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

ABSTRACT

By

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

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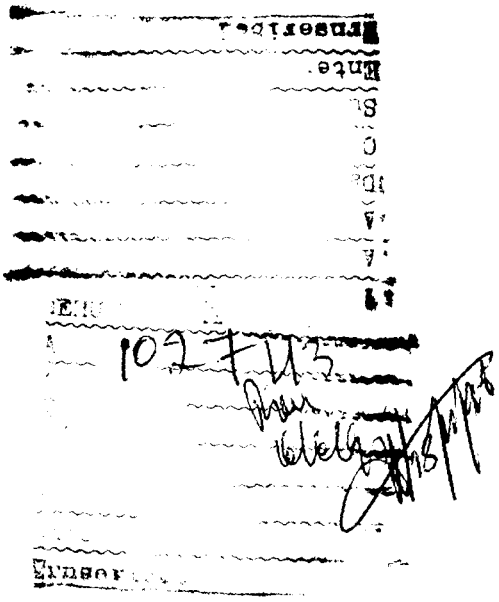
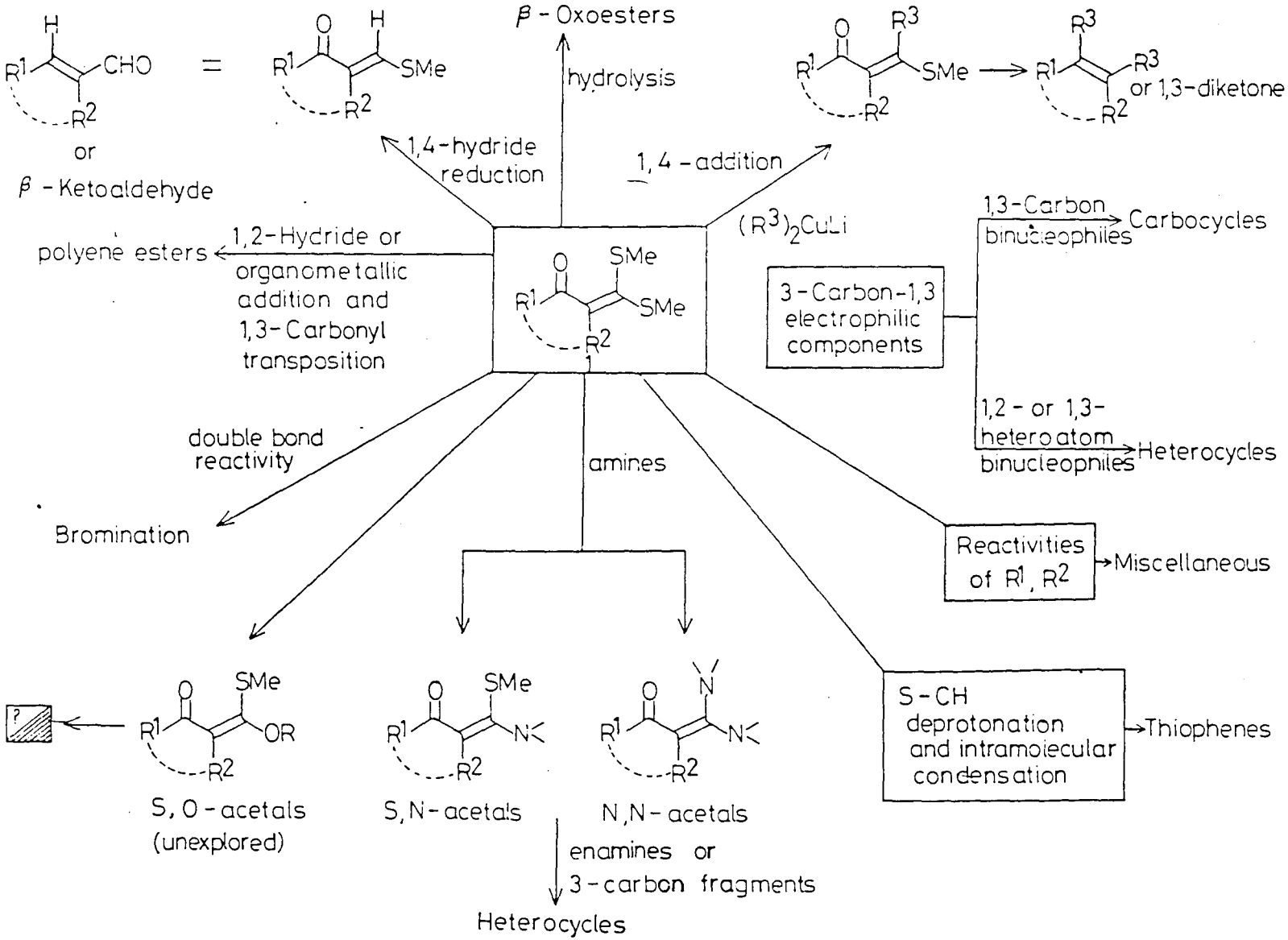
Chem.



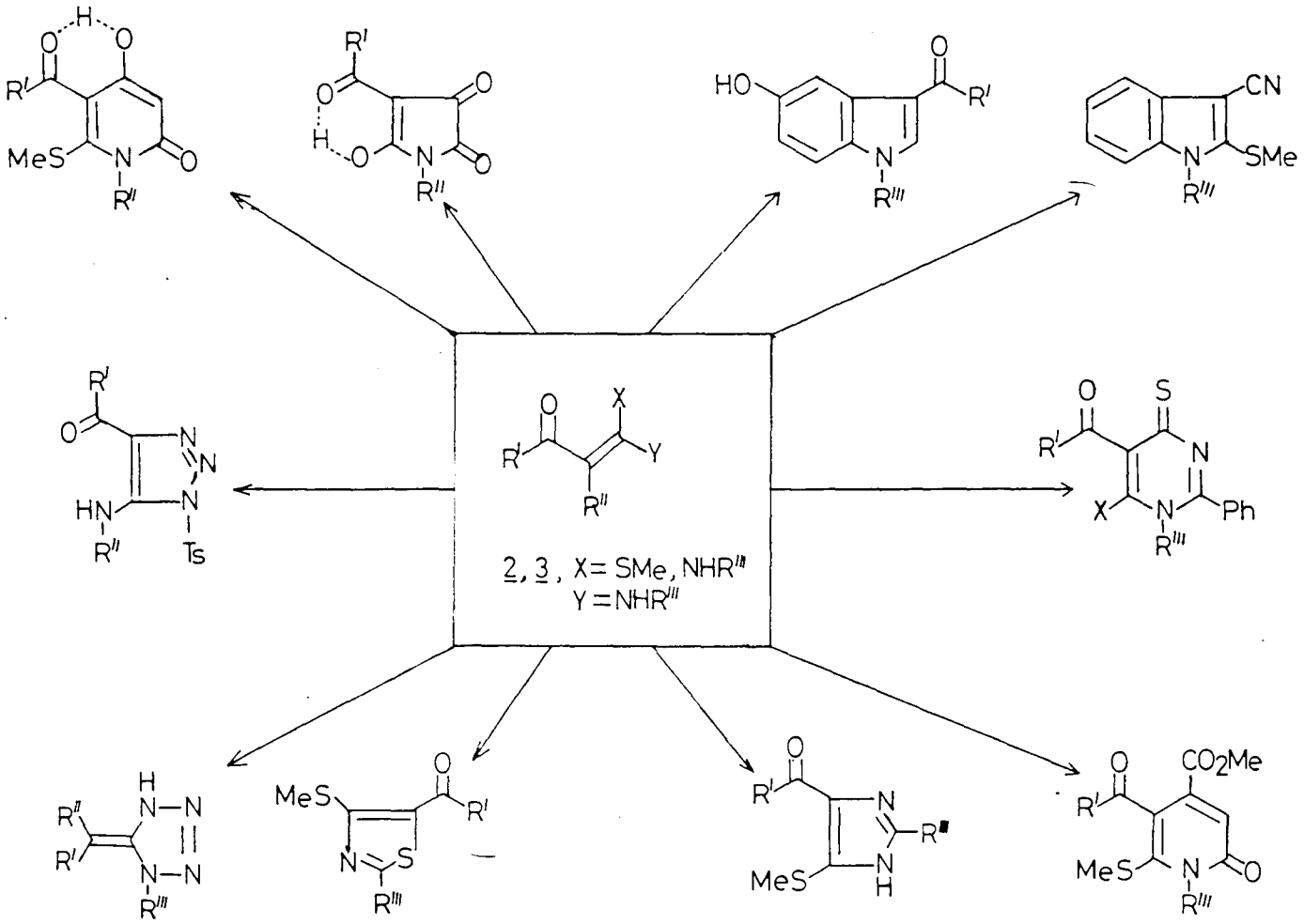
GUPJ-1

The synthesis of α-oxoketene S,S-acetals of the general formula 1 was first reported by Kelber and coworkers[1] in 1910. This class of compounds can be easily prepared from a wide variety of active methylene ketones and carbon disulfide in the presence of a suitable base followed by alkylation. Many experimental variations of this method are now available in the literature[2]. They are also called as polarized ketene S,S-acetals. The polarized ketene S,S-acetals possess 1,3-electrophilic centers with differing electrophilicity and, therefore, are excellent class of 3-carbon synthons. They have been extensively used to construct various carbocycles and heterocycles by reacting them with various 1,2- or 1,3-binucleophiles. A brief review on their utility as 3-carbon fragment has been shown in Scheme 1.

