluminium chloride, lanthanum triflate was equally ineffective; similarly the zeolites H-mordenite and RE-Y also could not bring about the required transformation. Neat reaction between the carbonimidodithioate **11b** and benzyl alcohol without any solvent or catalyst failed to give the required product. Changing the solvent in the above reaction to dimethyl formamide, tetrahydrofuran, dioxane, acetonitrile, diethyl ether, benzene or dimethyl sulfoxide also proved to be completely unsuccessful. In all the cases the starting material was recovered quantitatively without any change.

Successful conversion of carbonimidodithioate **11b** into N- (benzyloxycarbonyl) glycine methyl ester **12b** was finally achieved by the following protocol. Sodium benzyl alcoholate (2 mmol) was treated with carbonimidodithioate **11b** (2 mmol) in anhydrous THF at 30 °C for 6h. After complete disappearance of the starting material, water was added and the hydrolysis was allowed to proceed overnight at 30 °C. After acidic work-up the product **12b** was obtained as a colourless oil in 80% yield(Scheme 23). The ^1H NMR spectrum of a purified sample of **12b** showed a doublet at 1.40δ(d, 3H, J = 8.9Hz) due to the CH_3 protons, a singlet at 3.75δ(s, 3H) for OCH_3, followed by a multiplet at 4.40δ corresponding to NCH and a singlet at 5.10δ(s, 2H) for $\underline{CH_2}Ph$. The NH proton appeared as a broad singlet at 5.55δ and the aromatic protons appeared as a multiplet at

7.35δ(m, 5H). The IR spectrum of **12b** showed two sharp peaks at 1710 and 1740 cm^{-1} for the two carbonyl groups and a broad peak at 3360 cm^{-1} for NH. The mass spectrum of the product showed the molecular ion (M^+) peak at m/z 237. The above data proved the structure of the product to be **12b**(Figure 17). Similarly N- benzyloxycarbonyl glycinate (**12a**), N- benzyloxycarbonyl (L)- valinate (**12c**)(Figure 18), N- benzyloxycarbonyl (L)- phenylalaninate (**12d**) were prepared in 80-86 % yield and characterised by their spectral data.

Scheme 23



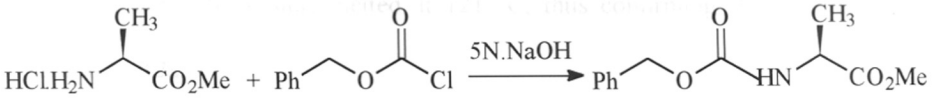
11b **12b**

12a **12c**

12d

An authentic sample of N- benzyloxycarbonyl (L)- alaninate was prepared by the reaction of (L)- alanine methyl ester hydrochloride with carbobenzoxy chloride at 0 °C in the presence of 5N sodium hydroxide solution(Scheme 24).

Scheme 24

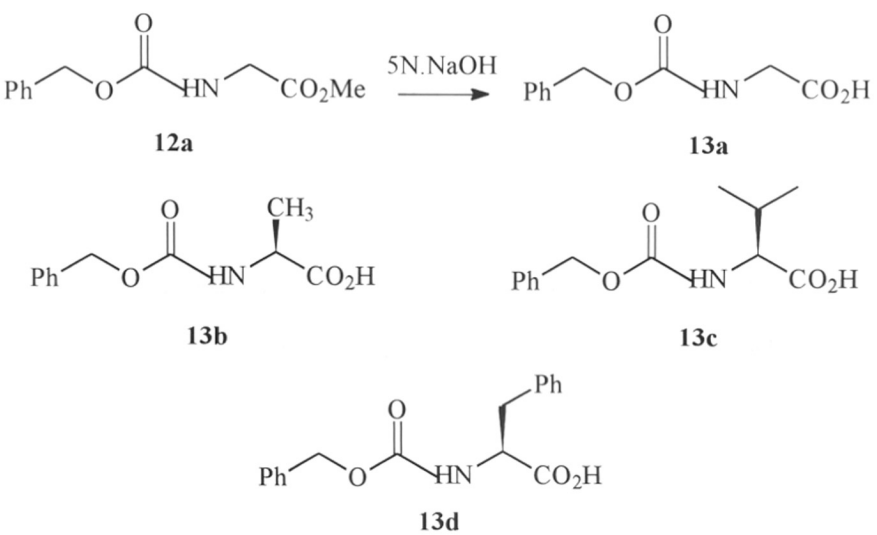


The IR and ^{1}H NMR spectra of the N- benzyloxycarbonyl (L)- alaninate **12b** prepared from carbonimididithioate **11b** and the authentic sample prepared above were identical.

2.3 Hydrolysis of the N- benzyloxycarbonyl amino acid methyl esters (12 a-d)

Alkaline hydrolysis of these methyl esters (**12 a-d**) at 30 °C led to the required N-benzyloxycarbonyl-α- amino acids (**13 a-d**)(Scheme 25). For example the reaction of N-benzyloxycarbonyl glycine methyl ester **12a** with 5N NaOH solution in methanol or tetrahydrofuran at 30 °C gave the required N-benzyloxycarbonyl glycine after 6h as a white solid in 71% yield.

Scheme 25



The mp of the solid N-benzyloxycarbonyl glycine was 120 °C, identical with that of an authentic sample prepared from glycine and carbobenzoxy chloride.[27] A mixture of **13a** and the authentic sample melted at 121 °C, thus confirming the structure of the product to be **13a**.

The hydrolysis could similarly be carried out with substrates **12b, 12c** and **12d** to give the corresponding N-benzyloxycarbonyl-α-amino acids. The melting point and

specific rotation of the N-benzyloxycarbonyl (L)- alanine (**13b**), N-benzyloxycarbonyl (L)- valine (**13c**) and N-benzyloxycarbonyl (L)- phenylalanine (**13d**) were compared with those of authentic samples prepared by the standard procedure. The yield, specific rotation and melting point of the Z- derivatives of amino acids are given in *Table 1*. Values within parentheses are those for authentic samples. The optical rotation was taken under the same conditions on the same instrument.

Table 1: Yields and physical properties of N-benzyloxycarbonyl ∝-amino acids (**13**)

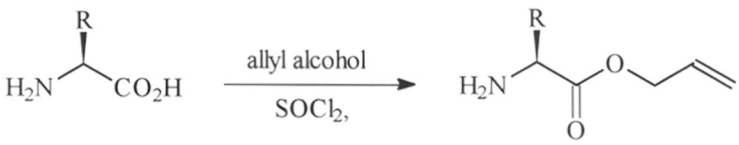
Product	Yield %	m.p ^{0} C	Specific Rotation$[\alpha]_D$
13a	71	121 [122-124]	-
13b	77	80 [82-84]	-14.1 ^{0} [-14.20^0] (c,2 in HOAc)
13c	69	62 [62-64]	+6.1 ^{0} [+6.20^0] (c, 4 in $CHCl_3$)
13d	75	86 [87-90]	+4.4 ^{0} [+4.45^0] (c, 5 in HOAc)

Although this marked the successful charting out of the synthetic route, we felt it was desirable to use a protecting group for the carboxy function, one which could be removed under non-racemising conditions. The allyl esters seemed ideal for this purpose, since mild procedures for de-allylation under Pd (0) catalysis have been reported in the literature.[28-32]

2.4 Preparation of allyl esters of α-amino acids

Allyl esters of α-amino acids were prepared by the published procedure.[33] For example glycine (10 mmol) was taken in allyl alcohol (50 ml) and thionyl chloride (15 mmol) was added dropwise at 0 °C; the mixture was allowed to stir at 30 °C for 24h (Scheme 26). Excess alcohol was removed *in vacuo* and the solid glycine allyl ester hydrochloride **14a** was used as such for further reaction.

Scheme 26



14 a-c

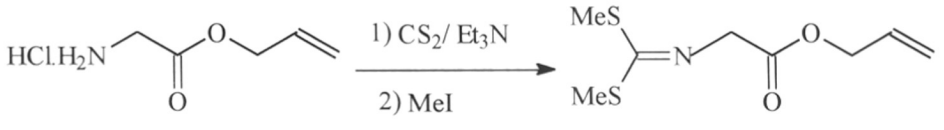
	a	b	c	d	e
R	H	CH_3	$CHMe_2$	CH_2CHMe_2	CH_2Ph

Similarly (L)- allyl alaninate **14b**, (L)- allyl valinate **14c**, (L)- allyl leucinate **14d** and (L)-allyl phenylalaninate **14e** were prepared.

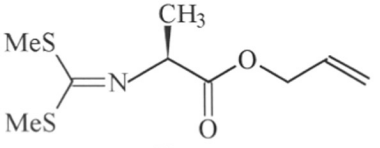
2.5 Synthesis of the carbonimidodithioic acid dimethyl esters (15 a-e) from amino acid allyl esters.

The allyl esters of α-amino acids were converted into the corresponding carbonimidodithioates (**15 a-e**) by the usual procedure.[23] Thus glycine allyl ester was condensed with CS_2; subsequent methylation with methyl iodide gave the product **15a** as a pale yellow oil in 69% yield(Scheme 27). The ^{1}H NMR spectrum of **15a** showed three singlets at 2.40(s, 3H), 2.60(s, 3H) and 4.25(s, 2H) corresponding to -SCH_3, -SCH_3 and -NCH_2 protons respectively in the ratio 3:3:2. Three multiplets were also observed at 4.75(m, 2H), 5.30(m, 2H) and 5.90(m, 1H) corresponding to -OCH_2, =CH_2 and =CH. The mass spectrum of the product showed the molecular ion (M^+) peak at m/z 219. The above data proved the structure of the product to be **15a**(Figure 19). By a similar procedure the bismethylthio methylene derivatives of (L)-alanine, (L)-valine, (L)- leucine and (L)- phenylalanine allyl esters (**15 b-e**) were prepared in 65-77% yields. All these compounds were characterised by their ^{1}H NMR spectra and other analytical data(**15e**-Figure 20).

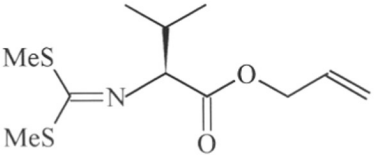
Scheme 27



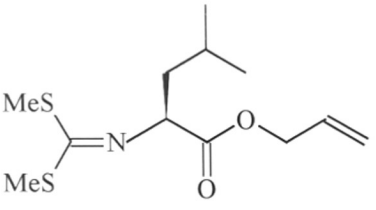
14a **15a**



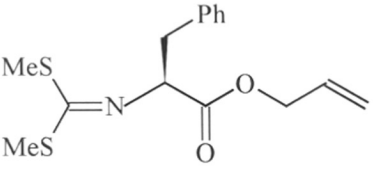
15b



15c



15d



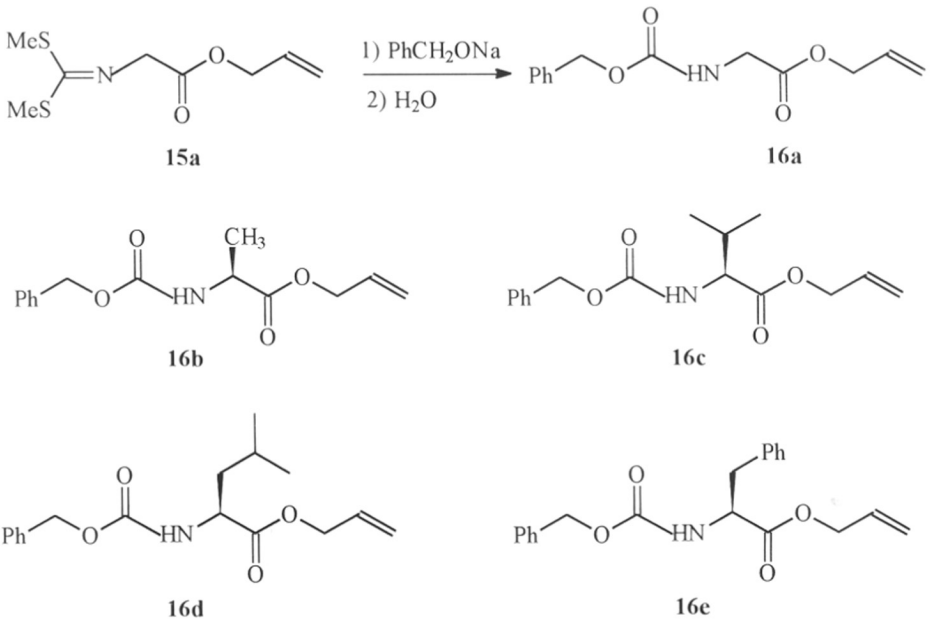
15e

2.6 Conversion of carbonimidodithioates of amino acid allyl esters (15 a-e) into benzyl carbamates (16 a-e)

The carbonimidodithioates derived from amino acid allyl esters (**15 a-e**) could be converted into the corresponding carbamates (**16 a-e**) as before. For example N-[bis(methylthio)-methylene] glycine allyl ester **15a** and sodium benzyl alcoholate were taken in THF and stirred at 30 °C. After the disappearance of the starting material, water was added and the mixture allowed to stir at 30 °C overnight, to give allyl N-(benzyloxycarbonyl) glycinate **16a** as a colourless oil in 79% yield(Scheme 28). The structure of **16a** was confirmed from the spectral data. The ^{1}H NMR spectrum of a purified sample of **16a** showed two doublets at 4.00(d, 2H) and 4.65(d, 2H) corresponding to NCH_2 and OCH_2 respectively. A singlet was observed at 5.15(s, 2H) for OCH_2Ph and three multiplets at 5.25(m, 2H), 5.90(m, 1H) and 7.35(m, 5H) corresponding to $=CH_2$, =CH and aromatic protons respectively. The NH proton appears

as a broad peak at 5.40δ. The mass spectrum showed the molecular ion (M^+) peak at m/z 249. The above data proved the structure of the compound to be **16a**(Figure 21). By a similar procedure bismethylthio derivatives of (L)- alanine, (L)- valine, (L)- leucine and (L)- phenylalanine allyl esters (**15 b-e**) were converted into the corresponding benzyl carbamates (**16 b-e**)(**16c**- Figure 22).

Scheme 28



15a **16a** **16b** **16c** **16d** **16e**

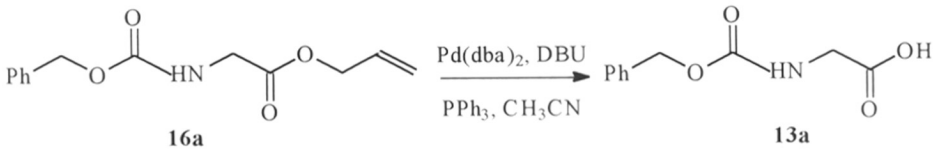
2.7 De-allylation of N- benzyloxycarbonyl-α-amino acid allyl esters (16a-e)

The N- benzyloxycarbonyl-α-amino acid allyl esters were subjected to Pd(0) catalysed de-allylation in the presence of morpholine as the allyl acceptor to get the N-benzyloxycarbonyl-α-amino acids. Thus allyl N- benzyloxycarbonyl glycinate **16a** was taken in degassed acetonitrile; to this 1, 8 diazabicyclo[5.4.0]undec-7-ene (DBU) and morpholine were added and stirred under argon at 30 °C. A mixture of $Pd(dba)_2$ and PPh_3 in acetonitrile was added and stirred at 30 °C for 12h to give N- benzyloxycarbonyl glycine **13a** in 83% yield, melting at 120 °C(Scheme 29). The melting point of an authentic sample was 122-124 °C. Similarly N- benzyloxycarbonyl derivatives of L-

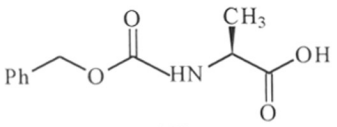
alanine, L- valine, L- leucine and L- phenylalanine allyl esters (**16 b-e**) were de-allylated to yield the corresponding N- carbobenzoxy-α-amino acids (**13 b-e**) in 74-81% yield.

The N- carbobenzoxy derivatives of α-amino acids obtained by this method showed identical specific rotation and melting point with those of authentic samples prepared by standard procedures. The physical properties and yields of N-benzyloxycarbonyl-α- amino acids **13** are given in *Table 2.*

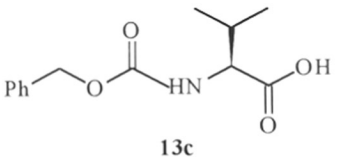
Scheme 29



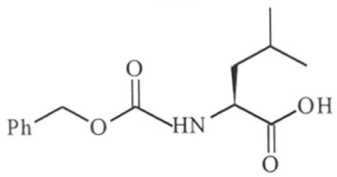
16a **13a**



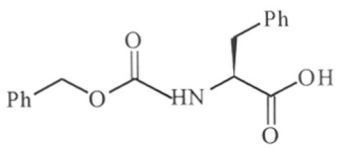
13b



13c



13d



13e

Table 2: Yields and physical properties of N-benzyloxycarbonyl ∝-amino acids (**13**)

Product	Yield %	m.p ^{0} C [a]	Specific Rotation$[\alpha]_D$ [a]
13a	83	121 [122-124]	-
13b	81	80 [82-84]	-14.1 ^{0} [-14.20^0] (c,2 in HOAc)
13c	79	62 [62-64]	+6.1 ^{0} [+6.20^0] (c, 4 in $CHCl_3$)
13d	74	50 [52-55]	-16.7 ^{0} [-16.85^0] (c, 2 in EtOH)
13e	80	86[87-90]	+4.4 ^{0} [+4.45 ^{0}] (C, 5 in HOAc)

a: Values within brackets are those for authentic samples prepared by standard procedures; the rotations were taken under the same conditions on the same instrument.

2.8 Determination of enantiomeric purity of the N- benzyloxycarbonyl-α- amino acids (13 b-e)

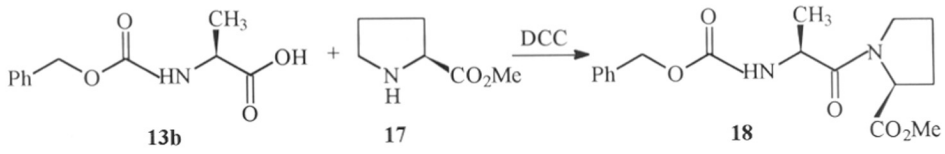
1. The specific rotation of the carbobenzoxy derivatives of the chiral amino acids (**13b-e**) were compared with those of authentic samples prepared by the standard procedure[26] from the corresponding α- amino acid and carbobenzoxy chloride in aqueous sodium hydroxide. For example the specific rotation of N- carbobenzoxy (L)-alanine **13b** prepared by de-allylation route was -14.1, while that of an authentic sample was -14.20 at the same concentration (c, 2 HOAc). The specific rotation of **13c** was +6.1 while the $[\alpha]_D$ of the corresponding authentic sample was +6.20 at the same concentration (c, 4 $CHCl_3$). The specific rotation of **13d** was determined as -16.7 while the authentic sample showed a specific rotation of -16.85 (c, 2 EtOH). The $[\alpha]_D$ of N- benzyloxycarbonyl (L)-leucine **13e** was +4.4, while that of the authentic product was +4.45 at the same concentration (c, 5 HOAc).

2. As a further check on the enantiomeric purity of the product N-benzyloxycarbonyl (L)- alanine **13b** prepared by the de-allylation route was subjected to HPLC analysis using a chiral column (DAICEL CHIRALCEL). This showed only one peak, which indicates the presence of only one enantiomer ie 100% *ee*. As a cross check, the HPLC analysis was also performed on a sample of N- benzyloxycarbonyl alanine prepared from (dl) alanine through the corresponding carbonimidodithioate. This showed two peaks in the ratio of 1:1. This study shows that the N- benzyloxycarbonyl (L)- alanine **13b** prepared by the de-allyaltion of N- benzyloxycarbonyl (L)- alanine allyl ester **16b** has not undergone any significant racemization(Figure 23).

3. Furthermore, the sample of N- benzyloxycarbonyl (L)- alanine **13b** prepared by the de-allylation route was coupled with freshly prepared (L)-proline methyl ester **17** using dicyclohexyl carbodiimide as coupling agent in dichloromethane(Scheme 30). The ^1H

NMR spectrum of the product dipeptide **18** was determined. The spectrum showed only one set of peaks. This again proves the presence of only one (S, S) diastereomer.

Scheme 30



13b **17** **18**

3. Conclusion

- A new route for the conversion of carbonimidodithioates to benzyl carbamates was described.
- The utility of this reaction for the preparation of N- benzyloxycarbonyl α- amino acids has also been demonstrated.

Experimental

General experimental techniques which have been described in the experimental section of Chapter 2 were followed.

General procedure for the conversion of carbonimidodithioates (11a-d) to benzyl carbamates (12 a-d)

Sodium benzyl alcoholate (2 mmol) was taken in dry THF (10 ml). To this was added the carbonimidodithioate (**11**) (2 mmol) and stirred at 30 ^{0}C for 6 h. The sodium salt slowly went into solution as the reaction progressed. The reaction was monitored by tlc. After the complete disappearance of the starting material, water (3 mmol) was added to the mixture and stirred overnight at 30 ^{0}C. The THF was removed by distillation *in vacuo*, and the aqueous residue extracted with EtOAc (25 ml). The organic layer was washed successively with water (2 x 20 ml), 1% HCl (2 x ml), and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product was purified by chromatography on a silica column (1:9-acetone:pet. ether).

Methyl N-benzyloxycarbonylglycinate (12a)

yield (%)	81
IR(Neat)/cm^{-1}	3360, 3040, 2960, 1740, 1710, 1520, 1510, 1440
^{1}H NMR ($CDCl_3$)	3.75(s, 3H, OCH_3), 4.00(d, 2H, NCH_2, J = 5.0), 5.15(s, 2H, OCH_2),
(200 MHz)	5.35(br, 1H, NH), 7.35(m, 5H, Ar)
^{13}C NMR($CDCl_3$)	42.40, 51.94, 66.75, 127.85, 128.29, 136.25, 156.48, 170.55
(50 MHz)	
MS (m/z)	223(M^+), 189, 164, 120, 108, 91(100%)
Analysis	Found, C, 59.15; H, 5.96; N, 6.12. $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.82; N, 6.27%

Methyl N-benzyloxycarbonyl-(S)-alaninate (12b)

yield (%)	86
IR(Neat)/cm^{-1}	3320, 2930, 1720, 1540, 1460, 1220
^1H NMR ($CDCl_3$)	1.40(d, 3H, CH_3, J = 8.7), 3.75(s, 3H, OCH_3), 4.40(m, 1H, NCH),
(200 MHz)	5.10(s, 2H, CH_2Ph), 5.55(br, 1H, NH), 7.35(m, 5H, Ph)
^{13}C NMR($CDCl_3$)	18.19, 49.55, 52.19, 66.71, 127.96, 128.36, 136.35, 155.69, 173.43
(50 MHz)	
MS (m/z)	237(M+), 218, 178, 156, 141, 115, 91(100%)
Analysis	Found: C, 60.64; H, 6.02; N, 5.69. $C_{12}H_{15}NO_4$ requires C, 60.75; H,
	6.32; N, 5.90%

Methyl N-benzyloxycarbonyl-(S)-valinate (12c)

Yield (%)	85
IR(Neat)/cm^{-1}	3360, 2990, 1730, 1540, 1510, 1450, 1220
^1H NMR ($CDCl_3$)	0.95(q, 6H, $2CH_3$, J = 8.5), 2.25(m, 1H, CH), 3.75(s, 3H, OCH_3),
(200 MHz)	4.30(q, 1H, NCH, J = 4.7), 5.15(s, 2H, CH_2Ph), 5.30(br, 1H, NH),
	7.40(m, 5H, Ph)
^{13}C NMR($CDCl_3$)	17.50, 18.79, 31.09, 51.86, 59.08, 66.78, 127.94, 128.35, 128.76,
(50 MHz)	136.35, 156.21, 172.41
MS (m/z)	265(M^+), 218, 206, 162, 108, 91(100%)
Analysis	Found: C, 63.51; H, 7.30; N, 5.37. $C_{14}H_{19}NO_4$ requires C, 63.39; H,
	7.16; N, 5.28%

Methyl N-benzyloxycarbony-(S)-phenylalaninate (12d)

yield (%)	80
IR(Neat)/cm^{-1}	3460, 3020, 1720, 1540, 1510, 1460, 1220
^1H NMR ($CDCl_3$) (200 MHz)	3.15(t, CH_2, 2H, J = 5.5), 3.75(s, 3H, OCH_3), 4.70(q, 1H, NCH, J = 7.8), 5.15(s, 2H, CH_2Ph), 5.30(br, 1H, NH), 7.10-7.45(m, 10H, 2Ph)
^{13}C NMR($CDCl_3$) (50 MHz)	38.00, 52.12, 55.21, 66.77, 127.00, 127.99, 128.46, 128.53, 129.30, 136.33, 136.58, 155.98, 172.23
MS (m/z)	313(M^+), 270, 252, 228, 210, 192, 178, 162, 91(100%)
Analysis	Found: C, 68.87; H, 6.01; N, 4.32. $C_{18}H_{19}NO_4$ requires C, 69.00; H, 6.07; N, 4.47%

Hydrolysis of N-benzyloxycarbonyl-α- amino acid methyl ester (12 a-d)

A solution of **(12a)** (1 mmol) in MeOH (5 ml) was stirred with NaOH (1.1 mmol) in water (5 ml) at 30 ^{0}C for 6 h. The MeOH was removed *in vacuo*, the residue diluted with water and acidified to pH 2 by adding conc. HCl. The product was extracted with EtOAc (3x15 ml), the combined organic layers washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed to give N-benzyloxycarbonylglycine (**13a**), m.p. 120 ^{0}C in 84% yield. The hydrolysis could similarly be carried out with **12b**, **12c** and **12d** to give the corresponding N-benzyloxycarbonyl α- amino acids.

Preparation of carbonimidodithioates 11(a-e) from α-amino acid allyl esters (10)

α-Amino acid allyl esters **10(a-e)** were prepared by the published procedure.[33] These were converted to the corresponding dimethyl carbonimidodithioates **11(a-e)** by the usual procedure [23] involving condensation with CS_2, followed by methylation.

