SYNTHETIC AND MECHANISTIC INVESTIGATIONS ON α- OXOKETENE DITHIOACETALS

BY

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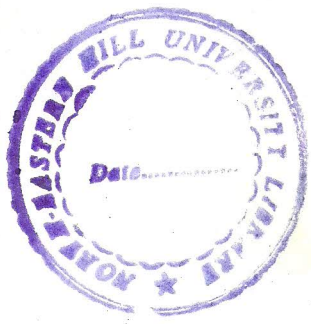

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THE NORTH-EASTERN HILL UNIVERSITY

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

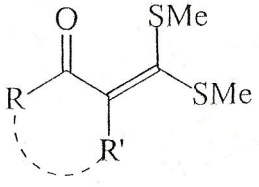
CHAPTER-I

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.

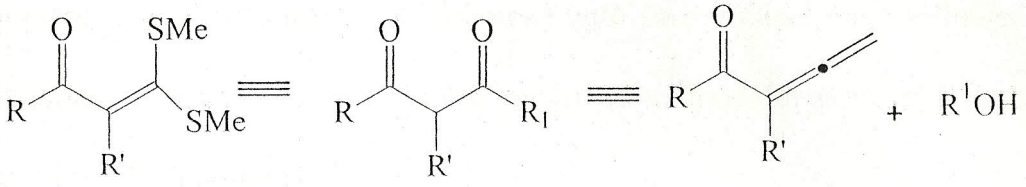
This chapter has been simplified into sections. The first section gives a brief review of α-oxoketene dithioacetals and the second section describes the present work.

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.

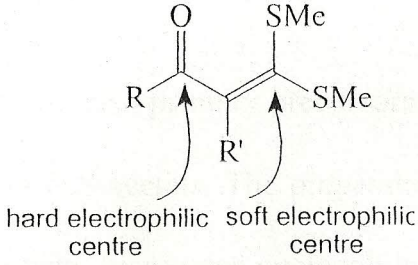


Kelber and co-workers[1, 2] had given the first report on α-oxoketene dithioacetals in the year 1910. Much of the earlier work on α-oxoketene dithioacetals was confined to their preparation and properties, while little attention was paid to their synthetic utility. Later on Thuillier and Vialle prepared 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.

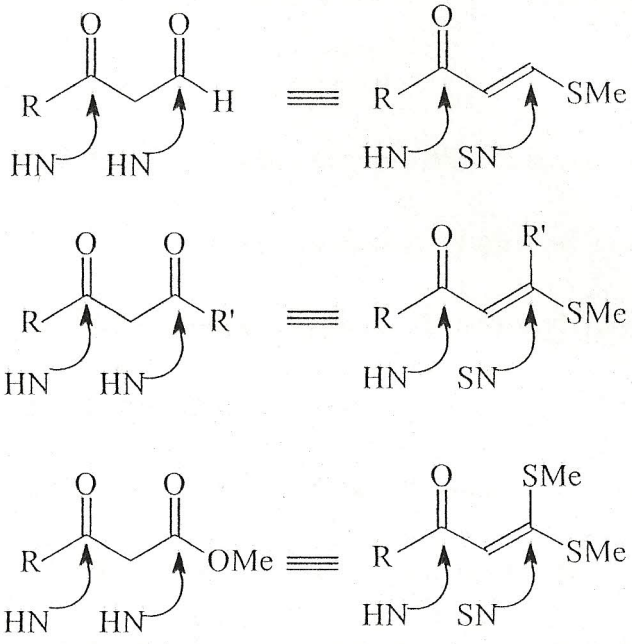
The α-oxoketene dithioacetals, generally exhibit well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stirred indefinitely without decomposition. The α-oxoketene dithioacetals have attained recognition 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-eletrophilic 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].

