SYNTHETIC STUDIES ON POLARIZED KETENE S, S- S, N- AND N, N- ACETALS

By

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A THESIS
SUBMITTED IN FULFILMENT OF THE REQUIREMENT
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

To

THE NORTH-EASTERN HILL UNIVERSITY

SHILLONG - 793 001

INDIA

1990

Dedicated to my Parents

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This is to certify that the work described in this thesis has been carried out by Mr. Akhilesh Kumar Gupta under my supervision. He has satisfactorily completed the pre-Ph.D. courses prescribed and 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.

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Title	Course No.
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2. Electrochemistry	Chem - 668
3. Experimental Techniques	SPS - 630
4. French Language	SPS - 601

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ACKNOWLEDGEMENT

First of all I am proud of being a research student in the Department of Chemistry, North-Eastern Hill University, Shillong, India. I express my sincere gratitude to Professor Dr. H. Junjappa for his kind supervision and encouragement. My sincere gratitude is also due to Professor Dr.(Mrs) H. Ila for giving helpful suggestions. I acknowledge the efficient services extended by the Regional Sophisticated Instrumentation Centres at Central Drug Research Institute, Lucknow and North-Eastern Hill University, Shillong for providing the spectral and analytical data of the compounds described in this thesis. I am grateful to Ms. Organon Research Centre, Calcutta, India for supplying estrone. Financial assistance from the Council of Scientific and Industrial Research, New Delhi is also thankfully acknowledged.

I am also indebted to all the teaching and non-teaching staff of the School of Physical Sciences as a whole and the Department of Chemistry in particular for their cooperation and help. I am deeply indebted and grateful to my colleagues: Dr. S. Apparao, Dr. B. Myrboh, Dr. S.S. Bhattacharjee, Dr. J.N. Vishwakarma, Dr. A. Rahman, Dr. G. Singh, Dr. L. W. Singh, Dr. A. Dutta, Dr. C.V. Asokan, Dr. M.L. Purkayastha, Dr. R.T. Chakrasali, Dr. A. Thomas, Dr.(Miss) D. Pooranchand, Mr. Arun K. Gupta, Mr. M.P. Balu, Md. Moffizuddin, Mr. B. Deb, Mrs. M. Chakraborty,

Mr. C.S. Rao, Mr. M. Chandrasekhar, Mr. K.R. Reddy, Mr. J. Satya Narayan, Mr. K. Mallaiah, Mr. B. Patro, Mr. D. Venkteshwarlu, Mr. S.K. Sharma, Mr. L.N. Bhat for their help and cooperation.

Special recognition and gratitude are due to Mr. Vijayan and Sivaprakashan. C.V. for the help extended by them in processing this thesis. I also express my gratitude to all my friends for their help.

Finally, I acknowledge the ever encouraging support and patience extended by parents, my wife and family members for which I remain indebted.

(Akhilesh K. Gupta)

C O N T E N T S

P R E F A C E

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- & 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- & N,N-acetals.

A brief survey of the recent reports on the work done on the polarized ketene S,S-, S,N- & N,N-acetals is presented in the first chapter. The second chapter describes the reaction of various polarized ketene, S,N- and N,N-acetals with maleic anhydride and maleimide resulting in the formation of structurally important pyrrole derivatives. A new route to variously substituted pyrroles utilizing the polarized ketene S,N-acetals has been described in the third chapter.

Fourth chapter of this thesis describes the synthesis of various benzo[c]quinolizinium tetrafluoroborates from α-oxoketene S,S-acetals. The last chapter describes various

synthetic transformations of the α-oxoketene S,S-acetals derived from estrone.

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.

CHAPTER I

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

Polarized Ketene S,S-, S,N- and N,N-acetals have been proved to be among the simplest synthetic intermediates. This chapter is devoted to a brief review and discussion on the chemistry of these synthons regarding their practical and potential application in organic synthesis. For convenience, this chapter is divided into three sections. 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. The present work has been described, in the third section.

A. The Polarized Ketene S,S-acetals:

Polarized Ketene S,S-acetals 1 have been recognized as useful building blocks in many synthetic operations[1]. 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-

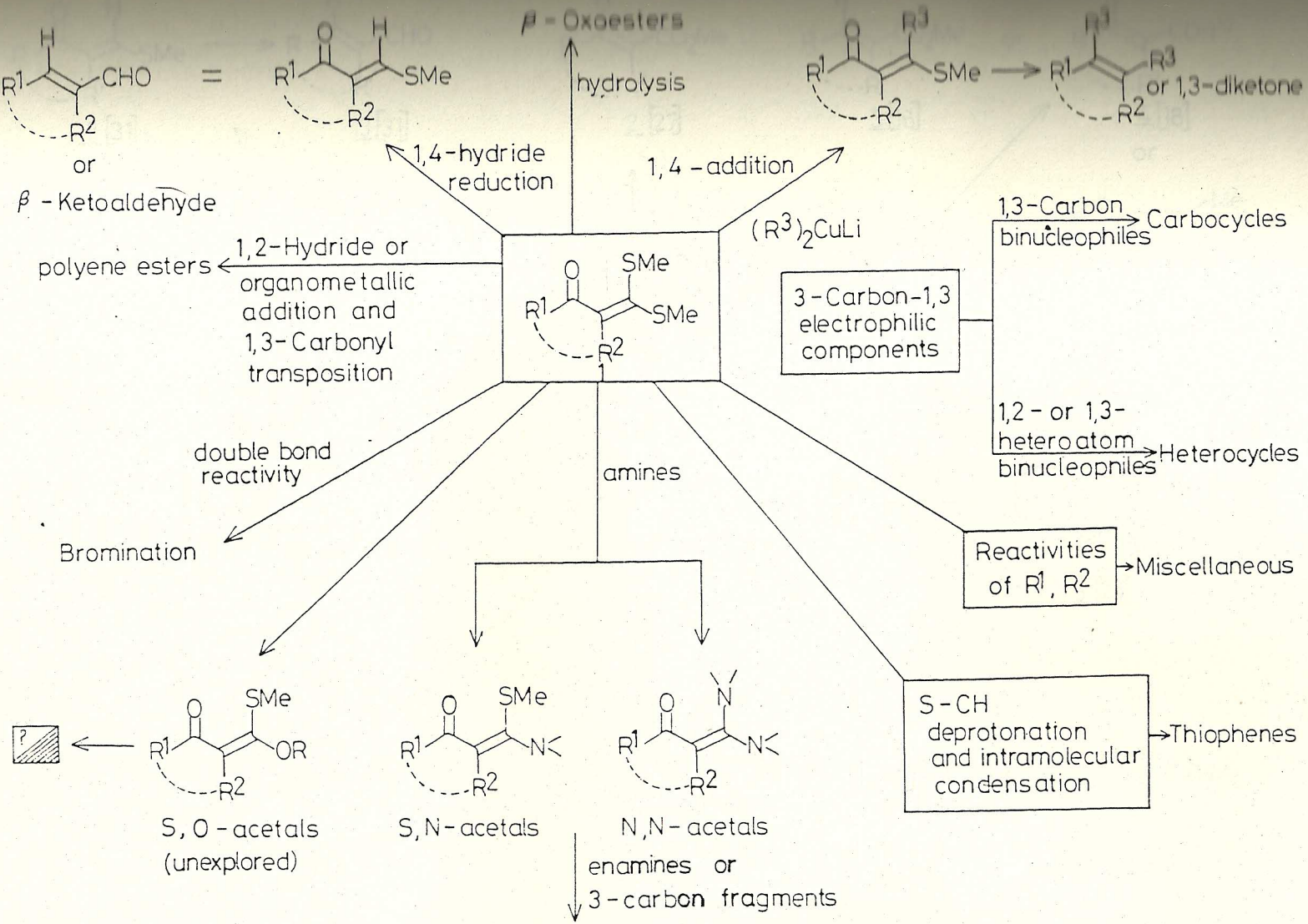
acetal is essentially a masked β-keto ester in which the ester functionality is protected as dithioacetal. Alternatively, it may be viewed as an α,β-unsaturated ketone containing highly functionalized β-carbon. They are versatile three carbon fragments having 1,3-electrophilic centres of differing electrophilicity. 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 precurssors 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 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

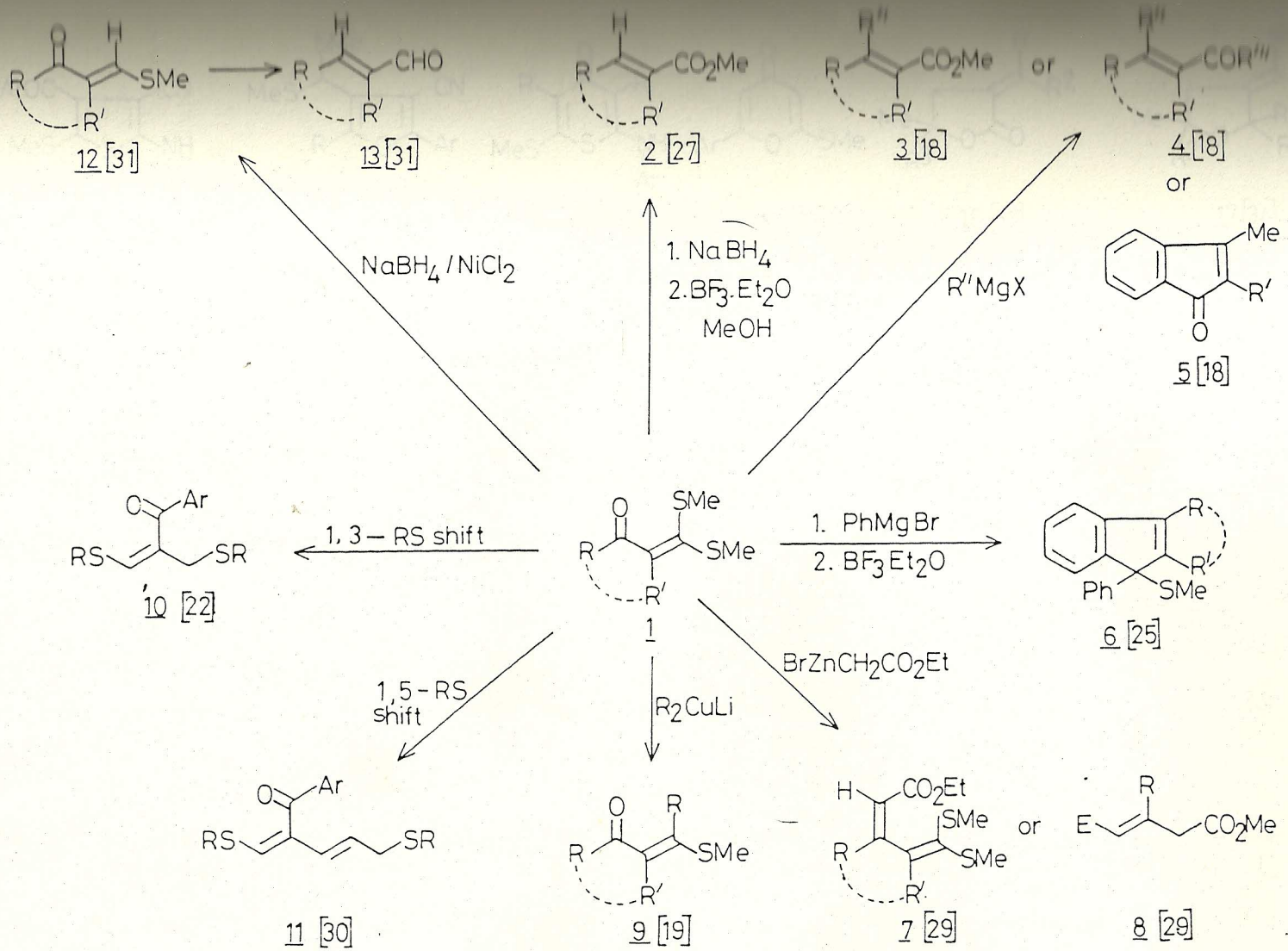
react with 1,2-and 1,3-heteroatom binucleophiles to give five and six membered heterocyclic compounds respectively. The 1,3-carbon nucleophiles, on the other hand, give carbocyclic compounds. The enolate ion formed by deprotonation (R^1 = alkyl) can undergo condensation with aldehydes to give α-enoylketene 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:

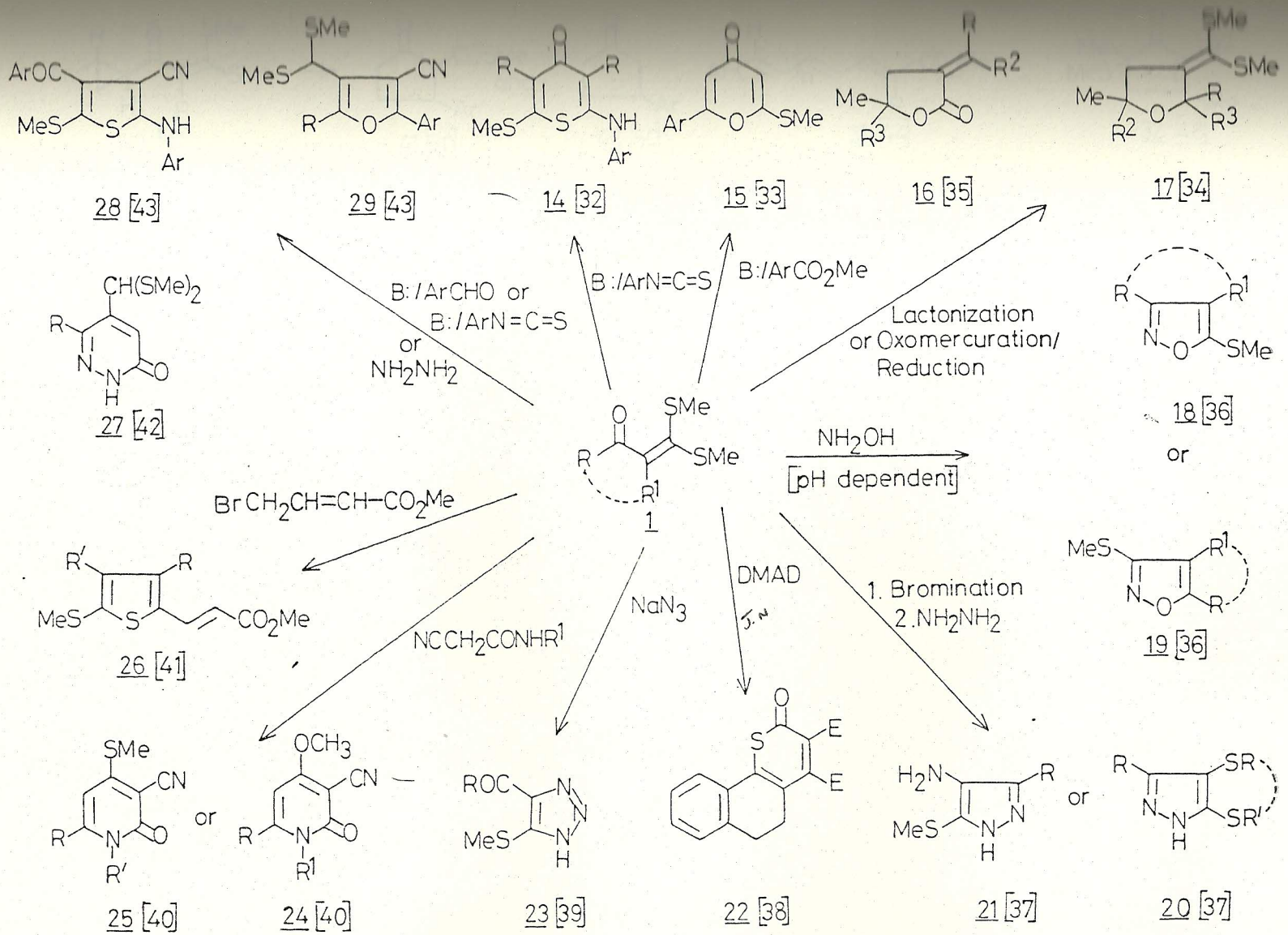
Like oxoketene S,S-acetals, the S,N- and N,N-acetals also possess 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. As stated in the preceding section, they can be prepared by displacement of one or both of the methylthio groups from oxoketene S,S-acetals by suitable amines under different reaction conditions. The S,N-acetals can alternatively be prepared directly


β - Oxoesters
hydrolysis
or
β - Ketoaldehyde
1,4-hydride reduction
1, 4 - addition
(R3)2CuLi
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

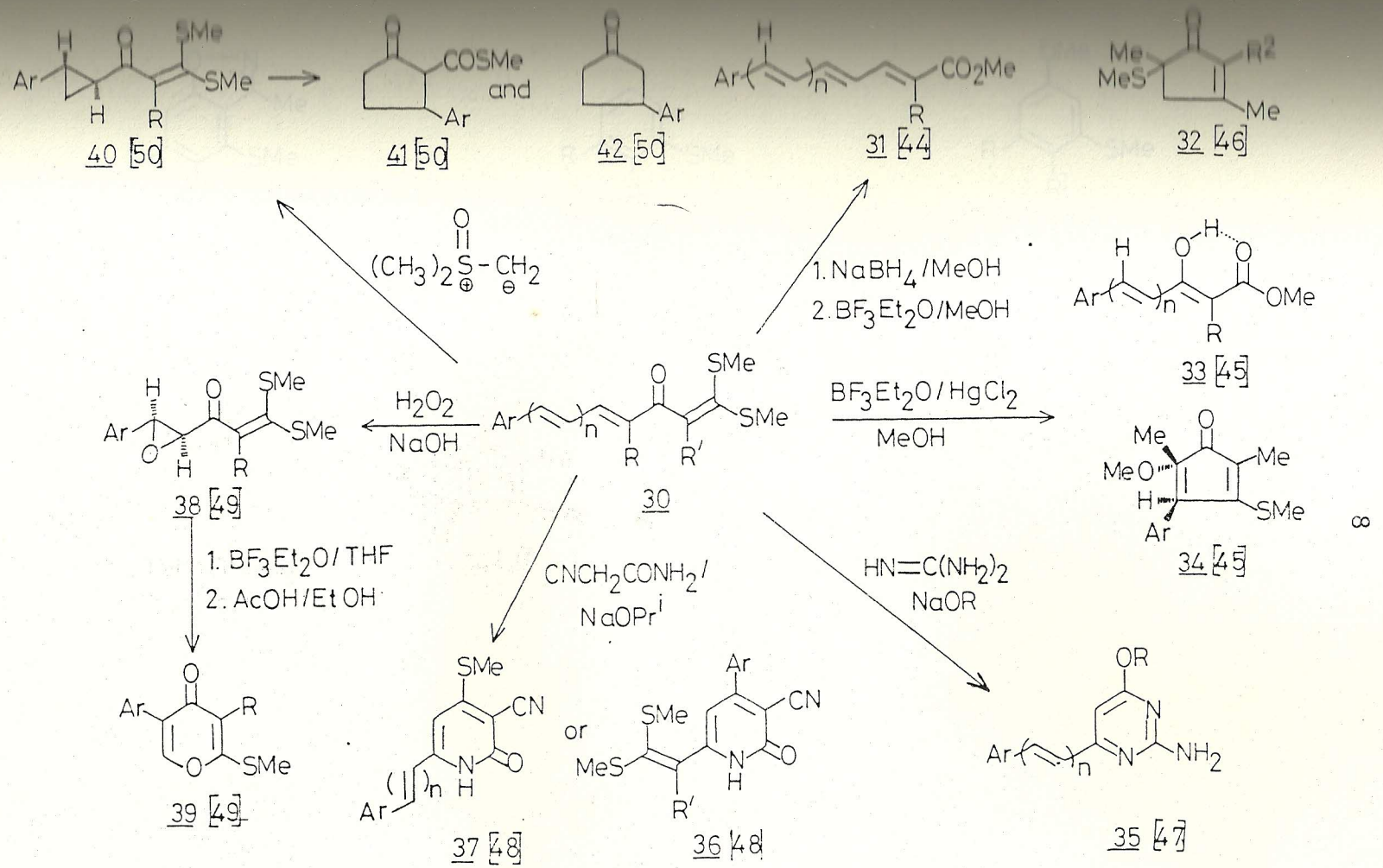
Scheme - 1


12 [31]
13 [31]
2 [27]
3 [18]
or
4 [18]
or
5 [18]
NaBH4 / NiCl2
1. NaBH4
2. BF3.Et2O
MeOH
R''MgX
1, 3 – RS shift
1. PhMgBr
2. BF3Et2O
10 [22]
1
6 [25]
1,5 – RS shift
R2CuLi
BrZnCH2CO2Et
11 [30]
9 [19]
7 [29]
or
8 [29]

