SYNTHETIC STUDIES ON HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTEREST

BY

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Dedicated to my Mother

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This is to certify that the work described in this thesis has been carried out by Mr. Sanjeev Kumar Sharma. He has satisfactorily completed the minimum period of two years of investigational 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.

(H. Junjappa)
Supervisor

Date : April 1993.

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(SANJEEV KUMAR SHARMA)

Date :

PREFACE

Polarized ketene S,S-acetals can be conveniently prepared from any active methylene compound. They can be converted to the corresponding polarized ketene S,N- and N,N-acetals. The S,N- and N,N-acetals can also be prepared directly by reacting active methylene compounds with alkyl or arylisothiocyanates. These polarized ketene S,S-, S,N- and N,N-acetals have been extensively explored in this laboratory for the development of several new synthetic methods for a variety of heterocyclic and carbocyclic compounds. The work described in this thesis highlights further new interesting transformations of polarized ketene S,S-, S,N-acetals.

A brief survey of the recent reports on the work done on the polarized ketene S,S-, S,N- and N,N-acetals is presented in the first chapter. In the second chapter a brief introduction on the recent development in the area of antiamebic drugs is presented. The third chapter describe the nitration of various substituted pyrroles, which are of biological interest. These nitropyrroles were screened for antiprotozoal activity. The results of these screening tests are discussed in this chapter. A new route to variously substituted imidazoles utilizing the aminoacetaldehyde diethylacetal has been described in the fourth chapter.

Fifth chapter of this thesis describes the synthesis of 7-substituted and 6,7-annulated-5-deazapteridines. Mannich reaction on α-oxoketene S,N-acetals for the synthesis of substituted and annulated tetrahydropyrimidine and tetrahydrotriazine has been described in the last chapter.

The entire documentation in this thesis is supported by appropriate references. The references of the published work of the present investigation are cited in the respective chapters.

CONTENTS

CHAPTER I

THE POLARISED KETENE S,S-, S,N- AND N,N-ACETALS : GENERAL INTRODUCTION

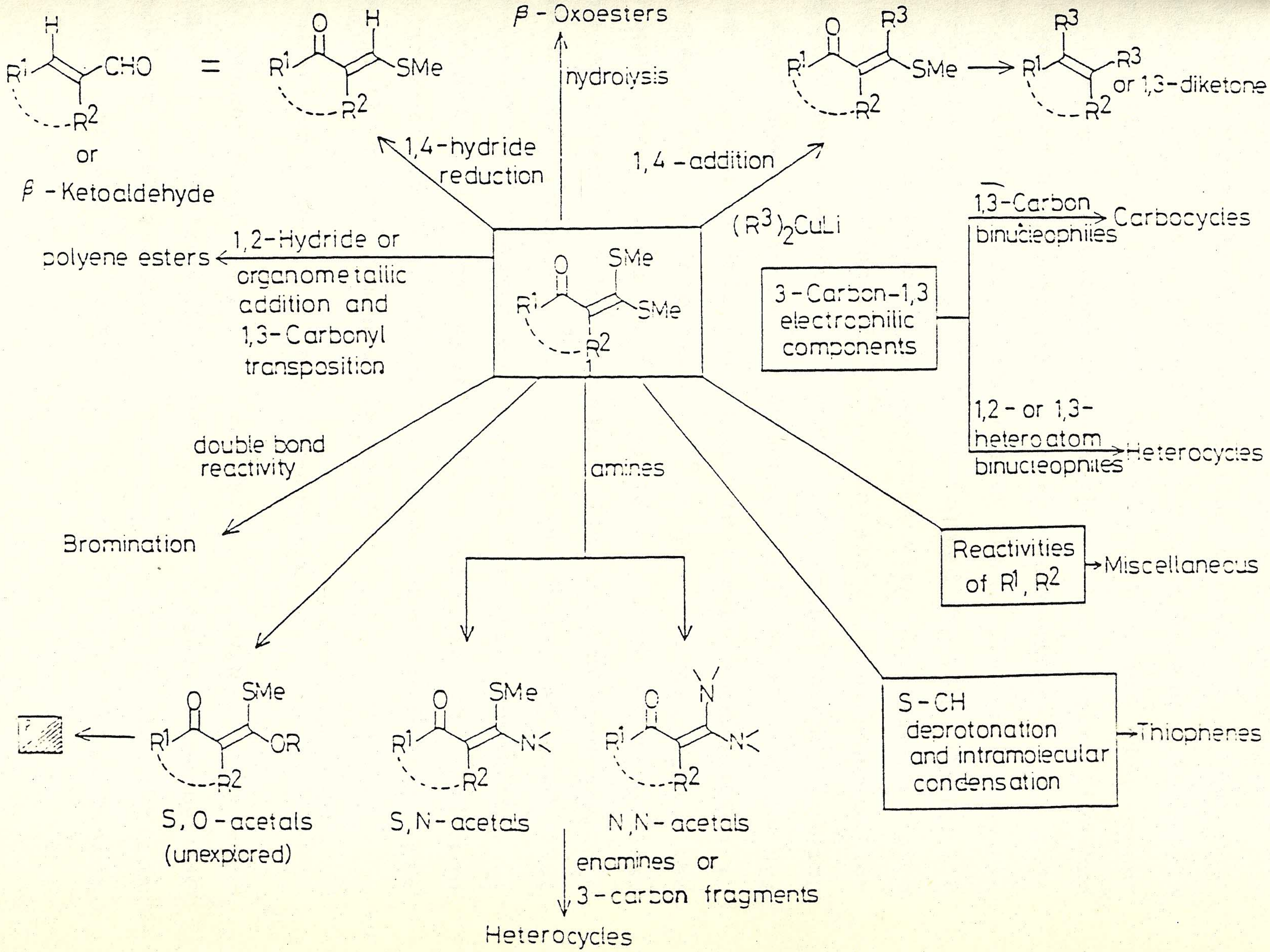
The polarized ketene S,S-, S,N- and N,N-acetals are the simplest synthetic intermediates derived from the active methylene compounds[1a]. The preparation of S,N-acetals and N,N-acetals could be achieved either from the parent S,S-acetals or directly from the active methylene ketones and the corresponding isothiocyanates followed by alkylation to afford the corresponding S,N-acetals. The N,N-acetals inturn are obtained by reacting the corresponding S,S-acetals or S,N-acetals with primary or secondary amines. These compounds have been extensively used in organic synthesis particularly for the synthesis of biologically important heterocycles. We have used these intermediates for the synthesis of nitro pyrroles (Chapter 3) and 5-aroyl-6-methylthio 1,2,3,4-tetrahydropyrimidines (Chapter 6). Also dimethyl iminodithiocarbonates derived from primary amines have been used in the synthesis of 1-substituted-2-methylthio imidazoles (chapter 4). In the first section a brief survey of polarized ketene S,S-acetals is described and the second section describes a survey of polarized ketene S,N- and N,N-acetals. A brief description of the present work is described at the end of this chapter.

A. The Polarized Ketene S,S-acetals:

Polarized Ketene S,S-acetals 1 have been recognized as useful building blocks in many synthetic operations[1b]. This class of compounds can be conveniently prepared[2-10] by reacting any active methylene compound with two equivalents of base and carbon disulphide followed by alkylation. The first synthesis of α-oxoketene S,S-acetal was reported by Kebler and co-workers in 1910[11-13]. Much of the earlier work on α-oxoketene S,S-acetals was confined to their synthesis and properties while little attention was paid to their synthetic utility. Later, Thuillier and Vialle prepared these compounds in high yields in a one-pot reaction by reacting the active methylene ketones with carbon disulphide in the presence of sodium amylate as base followed by alkylation[2-5]. Subsequently these reaction conditions have been greatly improved using different bases and reaction conditions[6-10]. A large number of α-oxoketene S,S-acetals have now been prepared and their chemistry has been reviewed by Dieter[1].

The oxoketene S,S-acetals generally exhibit well defined physical properties and can be easily purified by conventional methods. They are stable under mild acidic and alkaline conditions and can be stored indefinitely without apparent decomposition. The corresponding α-oxoketene O,O-acetals are moisture sensitive and undergo hydrolysis under mild conditions. The oxoketene S,S-acetal is essentially a masked β-keto ester in which the ester functionality is protected as dithioacetal. Alternatively, it may be viewed as an α,β-unsaturated ketone containing highly functionalized β-carbon. They are versatile three carbon fragments having 1,3-electrophilic centres of differing electrophilicity. These intermediates possess considerable potential in the stereo and regioselective construction of new bonds either by 1,2-nucleophilic addition to carbonyl group or by 1,4-conjugate addition to the β-carbon of the enone system. Also, they are primary precursors for the corresponding O,S-, S,N- and N,N-acetals. The preparation of the O,S-acetals is accomplished through the displacement, by an oxygen nucleophile, of the sulfonium salt[14]. The S,N-acetals can be prepared by the displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol[15,16]. The N,N-acetals can be prepared by displacing both the thiomethyl groups by amines in refluxing acetic acid[16,17].

In Scheme 1 various reactivity profiles of α-oxoketene S,S-acetals of the general formula 1 have been outlined. Hydrides and organometallic reagents give 1,2-addition reactions typical of carbonyl function reactivity[18]. These

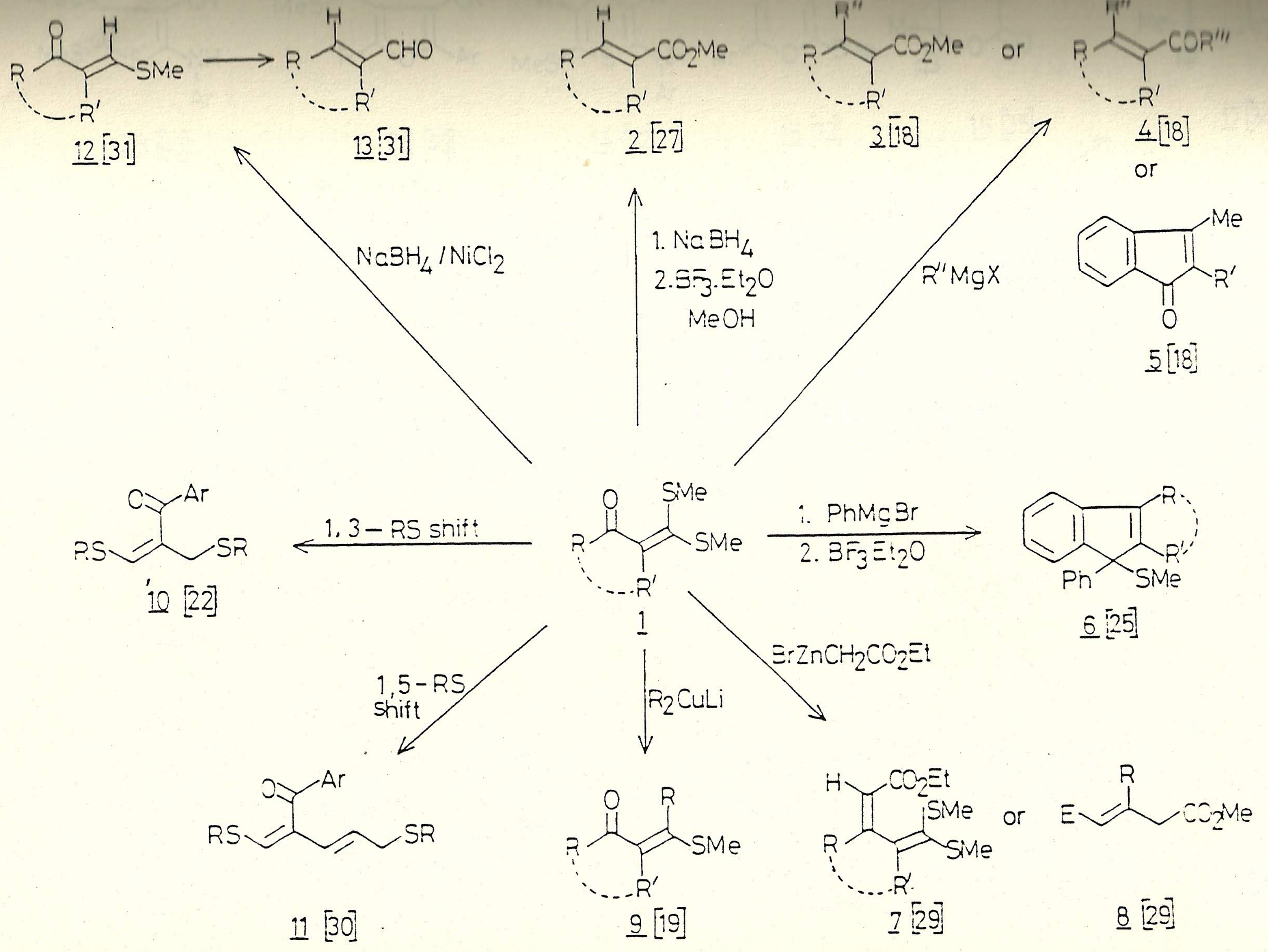

CHO
or
β - Ketoaldehyde
SMe
β - Oxoesters
hydrolysis
1,4-hydride reduction
1,4 - addition
$(R^3)_2CuLi$
or 1,3-diketone
1,2-Hydride or organometallic addition and 1,3-Carbonyl transposition
polyene esters
1,3-Carbon binucleophiles
Carbocycles
3-Carbon-1,3 electrophilic components
1,2 - or 1,3-heteroatom binucleophiles
Heterocycles
double bond reactivity
Bromination
amines
Reactivities of R1, R2
Miscellaneous
S-CH deprotonation and intramolecular condensation
Thiophenes
S, O - acetals (unexplored)
S, N - acetals
N, N - acetals
enamines or 3-carbon fragments
Heterocycles
1