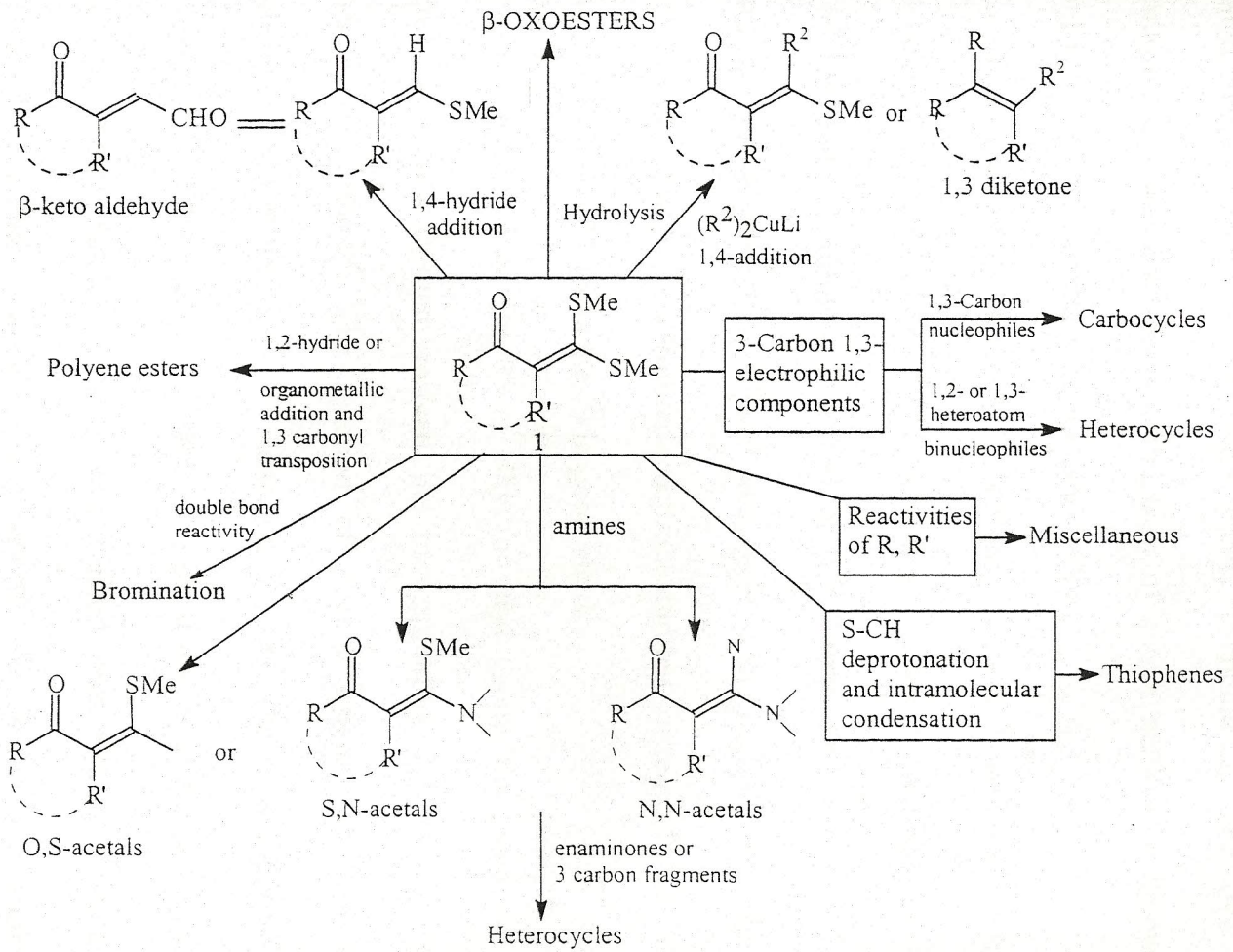
The α-oxoketene N,N-acetals can be prepared in high yields by displacing both the thiomethyl groups of α-oxoketene dithioacetal by amines in refluxing acetic acid[15,17]. The α-oxoketene S,S-, N,S- and N,N- acetals have