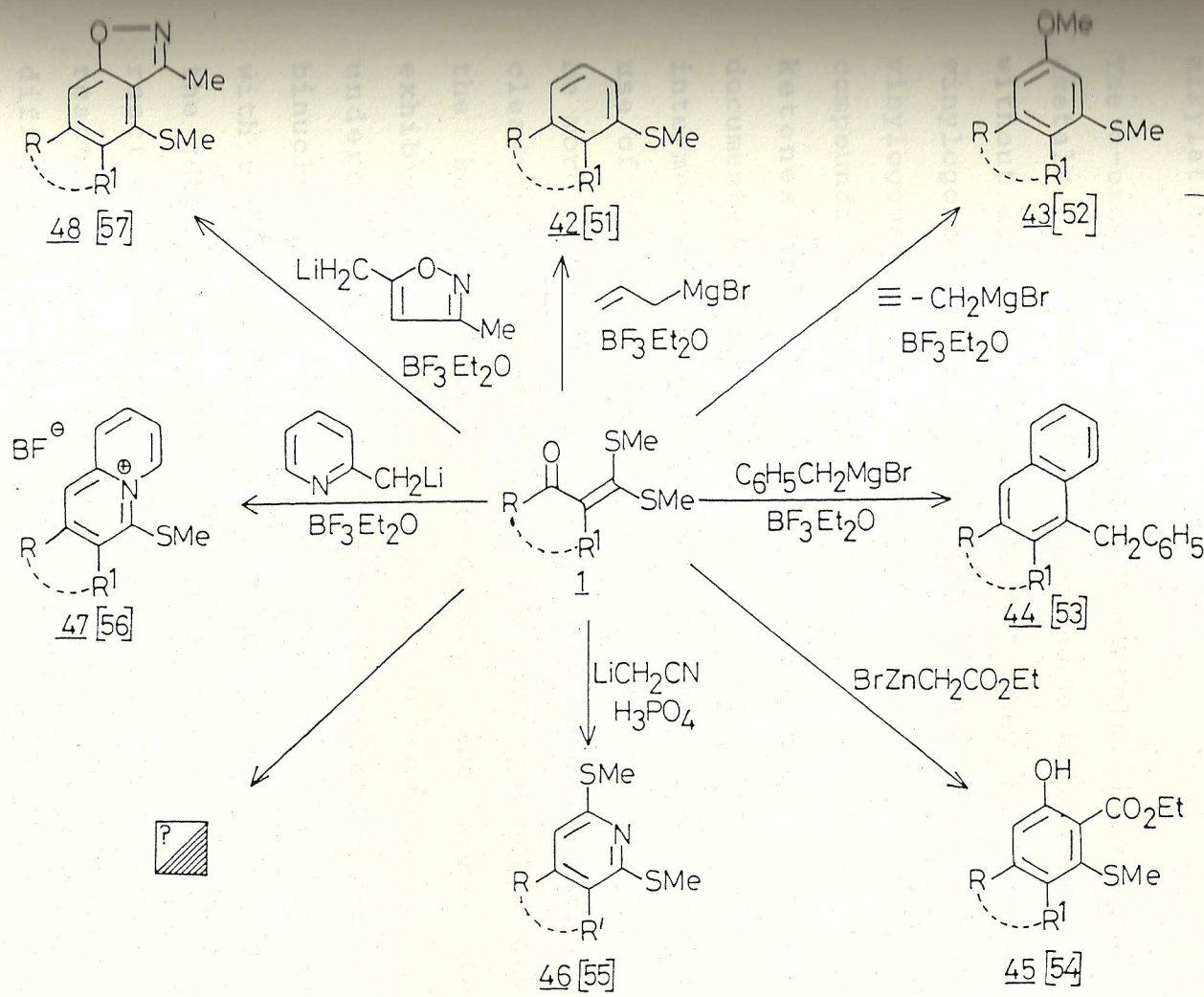
Scheme – 2


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

SCheme – 3


40 [50]
41 [50]
and
42 [50]
31 [44]
32 [46]
1. NaBH4 /MeOH
2. BF3Et2O/MeOH
33 [45]
H2O2
NaOH
30
BF3Et2O / HgCl2
MeOH
34 [45]
38 [49]
1. BF3Et2O / THF
2. AcOH / Et OH
39 [49]
CNCH2CONH2 /
NaOPr^i
or
37 [48]
36 [48]
HN=C(NH2)2
NaOR
35 [47]

Scheme - 4


48 [57]
42 [51]
43 [52]
LiH2C
Me
BF3 Et2O
MgBr
BF3 Et2O
≡ - CH2MgBr
BF3 Et2O
BF⊖
47 [56]
CH2Li
BF3 Et2O
1
C6H5CH2MgBr
BF3 Et2O
44 [53]
LiCH2CN
H3PO4
BrZnCH2CO2Et
?
46 [55]
45 [54]

Scheme – 5

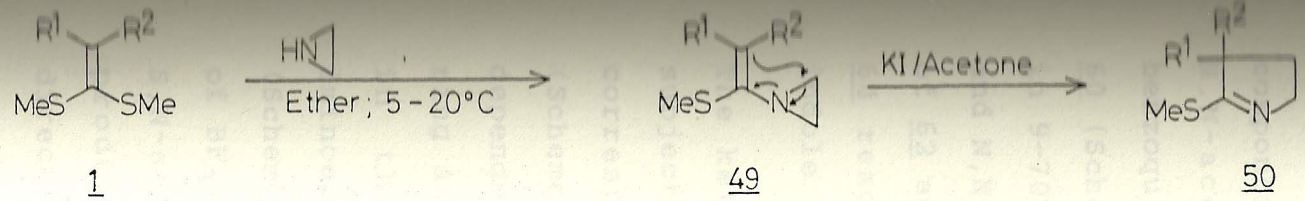
from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates followed by alkylation[58].

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 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 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.

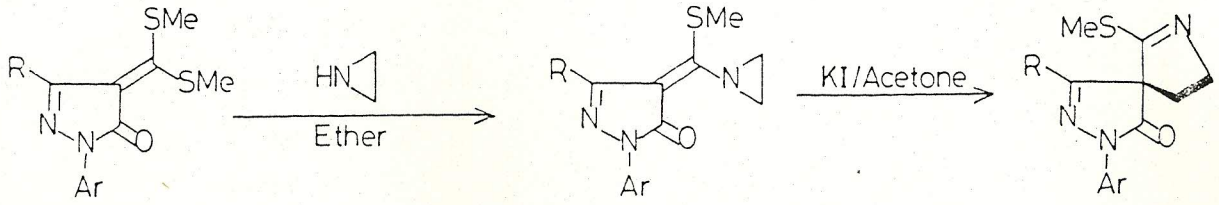
The doubly activated α-oxoketene S,S-acetal 1 underwent smooth displacement reaction at room temperature with aziridine[62] to give the corresponding S,N-acetal 49 in high yields (Scheme 6). The S,N-acetals 49 can be viewed as N-vinyl aziridine and undergo facile ring expansion to yield the corresponding pyrrolines 50 (Scheme 6). Similarly the α-oxoketene S,S-acetals 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 method suffered from limitations since it



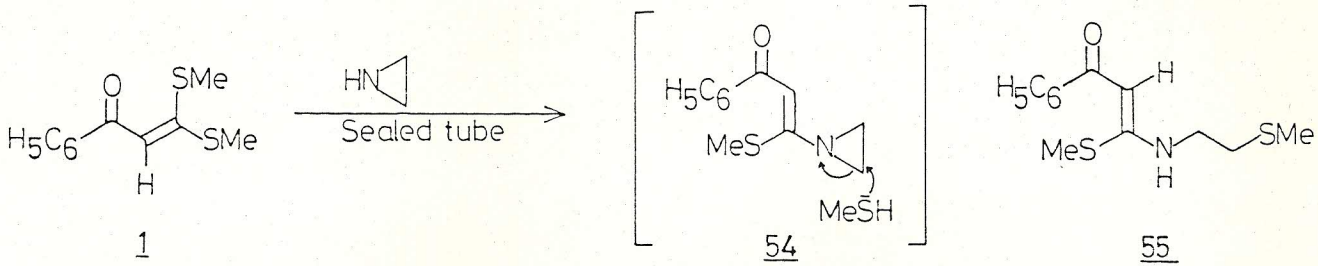
1 49 50

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 52 53

R = Ph ; 4 - MeC_6H_4 ; 4 - $MeOC_6H_4$; 4 - ClC_6H_4 ; Me

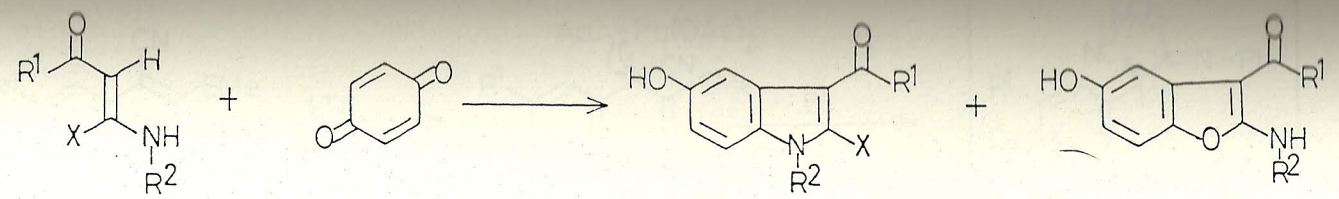


1 54 55

Scheme - 6

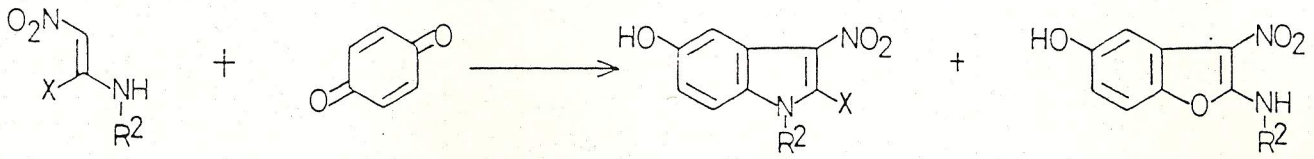
carried a substituent at 2-position arising from the enamine component. The α-oxoketene S,N- and N,N-acetals were considered as suitable alternatives to these enamine components in the Nenitzescu indole synthesis. Thus, the N,N-acetals 56 underwent smooth reaction with p-benzoquinone to yield a mixture 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-oxoketene S,N-acetals 57 underwent LTA oxidation[65] to yield the corresponding 72