N-[Bis (methylthio) methylene] glycine allyl ester (11a)

Yield (%)	69
IR(Neat)/cm^{-1}	2900, 2100, 1740, 1580, 1410, 1170
^1H NMR ($CDCl_3$) (200 MHz)	2.40(s, 3H, SCH_3), 2.60(s, 3H, SCH_3), 4.25(s, 2H, NCH_2), 4.75(m, 2H, OCH_2), 5.30(m, 2H, $=CH_2$)
^{13}C NMR($CDCl_3$) (50 MHz)	14.46, 14.75, 54.04, 65.16, 117.98, 132.02, 162.86, 169.43
MS (m/z)	219(M^+), 172(100%), 157, 144, 127, 116, 101, 87
Analysis	Found: C, 43.54; H, 5.92; N, 5.94. $C_8H_{13}NO_2S_2$ requires C, 43.83; H, 5.93; N, 6.39%

N-[Bis (methylthio) methylene]-(S)-alanine allyl ester (11b)

Yield (%)	73
IR(Neat)/cm^{-1}	2990, 2910, 2020, 1740, 1570, 1420, 1370
^1H NMR ($CDCl_3$) (200 MHz)	1.45(d, 3H, CH_3, J = 6.2), 2.40(s, 3H, SCH_3), 2.55(s, 3H, SCH_3), 4.55(q, 1H, NCH, J = 7.5), 4.65(m, 2H, OCH_2), 5.25(m, 2H, $=CH_2$), 5.95(m, 1H,=CH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.32, 14.53, 18.18, 19.13, 59.70, 64.77, 117.35, 118.80, 131.88, 160.77, 171.50
MS (m/z)	233(M^+), 186(100%), 158, 148, 130, 114, 89, 75, 60
Analysis	Found: C, 46.73; H, 6.62; N, 5.94. $C_9H_{15}NO_2S_2$ requires C, 46.35; H, 6.43; N, 6.00%

N-[Bis (methylthio) methylene]-(S)-valine allyl ester (11c)

Yield (%)	71
IR(Neat)/cm^{-1}	2960, 2920, 2080, 1730, 1580, 1430
^1H NMR ($CDCl_3$) (200 MHz)	1.00(m, 6H, $2CH_3$), 2.35(m, 1H, CH), 2.45(s, 3H, SCH_3), 2.60(s, 3H, SCH_3), 4.20(d, 1H, NCH, J = 6.7), 4.65(m, 2H, OCH_2), 5.35(m, 2H, $=CH_2$), 5.95(m, 1H, =CH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.38, 14.62, 17.82, 19.12, 32.17, 64.60, 65.11, 117.49, 131.86, 161.19, 170.31
MS (m/z)	261(M^+), 214, 199, 186, 171, 128, 114(100%), 103, 91
Analysis	Found: C, 50.91; H, 7.22; N, 5.79. $C_{11}H_{19}NO_2S_2$ requires C, 50.57; H, 7.27; N, 5.36%

N-[Bis (methylthio) methylene]-(S)-leucine allyl ester (11d)

Yield (%)	65
IR(Neat)/cm^{-1}	2920, 2060, 1740, 1570, 1430, 1560, 1220
^1H NMR ($CDCl_3$) (200 MHz)	0.90(d, 3H, CH_3, J = 7.8), 0.95(d, 3H, CH_3, J = 7.3), 1.55(m, 1H, CH), 2.60(dd, 2H, CH_2, J = 6.0, 8.0Hz), 2.40(s, 3H, SCH_3), 2.80(s, 3H, SCH_3), 4.50(t, 1H, NCH, J = 7.4), 4.65(m, 2H, OCH_2), 5.30(m, 2H, $=CH_2$), 5.95(m, 1H, =CH)
^{13}C NMR($CDCl_3$) (50 MHz)	14.34,14.60, 21.80, 22.70, 24.68, 42.21, 63.01, 64.70, 117.30, 131.92, 16.96, 170.99
MS (m/z)	275(M^+), 260, 228, 200, 172, 142, 95, 69(100%)
Analysis	Found: C, 52.59; H, 7.70; N, 5.20. $C_{12}H_{21}NO_2S_2$ requires C, 52.36; H, 7.63; N, 5.09%

N-[Bis (methylthio) methylene]-(S)-phenylalanine allyl ester (11e)

Yield (%)	77
IR(Neat)/cm^{-1}	3000, 2905, 2020, 2010, 1725, 1560, 1490, 1410
^1H NMR ($CDCl_3$) (200 MHz)	2.40(s, 3H, SCH_3), 2.50(s, 3H, SCH_3), 3.20(m, 2H, CH_2), 4.60(t, 1H, NCH, J = 5.7), 4.65(m, 2H, OCH_2), 5.25(m, 2H, $=CH_2$), 5.90(m, 1H, =CH), 7.25(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	14.65, 14,94, 39.59, 65.05, 66.38, 117.70, 126.30, 1237.99, 131.89, 137.56, 162.35, 170.52
MS (m/z)	309(M^+), 262, 218, 188, 162, 143, 128, 103, 91(100%)
Analysis	Found: C, 58.59; H, 6.09; N, 4.85; $C_{15}H_{19}NO_2S_2$ requires C, 58.25; H, 6.14; N, 4.53%

Allyl N-benzyloxycarbonylglycinate (12a)

Yield (%)	79
IR(Neat)/cm^{-1}	3350, 3020, 2940, 1740, 1720, 1520, 1480, 1230
^1H NMR ($CDCl_3$) (200 MHz)	4.00(d, 2H, NCH_2, J = 6.7), 4.65(d, 2H, OCH_2, J = 5.5), 5.15(s, 2H, OCH_2), 5.15(m, 2H, $=CH_2$), 5.40(br, 2H, OCH_2), 5.90(m, 1H, =CH), 7.35(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	42.39, 65.40, 66.57, 118.21, 127.71, 128.15, 131.45, 136.19, 156.41, 169.68
MS (m/z)	249(M^+), 206, 192, 170, 158, 107, 91(100%)
Analysis	Found: C, 62.47; H, 6.28; N, 5.35. $C_{13}H_{15}NO_4$ requires C, 62.65; H, 6.02; N, 5.62%

Allyl N-benzyloxycarbonyl-(S)-alaninate (12b)

Yield (%)	80
IR(Neat)/cm^{-1}	3360, 3080, 2980, 1740, 175, 1510, 1460, 1260
^1H NMR ($CDCl_3$) (200 MHz)	1.45(d, 3H, CH_3, J = 8.7), 4.45(t, 1H, NCH, J = 8.5), 4.65(d, 2H, OCH_2, J = 5.6), 5.10(s, 2H, OCH_2), 5.30(m, 2H, $=CH_2$), 5.45(br, 1H, NH), 5.90(m, 1H, =CH), 7.35(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	18.36, 49.69, 65.76, 66.80, 118.51, 128.04, 128.44, 131.64, 136.37, 155.72, 172.69
MS (m/z)	263(M^+), 172, 134, 108, 91(100%), 79, 65
Analysis	Found: C, 64.18; H, 6.44; N, 5.06. $C_{14}H_{17}NO_4$ C, 63.87; H, 6.46; N, 5.32%

Allyl N-benzyloxycarbony-(S)-valinate (12c)

Yield (%)	72
IR(Neat)/cm^{-1}	3320, 3060, 3020, 2940, 1725, 1710, 1510, 1450, 1290
^1H NMR ($CDCl_3$) (200 MHz)	0.90(d, 3H, CH_3, J = 6.7), 1.00(d, 3H, CH_3, J = 6.5), 2.20(m, 1H, CH), 4.35(br, 1H, NH), 4.15(d, 2H, $=CH_2$, J = 5.8), 5.15(s, 2H, OCH_2), 5.35(m, 2H, OCH_2), 5.40(br, 1H, NH), 5.95(m, 1H, =CH), 7.40(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	17.40, 18.78, 31.00, 59.08, 65.44, 66.66, 118.51, 127.84, 128.25, 131.59, 134.64, 136.33, 156.19, 166.19, 171.58
MS (m/z)	295(M^+), 206, 162, 127, 107, 91(100%)
Analysis	Found: C, 66.59; H, 7.54; N, 5.23. $C_{16}H_{21}NO_4$ requires C, 65.97; H, 7.21; N, 4.81%

Allyl N-benzyloxycarbonyl-(S)-leucinate (12d)

Yield (%)	74
IR(Neat)/cm^{-1}	3350, 3070, 3015, 2945, 1730, 1510, 1450
^1H NMR ($CDCl_3$) (200 MHz)	1.00(2d, 6H, $2CH_3$, J = 7.6), 1.65(m, 3H, CH, CH_2), 4.45(m, 1H, CH), 4.75(d, 2H, OCH_2, J = 7.7), 5.15(s, 2H, OCH_2), 5.30(m, 2H, $=CH_2$), 5.40(br, 1H, NH), 5.95(m, 1H, =CH), 7.35(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	21.85, 22.90, 24.79, 41.68, 52.68, 65.81, 66.96, 118.65, 128.12, 128.54, 131.77, 136.45, 156.11, 172.91
MS (m/z)	305(M^+), 220, 186, 171, 155, 141, 127, 107, 91(100%), 81
Analysis	Found: C, 66.85; H, 7.54; N, 4.54. $C_{17}H_{23}NO_4$ requires C, 66.88; H, 7.54; N, 4.59%

Allyl N-benzyloxycarbonyl-(S)-phenylalaninate (12e)

Yield (%)	73
IR(Neat)/cm^{-1}	3340, 3060, 3020, 2940, 1730, 1710, 1520, 1450, 1295
^1H NMR ($CDCl_3$) (200 MHz)	3.35(d, 2H, CH_2, J = 4.2), 4.65(d, 2H, OCH_2, J = 6.5), 4.75(m, 1H, NCH), 5.15(s, 2H, OCH_2), 5.30(m, 2H, $=CH_2$), 5.40(br, 1H, NH), 5.90(m, 1H, =CH), 7.25(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	38.17, 55.00, 65.95, 66.88, 118.87, 127.07, 128.04, 128.51, 129.35, 131.52, 135.89, 136.38, 155.74, 171.31
MS (m/z)	339(M^+), 296, 278, 254, 210, 188, 91(100%)
Analysis	Found: C, 70.70; H, 5.90; N, 4.06. $C_{20}H_{21}NO_4$ requires C, 70.79; H, 6.19; N, 4,12%

General procedure for de-allylation of N-benzyloxycarbonyl-α- amino acid allyl esters (16 a-e)

To a solution of the allyl ester (**16**) (1 mmol) in dry MeCN (5 ml), DBU (1 mmol), and morpholine (3 mmol) were added and stirred under argon at 30 ^{0}C. To this was added $Pd(dba)_2$ (5 mol%), followed by PPh_3 (10 mol%). The reaction mixture became clear in about 15-20 min. The mixture was stirred at 30 ^{0}C for 12 h. The progress of the reaction was monitored by tlc. After completion of the reaction, it was quenched by the addition of aq. HCl (5%, 5-6 ml). The aqueous solution was extracted with EtOAc (5 x15 ml), the organic layers combined and washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product (**13**) purified by recrystallisation. The yields and physical data are presented in ***Table 2***.

References

1. a) H. Ultrich, B.Tucker and A. A. R. Sayigh, *J. Org. Chem.*, **1967**, *2*, 3938.

   b) J. Wilson, *J. Am. Chem. Soc.*, **1942**, *64*, 2229.

2. N. Rainer, S. Holger, N. Hagen, F. Peter and S. Klaus, *Chem. Abstr.*, **1988**, *109*, 73158m.

3. J. Tadeusz, *Chem. Abstr.*, **1983**, *99*, 87844u.

4. Mitsubishi Chemical Ind. Co. Ltd. Japan. *Chem. Abstr* **1985**, *102*, 24304c.

5. T. Shioiri, K. Ninomiya and S. Yamada, *J. Am. Chem. Soc.*, **1972**, *94*, 6203.

6. a) S. Bunte, *Ann.*, **1891**, *151*, 181. b) A. Werner, *J. Chem. Soc.*, **1918**, *113*, 622.

   c) Hoffman, *Chem. Ber.*, **1871**, *4*, 262.

7. M. Paquin, Z. *Naturforsch.*, **1946**, *1*, 518.

8. a) H. G. Ashburn, A. R. Collect and L. C. Lazzell, *J. Am. Chem. Soc.*, **1938**, *60*, 2934. b) W. M.. Kraft and R. M. Herbst., *J. Org. Chem.*, **1953**, *18*, 1634.

   c) J. Thiele and F. Dent, *Ann.*, **1908**, *302*, 236.

9. a) N. G. Gaylord and C. C. Sroog., *J. Org. Chem.*, **1953**, *18*, 1634 b) M. Metaver, *Bull. Soc. Chim. Fr.*, **1951**, *18*, 1634.

10. W, M. Kraft, *J. Am. Chem. Soc.*, **1948**, *70*, 3569.

11. R. Hazard, J. Cheymol, P. Charbrier and A. Sekera, *Bull. Soc. Chim. Fr.*, ***1961***, 2087.

12. K. Kondo and N. Sonoda, *Chem. Lett.*, **1972**, 373.

13. R. Becker, J. Grolig and C. Rasp, *Chem. Abstr.*, **1981**, *97*, 297501.

14. S. Fukuoka, M. Chono and M. Kohno, *J. Chem. Soc., Chem.Commun.*, **1984**, 399.

15. H. Alper, *J. Chem. Soc., Chem. Commun.*, **1988**, 1141.

16. S. Fukuoka and S, Khona, *J. Org. Chem.*, **1984**, *49*, 1458.

17. T. Tsuda, H. Washita, K. Watanabe, M. Miwa and T. Saegusa, *J. Chem. Soc., Chem. Commun.*, **1978**, 815.

18. M. Aresta and E. Quaranta, *Tetrahedron,* **1992**, *48*, 1515.

19. A. Inersi, V. Mucciante and L. Rossi, *J. Org. Chem.*, **1998**, *63*, 1337.

20. D. Deiter, H. Heinz and S. Michael, *Chem. Abstr.*, **1987**, *106*, 146070b.

21. S. K. Tande., S. Rajappa and S. V. Pansare, *Tetrahedron*, **1993**, *49*, 7479.

22. a) T. I. Reddy, B. M. Bhawal and S. Rajappa, *Tetrahedron. Lett.*, **1992**, *38*, 2857.

    b) T. I. Reddy, Ph. D. Thesis, University of Poona, pune, India, **1992.**

23. a) D. Hoppe and L. Beckmann, Liebigs. *Ann. Chem.*, **1979**, 2066.

    b) T. I. Reddy, B. M. Bhawal and S. Rajappa, *Tetrahedron*, **1993**, *49*, 2101.

24. G. H. Kulkarni, R. H. Naik, S. K. Tandel and S. Rajappa, *Tetrahedron*, **1991**, *47*, 1249.

25. S. R. Deshpande, A. P. Likhite and S. Rajappa, *Tetrahedron*, **1994**, *50*, 10367.

26. T. I. Reddy and S. Rajappa, Unpublished results.

27. *Chemistry of Amino Acids*, Ed. By Greenstein and Winitz, John Wiley & sons, **1961**, Vol. *2*. P 891.

28. H. Kunz and H. Waldmann, *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 71.

29. H. Kunz and C. Unverzagt, *Angew. Chem., Int. Ed. Engl.*,**1984**, *23*, 437.

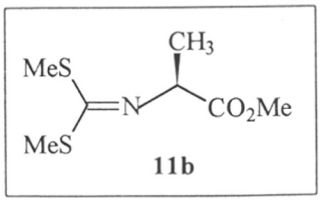
30. J. P. Genet, E. Blart, M. Savignac, S. Lemeune and J.- M. Paris, *Tetrahedron Lett.*,. **1993**, *34*, 4189.

31. J. P. Genet, E. Blart, M. Savignac, S. Lemeune, S. Lemaire-Audoire, J.- M. Paris and J.- M. Bernard, *Tetrahedron,* **1994**, *50*, 497.

32. S. Lemaire-Audoire, M. Savignac, E. Blart, G. Pourcelot and J. P. Genet, *Tetrahedron Lett.*, **1994**, *35*, 8783.

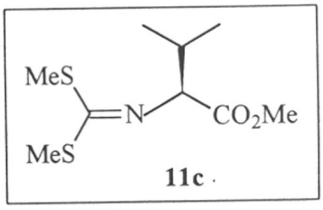
33. H. Waldmann and H. Kunz, *Liebigs Ann. Chem.*, **1983**, 1712.

Figure 15



11b

Figure 16



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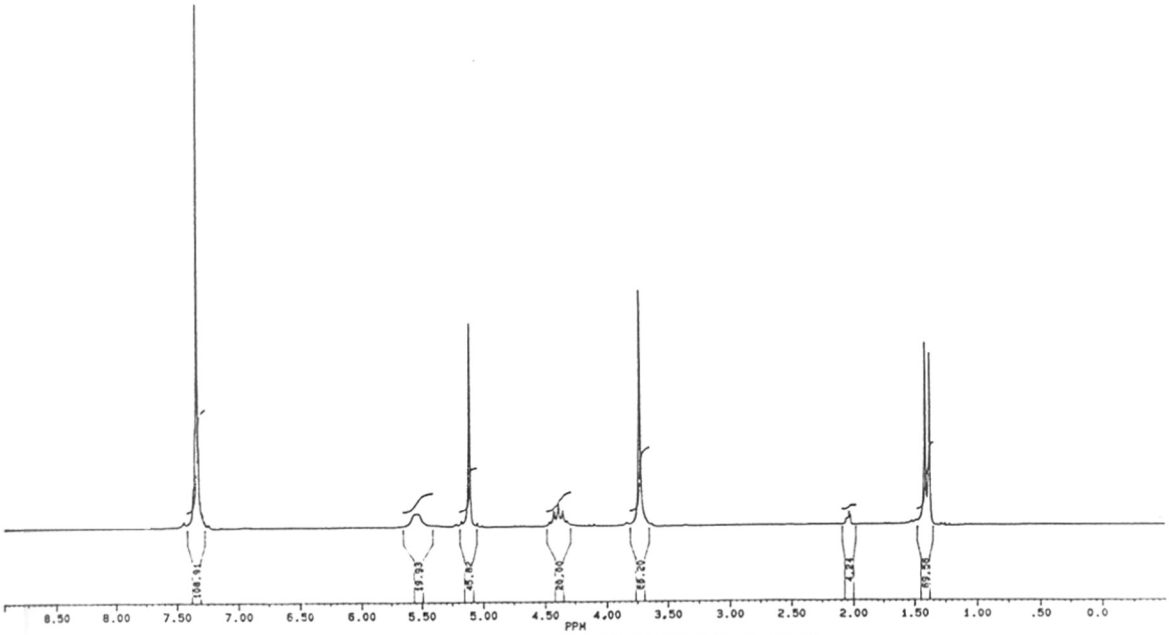
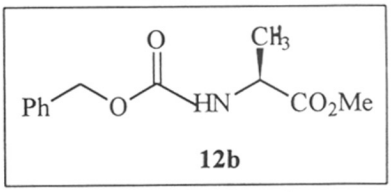


Figure 17



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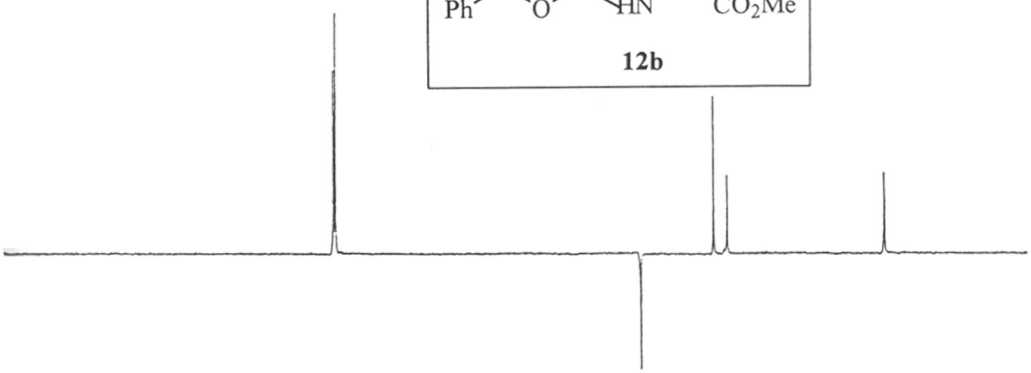

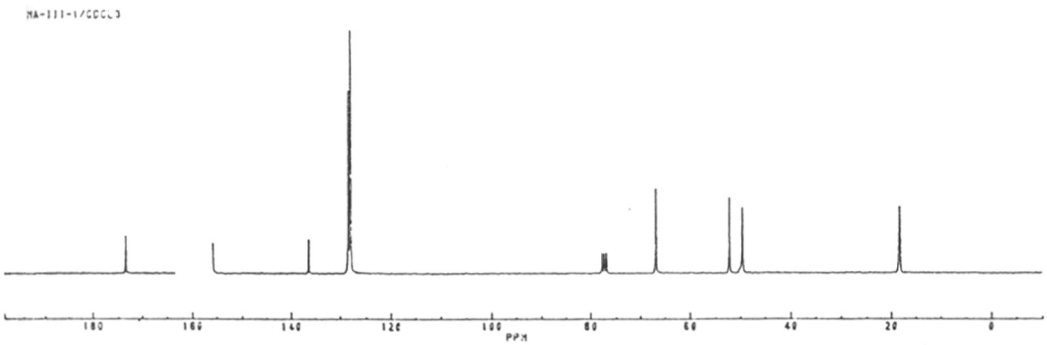

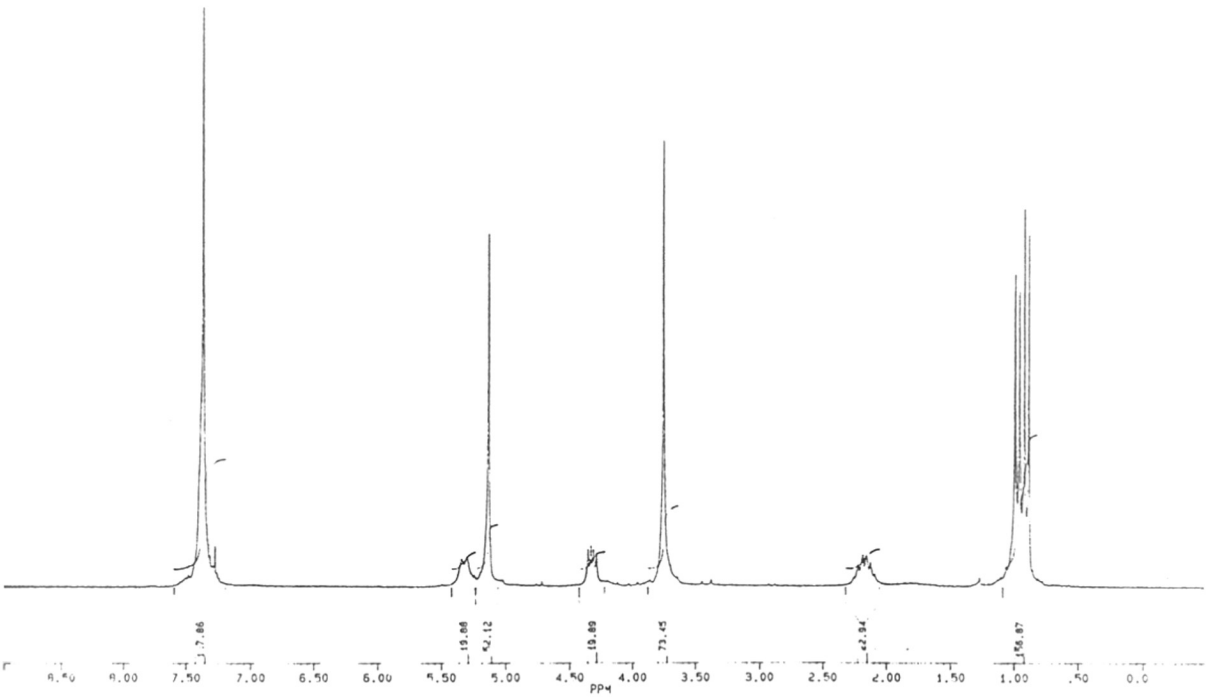

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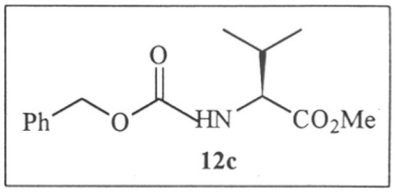

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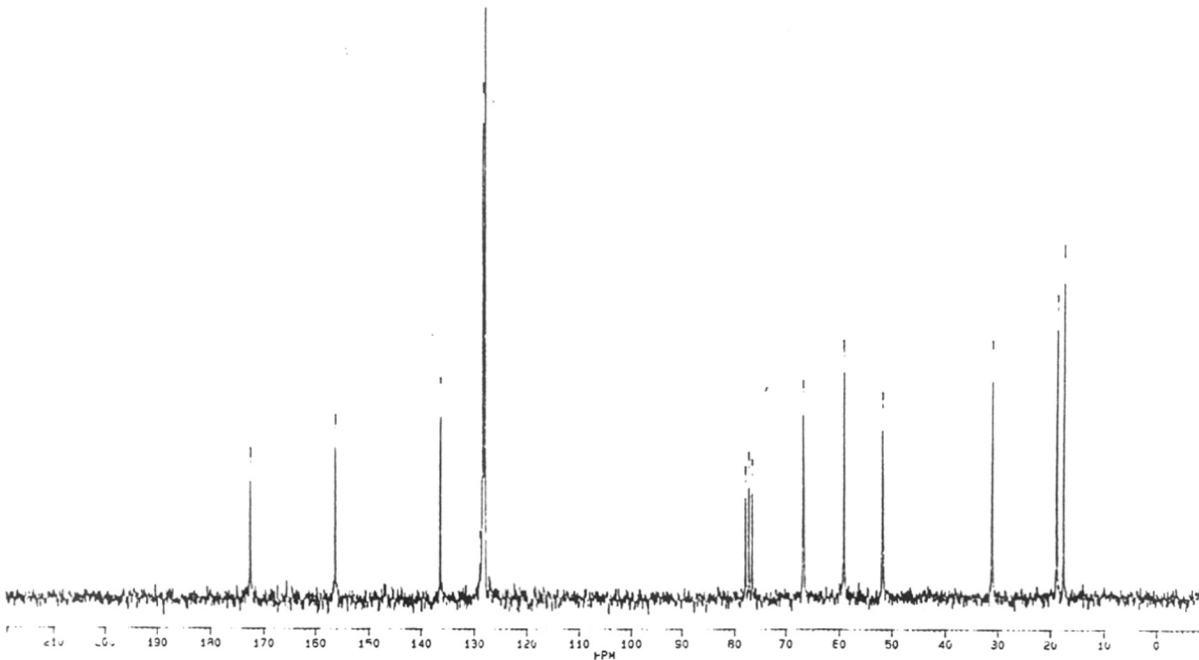


