SYNTHETIC AND MECHANISTIC INVESTIGATIONS ON α- OXOKETENE DITHIOACETALS

BY

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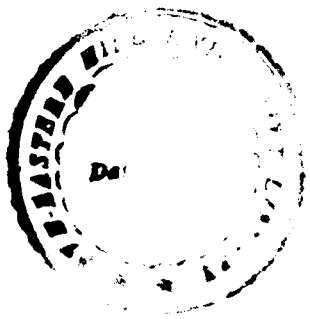

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LATE SAMIR K. SAMAL.

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July 1999

I, Sanchita Dhar do hereby declare that the subject matter of this thesis is the record of work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other University/Institute.

This is being submitted to the North-Eastern Hill University for the Ph.D. degree in Chemistry.

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" I cannot achieve anything alone. To gather ideas and build on them- I need others."

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" God is Great"

Shillong

July 1999

Sanchita Dhar

SANCHITA DHAR.

Preface

The α-oxoketene dithioacetals are versatile three carbon synthons with ambident 1,3-electrophillic centres permitting the designs of various carbocyclic and heterocyclic molecules. Our continuous interest in these class of compounds has centered around in exploiting the differential electrophilicity of 1,3-carbon centres for the regioselective construction of new C-H and C-C bonds involving either 1,2- or 1,4- nucleophilic additions leading to a number of synthetic routes for the synthesis of a wide range of organic compounds.

The work presented in this thesis has been carried out as a part of our ongoing investigations on α-oxoketene dithioacetals and their sister counterparts. The work undertaken describes the synthesis of β-oxodithioates, methyl dithiocarbamates, thioureas and also a synthetic transformation using α-oxoketene dithioacetal as the precursor.

The first chapter of this thesis provides a brief account on the general reactivity profile of α-oxoketene dithioacetals and some of the recently developed synthetic strategies employing these class of compounds.

The second chapter describes the reaction of 1-(methyldithiocarbonyl) imidazole and 3-methyl-1-(methyldithiocarbonyl)imidazolium iodide with active methylene compounds, to obtain β-oxodithioates using a new synthetic strategy.

An efficient route for the synthesis of methyl dithiocarbamates, symmetrical thioureas and unsymmetrical thioureas on reacting 1-(methyldithiocarbonyl) imidazole and 3-methyl-1-(methyldithiocarbonyl)imidazolium iodide with amines has been developed and the results of this investigation has been presented in the third chapter.

The last chapter of this thesis describes that α–oxoketene dithioacetals undergo 1,4-addition in a highly regio- and stereo- selective manner using organo zinc reagents to give β-alkyl-β-alkylthio-α,β-enones by the displacement of one methylthio group.

CONTENTS

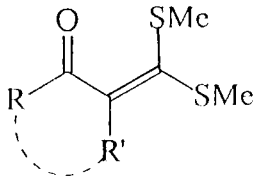
CHAPTER-I

INTRODUCTION

Study of the chemistry of α-oxoketene dithioacetals and the corresponding S,N-, N,N- and O,S-acetals has attracted increased attention in recent years because of their wide application in organic synthesis. This chapter gives a brief review and discussion on the chemistry of α-oxoketene dithioacetals in the context of their potential application to organic synthesis.

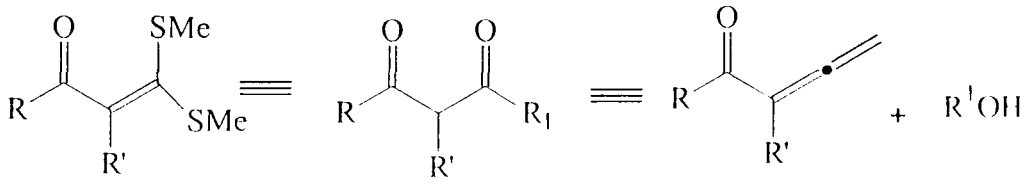
This chapter has been simplified into sections. The first section gives a brief review of α-oxoketene dithioacetals and the second section describes the present work.

Section I. α-oxoketene dithioacetals are having the structure



1

These are masked β-ketoesters in which the ester functionality is manifested as ketene dithioacetal moiety.

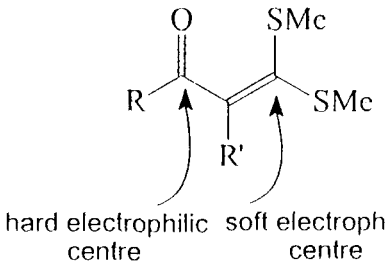


Kelber and co-workers[1, 2] had given the first report on α-oxoketene dithioacetals in the year 1910. Much of the earlier work on α-oxoketene dithioacetals was confined to their preparation and properties, while little attention was paid to their synthetic utility. Later on Thuillier and Vialle prepared these compounds in a one pot reaction by reacting the active methylene ketones with carbon disulphide in the presence of sodium tertiary amylate followed by alkylation[3-6]. Subsequently these reaction conditions have been greatly improved using different bases and reaction conditions[7-11]. A large number of α-oxoketene dithioacetals have now been reported and their chemistry has been reviewed by Dieter[12a] in 1986 and by Junjappa and co-workers[12b] in 1990.

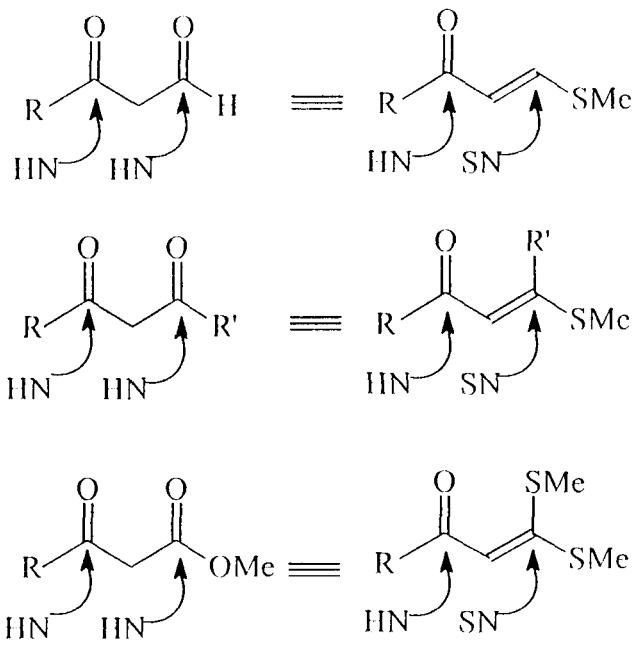
The α-oxoketene dithioacetals, generally exhibit well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stirred indefinitely without decomposition. The α-oxoketene dithioacetals have attained recognition in being used as building blocks in strategic synthetic

operations[12]. The reaction of enolate anions derived from active methylene carbonyl compounds in the presence of suitable base/solvent combination (coupled with temperature manipulation) with carbon disulphide followed by alkylation, continues to be the most preferred method for the preparation of this class of compounds [3-6 & 7-11].

The α-oxoketene dithioacetals are β,β-disubstituted α,β-unsaturated ketones having 1,3-electrophilic centres with differing electrophilic properties.



The carbonyl carbon can be regarded as the hard electrophilic centre since it is attached to oxygen atom which is a hard base. The β-carbon atom can be regarded as the soft electrophilic centre since it is flanked by two methylthio groups of which sulphur is a soft base. The 1,3-dicarbonyl compounds are attacked by nucleophiles at both carbonyl centers while their counter parts show differential electrophilicity permitting hard nucleophiles to attack via charge controlled 1,2-addition mode. The soft nucleophiles follow orbital controlled 1,4-addition-elimination sequence with the sulphur analogs. Thus the sulphur analogs display greater regioselectivity as compared to the oxygen analogs.



The α-oxoketene dithioacetals are also primary precursors for the synthesis of corresponding N,N-, N,S-, and O,S-acetals. The preparation of O,S-acetals is accomplished, by the displacement, by oxygen nucleophiles of the sulphonium salts[13] of the corresponding S,S-acetals. The N,S-acetals can be prepared from α-oxoketene dithioacetals by the displacement of one thiomethyl group by a suitable amine in refluxing ethanol[14,15]. Alternatively, they can be prepared directly from active methylene ketones by reacting their enolate anions with alkyl and aryl isothiocyanates followed by alkylation[16].

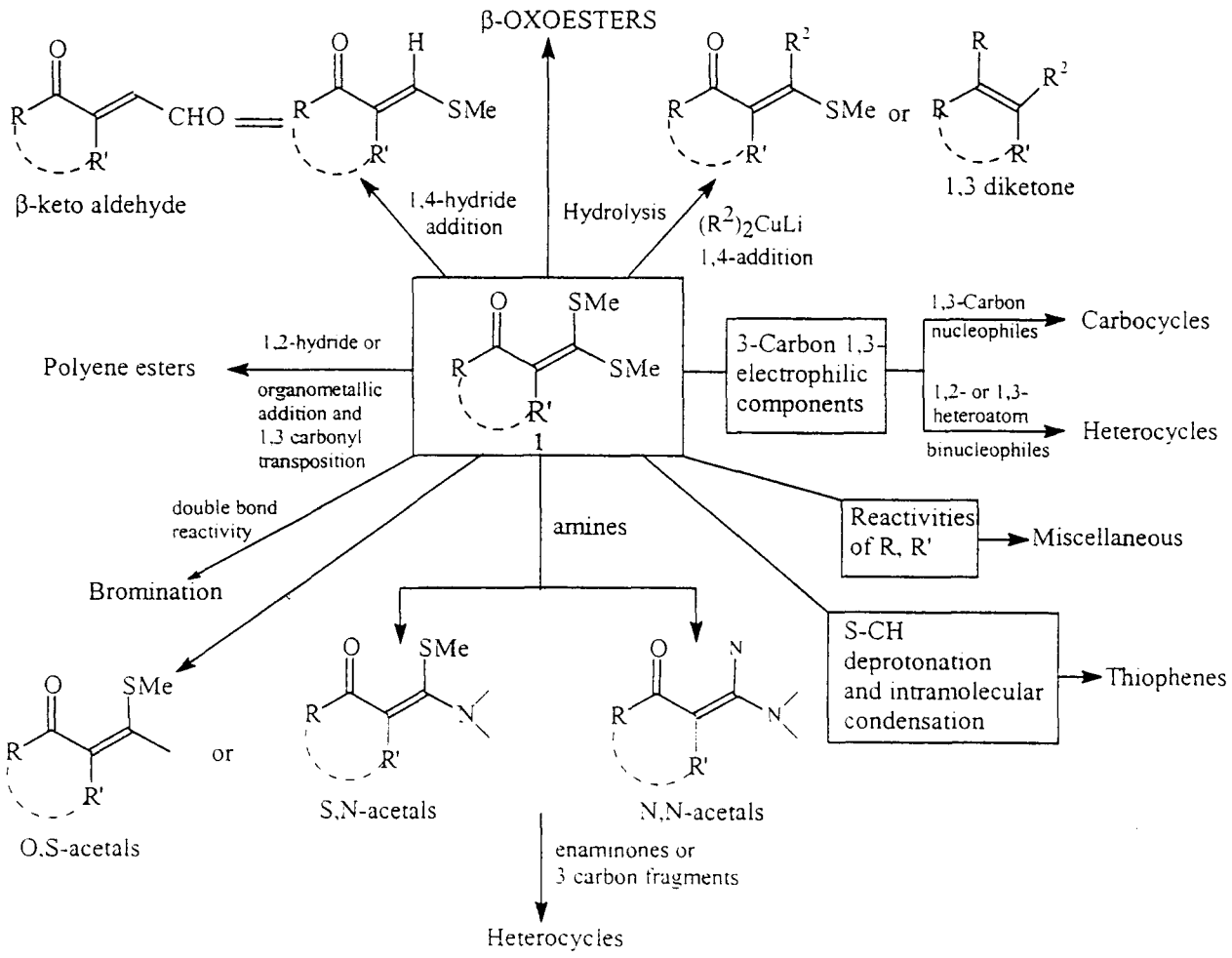
The α-oxoketene N,N-acetals can be prepared in high yields by displacing both the thiomethyl groups of α-oxoketene dithioacetal by amines in refluxing acetic acid[15,17]. The α-oxoketene S,S-, N,S- and N,N- acetals have

been extensively used in the laboratory for the synthesis of both heterocyclic and carbocyclic compounds[12].

In Scheme-1, various reactivity profiles of α-oxoketene S, S-acetals of general formula **1** have been outlined. Hydrides and organometallic reagents give 1,2-addition products typical of carbonyl function reactivity[18]. These additions can be directed in a 1,4-manner by suitably manipulating the reagent and reaction conditions[18,19]. Further transformations after the initial 1,2- or 1,4-addition are further reported[18]. Then enolate ion formed by the deprotonation (when R′=alkyl) can undergo condensation with aldehydes to give α-enoyl ketene dithioacetals[20].

Also deprotonation on the thiomethyl group followed by intramolecular aldol type condensation to thiophene is also reported[22,23]. The reactivity of the mercaptal double bond is also exploited with electrophiles. The α-oxoketene dithioacetals **1** undergo bromination at α-position with N-bromo succimide[24]. Thus, it is apparent that the α-oxoketene S,S-acetals of general formula **1** constitute an important class of synthons with reactive electrophilic and nucleophilic centers distributed in various centers of its skeleton permitting reactions of great synthetic importance. Some of the selected transformations reported from this laboratory are briefly described in the following section.

The carbonyl group of α-oxoketene dithioacetals can be selectively reduced using sodium borohydride in a 1,2-fashion to give the carbinol

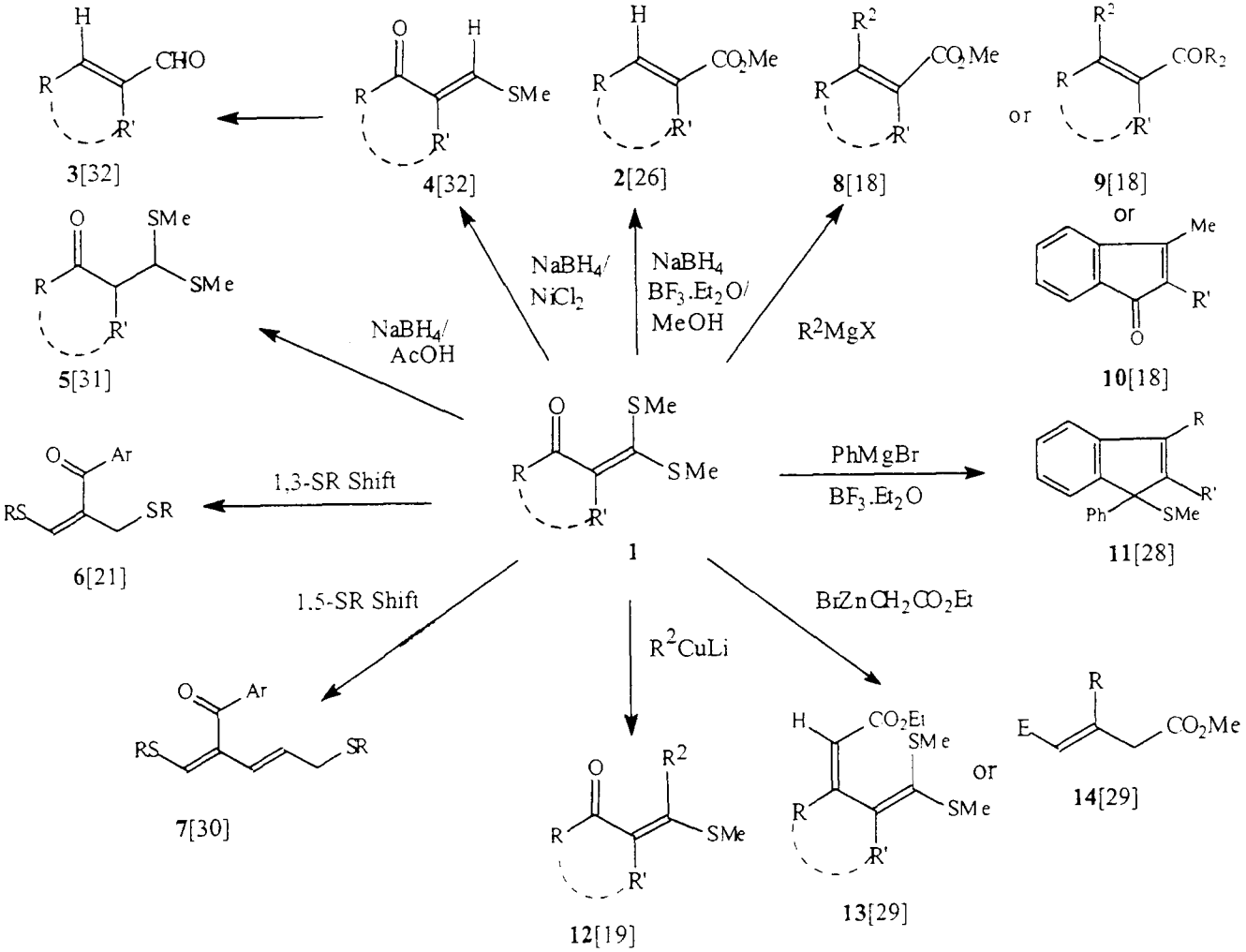

β-OXOESTERS
β-keto aldehyde
1,4-hydride addition
Hydrolysis
(R2)2CuLi 1,4-addition
1,3 diketone
Polyene esters
1,2-hydride or organometallic addition and 1,3 carbonyl transposition
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
double bond reactivity
Bromination
amines
Reactivities of R, R'
Miscellaneous
S-CH deprotonation and intramolecular condensation
Thiophenes
O,S-acetals
S,N-acetals
N,N-acetals
enaminones or 3 carbon fragments
Heterocycles

Scheme 1

acetals[25,26]. These carbinol acetals were shown to undergo smooth methanolysis in the presence of boron trifluoride etherate to afford α,β-unsaturated methyl esters **2**[26] in high yields (Scheme-2). The overall transformation is considered as homologation of active methylene ketones involving 1,3-carbonyl transformation methodology.

The Grignard and organolithium reagents undergo either regioselective 1,2-addition to afford α-hydroxy ketene dithioacetals or sequential 1,4- and 1,2-additions to afford the β-hydroxy vinyl sulfides[18,19,27]. The boron trifluoride etherate catalysed solvolysis or the hydrolysis of these carbinols yield either β-substituted α,β-unsaturated esters **8** or the corresponding ketones **9**[18] (Scheme-2) in good yields.

However, when the R′ is alkyl or aryl group the open chain cinnamates were not formed, instead the corresponding 2,3-disubstituted indenones were formed[18]. The reaction of phenyl magnesium bromide followed by $BF_3.Et_2O$ treatment is reported to give the 1-methylthio-1-phenylidenes **11**[28]. Diene esters **14** and α,β-unsaturated esters **13**[29] were reported when Reformatsky reaction was carried out with α-oxoketene dithioacetals. Dieter and co-workers have reported the chemo- and stereo-selective addition of organo cuprates to **1** which undergo conjugate addition to give β-alkyl thio-β-substituted α,β-unsaturated ketones **12**[19]. In another study from this laboratory, base catalysed rearrangement of α-oxoketene

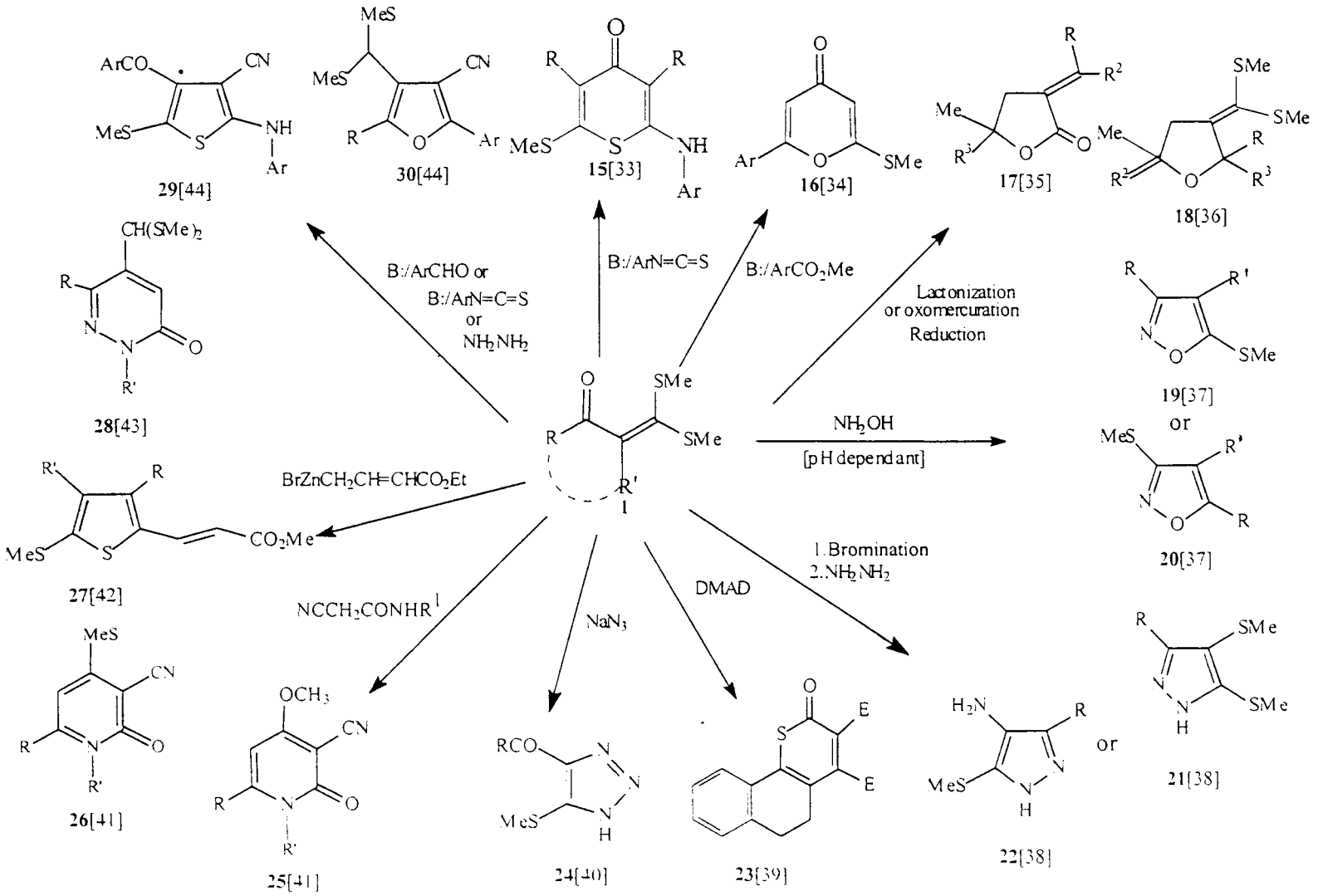

3[32]
4[32]
2[26]
8[18]
9[18]
5[31]
10[18]
6[21]
1
11[28]
7[30]
12[19]
13[29]
14[29]
NaBH4/ NiCl2
NaBH4 BF3.Et2O/ MeOH
R2MgX
NaBH4/ AcOH
1,3-SR Shift
PhMgBr
BF3.Et2O
1,5-SR Shift
R2CuLi
BrZnCH2CO2Et
or

Scheme 2

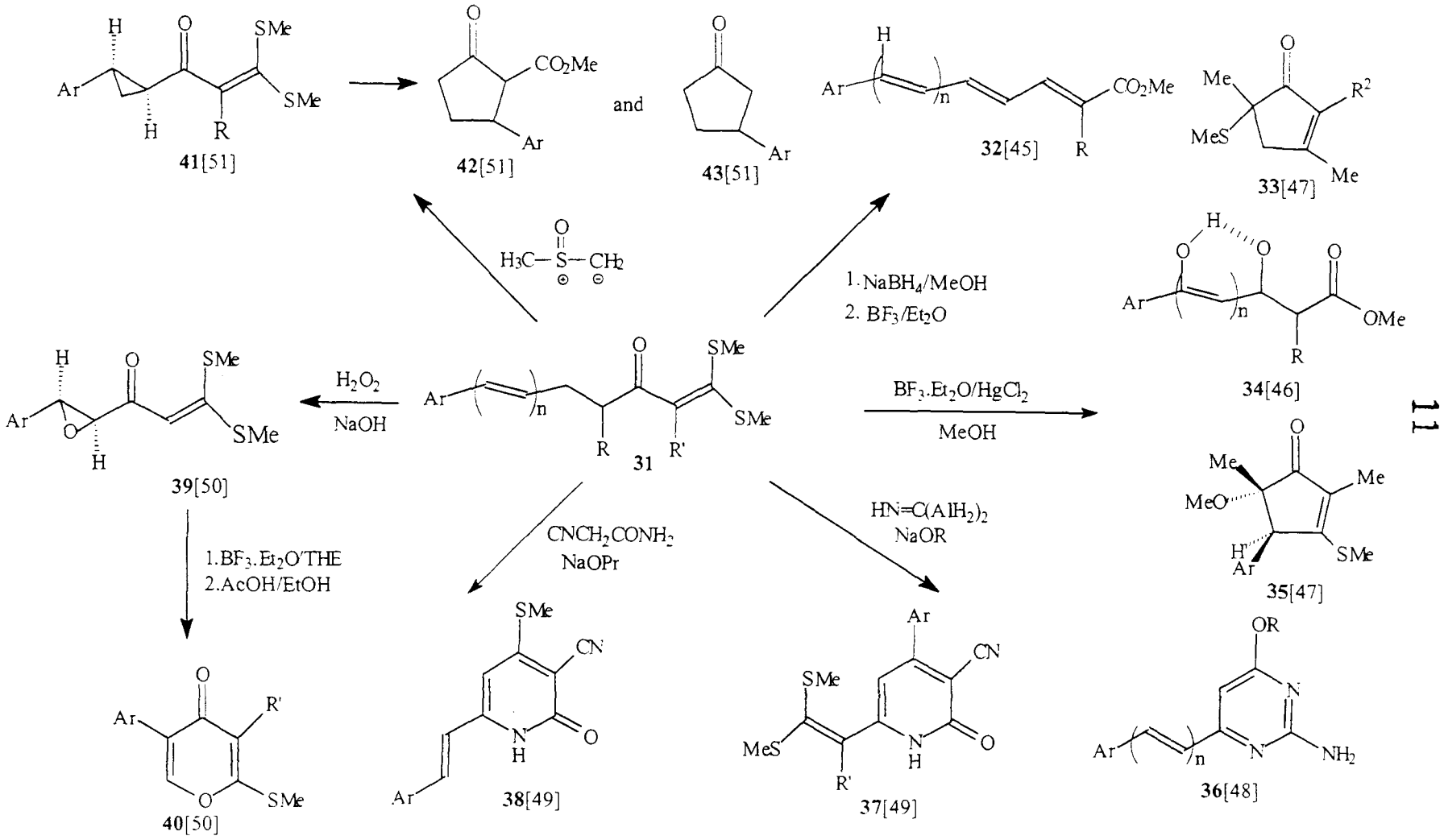
dithioacetals derived from propiophenone is reported[21]. The 2-alkyl thiomethyl acrylo-phenones **6** are formed by the 1,3-SR shift. A base assisted 1,5-SR shift to the dienes **7** is also reported[30]. The α-oxoketene dithioacetals **1** are shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to afford the corresponding β-methylthio alkenyl ketones **4**[32]. These intermediates are hydrolysed to α,β-unsaturated aldehydes **3**[32] (Scheme- 2).

The differential electrophilicities of the 1,3-carbon atoms of α-oxoketene dithioacetals have been exploited for the synthesis of various fused five and six membered heterocycles[33-34] by reacting with appropriate 1,2- and 1,3-hetero binucleophiles (Scheme-3). α-oxoketene dithioacetals on reaction with hydroxyl amine at pH 7-9 gave isomeric isooxazoles **20**[37] in good yields. From these transformations it is apparent that the α-oxoketene dithioacetals with wide functional variation and many easily accessible reagents and reaction intermediates manifest various possibilities leading to a diverse range of products.

Various transformations developed, based on α-cinnamoyl and 5-aryl 2,4-pentadienoyl ketene dithioacetals **31** are outlined in (Scheme-4). A general method for the synthesis of polyene esters **32**[20,45] has been reported by 1,2-reduction of **31** followed by methanolysis in the presence of boron trifluoride etherate. In Hg (II) assisted hydrolysis the corresponding γ,δ-unsaturated β-keto esters **34** are formed[46]. In the case of 2,4-disubstituted (R=


29[44]
30[44]
15[33]
16[34]
17[35]
18[36]
28[43]
19[37]
or
20[37]
27[42]
26[41]
25[41]
24[40]
23[39]
22[38]
or
21[38]
B:/ArCHO or
B:/ArN=C=S
or
NH2NH2
B:/ArN=C=S
B:/ArCO2Me
Lactonization
or oxomercuration
Reduction
NH2OH
[pH dependant]
BrZnCH2CH=CHCO2Et
NCCH2CONHR1
NaN3
DMAD
1.Bromination
2.NH2NH2

Scheme 3


41[51]
42[51]
and
43[51]
32[45]
33[47]
34[46]
35[47]
36[48]
37[49]
38[49]
39[50]
40[50]
31
1. NaBH4/MeOH
2. BF3/Et2O
H2O2
NaOH
BF3.Et2O/HgCl2
MeOH
1.BF3.Et2O'THE
2.AcOH/EtOH
CNCH2CONH2
NaOPr
HN=C(AlH2)2
NaOR

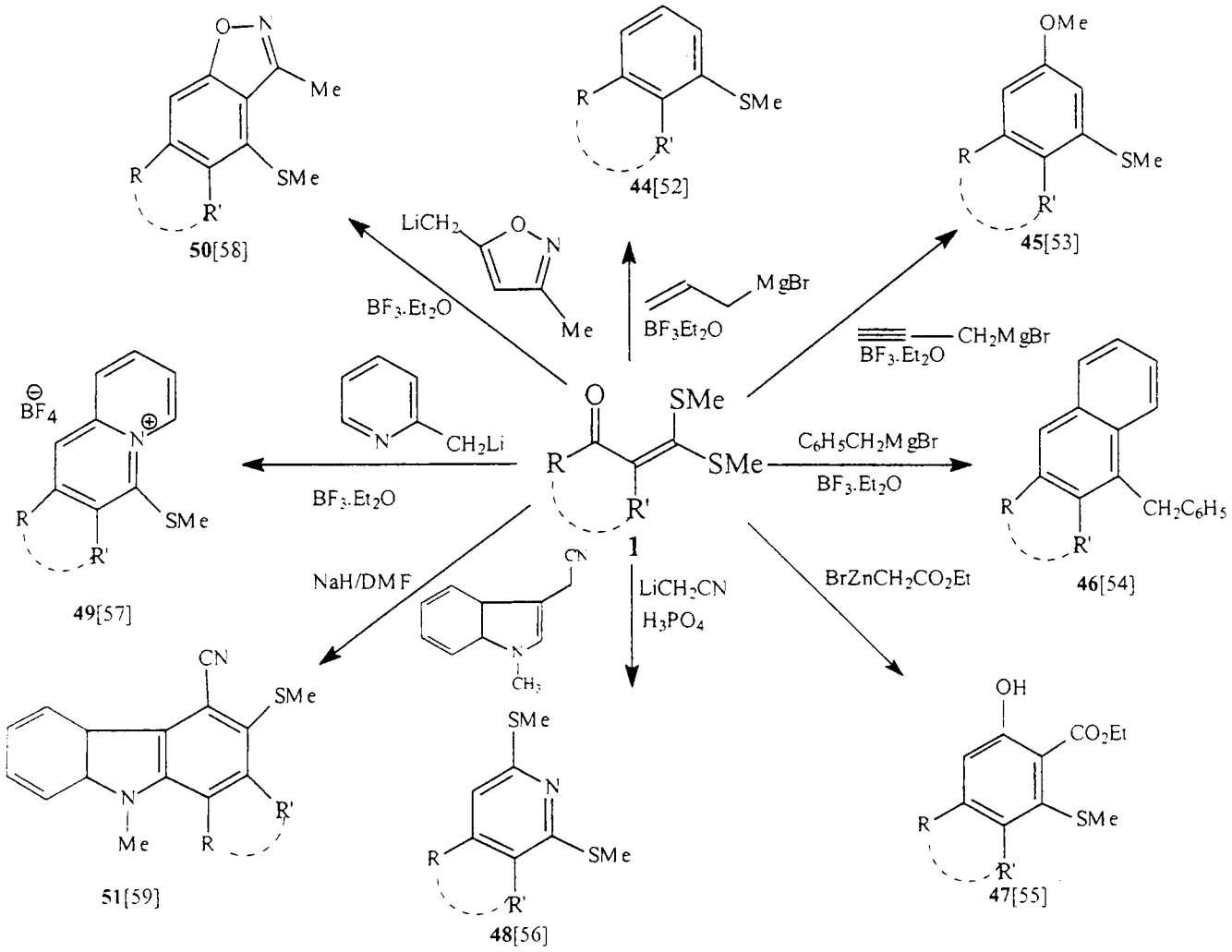
Scheme 4

R'= CH_3), the corresponding cyclopentanones **33** and **35** are formed in both reaction conditions[46,47]. Styryl pyrimidines **36**, pyridones **37** and **38** were also synthesized using these intermediates[48,49]. The cinnamoyl ketene dithioacetals **31** have been reported to undergo regio–selective epoxidation to give **39** and cyclopropanation to give **41** at the styryl double bond[50,51]. The intermediates **39** and **41** were further exploited for the synthesis of pyrones **40** and cyclopentanones **42** and **43** respectively[50,51].

The synthetic outcome of the aromatic annulation approach via α-oxoketene dithioacetals developed in this laboratory is depicted in (Scheme-5). Allyl magnesium bromide has been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetals in high yields, which on $BF_3.Et_2O$ assisted cationic cyclization afforded the substituted and fused benzene derivatives **44**[52]. The method is extended for the synthesis of other benzenoids **45, 46** and **47**[53-55]. The method is further shown to be extremely versatile and found general application for the synthesis of pyridines **48**[56], quinolizinium salts **49**[57], 1,2-benz isooxazoles **50**[58] and condensed indoles **51**[59].