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

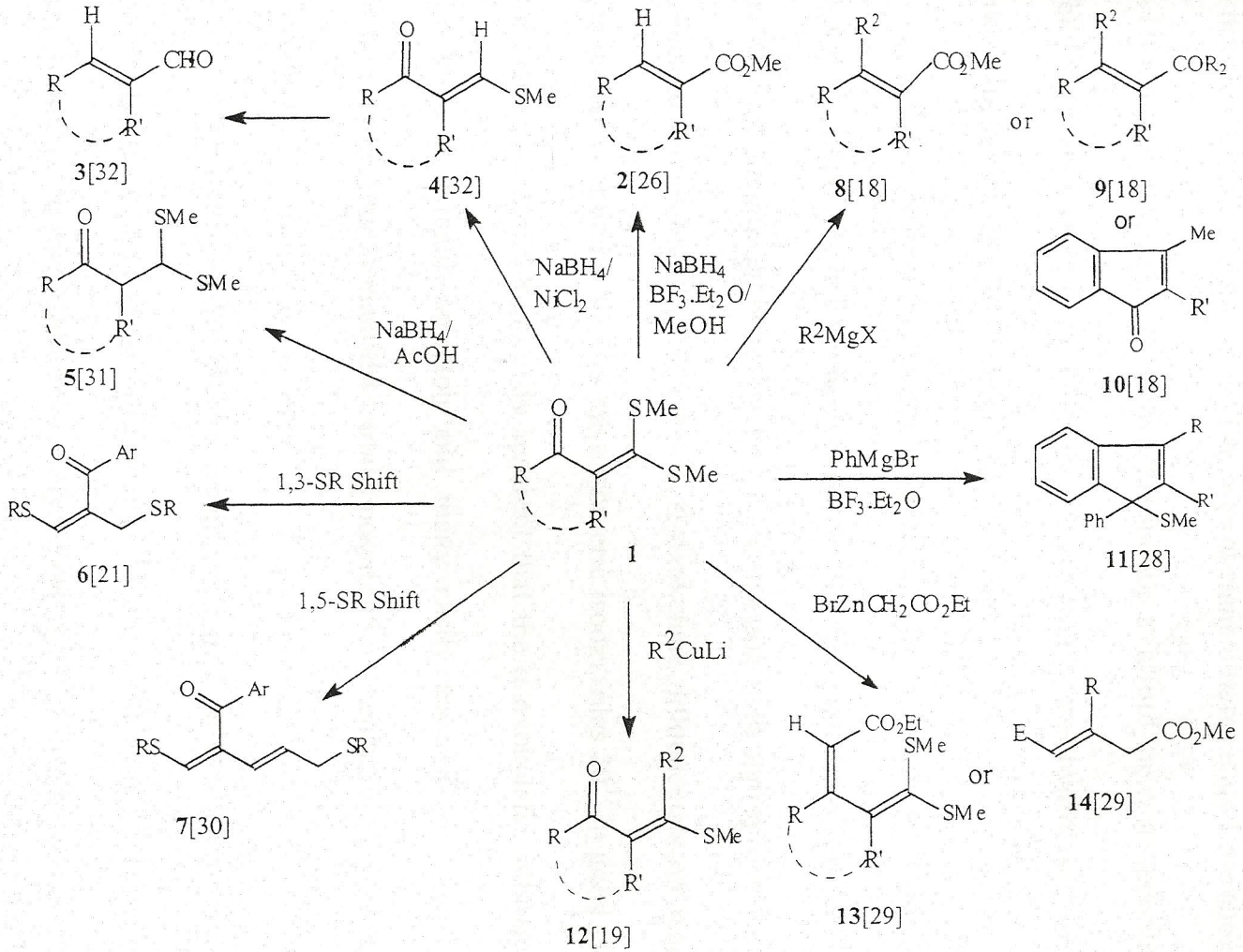

β-OXOESTERS
β-keto aldehyde
1,4-hydride addition
Hydrolysis
$(R^2)_2CuLi$ 1,4-addition
or
1,3 diketone
Polyene esters
1,2-hydride or organometallic addition and 1,3 carbonyl transposition
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
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