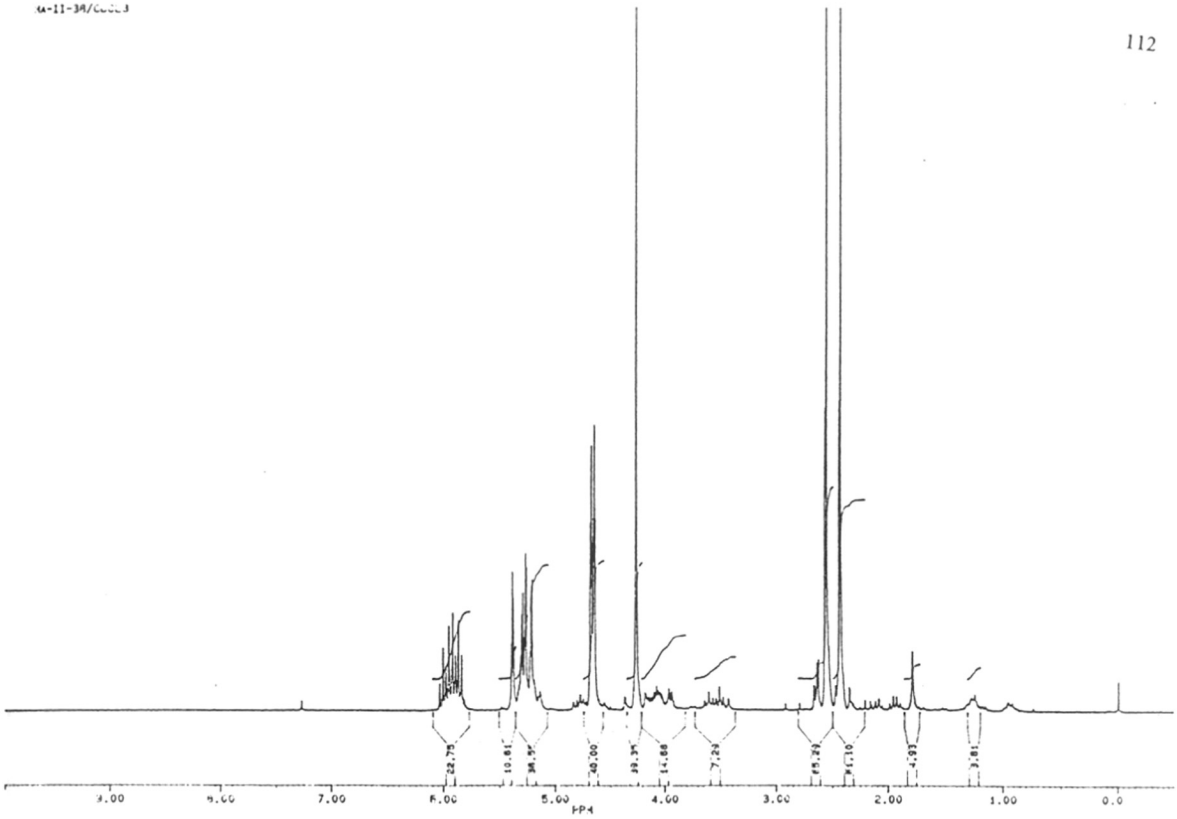
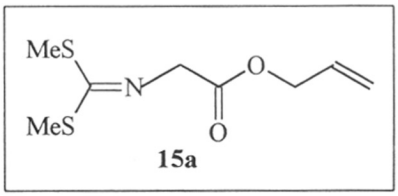


Figure 19



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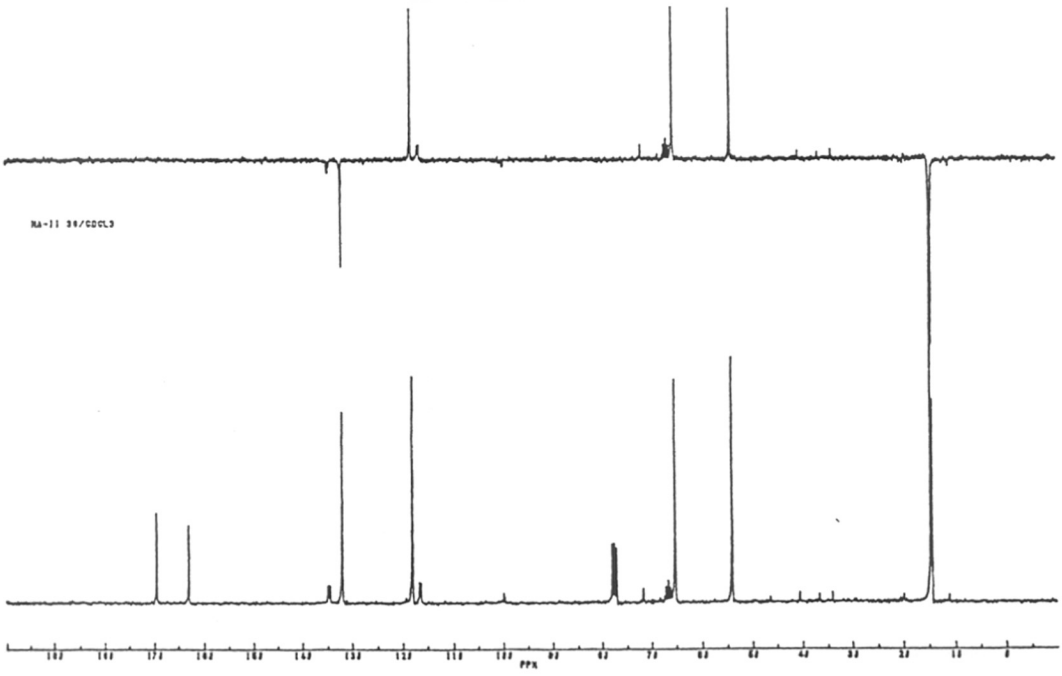


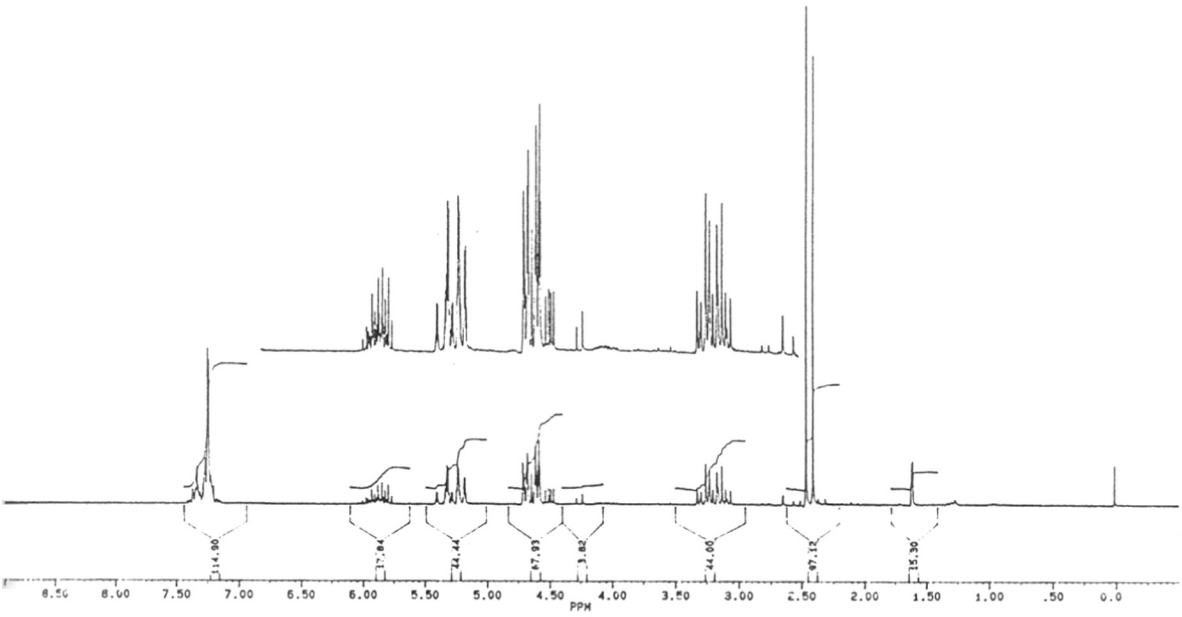
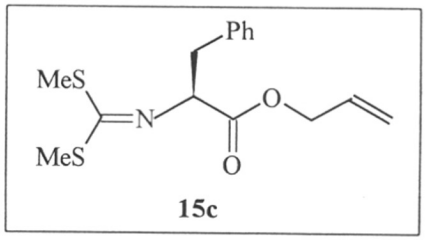
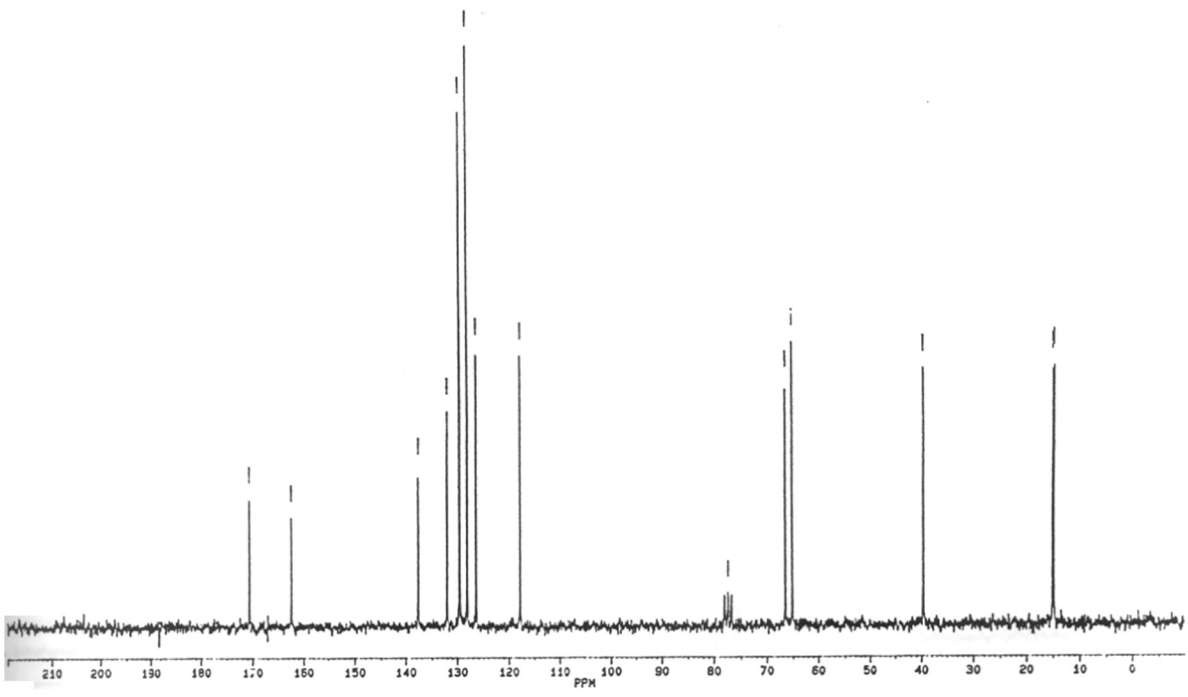


Figure 20



15c



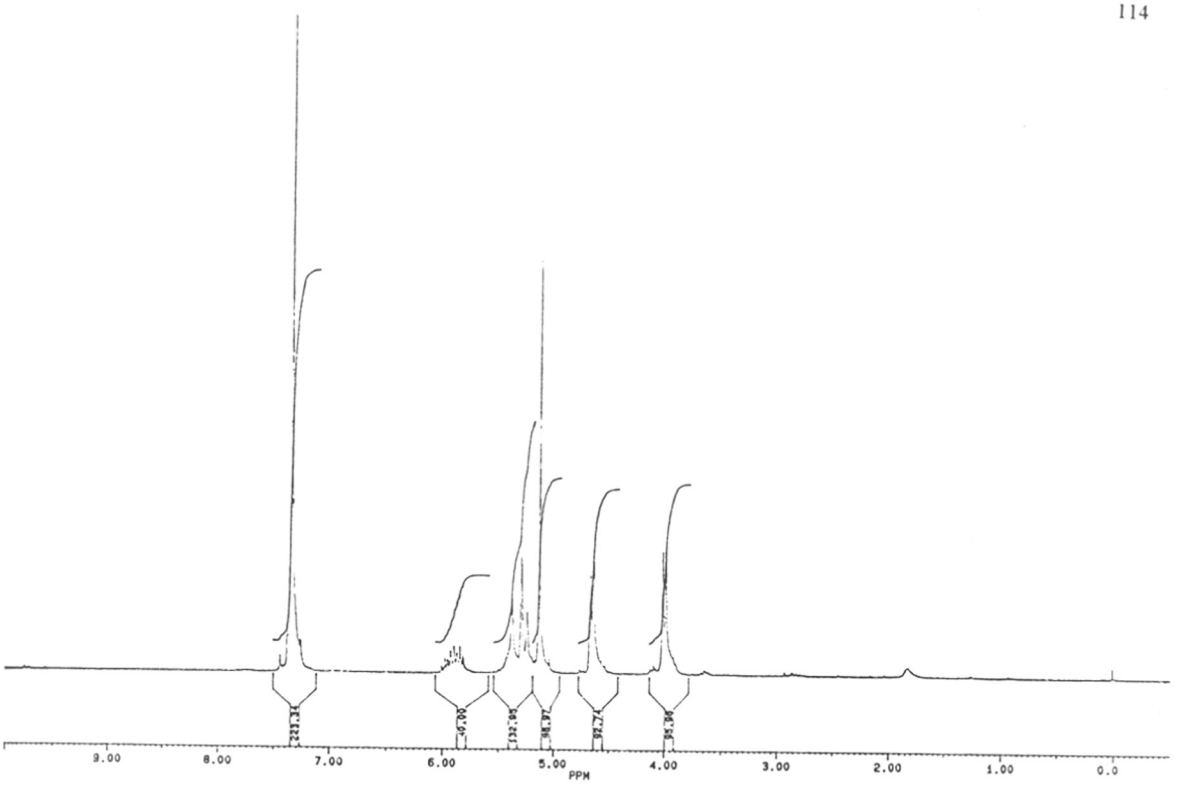
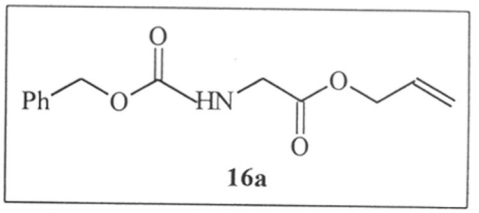
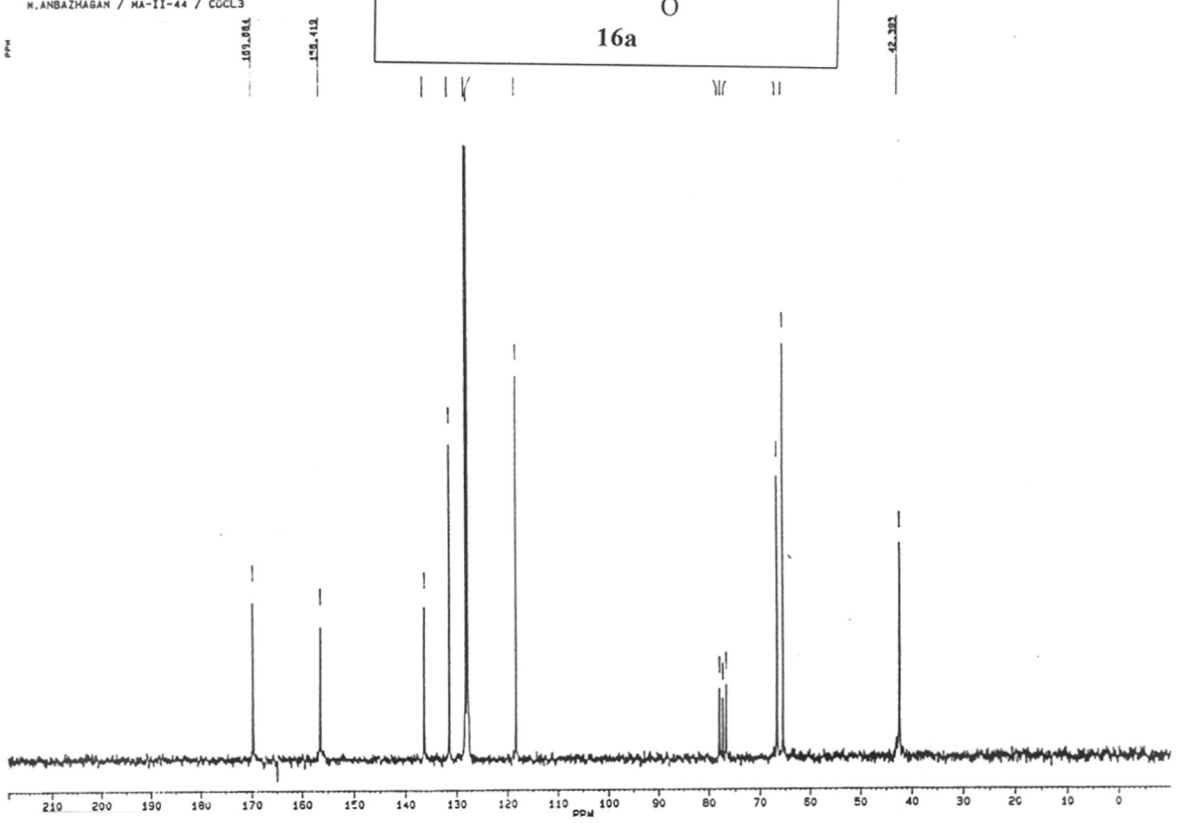


Figure 21



16a



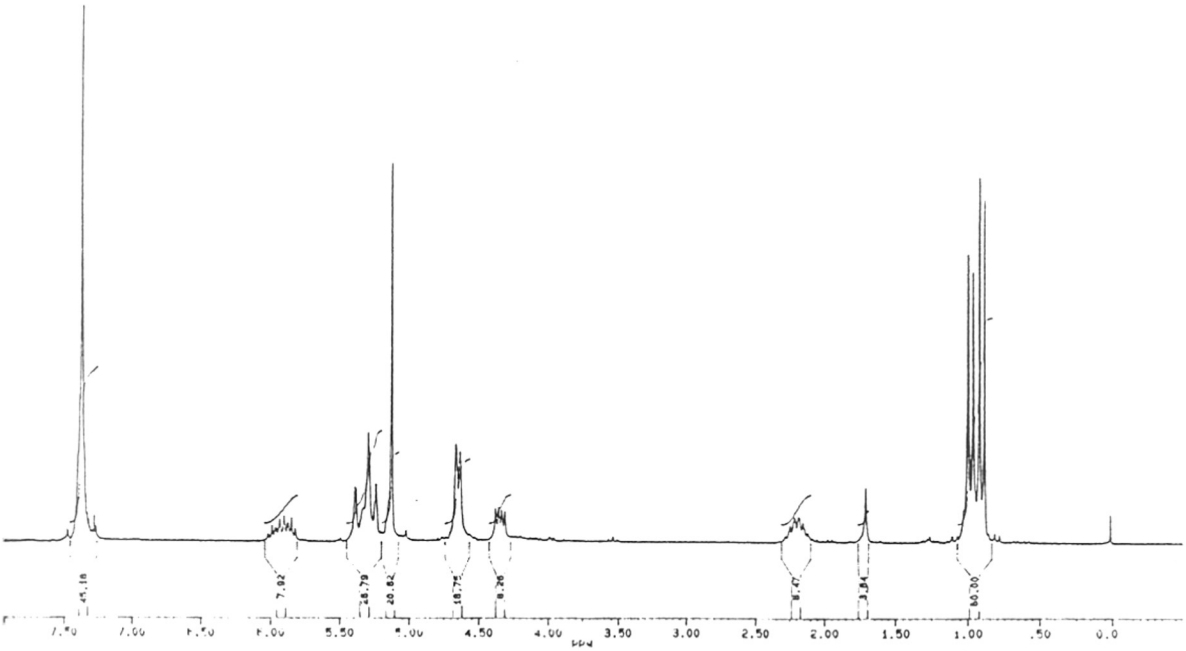
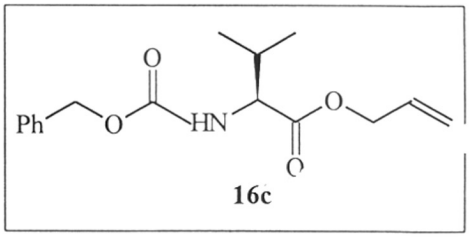


Figure 22



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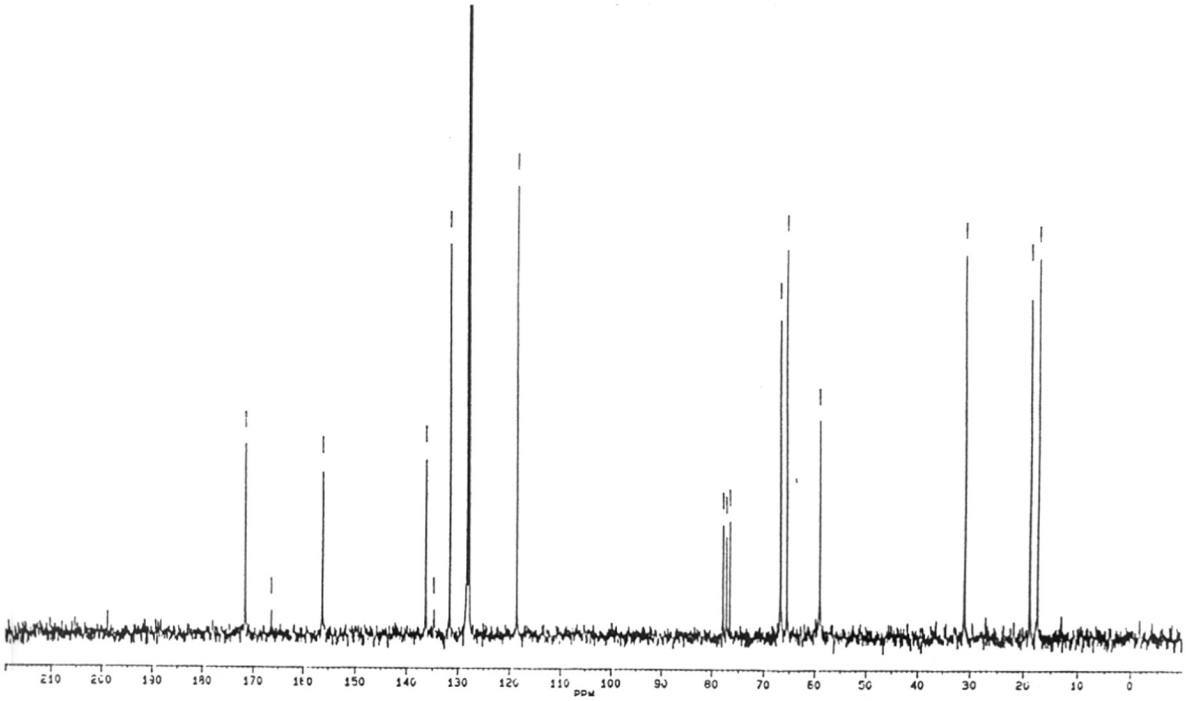
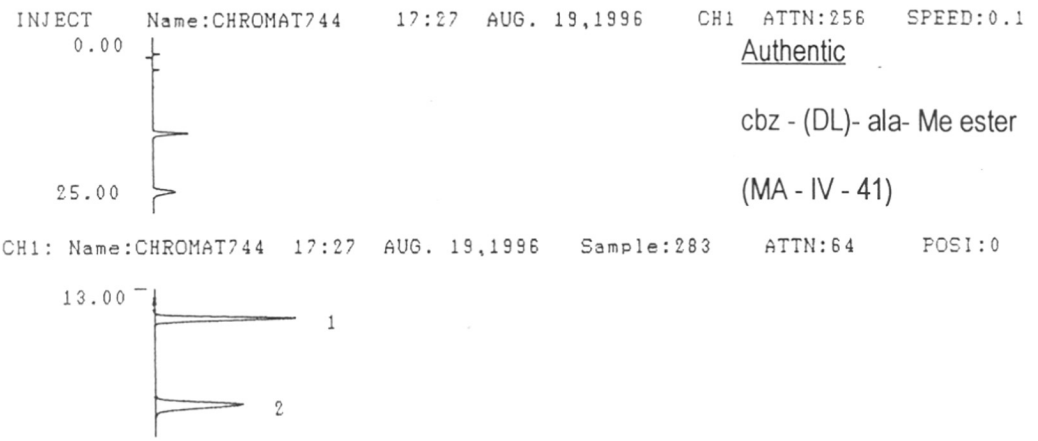


Figure 23 a) Concentration = 5 mg/ 0.5 ml in Isopropanol

b) Flow rate = 1 ml/ min., Solvent: Hexane : Isopropanol (20 : 1)

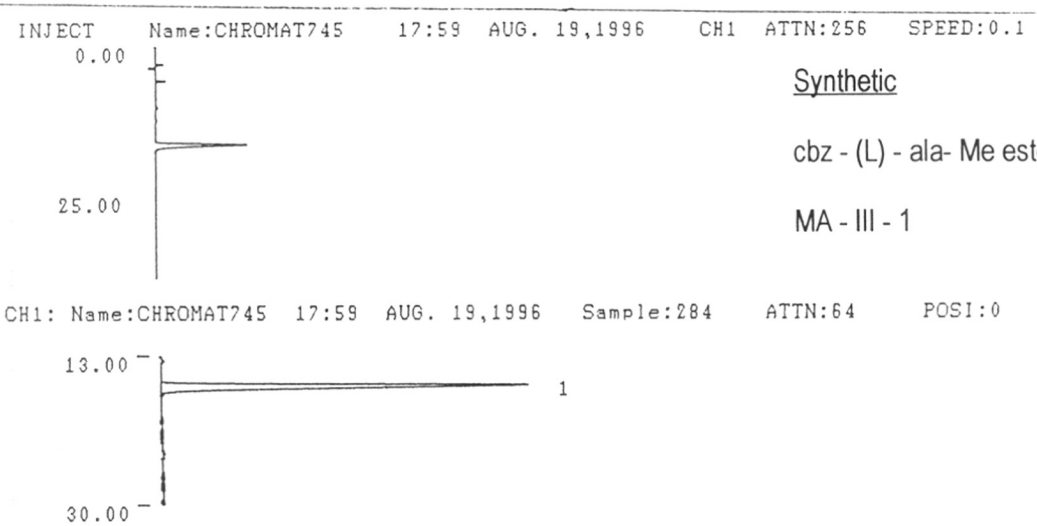
c) Column = DAICEL CHIRALCEL OD (uv detector - 254 nm)



CH1:
Conc.Level:0 Calc.Method:0(Area%) PA:1.00000 PB:1.00000

NO.	NAME	RT	AREA	MARK	CONC	HEIGHT
1		16.389	2869780		50.0239	96623
2		26.309	2867030		49.9760	59858
TOTAL			5736810		100.0000	156481

} racemic mixture



CH1:
Conc.Level:0 Calc.Method:0(Area%) PA:1.00000 PB:1.00000

NO.	NAME	RT	AREA	MARK	CONC	HEIGHT
1		16.469	7737460		100.0000	251704
TOTAL			7737460		100.0000	251704

} 100% ee

CHAPTER 4

Synthesis of chiral oxazolidin-2-ones from α- amino acid esters *via* carbonimidodithioates

1. Introduction

Chiral auxiliary based transformations are very important in synthesis because of the reliable prediction of stereochemistry possible in such steps.[1-8] These chiral auxiliaries can either be covalently bound to the substrate (substrate control) or can be part of the reagent (reagent control). Often these chiral additives (auxiliaries) are built from (L-) amino acids.[9] Amino acids are well suited for this purpose since most of them are cheap and commercially available. In addition, the variety of (L-) amino acids provides the opportunity of tuning additives for special purposes.