Section II The work presented in this thesis

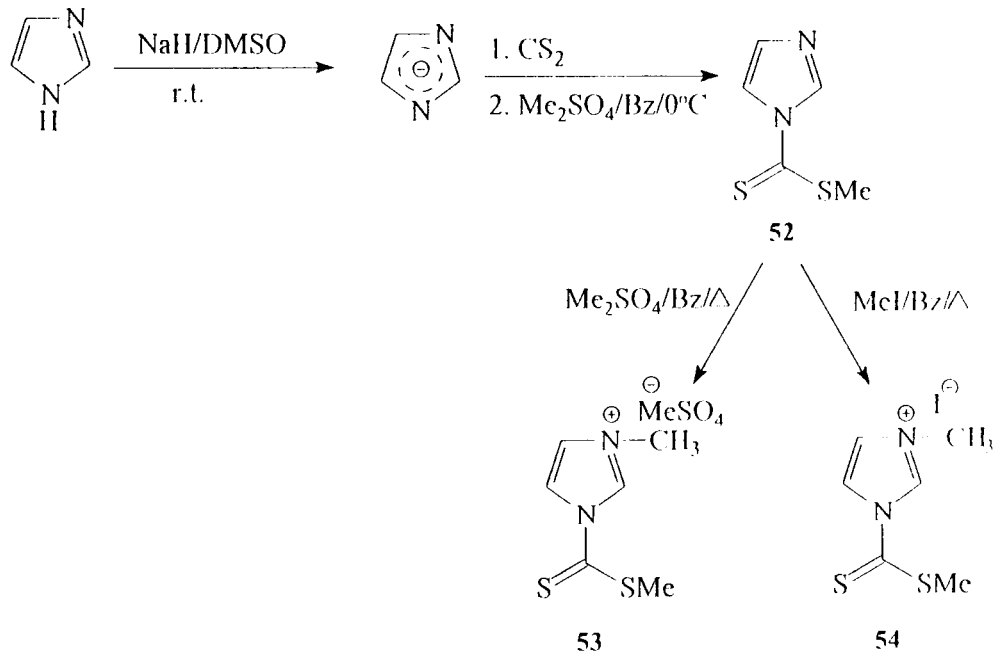
From a survey of the synthetic applicability of various α-oxoketene dithioacetals it is evident that they are versatile intermediates for performing carbon-carbon bond formation, synthesis of carbocycles, heterocycles etc. In our present investigation we have taken up the synthesis of β-oxodithioates, dimethyl dithiocarbamates and thioureas using a new novel method of


50[58]
44[52]
45[53]
LiCH2
Me
BF3.Et2O
MgBr
BF3Et2O
CH2MgBr
BF3.Et2O
BF4
CH2Li
BF3.Et2O
SMe
R
R'
1
C6H5CH2MgBr
BF3.Et2O
CH2C6H5
46[54]
49[57]
NaH/DMF
LiCH2CN
H3PO4
BrZnCH2CO2Et
CN
CH3
51[59]
48[56]
OH
CO2Et
47[55]

Scheme 5

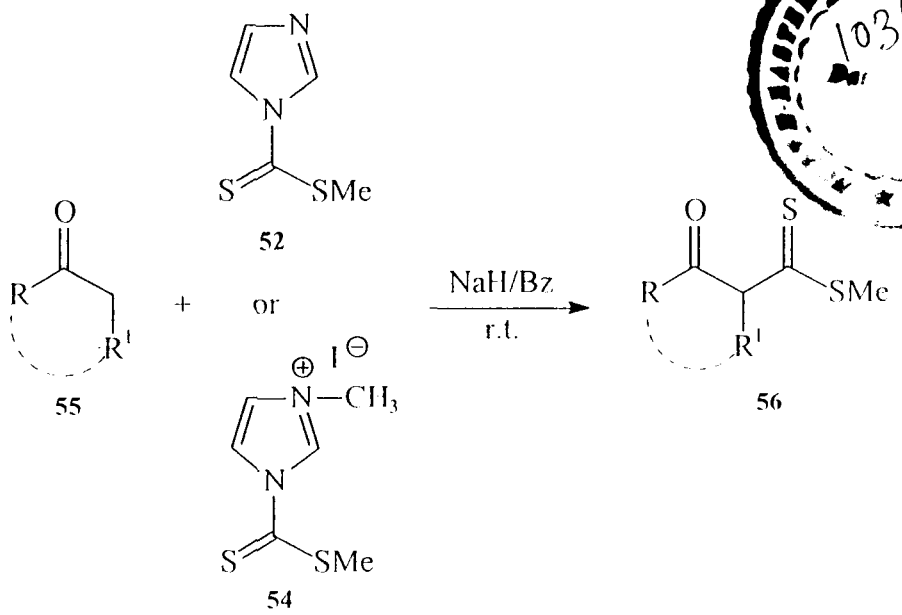
approach. We also attempted to undertake some transformations on α-oxoketene dithioacetals.

The second chapter deals with the reactions of 1-(methyldithiocarbonyl)imidazole **52** and 3-methyl-1-(methyldithiocarbonyl) imidazolium iodide **54** with active methylene ketones. The preparation of 1-(methyldithiocarbonyl)imidazole **52** can be achieved by the reaction of imidazole with carbondisulfide and dimethyl sulphate in the presence of sodium hydride using DMSO as solvent. Sun and co workers[60] had prepared the same compound using similar reagents and reaction conditions, but using THF as the solvent of chioce. The hitherto unreported salt **54** can be prepared by refluxing **52** with methyl iodide in dry benzene for few hours (Scheme-6).



Scheme 6

On refluxing **52** with Me_2SO_4 in dry benzene **53** was obtained. On reacting 1-(methyldithiocarbonyl)imidazole **52** with active methylene ketones in the presence of sodium hydride, DMSO and dry benzene at room temperature for a period of three to four hours the corresponding β-oxo dithioates **56** are obtained in good yields. When the quarternary salt **54** is reacted with active methylene ketones under the same reaction conditions excepting with reduced time period of reaction, the corresponding β-oxodithioates **56** were no doubt obtained, but this time in quantitative yields as compared to that when reacting 1-(methyldithiocarbonyl)imidazole **52** with active methylene ketones (Scheme-7).

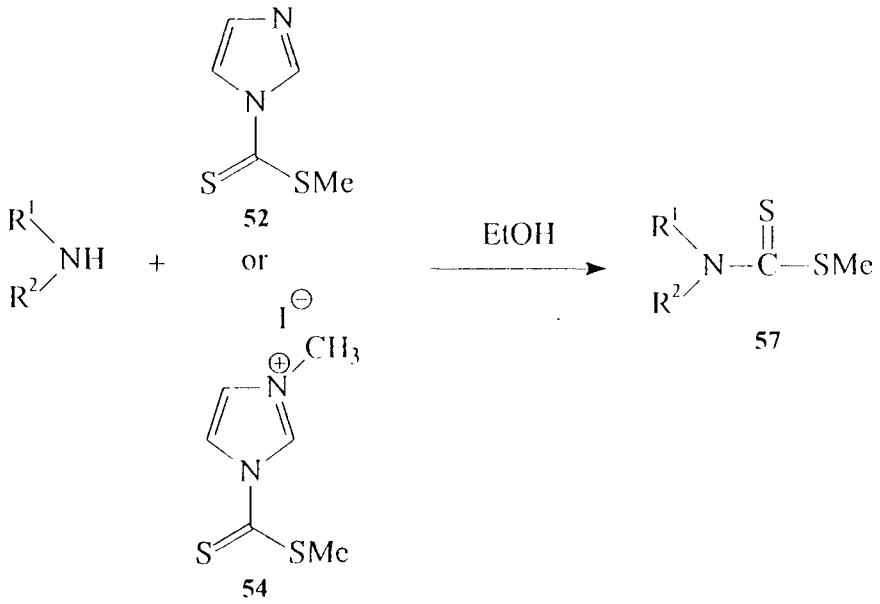


Scheme 7

These β-oxodithiotes could be further alkylated to obtain quantitative yields of *symmetrical and unsymmetrical α-oxoketene dithioacetals* which can be used further for multiple synthetic transformations. The novelty underlying this

method of approach for making β-oxodithiotes as compared to the literature methods[61] is highlighted in detail in the second chapter.

The third chapter describes the reactions of 1-(methyldithio carbonyl)imidazole **52** and its corresponding quarternary salt **54** with various amines. Taking advantage of the fact that **52** or **54** serves as effective dithiocarbonyl transfer reagents, we decided to react **52** or **54** with amines (R^1 =R^2 = alkyl/aryl group). Thus, when 1-(methyldithiocarbonyl)imidazole **52** or its quarternary salt **54** was treated with only one equivalent of primary or secondary amine in refluxing ethanol, a controlled reaction gave methyl dithiocarbamates **57** as the end products of the reaction (Scheme-8).

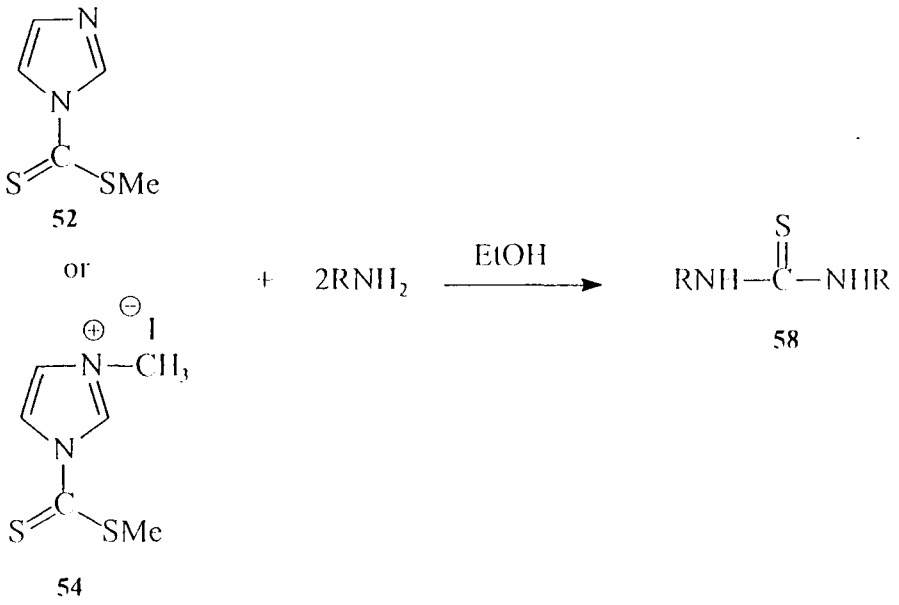


Scheme 8

A literature survey revealed that there exists no general satisfactory method for the preparation of alkyl/aryl dithiocarbamates, excepting by reacting carbon disulphide with various amines in the presence of a base followed by

alkylation. Also keeping in view that dithiocarbamates show fungistatic action as well as other important properties, we decided to prepare a number of derivatives of methyl dithiocarbamates to test the general applicability underlying our method of preparation of these compounds. The third chapter gives a broad view and discusses the important properties of this class of compounds.

Next when **52** or **54** was reacted with two equivalents of amines (R = alkyl/aryl group) in refluxing ethanol, symmetrical thioureas **58** were obtained in good yields (Scheme-9).

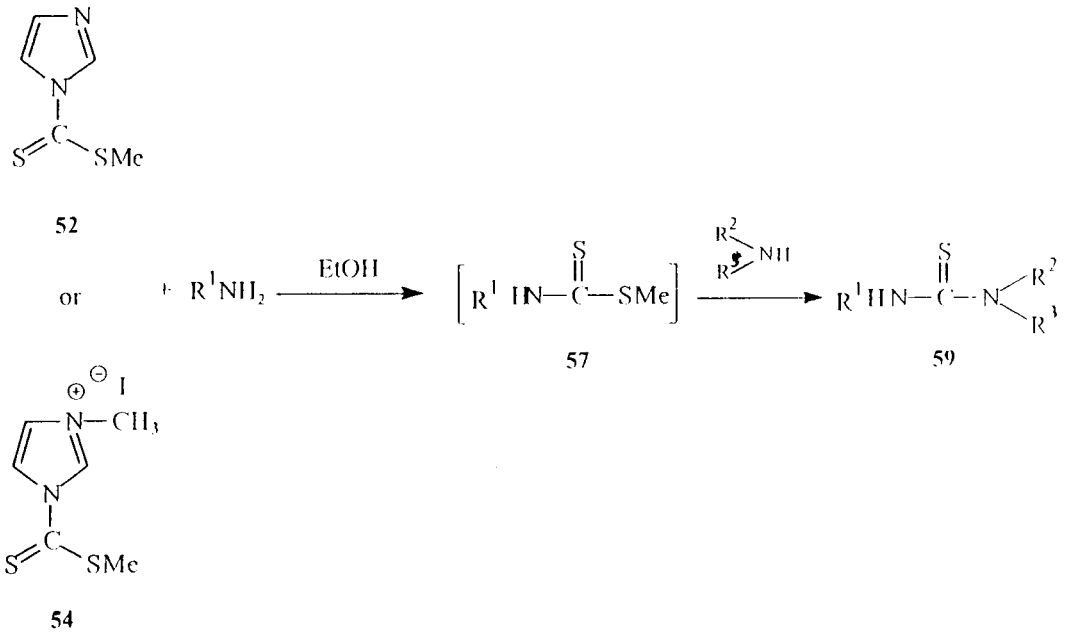


Scheme 9

Preparation of symmetrical thioureas usually involves the use of hazardous chemicals[62] or very severe reaction conditions[63]. Nonetheless thioureas display important industrial applications in both pharmaceutical and agrochemical sectors and hence the above described method can easily and economically be used to prepare such compounds quite effectively. The third chapter gives in

detail various literature methods of preparation, properties and also the synthetic and industrial aspects of symmetrical thioureas.

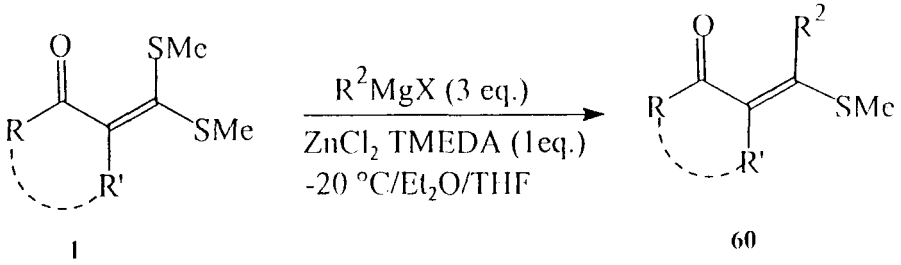
We next attempted to synthesize unsymmetrical thioureas **59** using 1-(methyldithiocarbonyl)imidazole **52** and 3-methyl-1-(methyldithio carbonyl)imidazolium iodide **54** and amines, because of their synthetic utility [64,65]. In order to synthesize various unsymmetrical thioureas starting from and amines (R^1 = alkyl/aryl group) and **52** and **54** we first prepared various methyl dithiocarbamates, as per earlier described procedure. Next without isolating that particular methyl dithiocarbamate we added our second alkyl or aryl amine of choice in one pot and further refluxed the reactants in ethanol for a few hours to obtain the desired unsymmetrical thioureas **59** (Scheme-10).



Scheme 10

To test the feasibility of this method we prepared a number of unsymmetrical thioureas, starting from 1-(methyldithiocarbonyl)imidazole **52** or its quarternary salt **54**. It was found that when **54** reacted with amines better yields of unsymmetrical thioureas **59** were obtained compared to that when **52** was reacted with amines. The details regarding their comparative yield and synthetic utility of unsymmetrical thioureas **59** have been described in detail in the third chapter.

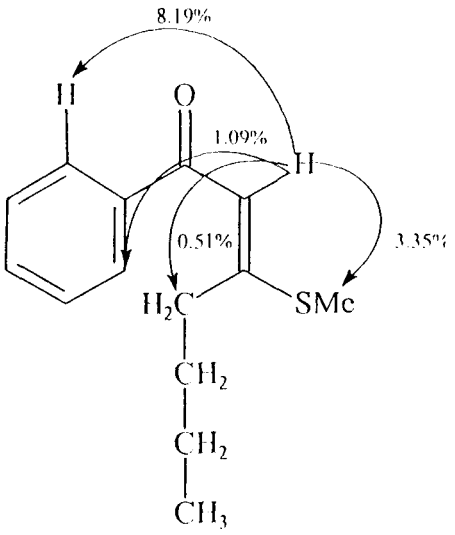
In the last chapter, the nucleophilic addition studies on α-oxoketene dithioacetals are described. The α-oxoketene dithioacetals when reacted with various Grignard reagents using $ZnCl_2$.TMEDA complex at -20^{0}C under nitrogen atmosphere, 1,4-addition products **60** were obtained in moderate to good yields in a stereospecific manner, by the displacement of one methylthio group (Scheme-11).



1 60

Scheme 11

Experiments in which the ratio of Grignard to $ZnCl_2$.TMEDA was 3:1 yielded good results. A number of additions were carried which are highlighted in the fourth chapter. From ^{1}H NMR and NOE experiments we have concluded that the product present is only the *E*-isomer (Scheme-12).



60a

E-isomer

Scheme 12

A broad survey of 1,2- and 1,4-additions and also the results of this study is presented in detail in the fourth chapter.

References

1. Kelber, C. *Chem. Ber.* **1910**, 43, 1252.
2. Kelber, C.; Schwarz, A. *Chem.Ber.* **1912**, 45, 137.
3. Thuiller, A.; Vialle, J. *Bull.Soc.Chim.Fr.* **1962**, 2187.
4. Thuiller, A.; Vialle, J. *Bull.Soc.Chim. Fr.* **1962**, 2194.
5. Saquet, M.; Thuiller, A. *Bull. Soc. Chim. Fr.* **1966**, 1582.
6. Thuiller, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1959**, 1398.
7. Gompper, R.; Schmidt, R.R.; Kutter, E. *Leibig. Ann. Chem.* **1965**, 648, 27.
8. Corey, E.J.; Chen, R.H.K. *Tetrahedron Letters* **1973**, 3817.
9. Shahat, I.; Sasson, Y. *Tetra. Lett.* **1973**, 4207.
10. Chauhan, S.M.S.; Junjappa, H. *Tetrahedron* **1976**, 32, 1779.
11. Dieter, R.K. *J.Org. Chem.* **1981**, 46, 5031.
12. For a review see (a) Dieter, R.K. *Tetrahedron* **1986**, 42, 3029.(b) Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron* **1990**, 46, 5423.
13. Spitzner, R.; Menzel, M.; Schroth, W. *Synthesis* **1982**, 206.
14. Gompper, R.; Schaefer, H. *Chem. Ber.* **1967**, 100, 591.
15. Borrmann D. In: *Houben-Weyl, Methoden der. Organischen. Chemie, 4th Edn, E. Muller, Ed., Vol. VII/4, George Thieme Verlag, Stuttgert.* **1968**, 421.
16. Rudof, W.D.; Schierhorn, A.; Augustin, M. *Tetrahedron* **1979**, 35, 551.

17. Thomas, A.; Vishwakarma, J.N.; Ila, H.; Junjappa, H. *Tetrahedron* **1988**, 44, 1667.

18. Singh, G.; Purkayastha, M.L.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin Trans. I* **1985**, 1289.

19. Dieter, R.K.; Silks, L.A.; Fishpaugh, J.R.; Kastner, M.E. *J.Am.Chem. Soc.* **1985**, 107, 4679.

20. Myrboh, B.; Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 50.

21. Apparao, S.; Rahman, A.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1982**, 23,971.

22. Marino, J.P.; Kostusyk, J.L. *Tetra. Lett.* **1979**, 20, 2489.

23. Marino, J.P.; Kostusyk, J.L.; *Tetra. Lett.* **1979**, 20, 2493.

24. Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 165.

25. Saquet, M.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1966**, 3969.

26. Myrboh, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, 48, 5327.

27. Dieter,R.K.; Fishpaugh, J. R.; Silks, L.A. *Tetra. Lett.* **1982**, 23, 3751.

28. Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1986**, 744.

29. Apparao, S.; Dutta, A.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 169.

30. Apparao, S.; Bhattacharjee, S.S.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin trans. I* **1985**, 641.

31. Srinivasa Rao, Ch.; Chakrasali, R.T.; Ila, H.; Junjappa, H. *Tetrahedron* **1990**, 46, 2195.

32. Myrboh, B.; Singh, L. W.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 307.

33. Singh, L.S.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 531.

34. Singh, L.W.; Ila, H.; Junjappa, H. *Synthesis* **1987**, 837.

35. Dutta, A.; Bhattacharjee, S.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 725.

36. Dutta, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1987**, 43, 5367.

37. Purkayastha, M.L.; Ila, H.; Junjappa, H. *Synthesis* **1989**, 919.

38. Singh, G.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin trans. I* **1987**, 1945.

39. Vishwakarma, J.N.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin trans.I* **1983**, 1099.

40. Chakrasali, R.T.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 453.

41. Rastogi, R.R.; Ila, H.; Junjappa, H. *J. Chem. Soc. Chem. Comm.* **1975**, 645.

42. Rastogi, R.R.; Kumar, A.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin trans. I* **1978**, 549.

43. Dutta, A.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 556.

44. Singh, L.W.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 89.

45. Singh, L.W.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin trans. I* **1988**, 2365.

46. Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* **1985**, 163.

47. Asokan, C.V.; Bhattacharjee, S.S.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 281.

48. Asokan, C.V.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1988**, 26, 1087.

49. Singh, L.W.; Gupta, A.K.; Ila, H.; Junjappa, H. *Synthesis* **1984**, 516.

50. Singh, L.W.; Ila, H.; Junjappa H. *Ind. J. Chem.* **1987**, 36B, 607.

51. Deb, B.; Asokan C.V.; Ila, H.; Junjappa H. *Synthesis* **1987,** 893.

52. Deb, B.; Asokan, C.V.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1988,** 29, 2111.

53. Singh G.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1984,** 25, 5095.

54. Gupta, A.K.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1987,** 1459.

55. Balu, M.P.; Singh, G., Ila, H.; Junjappa, H. *Tetra. Lett.* **1986,** 27, 1117.

56. Dutta, A.; Ila, H.; Junjappa H.; *Tetra. Lett.* **1988**, 29, 497.

57. Dutta A.K.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1988**, 29, 6633.

58. Balu, M.P.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1987**, 28, 3023.

59. Balu, M. P.; Pooranchand, D.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1988**, 29, 501.

60. Sun, W. Y.; Hu, J. Q.; Shi, Y. P. *Synlett* **1997,** 1279.

61. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693 and references therein.

62. Sharma, S. *Synthesis* **1978,** 802

63. Weville, R. G.; Mc. Gee, J.J. *Can. J. Chem.* **1963,** 41, 2123.

64. Sarkis, G.V.; Faisal E.D. *J. Heterocyclic chemistry* **1985**, 22, 137.

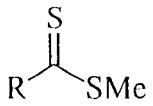
65. Makhsumov, A.G.; Safaev, A.S.; Abidova S.V. *Chem. Abstr.* **1969**, 71,101668v.

CHAPTER II

REACTION OF 1-(METHYLDITHIOCARBONYL)IMIDAZOLE AND 3-METHYL-1-(METHYLDITHIOCARBONYL)IMIDAZOLIUM IODIDE WITH ACTIVE METHYLENE COMPOUNDS: AN EFFICIENT METHOD FOR THE SYNTHESIS OF β-OXODITHIOATES

A brief review on the synthesis of dithioesters

The dithioesters of general formula **1** have recently attracted the attention of chemists due to their characteristic properties arising out of the two sulphur atoms in place of two oxygen atoms in the carboxylates.

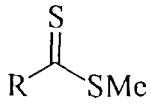


1

The dithioesters **1** are different in many ways from their oxygen counterparts and they have recently found application in organic synthesis[1,2] as well as in

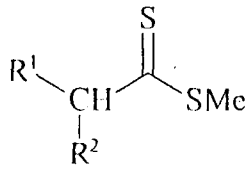
industries[3,4,5]. The corresponding dithioic acids however, are relatively unstable and undergo transformations characteristic of sulphur reactivity. For example, they may undergo oxidative coupling to yield the corresponding disulphides[6-9] or undergo intermolecular or intramolecular transformations, depending on the reaction conditions. The dithioesters can generally be classified in the following two categories;

Category I;



R = alkyl, aryl groups

Category II;

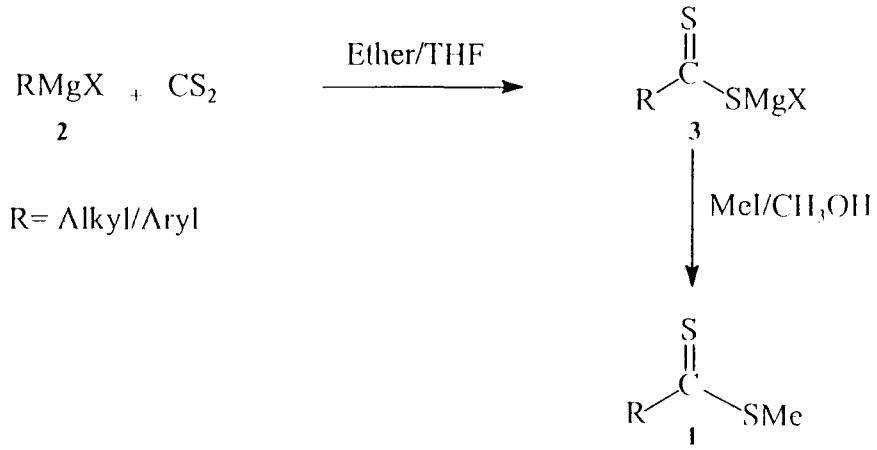


(R^1 = COR, COAr, COOR, CN, NO_2, SO_2R.)

(R^2 = H, Alkyl, Aryl, COOR, CN.)

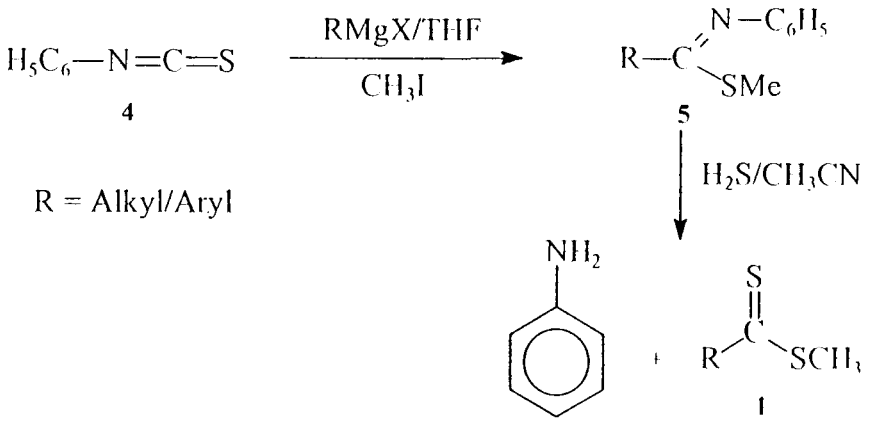
The (category I) dithioesters are generally prepared by reacting alkyl and aryl anions (derived from Grignard, Reformatsky, Gilman and other alkali metal reagents) with carbon disulphide followed by alkylation. The other dithioesters (category II) are generally obtained by reacting active methylene compounds with carbon disulphide followed by alkylation. The methods describing the synthesis of dithioesters have been reviewed[10] in 1983, and the present chapter briefly describes, selected examples of this category as

introductory information of this chapter. The organo Grignard reagents of general formula **2** (Scheme-1) are known to react with carbon disulphide to yield the corresponding dithioate salts **3**, which are generally alkylated with alkyl halides to yield the corresponding dithioesters **1** in good yields[11]. However, when the corresponding dithioic acids are required, salts **3** are acidified, to achieve the desired transformation. A number of dithioesters of this category have been prepared which are described in the review[10].



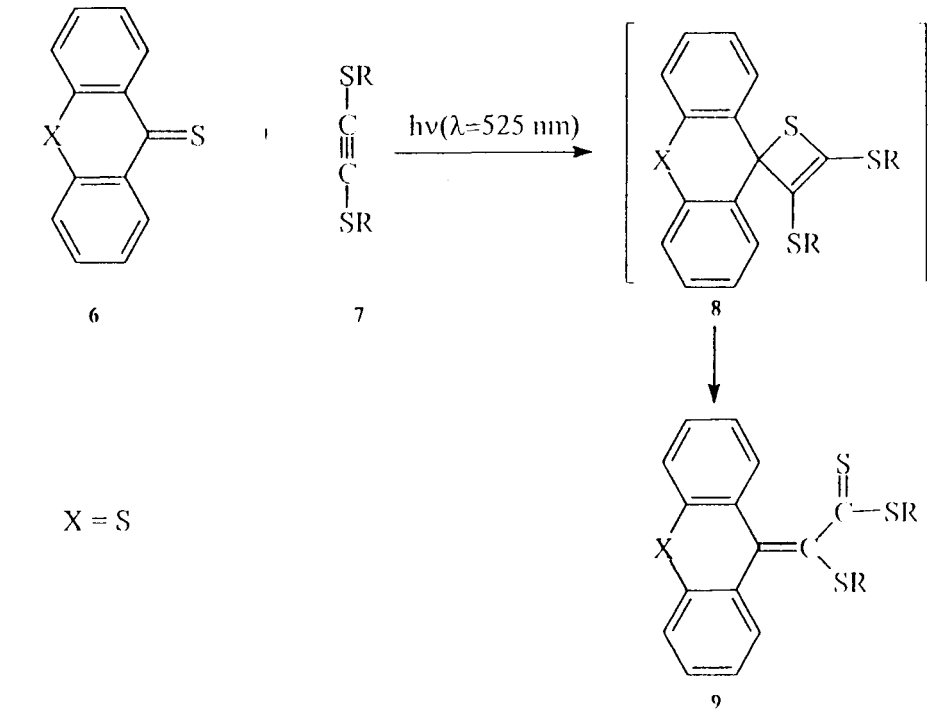
Scheme 1

In another type of reaction sequence, the easily available isothiocyanates of general formula **4** (Scheme-2) have been used for the synthesis of **1**. Thus the isothiocyanate **4** when reacted with Grignard reagents followed by alkylation yielded the corresponding imino methylthio compound **5** which after passing H_2S in acetonitrile, yielded the corresponding methyl dithioesters **1** in 59-72 % overall yields[12,13].



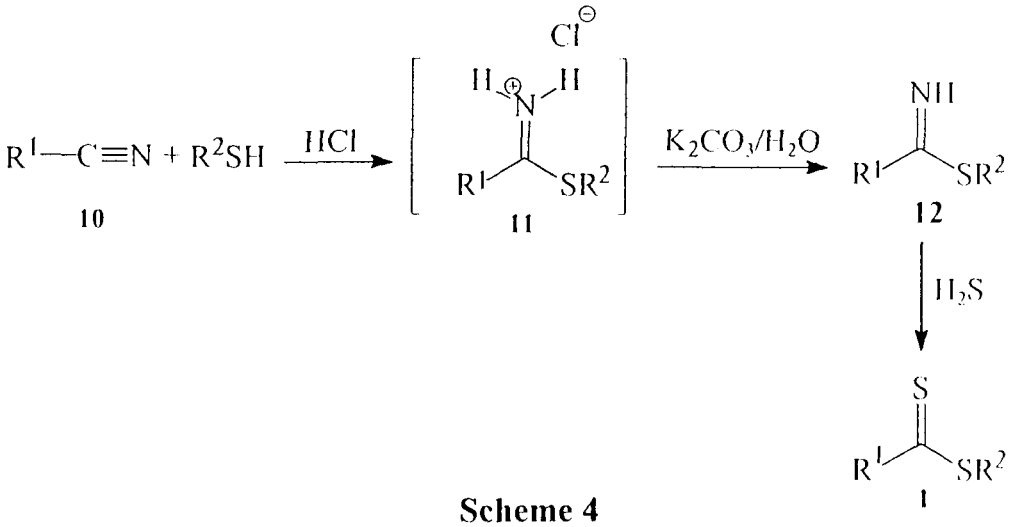
Scheme 2

An interesting example of the synthesis of α,β-unsaturated dithioesters involves [2+2] cycloaddition of aromatic thiones **6** with acetylenes having S-alkyl substituents **7**. The [2 + 2] cycloadduct **8** is unstable and rapidly cleaves to the corresponding α,β-unsaturated dithioester **9**[14,15,16] (Scheme-3).



Scheme 3

Aryl dithioates (R^1 = aryl) **1** (Scheme-4) have also been prepared starting from the corresponding nitriles **10**.



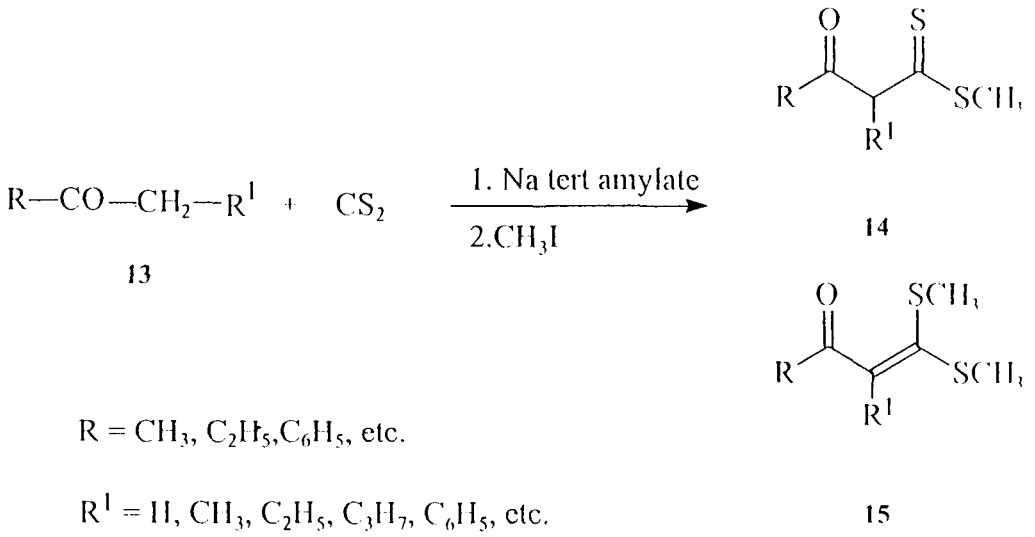
Scheme 4

Thus different mercaptals when added to nitriles **10** in the presence of hydrochloric acid yielded the corresponding immonium salts **11** which when *in situ* was treated with aqueous potassium carbonate afforded the corresponding immino ester **12** which were transformed to the corresponding dithioesters **1** by passing dry hydrogen sulphide[17].

The dithioates from active methylene compounds

Although the reaction of enolate anions derived from active methylene compounds particularly ketones with carbon disulphide was long reported by Kelber and co-workers in 1910, the well defined β-oxodithioates and the corresponding α-oxoketene dithioacetals were reported through a series of papers by Thuillier and co-workers.[18,19,20] They reported the reaction of active methylene ketones **13** with carbon disulphide in the presence of sodium tertiary amylate followed by alkylation to afford a mixture of β-

oxodithioates **14** and the corresponding α-oxoketene dithioacetals **15** (Scheme-5).

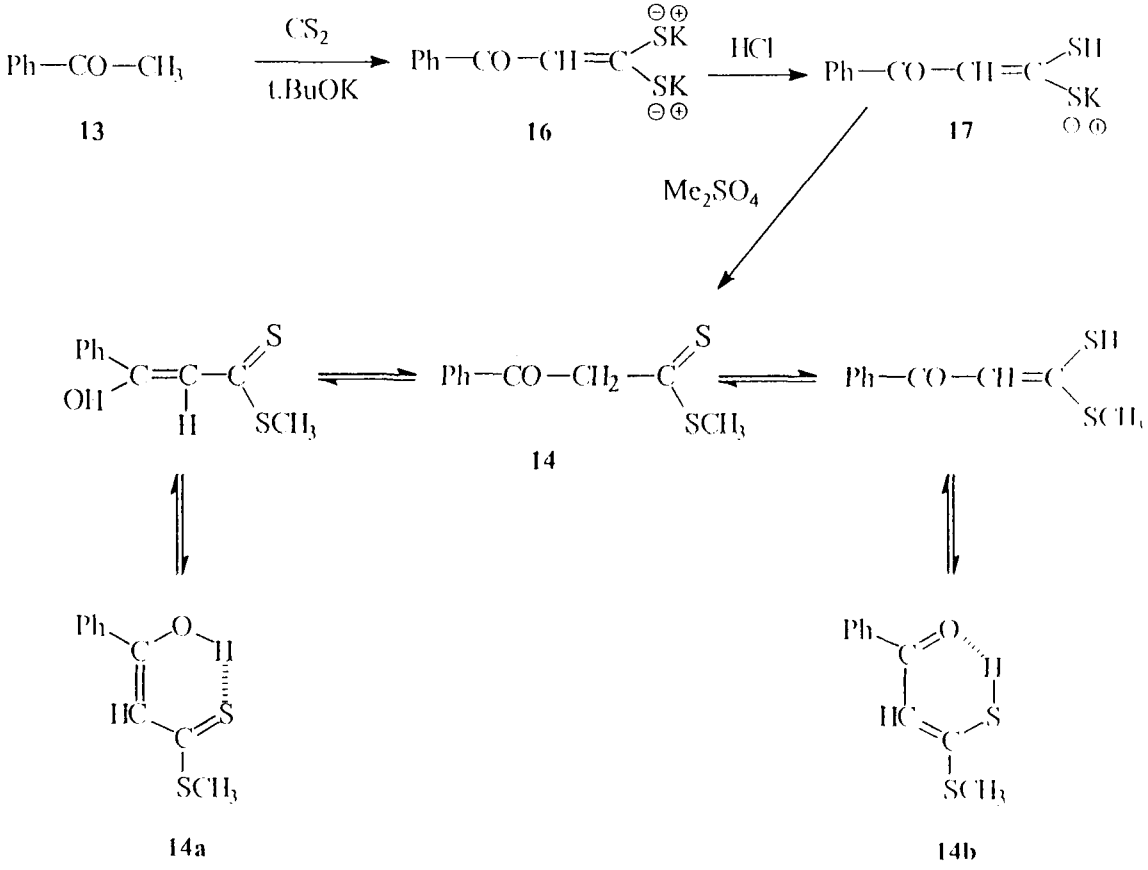


Scheme 5

Interestingly using one equivalent of alkylating agent the formation of **15** prevailed under the reaction conditions reported[19]. It was therefore not possible to use this direct approach to prepare exclusively β-oxodithioates **14** without having **15** as a mixture. However when excess of methyl iodide was used the entire reaction proceeded to yield **15** exclusively. Therefore Thuillier's method was good for the synthesis of α-oxoketene dithioacetals **15**, but not very efficient for the preparation of β-oxodithioates **14** from active methylene compounds.