The polarized ketene S,S-acetals can be converted into corresponding polarized ketene S,N- and N,N-acetals 2 and 3 respectively by reacting them with appropriate amines under different conditions[5-7]. These S,N- and N,N-acetals, in turn,are excellent enamines and have been used to synthesize various heterocycles. They can be considered as vinylogous amides if they are derived from ketones and as vinylogous amines if they are derived from other active methylene compounds. They also possess 1,3-electrophilic centers and have been used to construct various heterocycles. Their various transformations have been briefly shown in Scheme 2.

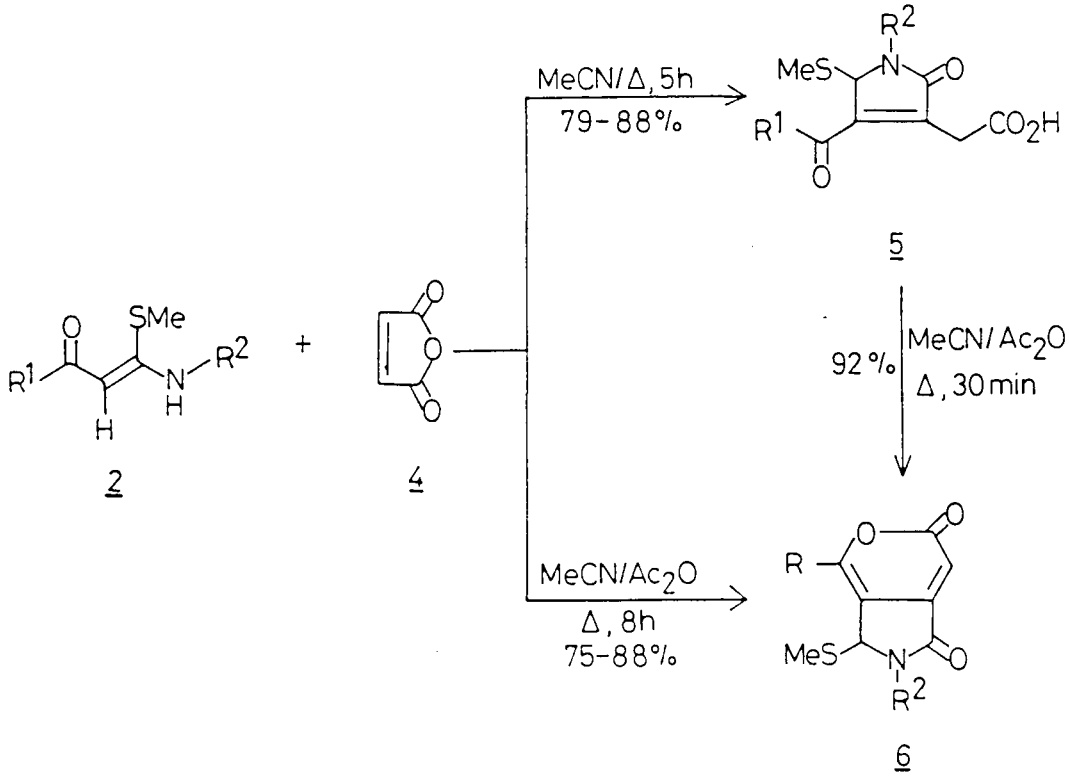

β - Oxoesters
hydrolysis
or 1,3-diketone
1,4-hydride reduction
1,4-addition
(R3)2CuLi
1,2-Hydride or organometallic addition and 1,3-Carbonyl transposition
polyene esters
1,3-Carbon binucleophiles
Carbocycles
3-Carbon-1,3 electrophilic components
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
double 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
or
β - Ketoaldehyde

Scheme-1



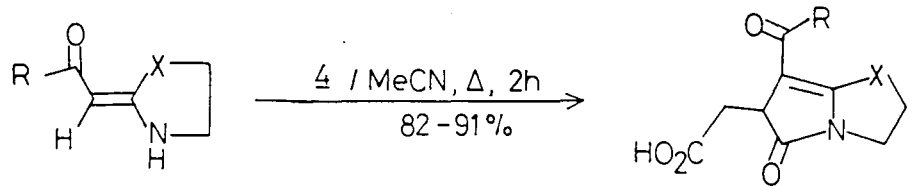
Scheme – 2

In the present study it was proposed to explore the enamine behaviour of the polarized ketene S,N- and N,N-acetals[9]. Thus, they are shown to react with maleic anhydride 4 in refluxing acetonitrile to afford various pyrrolin-3-acetic acids 5 in excellent yields (Scheme 3). Alternately, they yield various pyranopyrroles 6 when reacted with maleic anhydride in the presence of acetic anhydride in refluxing acetonitrile (Scheme 3). It is also shown that the pyrrolin-3-acetic acids 5 are cyclized to the corresponding pyranopyrroles 6 when heated with acetic anhydride (Scheme 3). Similarly, the cyclic S,N- and N,N-acetals 7 also react with maleic anhydride in refluxing acetonitrile to yield various pyrrolothiazoles 8a-c and pyrroloimidazoles 8d-f in good yields (Scheme 4). However, these pyrrolothiazoles and pyrroloimidazoles failed to cyclize in the presence of acetic anhydride. As a model reaction, the S,N-acetals 2a and 2d are shown to react with maleimide 9 in refluxing acetonitrile to yield the corresponding pyrrolin-3-acetamides 10a and 10b in good yields (Scheme 5). The corresponding pyrrolopyridines 11a and 11b were obtained when the refluxing time was increased (Scheme 5). Few N,N-acetals 3 are also shown to react with maleic anhydride 4 and maleimide 9 in refluxing acetonitrile to yield the corresponding pyrrolin-3-acetic acids 12 and pyrrolin-3-acetamides 13 in good yields (Scheme 6). However, 12 and 13 failed to cyclize in acetic anhydride. The scope and limitations of this method are discussed in detail in the second chapter.



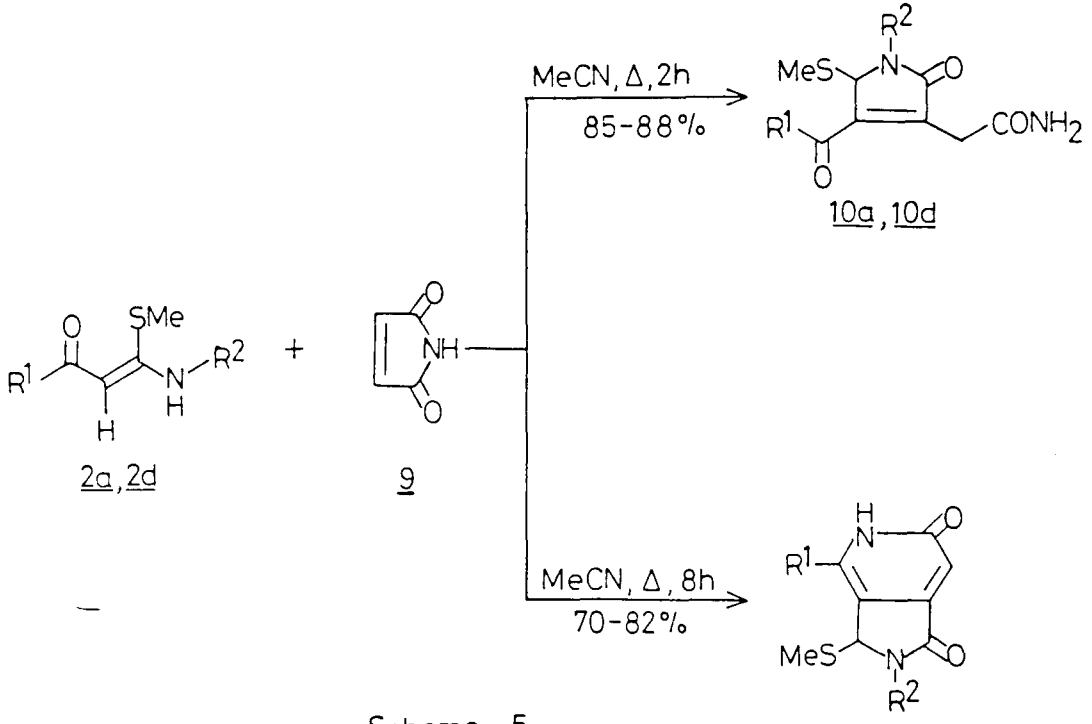
(4)