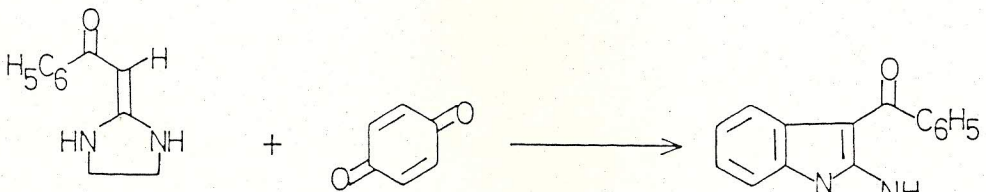


56,57 58 59 60

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

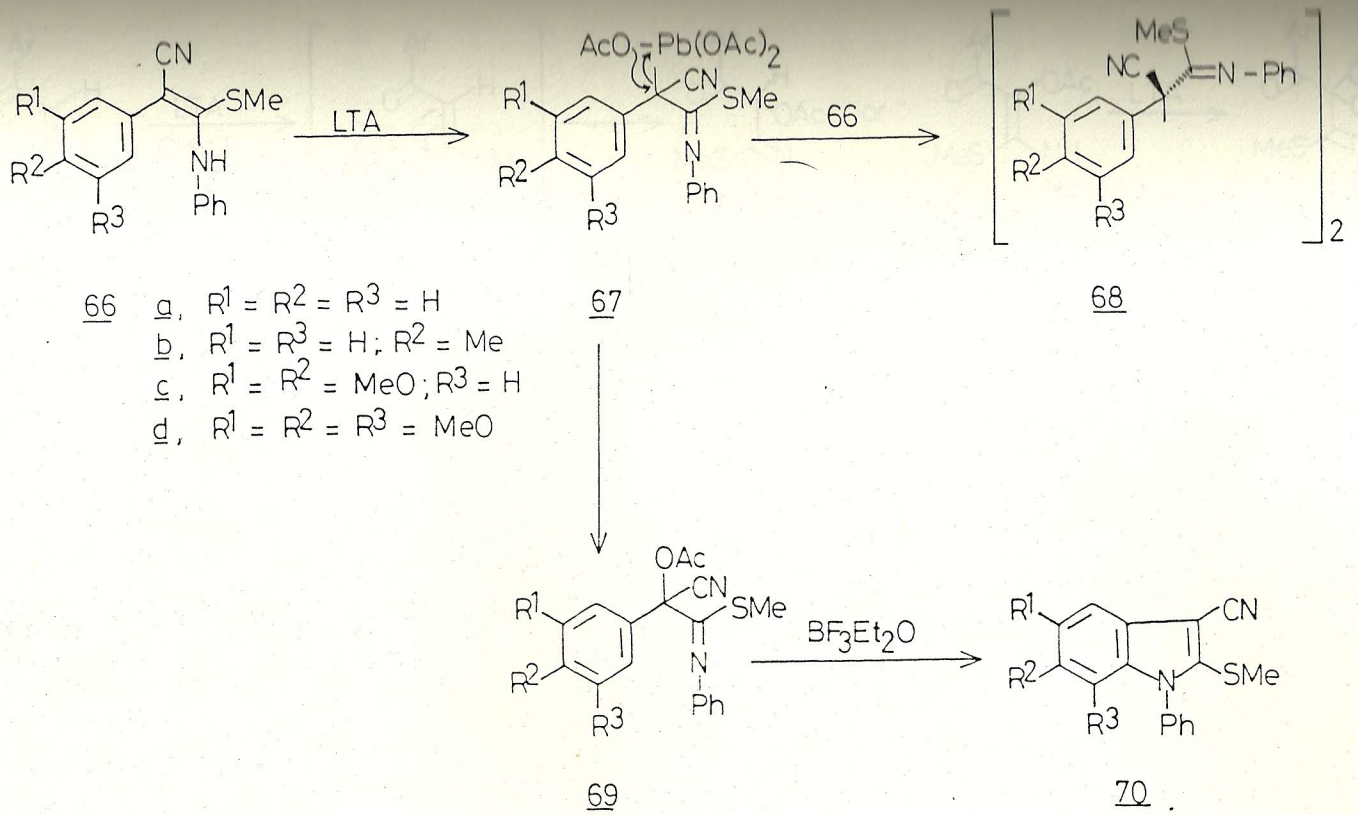


61 58 62 63



64 58 65

Scheme - 7



66 a, $R^1 = R^2 = R^3 = H$
b, $R^1 = R^3 = H$; $R^2 = Me$
c, $R^1 = R^2 = MeO$; $R^3 = H$
d, $R^1 = R^2 = R^3 = MeO$

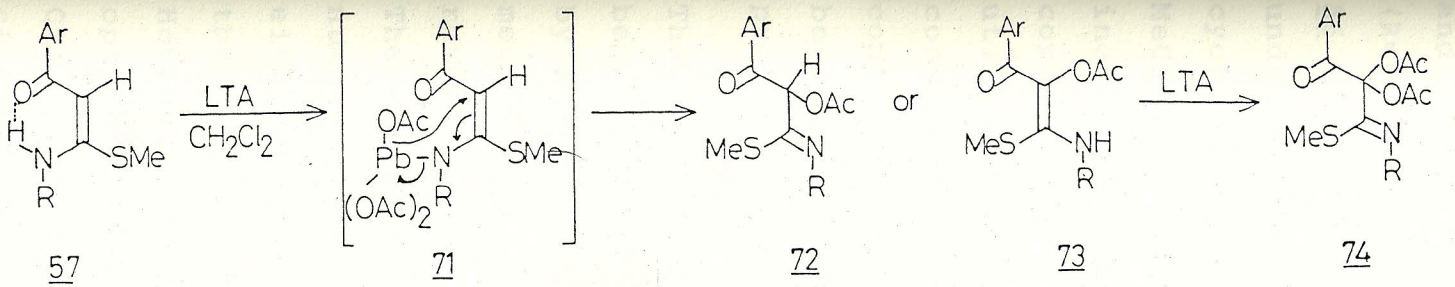
67

68

69

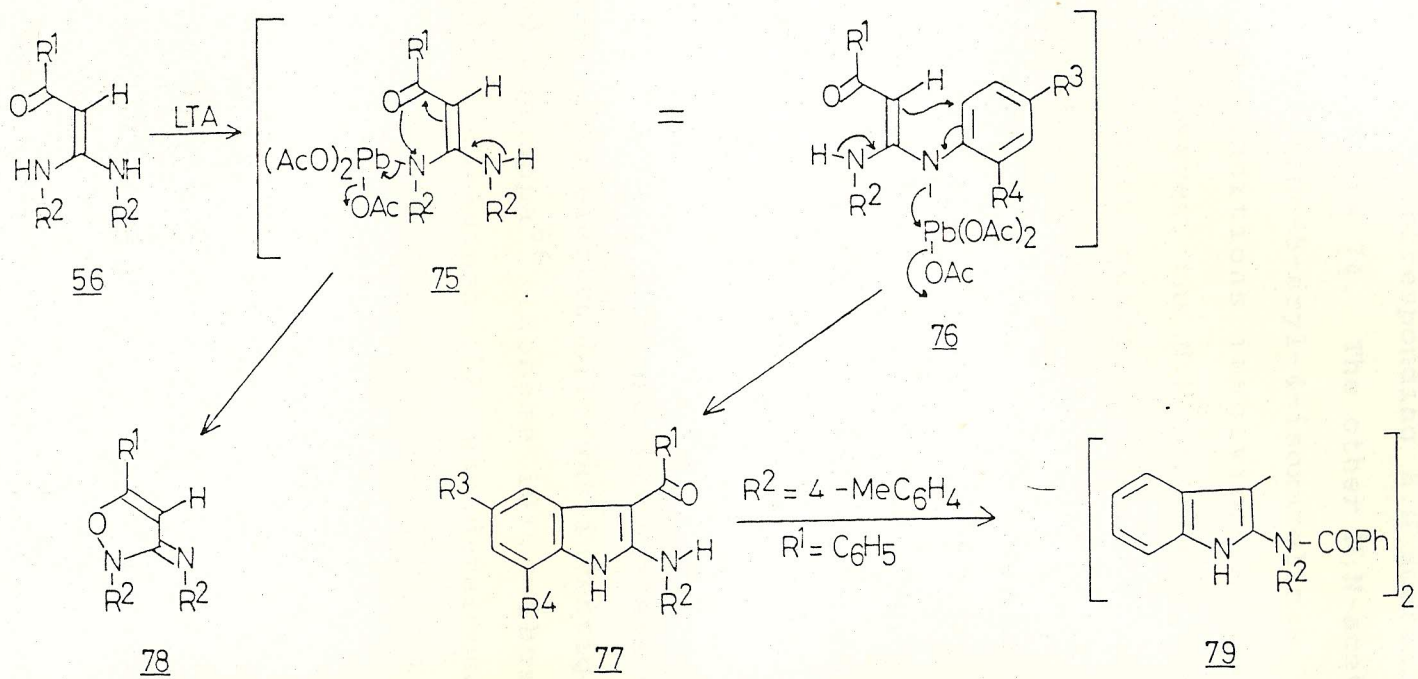
70

Scheme - 8



57 71 72 73 74

R = Et, C_6H_5, $C_6H_5CH_2$



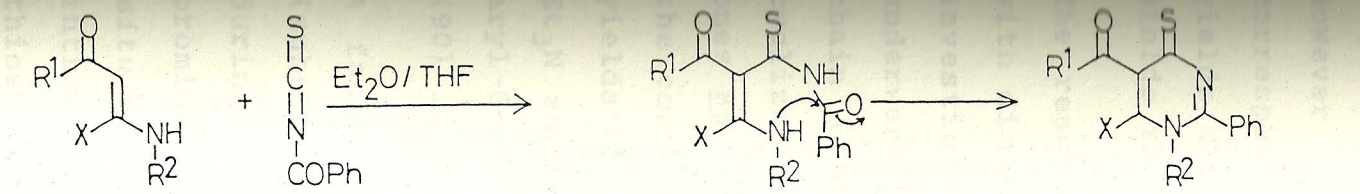
56 75 76 78 77 79

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

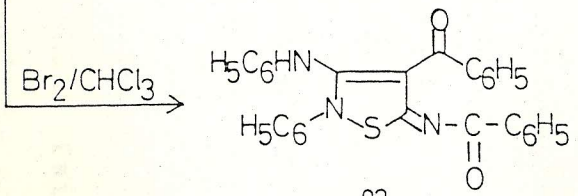
and 73 (Scheme 9) while the corresponding S,N-acetals 57 (R=Et) yielded the iminoacetate 74. The other N,N-acetals 56 afforded 2-aryl-3-arylamino-5-aryl-4-isoxazolines (78) under similar reaction conditions involving oxidative cyclization (Scheme 9). However, the N,N-acetals 56 (R^2=4-MeC_6H_4) yielded, 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 isothiazolines 83 in good yields. Similarly, the nitroketene S,N- and N,N-acetals 61 reacted with 80 in boiling THF to yield the corresponding

