SYNTHETIC STUDIES ON α-OXOKETENE DITHIOACETALS

(ABSTRACT)

By

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A THESIS
SUBMITTED IN FULFILMENT OF THE REQUIREMENT FOR
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TO

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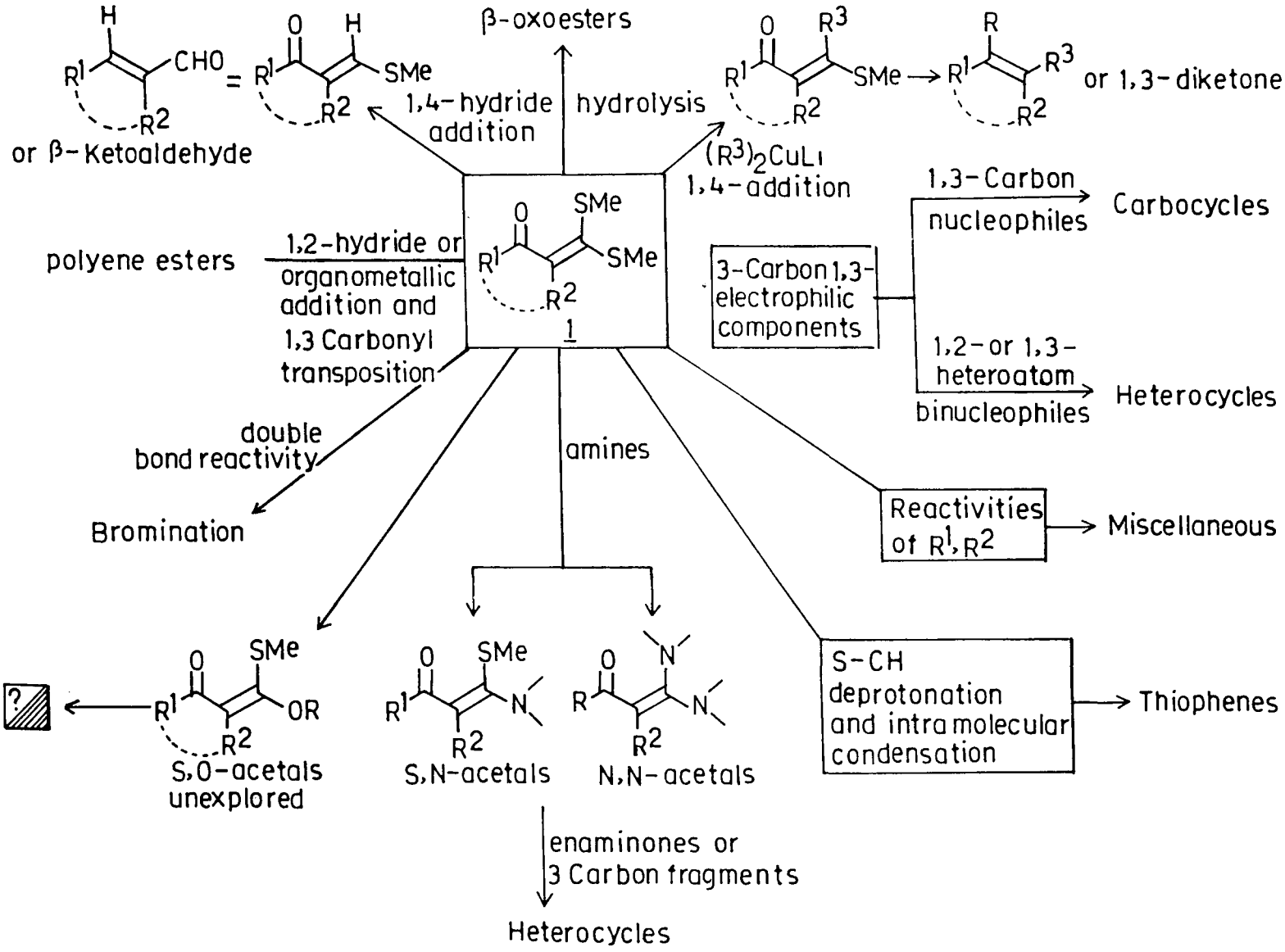
The work described in the thesis is part of an ongoing research programme in our laboratory since last twenty years. The thesis contains five chapters.

CHAPTER I : GENERAL INTRODUCTION

Polarized ketene dithio acetals **1** have been recognised as useful building blocks in many synthetic operations[1]. This class of compounds can be conveniently prepared by reacting any active methylene compound with two equivalents of base and carbon disulfide followed by alkylation. They have been shown to be excellent three carbon fragments with ambident 1,3-electrophilic centres thus permitting to design various methodologies for both carbocyclic and heterocyclic synthesis. the versatility of these intermediates has been already established and is highlighted in two recent reviews [1,2]. Scheme-1 highlights new interesting transformations of this polarized ketene dithioacetals.

CHAPTER II A: POLARIZED KETENE S,N- AND N,N-ACETALS : A BRIEF REVIEW.
B: REACTION OF LITHIOAMINO ANIONS WITH α-OXOKETENE DITHIOACETALS: AN IMPROVED AND A NEW GENERAL METHOD FOR THE SYNTHESIS OF α-OXOKETENE S,N- AND N,N-ACETALS.

Chapter II is divided into two parts. Part-I contains a brief review on polarised ketene S,N- and N,N-acetals regarding their practical and potential application in organic synthesis. In part II an improved method for the synthesis of S,N-acetals through metallation reactions is described. This method is superior to the earlier method developed in this laboratory which failed when extended to the synthesis of S,N-acetals can be readily prepared in high yields by using easily accessible α-oxoketene S,S-acetals in one step. It is generally known that aromatic amines are less readily reacted with α-oxoketene dithioacetals to give the corresponding S,N-

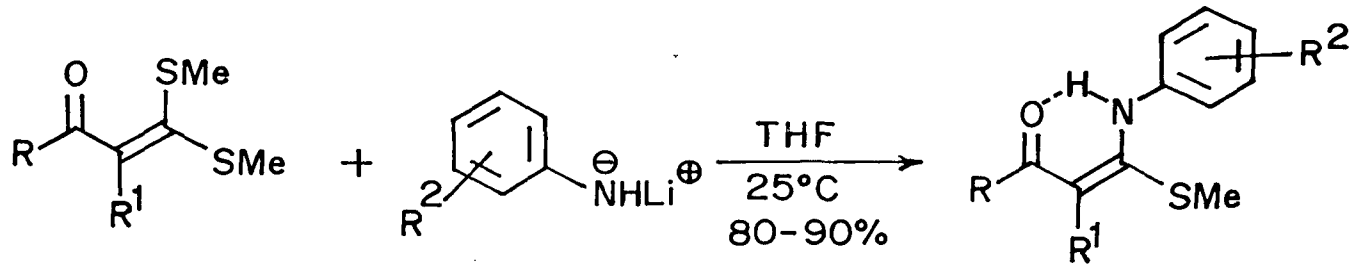

β-oxoesters
or β-Ketoaldehyde
1,4-hydride addition
hydrolysis
(R3)2CuLi 1,4-addition
or 1,3-diketone
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
1
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2-or 1,3-heteroatom binucleophiles
Heterocycles
double bond reactivity
Bromination
amines
Reactivities of R1, R2
Miscellaneous
S,O-acetals unexplored
S,N-acetals
N,N-acetals
S-CH deprotonation and intramolecular condensation
Thiophenes
enaminones or 3 Carbon fragments
Heterocycles

Scheme-1

acetals due to their reduced basicity. Under more rigorous conditions the corresponding N,N-acetals are formed sometimes resulting in the formation of a mixture of both S,N- and N,N- acetals. It was therefore, considered of interest to generate N-anions of these aromatic amines by metallation reactions and react with S,S-acetals so that only the corresponding S,N-acetals could be formed in high yields without resulting in a mixture of both S,N- and N,N-acetals.

Apparently, the lithio-anilines have been shown to react with S,S-acetals 1a-f to yield a variety of structural variants of the corresponding S,N-acetals **3a-j** exclusively in 80-90% overall yield. (Scheme-2). No trace of the corresponding N,N-acetals were formed in these reactions. Thus the method developed in the present investigation provides a convenient route for the synthesis of S,N-acetals of aromatic amines in high yields. Also these reactions were extended to prepare the corresponding S,N-acetals from lithio-amino pyridines **4** and **6**. It must be noted that the reaction of 2-amino and 3-amino pyridines with α-oxoketene S,S-acetals failed to yield even poor yields of the corresponding S,N-acetals **5a-j** and **7a-e** when we applied the earlier methods. When the same reaction was carried out with lithio amino pyridines the corresponding S,N-acetals were formed in good to excellent yields. (Scheme 3, Scheme 4). These results and discussions are described in the second part of chapter II. It is interesting to note that when 2-equimolar quantity of 2-lithioamino pyridine was reacted with 1-equimolar quantity of **1a** and refluxed for 3 hrs yielded the corresponding N,N-acetal **8a** in 79% yield. Similarly **8b** was also obtained in 80% yield (Scheme-5).

CHAPTER III A: A NEW VERSATILE AND EFFICIENT METHOD FOR THE SYNTHESIS OF PYRIDO [1,2-a] PYRIMIDINES VIA α-OXOKETENE S,N-ACETALS & N,N-ACETALS.



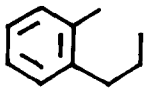
1a-f　　2 a-e　　3a-j

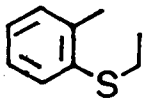
1 a, R = C_6H_5 R^1 = H

b, R = 4-MeOC_6H_4, R^1 = H

c, R = 4-ClC_6H_4, R^1 = H

d, R = 4-BrC_6H_4, R^1 = H

e, R = R^1 = 

f, R = R^1 = 

2 a, R^2 = H

b, R^2 = 2-Cl

c, R^2 = 4-Cl

d, R^2 = 4-Me

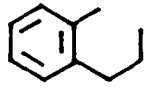
e, R^2 = 4-MeO

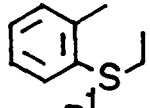
3 a, R = C_6H_5, R^1 = H, R^2 = H

b, R = 4-MeOC_6H_4, R^1 = H, R^2 = H

c, R = 4-ClC_6H_4, R^1 = H, R^2 = H

d, R = 4-Br C_6H_4, R^1 = H, R^2 = H

e, R = R^1 =  , R^2 = H

f, R = R^1 =  , R^2 = H

g, R = C_6H_5, R^1 = H, R^2 = 2-Cl

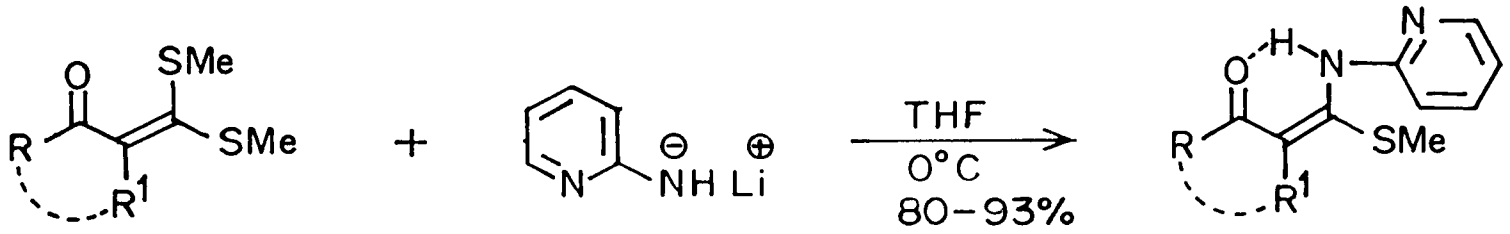
h, R = C_6H_5, R^1 = H, R^2 = 4-Cl

i, R = C_6H_5, R^1 = H, R^2 = 4-Me

j, R = C_6H_5, R^1 = H, R^2 = 4-MeO

Scheme-2

(See Table-1)



1 a-j 4 5, a-j

1 4, 5, a, R = C_6H_5, R^1 = H

b, R = 4-MeOC_6H_4, R^1 = H

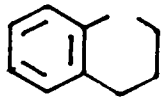
c, R = 4-Cl C_6H_4, R^1 = H

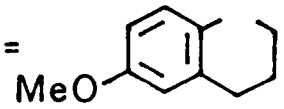
d, R = 4-MeC_6H_4, R^1 = H

e, R = 2-furyl, R^1 = H

f, R = 2-thienyl, R^1 = H

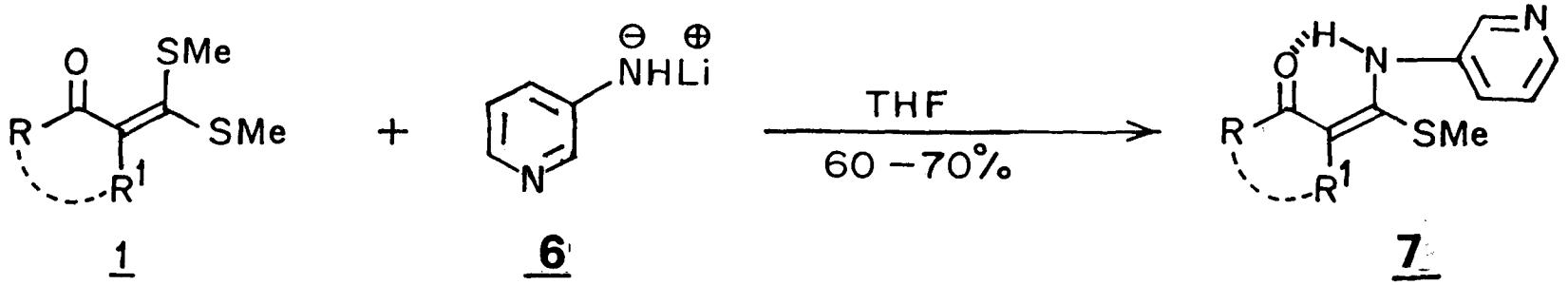
g, R = R^1 = $-(CH_2)_4-$

h, R = R^1 = 

i, R = R^1 = 

j, R = $C_6H_5-CH=CH$, R^1 = H

Scheme-3



1 6 7

6 , 7 , a , R = C_6H_5 , R^1 = H

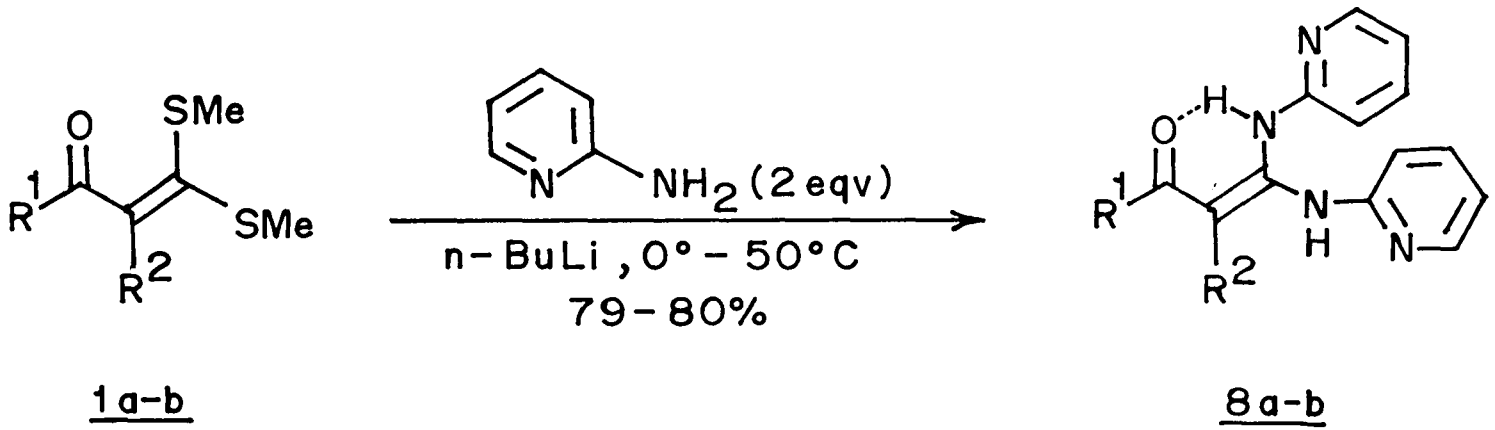
b , R = 4−$MeOC_6H_4$, R^1 = H

c , R = 4−MeC_6H_4 , R^1 = H

d , R = H_5C_2O− , R^1 = CN

e , R = 2− furyl , R^1 = H

Scheme-4



1a-b

8a-b

1, 8, a, $R^1 = C_6H_5$, $R^2 = H$

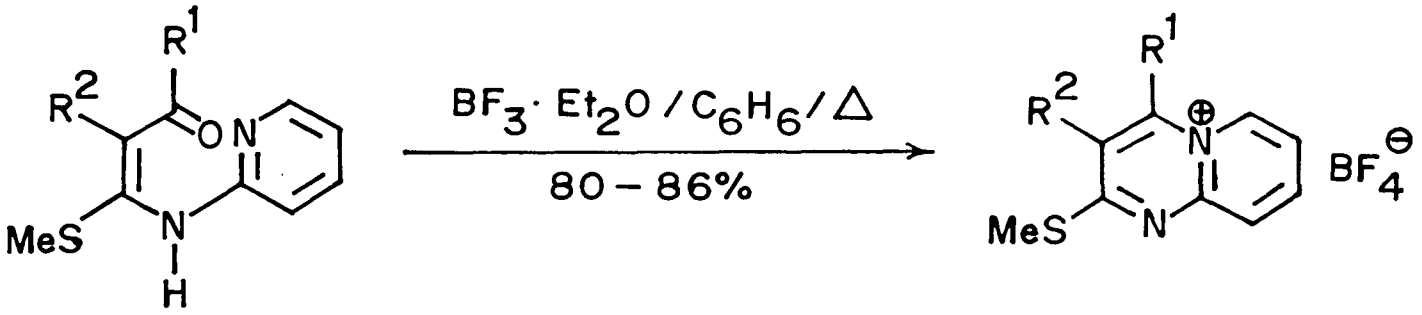
b, $R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$

Scheme-5

B: COPPER(I) ASSISTED INTRAMOLECULAR RING CLOSURE: A NEW GENERAL METHOD FOR IMIDAZO [1,2-a] PYRIDINES.

In chapter III, application of the S,N-acetals described in the preceding chapter for the synthesis of pyrido [1,2-a] pyrimidinium tetrafluoroborate salts and imidazo [1,2-a] pyridines is presented. Thus 3-methylthio-3-(2-pyridyl amino)-1phenyl-2-propene-1-one (Scheme 6) **5a** underwent smooth cycloaromatization in the presence of boron triflouride etherate to yield the corresponding 2-Methylthio-4-phenyl pyrido [1,2-a] pyrimidin-5-ium tetrafluoroborate salt in 82% overall yield. Thus S,N-acetals 5b-f yielded pyrido[1,2-a] pyrimidinium salts **9b-f** in 80-90% overall yields. Very few reports are available for the preparation of these compounds (see chapter III text) involving the reaction of 1,3 dicarbonyl compounds with 2-amino pyridines in the presence of perchloric acid under drastic conditions to get overall poor yields of the corresponding pyrido [1,2-a] pyrimidinium perchlorates. Thus the method developed in the present investigation is shown to provide convenient route for the synthesis of these compounds under mild reaction conditions with more flexible structural variants. S,N-acetals **5g** and **5h** derived from mercaptals of cyclohexanone and tetralone also yielded the pyrido [1,2-a] quinazolinium tetraflouroborates **10**(76%) and **11**(86%) respectively under the same reaction conditions (Scheme 7).

Also in the same chapter, a new general method for the synthesis of novel imidazo [1,2-a] pyridines is described. Thus S,N-acetals **5a-f** when treated with one equivalent of Copper (1) chloride in refluxing tetrahydrofuran the compounds obtained were characterised as imidazo [1,2-a] pyridines **12a-f** with excellent yields (85-93%) (Scheme-8). However the reaction mechanism governing these



5a-f

9a-f

5, 9, a $R^1 = C_6H_5$; $R^2 = H$ (82%)

b $R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$ (82%)

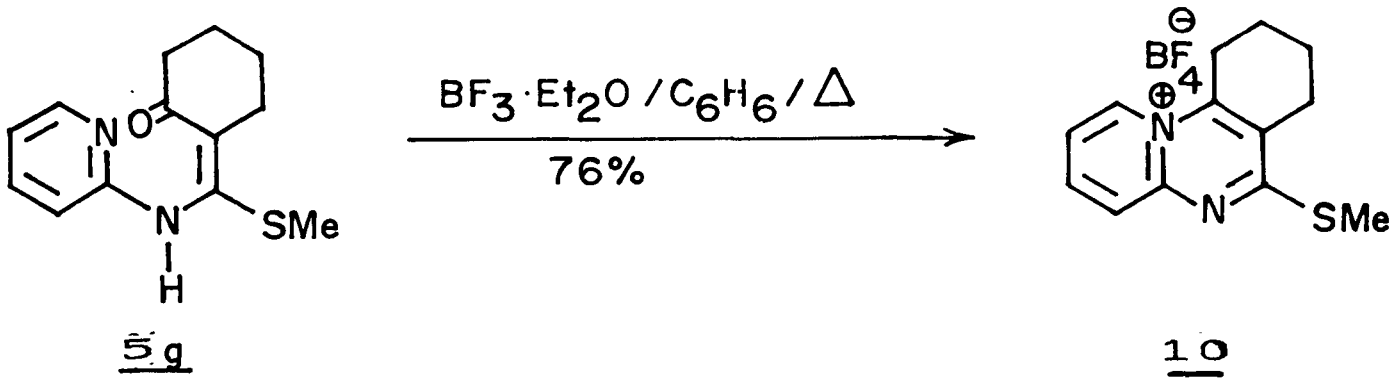
c $R^1 = 4\text{-}ClC_6H_4$; $R^2 = H$ (84%)

d $R^1 = 4\text{-}MeC_6H_4$; $R^2 = H$ (80%)

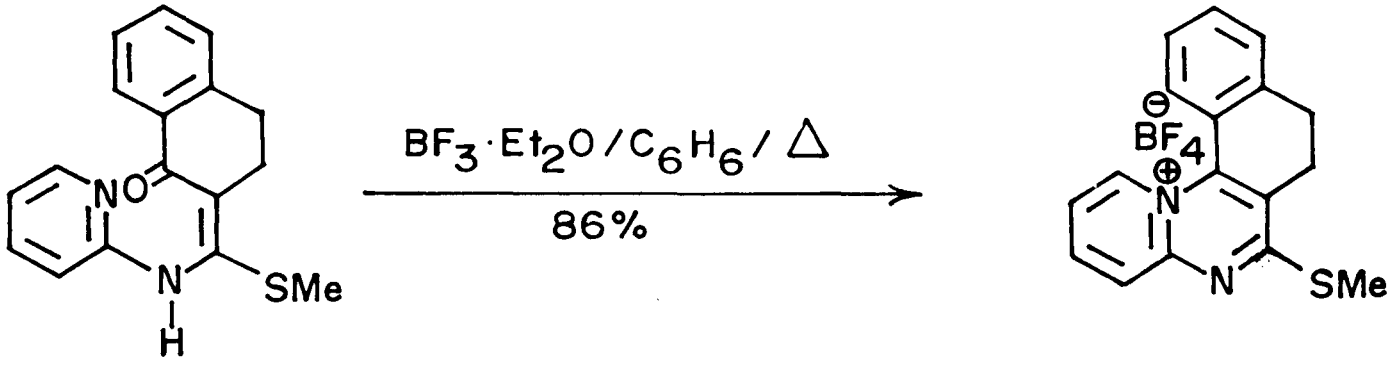
e $R^1 = 2\text{-}$furyl ; $R^2 = H$ (86%)

f $R^1 = 2\text{-}$thienyl ; $R^2 = H$ (80%)

Scheme-6

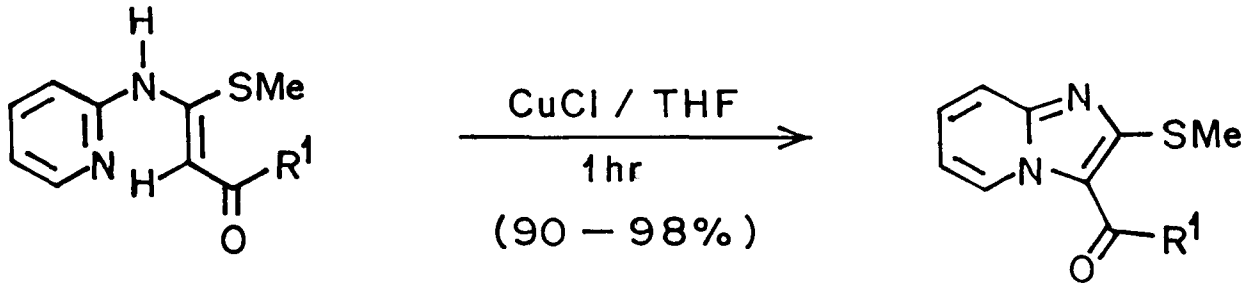


5g 10



5h 11

Scheme-7



5 a-f

12 a-f

5, 12, a, $R^1 = C_6H_5$

b, $R^1 = 4\text{-}MeOC_6H_4$

c, $R^1 = 4\text{-}clC_6H_4$

d, $R^1 = 4\text{-}Me\ C_6H_4$

e, $R^1 = 2\text{-}furyl$

f, $R^1 = 2\text{-}thienyl$

Scheme -8

transformations is not clearly understood and the possible tentative mechanism is discussed.

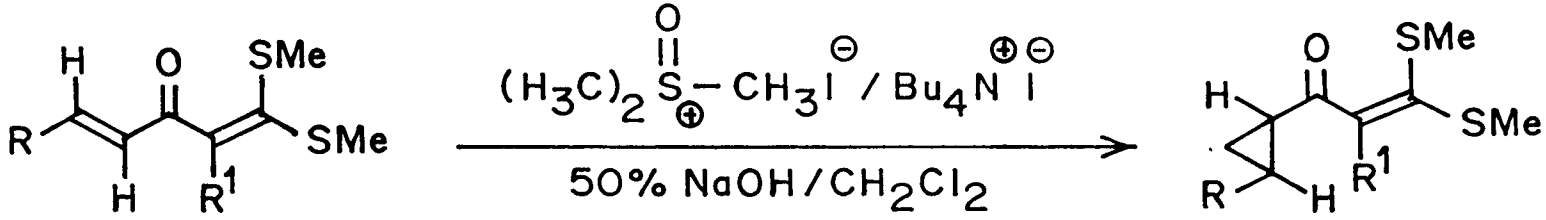
The results describing synthesis of both pyrido [1,2-a] pyrimidinium tetra floroborates and imidazo [1,2-a] pyridines are described in chapter - III.

CHAPTER IV REACTION OF α-BIS(METHYLTHIO)-METHYLENE CYCLOPROPYL KETONES WITH 1,2- AND 1,3-BINUCLEOPHILES: A GENERAL METHOD FOR THE SYNTHESIS OF CYCLOPROPYL RING SUBSTITUTED HETEROCYCLES.

As a part of our programmed studies on α-oxoketene dithioacetals it was considered of importance to prepare several cyclopropyl substituted heterocycles by using cyclopropyl ketene dithioacetals **14**. The α-bis (methylthio) methylene cyclopropyl ketones **14a-f** were obtained in excellent yields by regioselective cinnamoyl ketene dithioacetals **13a-f** under phase transfer conditions (Scheme 9). The 3-carbon 1,3-electrophilic structural frame is utilized for the synthesis of both 5- and 6-membered keterocycles by reacting with 1,2- and 1,3-heteroatom binucleophiles respectively. The cyclopropyl ketene dithioacetals **14** are reacted with hydrazine, hydroxylamine, guanidine and cyanoacetamide to obtain cyclopropyl substituted pyrazoles **15a-f**, isomeric isoxazoles **16a-e**, **17a-e**, pyrmidines **18a-f**, and the pyridones **19a-d** (Scheme 10) respectively. These results are described in chapter - IV.

CHAPTER V STUDIES ON REDUCTIVE CLEAVAGE OF C-O & C-S BONDS OF ACETALS AND DITHIOACETALS WITH ZINC IN ACETIC ACID.

In chapter V, some studies on the reductive cleavage of C-O and C-S bonds in the presence of zinc and acetic acid has been described. When acetals **20a-h** are



13 a–f

14 a–f

13, 14

a , R = C_6H_5 , R^1 = H

b , R = 4–MeOC_6H_4 , R^1 = H

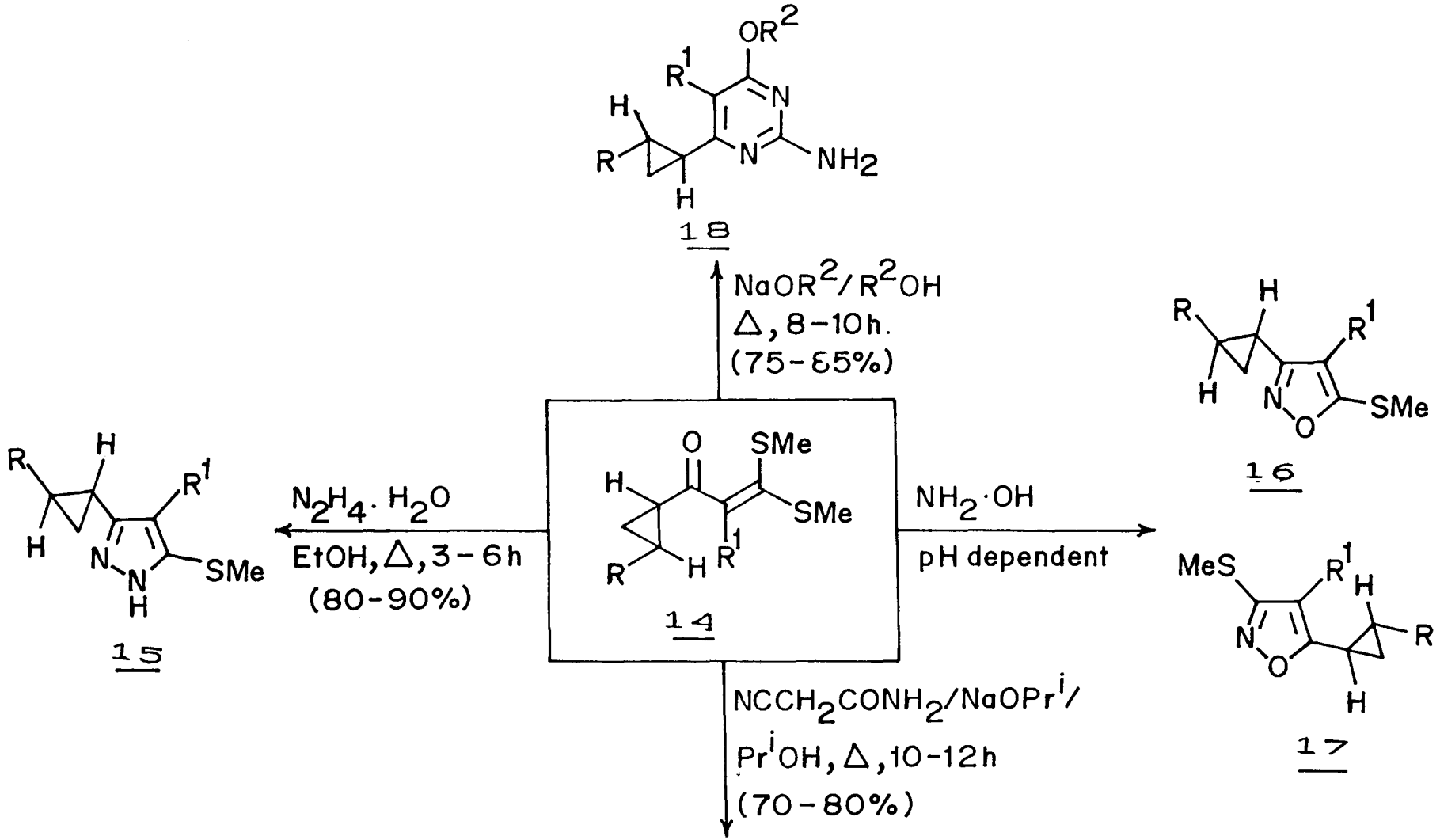
c , R = 3,4–$(MeO)_2$ C_6H_3 , R^1 = H

d , R = 3,4,5–$(MeO)_3$ C_6H_2 , R^1 = H

e , R = 4–ClC_6H_4 , R^1 = H

f , R = 4–Me C_6H_4 , R^1 = H

Scheme – 9


OR2
R1
N
H
R
N
NH2
H
18
NaOR2/R2OH
Δ, 8-10h.
(75-85%)
H
R
R1
H
N
O
SMe
16
O
SMe
H
SMe
R1
R
H
14
N2H4. H2O
EtOH, Δ, 3-6h
(80-90%)
NH2·OH
pH dependent
R
H
R1
H
N
N
H
SMe
15
MeS
R1
H
N
O
R
H
17
NCCH2CONH2/NaOPri/
PriOH, Δ, 10-12h
(70-80%)
SMe
R1
CN
H
R
N
H
O
H
19

Scheme-10

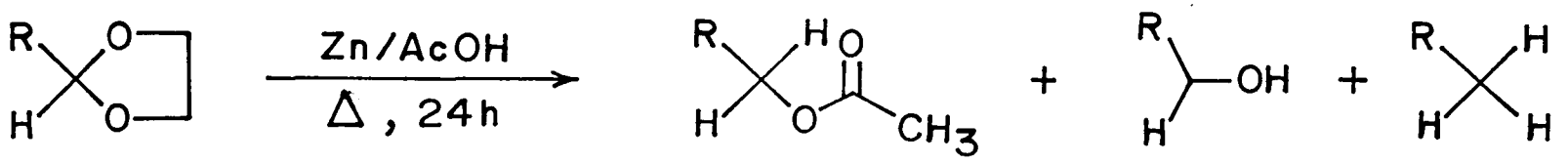
treated with zinc in acetic acid and refluxed for 20-24 hours the products obtained were characterised as a mixture of acetals **21a-d** alcohols **22a-c,h** and sometimes completely reduced products **23d-g** (Scheme 11). The acetals **20d-g** derived from alkoxy substituted benzaldehydes underwent facile cleavage under the same reaction condition to afford only the completely reduced products exclusively. However when the dithioacetals **24a-e** are treated with zinc in acetic acid under similar reaction conditions partially reduced mercaptans **25a-e** (Scheme 12) were obtained. Similarly dithioacetals **26a-c** derived from aromatic benzaldehydes and ketones and thiophenol also yielded the partially reduced products **27a-c** along with traces of thiophenol in the overall product mixture are (Scheme 13). The results of this study and the plausible mechanism are also described in this chapter.

Each chapter is divided into introduction, results and discussion, experimental and conclusion. Relevant reference have been included at the end of each chapter.

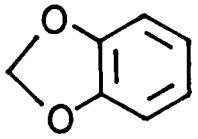
REFERENCE:

1. Dieter, R.K. *Tetrahedron* 1986, *43*, 3209.

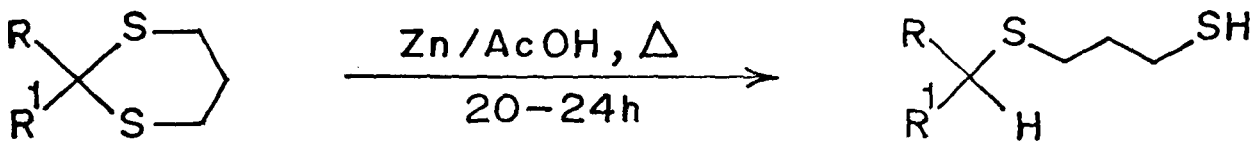
2. Junjappa, H; Ila, H; Asokan, C.V. *Tetrahedron*, 1990, *46*, 5423.



20 21 22 23

20	R	21(%)	22(%)	23(%)
a	C_6H_5	(45)	(35)	—
b	4-Me C_6H_4	(42)	(36)	—
c	4-Cl C_6H_4	(30)	(50)	—
d	4-MeO C_6H_4	(40)	—	(40)
e	3,4-$(MeO)_2$ C_6H_3	—	—	(78)
f	3,4,5-$(MeO)_3C_6H_2$	—	—	(63)
g		—	—	(65)
h	2-Naphthyl	—	(82)	—

Scheme-11



24 → 25

72 – 85%

24, 25 a, R = C_6H_5, R^1 = H

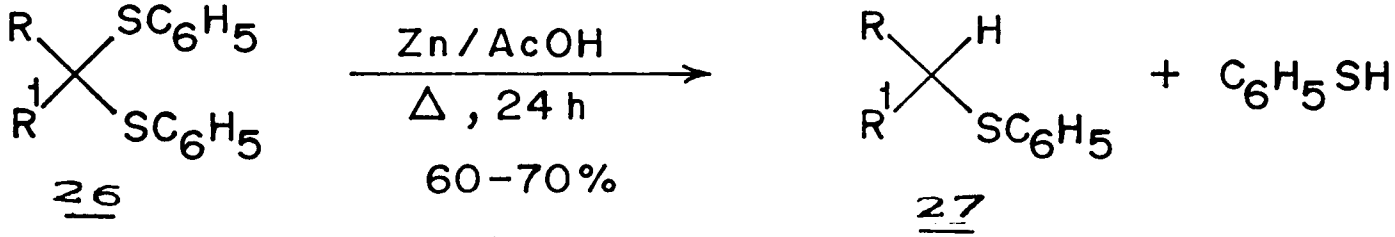
b, R = 4-ClC_6H_5, R^1 = H

c, R = 4$MeOC_6H_4$, R^1 = H

d, R = 2-naphthyl, R^1 = H

e, R = R^1 = C_6H_5

Scheme-12



26 27

26,27. a, $R = C_6H_5$, $R^1 = H$

b, $R = C_6H_5 - CH = CH$, $R^1 = H$

c, $R = R^1 = C_6H_5$

Scheme-13

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1996

Dedicated To
My Late Father & Mother
(in their loving memory)

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HEAD
DEPARTMENT OF CHEMISTRY

TO WHOM IT MAY CONCERN

This is to certify that Mr. Okram Mukherjee Singh, a Ph.D. student of the Department of Chemistry has satisfactorily completed the following courses as a part of his Ph.D. Programme.

Course No.	*Title*	*Grade*
1. SPS 601	French Language	O
2. SPS 629	Numerical Methods with application to Computer.	A
3. CHEM 620	Selected Topics in Physical Chemistry.	A
4. CHEM 622	Spectroscopic Methods in Chemistry	A

M K Mahanti
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Phone :
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PROF. H. JUNJAPPA
DEPARTMENT OF CHEMISTRY

This is to certify that the work described in this thesis has been carried out by Mr. Okram Mukherjee Singh, under my supervision. He has satisfactorily completed the Pre-Ph.D. courses prescribed and the minimum period of two years of investigation work for the award of Ph.D. degree in Chemistry.

The work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other University.

Shillong

H. Junjappa
Supervisor

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OMSingh

Dated. 16/12/96

OKRAM MUKHERJEE SINGH

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PREFACE

The α-oxoketene dithioacetals are a versatile group of 3-carbon synthons with ambident 1,3-electrophilic centres thus permitting to design various methodologies for both carbocyclic and heterocylic synthesis. They can be converted to the corresponding polarized ketone S,N- and N,N-acetals making them more important as precursors for a large variety of functionalized acetals. These polarized ketene S,S-, S,N- & N,N-acetals have been extensively explored in this laboratory for the development of new synthetic methods for a variety of heterocyclic and carbocyclic compounds. The work described in this thesis highlights further new interesting transformation of polarized ketene S,S-, S,N- & N,N-acetals.

The thesis consists of five chapters. The first chapter gives a general introduction to polarized ketene dithioacetals and some of the recent transformation reported from this laboratory.

The second chapter is divided into two parts. Part I contains a brief review on polarized ketene S,N- and N,N-acetals. In part II an improved and new method for the synthesis of polarized ketene S,N- and N,N-acetals in described.

The third chapter also, is divided into two parts. Part I contains a new versatile and efficient method for the synthesis of pyrido [1,2-a] pyrimidines via α-oxoketene S,N- and N,N-acetals.

In part II a new general method for novel imidazo [1,2-a] pyridines by copper (I) assisted intermolecular ring closure of S,N-acetals is described. Probable mechanism for the formation of various products is discussed.

In chapter IV, synthesis of cyclopropyl substituted heterocycles by reacting α-[bis (methylthio) methylene] cyclopropyl ketones with various 1,2- and 1,3- heteroatom bynucleophiles. The last chapter(CHAPTER V) of the thesis deals with studies on the reductive cleavage of C-O and C-S bonds of acetals and dithioacetals.

Each chapter is divided into introduction, results and discussion. experimental and conclusion. Relevant references have been included at the end of each chapter.

CHAPTER - I

GENERAL INTRODUCTION

The α-oxoketene dithioacetals and the corresponding S, N- and N, N- acetals are versatile synthetic intermediates in organic synthesis. This chapter is devoted to a brief review and discussion on the chemistry of these synthons in the context of their practical and potential application to organic synthesis. For convenience this chapter is divided into two sections. In the first section a brief survey of α-oxoketene dithioacetals is described and the present work has been described in the second section.

A. THE POLARIZED KETENE S, S - ACETALS

Polarized ketene S, S- acetals have been recognised as useful building blocks in many synthetic operations[1]. This class of compounds can be conveniently prepared by reacting any active methylene compound with two equivalents of base and carbon

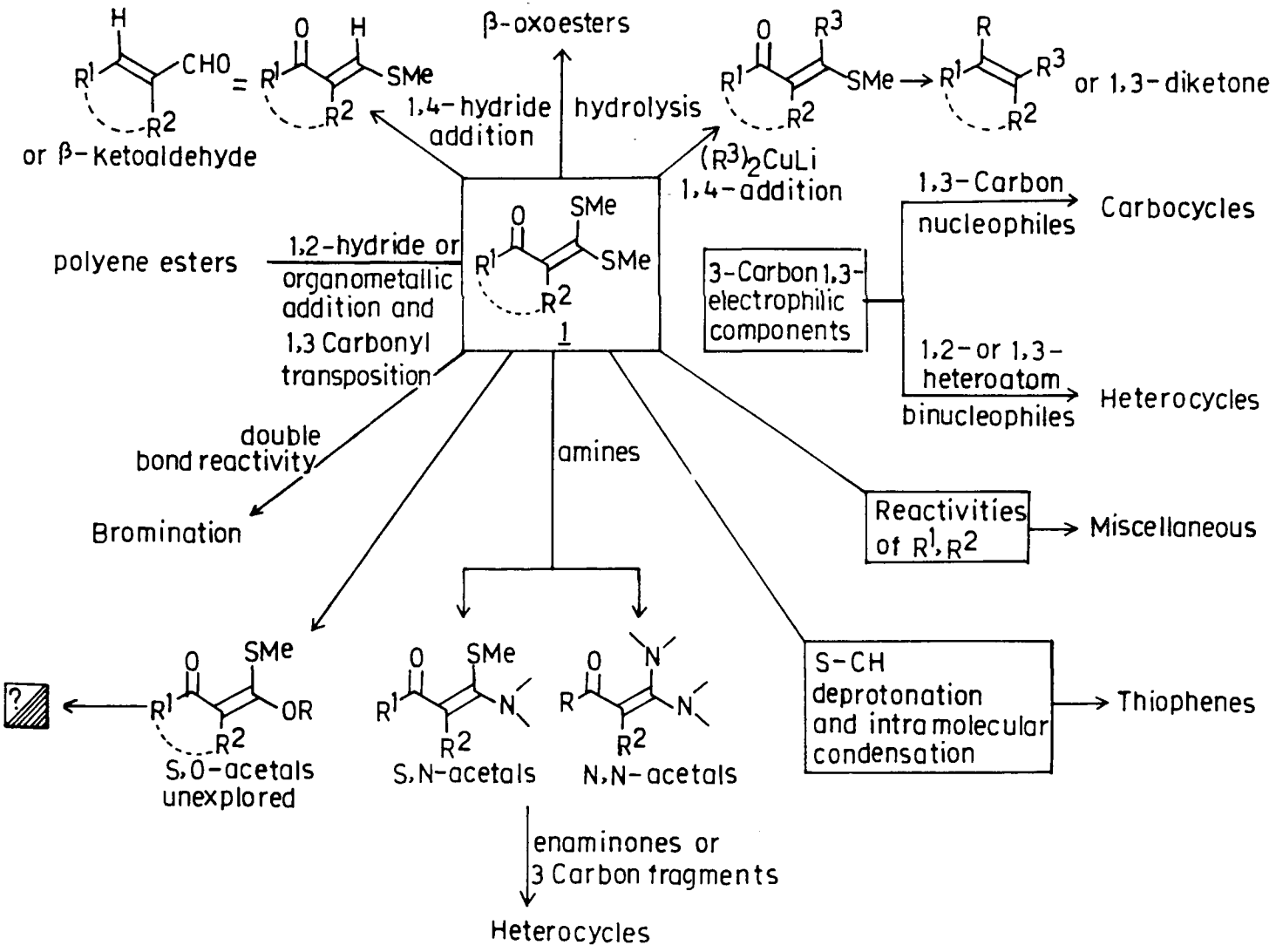
disulfide followed by alkylation[2,3,5]. Various bases and reaction conditions have been employed depending on the nature of the active methylene compound.

In 1910 Kelber and co-workers[10,11] reported the first synthesis of α-oxoketene dithioacetals. Much of the earlier works on oxoketene dithioacetals were confined to their preparation and properties, while little attention was paid for their synthetic utility. Hence, more than half a century the synthetic potential of these class of compounds remained unexplored. Later Thuillier and Vialle prepared these compounds in high yields in one pot reaction by reacting the active methylene ketone with carbondisulfide in the presence of sodium amylate followed by alkylation[2,3,5]. Subsequently, these reaction conditions have been greatly improved using different bases and reaction conditions[4,6-9]. A large number of α-oxoketene dithioacetals have now been reported and emerged as very useful synthetic intermediates over the last two decades and their chemistry has been reviewed by Dieter[1a] and Junjappa *et al.*[1b]

The α-oxoketene dithioacetals can be prepared by easier methods in one pot operation in high yields. They are stable compounds with well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stored indefinitely without decomposition. The corresponding α-oxoketene O,O- acetals[12] are moisture sensitive and undergo hydrolysis under mild conditions. The oxoketene dithioacetals are essentially a masked β-ketoester in which the ester functionality is protected as a ketene dithioacetal. Alternatively, it may be viewed as an α-β-unsaturated ketone containing a highly functionalised β-carbon. The oxoketene dithioacetals have been shown to be excellent three carbon fragments, with 1,3-carbon possessing differential electrophilic properties which is an important pre-requisite in designing various methodologies for both

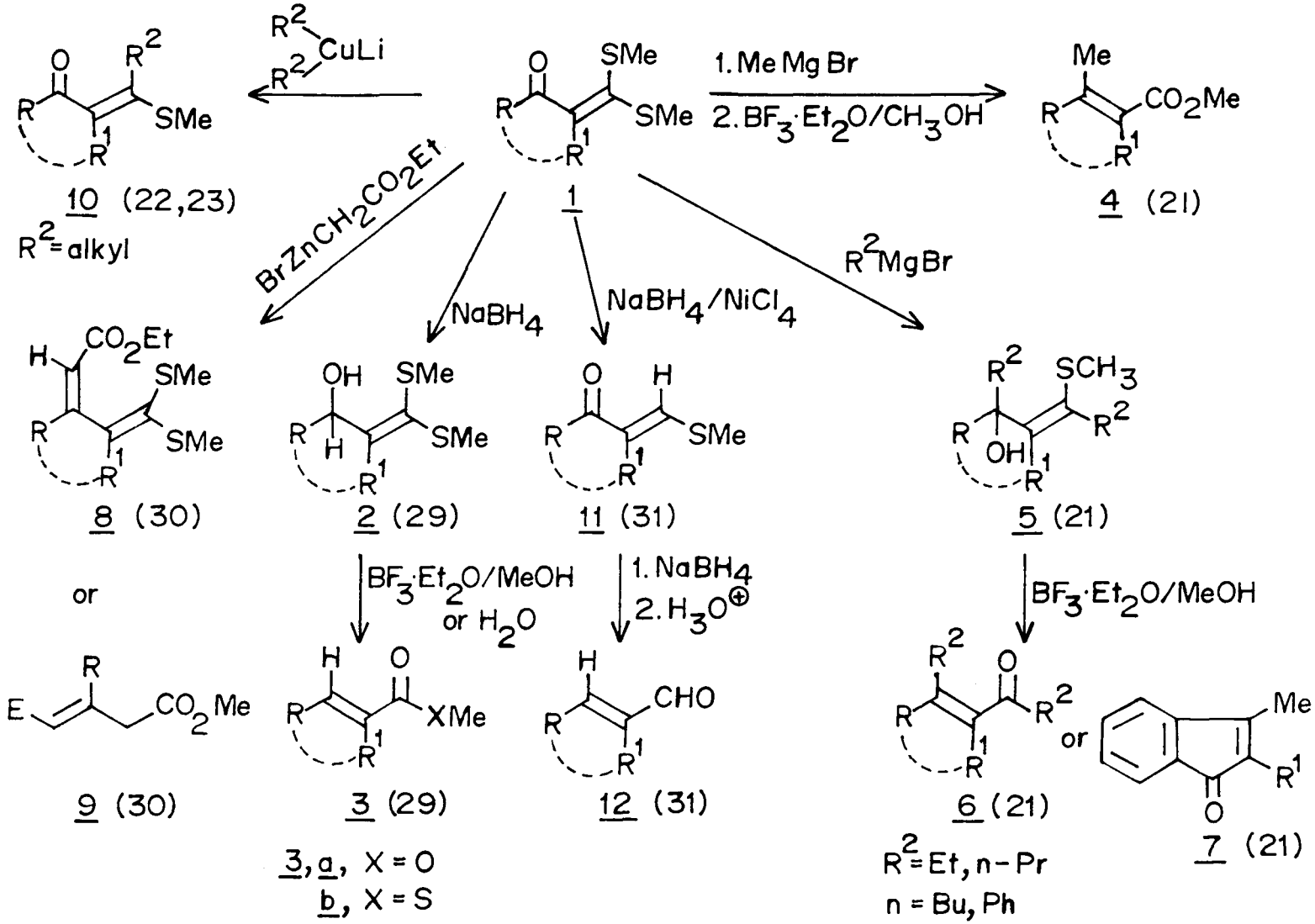
carbocyclic and heterocyclic compounds. They also possess considerable synthetic potential for the chemo-, stereo- and regioselective construction of new bonds via 1,2-nucleophilic additions to ketone carbonyl or by 1,4-conjugate addition to the β-carbon of the enone system. The intermediate allylic alcohols and enones can, in turn, be exploited in additional bond forming reactions. also, oxoketene dithioacetals can be further converted to the corresponding ketene dihalogenides[13,14], N,S[15] and N,N-acetals[16] making them more important as precursors for a large variety of functionalized acetals. The preparation of N,S-acetals is accomplished through the displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol[15,17]. Alternatively, they can be prepared directly from active methylene ketones by reacting their enolate anion with alkyl and arylisothiocyanates followed by alkylation[18]. The oxoketene N,N-acetals can be prepared in high yields by displacing both the thiomethyl groups by amines in refluxing acetic acid[17,19]. The preparation of O,S-acetals are accomplished through the displacement by an oxygen nucleophile of the sulfonium salt[2]. The oxoketene S,S- ,N,S- and N,N-acetals have been extensively used largely unexplored.