Scheme- 3



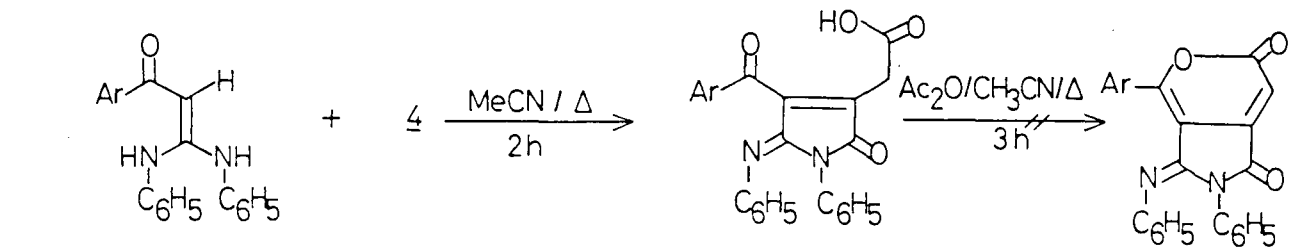
7 X = O, NH 8

Scheme-4



Scheme – 5

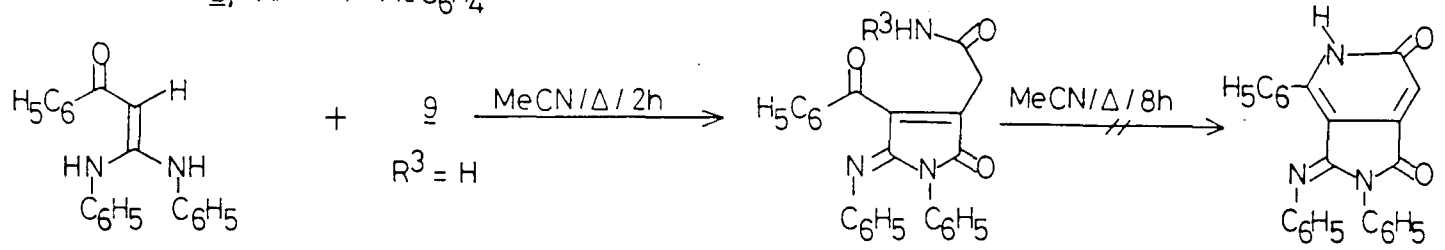
(vi)



3 a, Ar = C_6H_5
b, Ar = 4-MeC_6H_4

12 a-b

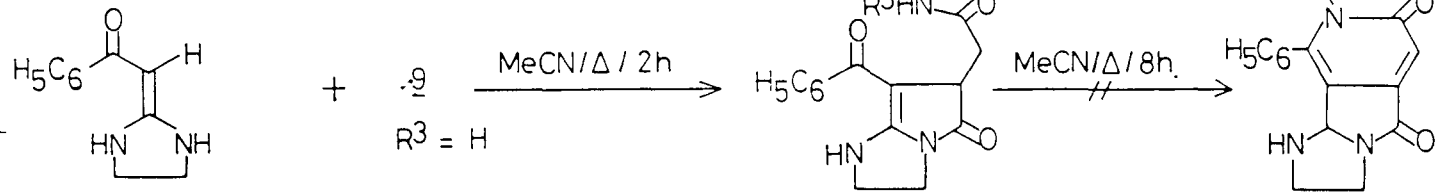
12A



3

13

13A



3c

13

13A

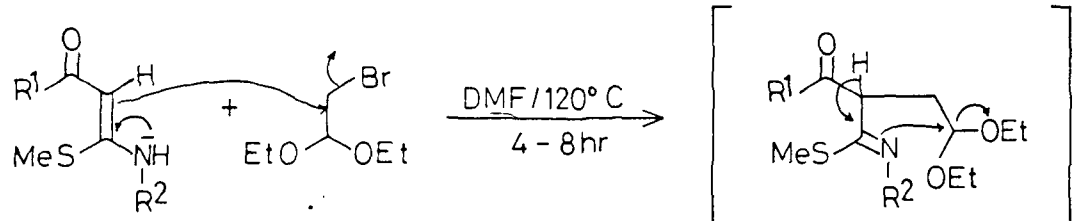
Scheme – 6

(vii)

In the third chapter, it was proposed to react various polarized ketene S,N-acetals 2 with bromoacetaldehyde diethylacetal 14[10]. Thus, 2 are shown to react with 14, in refluxing DMF, to yield the corresponding 1,2,3-trisubstituted pyrroles 15 in good to excellent yields (Scheme 7). The cyclic S,N-acetals 7 also reacted with 14 to yield various pyrroloimidazoles 16 in good yields (Scheme 8). Similarly, 2 also reacted with propargyl bromide 17, in the presence of refluxing dioxan, to yield the corresponding 5-methyl-1,2,3-trisubstituted pyrroles 18 in good to excellent yields (Scheme 9). The cyclic S,N-acetals 7 also reacted with 17 to yield various pyrroloimidazoles 19 in good yields (Scheme 10). The scope and limitations of this method are also described in this chapter.

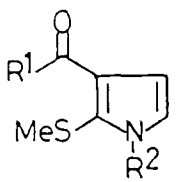
Thus, it has been shown, in the second and third chapter, that the polarized ketene S,N- and N,N-acetals can be conveniently used as enamines to construct various heterocycles.

In continuation of our study on the polarized ketene S,S-acetals 1, it was proposed to react them with azaallyl cations. Thus, the S,S-acetals are shown to react with 2-lithiomethylquinoline 20 to yield the corresponding carbinol acetals 21 in quantitative yields (Scheme 11). These carbinol acetals are conveniently cycloaromatized, in the presence of borontrifluoride etherate, to yield the corresponding benzo[c]quinolizinium and condensed



2 a-i 14 15A

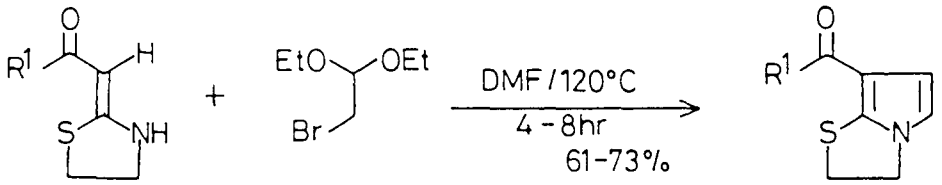
2	R^1	R^2	2	R^1	R^2
a	Me	Et	f	4-ClC_6H_4	i-Pr
b	Me	$PhCH_2$	g	Ph	n-Bu
c	Ph	Me	h	Ph	Ph
d	Ph	Et	i	Ph	$PhCH_2$
e	Ph	n-Pr			



15 a-i

(xx)

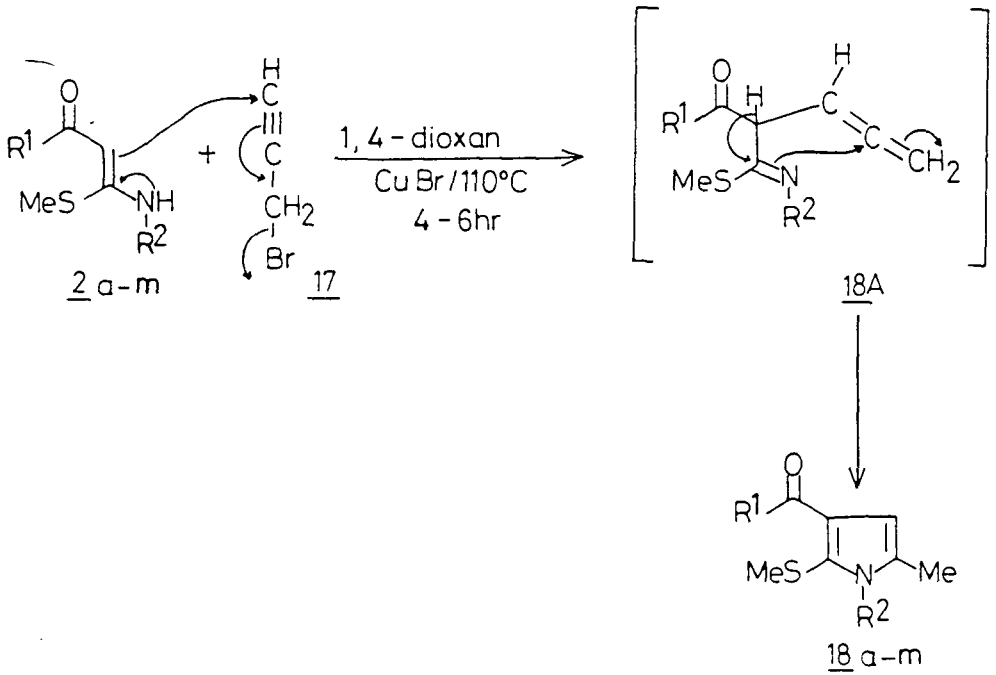
Scheme - 7



7 a-c 14 16 a-c (x)