Gompper and co-workers[21] observed that acetophenone **13** reacted with carbon disulfide in the presence of potassium tertiary butoxide to yield the corresponding dipotassium salt of dithioate **16** in excellent yields. The

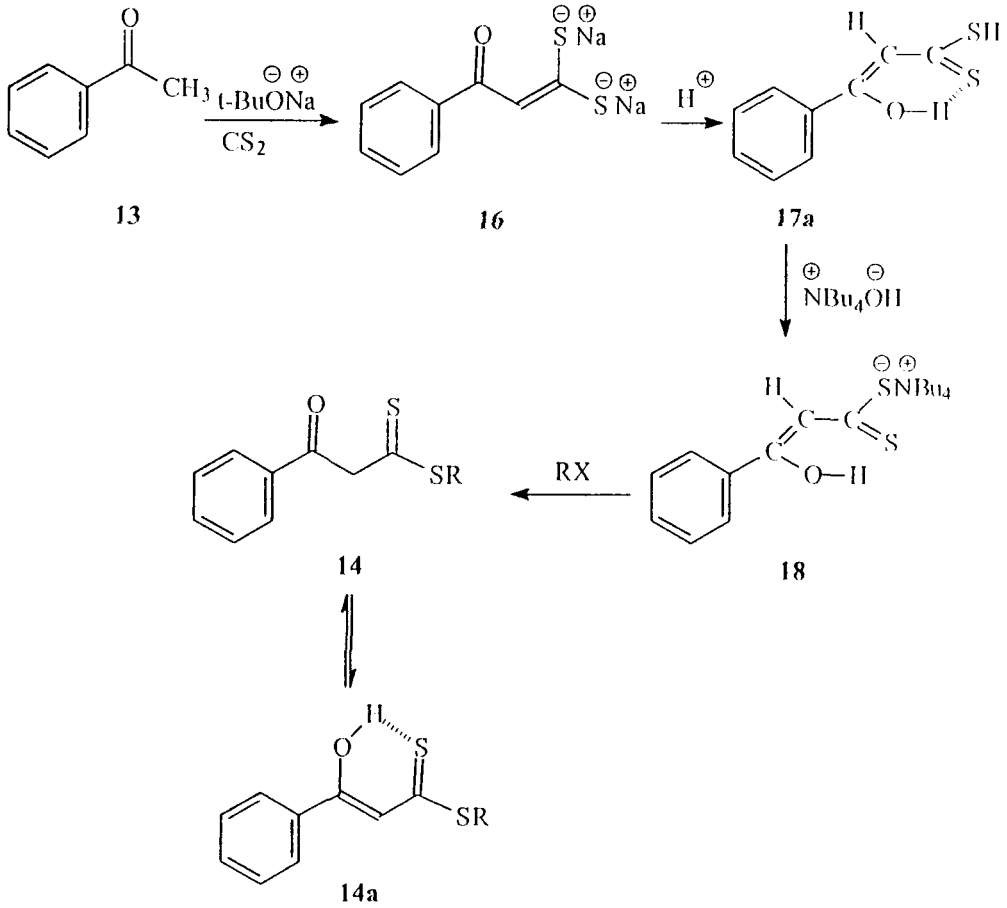
dipotassium salt **16** was carefully acidified with exactly one equivalent of hydrochloric acid to give the monopotassium salt **17** followed by its alkylation to afford the corresponding β-oxodithioates **14** in good yields. They have also shown that β-oxodithioates exist in tautomers **14a** and **14b** as shown in Scheme-6.



Scheme 6

Subsequently in 1972 Larsson and Lawesson[22] reported an efficient synthesis of β-oxodithioates as shown in Scheme-7. The method involves treatment of acetophenone **13** with base and carbon disulphide followed by acidification to get the dithioic acid **17a**. The dithioic acid **17a** was then treated with tetrabutylammonium hydroxide to obtain the monosodium salt of

dithioate **18** as intermediate followed by alkylation to obtain β-oxodithioates **14** in good yields.

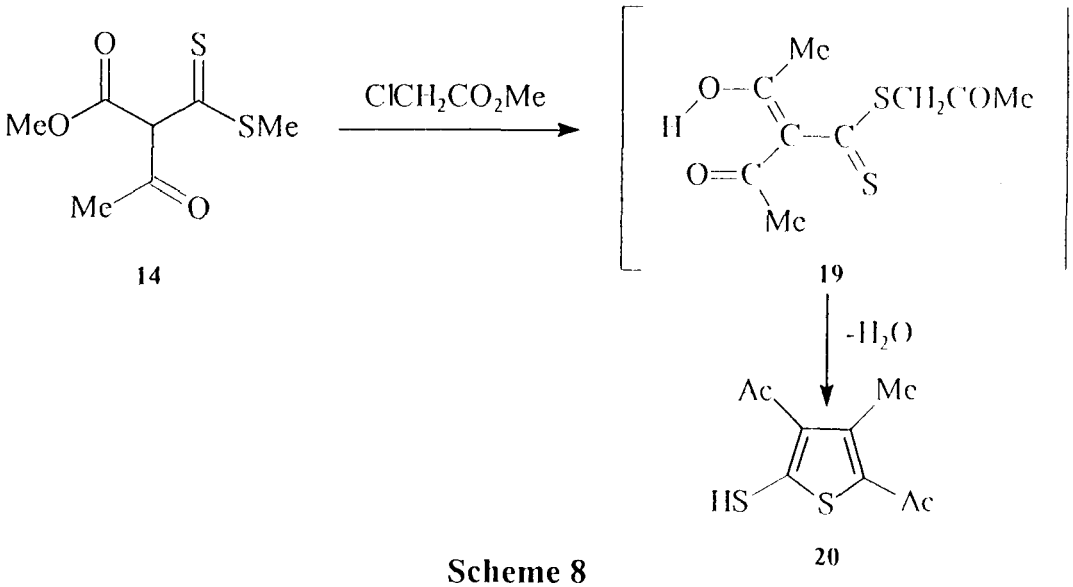


13 **16** **17a** **18** **14** **14a**

Scheme 7

By this time a large of active methylene ketones[19-31], aldehydes[32], lactones[33], β-ketoesters[34], sulfoxides[35], sulphones[34,35], nitromethane,[21] and doubly activated methylene compounds as malononitrile,[34,36] cyanoacetamide[21,23,30,34,37,38,39] were reacted with carbon disulphide. In all these cases, alkali metal hydroxides, alkali metal alkoxides, alkali metal hydrides and alkali metal amides were used as bases. In most of these cases it was noticed that only the corresponding dianion were formed exclusively, which yielded the corresponding α-oxoketene dithioacetals after alkylation.

However Gompper and co-workers had observed the formation of **17** by adding one equivalent of hydrochloric acid to **16**. They also observed that after complete acidification the resultant dithioic acids were often unstable and underwent decomposition. The unequivocal synthesis of alkyl dithioates are important as intermediates to prepare their corresponding mixed α-oxoketene dithioacetals which are in turn useful intermediates for various synthetic purposes. The β-oxodithioates are also excellent precursors for the synthesis of thiophenes **20**[40] as formulated in Scheme-8.

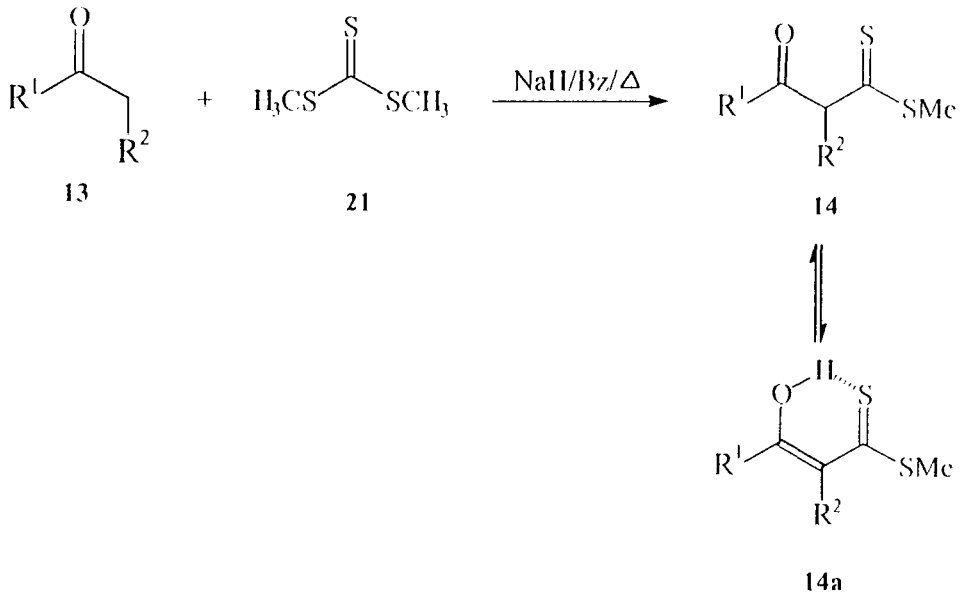


Scheme 8

Therefore the only methods available for the synthesis of β-oxodithioates were the ones developed by Gompper (Scheme-6) and the other by Lawesson and Larsson (Scheme-7). Both these methods involve careful acidification of the disodium or dipotassium salts to get the monosalt or dithioic acids followed by further alkylation to get the β-oxodithioates. The dithioic acids were further found to be unstable and thus resulted in overall poor yields of the β-

oxodithioates. Also Lawesson and co-workers have used these dithioates to prepare the corresponding mixed α-oxoketene dithioacetals with allyl alkylating group to examine their thioclaisen rearrangement[22]. Therefore Lawesson and co-workers developed an unequivocal method for the synthesis of alkyl dithioates applying ion-pair extraction technique discovered by Brandstrom[41,42] and Starks[43]. It was found that in order to have the monoester we have to get the corresponding monosalt and these monosalts should be alkylated to yield the desired dithioates. The Brandstrom's ion pair extraction technique was successfully applied as shown in Scheme-7. Thus instead of preparing the monoacid as Gompper and co-workers these investigators acidified **16** with excess of hydrochloric acid and the corresponding dithioic acid **17a** was then treated with tetrabutylammonium hydroxide when the corresponding mono tetrabutylammonium salt **18** was formed which was alkylated with appropriate alkylating agent to give excellent yields of β-dithioates **14**. The dithioates were then used for various other studies by these authors.

Another direct method for the synthesis of β-oxodithioates was reported from our laboratory itself in 1982. Thus, enolates derived from active methylene ketones when reacted with dimethyl trithiocarbonate **21** in boiling benzene it afforded the corresponding dithioate **14** in 50-60% overall yields[44] (Scheme-9).

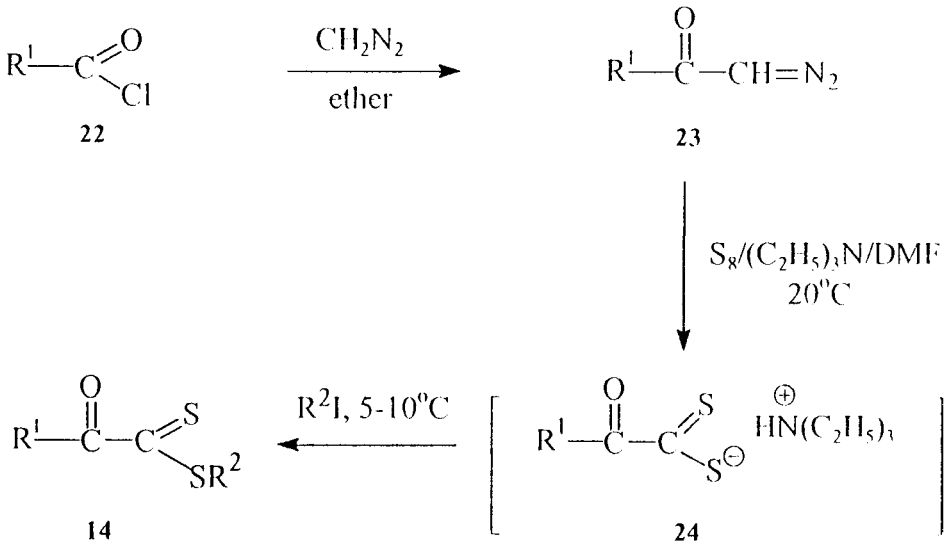


Scheme 9

The cyclic ketones also reacted under these conditions to afford moderate yields of the corresponding dithioates. However α-tetralone gave only 24% yield of the desired product. The alkyl ketones examined also did not give satisfactory yields of dithioates by this method. Phenyl acetonitrile also reacted with **21** to give the corresponding dithioate in only 45% yield. The method failed to yield the corresponding dithioates from methyl cyanoacetate, diethyl malonate, malononitrile, and nitromethane.

Recently Voss and co-workers have reacted acid chlorides **22** with diazomethane to get the corresponding diazoketones **23** and reacted these with elemental sulphur in the presence of triethylamine to afford *in situ* the corresponding dithioate salt **24** which was alkylated to afford the corresponding β-oxodithioates in good yields[45] (Scheme-10). Here again most of the examples selected were aromatic ketones and very few alkyl ketones

were used to make the corresponding dithioates. It is interesting to note that only hindered ketones in aliphatic category have been used by these authors.



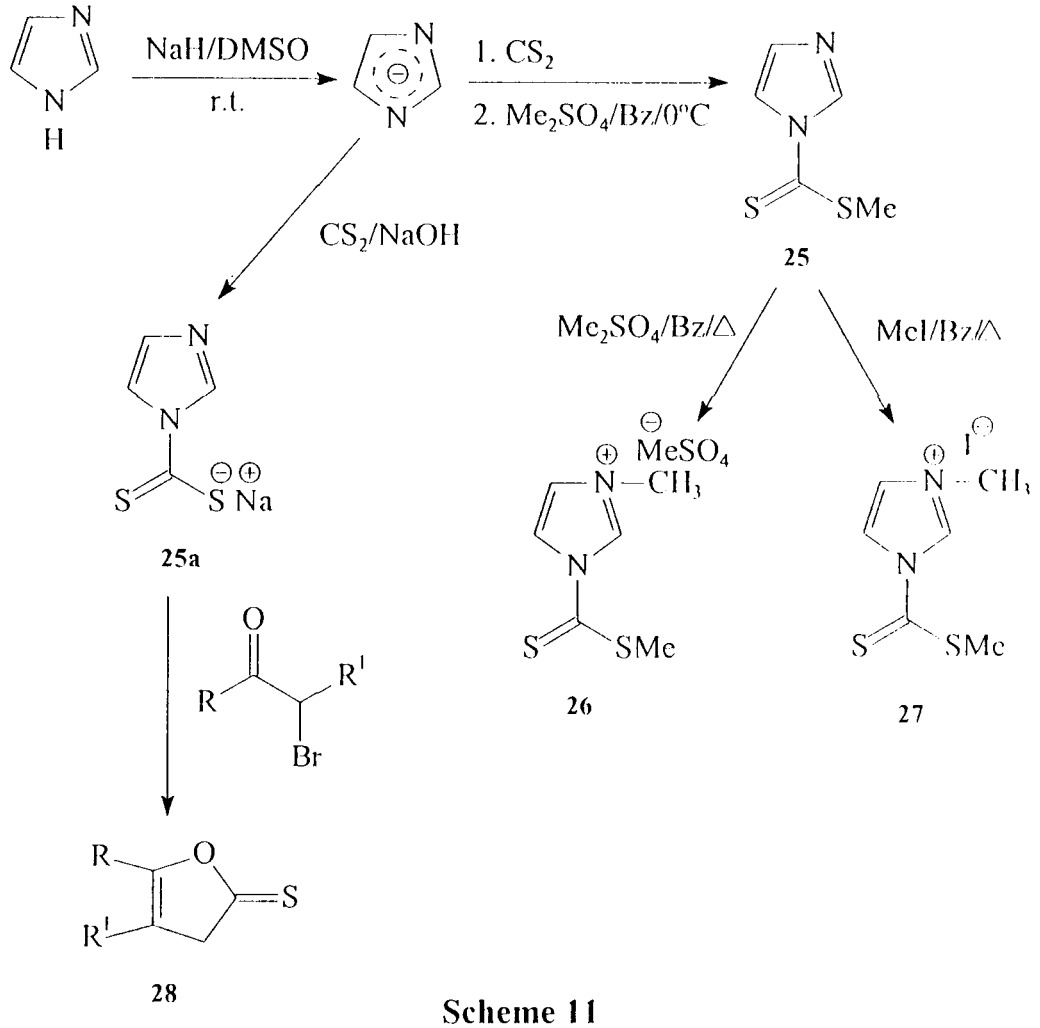
22 23 14 24

Scheme 10

From these selected reports on the synthesis of dithioates it is apparent that alkyl and aryl organometallic reagents react with carbon disulphide to afford the corresponding mono Grignard salts which are generally alkylated to yield the corresponding alkyl dithioates in excellent yields. The lack of active hydrogen in these systems has facilitated the synthesis of dithioates with mono alkylation. On the other hand when the active methylene compounds were the substrates in these reactions the mono alkali metal salts further activated the α-hydrogens with increased activity pushing forward competitive formation of dialkali metal salts instead of their mono alkali metal salts. In order to synthesize β-oxodithioates two approaches were therefore employed to circumvent this problem. One developed by Gompper generated the mono sodium salt by carefully acidifying the dialkali

metal salt with hydrochloric acid. The mono sodium salt so obtained was then alkylated using one equivalent of methyl iodide to obtain the corresponding β-oxodithioates. However, the use of hydrochloric acid to exactly neutralise one of the negative centers of the dithioate was not always an easy task, in many of the systems and no aliphatic system was ever examined by this method. Subsequently Larsson and Lawesson improved this method by using excess of acid to get the dithioic acid first and then treated this acid with tetrabutylammonium hydroxide to get the mono tetrabutylammonium salt which could be alkylated to afford the β-oxodithioates. However they have also examined only aromatic ketones possibly because their dithioic acids are more stable than their aliphatic counterparts. Our own past results did not give satisfactory yields of dithioates from aliphatic ketones or aldehydes, when reacted with dimethyl trithiocarbonate, while many active methylene compounds failed to yield the desired dithioates. Subsequent innovative discoveries by Voss and co-workers did not succeed to give aliphatic dithioates leaving the problem still unsolved. Thus there was a need to develop a satisfactory preparative methodology which could be applied for the preparation of both aromatic as well as aliphatic dithioates in high yields.

We have, in the present work, investigated the application of 1-(methyldithiocarbonyl)imidazole **25** and 3-methyl-1-(methyldithiocarbonyl) imidazolium iodide **27** (Scheme-11) as efficient reagents for dithioate synthesis.



Scheme 11

Thus enolates derived from both aliphatic and aromatic ketones when reacted with either **25** or **26/27** give high yields of desired dithioates. The expected improved yields of β-oxodithioates from the quaternary salt **26** or **27** are also observed through this investigation which are also presented in the following section.

RESULTS AND DISCUSSION

In the preceding section of this chapter a brief survey on the synthesis of simple and activated dithioates were described as reported in literature. The reported methods have been found to be unsatisfactory for the universal application for the synthesis of β-oxodithioates. Only aryl ketones have been found to give satisfactory results and therefore the literature methods for the synthesis of β-oxodithioates has remained limited only for these group of dithioates.

Many attempts were made in this laboratory to apply carbon disulphide or dimethyl trithiocarbonate methodology to enolates derived from aliphatic systems and obtain the corresponding dithioates which failed in most of the cases examined. The aliphatic β-oxodithioates derived from aliphatic ketones have been very important synthetic intermediates, for which there exists no satisfactory method of synthesis available in the literature. It was therefore considered of practical importance that one can explore possibilities to develop a new reagent which can circumvent these limitations. We have thus successfully developed reagents and applied them for the synthesis of dithioates without exception. 1-(methyldithiocarbonyl)imidazole **25** Scheme-11 was reported earlier by Pianka and co-workers in 1980[46]. They reacted heterocyclic methyl trithiocarbonate with imidazole in the presence of triethylamine to afford **25** in 93% overall yields. However the Japanese workers[47] have reported that imidazole reacts with carbon disulphide in the

presence of alkali metal to give sodium dithioate in quantitative yields. The sodium salt **25a** (Scheme-11) was reacted with α-bromoketones to afford the corresponding 1,3-oxathiol-2-thiones **28** in very high yields. Subsequently Sun and co-workers[48] also prepared **25** essentially by alkylating the sodium salt **25a** with methyl iodide in quantitative yield. We were using this intermediate **25** in the present investigation when the paper from Sun's group appeared and 1-(methyldithiocarbonyl)imidazole was being used by them to synthezise xanthates derived from higher alcohols. The reagent **25** was prepared essentially by us using the same method as Sun and co-workers but by only using DMSO instead of THF as solvent. The dithioate **25** was quaternised by reacting it with dimethyl sulphate or methyl iodide to afford the corresponding N-methyl salt **26** or **27** in near quantitative yields. The quaternary salts **26** or **27** were not reported earlier. The structure of 3-methyl-1-(methyldithiocarbonyl)imidazolium iodide **27** was characterised from its analytical and spectral data given below.

DATA

m.p. 75-76°C (decomposed)

I.R. (KBr) 3066, 1641, 1611, 1582, 1178, 1088 cm^{-1}

^1H NMR (300 MHz $CDCl_3$/DMSO) 2.96 (s, 3H, SCH_3), 4.02 (S, 3H, NCH_3), 7.95 (s, 1H, HC=CH), 8.34 (brs, 1H, NHC=N), 10.18 (s, 1H, NCH=N).

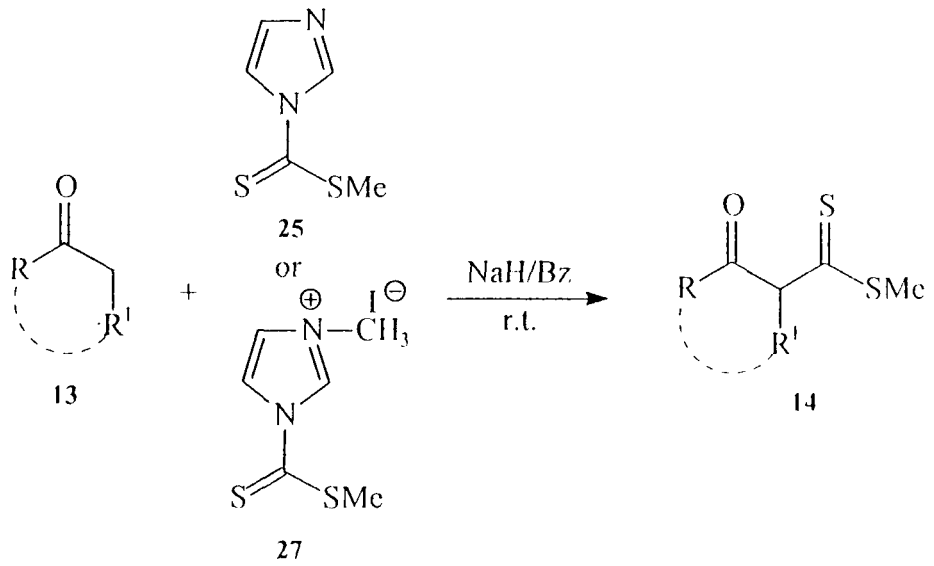
Mass (m /z, %) = 173 (M^+ -127, 97%)

Molecular formula $C_6H_9N_2S_2I$

Molecular weight = 300.18

Elemental analysis C 24.01, H 3.02 and N 9.33 %. Found C 24.20, H 2.98, N 9.47%.

The experimental procedure employed for the synthesis of β-oxodithioates **14** using **25** or **27** as useful dithioate transfer reagents to active methylene compounds is depicted in Scheme-12.

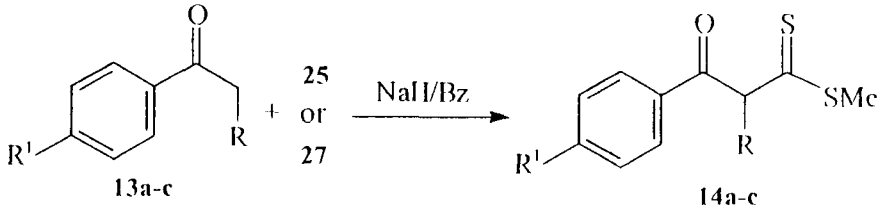


Scheme 12

The yields from both **25** and **27** are listed in the subsequent tables and the improved yield profile obtained from **27** are also depicted. Also the yields and methods of preparation of the reported dithioates are incorporated wherever available so that the superiority of the present method can be justified. Since earlier reported methods were generally satisfactory for aromatic ketones only a few have been reacted by our present method. Thus acetophenone **13a** when reacted with **25** in

benzene and sodium hydride and stirred for a few hours at room temperature, the reaction mixture after work up yielded the corresponding dithioate **14a** in 78% yield (Scheme-13). The properties of dithioate **14a** was fully in conformity with the properties reported earlier[22]. It may be noted that **13a** reacted with **27** in the presence of sodium hydride in benzene/DMSO solvent combination under the same reaction condition but with reduced time period of reaction to yield **14a** in a much improved i.e. 90% overall yield. Thus the quaternary salt **27** is more reactive and consequently the yield of **14a** is the best so far reported. Apparently the dimethyl trithiocarbonate method reported[44] earlier for the synthesis of **14a** yielded only 60% of the product. The present method is therefore superior to the trithiocarbonate method also. Similarly, paramethyl acetophenone **13b** yielded **14b** in two different reactions. The one with **25** and **13b** and the other **27** with **13b** under the conditions described above gave **14b** in 82 and 85% yields respectively. The dithioate **14b** was fully characterised from its analytical and spectral data with that reported earlier[44]. The dimethyl trithiocarbonate method yielded only 62% of the desired product. Also propiophenone **13c** when reacted with **25** and sodium hydride in benzene and after stirring for a few hours followed by work up yielded an impressive 83% yield of dithioate **14c** which was found to be identical with the data as reported earlier[44]. It may be noted that **13c** reacted with **27** in the presence of sodium hydride and benzene/DMSO solvent combination to give 87% of **14c.** The dimethyl trithiocarbonate method gave 61% yield of the desired β-oxodithioate (Scheme-13).

Very few cyclic ketones were studied by the trithiocarbonate method earlier with variably low yields. Thus when cyclopentanone was reacted with **25** under the same reaction condition as described earlier, it afforded the corresponding dithioate



13a-c 14a-c

13,14	% Yield from **25**	% Yield from **27**	% Yield $S=C(SMe)_2$	mp°C	Reported mp°C
a R = H, R^1 = H	78	90	60	56-57	57[22]
b R = H, R^1 = CH_3	82	85	62	55	54-55[44]
c R = CH_3, R^1 = H	83	87	61	liq	liq[44]

Scheme 13

13d in 71% yield which was fully in confirmity with the data reported earlier[44]. The yield with trithiocarbonate as can be seen from the table (Scheme-14) was only 57%.

13d-g 14d-g

13,14	%Yield from **25**	% Yield from **27**	% Yield $S=C(SMe)_2$	mp°C	Reported mp°C
d n = 3	71	79	57	41	40-41[44]
e n = 4	70	89	65	liq	liq[44]
f n = 6	70	88	-	liq	-
g n = 10	60	83	-	liq	-

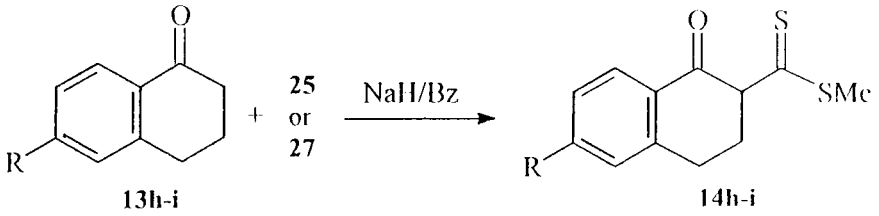
Scheme 14

The reaction of **13d** with **27** also yielded **14d** in an improved i.e. 79% yield. The other cyclic ketones **13e-13g** were reacted with both **25** and **27** using respective reaction conditions as described earlier to afford the corresponding dithioates **14e-14g** in 60 to 70% overall yields from **25** and 81-89% overall yields from **27**. The

trithiocarbonate method has only been reported with cyclopentanone **13d** and cyclohexanone **13e** to give 57% and 65% yield of the corresponding dithioates **14d** and **14e**, respectively (Scheme-14).

The analytical and spectral data of these dithioates are in conformity with that reported earlier[44]. The unreported dithioates **14f** and **14g** were characterised on the basis of its analytical and spectral data (see experimental). As seen from the table, an improved yield of β-oxodithioates is obtained when the corresponding ketones were reacted with **27**.

Tetralone **13h** reacted with trithiocarbonate to give only 24% yield of dithioate[44] while in the present method **13h** reacted with **25** to yield 62% of the corresponding dithioate **14h**, while it was improved to an impressive 80% when **13h** was reacted with **27**. 6-methoxy tetralone **13i** reacted with **25** and **27** to yield the corresponding dithioate **14i** in 69% and 82% yields respectively (Scheme-15). The analytical and spectral properties of these dithioates are in



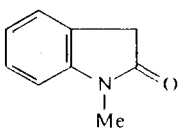
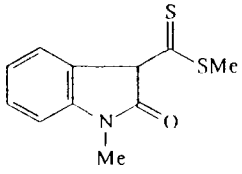
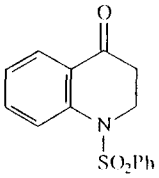
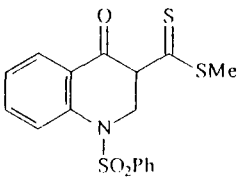
13h-i 14h-i

13,14	% Yield from **25**	% Yield from **27**	% Yield $S=C(SMe)_2$	mp °C	Reported mp °C
h R=H	62	80	24	76-77	76-77[44]
i R=OMe	69	82	-	96-98	-

Scheme 15

conformity with that reported[44]. The unknown dithioate **14i** is characterised on the basis of analytical and spectral data (see experimental).

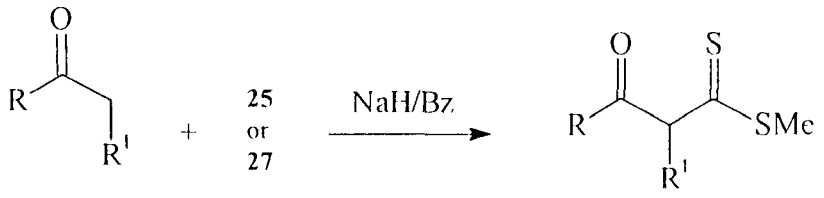
Similarly, the heterocyclic ketones **13j** and **13k** were reacted with **25** and **27** in respective reaction conditions as described earlier to afford the corresponding dithioates **14j** and **14k** in 80% and 65% overall yields from **25** and 95% and 80% overall yields from **27** (Scheme-16). These dithioates were not reported earlier and they were characterised from their analytical and spectral data (see experimental).

Starting Material Heterocyclic Ketones	Products	% Yield from **25**	% Yield from **27**	% Yield $S=C(SMe)(SMe)$	mp °C	Reported mp °C
 **13j**	 **14j**	80	95	-	120-121	-
 **13k**	 **14k**	65	80	-	110-112	-

Scheme 16

Interestingly, the present method for the synthesis of β-oxodithioates was very successful with the aliphatic ketones examined, which had earlier either failed or gave low yields by trithiocarbonate method. Thus when acetone **13l** was reacted with **25** and sodium hydride in benzene after stirring for a few hours at

r.t. followed by work up yielded 80% of the corresponding dithioate **14l**, which was obtained in only 40% yield by the earlier reported method[44]. The dithioate **14l** was confirmed for its structural assignment by analytical and spectral data which are identical with those reported in the literature. Acetone also reacted with **27** as described earlier to afford **14l** in an improved 88% yield. The other ketones which possibly failed by trithiocarbonate method reacted with **25** and **27** under the same reaction conditions as described earlier to afford the corresponding dithioate **14m** to **14o** in 64 to 91% overall yield from **25** and 84-95% overall yields from **27** (Scheme-17). The yields of



13 l-o **14 l-o**

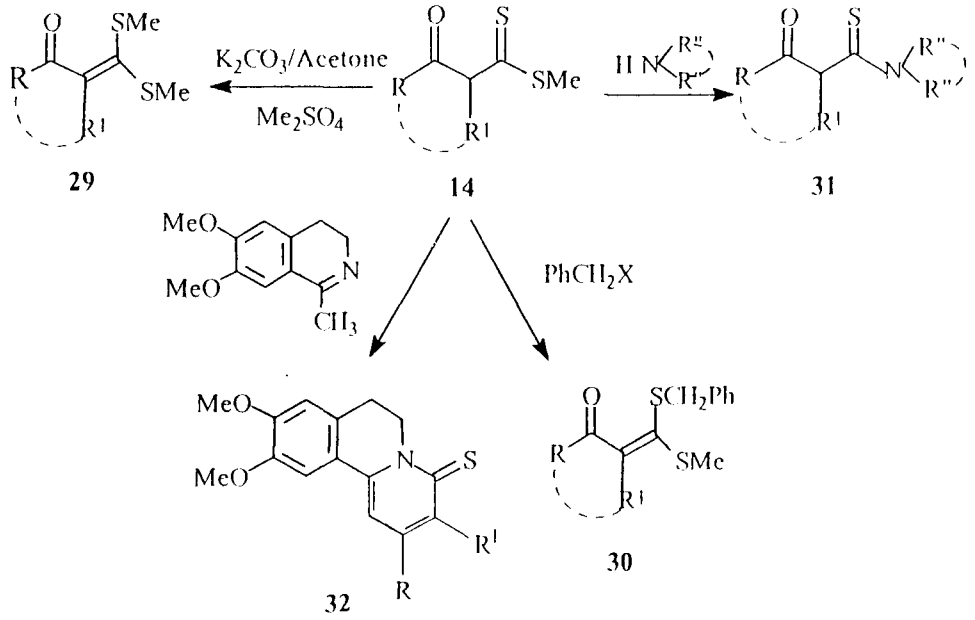
13, 14			% Yield from **25**	% Yield from **27**	% Yield $S=C(SMe)_2$	mp °C	Reported mp °C
l	$R = CH_3$,	$R^1 = H$	80	88	40	liq	liq
m	$R = CH_3$,	$R^1 = CH_3$	64	84	-	liq	-
n	$R = C_2H_5$	$R^1 = CH_3$	91	95	-	liq	-
o	$R = HC(OMe)_2$	$R^1 = H$	65	86	-	liq	-

Scheme 17

dithioates when **27** was reacted with aliphatic ketones is again much higher as observed for the other ketones also. It is to be noted that none of the systems examined in this investigation has failed to yield the corresponding dithioate.