Scheme 1 outlines various reactivity profiles of α-oxoketene dithioacetals of the general formula **1**. Hydrides and organo metallic reagents give 1,2- addition products typical of carbonyl function reactivity[21]. These additions can be directed in a 1,4- manner by suitably manipulating the reaction condition and reagents[21-23]. Further transformations of these 1,2- or 1,4- addition products have also been investigated extensively[21]. The differential electrophilicity at 1,3-carbon of the oxoketene dithioacetals have been judiciously utilized for the synthesis of both 5- and 6- membered heterocycles by reacting with 1,2- and 1,3 hetero atom binucleophiles respectively. The 1,3- carbon binucleophiles have been similarly used in the synthesis of carbocycles. The enolate


β-oxoesters
or β-Ketoaldehyde
1,4-hydride addition
hydrolysis
or 1,3-diketone
(R3)2CuLi 1,4-addition
1,3-Carbon nucleophiles
Carbocycles
polyene esters
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
3-Carbon 1,3-electrophilic components
1,2-or 1,3-heteroatom binucleophiles
Heterocycles
double bond reactivity
Bromination
amines
Reactivities of R1, R2
Miscellaneous
S,O-acetals unexplored
S,N-acetals
N,N-acetals
S-CH deprotonation and intra molecular condensation
Thiophenes
enaminones or 3 Carbon fragments
Heterocycles

Scheme-1

anoin formed by the deprotonation (when R=alkyl) can undergo condensation with aldehydes to give α-enoyl ketene dithioacetals[3b,24]. When R^1 is a methyl group and allylic anion is generated in the presence of strong bases leading to rearranged products[25]. Deprotonation of the thiomethyl group followed by intramolecular Aldol type condensation to afford thiophenes is also reported.[26] As discussed earlier they can be easily converted to oxoketene O,S-, N,S- and N,N- acetals. The reactivity of the mercapto double bond is also exploited with electrophiles with N-bromosuccinimide[27]. Thus, it is apparent that the oxoketene dithioacetals of general formula **1** constitute an important class of synthons with reactive electrophilic and nucleophilic centres distributed in various centers of its skeleton permitting reactions of great synthetic importance. In the following sections some of the selected transformations reported from this laboratory are briefly summarized. The oxoketene dithioacetals **1** have been reported to undergo chemoselective 1,2- reduction with sodium borohydride ($NaBH_4$) to give the corresponding carbinol acetals **2**[28,29] which were shown to undergo smooth methanolysis in the presence of boron triflouride eltherate to afford α-β- unsaturated methyl esters 3[29] in high yields (Scheme 2). The overall transformation can be viewed 90 as the homologation of active methylene ketones at the α- position, involving 1,3-carbonyl transposition. The Grignard and organo lithium reagents undergo either regioselective 1,2-addition to afford the α- hydroxy ketene dithioacetals or a sequential 1,4- and 1,2- addition to afford the β- hydroxyvinyl sulfides[21-23] the borontrifluride etherate catalysed solvolysis or the hydrolysis of these carbionols yield either β-substituted α-β unsaturated esters **4** or the corresponding ketene **6**[21] (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 7 were formed **21**. The Reformatsky reaction on dithioacetal **1** is reported to give the diene ester **8** and the β, γ-

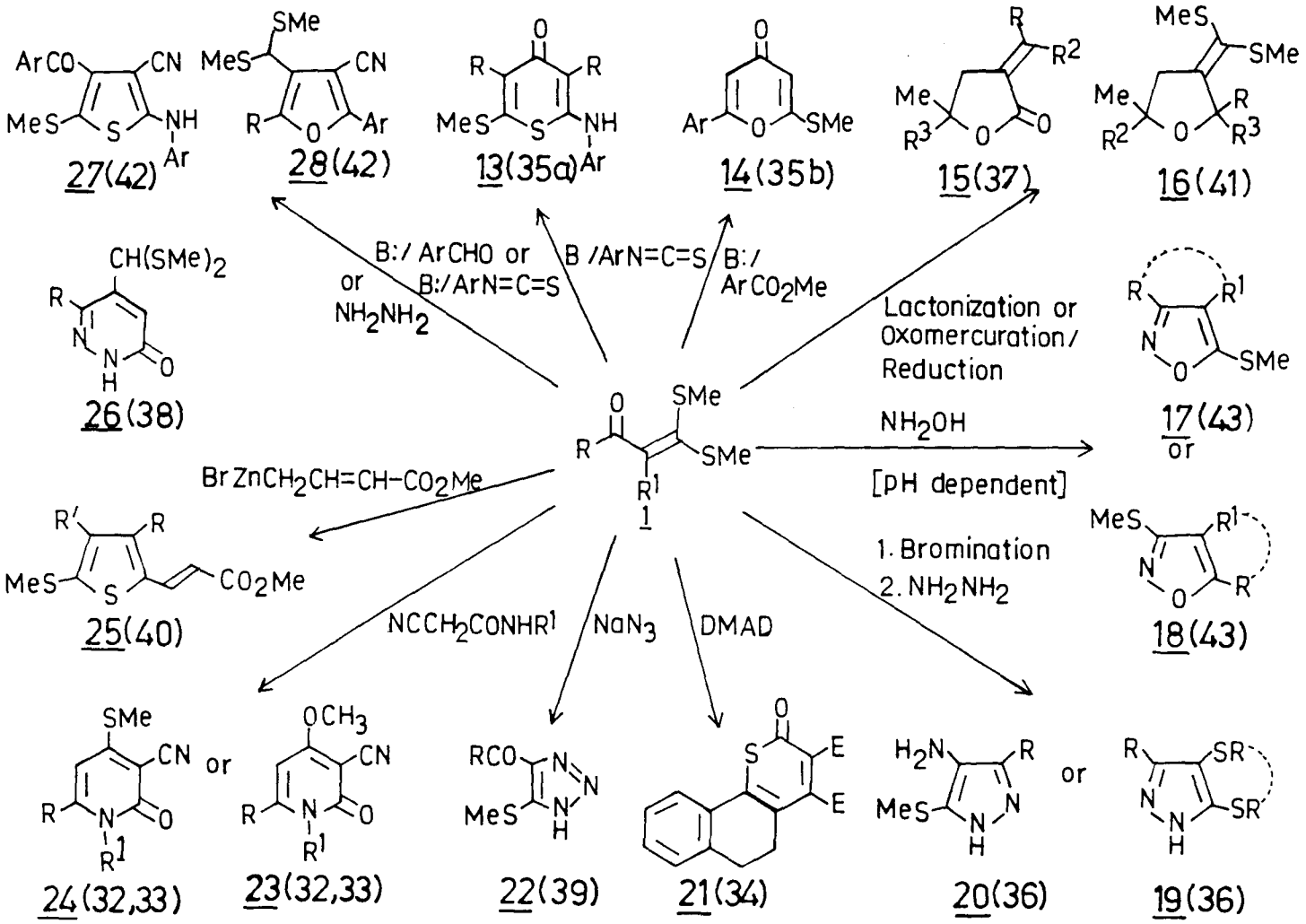

R2CuLi
1. MeMgBr
2. BF3·Et2O/CH3OH
BrZnCH2CO2Et
NaBH4
NaBH4/NiCl4
R2MgBr
10 (22,23)
R2=alkyl
1
4 (21)
8 (30)
2 (29)
11 (31)
5 (21)
or
BF3·Et2O/MeOH
or H2O
1. NaBH4
2. H3O⊕
BF3·Et2O/MeOH
9 (30)
3 (29)
12 (31)
6 (21)
or
7 (21)
3, a, X = O
b, X = S
R2=Et, n-Pr
n = Bu, Ph

Scheme-2

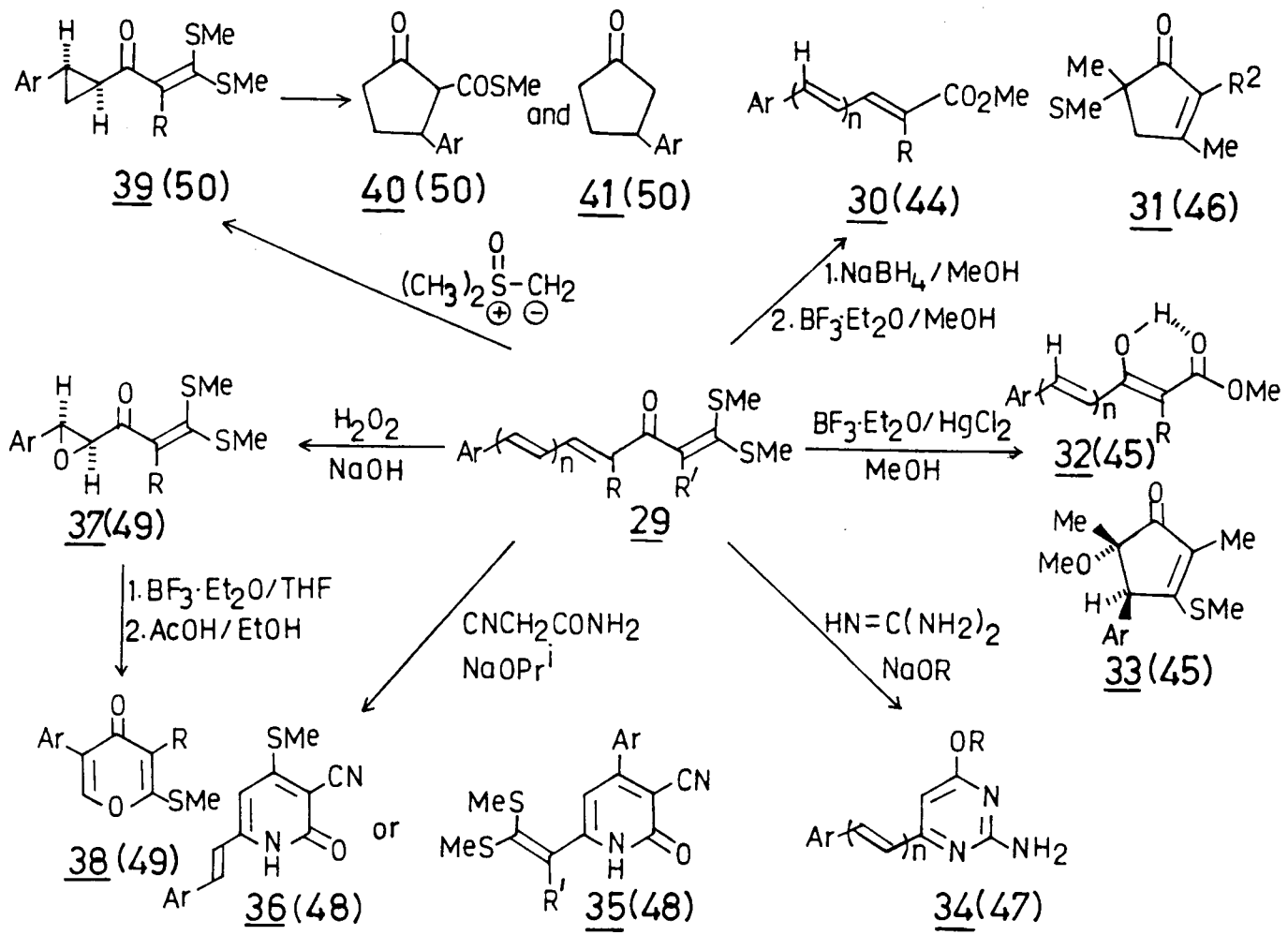
unsaturated ester **9**[30], these dienes hold considerable promise as useful synthetic intermediates. The overall transformation is considered as a double 1,3- alkylative carbonyl transposition. Dieter and co-workers have reported the chemo- and stereoselective addition of organo cuprates to dithioacetals **1**[22,23]. Thus, organo cuprates are shown to undergo conjugate addition to give β-alkythio β-substituted α, β-unsaturated ketones **10**. the oxoketene dithioacetals were shown to undergo nickel boride ($NaBH_4/NiCl_2$) reduction to the corresponding β-methylthio alkenyl ketones **11**. These intermediates are further transformed to the corresponding α,β- unsaturated aldehydes **12**[31] (Scheme 2).

The α-oxoketene dithioacetals have been extensively explored in this laboratory for the construction of numerous substituted and fused five and six membered heterocycles[32-43]. Some of the selected transformations developed recently are shown in Scheme 3. From these transformation is apparent that α-oxoketene dithioacetals with wide functional group variation and many easily accessible reagents and reaction intermediates manifest various possibilities leading to diverse product range.

Various transformation developed on α-cinnamoyl and 5-aryl-2,4-pentadienyl ketene dithioacetals **29** are outlined in Scheme 4. A general method for the synthesis of polyene esters **30**[24,44] have been reported by 1,2- reduction followed by methonolysis in the presence of boron trifluride etherate. In Hg(II) assisted hydrolysis the corresponding γ-δ-unsaturated β-keto esters are formed[45]. In the case of 2,4-disubstituted ($R=R^1=CH_3$), the corresponding cyclopentanones **40** and **41** were formed in both reaction conditions[45,46]. Styryl pyrimidines **345** pyridones **35** and **36** were also synthesised using these intermediates[47,48]. The cinnamoyl ketene dithioacetals **29** have been reported to undergo regioselective epoxidation and cyclopropanation at the styryl


27(42)
28(42)
13(35a)
14(35b)
15(37)
16(41)
26(38)
B:/ ArCHO or
or B:/ArN=C=S
NH2NH2
B /ArN=C=S
B:/
ArCO2Me
Lactonization or
Oxomercuration/
Reduction
17(43)
or
NH2OH
[pH dependent]
BrZnCH2CH=CH-CO2Me
25(40)
1. Bromination
2. NH2NH2
18(43)
NCCH2CONHR1
NaN3
DMAD
24(32,33)
23(32,33)
22(39)
21(34)
20(36)
or
19(36)

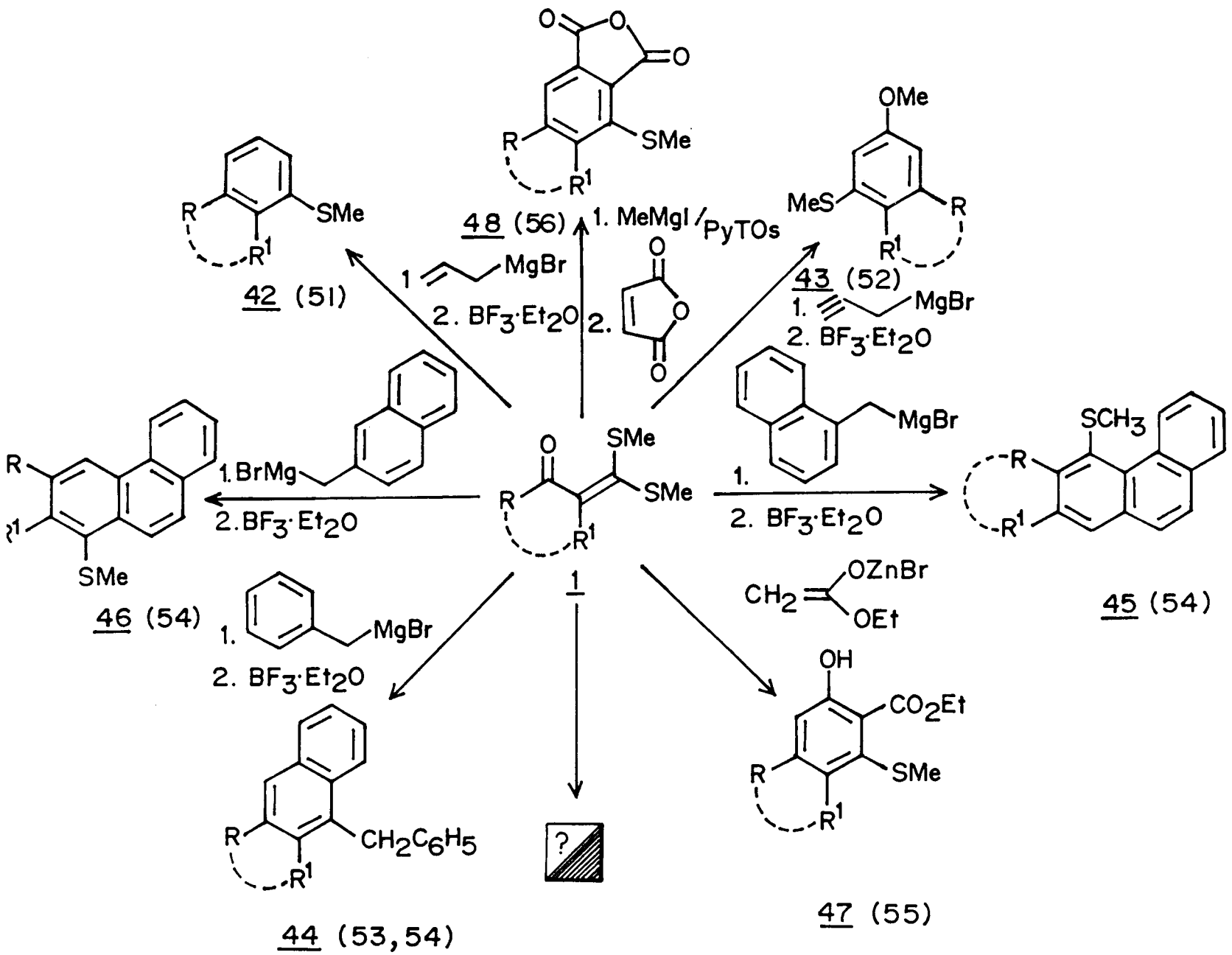
Scheme -3


39 (50)
40 (50)
41 (50)
30 (44)
31 (46)
1.NaBH4 / MeOH
2. BF3 Et2O / MeOH
(CH3)2 S-CH2
H2O2
NaOH
29
BF3·Et2O / HgCl2
MeOH
32 (45)
33 (45)
37 (49)
1. BF3·Et2O / THF
2. AcOH / EtOH
CNCH2CONH2
NaOPr^i
HN=C(NH2)2
NaOR
38 (49)
or
36 (48)
35 (48)
34 (47)

Scheme – 4

double bond[49,50]. The intermediates **37** and **39** were further explored for the synthesis of pyrones **38** and cyclopentanones **40** and **41** respectively.[49,50]

Aromatic annelation via α-oxoketene dithioacetals, developed from this laboratory has emerged as an area of great synthetic potential. Some of the important synthetic outcome of the aromatic annelation methodology is outlined in Scheme 5. The reaction of allymagnesium bromide with α-oxokeene dithioacetals have been shown to undergo exclusive 1,2- addition to yield the corresponding carbinol acetal in high yields, which on $BF_3.Et_2O$ assisted cationiccylization yield the substituted and fused benzene derivatives **42**[51]. This method is further shown to be extremely versatile and found general, when extended to propargyl magnesium bromide to afford methoxy substituted benzoannelated products **43**[52]. Subsequently, this method of aromatic annelation was extended to naphtho annelation. When benzyl magnesium chloride was reacted with α-oxoketene dithioacetals, which on treatment with BF_3Et_2O gave the corresponding naphthalene derivatives **44**[53,54] through benzene ring participation. This naphtho annelation methodology was extended to α-naphthyl methyl magnesium chloride and β-naphthyl methyl magnesium chloride to yield the corresponding phenanthrenes **45** and **46**[54]. With ethyl zinc bromoacetate α-oxoketene dithioacetals yielded the corresponding regiospecifically substituted and annelated 6-methylthio benzoates **47** in good yields[55]. The Diels-alder cyclo additions of vinyl ketene dithoacetals derived from the corresponding oxoketene dithioacetals **1** with maleic anhydride afforded the phthalic anhydrides **48** in good yields[56]. With a view to enhance the scope of aromatice annelation methodology for the synthesis of benzoheterocycles, heteroaromatic annelation methodology was developed in this laboratory by reacting appropriately substituted heteroallyl systems with α-oxoketene dithioacetals. Thus, the reaction of lithiomethylisoxazole with α-oxoketene dithioacetals


48 (56)
1. MeMgI / PyTOs
2.
42 (51)
1 MgBr
2. BF3·Et2O
43 (52)
1. MgBr
2. BF3·Et2O
1. BrMg
2. BF3·Et2O
46 (54)
1.
2. BF3·Et2O
45 (54)
1
1. MgBr
2. BF3·Et2O
CH2 OZnBr OEt
44 (53,54)
47 (55)
?

Scheme — 5

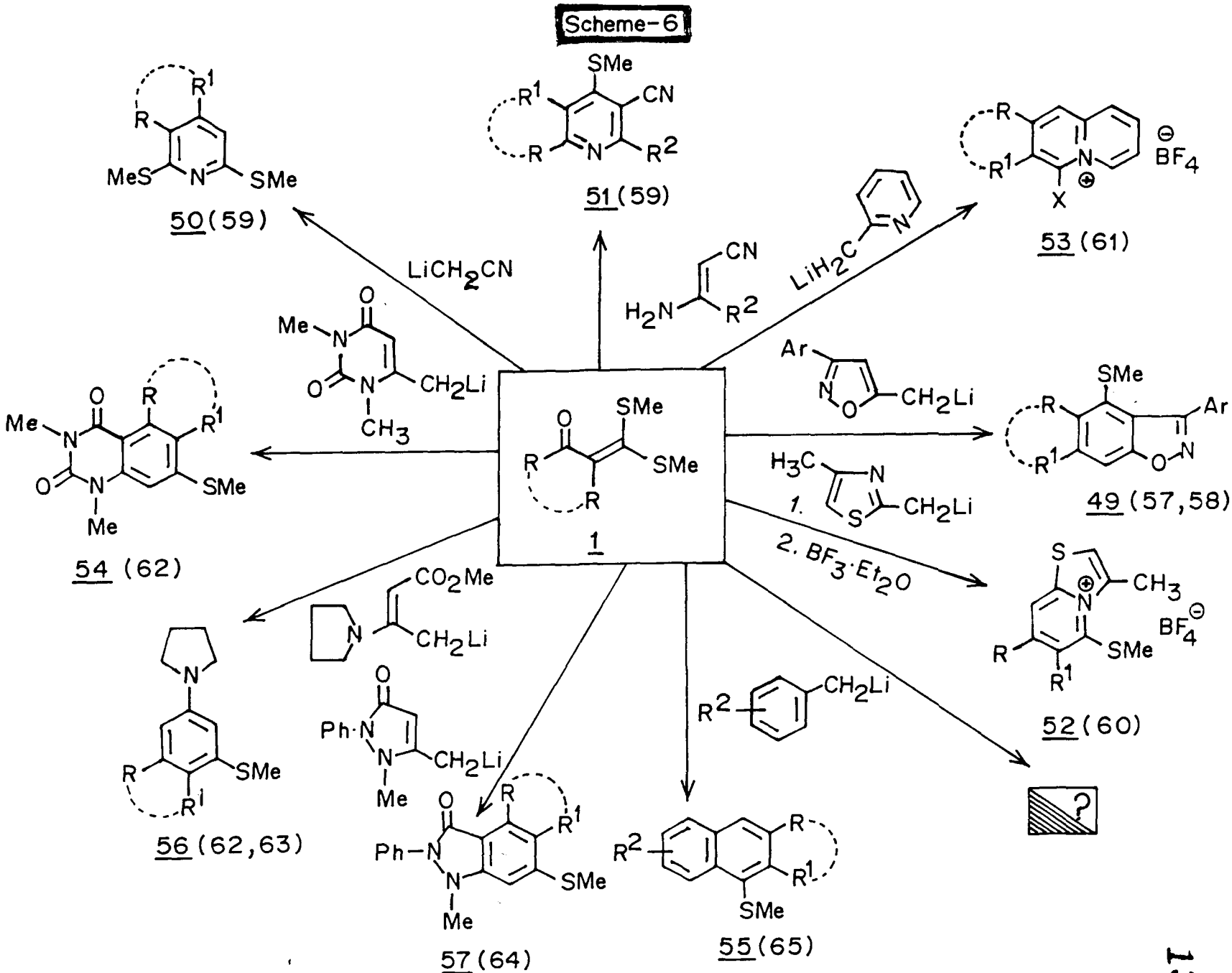
yielded the corresponding benzisoxazoles **49** in excellent yield[57,58] (Scheme 6). This method was further shown to be extremely versatile and general when extended for the synthesis of pyridines **50** and **51**[59], thiazolopyridinium salts **52**[60], quinolizinium salts **53**[61] and quinazolines **54**[62], amino benzenes **56**[63], indazolenes **57**[64], naphthalences **55**[65]. This methodology developed as considerable synthetic importance due to the fact that, a large number of azallyl anions could be used to construct various heteroaromatic compounds.

The α-oxoketene dithioacetals therefore with a wide ranging functional group variation and many easily accessible reagents and reactive intermediates manifestly hold many new synthetic possibilities leading to diverse product range, including carbocyclic, heterocyclic and benzoheterocyclic system.

B. WORK PRESENTED IN THIS THESIS

Chapter II is divided into two parts. Part-I contains a brief review on polarised ketene S,N- and N,N-acetals regarding their practical and potential application in organic synthesis. In part II an improved method for the synthesis of S,N-acetals through metallation reactions is described. This method is superior to the earlier method developed in this laboratory which failed when extended to the synthesis of S,N-acetals can be readily prepared in high yields by using easily accessible α-oxoketene S,S-acetals in one step. It is generally known that aromatic amines are less readily reacted with α-oxoketene dithioacetals to give the corresponding S,N-acetals due to their reduced basicity. Under more rigorous conditions the corresponding N,N-acetals are formed sometimes resulting in the formation of a mixture of both S,N- and N,N-acetals. It was therefore, considered of interest to generate N-anions of these aromatic amines by metallation reactions and react with S,S-acetals so that only the

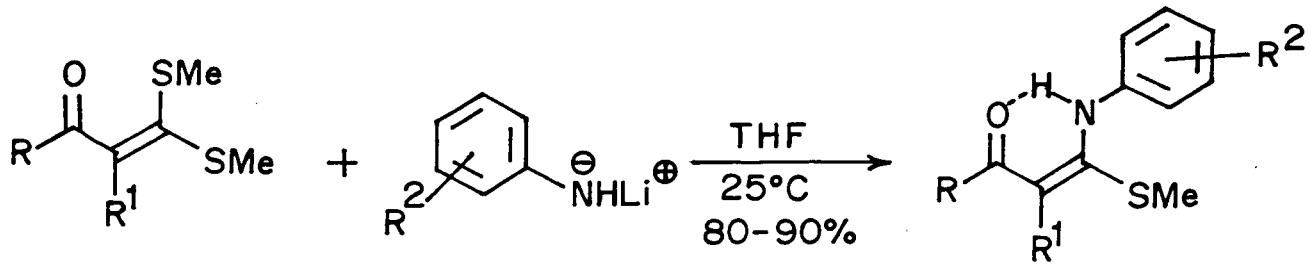
Scheme-6


SMe
R1
CN
R
N
R2
51 (59)
MeS
SMe
50 (59)
LiCH2CN
H2N
CN
R2
LiH2C
N
R
R1
N
X
BF4
53 (61)
Me
N
O
CH2Li
N
CH3
Ar
N
O
CH2Li
SMe
R
R1
Ar
N
O
49 (57,58)
O
R
Me
N
R1
O
N
SMe
Me
54 (62)
SMe
R
SMe
R
1
H3C
N
1.
S
CH2Li
2. BF3·Et2O
S
CH3
N
BF4
R
SMe
R1
52 (60)
CO2Me
N
CH2Li
N
SMe
R
R1
56 (62,63)
O
Ph·N
N
CH2Li
Me
R2
CH2Li
?
O
R
R1
Ph–N
N
SMe
Me
57 (64)
R2
R
R1
SMe
55 (65)

corresponding S,N-acetals could be formed in high yields without resulting in a mixture of both S,N- and N,N-acetals.

Apparently, the lithio-anilines have been shown to react with S,S-acetals 1a-f to yield a variety of structural variants of the corresponding S,N-acetals **59a-j** exclusively in 80-90% overall yield. (Scheme-7). No trace of the corresponding N,N-acetals were formed in these reactions. Thus the method developed in the present investigation provides a convenient route for the synthesis of S,N-acetals of aromatic amines in high yields. Also these reactions were extended to prepare the corresponding S,N-acetals from lithio-amino pyridines **60** and **62**. It must be noted that the reaction of 2-amino and 3-amino pyridines with α-oxoketene S,S-acetals failed to yield even poor yields of the corresponding S,N-acetals **61a-j** and **63a-e** when we applied the earlier methods. When the same reaction was carried out with lithio amino pyridines the corresponding S,N-acetals were formed in good to excellent yields. (Scheme 8, Scheme 9). These results and discussions are described in the second part of chapter II.

In chapter III, application of the S,N-acetals described in the preceding chapter for the synthesis of pyrido [1,2-a] pyrimidinium tetrafluoroborate salts and imidazo [1,2-a] pyridines is presented. Thus 3-methylthio-3-(2-pyridyl amino)-1phenyl-2-propene-1-one (Scheme 10) **61a** underwent smooth cycloaromatization in the presence of boron triflourideetherate to yield the corresponding 2-Methylthio-4-phenyl pyrido [1,2-a] pyrimidin-5-ium tetrafluoroborate salt in 82% overall yield. Thus S,N-acetals 61b-f yielded pyrido[1,2-a] pyrimidinium salts **64b-f** in 80-90% overall yields. Very few reports are available for the preparation of these compounds (see chapter III text) involving the reaction of 1,3 dicarbonyl compounds with 2-amino pyridines in the presence of perchloric acid under drastic conditions to get overall poor yields of the



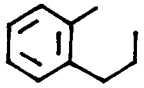
1a-f 58a-e 59a-j

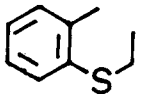
1a, R = C_6H_5 R^1 = H

b, R = 4-MeOC_6H_4, R^1 = H

c, R = 4-ClC_6H_4, R^1 = H

d, R = 4-BrC_6H_4, R^1 = H

e, R = R^1 = 

f, R = R^1 = 

58 a, R^2 = H

b, R^2 = 2-Cl

c, R^2 = 4-Cl

d, R^2 = 4-Me

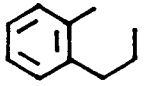
e, R^2 = 4-MeO

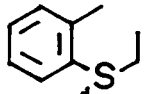
59 a, R = C_6H_5, R^1 = H, R^2 = H

b, R = 4-MeOC_6H_4, R^1 = H, R^2 = H

c, R = 4-ClC_6H_4, R^1 = H, R^2 = H

d, R = 4-Br C_6H_4, R^1 = H, R^2 = H

e, R = R^1 =  , R^2 = H

f, R = R^1 =  , R^2 = H

g, R = C_6H_5, R^1 = H, R^2 = 2-Cl

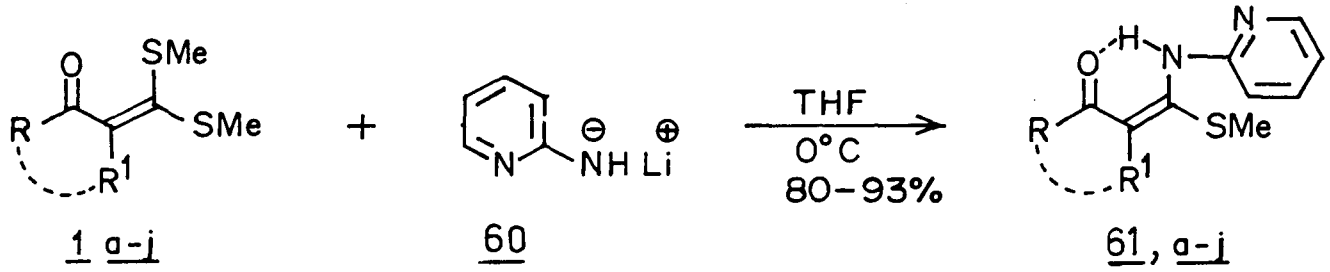
h, R = C_6H_5, R^1 = H, R^2 = 4-Cl

i, R = C_6H_5, R^1 = H, R^2 = 4-Me

j, R = C_6H_5, R^1 = H, R^2 = 4-MeO

Scheme-7

(See Table-1)



1 a-j 60 61, a-j

1 60,61, a, R = C_6H_5, R^1 = H

b, R = 4-$MeOC_6H_4$, R^1 = H

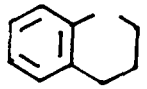
c, R = 4-Cl C_6H_4, R^1 = H

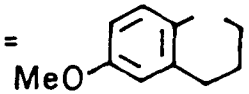
d, R = 4-MeC_6H_4, R^1 = H

e, R = 2-furyl, R^1 = H

f, R = 2-thienyl, R^1 = H

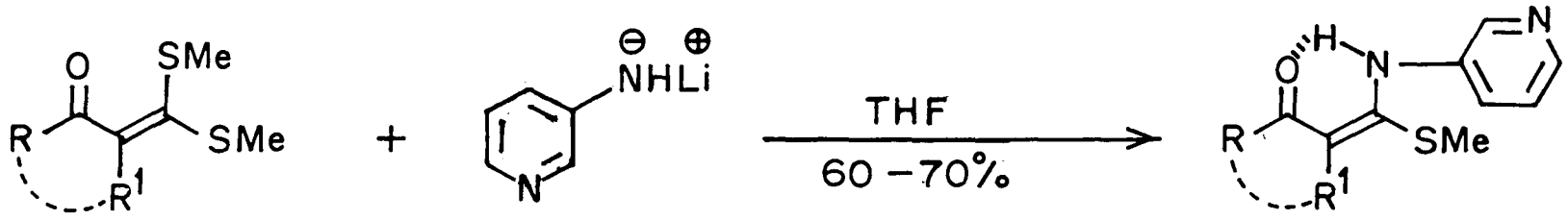
g, R = R^1 = $-(CH_2)_4-$

h, R = R^1 = 

i, R = R^1 = 

j, R = $C_6H_5-CH=CH$, R^1 = H

Scheme-8



1 62 63

62 , 63 , a , R = C_6H_5 , R^1 = H

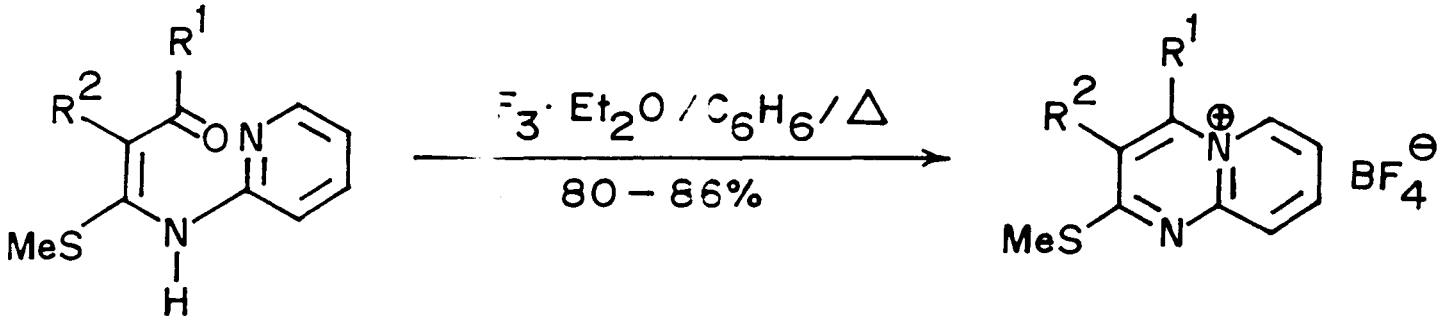
b , R = 4–$MeOC_6H_4$, R^1 = H

c , R = 4–MeC_6H_4 , R^1 = H

d , R = H_5C_2O– , R^1 = CN

e , R = 2– furyl , R^1 = H

Scheme–9



61a-f

64a-f

61,64, a $R^1 = C_6H_5$; $R^2 = H$ (82%)

b $R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$ (82%)

c $R^1 = 4\text{-}ClC_6H_4$; $R^2 = H$ (84%)

d $R^1 = 4\text{-}MeC_6H_4$; $R^2 = H$ (80%)

e $R^1 = 2$-furyl; $R^2 = H$ (86%)

f $R^1 = 2$-thienyl; $R^2 = H$ (80%)

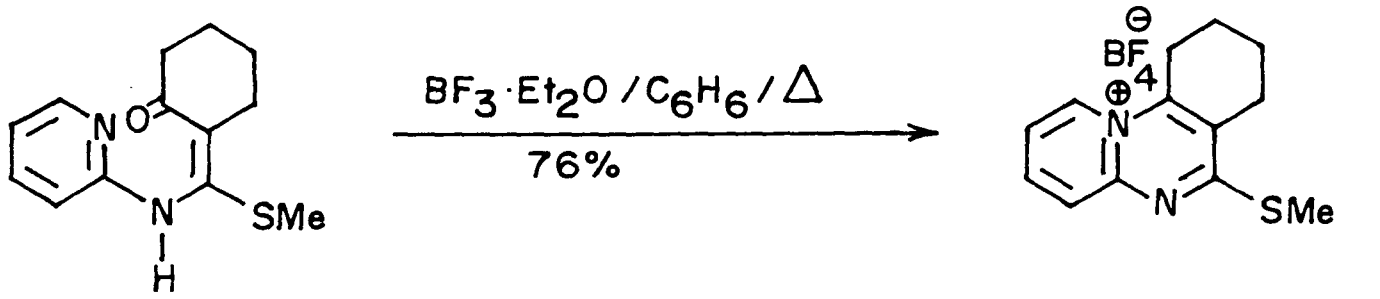
Scheme–10

corresponding pyrido [1,2-a] pyrimidinium perchlorates. Thus the method developed in the present investigation is shown to provide convenient route for the synthesis of these compounds under mild reaction conditions with more flexible structural variants. S,N-acetals **61g** and **61h** derived from mercaptals of cyclohexanone and tetralone also yielded the pyrido [1,2-a] quinazolinium tetraflouroborates 65(76%) and 66(86%) respectively under the same reaction conditions (Scheme 11).

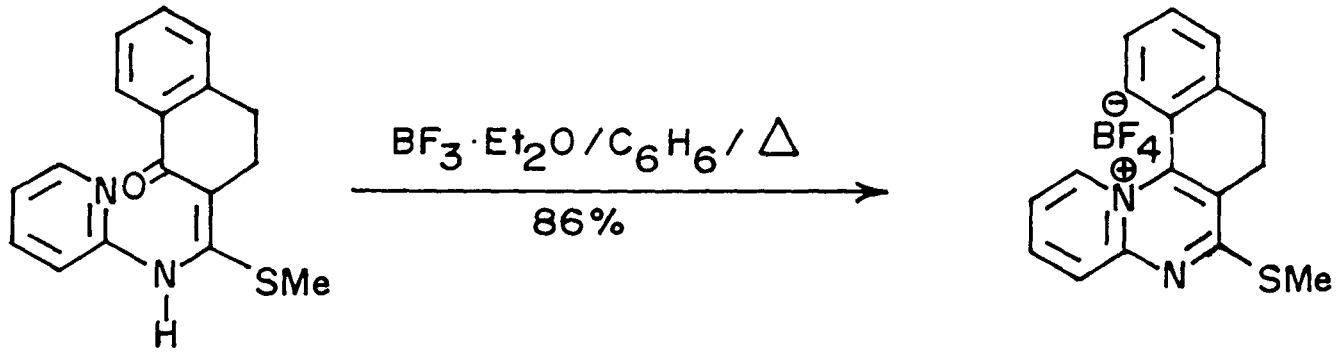
Also in the same chapter, a new general method for the synthesis of novel imidazo [1,2-a] pyridines is described. Thus S,N-acetals **61a-f** when treated with one equivalent of Copper (1) chloride in refluxing tetrahydrofuran the compounds obtained were characterised as imidazo [1,2-a] pyridines **67a-f** with excellent yields (85-93%) (Scheme-12). However the reaction mechanism governing these transformations is not clearly understood and the possible tentative mechanism is discussed.

The results describing synthesis of both pyrido [1,2-a] pyrimidinium tetra florobates and imidazo [1,2-a] pyridines are described in chapter - III.

As a part of our programmed studies on α-oxoketene dithioacetals it was considered of importance to prepare several cyclopropyl substituted heterocycles by using cyclopropyl ketene dithioacetals **69**. The α-bis (methylthio) methylene cyclopropyl ketones **69a-f** were obtained in excellent yields by regioselective cinnamoyl ketene dithioacetals 68a-f under phase transfer conditions (Scheme 13). The 3-carbon 1,3-electrophilic structural frame is utilized for the synthesis of both 5- and 6-membered keterocycles by reacting with 1,2- and 1,3-heteroatom binucleophiles respectively. The cyclopropyl ketene dithioacetals **69** are reacted with hydrazine, hydroxylamine, guanidine and cyanoacetamide to obtain cyclopropyl substituted pyrazoles **70a-f**,

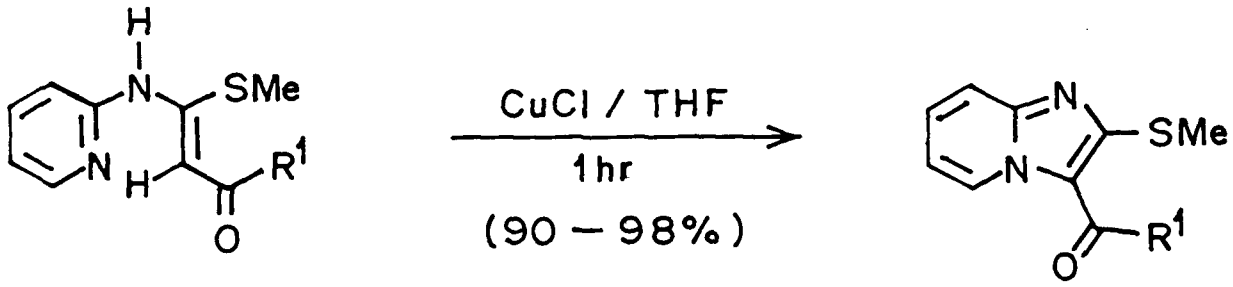


61g 65



61h 66

Scheme-11



61 a – f

67 a – f

61, 67, a, $R^1 = C_6H_5$

b, $R^1 = 4\text{-MeO}\,C_6H_4$

c, $R^1 = 4\text{-Cl}\,C_6H_4$

d, $R^1 = 4\text{-Me}\,C_6H_4$

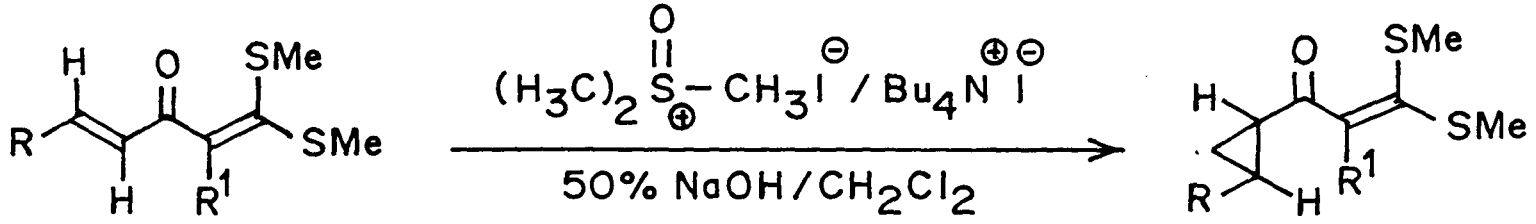
e, $R^1 = 2\text{-furyl}$

f, $R^1 = 2\text{-thienyl}$

Scheme – 12

isomeric isoxazoles **71a-e**, **72a-e**, pyrmidines **73a-f**, and the pyridones **74a-d** (Scheme 14) respectively. These results are described in chapter - IV.

In chapter V, some studies on the reductive cleavage of C-O and C-S bonds in the presence of zinc and acetic acid has been described. When acetals **75a-h** are treated with zinc in acetic acid and refluxed for 20-24 hours the products obtained were characterised as a mixture of acetals **76a-d** alcohols **77a-c,h** and sometimes completely reduced products **78d-g** (Scheme 15). The acetals **75d-g** derived from alkoxy substituted benzaldehydes underwent facile cleavage under the same reaction condition to afford only the completely reduced products exclusively. However when the dithioacetals **79a-e** are treated with zinc in acetic acid under similar reaction conditions partially reduced mercaptans **80a-e** (Scheme 16) were obtained. Similarly dithioacetals **81a-c** derived from aromatic bezaldehydes and ketones and thiophenol also yielded the partially reduced products **82a-c** along with traces of thiophenol in the overall product mixture are (Scheme 17). The results of this study and the plausible mechanism are also described in this chapter.



68 a–f

69 a–f

68, 69

a, R = C_6H_5, R^1 = H

b, R = 4–MeOC_6H_4, R^1 = H

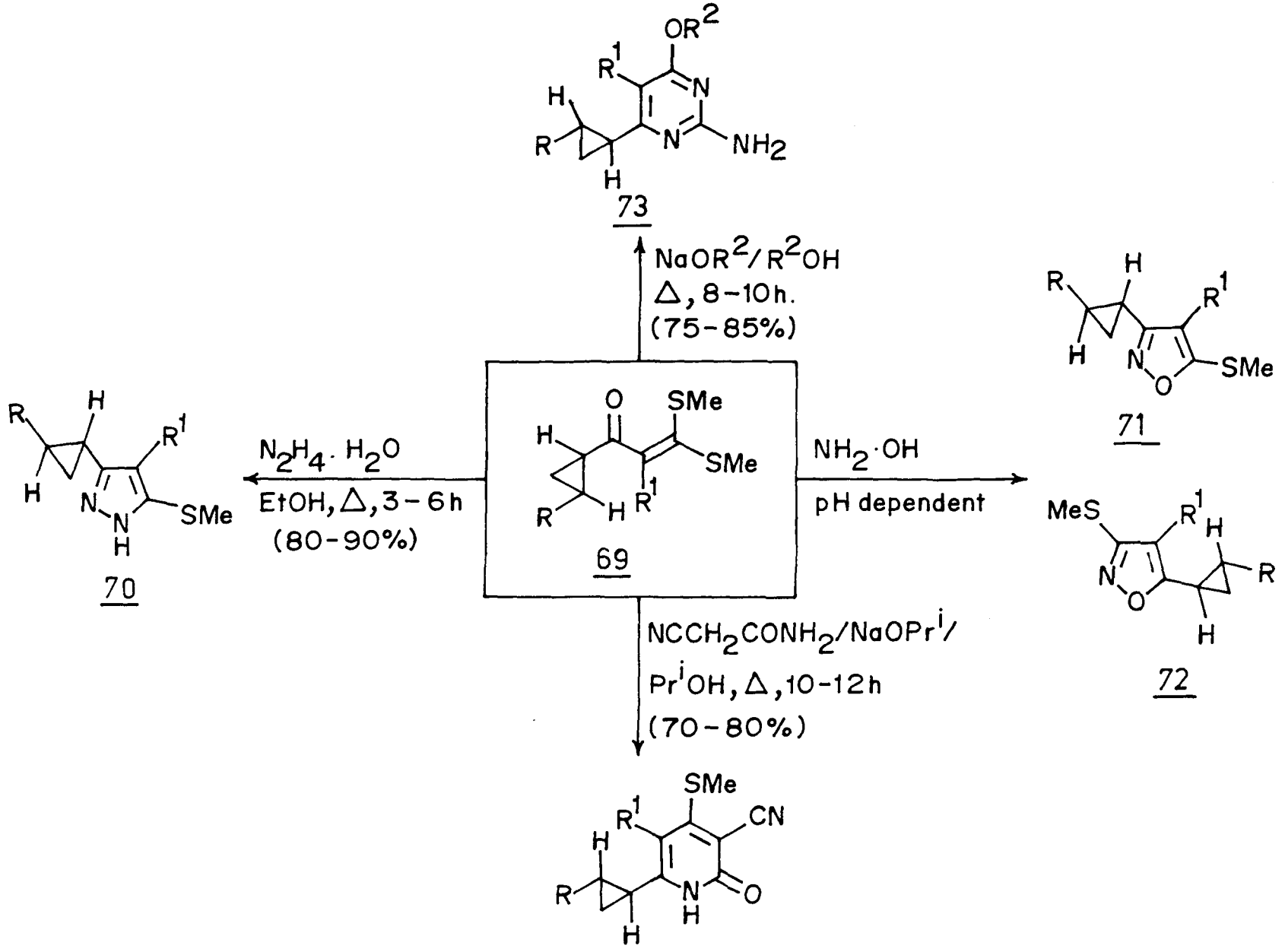
c, R = 3,4–$(MeO)_2$ C_6H_3, R^1 = H

d, R = 3,4,5–$(MeO)_3$ C_6H_2, R^1 = H

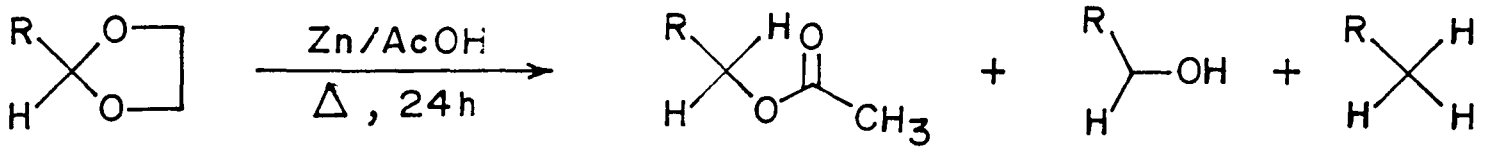
e, R = 4–ClC_6H_4, R^1 = H

f, R = 4–Me C_6H_4, R^1 = H

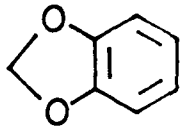
Scheme – 13


73
NaOR2/R2OH
Δ, 8-10h.
(75-85%)
71
N2H4·H2O
EtOH, Δ, 3-6h
(80-90%)
70
69
NH2·OH
pH dependent
72
NCCH2CONH2/NaOPri/
PriOH, Δ, 10-12h
(70-80%)
74

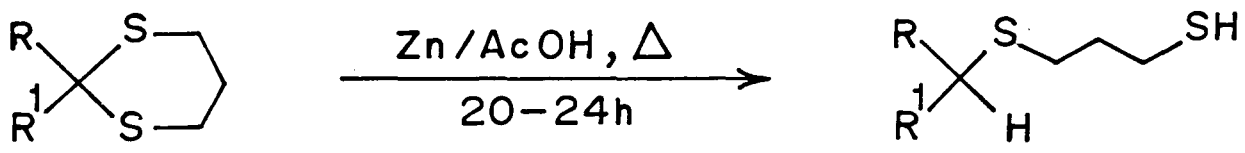
Scheme-14



75 76 77 78

75	R	76 (%)	77 (%)	78 (%)
a	C_6H_5	(45)	(35)	—
b	4-Me C_6H_4	(42)	(36)	—
c	4-Cl C_6H_4	(30)	(50)	—
d	4-MeO C_6H_4	(40)	—	(40)
e	3,4-$(MeO)_2$ C_6H_3	—	—	(78)
f	3,4,5-$(MeO)_3C_6H_2$	—	—	(63)
g		—	—	(65)
h	2-Naphthyl	—	(82)	—

Scheme-15



79 → 80

72 – 85%

79, 80, a, R = C_6H_5, R^1 = H

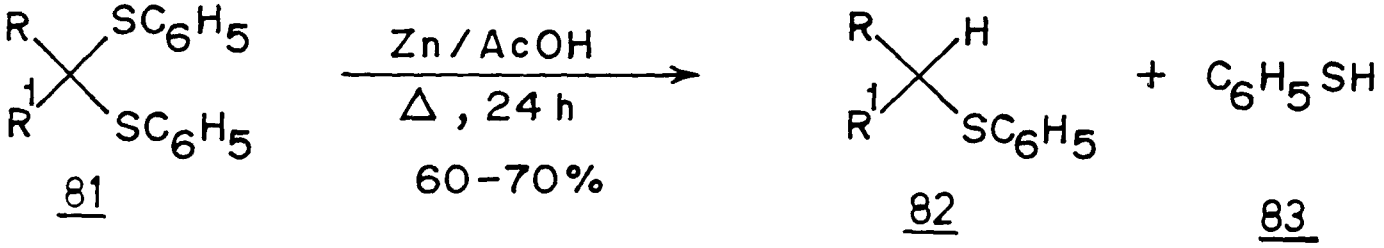
b, R = 4-ClC_6H_5, R^1 = H

c, R = 4$MeOC_6H_4$, R^1 = H

d, R = 2-naphthyl, R^1 = H

e, R = R^1 = C_6H_5

Scheme-16



81 82 83

81, 82, a, $R = C_6H_5$, $R^1 = H$

b, $R = C_6H_5 - CH = CH$, $R^1 = H$

c, $R = R^1 = C_6H_5$

Scheme-17

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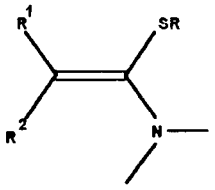
CHAPTER - II

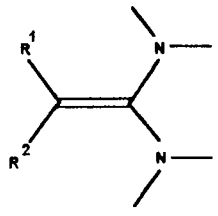
IIA: POLARIZED KETENE S,N- AND N,N - ACETALS : A REVIEW

IIB: REACTION OF LITHIOAMINO ANIONS WITH POLARIZED KETENE S,S- ACETALS: AN IMPROVED AND A NEW GENERAL METHOD FOR THE SYNTHESIS OF POLARIZED KETENE S,N- AND N,N -ACETALS.