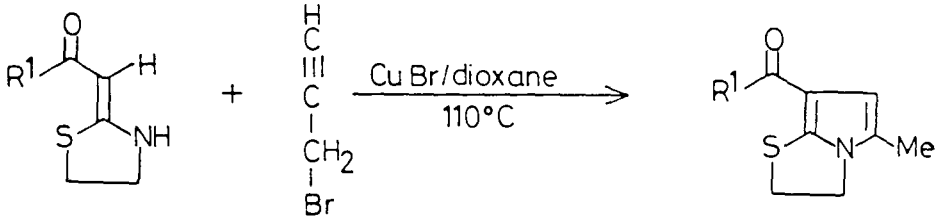
a, R^1 = Me
b, R^1 = 4-ClC_6H_4
c, R^1 = Ph

Scheme - 8


R1
O
MeS
NH
R2
2 a-m
H
C
C
CH2
Br
17
1, 4 - dioxan
Cu Br / 110°C
4 - 6hr
18A
18 a-m
Me
N

(xi)

Scheme – 9

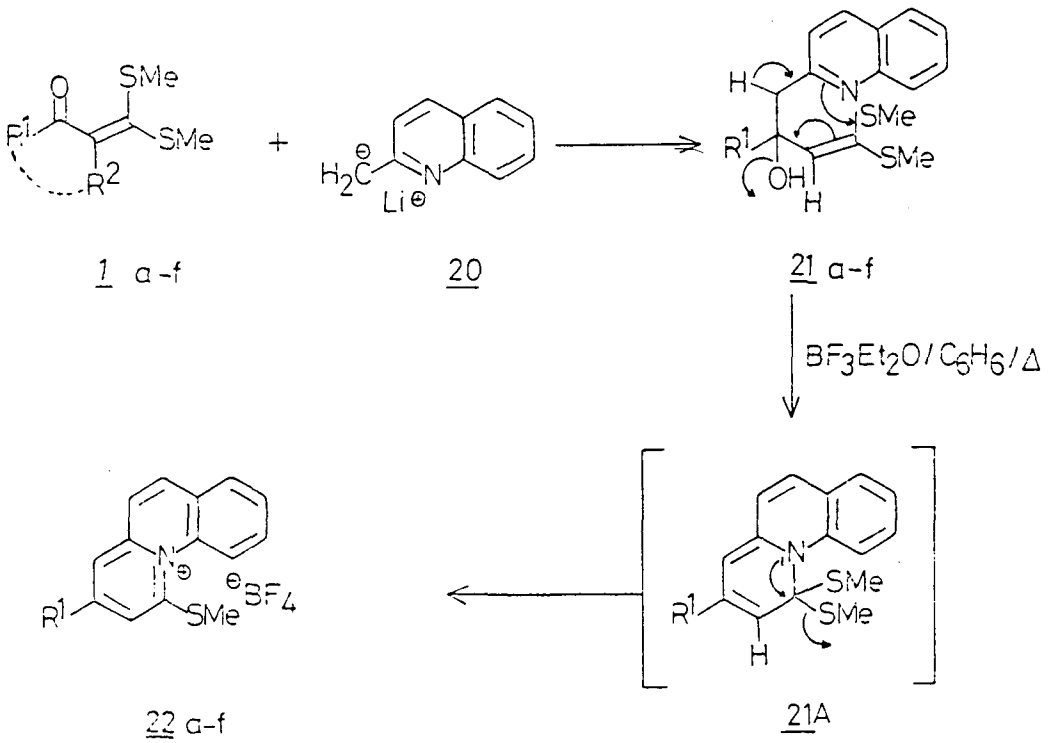


7 a-c 17 19a-c

a, R^1 = Me
b, R^1 = Ph
c, R^1 = 4-ClC_6H_4

(xii)

Scheme-10



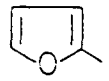
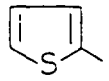
1 a-f

20

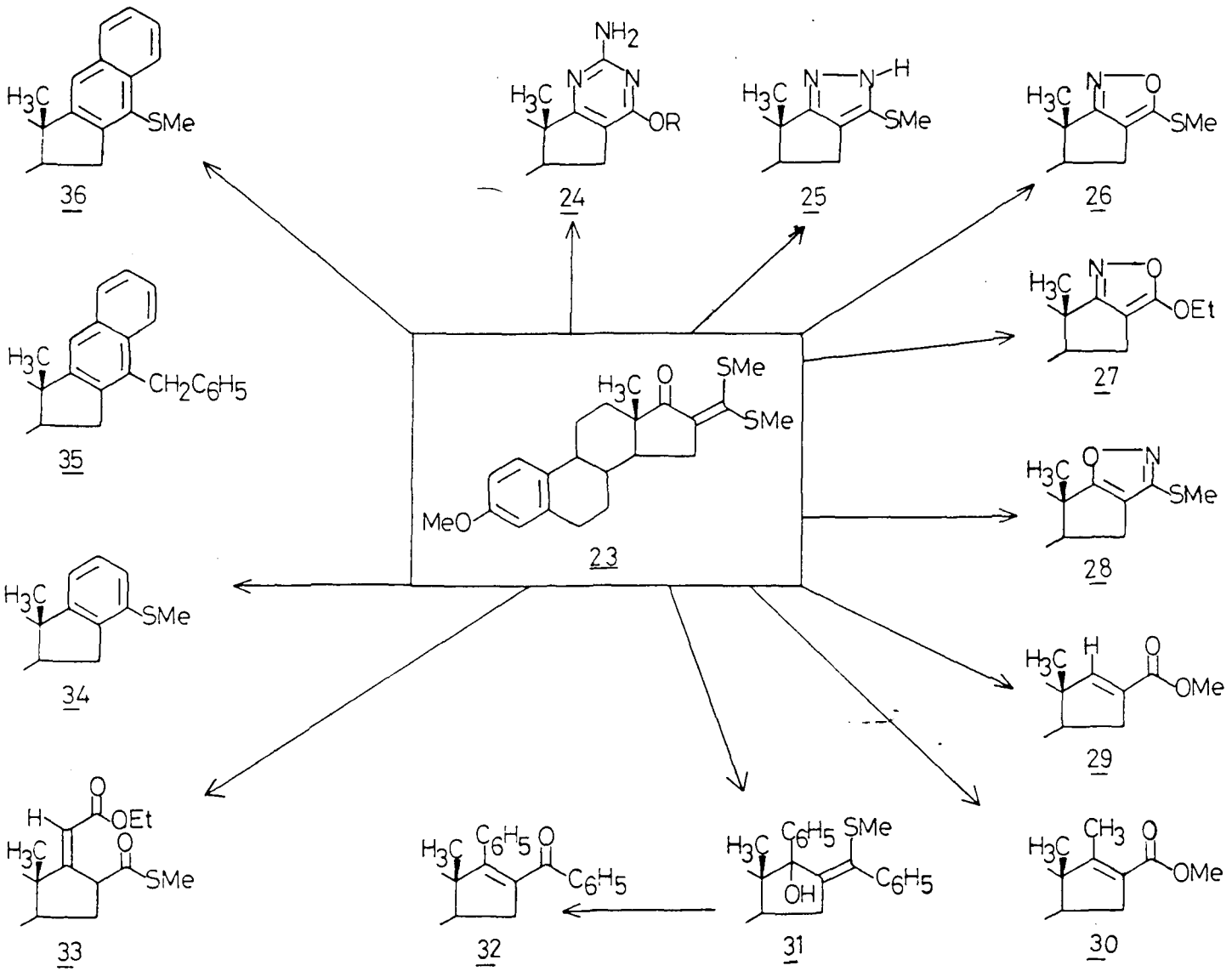
21 a-f

22 a-f

21A

a, R^1 = C_6H_5 ; R^2 = H
b, R^1 = 4-$MeOC_6H_4$; R^2 = H
c, R^1 = 4-MeC_6H_4 ; R^2 = H
d, R^1 = 2-naphthyl ; R^2 = H
e, R^1 =  R^2 = H
f, R^1 =  R^2 = H

Scheme - 11



(xiv)

Scheme - 12

derivatives 22 in good to excellent yields (Scheme 11). The scope and limitations of this method have been discussed in detail in the fourth chapter.