Scheme 1

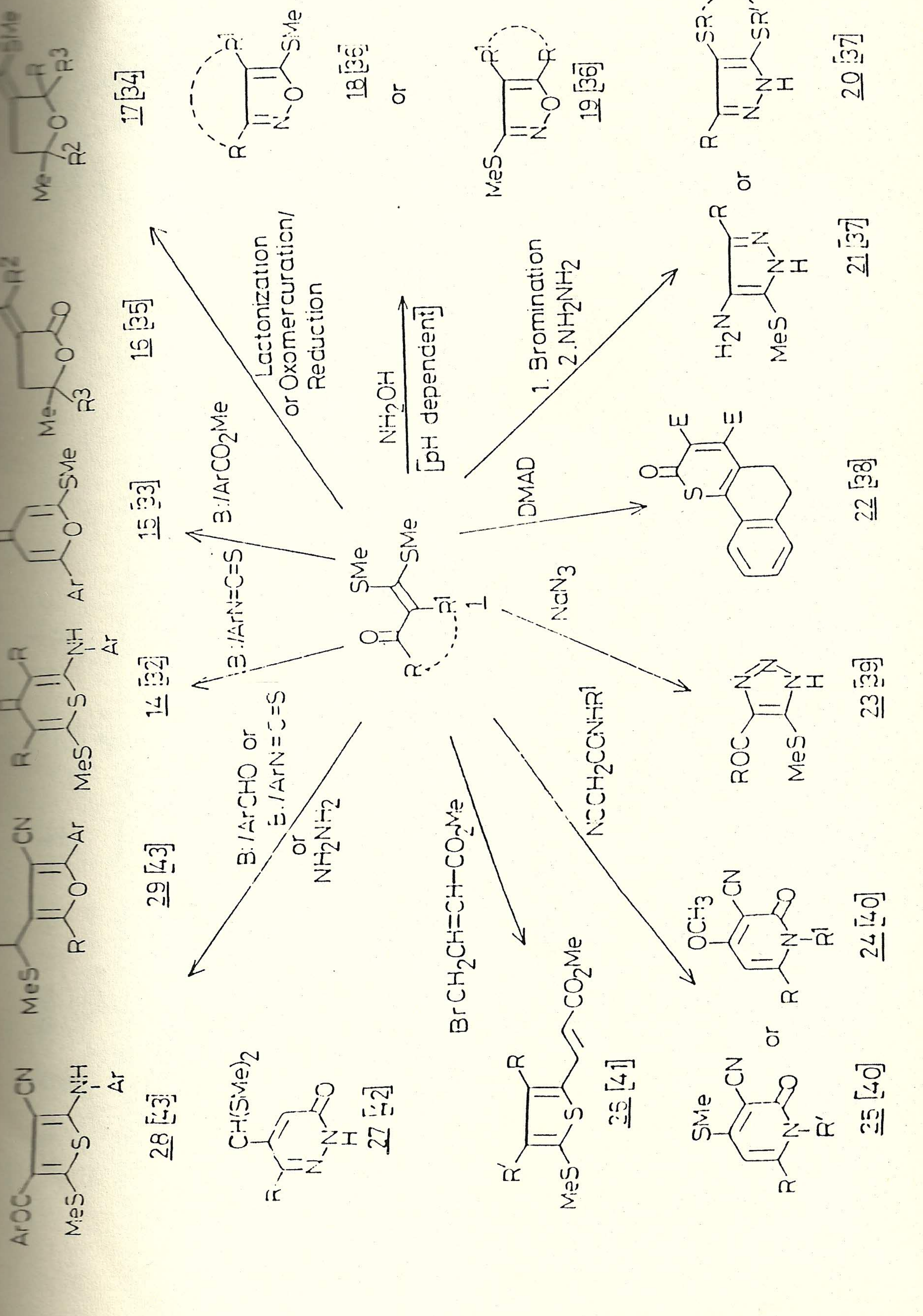
reactions can be directed in 1,4-manner by suitably manipulating the reagent and reaction conditions[18-20]. Further transformations after the initial 1,2- or 1,4-additions are also reported[18]. The α-oxoketene S,S-acetals possess typical 1,3-electrophilic centres and they react with 1,2- and 1,3-heteroatom binucleophiles to give five and six membered heterocyclic compounds respectively. The 1,3-carbon nucleophiles, on the other hand, give carbocyclic compounds. The enolate ion formed by deprotonation (R^1=alkyl) can undergo condensation with aldehydes to give α-enoylketene S,S-acetals[2,21]. An allylic anion formation has also been reported, when R^2 is a methyl group, leading to rearranged products[22]. Demethylation on the thiomethyl group followed by intramolecular Aldol type condensation to thiophene is also reported[23,24]. The reactivity of the mercapto double bond is also exploited with electrophiles. Thus, dithioacetals (R^2=H) undergo bromination at α-position with N-bromosuccinimide[25]. It is therefore, apparent that the oxoketene S,S-acetals of general formula 1 constitute an important class of synthons. Some of the related transformations[26-57] reported from this laboratory are briefly shown in Schemes 2,3,4 and 5.

B. Polarized Ketene S,N- and N,N-acetals:

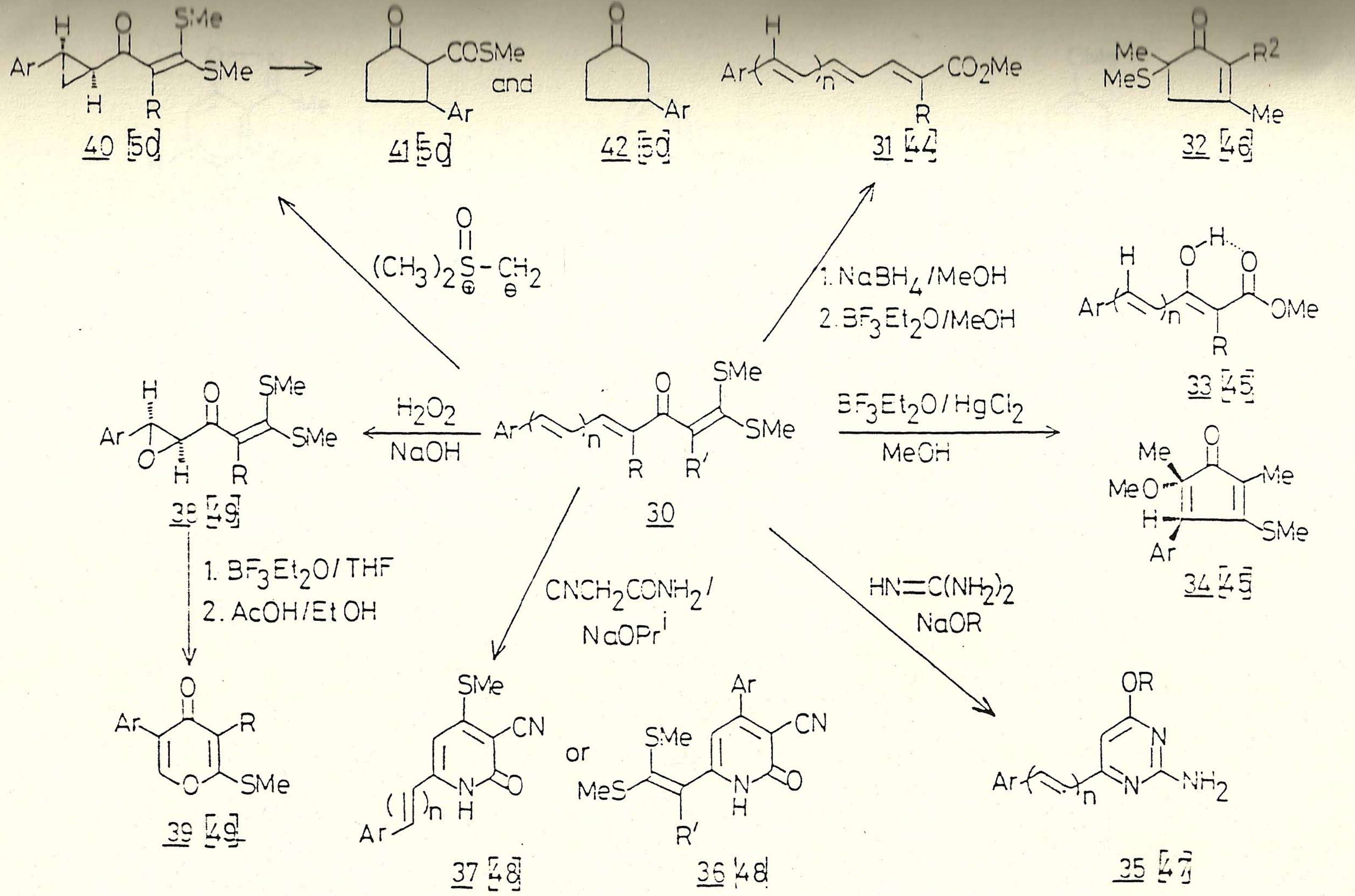
Like oxoketene S,S-acetals, the S,N- and N,N-acetals also possess 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. As stated in the preceding


12 [31]
13 [31]
2 [27]
3 [18]
or
4 [18]
or
5 [18]
NaBH$_4$ / NiCl$_2$
1. NaBH$_4$
2. BF$_3$.Et$_2$O
MeOH
R''MgX
1, 3 – RS shift
1
1. PhMgBr
2. BF$_3$ Et$_2$O
6 [25]
10 [22]
1,5 - RS shift
R$_2$CuLi
BrZnCH$_2$CO$_2$Et
11 [30]
9 [19]
7 [29]
or
8 [29]

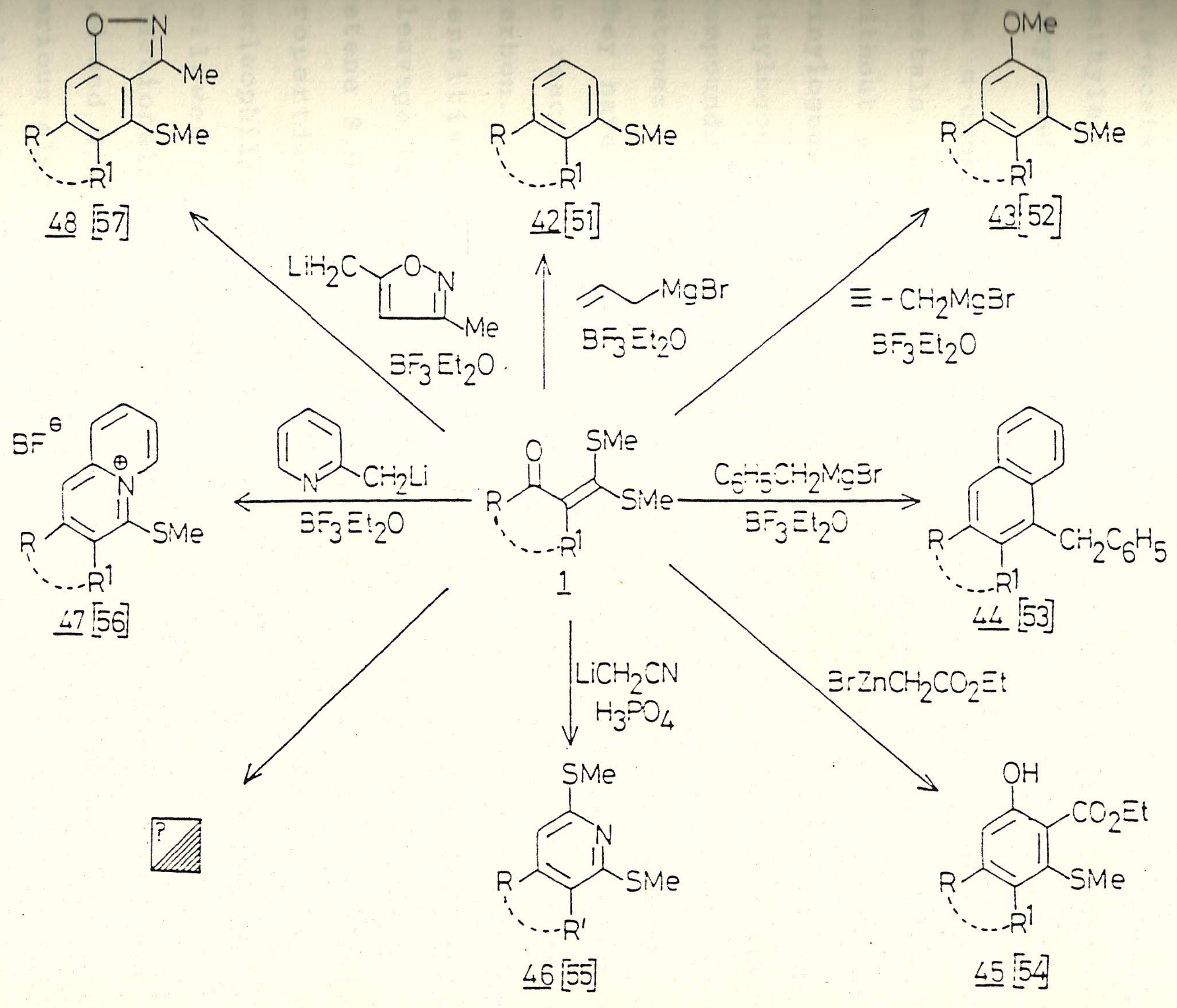
Scheme -2


1
Lactonization or Oxomercuration/ Reduction
NH2OH [pH dependent]
1. Bromination 2. NH2NH2
DMAD
NaN3
NCCH2CONHR1
BrCH2CH=CH-CO2Me
B:/ArCHO or B:/ArN=C=S or NH2NH2
B:/ArN=C=S
B:/ArCO2Me
17 [34]
16 [35]
15 [33]
14 [32]
29 [43]
28 [43]
27 [42]
26 [41]
25 [40]
24 [40]
23 [39]
22 [38]
21 [37]
20 [37]
19 [36]
18 [36]
or

SCheme - 3


40 [50]
41 [50]
and
42 [50]
31 [44]
32 [46]
$(CH_3)_2\overset{O}{\overset{\|}{S}}^{\oplus}-CH_2^{\ominus}$
1. $NaBH_4$/MeOH
2. BF_3Et_2O/MeOH
33 [45]
H_2O_2
NaOH
30
$BF_3Et_2O/HgCl_2$
MeOH
34 [45]
38 [49]
1. BF_3Et_2O/THF
2. AcOH/EtOH
$CNCH_2CONH_2$/
$NaOPr^i$
$HN{=}C(NH_2)_2$
NaOR
39 [49]
37 [48]
or
36 [48]
35 [47]

Scheme-4


48 [57]
42 [51]
43 [52]
LiH2C
O
N
Me
BF3 Et2O
MgBr
BF3 Et2O
≡ - CH2MgBr
BF3 Et2O
OMe
SMe
R
R1
BF⊖
CH2Li
BF3 Et2O
O
SMe
SMe
1
C6H5CH2MgBr
BF3 Et2O
CH2C6H5
47 [56]
44 [53]
?
LiCH2CN
H3PO4
BrZnCH2CO2Et
OH
CO2Et
N
R'
46 [55]
45 [54]