II A.1. INTRODUCTION



1



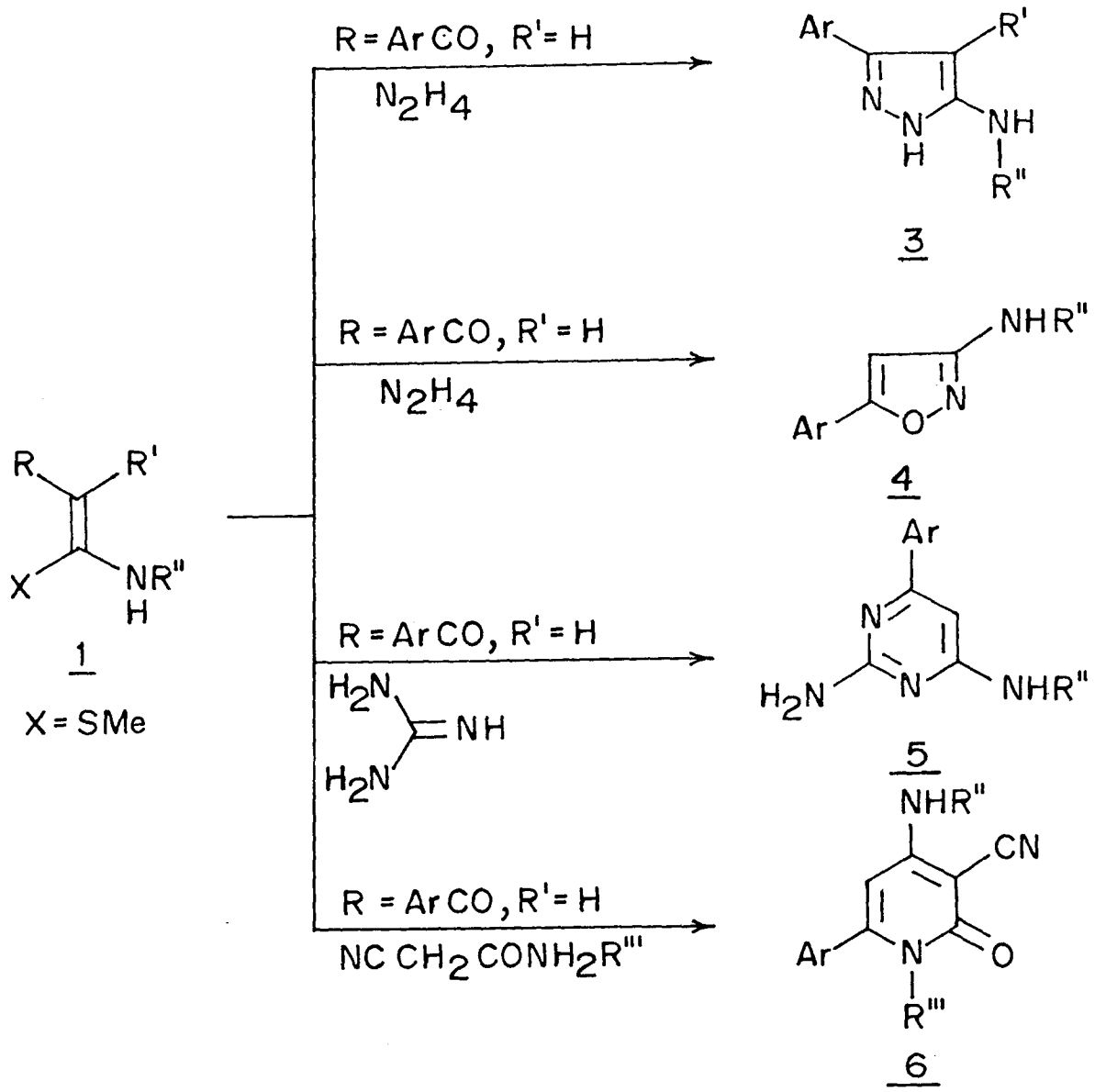
2

The polarized ketene S,N-**1** and N,N-acetals **2** like oxoketene S,S-acetals, are well defined compounds which can be preserved without apparent decomposition. They can be considered as vinylogous amides if they are derived from ketones and as

vinylogous amines if they are derived from other methylene compounds. The chemistry of enamines derived from various ketones and primary or secondary amines is well documented. They have been extensively used as synthetic intermediates to react with various electrophiles making use of α-carbon. However, these enaminones are found to be more sensitive to moisture and undergo ready hydrolytic cleavage to the starting materials. On the other hand, the ketene S,N- and N,N-acetals are more stable and exhibit properties identical to enamines. They can undergo nucleophilic dis placement with various binucleophiles 3-6 (Scheme-1)[1,2-6] followed by intra molecular cyclization with α-oxo functionality. Like enamines the α-carbon in the ketene S,N- and N,N-acetals is nucleophilic enough to react with various electrophilic species.so that these reactions can be utilized to construct heterocycles of different structural features.

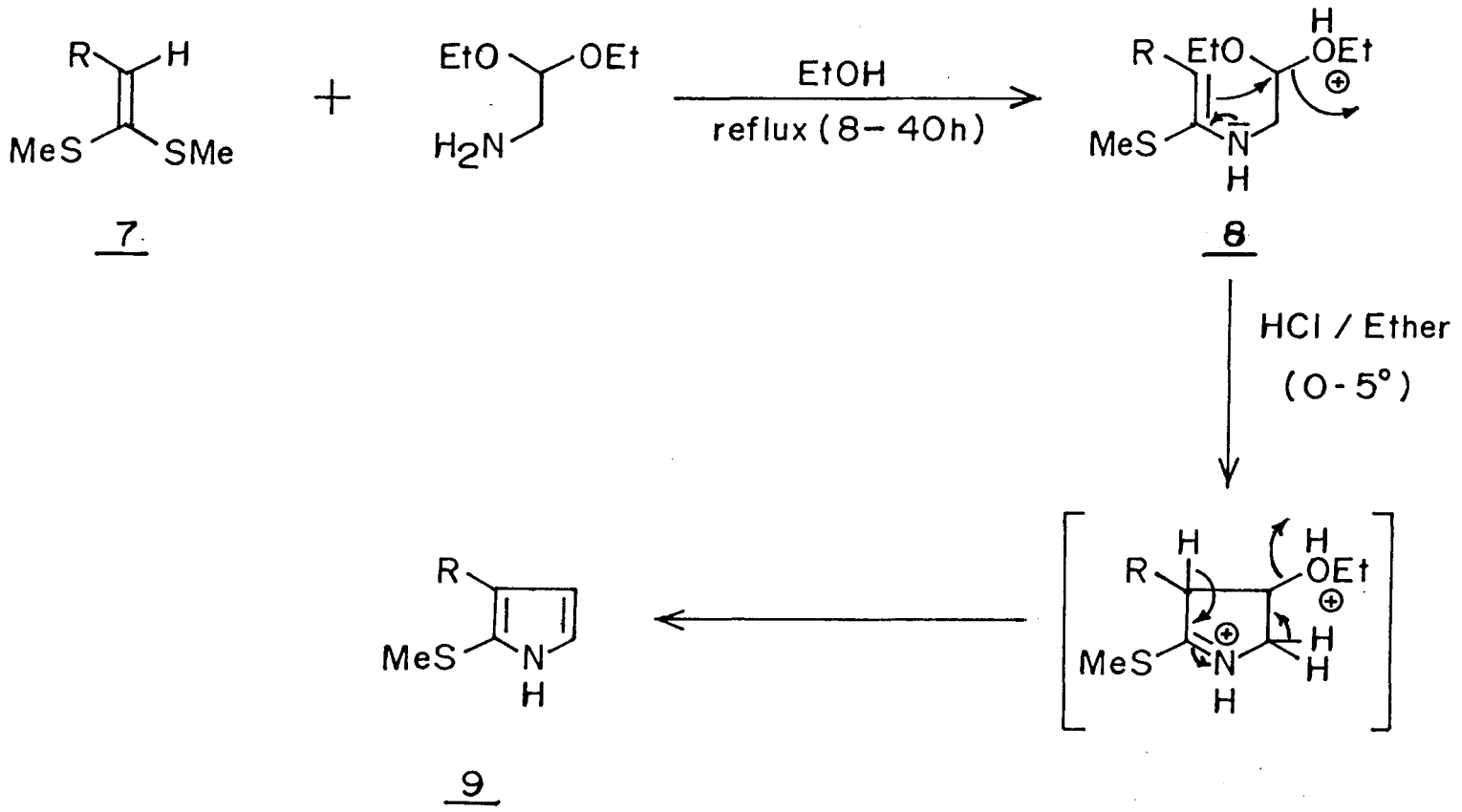
The behaviour of polarized ketene S,N and N,N-acetals as functionalized enaminones or enamines is manifested in the reaction of **1** and **2** with compounds having activated multiple bonds leading to the synthesis of a wide variety of heteocycles. Few of these transformation for the synthesis of pyrroles **9** via S,N-acetals **8** is shown in Scheme-2[7]. Another variation of this method for the synthesis of 2-amino pyrroles **12** starting with ketene S,S-acetals **10** condensed with various amines to give the pyrole via S,N-acetals **11** is also shown in Scheme-3[8].

The doubly activated polalrized ketene S,S-acetal **13** underwent smooth displacement reaction at room temperature with aziridine to yield the corresponding S,N-aziridino acetals **14** in excellent yields. These intermediates yielded the corresponding pyrrolines **15** through facile potassium iodide induced rearrangement. (Scheme-4)[9].



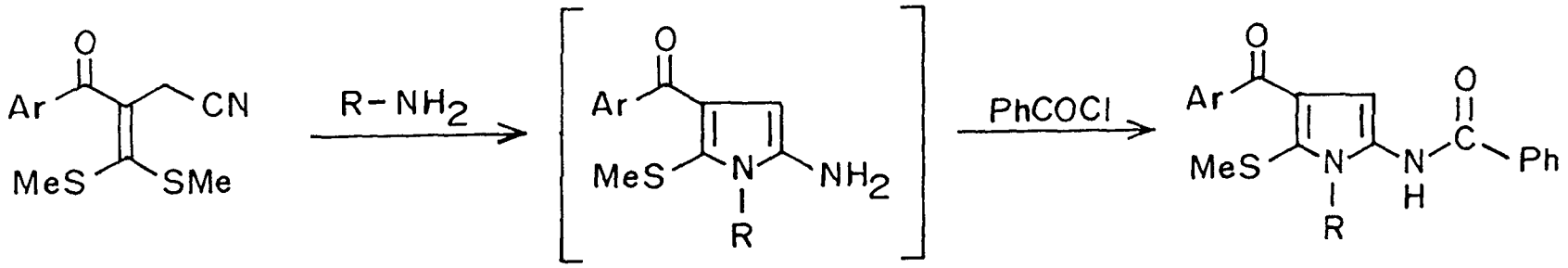
(Ref. 2 - 6)

Scheme-1



7, 9, R = ArCO, NO_2

Scheme – 2 (Ref.7)

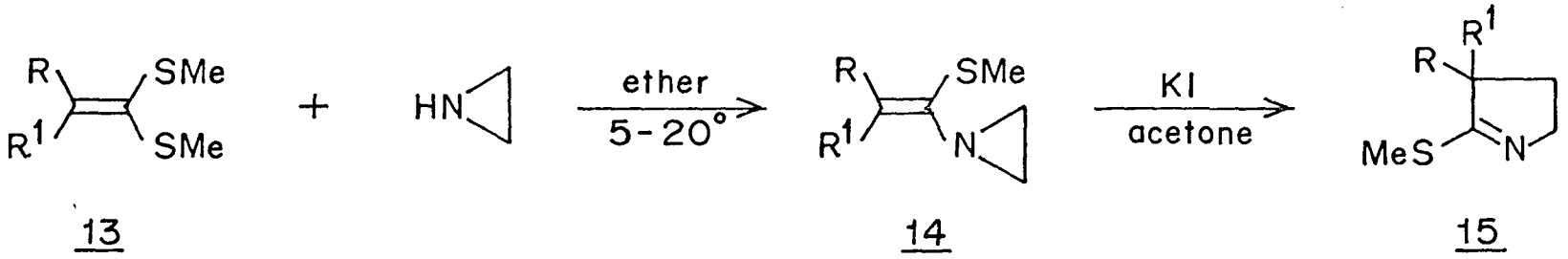


10 11 12

10,12 Ar = C_6H_5, P-ClC_6H_4, P-$MeOC_6H_4$;

R = CH_3, C_2H_5, $CH_2C_6H_5$ (Ref. 8)

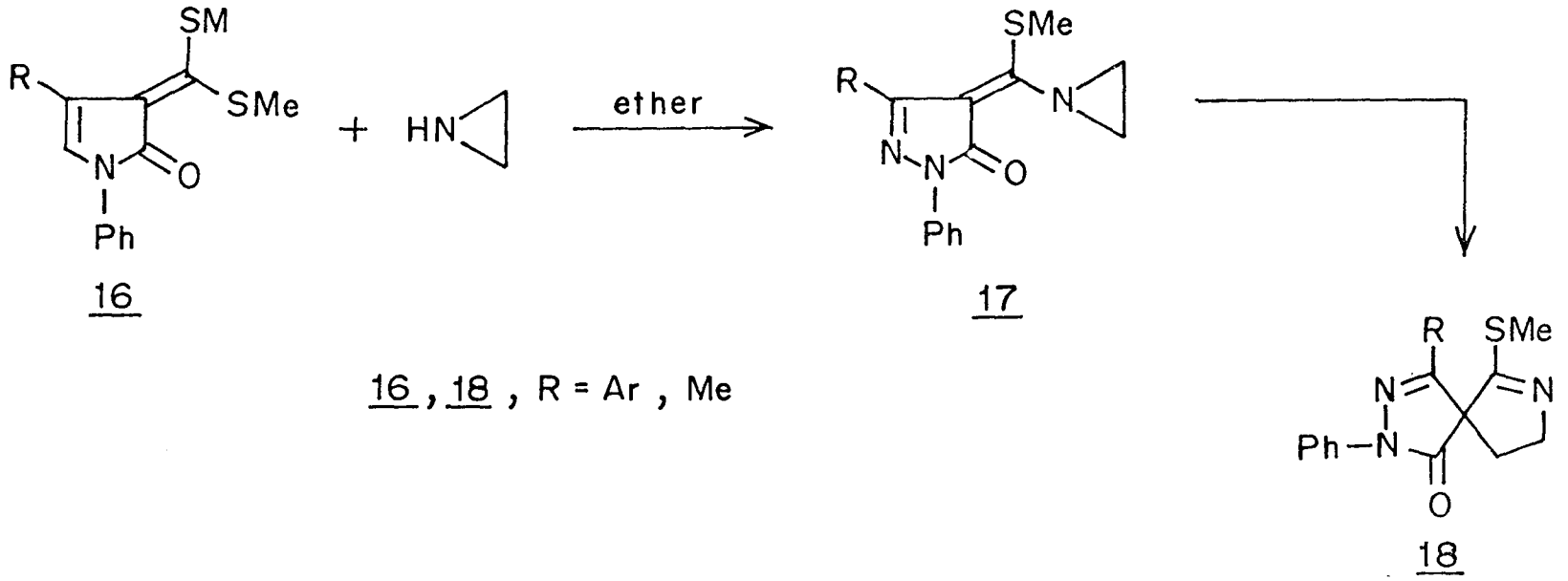
Scheme – 3



13 14 15

13 , 15 , R = CN ; R^1 = $CONH_2$

R = H , CN ; R^1 = COOEt



16 17 18

16 , 18 , R = Ar , Me

Scheme – 4

(Ref. 9)

The method is extended to accompalish identical transformation to give novel spiro pyrrolines **18** under identical reaction conditions(Scheme-4)[9].

It is evident that polarized ketene S,N- and N,N-acetals, in addition to their reactivcity as 1,3 electrophilic-3-carbon fragments, they differ from polarized ketene dithioacetla in their enamine reactivity profile providing C-C-N component in the product heterocycles. Based on this reactivity a number of reactions have been done in our laboratory for the synthesis of wide variety of amino and alkyl heterocycles **19-35** (Scheme 5 & 6)[10-24].

IIA.2. METHODS OF SYNTHESIS OF KETENE S,N- AND N,N-ACETALS

There are a number of methods described in the literature for the synthesis of ketene S,N- and N,N-acetals and they can be broadly classified in the following categories:

IIA.2.1 Direct method using isothiocyanates.

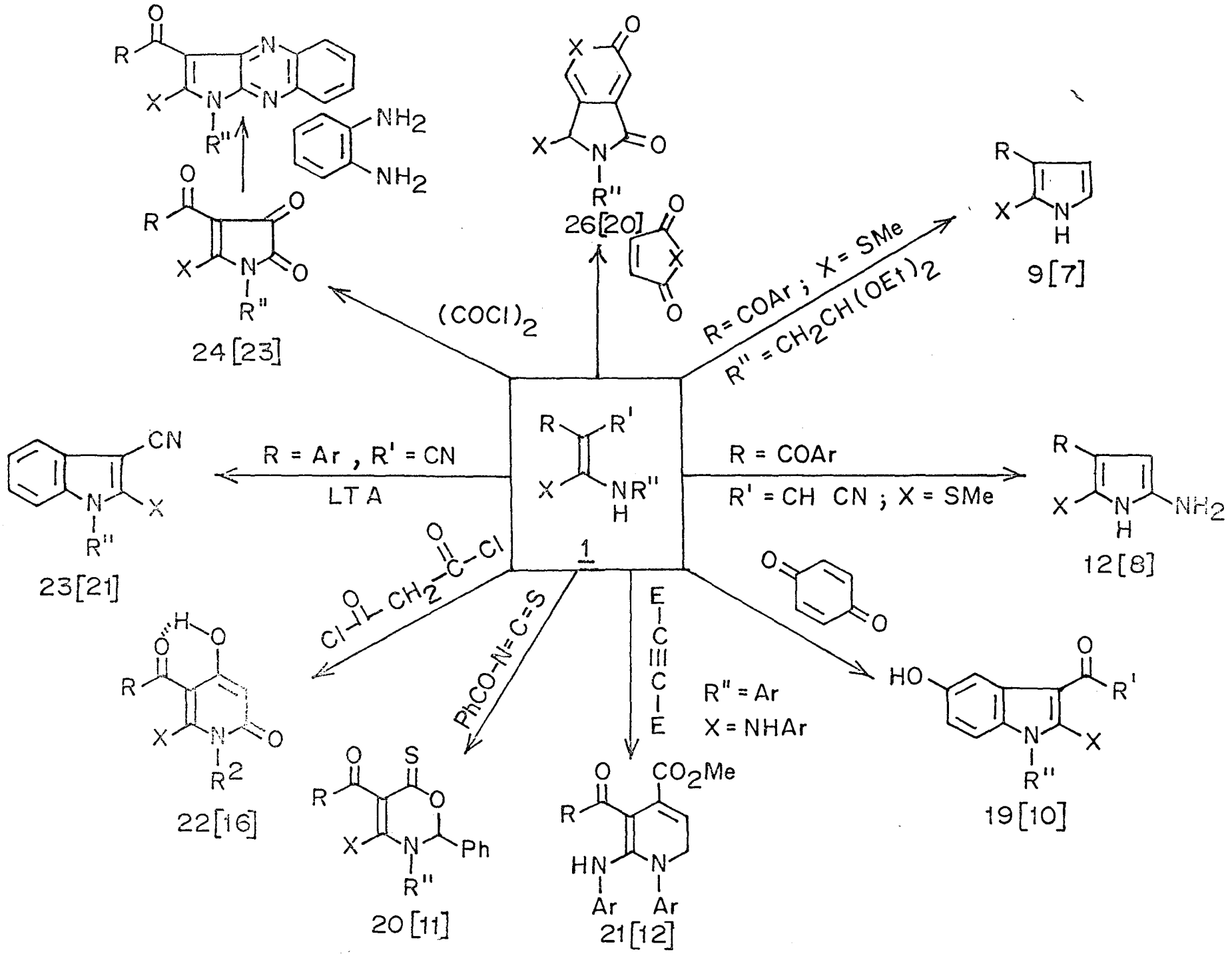
IIA.2.2 Displacement method.

IIA.2.3 Thioamide method.

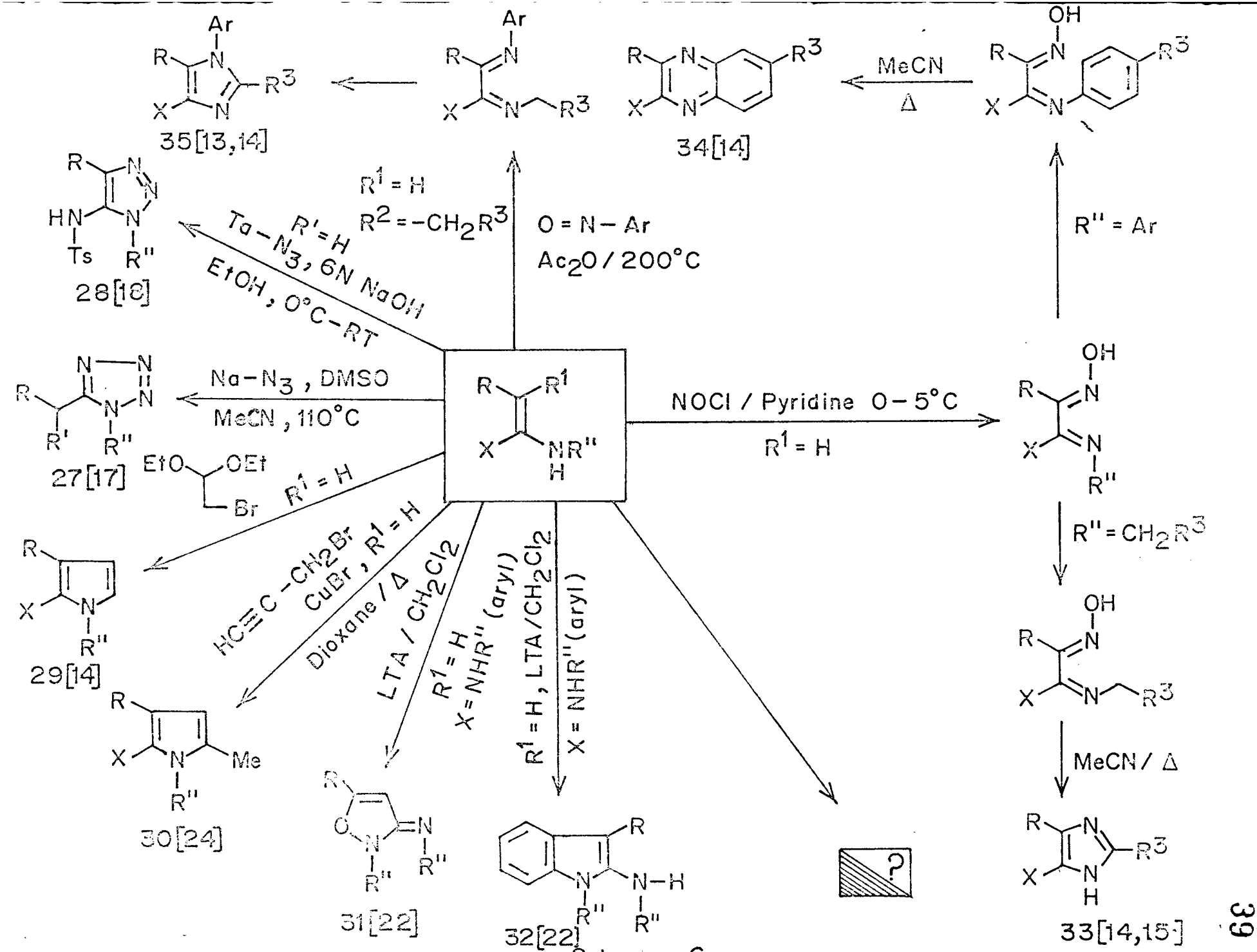
IIA.2.4 Miscellaneous methods.

IIA.2.1.1. Direct Synthesis Using Alkyl And Aryl Isothiocyanates.

The reaction of active methylene compounds **36** with alkyl or aryl isothiocyanate in the presence of a base followed by alkylation to yield the ketene S,N-acetals is one of the efficient methods reported in the literature[25-33]. Thus, when **36** was reacted in the presence of sodium hydride and dimethyl formamide, the sodium salt **37** separated, in situ, was alkylated with appropriate alkyl halides to yield the desired ketene S,N-


24[23]
(COCl)2
26[20]
R= COAr ; X= SMe
R'' = CH2CH(OEt)2
9[7]
23[21]
R = Ar , R' = CN
LTA
1
R = COAr
R' = CH CN ; X = SMe
12[8]
22[16]
PhCO-N=C=S
R'' = Ar
X = NHAr
19[10]
20[11]
21[12]

Scheme – 5


35[13,14]
34[14]
MeCN
Δ
R'' = Ar
R¹ = H
R² = -CH₂R³
O = N - Ar
Ac₂O / 200°C
28[16]
Ts
Ta - N₃, 6N NaOH
EtOH, 0°C - RT
R' = H
Na - N₃, DMSO
MeCN, 110°C
27[17]
NOCl / Pyridine 0 - 5°C
R¹ = H
R'' = CH₂R³
MeCN / Δ
33[14,15]
EtO
OEt
Br
R¹ = H
29[14]
HC≡C - CH₂Br
CuBr, R¹ = H
Dioxane / Δ
30[24]
Me
LTA / CH₂Cl₂
R¹ = H
X = NHR'' (aryl)
31[22]
R¹ = H, LTA/CH₂Cl₂
X = NHR'' (aryl)
32[22]
?

Scheme - 6

acetals **38** in good to excellent yields (Scheme 7). The methods is particularly useful for the preparation of S,N-acetals exclusively.

IIA.2.1.2. Using thiocarbamoyl chlorides and C-aryl sulfonyl thioformamides:

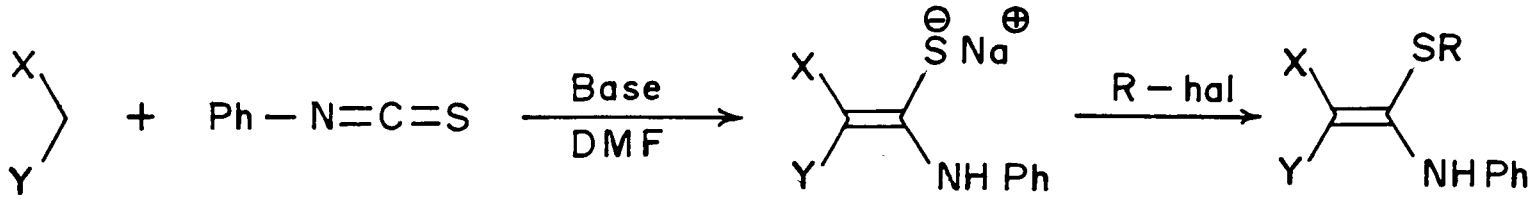
Active methylene compounds **36** (Scheme 8) have been reacted in the presence of sodium hydride and DMF benzene mixture with thiocarbamoyl chlorides **39a**[34-35] or C-arylsulfonylthio formamides **39b**[36a] to give the corresponding thiomides **40** which on subsequent alkylation gave S,N-acetals **41**.

IIA.2.1.3. Using S-alkyl isothiureas and dithiocarbonic acid diester-imides:

Active methylene compounds **3** are also shown to react with S-methyl isothiureas **39'a-b** (Scheme 8b)[26,36b,36c] in meutral medium to give directly the corresponding ketene N,N-acetals **41'a** and S,N-acetals **41'b** in good yields.

IIA.2.2. Displacement Method

The ketene S,S-acetals are known to undergo facile displacement reaction with primary or secondary amines to give the corresponding S,N- and N,N-acetals depending upon the reaction conditions and the stoichiometry of the amine used. Thus, the ketene S,S-acetals **42** (Scheme 9)[26,27,37-41] react with ammonia, primary or secondary (Scheme 7) aliphatic amines **43** and primary aromatic amines **45** in ethanol to give the corresponding ketene S,N-acetals **44** and , N,N-acetals **46**, or mixtures of S,N- and N,N-acetals. However, their reactivity with aromatic amines in boiling acetic acid is more selective. In most of the cases both S,N- **48** and N,N-acetals **47** are formed as mixtures and column chromatography is necessary to separate them (Scheme-10)[42].



36 37 38

X = NO_2; Y = H; R = Me

X = NO_2; Y = PhCO; R = CH_2Ph, CH_2NO_2, CH_2COMe, CH_2COPh.

X = CN, COOEt, $CONH_2$, Ph; Y = CN;

R = CH_2CN, CH_2COOR, CH_2CONH_2.

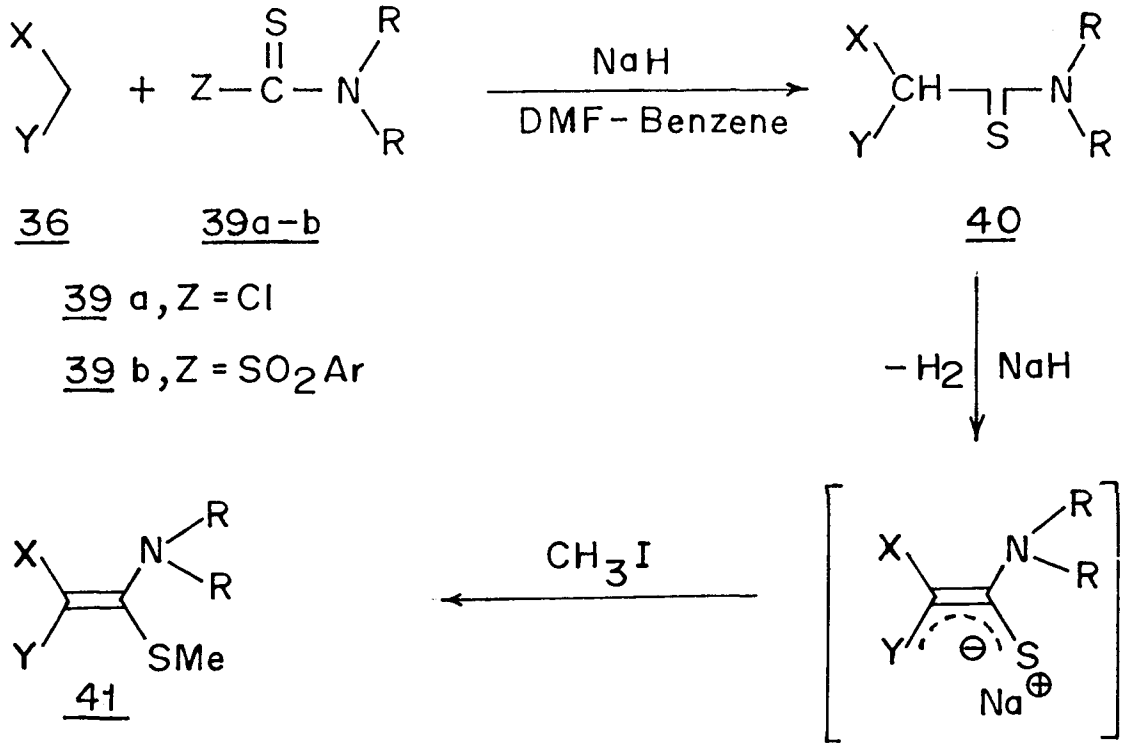
X = COOMe; Y = CN, COOMe; R = Me, allyl, crotyl.

X = COOEt; Y = COOEt, COMe; R = Me, allyl, crotyl.

X = COMe, Y = H, COMe; R = Me, allyl.

(Ref. 25-33)

Scheme–7



41 a, X = Y = CN ; R = Me

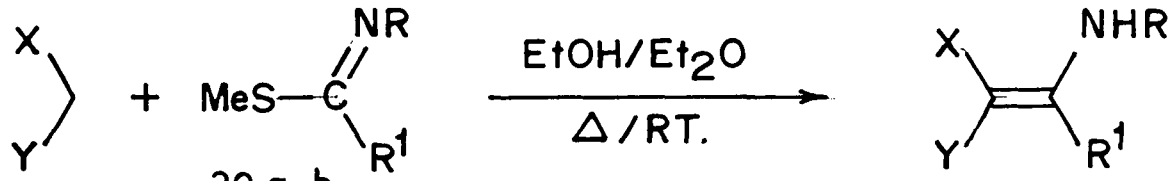
b, X = Y = CN; R = Me

c, X = Y = CN; Y = Ph; R = Me

d, X = Y = CN; R = CH_2Ph

(Ref. 34-36)

Scheme - 8



36 39 a-b 41′

a, R^1 = N<

b, R^1 = SMe

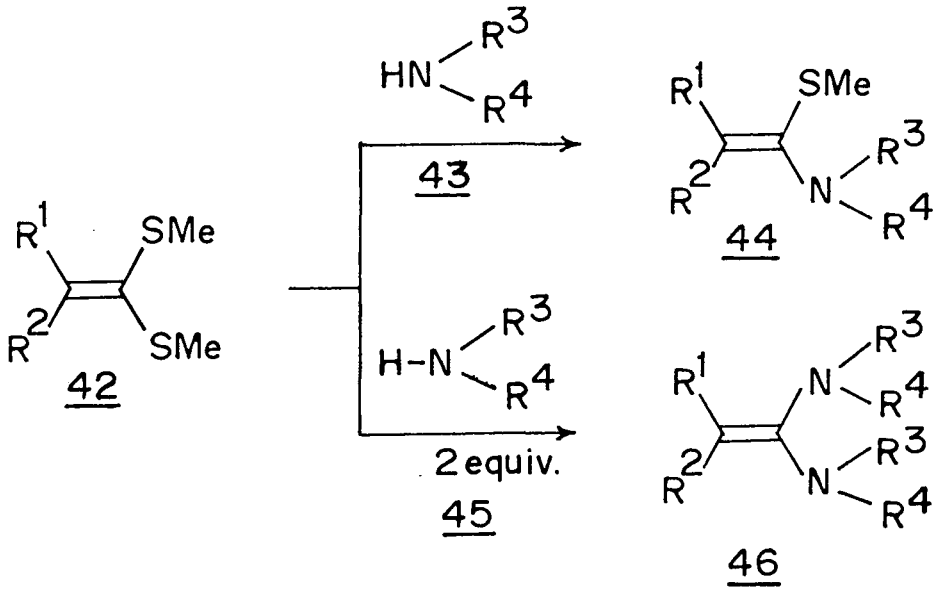
41′, X = C_6H_5CO, p-$CH_3C_6H_4CO$, pClC_6H_4CO, 1-thienyl-CO,
Y = CN; R, R^1 = $-(CH_2)_3-N(Me)-$
X = NO_2, Y = H, R = Me, R^1 = N(Me)(Ph), —N□

a X = Y = CN, R = Me; R^1 = NMe_2

b X = Y = CN, R = Me, R^1 = SMe

(Ref. 26,36b,36c)

Scheme-8B



42,44, R^1 = CN; R^2 = CN, CO_2 Alk ; R^3 = H, R^4 = alkyl, aryl.

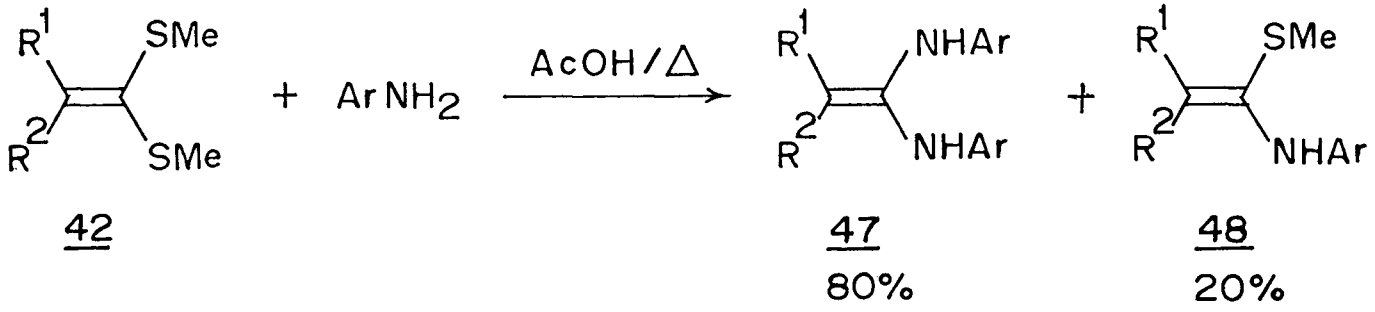
R^1 = MeCO, ArCO; R^2 = MeCO, ArCO, CN, SO_2Ar ; R^3 = H, R^4 = alkyl, aryl.

42,45, R^3 = R^4 = morpholino, pyrrolidino, piperdino, aziridino

R^1 = ArCO, MeCO; R^2 = H.

(Ref. 26,27,37-42)

Scheme-9



42

47
80%

48
20%

47 , 48 R^1 = substituted aryl , methyl

R^2 = H , CN , CO_2Alkyl

Ar = substituted aryl .

Scheme-10

IIA.2.3. Thioamide method

The displacement method failed to yield S,N-acetals of piperidine or morpholines, which could also not be prepared by the direct method. But the thioamide **50** (Scheme 11) derived from the corresponding dithioester **49** and amine are reported to be alkylated to the corresponding ketene S,N-acetals **52** in good yields. Similarly, the formation of **54** from **53** is described[43-46].

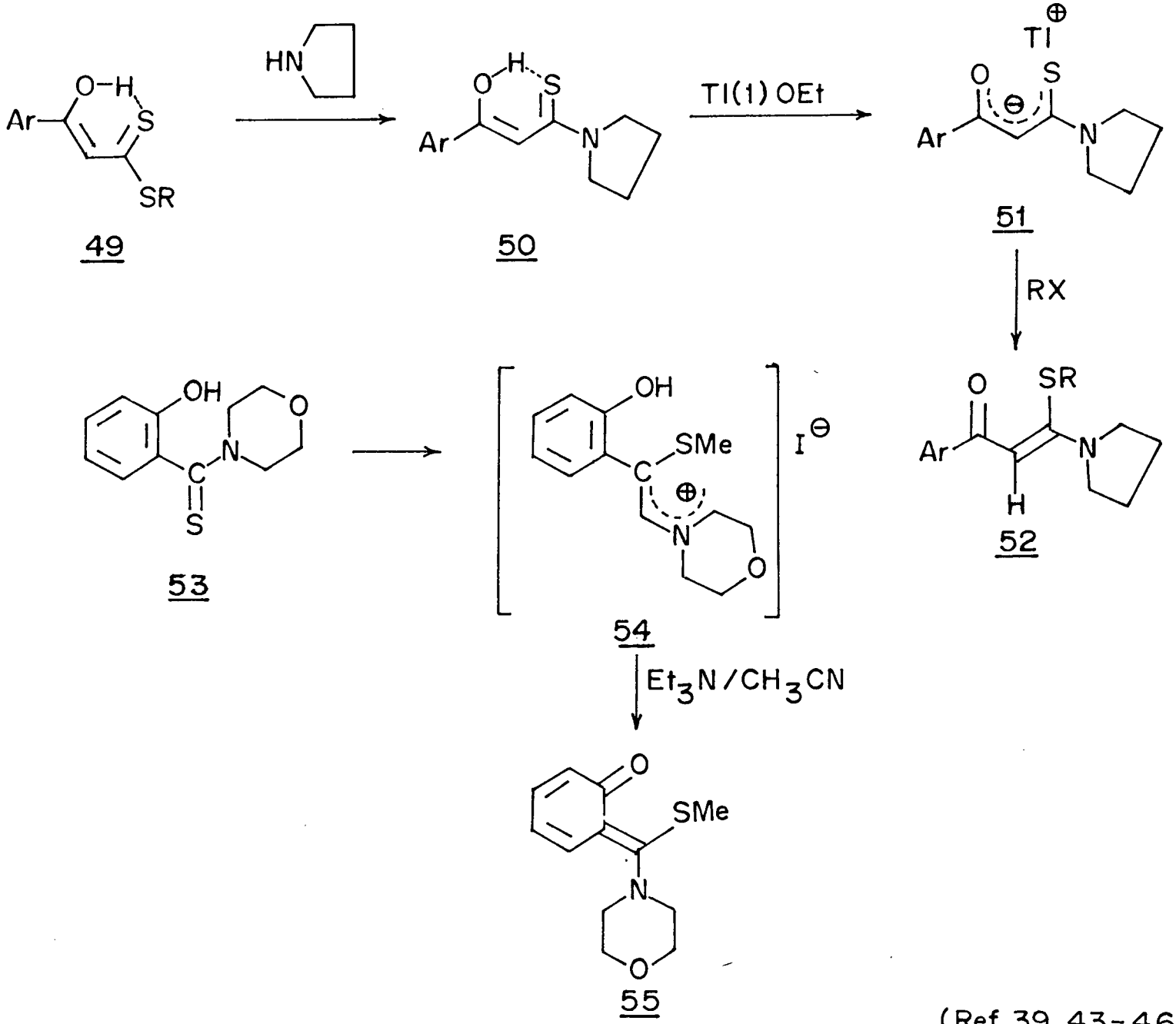
IIA.2.4. New methods developed in the laboratory for the synthesis of ketene S,N- and N,N-acetals

(a) Thioamide method

Recently Junjappa, Ila and co-workers reported[47] a facile preparation of dithioesters **56** (Scheme 12) by reacting ketones with trithiocarbonate in excellent yields. The dithioester **56** thus prepared, underwent smooth condensation with morpholine **57** in boiling ethanol to give the corresponding thioamide **58** which was subsequently alkylated with methyl iodide in the presence of sodium hydride to give **59** in high yield.

(b) Quaternisation method

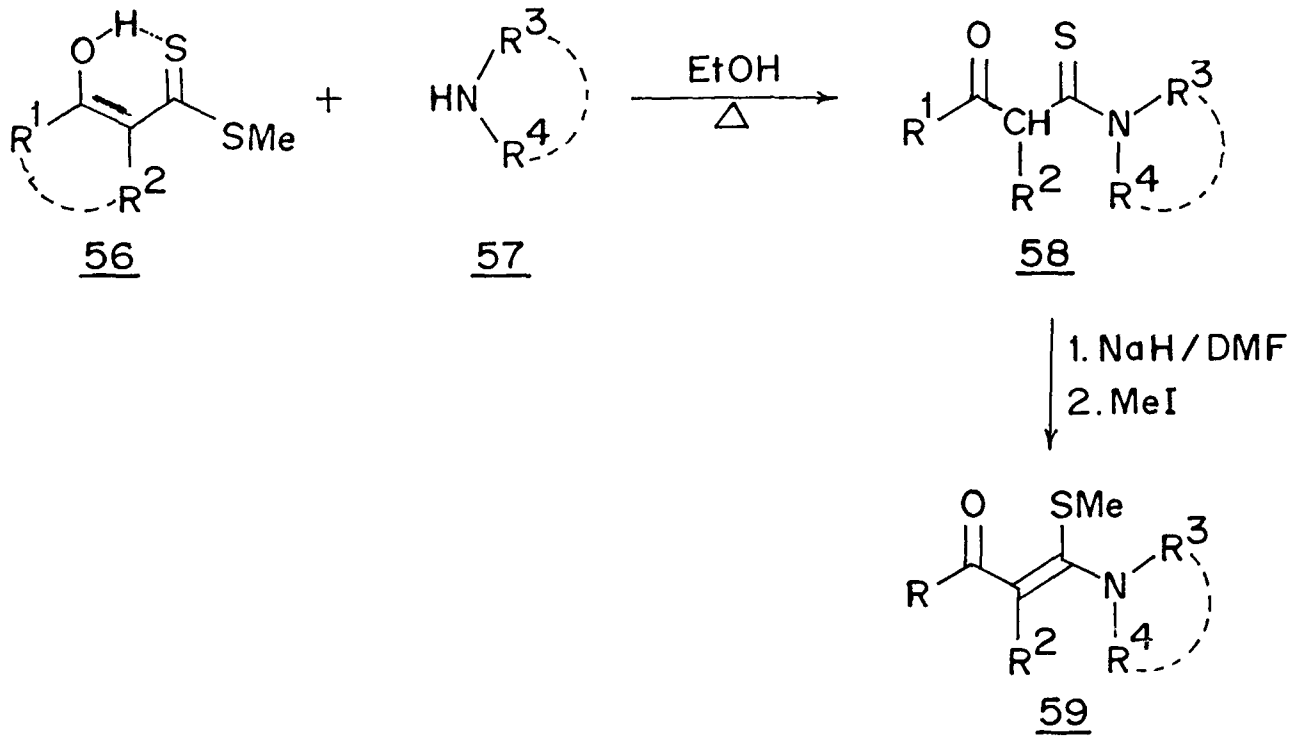
The displacement reaction as mentioned earlier when applied to less reactive a-oxoketene dithioacetal require more vigorous conditions and generally afford a mixture of S,N- and N,N- acetals. Therefore, an alternative method of preparation of ketene S,N-acetals by displacement method involves the reaction of dimethyl sulfonium salts derived from the respective dithioacetals[48] . Thus, the dimethyl sulfonium perchlorate **61** on reaction with amines in the presence of anhydrous potassium carbonate in acetone afforded the corresponding ketene S,N-acetals **62-63** in moderate to high yields (Scheme 13).



49 50 51 52 53 54 55

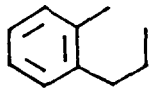
Scheme –11

(Ref. 39, 43-46)



56 57 58 59

R^1 = Me, substituted aryl, R^2 = H;

$R^1 = R^2 = -(CH_2)_4$, 

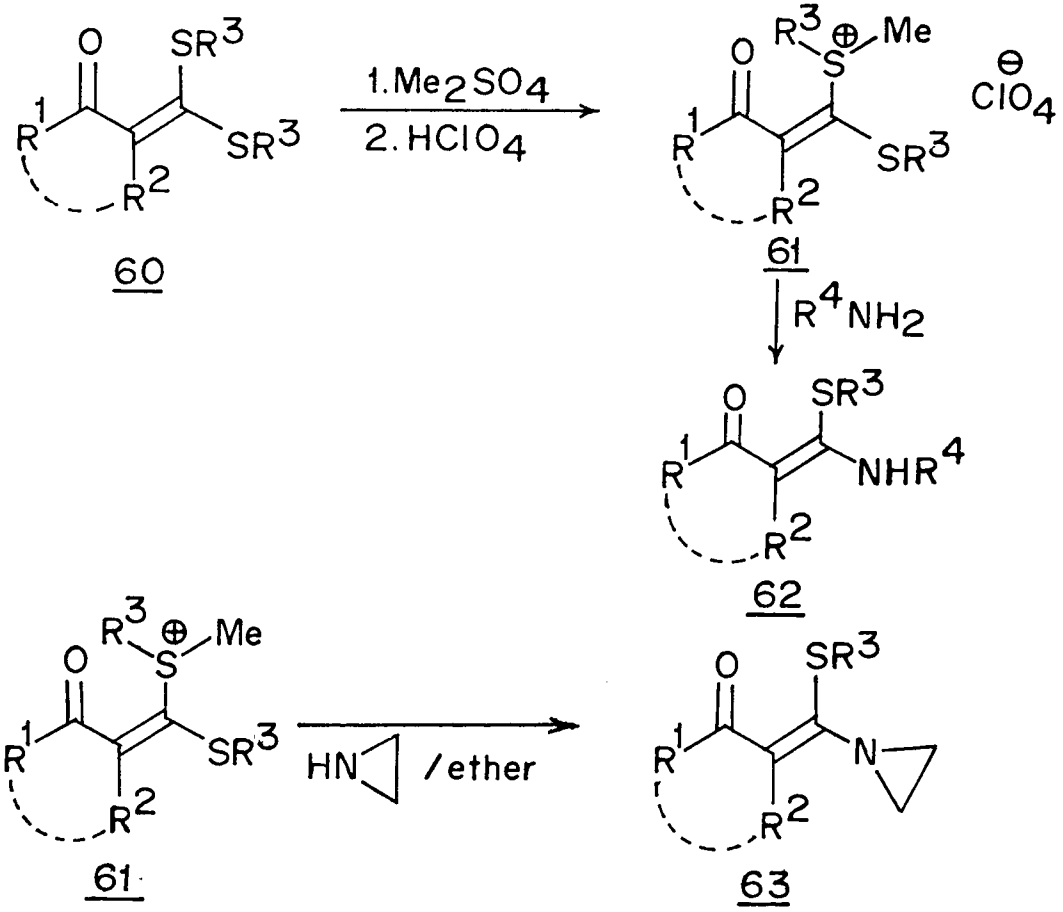
$R^3 = R^4$ = Me, Et; $R^3 = C_6H_5$, R^4 = Me;

$R^3 = R^4$ = pyrrolidino, morpholino, N-phenylpiperazine;

$R^3 = CH_2CO_2Et$, R^4 = H.

(Ref. 47)

Scheme-12



60 61 62 61 63

$R^1 = C_6H_6, 4ClC_6H_4, 4MeOC_6H_4$, $R^2 = H$

$R^1 - R^2 = -(CH_2)_4-$,

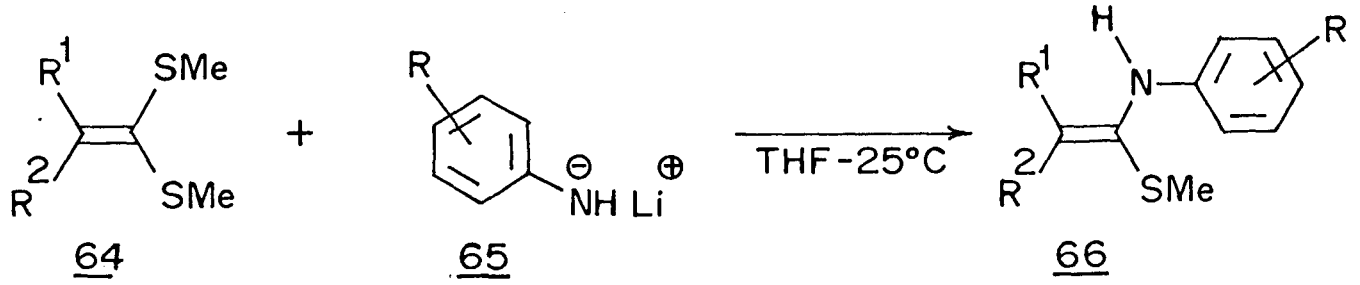
$R^3 = Me$

(Ref. 48,49)

Scheme-13

(c) Using Lithioamino anions

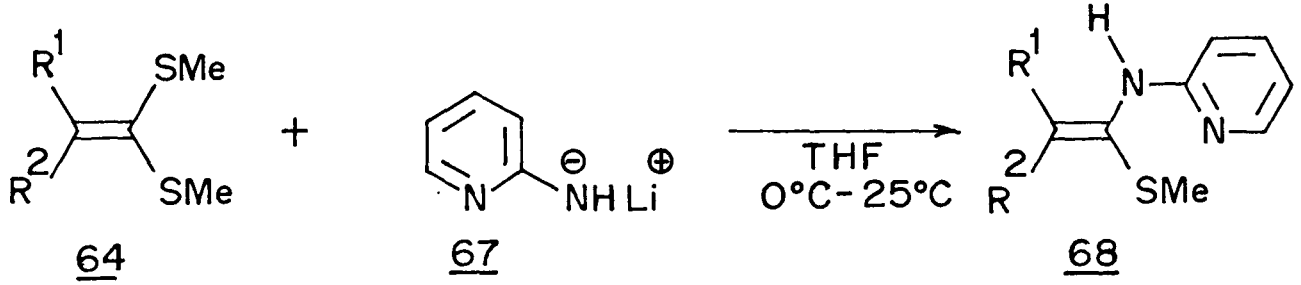
Attempts to prepare functionalized ketene S,N-acetals like 3- methylthio-3-(2-pyridylamino)-2-aryl-2-propene-1-ones **68** by using the methods reported earlier were unsuccessful. But recently we have developed[49] a new method for the preparation of ketene S,N- acetals **66, 68, 70** by displacement method using the lithio-amino anions **71, 73, 75** (Scheme 14)[49]. The preliminary study on these preparations and the scope of this new approach developed is discussed in detailed in part II of this chapter.

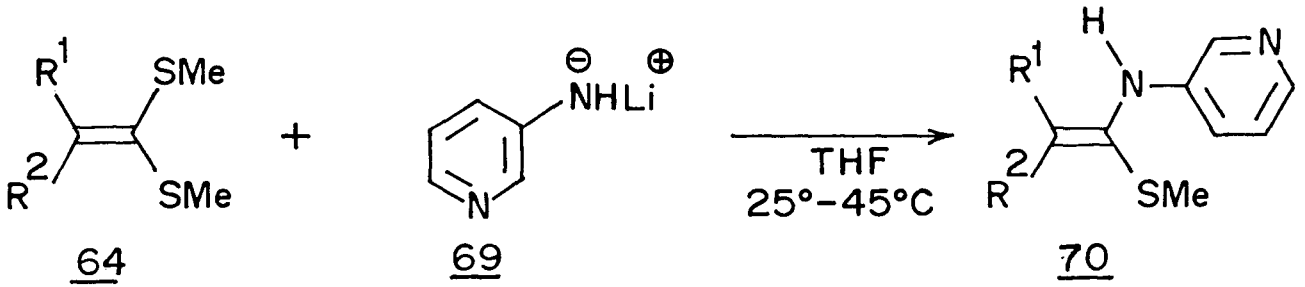


65, a. R = H d, R = 4-Me

b. R = 2-Cl e, R = 4-MeO

c. R = 4-Cl





(Ref. 56) 49

Scheme-14

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CHAPTER-II B

REACTION OF LITHIOAMINO-ANIONS WITH α-OXOKETENE DITHIOACETALS:

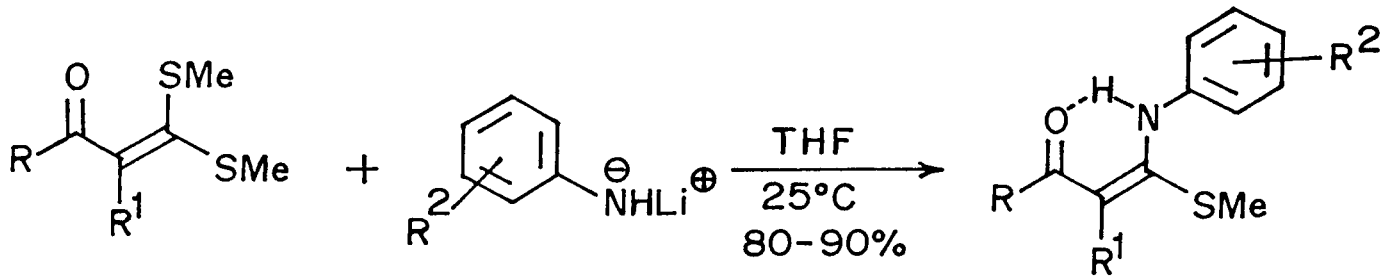
AN IMPROVED AND A NEW GENERAL METHOD FOR THE SYNTHESIS OF α-OXOKETENE S,N- AND N,N- ACETALS.

IIB.1. In the preceding part of the chapter a brief literature survey on the methods of the preparation of S,N and N,N- acetals is described. Although the preparation of S,N- acetals by reacting enolate anions with isothiocyanates and the reaction of amines with dithioates followed by alkylation to give the corresponding S,N-acetals appears to constitute the good methods for the preparation of S,N-acetals, the preparation of isothiocynates from amino heterocycles is not very satisfactory. Since α-oxoketene dithioacetals of wide structural diversity are available in large

quantities, it was considered of interest to examine the reaction of aromatic amines (aniline, 2- chloroaniline,4- chloroaniline, 4- methyl aniline and 4- methoxy aniline) and amino- heterocycles (2 -amino pyridine and 3- amino pyridine) with the α-oxoketene dithioacetals in the presence of n- butyl lithium.