The reagents **25** and **27** therefore possess superior reactivity towards a variety of enolates and serves as an efficient dithiocarbonyl transfer reagent to afford the corresponding dithioates in attractive yields.

The importance of these dithioates are briefly depicted in Scheme-18. The β-oxodithioates are excellent precursors for the synthesis of α-oxoketene dithioacetals both symmetrical **29** and unsymmetrical **30**[77]. The dithioates are reactive with various primary and secondary amines and affords the corresponding thioamides **31** (Scheme-18) in excellent yields.



Scheme 18

These thioamides **31** are excellent precursors for the synthesis of a variety of α-oxoketene S, N-acetals. The β-oxodithioates also react with 3,4-dihydro 6,7-dimethoxy-1-methyl isoquinolines in a one pot reaction to afford the corresponding condensed tricyclic heterocycles **32** in very high yields under mild reaction conditions. This is therefore of practical importance since it can

be applied to many natural products containing this structural moiety which are being currently explored in our laboratory.

In conclusion we have demonstrated the synthetic application of 1-(methyldithiocarbonyl)imidazole **25** as an efficient dithiocarbonyl transfer reagent to prepare β-oxodithioates **14** in high yields. We have for the first time prepared the reagent 3-methyl-1-(methydithiocarbonyl)imidazolium iodide **27** which has proved to be a better dithiocarbonyl transfer reagent and showed that it reacts with enolate anions to afford the corresponding dithioates **14** in further improved yields, which can serve as useful precursors for other synthetic transformations.

Experimental Section

General:

Melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian EM-390, 90 MHz spectrometer and are reported in δ units downfield from Me_4Si. The coupling constants are given in Hertz (Hz). TLC (silica gel, ACME's) was used for monitoring the reactions. Elemental analysis was carried out on a Heraeus CHN-O-Rapid instrument.

CHEMICALS AND REAGENTS

Commercially available NaH (SD) (75%) was used and all necessary precautions were taken while handling this reagent. Carbon disulphide and methyl iodide were used as such. DMSO was dried by refluxing with calcium hydride, distilling and then keeping over molecular seives[53], (prior to use). Dimethyl sulphate was used after neutralisation with K_2CO_3/$NaHCO_3$ and then passing through anhydrous sodium sulphate.

STARTING MATERIALS

Imidazole (Merck) mp 89-91°C was used as such. Acetophenone, p-methyl aacetophenone, cyclopentanone, cyclohexanone, acetone, ethyl

methyl ketone, dimethoxy acetone were purified by distillation under reduced pressure before use. p-methoxy 1-tetralone, b.p. 171°C (11mm) was used by distillation under reduced pressure. Propiophenone, b.p. 105-110 (8 mm)[50], 1-tetralone, b.p. 140-150°C (10 mm)[49], N-methyl oxindole (mp 126-127°C)[51] N-phenyl sulphonyl quinolone (mp 133-139°C)[52] were prepared according to reported procedures. Commercially available cyclooctanone (mp 38-41°C) cyclododecanone (mp 59-61°C) was used as such.

General Procedure for the Preparation of 1-(methyldithiocarbonyl) imidazole 25.

To a solution of imidazole (0.68g, 0.01 mol) in dry DMSO (50 ml) was added sodium hydride NaH (75%) (0.48g, 0.012 mol) at room temperature under an atmosphere of nitrogen. After stirring for 0.5 hour, carbon disulphide (CS_2) (0.93g, 0.01 mol) was added at 0°C and the reaction mixture was further stirred for 0.5 hour at room temperature followed by addition of dimethyl sulfate (Me_2SO_4) (1.9ml, 0.015 mol). The reaction mixture after stirring for 6 hours was poured into crushed ice, extracted with chloroform (3 × 25ml). The combined organic extracts were washed with water (2 × 75 ml), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. Purification of product was done by passing through a short column using hexane/ethyl acetate (80:20) as eluent to give the corresponding compound **25** (1.5g, 98%) as a yellow oil.

General Procedure for the Preparation of N-methyl salt 26 or 27.

To an ice cooled stirring solution of 1-(methyldithiocarbonyl)imidazole **25** (1.58g, 0.01 mol) in sodium dried benzene (30 ml), dimethyl sulphate (1.9 ml, 0.015 mol) or methyl iodide (2.5 ml, 0.04 mol) was added drop wise. After complete addition of Me_2SO_4 or MeI, the reaction mixture was refluxed for three hours, when orange colored crystals separated out. The salt was filtered and washed with dry benzene to yield 95% of pure compound **26 or 27**.

Preparation of β-oxodithioates

General procedure for the preparartion of β-oxodithioates using 1-(methyldithiocarbonyl)imidazole and 3-methyl-1-(methyldithiocarbonyl) imidazolium iodide and ketones.

To a well stirred suspension of sodium hydride (75%) (2.5 g, 0.05 mol) in dry benzene (25 ml) and DMSO (5 ml) appropriate ketone (0.01 mol) is added and stirred for 10 min. A solution of 1-(methyldithiocarbonyl)imidazole **25** (1.58g, 0.01mol) in dry benzene (25 ml) is slowly added drop wise and the mixture stirred for a period of four hours at room temperature. After completion of the reaction (TLC) the reaction mixture is poured in ice cold water. The aqueous layer is separated, acidified with 3N hydrochloric acid, and extracted with benzene (3 × 75 ml). The combined organic extracts were washed with water (2 × 75ml) dried (anhydrous Na_2SO_4) and evaporated under reduced pressure

to give the crude product. Purification of the crude product was achieved by column chromatography on silica gel (60g) using hexane ethyl acetate (3:1) as eluent to give the compound **14** in 60-91% overall yields. Under identical reaction conditions appropriate ketone and the quaternary salt **27** in DMSO/Benzene was stirred, for a period of 3 hours at room temperature and the reaction mixture after work up yielded the corresponding dithioates in 79-95% overall yield. All the known β-oxodithioates were characterised by comparision of their melting points, NMR, IR spectra with those reported and of authentic samples. The unknown β-oxodithioates are characterised from their analytical and spectral data. Their spectral and analytical data are given below.

Methyl 3-oxo-3-phenylpropanedithiocarboxylate (14a): colorless solid; m.p. 56-57°C; (lit[22] m.p. 57°C); yield using **25** 78%; yield using **27** 90%; IR (KBr):ν_{max} = 1235, 1554,1582 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.6 (s, 3H, SCH_3); 6.9 (s, 1H, =CH); 7.4 (m, 3H, ArH); 7.8-7.9 (m, 2H,ArH); 15.5 (s, 1H, OH). Anal. Calcd. for $C_{10}H_{10}OS_2$ (210) : C, 57.14 ; H, 4.7% . Found: C, 57.2; H, 4.5%.

Methyl 3-oxo-3-(p-methyl)phenylpropanedithiocarboxylate (14b):colorless solid; m.p. 55°C (lit[44] m.p. 54-55°C); yield using **25** 82%; yield using **27** 85%; IR (KBr): ν_{max} = 1227, 1557,1582 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.35 (s, 3H, CH_3); 2.6 (s, 3H, SCH_3); 6.85 (s, 1H, =CH); 7.15-7.8 (m, 4H, ArH); 15.05

(s, 1H, OH). Anal. Calcd. for $C_{11}H_{12}OS_2$ (224) : C,58.92; H, 5.36%. Found: C, 58.7, H, 5.12%.

Methyl 2-methyl-3-oxo-3-phenylpropanedithiocarboxylate (14c):viscous liquid; (lit[44] liq); yield using **25** 83%; yield using **27** 87%; IR (CCl_4) ν_{max} = 1218, 1546,1689 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 1.65 (d, 3H, J = 6 Hz, CH_3); 2.6 (s, 3H, SCH_3); 5.1 (q, 1H, J = 6Hz, $CHCH_3$); 7.5 (m, 3H, ArH); 7.95-8.15 (m, 2H, ArH). Anal. Calcd. for $C_{11}H_{12}OS_2$ (224) : C, 58.2 ; H, 5.36%. Found: C, 58.6, H, 5.2%.

Methyl 2-oxocyclopentane carbodithiocarboxylate (14d): yellow solid: mp 41°C mp (lit[44] 40-41°C); yield using **25** 71%; yield using **27** 79%; IR (KBr) ν_{max} = 1232, 1548,1578 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 1.8-1.93 (m, 2H, CH_2); 2.3 (m, 4H, CH_2); 2.61 (s, 3H, SCH_3); 14.26 (s, 1H, OH). Anal. Calcd. for $C_7H_{10}OS_2$ (174) : C, 48.28; H, 5.75%. Found C, 48.0, H, 5.5%.

Methyl 2-oxocyclohexanonedithiocarboxylate (14e): viscous liquid; (lit[44] liq); yield using **25** 70%; yield using **27** 89%; IR (CCl_4) ν_{max} = 1258, 1297,1540 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 1.8 (m, 4H, CH_2); 2.55 (s, 3H, SCH_3); 2.38-2.75 (m, 4H, CH_2); 15.9 (s, 1H, OH). Anal. Calcd. for $C_8H_{12}OS_2$ (188): C, 51.06; H, 6.38%. Found: C, 56.1; H, 6.0%.

Methyl 2-oxocyclooctanonedithiocarboxylate (14f): yellow liquid; yield using **25** 70%; yield using **27** 88%; IR (CCl_4) ν_{max} = 1132, 1333,1535 cm^{-1}; ^1H

NMR (90 MHz, CCl_4): δ = 1.4-1.95 (m, 12H, CH_2); 2.6 (s, 3H, SCH_3); 2.85 (t, 1H,CH); 16.0 (s, 1H, OH). Anal. Calcd. for $C_{10}H_{16}OS_2$ (216) : C, 55.56; H, 7.41%. Found: C, 55.3; H, 7.22%.

Methyl 2-oxocyclododecanonedithiocarboxylate (14g): viscous liquid; yield using **25** 60%; yield using **27** 83%; IR (CCl_4) ν_{max} = 1261, 1526,1651 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 1.35 (m, 20H, CH_2); 2.6 (s, 3H, SCH_3); 2.45-2.7 (m, 1H,CH). Anal. Calcd. for $C_{15}H_{24}OS_2$ (284): C, 63.38; H, 8.45%. Found: C, 63.5; H, 8.6%.

Methyl 1-tetralone-2-dithiocarboxylate (14h): yellow solid; m.p. 76-77°C; (lit[44] m.p. 76-77 °C); yield using **25** 62%; yield using **27** 80%; IR (KBr): ν_{max} = 1150, 1296,1519,1649 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.59 (s, 3H, SCH_3); 2.81 (m, 4H, CH_2CH); 7.1-7.36 (m, 3H,ArH); 7.9-8.01 (m, 1H,ArH); 16.0 (s, 1H, OH). Anal. Calcd. for $C_{12}H_{12}OS_2$ (263) : C, 54.75 ; H, 4.56%. Found: C, 54.92; H, 4.83%.

Methyl 6-methoxy-1-tetralone-2-dithiocarboxylate (14i) : yellow solid; m.p. 96-98°C; yield using **25** 69%; yield using **27** 82%; IR (KBr): ν_{max} 1195, 1248,1522, 1591, 1602 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.6 (s, 3H, SCH_3); 2.9 (m, 5H, CH_2CH); 3.8 (s, 3H, OCH_3); 6.65-6.9 (m, 2H,ArH); 8.0 (d, 1H, J=9 Hz). Anal. Calcd. for $C_{13}H_{14}O_2S_2$ (266) : C, 58.64 ; H, 5.26%. Found: C, 58.72; H, 5.33%.

Methyl 1-methyl oxindole-3-dithiocarboxylate (14j): colorless solid; mp 120-121°C; yield using **25** 80%; yield using **27** 95%; IR (KBr): ν_{max} 1213,1595, 1615 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.8 (s, 3H, S-CH_3); 3.6 (s, 3H, NCH_3); 6.61 (s, 1H,=CH); 7.45 (m, 3H, ArH); 8.35-8.55 (m, 1H, ArH); 16.1 (s, 1H, OH). Anal. Calcd. for $C_{11}H_{11}ONS_2$ (237) : C, 55.7 ; H, 4.64; N, 5.9 %. Found: C, 55.5; H, 4.43; N, 5.80 %.

Methyl 4-oxo-1-phenylsuphonyl-1,2,3,4-tetrahydroquinoline-3-dithiocarboxylate. (14k): colorless solid; m.p. 110-112°C; yield using **25** 65%; yield using **27** 80%; IR (KBr) ν_{max} = 1258,1542, 1602 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.69 (s, 3H, SCH_3); 5.0 (s, 2H, CH_2); 7.0 (s, 1H,=CH); 7.1 (m, 3H, ArH); 7.23 (m, 4H, ArH); 7.34 (m, 1H, ArH); 7.36 (m, 1H, ArH). Anal. Calcd. for $C_{17}H_{15}O_3NS_3$ (377) : C, 54.11; H, 3.98; N, 3.71%. Found: C, 54.2; H, 4.00; N, 3.8%.

Methyl 3-oxo butanedithiocarboxylate (14l): viscous liquid; (lit[44] viscous liq); yield using **25** 80%; yield using **27** 88%; IR (CCl_4): ν_{max} = 1215,1560, 1580 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.0 (s, 3H, CH_3); 2.52 (s, 3H, SCH_3); 6.25 (s, 1H, =CH); 15.0 (s, 1H, OH). Anal. Calcd. for $C_5H_8OS_2$ (148) : C, 40.54 ; H, 5.40%. Found: C, 40.52; H, 5.41%.

Methyl 2-methyl 3-oxo butanedithiocarboxylate (14m):viscous liquid; yield using **25** 64%; yield using **27** 84%; IR (CCl_4): IR ν_{max} = 1256,1354, 1545 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 1.49 (d, 3H, J = 6 Hz, CH_3); 2.2 (s, 3H, CH_3);

2.7 (s, 3H, SCH_3); 4.35 (m, 1H, CH); 16.0 (s, 1H, OH). Anal. Calcd. for $C_6H_{10}OS_2$ (162) : C, 44.44 ; H, 6.17%. Found: C, 44.24; H, 6.23%.

Methyl 2-methyl 3-oxo-pentanedithiocarboxylate (14n) : viscous liquid; yield using **25** 91%; yield using **27** 95%; IR (CCl_4) ν_{max} = 1258,1545, 1722 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 1.0 (t, 3H,CH_3); 1.5 (d, 3H, J = 6 Hz, CH_3); 2.5 (m, 1H, CH); 2.6 (s, 3H, SCH_3); 4.32 (q, J = 6Hz, 2H, CH_2). Anal. Calcd. for $C_7H_{12}OS_2$ (176) : C, 47.73 ; H, 6.82 %. Found: C, 47.43; H, 6.45%.

Methyl 3-oxo-4,4-dimethoxybutanedithiocarboxylate (14o): liquid; yield using **25** 65%; yield using **27** 86%; IR (CCl_4) ν_{max} = 1158,1329, 1594 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ = 2.6 (s, 3H, SCH_3); 3.38 (s, 6H, $(OCH_3)_2$); 4.86 (s, 1H, CH); 6.58 (s, 1H, =CH); 14.38 (s, 1H, OH). Anal. Calcd. for $C_7H_{12}O_3S_2$ (208) : C, 40.38 ; H, 5.77 %. Found: C, 40.2; H, 5.85%.

References

1. Doyle, K. M.; Kurzer, F. *Chem. Ind. (London)*, **1974,** 803.
2. Reid, E. E. *Organic Chemistry of Bivalent Sulphur*, Vols. 1-6, Chemical Publishing Co.Inc., New York., **1958-1966**.Scheithauer, S. .Mayer, R. *Thio- and Dithiocarboxylic Acids and Their Derivatives, Topics in Sulphur Chemistry*, Vol.4, A. Senning, Ed., Georg Thieme Verlag, Stuttgart, **1979**.
3. Donald, R.; Jerome, A. *U.S. Patent* 3479 299 **1969**, Cabot Corp.; *C. A.* **1970,** 72, 22 135.
4. Nishihara, A. *Japanese Patent* **1971**,7134 425, Asahi Electrochemical Co. Ltd.; *C. A.* **1972**, 76, 3832.
5. Gahler, S.; Junge, K. W.; Fischer, G.; Scheithauer, S.; Viola, H. *French Patent* **1977**, 2320 577, VEB Filmfabrik Wolfen-Fotochemisches Kombinat; *C. A.* **1982**, 96, 105 791.
6. Coucouvanis, D. *Prog. Inorg. Chem.* **1970,** 233.
7. Bruni, G.; Levi, T.G.; *Atti. Accad. Naz. Lincei* **1923**, 32, 5. *C. A.* **1924,** 18, 2693.
8. Houben, J.; Pohl, H. *Ber. Dtsch. Chem. Ges.* **1907,** 40, 1303, 1725.
9. Wheeler, A. S.; Thomas, C. L. *J. Am. Chem. Soc.* **1928,** 50, 3106.
10. Ramadas, S. R.; Srinivasan, P. S.; Ramachandran, J.; Sastry, V. V. S. K. *Synthesis* **1983**, 605.

11. Meijer, J.; Vermeer, P.; Brandsma, L. *Recl. Trav. Chim. Pays-Bays* **1973**, 92, 601.

12. Gosselin, P.; Masson, S.; Thuillier, A. *Tetra. Lett.* **1978**, 2715.

13. Masson, S.; Saquet, M.; Thuillier, A. *Tetra. Lett.* **1976**, 4179.

14. Brouwer, A. C.; Bos, H. J. T. *Tetra. Lett.* **1976**, 209.

15. Brouwer, A. C.; George, A.V.E.; Bos, H. J. T. *Recl Trav. Pays-Bas* **1983**, 102, 83.

16. Brouwer, A.C.; George, A.V.E; Bos, H.J.T. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 91.

17. Sakurada, Y; *Mem. Coll. Sci. Kyoto Imp. Univ. Ser. A.* **1926**, 10, 79; *C.A.* **1927**, 21, 3609.

18. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2182.

19. Thuillier, A.; Vialle, J.; *Bull. Soc. Chim. Fr.* **1962**, 2187.

20. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2194.

21. Gompper, R.; Schaefer, H. *Chem. Ber.* **1967**, 100, 591.

22. Larsson, F.C.V.; Lawesson, S-O. *Tetrahedron* **1972**, 28, 5341.

23. Gompper, R; Topfl, W. *Chem. Ber.* **1962**, 95, 2867.

24. Kelber, C. *Chem. Ber.* **1910**, 43, 1252.

25. Kelber, C.; Schwartz, A. *Ibid*, **1911**, 44, 1693.

26. Idem, *Ibid*: **1912**, 45, 137.

27. Thuillier, A.; Vialle, J.; *Bull. Soc. Chim. Fr.* **1959**, 1398.

28. Klingsberg, E.; Schreiber, A.M. *J. Am. Chem. Soc.* **1962**, 84, 2944.

29. Yates, P.; Moore, D.R.; Lynch, T.R. *Canad. J. Chem.* **1971**, 49, 1456.

30. Yates, P.; Lynch, T.R.; Moore, D.R. *Ibid.* **1971**, 49, 1467.

31. Yates, P.; Lynch, T.R. *Ibid.* **1971**, 49, 1477.

32. Saquet, M.; Thuillier, A. *Bull. Soc. Chim. Fr.* **1966**, 1582.

33. Rioult, P.; Vialle, J. *Ibid.* **1965**, 3315.

34. Foye, W. O. *J. Chem. Educ.* **1969**, 46, 841.

35. Truce, W.E.; Tracy, J.E.; Gorbaty, M.L. *J. Org. Chem.* **1971**, 36, 237.

36. Yokoyama, M. *J. Org. Chem.* **1971**, 36, 2009.

37. Soderback, E. *Acta. Chem. Scand.* **1963**, 17, 362.

38. Yokoyama, M. *J. Org. Chem.* **1970**,35, 283.

39. Yokoyma, M.; *Bull. Chem. Soc. Japan* **1970**, 43, 2938.

40. Dalgaard, L.; Jensen, L.; Lawesson, S-.O. *Tetrahedron* **1974**, 30,93.

41. Brandstrom, A.; Junggren, U. *Acta. Chem. Scand.* **1969**, 23, 2536.

42. Brandstrom, A. *Kem. Tidskr.* **1970**, 82 (5-6) 32.

43. Starks, C.M.; *J. Am. Chem. Soc.* **1971**, 93, 195.

44. Singh, G.; Bhattacharjee, S.S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693.

45. Sawluk, A.; Voss, J. *Synthesis* **1986**, 968.

46. Howes, P.D.; Pianka, M. *J. Chem. Soc. Perkin trans. I* **1980**, 762.

47. Ishida, M.; Suguira, K.; Takagi,K.; Hiraoka, H.; kato, S. *Chem. Lett.* **1988**, 1705.

48. Sun, W.Y.; Hu, J.Q.; Shi, Y.P. *Synlett* **1997**, 1279.

49. Olsen, C.E.; Bader, A.D. *Organic Synthesis Coll. Vol.4*, **1963**, 898.

50. Noller, C.R.; Adams, R. *J. Am. Chem. Soc.* **1924**, 46, 1889.

51. Abramoviten, R.A.; Hey, D.H. *J. Chem. Soc.* 1954, 1697.

52. Johnson, W.S.; Woroch, E.L.; Buell, B.G. *J. Am. Chem. Soc.* **1949**, 1901

53. Vogel's Text book of Practical Organic Chemistry 4 thEd., **1978.**

CHAPTER III

REACTION OF 1-(METHYLDITHIOCARBONYL)IMIDAZOLE AND 3-METHYL-1-(METHYLDITHIOCARBONYL)IMIDAZOLIUM IODIDE WITH AMINES: AN EFFICIENT SYNTHESIS OF DITHIOCARBAMATES, SYMMETRICAL AND UNSYMMETRICAL THIOUREAS.

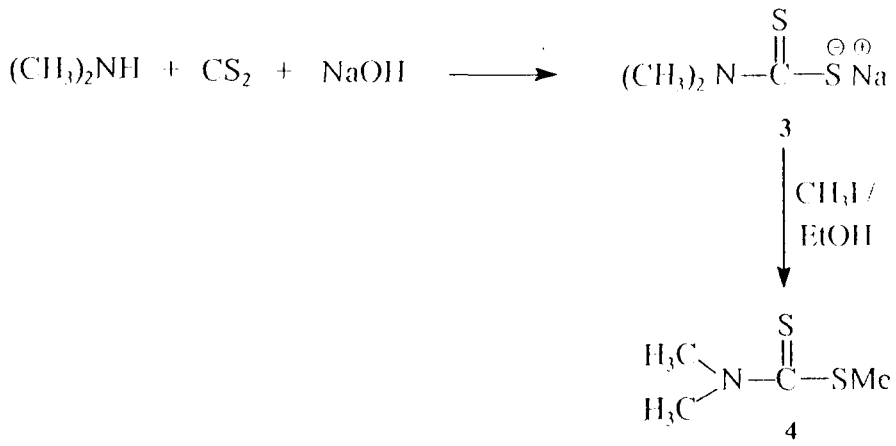
The reaction of carbon disulphide with ammonia and amine derivatives to yield the corresponding dithiocarbamates were described as early as 1850[1]. Soon after this discovery their strong affinity towards heavy metal binding and their properties were recognised largely by the work of Delepine[2] and co-workers. Due to the ability of dithiocarbamates to chelate with different metal ions many of the dithiocarbamates have found application in inorganic analysis[3]. A number of these dithiocarbamates have been used in

the rubber industry as vulcanization accelerators and antioxidants. Their application in the field of agriculture is unlimited. They have been found to display profound effect on biological systems and has been variously used as enzyme inhibitors. Their usefulness is largely due to their metal combining capacity and their interaction with sulphydryl groups. The tetramethylthiuram disulphides were found to be active against scabies as early as 1942[4]. Their application in soap industry as preventive ingredients is also very common. They are also recognised insecticides which are applied in agriculture against leaf feeding insects[5, 6].

The dithiocarbamates possess powerful fungicidal properties[7]. The biological application of the dithiocarbamate metal salts are well documented[8]. An extensive literature on both preparation and applications of these class of compounds are described in the Elsevier monograph by Thorn and Ludwig[9].

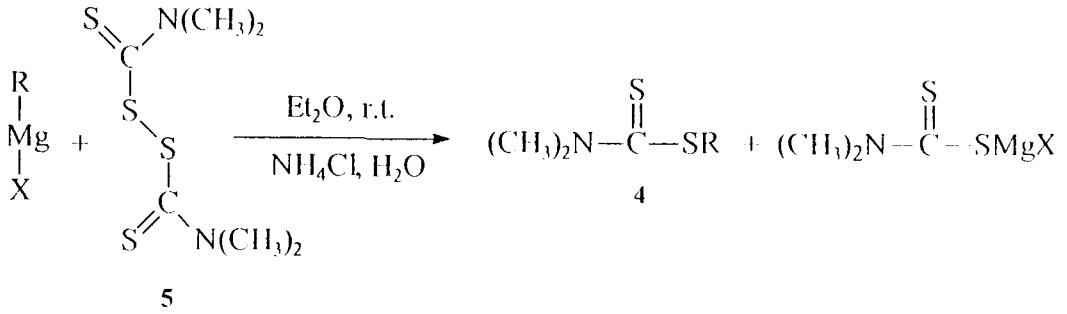
The alkyl dithiocarbamates are well defined liquids or solids which are stable enough to be stored without decomposition. These dithiocarbamates are extremely important intermediates since they can be the starting materials for the synthesis of isothiocyanates, symmetrical thioureas, unsymmetrical thioureas and a variety of heterocyclic compounds. In the present investigation reaction of 1-(methyldithiocarbonyl)imidazole **1** and N-(methyl)-N`-(methyldithiocarbonyl)imidazolium iodide **2** with various primary and secondary amines have been investigated, which under different reaction conditions yield dithiocarbamates, symmetrical and unsymmetrical thioureas.

A brief review on the reported methods of preparation and importance of alkyl/aryl dithiocarbamates, symmetrical thioureas and unsymmetrical thioureas has been presented in this section. One of the most common methods of preparation of dithiocarbamates, described in the literature as early as 1850 involves simple alkylation of sodium salt of N,N-dimethyl dithiocarbamate by methyl iodide in ethanol to yield the corresponding methyl dimethyl dithiocarbamate **4** in good yields. The sodium dithiocarbamate **3** was prepared by reacting dimethyl amine in carbon disulphide in the presence of NaOH (Scheme-1).



Scheme 1

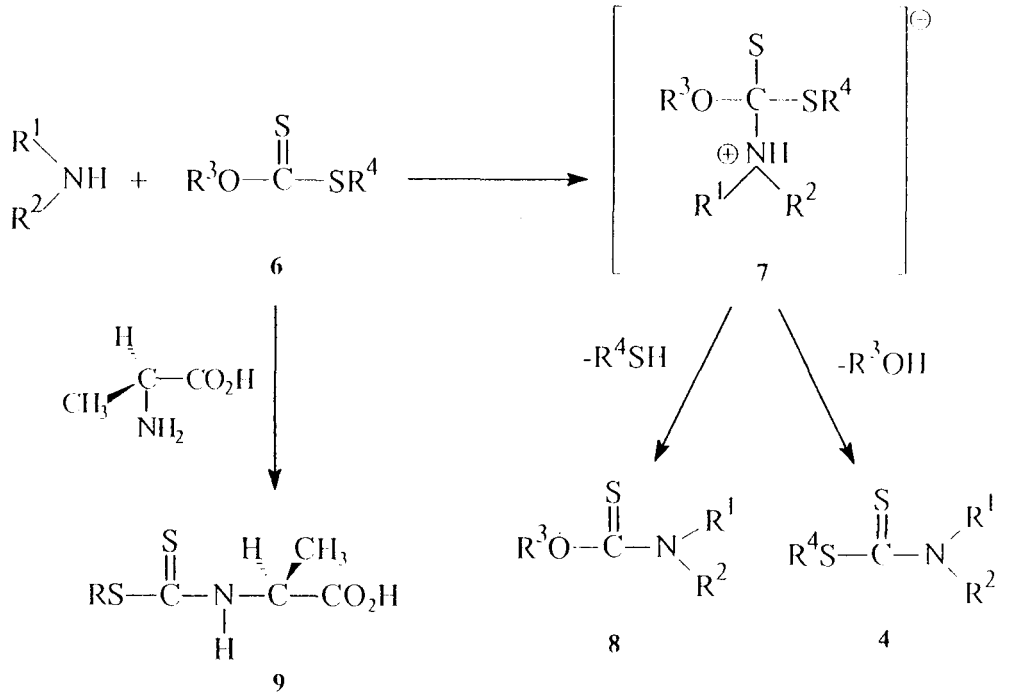
Subsequently Grunwell[10] has reported the reaction of various Grignard reagents with tetramethylthiuram disulphide **5** in diethyl ether. The reaction mixture after reaction and subsequent work up with ammonium chloride yielded the corresponding dithiocarbamate **4** in only 33% yield (Scheme-2).



Scheme 2

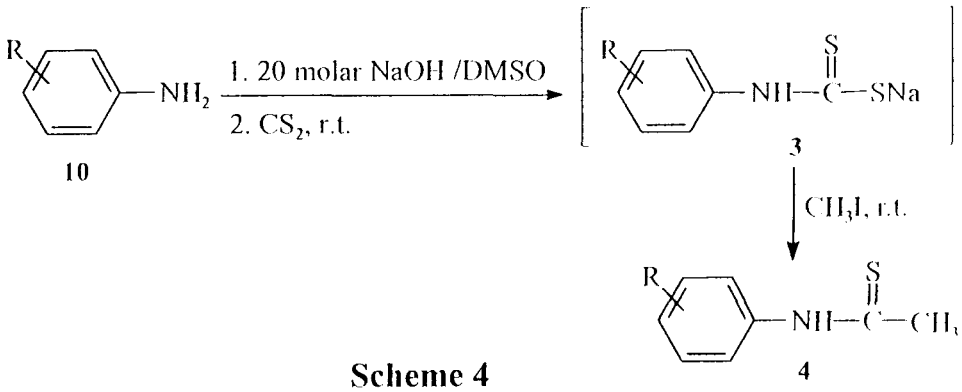
The synthetic advantage of this reaction is clearly understood since iso- and tertiary alkyl carbon atoms can be used for alkylation which are otherwise not easy to make by classical alkylation methods.

Barret and co-workers[11] developed a novel method for the synthesis of dithiocarbamates (dithiourethanes) **4** through aminolysis of tertiary alkyl xanthates **6**. Interestingly the xanthates when prepared from primary alcohols reacted with amines to afford the corresponding thioneurethanes **8** by the elimination of methyl mercaptan which is a good leaving group. On the other hand Barret and co workers[11] prepared the xanthates from tertiary alcohols and showed that the amines react with these xanthates to afford the corresponding dithiourethanes **4** in good yields. The steric hindrance of these tertiary alkyl group facilitates the elimination of alcohol during this reaction giving rise to dithiocarbamates **4.** Also secondary amines give high yields of dithiocarbamates. In this way hindered xanthates were also used as reagents of choice to prepare the dithiocarbamates **9** from L-α-amino acid. The synthetic application of tertiary butyl xanthates is of potential use in other areas which are not yet explored (Scheme-3).



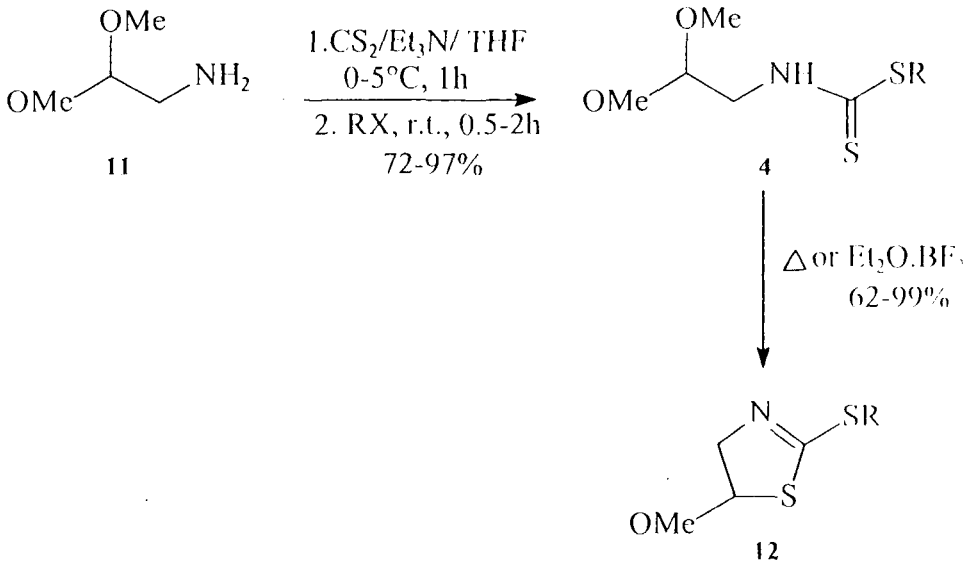
Scheme 3

A facile modification of the dithiocarbamate synthesis for the preparation of methyl N-aryl dithiocarbamates **4** (Scheme-4) was later on developed[12]. The reaction of anilines **10** with aqueous 20 M sodium hydroxide and carbon disulphide in DMSO as solvent yielded initially the corresponding sodium N-aryl dithiocarbamates **3** which are converted *in situ* to the corresponding methyl N-aryl dithiocarbamates **4** by alkylation with methyl iodide (Scheme-4).



Scheme 4

A series of 2-alkylthio-4,5-dihydro-5-methoxythiazoles **12** was prepared by thermal or BF_3.etherate assisted cyclization of the corresponding N-(2,2-dimethoxy ethyl) dithiocarbamic acid esters **4.** These dithiocarbamic acid esters are in turn prepared from aminoacetaldehyde dimethyl acetal with carbon disulphide in the presence of triethylamine[13] (Scheme-5). This paper represents the usefulness of functionalised **4** for the synthesis of important heterocycles.



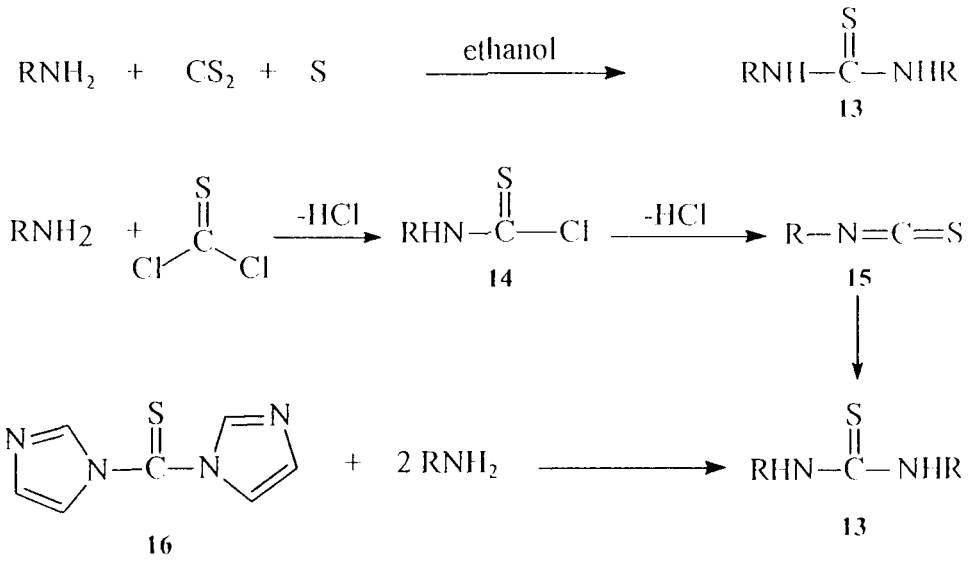
Scheme 5

A new synthesis of thioureas

The dithiocarbamate chemistry was further extended for the synthesis of symmetrical and unsymmetrical thioureas by reacting them *in situ* with various amines. As seen from literature thioureas have been prepared using different reagents and reaction conditions and many hazardous conditions were employed for thiourea synthesis. One of the earliest known

methods[14] for the synthesis of thioureas **13** has been described by Hugershof and co-workers in 1899, involving the heating of a primary arylamine with carbon disulphide and sulphur in ethanol (Scheme-6).