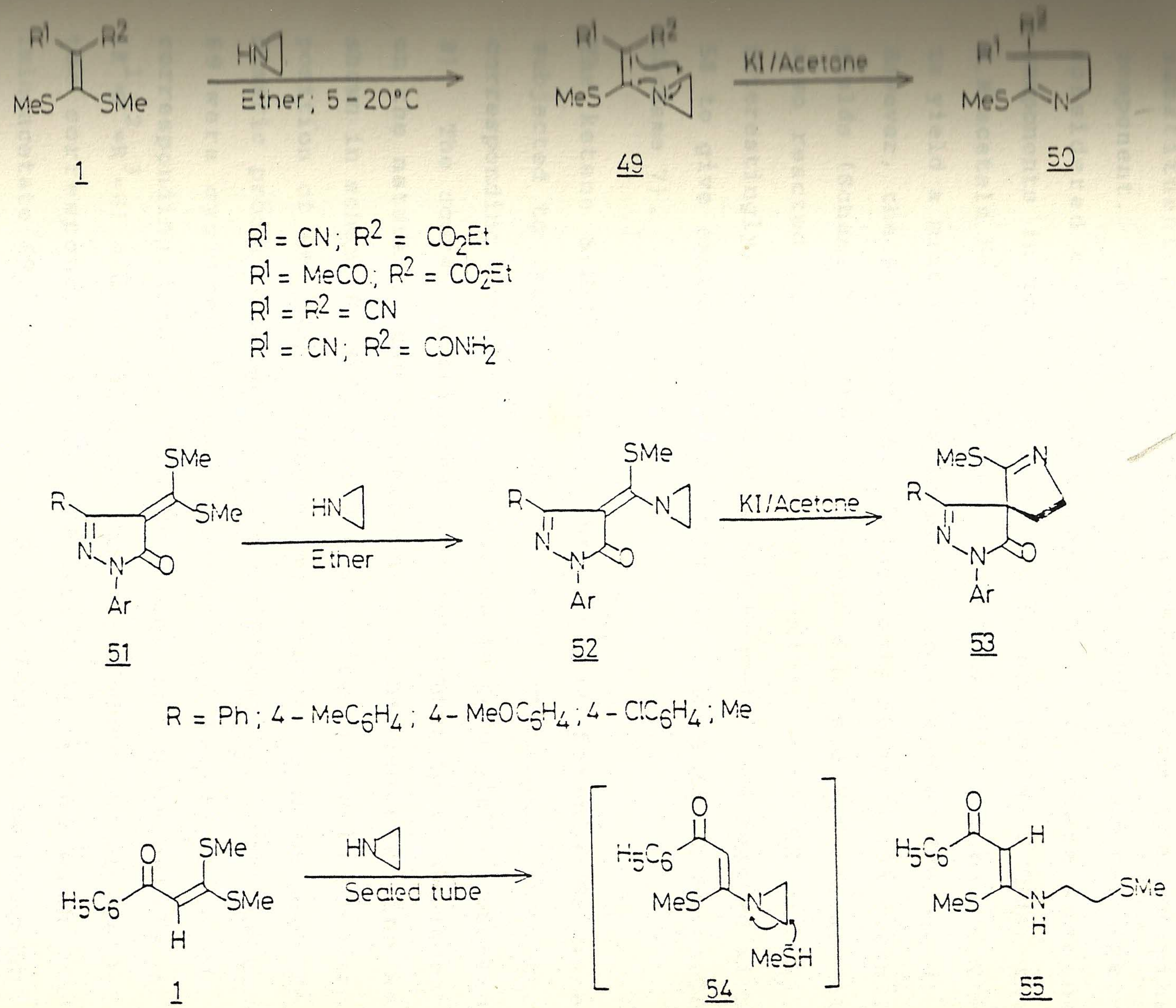
Scheme - 5

section, they can be prepared by displacement of one or both of the methylthio groups from oxoketene S,S-acetals by suitable amines under different reaction conditions. The S,N-acetals can alternatively be prepared direct from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates followed by alkylation[58].

The α-oxoketene S,N- and N,N-acetals, 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 the α-carbon. however, these enamines are found to be more sensitive to moisture and readily undergo 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 displacement with various binucleophiles[59-61] followed by intramolecular 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[62-75]. The chemistry and synthetic applications of the α-oxoketene S,N- and N,N-acetals have been reviewed[1] and a number of synthetic methods have been developed in this laboratory which are briefly discussed in the following section.

The doubly activated α-oxoketene S,S-acetal 1 underwent smooth displacement reaction at room temperature with aziridinek[62] to give the corresponding S,N-acetal 49 in high yields (Scheme 6). The S,N-acetals 49 can be viewed as N-vinyl aziridine and undergo facile ring expansion to yield the corresponding pyrrolines 50 (Scheme 6). Similarly the α-oxoketene S,S-acetal derived from pyrazolone 51 reacted with aziridine at room temperature to yield the intermediate aziridino S,N-acetal 52 followed by potassium iodide assisted rearrangement to yield the corresponding 1-aryl/alkyl-3-phenyl-6-methylthio-2,3,7-triazaspiro [4,4]non-6-ene-4-ones (53) in high yields (Scheme 6). However, singly activated s,S-acetals 1 did not give 54 at room temperature and the corresponding 3-methylthio-3-(2-methylthioethylamino)-1-phenyl-2-propene-1-one (55) was obtained in 54% yield (Scheme 6). Apparently, the formation of 55 was explained by ring opening by the attack of the nucleophile, methylmercaptan, as shown in Scheme 6.

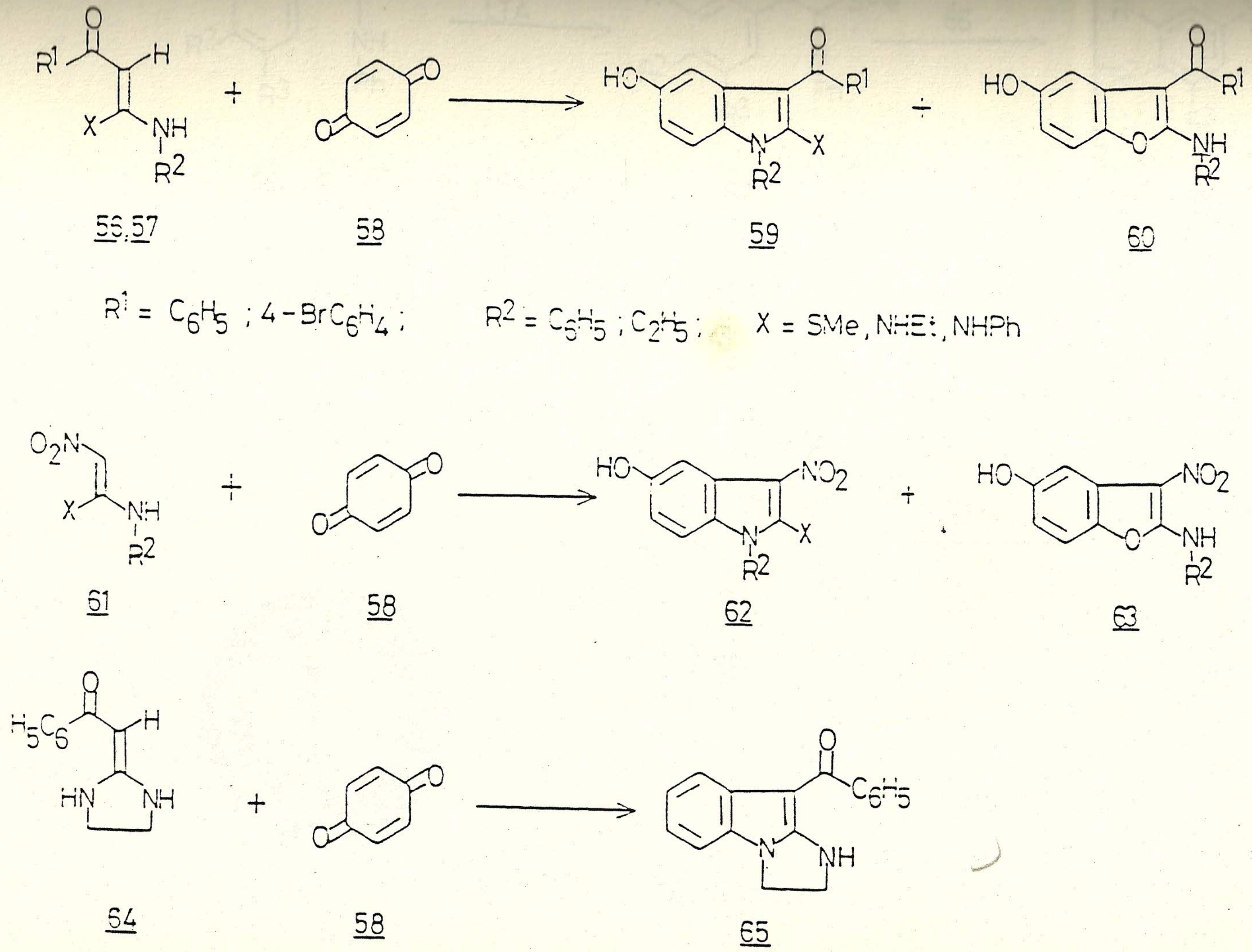
The application of the α-oxoketene S,N- and N,N-acetals in the Nenitzescu indole synthesis was reported[63] from this laboratory. The Nenitzescu indole synthesis required β-keto esters, linear and cyclic 1,3-diones to prepare the required enamines which react with p-benzoquinone 58 to yield the corresponding 2-substituted-5-hydroxy indoles (59). This


1
HN
Ether; 5-20°C
49
KI/Acetone
50
$R^1 = CN;\ R^2 = CO_2Et$
$R^1 = MeCO;\ R^2 = CO_2Et$
$R^1 = R^2 = CN$
$R^1 = CN;\ R^2 = CONH_2$
51
HN
Ether
52
KI/Acetone
53
$R = Ph;\ 4-MeC_6H_4;\ 4-MeOC_6H_4;\ 4-ClC_6H_4;\ Me$
1
HN
Sealed tube
54
MeSH
55

Scheme - 6

method suffered from limitations since it carried a substituent at 2-position arising from the enamine component. The α-oxoketene S,N- and N,N-acetals were considered as suitable alternatives to these enamine components in the Nenitzescu indole synthesis. Thus, the N,N-acetals 56 underwent smooth reaction with p-benzoquinone to yield a mixture of the indole 59 and furan 60 (Scheme 7). However, the S,N-acetal 57 yielded only 60 in 9-70% overall yields (Scheme 7). The nitroketene S,N- and N,N-acetals 61 also reacted with 58 to yield a mixture of 62 and 63. Interestingly, the cyclic ketene N,N-acetals 64 reacted with 58 to give exclusively the tricyclic indole 65 in 9% yield (Scheme 7).

The ketene S,N-acetals of the general formula 66 were subjected to lead tetra acetate (LTA) oxidation[64] when the corresponding acetals 69 were formed in good yields (Scheme 8). The course of this reaction was found to be dependent on the nature of the substituent in the benzene ring as shown in scheme 8. With electron donating groups in the para position of 66, the corresponding iminoacetates 69 and the dimeric products 68 were obtained (Scheme 8). The acetals 69 were cyclized in the presence of $BF_3.Et_2O$ to the corresponding indoles 70. However, the S,N-acetals 66 ($R^1=R^2=R^3=H$) did not give the dimeric product 68 but yielded the corresponding indole 70 directly along with the iminoacetate 69. The yield of 70 was found to be dependent on the substituents on the phenyl ring. Similarly, the α-



$R^1 = C_6H_5$; $4-BrC_6H_4$; $R^2 = C_6H_5$; C_2H_5 ; X = SMe, NHEt, NHPh

Scheme -7

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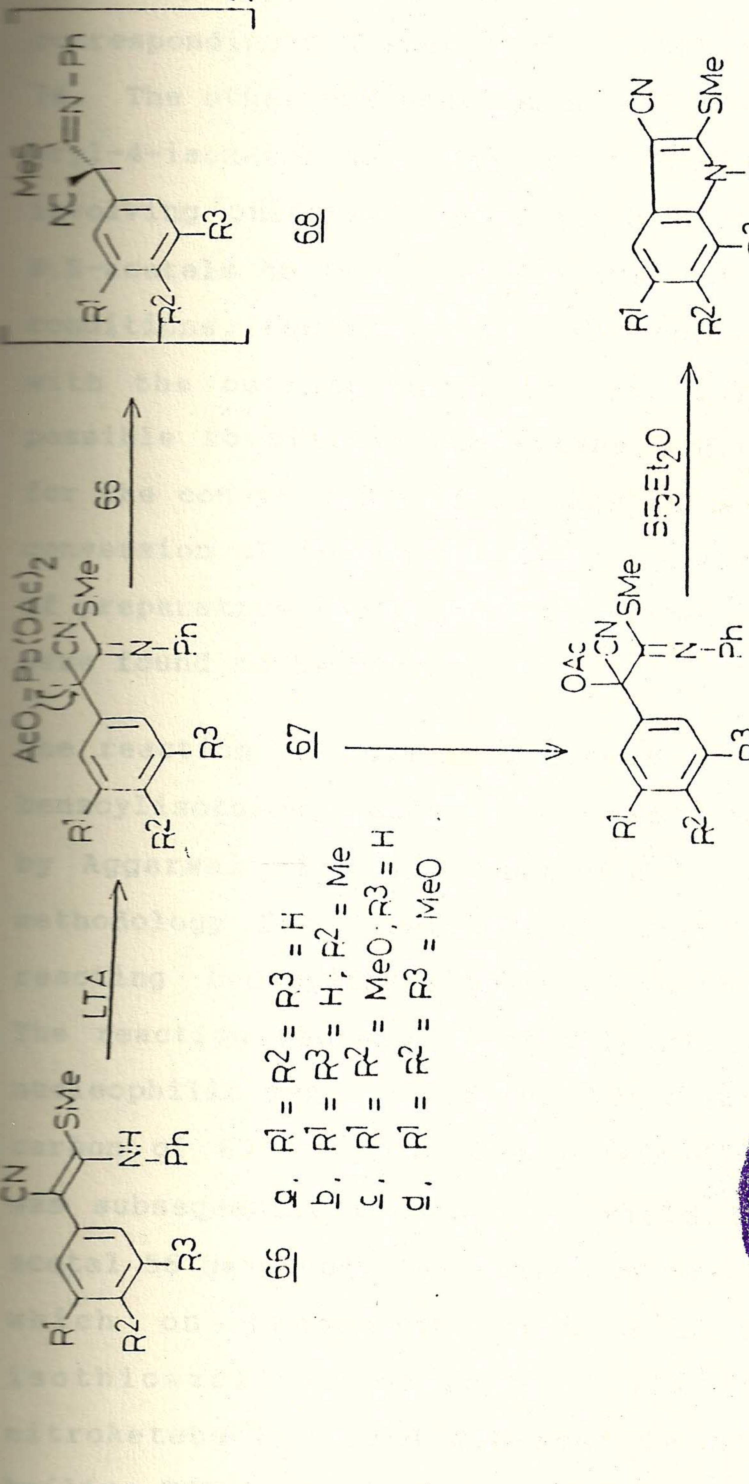