"Evans oxazolidinones" derived from chiral α-amino acids are certainly the most successful of the chiral auxiliaries currently available for asymmetric transformations. Beginning from the early 1980's, Evans and his group have shown that the use of 4-substituted oxazolidin-2-ones as chiral auxiliaries leads to excellent stereochemical control.[10-15] The synthetic methods currently available for the preparation of oxazolidin-2-ones are given below.

1.1 Methods for the preparation of oxazolidin-2-ones

Oxazolidin-2-ones are accessible from chiral α- amino acids. Three distinct steps are involved in this transformation:

i) reduction of the chiral α- amino acid to the corresponding 1,2- amino alcohol

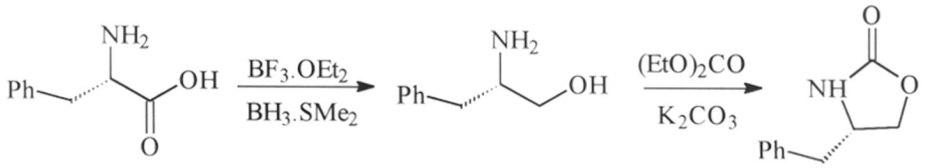
ii) introduction of a one-carbon unit at the carbon dioxide level of oxidation, and

iii) cyclisation to the oxazolidin-2-ones.

The sequence of steps one and two can be interchanged.

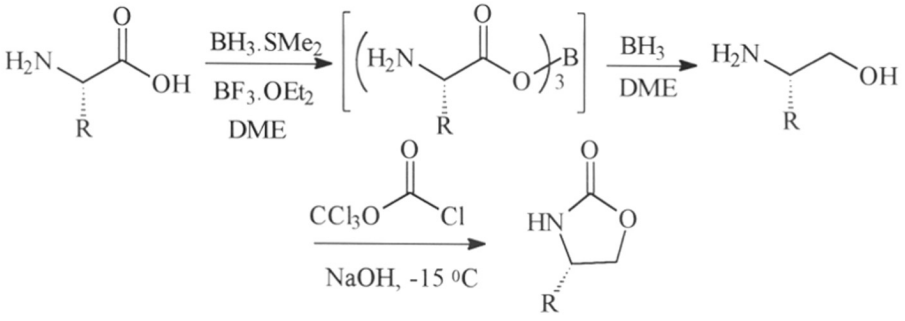
The first synthesis of chiral oxazolidin-2-ones was reported by Evans,[16] in which the α- amino acid was initially reduced to amino alcohols by means of borane in the presence of BF_3-etherate. The carbonyl unit was introduced using diethyl carbonate as the one-carbon synthon in the presence of potassium carbonate(Scheme 1).

Scheme 1



Modification of this procedure involving the use of trichloromethyl chloroformate (diphosgene) as one-carbon synthon was reported by Pridgen *et al.*[17] In this procedure the amino acid was reduced with borane in the presence of BF_3-etherate as in the Evans method(Scheme 2).

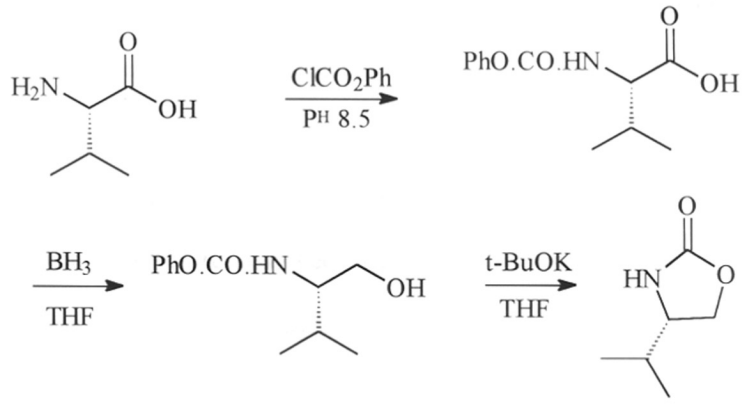
Scheme 2



The amino alcohol on treatment with trichloromethyl chloroformate (TCF or diphosgene) gave 4- substituted 2- oxazolidinone derivative directly.

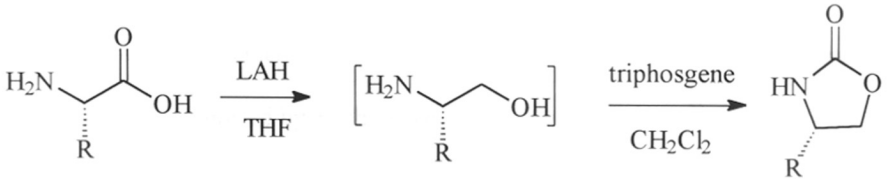
Another modification in the Evans procedure was reported by Wuts,[18] in which he has used phenyl chloroformate as the acylating agent. This synthesis begins with a Schotten-Baumann acylation of (S)- valine with phenyl chloroformate in aqueous sodium hydrogen carbonate, followed by borane reduction of the N-acylated amino acid to give the alcohol. Treatment of this alcohol with a catalytic amount of potassium *tert*-butoxide in THF afforded the crystalline oxazolidinone(Scheme 3).

Scheme 3



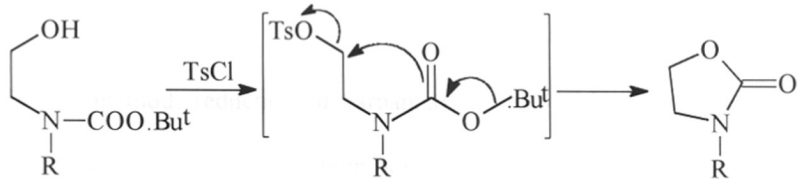
A further variant is the use of lithium aluminium hydride for reduction of the amino acids followed by treatment of the *in situ* generated β- amino alcohol with (bis trichloromethyl) carbonate (triphosgene) to form the oxazolidin-2-one. This procedure was reported by Carrea *et al*(Scheme 4).[19]

Scheme 4



A totally different mechanism is operative in the conversion of homochiral N-t-butoxycarbonyl-β- amino alcohols to oxazolidin-2-ones reported by Agami and coworkers(Scheme 5).[20]

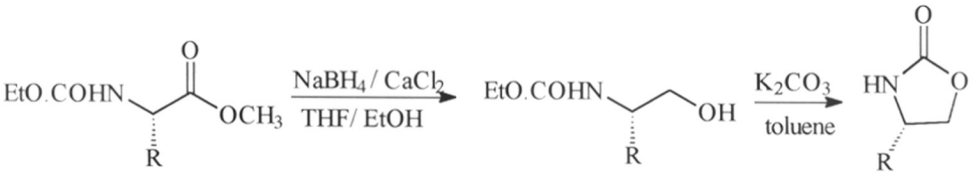
Scheme 5



In this procedure, the N-t-butoxycarbonyl derivatives of homochiral β- amino alcohols on treatment with p-toluenesulfonyl chloride afford 2- oxazolidinones. Here both the oxygen atoms of the oxazolidinone are derived from the N- Boc protecting group.

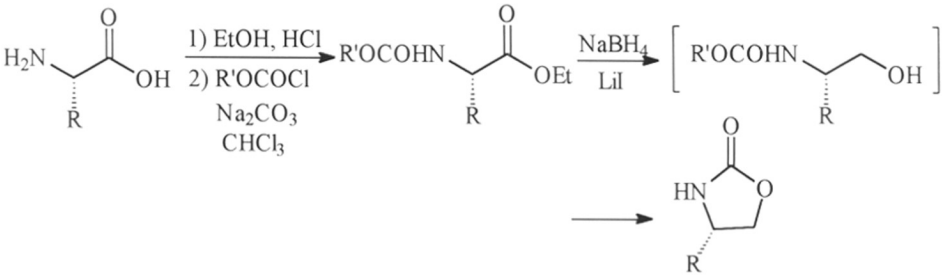
A significant improvement in terms of safety and ease of operation, especially for large-scale preparation has recently been achieved by McKillop and co-workers.[21] The crucial step was the calcium borohydride reduction of N- carbethoxy-α- amino acid esters, followed by base-catalysed cyclisation of the resultant N- carbethoxy-β- amino alcohols(Scheme 6).

Scheme 6



A further improvement on this procedure has been the use of $LiBH_4$ instead of $Ca(BH_4)_2$. This was reported by Sudharshan and Hultin(Scheme 7).[22]

Scheme 7



In this method, reduction of carbamate-blocked amino acid esters by lithium borohydride (made *in situ* from sodium borohydride and lithium iodide) leads to chiral 4- substituted oxazolidin-2-ones directly. The presence of iodide in the reaction mixture appears to promote the cyclisation of the intermediate alkoxyborohydride.

2. Objective

Existing methodologies for the synthesis of this important class of compounds generally start with expensive optically active α- amino alcohols and use either diethyl carbonate or phosgene as the acylating agent. The problem associated with the use of the existing procedures in large-scale experiments are two-fold

i) the exothermicity of the borane reduction, and

ii) the intermediate amino alcohols often possess considerable water solubility and can be difficult to isolate and purify.

These time-consuming procedures, often involve difficult work-ups, and require the use of hazardous or expensive reagents. There is clearly a need for a more convenient approach, especially for larger-scale work.

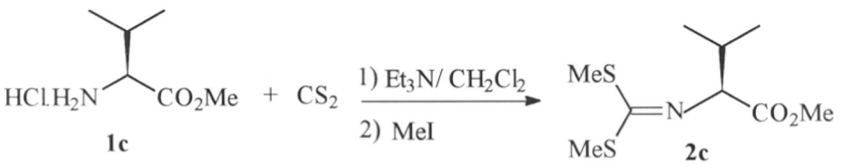
In this chapter we describe a simple, cost-effective procedure for the preparation of chiral oxazolidin-2-ones, in which the source of the carbonyl group is carbon disulfide. As part of our ongoing research on carbamates, we have recently reported the conversion of carbonimidodithioates to methyl or benzyl carbamates in a single step process.[23] The primary objective in that study was to develop a method for the preparation of N- carbobenzoxy α- amino acids. The concept has now been extended to provide a simple route for the synthesis of chiral 4- substituted oxazolidin-2-ones.

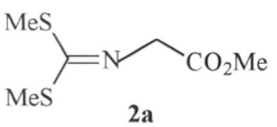
3. Results and Discussion

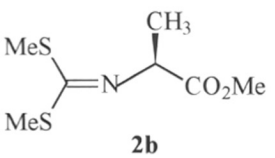
3.1 Synthesis of the carbonimidodithioic acid dimethyl esters from α- amino acid esters (2a-f)

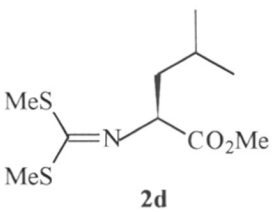
These carbonimidodithioates were prepared by the usual procedure[24] with appropriate modifications. A general procedure for the synthesis of these compounds has been given in chapter- 3(page 87).Thus (S)- valine methyl ester hydrochloride **1c** was condensed with carbon disulfide in the presence of triethylamine as the base in dichloromethane. Subsequent bismethylation with methyl iodide gave the product **2c** as a liqiud in 80% yield(Scheme 8). By a similar procedure the bismethylthio methylene derivatives of glycine, (S)-alanine, (S)-leucine, (S)-phenylalanine and (S)-phenylglycine methyl esters(**2a-b, d-f**) were prepared in more than 80% yield. All these compounds were characterised by their ^{1}H NMR spectra and other spectral data and compared with the reported values.

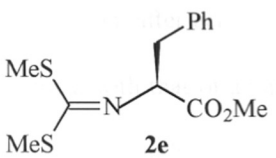
Scheme 8

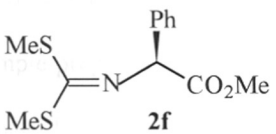










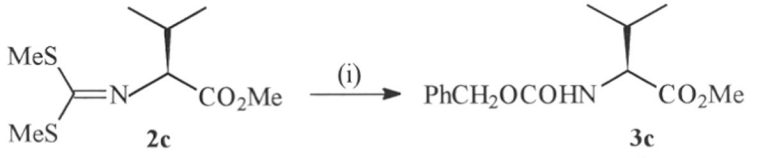


3.2 Synthesis of oxazolidin-2-ones from carbonimidodithioates

The above carbonimidodithioates (**2a-f**) could be converted to the benzyl carbamates (**3a-f**) by first treating with sodium benzyl alcoholate in THF at 30 °C, and subsequent hydrolysis at 30 °C. The N- carbobenzoxy amino acid methyl esters (**3a-f**) so generated could be reduced without purification to the corresponding alcohols (**4a-f**), which could then be directly cyclised to the desired oxazolidin-2-ones (**5a-f**)(Scheme 9). The whole process from the carbonimidodithioate stage to the oxazolidinone could be carried out as a one-pot reaction without the need to purify the intermediate product. For the reduction of the esters (**3a-f**), the protocol recently described by Sudharshan and Hultin,[22] involving the *in situ* generation of $LiBH_4$ from $NaBH_4$ and LiI has been used. However, under our reaction conditions, cyclisation of the N-carbobenzoxy-β- amino alcohols (**4a-f**) was slow and was complete only after 24h. The addition of dry NaOMe (10 mol%) to the refluxing THF solution accelerated the process; under these conditions cyclisation was complete in 8-10h. The use of n-BuLi (0.1 eq) or t-BuOK (0.1eq) in place of NaOMe in order to accelerate the reaction gave good yields of the products. However, NaOMe is preferred on a large scale because of its ease of handling. Thus for example, the carbonimidodithioate **2c** derived from (S)-valine methyl ester was treated with sodium benzyl alcoholate in anhydrous tetrahydrofuran at 30 °C for 8h; after the disappearance of the starting material on tlc, water (1.5eq) was added and the hydrolysis was allowed to proceed overnight at 30 °C, to give the benzyl carbamate (**4c**). This was then subjected to reduction by $LiBH_4$ (2eq) generated *in situ* from $NaBH_4$ and LiI in THF at 80 °C for 10h, after acidic work-up, a white solid was obtained, which melts at 70-72 °C, identical with that of an authentic sample prepared by the standard route.[15] A mixture of **5c** and the authentic sample also melted at 71-73 °C, thus confirming the structure of the product to be **5c**. The specific rotation of the purified sample was -17.2

(c 6.0, EtOH), while that of the authentic sample was -16.6(c 5.8, EtOH). By a similar procedure the bismethylthio derivatives of glycine, (S)-alanine, (S)-leucine, (S)-phenylalanine and (S)-phenylglycine methyl esters were converted to the corresponding oxazolidin-2-ones in good yields and optical purity.

Scheme 9

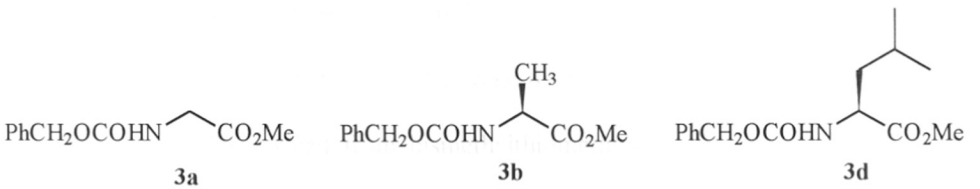


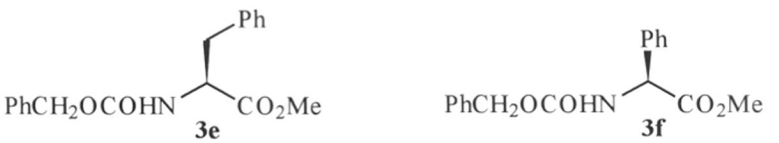
Reagents

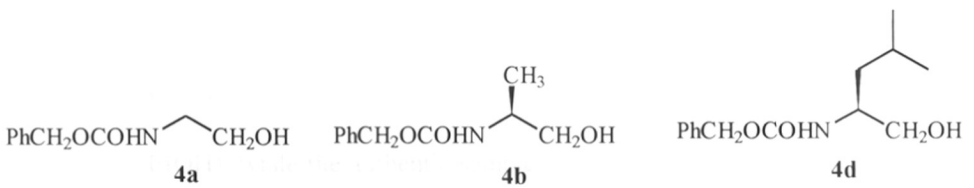
i) $PhCH_2ONa$, THF, then H_2O, 30 ^0C

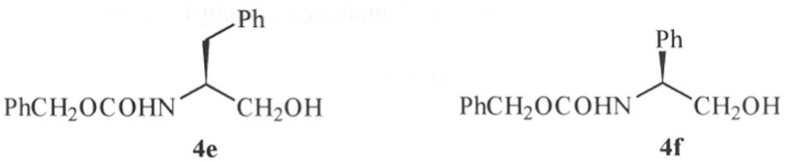
ii) $NaBH_4$, LiI, THF, 80 ^0C

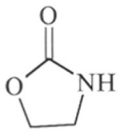
iii) NaOMe, THF, reflux











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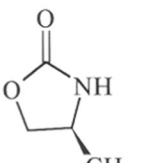

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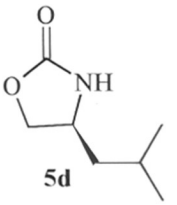

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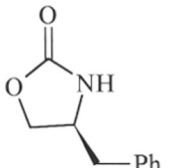

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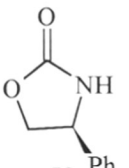


5f

The IR and ^{1}H NMR spectra of the oxazolidin-2-ones (**5a-f**) prepared from the carbonimidodithioates (**2a-f**) and those of authentic samples prepared for this purpose by the reported procedures were identical (**5a**-Figure 24, **5c**-Figure 25, **5e**- Figure 26 and **5f**- Figure 27). The melting points and the specific rotation have also been compared with those of authentic samples. The solid oxazolidin-2-one (**5a**) melted in the range 85-87 °C, while the mp of an authentic sample was 86-88°C. A mixture of **5a** and the authentic sample melted at 87-88 °C, thus confirming the structure of the product to be **5a**. The mp of the crystalline solid 4-benzyl oxazolidin-2-one (**5e**) ranged between 82-84 °C, while that of an authentic sample was 83-85 °C(mixed mp: 83-85 °C). The oxazolidin-2-one (**5f**) derived from bismethylthiomethylene (S)- phenylglycine methyl ester melted at 130-131 °C, while the mp of an authentic sample was 132-133 °C(mixed mp 129-131 °C). The specific rotation of the 4- methyloxazolidin-2-one (**5b**) was -11.7°(c 4.0, C_6H_6), while that of an authentic sample was -11.3°(c 3.98, C_6H_6). The specific rotation of **5c** was -17.2°(c 6.0, EtOH), while the $[\alpha]_D$ of the corresponding authentic sample was -16.6°(c 5.8, EtOH). The specific rotation of **5e** was determined as +4.81°(c 1.0, EtOH), while the authentic sample showed a specific rotation of +4.90°(c 1.1, EtOH). The $[\alpha]_D$ of 4-phenyloxazolidin-2-one (**5f**) was +48.8°(c 2.0, $CHCl_3$), while that of an authentic sample was +49.5°(c 2.1, $CHCl_3$). The yields and physical properties of (**5a-f**) are given in *Table 1*.

Table 1

Product	R	Yield (%)	Nature	mp (°C)	specific rotation $[\alpha]_D$ degree
5a	H	88	solid	85-87[86-88][25]	-
5b	CH_3	81	oil	-	-11.7(c 4.0, C_6H_6) [-11.3(c 3.98,C_6H_6)] [26]
5c	$CH(CH_3)_2$	83	needles	70-72[69-70]	-17.2(c 6.0, EtOH) [-16.6(c 5.8, EtOH)][15]
5d	$CH_2CH(CH_3)_2$	77	oil	-	+41.4(c 1, $CHCl_3$) 42.0(c 1, $CHCl_3$) [27]
5e	CH_2Ph	82	crystalline solid	82-84[84-86]	+4.81(c 1.0, EtOH) [+4.90(c 1.1, EtOH)][13]
5f	Ph	80	colourless prism	130-131 [132-133]	+48.8(c 2.0, $CHCl_3$) [+49.5(c 2.1, $CHCl_3$][14]

4. Conclusion

• A simple, cost-effective route for the conversion of carbonimidodithioates derived from α- amino acid methyl esters to chiral 4- substituted oxazolidin-2-ones was described.

Experimental

General

General experimental techniques which have been described in the experimental section of Chapter 2 were followed.

Synthesis of Carbonimidodithioates (2a-f) from amino acid esters.

General procedure for the synthesis of these compounds has been given in Chapter 3.

General procedure for the conversion of carbonimidodithioates (2a-f) to oxazolidin-2-ones (5a-f)

Sodium benzyl alcoholate (2 mmol) was taken in dry THF (10 ml). To this was added the carbonimidodithioate (**2a-f**) (2 mmol) and stirred at 30 ^{0}C for 6 h. The reaction was monitored by tlc. After the complete disappearance of the starting material, water (3 mmol) was added to the mixture and stirred overnight at 30 ^{0}C. The THF was removed by distillation *in vacuo* and dried completely. The reaction mixture was dissolved in anhydrous THF(10 ml) and then sodium borohydride (5 mmol), anhydrous lithium iodide (5 mmol) and sodium methoxide (0.2 mmol) was added and the resulting suspension was stirred and refluxed for 8-10h. The reaction mixture was cooled and acidified with 2N HCl (10 ml) and the organic solvent was evaporated. The residue was diluted with water (5 ml) and extracted with CH_2Cl_2. The combined extracts were washed with saturated $NaHCO_3$ (2 x 10 ml), aqueous $Na_2S_2O_3$ (10 ml), water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the product (**5a-f**) was purified either by column or by crystallisation.

Oxazolidin-2-one (5a)

Yield (%)	88
mp (mixed mp)	85-87 °C (87-88 °C)
IR(Neat)/cm^{-1}	3280, 3017, 2918, 1753, 1556, 1483, 1402, 1327, 1215
^1H NMR ($CDCl_3$) (200 MHz)	3.60(t, 2H, NCH_2, J = 8.0Hz), 4.45(t, 2H, OCH_2, J = 8.0Hz), 6.50(br, 1H, NH)

(S)- 4-Methyl oxazolidin-2-one (5b)

Yield (%)	81
IR(Neat)/cm^{-1}	3284, 2968, 1751, 1678, 1544, 1483, 1384, 1236
^1H NMR ($CDCl_3$) (200 MHz)	1.00(d, 3H, CH_3, J = 9.0Hz), 3.80(m, 1H, CHNH), 4.00(dd, 1H, J = 6.0, 8.0Hz), 4.45(t, 1H, J = 8.0Hz), 6.95(br, 1H, NH)

(S)- 4-Isopropyl oxazolidin-2-one (5c)

Yield (%)	83
mp (mixed mp)	70-72 °C (70-72 °C)
IR(Neat)/cm^{-1}	3267, 3141, 2966, 1751, 1471, 1440, 1381, 1217, 1087
^1H NMR ($CDCl_3$) (200 MHz)	0.9(d, 3H, CH_3, J = 7.0Hz), 1.0(d, 3H, CH_3, J = 7.0Hz), 1.72(m, 1H, CH), 3.60(m, 1H, NCH), 4.10(dd, 1H, J = 6.0, 8.0Hz), 4.40(t, 1H, J = 8.0), 7.05(br, 1H, NH)
^{13}C NMR($CDCl_3$) (75 MHz)	17.24, 17.43, 32.29, 57.99, 68.21, 160.51

(S)- 4-Isobutyl oxazolidin-2-one (5d)

Yield (%)	77
IR(Neat)/cm^{-1}	3260, 2958, 2872, 1754, 1466, 1426, 1384, 1260
^1H NMR ($CDCl_3$) (200 MHz)	0.9(d, 3H, $CHCH_3$, J = 7.0Hz), 1.0(d, 3H, $CHCH_3$, J = 7.0Hz), 1.20-1.55(m, 3H, CH, CH_2), 4.00-4.60(m, CH, OCH_2), 6.35(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	21.44, 22.43, 24.23, 43.94, 50.40, 70.14, 160.04

(S)- 4-Phenylmethyloxazolidin-2-one (5e)

Yield (%)	82
mp (mixed mp)	82-84 °C (83-85 °C)
IR($CHCl_3$)/cm^{-1}	3274, 3018, 2918, 1751, 1604, 1479, 1406, 1217
^1H NMR ($CDCl_3$) (200 MHz)	2.90(d, 2H, CH_2Ph, J = 8.0Hz), 4.00-4.50(m, 3H, CH, CH_2O), 6.15(br, 1H, NH), 7.10-7.50(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	40.88, 53.45, 69.21, 126.84, 128.64, 129.00, 135.93, 159.85

(S)- 4-Phenyloxazolidin-2-one (5f)

Yield (%)	80
mp (mixed mp)	130-131 °C(129-131 °C)
IR(Neat)/cm^{-1}	3460, 3250, 2950, 2853, 1740, 1650, 1375, 1218
^1H NMR ($CDCl_3$) (200 MHz)	4.15(dd, 1H, J = 6.0, 8.0Hz), 4.65(t, 1H, J = 8.0Hz), 4.95(m, 1H, NCH), 6.50(br, 1H, NH), 7.25-7.55(m, 5H, Ar)

References

1. D. Seebach, J. Zimmermann, U. Gysel, r. Ziegler and T.-K. Ha, *J. Am. Chem. Soc.*, **1988**, *110*, 4763.
2. M. Sato, M. Murakami, S. Sunami, C. Kaneko. T. Furuya and H. Kurihara, *J. Am. Chem. Soc.*, **1995**, *117*, 4279.
3. M. Demuth, A. Palomer, H. D. Sluma, A. K. Dey, C. Kruger and Y. H. Tsay., *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 1117.
4. a) J. K. Whitesell, A. Bhattacharya, and K. Henke, *J. Chem. Soc., Chem. Commun.*, **1982**, 988.

   b) J. K. Whitesell, A. Bhattacharya, D. A. Aguilar and K. Henke, *J. Chem. Soc., Chem. Commun.*, **1982**, 989.
5. W. Oppolzer, C. Chapuis and G. Bernardinelli, *Helv. Chim. Acta.*, **1984**, *67*, 1397.
6. D. Enders in *Asymmetric Synthesis*, Ed. J. D. Morrison, Academic Press, **1984**, *3*, 275.
7. a) A. I. Meyers, M. Harre and R. Garland, *J. Am. Chem. Soc.*, **1984**, *106*, 1146.

   b) A. I. Meyers, R. Henreich and K. Th. Wanner, *J. Am. Chem. Soc.*, **1985**, *107*, 7776.

   c) A. I. Meyers and S. I. Fleming, *J. Am. Chem. Soc.*, **1986**, *108*, 306.

   d) A. I. Meyers and B. A. Lefker, *Tetrahedron.*, **1987**, *43*, 5363.

   e) A. I. Meyers and R. H. Wallace, *J. Org. Chem.*, **1989**, *54*, 2509.
8. a) D. A. Evans, K. T. Chapman and J. Bisaha, *Tetrahedron Lett.*, **1984**, *25*, 4071.

   b) D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, **1984**, *106*, 4261.
9. A. Studer, *Synthesis*, **1996**, 793.
10. D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, **1981**, *103*, 2127.
11. D. A. Evans, *Aldrichimica Acta.*, **1982**, *15*, 23.
12. J. R. Gage and D. A. Evans, *Org. Synth.*, **1990**, *68*, 83.
13. D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, **1986**, *108*, 6757.