The results of these investigations are described in this chapter. In an optimized reaction condition,the lithio- amino anion **2a** was generated by deprotonation at amino group of aniline by n- butyllithium in dry tetrahydrofuran (THF) at 25°C under an efficient atmosphere of nitrogen. The α-oxoketene dithioacetal **1a** was added as a THF solution over a period of 30 minutes. The reaction mixture, after work-up and purification, yielded the corresponding S,N- acetals (**3a**) as **3-Methylthio-3- (phenylamino)-1- pheny l-2-propen -1-one** as bright yellow needles ($CHCl_3$ -ether), m.p. 57°C. The structure of S,N- acetals **3a** was fully established from its spectral and analytical data. The overall yield of **3a** was 89% and the structure was further confirmed by comparing its properties with the authentic sample prepared by the other reported methods[1,2], (mixed m.p. superimposable IR and NMR). Similarly, the α-oxoketene dithioacetals **1b-f** were reacted with aniline in the presence of n- butyllithium (1 eqv) at 25°C to yield the corresponding α-oxoketene S,N- acetals **3b-f** in 80-89% overall yields (Scheme-1).

Substituted anilines 2-chloroaniline, 4-chloro-aniline, 4-methyl aniline and 4-methoxy aniline also reacted with **1a** in the presence of n- butyl lithium under the same reaction conditions to yield the corresponding S, N -acetals **3g-j** in 80-83% overall yield (Scheme-1 and Table -1). The structure of the unreported S,N- acetal **3g** was fully established on the basis of the spectral and analytical data which is given in the experimental section.



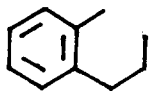
1a-f 2a-e 3a-j

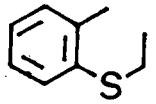
1a, R = C_6H_5 R^1 = H

1b, R = 4-MeOC_6H_4, R^1 = H

1c, R = 4-ClC_6H_4, R^1 = H

1d, R = 4-BrC_6H_4, R^1 = H

1e, R = R^1 = 

1f, R = R^1 = 

2a, R^2 = H

2b, R^2 = 2-Cl

2c, R^2 = 4-Cl

2d, R^2 = 4-Me

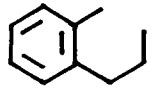
2e, R^2 = 4-MeO

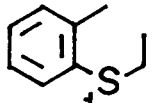
3a, R = C_6H_5, R^1 = H, R^2 = H

3b, R = 4-MeOC_6H_4, R^1 = H, R^2 = H

3c, R = 4-ClC_6H_4, R^1 = H, R^2 = H

3d, R = 4-Br C_6H_4, R^1 = H, R^2 = H

3e, R = R^1 =  , R^2 = H

3f, R = R^1 =  , R^2 = H

3g, R = C_6H_5, R^1 = H, R^2 = 2-Cl

3h, R = C_6H_5, R^1 = H, R^2 = 4-Cl

3i, R = C_6H_5, R^1 = H, R^2 = 4-Me

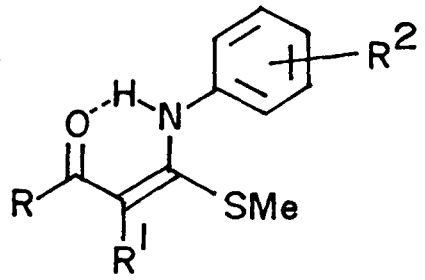
3j, R = C_6H_5, R^1 = H, R^2 = 4-MeO

Scheme-1

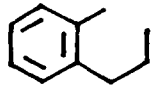
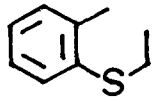
(See Table-1)

Table - 1

Polarised Ketene S,N - acetals prepared by direct displacement using metallated amines.

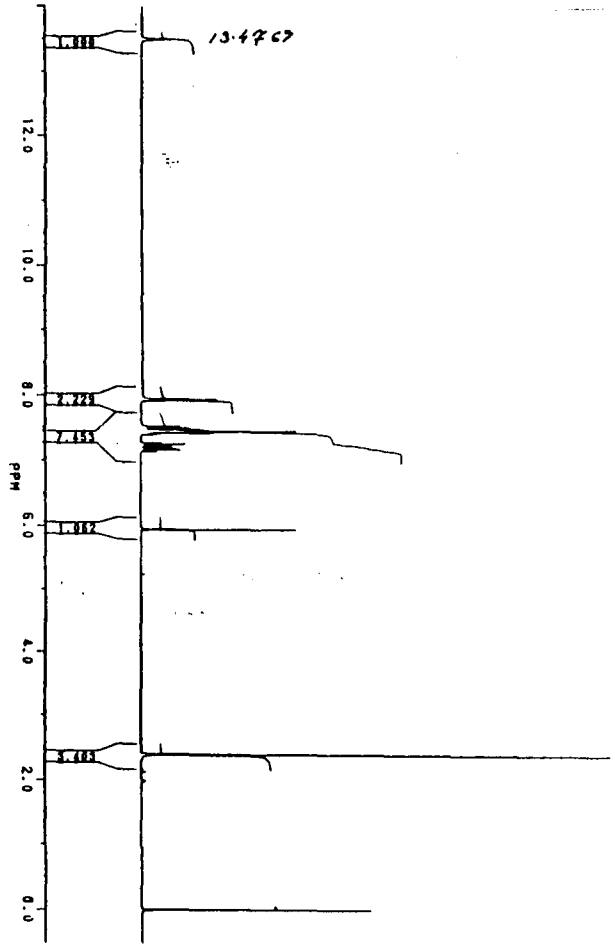


3

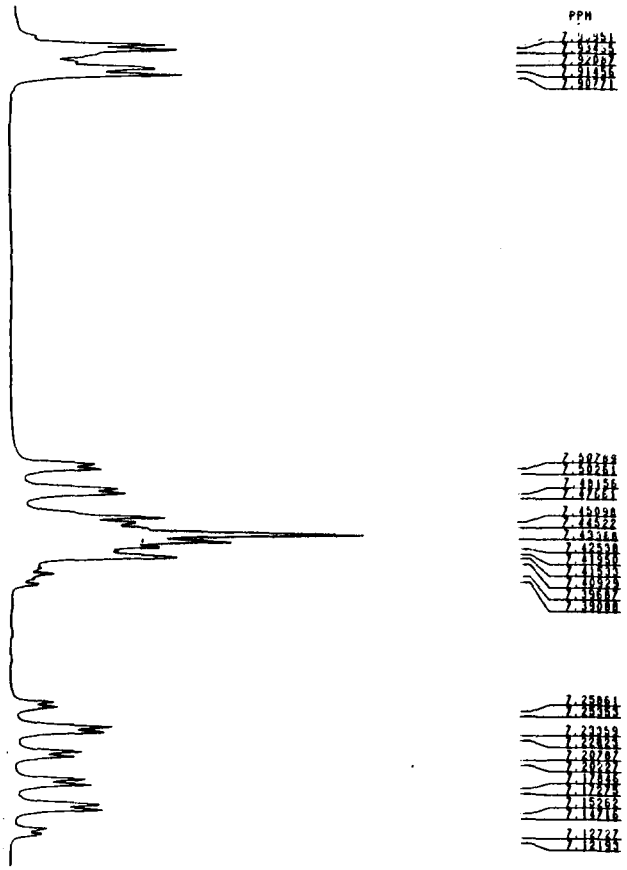
Sl. No	Product 3	R	R^1	R^2	Yied (%)
1.	a	C_6H_5	H	H	89
2.	b	4-$MeOC_6H_4$	H	H	90
3.	c	4-ClC_6H_4	H	H	85
4.	d	4-BrC_6H_4	H	H	80
5.	e			H	80
6.	f			H	80
7.	g	C_6H_5	H	2-ClC_6H_4	82
8.	h	C_6H_5	H	4-MeC_6H_4	80
9.	i	C_6H_5	H	4-MeC_6H_4	82
10.	j	C_6H_4	H	4-$MeOC_6H_4$	85

3a-f, 3h-j reported[1,2] earlier

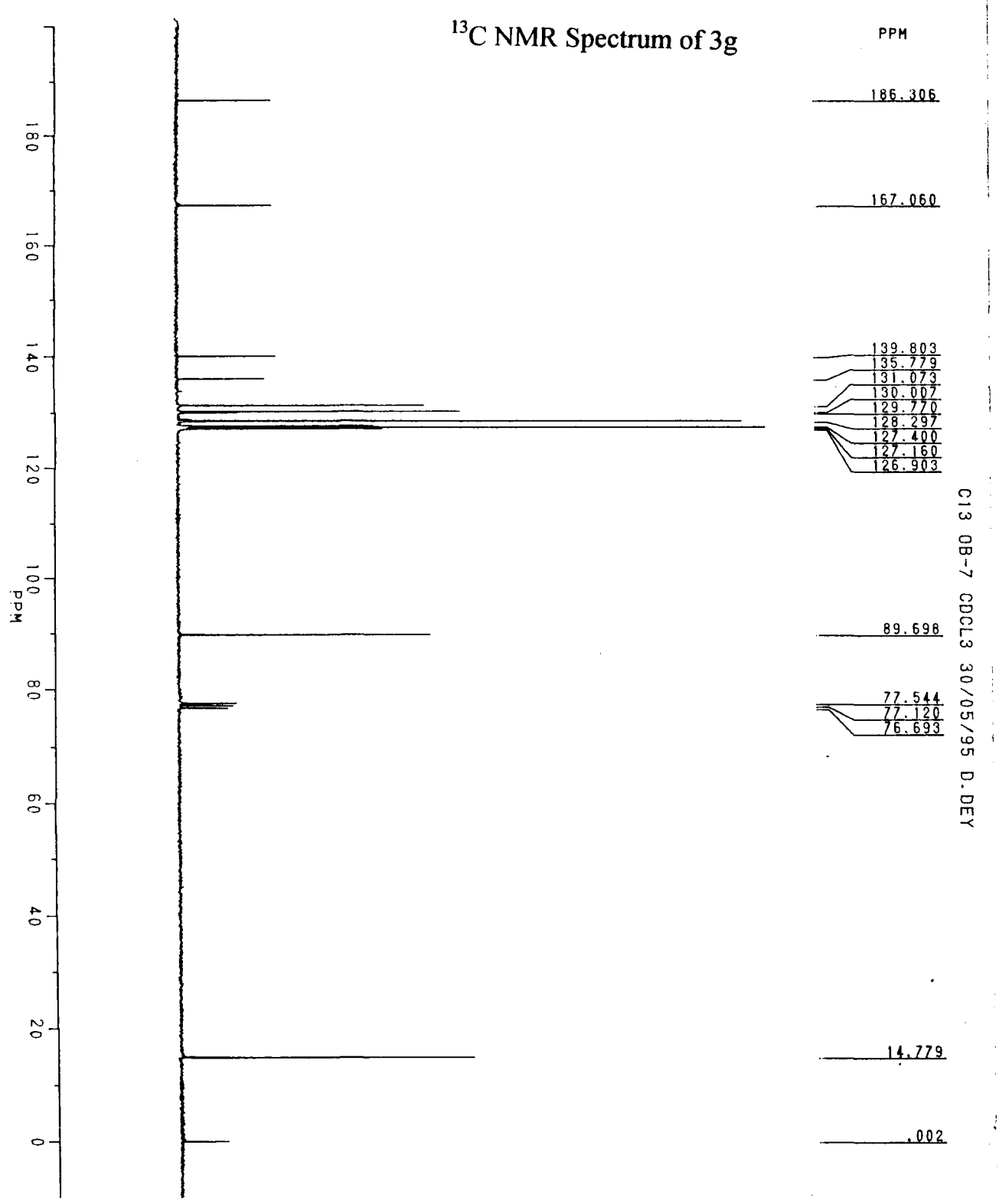
^{1}H NMR Spectrum of 3g



^{1}H NMR Spectrum of 3g



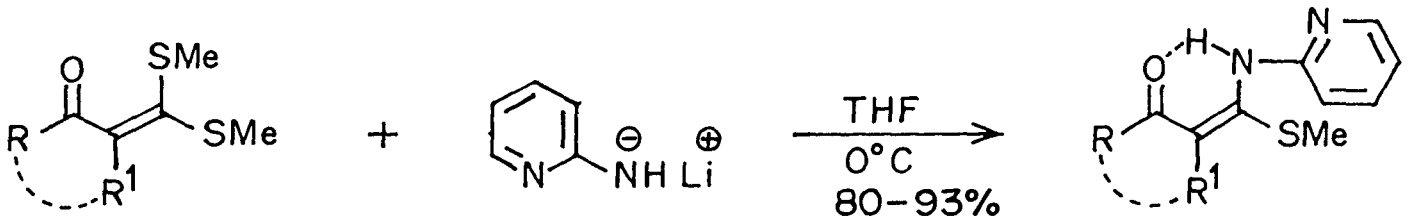
^{13}C NMR Spectrum of 3g



Interestingly, when **1a** was reacted under similar.reaction conditions with 2- lithio-aminopyridine **4**, the corresponding 3- methylthio-3- (2- pyridyl amino)-1- phenyl- 2 propene 1-one **5a** was obtained in 92% yield. The S,N acetal **5a** was not reported in the literature and its structure was established on the basis of analytical and spectral data.The compound was analysed for the molecular formula $C_{15}H_{14}N_20S$ with a molecular weight 270.1.

It's IR (KBr) spectrum showed bands for γNH associated with intra molecular hydrogen bonding with carbonyl oxygen at 3351 cm^{-1}. The very low frequency carbonyl stretching at 1588 cm^{-1} was attributed to the enamino form. (See Scheme-6). The other absorption at 1537 (c= N), 1244^{-1} cm were also noted. The structure of **5a** was further confirmed by its ^{1}HNMR ($CDCl_3$) spectrum (Fig.1).The singlet at ppm 2.37 was assigned to the three SMe protons. The vinylic proton appeared as a singlet at (15.93. The signal due to - NH proton associated with intramolecular hydrogen with carbonyl oxygen appeared at δ14.64. The aromatic protons appeared at δ7.38-7.42 (m,3H, ArH), 7.86-7.89 (m,1H, ArH) and the 4-pyridyl protons show clearly ABMX system at δ6.85 (m,1H, 5-H) 6.93 (d,1H,3H), 7.53 (ddd,1H,4-H) and 8.27 (dt,1H,6-H) with the coupling constants, $J_{3,4}$=8.7, $J_{4,6}$=0.3 J =6.0, $J_{5,6}$ = 0.01 3,4 4,6 5,6 3,5Hz. ^{13}CNMR spectrum of compound **5a** was also in conformity with the assigned structure (Fig.2). ^{13}CNMR (75.5MHz, $CDCl_3$) δppm.15.9(SCH_3), 90.63 (=CH), 113.6, 118.0 (C=5 and C-3 of pyridyl), 127.0, 128.5. 131.4 (C-2,C-3 & C-4 of Ar), 137.6 (C-4pyridyl 139.8 (C-1 Ar), 146.6 (C-6 pyridyl), 151.2, 185.67 for carbonyl carbon.

Similarly, 2-lithio aminopyridine was reacted with various α-oxoketene dithioacetals 1b-j under the described reaction conditions to yield the corresponding S,N- acetals **5b-j** in 80-93% overall yield (Scheme-2).The structure of all these compounds were



1 a-j 4 5, a-j

1, 5, a, R = C_6H_5, R^1 = H

b, R = 4-MeOC_6H_4, R^1 = H

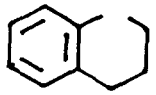
c, R = 4-Cl C_6H_4, R^1 = H

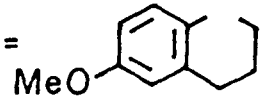
d, R = 4-MeC_6H_4, R^1 = H

e, R = 2-furyl, R^1 = H

f, R = 2-thienyl, R^1 = H

g, R = R^1 = $-(CH_2)_4-$

h, R = R^1 = 

i, R = R^1 = 

j, R = $C_6H_5-CH=CH$, R^1 = H

Scheme-2

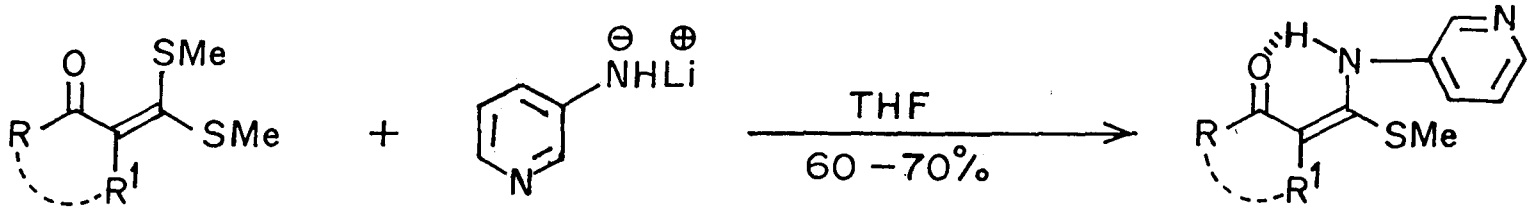
fully established by their analytical and spectral data which are described in the experimental section.

Under similar reaction conditions, 3- lithio- amino pyridine **6** also reacted with α-oxoketene dithioacetals **1a-e** to yield the corresponding S,N- acetals **7a-e** in 60-70% over all yields. (Seheme -3). The structures of **7a-e** were fully established by their analytical and spectral data and were in agreement with the assignment (see in experimental section).

It is interesting to note that when 2- equimolar quantity of 2- lithioamino pyridine was reacted with 1- equimolar quantity of **1a** and refluxed for three hours yielded the corresponding N,N- acetals **8a** in 79% yield. (Scheme-4). Similarly **8b** was also obtained in 80% yield. The analytical and spectral data of both **8a** and **8b** are described in experimental section.

Also, in a typical experiment, S,N- acetal **5a** was refluxed in methanol in the presence of sodium methoxide (1eqv), the corresponding S,N-acetal **10a** was formed in 61% yield.(Scheme-5). This reaction is unusual since such displacement of methylthio group of S,N- acetals is not reported in earlier literature. In all the S,N-acetals described in Scheme -1 did not undergo such displacement reactions even on prolonged heating of methanol under identical conditions.

However, the 2- amino pyridine moeity because of the electron deficient character of the pyridine ring makes C-4 more electrophilic thus facilitating the displacement of methylthio group by methoxy group.



1 6 7

1, 6, 7, a, R = C_6H_5, R^1 = H

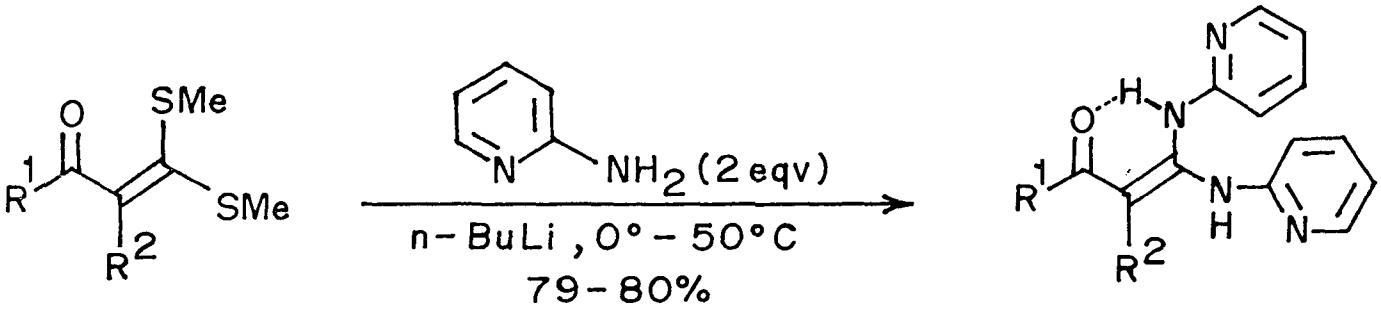
b, R = 4−$MeOC_6H_4$, R^1 = H

c, R = 4−MeC_6H_4, R^1 = H

d, R = H_5C_2O−, R^1 = CN

e, R = 2-furyl, R^1 = H

Scheme-3



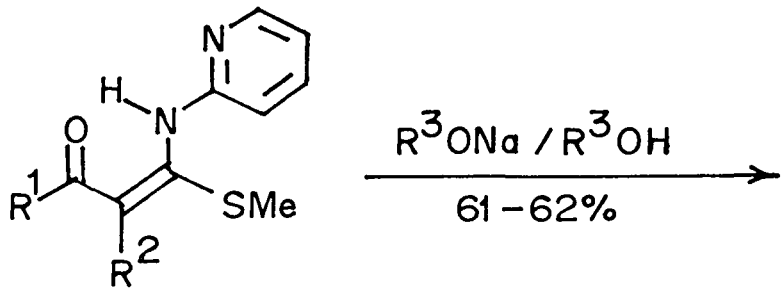
1a-b

8a-b

1, 8, a, $R^1 = C_6H_5$, $R^2 = H$

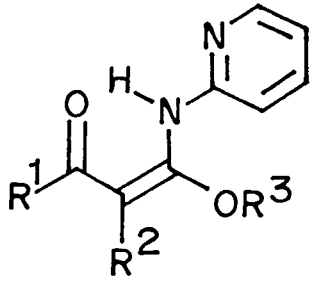
b, $R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$

Scheme-4



R^3ONa / R^3OH

61 – 62%



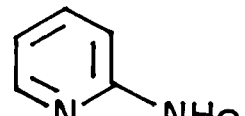
5 a-b

10 a-b

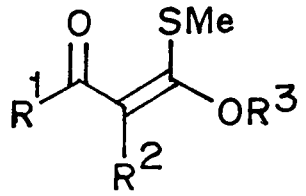
5, a, $R^1 = C_6H_5$, $R^2 = H$

b, $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$

80 – 81%

1. 

2. n-BuLi / THF



9 a-b

9, 10, a; $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$

b, $R^1 = 4\text{-}ClC_6H_4$, $R^2 = H$, $R^3 = CH_3$

Scheme – 5

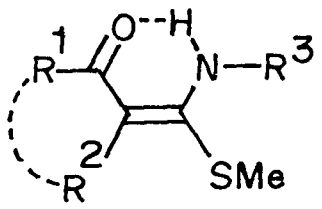
The O,N- acetal **10a** was also alternatively prepared in 81% yield by reacting O,S-acetals **9a** with 2-lithio amino pyridine (Scheme-5) (The required O.S-acetals **9a-b** were prepared by earlier reported method). Similarly the O,S-acetals **9b** was reacted with 2 lithio-amino pyridine to yield the corresponding O,N-acetal **10b** in 81% yield. The analytical and spectral data of both **10a** and **10b** are described in experimental section.

IIB.2. SPECTRAL STUDIES AND CONFIGURATIONAL ASSIGNMENTS.

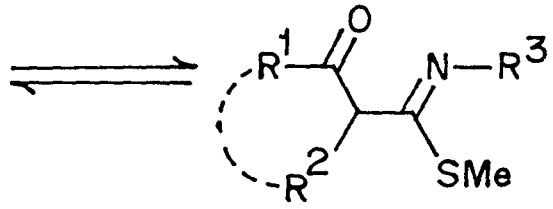
All the S,N- acetals formed **3a-j**, **5a-j** and **7a-e** displayed the formation of only one stereoisomer which was evident from their sharp melting points. The chemical shift values of SMe and vinylic protons appeared as sharp singlets in all the cases indicating the purity of their geometrical isomerism. The geometry of the S,N-acetals thus formed,was assigned E- configuration on the basis of IR and NMR data.

Polarized keten- S,N- acetals are known[4] to exist in tautomeric equilibriun between enamino A and imino form B (Scheme-6) which can be easily distinguished with the help of IR and NMR spectroscopy. The spectral studies on α- oxoketene S,N-acetals **3a-j** (Scheme-1), **5a-j** (Scheme-2) and **7a-e** (Scheme-3) prepared for the present investigation, indicated that all of them exist in the enamino form A which supports the E- configuration. The IR spectrum strongly indicate the hydrgen bonded NH stretching, vibration at 3330-3350cm^{-1} suggesting its position with the intramolecularly associated hydrogen. The carbonyl stretching vibration in these compounds was merged with bands around and below 1600 cm^{-1} reflecting characteristic conjugation effect of the amino group and strong intramolecular hydrogen bonding. In ^{1}HNMR spectrum, the downfield shift of the - NH proton signal at δ13-15 ppm was attributed to its intramolecular hydrogen bonding. It is interesting to note that all the S,N- acetals were found to be exclusively in E-configuration and the corresponding isomers were not formed in any of the experiments.

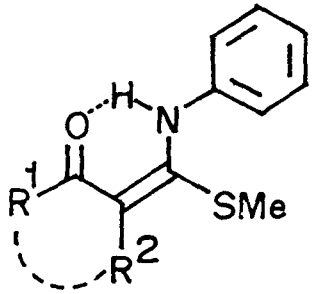
Apparently it appears that the strong intramolecular hydrogen bonding directs the overall configuration of the S,N-acetals (Scheme- 6).



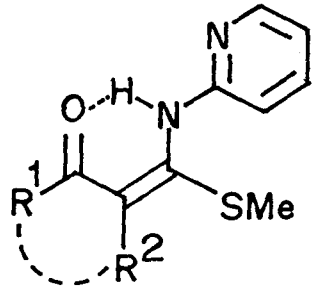
Enamino
A



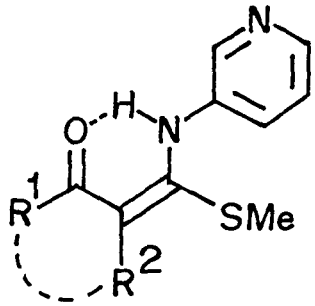
Imino
B



3



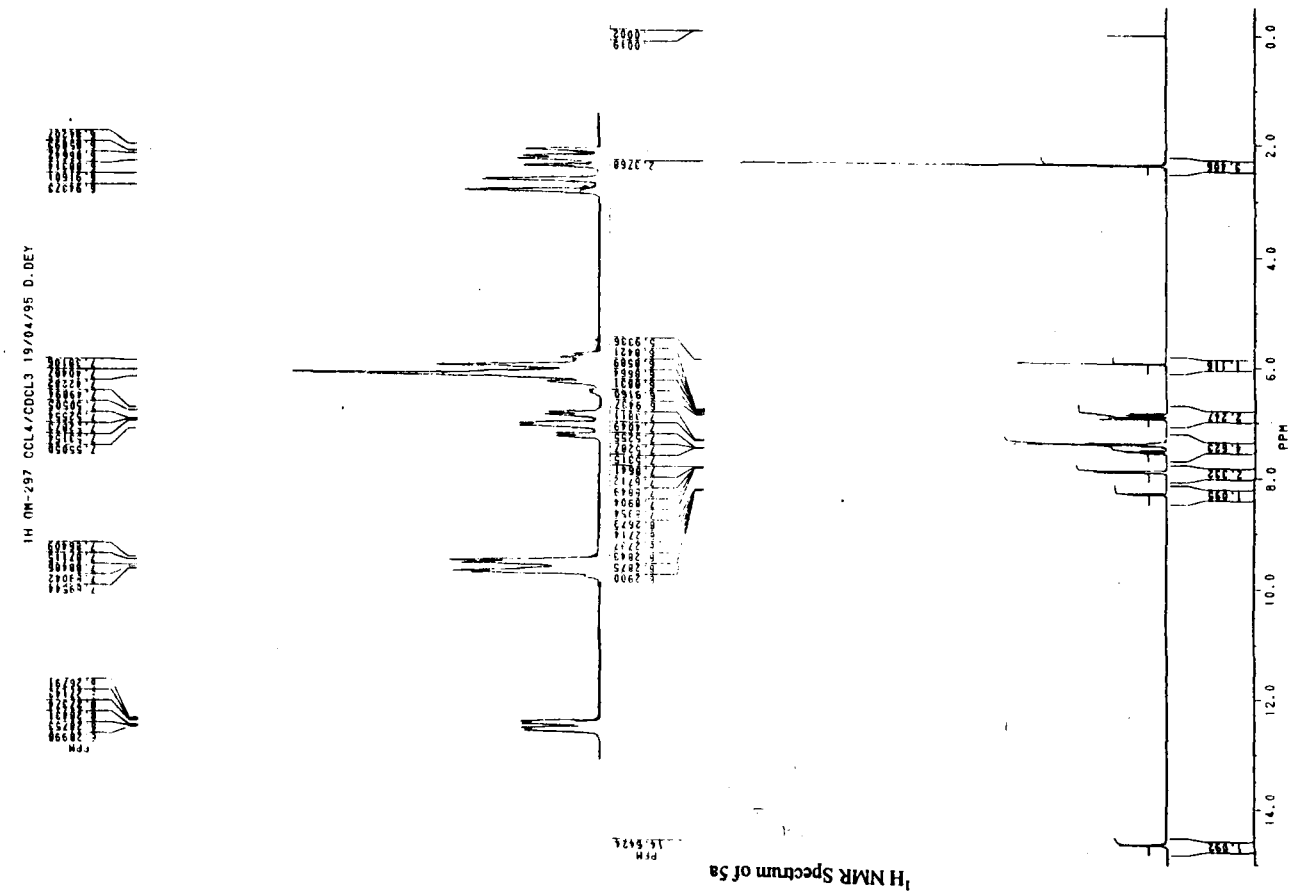
5



7

All E – configuration

Scheme – 6



^{1}H NMR Spectrum of 5a

^{13}C NMR Spectrum of 5a

IIB.3. CONCLUSION

A new efficient method for the synthesis of various S,N-acealsinvolving α-oxoketene dithioacetals and lithio-amino anions has been developed. The examples, examined in these studies demonstrate that the method is very versatile since the reaction condtions are mild and the displacement is highly stereoselective (E- configuration). The hitherto unreported S,N- acetals derived from amino pyridines could also be prepared by this method in improved yields. The S,N- acetals derived from 2- amino pyridines **5a-j** displayed characteristic properties undergoing easy displacement of the methylthio group by alkoxy group while others do not undergo these displacement reactions under similar reaction conditions.

IIB.4. EXPERIMENTAL SECTION

Melting points were determined on a "Thomas-Hoover" capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 and Perkin-Elemer 983 spectrometers. ^{1}HNMR (90 MHz) were recorded on Varian EM-390 high resolution ^{1}H NMR (300 MHz) and ^{13}CNMR (75.5 MHz) spectra were recorded on Brucker ACF 300 spectrometer. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethyl silane or DMSO-d_6 in ^{13}CNMR. The following abbreviations are used to describe peak patterns when appropriate : br=broad, s = singlet, d=doublet, d=double doublet, dt = double triplet, t=triplet, q=quartet, m=multiplet. Mass measurements were carried out with Jeol JMS D-300 spectrometer. Masses (MS) are reportedin unit of mass over charge (m/z), the molecular or base peaks and relative intensities are indicated by (M)and (%) respectively. Elemental analysis were performed on a Heracus CHN-O-Rapid Analyzer. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Dry ether was obtained by keeping over calcium chloride (fused) and stored over sodium wire. Lithium Ingot (Aldrich) were cut into smaller pieces and washed with dry ether twice before use n-Butyl lithium was prepared according to the reported[5] procedure.

Starting materials:

Commercially available ketones p-methoxybenzaldehyde acetophenone, 4-chloroacetophenone, 4-methoxy acetophenone, acetone, cyclohexanone and cycloheptanone were purified either by simple distillation/distillation under reduced pressure or crystalliza tion before use. 2-Acetyl furan & 6 methoxy tetralone

was pur chased from Aldrich and used as such 1-tetralone bp 140°-150°C (10 mm), 2-acetyl thiophene bp 214°C, were prepared according to the earlier reported[6] procedures. Aniline, O-chloroaniline,p-chloroaniline were distilled prior to use. p-Toludine, p-anisi dine and p-bromoaniline, 2-aminopyridine, 3-aminopyridine were recrystallised before use. α-Oxoketene S,S-acetals required for the present investigation were prepared according to the earlier reported[7] literature pro cedures which are given below.

General procedure for the preparation of oxoketene dithioacetal (1a-f of Scheme-1, 1a-i of Scheme-2,1a-e of Scheme-3) using sodium tert.butoxide. A mixture of ketone (0.2 mol) and carbon disulphide (0.2 mol) was added dropwise to an ice-cold and well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (200 ml) and the reaction mixture was allowed to stirr at room temperature for 5-6 hours. Acid free dimethyl sulphate (0.2 mol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stir at room temperature for 6-10 hours. The reaction mixture was poured over aqueous saturated ammonium chloride solution (250 ml) and the layers were separated. The aqueous layer was extracted with benzene (100 ml) and combined benzene extracts were washed with water (4x250 ml), dried (Na_2SO_4) and evaporated. Trituration of the oil residue with hexane gave the dithioacetals as yellow crystalline solid in good yields. Liquid dithioacetals were purified by passing through silica gel column using hexane- ethylacetate (9:1 to 8:2) as eluent. All the known dithioacetals were charaterized by comparison of their melting points, NMR, IR spectra with those of reported data and of authentic sample.

Condensation of -acylketene dithioacetals with aldehydes : General procedure for the preparation of 5-aryl, 1-bis(methylthio) 1,4-pentadiene-3-ones (**1j** Scheme-2). To a cooled and stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (0.06 mol) in ethanol (30 ml), a solution of the -acylketene dithioacetal (0.03 mol) and aldehyde (0.03 mol) in minimum ethanol was added dropwise over a period of 5 minutes. The reaction mixture was brought to room temperature over a period of 20 minutes and further stirred at room temperature for 4-5 hr. The mixture was diluted with cold water (100 ml) and solid separates out was filtered, washed with water (4x50 ml) and dried.

General procedure for the generation and reaction of 1-lithioamino benzenes and substituted 1-lithioamino benzenes with α -oxoketene dithioacetal: preparation of S,N-acetals (3a-j). To a stirred solution of 1-aminobenzene (aniline) or substituted aniline (10 mmol) in dry THF (20 ml) n-butyllithium was added undeer dry and inert atmosphere, over 20 minutes at room temp. (25°C). The reaction mixture was stirred for 30 minutes at the same temp. The lithiation was indicated by the appearance of reddish brown colour. A solution of oxoketene S,S-acetal (10 mmol) in dry THF (25 ml) was added. The contents were stirred at room temperature for 5-6 hours. In case of S,N-acetals (**3e-g**), after addition of oxoketene S,S-acetals the reaction mixture was refluxed with stirring at 60°C for 2-3 hours to complete the reaction. Then it was brought to room temperature, worked up by pouring into saturated aqueous NH_4Cl solution (100 ml), extracted with chloroform (2x50 ml) and the combined extracts were washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give the crude product, which was purified by crystallization from chloroform-hexane mixture or by passing through column of silica gel using

ethylacetate - hexane (1:9) as eluent (**3e-g**).Analytical and spectral data of the hitherto unreported S, N-acetal **3h** is given below:

3-Methylthio-3-(2-chlorophenylamino)-1-phenyl-2-propen-1-one (3h) was isolated as light yellow crystals (chloroform-hexane) m.p. 110°C; yield 2.50g (82%). υ_{max} (KBr) : 3320 (NH), 1603, 1592, 1240 cm^{-1}. δ_H(300 MHz, $CDCl_3$): 2.38 (s, 3H, SCH_3), 5.93 (s, 1H, vinylic), 7.15 [(ddd, 1H, J = 17Hz ($J_{3,4}$+ $J_{4,5}$+ $J_{4,6}$)], 7.23 [(ddd, 1H, J = 16.5 Hz ($J_{4,8}$+$J_{5,6}$ +$J_{3,5}$), H-5], 7.39-7.45 (m, 4H, H-6 & ArH, 7.50 (m, 2H, ArH), 7.92 (dd, 1H, J = 9.6 Hz, H-3), 13.4769 (s, 1H, NH, exchanges D_2O). δ_C(75.5 MHz, $CDCl_3$) : 14.77 (SCH_3), 89.69 (=CH), 126.90 (C-6 anil), 127.1 (C-2'Ar), 127.46, 128.29 (C-3'Ar), 129.7 (C-4Am) 130.0 (C-5anil), 131.07 (C-3aniline) 135-77 (C-2 aniline) 139.80 (C-1'Ar), 167-06 (=C), 186.30 (C=O). Anal. Calcd. for $C_{16}H_{14}ClNOS$ (303.5), C 63.26, H 4.6, N 4.6. Found. C 63.37, H 4.5, N 4.80.

Generation of 2-lithio-amino pyridine and its reaction with α-oxoketene dithioacetal: General procedurre for the preparation of ketene S,N-acetals **5a-j**. To a stirred solution of 2-aminopyridine (0.94g, 10 mmol) in anhydrous tetrahydrofuran (THF) (20 ml), n-butyllithium (15 mmol) was added with stirring and maintaining the temperature at 0°C. The lithiation was indicated by the appearance of reddish brown colour. The reaction mixture was stirred at the same temperature for 30 minutes. A solution of oxoketene dithioacetal (10 mmol) in dry THF (25 ml) was added and stirred for 30-45 minutes (0°C) and then allowed to warm to room temperature. The reaction mixture was further stirred at the same temperature for one hour, worked up by pouring into saturated aquous NH_4Cl solution 50ml) extracted with chloroform (2x50 ml) and the combined extracts were washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give the crude product, which

was purified by crystallization from chloroform/hexane mixture or by passing through silica gel column using ethylacetate-hexane (1:9) as eluent(**5g-j**). The structures (**5a-j**) were fully established from their spectral and analytical data which are given below:

3-Methylthio-3-(2-pyridyl amino)-1-phenyl-2-propene-1-one (5a) was isolated as light yellow crystals (chloroform-hexane), yield 12.50g (92%), m.p. 90°C. υ_{max} ((KBr) : 3496, 3351 (NH), 1588, 1537, 1244 cm^{-1}, δ_H (300 MHz, $CDCl_3$): 2.37 (s, 3H, SCH_3), 5.93 (s, 1H, vinylic), 6.85 (m, 1H, 5-H pyridyl), 6.93 (d, 1H, J = 9Hz, 3-H pyridyl), 7.38-7.42 (m, 3H, ArH), 7.53 (ddd, 1H, J=15.6 Hz, 4-H pyridyl), 7.86-7.89 (m, 2H, ArH), 8.27 (dt, 1H, J = 6.6 Hz), 6-H pyridyl), 14.64 (s, 1H, NH, exchanges D_2O).,[3-H, 5-H, 4-H and 6-H pyridyl = ABMX system; from first order analysis, $J_{3,4}$ = 8.7, $J_{4,6}$ = 0.3, $J_{5,6}$ = 6.0, $J_{3,5}$ = 0.01 Hz] δ_C (75.5 MHz, $CDCl_3$)=15.9 (SCH_3), 90.63 (=CH), 113.6, 118.0 (C-5 and C-3 of pyridyl), 127.0, 128.5, 131.4 (C-2′, C-3′ & C-4′ of Ar), 137.6 (C-4 pyridyl), 139.8 (C-1′Ar), 146.6 (C-6 pyridyl), 152.2 (= C), 165.8 (=C), and 185.67 (C=0). Anal. Calcd. for $C_{15}H_{14}N_2OS$ (270.1) C 66.66, H 5.18, N 10.37. Found: C 66.69, H 5.15, N 10.38.

3-Methylthio-3(2-pyridylamino)-1-(4-methoxypneyl)-2-propene-1-one (5b) was isolated as yellow crystals, yield 2.80g (93%), m.p. 105°C. υ_{max} (KBr) : 3491, 3325 (NH), 1580, 1534, 1238 cm^{-1}. δ_c(300 MHz, $CDCl_3$) : 2.43 (s, 3H, SCH_3), 3.82 (s,3H, OCH_3), 6.91 (d, 2H, J = 9 Hz, ArH), 6.93-6.98 (m, 2H, 6-H & 3-H pyridyl), 7.59 (ddd, 1H, $J_{4,5}$, $J_{4,6}$, $J_{4,3}$ = 17.3 Hz, 4-H pyridyl) 7.88-7.91 (d, 2H, J = 9Hz, ArH), 8.32 (dt, 1H, $J_{5,6}$, $J_{4,6}$=6.9 Hz, 6-H pyridyl), 14.56 (s, 1H, NH, exchanges D_2O). ^{13}CNMR (75.5 MHz, $CDCl_3$) : 16.10 (SCH_3), 55.3 (OCH_3), 90.5 (=CH), 113.61 (C-2′of Ar), 113.84, 118.13

(C-5 and C-3 pyridyl), 129.08 (C-3′ of Ar), 132.46 (C-1′ of Ar), 137.96, 146.81 (C-4 & C-6 pyridyl) 152.50 (=C), 162.19 (C-9′ Ar), 165.13 (=C) and 185.25 (C=O). Anal. Calcd. for $C_{16}H_{16}N_2OS$ (300.1) C 63.97, H 5.33, N 9.33. Found: C 63.95, H 5.29, N 9.50.

3-Methylthio-3-(2-pyridyl amino)-1-(4-chlorophenyl)-2-propene-1-one (5c) was isolated as bright yellow crystals (chloroform-hexane) m.p.=116°C, yield 2.75g (90%). υ_{max} (KBr): 3498, 3347(NH), 1579, 1538, 1248 cm^{-1}. δ_H (90 MHz, $CDCl_3$) : 2.38 (s, 3H, SCH_3) 5.91 (s,1H, vinylic), 6.91-7.10 (m, 2H, 5-H & 3-H pyridyl), 7.49 (d, 2H, J = 9Hz, ArH), 7.59 (ddd, 1H, $J_{4,5}$ $J_{4,6}$ $J_{4,3}$=17.5 Hz, 4-H pyridyl) 8.00 (d, 2H, J = 9Hz, ArH), 8.32 (dt, 1H, J = 6.9 Hz, 6-H pyridyl), 14.60 (s, 1H, NH). δ_C (75 MHz, $CDCl_3$) : 16.1 (SCH_3), 114.01, 118.5 (C-5, C-3 pyridyl), 128.5, 128.59, 137.28 (C-2′, C-3′ and C-1′ of Ar), 138.03 (C-4 pyridyl), 138.35 (C-4′ Ar), 146.0 (C-6 pyridyl), 152.2 (=C), 166.58 (= C), 184.52 (C=O). Anal. Calcd.for $C_{15}H_{13}N_2OSCl$ (304.6), C 59.06, H 4.2, N 9.12. Found : C 59.13, H 4.1, N 9.10.

3-Methylthio-3-(2-pyridyl amino)-1-(4-methylphenyl)-2-propene-1-one (5d) was isolated as yellow solid (chloroform-hexane) m.p. 110°C yield 2.56g (90%). υ_{max} (KBr) : 3487, 3320 (NH), 1748, 1522, 14556, 1250 cm^{-1}. δ_H (90 MHz, $CDCl_3$) : 2.58 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 5.99 (s, 1H, vinylic), 7.15 (m, 1H, 5-H pyridyl), 7.25 (d, 1H, J = 9Hz, 3-H pyridyl), 7.45 (d, 2H, J = 8.9 Hz, ArH), 7.75 (ddd, 1H, J = 17.3 Hz ($J_{4,5}$+$J_{4,6}$+$J_{4,3}$), 4-H pyridyl), 8.05 (d, 2H, J = 8.9 Hz, ArH), 8.51 (dt, 1H, J = 6.9 Hz, H-6 pyridyl), 14.95 (s, 1H, NH, exchanges D_2O). Anal. Calcd. for $C_{16}H_{16}N_2OS$ (284.1) C 67.60, H 5.6, H 5.7, N 9.75.

3-Methylthio-3-(2-pyridylamino)-1-(2-furyl)-2-propene-1-one 5e was isolated as yellow crystals (EtOAc - hexane); m.p. 120°C, yield 2.30g (88%). υ_{max} (KBr) : 3460, 3247 (NH), 1678, 1599, 1230 cm^{-1}. δ_H (300 MHz, $CDCl_3$ d (ppm) : 2.40 (s, 3H, SCH_3),

5.92 (s, 1H, vinylic), 6.51 (dd, 1H, H-4′ furyl, J = 4.5 Hz), 6.82 (m, 1H, H-5 pyridyl), 6.88 (d, 1H, J = 9Hz, H-3 pyridyl), 7.10 (d, 1H, J = 4.5 Hz, H-3′ furyl), 7.48 (d, 1H, J = 3Hz, H-5′ furyl), 7.00 (ddd, 1H, J = 16.6 Hz, H-4 pyridyl), 8.30 (dt, 1H, J = 6.9Hz, H-6 pyridyl), 14.80 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{12}N_2O_2S$ (260.1), C 59.99, H 4.6, N 10.76. Found : C 59.8, H 4.70, N 10.71.

3-Methylthio-3-(2-pyridylamino)-1-(2-thienyl)-2-propene-1-one 5f was isolated as light yellow solid (EtOAc-hexane) m.p. 109°C, yield 2.17g (89%). υ_{max} (KBr) : 3386, 3343 (NH), 175, 1591, 1281 cm^{-1}. δ_H (300 MHz, $CDCl_3$) : 2.51 (s, 3H, SCH3), 5.91 (s, 1H, vinylic), 6.98 (m, 1H, H-5 pyridyl), 7.14 (dd, 1H, J = 8Hz, H-4′ thienyl), 7.25 (d, 1H, J = 8.9 Hz, H-3 pyridyl), 7.60 (d, 1H, J = 4.5 Hz, H-3′ thieyl), 7.75 (d, 1H, J = 6.0 Hz, H-5′ thienyl), 7.80 (ddd, 1H, J = 16.5 Hz, H-4 pyridyl), 8.50 (dt, 1H, J = 6.9 Hz, H-6 pyridyl). Anal. Calcd. for $C_{13}H_{12}N_2OS_2$ (276) C 56.52, H 4.3, N 10.4. Found: C 56.50, H 4.2, N 10.21.

2-Methylthio-2-(2-pyridylamino)methylene cyclohexanone 5g was isolated as viscous oil, yield 1.50g (60.4%). υ_{max} (CCl_4): 3460, 3335 (NH), 1661, 1628, 1521 cm^{-1}. δ_H(90 MHz, CCl_4); d ppm : 1.86-2.03 (m, 4H, 2xCH), 2.30 (s, 3H, SCH_3), 3.12-3.24 (m, 4H, 2xCH_2), 7.03 (m, 1H, H-5 pyridyl), 7.42-7.48 (m, 2H, H-3 & H-4 pyridyl), 9.08 (d, 1H, J = 9Hz, H-6 pyridyl), 14.00 (brs, 1H, NH, exchanges D_2O). Anal. Calcd. for $C_{13}H_{16}N_2OS$ (248); C 62.9, H 6.4, N 11.2. Found C 62.7, H 6.1, N 11.5.

2-[Methylthio-(2-pyridylamino)]methylene tetralone 5h was isolated as viscous yellow oil (3h), yield 2.6g (91%). υ_{max} ((CCl_4) : 3382, 1675, 1609, 1586, 1236 cm^{-1}. δ_H (90 MHz, CCl_4): 2.15 (s, 3H, SCH_3), 2.80-2.95 (m, 4H, 2xCH_2), 7.00 (ddd, 1H, J = 16 Hz, H-5 pyridyl), 7.20-7.31 (m, 3H, ArH), 7.40-7.50 (m, 2H, H-3 and H-4 pyridyl), 8.09 (m, 1H, ArH), 8.43 (dd, 1H, 7=8.9 Hz, H-6 pyridyl), 13.1 (brs, 1H, NH,

exchanges D_2O).Anal. Calcd. for $C_{17}H_{16}N_2OS$ (296) C 68.91, H 5.4, N 9.4.Found : C 68.50, H 5.5, N 9.3.

2-[Methylthio-(2-pyridylamino)]methylene-6-methoxy-1-tetralone (5i) was isolated as an oil yield 2.50g (76.6%). υ_{max} (CCl_4) : 3382, 3066, 1634, 1598, 1490, 1270 cm^{-1}. δ_H(90 MHz, CCl_4): 2.67 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 3.90-3.93 (m, 4H, 2xCH_2), 7.20 (ddd, 1H, J=15.6 Hz, H-5 pyridyl), 7.31 (m, 2H, H-3 & H-4 pyridyl), 7.40-7.45 (m, 2H, ArH), 7.89 (s, 1H, ArH), 8.55 (dd, 1H, J = 9Hz, H-6 pyridyl), 13.00 (brs, 1H, NH). Anal. Calcd. for $C_{18}H_{18}N_2O_2S$. C66.25, H 5.5, N 8.5. Found : C 65.5, H 5.9, N 8.40.

1-Methylthio-1-(2-pyridyl amino)-3-oxo-5(4methoxy phenyl)-1,4-pentadiene (5j) was isolated as yellow crystals(chloroform-Hexane), m.p 120°C yield 2.77g (85%) υ_{max} (KBr):3414, 3370, 1606, 1545, 1476 cm^{-1}. δ_H(300MHz, $CDCl_3$): 2.41(s,3H, SCH_3), 3.82 (s,3H,OCH_3) ,5.43(s,1H,H-2vinylic), 6.64 (d,1H,J=15Hz,H-4) ,6.8(d,2H,J=9Hz, ArH 6.92-6.97 (m,H-3, H-4 pyridyl), 7.5 (d, 2H, J=9Hz,ArH), 7.56 (d,1H, J= 15Hz, H-5),7.62(ddd,1H,J= 15.6Hz,H-5 pyridyl),8.32 (dd,1H,J= 9Hz, H-6 pyridyl, 14..7 (s,1H,NH,exchanges D_2O.(75MHz) d: 16.05 (SCH_3),55.26 (OCH_3), 113..84, 114.1 ^{13}CNMR CHAr), 118.13, 125.7, 128.2 (CH,Ar), 129.5,137.9, 139, 146.7, 152.5, 160.8, 165.5,183.84 (C=O).Anal : Calcd for $C_{18}H_{18}N_2O_2S$ (326): C 66.5, H. 5.6, N 8.4. Found: C 66.2,H 5.5,N 8.2.

Generation of 3-lithio-aminopyridine and it's reaction with α-oxoketene dithioacetals: General procedure for the preparation of S,N-acetals (**7a-e**). To a solution of 3-aminopyridine (1.41g, 15 mmol) in dry THF (25 ml) n-butyllithium (15 mmol) was added under nitrogen and inert atmosphere with stirring at room temperature. The reaction mixture was gradually warm upto 45°C and stirred for 30

minutes at the same temperature. Then it was brought to room temperature (25°C) and a solution of S,S-acetal (10 mmol) in dry THF (25 ml) was added. The reaction mixture was further stirred for 5 hours at ambient temperature. It was then quenched with saturated NH_4Cl solution (50 ml) and extracted with chloroform (2x50 ml). The combined extracts were washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give the crude product which were chromatographed on silica gel using ethylacetate-hexane (2:8) as eluent.

3-Methylthio-3-(3-pyridylamino)-1-phenyl-2-propene-1-one (7a) was isolated as low melting solid, yield 2.00g (70%). IR ν max (CCl_4): 3416, 3034, 1693, 1549, 1256 cm^{-1}. ^{1}HNMR (90 MHz, $CDCl_3$) : 2.31 (s, 3H, SCH_3), 5.91 (s, 1H, vinyl), 7.20-7.26 (m, 1H, H-5 pyridyl), 7.29-7.35 (m, 1H, H-4Py) 7.35-7.50 (m, 3H, ArH), 7.91-8.12 (m, 2H, ArH) 8.45 (dd, 1H, J = 9.6Hz, H-6pyridyl), 8.62 (s, 1H, H-2 pyridyl), 14.01 (1H, NH, exchanges D_2O). Found : C 66.69, H 5.15, N 10.38.

3-Methylthio-3-(3-pyridylamino)-1-(4-methoxyphenyl)-2-propene-1-one (7b) isolated as yellow crystal m.p. 95°C, yield 2.10g (70%). υ_{max} (KBr) : 3421, 3055, 1603, 1541, 1246 cm^{-1}. δ_H(90 MHz, $CDCl_3$) : 2.34 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 5.83 (s, 1H, vinylic), 6.84 (d, 2H, J = 9Hz, ArH), 7.19 (dd, 1H, J = 9Hz, H-5 pyridyl), 7.56 (dd, 1H, J = 9Hz, H-4 pyridyl), 7.81 (d, 2H, J = 9Hz, ArH), 8.35 (dd, 1H, J = 8.5Hz, H-6 pyridyl), 8.36 (s, 1H, H-2 pyridyl), 13.44 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{16}N_2OS$ (300.1) C 63.97, H 5.33, N 9.33. Found : C 63.95, H 5.30, N 9.50.

3-Methylthio-3-(3-pyridylamino)-1-(4-methylphenyl)-2-propene-1-one(7c) was isolated as low melting solid, yield 1.95g (68%). υ_{max} (CCl_4): 3385, 3049, 1609, 1544, 1184 cm^{-1}. ^{1}HNMR (90 MHz, $CDCl_3$): 2.35 (s, 3H, SCH_3), 5.81 (s, 1H, vinylic), 7.01 (d, 2H, J = 9Hz, ArH), 7.45-7.50 (dd, 1H, H-5 pyridyl), 7.55 (dd, 1H, H-3 pyridyl), 7.65

(d, 2H, J = 9Hz, ArH), 8.35 (dd, 1H, J = 8Hz, H-6 pyridyl), 8.56 (s, 1H, H-2Py), 14.0 (1H, NH). Anal. Calcd. for $C_{16}H_{16}N_2OS$ (284.1) C 67.60, H 5.61 N 9.81. Found : C 67.50, H 5.7 N 9.75.