$\underline{a}$, $R^1 = R^2 = R^3 = H$

$\underline{b}$, $R^1 = R^3 = H$, $R^2 = Me$

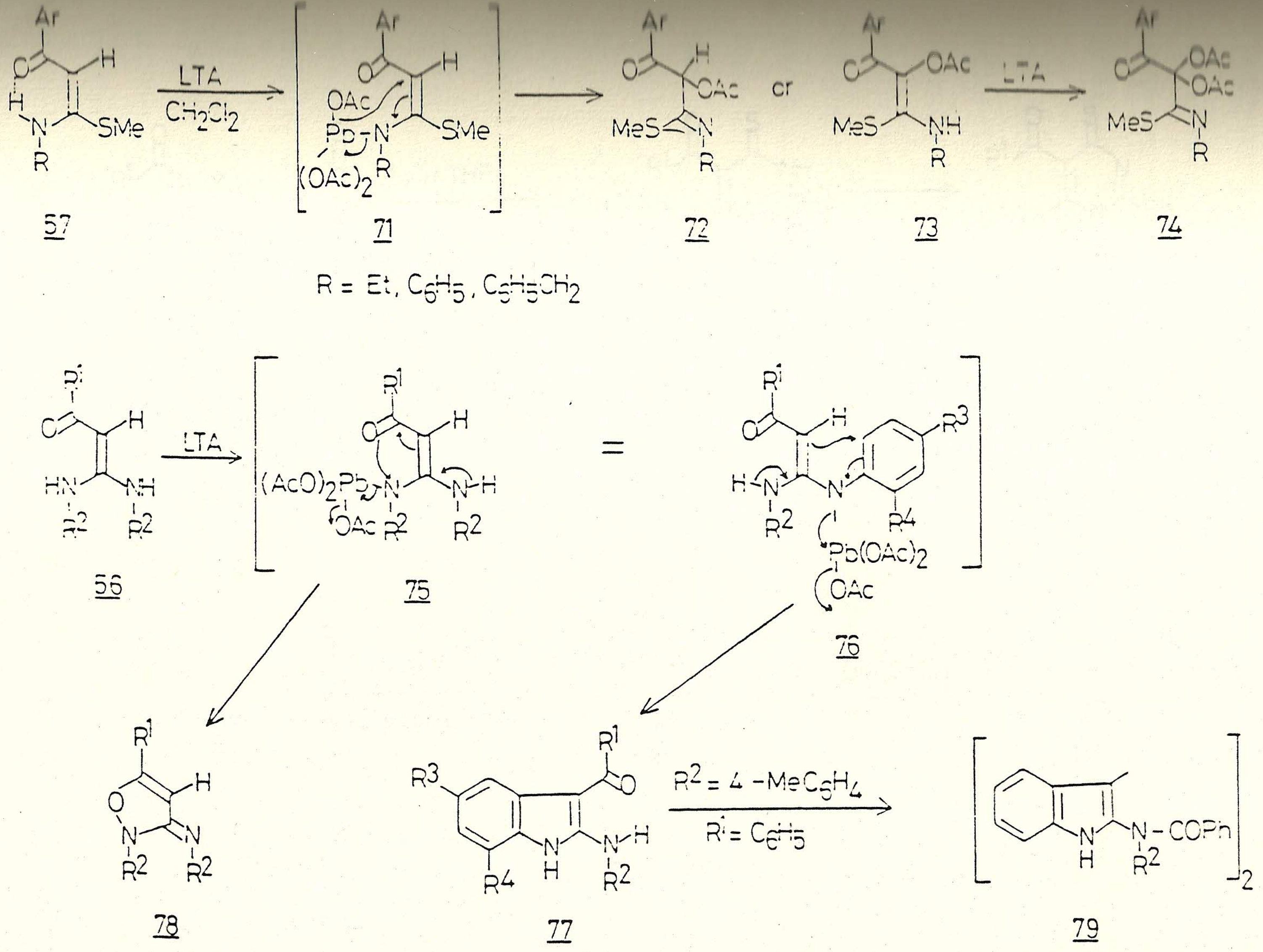
$\underline{c}$, $R^1 = R^2 = MeO$; $R^3 = H$

$\underline{d}$, $R^1 = R^2 = R^3 = MeO$

Scheme -8

oxoketene S,N-acetals 57 underwent LTA oxidation[65] to yield the corresponding 72 and 73 (Scheme 9) while the corresponding S,N-acetals 57 (R=Et) yielded the iminoacetate 74. The other N,N-acetals 56 afforded 2-aryl-3-arylamino-5-aryl-4-isoxazolines (78) under similar reaction conditions involving oxidative cyclization (Scheme 9). However, the N,N-acetals 56 (R^2=4-MeC_6H_4) yielded, under similar reaction conditions, the indoles 77 and the dimeric indole 79 along with the corresponding iminoacetate 74. Thus, it was possible to utilize the ketene S,N-acetals and N,N-acetals for the construction of indoles as one of the products. The conversion of iminoacetates to isoxazolines was found to be of preparative importance since the yields of these products were found to be high.

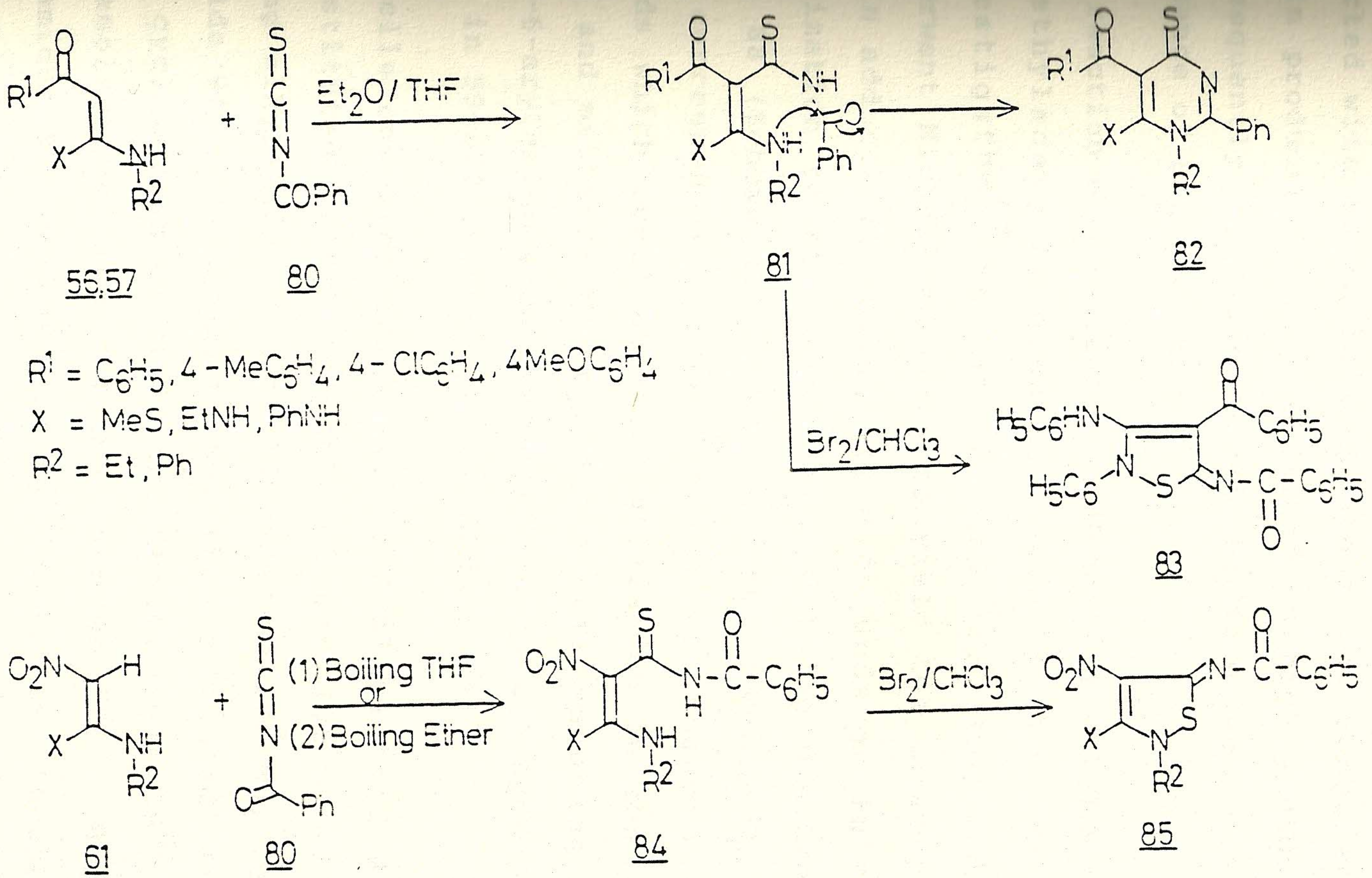
The reaction of polarized ketene S,N- and N,N-acetals with benzoylisothiocyanates 80 as electrophile was investigated by Aggarwal, Ila and Junjappa[66] (Scheme 10). Thus, a methodology for 4-thioxopyrimidines (82) was developed by reacting benzoylisothiocyanate with various S,N-acetals. The reaction proceeds initially through the attack of the nucleophilic α-carbon of the S,N-acetal on the electrophilic carbon of 80 to yield the intermediate thioamide 81 which was subsequently cyclized to yield 82. However, the N,N-acetal 56 gave only the corresponding open chain products 81 which on treatment with Br_2 in $CHCl_3$ gave the isothioazolines 83 in good yields. Similarly, the nitroketene S,N- and N,N-acetals 61 reacted with 80 in boiling THF to yield the corresponding isothiazolines 85 in



R = Et, C_6H_5, $C_6H_5CH_2$

$R^1 = C_6H_5$, $4-MeC_6H_4$, $4-ClC_6H_4$; $R^2 = Ph$, $4-BrC_6H_4$, $3-MeC_6H_4$, $2-MeC_6H_4$

Scheme - 9



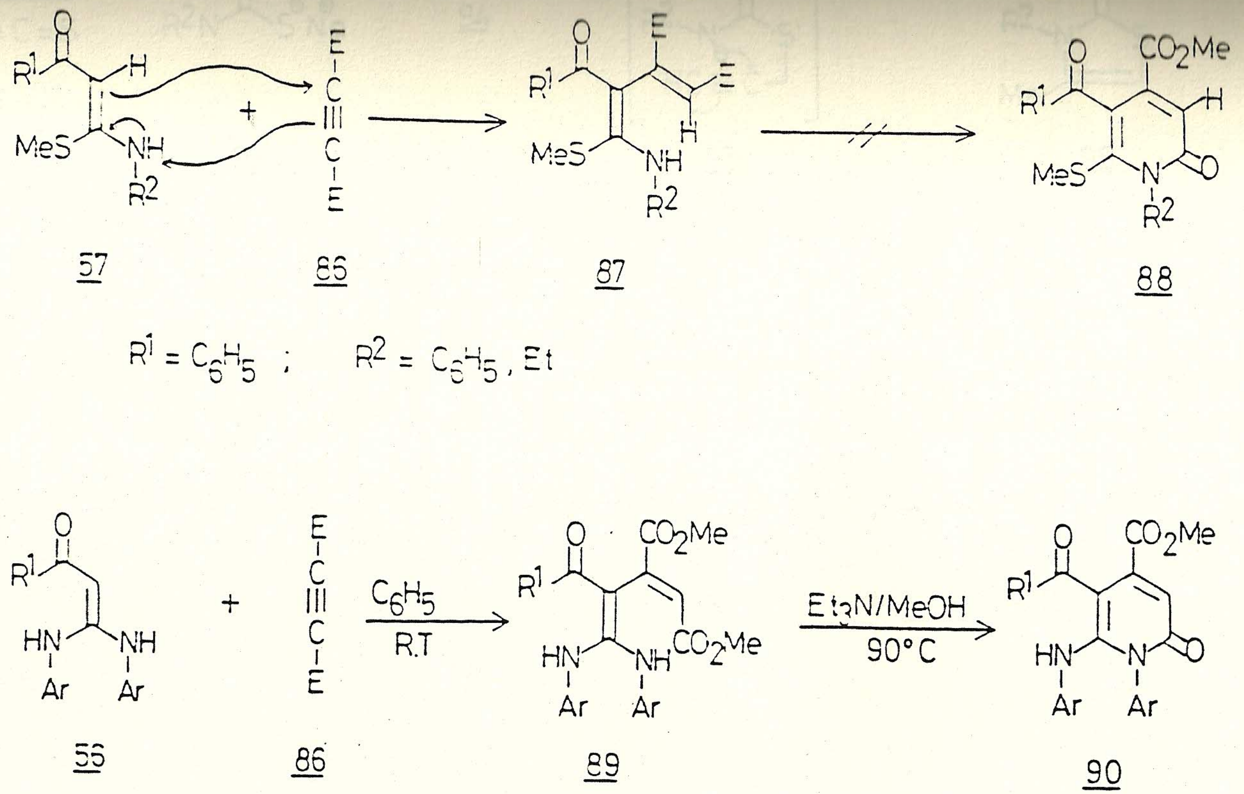
$R^1 = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4MeOC_6H_4$
$X = MeS, EtNH, PhNH$
$R^2 = Et, Ph$

Scheme - 10

46-55% overall yields (Scheme 10). However, when 61 were reacted with 80 in boiling ether the corresponding open chain products 84 were obtained in high yields which were subsequently cyclized to 85 in improved yields in the presence of Br_2 and $CHCl_3$.