14. D. A. Evans and E. B. Sjogren, *Tetrahedron Lett.*, **1985**, *26*, 3783.

15. D. A. Evans, D. J.- Mathre and W. L. Scott, *J. Org. Chem.*, **1985**, *50*, 1830.

16. J. R. Gage and D. A. Evans, *Org. Synth.*, **1990**, *68*, 77.

17. L. N. Pridgen, J. Prol. Jr, B. Alexander and L. Gillyard, *J. Org. Chem.*, **1989**, *54*, 3231.

18. P. G. M. Wuts and L. E. Pruitt, *Synthesis.*, **1989**, 622.

19. A. Correa, J. -N. Denis and A. E. Greene, *Synth. Commun.*, **1991**, *21*, 1.

20. A. Agami, F. Couty, L. Hamon and O. Venier, *Tetrahedron Lett.*, **1993**, *34*, 4509.

21. N. Lewis, A. McKillop, R. J. K. Taylor and R. J. Watson, *Synth. Commun.*, **1995**, *25*, 561.

22. M. Sudharshan and P. G. Hultin, *Synlett.*, **1997**, 171.

23. M. Anbazhagan, T. I. Reddy and S. Rajappa, *J. Chem. Soc., Perkin Trans 1*, **1997**, 1623.

24. a) H. Waldmann and H. Kunz, *Liebigs. Ann Chem.*, **1983**, 1712.

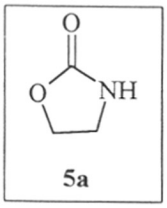
    b) T. I. Reddy , B. M. Bhawal and S. Rajappa, *Tetrahedron Lett.*, **1992**, 33, 2857.

25. K. -H. Schotz, H. -G. Heine and W. Hartman, *Org.Synth.Coll.Vol.* **1990**, *8*, 4

26. P. F. Alewood, M. Benn and R. Reinfried, *Can. J. Chem.*, **1974**, *52*, 4083

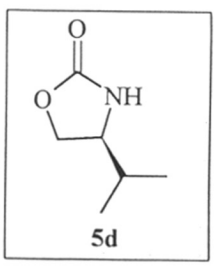
27. B. R. Nicolaus, L. Mariani, G. Gallo and E. Testa, *J. Org. Chem.*, **1961**, *26*, 2253.

Figure 24



5a

Figure 25



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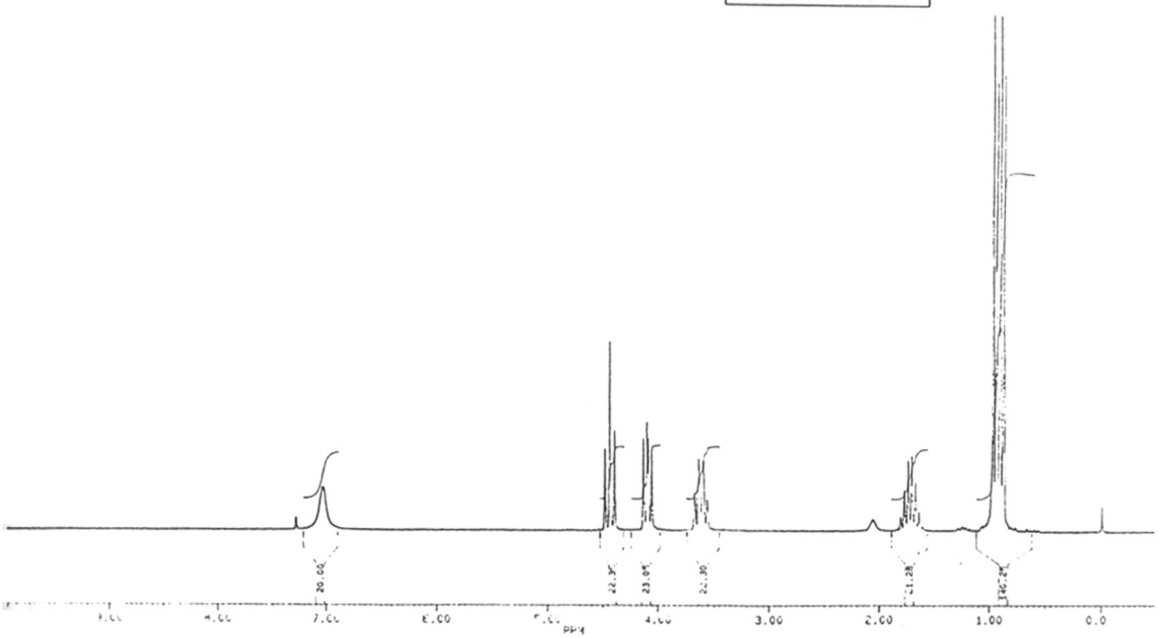
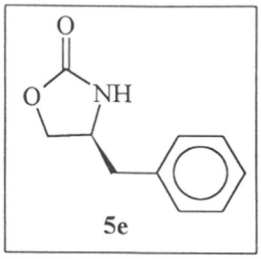
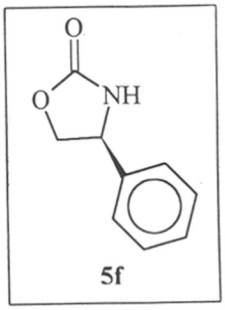


Figure 26

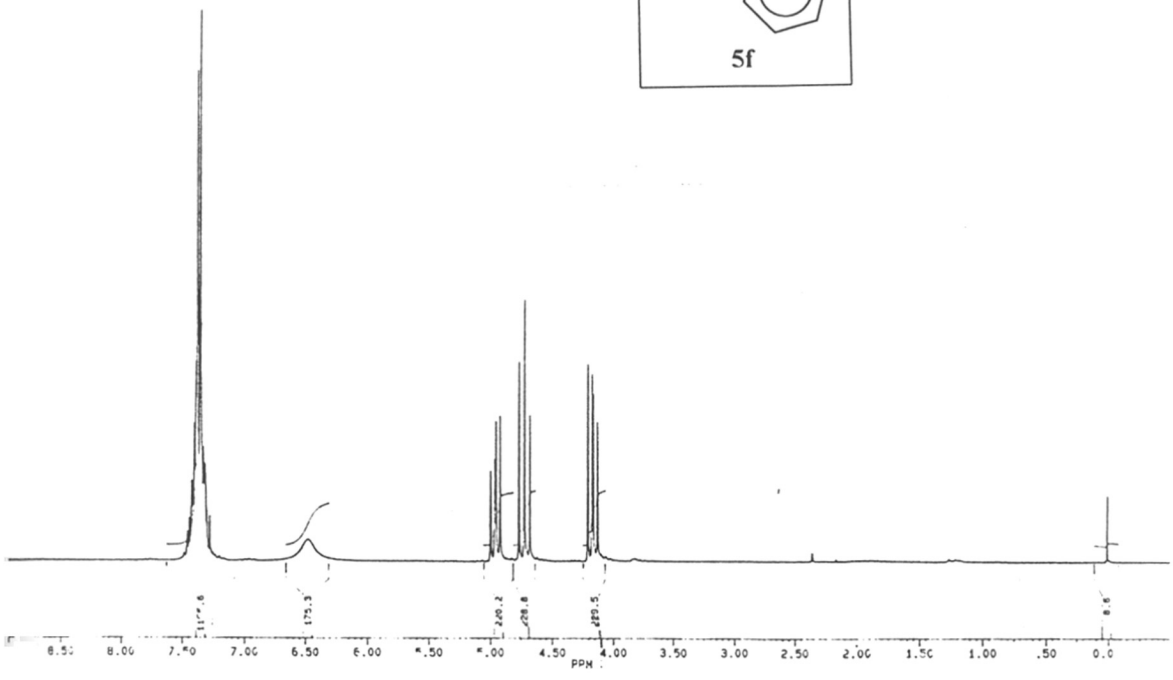


5e

Figure 27



5f



Chapter 5

Preparation of unsymmetrical di-, and tri- substituted ureas including urea dipeptides from carbonimidodithioates

1. Introduction

Substituted ureas have attracted attention because of the wide variety of their applications in industry, engineering, agriculture and medicine; they are used as antioxidants in gasoline for automobiles, in dyeing of hair and cellulose fibres, as additives in detergents to prevent carbon deposits and as corrosion inhibitors.[1] Ureas are reported to possess a wide spectrum of biological activities; for instance, they can act as plant growth regulators, pesticides, herbicides,[2] transquillizers, anticonvulsants and as oral anti-diabetics.[3,4] Recently some unsymmetrical ureas have been shown to be potent HIV-1 protease inhibitors.[5-7] A brief account of the synthesis of substituted ureas is given below.

1.1 Methods of synthesis of substituted ureas

Several methods are available for the preparation of symmetrical and unsymmetrical di-, or tri- substituted ureas in good yields.[8] The synthesis of urea derivatives essentially involves two steps;

i) reaction of an amine with a one-carbon reagent at the carbon dioxide oxidation level to form a reactive molecule still possessing a leaving group attached to the carbonyl, and

ii) treatment of this intermediate with either the same or another amine to form the urea.

Two types of reagent have been evolved for this purpose.

1.2 Using reagents of the type COX_2

A. Symmetrical ureas by reaction of two moles of the same amine

1.2.1 From phosgene

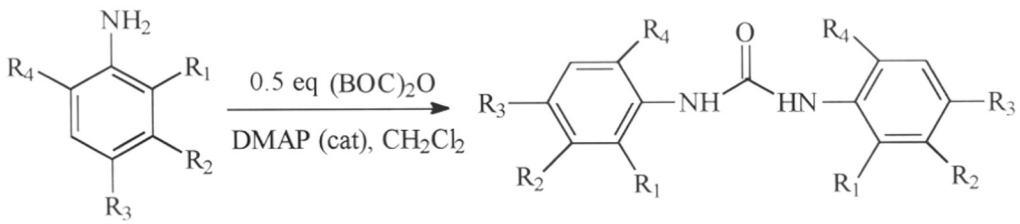
Symmetrical dialkyl-, diaryl ureas are obtained by treating the corresponding amines with phosgene.[1] By passing phosgene through a saturated aqueous solution of aniline, diphenyl urea was obtained(Scheme 1). The reaction proceeds through the intermediate phenylcarbamoyl chloride, which readily reacts with another molecule of the amine to form the symmetrically substituted ureas.

Scheme 1

1.2.2 From Di-*t*-butyl dicarbonate

The reaction of arylamine with 0.5 equivalent of di-tert-butyldicarbonate and a catalytic amount of DMAP in dichloromethane provided symmetrical N, N′ diarylureas in 87-96% yield(Scheme 2).[9]

Scheme 2



1.2.3 From S, S- Dimethyl dithiocarbonate

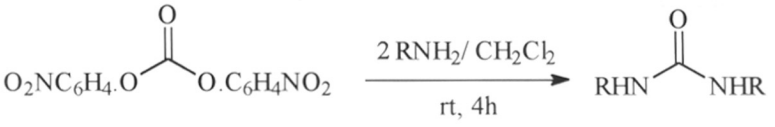
The reaction of S, S- dimethyl dithiocarbonate with 2 equivalents of a primary amine in methanol or ethanol at 60 °C gave the corresponding symmetrical urea as the only product(Scheme 3).[10]

Scheme 3

1.2.4 From Bis(4-nitrophenyl) carbonate

When bis(4-nitrophenyl) carbonate was allowed to react with an excess of amine (1:2) in dichloromethane at ambient temperature, symmetrical ureas were formed directly (Scheme 4).[11]

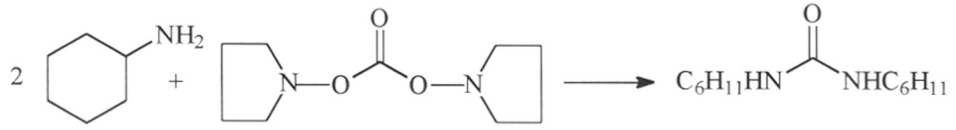
Scheme 4



1.2.5 From Disuccinimido carbonate

Takeda *et al*[12] have used disuccinimido carbonate (DSC) as a carbonyl insertion reagent for the synthesis of symmetrically substituted ureas. This reagent was treated with amines and diamines yielding urea derivatives (Scheme 5).

Scheme 5



1.2.6 From N, N′- Carbonyl diimidazole

In inert solvents, N, N′- carbonyl diimidazole reacts rapidly and quantitatively with primary aliphatic and aromatic amines at 20 °C yielding substituted symmetrical ureas(Scheme 6).[13]

Scheme 6

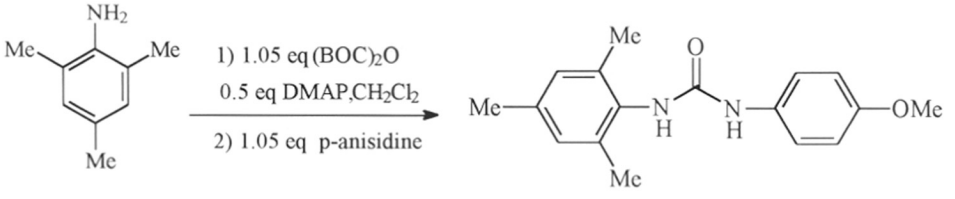
B. Unsymmetrical ureas by reaction with two different amines

1.2.7 From Di-*t*-butyl dicarbonate

The intermediate isocyanate formed in the reaction of a primary amine with $(BOC)_2O$ can be trapped *in situ* by another amine. This concept was used for the synthesis of unsymmetrical diaryl and dialkyl ureas. For this purpose 1 equivalent of the

first amine was treated with 1.05 equivalent of $(BOC)_2O$ in the presence of 0.1 equivalent of DMAP. The isocyanate was converted into the unsymmetrical urea by the addition of 1.05 equivalent of the second amine(Scheme 7).[9]

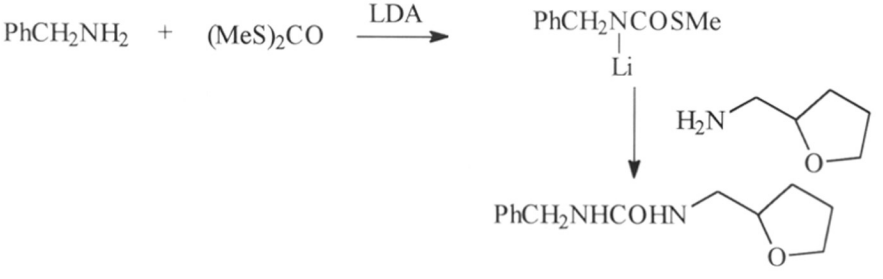
Scheme 7



1.2.8 From S, S- Dimethyl dithiocarbonate

Under basic conditions, S, S- dimethyl dithiocarbonate reacts with benzylamine to form N- benzyl-S-methyl thiocarbamate, which on condensation with a different amine give an unsymmetrical urea(Scheme 8).[10]

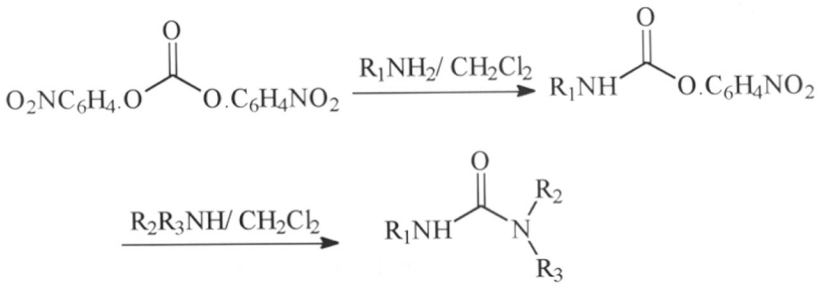
Scheme 8



1.2.9 From Bis(4-nitrophenyl) carbonate

This carbonate reacts in dichloromathane at ambient temperature with equimolar amounts of primary amines to give 4-nitrophenyl-N-alkyl carbamates. These carbamates, on treatment with a different amine lead to N, N′-disubstituted unsymmetrical ureas.[11] This second reaction is considerably slower than the carbamate formation(Scheme 9).

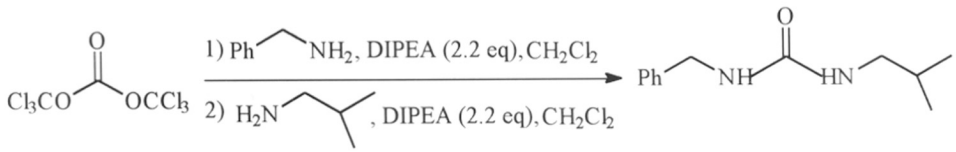
Scheme 9



1.2.10 From Triphosgene

A facile one-pot synthesis of unsymmetrically substituted ureas by sequential addition of two different amino components to a solution of triphosgene in dichloromethane has been reported by Majer *et al*(Scheme 10).[14]

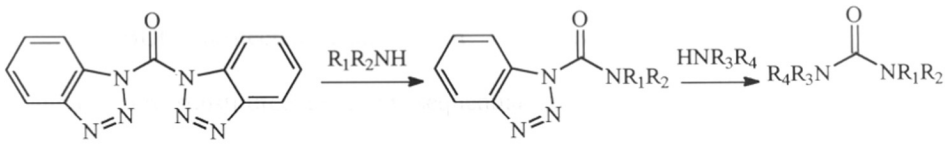
Scheme 10



1.2.11 From 1, 1′ Carbonyl bisbenzotriazole

Trisubstituted or tetrasubstituted ureas have been synthesized by a one-pot reaction of 1, 1′ carbonyl bisbenzotriazole initially with a primary or a secondary amine followed by treatment with a secondary amine as reported by Katritzky *et al* (Scheme11).[15]

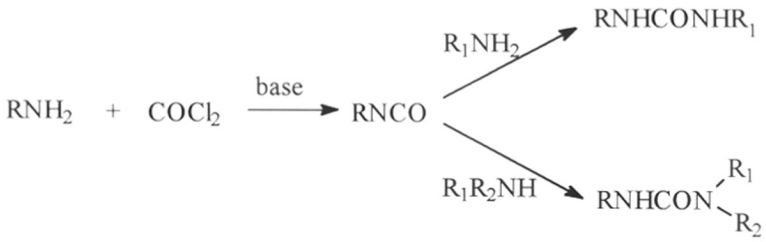
Scheme 11



1.2.12 From Isocyanates

The most common general procedure for the synthesis unsymmetrical di- or trisubstituted ureas involves the reaction of an isocyanate with an amine.[8] Isocyanates are usually prepared by bubbling phosgene gas through a solution of a primary amine at elevated temperature.[16] An improved method for the perparation of isocyanates involves the reaction of primary amines with phosgene in the presence of a base(Scheme 12).[17]

Scheme 12

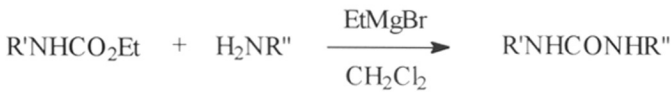


1.3 Using reagent of the type COXY

1.3.1 From Carbamates

A simple synthesis of N, N'- disubstituted ureas from carbamates has been described by Basha.[18] The reaction involves the displacement of an alkoxy group from a carbamate by the magnesium salt of an amine generated *in situ* (Scheme 13).

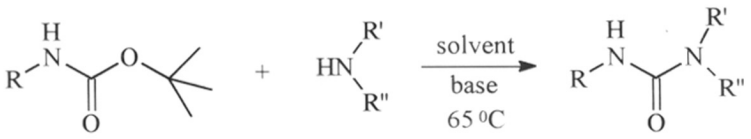
Scheme 13



1.3.2 From N- BOC protected amines

N- BOC protected amines can be converted efficiently into N, N'- unsymmetrically substituted ureas by sequential deprotonation and condensation with amines at 65 °C as reported by Lamothe *et al*(Scheme 14).[19]

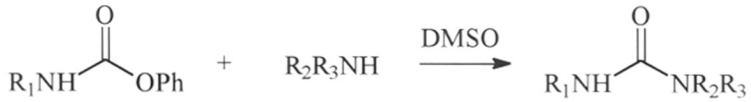
Scheme 14



1.3.3 From Phenyl carbamate

Thavonekham[20] has described a mild approach for the synthesis of urea derivatives under neutral conditions from a phenyl carbamate and a stoichiometric amount of amine in DMSO at room temperature(Scheme 15).

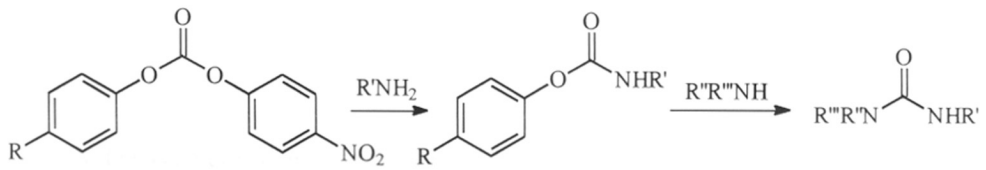
Scheme 15



1.3.4 From Unsymmetrical diaryl carbonates

Appropriately substituted unsymmetrical diaryl carbonates react smoothly with primary amines to give the carbamates; subsequent treatment of the carbamate with a primary or secondary amine gives symmetrical or unsymmetrical ureas in good yields (Scheme 16).[21]

Scheme 16



1.4 Synthesis of ureas from carbon monoxide

The reaction of aliphatic primary or secondary amines with carbon monoxide in the presence of selenium produces the substituted ureas in good yields(Scheme 17).[22]

Scheme 17

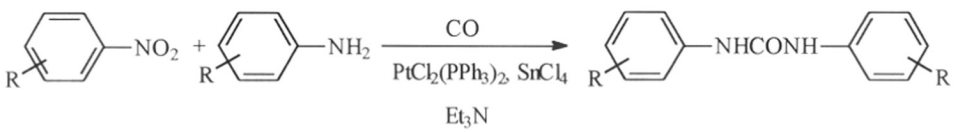
$$RNH_2 + Se + CO \longrightarrow (RNH_3)^+ (RNHCOSe)^-$$

$$(RNH_3)^+ (RNHCOSe)^- + O_2 \longrightarrow (RNH)_2CO + H_2O + Se$$

The intermediate selenocarbamate salts have been isolated, suggesting that the process goes in atleast two steps.

N, N′- Diaryl ureas have been obtained in good yields from nitroarenes, aminoarenes and carbon monoxide at 140 °C in the presence of catalytic amount of dichlorobis (triphenylphosphine) platinum (II)(Scheme 18).[23]

Scheme 18



N, N′- disubstituted ureas have been prepared in good yields by the reaction of aromatic or aliphatic primary amines in alcohol solution with CO and O_2 under mild conditions (70-90 °C, 1 atm) in the presence of catalytic amount of $PdCl_2$ or a palladium (II) complex(Scheme 19).[24]

Scheme 19

$$PdCl_2(PhNH_2)_2 + CO + PhNH_2 \longrightarrow CO(NHPh)_2 + 2[PhNH_3^+][Cl^-] + Pd$$

$$Pd + 2\,PhNH_3^+Cl^- + 0.5\,O_2 \longrightarrow PdCl_2(PhNH_2)_2 + H_2O$$

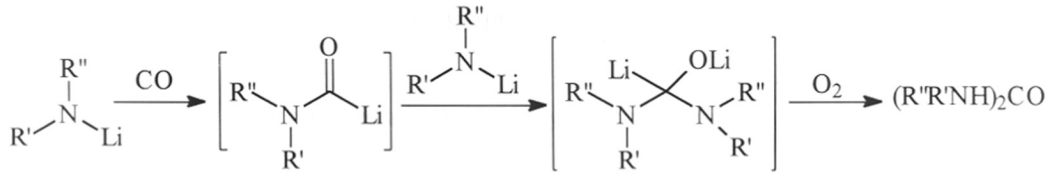
Iodine is an effective promoter for the Pd- catalysed carbonylation of primary and secondary amines to ureas, in acetonitrile as reported by Alper *et al*(Scheme 20).[25]

Scheme 20

$$R'R''NH + CO + I_2 \xrightarrow[CH_3CN,\ 95\ ^oC]{Pd(OAc)_2,\ K_2CO_3} (R'R''N)_2CO + 2HI$$

N, N, N′, N′- tetrasubstituted ureas have been obtained by the reaction of lithium aliphatic amides in tetrahydrofuran solution with carbon monoxide at 0 °C, followed by oxidation with oxygen(Scheme 21).[26]

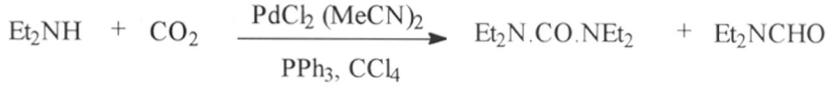
Scheme 21



1.5. Synthesis of ureas from carbon dioxide

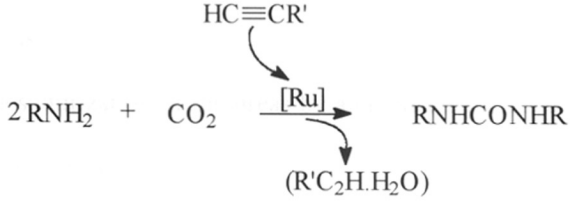
The reaction of dialkyl amines with carbon dioxide in the presence of $PdCl_2(MeCN)_2$ as catalyst and PPh_3 as additive gave tetrasubstituted ureas. N, N-diethyl formamide was obtained as a minor product(Scheme 22).[27]

Scheme 22



Aliphatic and araliphatic primary amines have been treated with CO_2 at 120-140 °C in the presence of ruthenium compelxes and terminal alkynes especially propargyl alcohols to give N, N′- disubstituted symmetrical ureas. The alkyne ruthenium intermediate acts as a dehydrating agent(Scheme 23).[28]

Scheme 23



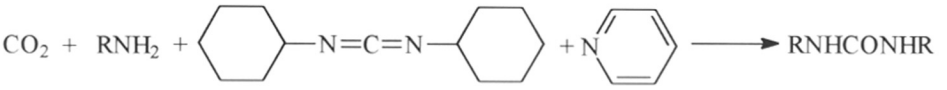
Yamazaki[29] has reported a method for the preparation of N, N′- diphenyl urea by passing carbon dioxide through a pyridine solution of diphenylphosphite and aniline at 40 °C (Scheme 24).

Scheme 24

$$2\ PhNH_2 + CO_2 + HPO(OPh)_2 \xrightarrow[3\ atm]{40\ ^oC} PhNHCONHPh$$

Ogura *et al*[30] have reported a large- scale synthesis of disubstituted ureas directly from CO_2 and amine using dicyclohexyl carbodiimide as a condensing agent in the presence of a tertiary amine(Scheme 25).