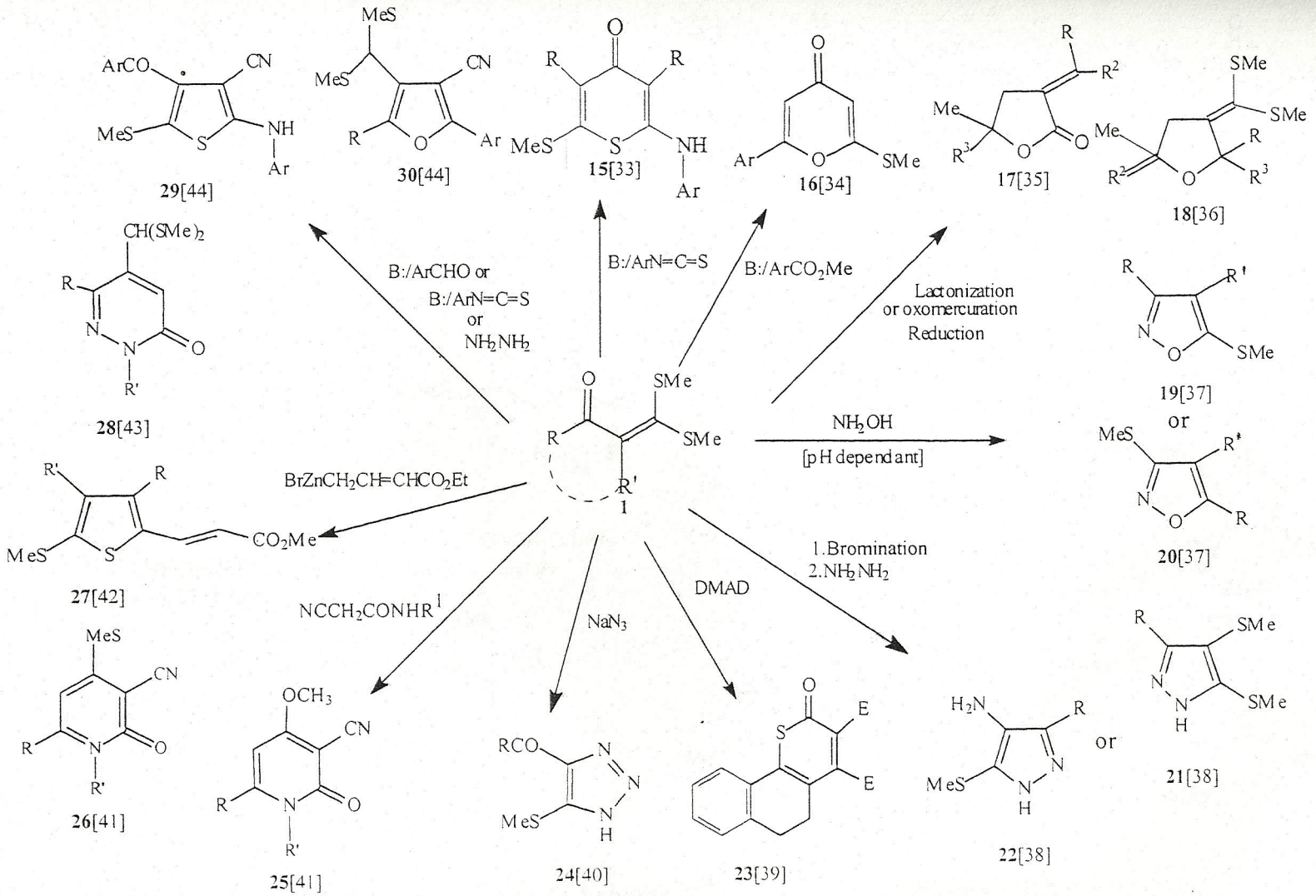

3[32]
4[32]
2[26]
8[18]
or
9[18]
5[31]
NaBH4/ NiCl2
NaBH4 BF3.Et2O/ MeOH
R2MgX
NaBH4/ AcOH
or
10[18]
1,3-SR Shift
PhMgBr
BF3.Et2O
6[21]
1
11[28]
1,5-SR Shift
R2CuLi
BrZnCH2CO2Et
7[30]
12[19]
13[29]
or
14[29]

Scheme 2

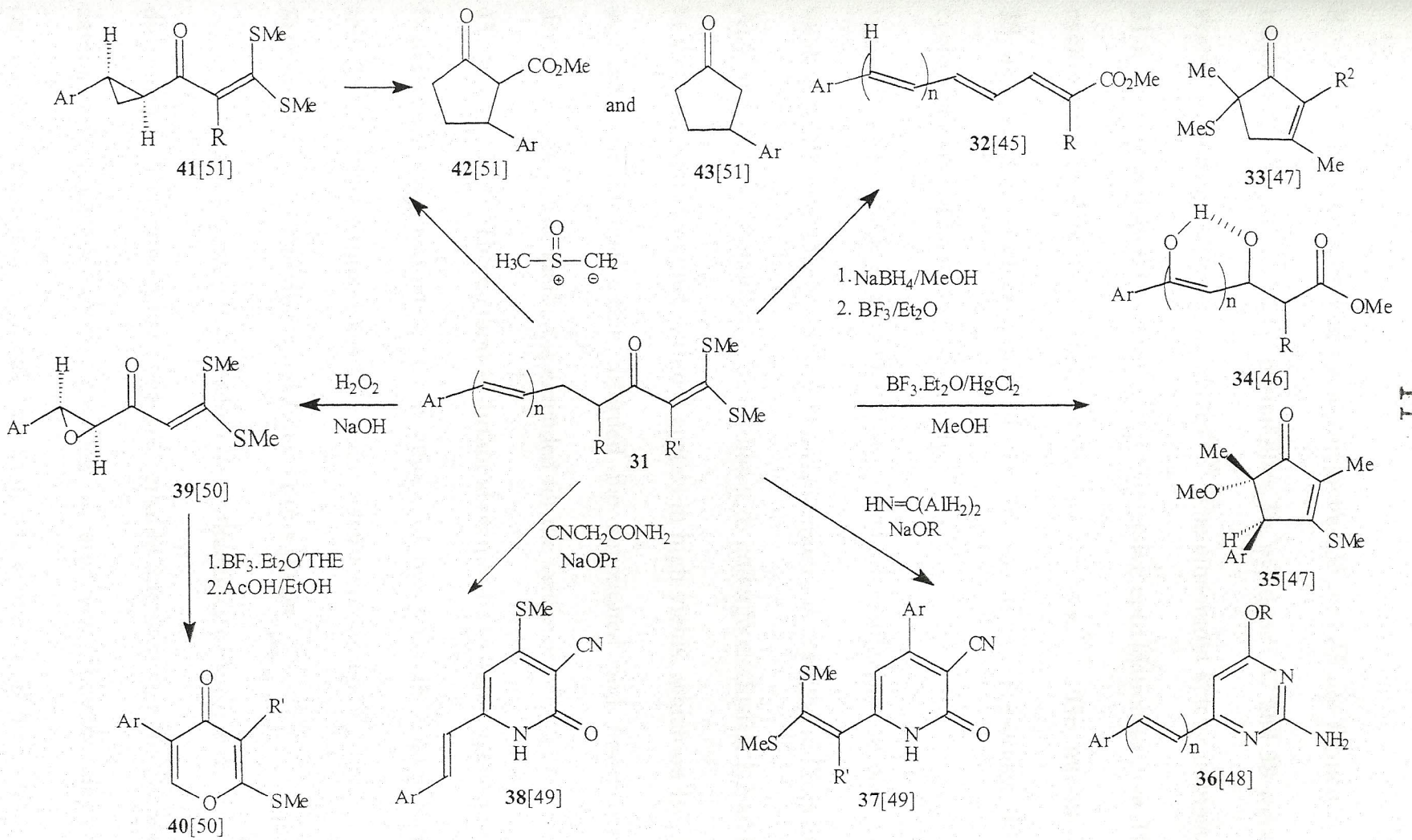
dithioacetals derived from propiophenone is reported[21]. The 2-alkyl thiomethyl acrylo-phenones **6** are formed by the 1,3-SR shift. A base assisted 1,5-SR shift to the dienes **7** is also reported[30]. The α-oxoketene dithioacetals **1** are shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction 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]
B:/ArCHO or
B:/ArN=C=S
or
NH2NH2
B:/ArN=C=S
B:/ArCO2Me
Lactonization
or oxomercuration
Reduction
19[37]
or
20[37]
NH2OH
[pH dependant]
1
BrZnCH2CH=CHCO2Et
27[42]
NCCH2CONHR1
NaN3
DMAD
1.Bromination
2.NH2NH2
26[41]
25[41]
24[40]
23[39]
22[38]
or
21[38]