The reaction of α-oxoketene S,N-acetals and N,N-acetals with dimethylacetylenedicarboxylate (DMAD) 86 has been investigated[67] in this laboratory. The S,N-acetal 57 underwent Michael addition to yield the corresponding open chain adducts 87 which failed to undergo intramolecular cyclization to afford the corresponding dihydropyridine-2-ones 88 (Scheme 11). However, the N,N-acetals 56 yielded the corresponding Michael addition products 89 in high yields which could undergo cyclization in the presence of Et_3N and methanol to afford the corresponding 5-aroyl-1-aryl-6-arylamino-4-carbmethoxy-2-oxo-1,2-dihydropyridines (90) in 59-67% overall yields (Scheme 11).

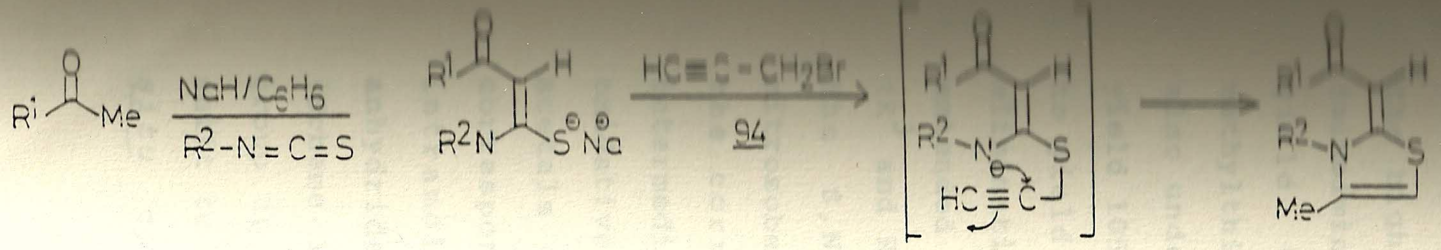
A facile one step synthesis of 3-alkyl/aryl-4-methyl-2-(substituted methylene)-thiazolines (96) was developed during alkylation of the sodio derivative 93, by propargyl bromide 94. The products 95, thus alkylated, underwent *in situ* cyclization to yield the thiazolines 96[68] involving intramolecular ring closure (Scheme 12). However, the thioamides 97 derived from cyclic amines, though underwent initial alkylation to yield the corresponding s-propargyl aminoacetals 98, underwent *in situ* rearrangement to an allenic functionality 99 followed by intramolecular



$R^1 = C_6H_5$; $R^2 = C_6H_5$, Et

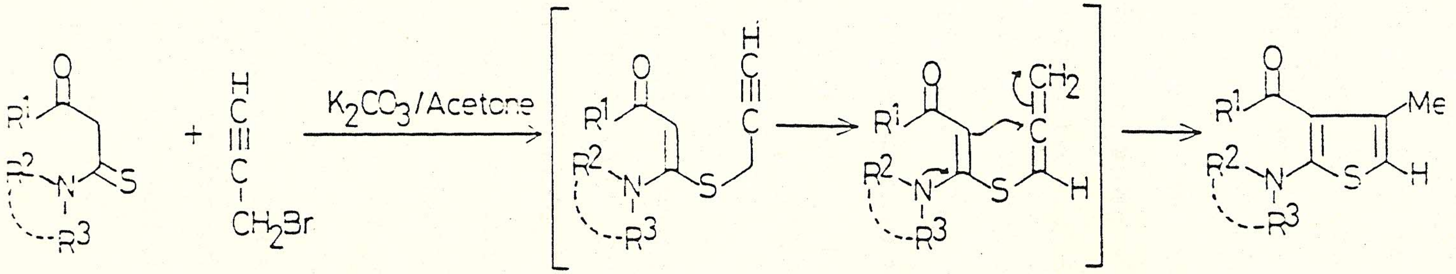
$R^1 = Ar = C_6H_5$, 4 - MeC_6H_4, 4 - $MeOC_6H_4$, 4 - ClC_6H_4

Scheme -11



91 92 93 95 96

$R^1 = C_6H_5$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4
$R^2 = C_6H_5$, Et



97 94 98 99 100

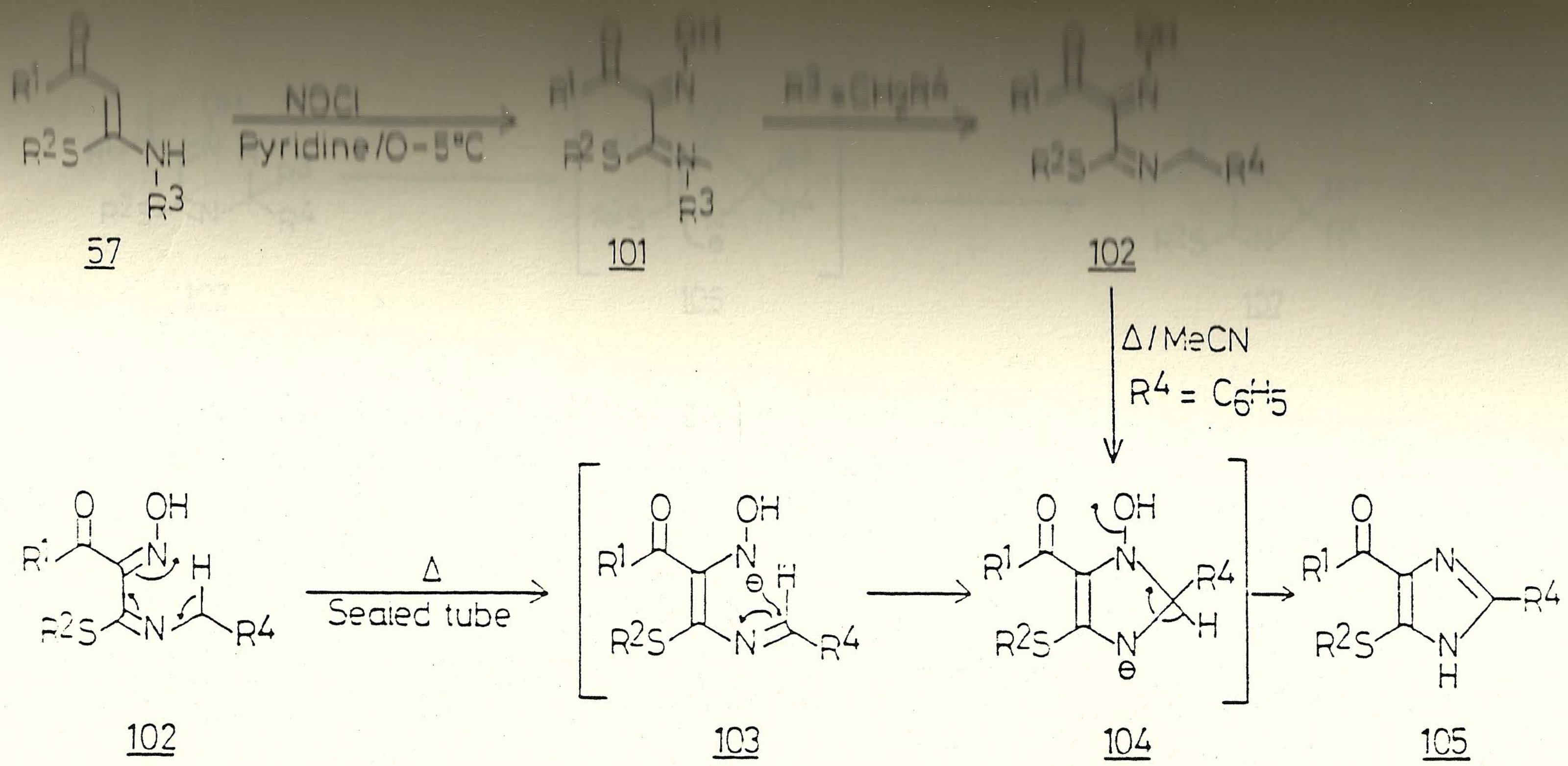
$R^1 = C_6H_5$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

$R^2R^3N- = -(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$
$-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$

Scheme -12

cyclization to afford the corresponding thiophenes **100** (Scheme 12).

The α-oxoketene S,N-acetals were found to undergo facile nitrosation directly from nitrosyl chloride (NOCl) to yield the highly functionalized hydroxyiminoimines **101**. The iminoimines **102** (R^3=CH_2R^4) underwent facile ring closure to yield the corresponding 2-substituted-4-aroyl-5-methylthioimidazoles[70] **105** (Scheme 13). The iminoimines **101** also underwent cyclization when heated in sealed tube to yield **105**. the method involves 1,5-sigmatropic proton shift to yield the intermediate **103** followed by cyclization and elimination of water (Scheme 13). The reaction was further extended to prepare the imidazolines **107** by subjecting **102** (R^3 and R^4=H) to heat treatment in sealed tube (Scheme 14). The S,N-acetals 57 (R^3=CH_2R^4) also reacted with nitrosobenzene in the presence of acetic anhydride to yield the corresponding N-aryl-imidazoles **112** through the intermediates **109**, **110** and **111** (Scheme 14) which underwent oxidative aromatization to yield **112**. Similarly, the S,N-acetals derived from various anilines also yielded the corresponding hydroxyiminoimines **113**, which underwent intramolecular cyclization in the presence of acetic anhydride to yield the corresponding quinoxalines **115** (Scheme 15) in high yields. However, when R^2 was benzyl group in **113**, it rapidly underwent 1,5-sigmatropic proton shift to yield reactive intermediate **116** which underwent *in situ* cyclization to yield the corresponding 5-