In continuation of our study on the synthetic utility of polarized ketene S,S-acetals, it was proposed to prepare the hitherto unknown S,S-acetal 23 from the 3-methyl ether of estrone, a potent female sex hormone. The estrone molecule has been greatly modified synthetically to design some compounds which can separate the antifertility property from estrogenic property. While much of the literature is devoted to the construction of rings on the A ring of estrone, there is virtually no attempt to construct aromatic ring on the D ring. In the fifth chapter various carbocycles and heterocycles have been prepared by reacting the estrone S,S-acetal 23 with various binucleophiles (Scheme 12). The details of all these transformations have been described in the fifth chapter.

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10. Akhilesh K. Gupta, R.T. Chakrasali, H. Ila, H. Junjappa, *Synthesis*, 141 (1989).

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Professor H. Junjappa, FNA
Department of Chemistry

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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This is to certify that Mr. Akhilesh Kumar Gupta, a Ph.D. student of the Department of Chemistry has satisfactorily completed the following courses as a part of his Ph.D. programme.

Title	Course No.
1. Pericyclic Reactions	Chem - 624
2. Electrochemistry	Chem - 668
3. Experimental Techniques	SPS - 630
4. French Language	SPS - 601

(H. Ila)
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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.

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(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-

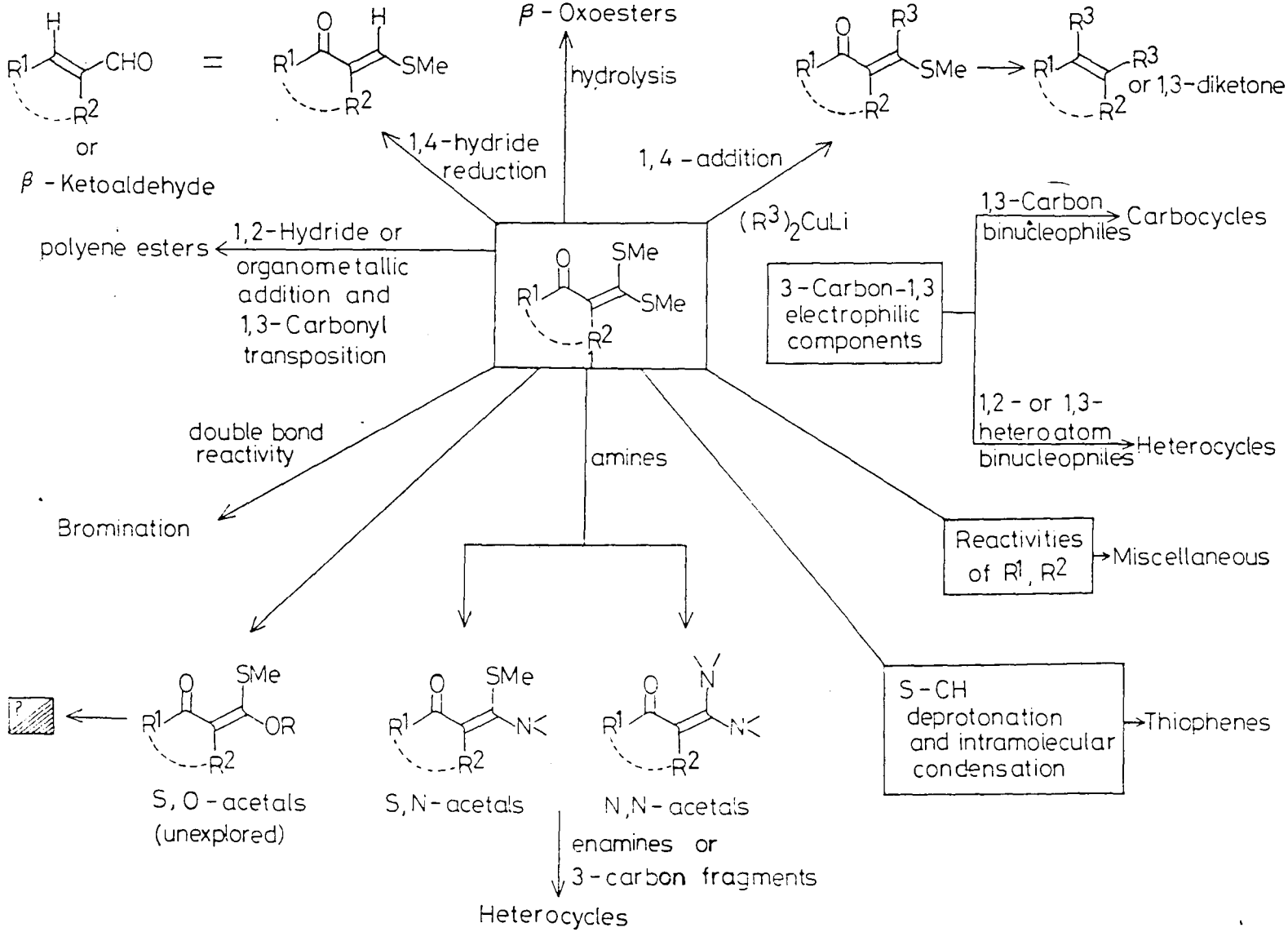
acetal is essentially a masked β-keto ester in which the ester functionality is protected as dithioacetal. Alternatively, it may be viewed as an α,β-unsaturated ketone containing highly functionalized β-carbon. They are versatile three carbon fragments having 1,3-electrophilic centres of differing electrophilicity.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

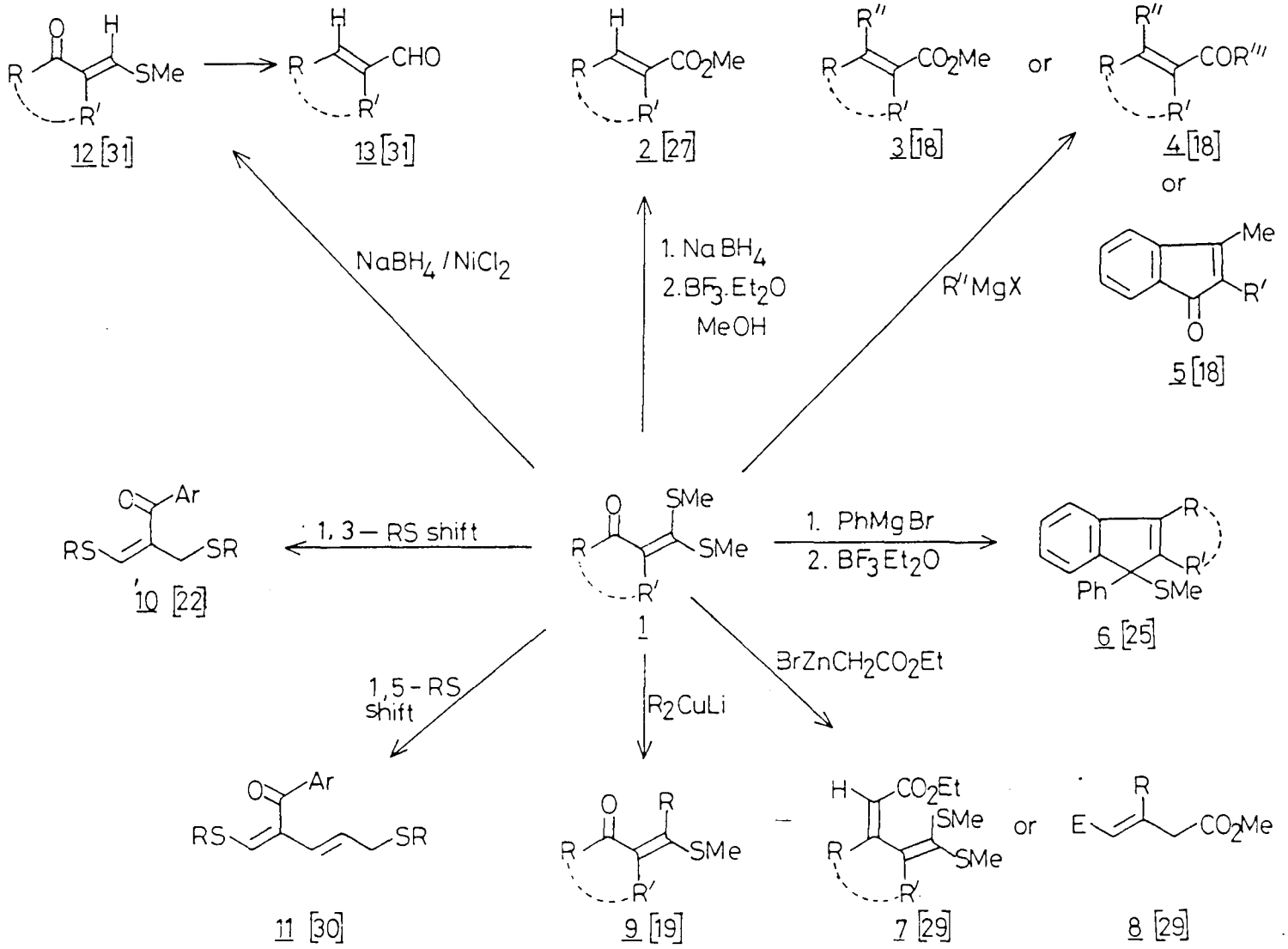
react with 1,2-and 1,3-heteroatom binucleophiles to give five and six membered heterocyclic compounds respectively. The 1,3-carbon nucleophiles, on the other hand, give carbocyclic compounds. The enolate ion formed by deprotonation (R^1 = alkyl) can undergo condensation with aldehydes to give α-enoylketene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