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

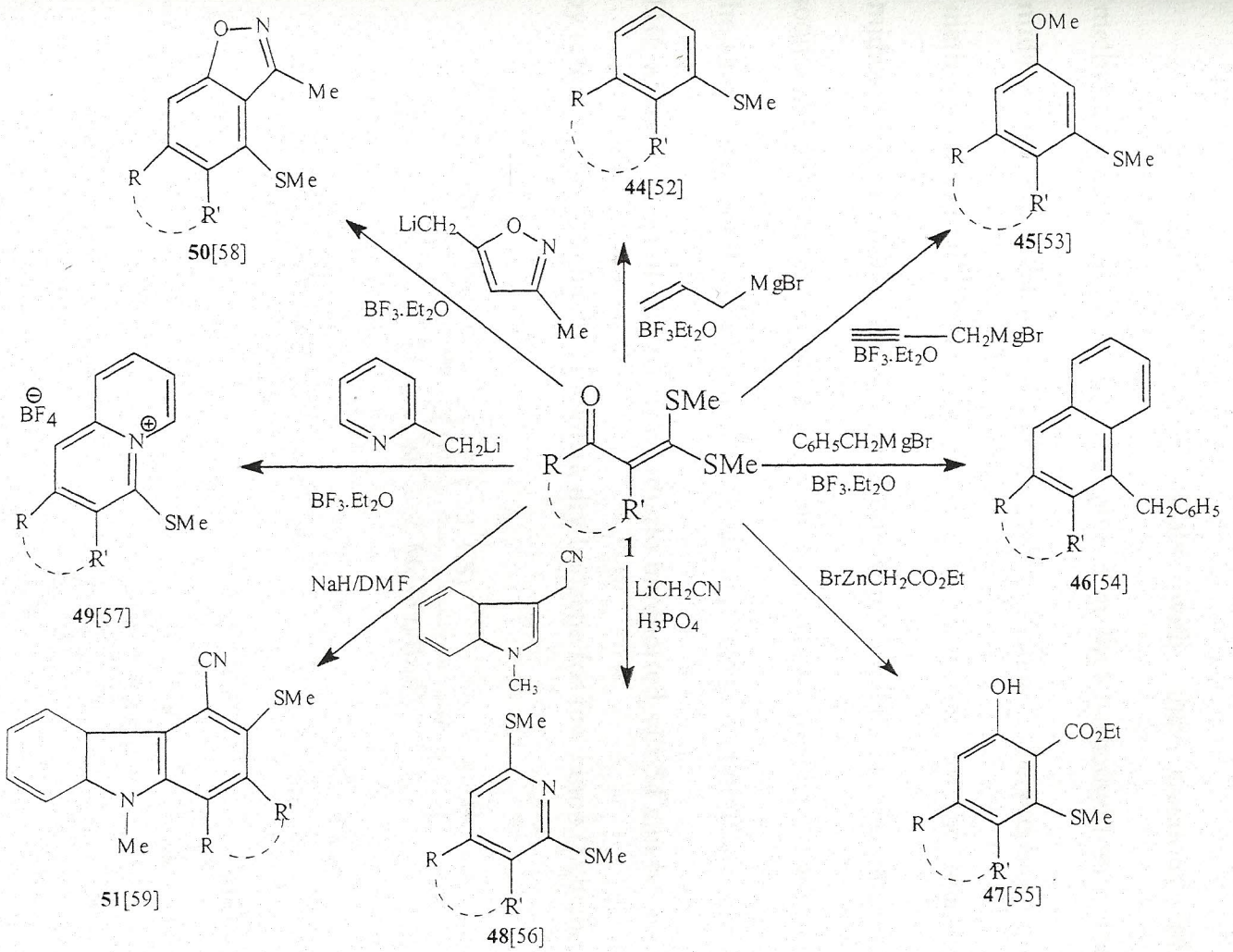
Scheme 4

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

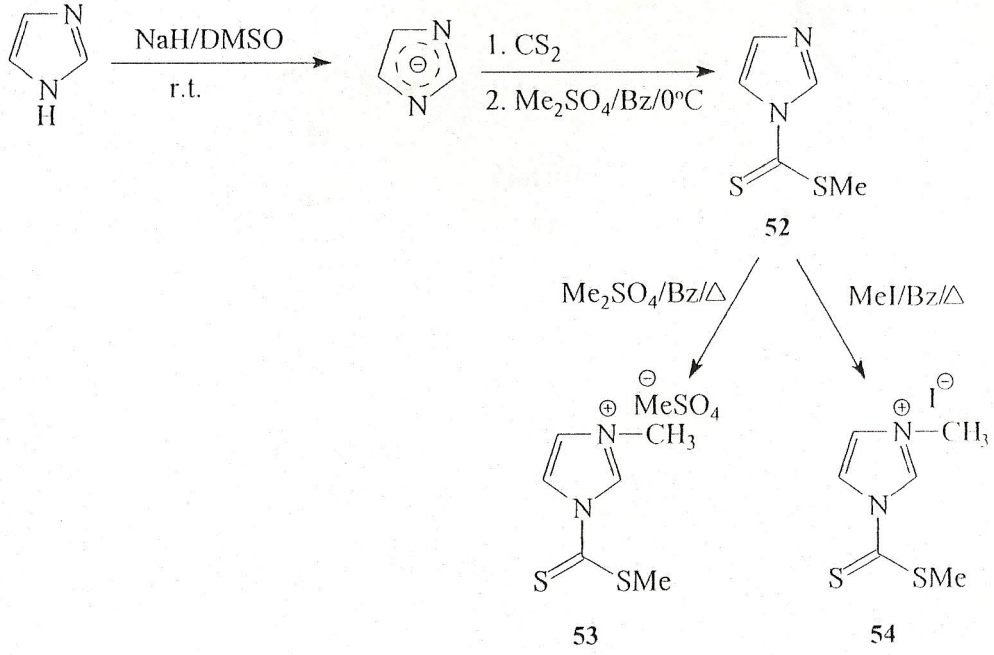
From a survey of the synthetic applicability of various α-oxoketene dithioacetals it is evident that they are versatile intermediates for performing carbon-carbon bond formation, synthesis of carbocycles, heterocycles etc. In our present investigation we have taken up the synthesis of β-oxodithioates, 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
C6H5CH2MgBr
BF3.Et2O
CH2C6H5
46[54]
49[57]
NaH/DMF
CN
LiCH2CN
H3PO4
BrZnCH2CO2Et
OH
CO2Et
51[59]
48[56]
47[55]