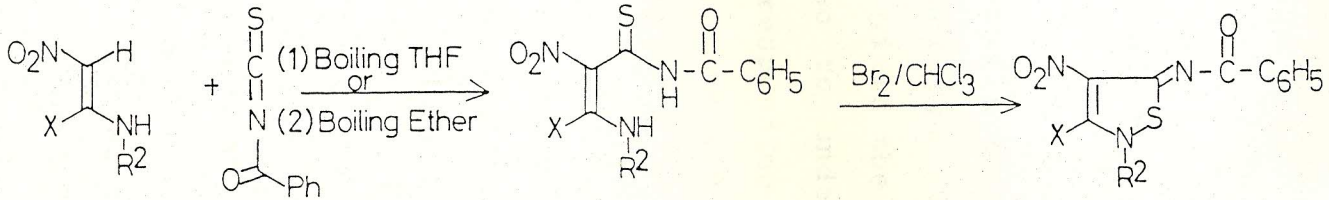


56,57 80 81 82

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



83



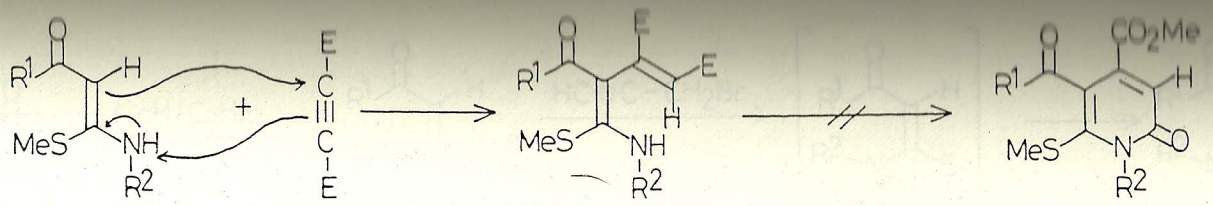
61 80 84 85

Scheme - 10

isothiazolines 85 in 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 $CHCl_3$.

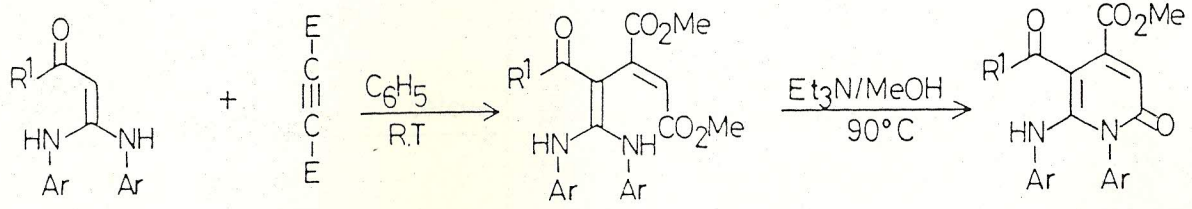
The reaction of α-oxoketene S,N-acetals and N,N-acetals with dimethylacetylenedicarboxylate (DMAD) 86 has been investigated[67] in this laboratory. The S,N-acetal 57 underwent Michael addition to yield the corresponding open chain adducts 87 which failed to undergo intramolecular cyclization to afford 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)-thizolines (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



57 86 87 88

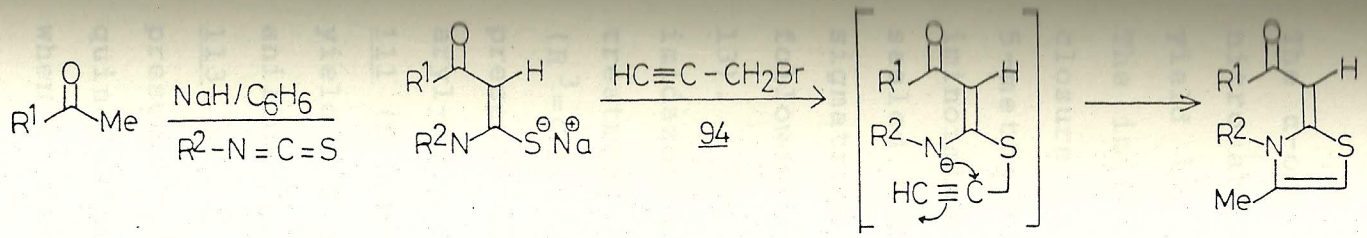
$R^1 = C_6H_5$; $R^2 = C_6H_5$, Et



56 86 89 90

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

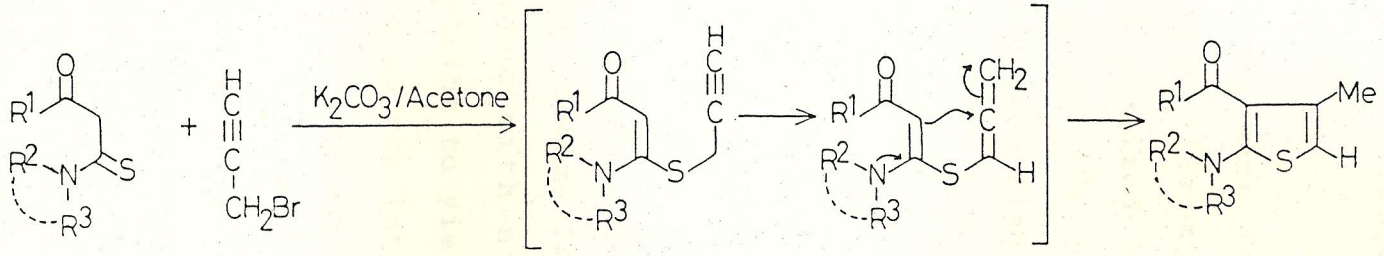
Scheme -11



91 92 93 94 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

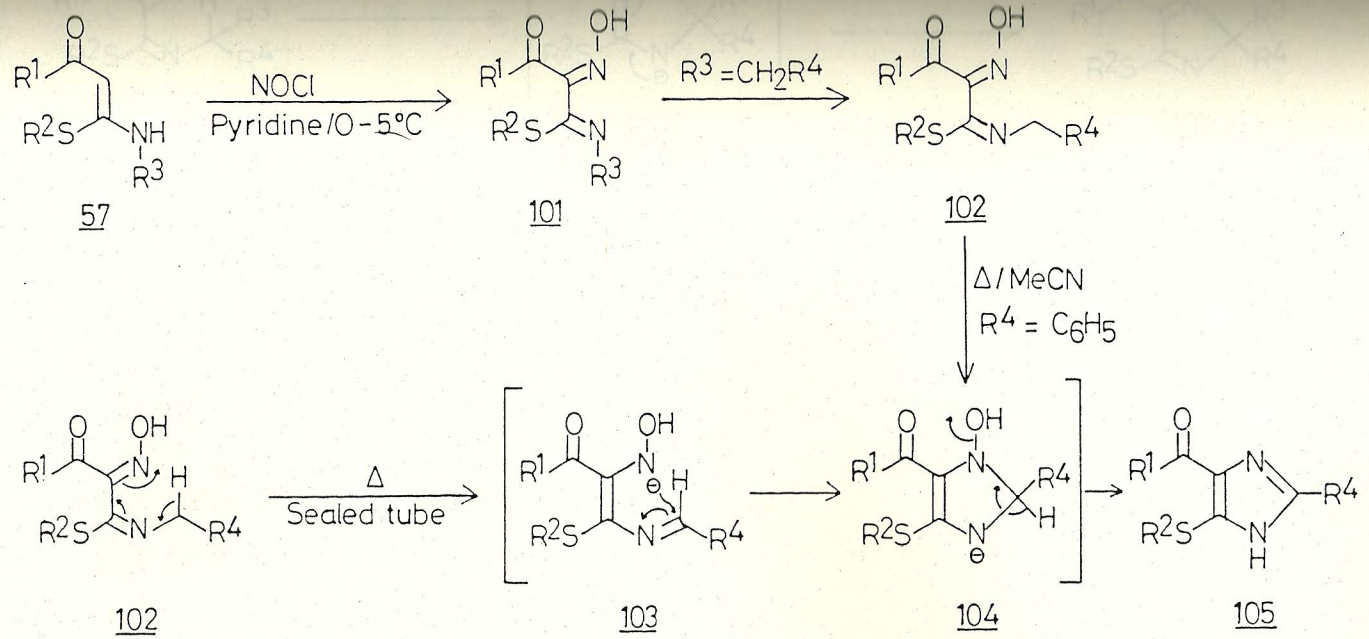
R^2, R^3N - = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$

$-(CH_2)_2-N(C_6H_5)-(CH_2)_2-$

Scheme -12

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

The α-oxoketne 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 102 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-anilinothiazoles (117) in excellent yields



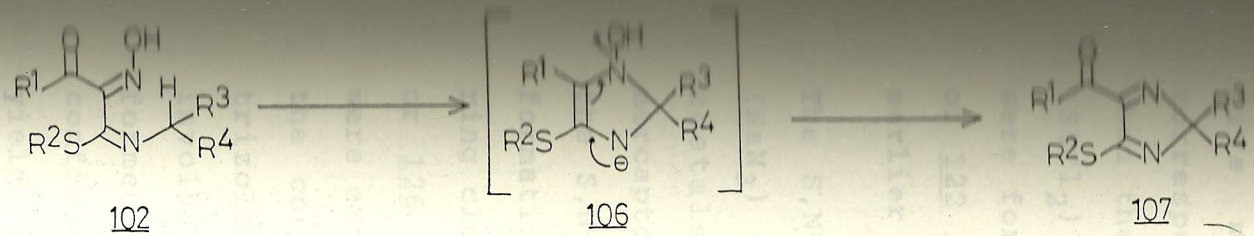
57 101 102 102 103 104 105

R^1 = substituted aryl, Me, CO_2Et

R^2 = Me, Et

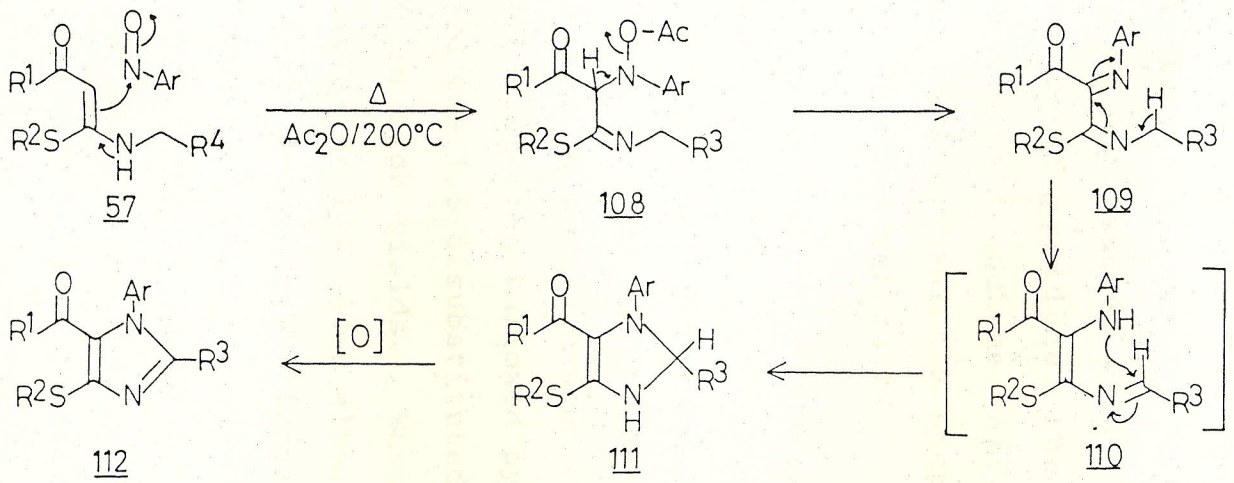
R^4 = H, Me, Et, C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme -13