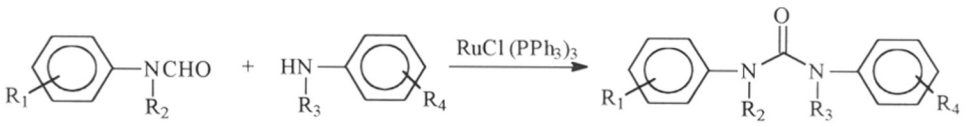
Scheme 25



1.6. Oxidative insertion of amine in formanilide

Watanabe *et al*[31] have reported that N- aryl substituted formamides react smoothly with aminoarenes in the presence of a catalytic amount of dichlorotris (triphenylphosphine) ruthenium affording various N, N′- diarylaureas in good yields (Scheme 26).

Scheme 26



1.7 From Thoiureas

Recently desulfurization of thioureas by ammonium persulfate to ureas has been reported by Ramdas *et al*(Scheme 27).[32]

Scheme 27

$$RNHCSNHR \xrightarrow[DMF/\ H_2O]{\text{ammonium persulfate}} RNHCONHR$$

2 Objective

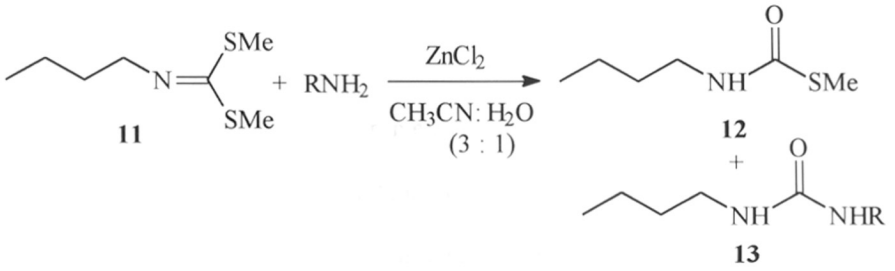
Most of the methods summarised above have several drawbacks. Due to their high toxicity and reactivity, phosgene and isocyanates are difficult to handle in the laboratory. Although several substitutes for phosgene such as triphosgene, carbonates and carbonyl diimidazole have been developed during the last few decades, these reagents are themselves prepared from phosgene. Alternatively, methods for the preparation of unsymmetrical ureas based on carbonic acid derivatives have been reported. These methods are also not totally satisfactory since they require preparation of reagent, long reaction time, use of large excess of reagent and isolation of the reactive intermediate from excess of the reagent. Our efforts have therefore been directed toward the development of a mild method for the synthesis of substituted ureas.

3. Results and Discussion

Recently, we have reported the conversion of carbonimidodithioates into carbamates in one-step.[33] The method consists of the $ZnCl_2$- catalysed hydrolysis of the imino sulfide unit of the carbonimidodithioate at 60 °C in MeOH-water (3:1) followed by nucleophilic displacement of SMe by methanol to give the carbamates directly.

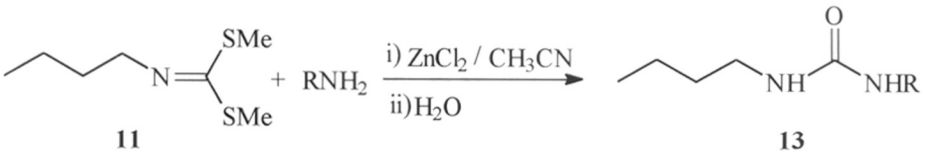
The next logical step was to extend this reaction to nitrogen nucleophiles instead of the oxygen nucleophile to provide urea derivatives. The first attempt in this direction, by replacing methanol with an amine in the $ZnCl_2$- catalysed reaction of carbinimidodithioates **11** derived from n-butylamine was disappointing. The major portion of the product consisted of the partially hydrolysed thiocarbamate **12** with only a small quantity of the urea derivative (less than 5%) **13**(Scheme 28).

Scheme 28



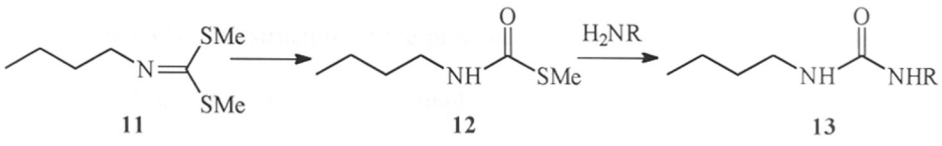
It was therefore decided to run the $ZnCl_2$- catalysed reaction of cabonimidodithioates **11** with an amine in anhydrous acetonitrile solution. It took more than 48h for the complete disappearance of the starting material at 80 °C; then water (2 eq) was added and the hydrolysis was allowed to proceed overnight at 80 °C to give a moderate yield (52%) of urea **13**(Scheme 29).

Scheme 29



Meanwhile the thiocarbamate **12** obtained in the first attempt was treated with n-propyl amine in acetonitrile at 30 °C to give the required urea derivative **13** in 80% yield (Scheme 30). Hence, it was decided to hydrolyse the carbonimidodithioates **11** first into S-methyl thiocarbamate **12** and then convert this thiocarbamate **12** to an urea derivative by treatment with an appropriate amine.

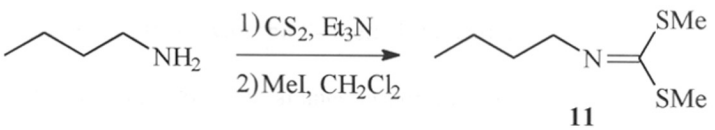
Scheme 30



3.1 Synthesis of carbonimidodithioate (11)

Carbonimidodithioate **11** was prepared by the reported procedure[34] with appropriate modifications. n-Butylamine was reacted with carbon disulfide in the presence of triethylamine in dichloromethane followed by methylation with methyl iodide. This gave the carbonimidodithioic acid dimethyl ester (**11**) in 76% yield, as a clear liquid(Scheme 31). The structure of the product was confirmed by its spectral data. The ^{1}H NMR spectrum of a purified sample of **11** showed a triplet at 0.85δ (t, 3H, J = 8Hz) due to the CH_3, followed by a multiplet at 1.35-1.40δ(m, 4H) for the methylenes of the chain. Two sharp singlets were seen at 2.40 and 2.55δ corresponding to the two SCH_3 groups, followed by a quartet at 3.20δ (q, 2H, J = 7Hz) due to the NCH_2 protons. The mass spectrum of **11** showed the molecular ion (M^+) peak at m/z 177. The above data proved the structure of the product to be **11**.

Scheme 31



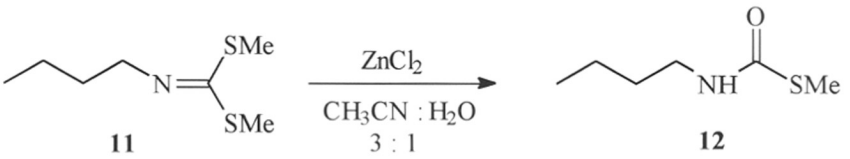
11

3.2 Hydrolysis of carbonimidodithioic acid dimethyl ester (11) to S-methyl thiocarbamate (12)

Carbonimidodithioates can be converted to the corresponding S-methyl thiocarbamates according to the reported procedure.[33] Thus $ZnCl_2$ was taken in acetonitrile-water (3:1); to the mixture was added carbonimidodithioate **11** in the same solvent and stirred at 80 °C for 8h to give S- methyl N-butyl thiocarbamate **12** in 73% yield(Scheme 32). The structure of the product **12** was confirmed by the spectral data. The ^{1}H NMR spectrum of a purified sample of **12** showed a triplet at0.85δ (t, 3H, J = 8Hz) due to the CH_3, followed by a multiplet at 1.25-1.40δ for the CH_2-CH_2 protons, a singlet at 2.30δ corresponding to SCH_3 and a quartet at 3.15δ(q, 2H, J = 7Hz) for the

NCH_2 protons. The NH proton appears as a broad peak at 4.85δ. The mass spectrum of the product showed the molecular ion (M^+) peak at m/z 147. The above data proved the structure of the product to be **12**(Figure 28).

Scheme 32



11 **12**

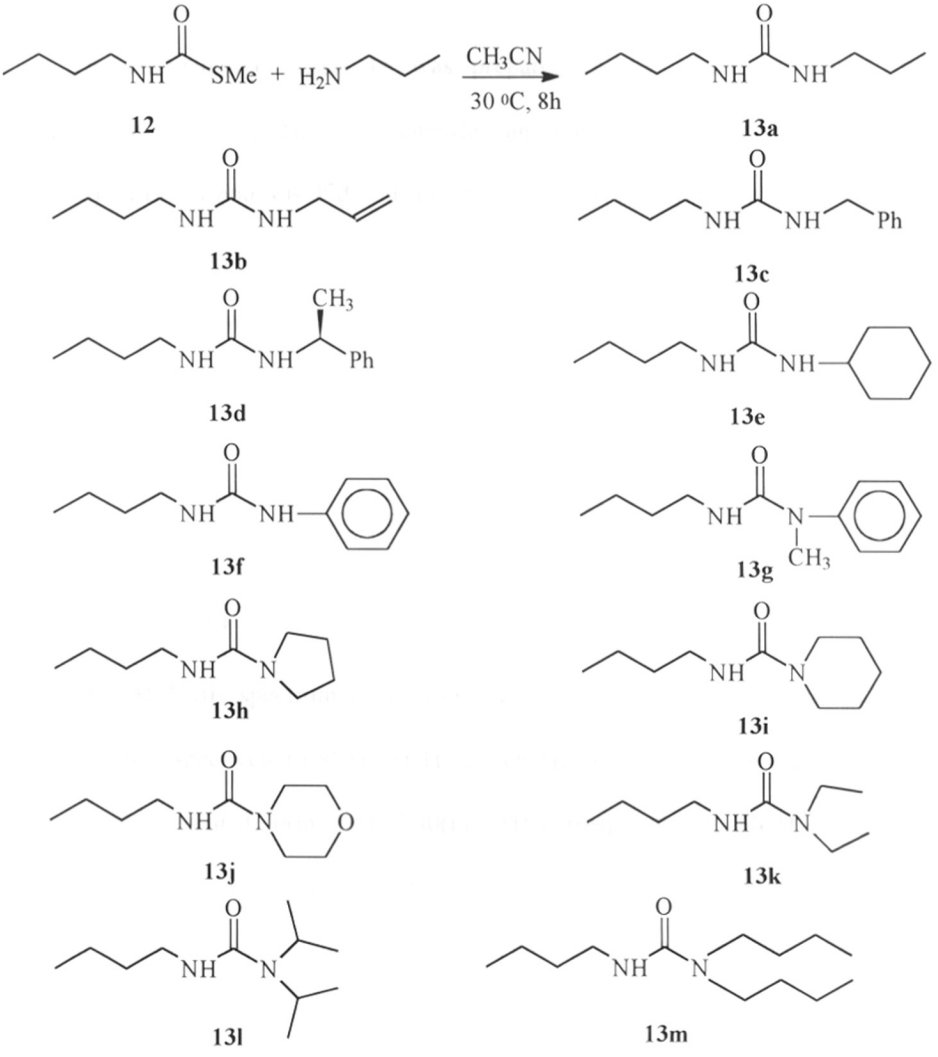
This hydrolysis can also be effected with $HgCl_2$, but the reaction was not as clean as the $ZnCl_2$- catalysed hydrolysis and more importantly the yield of S- methyl thiocarbamate **12** was only 55%.

3.3 Synthesis of urea derivatives (13) from S-methyl thiocarbamate (12)

S-Methyl thiocarbamate **12** on treatment with an appropriate amine in acetonitrile at 30 °C or 80 °C gave the required di-, or trisubstituted urea derivatives. Aliphatic amines were reacted at 30 °C with the S- methyl thiocarbamate yielding urea derivatives (**13a-k**) in 64-89% yield. Aromatic amines in contrast required higher temperature for the reaction to proceed; in refluxing acetonitrile the ureas (**13 l-m**) were obtained in 60-63% yields. Generally two equivalents of the amine were used. For example, the S-methyl thiocarbamate **12** (2 mmol) was treated with n-propylamine (4 mmol) in acetonitrile solution (5 ml) at 30 °C for 8h to give the urea **13a** in 80% yield(Scheme 33). The structure of the product was confirmed from its spectral data. The ^1H NMR spectrum of **13a** shows a triplet at 0.85δ(t, 3H, J = 8.2Hz) due to the two CH_3 groups, followed by a multiplet at 1.40δ (m, 6H) for the three methylene group protons and a quartet at 3.15δ (q, 4H, J = 7.2Hz) corresponding to two NCH_2. The NH proton appears as a broad singlet at 5.20δ (br, 2H, 2NH). The mass spectrum of the product showed the

molecualr ion (M^+) peak at m/z 158. From the above data the structure of the product was proved to be **13a**(Figure 30).

Scheme 33



By a similar procedure the di- and trisubstituted urea derivatives **13b-m** were prepared and characterised from their spectral data(**13f-** Figure 31: **13l-** Figure 32). Isolated and purified yields of the urea derivatives **13a-m** are given *Table 1*.

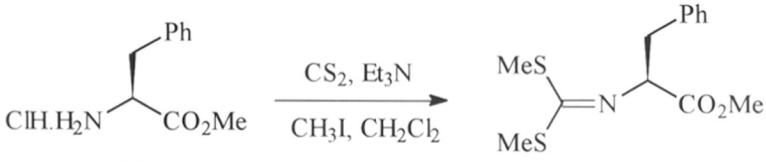
The next step was to utilise this methodology for the synthesis of urea dipeptides.[35] Recently some urea dipeptides have been shown to be potent HIV-1

protease inhibitors.[7] For the synthesis of urea dipeptides, the starting thiocarbamate has to be prepared from carbonimidodithioates of an α- amino acid ester.

3.4 Synthesis of carbonimidodithioic acid dimethyl ester (15) of (S)- phenylalanine methyl ester (14)

The carbinimidodithioate **15** was prepared by the usual procedure[34] with appropriate modification. Thus (S)- phenylalanine methyl ester hydrochloride **14** was condensed with carbon disulfide in the presence of triethylamine as the base in dichloromethane. Subsequent bismethylation with methyl iodide gave the product **15** as a colourless oil in 90% yield(Scheme 34).

Scheme 34



14 **15**

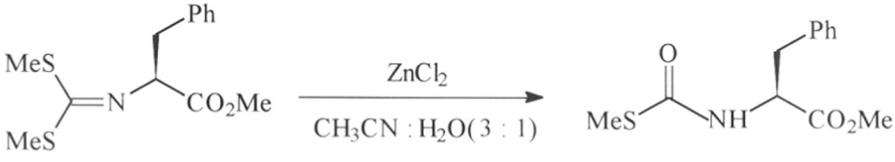
The ^{1}H NMR spectrum of **15** showed three singlets at 2.35, 2.40 and 3.70δ corresponding respectively to SCH_3, SCH_3 and OCH_3. A doublet at 3.15 (d, 2H) for CH_2 and two multiplets at 4.70(m, 1H), 7.30(m, 5H) corresponding to NCH and aromatic protons respectively. Further support to the structure was provided by the mass spectrum which showed the molecular ion (M^+) peak at m/z 283. The above data proved the structure of the product to be **15**.

3.5 Hydrolysis of the carbonimidodithioate (15) to the methyl (S)-N-(methylthiocarbonyl) phenylalanine (16)

The hydrolysis of carbonimidodithioate **15** into S-methyl thiocarbamate **16** was performed as before in the presence of $ZnCl_2$ catalyst in acetonitrile-water (3:1) solution. Thus $ZnCl_2$ and carbonimidodithioate were taken in acetonitrile-water (3:1) and stirred at 80 °C for 12h, to give methyl (S)- N-(methylthiocarbonyl) phenylalaninate in 72%

yield as a low melting solid(Scheme 35). The structure of the product was confirmed from its spectral data. The ^{1}H NMR spectrum of **16** showed a sharp singlet at 2.35δ due to the SCH_3, followed by a doublet at 3.10δ (d, 2H, J = 8.5Hz) for $PhCH_2$ protons, a sharp singlet at 3.70δ due to the OCH_3 and a quartet at 4.90δ(q, 1H, J = 7.2Hz) corresponding to NCH proton. NH proton appears as a broad peak at 5.95δ and the aromatic protons were seen as a multiplet at 7.30δ. The mass spectrum showed the molecular ion (M^+) peak at m/z 253. The above data proved the structure of the product to be **16**(Figure 29).

Scheme 35



15 **16**

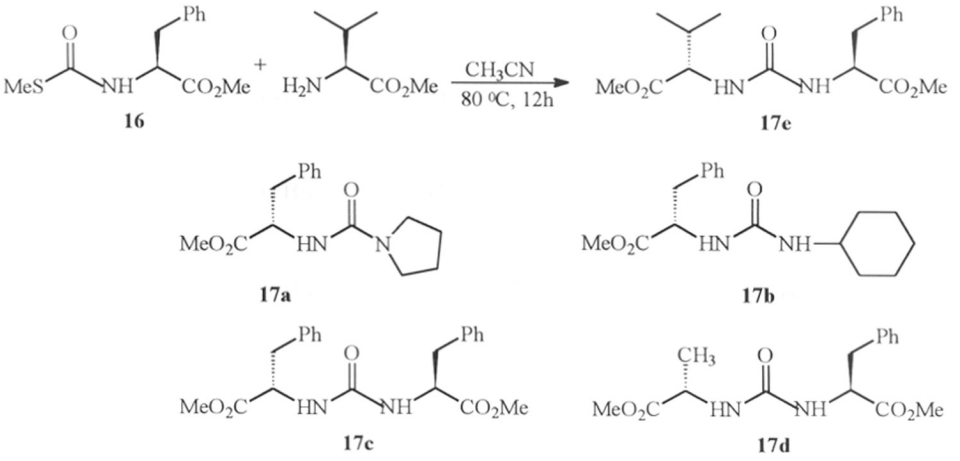
3.6 Synthesis of urea derivatives (17a-b) and urea dipeptides (17c-e) from S-methyl thiocarbamate (16)

The S- methyl thiocarbamate **16** was transformed into urea derivatives (**17a-b**) and urea dipeptides (**17c-e**) by a similar procedure as described above. This thiocarbamate **16** reacts with primary and secondary amines at 30 °C, but with α- amino acid esters, the reaction proceeds only at 80 °C. For example S-methyl thiocarbamte **16** (1eq) and freshly prepared (S)- valine methyl ester (2eq) were taken in acetonitrile and stirred at 80 °C for 12h to give the urea dipeptide **17e** in 79% yield(Scheme 36). The structure of the product was proved from the spectral data. The ^{1}H NMR spectrum of **17e** showed two doublets at 0.80δ (d, 3H) and 0.90δ (d, 3H) for the isopropyl group followed by a multiplet at 2.10δ for the CH of the isopropyl, a triplet at 3.00δ (t, 2H, J = 7.2Hz) due to the $PhCH_2$, a sharp singlet for the two methoxy groups at 3.60δ, a doublet

of doublet at 4.40δ (dd, 1H, J = 6.0, 8.0Hz) for the NCH, and a quartet at 4.80δ (q, 1H, J = 7.0Hz) corresponding to NCH-CH_2Ph. The two NH protons appeared as a broad peak at 5.40δ and 5.60δ followed by a multiplet at 7.15 for the aromatic protons. The mass spectrum of the product showed the molecular ion (M^+) peak at m/z 336. The above data proved the structure of the product to be **17e**(Figure 35). By a similar procedure other urea derivatives(**17a-b**) and urea dipeptides (**17c-d**) were prepared and characterised from their spectral data(**17b**- Figure 33: **17d**- Figure 34: **17e**- Figure 35). Isolated and purified yields of urea derivatives (**17a-b**) and urea dipeptides (**17c-e**) are given in

Table 2.

Scheme 36

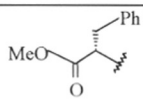
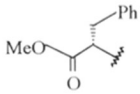
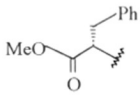
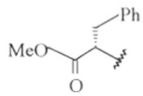
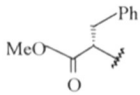
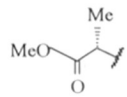
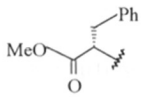
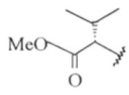


It is obvious that for the preparation of urea dipeptides, it would be preferable to consume just one equivalent of the second amino acid ester. Accordingly, freshly prepared methyl esters of (S)- phenylalanine (1eq), (S)- alanine and (S)- valine were reacted with the thiocarbamate (**16**) derived from (S)- phenylalanine methyl ester. The products **17c-e** were obtained in marginally lower yields, 75, 77, and 75% respectively.

Table 1. Isolated and purified yields of urea derivatives $R^1NHCONR^2R^3$ (**13**)

Product (**13**)	R^1	R^2	R^3	conditions	Yeld (%)
a	n-Bu	H	n-Pr	30 °C, 8h	80
b	n-Bu	H	allyl	30 °C, 10h	76
c	n-Bu	H	$PhCH_2$	30 °C, 12h	75
d	n-Bu	H	Ph-CH(Me)-	30 °C, 12h	73
e	n-Bu	H	cyclohexyl	30 °C, 10h	82
f	n-Bu	H	Ph	80 °C, 12h	60
g	n-Bu	Me	Ph	80 °C, 12h	63
h	n-Bu	- (CH_2)$_4$ -		30 °C, 6h	89
i	n-Bu	- (CH_2)$_5$ -		30 °C, 6h	89
j	n-Bu	- $CH_2CH_2OCH_2CH_2$ -		30 °C, 10h	64
k	n-Bu	Et	Et	30 °C, 10h	78
l	n-Bu	i-Pr	i-Pr	30 °C, 10h	67
m	n-Bu	n-Bu	n-Bu	30 °C, 8h	72

Table 2. Isolated and purified yields of urea derivatives $R^1NHCONR^2R^3$ (**17**)

17	R^1	R^2	R^3	conditions	yield(%)
a		- (CH_2)$_4$ -		30 °C, 6h	69
b		H	cyclohexyl	30 °C, 8h	85
c		H		80 °C, 12h	79
d		H		80 °C, 12h	81
e		H		80 °C, 12h	79

4. Conclusion

• S- Methyl thiocarbamate **12** gave di- or trisubstituted ureas(**13a-m**) on reaction with primary or secondary amines.

• S- Methyl thiocarbamate **16** derived from (S)- phenylalanine methyl ester gave urea derivatives(**17a,b**) on reaction with amines and gave urea dipeptides(**17c-e**) on reaction with α- amino acid methyl esters.

Experimental

General

General experimental techniques which have been described in the experimental section of Chapter 2 were followed.

Synthesis of Carbonimidodithioates (11 & 15)

General procedure for the synthesis of these compounds has been given in Chapter 3.

Hydrolysis of carbonimidodithioates (11 & 15) to S-methyl thiolcarbamates (12 & 16)

Carbonimidodithioates could be converted to S-methyl thiolcarbamate by known procedure.[33] Accordingly, $ZnCl_2$ (10 mmol) was taken in acetonitrile-water (3:1) (15 ml). To that was added carbonimidodithioate (**11**) (10 mmol) in the same solvent and stirred at 80 °C for 8h. The progress of the reaction was monitored by tlc. After the complete disappearance of the starting material, the mixture was cooled and filtered through celite. The solvent was removed and the residue was taken in EtOAc (50 ml), washed thrice with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using 5-10% EtOAc- pet-ether to give S- methyl thiolcarbamate (**12**) in 73% yield. Similarly, carbonimidodithioate (**15**) was also converted to Methyl (S)-N-(methylthiocarbonyl) phenylalanine (**16**) in 72% yield.

S-Methyl N-n-butyl thiolcarbamate (12)[33]

Yield (%)	73
IR(Neat)/cm^{-1}	3309, 3012, 2960, 1654, 1525, 1438, 1379, 1215
^1H NMR ($CDCl_3$)	0.85 (t, 3H, CH_3, J = 5.7Hz), 1.35 (m, 2H, CH_2), 1.40 (quintet, 2H,

(200 MHz)	CH_2), 2.30 (s, 3H, SCH_3), 3.15 (q, 2H, NCH_2, J = 5.7Hz), 4.85 (br, 1H, NH)
MS (m/z)	147 (M+), 132, 114, 108, 88, 73, 70 (100%), 61

Methyl N-(thiomethyl carbonyl)-(S)-phenylalaninate (16)

Yield (%)	72
IR(Nujol)/cm^{-1}	3400, 1740, 1670, 1500, 1220
^1H NMR ($CDCl_3$)	2.35 (s, 3H, SCH_3), 3.10 (d, 2H, CH_2, J = 6.4Hz), 3.70 (s, 3H, OCH_3),
(200 MHz)	4.90 (q, 1H, NCH, J = 5.4Hz), 5.95 (br, 1H, NH), 7.10-7.45 (m, 5H, Ar)
^{13}C NMR($CDCl_3$)	12.04, 37.87, 52.11, 54.74, 126.88, 128.33, 129.05, 135.61, 167.72,
(50 MHz)	171.40
MS (m/z)	253 (M^+, 02%), 206, 194, 162 (100), 146, 134, 91
Analysis	Found: C, 56.77; H, 6.31; N, 5.46. $C_{12}H_{15}NO_3S$ requires C, 56.91; H, 5.92; N, 5.53%.

Synthesis of urea derivatives (13a-m) from S- methyl thiolcarbamate (12)

S-Methyl thiolcarbamate (**12**) (2 mmol) was taken in acetonitrile (5 ml), an appropriate amine (4 mmol) was added to the solution and stirred at 30 °C. The progress of the reaction was monitored by tlc. After the complete disappearance of the starting material, the solvent was removed under pressure and the mixture was taken in EtOAc (20 ml), washed with 2N HCl (1 x 10 ml) and with water (2 x 10 ml), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude compound was purified by column chromatography using 35-40% EtOAc : pet-ether to

give the urea derivative (**13a-m**) in 60-89% yield. The aromatic amines were reacted at 80 °C to give the urea derivatives.

N- (n-Butyl)-N′-(n-propyl) urea (13a)

Yield (%)	80
IR(Neat)/cm^{-1}	3332, 3180, 3051, 2945, 2821, 1630, 1533, 1435, 1329, 1215
^{1}H NMR ($CDCl_3$) (200 MHz)	0.85(t, 6H, $2CH_3$, J = 8.0Hz), 1.20-1,55(m, 6H, $3CH_2$), 3.15(q, 4H, $2NCH_2$, J = 7.3Hz), 5.25(br, 2H, 2NH)
^{13}C NMR($CDCl_3$) (50 MHz)	11.20, 13.64, 19.96, 23.48, 32.44, 39.74, 41.76, 159.63
MS (m/z)	158(M^+, 100%), 143, 129, 115, 100, 87, 73, 55
Analysis	Found: C, 60.79; H, 12.01; N, 17.76. $C_8H_{18}N_2O$ requires C, 60.75; H, 11.39; N, 17.72%.