Scheme 5

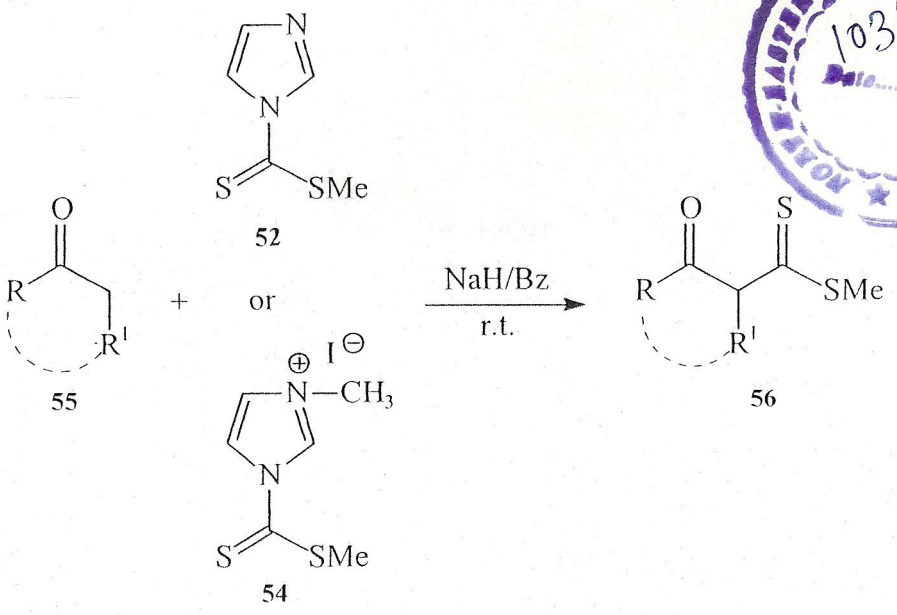
approach. We also attempted to undertake some transformations on α-oxoketene dithioacetals.

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).

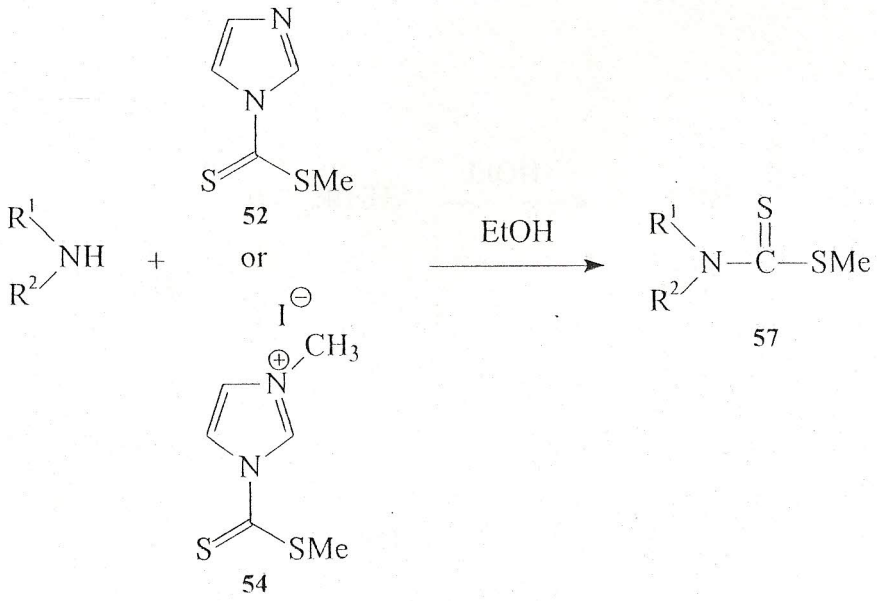


Scheme 7

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).

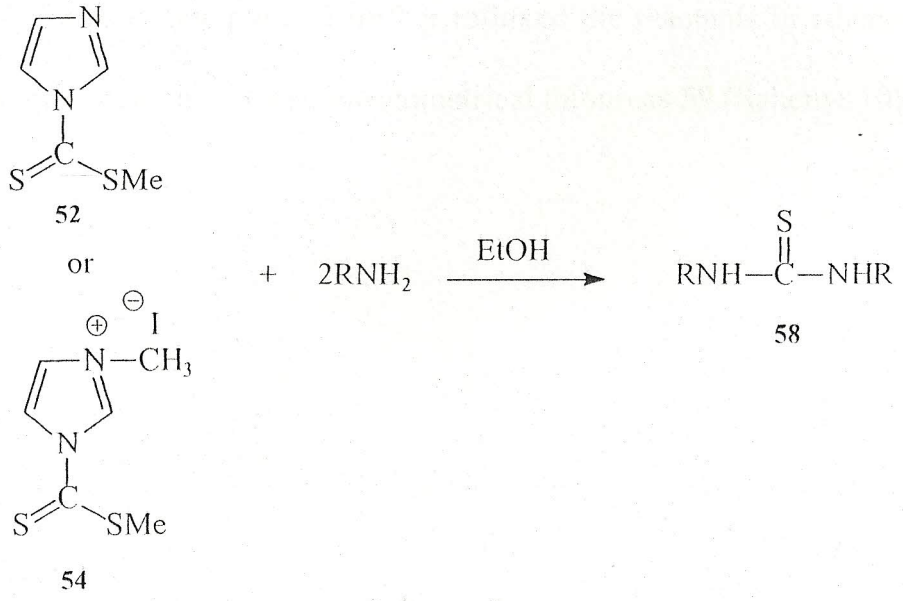


Scheme 8

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).