102 106 107

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 = $-(CH_2)_5-$



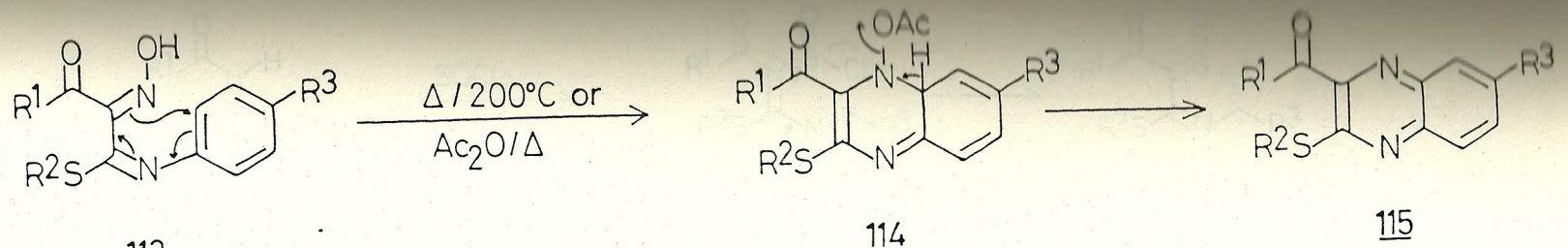
57 108 109 110 111 112

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

(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.

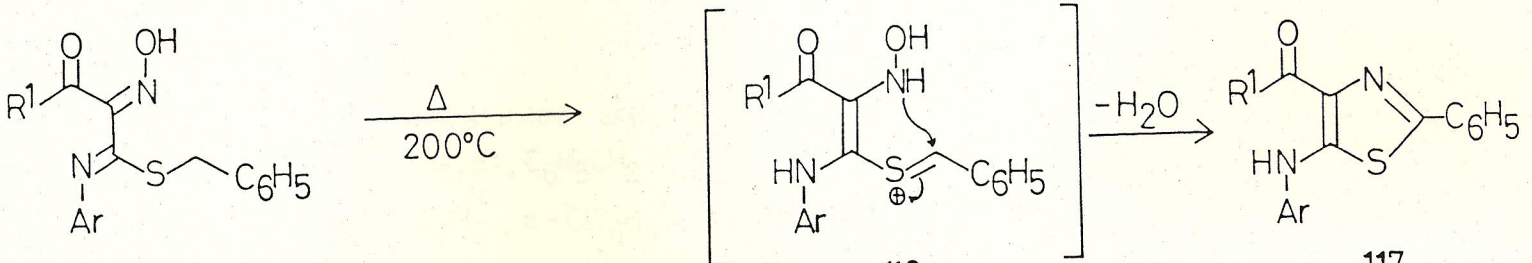
The S,N-acetals 57 behave differently with sodium azide (NaN_3) than the corresponding S,S-acetals. The S,S-acetals generally undergo 3+2 cycloaddition to the mercapto double bond to yield the triazoles[72]. However, the S,N-acetals react with NaN_3 through the intermediate formation of the azide 123⇌124 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).



113 114 115

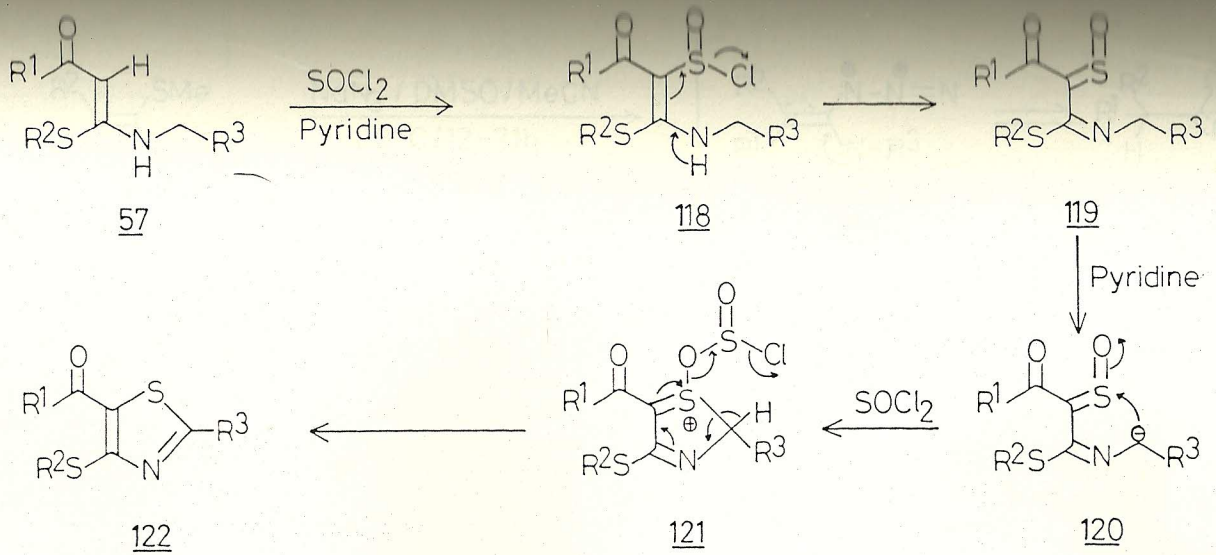
R^1 = substituted aryl; R^2 = Me
R^3 = H, Me, Cl, MeO