N- (n-Butyl)-N′-allyl urea (13b)

Yield (%)	76
IR(Neat)/cm^{-1}	3342, 3130, 3084, 2960, 2873, 1633, 1573, 1465, 1379
^{1}H NMR ($CDCl_3$) (200 MHz)	0.85(t, 3H, CH_3, J = 8.0Hz), 1.25-1,55(m, 4H, $2CH_2$), 3.15(q, 2H, NCH_2, J = 7.2Hz), 4.80(t, 2H, NCH_2, J = 6.5Hz), 5.05-5.20(m, 2H, $=CH_2$), 5.35(br, 2H, 2NH), 5.85(m, 1H, -CH=)
^{13}C NMR($CDCl_3$) (50 MHz)	13.31, 19.66, 32.04, 39.67, 42.31, 114.62, 135.39, 159.27
MS (m/z)	156(M^+), 141, 127, 113, 99, 85, 57(100%)
Analysis	Found: C, 61.17; H, 10.81; N, 17.67. $C_8H_{16}N_2O$ requires C, 61.53; H, 10.45; N, 17.94%.

N- (n-Butyl)-N′-benzyl urea (13c)

Yield (%)	75
IR(Neat)/cm^{-1}	3350, 3018, 2960, 2873, 1629, 1577, 1498, 1454, 1936
^1H NMR ($CDCl_3$) (200 MHz)	0.85(t, 3H, CH_3, J = 8.0Hz), 1.20-1,50(m, 4H, $2CH_2$), 3.05(q, 2H, NCH_2, J = 7.5Hz), 4.30(d, 2H, $PhCH_2$, J = 7.1Hz), 5.10(br, 1H, NH), 5.45(br, 1H, NH), 7.25(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	13.72, 19.97, 32.36, 39.78, 43.66, 126.67, 126.81, 128.24, 139.92, 159.63
MS (m/z)	206(M^+), 177, 164, 149, 132, 106,(100%), 91, 77
Analysis	Found: C, 69.94; H, 9.31; N, 13.43. $C_{12}H_{18}N_2O$ requires C, 69.90; H, 8.73; N, 13.59%.

N- (n-Butyl)-N′-(α- methylbenzyl) urea (13d)

Yield (%)	73
IR(Neat)/cm^{-1}	3332, 3028, 2996, 2870, 1630, 1566, 1450, 1250
^1H NMR ($CDCl_3$) (200 MHz)	0.90(t, 3H, CH_3, J = 8.0Hz), 1.15-1,40(m, 4H, $2CH_2$), 1.45(d, 3H, $CH\underline{CH_3}$, J = 7.3Hz), 3.05(q, 2H, NCH_2, J = 7.2Hz), 4.75(t, 1H, $\underline{CH}CH_3$, J = 7.3Hz), 5.00(br, 1H, NH), 5.45(br, 1H, NH), 7.30(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	13.88, 20.12, 23.39, 32.54, 39.92, 49.42, 125.86, 126.74, 128.43, 145.26, 158.90
MS (m/z)	220(M^+), 205, 177, 147, 132, 120, 106(100%), 77
Analysis	Found: C, 71.08; H, 9.78; N, 12.62. $C_{13}H_{20}N_2O$ requires C, 70.87; H, 9.18; N, 12.71%.

N- (n-Butyl)-N′-cyclohexyl urea (13e)

Yield (%)	81
IR(Neat)/cm^{-1}	3334, 2931, 2856, 1624, 1569, 1450, 1315, 1253, 1217
^1H NMR ($CDCl_3$) (200 MHz)	0.90(t, 3H, CH_3, J = 8.1Hz), 1.10-1,80(m, 14H, $7CH_2$), 3.10(q, 2H, NCH_2, J = 7.4Hz), 3.50(m, 1H, CH), 4.75(br, 2H, 2NH)
^{13}C NMR($CDCl_3$) (50 MHz)	13.64, 20.01, 24.93, 25.56, 32.56, 33.85, 39.73, 48.73, 158.85
MS (m/z)	198(M^+), 169, 156, 137, 117, 99, 70, 56(100%)
Analysis	Found: C, 66.56; H, 12.04; N, 14.09. $C_{11}H_{22}N_2O$ requires C, 66.66; H, 12.11; N, 14.14%.

N- (n-Butyl)-N′-phenyl urea (13f)

Yield (%)	60
IR(Neat)/cm^{-1}	3750, 2962, 2933, 1631, 1529, 1487, 1368, 1217
^1H NMR ($CDCl_3$ + DMSO-d_6) (200 MHz)	0.90(t, 3H, CH_3, J = 8.0Hz), 1.20-1.50(m, 4H, $2CH_2$), 3.10(q, 2H, NCH_2, J = 7.2Hz), 5.57(br, 1H, NH), 6.9-7.40(m, 5H, Ar), 7.80(br, 1H, NH)
^{13}C NMR(DMSO-d_6) (50 MHz)	19.30, 25.29, 37.67, 44.51, 123.45, 126.64, 134.23, 146.33, 161.09
MS (m/z)	192(M^+), 169, 157, 135, 119, 93(100%), 77, 65, 57
Analysis	Found: C, 68.93; H, 8.30; N, 14.38. $C_{11}H_{16}N_2O$ requires C, 68.72; H, 8.38; N, 14.57%.

N- (n-Butyl)-N′-methyl-N′-phenyl urea (13g)

Yield (%)	63
IR(Neat)/cm^{-1}	3383, 3019, 2868, 1655, 1552, 1440, 1316, 1215
^1H NMR ($CDCl_3$) (200 MHz)	0.90(t, 3H, CH_3, J = 8.0Hz), 1.20-1,50(m, 4H, $2CH_2$), 3.10(q, 2H, NCH_2, J = 7.4Hz), 3.30(s, 3H, NCH_3), 4.30(br, 1H, NH), 7.20-7.50(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	13.25, 19.49, 31.81, 36.54, 40.00, 126.52, 126.63, 129.39, 143.20, 156.54
MS (m/z)	206(M^+), 177, 157, 134, 107(100%), 91, 77, 57
Analysis	Found: C, 70.27; H, 9.08; N, 13.53. $C_{12}H_{18}N_2O$ requires C, 69.90; H, 8.73; N, 13.549%.

N- (n-Butyl)-N′- tetramethylene urea (13h)

Yield (%)	89
IR(Neat)/cm^{-1}	3305, 2959, 2931, 2872, 1659, 1528, 1465
^1H NMR ($CDCl_3$) (200 MHz)	0.90(t, 3H, CH_3, J = 8.0Hz), 1.25-1,60(m, 4H, $2CH_2$), 1.85-1.95(m, 4H, $2CH_2$), 3.15-3.45(m, 6H, NCH_2, CH_2NCH_2), 4.20(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	13.64, 19.89, 25.37, 32.44, 40.19, 45.33, 156.79
MS (m/z)	170(M^+), 141, 127, 114, 98, 70(100%)
Analysis	Found: C, 62.89; H, 10.25; N, 15.39. $C_9H_{18}N_2O$ requires C, 63.15; H, 10.58; N, 15.47%.

N- (n-Butyl)-N′- pentamethylene urea (13i)

Yield (%)	89
IR(Neat)/cm^{-1}	3300, 3005, 2945, 2895, 1663, 1515, 1500, 1470
^1H NMR ($CDCl_3$) (300 MHz)	0.90(t, 3H, CH_3, J = 8.0Hz), 1.25-1,70(m, 10H, $5CH_2$), 3.20-3.40(m, 4H, CH_2NCH_2), 4.40(br, 1H, NH)
^{13}C NMR($CDCl_3$) (300 MHz)	13.17, 19.47, 23.86, 25.03, 31.83, 39.98, 44.12, 157.46
MS (m/z)	184(M^+), 155, 128, 112, 100, 84(100%), 69, 56
Analysis	Found: C, 65.60; H, 10.98; N, 14.95. $C_{10}H_{20}N_2O$ requires C, 65.21; H, 10.86; N, 15.21%.

N- (n-Butyl)-N′-[bis(bismethylene)]oxo urea (13j)

Yield (%)	64
IR(Neat)/cm^{-1}	3349, 2959, 2930, 2898, 1640, 1628, 1547, 1456
^1H NMR ($CDCl_3$) (200 MHz)	0.88 (t, 3H, CH_3, J = 8.0Hz), 1.20-1.45(m, 4H, $2CH_2$), 3.10(q, 2H, NCH_2, J = 7.5Hz), 3.25(t, 4H, CH_2NCH_2 J = 7.5), 3.55(t, 4H, CH_2OCH_2, J = 7.5Hz), 5.00(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	13.57, 19.82, 32.10, 40.37, 43.82, 66.31, 158.05
MS (m/z)	186(M^+), 171, 155, 143, 129, 114, 100, 70, 57(100%)
Analysis	Found: C, 58.02; H, 10.33; N, 15.01. $C_9H_{18}N_2O_2$ requires C, 58.06; H, 9.67; N, 15.05%.

N- (n-Butyl)-N′, N′- diethyl urea (13k)

Yield (%)	78
IR(Neat)/cm^{-1}	3491, 9274, 2874, 1623, 1571, 1370, 1302, 1215
^1H NMR ($CDCl_3$) (200 MHz)	0.85(t, 3H, CH_3, J = 8.0Hz), 1.10(t, 6H, $2CH_3$, J = 8.2Hz), 1.20-1.50(m, 4H, $2CH_2$), 3.15(m, 6H, NCH_2, CH_2NCH_2), 4.35(br, 1H, NH)
^{13}C NMR($CDCl_3$) (50 MHz)	12.77, 19.16, 64.39, 39.81, 156.65
MS (m/z)	172(M^+), 157, 143, 129, 100, 87, 72(100%), 58
Analysis	Found: C, 62.64; H, 11.92; N, 16.09. $C_9H_{20}N_2O$ requires C, 62.79; H, 11.62; N, 16.51%.

N- (n-Butyl)-N′, N′- diisopropyl urea (13l)

Yield (%)	67
IR(Neat)/cm^{-1}	3354, 2931, 2873, 1624, 1530, 1419, 1367
^1H NMR ($CDCl_3$) (200 MHz)	0.85(t, 3H, CH_3, J = 8.0Hz), 1.20(d, 12H, $4CH_3$, J = 8.5Hz), 3.20(q, 2H, NCH_2, J = 7.2Hz), 3,70(m, 2H, 2CH), 4.20(br, 1H, NH)
^{13}C NMR($CDCl_3$) (75 MHz)	13.28, 19.73, 20.87, 31.95, 39.85, 44.42, 156.82
MS (m/z)	200(M^+), 185, 157, 128, 86(100%), 70, 58
Analysis	Found: C, 65.90; H, 11.84; N, 13.52. $C_{11}H_{24}N_2O$ requires C, 66.00; H, 12.00; N, 14.00%.

N- (n-Butyl)-N′, N′- di(n-butyl) urea (13m)

Yield (%)	72
IR(Neat)/cm^{-1}	3346, 2931, 1624, 1537, 1492, 1465, 1375, 1292
^1H NMR ($CDCl_3$) (200 MHz)	0.90(t, 9H, $3CH_3$, J = 8.1Hz), 1.20-1,70(m, 12H, $6CH_2$), 3.20(q, $3NCH_2$, J = 7.5), 4.30(br, 1H, NH)
^{13}C NMR($CDCl_3$) (75 MHz)	13.10, 19.52, 30.24, 31.99, 39.97, 46.33, 157.29
MS (m/z)	228(M^+), 185, 156, 126, 100, 86(100%), 57
Analysis	Found: C, 68.47; H, 12.47; N, 12.00. $C_{13}H_{28}N_2O$ requires C, 68.42; H, 12.28; N, 12.28%.

Synthesis of urea derivatives (17a-b) and urea dipeptides (17c-e) from Methyl (S)-N-(Methylthiolcarbonyl) phenylalaninate (16)

S-Methyl thiolcarbamate (**16**) (2 mmol) was taken in acetonitrile (5 ml), an appropriate amine or an α- amino acid methyl ester (4 mmol) was added to the solution and stirred at 30 °C. The progress of the reaction was monitored by tlc. After the complete disappearance of the starting material, the solvent was removed under pressure and the mixture was taken in EtOAc (20 ml), washed with 2N HCl (1 x 10 ml) and with water (2 x 10 ml), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude compound was purified by column chromatography using 35-40% EtOAc : pet-ether to give the urea derivative (**17a-b**) or urea dipeptide (**17 c-e**). The amino acid estrers were reacted at 80 °C to give the urea dipeptides.

Urea derivative (17a)

Yield (%)	69
IR(Neat)/cm^{-1}	3379, 2976, 2952, 1730, 1639, 1521, 1487, 1338, 1201
^1H NMR ($CDCl_3$) (200 MHz)	1.80-2.10(m, 4H, $2CH_2$), 3.10(d, 2H, CH_2, J = 8.3Hz), 3.20-3.40(m, 4H, CH_2NCH_2), 3.70(s, 3H, OCH_3), 4.60(br, 1H, NH), 4.80(q, 1H, NCHCO, J = 7.5Hz), 7.10-7.40(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (75 MHz)	24.82, 37.87, 44.83, 51.30, 53.71, 126.21, 127.77, 128.62, 136.03, 155.30. 172.61
MS (m/z)	276(M^+), 252, 228, 217, 185, 162, 146, 131, 114, 98(100%), 86, 77
Analysis	Found: C, 65.19; H, 7.76; N, 10.20. $C_{15}H_{20}N_2O_3$ requires C, 65.21; H, 7.24; N, 10.14%.

Urea derivative (17b)

Yield (%)	85
IR(Neat)/cm^{-1}	3372, 3018, 2933, 1641, 1552, 1450, 1352, 1215
^1H NMR ($CDCl_3$) (300 MHz)	1.00-1.40(m, 6H, $3CH_2$), 1.50-1.95(m, 4H, $2CH_2$), 3.00(d, 2H, $PhCH_2$, J = 8.0Hz), 3.40(m, 1H, NCH), 3.65(s, 3H, OCH_3), 4.70(q, 1H, NCHCO, J = 7.5Hz), 5.15(d, 1H, NH, J = 10Hz), 7.10-7.40(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (300 MHz)	24.19, 25.06, 33.03, 38.14, 47.96, 50.99, 53.63, 125.96, 127.62, 128.69, 136.30, 156.79, 172.64
MS (m/z)	304(M^+), 284, 272, 258, 245, 213, 191, 162, 142, 120, 99, 88(100%), 77
Analysis	Found: C, 67.04; H, 8.30; N, 9.31. $C_{17}H_{24}N_2O_3$ requires C, 67.10; H, 7.89; N, 9.21%.

Urea dipeptide (17c)

Yield (%)	79
IR(Neat)/cm^{-1}	3343, 2945, 2895, 1732, 1632, 1515, 1505, 1475, 1364, 1219
^1H NMR ($CDCl_3$) (200 MHz)	3.00(d, 4H, $2PhCH_2$, J = 8.0Hz), 3.60(s, 6H, $2OCH_3$), 4.80(q, 2H, 2NCHCO, J = 7.5), 5.65(d, 2H, 2NH, J = 9.4Hz), 7.10-7.40(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (75 MHz)	38.19, 51.90, 54.10, 125.98, 127.75, 128.91, 136.62, 156.98, 173.01
MS (m/z)	384(M^+), 352, 320, 293, 264, 222, 190, 162(100%), 146, 130,99,77
Analysis	Found: C, 65.89; H, 6.61; N, 7.62. $C_{21}H_{24}N_2O_5$ requires C, 65.62; H, 6.25; N, 7.29%.

Urea dipeptide (17d)

Yield (%)	81
IR(Neat)/cm^{-1}	3370, 2969, 2947, 1729, 1628, 1517, 1480, 1335, 1200
^1H NMR ($CDCl_3$) (200 MHz)	1.15(d, 3H, CH_3, J = 8.2Hz), 3.00(d, 2H, $PhCH_2$, J = 7.5Hz), 3.70(s, 3H, OCH_3), 4.41(m, 1H, NCHCO), 4.80(q, 1H, NCHCO, J = 7.3Hz), 5.40(d, 1H, NH, J = 9.0Hz) 5.50(d, 1H, NH, J = 9.0Hz), 7.10-7.40(m, 5H, Ar)
^{13}C NMR($CDCl_3$) (50 MHz)	18.73, 38.68, 48.67, 52.06, 52.27, 54.04, 126.85, 128.36, 129.42, 136.29,156.78, 173.38, 174.94
MS (m/z)	308(M^+), 276, 249, 217, 189, 162(100%), 145, 131, 102, 77
Analysis	Found: C, 59.08; H, 6.89; N, 9.53. $C_{15}H_{20}N_2O_5$ requires C, 58.44; H, 6.49; N, 9.09%.

Urea dipeptide (17e)

Yield (%)	79
IR(Neat)/cm^{-1}	3326, 2956, 2860, 1732, 1638, 1595, 1475, 1352, 1217
^1H NMR ($CDCl_3$) (300 MHz)	0.80(d, 3H, CH_3 J = 8.0Hz), 0.90(d, 3H, CH_3 J = 8.0 Hz), 2.10(m, 1H, CH), 3.0(t, 2H, NCH_2, J = 7.0Hz), 3.60(s, 6H, $2OCH_3$), 4.40(dd, 1H, NCH J = 8.9, 7.0Hz), 4.80(q, 1H, J = 8.0), 5.4(d, NH, J = 8.0Hz), 5.6(d, NH, J = 8.0Hz), 7.0-7.30(m, 5H
^{13}C NMR($CDCl_3$) (50 MHz)	174.58, 73.53, 157.20, 136.43, 129.66, 128.61, 127.13,58.13, 54.27, 52.32, 39.12, 31.78, 19.20, 18.00
MS (m/z)	336(M^+), 304, 277, 245, 233, 202, 191,175,162(100%), 146, 130, 115.
Analysis	Found: C, 60.99; H, 7.57; N, 8.23. $C_{17}H_{24}N_2O_5$ requires C, 60.71; H, 7.14; N, 8.23%.

References

1. T. P. Vishnyakova, I. A. Glubeva andE. N. Glebova, *Russ.Chem. Rev.(Engl. Trans)*. **1985**, *54*, 249.
2. E. M. Beyer, M. F. Duffy, J. V. Hay, D. D. Schlueter in *Herbicides: Chemistry, Degradation and Mode of action*, Ed. P. C. Kearney and D. D. Kautman, Marcel Dekker, New York, **1988**, Vol. *3*, p117.
3. E. Mutschler, *Arzneimittelwirkungen*, 7th edn, Wissenchaffliche Verlagagesell Schaft, Stuttgart, **1996**.
4. K. Matsuda, *Med. Chem. Rev.*, **1994**, *14*, 271.
5. D. J. Kempf, K. C. Marsh, D. A. Paul, M. F. Knigge, D. W. Nerbeck. W. E. Kohlbenner, L. Codacovi, S. Vasavanonda, P. Bryant, X. C. Wang, N. E. Wideburg, J. J. Clement, J. J. Plattner and Erickson, *J. Antimoicrob. Agents. Chemother.*, **1991**, *35*, 2209.
6. D. P Getman, G. A. Decrescenzo, R. M. Heintz, K. L. Reed, J. J. talley, M. L. Bryant, M. Clare, K. A. Houseman, J. J. Marr, R. A. Mueller, M. L. Vazquer, H.-S. Shieh, W. C. Stallings and R. A. Stegemann, *J. Med. Chem.*, **1993**, *36*, 288.
7. S. Stefanelli, L. Cavoletti, E. Sarubbi, E. Ragg, L. Colombo and E. Selva, *J. Antibiot.*, **1995**, 48, 332.
8. U. Petersen, In *Methoden der Organishen Chemie*, Houben-weyl, E 4; G. Thieme Verlag; New York, **1983**, p334.
9. H. J. Knolker, T. Braxmeier and S. Schlechtingen, *Synlett.*, **1996**, 502.
10. M. K. Leung, J. -L. Lai, H. -K. Lau, H. -h. Yu and H. J. Hsiao, *J. Org. Chem.*,**1996**, *61*, 4175.
11. J. Izdebski and D. Pawlak, *Synthesis*, **1989**, 423.
12. K. Takeda and H. Ogura, *Synth. Commun.*, **1982**, *12*, 213.

13. a) H. A. Stabb, *Liebigs. Ann Chem.* **1957**, *609*, 75.

b) H. A. Stabb, *Angew. Chem. Int. Ed. Engl.*, **1962**, *1*, 351.

14. P. Majer and R. S. Randad, *J. Org. Chem.*, **1994**, *59*, 1937.

15. A. R. Katritzsky, D. P. M. Pleynet and B. Yang, *J. Org. Chem.*, **1997**, *62*, 4155.

16. R. L. Shriner, W. H. Horne and B. F. Cox., *Organic Synthses*; New York; **1994**, Vol. *2*, p 453.

17. J. S. Norwich, N. A. Powell, T. M. Ngugen and G. Noronba, *J. Org. Chem.*, **1992**, *52*, 7364.

18. A. Basha, *Tetrahedron Lett.*, **1988**, *29*, 2525.

19. M. Lamothe, M. Perez, V. Colovray-Gotteland and S. Halazy, *Synlett.*, **1996**, 507.

20. B. Thavonekham, *Synthesis*, **1997**, 1189.

21. R. Freer and A. Mc Killlop, *Synth. Commun.*, **1996**, *26*, 331.

22. N. Sonoda, T. Yasuhara, K. Konda, T. Ikeda and S. Tsutsumi, *J. Am. Chem. Soc.*, **1971**, *93*, 6344.

23. T. Tsujii, R. Takeuchi and Y. Watanabe, *J. Organomet. Chem.*, **1985**, *290*, 249.

24. P. Giannoccaro, *J. Organomet. Chem.*, **1987**, *336*, 271.

25. I. Pri-Bar, and H. Alper, *Can. J. Chem.*, **1990**, *68*, 1544.

26. N. S. Nudetman, E. S. Lewkowicz, D. G. Perez, *Synthesis*, **1990**, 917.

27. Y. Morimoto, Y. Fujiwara, H. Taniguchi, Y. Hori and N. Nagano, *Tetrahedron Lett.*, **1986**, *27*, 1809.

28. F. Fournier, C. Bruneau, P. H. Dixneaf and Lacolier, *J. Org. Chem.*, **1991**, *56*, 4456.

29. N. Yamazaki, T. Iguchi and F. Higashi, *Tetrahedron Lett.*, **1974**, 1191.

30. H. Ogura, K. Takeda, R. Tokue and T. Kobayashi, *Synthesis,* **1978**, 394.

31. S. Kotachi, Y. Tsuji, T. Konda and Watanabe, *J. Chem. Soc., Chem. Commun.*, **1990**, 549.

32. K. Ramdas and N. Janarthanam, *Synth. Commun.*, **1997**, *27*, 2357.

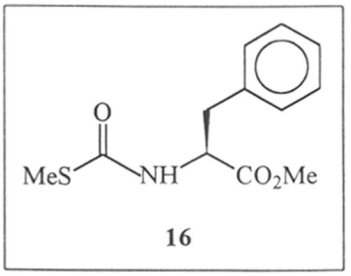
33. M. Anbazhagan, T. I. Reddy and S. Rajappa, *J. Chem. Sco., Perkin Trans 1*, **1997**, 1623.

34. a) D. Hoppe and L. Beckmann, *Liebigs. Ann chem.*, **1979**, 2066.

b) T. I. Reddy, B. M. Bhawal and S. Rajappa, *Tetrahedron*, **1993**, *49*, 2101.

35. X. Zhang, R. Rodirigcus, L. Evans, B. Hinkle, L. Ballantyne and M. Pena, *J. Org. Chem.*, **1997**, *62*, 6420.

Figure 29



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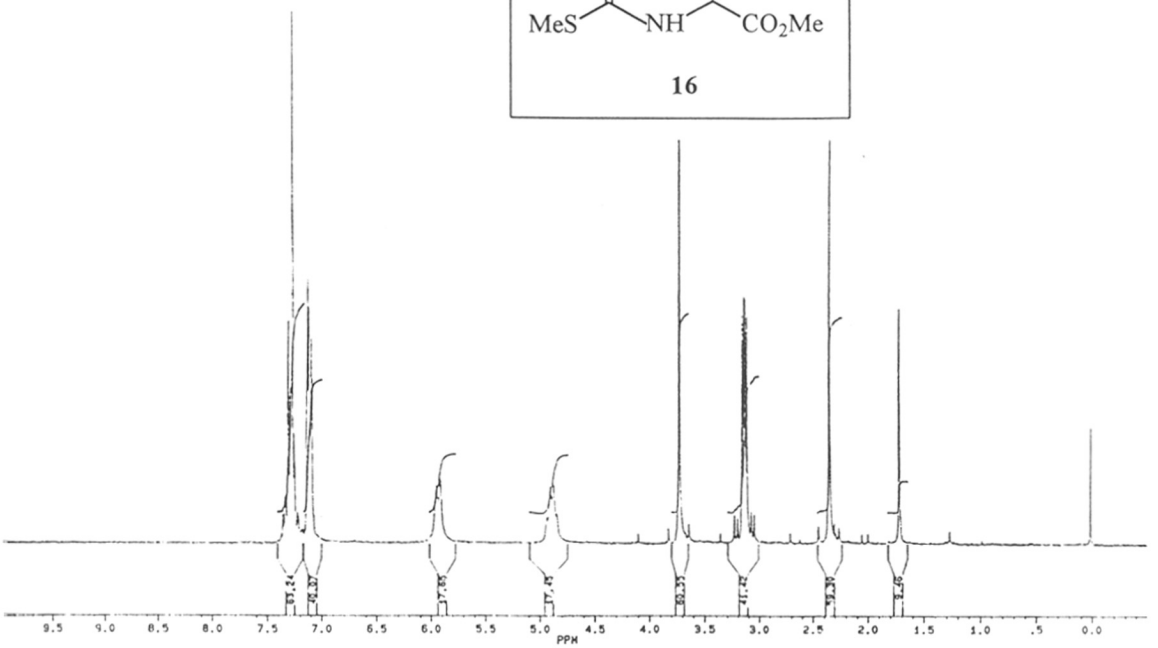

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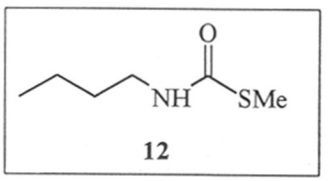

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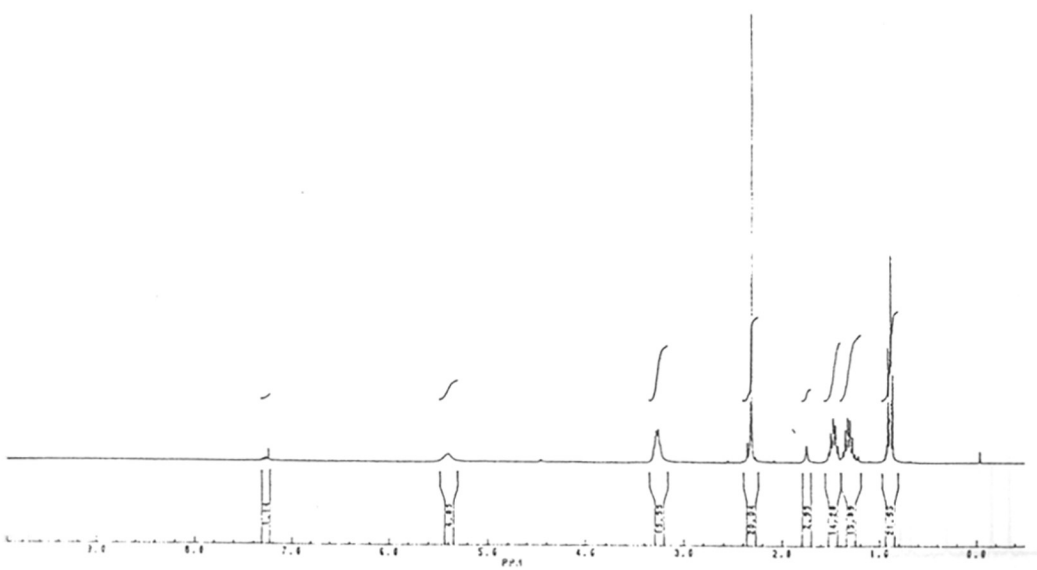