1-(3-pyridylamino)-2-carboethoxy-2-cyano-1-methylthiomethylene (7d) was isolated as colourless solid, m.p. 110°C, yield 2.40g (91.2%). υ_{max} (KBr): 3302, 2264, (C=N) 1670, 1621 cm^{-1}. δ_H(90 MHz, $CDCl_3$): 1.30 (t, 3H, CH_2CH_3, J = 7Hz), 2.30 (s, 3H, SCH_3), 4.36 (q, 2H, CH_2CH_3, J = 7 Hz), 7.40 (dd, 1H, J = 9.6 Hz, H-5 pyridyl), 7.75 (d, 1H, J = 8Hz, H-4 pyridyl), 8.65 (m, 2H, s and d overlapped, H-2 & H-6 pyridyl), 12.10 (brs, 1H, NH). Anal. Calcd. for $C_{12}H_{13}N_3O_2S$ (263) C 54.75, H 4.9, N 15.96. Found : C 54.66, H 4.7, N 16.10.

3-Methylthio-3-(3-Pyridylamino)-1-(2-furyl)-2-propen-1-one (7e) was isolated as yellow solid m.p. 105°C, yield 1.65g (62%). υ_{max} (KBr) : 3436, 3104, 1723, 1670, 1017 cm^{-1} .δ_H (90 MHz, $CDCl_3$) : 2.50 (s, 2H, SCH_3), 5.91 (s, 1H, vinylic), 6.60 (dd, 1H, J = 4.5 Hz, H-3' furyl), 7.30 (dd, 1H, J = 5.5 Hz, H"-4' furyl), 7.50 (dd, 1H, $J_{4,5}$ =9Hz, $J_{4,6}$ =1.8Hz, H-4 pyridyl), 7.52 (dd, 1H, $J_{5,4}$ =9Hz,$J_{5,6}$ =6Hz), H-5 pyridyl) 7.70 (d, 1H, J=3Hz, H-5'furyl), 8.40 (dd, 1H, $J_{6,5}$ =6Hz, $J_{6,4}$ =1.8Hz, H- 6pyridyl), 8.60 (s, 1H, H-2 pyridyl). Anal. Calcd. for $C_{13}H_{12}N_3O_2S$ (260.1) C 59.9, H 4.6, N 10.76. Found : C 59.8, H 4.70, N 10.71.

General procedure for the preparation of N,N-acetals (8a-b): To a solution of 2-amino pyridine (1.88g, 20 mmol) in anhydrous THF (25 ml), n-butyllithium (20 mmol) was added under dry and inert atmosphere, over 20 minutes with stirring at room temperature (25°C). After 30 minutes, a solution of oxoketene dithioacetal (10 mmol) in dry THF (25 ml) was added and continued stirring for another 1 hr at the same temperature. Then the reaction mixture was refluxed for 5 hours at 60°C

(monitored by TLC). After cooling to room temperature, the reaction mixture was quenched with saturated NH_4Cl solution (100 ml), extracted with chloroform (2x50 ml) and the combined extracts were washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to give the crude product, which was purified by column chromatography (silica gel) using ethylacetate-hexane (2:8) as eluent.

3,3-Bis(2-pyridyl amino)-1-(phenyl)-2-propen-1-one (8a) was isolated as yellow crystals (EtoAc-hexane), yield 2.50g (79%) m.p.125°C υ_{max}(KBr) : 3427, 1653, 1611, 1592, 1545 cm^{-1}.δ_{H} (90 MHz, $CDCl_3$): 6.95-7.35 (m, 5H, olefinic, ArH, & H-5 pyridyl), 7.50 (m, 2H, H-3, pyridyl), 7.65-8.10 (m, 5H, ArH, 2xH-4, H-5) 8.40 (d, 1H, J = 6.9Hz, H-6 pyridyl), 8.60 (d, 1H, J = 6.9Hz, H-6 pyridyl), 13.30 (brs, 1H, NH), 14.63 (brs, 1H, NH). Anal. Calcd. for $C_{19}H_{16}N_4O$ (316), C 72.15, H 5.06, N 17.72. Found : C 72.25, H 5.09, N 17.61.

3,3-Bis(2-pyridylamino)-1-(4-methoxyphenyl)-2-propen-1-one (8b) was isolated as yellow coloured solid, yield 2.80g (80.9%), m.p.130°C υ_{max} (KBr): 3401, 1659, 1608, 1589, 1532 cm^{-1}. δ_{H}($CDCl_3$): 3.80 (s, 3H, OCH_3), 6.90-7.30 (m, 5H, olefinic, ArH, 2xH-5 pyridyl), 7.60 (m, 4H, 2xH-3 & 2xH-4 pyridyl), 8.00 (d, 2H, J = 9Hz, ArH), 8.25 (d, 1H, J = 9Hz, H-6 pyridyl), 8.55 (d, 1H, J = 6.9 Hz, H-6 pyridyl), 13.20 (brs, 1H, NH), 14.80 (brs, 1H, NH). Anal. Calcd. for $C_{20}H_{18}N_4O_2$ (346) C 69.36, H 5.20, N 16.18. Found : C 69.40, H 5.12, N 16.21.

General procedure for the preparation of O,N-acetals (10 a-b)

Method A: (N,S-acetal as precursor): To a cooled and stirred solution of sodium alkoxides (prepared by dissolving sodium, 0.01 mol, in 20 ml of respective alcohol) in the respective alcohol (10 ml), the ketone S,N-acetal (0.01 mol) was added and stirred for 10-15 minutes. The reaction mixture was refluxed for 8-10 hours

(monitored by TLC). The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform (2x50 ml), washed (H_2O), dried (Na_2SO_4) and distilled off to give the crude O,N-acetals which were purified either by crystallization or chromatography on silica gel using EtOAc-hexane (1:2) as eluent.

Method B: (O,S-acetal as precursor): To a solution of 2-aminopyridine (0.94g, 10 mmol) in anhydrous THF (20 ml), n-butyllithium (15 mmol) was added under dry and inert atmosphere at ambient temperature. After stirring for 30 minutes, a solution of a-oxoketene O,S-acetal (prepared by reported procedure) in dry THF (25 ml) was added and stirred for another 1 hour at the same temperature. The reaction mixture was quenched with sat. NH_4Cl solution (100 ml), extracted with chloroform (2x50 ml) and the combined extracts were washed with water (100 ml), dried (Na_2SO_4) and evaporated to give the crude O,N-acetals, which were purified by column chromatography.

3-Methoxy-3-(2-pyridylamino)-1-phenyl-2-propene-1-one (10a) was isolated as light yellow crystals (chloroform-hexane), yield 1.56g (61.4%), m.p. 130°c υ_{max}(KBr) : 3918, 3258, 1627, 1599, 1339 cm^{-1}. δ_H(90 MHz, $CDCl_3$) : 3.63 (s, 3H, OCH_3), 5.30 (s, 1H, vinylic), 6.70 (ddd, J = 15.4 Hz, H-5 pyridyl), 7.10-7.50 (m, 4H, 3-arH & H-3), 7.80-8.15 (m, 3H, 2 ArH), H-4), 8.35 (td, 1H, J = 8.0 Hz, H-6), 14.0 (brs, 1H, NH, exchanges D_2O). Anal. Calcd. for $C_{15}H_{14}N_2O_2$ (254) C 70.86, H 5.51, N 11.02. Found : C 70.65, H 5.60, N 11.20.

3-Methoxy-3-(2-pyridylamino)-1-(4-chlorophenyl)-2-propene-1-one (10b) was isolated as light yellow crystals ($CHCl_3$ -hexane), m.p. 137°c yield 1.80g (62%).υ_{max} (KBr) : 3417, 1617, 1589, 1213 cm^{-1}. δ_H(90 MHz, $CDCl_3$) : 3.90 (s, 3H, OCH_3), 5.60 (s,

1H, vinylic) 6.90 (ddd, 1H, $J_{5,6}$ $J_{4,5}$ = 15Hz, H-5), 7.40 (d, 2H, J = 9Hz, ArH), 7.50-7.75 (m, 2H, H-3 & H-4), 7.95 (d, 2H, J = 9Hz, ArH), 8.35 (dd, J = 6.9Hz, H-6 $J_{5,6}$+$J_{4,6}$ pyridyl). Anal. Cacld. for $C_{15}H_{13}N_2O_2Cl$ (288.5), C 62.39, H 4.50, N 9.70. Found : C 62.45, H 4.42, N 9.69.

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CHAPTER-III

A. *A NEW VERSATILE AND EFFICIENT METHOD FOR THE SYNTHESIS OF PYRIDO [1,2-a] PYRIMIDINES VIA α-OXOKETENE S,N-ACETALS.*

B. *COPPER (1) ASSISTED INTRAMOLECULAR RING CLOSURE: A NEW GENERAL METHOD FOR IMIDAZO [1,2-a] PYRIDINES.*

III.A.I. INTRODUCTION

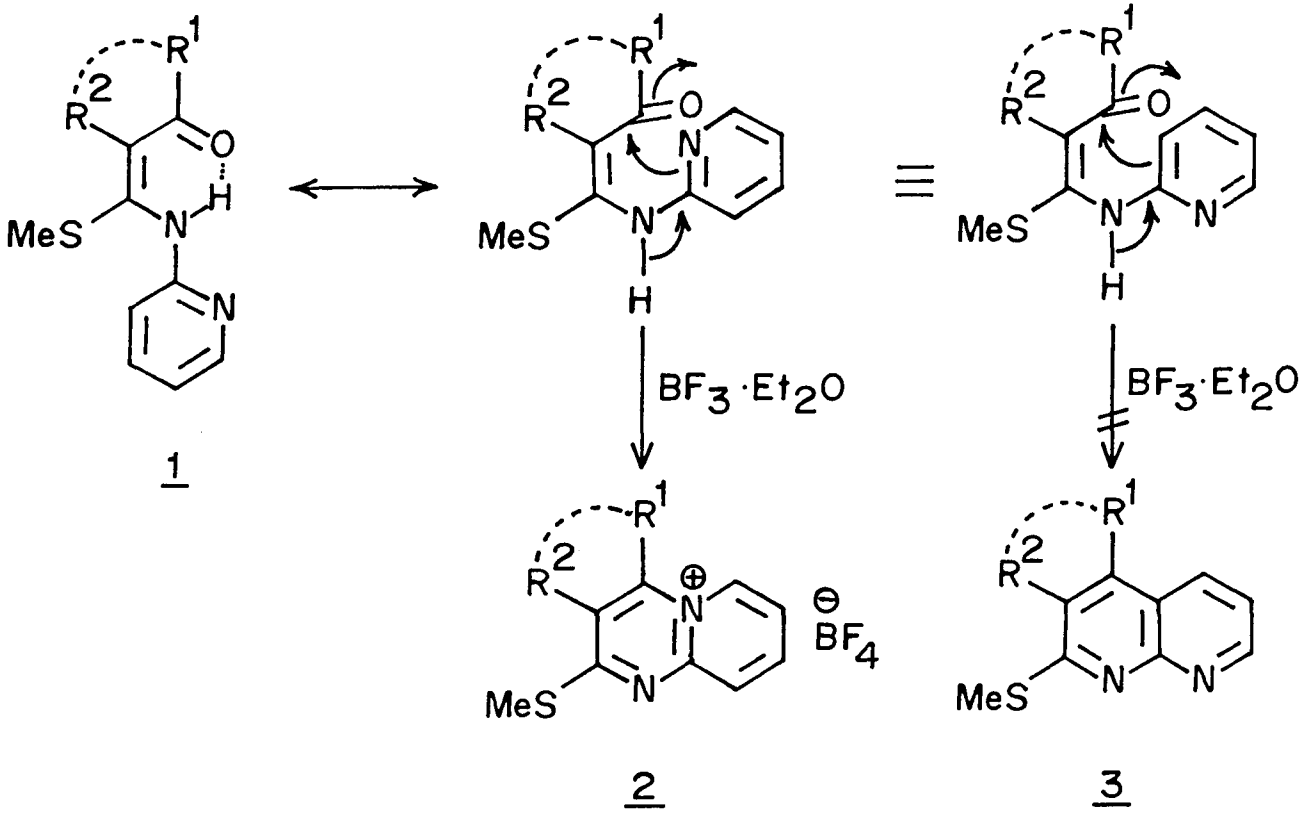
In the preceding chapter an efficient method for theconversion of α-oxoketene dithioacetals to the corresponding S,N,-acetals in high yields was described. The amines were reacted in the presence of n-butyl lithium so that the lithio amino anions were the reacting species in these reactions. Reaction conditions were extremely mild with overall improved yield of the S,N-acetals. The method was applicable to 2-amino pyridines also to yield the corresponding S,N-acetals. The S,N-acetals derived from 2-amino pyridine are of interest since it forms an excellent precursor to undergo further

cyclization under suitable conditions to yield the corresponding bicyclic heterocycles. 2-amino-pyridine behaves as a cyclic amidine functionality and on electrochemical grounds alone, its converion into a 1,8-naphthyridine appears highly improbable[1]. Thus the normal mode of ring closure involved the ring nitrogen of the imino form of the amino-pyridine leading to the formation of pyrido [1,2-a] pyrimidinium compounds. (Scheme -1). Present chapter discribes this new method for the synthesis of pyrido [1,2-a] pyrmidines and its condensed analogues.

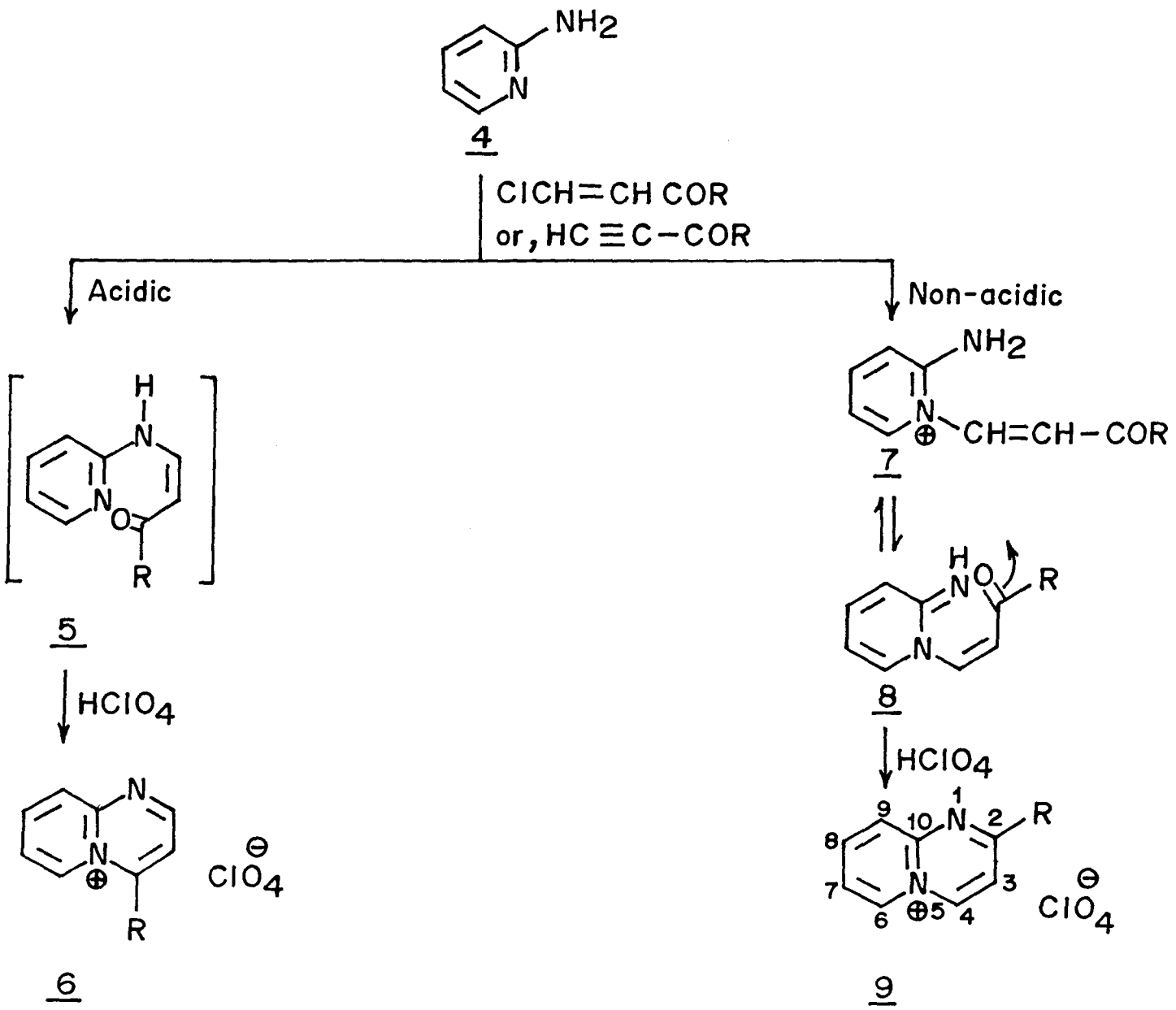
Much work has been done in the recent past and the chemistry of these compounds has been reviewed[2-3]. A number of methods have been reported for the synthesis of pyrido [1,2-a] pyrimidine 2-and 4-ones by the methods concerning pyrido [1,2-a] pyrimidinium salts not bearing an oxo or an imino-substituent have been few in number. Most methods revolved around the condensation of 2-amino pyridines with 1,3-dielectrophilic carbon fragments.

Fischer prepared[4] the unsubstituted pyrido [1,2-a] pyrimidine perchlorate salt (3, R=H) but its 2 & 4-substituted derivatives by reacting 2-aminopyridines with proparagyldehyde and with β-chloro-vinyl ketones. (Scheme-2). In non-acidic medium (acetone-methanol mixture) the pyridinium salt **7** was formed which was cyclized by $HClO_4$ to the 2-subsitituted pyrido [1,2-a] pyrimidinium salt **9** via **8**. In acidic medium, however the 4-substituted pyrido [1,2-a] pyrimidinium salt **6** was formed via the enamine intermeidiate **5**. Similarly, when 2-amino pyridine was reacted with aroyl acetylenes the reaction was found to follow the same route involving initial Micheal addition followed by cyclization (Scheme-2).

Among the variants of 1,3-diketones, ketoaldehyde acetals **10** reacted with 2-amino pyridine **4** to yield 4-substituted pyrido [1,2-a] pyrimidines **12**[5]. The initial reaction of **4**



Scheme – 1


NH2
N
4
ClCH=CH COR
or, HC≡C–COR
Acidic
Non-acidic
H
N
O
R
5
HClO4
N
⊕
ClO4
6
NH2
CH=CH–COR
7
8
9
10
1
2
3
4
5
6
7
8

Scheme-2

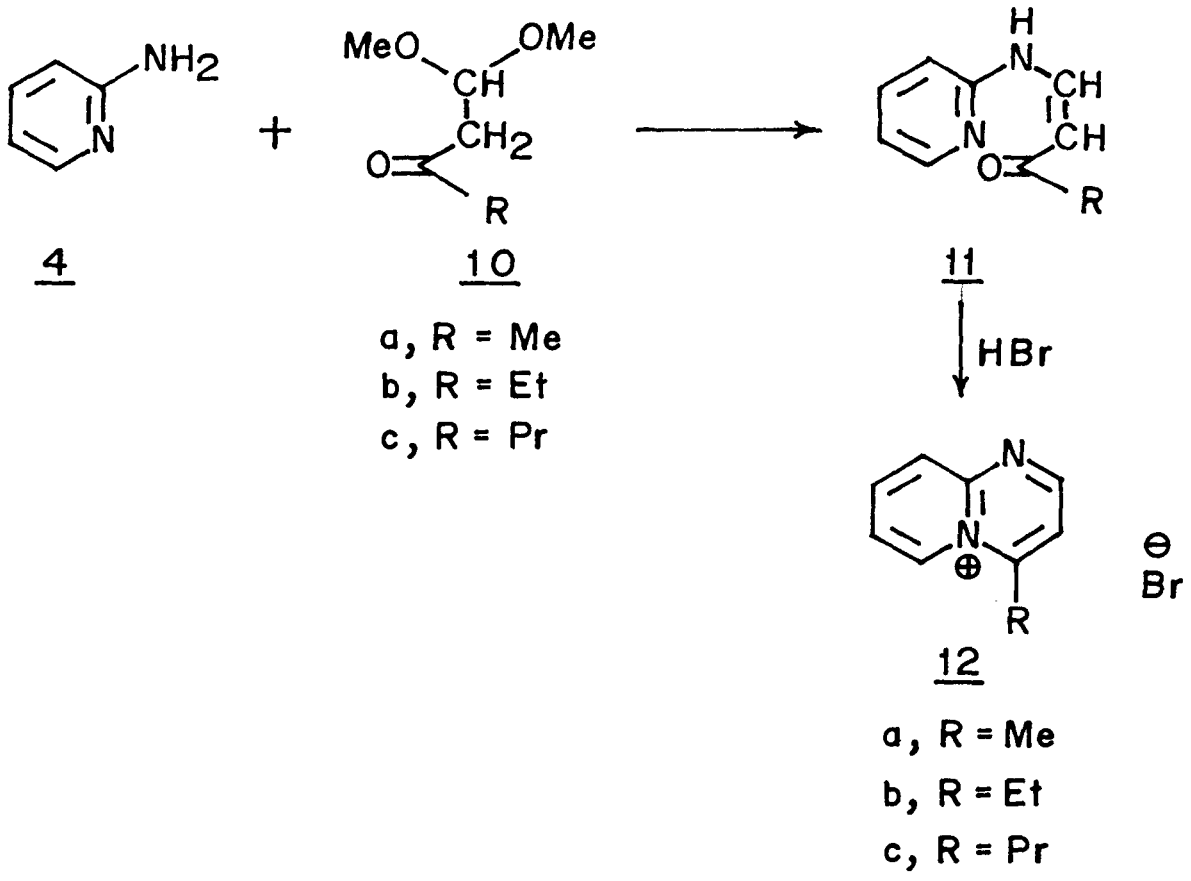
with **10** appears to go theough intermediate **11** exchusively which on treatment with HBr cyclised to pyrido [1,2-a] pyrimidinium salt **12** were formed (Scheme-3).

The 1,3-diketones were also reacted with 2-aminopyridine **4** in perchloric acid to yield the corresponding **14** (Scheme-4)[6]. The work was reinvestigation of the earlier erroneous results that the reaction between 2-amino pyridines and 1,3-diketones to yield the corresponding 1,8-napthyridines **14a**. The products obtained by these authors were not naphythyridines but the corresponding pyrides [1,2-a] pyrimidinium salts **14**.

III.A.2. RESULTS AND DISCUSSION

The methods employed for the synthesis of pyrido [1,2-a] pyrmidines have drawn the precursors generally from the 1,3-dielectrophilic fragments. It must be noted that α-oxoketene S,S-acetals and the corresponding S,N.-acetals provide a more versitile structural variation that the precusrsors described in the preceding paragraphs. The facile displacement of methylthio groups of S,S-acetals by 2-amino pyridines is already described in chapter II and these intermediates were subjected to acid assisted cyclization to yield regioselectively substituted pyrido [1,2-a] pyrimidinium salts and the results are presented as follows.

When the S,N-acetals **1a** was treated with BF_3Et_2O in refluxing benzene, after workup the product was characterised as 2-methylthio-4-phenyl [1,2-a] pyrimidin-5-ium tetrafloroborate **15a** in 82% yield as colourless needles with m.p. 155°C (AcOH). The structure of **15a** was established on the basis of its analytical and spectral data. It was analysed for $C_{15}H_{13}N_2SBF_4$ and molecular weight 340.14. It showed in its mass spectrum peaks at m/Z 253 (M^+-BF, 2.0%), 238 (M^+-102, 7.6%). The compound displayed strong absorptions in its IR (KBr) spectrum as γ_{max} 3330, 1619 (C=N), 1147,



4

10

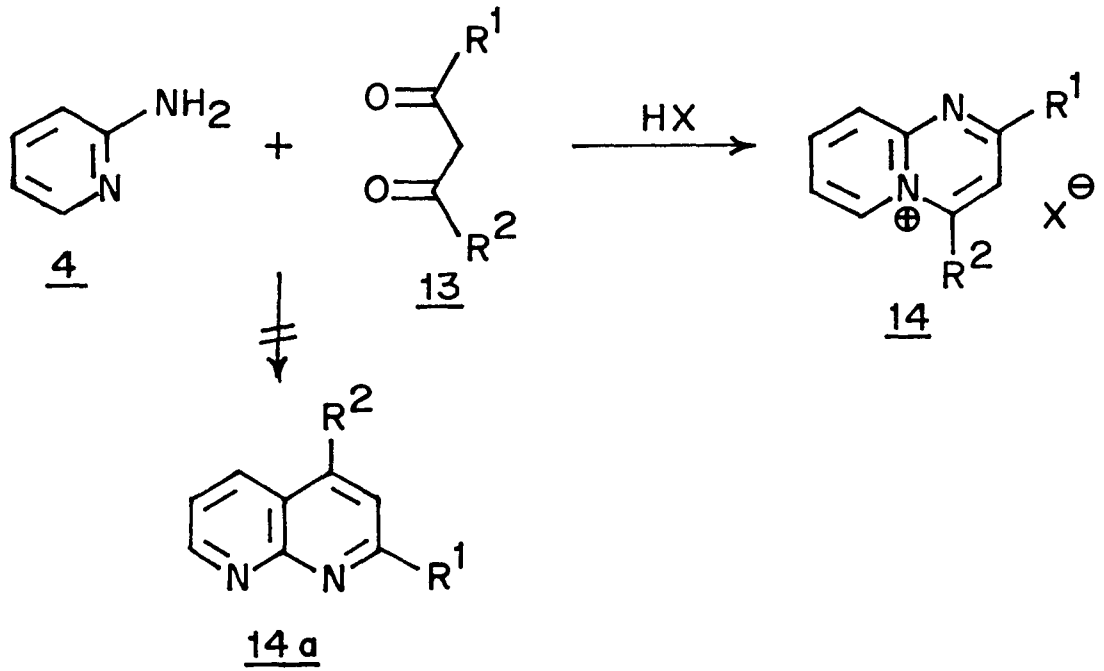
a, R = Me
b, R = Et
c, R = Pr

11

12

a, R = Me
b, R = Et
c, R = Pr

Scheme – 3



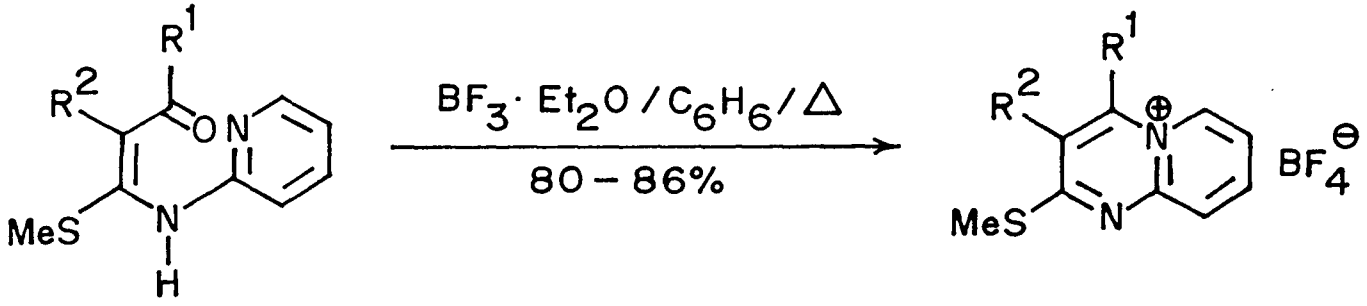
Scheme-4

1093, 1039 (BF_4)cm^{-1}. Tetrafloroborate showed a very strong absorption at 1039 cm^{-1}. The ^{1}HNMR (DMSO-d_6) of **15a** exhibited a singlet at δppm 2.90 (3H) which was assigned to the SMe groups protons. The multiplet between δ-7.77-7.89 for 5 protons was assigned to substituted pheynyl protons. The pyrido [1,2-a] pyrimidine ring protons showed the following pattern: 7.91 (ddd,1H,$J_{6,7}$= 6.5, $J_{7,8}$= 7.5, 6.7, 7.8, $J_{7,9}$ = 1.0 Hz, H=7), 8.20 (s,1H, H,-3), 8.22 (d,1H,J = 9Hz, H-9), 8.60 (ddd, $J_{7,8}$=7.5, $J_{8,9}$=8.0, $J_{6,8}$= 1, 5Hz, 1H, H-8), 8.75 (dd, 1H, $J_{6,7}$=6.5, $J_{6,8}$=1.5Hz, H-6). The four protons of pyrido [1,2-a] pyrimidines H-4, H-5, H-7 and H-8 clearly showed the ABMX system and their coupling constants are calculated from the first order analysis. The structure was further confirmed by ^{13}CNMR spectrum with the chemical shifts: δ-13.64 (SCH_3), 119.20,122.1, 126.9 (= CH, C-3, C-7, C-9);, 128.3, 129, 130, 132.21 (C-1 ,C-2 , C-3 and C-4 of of phenyl), 132.5, 142.5, (C-8, C-6), 148.9, 149.1, 174.15 (C-2, C-4 and C-10).See fig. 1 for ^{1}HNMR & Fig. 2 for ^{13}CNMR.

Similarly, the S,N-acetals **1b-f** yielded the corresponding 2-methyl thio-4 substituted pyrido [1,2-a] pyrimidinium tetrafluoroborate salts in 80-86% overall yields (Scheme 5). The spectral and analytical data for all these compounds were found to agree with the assigned structures which are given in the experimental section.

The S,N-acetals derived from cyclohexanone mercaptal and tetralone mercaptal yielded pyrido fused quinazolinium tetrafloroboratre salts when treated with boron triflouride etherate under the same reaction condtion.

Thus, S,N-acetal **1g** and **1h** yielded the corresponding annelated products 5-methylthio 1,2,3, 4-tetralydropyrido [1,2-a] quinazolin 11-ium (**16**) and 7-methylthio, 5,6-dilydro benzo [b] pyrido [1,2-a] quinazolin 13-ium (**17**) tetrafloroborate salts in 76% and 86% yield respectively (Scheme-6).



1a-f

15a-f

1,15, a $R^1 = C_6H_5$; $R^2 = H$ (82%)

b $R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$ (82%)

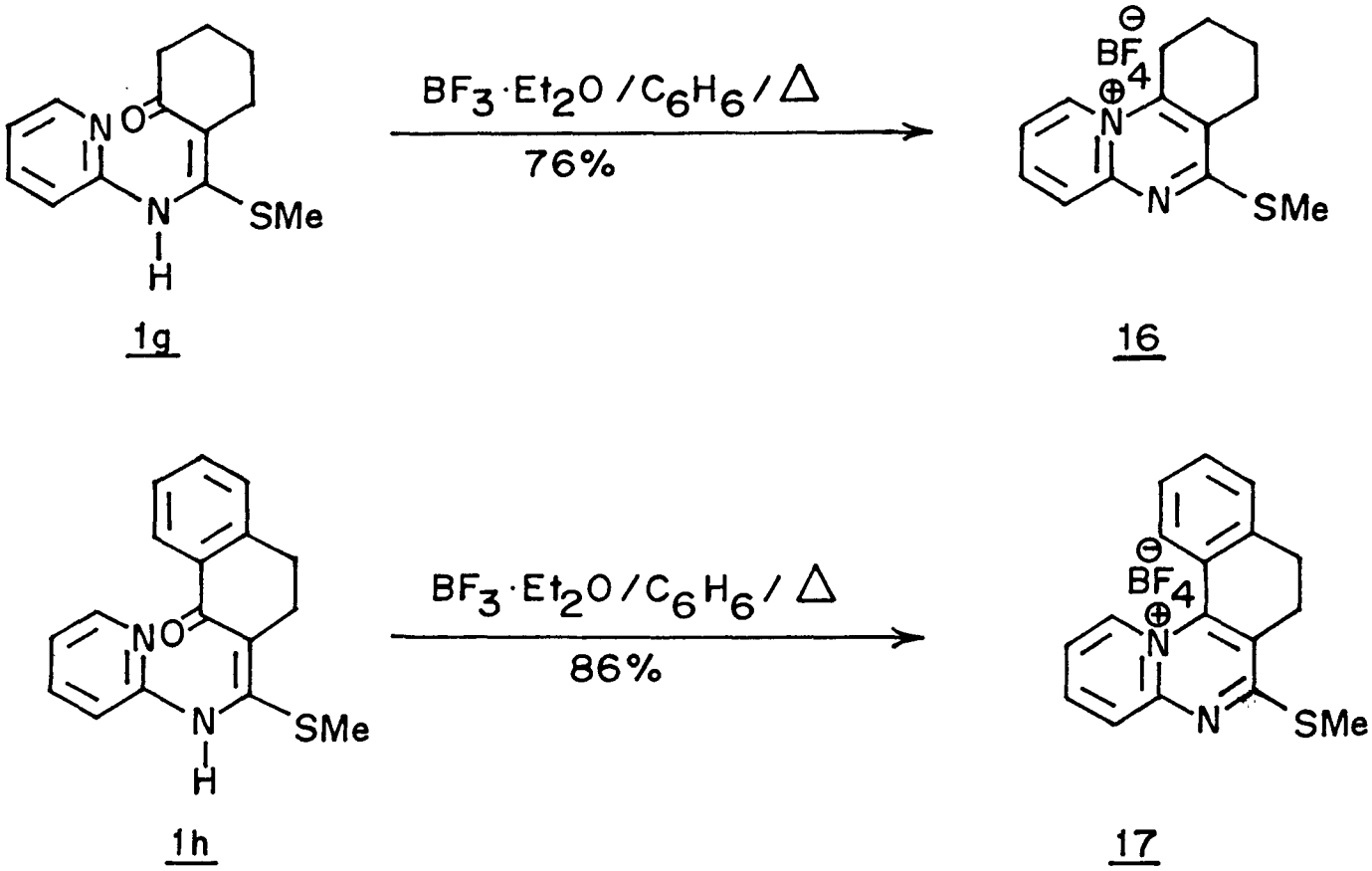
c $R^1 = 4\text{-}ClC_6H_4$; $R^2 = H$ (84%)

d $R^1 = 4\text{-}MeC_6H_4$; $R^2 = H$ (80%)

e $R^1 = 2\text{-furyl}$; $R^2 = H$ (86%)

f $R^1 = 2\text{-thienyl}$; $R^2 = H$ (80%)

Scheme-5

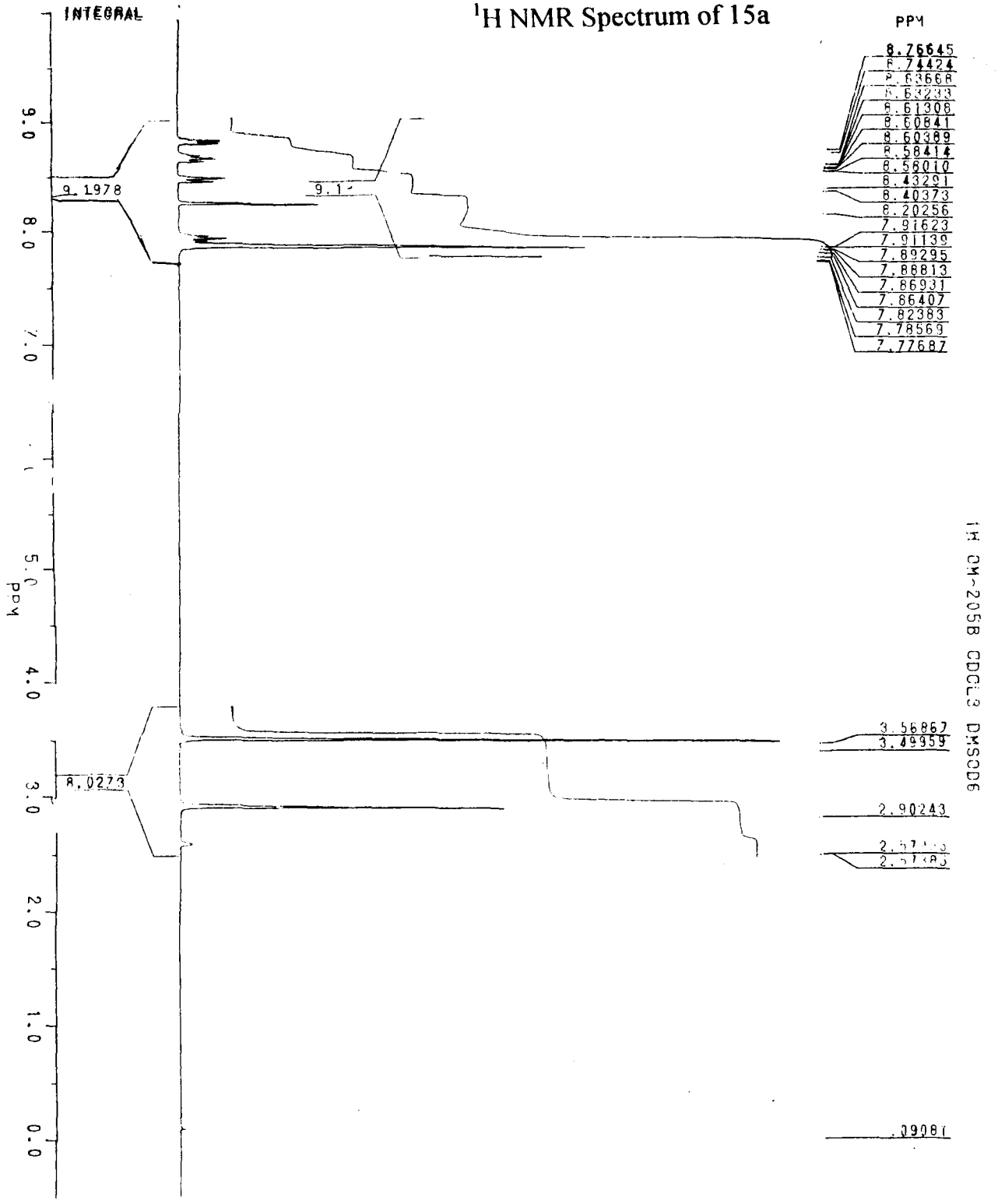


1g 16

1h 17

Scheme-6

^{1}H NMR Spectrum of 15a



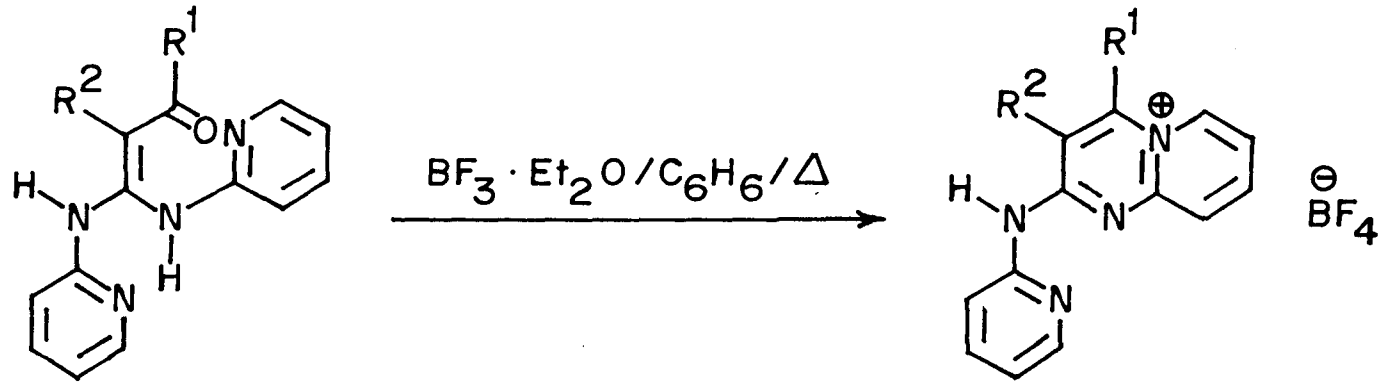
10/5-/94

^{13}C NMR Spectrum of 15a

The N,N-acetals **18a** and **18b** also yielded the corresponding pyrido [1,2-a] pyrimidinium tetraflorobarate salts in 72% and 86% respectively under the described reaction conditions (Scheme-7). The analytical and spectral data in support of these compounds are described in the experimental section.

III.A.3. CONCLUSION

It is demonstrated that the S,N-acetals derived from the 2-amino pyrdines proved to be excellent precursors for pyrido [1,2-a] pyrimidines and their condensed analognes. 2-amino pyridine behaves as a cyclic amidine in these reactions, and ring cosure involved the ring nitrogen of the imino form of the amino pyridine leading to the formation of bicyclic pyrido [1,2-a] pyrimidine compounds have been listed[7] as biologically important compounds particularly in the area of anti-parasitic, hypoglycemic and antihypertensive activities. Certain pyrido [1,2-a] pyrimidinium salts have been patented[8] as dyes and additives to photographic materials. Therefore the present method should prove to be useful in making large structural variants of these compounds.



18 a-b

19 a-b

		Yield
18,19, a.	$R^1 = C_6H_5$; $R^2 = H$	72%
b.	$R^1 = 4\text{-}MeOC_6H_4$; $R^2 = H$	86%

Scheme-7

CHAPTER-III B

B. COPPER (1) ASSISTED INTRAMOLECULAR RING CLOSURE : A NEW GENERAL METHOD FOR NOVEL IMIDAZO [1,2-a] PYRIDINES.

III.B.1. When the S,N-acetals derived from 2-aminopyridines were treated with Cu(1) Cl the acetals were transformemd into functionalised imidazo [1,2-a] pyridines in excellent yields. This is the first report for the synthesis of imidazo [1,2-a] pyridines by using S,N-acetals derived from 2-amino pyridines involving copper (I) halide as promoter for the imidazo ring closure. This reaction seems unusual and the role of copper (I) halide is not clearly understood. Before the actual results of these investigations are presented a brief literature on recent development of these class of compunds is presented.

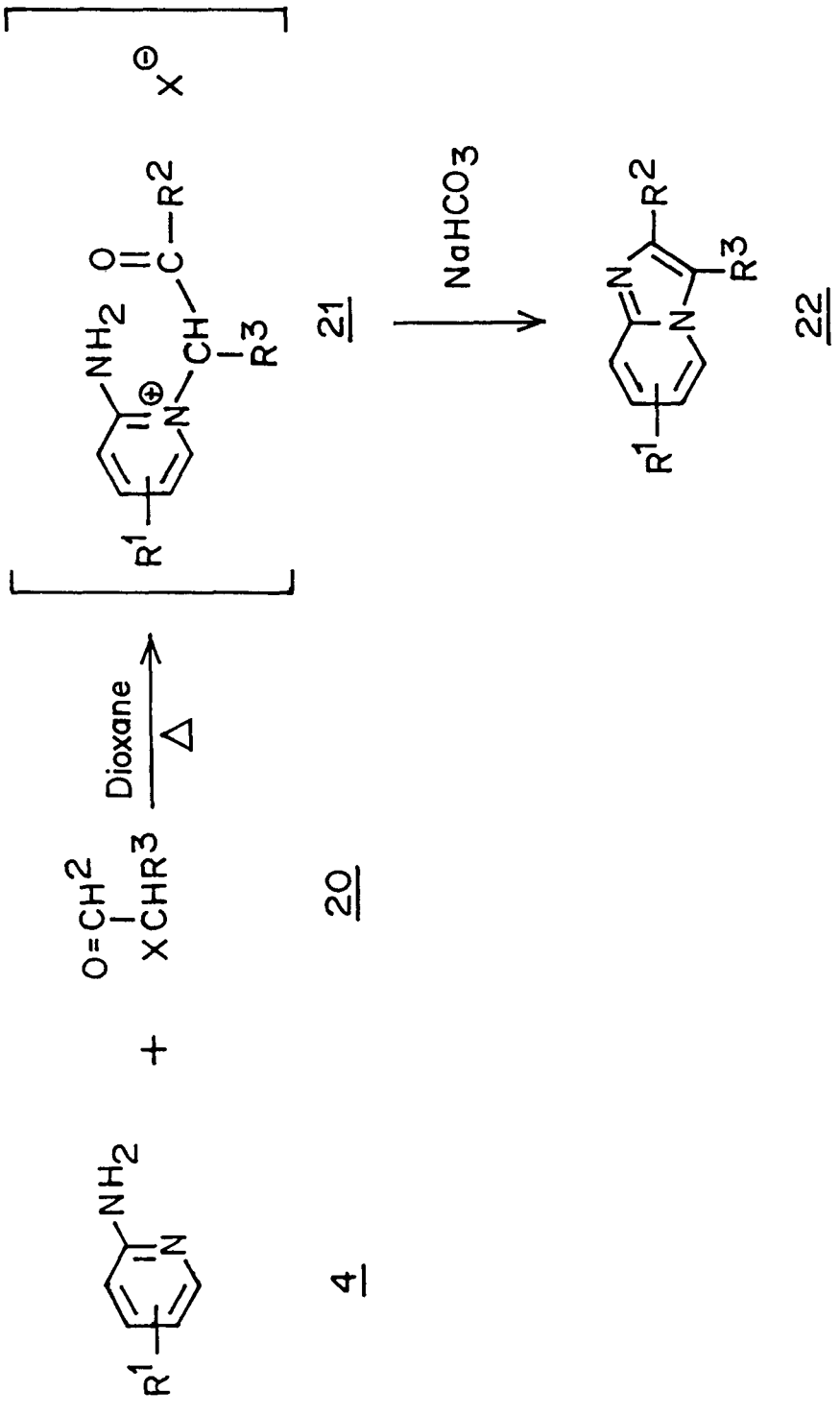
Imidazo [1,2-a] pyridine **22** contains both (excessive imidazole and the π-deficient pyridine rings. (Scheme-1). In fact these compounds exhibit the properties of ten π-electron nitrogen heterocycles and attracted much recent interest because of their broad range of pharma cological activities[9,10].

The majority of imidazo [1,2-a] pyridines **22** have been prepared by the reaction of a 2-amino pyridine **4** with a α-halocarbonyl compound **20** according to the. Tschitschibabin method[11] (Scheme-8).

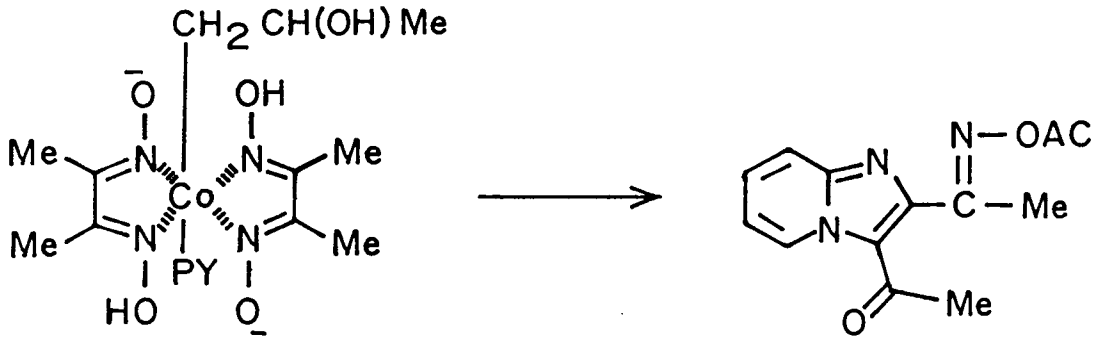
Apparently, the methodology described in the literature largely confined to several variation of the imidazole ring closure as shown in Scheme-8. But recently some publications for the synthesis of imidazo [1,2-a] pyridines involving pyridine ring construction have appeared.

An interesting degradation reaction of cobalto oximes was observed[12] to yield the corresponding imidazo [1,2,-a] pyridines in good yields.Thus alkylcobaloximes **23** with acetic anhydride in pyridine afford an imidazo [1,2-a] pyridine. The mechanism involving in the decomposition and generality of the method is discussed in the report[12] (Scheme-9).

Recently, Knolker *et al.* developed[13] a simple one step procedure furnishing regioslectively functionalized imidazo [1,2-a] pyridines **27** by a novel condensation reaction of 1-phenyl acetyl imidazole **25** with acetylenic dicarboxylic esters **26** (Scheme-10). The mechanism governing these transformations has been discussed by the authors[13].



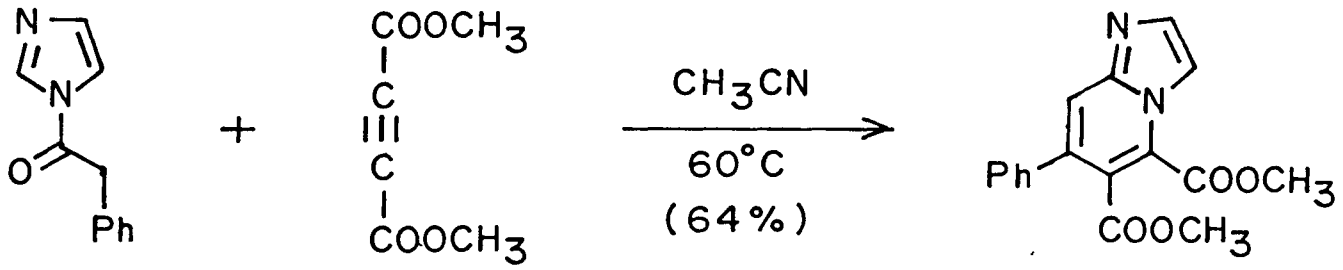
Scheme – 8



23 24

PY = 

Scheme – 9



25 26 27

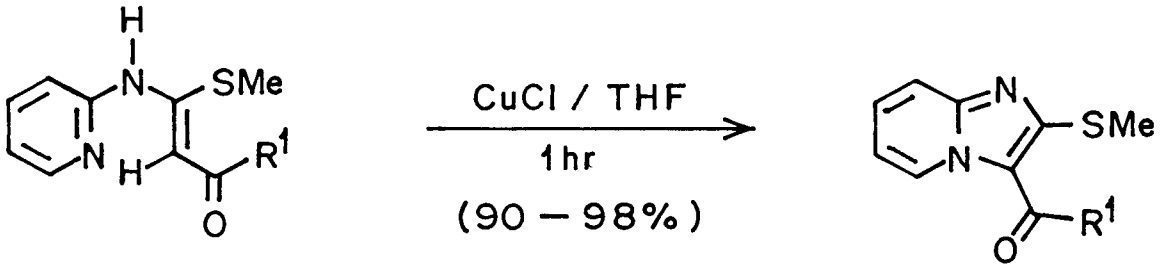
Scheme—10

III. B.2. RESULT AND DISCUSSION

The observation made in the present investigation that the S,N-acetals of the general formula **1** behave totally different in the presence of Cu(I)Cl to yield the corresponding imidazo, [1,2-a] pyridine in very high yields. Thus, when S,N-acetal **1a** was refluxed with Copper (I) chloride in dry THF for 1h, after work-up, the the corresponding 2-methylthio-3-benzoyl imidazo [1,2-a] pyridine **28a** was obtained in 93% yield as colourless needles with a sharp m.p. 140°C. It was analysed for the molecular formula $C_{15}H_{12}N_2OS$ and molecular weight of 268.1. It was confirmed by the mass spectrum with a molecular ion peaks at m/Z 268 (M^+, 25 3%), 267 (M^+-1, 100%). The presence of strong absorptions at γmax 1627 cm^{-1} and γmax 1590 cm^{-1} in the IR spectrum indicates the presence of benzoyl carbonyl function and C=N of the imidazo [1,2-a] pyridine ring respectively. ^{1}HNMR ($CDCl_3$) of **28a** exhibited a singlet at δppm 2.53 (3H) which was assigned to the 3 protons of SMe group. The five aromatic protons of the benzoyl group showed multiplets at 7.47-7.51 (m. 3H) and 7.53-7.60 (m,2H). The remaining protons of the imidazo [1,2a] pyridine ring displayed the following pattern. 6.99 (ddd,1H, $J_{5,6}$ = 6.6 Hz, $J_{6,7}$=6.9 Hz. $J_{5,7}$=0.9Hz, H-6), 7.45 (ddd, 1H, $J_{6,7}$= 9Hz, $J_{5,7}$= 0.9 Hz, $J_{7,8}$= 9Hz, H-7), 7.65 (dt, 1H, J=9Hz, J= 0.9Hz, H-8),and 9.52 (dt,1H, J=6.6Hz,J=0.9Hz,H-5) ABXY system.

The structure was further confirmed by the ^{13}CNMR which displayed the following pattern, 14.8 (SCH_3),114, 115.7, 120 (C-6, C-7, C-3),28.1, 128.54, 128.59 (C-2'2,1C-3'2, 1C-4' of Ar), 129.56, 131.5, (C-8, C-5), 139.8 (C-1' of Ar). 148.01, 153.97 (C-9 & C-2), 185.48 (C=0).

Similarly, the S,N-acetals **1b-f** yielded the corresponding 2,3 disubstituted imidazo [1,2-a] pyridines in 90-98% overall yields. (Scheme-11). The O,N-acetals **29** (preparation was



1a–f

28 a–f

1, 28, a, $R^1 = C_6H_5$

b, $R^1 = 4\text{-MeO}C_6H_4$

c, $R^1 = 4\text{-cl}\,C_6H_4$

d, $R^1 = 4\text{-Me}\,C_6H_4$

e, $R^1 = 2\text{-furyl}$

f, $R^1 = 2\text{-thienyl}$

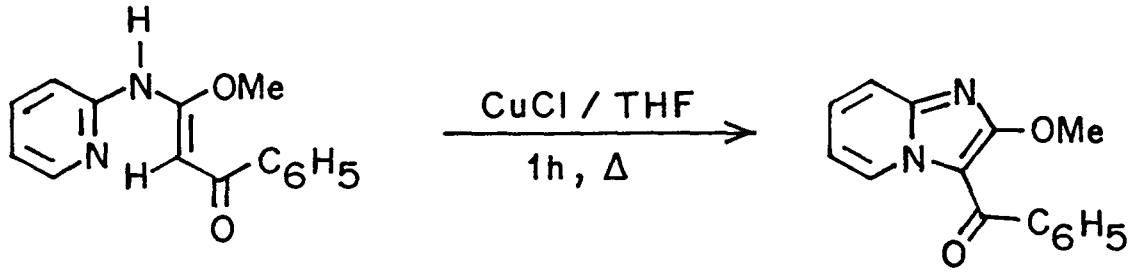
Scheme – 11

shown in chapter 11-B) also underwent the observed transformation under the described condition to yield the imidazo [1,2-a] pyridine **30** in 90% yield. (Scheme-12). The analytical and spectral data for, all these compounds are fully in conformity with the assigned structures which are explained in the experimental section.