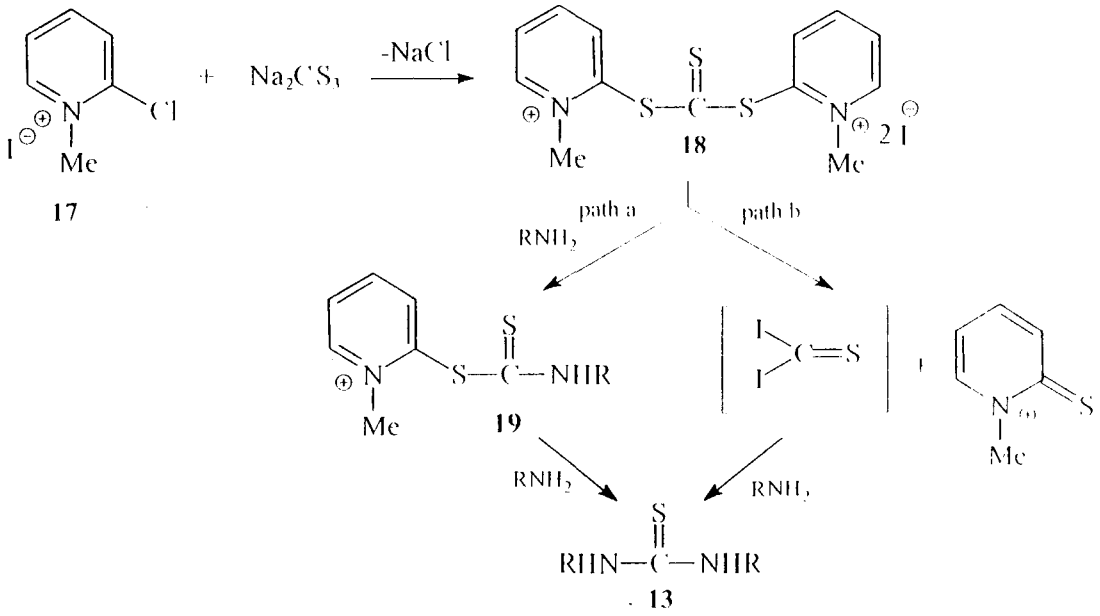
The application of thiophosgene for the synthesis of thioureas[15,16] has been described in a patent literature published in 1973 and 1977. Thiophosgene readily reacts with primary amines to afford the corresponding aminothiocarbonyl chloride **14** which readily undergo dehydro halogenation upon heating or in aqueous medium to yield isothiocyanates **15** in good yields. These isothiocyanates **15** are readily converted to the corresponding thioureas **13** in the presence of excess amine (Scheme-6).



Scheme 6

Heterocyclic thiocarbonyl transfer reagents such as 1,1'-thiocarbonyldiimidazole **16** was prepared by Staab and co-workers. These reagents have been reacted with primary amines to give the corresponding N,N'-disubstituted thioureas[17,18,19] in good yields (Scheme-6).

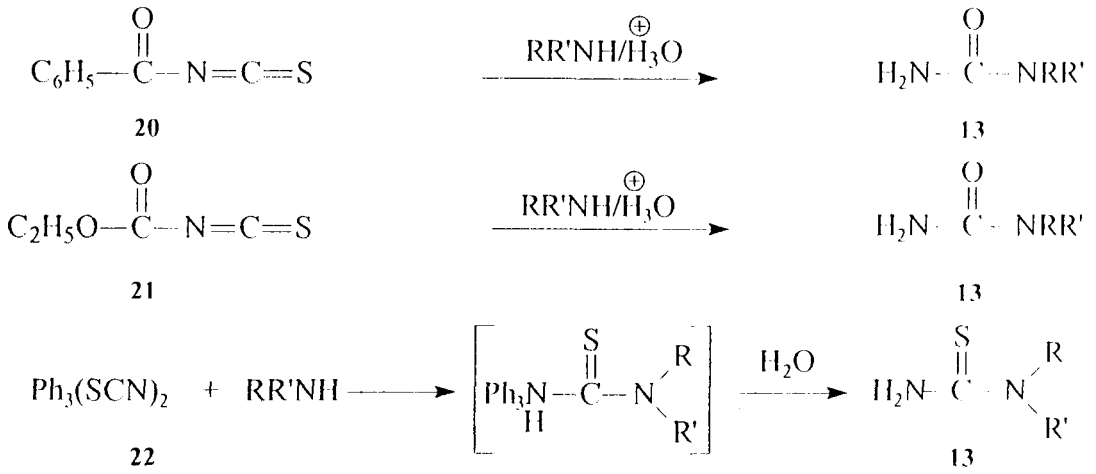
Takikawa and co-workers[20] have reported a novel method for the preparation of N, N'-disubstituted thioureas. The method involves the reaction of 2-chloropyridinium iodide **17** with sodium trithiocarbonate to afford the corresponding trithiocarbonate derivative **18** in high yields. This was further reacted with various primary amines to yield the intermediate dithiocarbamate **19**. This dithiocarbamate on subsequent heating with amines afforded the corresponding symmetrical thioureas **13** in good yields (Scheme-7).



Scheme 7

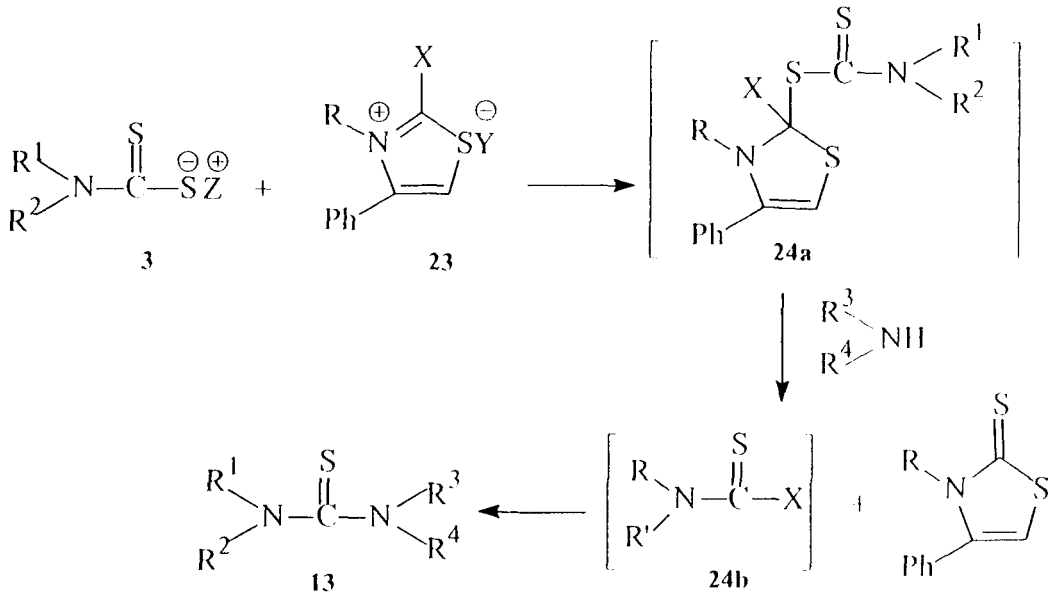
Specific methods have also been developed to make exclusively unsymmetrically substituted thioureas **13**. Thus, benzoyl isothiocyanate **20** or ethoxycarbonyl isothiocyanate **21** when reacted with secondary amines followed by acid hydrolysis yielded unsymmetrical thioureas in both the cases[21, 22] (Scheme-8).

Tamura and co-workers[23] reacted secondary amines with a combined reagent triphenylphosphine and thiocyanogen (TPPT) **22** in acetonitrile to afford the corresponding 1,1'-disubstituted thioureas **13** in good yields (Scheme 8).



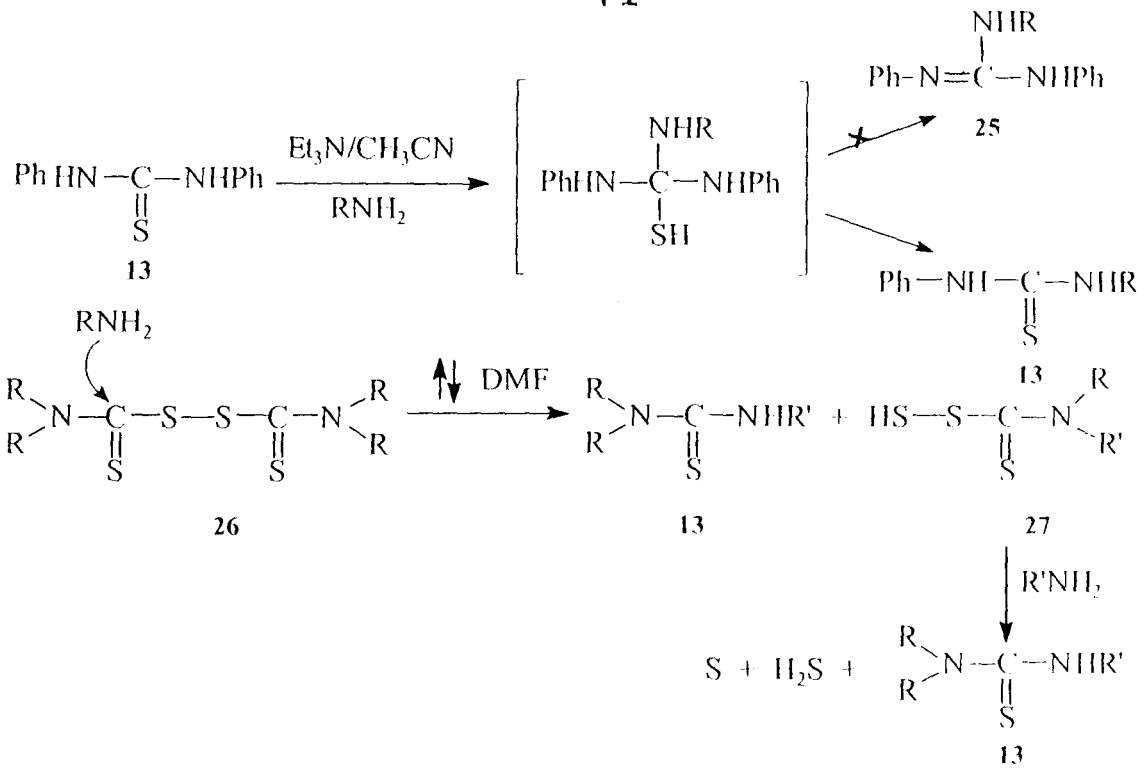
Scheme 8

Another novel method for the synthesis of unsymmetrical thioureas **13** was been reported by Hirai and co-workers[24] involving activation of salts of dithiocarbamate by 2-halothiazolium salt **23** to yield the corresponding addition product **24a** which in turn generated the active species **24b** in quantitative yield which was used for the synthesis of unsymmetrical thioureas and thiocarbamates depending on reaction conditions. These reactions represent a useful thiocarbonyl transfer process by activation with 2-halothiazolium salts (Scheme-9).



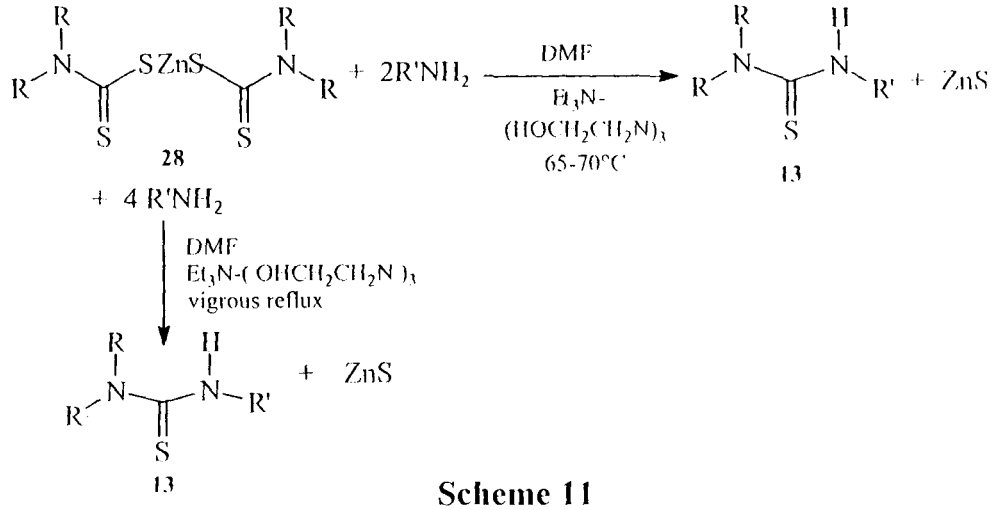
Scheme 9

A facile conversion of symmetrical thioureas to the corresponding unsymmetrical thioureas have been reported by Ramadas and co-workers[25]. In their attempt to prepare guanidines **25** by adding primary amines to diphenyl thiourea in triethylamine they obtained unsymmetrically substituted thioureas **13**. Probably the free –SH group in the presence of triethylamine facilitates elimination of bulkier phenylaniline to give the unsymmetrical thioureas **13** (Scheme-10). The same authors prepared a variety of substituted thioureas[26] by reacting thiuramdisulphides **26** with various amines in refluxing DMF (Scheme-10).



Scheme 10

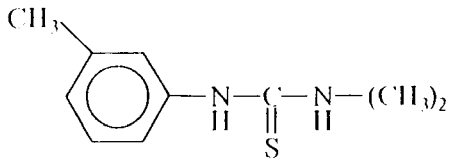
Ramadas and co-workers[27] have reported yet another method of thiourea synthesis from dialkyl dithiocarbamate zinc salt **28** and amines as formulated in (Scheme-11). The dialkyl dithiocarbamate zinc salt is commercially available and the synthesis is of commercial importance.



Scheme 11

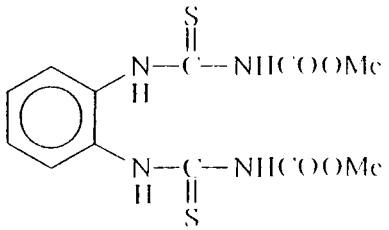
RESULTS AND DISCUSSION

In the preceding section we have described various synthesis of methyl dithiocarbamates, symmetrical thioureas and unsymmetrical thioureas using different reagents and reaction conditions. Thioureas have found application in agriculture as herbicides **29**, and fungicides **30**[28,29,30]. Some of them are phenoloxidase enzymatic inhibitors **32**[31,32a] besides their application as biomimetic models[32b,c]. They are also found to be active against bacterial and microbial infection such as RSV-37 as potential antitubercular reagents[28,30]. Also the antithyroid drug **31** is well known (Scheme-12).



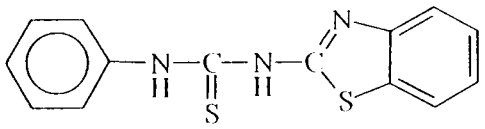
Methiuran
(Herbicide)

29



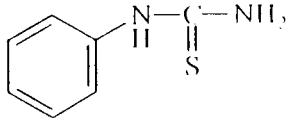
Thoiphanate Methyl
(Fungicide)

30



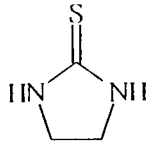
N- (benzothiozolyl) N'-phenyl thiourea
(Antithyroid activity)

31



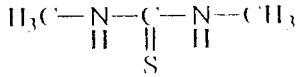
Phenyl thiourea
(phenol oxidase inhibitor)

32



Ethylene thiourea
(Corrosion Inhibitor)

33a



1,3-dimethyl thiourea
(Corrosion Inhibitor)

34

Scheme 12

Also cyclic thiourea **33a** and 1,3-dimethyl thiourea **34** are well known corrosion inhibitors[32a]. There are many thiourea derivatives used variously in many areas of modern life. They are also excellent building blocks for the construction of five and six membered heterocycles[33,34]. The reported methods for the synthesis of thioureas suffer from limitations due to many parameters such as availability of cheaper raw materials and handling problems due to environmental conditions. We have therefore investigated the reaction of **1** and **2** with various amines and shown that the yields obtained by both the methods are extremely attractive and the results of these studies are described in the following section.

The synthesis of reagents **1** and **2** are described in details in chapter II and they are directly used as dithiocarbonyl and thiocarbonyl transfer reagents in this section. Thus when an equimolar mixture of reagent **1** and benzyl amine was refluxed in ethanol for a few hours, and the reaction mixture after work up yielded the corresponding methyl N-benzyldithiocarbamate **4a** in 70% yield. However when reagent **2** was reacted with benzylamine under similar reaction conditions **4a** was obtained in an improved i.e. 98% yield. Both compounds were found identical (m.m.p. superimposable IR). **4a** was reported earlier in the literature as a white solid and the dithiocarbamate prepared by the present method was found to identical to the reported compound. The reagents **1** and **2** were also reacted with various aliphatic/aromatic primary and secondary amines **35b-j** to yield the

corresponding dithiocarbamates **4b-j** (Table I) in 67-87% overall yields from **1** and 85-98% overall yields from **2**. The mp's of various dithiocarbamates and the literature mp's for the known dithiocarbamates have also been listed in the table. The properties of the known dithiocarbamates were identical with that reported in the literature. The unknown dithiocarbamates were fully established for their structural assignment (see experimental).

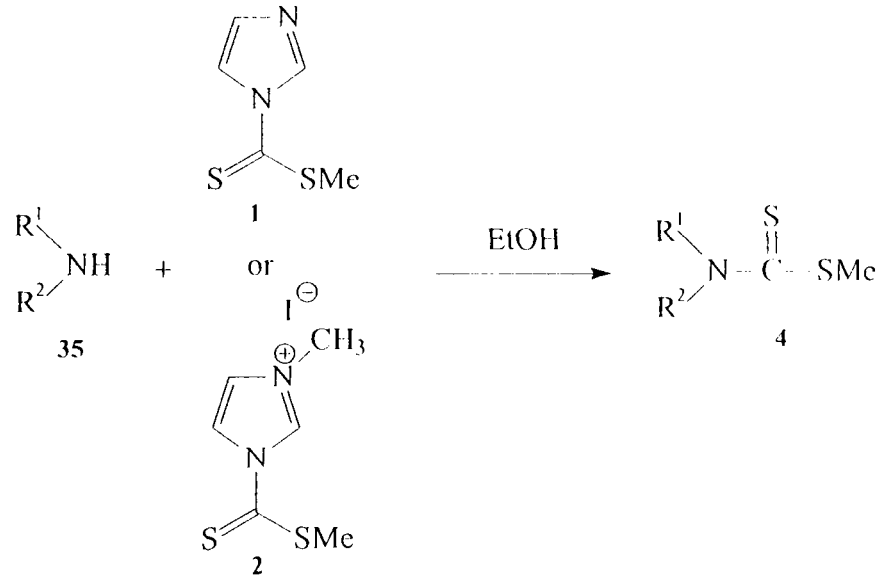
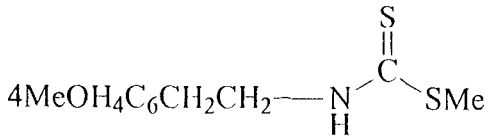
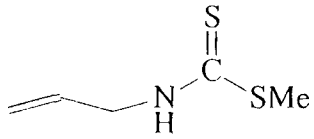
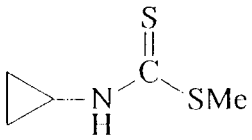
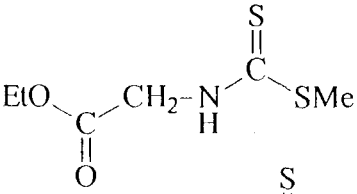
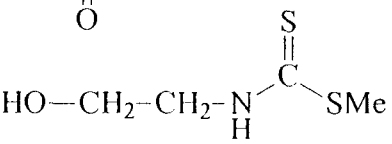
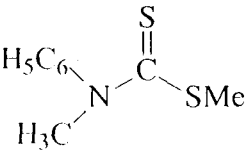
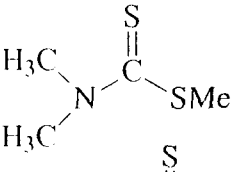
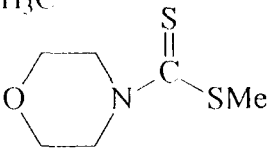


Table I

Methyl dithiocarbamates	% Yield from **1**/**2**	mp °C	Reported mp °C
35, 4a $H_5C_6CH_2$—N(H)—C(=S)—SMe	70/98	55-56	57[36]
4b H_5C_6—N(H)—C(=S)—SMe	76/86	92-93	94-95[34]

Table I

	Methyl dithiocarbamates	% Yield from 1/2	mp °C	Reported mp °C
35, 4c		75/90	58-59	-
4d		76/86	oil	oil
4e		80/97	67-68	-
4f		80/93	78-79	-
4g		67/92	76-77	-
4h		87/98	79-80	-
4i		81/94	47-48	47[10]
4j		76/84	84-85	82.5-83.5[15]

Application of reagents 1 and 2 for the synthesis of symmetrical and unsymmetrical thioureas.

1-(methyldithiocarbonyl)imidazole **1** when reacted with two equivalents of aniline in refluxing ethanol (6h) (Table-2) the reaction mixture

after work up yielded the corresponding symmetrical thiourea **13a** in 86% yield. An improved yield of 96% of this thiourea **13a** was obtained when the reagent **2** was reacted with aniline under similar reaction conditions but with reduced time period of reaction i.e. (4.5h). The thiourea was reported as a white solid purified by recrystalisation from ethanol and it was found identical in its analytical data with that reported in the literature. Our analytical and spectral data of **13a** were in conformity with the assigned structure. Our present method for the preparation of **13a** using safe reagents **1** or **2** under mild reaction conditions is definitely superior to the earlier reported methods. Similarly the other acyclic or cyclic aliphatic and heteroaromatic primary amines reacted with **1** and **2** in a 2:1 ratio under the described reaction conditions to afford N,N-disubstituted thioureas **13b-j** (Table-2) in 40-82% yield from **1** and 60-94% yields from **2** respectively.

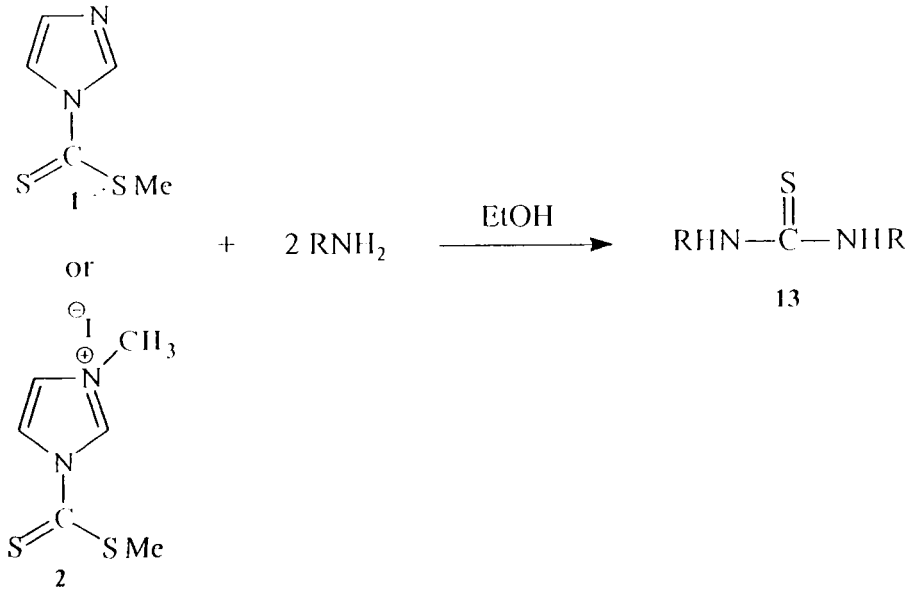
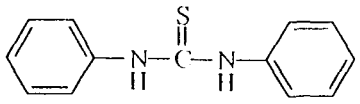
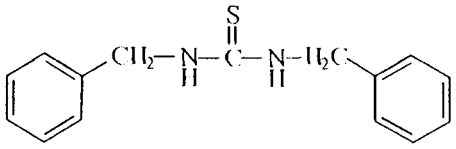
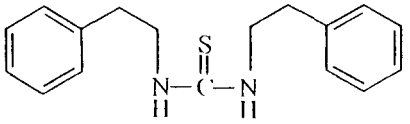
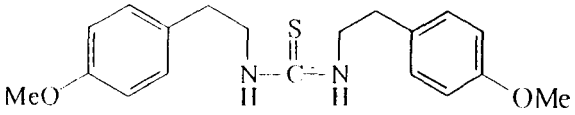
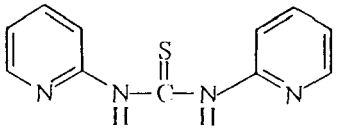
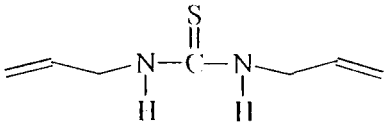
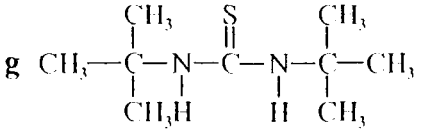
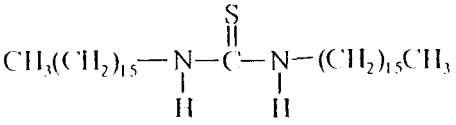
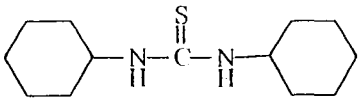
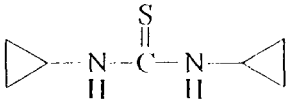
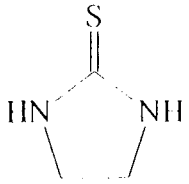


Table-2

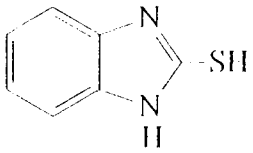
	1,3-disubstituted thioureas (symm)	%yield using 1/2	mp°C	Reported mp°C
13, **a**		86/96	151-152	152-153[38b]
b		79/92	146-147	145-147[38b]
c		80/91	91-92	90[39]
d		75/89	125-126	123-125[40]
e		70/80	153-154	152-153[38b]
f		75/90	48-49	47-49[37]
g		40/60	128-129	129-131[38b]
h		78/86	88-89	-
i		82/94	179-180	179-180[38b]
j		79/91	130-131	-

The melting points of N, N'-disubstituted thioureas reported in the literature are found to be identical with those prepared by the present method. The unreported thioureas were confirmed from their analytical and spectral data (see experimental).

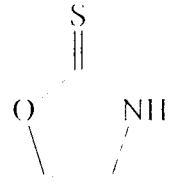
However, secondary amines like N-methylaniline and morpholine failed to give N,N'-tetrasubstituted thioureas under identical conditions and stoichiometry and yielded only dithiocarbamates **4h** and **4j** in 87% and 76% yields, respectively. The diamines such as o-phenylenediamine, ethylenediamine and ethanolamine reacted with **1** or **2** in refluxing ethanol (4-5h) to give imidazolidine-2-thione **33a,** 2-mercaptobenzimidazole **33b**, and oxozolidine-2-thione **33c**, in high yields (Scheme-13).



33a (77%)
m.p. 196-197°C
(lit[41] m.p. 195-196°C)



33b (74%)
m.p. 301-302°C
(lit[42a] m.p. 301-303°C)



33c (80%)
m.p. 97-98°C
(lit[42b] m.p. 98-99°C

Scheme 13

The overall yields obtained by using reagent **1** in some cases are certainly much higher than those reported in the literature for the known thioureas. The yields from reagent **2** are decidedly far higher than the methods described in the literature, making the present method superior to the hitherto described methods in the literature.

The application of reagents **1** and **2** for the synthesis of unsymmetrical N,N'-di- and tri-substituted thioureas was next examined. Thus an equimolar mixture of aniline and **1** was refluxed in ethanol for 1.5h (monitored by TLC) followed by addition of benzylamine (1 eqv) and further refluxing (2.5h) till the disappearance of N-phenyldithiocarbamate **4b** (TLC). The reaction mixture after work up afforded the corresponding N-benzyl-N'-phenylthiourea **13k** (Table 3) in 75% yield. The other unsymmetrical N, N'-di-(**13l-q**) and tri-substituted (**13r-t**) thioureas were similarly obtained in 61-89% and 79-88% overall yields respectively by reacting **1** first with primary amine followed by treatment with second amine in sequential manner (Table 3). The methodology could be extended further for the synthesis of mono (**13u-v**) and N,N-disubstituted (**13w-x**) thioureas by reacting **1** and **2** with ammonia and primary or secondary amine sequentially under identical conditions. Here also the melting points of the unsymmetrical thioureas prepared by our method are found identical with those reported in the literature. They were further confirmed from the spectral and analytical data (see experimental).

Here again the reported methods of preparation of unsymmetrical thioureas and the yields reported in the literature are not as satisfactory as the yields obtained from **1** and amines. The yields of unsymmetrical thioureas from amines and **2** are undoubtedly near quantitative making this method better than the reported procedures.

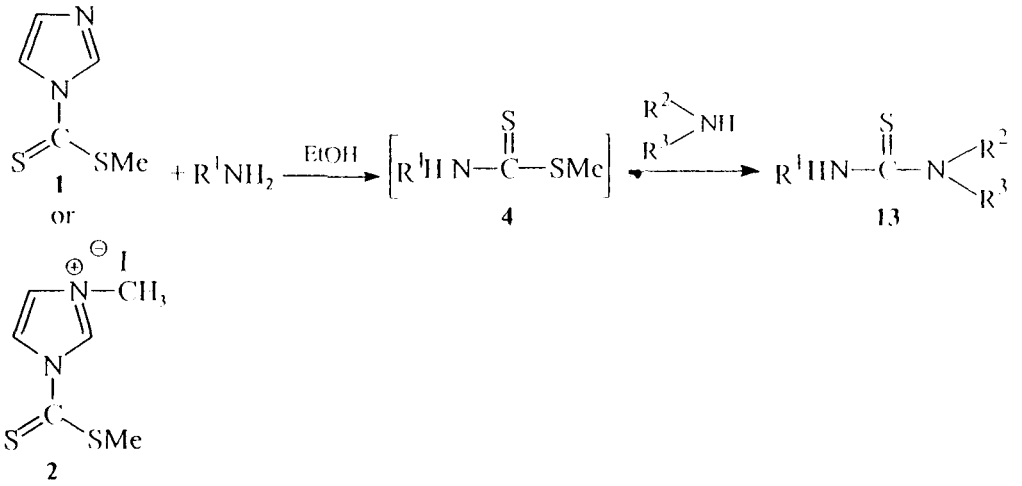


Table-3

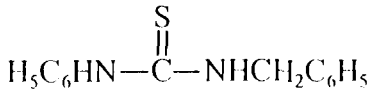
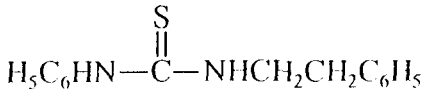
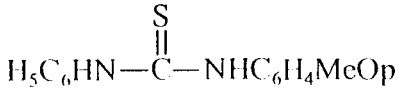
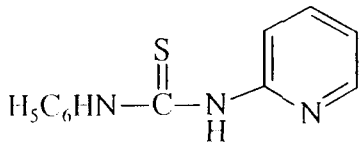
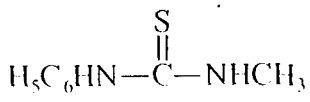
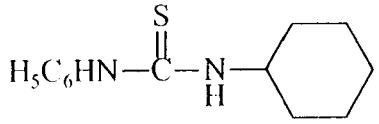
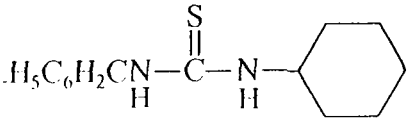
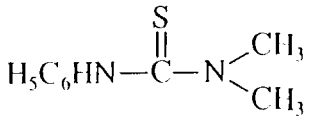
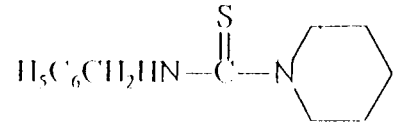
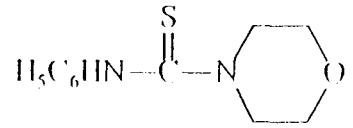
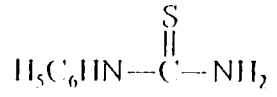
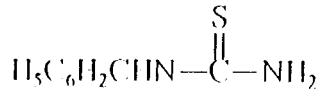
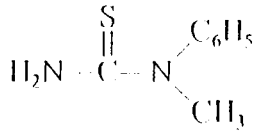
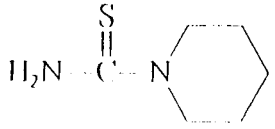
	1,3-disubstituted thiourea (unsymm)	%yield using **1/2**	mp°C	Reported mp° C
13, **k**		75/92	165-166	162-164[43]
l		73/93	106-107	106[45]
m		74/86	142-143	143[44]
n		89/91	167-168	167[46]
o		65/94	153-154	154-157[43]
p		65/82	152-153	150-151[43]
q		61/96	91-92	93-94[48]
r		79/94	137-138	136-138[43]

Table-3

	1,3-disubstituted thiourea (unsymm)	%yield using 1/2	mp°C	Reported mp° C
13, s		87/96	86-87	88[47]
t		88/90	131-132	132[43]
u		66/94	153-154	154[43]
v		66/84	164-165	165[38a]
w		72/78	107-108	107[38a]
x		76/87	125-126	126-128[49]

In conclusion we have amply demonstrated with a large number of examples the versatile reactivity of reagents **1** and **2** as useful dithiocarbonyl and thiocarbonyl transfer reagents for high yield general synthesis of methyl-dithiocarbamates, symmetrical thioureas and unsymmetrical mono-, di-, and tri-substituted thioureas in one pot procedure. The comparison of yields between the reagents **1** and **2** is evident from the tables listed. The yields from reagent **2** with amines is much higher compared to the yields of reagent **1** with amines thus proving the superiority of reagent **2** from **1**. Thus the above procedure represents a convenient least hazardous procedure for a variety of thioureas with wide structural variation.

EXPERIMENTAL SECTION

General

Melting points were determined on a Thomas Hoover Capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 983 spectrometer. ^{1}H NMR spectra were recorded on a Varian EM-390, Bruker-ACF-300 and Jeol-LA-400 spectrometer in CCl_4/$CDCl_3$/DMSO-d_6 and the chemical shifts are reported in δ (ppm) relative to tertamethyl silane. The coupling constants are given in Hertz (Hz). Mass spectra were obtained on a Jeol JMS-D-300 mass spectrometer. Elemental analysis was carried out on a Heracus CHN-O-Rapid analyser.

CHEMICALS AND REAGENTS

Commercially available NaH (SD's) (75%) was used and all necessary precautions were taken while handling this reagent. Carbon disulphide and methyl iodide were used as such. Benzene was dried by keeping over sodium wire followed by distillation before use. DMSO and ethanol were dried as reported[50].

STARTING MATERIALS

Imidazole (Merck) mp 89-91°C was used as such. Dimethylamine, allylamine, ethanolamine, cyclopropylamine, morpholine, aniline, benzylamine, p-methoxy phenylethylamine, N-methylphenylamine, tert.butylamine, phenylethylamine, cyclohexylamine, ethylenediamine, methylamine, piperidine were purified by distillation under reduced pressure before use.

The solid amines like 2-aminopyridine, p-anisidine, o-phenylenediamine, hexadecyl amine were used as such.