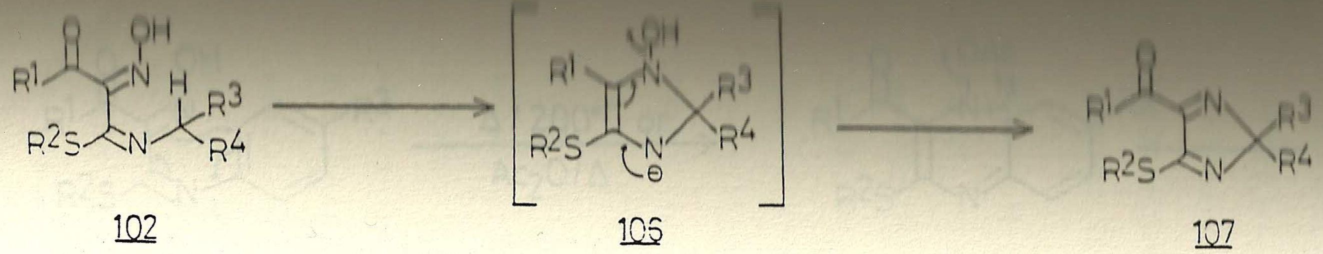


R^1 = substituted aryl, Me, CO_2Et

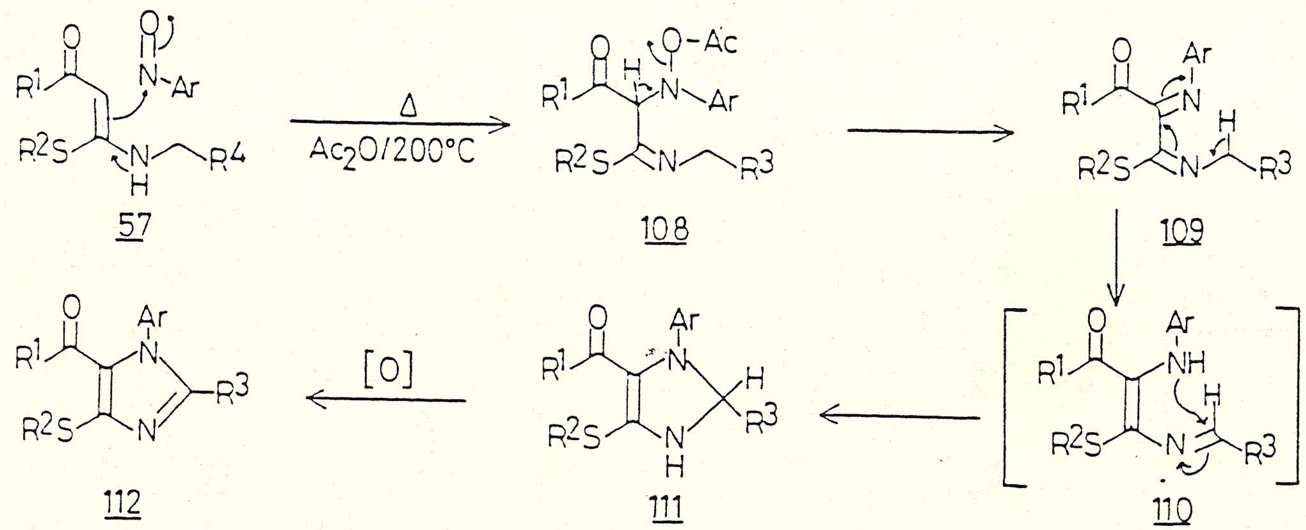
R^2 = Me, Et

R^4 = H, Me, Et, C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme -13

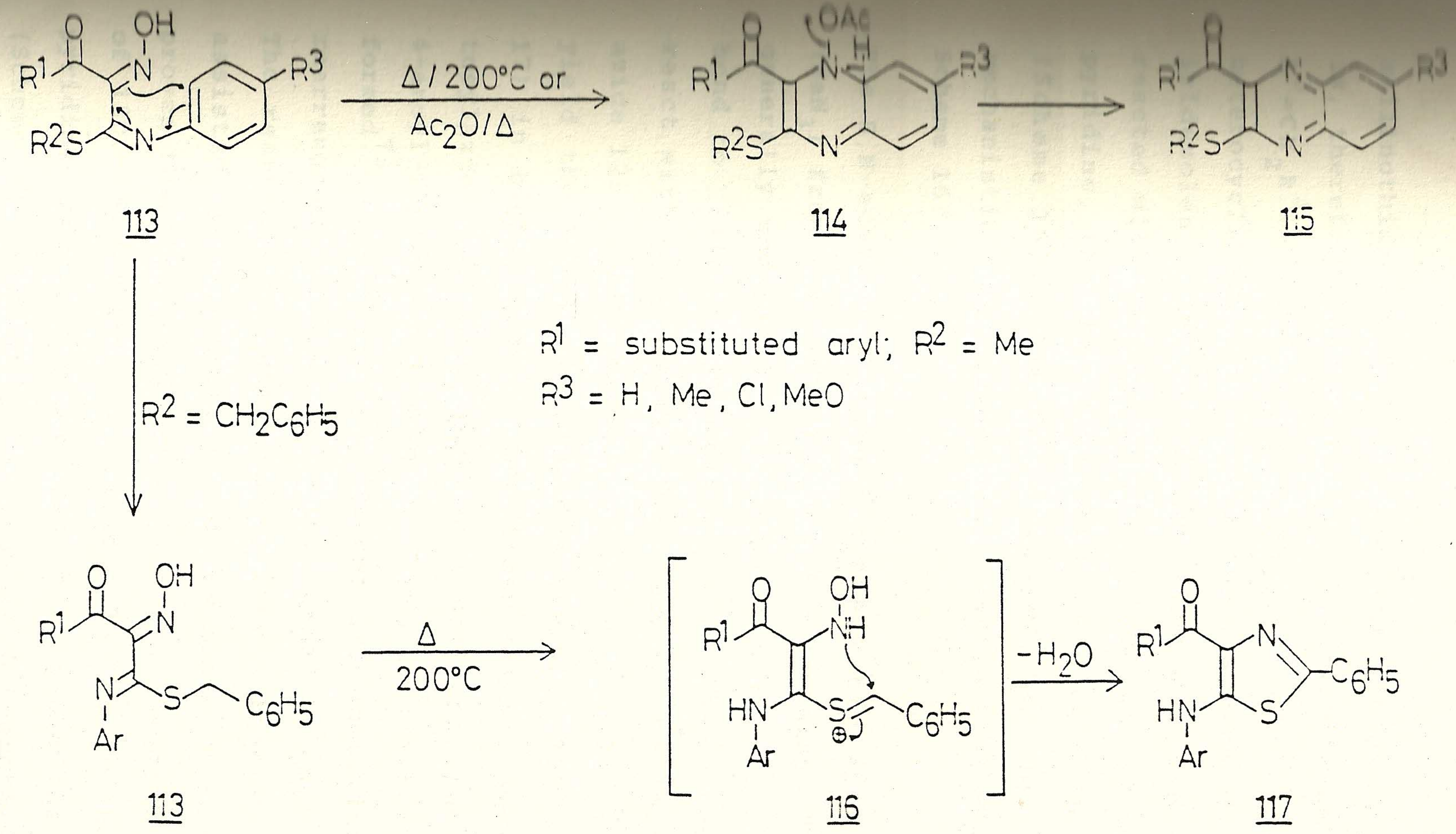


R^1 = substituted aryl; R^2 = Me, Et;
R^3 = R^4 = Me; R^3 = C_6H_5; R^2 = Me; R^3 = R^4 = $-(CH_2)_5-$



R^1 = substituted aryl, Me
R^2 = Me, Et, SCH_2
R^3 = Me, Et, substituted aryl
Ar = C_6H_5, 4 - MeC_6H_4

Scheme - 14



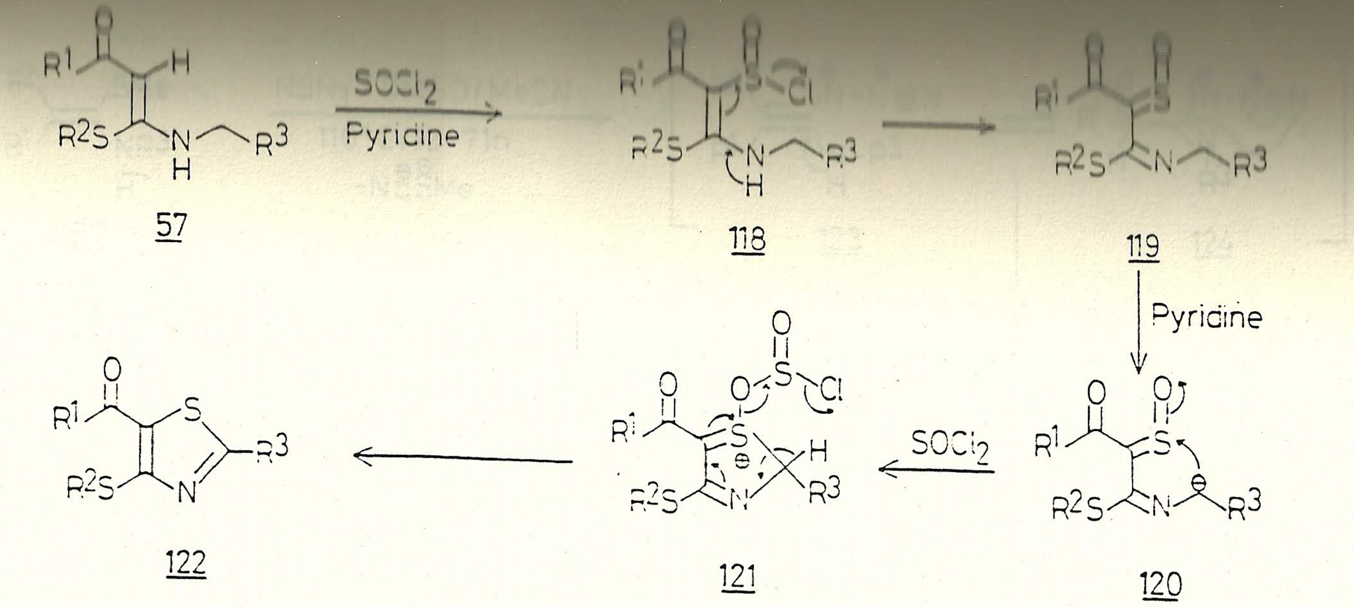
R^1 = substituted aryl; R^2 = Me

R^3 = H, Me, Cl, MeO

SCheme - 15

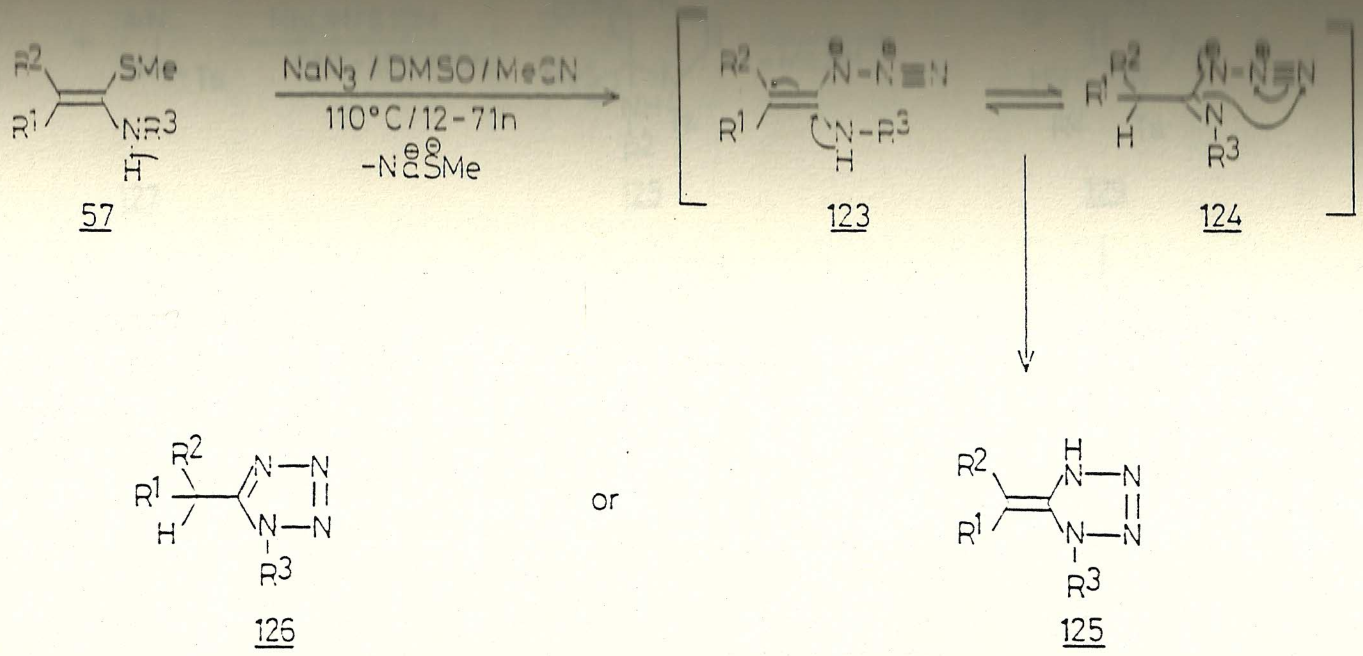
anilinothiazoles **117** in excellent yields (Scheme 15). It is, therefore, apparent that the iminoimines ($R^2=CH_2C_6H_5$ or $R^3=CH_2R^4$) undergo preferential five membered heterocyclization to afford the corresponding thiazoles or imidazoles. Interestingly, when the S,N-acetal **57** was reacted with thionyl chloride ($SOCl_2$) in the presence of pyridine, the thiazoles **122** were formed in high yields[71] (Scheme 16). The formation of **122** involves the same mechanistic steps as described earlier and they are shown in Scheme 16.

The S,N-acetals **57** behave differently with sodium azide (NaN_3) from the corresponding S,S-acetals. The S,S-acetals generally undergo 3+2 cycloaddition to the mercapto double bond to yield the triazoles[72]. However, the S,N-acetals react with NaN_3 through the itermediate formation of the azide **123**, **124** followed by intramolecular ring closure to yield the 1,5-disubstituted tetrazoles **125** or **126** (Scheme 17) in high yields. When these studies were extended to tosylazide **127** under alkaline conditions, the corresponding 4-aroyl-1-phenyl-5-tosylamino-1H-1,2,3-trizoles **130** were formed[73] in high yields (Scheme 18) involving the Dimroth rearrangement of the initially formed N-tosyl triazole **129**. The rearrangement was confirmed by subjecting **130** to acid assisted hydrolysis to yield the aminotriazole **131** which proves that the tosyl group is on the exocyclic amino group of **130**. The free aminotriazole **131** on further heating in pyridine underwent rearrangement to yield the triazole **132** (Scheme 18). Similarly, the cyclic S,N-acetals **133** reacted



R^1 = substituted aryl, Me
R^2 = Me, Et, $C_6H_5CH_2$
R^3 = C_6H_5 , 4-ClC_6H_4 , 4-$MeOC_6H_4$, CO_2Et

Scheme - 15

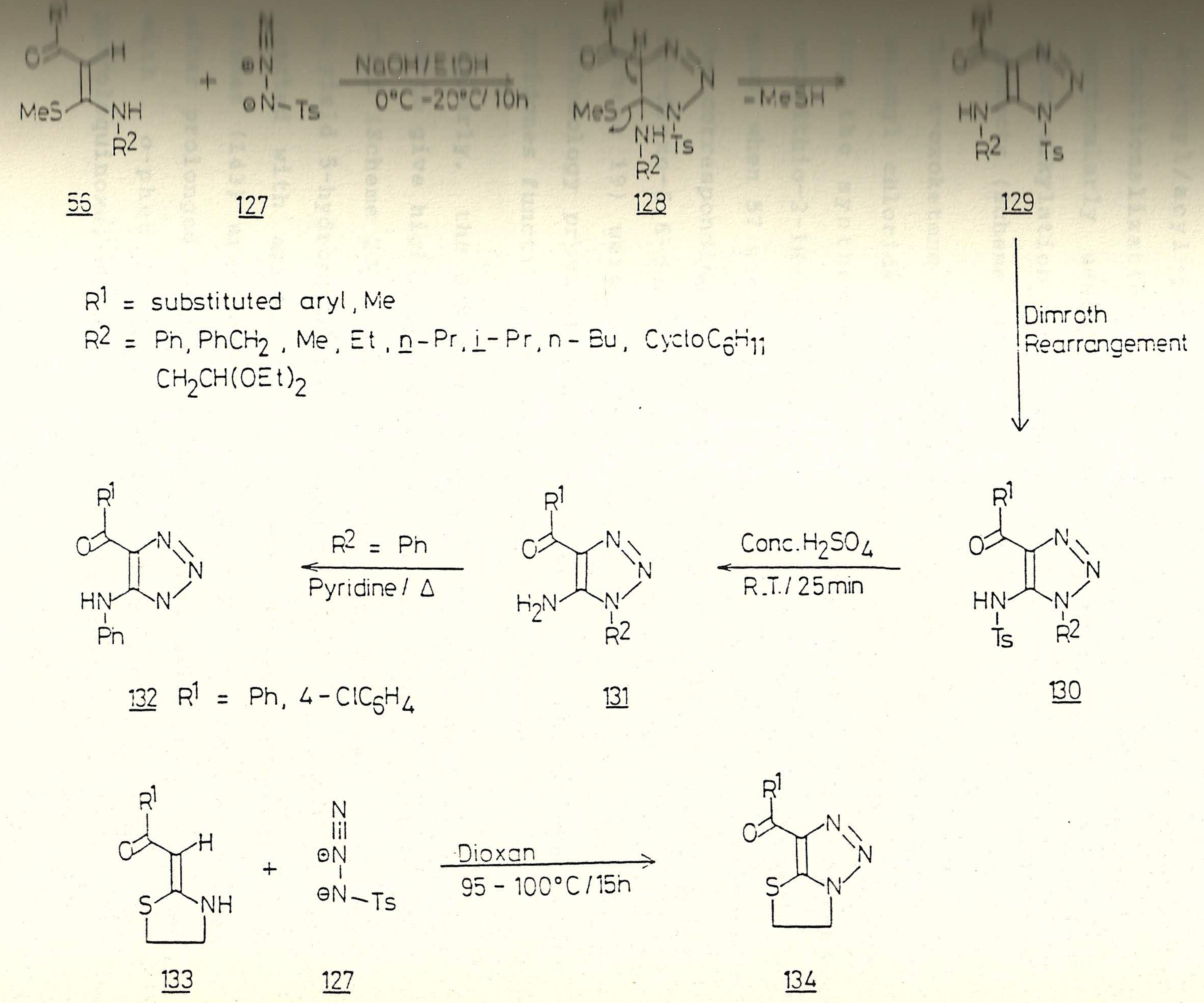


R^1 = ArCO, MeCO ; R^2 = H ; R^3 = Me, Et, n-Pr, i-Pr, C_6H_{11}, C_6H_5, $C_6H_5CH_2$

R^1 = C_6H_5 ; R^2 = CN;

R^1 = CO_2Et; R^2 = CN; R^3 = C_6H_5, $C_6H_5CH_2$

Scheme - 17



R^1 = substituted aryl, Me

R^2 = Ph, PhCH$_2$, Me, Et, n-Pr, i-Pr, n-Bu, CycloC$_6$H$_{11}$, CH$_2$CH(OEt)$_2$