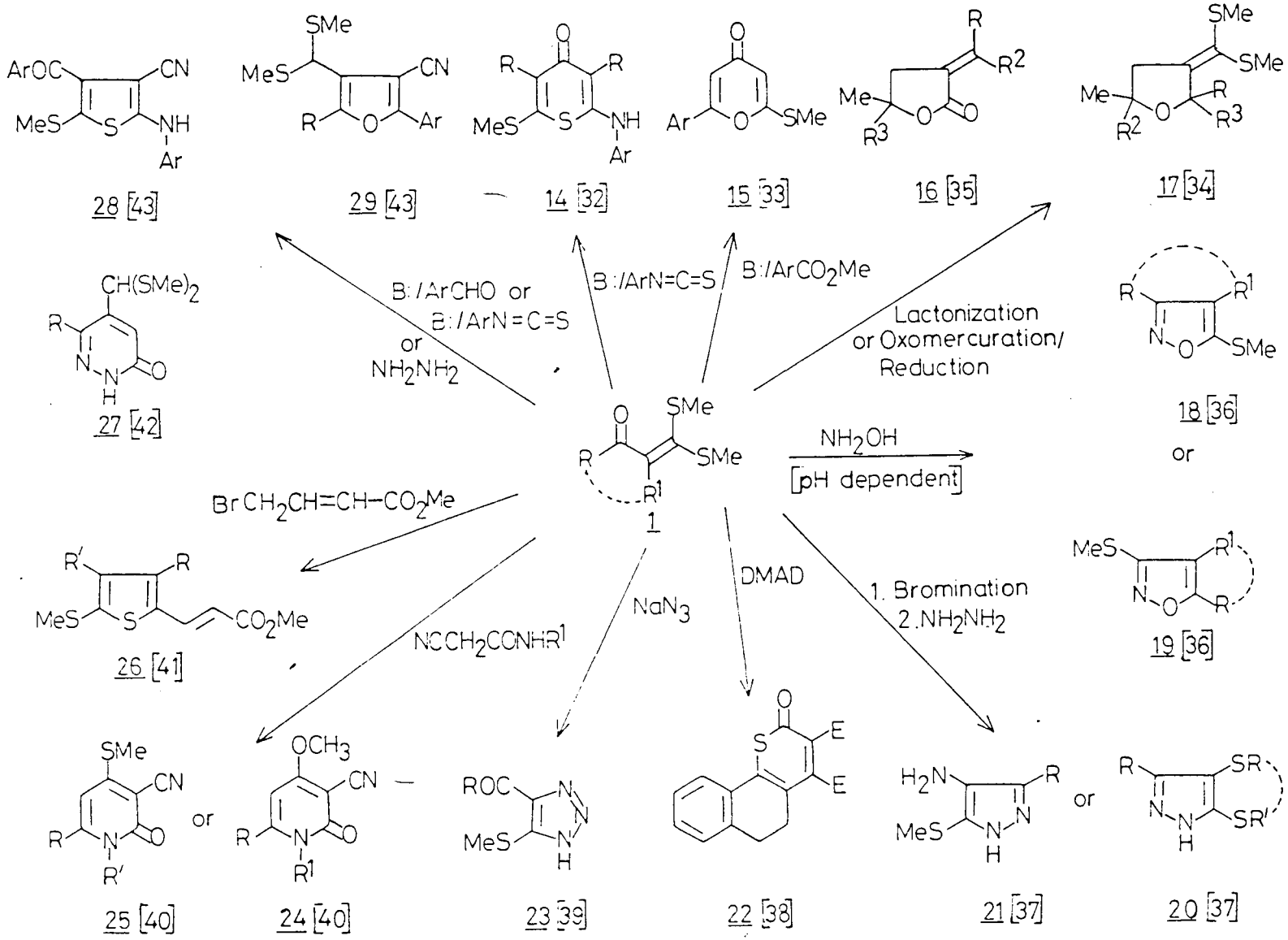
Like oxoketene S,S-acetals, the S,N- and N,N-acetals also possess 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. As stated in the preceding section, they can be prepared by displacement of one or both of the methylthio 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 1,3-diketone
1,4-hydride reduction
1, 4 - addition
or
β - Ketoaldehyde
polyene esters
1,2-Hydride or organometallic addition and 1,3-Carbonyl transposition
(R3)2CuLi
1,3-Carbon binucleophiles
Carbocycles
3-Carbon-1,3 electrophilic components
1,2 - or 1,3- heteroatom binucleopniles
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

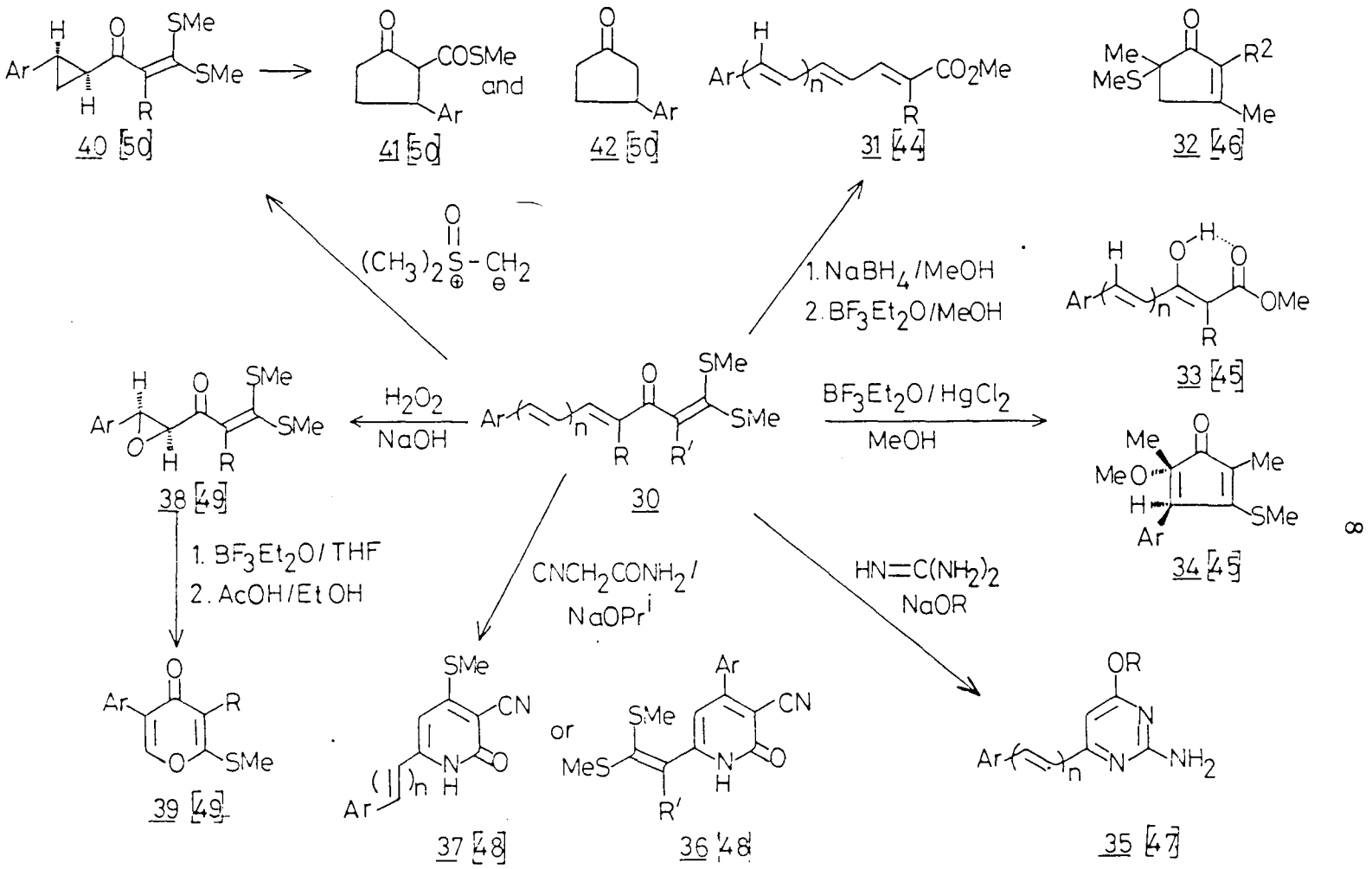
Scheme - 1


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
6 [25]
10 [22]
1
1,5 - RS shift
R2CuLi
BrZnCH2CO2Et
11 [30]
9 [19]
7 [29]
or
8 [29]