General method for the preparation of 1-(methyldithiocarbonyl)imidazole 1

To a solution of imidazole (0.68g, 0.01 mol) in dry DMSO (50 ml) was added sodium hydride NaH (75%) (0.48g, 0.012 mol) at room temperature under an atmosphere of nitrogen. After stirring for half an hour, carbon disulphide (CS_2) (0.93g, 0.01 mol) was added at 0°C followed after half an hour by dimethyl sulphate (Me_2SO_4) (1.9ml, 0.015 mol). The reaction mixture after stirring for 6 hours was poured into crushed ice, extracted with chloroform (50 ml). The combined organic extracts were washed with water (75 ml), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford crude 1-(methyldithiocarbonyl)imidazole **1** which was purified by passing through a short silicagel column using hexane/ethylacetate (80:20) as eluent to give the corresponding compound (1.5g, 98%) as a yellow oil.

General procedure for the preparation of N-(methyl)-N'-(methyldithiocarbonyl) imidazolinium iodide 2 .

To an ice cooled stirring solution of 1-(methyldithiocarbonyl)imidazole **1** (1.58g, 0.01mol) in sodium dried benzene (30 ml), methyl iodide (MeI) (2.5 ml, 0.04 mol) was added dropwise. After complete addition of MeI, the

reaction mixture was brought to room temperature and refluxed for three hours, when the orange colored crystals separated out which were filtered and washed with dry benzene to give 95% of pure **2.**

General procedure for the preparation of methyl dithiocarbamates (4a-j)

To a solution (or suspension) of **1** (1.58g, 0.01 mol) or its salt **2** (3.00g, 0.01 mol) in absolute ethanol, appropriate amine (0.01 mol) in 20 ml of absolute ethanol was added and the reaction mixture was refluxed between for 0.5-6 hours (monitored by TLC). Ethanol was removed under pressure and the residue was poured into water, extracted with chloroform (3 × 25 ml), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to afford methyl dithiocarbamates which were passed through a silicagel column using hexane/ethyl acetate (97:3) as eluent to give pure products. The analytical and spectral data of methyl dithiocarbamates **4** are given below.

Methyl benzyldithiocarbamate 4a: Colorless crystals; yield 1.38g (70%) using **1**; yield 1.91g (98%) using **2**; m.p. 55-56°C (lit[36] 57°C). IR (KBr): ν_{max} = 3653, 3086, 3064, 1698, 1371, 1093, 941 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$):δ = 2.65 (s, 3H, SCH_3); 4.87 (d, 2H, CH_2); 7.3 (m, 5H, ArH); 7.4 (brs, 1H, NH). Anal. Calc. for $C_9H_{11}NS_2$ (197): C, 54.82; H, 5.58; N, 7.12%. Found C, 54.72; H, 5.57; N, 7.3%.

Methyl phenyldithiocarbamate 4b: Colorless crystals; yield 1.39g (76%) using **1**; yield 1.57g (86%) using **2**; m.p. 92-93°C, (lit[34] 94-95°C). IR (KBr): ν_{max} = 3110, 3080, 1103, 1613, 1090, 957 cm^{-1}. ^1H NMR (90 MHz, CCl_4):δ =

2.6 (s, 3H, SCH_3); 7.48 (m, 5H, ArH), 9.56 (brs, 1H, NH). Anal. Calc. for $C_8H_9NS_2$ (183): C, 52.46; H, 4.92; N, 7.65%. Found C, 52.82; H, 5.0; N, 7.93%.

Methyl (4'-methoxyphenyl)ethyl dithiocarbamate 4c: Colorless crystals; yield 1.69g (75%) using **1**; yield 2.02g (90%) using **2**; m.p.58-59°C.IR (KBr): ν_{max} = 3245, 2991, 1607, 1506, 1384, 1247, 936 cm^{-1}. ^1H NMR (90 MHz, CCl_4):δ = 2.6 (s, 3H, SCH_3); 2.8 (t, J = 7Hz, 2H, CH_2); 3.6 (t, J = 7Hz, 2H, CH_2); 3.75 (s, 3H, OMe); 6.88 (dd, J = 8Hz, J = 2Hz, 2H, ArH); 7.1 (dd, J = 8Hz, J = 2Hz, 2H, ArH); 7.8 (brs, 1H, NH). Anal. Calc. for $C_{11}H_{15}NOS_2$ (241.37): C, 54.73; H, 6.26; N, 5.80%. Found C, 54.52; H, 6.18; N, 5.92%.

Methyl allyldithiocarbamate 4d: viscous liquid; yield 1.12g (76%) using **1**; yield 1.41g (86%) using **2**; IR (neat): ν_{max} = 3225, 2916, 1637, 1495, 1370, 1318, 1225, 931 cm^{-1}. ^1H NMR (90 MHz, CCl_4):δ = 2.55 (s, 3H, SCH_3); 4.35 (d, J = 7.4 Hz, 2H, CH_2); 5.25 (m, 1H, $CH{=}CH_2$); 5.85 (m, 2H, $CH_2{=}CH$); 7.5 (brs, 1H, NH). Anal. Calc. for $C_5H_9NS_2$ (147.27): C, 40.78; H, 6.16; N, 9.51%. Found C, 40.91; H, 6.35; N, 9.35%.

Methyl cyclopropyldithiocarbamate 4e: Colorless crystals; yield 1.2g (80%) using **1**; yield 1.4g (97%) using **2**; m.p. 68°C. IR (KBr): ν_{max} = 3158, 2960, 1605, 1499, 1446, 1409, 1330, 967 cm^{-1}. ^1H NMR (90 MHz, CCl_4):δ = 0.85-1.1 (m, 5H, $(CH_2)_2CH$-); 2.65 (s, 3H, SCH_3); 8.85 (brs, 1H, NH) Anal. Calc. for $C_5H_9NS_2$ (147.27): C, 40.78; H, 6.16; N, 9.51%. Found C, 40.86; H, 6.23; N, 9.67%.

Methyl (N-carboethoxymethyl) dithiocarbamate 4f: Colorless crystals; yield 1.54g (80%) using **1**; yield 1.83g (93%) using **2**; m.p. 79°C. IR (KBr): ν_{max} = 3273, 3210, 2977, 1722, 1641, 1522, 1413, 1304, 1258, 1220 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3/CCl_4$):δ = 1.31 (t, *J* = 7.5 Hz, 3H, CH_3); 2.64 (s, 3H, SCH_3); 4.27 (q, *J* = 7.5 Hz, 2H, OCH_2); 4.46 (d, *J* = 7.5Hz, 2H, CH_2NH); 7.5 (brs, 1H, NH). Anal. Calc. for $C_6H_{11}NO_2S_2$ (193.30): C, 37.28; H, 5.74; N, 7.25%. Found C, 37.08; H, 5.96; N, 7.45%.

Methyl N-(2-hydroxyethyl) dithiocarbamate 4g: Colorless crystals; yield 1.01g (67%) using **1**; yield 1.39g (92%) using **2**; m.p. 76-77°C. IR (KBr): ν_{max} = 3301, 2921, 2674, 1630, 1514, 1464, 1400, 1227, 1213, 1079 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3/CCl_4$):δ = 2.4 (s, 3H, SCH_3); 2.65 (brs, 2H, CH_2NH); 3.5 (brs, 2H, CH_2OH); 6.0 (brs, 1H, NH). Anal. Calc. for $C_4H_9NOS_2$ (151.25): C, 31.76; H, 5.99; N, 9.26%. Found C, 31.87; H, 6.11; N, 9.42%.

Methyl N-methyl-N-phenyldithiocarbamate 4h: Colorless crystals; yield 1.71g (87%) using **1**; yield 1.9g (98%) using **2**; m.p. 79-80°C. IR (KBr): ν_{max} = 2931, 1588, 1485, 1426, 1355, 1101 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$):δ = 2.54 (s, 3H, SCH_3); 3.70 (s, 3H, NCH_3); 7.2 (dd, *J* = 7.2Hz, 3.4Hz, 2H, ArH); 7.45(m, 3H, ArH). Anal. Calc. for $C_9H_{11}NS_2$ (197.33): C, 54.78; H, 5.62; N, 7.10%. Found C, 54.67; H, 5.68; N, 7.29%.

Methyl dimethyldithiocarbamate 4i: Colorless crystals; yield 1.09g (81%) using **1**; yield 1.27g (94%) using **2**; m.p. 47-48°C, (lit[19] 47°C). IR (KBr): ν_{max}

= 1658, 1311, 1054 cm^{-1}. ^1H NMR (90 MHz, CCl_4):δ = 2.62 (s, 3H, SCH_3); 3.58 (s, 6H, $(CH_2)_3N$). Anal. Calc. for $C_4H_9NS_2$ (135): C, 35.55; H, 6.67; N, 10.37%. Found C, 35.50; H, 6.32; N, 10.0%.

Methyl morpholine-N-dithiocarbamate 4j: Colorless crystals; yield 1.34g (76%) using **1**; yield 1.74g (84%) using **2**; m.p. 84-85 °C (lit[35] 82.5-83.5°C). IR (KBr): ν_{max} = 2980, 2960, 2860, 1444, 1420, 1263, 1226, 1113, 1040, 999 cm^{-1}. ^1H NMR (90 MHz, CCl_4):δ = 2.65 (s, 3H, SCH_3); 3.75 [t, *J* 7.4Hz, 4H, $N(CH_2)_2$]; 4.2 [(t, *J* =7.4Hz, 4H, $O(CH_2)_2$]; Anal. Calc. for $C_6H_{11}NOS_2$ (177.30): C, 40.65; H, 6.25; N, 7.9%. Found C, 40.25; H, 6.21; N, 8.12%.

General procedure for the preparation of Symmetrical thioureas (13a-j). In a typical experiment, a solution (or suspension) of **1** (1.58g, 0.01 mol) and **2** (3.00g, 0,01 mol) and the appropriate amine (0.02 mol) in absolute ethanol (20 ml) was refluxed for 2.5-6 hours (monitored by TLC). The excess solvent was evaporated under reduced pressure to give crystalline thioureas which were filtered and washed with ethanol. Recrystilization from ethanol yielded pure symmetrical thioureas in 40-82% yields from **1** and 60-80% of pure thioureas from **2**. Their spectral and analytical data are given below.

N,N'-Diphenylthiourea 13a: Colorless crystals; yield 1.96g (86%) using **1**; yield 2.19g (96%) using **2**; m.p.151-152°C; (lit[38b] 152-153°C). IR (KBr): ν_{max} = 3207, 2984, 3032,1313, 1069 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.5(brs,

10H, ArH); 8.35 (brs, 2H, NH). Anal. Calc. for $C_{13}H_{12}N_2S$ (228): C, 68.42; H, 5.26; N, 12.28%. Found C, 68.80; H, 5.50; N, 12.44%.

N,N'-Dibenzylthiourea 13b: Colorless crystals; yield 2.02g (79%) using **1**; yield 2.36g (92%) using **2**; m.p.146-147°C; (lit[38b] 145-147°C). IR (KBr): ν_{max} = 3058, 2912, 1326, 1077 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 4.64 (d, 4H, $(CH_2)_2$); 6.25 (brs, 2H, NH). 7.34 (brs, 10H, ArH); Anal. Calc. for $C_{15}H_{16}N_2S$ (256): C, 70.31; H, 6.25; N, 10.94%. Found C, 69.9; H, 6.11; N 11.2%.

N,N'-Diphenyl ethylthiourea 13c: Colorless crystals; yield 2.27g (80%) using **1**; yield 2.58g (91%) using **2**; m.p.91-92°C; (lit[39] 90°C). IR (KBr): ν_{max} = 3247, 1319, 1098 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$):δ = 3.0 (t, *J* = 7Hz, 4H, $(CH_2)_2$); 3.65 (t, *J* = 7Hz, 4H, $(CH_2)_2$); 6.9 (dd, *J* = 8Hz, *J* = 2Hz, 6H, ArH); 7.35 (dd, *J* = 8Hz, *J* = 2Hz, 4H, ArH); 7.9 (brs, 2H, NH). Anal.Calc.for $C_{17}H_{20}N_2S$ (284): C, 71.83; H, 7.04; N, 9.86%. Found C, 70.92; H, 6.89; N, 9.45%.

N,N'-(4'-methoxy)diphenylethylthiourea 13d: Colorless crystals; yield g (75%) using **1**; yield g (89%) using **2**; m.p.125-126°C; (lit[40] 123-125°C). IR (KBr): ν_{max} = 3037, 3018,1332, 1099 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$):δ = 2.7 (t, *J* = 7Hz, 4H, $(CH_2)_2$); 3.5 (t, *J* = 7Hz, 4H, $(CH_2)_2$); 3.9 (s, 6H, $(OMe)_2$); 7.0 (dd, *J* = 8Hz, *J* = 2Hz, 6H, ArH); 7.3 (dd, *J* = 8Hz, *J* = 2Hz, 4H, ArH); 7.9 (brs, 2H, NH). Anal. Calc. for $C_{15}H_{18}N_2SO_2$ (344): C, 66.28; H, 6.98; N, 8.14%. Found C, 66.0; H, 6.48; N, 7.92%.

N,N'-Bis(2-pyridyl)thiourea 13e: Colourless crystals; yield 1.61g (70%) using **1**; yield 1.84g (80%) using **2**; m.p.153-154°C; (lit[38b] 152-153°C). IR (KBr): ν_{max} = 3201, 3036, 2823, 1317, 1090 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$/DMSO d_6):δ = 6.88 (brs, 1H,ArH);7.71 (dd, J =8Hz, J =4.0Hz, 2H, ArH); 8.42 (dd, J =12Hz, J =4Hz, 4H, ArH); 8.8 (brs, 2H, NH). Anal. Calc. for $C_{11}H_{10}N_4S$ (230): C, 57.39; H, 4.35; N, 24.35%. Found C, 57.73; H, 4.61; N, 24.55%.

N,N'-Diallylthiourea 13f: Colorless crystals; yield 1.71g (75%) using **1**; yield 1.4g (90%) using **2**; m.p. 48-49°C; (lit[37] 47-49°C). IR (KBr): ν_{max} = 2993, 2924, 1646, 1325, 1254, 756 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$):δ = 5.1 (m, 4H, $(CH_2)_2$); 5.9 (m, 2H, $(CH)_2$); 7.0 (s, 4H, $(CH_2)_2$); 8.9 (brs, 2H, NH). Anal. Calc. for $C_7H_{12}N_2S$ (156): C, 53.85; H, 7.69; N, 17.95%. Found C, 53.92; H, 7.99; N, 18.2%.

N,N'-Di-tert-butylthiourea 13g: Colorless crystals; yield 0.75g (40%) using **1**; yield 1.13g (60%) using **2**; m.p.128-129°C; (lit[38b] 129-131°C). IR (KBr): ν_{max} = 3265, 2960, 2922, 1537, 1317, 1055 cm^{-1} .^1H NMR (90 MHz, $CDCl_3$):δ = 1.4 (s, 9H, $C(CH_3)_3$); 5.7 (brs, 1H, NH). Anal. Calc. for $C_9H_{20}N_2S$ (188): C, 57.45; H, 10.64; N, 14.89. Found C, 57.72; H, 10.93; N, 15.2%.

N,N'-Dihexadecylthiourea 13h: Colorless crystals; yield 4.09g (78%) using **1**; yield 4.51g (86%) using **2**; m.p. 88-89 °C. IR (KBr): ν_{max} = 3072, 2953,

2912, 2848, 1570, 1338 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$):δ = 1.48-1.96 (brs, 66H, $\{CH_3(CH_2)_{15}\}_2$); 6.66 (brs, 2H, NH). Anal. Calc. for $C_{33}H_{68}N_2S$ (524.98): C, 75.50; H, 13.06; N, 5.34%. Found C, 75.42; H, 13.13; N, 5 .28%.

N,N'-dicyclohexylthiourea 13i: Colorless crystals; yield 1.97g (82%) using **1**; yield 2.26g (94%) using **2**; m.p.179-180 °C; (lit[38b] 179-180°C). IR (KBr): ν_{max} = 3242, 2926, 1548, 1408, 1320, 1077 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$):δ = 1.27(m, 2H,CH); 1.61 (m, 12H, $(CH_2CH_2CH_2)_2$);2.0 (m, 8H, $(CH_2CH_2)_2$); 5.9 (brs, 2H, NH). Anal. Calc. for $C_{13}H_{24}N_2S$ (240): C, 65.0; H, 10.0; N, 11.67%. Found C, 65.51; H, 10.48; N, 11.92%.

N,N'-Dicyclopropylthiourea 13j: Colorless crystals; yield 1.23g (79%) using **1**; yield 1.42g (91%) using **2**; m.p.130-131°C. IR (KBr): ν_{max} 3394, 3202, 2984, 2215, 1521, 1322, 1255, 1215, 1022, 900 cm^{-1} .^1H NMR (400 MHz, $CDCl_3$):δ = 0.6-0.7 (m, 6H, cyclopropyl); 0.8-0.95 (m, 4H, cyclopropyl); 6.53 (brs, 2H, NH). Anal. Calc. for $C_7H_{12}N_2S$ (156.25): C, 53.81; H, 7.73; N, 17.93. Found C, 53.92; H, 7.67; N, 18.18%.

General Procedure for the preparation of unsymmetrical thioureas13k-x

To a solution (or suspension) of imidazole dithioate **1** (1.58g, 0.01 mol) and its salt (3.0g, 0.01 mol) an appropriate amine (0.01 mol) in absolute ethanol was added and refluxed for 0.5-1.5. After disappearance of amine

(monitored by TLC), a solution of the second amine (0.01 mol) or ammonia solution (25%, 1 ml) in ethanol was added and the reaction mixture was further refluxed and worked up as described earlier for symmetrical thioureas. The crude thiourea is recrystallised from ethanol to obtain pure crystals of pure unsymmetrical thioureas **13k-x** in 62-96% yields from **1** and 90-98% yields from **2**. Their spectral and analytical data are given below.

1-Phenyl-3-benzylthiourea 13k: Colorless crystals; yield 1.81g (75%) using **1**; yield 2.23g (92%) using **2**; m.p.165-166°C; (lit[43]162-164°C). IR (KBr): ν_{max} = 3361, 3147,1329, 1068 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 4.9 (d, J=6 Hz, 2H, CH_2); 7.4 (m, 10H, ArH); 7.6 (brs, 2H, ArH). Anal. Calc. for $C_{14}H_{14}N_2S$ (242): C, 69.42; H, 5.79; N, 11.57%. Found C, 70.1; H, 5.99; N, 11.73%.

1-Phenyl-3-phenylethylthiourea 13l: Colorless crystals; yield 1.87g (73%) using **1**; yield 2.38g (93%) using **2**; m.p. 106-107°C; (lit[45]106°C). IR (KBr): ν_{max} = 3371, 3021, 1312, 1066 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 2.9 (t, *J* = 7Hz, 2H, CH_2); 3.92 (t, *J* = 7Hz, 2H CH_2); 6.15 (brs, 1H, NH); 7.46(m, 10H, ArH); 8.62 (brs, 1H, NH). Anal. Calc. for $C_{15}H_{16}N_2S$ (256): C, 70.31; H, 6.25; N, 10.94%. Found C, 70.59; H, 6.45; N, 11.2%.

1-Phenyl-3-(4'-methoxy)phenylthiourea 13m: Colorless crystals; yield 1.9g (86%) using **1**; yield 2.22g (86%) using **2**; m.p.142-143°C; (lit[45]143°C). IR (KBr): ν_{max} = 3217, 2934, 1310, 1105 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 3.97 (s, 3H, OCH_3); 7.72 (brs,10H, ArH); 8.21 (brs,2H, NH) . Anal. Calc. for

$C_{14}H_{14}N_2SO$ (258): C, 65.11; H, 5.43; N, 10.85%. Found C, 65.22; H, 5.21; N, 10.48%.

1-Phenyl-3-pyridylthiourea 13n: Colorless crystals; yield 2.04g (89%) using **1**; yield 2.08g (91%) using **2**; m.p.167-168°C; (lit[46]167°C). IR (KBr): ν_{max} = 3217, 3100, 3073, 1323, 1098 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 7.3 (brs, 2H, ArH); 7.4 (dd, *J* = 7.5Hz, *J* = 4.2Hz, 1H, ArH); 7.44 (m, 5H, ArH); 7.6(dd, *J* = 11.64Hz, *J* = 4.7Hz, 1H, ArH); 10.0 (brs, 1H, NH) 13.7 (brs,1H, NH). Anal. Calc. for $C_{12}H_{11}N_2S$ (229): C, 62.88; H, 4.8; N, 18.34%. Found C, 63.1; H, 5.0; N, 18.62%.

1-Phenyl-3-methylthiourea 13o: Colorless crystals; yield 1.03g (65%) using **1**; yield 1.54g (94%) using **2**; m.p. 153-154°C; (lit[43]154-157°C). IR (KBr): ν_{max} = 3257, 3215, 1306, 1068 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$):δ = 3.1 (d, 3H, CH_3); 7.39 (m, 5H, ArH); 8.75 (brs, 1H, NH) 13.7 (brs, 1H, NH). Anal. Calc. for $C_8H_{10}N_2S$ (166): C, 57.83; H, 6.02; N, 16.87%. Found C, 57.85; H, 5.99; N, 16.90%.

1-Phenyl-3-cyclohexylthiourea 13p: Colorless crystals; yield 1.43g (65%) using **1**; yield 2.25g (82%) using **2**; m.p.152-153°C; (lit[43]150-151°C). IR (KBr): ν_{max} = 2987, 2926, 1314, 1110 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 1.35 (m, 4H, $(CH_2)_2$); 1.6 (m, 3H, $CHCH_2$); 2.1 (m, 4H $(CH_2)_2$); 7.39 (m, 5H, ArH); 8.49 (brs, 2H, NH) . Anal. Calc. for $C_{13}H_{18}N_2S$ (234): C, 66.67; H, 7.69; N, 11.97%. Found C, 66.82; H, 7.91; N, 12.0%.

1-Benzyl-3-cyclohexylthiourea 13q: Colorless crystals; yield 1.51g (61%) using **1**; yield 2.38g (96%) using **2**; m.p.91-92°C; (lit[48]93-94°C). IR (KBr): ν_{max} = 2992, 2934, 1320, 1118 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 1.33 (m, 4H, $(CH_2)_2$); 1.58 (m, 3H, $CHCH_2$); 2.0 (m, 4H $(CH_2)_2$); 4.6 (d, 2H, CH_2); 7.34 (m, 5H, ArH); 8.5 (brs, 2H, NH). Anal. Calc. for $C_{14}H_{20}N_2S$ (248): C, 67.74; H, 8.06; N, 11.29%. Found C, 67.98; H, 8.26; N, 11.42%.

1-Phenyl-3-dimethylthiourea 13r: Colorless crystals; yield 1.42g (79%) using **1**; yield 1.69g (94%) using **2**; m.p. 137-138°C; (lit[43]136-138°C). IR (KBr): ν_{max} = 2923, 1304, 1056 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 3.3 (s, 6H, $(CH_3)_2$); 7.35 (brs, 5H, ArH); 7.45 (brs, 1H, NH). Anal. Calc. for $C_9H_{12}N_2S$ (180): C, 60.0; H, 6.67; N, 15.56%. Found C, 59.9; H, 6.58; N, 15.5%.

1-Benzyl-3-pipyridylthiourea 13s: Colorless crystals; yield 2.04g (87%) using **1**; yield 2.25g (96%) using **2**; m.p.86-87°C; (lit[47]88 °C). IR (KBr): ν_{max} = 3052, 2932, 1324, 1075 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 1.54 (brs, 6H, CH_2); 3.78 (brs, 4H, CH_2); 4.87 (brs, 2H, CH_2); 5.70(brs, 2H, NH exchangeable with D_2O); 7.28 (m, 5H, ArH). Anal. Calc. for $C_{13}H_{18}N_2S$ (234): C, 66.62; H, 7.74; N, 11.95%. Found C, 66.53; H, 7.62; N, 12.03%.

1-Phenyl-3-morpholinylthiourea 13t: Colorless crystals; yield 1.95g (88%) using **1**; yield 2.0g (90%) using **2**; m.p.131-132°C; (lit[43]132°C). IR (KBr): ν_{max} = 3193, 3111, 1305, 1110 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 3.7 (brs,

8H, $(CH_2)_4$); 7.29 (m, 5H, ArH); 7.85 (brs, 1H, NH). Anal. Calc for $C_{11}H_{14}N_2SO$ (222): C, 59.46; H, 6.31; N, 12.61%. Found C, 59.47; H, 6.45; N, 12.65%.

Aniline thiourea 13u: Colorless crystals; yield 1.0g (66%) using **1**; yield 1.43g (94%) using **2**; m.p.153-154°C; (lit[43]154°C). IR (KBr): ν_{max} = 3419, 3254,1312, 1060 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 7.45 (brs, 5H, ArH); 8.48 (brs, 2H, NH). Anal. Calc. for $C_7H_8N_2S$ (152): C, 55.26; H, 5.26; N, 18.42%. Found C, 55.51; H, 5.45; N, 18.53%.

Benzyl thiourea 13v: Colorless crystals; yield 1.10g (66%) using **1**; yield 1.39g (84%) using **2**; m.p.164-165°C; (lit[38a]165°C). IR (KBr): ν_{max} = 3298, 3040, 1325, 1077 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 4.6 (d, *J* = 6Hz, 2H, CH_2); 6.35 (brs, 1H, NH); 7.35 (s, 5H, ArH); 6.3 (brs, 2H, NH). Anal Calc. for $C_8H_{10}N_2S$ (166): C, 57.83; H, 6.02; N, 16.87%. Found C, 58.99; H, 6.31; N, 16.94%.

N-methyl-N-Phenylthiourea 13w: Colorless crystals; yield 1.19g (72%) using **1**; yield 1.29g (78%) using **2**; m.p. 107-108°C; (lit[38a] 107°C). IR (KBr): ν_{max} = 3398, 3255, 1612, 1525, 1360 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 3.65 (s, 3H, CH_3); 6.12 (brs, 2H, NH); 7.64 (m, 5H, ArH). Anal. Calc. for $C_8H_{10}N_2S$ (166): C, 57.83; H, 6.02; N, 16.87%. Found C, 58.05; H, 6.05; N, 17.10%.

Pipyridylthiourea 13x: Colorless crystals; yield 1.09g (76%) using **1**; yield 1.25g (87%) using **2**; m.p. 125-126°C; (lit [49]126-128°C). IR (KBr): ν_{max} =

3332, 3170, 1648, 1515, 1362 cm^{-1} .^{1}H NMR (90 MHz, $CDCl_3$):δ = 1.74 (m, 6H, $(CH_2)_3$); 3.79 (m, 4H $(CH_2)_2$); 6.1 (brs, 2H, NH_2). Anal. Calc. for $C_6H_{12}N_2S$ (144): C, 50.0; H, 8.33; N, 19.44%. Found C, 50.32; H, 8.62; N, 19.50%.

References

1. Debus, H.; Uber die Verbindungen der Sulfocarbaminsaure. *Ann. Chem. (Leibigs)* **1850,** 73, 26.
2. Delepine, M. Metallic salts of dithiocarbamic acids; preparation of aliphatic isothiocyanates. *Compt. rend.* **1907,** 144, 1125.
3. Delepine, M. Sulphur and nitrogen compounds derived from carbon disulphide. XII metallic thiosulfocarbamates. *Bull. Soc. Chim. France* **1908,** [4] 3, 643.
4. Gordon, R.M. Observations on the treatment of scabies. *Brit. Med. J.* **1942,** 685.
5. Guy, H.G. Thiuram sulphides as repellents to leaf feeding insects. *J. Econ. Entomol.* **1936,** 29, 467.
6. Guy, H.G. investigation of organic compounds as insecticides. *Univ. Del. Agr. Exptl. Sta. Bull.* **1937,** 206.
7. Tisdale, W.H.; Williams, I. to E. I. Du Pont de Numerous & Co. Disinfectant and fungicide *U.S.P*, **1934**, Sept. II , 961.
8. Horsfall, J.G.; Fungicides and their action. *Chrocina Botanic* Co., Waltham, Mass, **1945,** 135.
9. *The dithiocarbamates and related compounds* by G.D. Thorn and R.A. Ludwig, Elsevier Publishing company, Amsterdam- New York, **1962,** 82.
10. Grunwell, J. R.; *J. Org. Chem.* **1970**, 35, 1500.

11. Barret, G.C.; Martins, C.M.O.A.; *J.C. S. Chem. Comm.* **1972,** 638.

12. Garin, J.; Martinez, V.; Mayoral, J.; Melendez, E.; Merchan, F.; *Synthesis* **1981.**

13. Lee, K.J.; Jeong, J.U.; Choi, D.O.; Kim, S.H.; Park, H.; *Synthesis* **1991,** 494.

14. Hugershof, *Chem. Ber.* **1899,** 32, 2246.

15. Japelj, M.; *Ger. Ofen.* 2209822 **1973.** C.A. **1973,** 79, 136866.

16. Beecham Group Ltd. *Belg. Patent.* **1975** 819436; *C.A.* **1977,** 87, 201318e.

17. Staab, H.A.; *Angew. Chem.* **1961,** 73, 148.

18. Staab, H.A.; Walther, G.; *Justus Leibigs Ann. Chem.* **1962,** 657, 98.

19. Staab, H.A.; Walther, G.; *Justus Leibigs Ann. Chem.* **1962,** 657, 104.

20. Takikawa, Y.; Inoue, N.; Sato, R.; Takizawa, S.; *Chemistry Lett.* **1982,** 641.

21. Hartmann, H.; Reuther, I.; *J. Prakt. Chem.* **1973,** 315, 44.

22. Reid, D. H.; et al., *Organic compounds of sulfur, Selenium and Tellurium, The chemical Society, London,* **1975,** *Vol. 3,* p 267 Esmail, R.; Kurzer,F.; *Synthesis* **1975,** 301.

23. Tamura, Y.; Adachi, M.; Kawasaki, T.; Kita, Y. *Tetra. Lett.* **1978,** 1753.

24. Sugimoto, H.; Makino, I.; Hirai, K.; *J. Org. Chem* . **1988,** 53, 2263.

25. Ramadas, K.; Srinivasan, N.; Janarthanan, N.; *Tetra. Lett.* **1993,** 34, 6447.

26. Ramadas, K.; Srinivasan, N.; *Synthetic Comm.* **1995,** 25 (21), 3381.

27. Ramadas, K.; Janarthanan N.;, *J. Chem. Research(s).* **1998,**, 228.

28. Schroeder, D.C.; *Chem. Rev.* **1955,** 55, 181.

29. Sarkis, G.V.; Faisal, E. D.; *J. Heterocycl . Chem.* **1985**, 22, 137.

30. Walpole, C.; Ko, S.V.; Brown, M.; Beattie, D.; Campbell, E.; Diickenson, F.; Ewen, S.; Hughes, G.A;, *J. Med. Chem.* **1998**, 41, 3159.

31. Makhsumov, A.G.; Safaev, A.S.; Abidova, S.V.; *Katal Pererab. Uglevodeordn .Syrya.* **1968,** 2, 101; *C.A.* **1969**, 71, 101 668v.

32. (a) Alder A, *Eur. Pat.* Appl. EP 307, 361;C.A. **1989,** 111, 173788b. (b) Tobe, Y.; Sasaki, S.; Hirose, K.; Naemura, K. *Tetrahedron Lett.* **1997**, 38, 4791. (c) Smith, J.; Liras, J.L.; Schneider, S.E.; Anslyn, E.V. *J. Org. Chem.* **1996**, 61, 8811.

33. Griffin, T. S.; Woods, T.S.; Klayman, D.L.; Thioureas in the synthesis of heterocycles. In Katritzky.A.R., Boulton A.J., editors. *Adv. Heterocycl. Chem.* **1975,** 18, 99 and references therein.

34. Garin, J.; Martinez, V.; Mayoral, J.; Melendez, E.; Merchan, F. *Synthesis* **1981**, 961.

35. McMillan, F. H.; King, J. A. *J. Am. Chem. Soc.* **1948**, 70, 4143.

36. Burrows, A. A.; Hunter, J. *J. Chem. Soc.* **1952**, 4118.

37. Williams, R. H.; Frame, E. G.; *Bull. Johns Hopkins Hosp.* **1945**, 77, 314 *C.A.* **1946**, 40, 5490.

38. (a) Neville, R. G.; Mc Gee, J. J. *Can. J. Chem.* **1963**, 41, 2123. (b) Ballabeni, M.; Ballini, R.; Bigi, F.; Maggi, R.; Parrini, M.; Predieri, G.; Sartori, G. *J. Org. Chem.* **1999**, 64, 1029.

39. Dyson, G. M.; George, H. J. *J. Chem. Soc.* **1924**, 125, 1702.

40. Bernstein, J.; Yale, H.L.; Losee, K.; Holsing, M.; Martins, J.; Lott, W. A. *J. Am. Chem. Soc.* **1951**, 73, 906.

41. Yamazaki, N.; Hagashi, F.; Iguchi, T. *Tetra. Lett.* **1974**, 13, 1191.

42. (a) Buckingham, J. "Dictionary of Organic Compounds"; 5th edition, Chapman and Hall, New York. 1982, vol. 1, 544. (b) Ettlinger, M.G. *J. Am. Chem. Soc.* **1950**, 72, 4792.

43. Xian, M.; Zhu, X.; Li, Q.; Cheng, J-P. *Tetrahedron Lett.* **1999**, 40, 1957. K.Daniel. *Bull. Soc. Chim. Fr.* **1970**, 2377.

44. Campbell, K. N.; Campbell, B. K.; Patelski, S.J. *C. A.* **1945**, 39, 881.

45. Braun, J.V.; Deutsh, H. *Chem. Ber.* **1912**, 2188.

46. Roy, A. C.; Guha, P.C. *J. Sci. Ind. Research (India).* **1950**, 9B, 262. *C. A.* **1951**, 45, 6636b.

47. Tisler, M. *Croat. Chem. Acta.* **1957**, 29, 409. *C.A.* **1959**, 53, 16130g.

48. Finnegan, W.G.; Henry, R.A. Euegene Leiber E. *J. org. Chem.* **1953**, 18, 779.

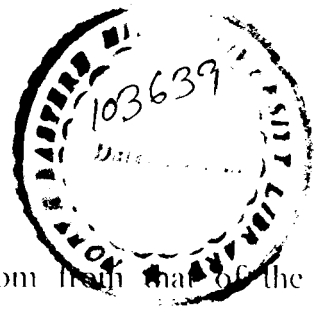
49. Mameli, E.; Ferruccio, D' Angeli, Richter, K. F. *Ann. Chim. (Rome)* **1956**, 46, 545. *C.A.* **1957**, 51, 13868d.