$R^2 = CH_2C_6H_5$



113 116 117

SCheme - 15



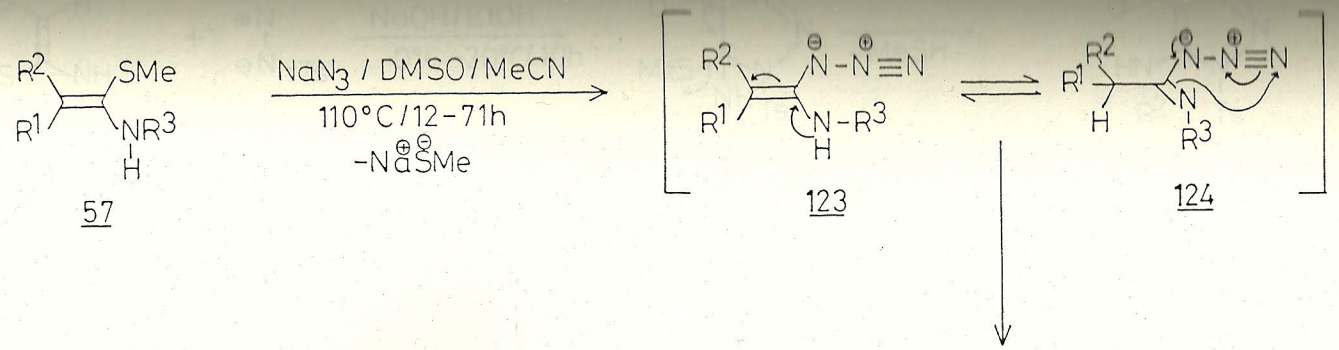
57 118 119 120 121 122

R^1 = substituted aryl, Me

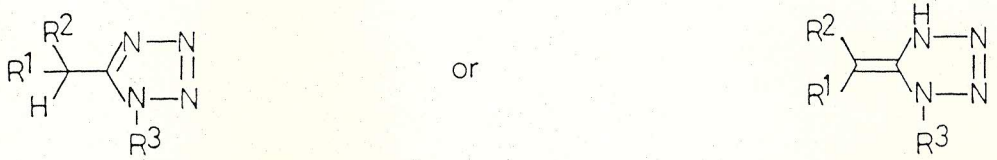
R^2 = Me, Et, $C_6H_5CH_2$

R^3 = C_6H_5 , 4-ClC_6H_4 , 4-$MeOC_6H_4$, CO_2Et

Scheme - 16



57 123 124



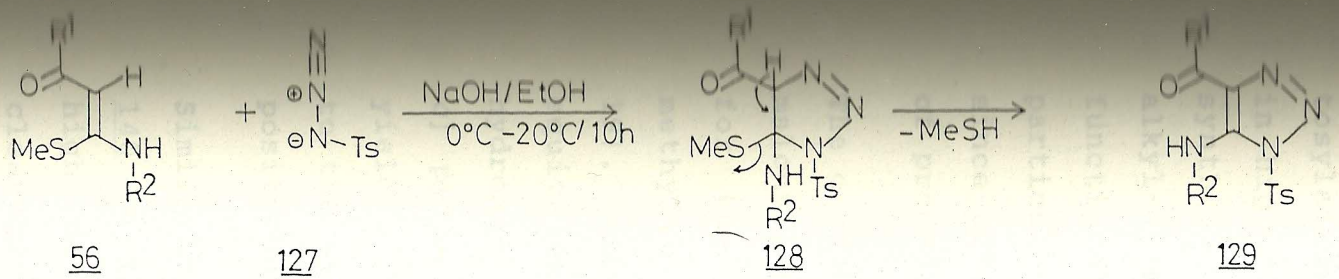
126 or 125

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

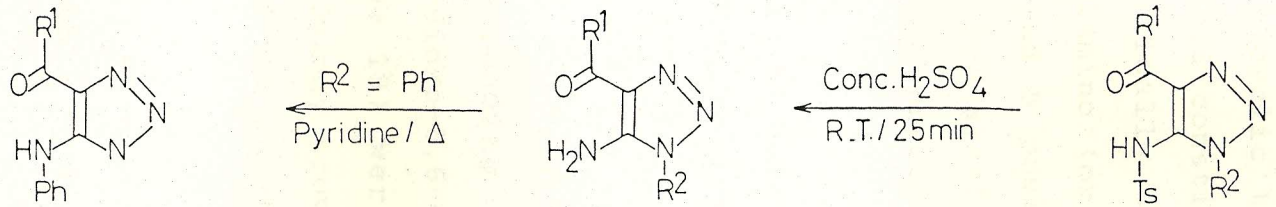


56 127 128 129

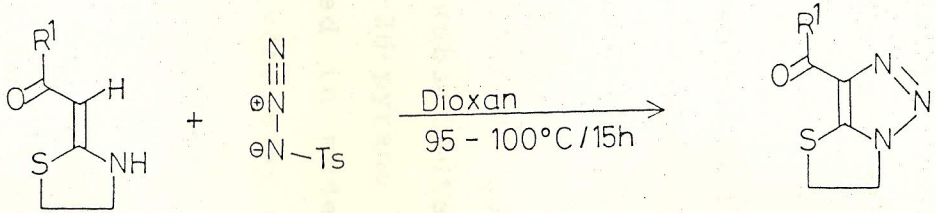
R^1 = substituted aryl, Me

R^2 = Ph, $PhCH_2$, Me, Et, n-Pr, i-Pr, n-Bu, $CycloC_6H_{11}$, $CH_2CH(OEt)_2$

Dimroth Rearrangement



132 R^1 = Ph, 4-ClC_6H_4 131 130



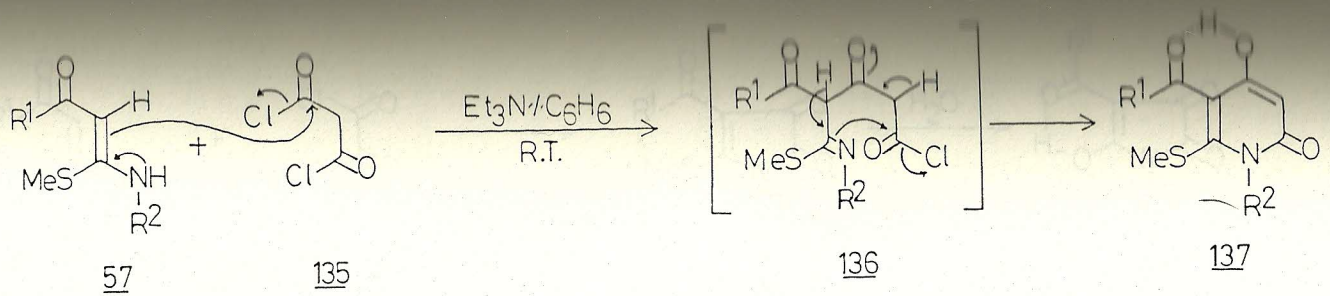
133 127 134

Scheme -18

Similarly, the cyclic S,N-acetals 133 reacted 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.

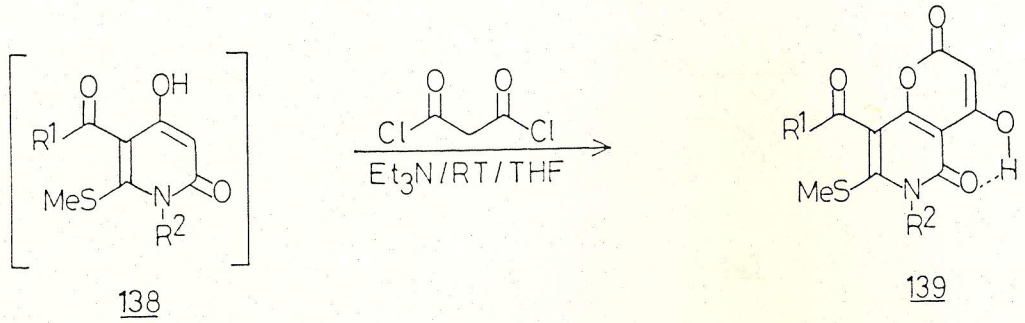
Similarly, the S,N-acetals 57 reacted with oxalyl chloride 140 to give highly unstable pyrrolo-2,3-diones[75] 141 in high yield (Scheme 20). They underwent easy hydrolytic cleavage to yield 5-hydroxy pyrrole diones 142. However, when 141 was reacted with amines the corresponding amino pyrrole-2,3-diones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



57 135 136 137

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

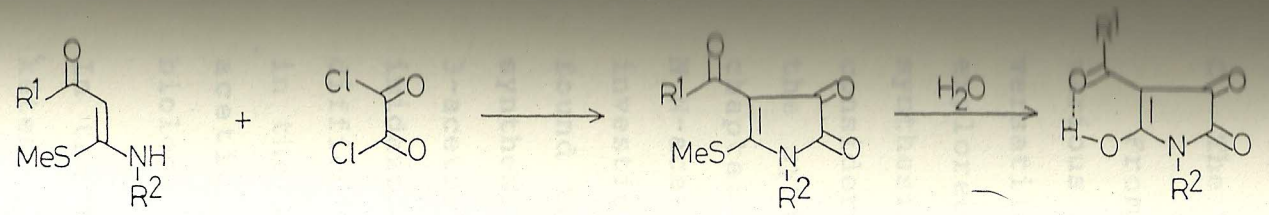


138 139

R^1 = Me, C_6H_5

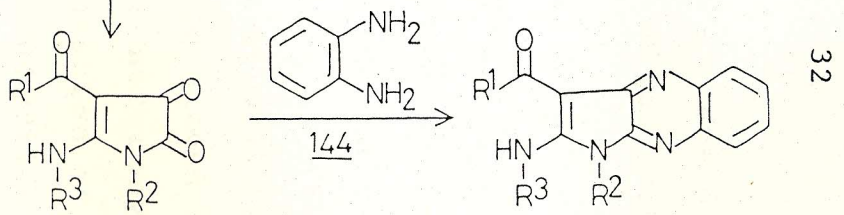
R^2 = Me, Et, $C_6H_5CH_2$

Scheme -19



57 140 141 142

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
$C_6H_5CH_2$



143 144 145

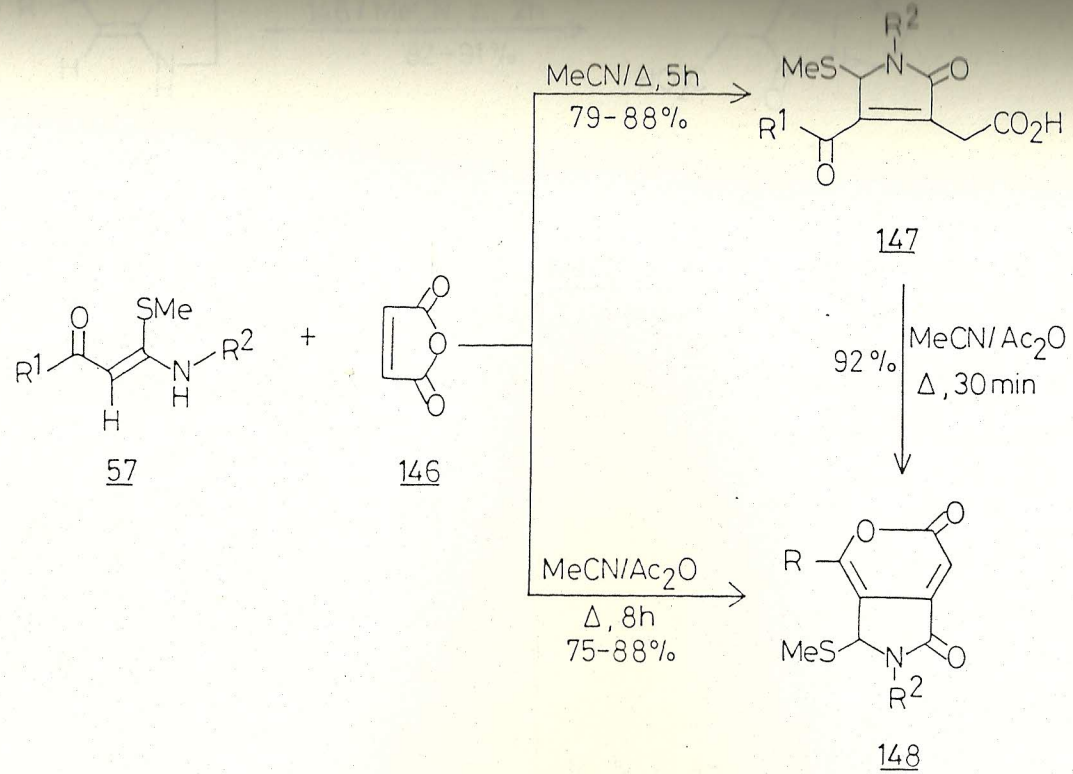
Scheme - 20

then condensed with o-phenylene diamine 144 to yield the pyrroloquinoxalines 145 in good yields (Scheme 20).

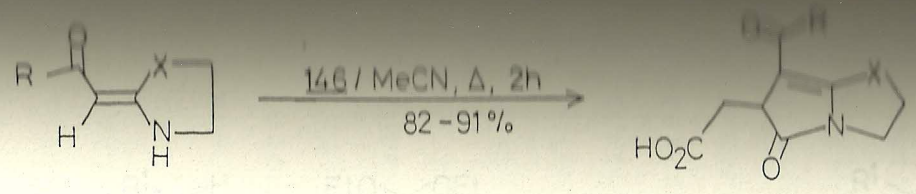
C. The Work Presented in this Thesis:

From the studies on the synthetic applications of various S,N- and N,N-acetals it is evident that they are versatile synthetic intermediates which could further be explored to develop novel synthetic methods for the synthesis of various heterocyclic molecules. Thus, it was considered of interest to extend some of these ideas for the synthesis of novel heterocycles. In the second chapter the cyclocondensation of α-oxoketene S,N- and N,N-acetals with maleic anhydride and maleimide has been investigated[76] (Schemes 21 and 22). These results were found to be fairly successful since they lead to the synthesis of various pyrroline-3-acetic acids, pyrroline-3-acetamides, pyranopyrroles, pyrrolopyridines, pyrrolo imidazoles and pyrrolothiazoles which are otherwise very difficult to synthesize by the reported methods available in the literature and particularly the pyrrolothiazole-6-acetic acids have structural features similar to biologically important molecules.