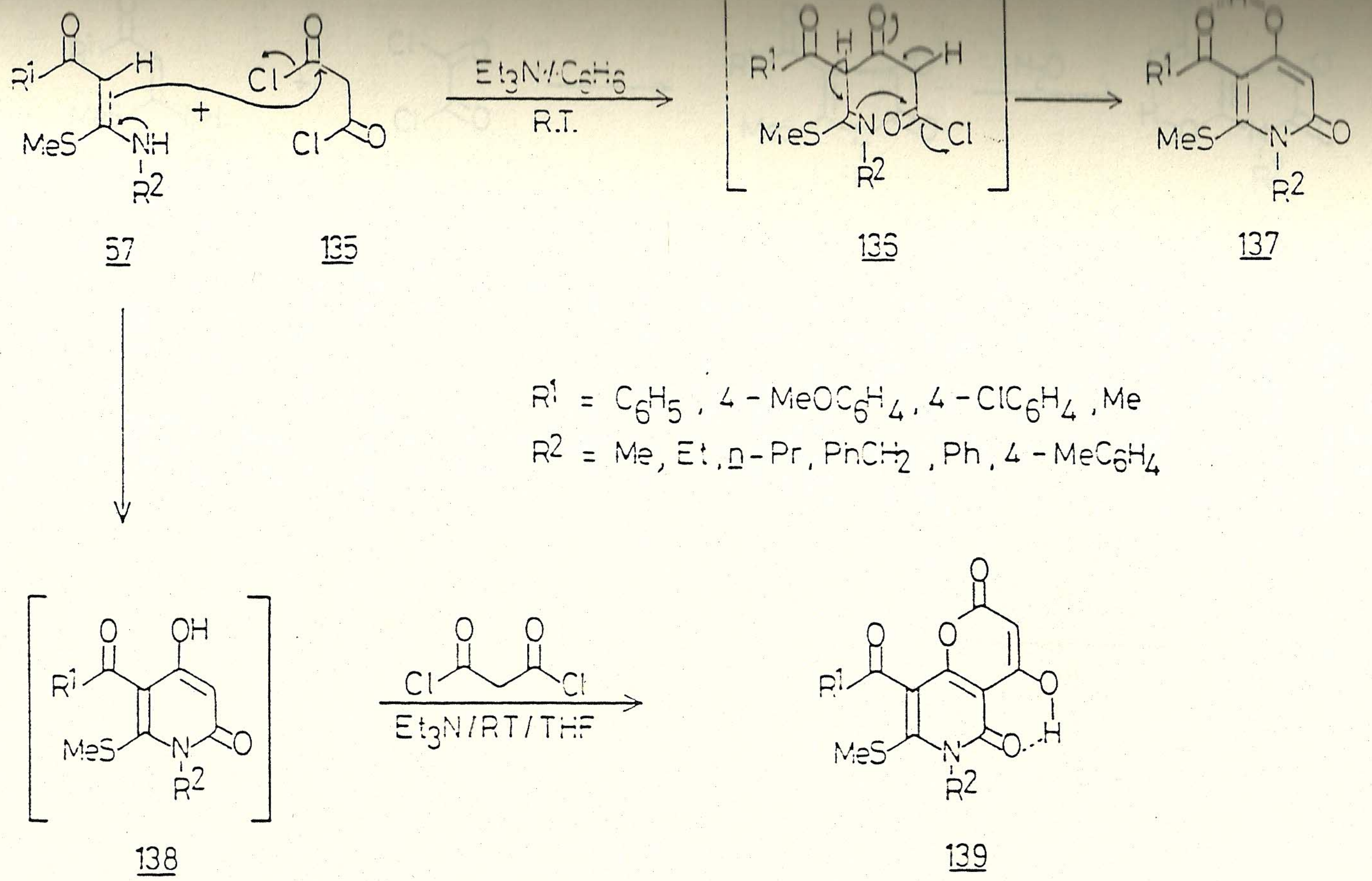
132 R^1 = Ph, 4-ClC$_6$H$_4$

Scheme -18

with tosylazide to yield the bicyclic triazolothiazolines 134 in high yields. The method constitutes an entry to the synthesis of regio-specifically substituted 1-phenyl/alkyl-4-aroyl/acyl-5-tosylamino (or amino) triazoles with functionalizations at 4 and 5 positions. This method is particularly useful when 1-N-alkyltriazoles are required since alkylation procedures generally result in a mixture of products (Scheme 18).

The α-oxoketene S,N-acetals 57 have also been reacted with malonyl chloride 135 leading to a new general methodology for the synthesis of 1,5-disubstituted-4-hydroxy-6-methylthio-2-1H-pyridones[74] 137 in high yields (Scheme 19). Also, when 57 was reacted with excess of 135 (3 equivalents) the corresponding 6,8-disubstituted 4-hydroxy-7-methylthio-2,5-dioxo-5,6-dehydro-2H-pyrano [2,3-*c*] pyridones 139 (Scheme 19) were formed in moderate yields. Thus, the methodology provides a very easy entry to the synthesis of pyridones functionalized at 4,5 and 6 positions.

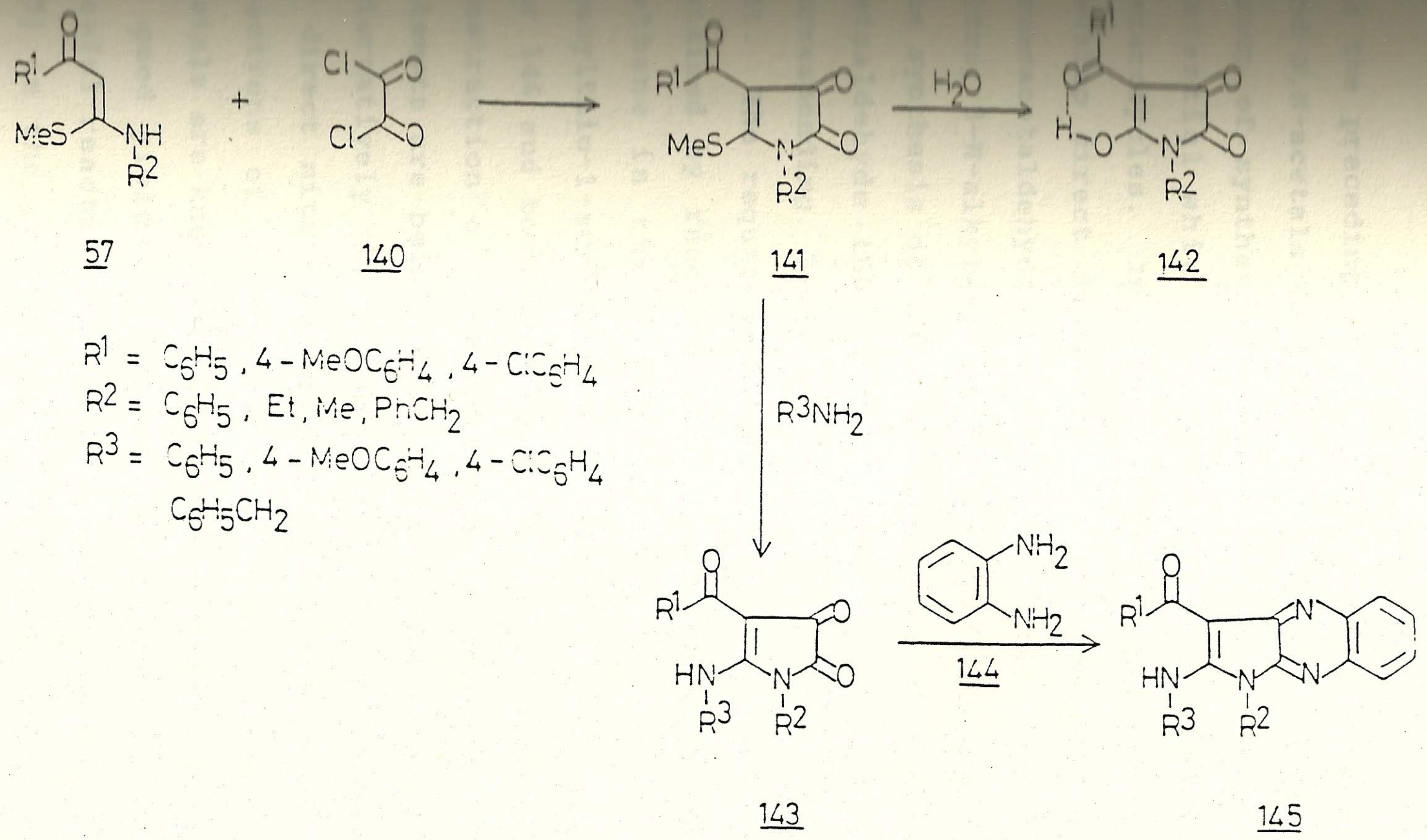
Similarly, the S,N-acetals 57 reacted with oxalyl chloride 140 to give highly unstable pyrrole-2,3-diones[75] 141 in high yield (Scheme 20). They underwent easy hydrolytic cleavage to yield 5-hydroxy pyrrole diones 142. However, when 141 was reacted with amines the corresponding amino pyrrole-2,3-diones (143) are formed which are found to be stable even after prolonged keeping. These diones were then condensed with *o*-phenylene diamine 144 to yield the pyrroloquinoxalines 145 in good yields (Scheme 20).



R^1 = C_6H_5 , 4 - $MeOC_6H_4$, 4 - ClC_6H_4 , Me
R^2 = Me, Et, n-Pr, $PhCH_2$, Ph, 4 - MeC_6H_4

R^1 = Me, C_6H_5
R^2 = Me, Et, $C_6H_5CH_2$

Scheme - 19



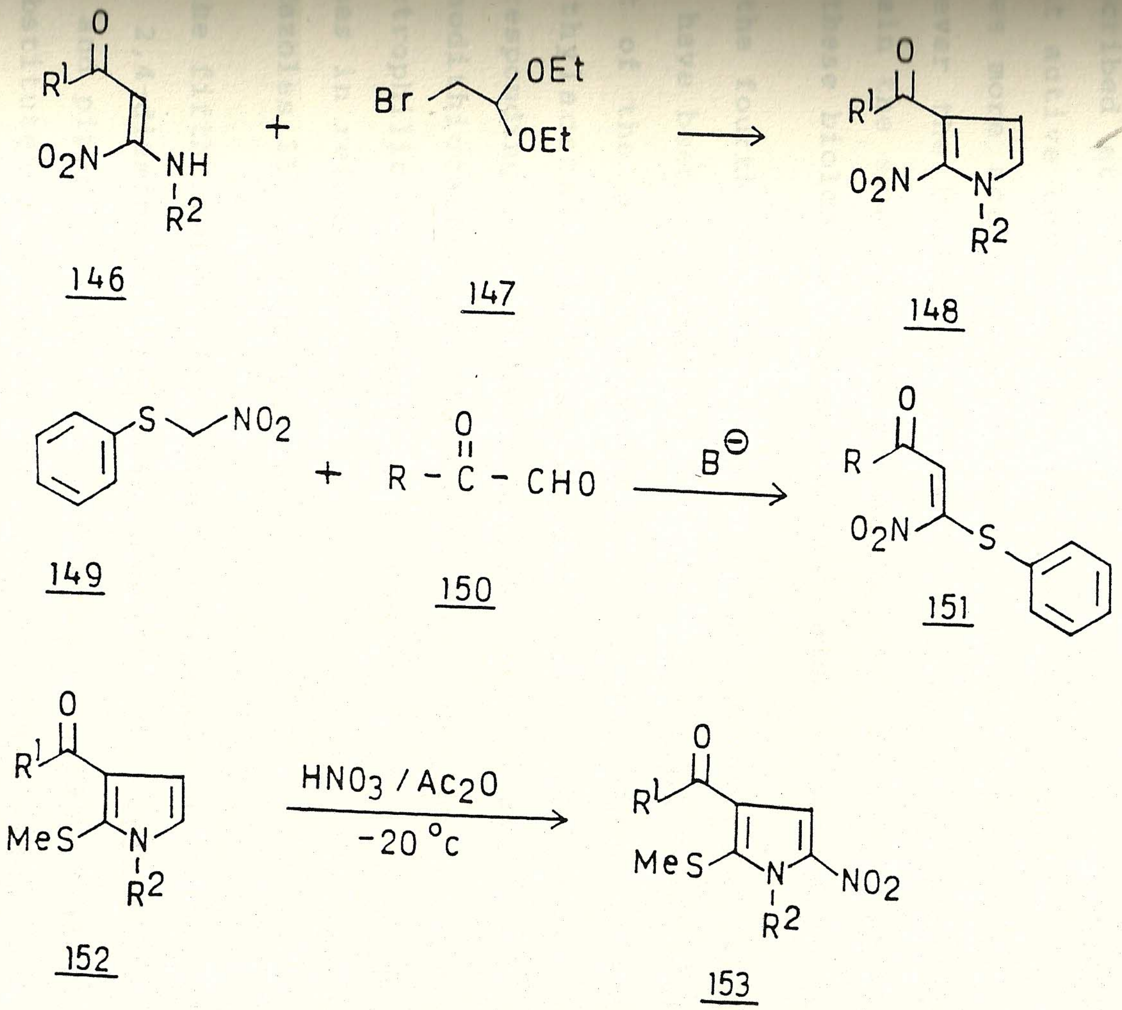
57 140 141 142 143 144 145

$R^1 = C_6H_5$, 4 - $MeOC_6H_4$, 4 - ClC_6H_4
$R^2 = C_6H_5$, Et, Me, $PhCH_2$
$R^3 = C_6H_5$, 4 - $MeOC_6H_4$, 4 - ClC_6H_4
$C_6H_5CH_2$

Scheme - 20

The Work Presented in this Thesis:

In the preceding sections a brief discussion on S,S-, S,N- and N,N-acetals is given and they are therefore a versatile group of synthetic intermediates of considerable synthetic potential which could be further used for many novel heterocycles. In chapter three an attempt has been made to develop direct synthesis of nitro pyrrole **148** by reacting bromoacetaldehyde diethyl acetal **147** with hypothetical 3-nitro, 3-N-alkyl/arylamino-1-alkyl/aryl-2-propene-1-one **146**. The synthesis of **146** was attempted by reacting **149** with aryl ketoaldehyde **150** in the presence of a base to get the corresponding 3-nitro-3-phenyl thio,1-aryl-2-propene-1-one **151**. The required thiophenyl nitromethane **149** was in turn obtained by reacting phenyl sulphenyl chloride with nitro methane in the presence of a base. The 3-nitro-3-phenylthio-1-aryl-2-propene-1-one **151** is also a precursor for **146** and both are important intermediates for the direct construction of 5-membered nitro heterocycles and further attempts are being made for the synthesis of **151** and **146**. Alternatively the synthesis of nitro pyrroles was conceived by direct nitration of preconstructed pyrroles. Thus the reactions of bromoacetaldehyde diethylacetal with S,N-acetals are known to afford the 2-methylthio-3-acyl pyrroles in good yields[76]. These pyrroles were nitrated under careful reaction conditions using fuming nitric acid (d, 1.5) in the presence of acetic anhydride to afford the corresponding 5-nitro pyrroles in moderate to good yields.