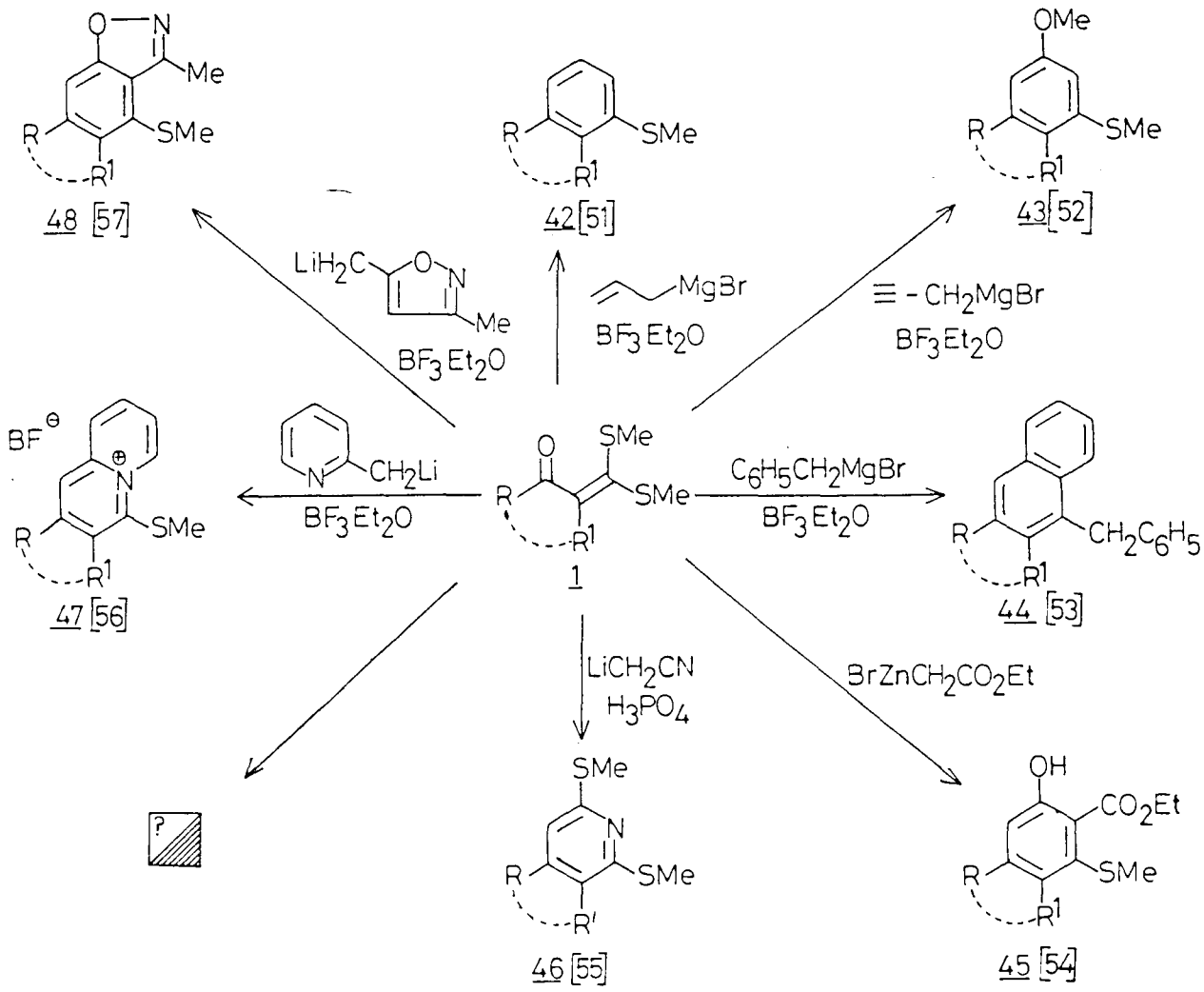
Scheme - 2


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]
24 [40]
23 [39]
22 [38]
21 [37]
or
20 [37]

SCheme - 3


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

Scheme - 4


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

Scheme - 5

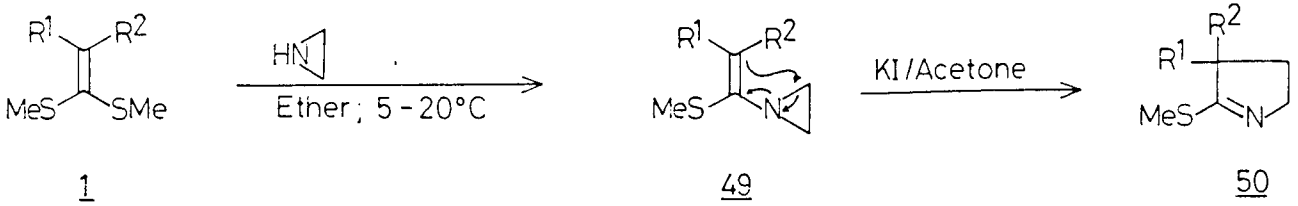
from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates followed by alkylation[58].

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.

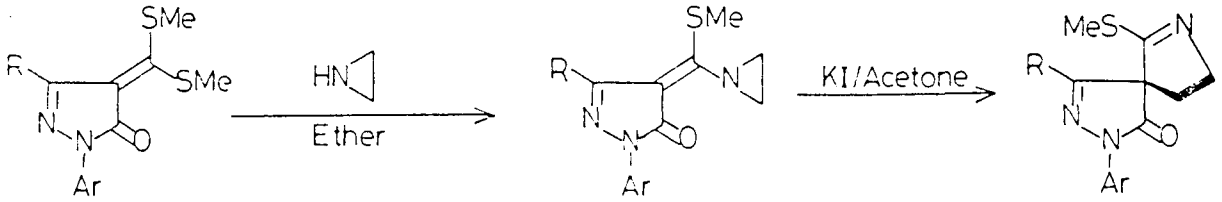
The doubly activated α-oxoketene S,S-acetal 1 underwent smooth displacement reaction at room temperature with aziridine[62] to give the corresponding S,N-acetal 49 in high yields (Scheme 6). The S,N-acetals 49 can be viewed as N-vinyl aziridine and undergo facile ring expansion to yield the corresponding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



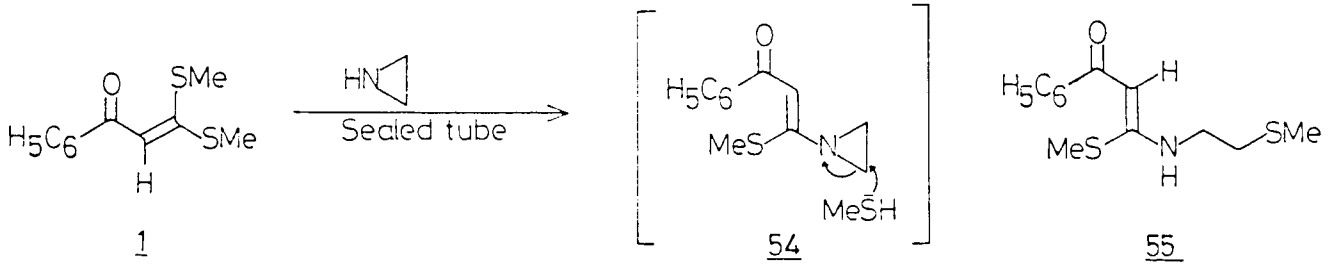
1 49 50

$R^1 = CN$; $R^2 = CO_2Et$
$R^1 = MeCO$; $R^2 = CO_2Et$
$R^1 = R^2 = CN$
$R^1 = CN$; $R^2 = CONH_2$



51 52 53

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

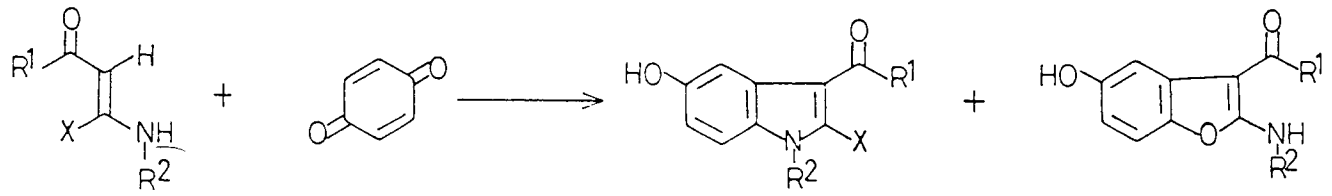


1 54 55

Scheme - 6

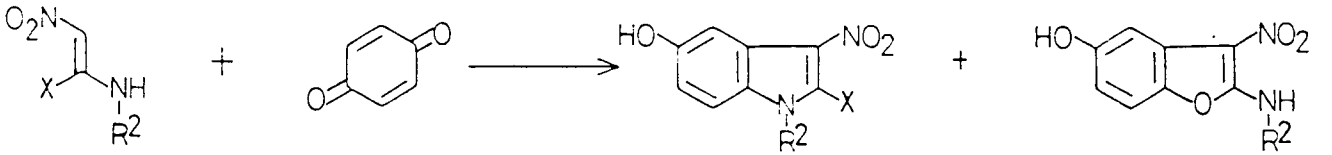
carried a substituent at 2-position arising from the enamine component. The α-oxoketene S,N- and N,N-acetals were considered as suitable alternatives to these enamine components in the Nenitzescu indole synthesis. Thus, the N,N-acetals 56 underwent smooth reaction with p-benzoquinone to yield a mixture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