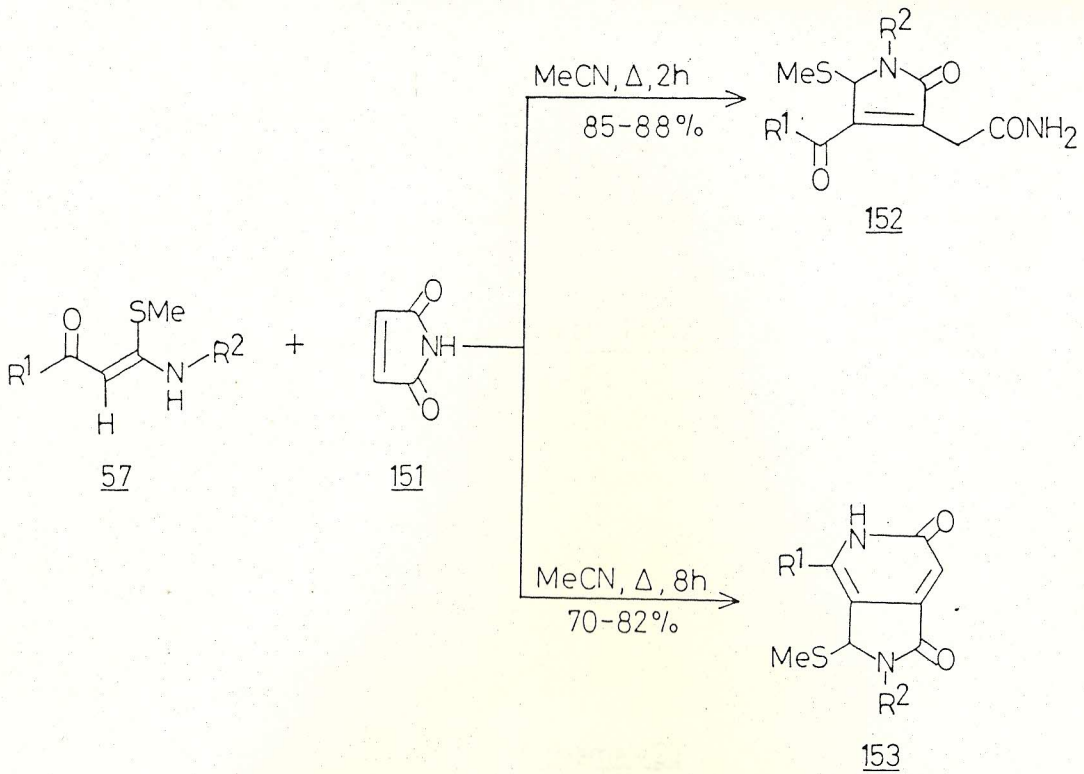
In the third chapter the application of the polarized ketene S,N- and N,N-acetals for the synthesis of various pyrroles[77] is discussed (Scheme 23). This method is superior to the earlier method developed in this laboratory which failed when extended to the synthesis of N-substituted pyrroles. Interestingly, the reaction of


MeCN/Δ, 5h
79-88%
MeS
N
R2
O
R1
CO2H
147
92 %
MeCN/Ac2O
Δ, 30 min
SMe
R1
R2
H
57
146
MeCN/Ac2O
Δ, 8h
75-88%
R
MeS
148

Scheme-21

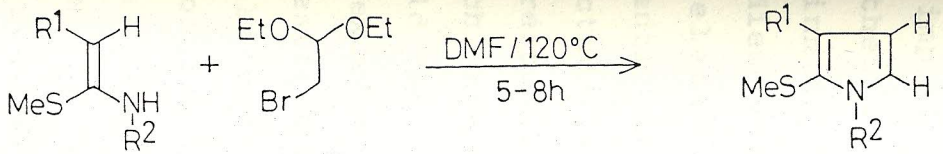


149 150

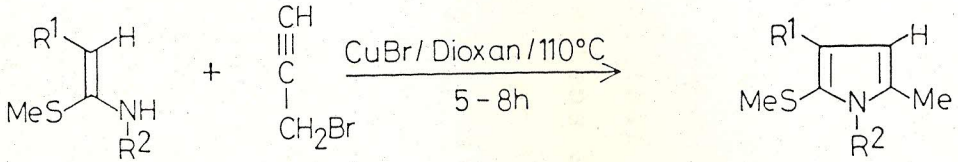


57 151 152 153

Scheme -22



57 154 155



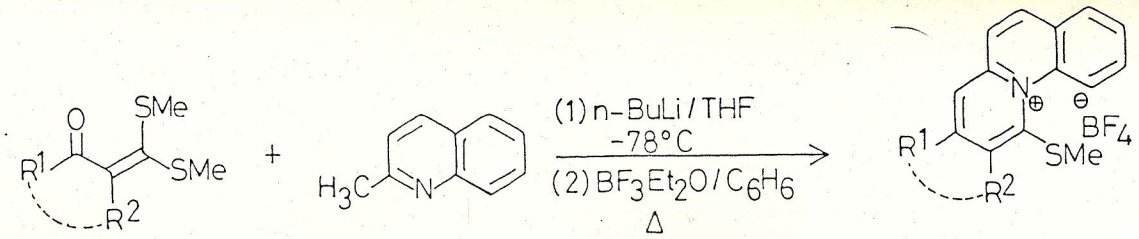
57 94 156

Scheme - 23

the polarized ketene S,N-acetals with propargyl bromide afforded 2-methyl pyrroles.

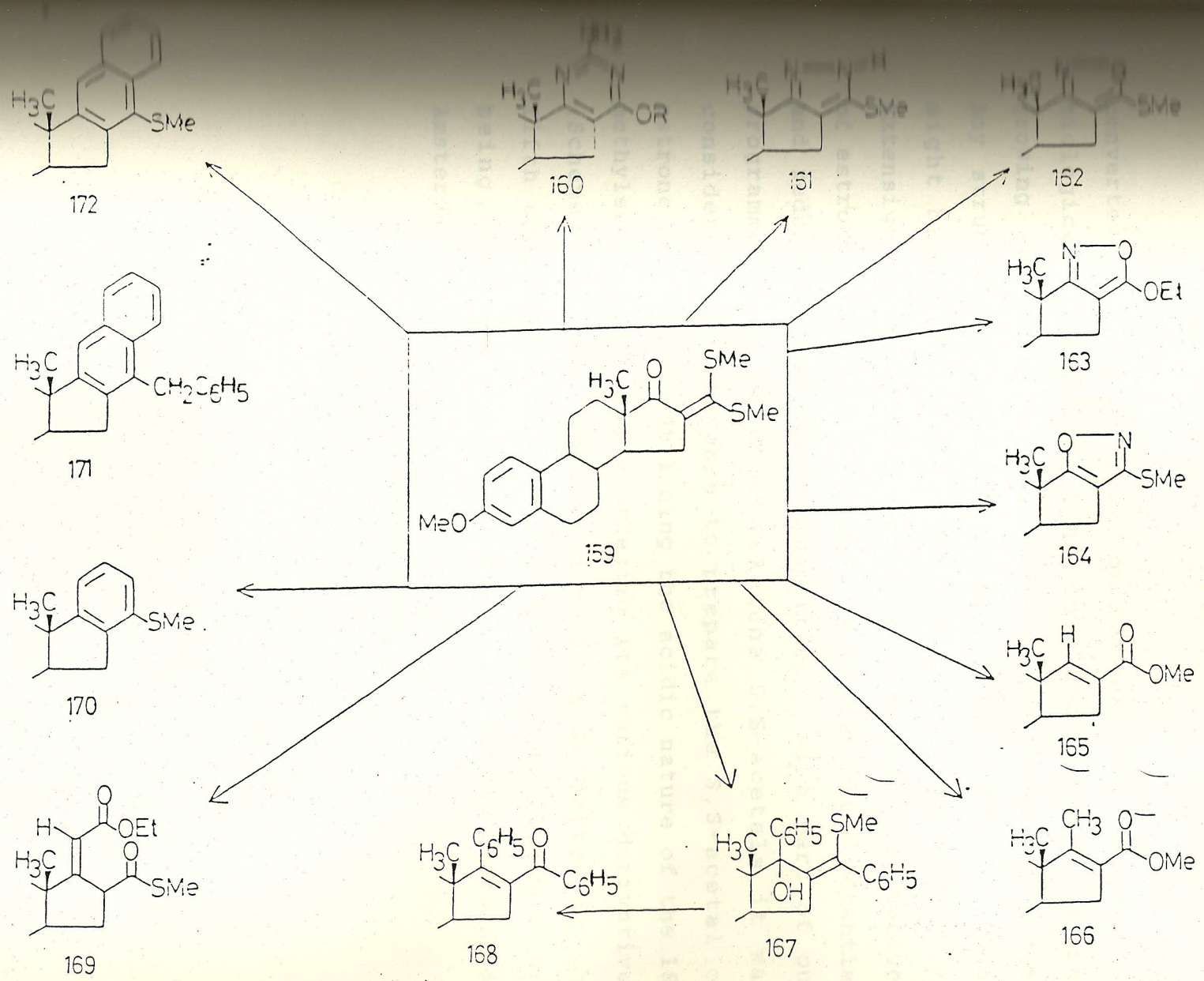
Like S,N-and N,N-acetals, the S,S-acetals also constitute an important class of synthetic intermediates whose synthetic importance has been reviewed briefly in the beginning of this chapter. In continuation of these studies various methods for aromatic and heteroaromatic annelation have been developed in this laboratory. Recently it was reported that the 2-lithiomethylpyridine reacted with the α-oxoketene S,S-acetals to afford the corresponding 1,2-addition products in quantitative yields which underwent $BF_3.Et_2O$ assisted cycloaromatization to yield the corresponding quinolizinium tetrafluoroborates[78], in excellent yields. This methodology required further investigation to study the scope and limitations of its application for the synthesis of several alkaloids belonging to berberine and isoquinoline series. Thus, model experiments were carried out to examine the scope of this reaction for the synthesis of condensed quinoline derivatives. Thus, 2-lithiomethyl quinoline and 2-lithiomethyl-4-methyl-6-methoxy quinoline were reacted with various α-oxoketene S,S-acetals to yield the corresponding benzo[*c*]quinolizinium, benzo[*c*]phenanthridizinium and condensed quinolizinium salts in good to excellent yields. These results have been discussed in the fourth chapter of this thesis (Scheme 24).

It is evident that any active methylene compound could be



1 157 158

Scheme - 24



Scheme - 25

converted to its S,S-, N,N-, or S,N-acetals. Estrone is biologically very important compound because of its growing importance in the field of antifertility drugs. Any structural change in a biologically active compound might bring about a marked effect on its activity. Extensive studies are reported to synthesize derivatives of estrone which could enhance its antifertility potential and reduce its estrogenic properties. As a part of our programmed studies on α-oxoketene S,S-acetals it was considered of importance to prepare the S,S-acetal of estrone molecule by utilizing the acidic nature of the 16-methylene protons and synthesize its various derivatives (Scheme 25). These results have been described in the fifth chapter of this thesis, and the derivatives are being screened, by Ms. Organon International, Oss. Amsterdam.

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