50. Vogel's Text book of Practical Organic Chemistry 4th; **1978**.

CHAPTER IV

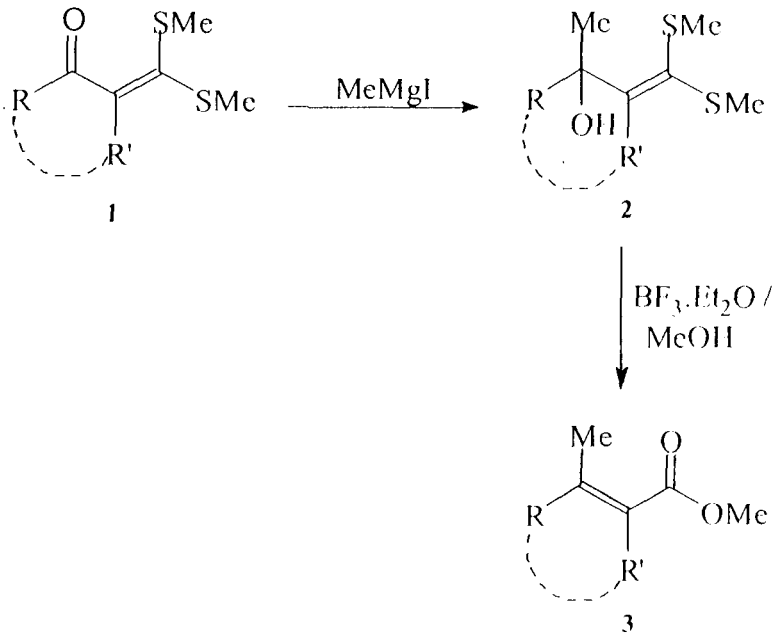
REACTION OF ORGANO GRIGNARD REAGENTS WITH α - OXOKETENE DITHIOACETALS IN THE PRESENCE OF $ZnCl_2$. TMEDA COMPLEX. A NEW GENERAL METHOD FOR THE SYNTHESIS OF HIGHLY STEREOSELECTIVE β-ALKYL-β-ALKYLTHIO-α,β-ENONES WITH *E*-CONFIGURATION

The α-oxoketene dithioacetals[1] of general formula **1** (Scheme-1) possess ambident 1,3-dielectrophilic centers with two methylthio leaving groups at the β-carbon atom. The differential reactivity of various nucleophiles with α-oxoketene dithioacetals is an area of recent interest and a number of reagents have been developed for directed 1,2-attack or 1,4-attack so that these addition products from 1,2-attack and addition-elimination products from 1,4-attack could be used as important synthetic intermediates. The presence of β,β-methylthio groups in α-oxoketene dithioacetals has



immensely altered the electrophilicity of β-carbon atom than that of the carbonyl carbon. Generally, the soft sulfur atoms have contributed to the softness of β-carbon atom while carbonyl carbon remains either unaltered or even more electrophilic towards nucleophiles. If it were oxygen the greater resonance interaction of non-bonded electrons would have rendered the carbon atom less electrophilic. On the other hand, the poor donor property of sulfur atoms has left carbonyl carbon more electrophilic towards nucleophiles. Thus α-oxoketene dithioacetals are unique 1,3-dielectrophilic structural units displaying differential electrophilicity towards various nucleophiles. The reaction of various hydride reagents and carbon nucleophiles with α-oxoketene dithioacetals has been examined in this laboratory to ascertain their regioselectivity towards **1**. The metal borohydrides examined have been known to add exclusively in a 1,2-manner to afford the corresponding carbinol acetals in near quantitative yields. These carbinol acetals underwent facile methanolysis to yield α,β-unsaturated esters in good yields[2].

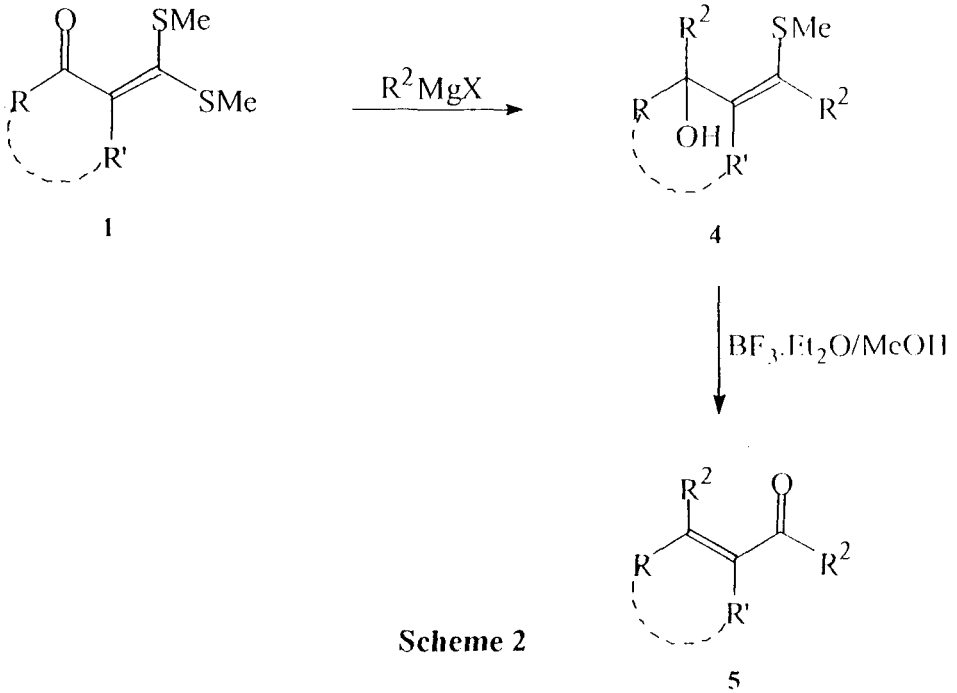
Subsequently it was shown in our laboratory that Grignard reagents particularly methyl magnesium iodide reacts with **1** in an exclusive 1,2-fashion to yield the carbinol acetals **2** which on methanolysis in the presence of $BF_3.Et_2O$ yielded crotonates **3** in excellent yields[3] (Scheme-1).



1 2 3

Scheme 1

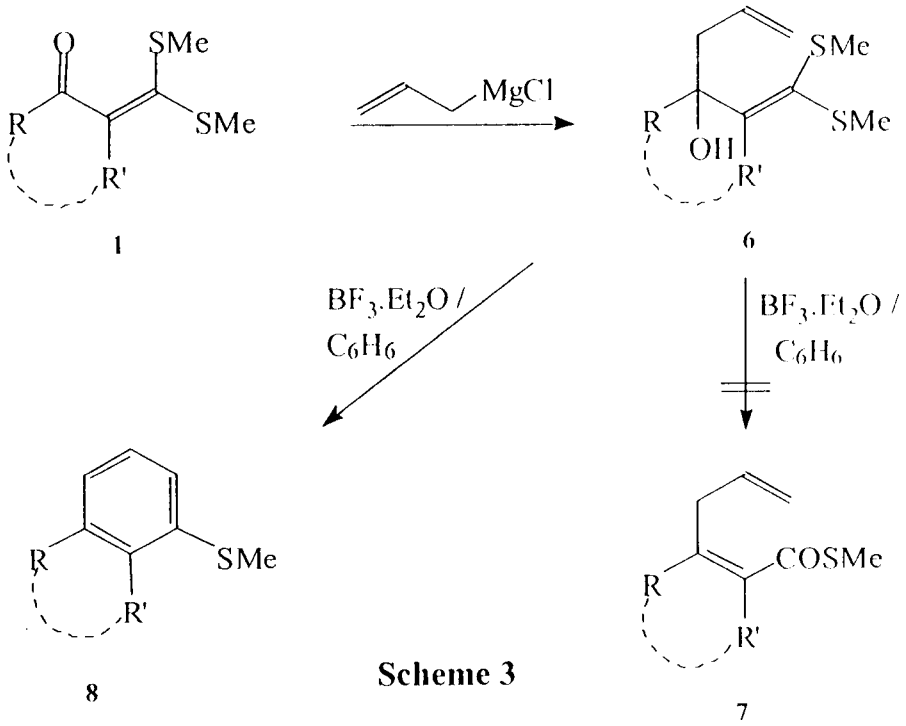
The higher alkyl Grignard reagents, i.e. ethyl, *n*-propyl, *n*-butyl etc. however followed sequential 1,4- and 1,2-addition modes to give the corresponding carbinols **4** which on hydrolysis in the presence of $BF_3.Et_2O$ and methanol yielded the α,β-unsaturated ketones **5** in good yields[3] (Scheme-2).



1 4 5

Scheme 2

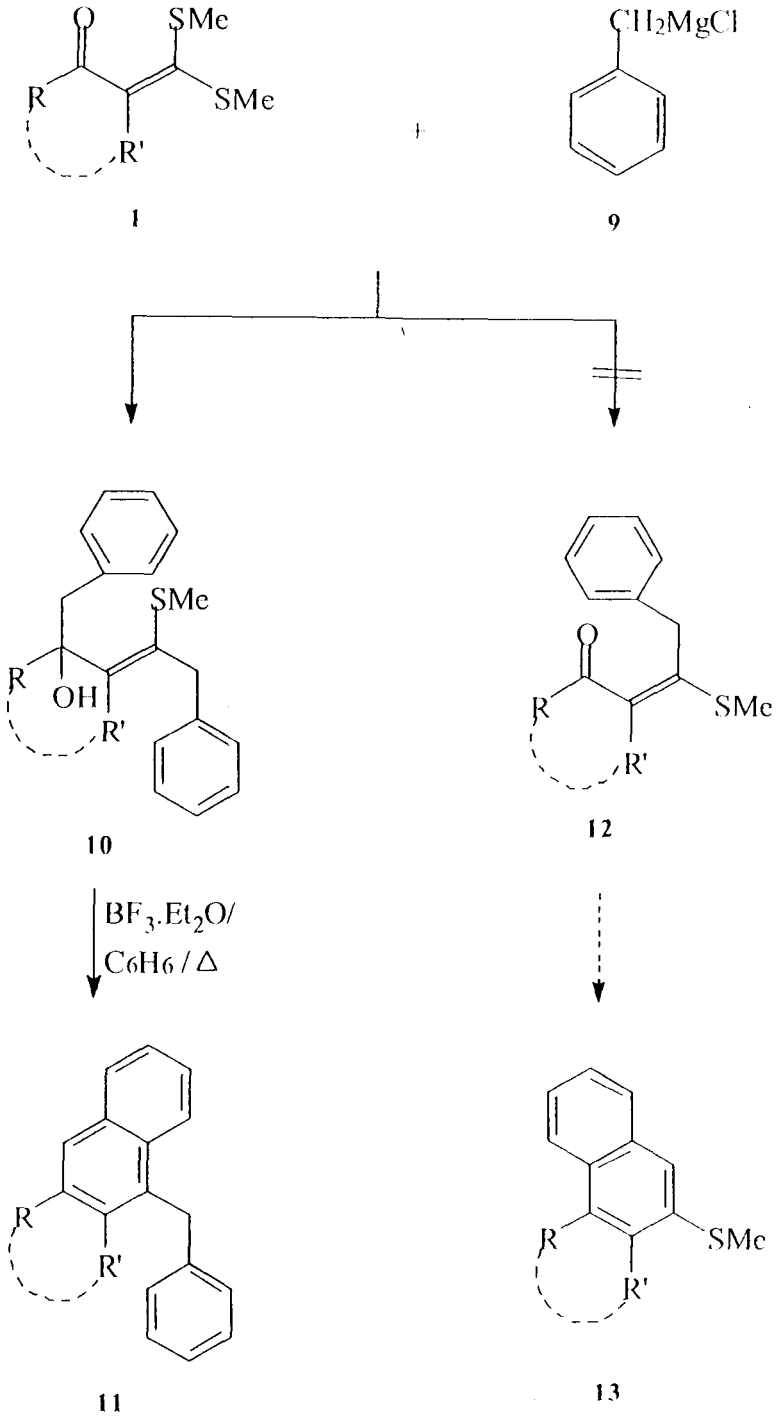
The higher alkyl Grignard reagents unlike the lower ones have followed 1,4-addition-elimination mode followed by 1,2-addition. These controlled addition modes were subsequently extended to allyl anions which followed exclusively 1,2-addition mode to give the corresponding carbinol acetals **6** (Scheme-3). These carbinol acetals **6** when treated with $BF_3.Et_2O$ in refluxing benzene underwent ring closure instead of simple dehydration to give substituted benzenes **8**. Thus a new aromatic annelation methodology was discovered which has been extensively studied in our laboratory[4]. These reactions were extended to benzyl Grignard reagent **9** to afford the carbinols **10** which underwent acid assisted cyclization to yield the benzyl substituted



1 6 8 7

Scheme 3

naphthalenes **11** in good yields[5] (Scheme-4). Obviously the benzyl Grignard reagent **9** followed sequential 1,4- and 1,2-addition modes with **1** to yield **10**,

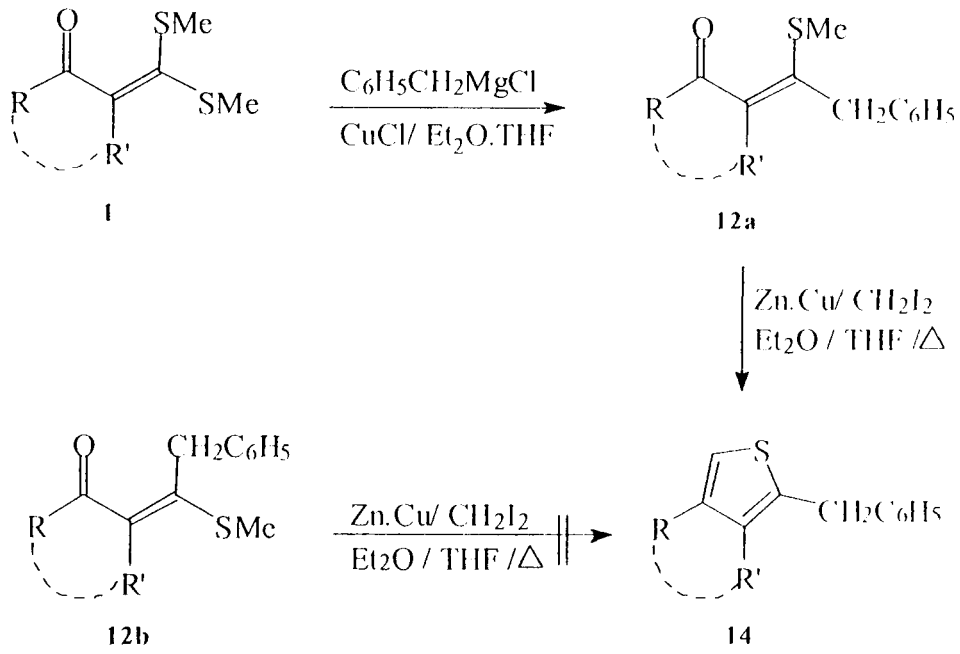


Scheme 4

followed by $BF_3.Et_2O$ cyclization to yield benzyl substituted naphthalenes **11** in good yields. By changing the stoichiometry of **9** with **1** it was not possible

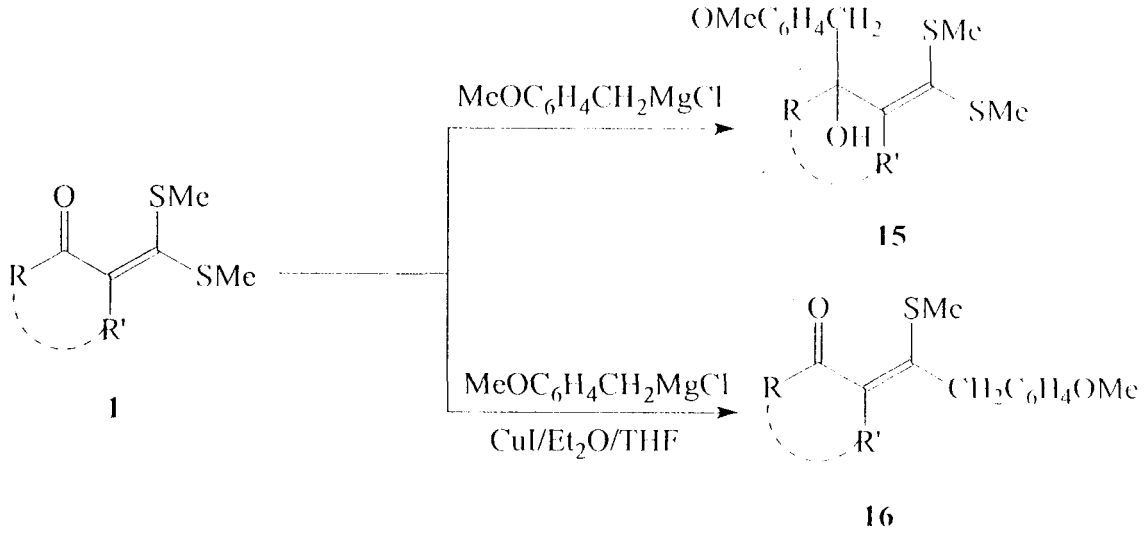
to isolate exclusively the 1,4-addition-elimination product **12** and indeed **12** was found to compete with **1** in its reactivity towards **9**. Thus even with one equivalent of **9** only **10** was obtained and not **12**. The 1,4-addition-elimination products **12** were considered of interest due to the fact that these intermediates can be cyclized to get angularly substituted and annelated naphthalenes **13** and also 1-aryl naphthalenes (**13**, R = Ar), the skeleton of which is present in *many naturally occuring lignans.*

However, it was possible to achieve the 1,4-addition-elimination product **12** by reacting **1** with organo copper reagent derived from **9** instead of **9** itself. Thus when **1** was reacted with **9** in the presence of CuCl, in THF/Et_2O as reaction medium, the 1,4-addition-elimination product **12a** was obtained in good yield[6] (Scheme-5). Also the stereochemistry of the product was found to be exclusively *Z* configuration and no traces of *E*-isomer was detected in the reaction mixture. The *Z* configuration of **12a** was confirmed on the basis of NOE studies and also by its conversion to thiophene by the method developed in our laboratory as shown in scheme-5[7,8,9]. Thus **12a** with thiomethyl group lying cis- to carbonyl function undergoes intramolecular aldol addition-elimination sequence when treated with Simmon-Smith reagent to yield the corresponding thiophene **14** in good yields. The *E*-isomer **12b** however did not undergo thiophene formation because thiomethyl group is trans- to carbonyl functionality. Thus the *Z* configuration of the addition-elimination product **12a** was fully established.



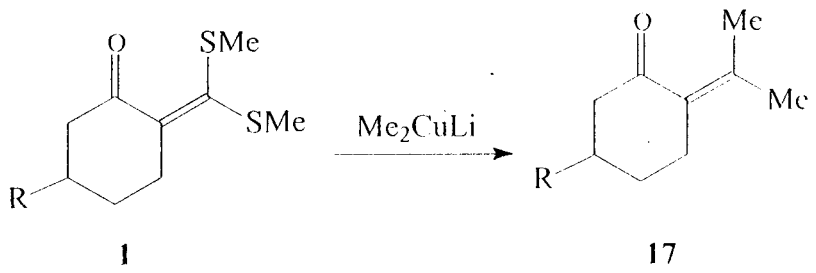
Scheme 5

Subsequently a number of alkyl and benzyl copper reagents derived from Grignard reagents were reacted with various α-oxoketene dithioacetals, and in all the cases 1,4-addition-elimination products were obtained with exclusive *Z* configuration. Methoxy substituted benzyl copper reagents also reacted with α-oxoketene dithioacetals and the 1,4-addition-elimination product **16** was obtained exclusively, though the corresponding Grignard reagents are known to add exclusively in a 1,2-fashion to give **15** in good yields (Scheme-6).



Scheme 6

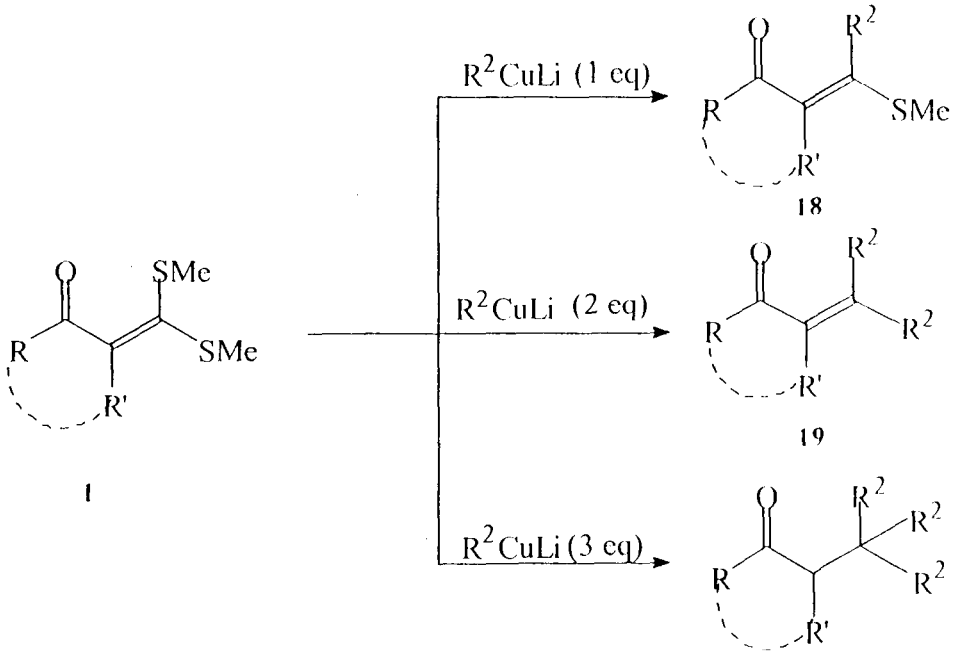
The displacement of alkylthio group of α-oxoketene dithioacetals **1**, on the other hand by alkyl groups were indeed known in the literature and one of the earlier studies for the displacement of methylthio group by methyl group was investigated by Corey and Chen as early as 1973[10]. They reacted dimethyl lithiocuprates with two equivalents of **1** to afford the corresponding 2-isopropylidine cyclohexanone **17** in 96% overall yields (Scheme-7).



Scheme 7

Subsequently Dieter and co-workers[11,12,13] made some detailed investigation of organo cuprates with **1**. When they reacted one equivalent of

organo cuprates with **1**, the product isolated (**18**) was found to be a mixture of *E* and *Z*-isomers. Similarly, when α-oxoketene dithioacetals were reacted with two equivalents of organo cuprates, both thiomethyl groups were displaced to give the β,β-dialkyl-α,β-unsaturated carbonyl compound **19**. They also reacted three equivalents of organo cuprates with **1** to afford β-tertiary alkyl ketones **20** in high yields involving the third addition in the Michael fashion (Scheme-8).



1 **18** **19** **20**

Scheme-8

Apparently in the preceding examples the organo Grignard reagents have shown 1,4-addition mode exclusively, when reacted in the presence of Cu (I) salts. A literature survey revealed that that there are no specific reagents or methods available for the preparation of 1,4-addition-elimination products

derived from α-oxoketene dithioacetals in their exclusive *E* configuration. In search of these reagents as well as in continuation of a programmed study of the C-C bond forming reactions of organometallic reagents with α-oxoketene dithioacetals, we examined the reactivity of organo Grignard reagents with α-oxoketene dithioacetals in the presence of (N,N,N',N'-Tetramethylethylenediamine)Zinc(II) chloride[21]. Surprisingly when α-oxoketene dithioacetals **1** were reacted with Grignard reagents in the presence of $ZnCl_2$.TMEDA complex, 1,4-addition-elimination products **22** were obtained exclusively in *E* configuration which proved to be a general method for the synthesis of *E*-β-alkyl-β-methylthio-α,β-enones. It may be noted here that *Z*-isomers **21** were not formed at all in these reactions. The results of this study are described in the following section.

RESULTS AND DISCUSSION

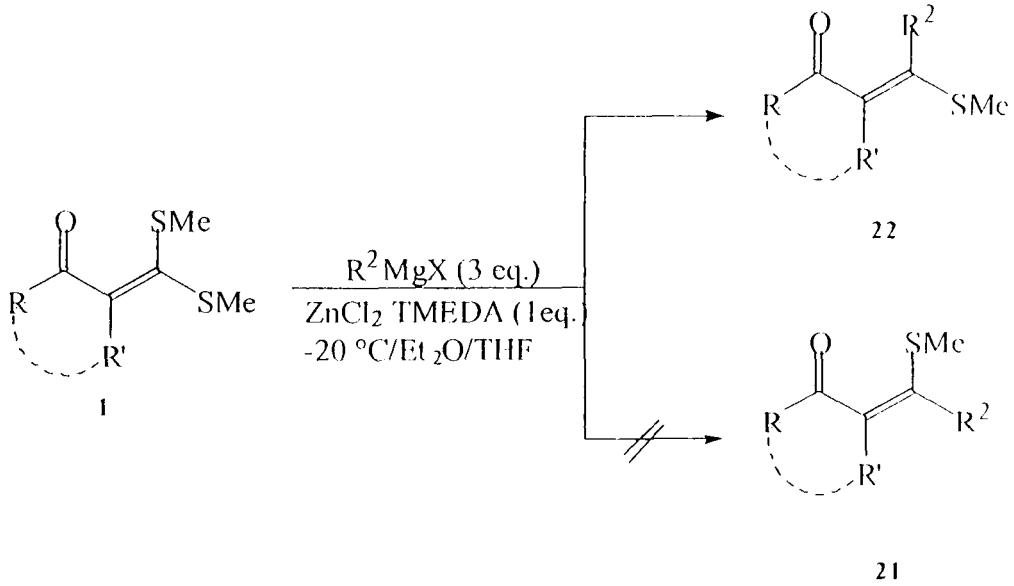
In the preceding section of this chapter the nucleophilic addition studies on α-oxoketene dithioacetals have been described. α-oxoketene dithioacetals have been found to react with organo Grignard reagents, showing variation of preference depending on the nature of the reagent. Bulkier organo Grignard reagents generally followed sequential 1,4- followed by 1,2-addition mode while the smaller groups generally followed 1,2-addition mode with α-oxoketene dithioacetals. The presence of Cu (I) salts however directed the organo Grignard reagents to react in a 1,4-fashion yielding exclusively 1,4-addition-elimination products of *Z* configuration.

We have in the present investigation thus found that when α-oxoketene dithioacetals reacted with organo Grignard reagents in the presence

of $ZnCl_2$.TMEDA complex 1,4-addition-elimination products were obtained but exclusively in the *E* configuration. Thus in a typical experiment magnesium triorganozincate, was prepared by reacting three equivalents of Grignard reagents with with one equivalent of $ZnCl_2$.TMEDA complex using diethyl ether/THF (solvent combination) 50: 50 at -20°C.

$$3\ RMgX + 1\ ZnCl_2.TMEDA \longrightarrow R_3ZnMgX \qquad \text{(equation 1)}$$

Since there is no indication of the formation of magnesium triorganozincate, trial experiments were carried out and it was found that generally the magnesium triorganozincates formed within twenty minutes of the reaction. The magnesium triorganozincate prepared in this way were reacted with α-oxoketene dithioacetals at -20°C in ether/ THF solvent combination and stirred for 45 minutes to yield 1,4-addition-elimination products **22** (Scheme-9).



Scheme 9

Acetophenone mercaptal was first reacted with $nBu_3ZnMgCl$. To a cooled solution i.e. -20°C of $nBu_3ZnMgCl$ in Et_2O/THF solvent combination a

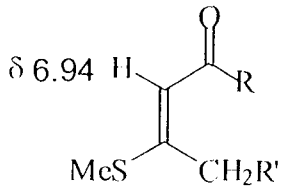
solution of acetophenone mercaptal was slowly added maintaining a temperature of -20°C, until the addition was complete. The temperature of the reaction mixture was gradually raised to 0°C and stirring continued for another 45 minutes. The reaction mixture after work up yielded 1-phenyl-3-methylthio-2-hepten-1-one **22d** in 71% yield. The structure of **22d** was confirmed from its analytical and spectral data.

DATA

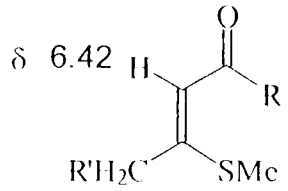
IR (CCl_4) ν_{max} = 2950, 1670, 1560, 1240 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 0.9 (t, J = 6Hz, 3H, CH_3); 1.40-1.62 (m, 4H, CH_2CH_2); 2.29 (s, 3H, SCH_3); 2.8 (q, J = 6Hz, 2H, CH_2); 6.42 (s, 1H, =CH); 7.31-7.49 (m, 3H, ArH); 7.8-7.91 (m, 2H, ArH). MS m/z (235.74) (M+, 37.6) 187 (18.3), 117 (100); Anal. Calcd. for $C_{14}H_{18}OS$ (234): C, 71.32; H, 8.29%. Found C, 71.48; H, 8.50%.

Assignment of E configuration

1-phenyl-3-methylthio-2-hepten-1-one **22d** was found to be a single geometrical isomer since all the signals in ^1H NMR spectrum were found to be sharp and near overlapping signals were not detected. Therefore it was presumed that the compound must be a single geometrical isomer. The vinylic proton of **22d** was observed at δ 6.42 which is far below from those systems for which we had assigned *Z* configuration, which was in turn obtained by reacting Grignard reagents in the presence of Cu (I) chloride with α-oxoketene dithioacetals as described earlier. The *Z*-isomers generally displayed the vinylic protons at δ 6.94, indicating approximate idea of the possible trans



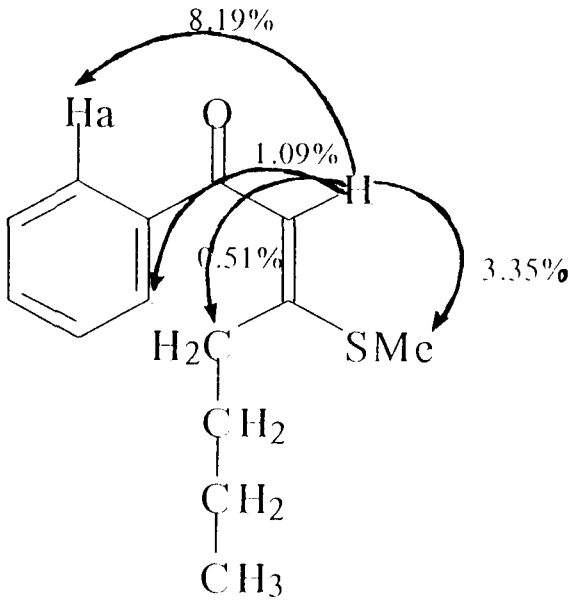
Z



E

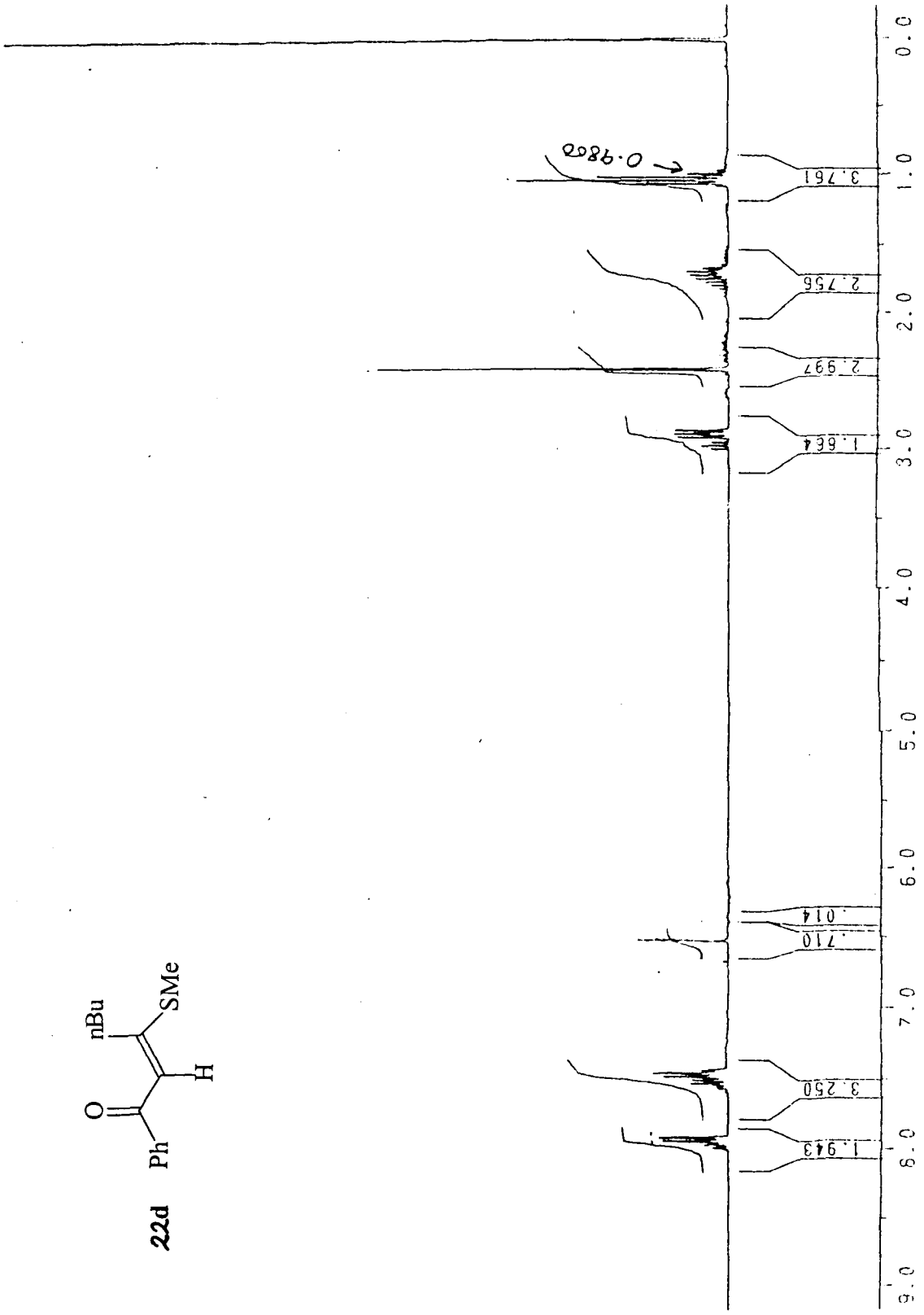
22d R = Ph, R' = $CH_2CH_2CH_3$

geometry for **22d**. This was further confirmed by subjecting **22d** for NOE studies.



22 d

From NOE studies carried out, the absorption signals of appropriate proton centres indicated the compounds **22** in its *E* configuration. The detailed studies are graphically represented in the structure **22d** where the enhancement of the vinylic protons was 3.35% when thiomethyl protons were irradiated. The vinylic proton showed an enhancement of 8.19% when Ha was irradiated. On the other hand enhancement of the proton of n-butyl group was a minimal


0.9802
3.761
2.756
2.937
1.664
.014
.710
3.250
1.943
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0

nBu
SMe
H
O
Ph

22d

0.5% when the vinylic proton was irradiated, confirming the thiomethyl group and H-atom on the same side of the double bond. Thus *E* configuration was confirmed unequivocally for **22d**. It is also important to note that the chemical shifts of the vinylic protons at δ 6.4 or values below this were taken as markers to assign *E* configuration to the other open chain systems examined in this work.

Similarly magnesium trimethyl, triethyl, *n*-tripropyl zincates were prepared and reacted with acetophenone mercaptal as described earlier to afford the corresponding 1,4-addition-elimination products **22a-22c** in 66-80% overall yields. The vinylic protons in **22a** appeared at δ 6.40, of **22b** appeared at δ 6.50 and **22c** at δ 6.48 confirming *E* conformation of the products **22a-22c** (Table I). Acetone mercaptal was next examined as a typical example of aliphatic ketone derivative. Thus when acetone mercaptal was reacted with magnesium trimethylzincate under similar reaction conditions as described above the unreacted reagent, acetone mercaptal was observed (TLC). The reaction did not proceed even after prolonging the reaction time and raising the temperature of the reaction. In a particular attempt the reaction mixture containing magnesium trimethylzincate and acetone mercaptal was cooled to -78°C, but the reaction failed in our hands. It was then decided to examine some of the higher alkyl magnesium zincate reagents and react it with acetone mercaptal.