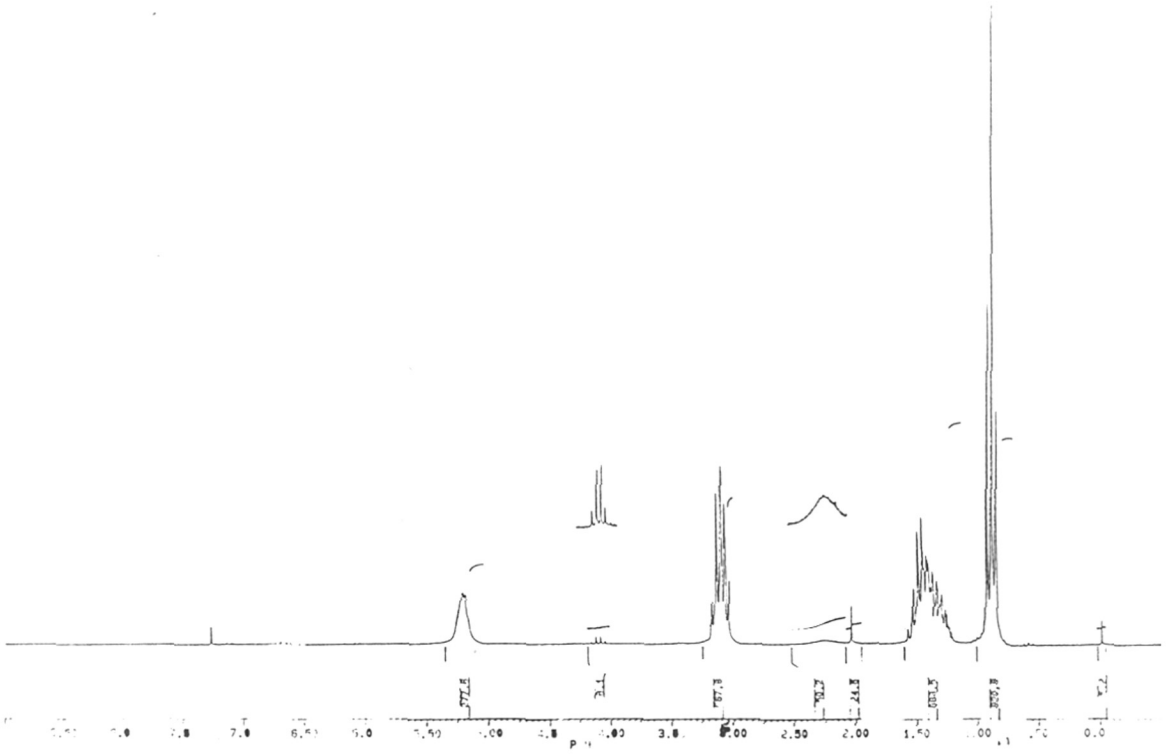

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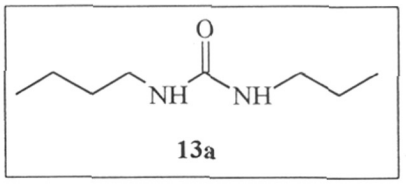

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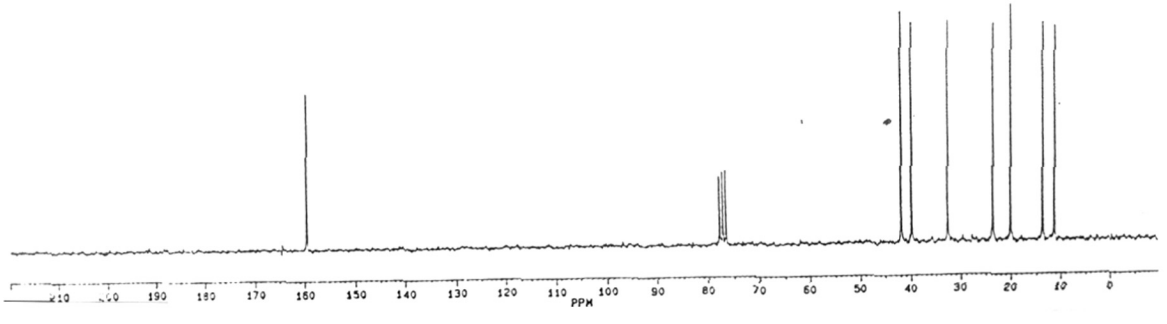

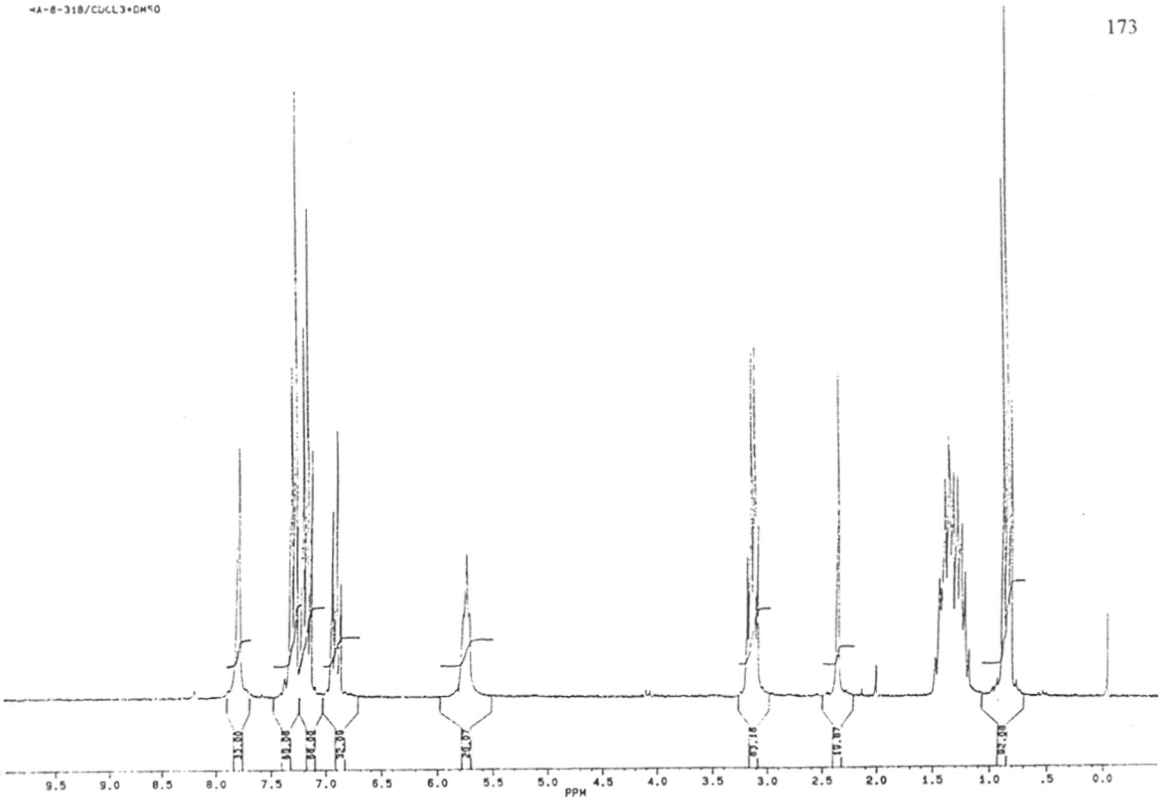

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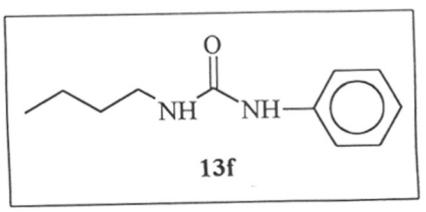

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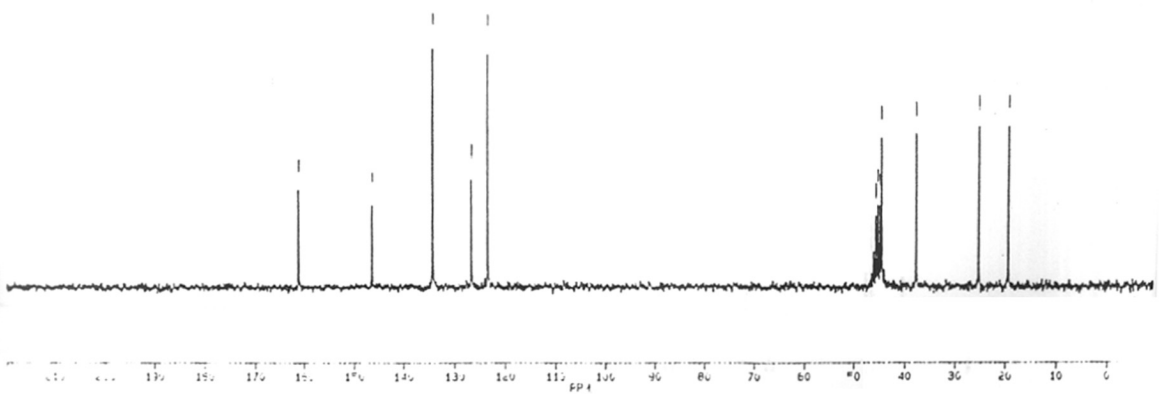


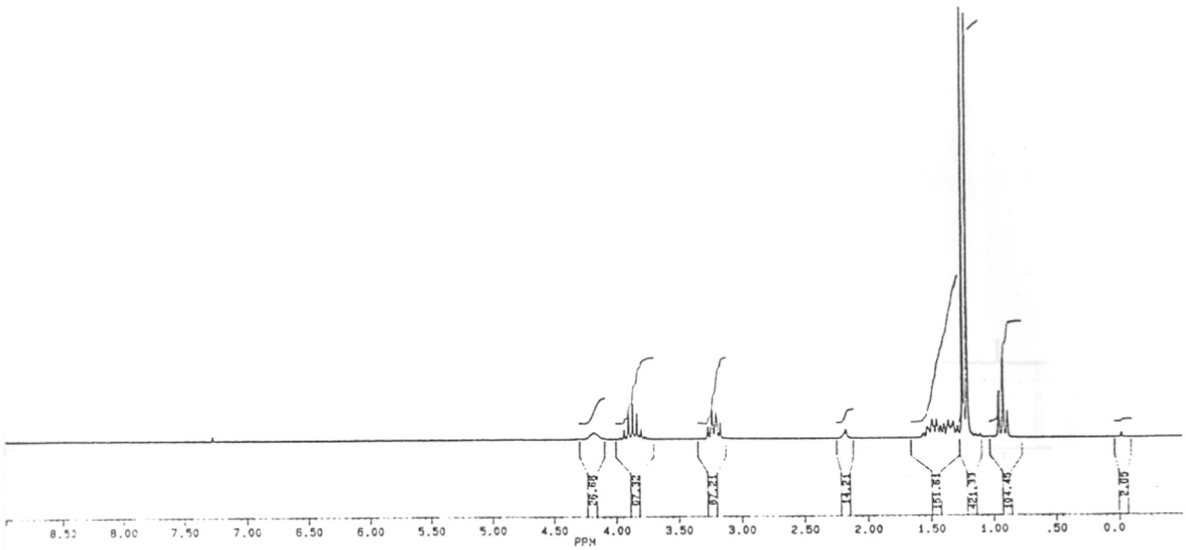
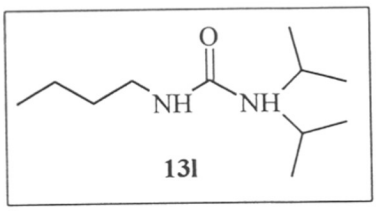


Figure 32



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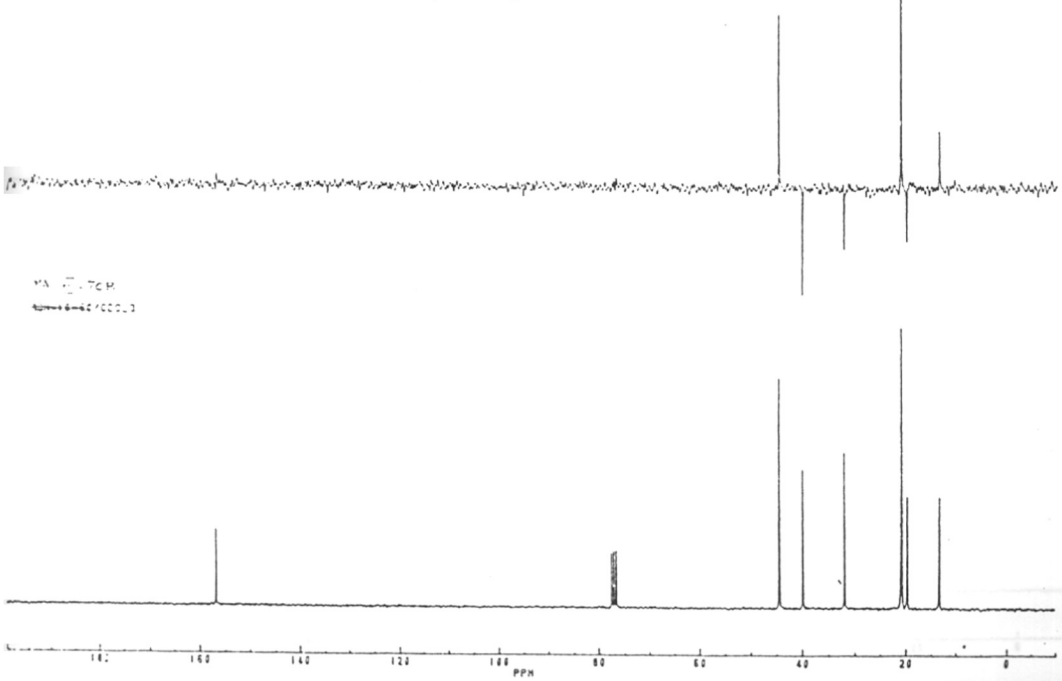

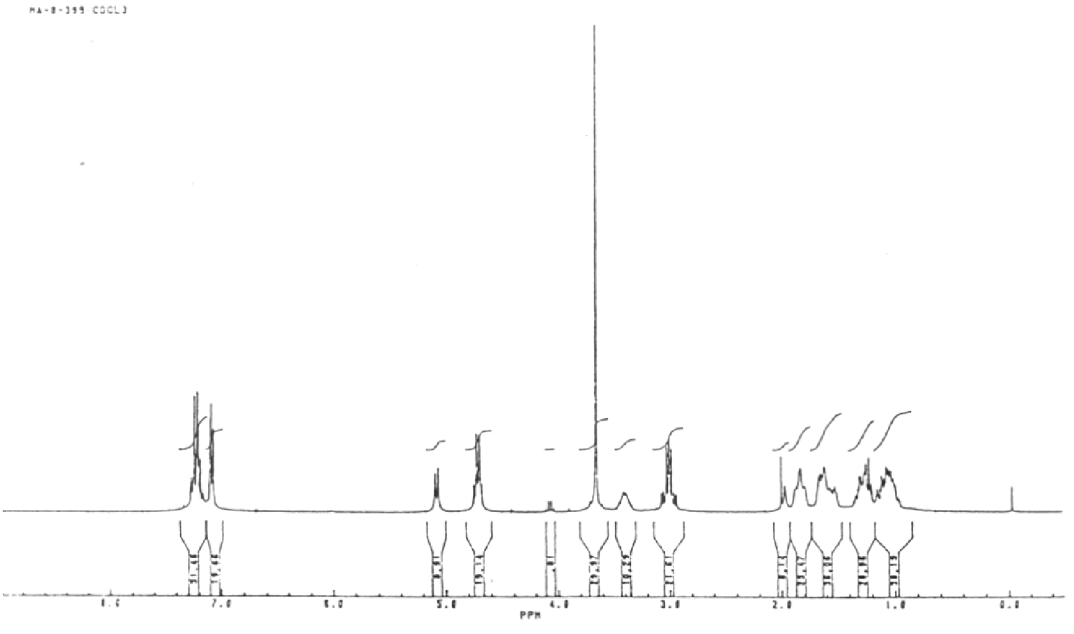

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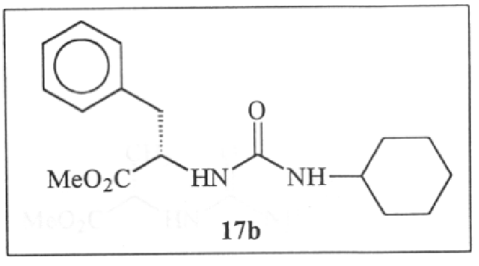

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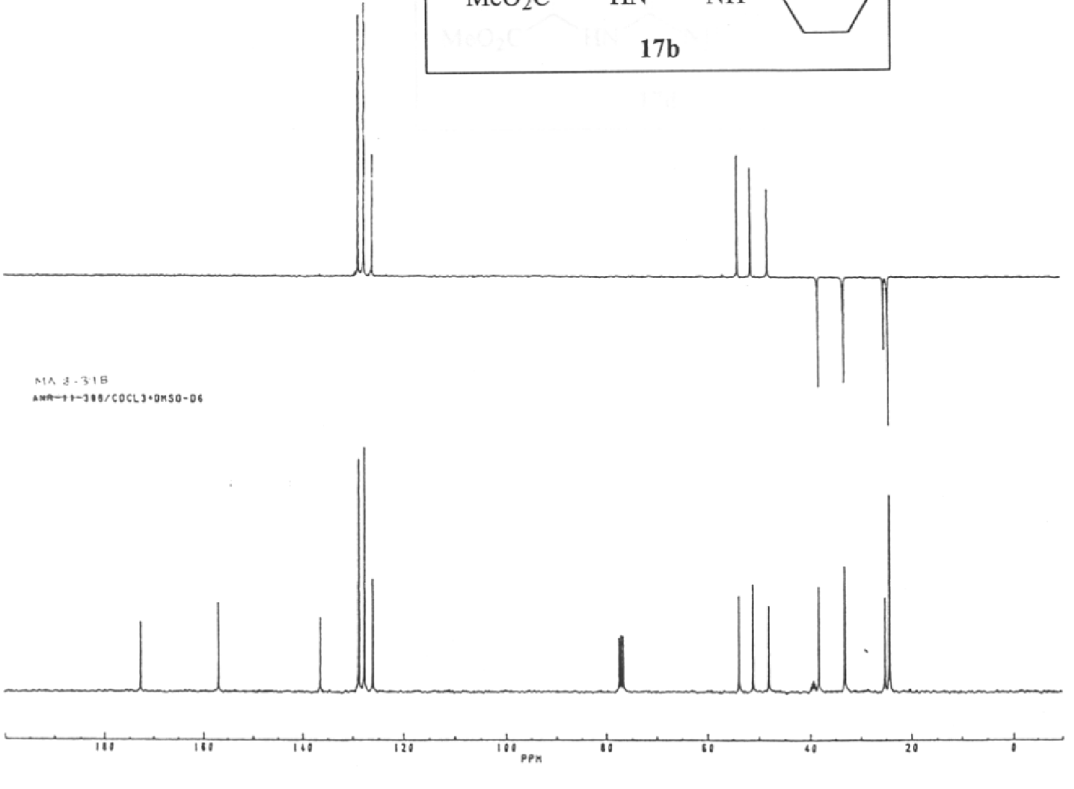

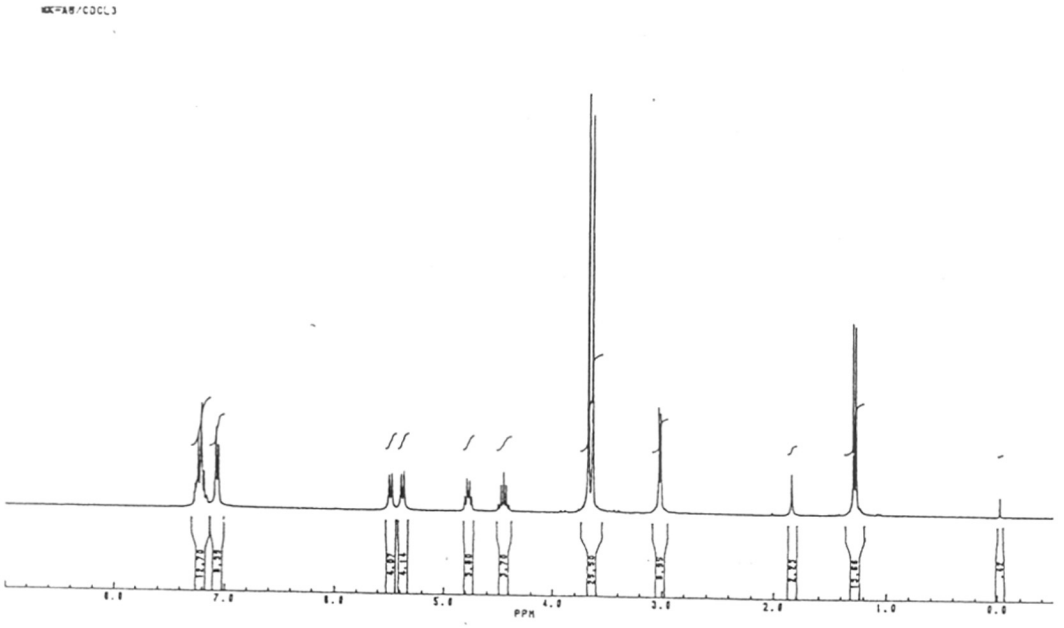

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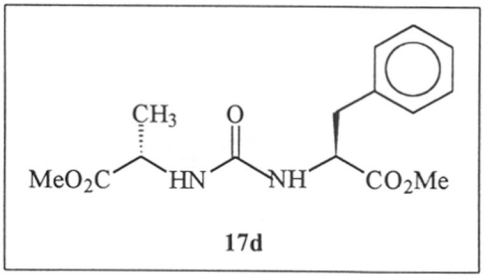

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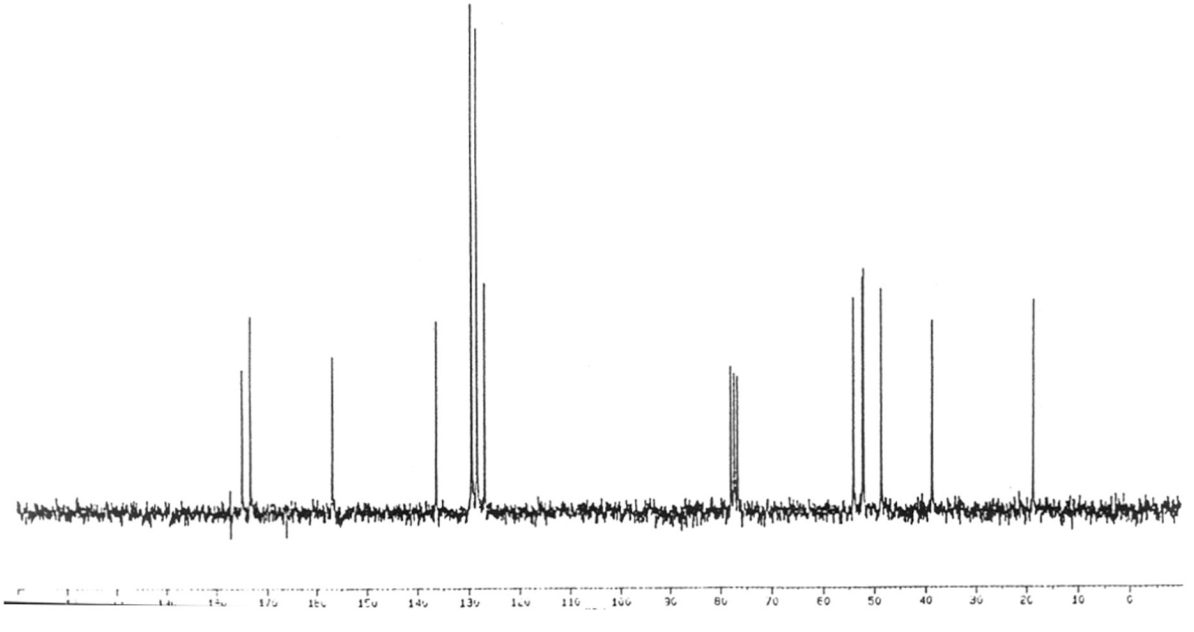

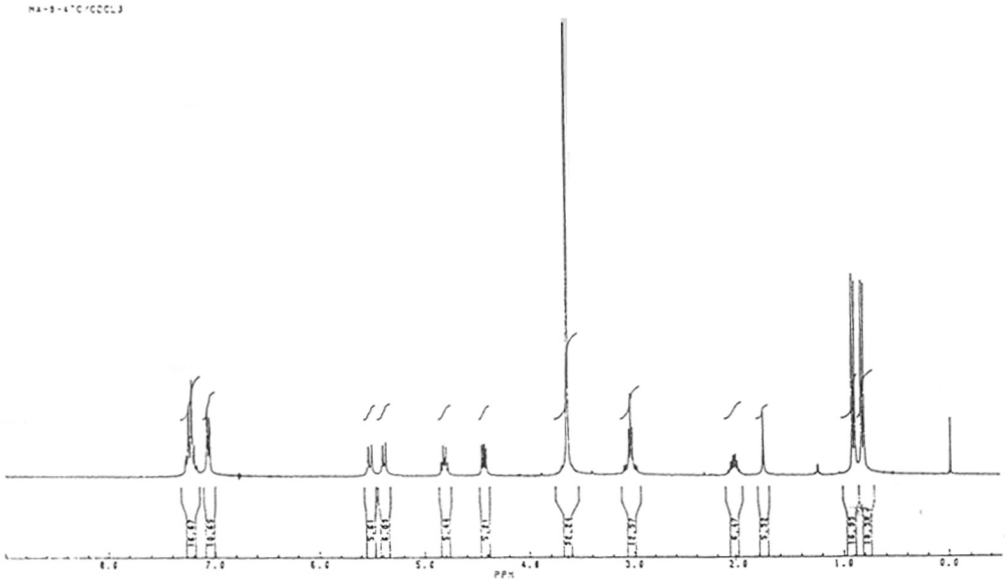

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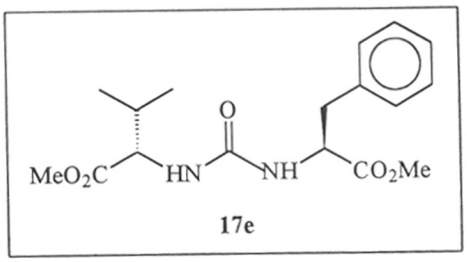

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