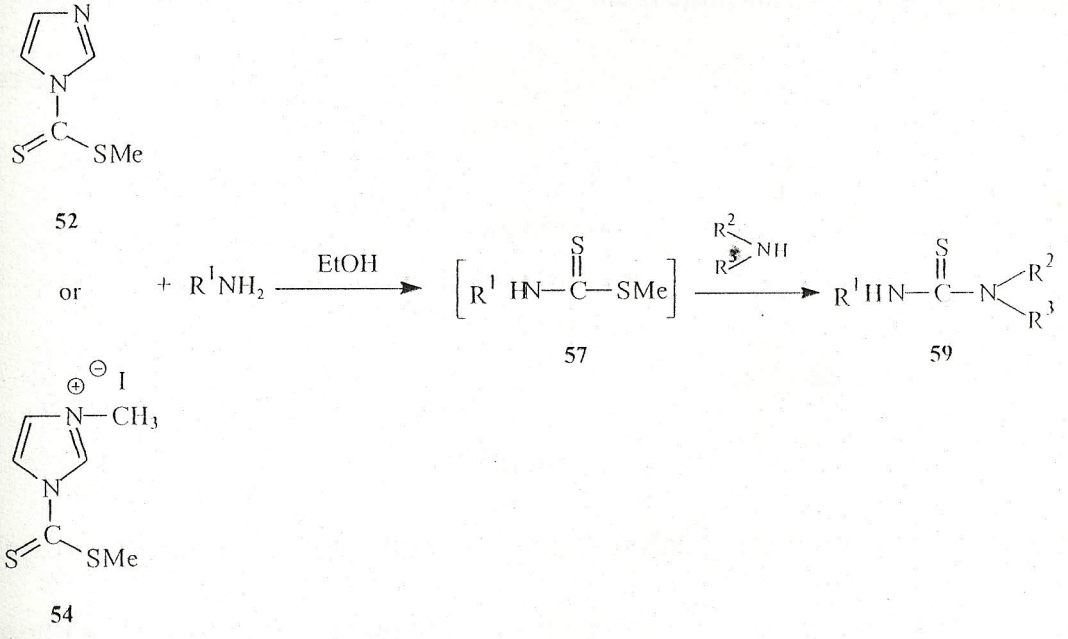


Scheme 9

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.

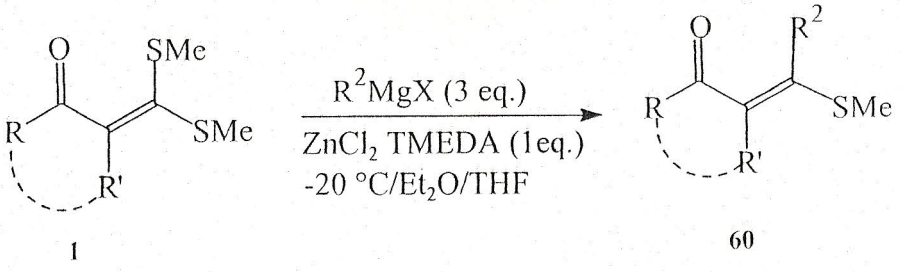
We next attempted to synthesize unsymmetrical thioureas **59** using 1-(methyldithiocarbonyl)imidazole **52** and 3-methyl-1-(methyldithio carbonyl)imidazolium iodide **54** and amines, because of their synthetic utility [64,65]. In order to synthesize various unsymmetrical thioureas starting from and 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.

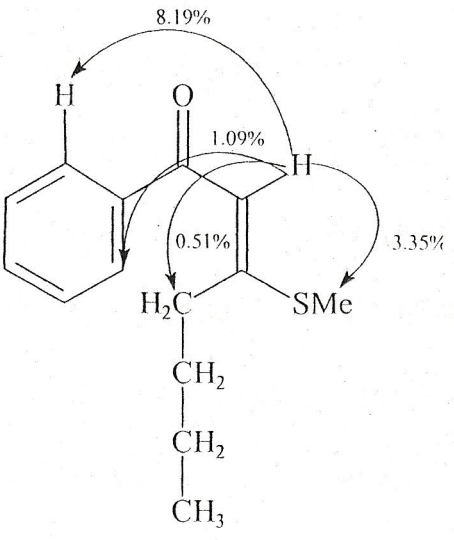
In the last chapter, the nucleophilic addition studies on α-oxoketene dithioacetals are described. The α-oxoketene dithioacetals when reacted with various Grignard reagents using $ZnCl_2$.TMEDA complex at -20^{0}C under nitrogen atmosphere, 1,4-addition products **60** were obtained in moderate to good 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.

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