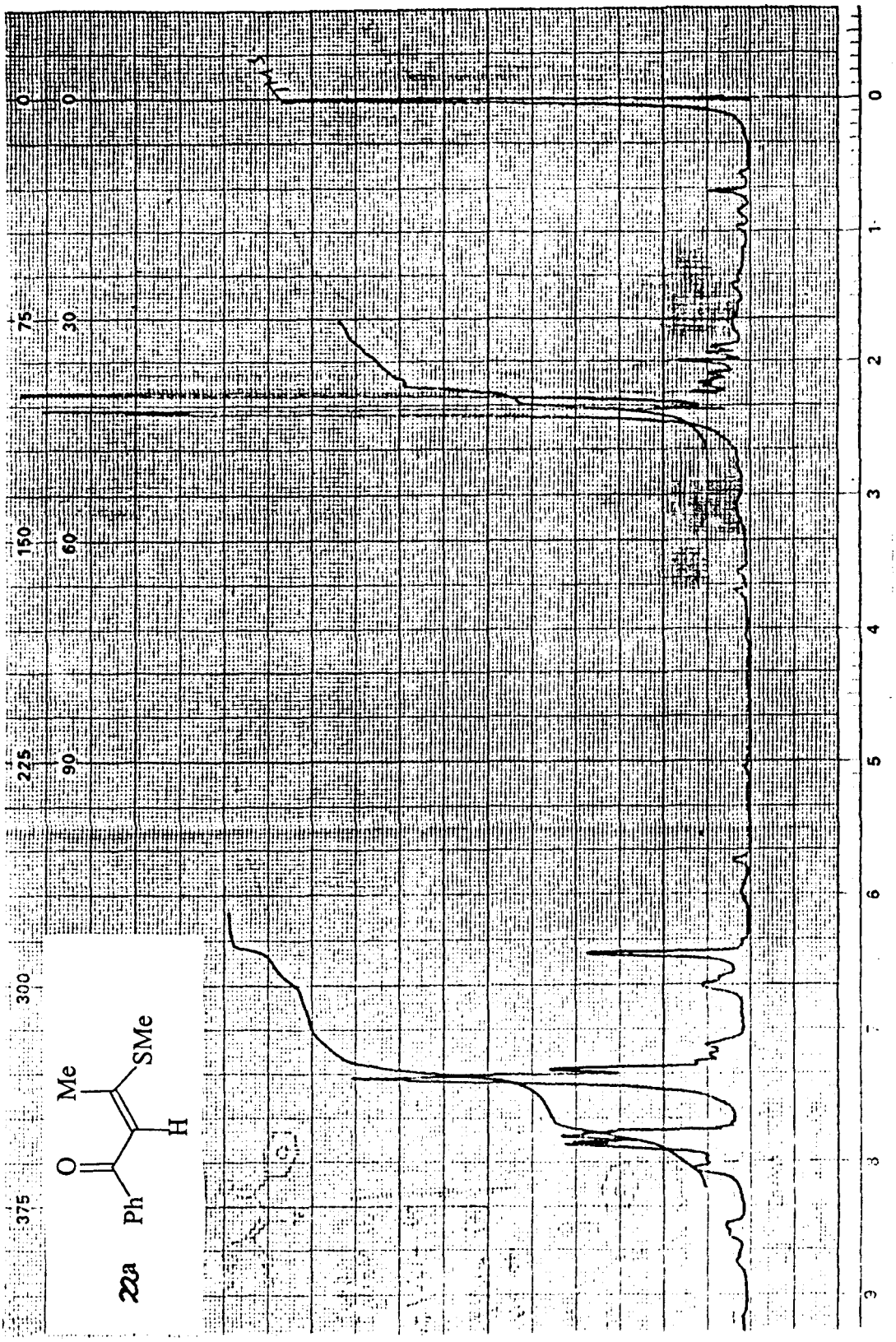
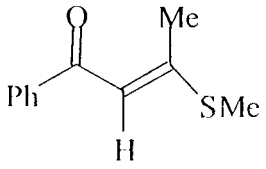
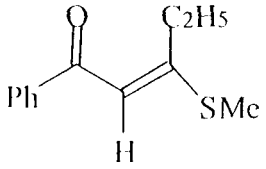
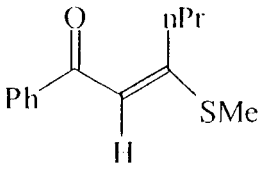
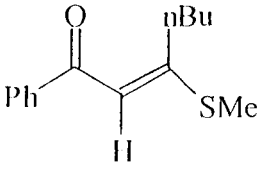
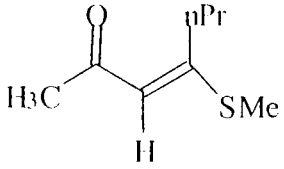
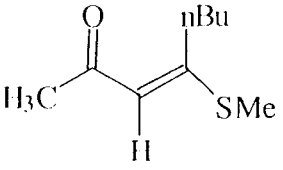
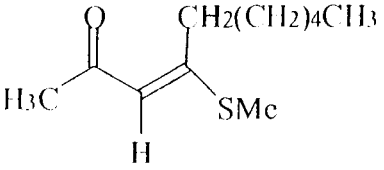
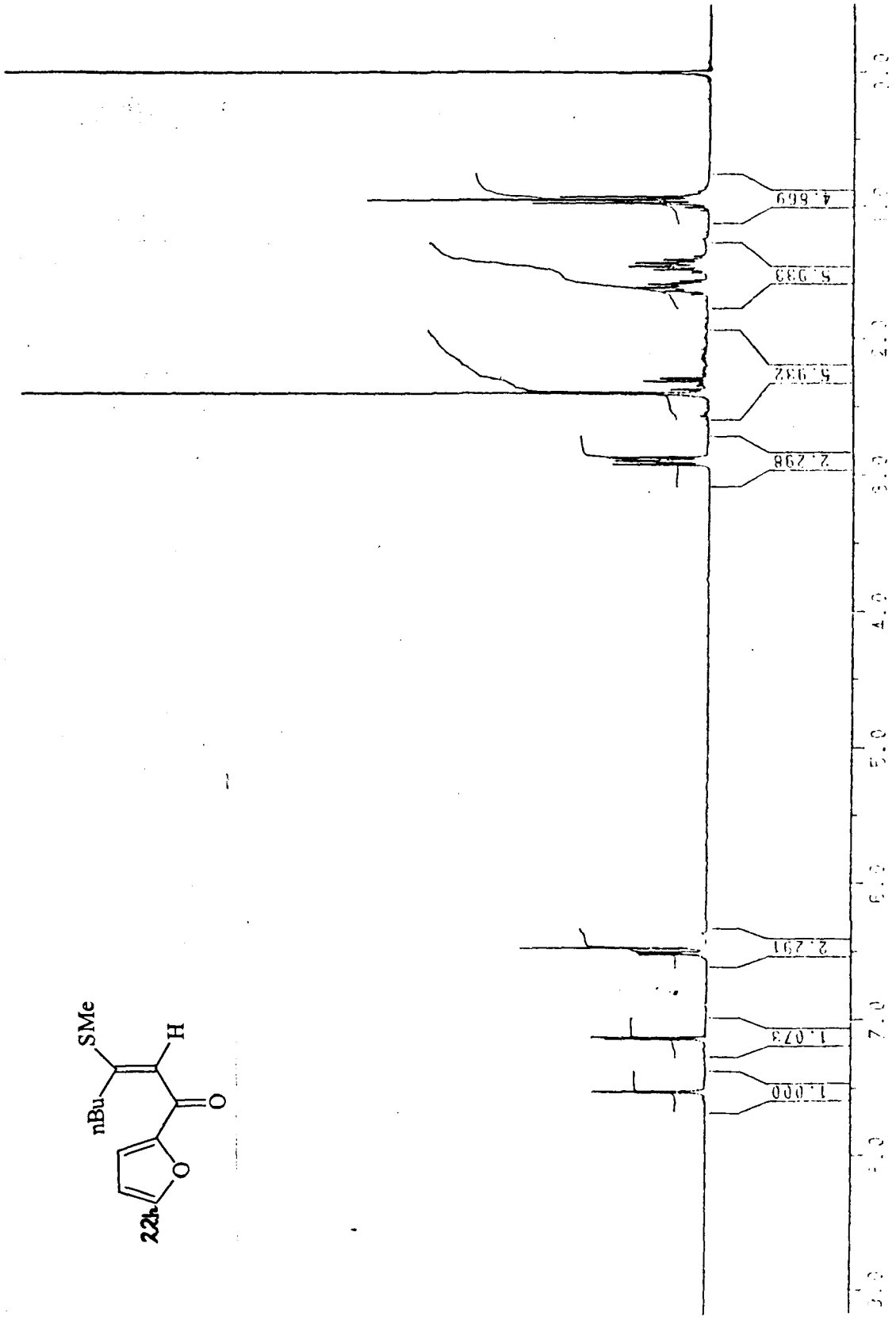

Me
SMe
O
H
Ph
22a

Table-I

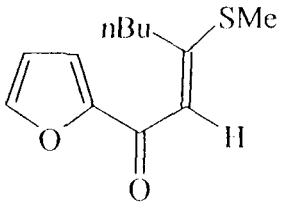
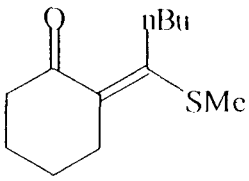
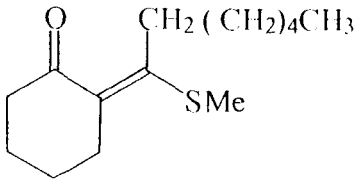
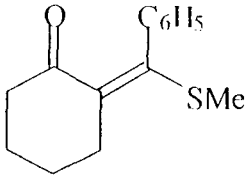
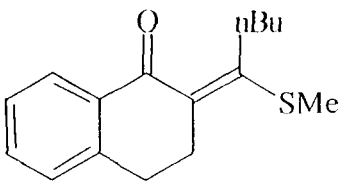
22	E isomers of β-alkyl thio α,β-enoens	% yield	δ_H vinylic
a		67	6.40
b		66	6.50
c		80	6.48
d		71	6.45
e		66	5.70
f		67	5.70
g		65	5.70

Thus magnesium *n*-tripropylzincate reagent was prepared as described earlier followed by addition of acetone mercaptal maintaining reaction temperature at -20°C. The reaction temperature was raised to 0°C and stirring continued for an additional 45 minutes and subsequent work up yielded the compound **22e** which was characterised as 4-methylthio-3-hepten-2-one in 66% overall yields. The structure and configuration of **22e** was confirmed from its spectral and analytical data (see experimental). The vinyl protons appeared at δ 5.7 on the basis of which *E* configuration was assigned to **22e** (Table I). Similarly **22f** was prepared by reacting magnesium *n*-tributylzincate with acetone mercaptal to yield the corresponding 4-methylthio-3-octen-2-one **22f** in 67% overall yields. The position of the vinylic proton in this compound also appeared at δ 5.7 confirming the assignment of *E* configuration (Table I). Also acetone mercaptal was reacted with magnesium *n*-trihexyl zincate to yield the corresponding 4-methylthio-3-decen-2-one **22g** in 65% overall yields (Table I). The position of the vinylic proton in this compound also appeared at δ 5.7 confirming the assignment of *E* confirmation. It is thus evident that the higher alkyl magnesium zincates reacted in a facile manner with α-oxoketene dithioacetals to yield the desired products.

Magnesium *n*-tributylzincate was next reacted with mercaptal derived from 2-acetyl furan which, under the described reaction conditions to yield the desired product **22h** in 82% overall yields. The position of vinylic


4.869
5.933
5.932
2.298
2.291
1.073
1.000
SMe
H
nBu
O
O
22h

proton at δ 6.46 was again used as a marker to assign *E* configuration to the product enone (Table II).

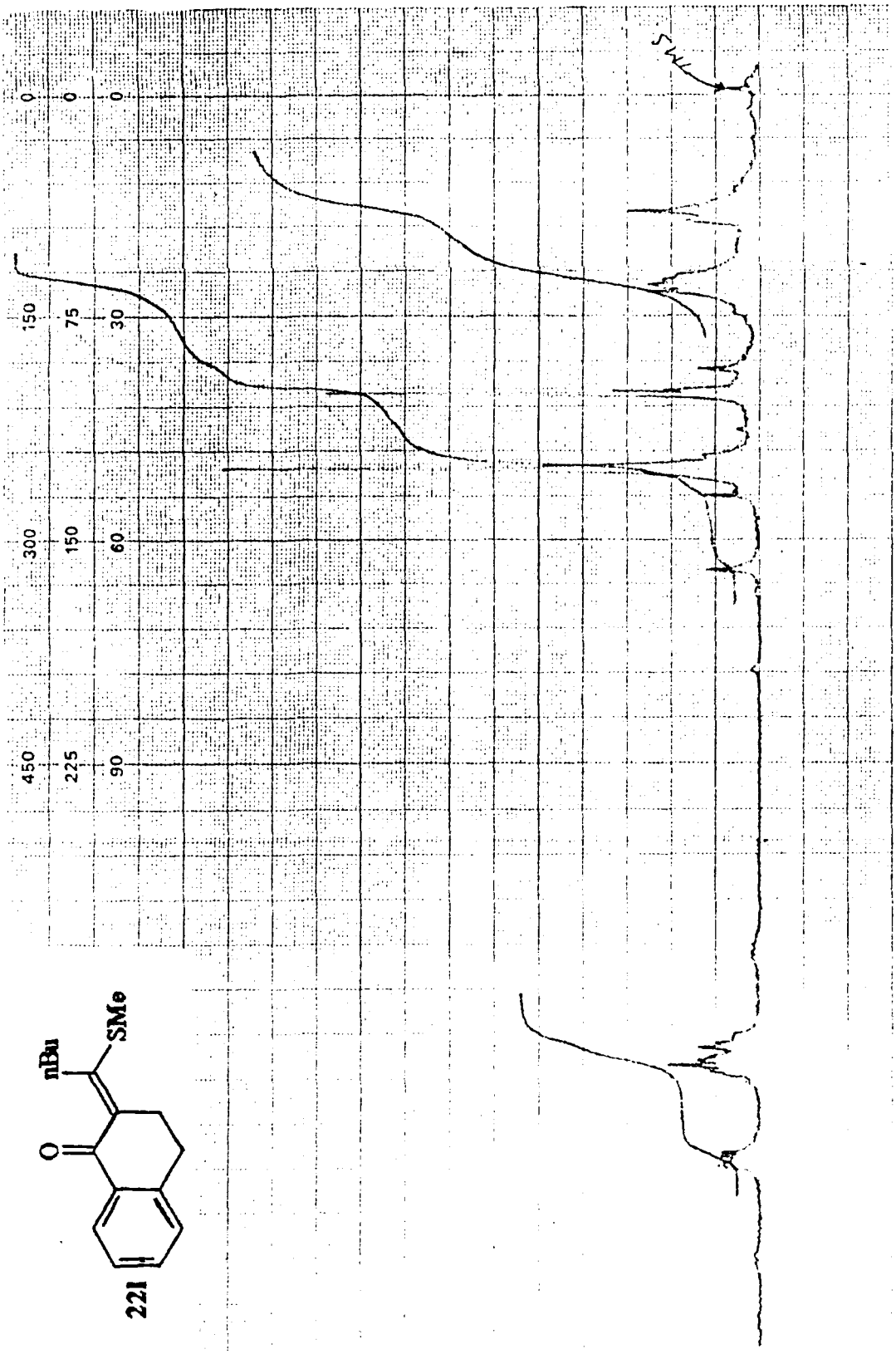
(Table II) **22**	E isomers of β-alkylthio α,β-enones	% yield	δ H vinylic
h		82	6.46
i		63	-
j		82	-
k		50	-
l		89	-

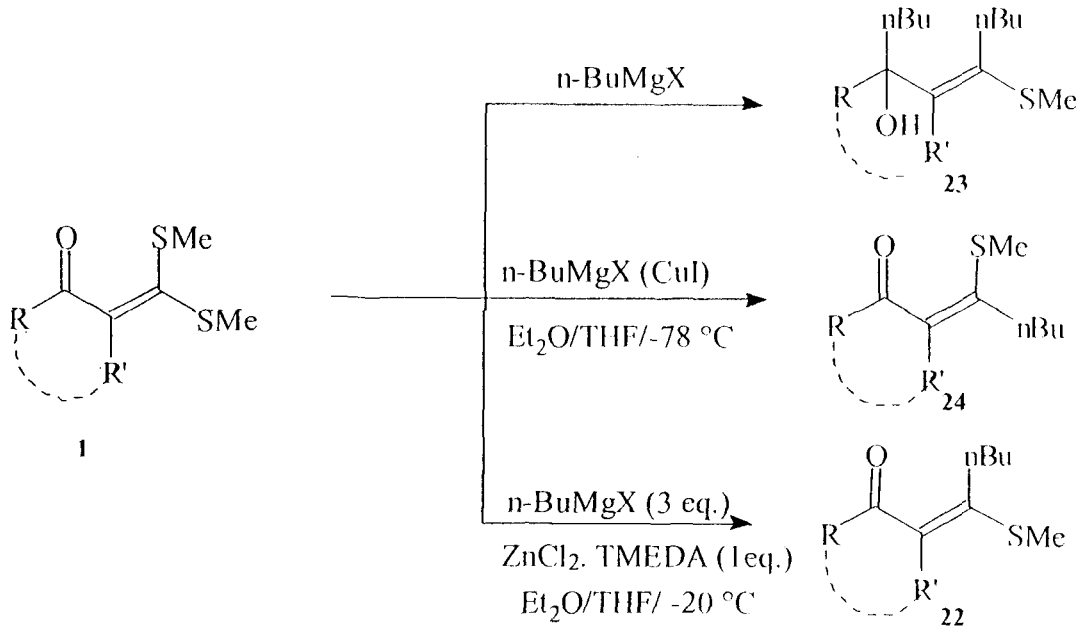
The reactivity of these magnesium zincate reagents with cyclic α-oxoketene dithioacetals was next examined. Thus when cyclohexanone mercaptal was reacted with magnesium *n*-tributyl, *n*-trihexyl and triphenyl

zinc reagents under similar reaction conditions as described earlier it afforded the corresponding β-alkyl-β-methylthio-α,β-enones **22i, 22j** and **22k** in 63, 82 and 50% yields respectively (Table II). The structures of **22i, 22j** and **22k** were in conformity with their analytical and spectral data (see experimental). The *E* configuration is tentatively assigned on the basis of the geometry observed in the open chain systems.

Tetralone mercaptal **22l** was also reacted with magnesium *n*-tributyl zincate and it yielded the corresponding β-n-butyl-β-methylthiotetralone **22l** in 89% overall yields (Table II). The structure of **22l** was confirmed from its analytical and spectral data (see experimental). The NMR and IR data of all these compounds **22a-22l** however, could not be used to distinguish between *E* and *Z*-isomers. The exact geometry needs to be confirmed possibly by X-ray studies of one of the crystalline compounds. All these compounds derived from alkyl, aryl, cyclic ketones etc. were liquids and efforts are being made to prepare one of the solid derivatives to get good crystals suitable for X-ray analysis.

In Scheme-10 we have described that simple n-butyl magnesium chloride is shown to react with **1** due to its bulk in a sequential 1,4- and 1,2-addition mode to yield **23**. However when *n*-butyl magnesium halide is reacted with **1** in the presence of Cu (I) iodide the reaction assumes full regio- and stereo control to afford the corresponding *Z*-β-methylthio-β-n-butyl α,β-enones **24** exclusively. Under these conditions no 1,2-adducts were detected.


0
0
0
150
75
30
300
150
60
450
225
90
SMe
nBu
O
221



Scheme 10

Under no circumstances it was possible to alter the course of the reaction using these conditions of Cu (I) assisted organo Grignard reagents to obtain 1,2-addition products. It was found that these reactions yielded 1,4-addition-elimination products exclusively in its *Z* configuration. It therefore became necessary to develop another reagent to get only *E*-isomers of these 1,4-addition-elimination products so that we have ready methods in hand to prepare either *Z*- or *E*-isomers as the case may be. In this context the work described in this chapter using magnesium triorganozincate as reagent of choice is a good method to obtain only the corresponding *E*-isomers without any trace of *Z*-isomers. Thus we have methods to prepare either *cis*- or *trans*-β-alkyl-β-methylthio-α,β-enones in good yields.

In conclusion we have been able to make some important generalisations on the stereoelectronic control process of reagents and their reactivity towards ambident 1,3-electrpophilic centers in α-oxoketene dithioacetals.

EXPERIMENTAL SECTION

General

Proton NMR spectra were recorded as CCl_4 or $CDCl_3$ solutions either on a Varian EM-390 or Bruker 300 MHz spectrometer instrument. Chemical shifts are reported relative to tetramethyl silane as internal standard. IR spectra were recorded on a Perkin-Elmer 297 and 983 spectrometer in CCl_4 solutions. Mass spectra were recorded on a Jeol JMS-D-300 spectrometer. Elemental analysis were carried out on a Hearaeus CHN-O-RAPID analyser.

CHEMICALS AND REAGENTS

Grignard grade magnesium turnings (SISCO) were used for, preparing various Grignard reagents which were carried out under an atmosphere of oxygen free dry nitrogen. Methyl iodide, ethyl bromide, n-propyl bromide, n-butylchloride, hexyl chloride, phenyl bromide, were purchased and used as supplied. Tetramethylethylenediamine (TMEDA) was purchased (E Merck) and purified before use by distillation under reduced pressure. THF was initially deperoxidised and then dried by keeping over sodium wire followed

by distillation. $ZnCl_2$ (E Merck) was used as such. TLC (silica gel Acme's) was used for monitoring the reactions.

STARTING MATERIALS

The commercially available acetophenone, acetone, cyclohexanone were purified by distillation under pressure before use. 1-Tetralone, bp.140-150°C (10mm)[14] were prepared according to reported procedures. Furfuraldehyde was distilled before use. The α-oxoketene dithioacetals required for the present investigation were prepared according to the earlier reported procedures[15-17]. The following α-oxoketene dithioacetals were prepared according to the general procedure described in the following section, 3,3-[Bis (methylthio)]-1-phenyl-2-propen-1-one, mp 93°C[18], 4,4-[bis (methylthio)]-3-buten-2-one mp 57°C[19], 2-[bis (methylthio) methylene] cyclohexanone bp 118°C (1mm)[20], 3,3-[bis (methylthio)]-1-(2'-furyl)-2-propen-1-one[18], 2-[bis (methylthio)] methylene-1-tetralone mp 58°C[15].

General method for the preparation of α-oxoketene dithioacetals using sodium-t-butoxide

A mixture of corresponding ketone (0.5 mol) and carbon disulphide (0.5 mol) in dry benzene (100 ml) was added drop wise to an ice cooled and well stirred suspension of sodium-t-butoxide (1.0 mol) in dry benzene and the reaction mixture was stirred for 4-5 hrs. Methyl iodide (1.1 mol) was then gradually added with cooling and the reaction mixture was further stirred for 6 hrs, cooled and poured into ice cold water. The benzene layer was separated

and the aqueous phase was extracted with benzene (200 ml), dried (anhydrous Na_2SO_4) and evaporated to give the crude dithioacetals which were purified either by crystallization or by distillation under reduced pressure.

General procedure for the preparation of N,N,N',N'-TMEDA Zn(II) chloride.

Five ml TMEDA was added to 10 ml saturated $ZnCl_2$.THF solution and allowed to stand for several hours at room temperature. The crystalline product was filtered and recrystallised from THF mp 177 °C[21].

General procedure for the reaction of α-oxoketene dithioacetals with organozinc reagents :

The reaction of α-oxoketene dithioacetals with organozinc reagents is representative. To a stirred suspension of N,N,N',N'-TMEDA Zinc(II) chloride (0.01 mol) in 25 ml of dry THF, under nitrogen atmosphere at -20°C, n-butyl magnesium chloride (0.03 mol), prepared from magnesium (0.5 g, 0.02 mol) and *n*-butyl chloride (0.92 ml, 0.01 mol) in 150 ml of Et_2O:THF (1:1) was added drop wise and the reaction mixture was further stirred for 20 min followed by addition of acetophenone mercaptal (0.005 mol) in THF (15 ml) at -20°C. The reaction mixture was continuously stirred for 45 min (monitored by TLC) at 0°C and poured into saturated NH_4Cl solution (100 ml), extracted with chloroform (3 × 50ml) and the organic extracts were

washed with water (2 × 50ml), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure to give the crude product which was purified by column chromatography over silica gel using hexane as eluent. Similar reaction conditions were maintained when other α-oxoketene dithioacetals were reacted with organozinc reagents to afford crude thiomethyl displaced products which after purification gave analytically pure β-alkyl-β-methylthio-α,β-enones. The analytical and spectral data of β-alkyl-β-methylthio-α,β-enones **22** are given below.

1-phenyl-3-methylthio-2-buten-1-one (22a): yield 67%; brown dense oil; IR (CCl_4) ν_{max} = 2950, 1760, 1720, 1620, 1420, 1290, 820, cm^{-1}. ^1H NMR (90 MHz, CCl_4) δ = 0.9 (t, 3H, CH_3); 1.4-1.6 (m, 4H, $(CH_2)_2$); 2.25 (s, 3H, CH_3); 2.35 (s, 3H, SCH_3); 6.40 (s, 1H, =CH); 7.2-7.4 (m, 3H, ArH); 7.66-7.90 (m, 2H, ArH). Anal. Calcd. for $C_{11}H_{12}OS$ (193.19): C, 68.38 ; H 6.75%. Found C, 68.55; H, 6.90%.

1-phenyl-3-methylthio-2-pente-1-one (22b): yield 66%; yellow liquid; IR (CCl_4) ν_{max} = 2913, 2367, 1566, 1232, 1177, 780, 760 cm^{-1}. ^1H NMR (90 MHz, CCl_4) δ = 1.26 (t, 3H, CH_3); 2.36 (s, 3H, SCH_3); 2.9 (q, 2H, CH_2); 6.50 (s, 1H, =CH); 7.48-7.64 (m, 3H, ArH); 7.2- 8.1 (m, 2H, ArH). MS m/z (207.37); (M^+, 18.5%) 157 (71.1), 105 (84.8), 77 (100); Anal. Calcd. for $C_{12}H_{14}OS$ (207.37): C, 69.50; H, 7.33%. Found C, 70.0; H, 7.68%.

1-phenyl-3-methylthio-2-hexen-1-one (22c): yield 80%; brown viscous liquid; IR (CCl_4) ν_{max} = 2930, 1645, 1552, 1226, 700 cm^{-1}. ^1H NMR (90 MHz,

CCl_4) δ = 1.0 (t, 2H, CH_2); 1.65 (q, 3H, CH_3); 2.35 (s, 3H, SCH_3); 2.85 (t, 2H, CH_2); 6.48 (s, 1H, =CH); 7.35-7.52 (m, 3H, ArH); 7.84-8.0 (m, 2H, ArH). Anal. Calcd. for $C_{13}H_{16}OS$ (221.56): C, 70.47; H, 7.84%. Found C, 70.23; H, 7.52%.

1-phenyl-3-methylthio-2-hepten-1-one (22d): yield 71%; yellow oil; IR (CCl_4) ν_{max} = 2950, 1670, 1560, 1240 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.9 (t, J = 6Hz, 3H, CH_3); 1.40-1.62 (m, 4H, CH_2CH_2); 2.29 (s, 3H, SCH_3); 2.8 (q, J = 6 Hz, 2H, CH_2); 6.45 (s, 1H, =CH); 7.31-7.49 (m, 3H, ArH); 7.8- 7.91 (m, 2H, ArH). MS m/z (235.74) (M^+, 37.6) 187 (18.3), 117 (100); Anal. Calcd. for $C_{14}H_{18}OS$ (235.74): C, 71.32; H, 8.29%. Found C, 71.48; H, 8.50%.

4-methylthio-3-hepten-2-one (22e): yield 66%; yellow oil; IR (CCl_4) ν_{max} = 2926, 1673, 1427, 1353, 1188, 867 cm^{-1}. ^1H NMR (90 MHz, CCl_4) δ = 0.9 (t, 3H, CH_3); 1.46 (m, 2H, CH_2); 2.0 (s, 3H, CH_3); 2.18 (s, 3H, SCH_3); 2.6 (t, 2H, CH_2) 5.70 (s, 1H, =CH). Anal. Calcd. for $C_8H_{14}OS$ (159.33): C, 60.30; H, 9.54%. Found C, 60.72; H, 9.73%.

4-methylthio-3-octen-2-one (22f): yield 67%; yellow oil; IR (CCl_4) ν_{max} = 2940, 1690, 1590, 1365, 925 cm^{-1}. ^1H NMR (90 MHz, CCl_4) δ = 0.9 (t, 2H, CH_2); 1.31-1.5 (t, 2H, CH_3); 2.1 (s, 3H, CH_3); 2.2 (s, 3H, SCH_3); 2.69 (t, 2H, CH_2); 5.70 (s, 1H, =CH). Anal. Calcd. for $C_9H_{16}OS$ (173.52): C, 62.29; H, 10.01%. Found C, 62.08; H, 9.89%.

4-methylthio-3-decen-2-one (22g): yield 65%; yellow oil; IR (CCl_4) ν_{max} = 2925, 1673, 1556, 1454, 1256, 1010, 971 cm^{-1}. ^1H NMR (90 MHz, CCl_4) δ =

0.74-0.94 (m, 2H, CH_2); 1.3-1.46 (m, 8H, $(CH_2)_4$); 2.1 (s, 3H, CH_3); 2.2 (s, 3H, SCH_3); 2.66 (q, 3H,CH_3); 5.70 (s, 1H, =CH). Anal. Calcd. for $C_{11}H_{20}OS$ (201.88): C, 65.44; H, 10.76%. Found C, 65.12; H, 10.45%.

1-(2-furyl)-3-methylthio-2-hepten-1-one (22h): yield 82%; yellow oil; IR (CCl_4) ν_{max} = 2923, 1623, 1542, 1431, 1248, 883 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.95 (t, 3H, CH_3); 1.43 (m, 2H, CH_2); 1.61 (m, 2H, CH_2); 2.40 (s, 3H, SCH_3); 2.86 (t, 3H,CH_3); 6.46 (s, 1H, =CH) 6.5 (m, 1H, furfuryl); 7.14 (d, 1H, furfuryl); 7.51 (d, 1H, furfuryl). MS m/z (225.54) (M^+, 18.0) 195 (74.9), 147 (38.2), 95 (100). Anal. Calcd. for $C_{12}H_{16}O_2S$ (225.54): C, 63.90; H, 7.70%. Found C, 64.0; H, 7.88%.

2-[1'-(methylthio)pentylidene]cyclohexanone (22i): yield 63%; yellow oil; IR (CCl_4) ν_{max} = 2933, 2826,1716, 1566, 1448, 1420, 1323, 1245, 1119, 1067, 970, 888 cm^{-1}. ^1H NMR (90 MHz, CCl_3) δ = 0.9-1.2 (t, 3H, CH_3); 1.32-1.56 (m, 4H, $(CH_2)_2$); 1.78 (t, 2H, CH_2); 2.28 (s, 3H, SCH_3); 2.2-2.4 (m, 4H,$(CH_2)_2$); 2.41-2.78 (m, 4H, $(CH_2)_2$). MS m/z (212) (M^+, 40.6); 197 (100) 165 (19.8); 135 (39.0). Anal. Calcd. for $C_{12}H_{20}OS$ (213.89): C, 67.38; H, 10.15%. Found C, 67.59; H, 10.48%.

2-[1'-(methylthio)heptylidene]cyclohexanone (22j): yield 82%; yellow oil; IR (CCl_4) ν_{max} = 2853,1651, 1456, 1265, 1135, 968, 889, 682 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.89 (t, 3H, CH_3); 1.26 (brs, 18H, $(CH_2)_9$); 2.35 (s, 3H, SCH_3). Anal. Calcd. for $C_{14}H_{24}OS$ (242.25): C, 69.41; H, 10.76%. Found C, 70.02; H, 10.93%.

2-[1'-(methylthio)benzylidine]cyclohexanone (22k): yield 50%; yellow oil; IR (CCl_4) ν_{max} = 2925, 1658, 1564, 1002, 978, 698 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 1.2-1.32 (m, 2H, CH_2); 1.77-2.09 (m, 6H, $(CH_2)_3$); 2.32 (s, 3H, SCH_3) 7.15-7.2 (m, 5H, ArH). Anal. Calcd. for $C_{14}H_{16}OS$ (233.57): C, 71.99; H, 7.44%. Found C, 72.0; H, 7.63%.

3,4-Dihydro-2-[1'-(methylthio)pentylidene]naphthalene-1-one (22l): yield 89%; yellow oil; IR (CCl_4) ν_{max} = 2945, 1660, 1640, 1420, 1300, 1260, 915 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.90 (t, 2H, CH_2); 1.48 (q, 3H, CH_3); 2.3 (s, 3H, SCH_3); 2.6 (d, 2H, CH_2); 2.82 (m, 6H, $(CH_2)_3$); 7.5-7.35 (m, 3H, ArH); 7.9 (m, 1H, ArH). Anal. Calcd. for $C_{16}H_{20}OS$ (261.93): C, 73.36; H, 8.29%. Found C, 73.82; H, 8.32%.

References

1. Reviews: Asokan, C.V.; Ila, H.; Junjappa, H. *Tetrahedron* **1990**, 46, 5423.
2. Myrboh, B.; Ila, H.; Junjappa, H. *J.Org. Chem.* **1983**, 48, 5327.
3. Singh, G.; Purkayastha, M. L.; Ila, H.; Junjappa, H. *J. Chem. Soc. Perkin. Trans. I* **1985**, 1289.
4. Singh, G.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1984**, 25, 5095.
5. Balu, M. P.; Singh, G.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1986**, 27, 117.
6. Mehta, B. K.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1995**, 36, 1925.
7. Thomas, A.; Singh, G.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1989**, 30, 3093.
8. Bhat, L. N.; Thomas, A.; Ila, H.; Junjappa, H. *Tetrahedron* **1992**, 48, 10377.
9. Bhat, L. N.; Ila, H.; Junjappa, H. *Synthesis* **1993**, 959
10. Corey, E. J.; Chen, R. H. K. *Tetra. Lett.* **1973**, 3817.
11. Dieter, R. K.; Fishpaugh, J. R.; Silks, L. A. *Tetra. Lett.* **1982**, 23, 3751.
12. Dieter, R. K.; Silks, L. A. III; Fishpaugh, J.R.; Kastner , M. E. *J. Am. Chem. Soc.* **1985**, 107, 4697.
13. Dieter, R. K.; Silks, L. A. *J. Org. Chem.* **1983**, 48, 2786.
14. Olson, C. E.; Bader, A. D. *Organic Synthesis Coll. Vol. 4*, **1963**, 898.
15. Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, 32, 1779.
16. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1962**, 2182, 2187.
17. Maignan, J.; Vialle, J. *Bull. Soc. Chim. Fr.* **1973**, 2388.

18. Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1959**, 1398.

19. Noller, C.R.; Adams, R. *J. Am. Chem. Soc.* **1924**, 46, 1398.

20. Thuillier, A.; Vialle, J. *Bull.Soc. Chim. Fr.* **1962**, 2194.

21. Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**.

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B.Sc.	1991	NEHU	Chemistry	I (63.37)
M.Sc.	1993	NEHU	Chemistry	I (72.50)
Ph.D (Synthetic Organic Chemistry)	1999	NEHU	Submitted	-

Thesis Work

Synthesised useful compounds viz. β-oxodithioates, methyl dithiocarbamates, symmetrical & unsymmetrical thioureas using 1-(methyldithiocarbonyl)imidazole and 3-methyl-1-(methyldithiocarbonyl)imidazolium iodide by economical synthetic strategy. Also using organo zinc reagents synthesis of β-alkyl-β-methylthio-α,β-enones was carried out.

Research Publications

1. Mehta, B. K.; Dhar, S.; Ila, H.; Junjappa, H. *Tetra. Lett.* **1995**, 36, 9377.

2. Dhar, S.; Mahanta, P. K.; Samal, S. K.; Ila, H.; Junjappa, H. *Tetrahedron* **1999**, 000 (accepted for publication).

3. 1-(methyldithiocarbonyl)imidazole : An efficient reagent for the synthesis of β-oxodithioates. (manuscript under preparation)

4. Highly Efficient and Selective Displacement of Alkylthio group on S, S-acetals by organo zinc reagents: A novel route to β-alkyl-β-methylthio-α,β-enones. (manuscript under preparation).

Other exams/interviews qualified:

1. GATE – 1996, Percentile score-88.73%.
2. CSIR (SRF) – 1996.

Fellowships/Awards

1. NEHU PG Scholarship, 1991-93.
2. Fellowship under SAP, NEHU, 1995-1996.
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