Further, the dethiomethylation results of these compounds was also observed. The 3-Benzoyl-2-Methythio Imidazo [1,2-a] pyridine **28** a was selected as a typical example for Raney Nickel assisted desulphurization when the corresponding sulphur free 3-benzoyl imidazo [1,2-a] pyridine **31** was oobtained in 81% (Scheme 13) yield. The analytical and spectral data of **31** was in conformity with the assigned structure. (See experimental section).

III.B.3. MECHANISM

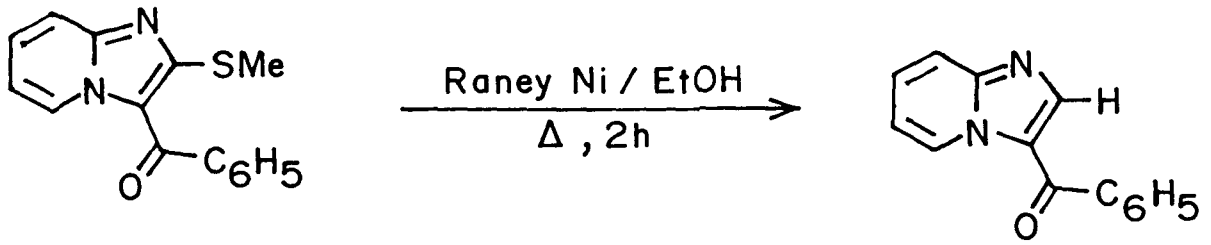
The exact mechanism governing these instructing transformation is not clearly understood. Undoubtedly, Copper(I) is playing the crucial role in the new C-N bond forming reaction. Cu(I)Cl is well known for using as promoter in many C-C bond forming and intramolecular cyclization reactions. These reactions are believed to proceed via generation of free radical. Sandmeyer reaction[14] on dediazonization of arene diazonium salts, Meerwein arylation[15] to yield substituted indoles, Kochis demonstrations[16] on addition of arene diazonium compounds to yield variety of olefines etc are all involved Cu(I)Cl as radical promoter and the mechanisms are proposed via radical process. Many recent reports on the generation of iminyl radicals and its role in intramolecular cyclization reactions to yield nitrogen heterocycles are also available in the literature. Therefore,a probable mechanism is depicted in Scheme-14 involving a diractical intermediate **1c** via **1a** and **1b** which eventually will couple to yield the product imidazo [1,2-a] pyridine **28a-f** and **30**. The mechanism is however



29 30

(90%)

Scheme – 12



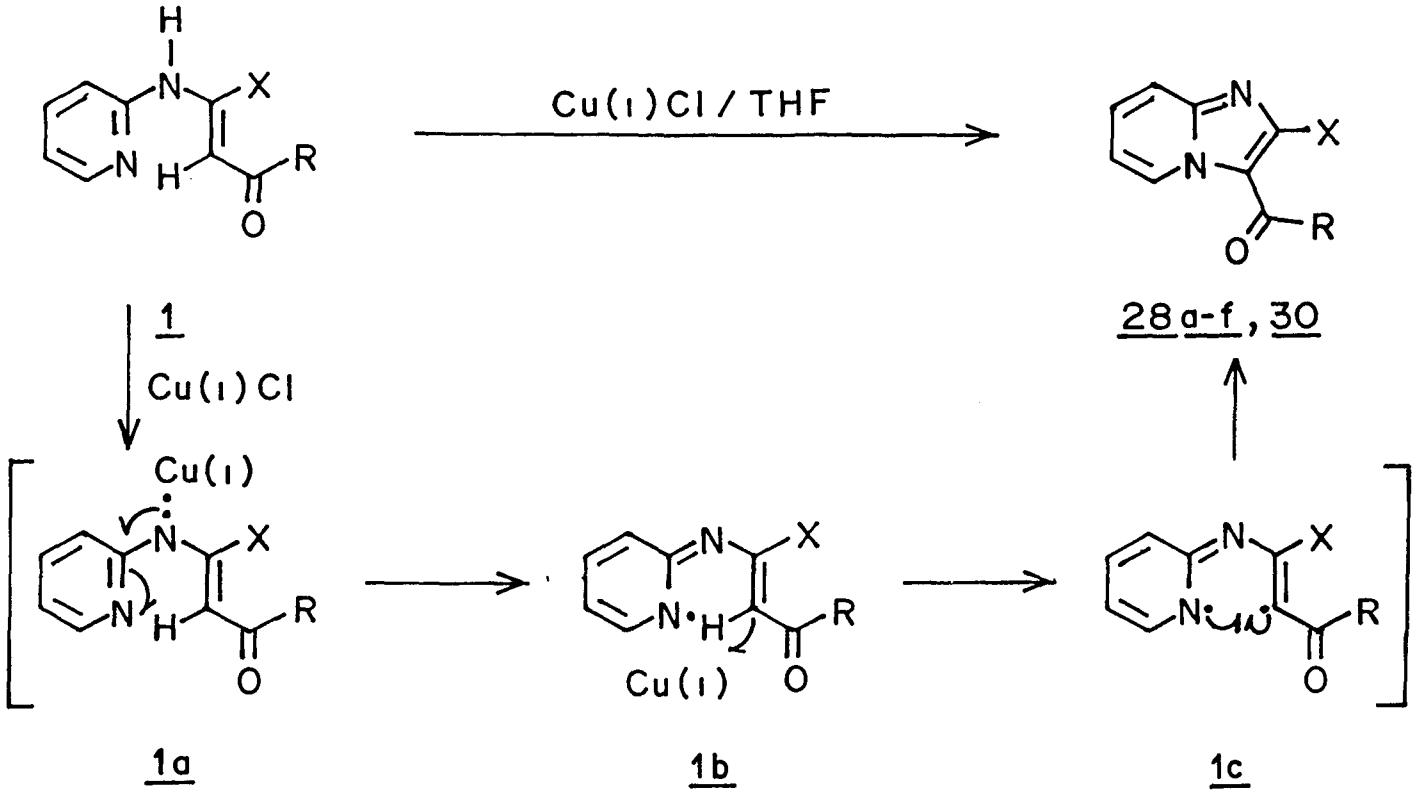
28a

31

Scheme – 13

tentative and requires further studies to fully establish the true pathway associated with these transformation.

In conclusion, a new general method for the synthesis of imidazo [1,2-a] pyridines is developed. The starting precursors for this methodology are readily available as described and undergo desired transformations under very mild reaction conditions.

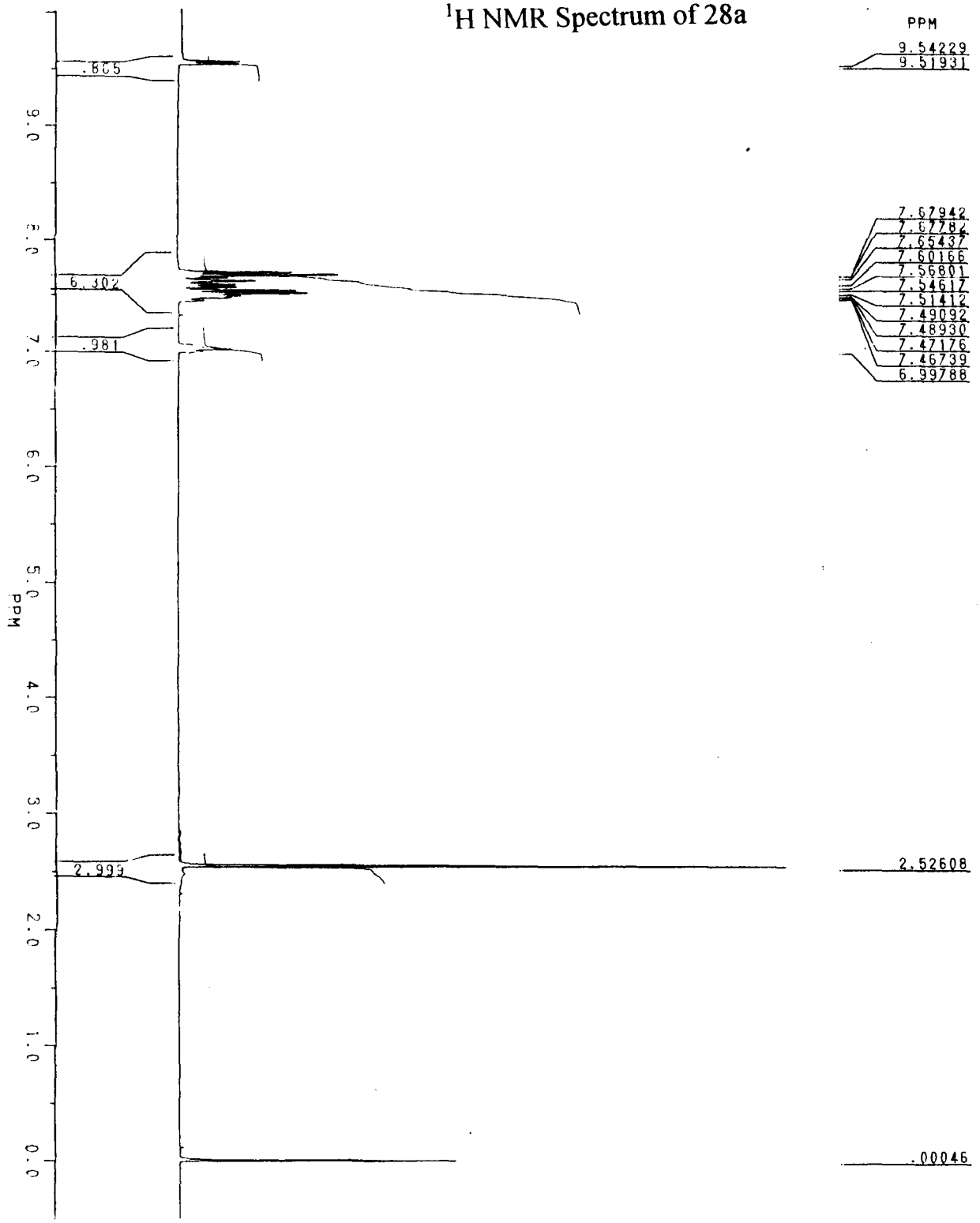


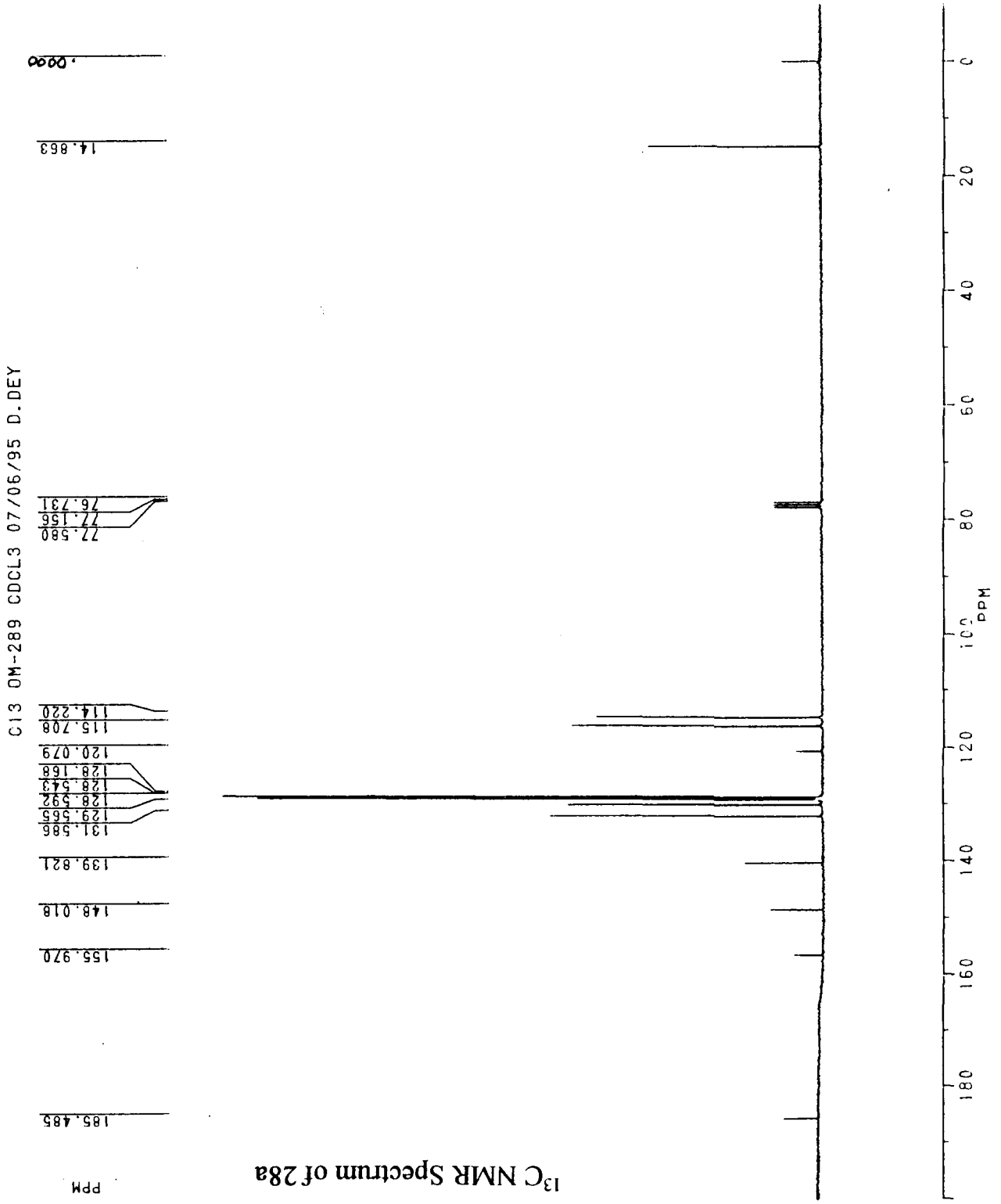
1, 28a–f, X = SMe

1, 30, X = OMe

Scheme – 14

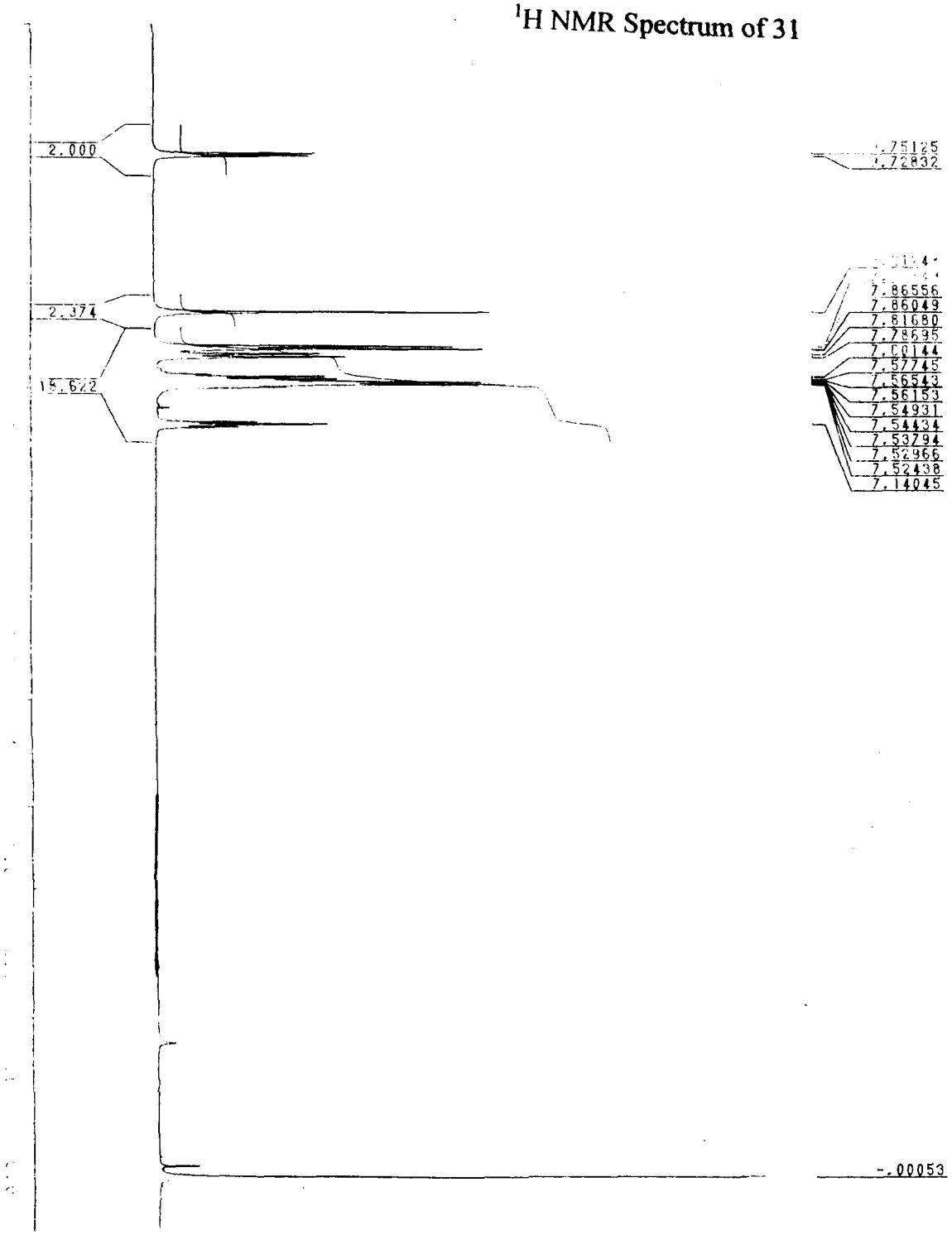
^{1}H NMR Spectrum of 28a



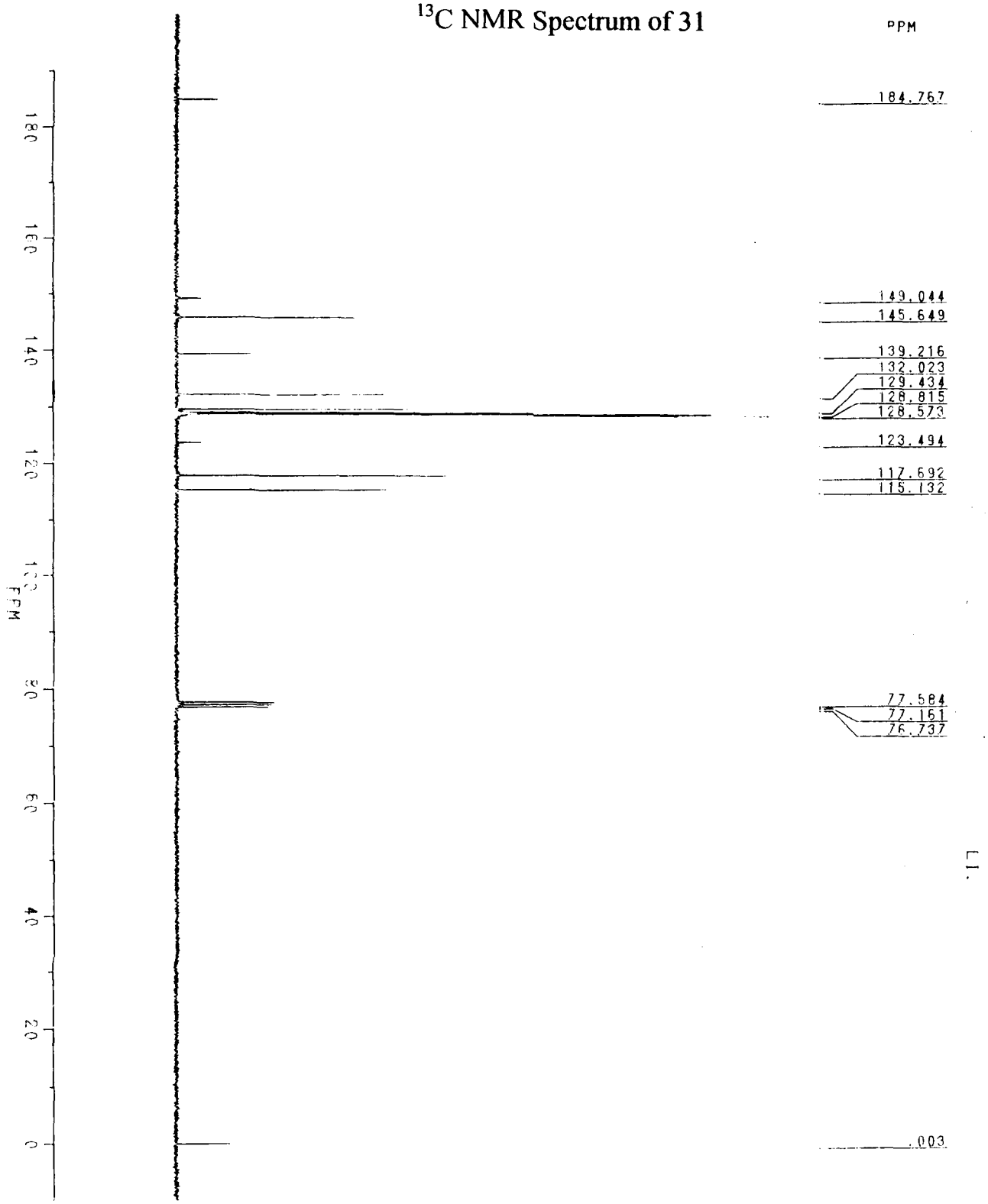


^{13}C NMR Spectrum of 28a

^{1}H NMR Spectrum of 31



^{13}C NMR Spectrum of 31



EXPERIMENTAL SECTION (IIIA+IIIB)

Melting points were determined on a "Thomas-Hoover" capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 297 and Perkin-Elemer 983 spectrometers. ^{1}HNMR (90 MHz) were recorded on Varian EM-390 high resolution ^{1}H NMR (300 MHz) and ^{13}CNMR (75.5 MHz) spectra were recorded on Brucker ACF 300 spectrometer. The chemical shifts (δppm) and the coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethyl silane or DMSO-d_6 in ^{13}CNMR. The following abbreviations are used to describe peak patterns when appropriate : br=broad, s = singlet, d=doublet, d=double doublet, dt=double triplet, t=triplet, q=quartet, m=multiplet. Mass measurements were carried out with Jeol JMS D-300 spectrometer. Masses (MS) are reportedin unit of mass over charge (m/z), the molecular or base peaks and relative intensities are indicated by (M)and (%) respectively. Elemental analysis were performed on a Heracus CHN-O-Rapid Analyzer. Dry benzene was obtained by washing with concentrated sulphuric acid followed by azeotropic distillation and stored over sodium wire. Dry ether was obtained by keeping over calcium chloride (fused) and stored over sodium wire. $BF_3.Et_2O$ was redistilled before use and Cu(I)Cl (AR grade, moisture free) supplied by E-Merck India was used as such.

Starting Materials:

Commercially available ketones p-methoxybenzaldehyde acetophenone, 4-chloroacetophenone, 4-methoxy acetophenone, acetone, cyclohexanone and cycloheptanone were purified either by simple distillation/distillation under reduced pressure or crystalliza tion before use. 2-Acetyl furan & 6 methoxy tetralone was pur chased from Aldrich and used as such 1-tetralone bp 140°-150°C (10 mm), 2-acetyl

thiophene bp 214°C, were prepared according to the earlier reported procedures. Aniline, O-chloroaniline,p-chloroaniline were distilled prior to use. p-Toludine, p-anisi dine and p-bromoaniline, 2-aminopyridine, 3-aminopyridine were recrystallised before use. α-Oxoketene S,S-acetals required for the present investigation were prepared according to the earlier reported literature pro cedures which are given below.

General procedure for the preparation of oxoketene dithioacetal (1a-f of Scheme-1, 1a-i of Scheme-2,1a-e of Scheme-3) using sodium tert.butoxide. A mixture of ketone (0.2 mol) and carbon disulphide (0.2 mol) was added dropwise to an ice-cold and well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (200 ml) and the reaction mixture was allowed to stirr at room temperature for 5-6 hours. Acid free dimethyl sulphate (0.2 mol) was then gradually added with stirring and cooling and the reaction mixture was allowed to stir at room temperature for 6-10 hours. The reaction mixture was poured over aqueous saturated ammonium chloride solution (250 ml) and the layers were separated. The aqueous layer was extracted with benzene (100 ml) and combined benzene extracts were washed with water (4x250 ml), dried (Na_2SO_4) and evaporated. Trituration of the oil residue with hexane gave the dithioacetals as yellow crystalline solid in good yields. Liquid dithioacetals were purified by passing through silica gel column using hexane- ethylacetate (9:1 to 8:2) as eluent. All the known dithioacetals were charaterized by comparison of their melting points, NMR, IR spectra with those of reported data and of authentic sample.

Preparation of S,N, N,N and O,N-acetals:

All the S,N-acetals (**1a-h**), N,N-acetals (**18a-b**) and O,N-acetal **29** required for the present investigation were prepared according to the procedures given in the exprimental section of chapter II-B.

Cycloaromatization of the S,N-acetals (1a-h) & N,N-acetals (18a-b): General procedure for the synthesis of pyrido [1,2-a] pyrimidinium (**15a-f**), (**19a-b**) and pyrido [1,2-a]quinazolinium salts **16, 17**. To a solution of S,N-or N,N-acetal (10 mmol) in dry benzene (30 ml), boron trifluoride etherate (3 ml) was added and the reaction mixture was refluxed with stirring for 45 min - 1 hour. The reaction mixture was then cooled, benzene layer was separated and distilled off under reduced pressure.The remaining residue was dissolved in minimum amount of acetone, neutralized with saturated sodium bicarbonate solution (20ml) and the solid separated was collected by filtration, washed with water (50 ml) and then with ether (2x10ml). Analytically pure products were obtained by recrystallization from glacial acetic acid.The structures **5a-f, 16, 17, 19-a-b**, were fully established from their spectral and analytical data which are given below.

2-Methylthio-4-phenyl[1,2-a] pyrimidin-5-ium tetrafluoroborate (15a) was isolated as colourless crystals (AcOH), m.p.155°C yield 2.80g (82.3%). IR ν_{max}(KBr): 3033, 1619 (C=N), 1147, 1093, 1039 (BF_4)cm^{-1}. ^{1}HNMR (300 MHz, DMSO-d6) $^{\delta}$H : 2.90 (s, 3H, SCH_3), 7.77-7.89 (m, 5H, ArH), 7.91(ddd, 1H, $J_{6,7}$ =6.5Hz, $J_{7,8}$ =7.5, $J_{7,9}$ =1.0Hz, H-7), 8.20(s, 1H, H-3), 8.22 (d, 1H, J = 9Hz, H-9), 8.60(ddd, $J_{7,8}$ =7.5Hz, $J_{8,9}$ =8.0, $J_{6,8}$ =1.5Hz, 1H, H-8), 8.75(dd, 1H, J= 6.5Hz, H-6). ^{13}CNMR (75.5 MHz, DMSO-d6) : 13.64 (SCH_3), 119.20, 122.1, 126.9 (CH, C-3, C-7, C-9); 128.3, 129, 130, 132.21 (C-1',C-2',C-3' and C-4' of phenyl); 132.54, 142.5 (CH, C-8, C-6), 148.9, 149.16, 174.15 (C-2, C-4 and C-10). Anal.Calcd. for $C_{15}H_{13}N_2SBF_4$ (340.14) C 52.9, H 3.8, N 8.23. Found: C 52.83, H3.86, N8.30. MS:m/z(%)=253(M^+-BF_4, 2.2); 238 (M^+-102, 7.6); 77(100).

2-Methylthio-4-(4-methoxy phenyl) pyrido [1,2-a]-pyrimidin-5-ium tetrafluoroborate (15b) was isolated as colourless crystals (AcOH) m.p. 130°C yield 3.05g

(82.4%).IR γ(KBr) : 3325, 1617, 1105, 1072, 1030 (BF_4)cm^{-1}. ^1H NMR(300 MHz, DMSO-d_6) : 2.88 (s, 3H, SCH_3), 3.96 (s, 3H, OCH_3), 7.19(d, 2H, J=9Hz, ArH), 7.65 (d, 2H, J = 9Hz, ArH), 3.76(s, 1H, H-3), 7.80 (dd, 1H, $J_{6,7}$=7.0Hz, $J_{7,8}$ =7.4Hz, $J_{7,9}$=0.6Hz, H-7), 8.29 (d, 1H, $J_{8,9}$=8.6Hz, $J_{7,9}$ =0.6Hz, H-9), 8.79 (d, 1H, $J_{7,8}$ = 7.4Hz, $J_{8,9}$ =8.6Hz, $J_{6,8}$ =0.6Hz, H-8), 8.80 (dd, 1H,J = 7.0Hz, $J_{6,8}$ =0.6Hz, H-6)[typical ABMX pattern]. ^{1}HNMR (300 MHz, DMSO-d_6): 13.48 (SCH_3), 55.5 (OCH_3), 115.30 (CH C-2′ of phenyl), 119.0 (C-3), 120.2 (C-1′ of phenyl), 121.8, 126.7 (C-7,C-9), 130.78, (C-3′ of phenyl), 132.7, 142.2 (C-8,C-6); 149.0, 150.1 (C-2, C-4), 162.3 , (C-4′ of henyl), 174.1(C-10). Anal. Calcd. for $C_{16}H_{15}N_2OSBF_4$ (370.17), C 51.8, H4.0, N 7.5. Found: C 52.1, H 4.1, N 6.9.MS : M/z (%), 283 ,(M^+ -BF_4,3.3), 268(2.4) 77(100).

2-Methylthio-4-(4-chlorophenyl) pyrido[1,2-a] pyrimidin-5-ium tetrafluoroborate (15c) was isolated as colourless crystals, (EtOH) m.p. 140°C; yield 3.15g (84%). IR (KBr): 3230, 1613 (C=N), 1150, 1081, 1035 (BF_4) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-d_6) : 2.84 (s, 3H, SCH_3), 7.64-7.66 (d, 2H, J = 9Hz, ArH), 7.68 (s, 1H, H-3), 7.69-7.71 (d, 2H, J=9Hz, ArH), 7.78 (ddd, 1H, $J_{6,7}$ =6.6Hz, $J_{7,8}$ =7.4Hz, $J_{8,9}$=1.0 Hz, H-7), 8.26 (d, 1H, J=9Hz, H-9), 8.45(dd, 1H, $J_{8,9}$ =8Hz, $J_{7,8}$ =7.4Hz, $J_{6,7}$ =1.0Hz,H-8), 8.62 (dd, 1H, $J_{6,7}$ =6.6Hz, $J_{6,8}$ =1.0Hz, H-6). [Includes ABMX spectrum]. CNMR (75.5 MHz, DMSO-d): 13.6 (SCH), 119.3, 122.1, 122.1, 126.9 (CH, C-3, C-7, C-9); 129, 130.2, 131.22, 132.6 (C-1′, C-2′, C-3′ and C-4′ of phenyl); 136.39, 142.46 (C-8, C-6), 146, 148 (C-2, C-4), 174.4 (C-10). Anal. Calcd. for $C_{15}H_{12}N_2$ SClBF(374.58) C 48.1, H 3.2, N 7.4. Found : C 48.3, H 3.1, N 7.5. MS : m/z (%) 287 (M^+-BF_4 , 10.7), 272 (M^+-102, 12.8%) 91 (100).

2-Methylthio-4-(4-methylphenyl) pyrido [1,2-a] pyrimidin-5-ium tetrafluoroborate (15d) was isolated as colourless crystals J(AcOH), m.p. 150°C, yield 2.85g (80%). IR δmax(KBr) : 3372, 1616 (C=N), 1150, 1063 (BF) 1034 cm. HNMR (300 MHz, DMSO-d_6)

δ(ppm) 2.50 (s, 3H, CH), 2.82(s, 3H, SCH_3), 7.46-7.49 (d, J = 9Hz, ArH), 7.55 (s, 1H, H-3), 7.56-7.59 (d, J = 9Hz, ArH), 7.75 (ddd, 1H, $J_{6,7}$ =6.5 Hz, $J_{7,8}$=7.0Hz, $J_{6,7}$ =6.5Hz, $J_{7,8}$ =7.0Hz, $J_{7,9}$=0.6Hz, H-7), 8.25 (d, 1H, J = 8.9Hz,H-9), 8.45 (dd, 1H, $J_{7,8}$ =7.0Hz, $J_{8,9}$ =8.3Hz , $J_{6,8}$=0.5Hz, H-8), 8.66 (d, 1H, $J_{6,7}$ = 6.5Hz, $J_{6,8}$ =0.5Hz, H-6). ^{13}CNMR(75 MHz, DMSO-d_6) : 13.6 (CH),21.5(SCH),119.06, 122.0(C-3, C-7), 125.36 (C-1′ of phenyl), 126.9 (C-9),129.27, 130.6 (C′-2, C′-3 of phenyl), 132.45, 142.4 (C-8, C-6), 143.0 (C-4′ of phenyl), 148.9, 149.47, 174.10 (C-2, C-4 and C-10). Anal. Calcd. for $C_{16}H_{15}N_2SBF_4$ (354.17) C 54.2, H 4.2, N 7.9. Found : C 54.3, H 4.3, N 7.70. Ms : m/z (%) : 267 (M^+-BF_4, 2.1), 252 (M^+-102, 2.1) 41(100).

2-Methylthio-4-(2-furyl)-pyrido [1,2-a] pyrimidin-5ium tetrafluoroborate(15e) was isolated as yellowcrystals(AcOH) m.p. 200°C; yield 2.86g (86%). IR ν_{max}(KBr) : 3448, 1602 (C=N), 1152, 1056 (BF_4) cm.$^{-1}$. ^{1}HNMR (90 MHz, DMSO-d_6): 2.70 (s, 3H, SCH_3), 6.90 (dd, 1H, J= 3.5and 1.5 Hz, H-4′ furyl), 7.80 (d, 1H, J = 3Hz, H-3′furyl), 8.10 (ddd, 1H, H-7), 8.21 (s, 1H, H-3), 8.30 (d, 1H, J =1.4Hz, H-5′furyl), 8.50 (dd, 1H, H-9), 8.61 (ddd, 1H, H-8),9.50(d, 1H, H-6). [ABMX spectrum, J values found in the typical region $J_{6,7}$ = 7.5, $J_{7,8}$ = 8.0, $J_{6,8}$ = 0-1, $J_{7,9}$ = 0-1.03 Hz]. Anal. Calcd. for, $C_{13}H_{11}N_2OSBF_4$(330.10) C47.2, H 3.3, N 8.4. Found :C 47.3, H 3.2, 8.50.MS : m/z (%) 259 (M^+-BF_4 , 1.8), 244 (M^+ -102, 1.8) 91(100).

2-Methylthio-4-(2-thienyl) pyrido [1,2-a] pyrimidin-5-ium tetrafluoroborate (15f) was isolated as yellow crystals m.p. 170°C (AcOH). IR (KBr) : 3424, 1601 (νC=N), 1148, 1085 (BF_4),1057 cm^{-1} .^{1}HNMR (90 MHz, DMSO-d_6) : 2.80 (s, 3H, SCH_3), 7.50 (dd, 1H, J= 4.5 and 1.5 Hz, H-4′ furyl), 7.86 (d, 1H, J = 3Hz, H-3′furyl), 8.25 (s, 1H, H-3), 8.26-8.56 (m, H-7, H-9, H-5′ furyl), 8.70 (dd, 1H, H-8), 9.30 (d, 1h, J = 9Hz, H-6). [J 6,7 =7.5Hz,J 7,8 =8.5=1.5, J 7,9= 1.0Hz]. Anal. Calcd. for $C_{13}H_{11}N_2S_2BF_4$ (346.16) C 45.01, H 3.1, N 8.0. Found : C 45.3, H 3.05, N 8.26.

5-methylthio,1,2,3,4 tetrahydro pyrido [1,2,-a]quinazolin-11-ium, tetraflouroborate (16) was isolated as colourlesscrystal (AcOH), m.p. 159°C. IRν_{max} (KBr): 3421, 1628, (C=N), 1421, 1099 (BF_4) cm^{-1}. ^{1}HNMR (90MHz, DMSO-d_6); 1.82-2.01 (m, 4H, $2CH_2$), 2.76(brs, 2H, CH_2) 2.80, (s, 3H, SCH_3), 2.92 (brs, 2H, CH_2), 7.80 (ddd, 1H, $J_{9,7}$= 1.5, $J_{9,8}$ = 7.5, $J_{9,10}$ = 6.6, H-9),8.15(dd, 1H, $J_{7,8}$ = 7.5, $J_{7,9}$ = 1.5, H-7), 8.50 (dt, 1H, $J_{7,8}$ = 7.5, $J_{8,9}$ = 7.5, $J_{8,10}$ =0.3, H-8), 9.30 (d, 1H, $J_{10,9}$ = 8.7, $J_{8,10}$ =0.3 Hz, H-6). Anal: Calcd. for $C_{13}H_{15}N_2SBF_4$ (318), C 48.0H 4.6, N 9.7 Found: C 48.5, H 4.6, N 8.9, 13 15 2 4/ Ms: M/z (%) 230 (M^+-BF_4, 1.6%), (M^+ -102, 10.9).

5,6-dihydro-7-methylthio benzo [h] pyrido [1,2-a] quinazolin-13-ium tetrafluoroborate (17) was isolated as yellow crystalline solid, (AcOH), m.p. 205°C, yield 2.15g (86%). IR(KBr): 3421, 1629(νC=N), 1561, 1081(BF_4) 1019 cm^{-1}. ^{1}HNMR (90 MHz, DMSO-d_6): 2.81 (s, 3H, SCH_3), 3.04 (t, J =8Hz, 2H,CH_2), 7.80 (m, 3H, H-2, H-3, H-4), 8.15 (m,2H,H-1,H-11), 8.42(ddd, 1H, J 10,9 =7.5Hz, J 10,11 =6.6Hz,J 10,12 =0.6Hz,H-10), 9.56 (d, J = 9.5Hz, 1H, H-12). Anal. Calcd. for $C_{17}H_{15}N_2SBF_4$(366.18) C55.73, H 4.01, N 7.60. Found : C 55.50, H 4.23, N 7.56. MS : m/z (%) 279 (M^+ -BF_4, 11.4), 278 (M^+-102, 31.4), 78 (100).

2-(2-Pyridylamino)-4-phenyl pyrido [1,2-a]pyrimidin-5-ium tetrafluoroborate (19a) was isolated as colourless crystals (EtOH), m.p. 201°C; yield 2.80g (72%). IR (KBr): 3437, 3299, 1644 (νC=N), 1582, 1072(BF_4), 1021cm^{-1}. ^{1}HNMR(300 MHz, DMSO-d_6): 7.30 (ddd, J= 7.6, J = 6.0, J = 0.5Hz, 1H, H-5′ of pyridyl); 7.51 (m, 2H, H-3′ of pyridy l3, 5 and H-7), 7.70-7.89 (m, 6H, 5H atom , & H-3), 7.90-8.25 (m, 2H,H-4′ of pyridyl and H-9), 8.31 (dd, 1H, J 9.5 and 8.6Hz, H-8), 8.43 (dd, 1H, J 8.2 and 1.5 Hz, H-6) 8.80 (brs, NH). Anal. Calcd. for $C_{19}H_{15}N_4BF_4$ (386) C 59.06, H 3.8, N 14.50. Found : C 59.5, H 3.2, N 14.31.

2-(2-Pyridylamino)-4-(4-methoxy phenyl) pyrido [1,2-a] pyrimidin-5-ium tetrafluoroborate (19b) was isolated as colourless crystals (EtOH) m.p. 200°C yield 3.60g (86%). IR(KBr) : 3471, 3114, 1641 (C=N) 1600, 1082 (BF) cm^{-1}. ^{1}HNMR (300 MHz, DMSO-d_6 δ (ppm) : 3.90 (s, 3H, OCH), 7.65-7.68 (d, 2H, J = 9Hz, ArH), 6.60 (brs, NH), 7.61 (dd, 1H,J 6,7 =6.6Hz, J 7,8 =7.4Hz,J 7,9 =0.9Hz, H-7), 7.35 (s, 1H, H-3), 7.22-7.25 (d, 2H, J = 9Hz, ArH), 8.08 (dd, 1H, J 8,9 =7.6, J 8,7 =7.4,J 8,6 =1.0Hz, H-9) 8.24-8.35 (m, H-3′, H-4′, H-5′ of pyridyl and H-8), 8.51 (d, J = 8Hz, H-6′ of pyridyl), 8.60 (dd, 1H, J 6,7 =6.61, J 6,8 =1.5Hz, H-6). ^{13}CNMR (75.5 MHz, DMSO-d_6) δ(ppm) : 111.4 (c-5′ of pyridyl), 115.1 (C-2′ of phenyl), 115.9 (C-3′ of pyridyl), 119.6(C-3), 120.5(C-1′ of phenyl), 121.2, 125.8 (C-7, C-9); 130.9 (C-3′of phenyl), 132.3(C-4′ of pyridyl) 137(C-8), 141(C-2′of pyridyl), 143 (C-6), 146 (C-6′ of pyridyl), 150.2 (C-4), 152.1 (C-2), 155 (C-10), 161.9 (C-4′ of phenyl). Anal. Calcd. for $C_{20}H_{17}N_4OBF_4$(416) C 57.69, H 4.08, N 13.96. Found : C 57.50, H 4.15, N 13.60.

Copper(I) promoted intramolecular radical cyclization of S,N & O,N-acetals (1a-f) & 29:

General procedure for the preparation of imidazo [1,2-a] pyridines (**28a-f**) & **30**. A mixture of anhydrous copper(I) chloride (1.47g, 15 mmol), S,N-or O,N-acetal (10 mmol) and dry tetrahydrofuran (THF) was stirred with refluxing at 67-70°C for 3-4 hours under argon. The initial pale green colour of the reaction mixture faded away and after 1 hour it gradually turned reddish brown. The progress of the reaction mixture was monitored by TLC. The reaction mixture was cooled, poured into water (50 ml) and extracted with benzene (2x50 ml) after removing the insoluble substances by filtration. The organic layer was washed several times with water, dried (Na_2SO_4) and evaporated to give the crude residue. The crude product was purified by column chromatographyon silica gel using hexane/ethylacetate (9:1) as the eluent to afford the imidazo [1,2-a] pyridine in high yield [Compound **28a** 2.50g (93%)]. Analytical & Spectral. Data for the purified compounds are reported below:

3-Benzoyl-2-Methylthio-imidazo [1,2-a] pyridine (28a) was isolated as colourless solid, recrystallisation from ethylacetate-hexane gave needles, m.p. 140°C; yield 2.50g (93%). IPγ_{max} (KBr): 3434, 1627, 15900, 1224 cm^{-1}. ^1H NMR (300 MHz), $CDCl_3$), δ(ppm): 2.53 (s, 3H, SCH_3), 6.99 (ddd, 1H, $J_{5,6}$=6.6 Hz, $J_{6,8}$-0.9 Hz, H-6), 7.45 (add, 1H, $J_{6,7}$=6.9 Hz, $J_{5,7}$=0.9 Hz, $J_{7,8}$=9Hz, H-7), 7.48-7.51 (m, 3H, ArH), 7.53-7.60 (m, 2H, ArH), 7.56 (dt, 1H, $J_{7,8}$=9Hz, $J_{6,8}$=0.9Hz, H-8), 9.52 (dt, 1H, $J_{5,6}$=6.6Hz, $J_{5,7}$=0.9Hz, H-5). [$J_{5,6}$=6.6, $J_{6,7}$=6.9, $J_{7,8}$=9, $J_{5,7}$=0.9, $J_{6,8}$=0.9Hz].^{13}C NMR (75.5 MHz, $CDCl_3$): 14.8 (SCH_3), 114, 115.7, 120(C-6, C-7, & C-3), 128,1, 128.54, 128.59 (C-2′, C-3′, C-4′ of ArH), 129.56, 131.5 (C-8, C-5), 139.8 (C-1′ of ArH), 148.01, 153,97 (C-9 & C-2), 185.48 (C=0). Anal. Calcd. for $C_{15}H_{12}N_2OS$ (268.3). C 67.3, H 4.47, N 10.44. Found: C 67.4, H 4.45, N 10.45. Ms: m/z(%) 268 (M^+, 25.3), 267 (M^+-1, 100), 253 (M^+-15.4), 252 (M^+-16, 18.5), 234 (M^+-33, 87.6).

3-(4-Methoxy benzoyl)-2-methylthio-imidazo [1,2-al pyridine (28b) was isolated as colourless crystals (EtOAc-hexane), m.p. 140°C, yield 2.70g (90%). IRγ_{max} (KBr): 3426, 1670, 1604, 1339, 1222 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): ((ppm): 2.56 (s, 3H, SCH_3), 3.88 (s, 3H, OCH_3), 6.98 (ddd, 1H, J=6.5, J=6.8 and j=0.9 Hz, H-6), 7.01 (d, 2H, J=9Hz, ArH), 7.44 (ddd, 1H, J=0.9 Hz, J=6.8 Hz, J=9.6 Hz, H-7), 7.62 (dt, 1H, J=0.9 Hz, J=9.6Hz, H-8), 7.70 (d, 2H, J=9 Hz, ArH), 9.41 (dt, 1H, J=6.5, J=0.9, H-5). [$J_{5,6}$6.5, $J_{6,7}$=6.8, $J_{7,8}$=9.6, $J_{6,8}$=0.9, $J_{5,7}$=0.9Hz]. ^{13}C NMR (75 MHz, $CDCl_3$), 14.96 (SCH_3), 55.4 (OCH_3), 113.81 (C-2′ of Ar), 113.9, 115.77, 120.36, 128.3, 129.1 (C-6, C-7, C-3, C-5), 130.8 (C-3′ of ArH), 132.36, (C-1′ Ar), 147.8 (C-9), 154-5 (C-2), 162.8 (C-4′ Ar), 184.74 (C=0). MS: m/z (%) 298 (M^+, 19.7), 297 (M^+-1, 100), 283 (M^+-15, 12.9), 265 (M^+-33, 47.5). Anal. Calcd. for $C_{16}H_{14}N_20_2S$ (298), C 64.4, H 4.6, N 9.39. Found: C 64.6, H 4.5, N 9.38.

3-(4-Chlorobenzoyl)-2-methylthio-imidazo [1,2-a] pyridine 28c was isolated as colourless solid (ĖtoAc-hexane), m.p. 152°C; yield 2.75g (91%). IRγ_{max} (KBr): 3416, 1670, 1627, 1599, 1221 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 2.55 (s, 3H, SCH_3), 7.05 (ddd, 1H, J=6.6, J=6.9, J=1.1 Hz, H-6), 7.47 (ddd, 1H, J=6.9, J-9.6, J=1.1 Hz, H-7), 7.50 (d, 2H, J=9Hz, ArH), 7.61 (d, 2H, J=9Hz, ArH), 7.66 (dt, 1H, J=1.1 Hz, J=9.6 Hz, H-8), 9.53 (dt, J=6.6, J=1.1 Hz, H-5). [$J_{5,6}$ =6.6, $J_{6,7}$=6.9, $J_{6,8}$= $J_{5,7}$=1.1Hz $J_{7,8}$=9.6 Hz]. ^{13}C NMR (75 MHz, $CDCl_3$): 14.81 (SCH_3), 114.4, 115.8, 119.8, 128.6 (C-6, C-7, C-3 & C-8), 128.9(C-2′ of Ar), 129.7 (C-3′ of Ar), 129.9 (C-5), 137.9, 138.0 (C-1′ & C-4 Ar). 148.1, 156.1 (C-9 & C-2), 184/1 (C=0). MS: m/z (%) = 303 (M^+, 100), 288 (M^+-15, 14.4) 270 (M^+-33, 51). Anal. Calcd. for $C_{15}H_{11}N_2OCl$ (302.6). C 59.5, H 3.6, B 9.2. Found: C 59.6, H 3.5, N 9.33. 3-(4-Methylbenzoyl)-2-methylthio-imidazo [1,2-a] pyridine 28d was isolated as colourless solid (ethylacetate-hexane); m.p. 152°C, yield 2.45j (87%). IR γ_{max} (KBr): 3432, 1627, 1601, 1336, 1223 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) ((ppm): 2.44 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 6.99 (ddd, 1H, J=6.6, J=6.9, J=0.9 Hz and J=1.1 Hz, H-6), 7.29 (d, 2H, J=9 Hz,

ArH), 7.43 (ddd, 1H, J=6.9, J=9, J=1.1 Hz, H-7), 7.59 (d, 2H, J=9 Hz, ArH), 7.61 (dt, 1H, J=9, J=1.1 Hz, H-8), 9.47 (dt, 1H, J=6.6, J=1.1 Hz, H-5). [$J_{5,6}$ =6.6, $J_{6,7}$=6.9, $J_{6,8}$= $J_{5,7}$=1.1Hz $J_{7,8}$=9.6 Hz].

^{13}C NMR (75 MHz, $CDCl_3$): 14.8 (CH_3), 21.7 (SCH_3), 114.0, 115.7, 120.2 (C-6, C-7, C-3), 128.5, 129.25 (C-2′ & C-3′ of Ar), 129.28, 131.7 (C-8, C-5), 137.03, 142.3 (C-1′, C-4′ of Ar), 147.9 (C-9), 155.3 (C-2), 185.47 (C-0). MS: m/z (%) =282 (M^+, 7.6), 281 (M^+-1, 19.3), 280 (M^+-2, 100), 247 (M^+-33, 70.3). Anal. Calcd. for $C_{16}H_{14}N_2OS$ (282), C 66.08, H 4.9, N 9.9. Found: C 68.1, H 4.7, N 9.8.

3(2-furoyl)-2-methylthio-imidazo [1,2-a] pyridine 28e was isolated as colourless crystals (chloroform-hexane) m.p. 141°C, yield 2.19g (85%). IR γ_{max} (KBr): 3433, 1687, 1627, 1606, 1232 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 2.64 (s, 3h, SCH_3). 6.60 (dd, 1H, J=4Hz, J=2Hz, H-4′ furyl), 6.98 (ddd, 1H, J=6.7, J=6.9, J=1.1 Hz, H-6),. 7.32 (d, J=4Hz, H-3′ furyl), 7.44 (ddd, 1H, J=6.9, J=9.6 & J=1.1 Hz, H-7), 7.62 (dt, 1H, J=9.6, J=1.1 Hz, H-8), 7.69 (d, J=3Hz, H-5′ furyl), 9.26 (dt, 1H, J=6.7, J=1.1 Hz, H-5). [$J_{5,7}$ =6.7, $J_{6,7}$=6.9, $J_{7,8}$= 9.6, $J_{5,7}$= $J_{6,8}$=1.1 Hz]. ^{13}C NMR (75 MHz, $CDCl_3$): 15.0 (SCH_3), 112.1 (C-4′ furyl), 114.0, 115.9 (C-6, C-7), 118.0 (C-3′ furyl), 120.3 (C-3), 128.1 129.2 (C-8, C-5), 146.1 (C-5′ furyl), 147.9 (C-9), 151.6 (C-2′ furyl), 154.0 (C-2), & 171.9 (C=0). MS. m/z (%) =258 (M^+, 100), 243 (M^+-15, 218), 230 (M^+-28, 95.8), 225 (M^+ -33, 12.7). Anal. Calcd. for $C_{13}H_{10}N_2O_2S$ (258) C 60.46, H 3.87, N 10.85. Found: C 60.56, H 3.73, N 10.90.

3-(2-Thienoyl)-2-methylthio-imidazo [1,2-a] pyridine 28f was isolated as light yellow solid (chloroform-hexane), m.p. 152°C; yield 2.60g (94.8%). IR γ_{max} (KBr): 3443, 1670, 1649, 1583, 1236 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 2.60 (s, 3H, SCH_3), 6.98 (ddd, J=6.9Hz, J=6.9 Hz, J=1.2 Hz, H-6), 7.15 (dd, J=4.9 and J=3.8, H-4′ thienyl) 7.45 (ddd, 1H, J=6.9, J=9.2, J=1.1, H-7), 7.63 (dt, 1H, J=9.2, J=1.2 Hz, H-8), 7.70 (dd, 1H, J=4.3 Hz, J=1.2

Hz, H-3′ thienyl), 7.77 (dd, 1H, J= 1.2 Hz & J=4.3 Hz, H-5′ thienyl) 9.29 (dt, 1h, j=6.9, J=1.1 Hz, H-5). [$J_{5,6}$ =6.9, $J_{6,7}$=6.9, $J_{7,8}$= 9.2, $J_{5,7}$=1.1, $J_{6,8}$=1.2 Hz]. ^{13}C NMR: 15.13 (SCH_3), 114.08, 115.8, 120.42 (C-6, C-7, C-3), 127.36 (C-4′ thienyl), 128.2, 129.29 (C-8, C-5), 132.72, 133.0, 142.83 (C-3′, C-5 & C-2′ thienyl), 147.9 (C-9), 154.16 (C-2), 177.04 (c=0). MS: m/z (%) : 274 (M^+, 100), 259 (M^+-15, 13.9), 241 (M^+-33, 84.4). Anal. Calcd. for $C_{13}H_{10}N_2OS$ (274.2), C 56.91, H 3.64, N 11.66. Found: C 56.90, H 3.65, N 11.65.