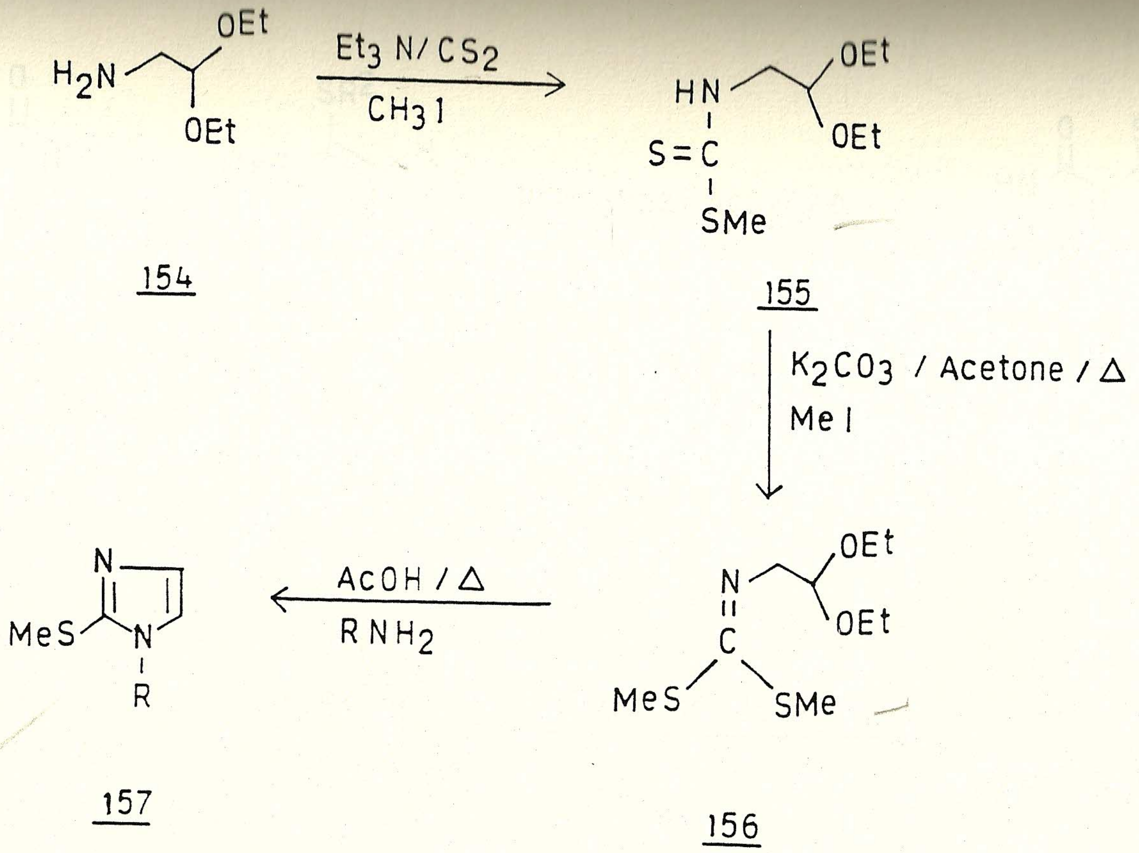
Scheme - 21

A number of unknown pyrroles were also prepared and nitrated to provide the corresponding nitro pyrroles 153 in moderate yields. These pyrroles have been screened for their anti-protozoal activity and the results of these studies are described at the end of this chapter. Interestingly the most active compound *invitro* test was found to be three times more active than the metronidazole i.e. 3.13 ug/ml. However the biological profile of these compounds did not remain the same when they were tested *invivo*. The results of these biological screening were also presented.

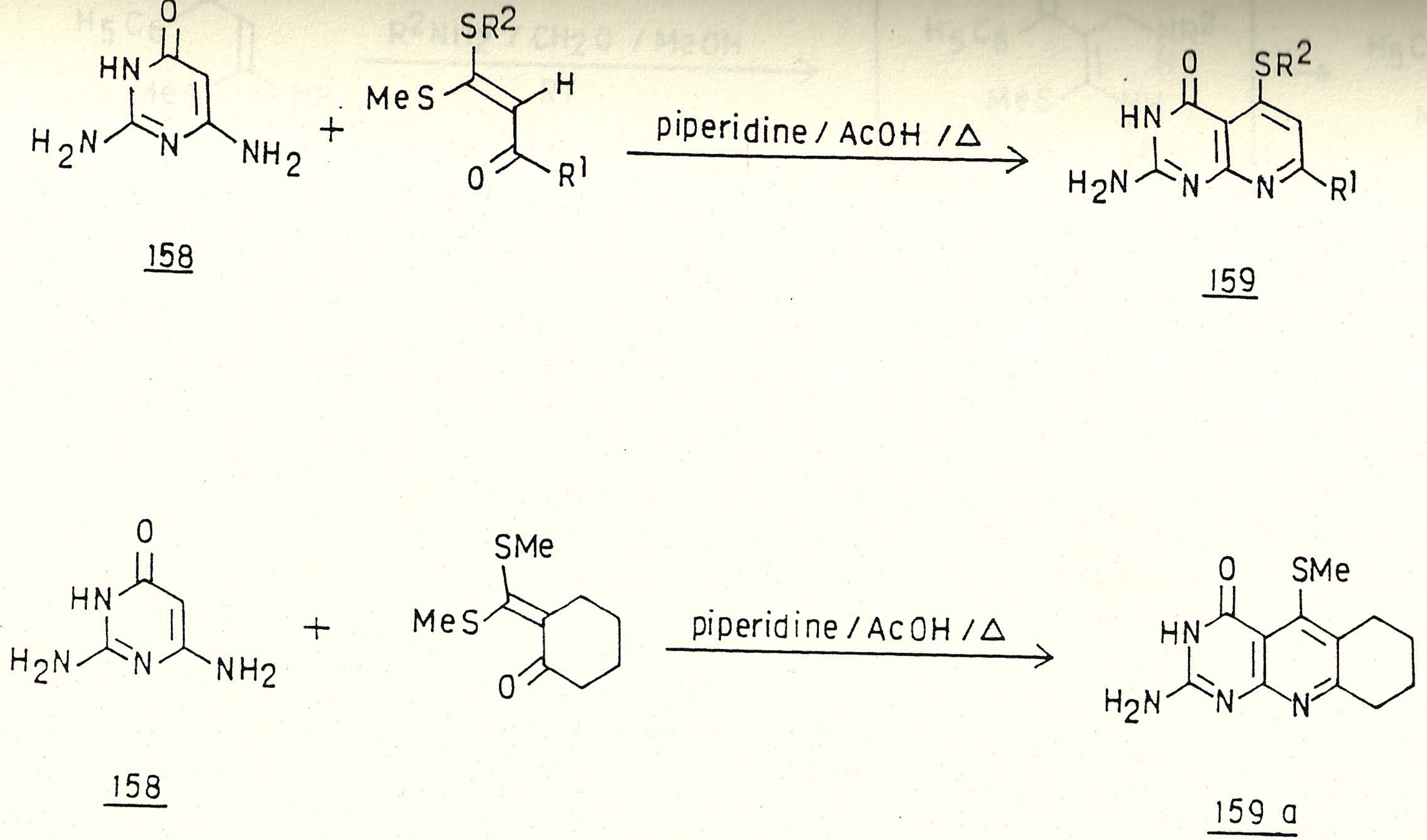
In the fourth chapter 1-substituted 2-methylthio imidazoles **157** have been prepared by new general method developed as a part of the present investigation. The aminoacetaldehyde diethylacetal **154** was convinienty converted to the corresponding iminodithiocarbonate **156** in 87% yield. The iminodithiocarbonate **156** is an interesting 4 atom 1,4-electrophilic synthon which is reacted with various primary amines in refluxing acetic acid to afford the corresponding imidazoles **157** in high yields.

In the fifth chapter, reaction of α-oxoketene dithioacetals with 2,4-diamino 6(1H)pyrimidinone **158** in refluxing acetic acid and piperidine to afford the corresponding 5-alkylthio-7-substituted-5-deazapteridine **159** in high yields. A number of pyrido (2,3-*d*)pyrimidinone and condensed pyrido (2,3-*d*)pyrimidinone **159a** have been synthesised[77] in the present work, the results of which are described in the chapter. The biological screening of these compounds were carried out

wrong


H$_2$N
OEt
OEt
154
Et$_3$ N/CS$_2$
CH$_3$ I
HN
S=C
SMe
OEt
OEt
155
K$_2$CO$_3$ / Acetone / Δ
Me I
N
C
MeS
SMe
OEt
OEt
156
AcOH / Δ
RNH$_2$
N
N
MeS
R
157

Scheme - 22



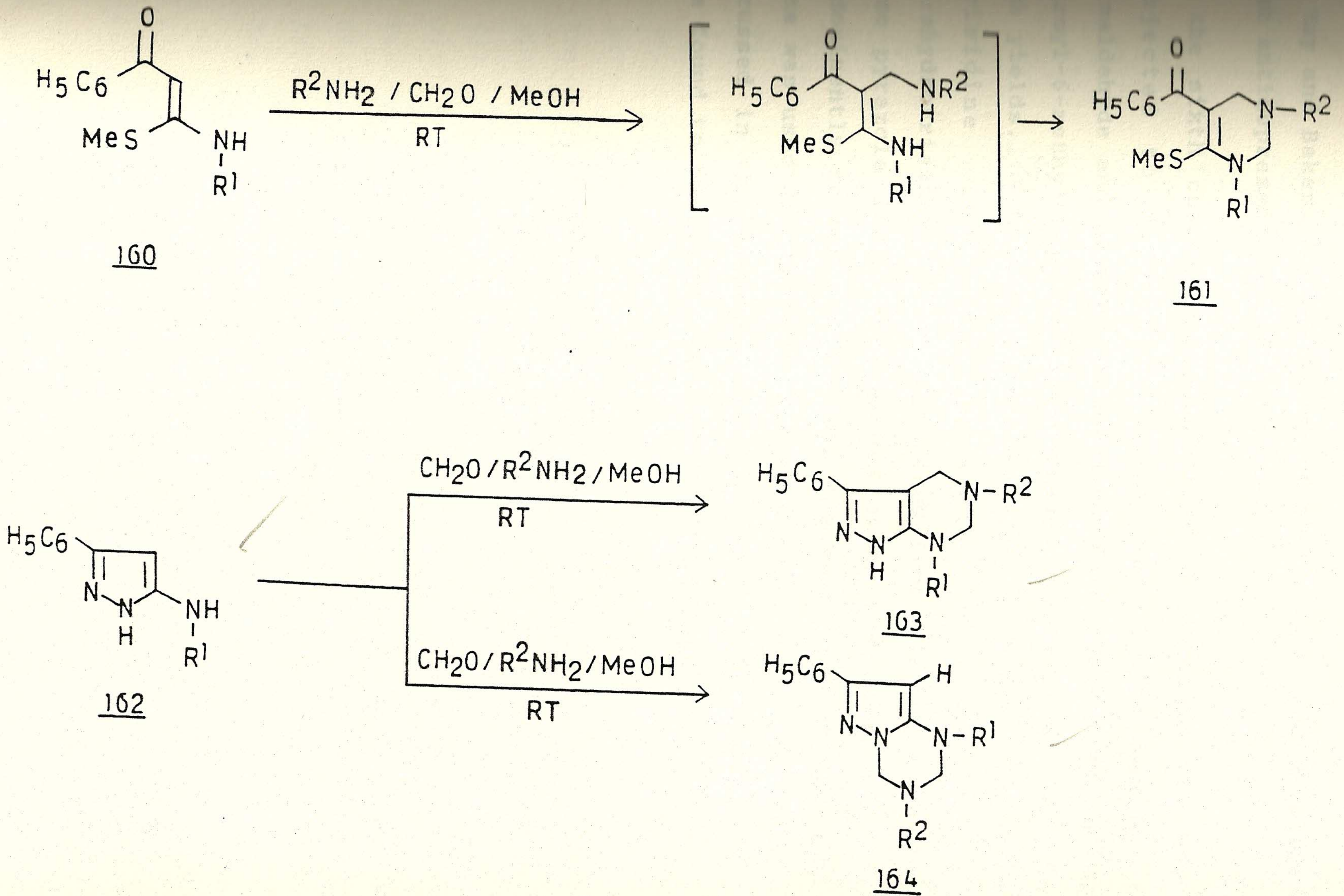
158

159

158

159 a

Scheme - 23


H5C6
O
MeS
NH
R1
160
R2NH2 / CH2O / MeOH
RT
H5C6
O
NR2
H
MeS
NH
R1
H5C6
O
N-R2
MeS
N
R1
161
H5C6
N
N
H
NH
R1
162
CH2O/R2NH2/MeOH
RT
H5C6
N-R2
N
N
H
N
R1
163
CH2O/R2NH2/MeOH
RT
H5C6
H
N
N
N-R1
N
R2
164

Scheme-24

by May and Baker, London. Some of these compounds displayed high antidepresent activity.

In the sixth chapter a number of S,N-acetals 161 were subjected to Mannich reaction in the presence of formaldehyde and primary amines to afford the corresponding 5-aroyl-6-methylthio 1,2,3,4-tetrahydropyrimidines 161 in high yields. similarly pyrazole (3,4-*d*)-4,5,6,7-tetrahydro pyrimidine 163 and pyrazolo (1,5-*a*)-1,2,3,4-tetrahydrotriazine 167 were prepared from the corresponding amino pyrazole 162. When excess amine was used, 164 was predominently formed and 163 was the main product when the amine was used in stachiometric amounts. These results are discussed in the chapter. All the tetrahydro pyrimidines were found to be inactive against *E. Histolytica*.

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