2-Methoxy-3-(4-chlorobenzoyl)-imidazo [1,2-a] pyridine (30) was isolated as yellow crystals ($CHCl_3$-hexane), m.p. 156°C, yield 2.50g (87%). IR γ_{max} (KBr): 3135, 1600, 1559, 1402, 1226 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 3.97, (s, 3H, OCH_3), 7.04 (ddd, 1h, J=6.6, J=6.9, J=1.1 Hz, H-6), 7.39 (d, 2H, J=9Hz, ArH), 7.45 -7.54 (m, H-7 and H-8), 7.65 (d,2H,J = 9 Hz, ArH) 9.68 (dt, 1h, J=6.6, J=1.1 Hz, H-5). ^{13} CNMR (75 MHz, $CDCl_3$): 56.03 (OCH_3), 114.1, 115.4 (C-6, C-7), 127.7 (C-2′ ArH), 128.9, 129.5 (C-8, C-3), 130.02, 137.1, 137.9 (C-3′, C-1′ & C-4′ Ar), 144.8 (C-9), 163.2 (C-2), 182.2 (C=0). Anal. Calcd. for $C_{15}H_{11}N_2O_2Cl$ (286.5). C 62.8, H 3.83, N 9.77. Found: C 62.78, H 3.79, N 9.95.

General procedure for dethiomethylation of 28a:

To a stirred solution of 3-benzoyl-2-methylthioimidazo [1,2-a] pyridine (**28a**) (2.5 mmol) in ethanol (25 ml) was added Raney Nickel (W4, 3 times by weight) and the mixture was stirred with refluxing for 6 hours (monitored by TLC). The reaction mixture was filtered through G-3 cintered funnel and the residue was washed with ethanol (10 ml). Ethanol was distilled off and chloroform (20 ml) was added and washed with water (2x50 ml), dried over Na_2SO_4 and evaporated. Analytically pure compound **31** was obtained by passing through a silica gel column using ethylacetate-hexane (1:9) as eluent.

3-Benzoyl-imidazo [1,2-a] pyridine (31) was isolated as colourless solid m.p.150, yield 1.8g (81%). IR γ_{max} (KBr): 3340, 1689, 1597, 1223 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ(ppm) 7.14 (ddd, 1H, $J_{5,6}$=6.6, $J_{6,7}$= 6.9 & $J_{6,8}$=1.0 Hz, H-6), 7.50-7.60 (m, 4H, 3H arom + H-7), 7.79 (dt, 1H, $J_{7,8}$=8.8, $J_{6,8}$=1.1 Hz, H-8), 8.21 (s, 1H, H-2), 9.74 (dt, 1H, $J_{5,6}$=6.6, $J_{5,7}$=0.3Hz, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): 115.13, 117.69, 123.49 (C-6, C-7, X-3); 128.5, 128.8, 129.43 (C-2', C-3' & C-4' Ar); 132.02 (C-8), 139.21 (C-1' Ar), 145.64 (C-5), 149.64 (C-9), 189.7 (C=0). Anal. Calcd. for $C_{14}H_{10}N_2$ (222). C 75.67, H 4.50, N 12.61. Found: C 75.70, H 4.35, N 12.50.

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CHAPTER-IV

REACTION OF α-BIS (METHYLITHIO)-METHYLENE CYCLOPROPYL KETONES WITH 1,2-AND 1,3- BINUCLEOPHILES:

GENERAL METHOD FOR THE SYNTHESIS OF CYCLOPROPYL RING SUBSTITUTED HETEROCYCLES.

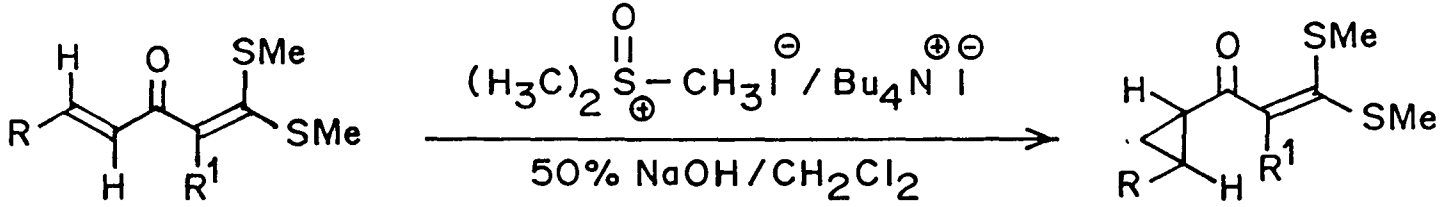
IV.1. INTRODUCTION

It has been shown[1] from this laboratory that cinnamoyl ketene dithioacetals of the general formula **1** (Scheme-1) undergo facile conjugate cyclopropantion regioselectively on thearyl substituted double bond instead of bis-(methylthio) double bond. These cinnamoyl α-oxoketene dithioacetals were prepared by condensing appropriate aryl benzaldehydes with α-oxoketene dithioacetals derived from aliphatic methylene ketones. The cyclopropanation of **1** have been achieved by reacting **1** with dimethyl sulphoxonium methylide in the presence of phase transfer catalyst in 88-98%overall

yields. These interesting cyclopropyl ketones **2** have been extensively used in Lewis-acid assisted rearrangements where the interaction of the mercapto double bond with the developing carbocation leads to the formation of cyclopentanones **5** in excellent yields(Scheme-1,2). The combination of other acids such as H_3P0_4/Formic acid also yields cyclopentanones with the variation in the side chain in the bis-methylthio functionality. Extensive studies have been made on the structrual variations in the aryl group attached to cyclopropane ring and the method hasbeen shown to be successful not only for the synthesis of functionalised cyclopentanones but also their singly and doubly annclated cyclopentanoids[3]. The α-oxoketene dithioacetals as 3-carbon dielectrophilic intermediate have been proved to be useful intermediates to yield a variety of heterocyclic systems of biological interest. Theyundergo facile cyclocondensation reaction with 1,2- and 1,3-binucleophiles to yield the corresponding five membered and six memberedheterocycles (See chapter -1, Scheme -3)[4]. It was therefore, considered of interest to utilize these easily accessible bis-(methylthio) methyline cyclopropyl ketones to prepare both five and six membered heterocycles having cyclopropyl group as one of the substituents. Such molecules would be of particular interest in thermal rearrangement studiesto yield the corresponding heterocycles with annelation of the cyclopentane ring. However these studies could not be accompalished and the proposed heterocycles have been synthesized and described in the present chapter.

IV.2. RESULTS AND DISCUSSIONS

The α-bis (methylthio) methylene cyclopropyl ketone **2a** was, refluxed in hydrrazine hydratre in ethanol to afford the corresponding **5(3)** - methylthio **3(5)** phenyl cyclopropyl pyrazole (Scheme-3) in 80% yield. The structure of **6a** was established from its analytical and spectral data. It was analysed for $C_{13}H_{14}N_2S$ for molecular weight

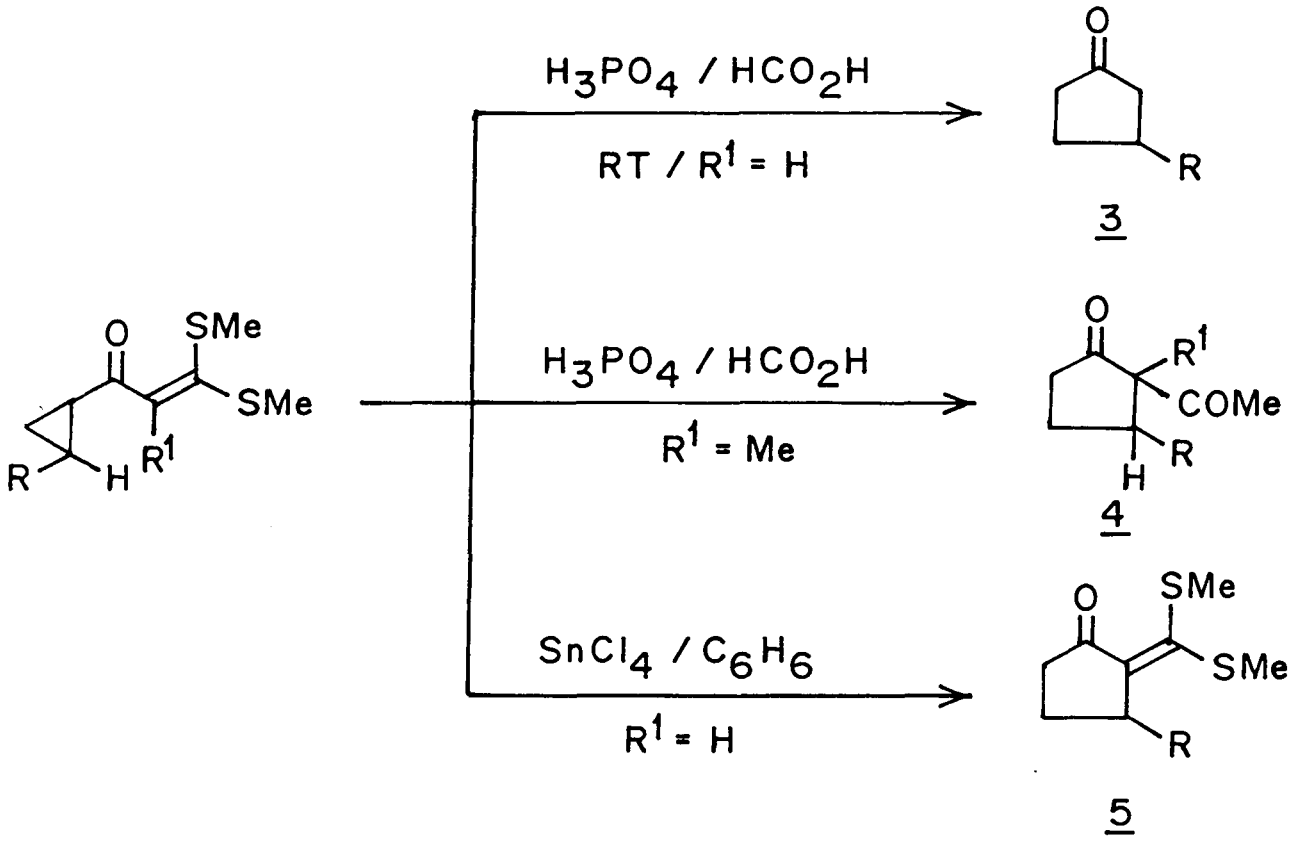


1a–f

2a–f

1a , 2a , R = C_6H_5 , R^1 = H
1b , 2b , R = 4–MeOC_6H_4 , R^1 = H
1c , 2c , R = 3,4–$(MeO)_2$ C_6H_3 , R^1 = H
1d , 2d , R = 3,4,5–$(MeO)_3$ C_6H_2 , R^1 = H
1e , 2e , R = 4–ClC_6H_4 , R^1 = H
1f , 2f , R = 4–Me C_6H_4 , R^1 = H

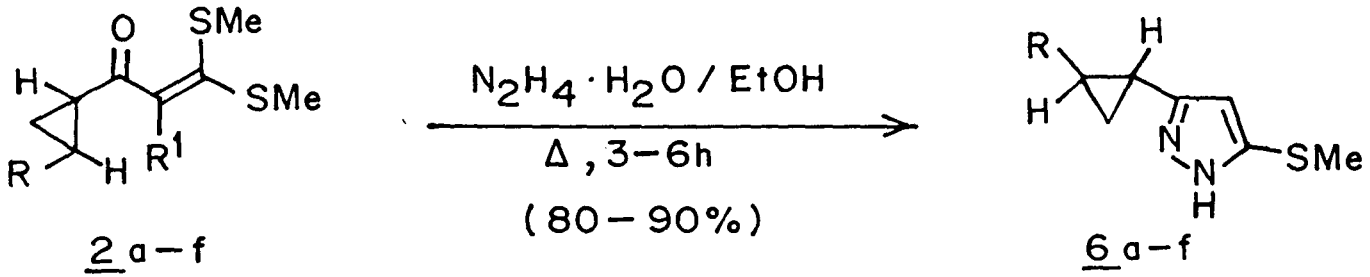
Scheme – 1


H3PO4 / HCO2H
RT / R1 = H
3
H3PO4 / HCO2H
R1 = Me
4
SnCl4 / C6H6
R1 = H
5
SMe
SMe
O
R
H
R1
COMe

Scheme – 2

230.2. In its IR(neat) spectrum strong bands appeared at 3176, 3123, 1609, 1510 cm^{-1}. The structure was further confirmed from its ^{1}HNMR spectrum ($CDCl_3$). The singlet at δppm 1.20-1.50 (2H) appeared as multiplets, were assgned to the cyclopropyl methylene protons. The two cyclooopropyl methine protons appeared as two multiplets between δ1.89-2.15 (1H) and δ2.33-2.58 (1H). The three protons of SMe group appeared as a singlet at 2.35. The sharp singlet at 5.90 was assigned to H-4 proton of the pyrazole ring. The aromatic protons appeared as multiplet between 7.0-7.51. Similarly, the other **bis (methylthio)-cyclopropyl ketones 1b-f** were also transformed to the corresponding pyrazoles **6b-f** in 80-90% (Schemme-3) overall yields. The analytical and spectral data which were in accord with the assigned structre are described in the experimental section.

The reaction of these cyclopropyl ketones **2** with 1hydroxylamine gave more interesting results. When α-bis(methylthio) cyclopropyl ketone **2b** was reacted with hydroxylamine hydrochloride in the presece of sodium methoxide in methanol (pH 7-9), the corresponding isoxazole **7b** was obtained in 80% yield, which was characterised as **5-methylthio 3(4-methoxy phenyl) cyclopropyl isoxazole** as colourless needlels (EtOH), m.p.156°C. The structure of **7b** was established on the basis of its analytical and spectral data. Similarly, cyclopropyl ketones **1a, 1c-f** in 70-80% overall yields under the described reaction conditions. All the isoxazoles were obtained exclusively with these regioslectivity under the described alkaline (pH >7) conditions. On the other hand, the α-bis(methylthio) cyclopropyl ketones **2a-f** when reacted with hydroxylamine hydrochloride under ambidend pH conditions (2.2) in sodium acetate-acetic acid-water and refluxed in benzene, the isoxazoles **3-methylthio-5(4- aryl)cyclopropyl isoxazoles 8a-f** were formed in 50-60% overall yield. In some of these experiments isomeric isoxazole **7a-f** was detected. The analytical and spectral data of these isoxazoles **8a-f**



2 a–f

6 a–f

2, 6, a R = C_6H_5, R^1 = H

b, R = 4-$MeOC_6H_4$, R^1 = H

c, R = 3,4-$(MeO)_2$ C_6H_3, R^1 = H

d, R = 3,4,5-$(MeO)_3$ C_6H_3, R^1 = H

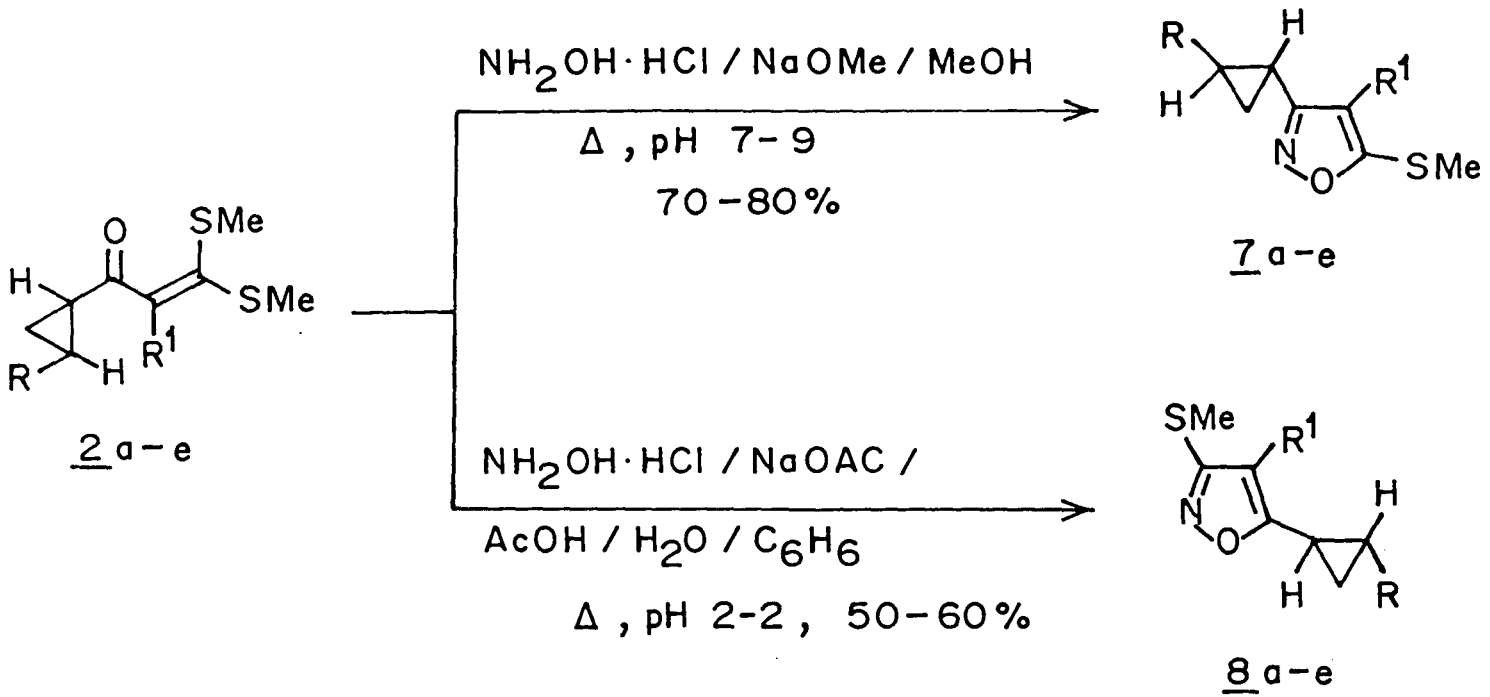
e, R = 4-ClC_6H_4, R^1 = H

f, R = 4-MeC_6H_4, R^1 = H

Scheme – 3

were in conformity with the assigned structure are described in the experimental section. Moreover the different isomers 7 and 8 were clearly distiguished by comparing their melting points, superimposable IR and NMR spectra. The mechanism for the formation of these different regiosomers is depicted in Scheme-5. It is interesting to note that the initial bond formation between oxoketene dithioacetal and hydroxylamine is controlled largely by the pH of the medium. At pH 7-9 the free hydroxylamine does not exert an effect on oxoketene dithioacetal. The course of attack of H_2NOH on oxoketene dithioacetal under these conditions therefore follows the oxime pathway to yield exclusively 7. Alternatively, we can described this reaction as a combination between hard electrophilic carbonyl carbon, hard mucleophilic nitrogen so that the formation of oxime was a possible intermediate can be appreciated. At pH 2.2 though hydroxylamine still remains protonated a small fraction of the free base appears to remain in equilibrium with protonated hydroxylamine. So that at the same the oxoketene dithioacetal also gets protonated to give the resonance form having greater positive charge at C-4 atom stablized by two sulphur atoms. Consequently there is a hard-soft affinity inversion (HSAB)[5] (Scheme 5A) permitting hard muclophilic nitrogen at C-4 carbon followed by ring closure to give the product isomeric isoxazoles **8** exclusively. It is therfore interesting to use this cyclopropyl ketones for the synthesis of isomeric isoxazoles having cyclopropyl group attached to carbon with C=N structural frame whereas in the other isomer the cuyclopropyl ring is attached to the other carbon next to the C=C of the structural frame of the isoxazole ring. These isomers will be very useful in the thermal and other rearrangement studies.

The reaction of bis (methylthio) cyclopropyl ketones **2a-f** with guanidine in the presence of the corresponding alkanol- alkoxide medium yielded 2-amino-4- alkoxy 6-aryl cyclopropyl pyrimidines in good yields. Guanidine reacts with α-oxoketene O,S-



2 a-e

7 a-e

8 a-e

2 , 7 , 8 , a , R = C_6H_5 , R^1 = H

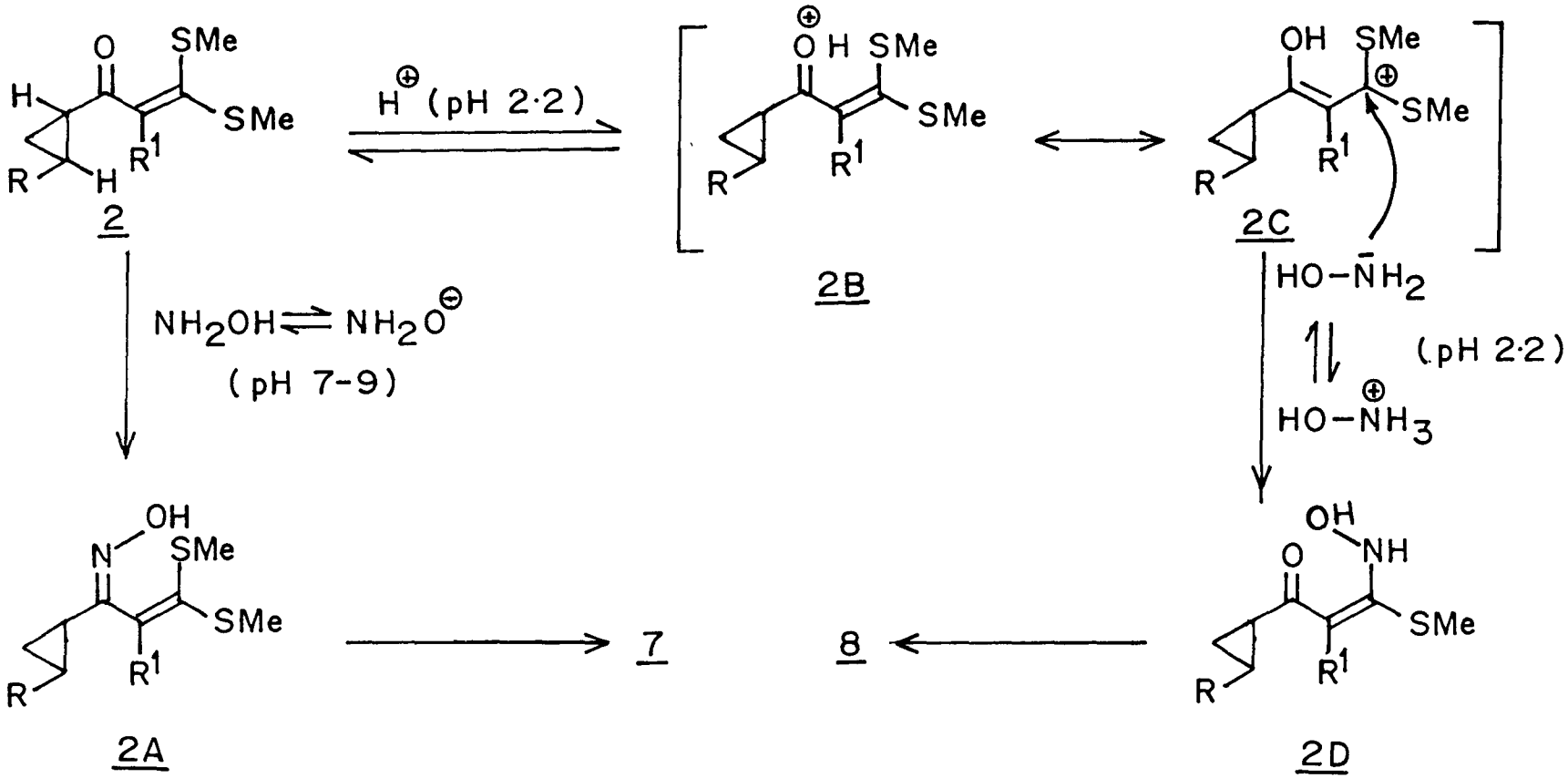
b , R = 4-$MeOC_6H_4$, R^1 = H

c , R = 3,4-$(MeO)_2C_6H_3$, R^1 = H

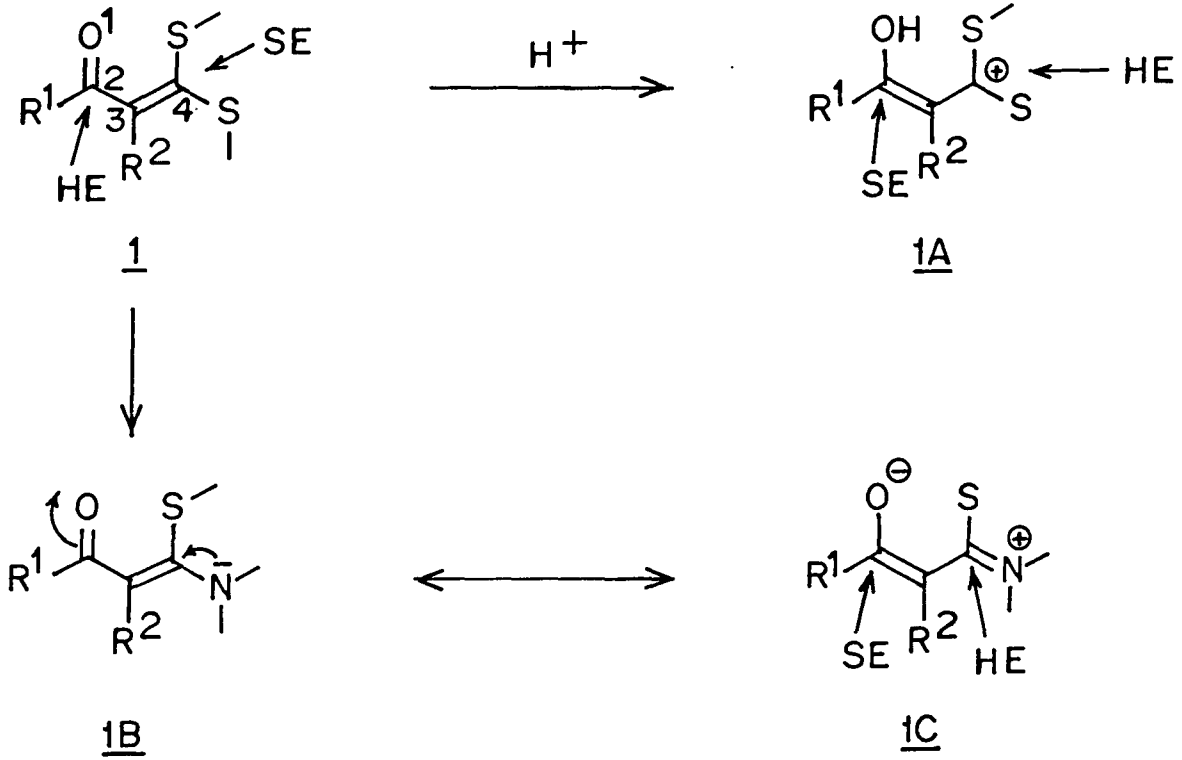
d , R = 4-MeC_6H_4 , R^1 = H

e , R = 4-ClC_6H_4 , R^1 = H

Scheme.- 4


SMe
O
H
SMe
R
H
R1
2
H⊕ (pH 2·2)
OH
SMe
SMe
R
R1
2B
OH
SMe
SMe
R
R1
2C
HO–NH2
(pH 2·2)
HO–NH3⊕
NH2OH ⇌ NH2O⊖
(pH 7-9)
OH
N
SMe
SMe
R
R1
2A
7
8
OH
O
NH
SMe
R
R1
2D

Scheme – 5



1 1A

1B 1C

Hard Soft Affinity Inversion through

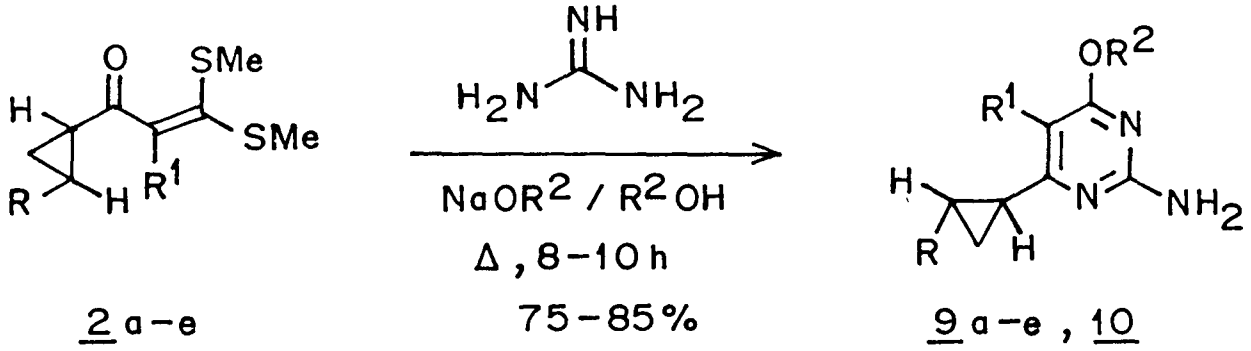
α oxoketene S, S-acetals

HE = Hard Electrophile ; SE = soft electrophile

Scheme – 5A

acetals formed *in situ* by displacement of methylthio group by alkoxide ion. Thus when **2b** was refluxed with guanidine nitrate in the presence of sodium methoxide in methanol the corresponding 2-amino-4-methoxy-6(p-methoxy phenyl) cyclopropyl pyrimidine **9b** was obtained in 82% yield (Scheme -6). the structure of **9b** was fully established by its analytical and spectral data. it was analysed for $C_{15}H_{17}N_30_2$ and molecular weight 271. In its mass spectrum the prominent molecular ion peaks are m/2, 271 (M^+,73.4), 256 (M^+-115, 100). In the IR spectrum the strong absorption bonds at γ_{max} 3180, 1640, 1600 cm^{-1} were characterised for γ-NH and δ-NH stretching frequencies. It was further confirmed by its ^{1}HNMR specterum which displayed the following pattern : δppm 1.15-1.68 (m, 2H, cyclopropyl methine protons) 3.74 (5, 3H), 3.80 (s, 3H) for two methoxy groups, 4.75 (broad s, NH_2 exchanges D_20), 6.0 (s, 1H, H-5) 6.75 (d, 2H, J=9Hz), 7.05 (d,2h, J=9Hz), for 4-aromatic protons with A_2B_2 pattern. [The incorporation of the appropriate alkoxy group in the ketene dithioacetal has been proved experimentally by using different alcohol. Thus the homologous 4-ethoxy pyrimidine **10** was prepared from **2b** by reacting exectlywith guanidine nitrate in presence of sodium ethoxide in refluxing ethanol. All the pyrimidines **9a**, **9b-f** and **10** were characterised by analytical and spectral data which are given in the experimental section.

The α-bis (methylthio) methylene cyclopropyl ketone **2a** also reacted with the enolate anion of cyanoacetamide in refluxing isopropyl alcohol to yield the corresponding 3-cyano-4-methylthio-6(4-methoxy phenyl) cyclopropyl-2 (1H) pyridone **11b** in 74% yield. The structure of **11b** was fully established by its analytical and spectral data. It was analyzed for $C_{17}H_{16}N_20_2S$ and molecular weight 312. It was confirmed by the molecular mass spectrum with molecular ion peaks at m/Z 312 (M^+, 100%), 297 (M^+-156, 40.1 %). The presence of C=N is confirmed by a strong absorption band γ_{max} 2209



2 a-e

9 a-e, 10

2, 9, a, R = C_6H_5, R^1 = H, R^2 = OCH_3

b, R = 4-MeO, R^1 = H, R^2 = OCH_3

c, R = 3,4-$(MeO)_2C_6H_3$, R^1 = H, R^2 = OCH_3

d, R = 3,4-5$(MeO)_3C_6H_2$, R^1 = H, R^2 = OCH_3

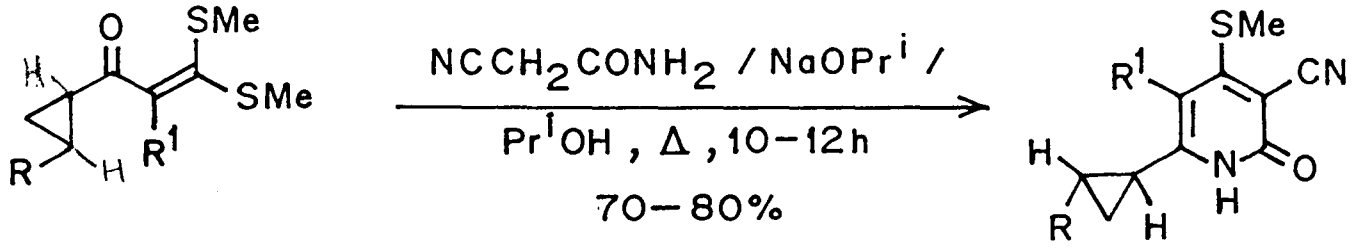
e, R = 4-ClC_6H_4, R^1 = H, R^2 = OCH_3

2b, 10, R = 4-MeO, R^1 = H, R^2 = OC_2H_5

Scheme – 6

cm^{-1} in the IR (KBr) spectrum. The structure of **11b** was further confirmed by its ^{1}HNMR (DMSO-d_6) spectrum. A three proton singlet at δppm 2.45 was assigned to SMe protons and also another singlet 3.60 for three protons was assigned to the methoxy group. A sharp singlet at 5.90 was assigned to 5-H proton of pyridone ring. The four aromatic protons displayed the characteristic chemical shifts of A_2B_2 pattern with two doublest at (6.80 (2H, J=9Hz) and 7.00 (d, J= 9Hz). The other substituted pyridones were obtained by reacting **2a**, **2c-e** with cyanoacctamide, in presence of isopropoxide ,and isopropyl alcohol and refluxing for 10-12 h. (Scheme-7) The nalytical and spectral spectral data of these pyridones are escribed in the experimental section.

In conclusion, The α-bis (methylthio) methylene cyclopropyl ketones undergo heterocyclisation through their 1,3 dielectrophilic carbon centres by reacting with various binucleophiles. In all these reactions it is shown that the cyclopropane ring remains unaltered in the product hetero cycles. Thus the method should be useful for the preparation of a wide variety of heterocycles which might be of interest in their thermal, acid, catalyzed or photochemical rearrangement studies.



2a–e

11a–e

2, 11, a, R = C_6H_5, R^1 = H

b, R = 4–MeOC_6H_4, R^1 = H

c, R = 3,4–$(MeO)_2C_6H_3$, R^1 = H

d, R = 4–ClC_6H_4, R^1 = H

e, R = 4–MeC_6H_4, R^1 = H

Scheme – 7

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 297 and Perkin-Elmer 983 spectrometers. ^{1}HNMR spectra were recorded on a varianEM- 390 (90 MHz) spectrometer using TMS as internal standard. The following abbreviations are used to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m= multiplet. Mass spectra were obtained on a Jeol JMS D-300 spectrometer. Masses (MS) are reported in unit of mass over charge (m/z), the molecular mass by(M). Elemental analysis were carried out on a Heraeus CHN-O-RAPID instrument.

Starting Materials

Commercially available acetone was purchased and redistilled before use. All liquid aldehydes were distilled and purified before use. Benzaldehydes, Anisaldehyde, 3-4-dimethoxy benzaldehyde, 4-methylbenzaldehyde,4-chloro benzaldehyde, 3,4,5, trimethoxy dithioacetals were purified before use.The α-oxoketene dithioacetals were prepared according to the procedure described in chapter II. The cinnamoyl ketene dithioacetals were prepared according to the reported procedure[1,6]. The cyclopropyl ketones were prepared according to the reported procedure[1,2]. Condensation of (-acylketene dithioacetals with aldehydes:

General procedure for the preparation of compounds 1(a-e):

To a cooled and stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (0.06 mol) in ethanol (30 ml), a solution of the acylketene dithioacetal (0.03 mol) and aldehyde (0.031 mol) in minimum amount of ethanol was added dropwise over a period of 5 minutes.The reaction mixture was brought over a period of 20 minutes and

further stirred at room temperature for 4-5 hr. The mixture was diluted with cold water (100 ml) and solid separates out was filtered, washed with water (4x50ml) and dried. The physical and spectral data were compared with that of the reported values.

Synthesis of cyclopropyl ketones **2a-e** from α-cinnamoyl ketene dithioacetal and dimethyl sulphoxonium methylide. General procedure: A suspension of the appropriate ketene dithioacetal (10 mmol), dimethyl sulphoxonium iodide (13 mmol), tetrabutyl ammonium iodide (15 mmol) in an aqueons solution of 50% NaOH(70 ml) and CH_2Cl_2 (70 ml) was stirred at 50°C for 7hrs. The organic layer was separated and concentrated, the residue diluted with - EtOAC to preciptitate tetrabutyl ammonium iodide which was filtered off. The filtrate was evaporated to give crude cyclopropyl ketones which were purified by column chromatography over silica gel using EtOAC/Hexane (1:20) as eluent. The analytically pure samples of cyclopropyl ketones were obtained by recrystallization from chloroform-hexane.The analytical and spectral data were in accordance with the reported values.

Preparation of 5(3)-alkylthio-3(5) (aryl substituted) cyclopropyl pyrazole 6a-f:

General Method: Hydrazine hydrate (6mmol) was added to a solution of the appropriate S,S-acetal (5mmol) in distilled ethanol (20 ml) and the reaction mixture was refluxed for 3-4 hrs (monitored by TLC). The solvent was removed under reduced pressure and the residue was diluted with water (100 ml), extracted with Chloroform (2x50 ml). The organic layer was washed with water (100 ml), dried (Na_2SO_4), and evaporated to give crude pyrazoles which were further purified by column chromatography over silica gel using hexane/ethyl acctate (20:1) as eluent.

5(3)-Methylthio-3(5) (Phenyl) cylopropyl pyrazole 6a was isolated as red oil, yield (90%). IRν_{max}(CCl): 3156(νNH), 1587 (νC=N), 1430 cm^{1}. ^{1}HNMR($CDCl_3$): δ 1.10-1.25(m, 2H, CH_2), 1.85-2.0 (m, 2H, 2CH), 2.29 (s, 3H, SCH_3). 5.85(s, 1H, H-4), 7.0 - 7.30 (m, 5H, ArH). Anal : calcd for $C_{13}H_{14}N_2S$, (230) C 67.8, H6.08, N 12.1. Found : C 66.7, H 6.6, N 11.9.

5(3)-Methylthio-5(4 methoxy phenyl) cyclopropyl pyrazole 6b was isolated as yellow oil. Yield 2.40g (92%). IRν_{max} (CCl_4): 3176, 3130 (νNH), 1609 (νC=N), 1510 cm^{-1}. ^{1}HNMR (90MHz, CCl_4): δ 1.20(m, 2H, CH_2),2.1(m, 2H,2xCH),2.3(s, 3H,SCH_3), 3.70 (s, 3H, OCH_3), 5.90(s, 1H, H-4), 6.75 (d, 2H, J=9Hz, ArH). 6.95 (d, 2H, J=9Hz, ArH). Anal: Calcd. for $C_{14}H_{16}N_2OS$ (260) C64.6, H 6.1, N 10.76. Found : C 64.45, H 6.3, N 10.51. MS: m/z (%) 260 (M^+, 80), 245 (M^+-15, 100).

5(3) Methylthio-3(5) (3, 4-dimetheoxyphenyl) cyclopropyl pyrazole 6c was isolated as a viscous redoil; yield 2.64g (91.3%). IRν_{max} (CCl_4): 3155 (νNH), 1590 (νC=N), 1280cm^{-1}. ^{1}HNMR (90 MHz, CCl_4) : 1.20 (m, 2H, CH) 2.0 (m, 2H, 2x CH), 2.23(s, 3H, SCH_3), 3.65

(s, 3H, OCH_3), 5.85 (s, 1H, H-4), 6.50- 6.65(m,3H, ArH). Anal : Calcd. for $C_{15}H_{18}N_20_2S$ (290) C 62.06, H 62.0, N 9.65.Found : C 62.20, H 61.6, N 9.70.

5(3)-methylthio-3(5) (3-4-5,Trimethoxy phenyl) cyclopropyl pyrazole 6d was isolated as red oil, yield 2.85g(89%). IRν_{max} (CCl_4): 3133 (νNH) 1576 (νC=N), 1499, 1232 cm^{-1}. ^{1}HNMR(CCl_4): 1.20 (m, 2H, CH_2), 1.98- 2.20 (m, 2H, 2xCH), 2.29 (s, 3H, SCH_3), 3.65 (s, 3H, OCH_3), 3.70(s, 6H, 2xOCH_3), 5.83 (s, 1H,H-4),6.22(s, 2H, ArH). Anal: Calcd. for $C_{16}H_{20}N_2O_3S$ (320) C 60.0 H 6.25,N 8.75 Found: C 60.3, H 6.30, N 8.65.

5(3)-methylthio-3(5) (4-chlorophenyl) cyclopropyl pyrazole 6e was isolated as viscous red oil, Yield 2.40g(90%). IR (CCl_4): 3125 (νNH), 1568 (νC=N), 1449, 1488cm^{-1}. ^{1}HNMR (CCl_4): 1.15-1.35 (m, 2H, CH_2), 2.01-2.20 (m, 2H, 2CH), 2.29 (s, 3H, SCH_3), 5.89 (s, 1H, H-4), 6.95 (d, 2H, J=9Hz,ArH),7.20(d, 2H, J=9Hz, ArH). Anal: Calcd. for $C_{13}H_{13}N_2SCl$ (264.5), C 58.97, H 4.91, N=10.58 Found: C 58.85 H 4.93, N 10.63.

5(3)-Methylthio-3(5) (4methylphenyl) cyclopropyl pyrazole 6f was isolated as a viscous oil, yield 2.10g (86%). IR(CCl):3129 (νNH), 2919, 1565 (νC=N), 1430 cm^{-1}. ^{1}HNMR (CCl_4): 1.20, (m, 2H, CH_2), 2.0-2.11 (m, 2H, 2CH), 2.29(s, 6H, SCH_3, CH_3). 5.86 (s, 1H, H-4), 6.90-6.99 (m, 4H, ArH). Anal: Calcd. for $C_{14}H_{16}N_2S$, (244) C 68.85, H 6.55, N 11.47 Found: C 68.86, H 6.75, N 11.37.

Preparation of 5(3)methylthio-3(5)-substituted arylcyclopropyl isoxazoles 7a-e:

General procedure: Hydroxy lamine hydrochloride (2.80g, 0.04mol) was added to a stirred suspension of NaOMe [prepared by dissolving Na(1.38g, 0.06 mol) in absolute MeOH (30 ml)] and stirring was continued for 10 minutes. The appropriate cyclopropyl substituted ketene dithioacetal (0.01 mol) was added and the mixture was refluxed with stirring for 10-15hrs. Methanol was removed under reduced pressure and the residue was poured into ice-cold H_2O(200ml), extracted with $CHCl_3$ (2x50 ml), and the organic layer was washed with H_2O (1x100 ml), dried (Na_2SO_4), and evaporated to give the isoxazoles as pale-colored solids which were recrystallised from $CHCl_3$-hexane to give the analytically pure products.

5-Methylthio-3(phenyl) cyclopropyl isoxazole 7a was isolated as colourless needles m.p. 99°C, yield 78%. IRν_{max} (KBr) : 1603, 1546, 1413 cm^{-1}. ^{1}HNMR ($CDCl_3$) : 1.23-1.51(m, 2H, CH_2), 2.15-2.39 (m, 2H, 2CH), 2.57 (s, 3H, SCH_3), 5.85 (s, 1H, H-4), 7.20-7.41 (m, 5H, ArH). Anal. Calcdfor $C_{13}H_{13}NSO$(231).C67.53, H5.6, N 6.06 Found : C 68,H 5.7, N 6.

5-Methylthio-3(4-methoxyphenyl) cyclopropyl isoxazole 7b was isolated as a colourless crystals ($CHCl_3$ -hexane) m.p. 150°C, yield 2.05g (80%). IR ((KBr) : 1600, 1500, 1430, 1250 cm^{-1}. ^{1}HNMR (90MHz, $CDCl_3$): 1.10-1.32 (m, 2H, CH_2) 1.85-2.20(m, 2H, 2x CH), 2.40 (s, 3H, SCH_3), 3.65(s, 3H, OCH_3), 5.72 (s, 1H, H-4), 6.70 (d, 2H, J=9Hz, ArH), 6.95 (d, 2H,J=9Hz,ArH). Anal: Calcd. for $C_{14}H_{15}NO_2S$(261) C 64.36, H.5.74, N, 5.36.Found :C63.9H 5.60 N 5.60.

5-Methylthio-3 (3, 4, dimethoxy phenyl) cyclopropyl isoxazole 7c was isolated as colourless crystals($CHCl_3$ -hexane) m.p.100°C, yield=2.10g (72%). IR (KBr) = 1600, 1530,

1420, 1230 cm^{-1}. ^{1}HNMR (90 MHz, $CDCl_3$): 1.25-1.50 (m, 2H, CH_2), 2.10-2.36 (m, 2H, 2xCH), 2.65 (s, 3H, SCH_3), 5.90 (s, 1H, H-4),6.75-6.86(m, 3H, ArH). Anal: Calcd. for $C_{15}H_{17}NO_3S$ (291) C 61.85, H 6.0, N 4.8 Found: C61.75, H 5.76, N 4.90.

5-Methylthio-3(4-methyl phenyl) cyclopropyl isoxazole 7d was isolated as colourless crystals m.p. 105°C, yield70%. IR (KBr) : 1601, 1500, 1459, 1258cm^{-1}. ^{1}HNMR ($CDCl_3$) :1.15-1.30 (m, 2H, CH_2), 1.87-2.26 (m, 2H, 2CH), 2.48 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 5.75 (s, 1H, H-4). 6.90-7.01 (m, 4H, ArH).Anal:Calcd. for $C_{14}H_{15}NOS$ (245) C 68.29, H 6.0, N 5.6 Found: C 68, H 6.1,N 5.6.

5-Methylthio-3 (4- chlorophenyl) cyclopropyl isoxazole 7e was isolated as colourless crystals m.p. 120°C yield 2.1g (79%). IR(KBr): 1602, 1545, 1418 cm^{-1}. ^{1}HNMR: 1.21-1.45(m, 2H, CH_2) 2.10-2.35 (m, 2H, 2xCH). 2.50 (s, 3H, SCH_3), 5.80 (s, 1H, H-4), 7.05 (d, 2H, J=9Hz, ArH), 7.25 (d, 2H, J=9Hz, ArH).Anal :Calcd. for $C_{13}H_{12}NSCl$ (265.5), C 58.75, H 4.51, N 5.27. Found: C58.80, H 4.60, N 5.10.

3-Alkylthio-5-Aryl Cyclopropyl Isoxazoles 8a-e. General Procedure: To a stirred solution of the cyclopropyl ketene dithioacetal 2a-e (0.01 mol) in benzene (100 ml) AcOH (100ml), a solution of NaOAc (2.80g, 0.034mol) and NH_2OH. HCl (2.80g, 0.04 mol) in H_2O(10 ml) was added, The mixture was made homogenous by the addition of EtOH (55ml) and refluxed for 8-10 hrs. It was then evaporated to dryness under reduced pressure, and extracted with $CHCl_3$ (2x50ml). The chloroform layer was washed with water (2x100 ml), dried (Na_2SO_4), and evaporated to give a dark brown residue, which were purified by passing through colomn chromatography using Hexane EtOAc (1:1) as eluent. Analytical and spectral data of products **8a-e** are given below:

5-Methylthio-3(phenyl) cyclopropyl isoxazole 8a was isolated as colourless needles m.p. 69°C, yield 58%. IR γ_{max} (KBr) : 1616, 1537, 1400 cm^{-1}. ^{1}HNMR ($CDCl_3$) : 1.32-1.51(m, 2H, CH_2), 2.15-2.39 (m, 2H, 2CH), 2.50 (s, 3H, SCH_3), 5.88 (s, 1H, H-4), 7.30-7.50 (m, 5H, ArH). Anal. Calcd. for $C_{13}H_{13}NSO$ (231). C 67.53, H 5.6, N 6.06 Found: C 68, H 5.7, N 6.

5-Methylthio-3(4-methoxyphenyl) cyclopropyl isoxazole 8b was isolated as a colourless crystals ($CHCl_3$-hexane) m.p. 100°C, yield 60%. IR(KBr) : 1612, 1520, 1430, 1230 cm^{-1}. ^{1}HNMR (90MHz, $CDCl_3$): 1.10-1.32 (m, 2H, CH_2) 1.85-2.20 (m, 2H, 2xCH), 2.35 (s, 3H, SCH_3), 3.65- (s, 3H, OCH_3), 5.85 (s, 1H, H-4), 6.70 (d, 2H, J=9Hz, ArH), 6.90 (d, 2H,J=9Hz,ArH). Anal: Calcd. for $C_{14}H_{15}NO_2S$(261) C 64.36, H 5.74, N 5.36. Found: C63.9H 5.60 N 5.60.

5-Methylthio-3 (3, 4, dimethoxy phenyl) cycloproppyl isoxazole 8c was isolated as colourless crystals($CHCl_3$-hexane) m.p. 70°C, yield (52%). IR (KBr) = 1613, 1542, 1420, 1230cm^{-1}. ^{1}HNMR (90 MHz, $CDCl_3$): 1.35-1.50 (m, 2H, CH_2), 2.10-2.36 (m,2H, 2xCH), 2.55 (s, 3H, SCH_3), 5.93 (s, 1H, H-4), 6.75-6.86 (m,3H, ArH). Anal: Calcd. for $C_{15}H_{17}NO_3S$ (291) C 61.85. Found: C61.75, H 5.76, N 4.90.

5-Methylthio-3(4- methyl phenyl) cyclopropyl isoxazole 8d was isolated as colourless crystals m.p. 60°C,yield70%. IR (KBr): 1615, 1532, 1435, 1230 cm^{-1}. ^{1}HNMR (CDCl):1.25-1.30 (m, 2H, CH_2), 1.87-2.26 (m, 2H, 2CH), 2.48 (s, 3H, CH_3), 2.51 (s, 3H, SCH_3), 5.85 (s, 1H, H-4). 6.90-7.00 (m, 4H, ArH). Anal. Calcd. for $C_{14}H_{15}NOS$ (245) C 68.29, H 6.0, N 5.6. Found: C 68 H6.1N, 5.6

5-Methylthio-3(4-chlorophenyl) cyclopropyl isoxazole 8e was isolated as colourless crystals m.p. 57°C yield 2.1g(79%).IR (KBr): 1615, 1536, 1425 cm^{-1}. ^{1}HNMR: 1.25-1.45(m,

2H, CH_2), 2.15-2.40 (m, 2H, 2xCH). 2.46 (s, 3H, SCH_3), 5.85 (s, 1H, H-4), 7.00 (d, 2H, J=9Hz, ArH), 7.25 (d, 2H, J=9Hz, ArH). Anal. Calcd. for $C_{13}H_{12}NSCl$ (265.5), C 58.75, H 4.51, N 5.27. Found: C58.70, H 4.65, N 5.20.

Preparation of 2-amino 4-alkoxy-6(aryl) cyclopropyl pyrimidines 9a-e, 10:

General procedure: To a solution of sodium alkoxide (prepared by dissolving sodium, 0.04 mol, in 75ml of respective alcohol), guanidine nitrate (2.44g, 0.02 mol) was added and the reaction mixture was stirred for 10-15 minutes. The appropriate cyclopropyl substituted ketene S,S-acetal (0.2 mol) was then added and the reaction mixture was refluxed for 8-9hours.The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform washed (H_2O), dried (Na_2SO_4) and distilled off to give the crude pyrimidines which were purified either by crystallisation or chromatography. Spectral and analytical data are given below:

2-amino-4 methoxy -6(phenyl) cyclopropyl pyrimidine 9a was isolated as colourless needles (EtOAc) m.p. 102°C, yield 83% IRν_{max} (KBr): 3297, 3143 (νNH), 1634, 1559 (δNH), ^{1}HNMR(CCl_4): δ1.20-1.65 (m, 2H, CH_2), 1.75-2.1 (m, 1H, CH), 2.40-2.59 (m, 1H, CH), 3.89 (s, 3H, OCH_3), 5.0(brs, 2H, NH),6.50(s, 1H, H-5), 7.15-7.50 (m, 5H, ArH). Anal.Calcd. for$C_{14}H_{15}N_3O$ (241):C69.70, H 6.2, N 17.4. Found : C 69.6, H 6.2, N 17.0,

2-amino-4-methoxy-6(4-methoxy phenyl) cyclopropyl pyrimidine 9b (EtOH) was isolated as colourless solid m.p. 80°C, yield 2.06g (82%). IR(KBr): 3390, 3180, (νNH), 1640, 1600cm^{-1} (δNH). ^{1}HNMR (90 MHz, $CDCl_3$): 1.15-1.68 (m, 2H, CH_2). 1.70-1.90 (m, 1H, CH), 2.30-2.55 (m, 1H, CH),3.74(s, 3H,OCH_3),3.80(s, 3H, OCH_3), 4.75 (brs, 2H, NH, exchanges D_2O). 6.0 (d, 2H, J=9Hz, ArH). Anal: Calcd. for $C_{15}H_{17}N_3O_2$ (271) C 66.42, H. 6.27, N15.49. Found : C 66.60, H 6.10, N 15.60. MS: m/z(%)271(M^+ ,73.4), 256(M^+ -15, 100).

2-amino-4-methoxy-6(3, 4-dimethoxy phenyl) cyclopropyl pyrimidine (9c) was isolated as colourless solid (EtOH), m.p. 110°C, yield 2.20g (75%). IR (KBr): 3401, 3185 (NH), 1590 cm^{-1}. ^{1}HNMR (90 MHz,$CDCl_3$): 1.20-1.61(m, 2H, CH_2), 1.80-2.10 (m, 1H,

CH), 2.35-2.55 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 3.95 (s,6H, 2xOCH_3), 5.20(brs, 2H, NH), 6.10 (s, 1H, H-5), 6.85 (m, 3H, ArH). Anal: Calcd. for $C_{16}H_{19}N_3O_3$ (301) C 63.78,H6.31,N 13.95, Found C 63.65, H 6.32, N 14.0.

2-amino-4-methoxy-6 (3, 4, 5 trimethoxy phenyl) cyclopropyl pyrimidine (9d) was isolated as colourless crystals (EtOH). m.p. 112°C, yield 2.35g (78%) IR(KBr): 3481, 3173, (γNH), 1559 (δNH), 1446 cm^{-1}. ^{1}HNMR ($CDCl_3$) 1.10-1.65, (m, 2H, CH), 1.75-1, 90 (m, 1H, CH), 2.30 - 2.50 (m, 1H, CH), 3.65,(s, 3H, OCH_3), 3.85 (s, 6H, 2xOCH_3), 5.15 (brs, 2H, NH) 5.95 (s, 1H, H-5), 6.30(s, 2H, Arh). Anal: Calcd. for $C_{17}H_{21}N_3O_4$ (331). C 61.63, H 6.34, N 12.68. Found : C 62.5, H 6.10, N 12.65.

2-amino-4-methoxy-6 (4- chlorophenyl) cyclopropyl pyrimidine (9e) was isolated as colourless crystals, (EtOAC-hexane), m.p. 105°C. Yield 2.0g(80%). 1R (KBr) : 3465, 3147, (γNH_2), 3131, 1559, (δNH_2), 1454 cm^{-1}. ^{1}HNMR (90 MHz, CCl_4): 0.85-1.0 (m, 1H, CH), 1.15-1.65 (m, 2H, CH_2), 1.95-2.15(m, 1H, CH), 3.45 (s, 3H, OCH_3), 4.55 (brs, 2H, NH_2), 5.55 (s, 1H, J-5), 6.75 (d, 2H, J=9Hz, ArH), 6.95(d, 2H, J= 9Hz, ArH). Anal: Calcd. for$C_{14}H_{14}N_3OCl$ (275.5), C 60.98, H 5.08, N 15.24. Found:C61.0,H5.12,N 15.05.

2-amino-4-ethoxy-6 (4-methoxy phenyl) cyclopropyl pyrimidine 10 was isolated as colourless solid (EtOAC-hexane) m.p. 195°C, yield 2.14g (75%). IR (KBr): 3400, 3210(γNH_2), 1645, 1601(δNH_2). ^{1}HNMR (90 MHz, CCl_4): 1.25 (t, 3H, J=7. OHz, OCH_2CH_3), 1.39-1.55 (m, 2H, CH), 1.65- 1.85 (m, 1H, CH), 2.20-2.30 (m, 1H, CH), 3.69 (s, 3H, OCH_3), 4.25 (q, 2H, J= 7.OHz,OCH_2), 5.15 (brs,2H, NH), 5.89 (s, 1H, H-5) 6.65 (d, 2H, J=9Hz, ArH), 6.95 (d,2H, J=9Hz, ArH). Anal: Calcd. for $C_{16}H_{19}N_3O_2$ (285), C 67.36,H6.6, N 14.73. Found C 66.50, H 6.5, N 14.95.

Preparation of 3-cyano-4-methylthio-6-(substituted aryl) cyclopropyl-2(1H)- pyridones (11a-e):

General Procedure: To a solution of sodium isoproxide (prepared by dissolving 0.23g,0.01 mol sodium in 40 ml of dry isopropanol) in isopropanol, cyanoacetamide (0.01 mol) was added and the mixture was shaken for 5-10 min. The appropriate cyclopropyl ketene S,S-(0.01 mol) was then added and the reaction mixiture was refluxed for 8-15 hr. Evaporation of the solvent yielded bright orange sodium salt, which was diluted with water (20-30 ml) and filtered. The residue obtained was acidified with dil.HCl (30%) to give crude pyridones **11a-e** as pale yellow amorophous solids which were crystallized from acetic acid.

3-cyano-4-Methylthio-6 (Phenyl) cyclopropyl-2(1H) pyridone 11a was isolated as colourless needles m.p.151°C, yield 75%. IR ν_{max}(KBr): 3290 (νNH), 2201 (νC≡N), 1670, 1596 cm^{-1}. ^{1}HNMR (DMSO-d_6) (δppm): 1.29-1.56(m, 2H, CH_2), 1.61-1.71 (m, 1H, CH) 1.98-2.40 (m, 1H, CH), 2.50 (s, 3H, SCH_3),5.98 (s, 1H, H-5), 7.05-7.21 (m, 5H, ArH). Anal. Calcd. for: $C_{16}H_{14}N_2OS$ (282),C68.32, H4.6, N 9.9. Found : C 68.5, H 4.6, N 9.6.

3-Cyano-4-Methylthio-6(4-methoxy phenyl) cyclopropyl2(1H) pyridone 11b was isolated as yellow solid (AcOH), yield 2.35g(74%). IR (KBr): 3292, 2209, (νCN), 1632, 1586, (νCO and pyridone ring). ^{1}HNMR (90 MHz, (DMSOd_6) (δppm): 1.25-1.50 (m, 2H, CH_2) 1.56-1.65(m, 1H, CH), 1.90-2.25 (m, 1H, CH), 2.43 (s, 3H, SCH_3), 3.65 (s, 3H, OCH_3), 5.90 (s, 1H, H-5), 6.70 (d, 2H, J=9Hz,ArH),7.00 (d, 2H, J=9Hz, ArH). Anal: Calcd. for $C_{17}H_{16}N_2O_2S$ (312) C65.38, H 5.12, N 8.97. Found: C 65.40, H5.01, N8.99MS :m/z(%)312 (m ,100), 297 (m -15, 40.1), 180 (64.7).

3-Cyano 4-methylthio-6(3, 4-dimethoxyphenyl) cyclopropyl-2(1H) pyridone 11c was isolated as yellow crystals, m.p.140°C, yield 75%. IRν(KBr) = 3298, 2209 (νCN),

1659, 1589 cm^{-1}. ^{1}HNMR (DMSO-d_6): 1.35-1.65 (m, 1H, CH), 1.85-2.10 (m, 1H, CH), 2.28-2.51 (m, 1H, CH), 3.80 (s, 6H, $2OCH_3$), 6.10 (s, 1H, H-5),6.90(m, 3H, ArH). Anal. Calcd. for: $C_{18}H_{18}N_2O_3S$ (342),C63.1,H5.21,N8.18 Found: C 62.6, H 5.3, N8.05.

3-cyano-4-methylthio-6 (4-Chlorophenyl) cyclopropyl-2(1H)-pyridone 11d was isolated as colourless needles, m.p. 150°C, yield 80%. IR (KBr): 3294, 2213 (νCN), 1652, 1597 cm^{-1}. ^{1}HNMR (DMSO-d_6): 1.35-1.60 (m, 2H, CH_2), 1.70-1.89 (m, 1H, CH), (m,1H,CH), 2.59 (s, 3H, SCH_3), 6.10(s, 1H, H-5), 7.20-7.50 (m, 4H, ArH). Anal. Calcd. for: $C_{16}H_{13}N_2SCl$, (300.5), C64.5, H4.3, N9.33, Found: C 64, H 4.1, N 9.2.

3-Cyano-4-methylthio-6 (4-methyl phenyl) cyclopropyl 2 (1H) pyridone 11e was isolated as yellow crystals (AcOH), m.p.145°C, yield 2.10g (70%). IR (KBr): 3128, 1651, 1595 (νco and pyridone ring). ^{1}HNMR (90 MHz, DMSO d_6): 1.35-1.65 (m, 2H, CH_2), 1.80-2.01 (m, 1H, CH), 2.25-2.45 (m, 1H, CH), 2.50 (s, 3H, CH_3), 2.68(s, 3H, SCH_3), 6.20 (s, 1H, H-5), 7.20-7.45 (m, 4H, Ar).Anal:Calcd. for $C_{17}H_{16}N_2OS$ (296), C 68.91, H 5.40, N 9.45. Found :C 68.85, H 5.30, N9.5.

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CHAPTER-V

STUDIES ON REDUCTIVE CLEAVAGE OF C-0 AND C-S BONDS OF ACETALS AND DITHIOACETALS WITH ZINC IN ACETIC ACID.

V.1. INTRODUCTION

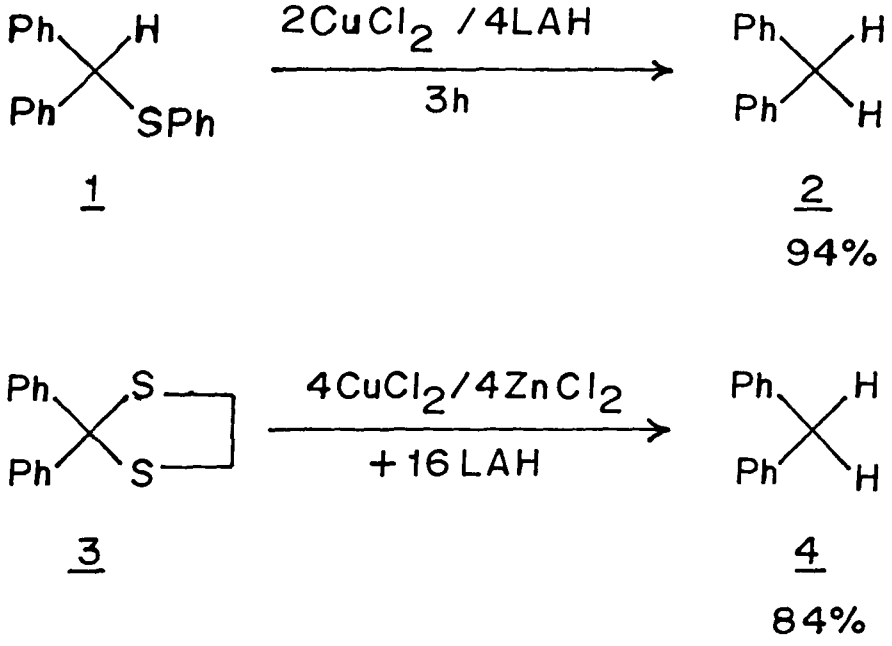
The acetals and dithioacetals are the most commonly used protecting groups for aldehydes and ketones[1,2] . They also play an important role as precursors of masked acylanions in organic synthesis. In both the cases the ultimate step involves the cleavage of the acetal and dithioacetal functionality to restore the original carbonyl group. Acetals and ketals generally revert to the carbonyl compounds upon treatment with acids, but different types may show widely different sensitivity to cleavage conditions. The stability of the dioxolan group to drastic alkaline reaction conditions has been utilized in synthesis of sensitive α, β-unsaturated carbonyl compounds particularly cyclopentenes, the cleavage of dioxolans is facilitated in the presence of periodic acid, whose further oxidation of the elthyene glycol formed drives the

reaction to completion. Both the selective formation and selective cleavage of dioxolans have been well reviewed[3] in the steroid field.

The reductive cleavage of carbon-sulphur bonds is an established synthetic method of considerable utility. the main interest in dithioacetals and ketals has been in connection with their hydrogenolysis by Raney-Nickel to give the corrsponding hydrocarbons, as an alternative to the Clemmensen or Wolff Kishner reduction on the parent carbonyl compound. This subject has been throughly reviewed[4-7]. Hydrogenolisis of thioketals has also been effected by hydrazone and by alkali metals in liquid ammonia[8]. Cleavage of the dithioacetals could better be accomplished using mercury(II) chloride and cadmium carbonate in various solvents[9-13].

Although the sulphides and thioacetals are not generally attacked by sodium borohydride or lithum aluminium hydride, the application of thesehydrides in combination with transition metal halides have been frequently used in organic synthesis to cleave the carbon- sulphur bond selectively in recent years[14]. Thus the sulphide **1** (Scheme-1) is reported[14] to undergo facile carbon- sulphur bond cleavage in the presence of lithium aluminium hydride and copper(II) chloridetogivethe corresponding hydrocarbon **2** in 94% yield.

Similarly, **3** underwent complete reduction in the presence of lithum aluminium hydride and either copper(II) chloride or Zinc(II) chloride to give the corresponding hydrocarbon **4** in 84% yield. Another reagent Nickel (II) chloride in the presence of sodium borohydride has been extensively used[15-16] for selective reduction of carbon-sulphur bonds in yields comparable to those obtained by Raney Nickel methods.


Ph
H
Ph
SPh
1
2CuCl2 / 4LAH
3h
Ph
H
Ph
H
2
94%
Ph
S
Ph
S
3
4CuCl2/4ZnCl2
+16 LAH
Ph
H
Ph
H
4
84%

Scheme-1

Recently mumerous reports concerning the cleavage of C-S bonds by using Zinc as promoter have appeared[17]. The role of Zinc in the selective cleavage of[18-19] C-0 bond of poly acetals and ketals in the steroid field is also well known.

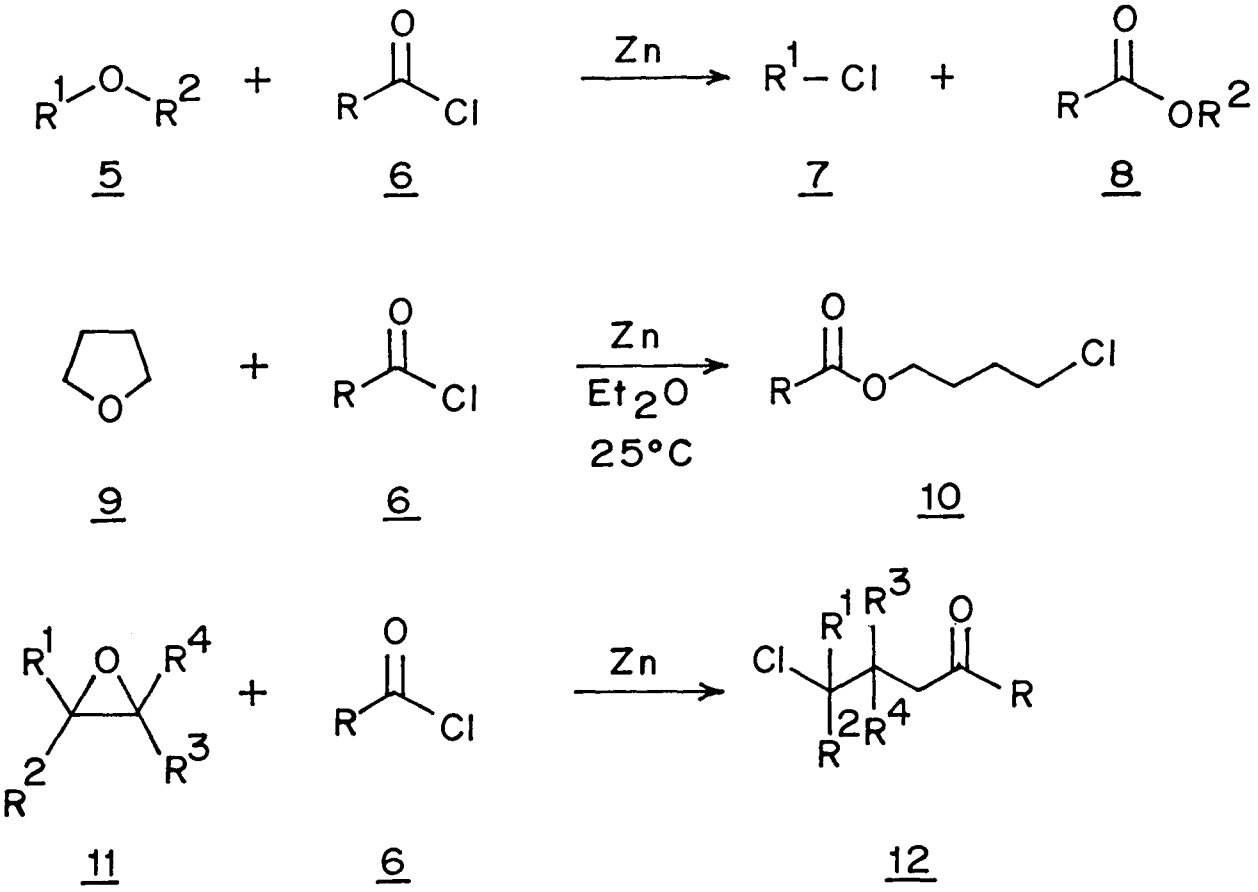
B.C. Ranu *et al.* reported[20] a facile selective cleavage of C-0 bond of other, tetrahydro furan and epoxides in the presences of acyl chloride by zinc. Thus dialkyl ethers **5** in the presence of acid chlorides **6** including acyclic, cyclic and aromatic ones underwent cleavage by zinc toproduce the corresponding alkyl chlorides **7** and alkanoates **8** (Schemes-2).

Similarly, tetrahydrofuran **9** and epoxides **11** yielded the corresponding alkanoates **10** and **12** respectively in thepresence of acylchloride **6** and zinc under the same reaction condition.

A.Schmitt *et al.* reported[21] the reduction of activated thiopyridyl compounds by zinc metal in acetec acid.Thus compounds **13** with thiopyridyl functional group was reactedwith commercial zinc- powder in acetic acid at 80°C to yield the corresponding partial reduction products **14** in 80-98% overall yields as shown in Scheme-3.

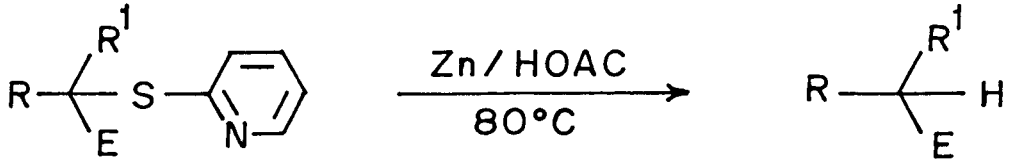
Recent works developed in our laboratory for dethioacetalisation, C-S cleavage and Zinc - acetic acid reduction:

The reagents which could achieve deprotections of both thioacetals and ketals under mild and neutral conditions and ketals under mild and neutral condition in high yields are always on demand. In our laboratory, we have observed[22] a mild and neutral reagent, dimethyl sulfoxide alone can affect the cleavage of dithioacetals to afford the carbonyl compounds in excellent yields.

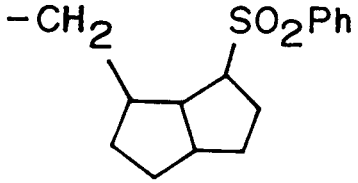


Zinc promoted selective cleavage of ethers.

Scheme-2



13 14

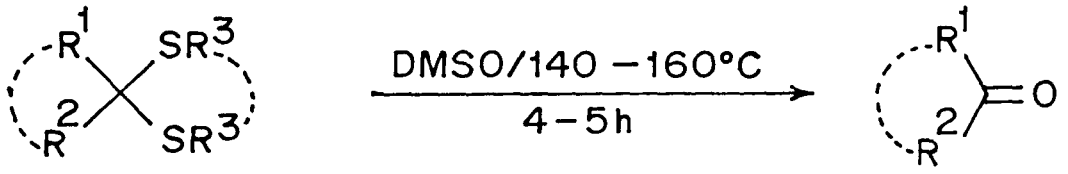
13,14, R	R^1	E
$-CH_2CHPh_2$	H	H
$-CH_2CHPh_2$	H	SO_2Ph
$-(CH_2)_{15}CH_3$	H	SO_2Ph
	H	SO_2Ph
$-(CH_2)_2CHPh_2$	H	CO_2Me
$-(CH_2)_2CHPh_2$	H	CN

Scheme-3

Thus the dithioacetals or ketals **15** on merely heating with dry dimethyl sulfoxide at 140-150°C afforded the aldehydes or ketones **16** in high yields as shown in Scheme-4. The probable mechanism proposed depicting transfer of oxygen from the solvent DMSO to regenerate the original aldehydes and ketones **16** is also depicted in Scheme-5.

The use of Nickel (II) chloride in sodium borohydride to reduceC-Sbondis already mentioned. The partial dethiomethylation of α- oxoketene dithioacetals **17** was developedin the presence of Nickel (II) chloride to give the corresponding mehthyl thiomethylene ketones **18** as a mixture of cis and trans isomeres **18a** and **18b** in 60-70% yields (Scheme-6)[23]. The reducing agent in this reaction was proposed to be nickel boride derived from the reaction of sodium borohydride and nickel (II) chloride.

In another recent work developed in our laboratory[24] related to zinc-acetic acid reductions, β-oxodithioacetals were obtained in high yields by chemoselective conjugate reduction of β-oxoketene dithioacetals. Thus when β-oxoketene dithioacetals **17** were treated with 2-5 equivalents of zinc in 8ml of acetic acid and water at room temperature for **3-5h** to afford the corresponding β-oxodithioacetals **19** in 60-94% overall yields. In fact these β-oxodithioacetals **19** could also be prepared[25] by reducing the β-oxoketene dithioacetals **17** withsodium borohuydride in acetic acid (Scheme-7)[25].

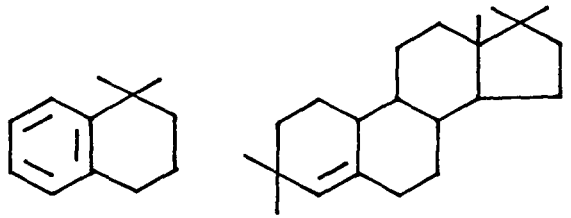


15 16

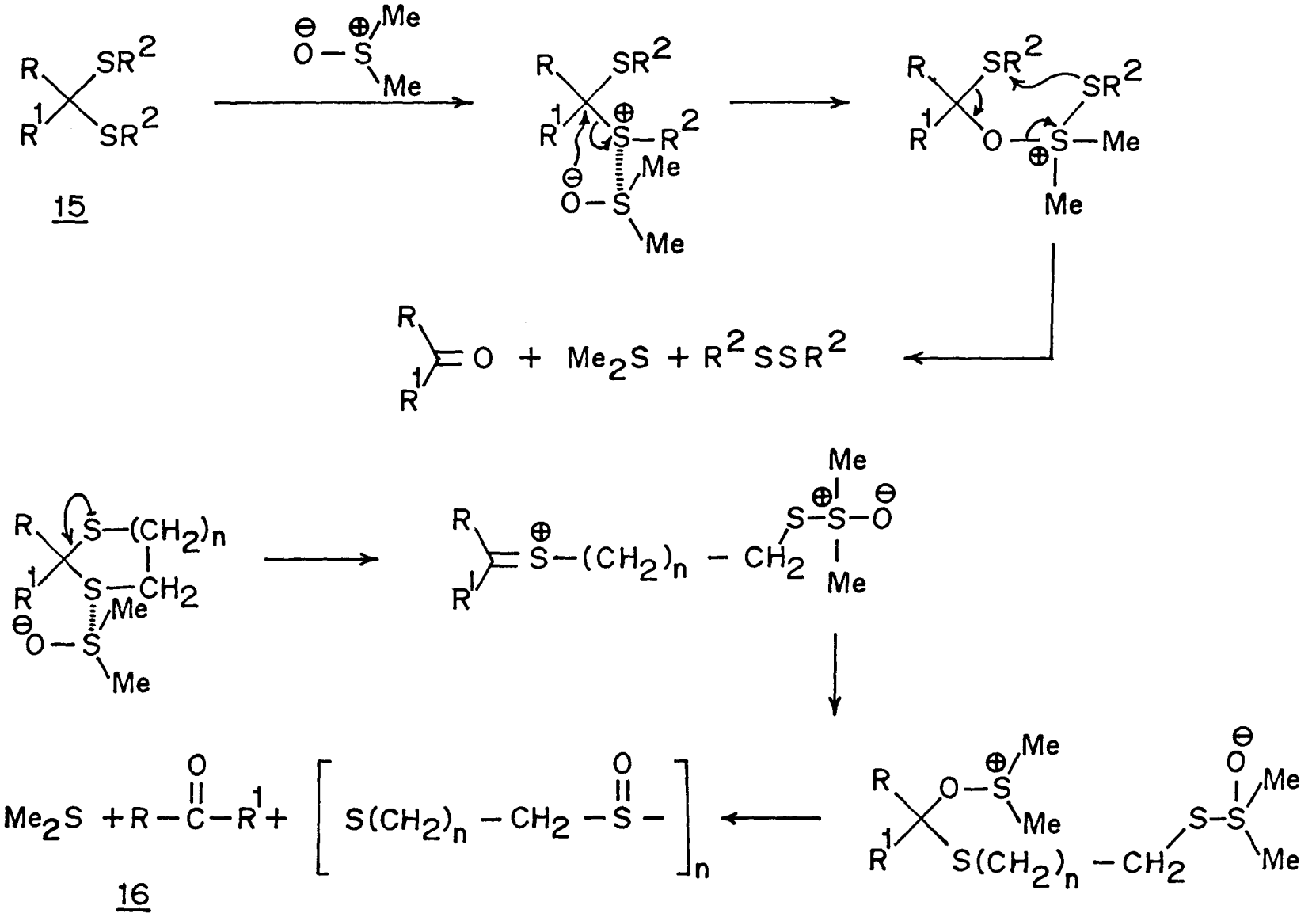
66-94%

$R^1 = C_6H_5$; $C_6H_5-CH=CH-$; Et ; $Me(CH_2)_2-$; $Me(CH_2)_{10}$;
R^2 = H , Me , Et .

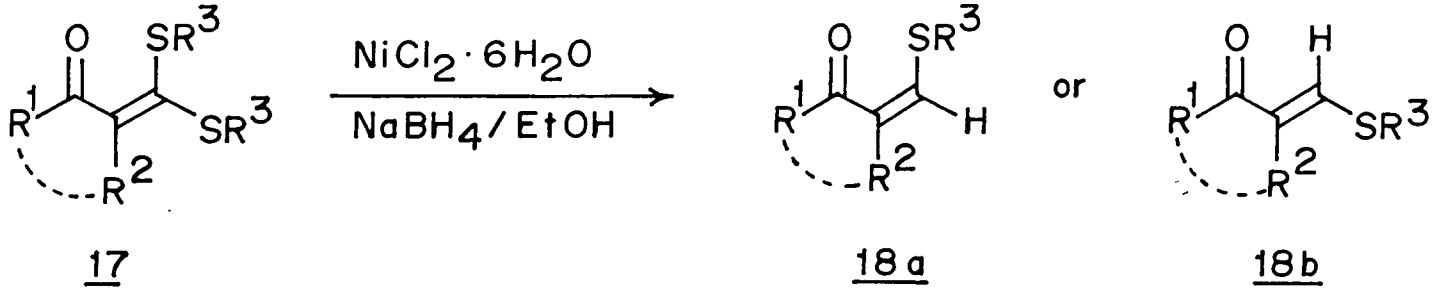
$R^1 - R^2 = -(CH_2)_5-$;



Scheme-4



Scheme-5

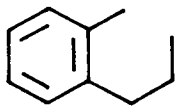
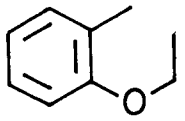


17 18a 18b

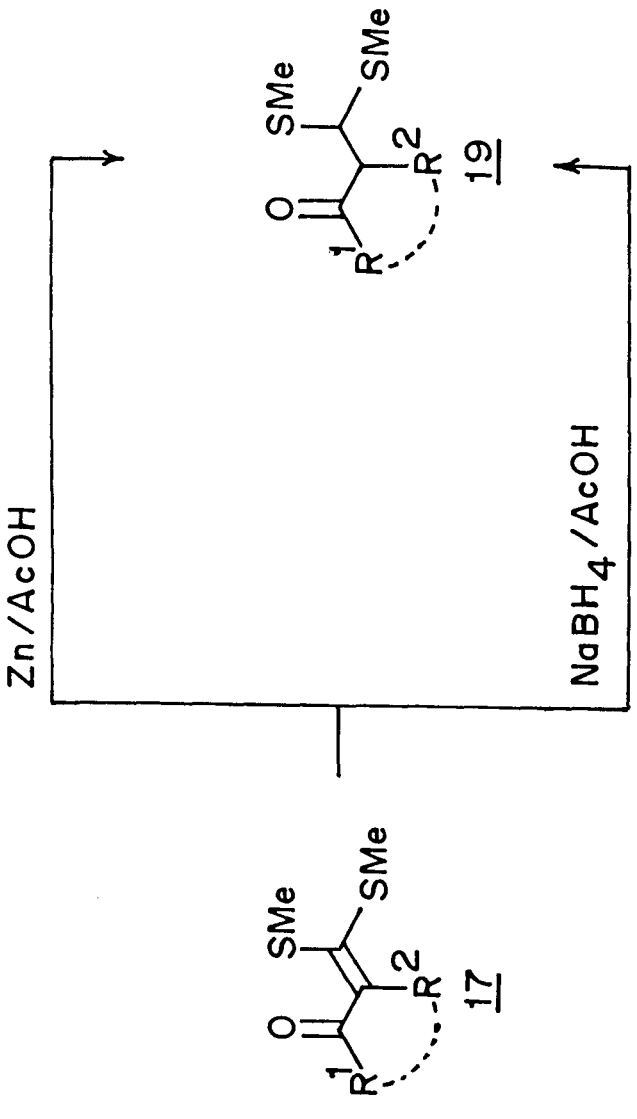
$R^1 = C_6H_5$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, Me ;

$R^2 = H$; $R^3 = Me, Et$.

$R^1 = C_6H_5$, Me, $R^2 = Me, Et, n-C_3H_7$, $R^3 = Me$.

$R^1 = R^2 = -(CH_2)_3-, -(CH_2)_4-$;  ; 

Scheme-6



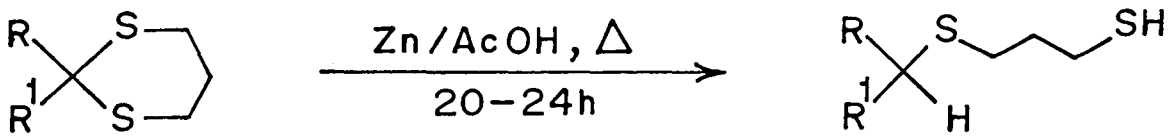
Scheme-7

V.2. RESULTS AND DISCUSSION

From the literature, it is apparent that many reagents have been used to cleave carbon sulphur and carbon-oxygen bonds. It was further contemplated that the thioacetls could be subjected to partial reduction in the presence of zinc in boiling acetic acid. The cyclic dithioacetals **20a-e** which wereprepared by treating appropriate aldehyde or ketone with propane 1,3-dithiol according to the reported[1,26] literature method were examined first. In a typical experiments when dithioacetals **20** (Scheme-8) was refluxed with zinc (10eqv) in acetic acid for 20 hours and the reaction mixture after work up yielded a single compound in 72% yield. The compound was assigned as 4-phenyl-3-thiabutane-1-thiol **21a** in 72% yield. The structure of **21a** was fully established by its analytical and spectral data: IR $(CCl_4)\gamma_{max}$: = 3019, 2915, 1535, 1487cm^{-1} , ^{1}HNMR (CCl): δppm 1.13 (t, 1H, J= 7HZ = SH), 1.70 (m,2H, C CH_2 C), 2.40 (m, 4H, SCH_2), 3.58 (S, 2H, Ph CH_2 -), 7.20 (m, 5H, ArH).

The quantity of zinc (10 mmol) used in these transformations remains critical since any variation made in quantities will affect the quantity of overall yield of product **21**. The other acetals **20b-d** also underwent partial reduction to yield the corresponding sulphides **21b-d** in 72-85%. The structure of these compounds were confirmed by their analytical and spectral data as given in the experimental section. In case of aliphatic acetals and ketals the method fails to observe the C-S bond cleavage reactions.

In case of dithioacetals **20d** derived from naphthyldehyde and ketal **20e** derived from benzophenone the over reduction and completely sulphur free products were also obtained along with the partially reduced products.Thus under the same reaction conditions **20d** yielded **21d** and **2- methyl naphthalene 22** as a 1:1 mixture of the



20 21

72 – 85%

20,21, a, R = C_6H_5, R^1 = H

b, R = 4-ClC_6H_5, R^1 = H

c, R = 4MeOC_6H_4, R^1 = H

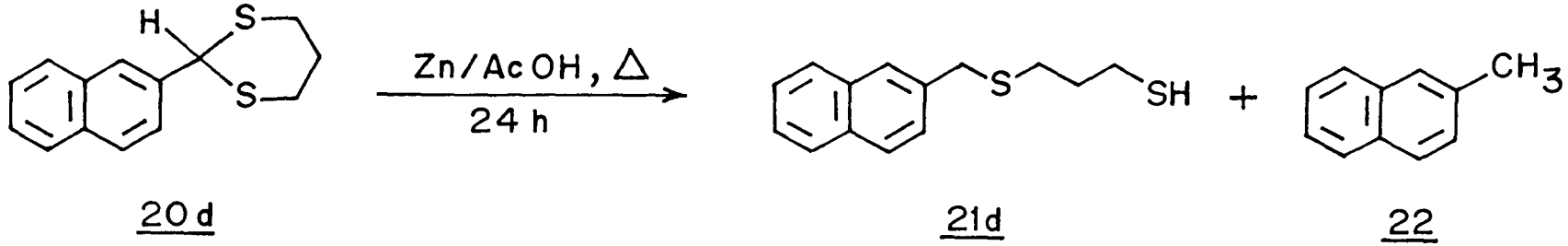
d, R = 2-naphthyl, R^1 = H

e, R = R^1 = C_6H_5

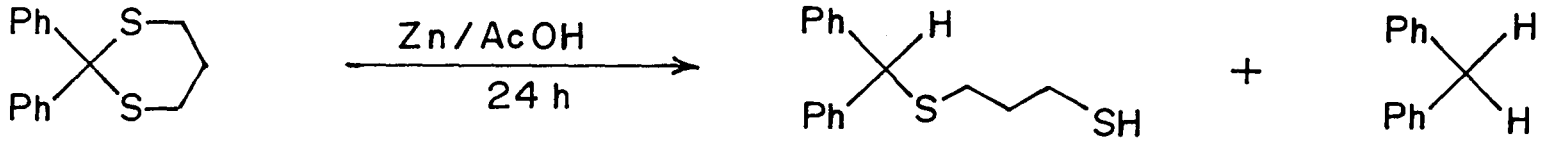
Scheme-8

overall 80% yield. Similarly **20e** yielded **21e** and diphenyl **methane 23** in 1:1 ratio of 75% overall total yield as shown in Scheme - 9.

When the thioacetals **24a,b** and ketals **24c** (Scheme-10) derived from the respective aldehyels, ketone and thiophenol were subjected under the described conditions the corresponding sulphides **25a-c** were obtained in 60-70% overall yields along with the traces of thiophenol. The structures of these compounds were confirmed by comparing their spectral properties with the data reported in the literature.

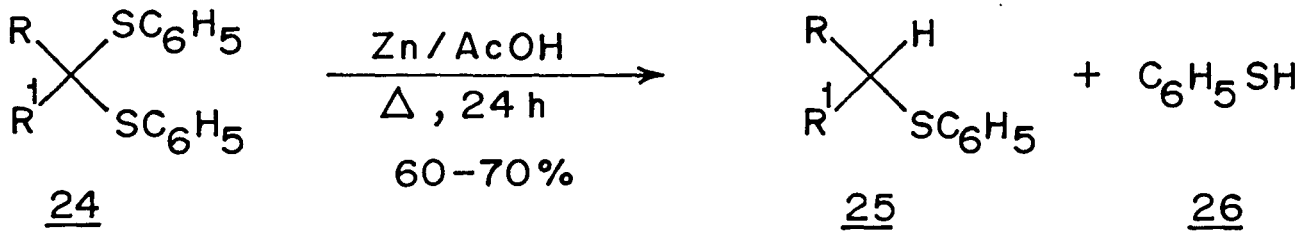


20d 21d 22



20e 21e 23

Scheme-9



24 25 26

24, 25, a, $R = C_6H_5$, $R^1 = H$

b, $R = C_6H_5 - CH = CH$, $R^1 = H$

c, $R = R^1 = C_6H_5$

Scheme-10

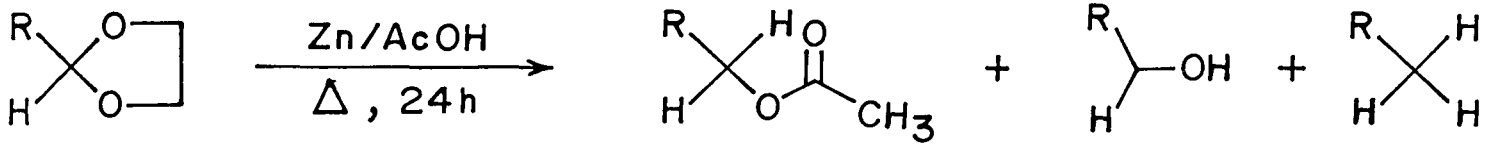
Zn-AcOH reduction studies of Cyclic acetals:

A number of 2-(substituted aryl) 1,3-dioxolan **27a-h** were prepared by reacting the appropriate aldehydes with ethyleneglycol according to the reported[27] procedure. In a typical study, when **27a** was refluxed with **10** equivalent quantity of zinc in acetic acid for 24h after work up yielded two products benzylacetate **28a** and benzyl alcohol **29a**. The overall yield of the mixture was 80% out of which acetate was 45% and the benzyl alcohol was 35% (Scheme-II).

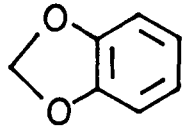
Both the compounds were separated by column chromatography and the structures were confirmed from analytical and spectral data. Similarly **27b** and **27c** yielded a mixture of **28b+29b** and **28c+29c** in 78% and 80% yields respectively. Their further product distributions are shown in Scheme-II. However, the compound 2-(4- methoxy phenyl) 1,3 dioxolan **27d** gave a mixture of two products for acetate **28d** and completely reduced product **30d** instead of the clcohol in 1:1 ratio of overall 80% yield of the mixture. Interestingly compounds **27e-g** with more than one alkoxy substituted groups in the aryl ring gave only completely reduced products **30e-g** in 63-78% overall yields. 2-Naphthyl 1,3-dioxolan **27** however yielded only the naphthyl alcohol **29h** in 82% yield.

The structures of all these compounds were confirmed by comparing their analytical and spectral properties with authentic samples.

The reaction however failed when applied to the corresponding Ketals. Therefore only the aromatic aldehyde acetals were selected to demonstrate the C-0 bond cleavage by Zinc in acetic acid. From the results described above, Zn-in acetic acid reduces the acetals to give either a mixture of acetate or the true alcohol or sometimes the



27 28 29 30

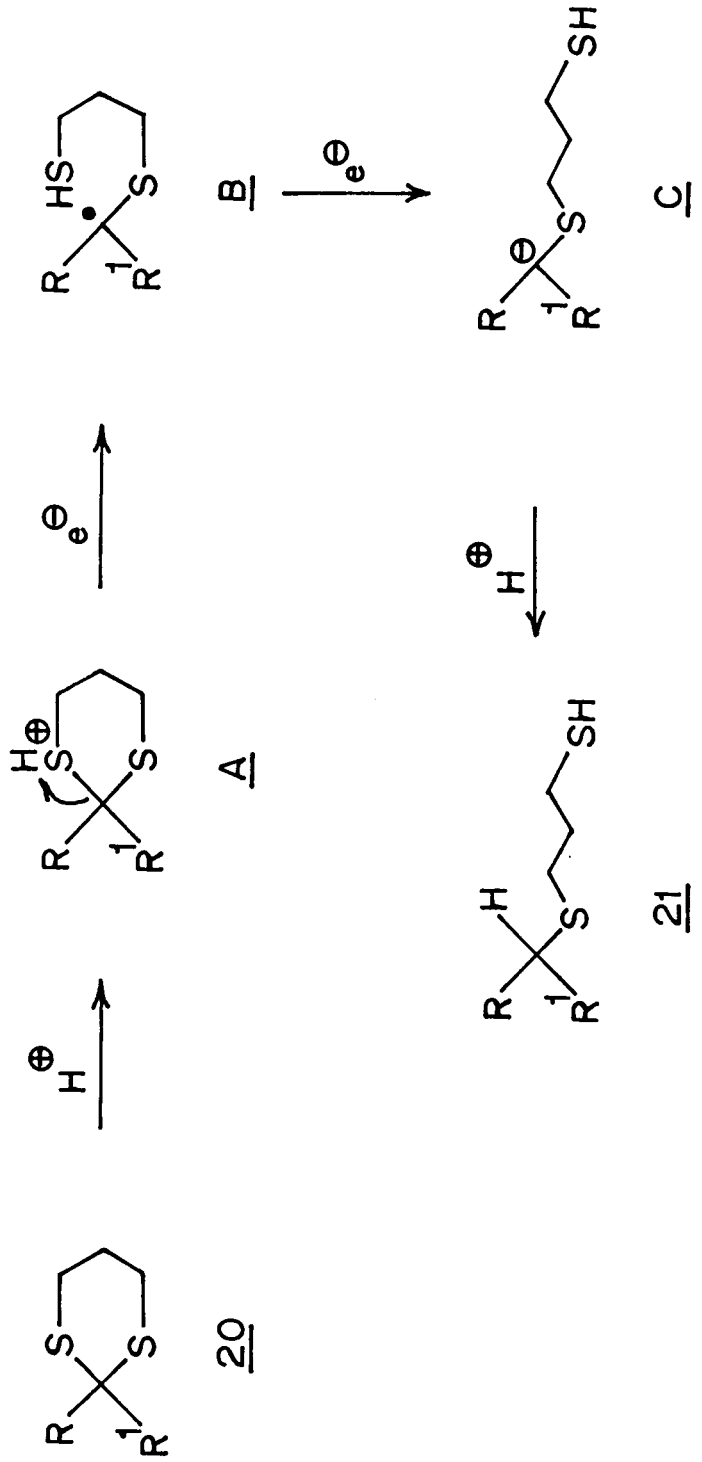
27	R	28(%)	29(%)	30(%)
a	C_6H_5	(45)	(35)	—
b	4-Me C_6H_4	(42)	(36)	—
c	4-ClC_6H_4	(30)	(50)	—
d	4-MeOC_6H_4	(40)	—	(40)
e	3,4-$(MeO)_2$ C_6H_3	—	—	(78)
f	3,4,5-$(MeO)_3C_6H_2$	—	—	(63)
g		—	—	(65)
h	2-Naphthyl	—	(82)	—

Scheme-11

completely reduced products under similar reaction conditions It appears that electron donating substituents appear to favour faster rate of reduction by complete cleavage of the C-O bond of the protecting group.

In conclusion, the reduction of dithioacetals under similar reaction condition was more consistant yielding exclusively one product in high yields.Therefore, the method is useful for partial reduction of dithioacetals to the corresponding sulphides.

The plausible reaction pathway is depicted as shown in Scheme-12 assuming a radical mechanism. Initially compound **20** would be protonated to yield the intermediate **A** which then could be reduced to the radical **B** by rupture of the alkyl-thio bond. Radical **B** could than be further reduced to the stablized carbanion **C**. Protonation of **C** would then yeild the corresponding partial reduced prduct **21** (Scheme-12). However the mechanism governing the reduction of acetals (dixolans) appear to be different since in the acetic acid medium the acetals yield the corresponding acetates as one of the products. These studies are still to be concluded.



Scheme-12

EXPERIMENTAL SECTION

Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on Perkin Elumer- 983 spectrophotometer HNMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as internal standard and chemical shifts are expressed in δ(ppm) units downfield from TMS. The following abbreviation areused to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q= quartet, m= multiplet. Elemental analysis were performed on a Heraeus HN-O-rapid elemental analyser.

Chemical and Reagents:

Zn (AR grade) used in the reaction was suppliedby E-Merck (India) and was activated before use. Commercially available AR grade acetic acid, benzaldehyde, cinnamaldehyde, 4-chlorobenzaldehyde, 4-methoxy benzaldehyde 4-methyl, 2-napthyl aldehyde, Thiopheno 1,1,3- propan dithiol was supplied by E- Merck, Germany and was used as such.

Starting Materials:

All the starting thioacetals, 1,3-dithianes of the corresponding aromatic aldehydes and ketones and acetals 1,3-dioxolans of the corresponding aromatic aldehydes were prepared according to the reported[1,26,27] procedures, and a typical procedure for each class of dithioacetal and acetal mentioned above is given as representative examples in the following sections.

General Procedure for the Preparation of 1,3-dithioactals, (20a-e, Scheme 8) from carbonyl compounds:

To a well stirred solution of carbonyl compound (0.01 mol) in dichloromethane (20ml) was added $BF_3.Et_20$ (2-3 drops) and stirred for 10-15 min. at room temp.The reaction mixture was cooled to 0°C and was added the 1,3-propan dithiol (0.011mol) in dichloromethane (10ml) dropwise over a period of 10 min. The reaction mixture was allowed to come to room temp and stirred for 2-3 hr. (monitored by TLC) worked up with a solution of sat $NaHCO_3$ and product was chromotographed (silicagel column) using hexane as eleuent to obtain pure product. The compounds were characterised by comparison of their physical and spectral data with that of literature methods.

General procedure for the preparation of dithioacetals (24a-c). To a well stired mixture of corresponding aldehyde or ketone (0.01 mol) and thiophenol (0, 0.022 mol) in dichloromethane (10/ml) was added BF_3 Et_2 0 (2-3 drops) at 0°C, stirring continued for further 10 min, allowed to come to room temp during a period of 3 hrs (monitored by TLC). The reaction mixture was then poured into a cold sat. $NaHCO_3$ sol. (50 ml), extracted with dichlorometahane 92x50 ml) washed with water (2x50 ml), dried (Na_2SO_4) and evaporated to obtain the corresponding dithioacetals **24a-c**, which were purified over silica gel column using hexane as eluent. All the dithioacetals thus prepared were well characterized by comparing their spectral and analytical data with that of reported ones.

General procedure for the preparatiom of 1,3- dioxolans **27a-h** (Scheme-II). 12-(substituted aryl)-1,3- dioxolans were prepared by reacting the appropriate aromatic aldehyde with ethyene glycol in refluxing benzene. A trace of p-toluene sulphonic acid was added as catalyst. Water was removed by azeotrope distillation with the benzene.

At the conclusion of the reaction, the mixture was washed with 1M NaOH solution. The benzene layer was dried (Na_2SO_4) and evaporated to yield the residual liquids which were purified by column chromatography. All these dioxolans prepared were found to be identical in their physical and spectral data with the literature data.

General Procedure for reduction of dioxolans 27a-h (Scheme-11) with Zinc in acetic acid:

To a solution of the dioxolane (2 mmol) in acetic acid (10 ml) zinc dust (20 mmol) was added and stirred with refluxing for 24 hours. It was then cooled and poured into crushed ice, extracted with benzene. The benzene layer was washed with saturated aqueous $NaHCO_3$ and 3-4 times with water, dried (Na_2SO_4) and evaporated to give the corresponding acetals **28a-d**, alcohol **29a-c**, **29h** and completely acetal reduced products **30d-g** which were separated and purified by passing through silica gel column using hexane as eluent (Scheme-11 shows the product distribution). All the acetals, alcohols and substituted alkanes are known and were characterised by comparison of their physical and spectral data with those reported in the literature (mixed m.p., b.p., superimposable IR and NMR etc.).

General Procedure for Reduction of 1,3-dithianes 20a-e, 24a-c (Scheme 10) with zinc in acetic acid:

Zinc dust (20 mmol) was added to a solution of dithioacetal (2mmol) in 10 ml of acetic acid. The reaction mixture was refluxed for 24 h. It was then cooled and poured into crushed ice, extracted with benzene. The benzene layer was washed with saturated aqueous NaHCO solution, dried (Na_2SO_4) and evaporated to give the corresponding partially reduced products **21a-e** & **25a-c** and completely reduced products **22** and **23**. The column chromatography over silica gel using hexane as eluent afforded the products in very pure form. Their spectral and analytical data are given below:

5-Phenyl-4-thia pentane-1-thiol (21a) was isolated as yellow viscous oil IR γ_{max} (CCl_4) : 3019, 2915, 1585 cm^{-1} ^{1}HNMR (CCl_4) : 1.13 (t, 1H, J=7Hz, SH) 1.70 (m, 2H, CCH_2C), 2.40 (m, 4H, S CH_2), 3.58 (S, 2H, Ph CH_2), 7.18 (S, 5H, ArH). Anal : Calcd. for $C_{10}H_{14}S_2$: C 60.56, H 7.11, S 32.33. Found: C 60.54, H 7.09, S 32.57.

5-(4 chloro phenyl)-4 thio pentane-1-thiol (21b) was isolated as thick viscous oil. IR γ_{max}(CCl_4): 3013, 2900, 2580, 1575 cm^{-1}. ^{1}HNMR(CCl_4) : 1.13 (t, 1H, J=7.5Hz, SH). HNMR 41.70 (m,2H, J= 7.5 Hz, -CH_2), 2.50 (m, 4H, SCH). 3.50 (s, 2H, Ar-CH_2), 7.25 (m, 4H, ArH). Anal: Calcd. for $C_{10}H_{13}ClS_2$.

5-(4-methoxy phenyl)-4 thio pentane-1- thiol (21c) was isolated as thick viscous oil. IR γ_{max} (CCl_4): 3179, 2923, 2536, 1598, 1102 cm^{-1}. ^{1}HNMR (CCl_4): 1.2 (t, 1H, J= 7.5Hz, SH). 1.70 (m, 2H, CH_2), 2.45 (m, 4H, S-CH_2 -) 3.50 (S,2H, Ar CH_2), 3.70 (S, 3H, OCH_3) 6.85 (d,2H, J=9Hz, ArH), 7.20 (d,2H, J=9Hz, ArH). Anal Calcd. for $C_{11}H_{16}OS_2$ (228,0), C 57.87 H 7.01, C 58, H 6.6. 11 16.

5-naphthyl-4-thia pentane1-1 thiol (21d) was isolated as thick oil. IR (CCl_4) 3103, 3057, 2905, 1656, 1616 cm^{-1}. ^{1}HNMR(CCl_4): 1.20 (t, 1H, J= 7Hz, SH), 1.80 (m, 2H, CH), 2.50 (m, 4H, SCH_2). 3.80 (S, 2H, Ar-CH_2), 7.35 - 7.90 (m, 6H, ArH). Anal: Calcd. for $C_{14}H_{16}S_2$ (248.0), C 67.74, H 6.41, C 66.5, H 6.7.

5,S-diphenyl-4-thia pentan-1-thiol (21e) was isolated as yellow viscous liquid. IR (CCl_4): 3056, 3019, 2918, 1651, 1488 cm^{-1}. ^{1}HNMR: 1.12 (t,1H, J= 7.5 Hz, SH), 1.65 (m, 2H, CH_2), 2.45 (m, 4H, SCH_2) 5.0 (s, 1, Ar- CH), 7.20-7.50 (m, 10H, ArH). Anal: Calcd. for $C_{16}H_{18}S_2$ (274.0) C 70.07, H 6.5, C 71.2, H 6.3.

Benzyl phenyl sulfide (25a) was isolated as a low melting solid (lit. m.p. 41-43.5°C) m.p. 43-44°C. IRν_{max} (KBr) : 3015, 1567, 1466, 1075 cm^{-1}. ^{1}HNMR (CCl_4): 3.98 (S, 2H, $PhCH_2$), 7.15-7.20 (m,10H, ArH). Anal Caled for $C_{13}H_{12}S$ (200.0) C 78 H 6.00 Found C 76 H 6.5.

1-Phenyl-3(phenylthio)-1-propene (25b) was isolated as lowmelting soild. IRν_{max} (CCl_4): 3014, 2900, 1541 cm^{-1}. ^{1}HNMR (CCl_4) : 3.50 (d,2H, J = 6HZ, -CH_2SPh), 5.8 - 6.20 (m, 1H, = CH), 6.30 (d,1H, J = 15HZ, = CH), 7.20-7.50 (m, 10H, ArH). Anal Calcd for $C_{15}H_{14}S$ (226.0) C 79.64 H 6.19 found C 79.1 H 5.9.

Phenyl - [1,1 - diphenyl] methyl sulfide (25c) was isolated as oil. IRν_{max} (neat) : 3512 3019, 1481 cm^{-1}. ^{1}HNMR (CCl_4) : 5:35 (S, 1H, CH), 7.10 - 7.50 (m, 15H, ArH). Anal Caled for $C_{19}H_{16}S$ (276) C 82.60, H 5.79. Found : C 82.5 H 5.8.

Diphenyl methane (23) was isolated as lowmelting solid (lit . m.p. 22-24°C) m.p. 24-25°C. IR (CCl_4) : 3018, 2907, 1712, 1592. ^{1}HNMR (CCl_4): 3.8 (S,2H, CH_2), 7-7.25 (m, 10H, ArH). Anal Calcd for $C_{13}H_{12}$(168.24) C 82.9, H 7.14. Found C 83.2 , H 6.8.

2-Methyl naphthalene (22) was isolated as colourless needles. (m.p lit 34-36) m.p. 35-37°C. IR ν_{max} (CCl_4): 3335, 3090, 2901, 1592 cm^{-1}. ^{1}HNMR (CCl_4): δ(ppm: 2.45 (S, 3H, CH_3), Anal Calcd for $C_{11}H_{10}$ (142.20) C 92.9, H 7.04. Found C 92.8,H 7.26.

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