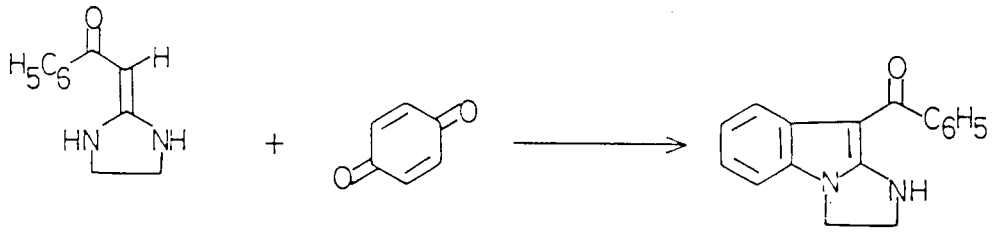


56,57 58 59 60

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

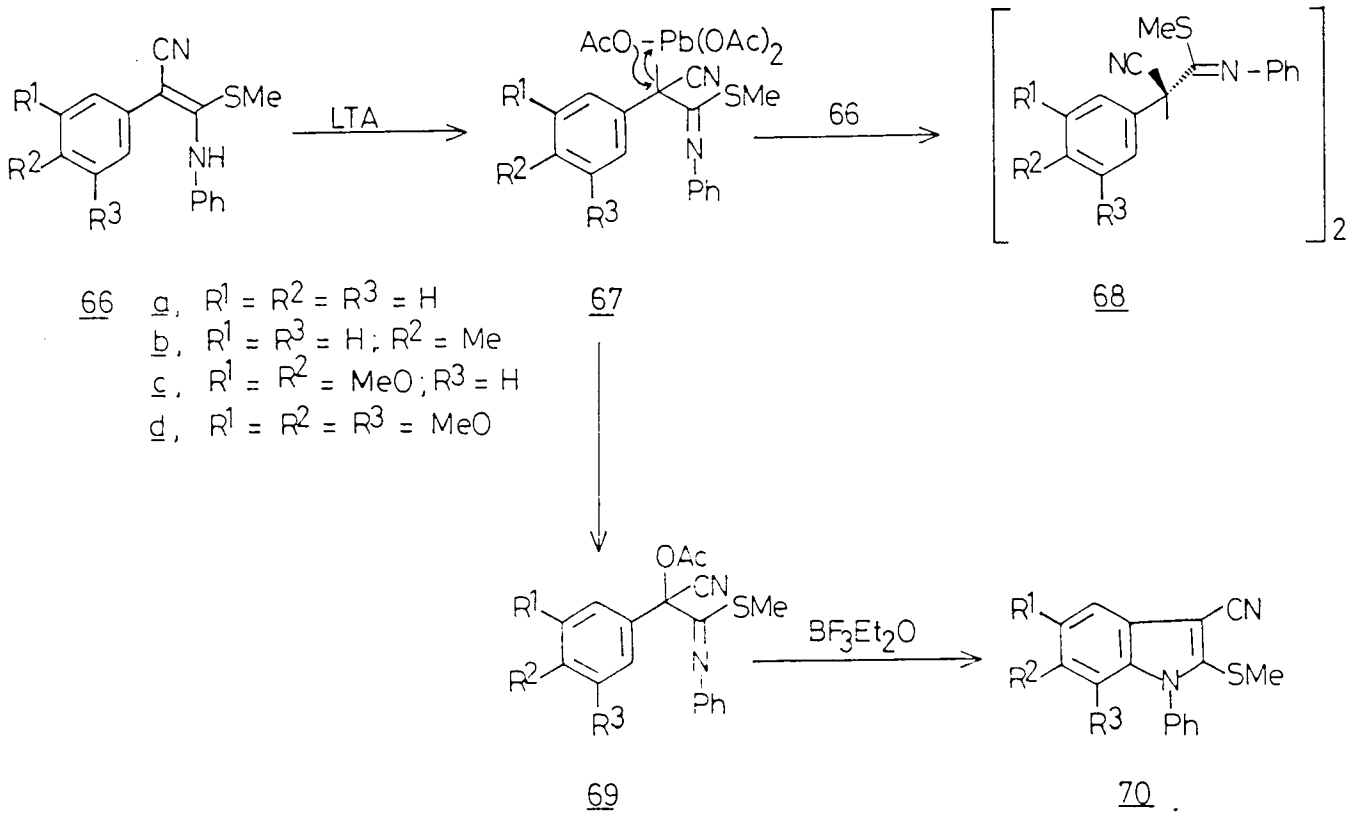


61 58 62 63



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, $R^1 = R^2 = R^3 = MeO$

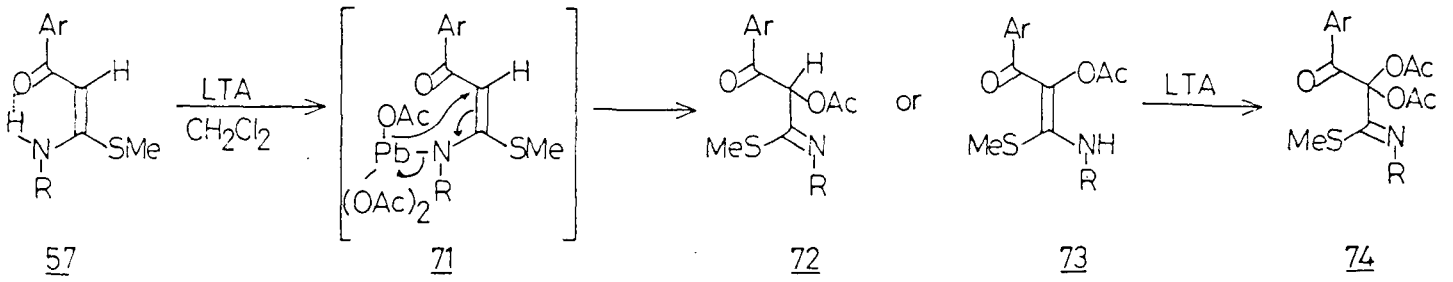
67

68

69

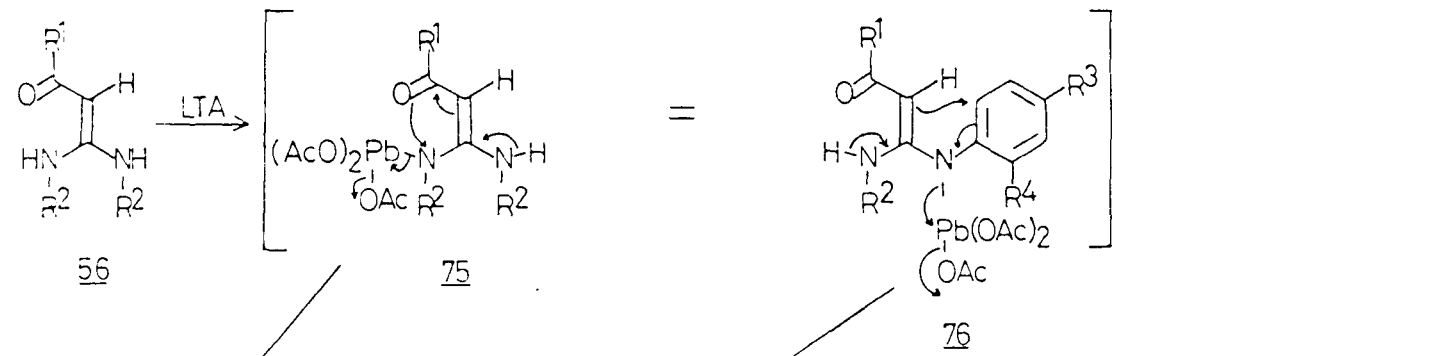
70

Scheme - 8

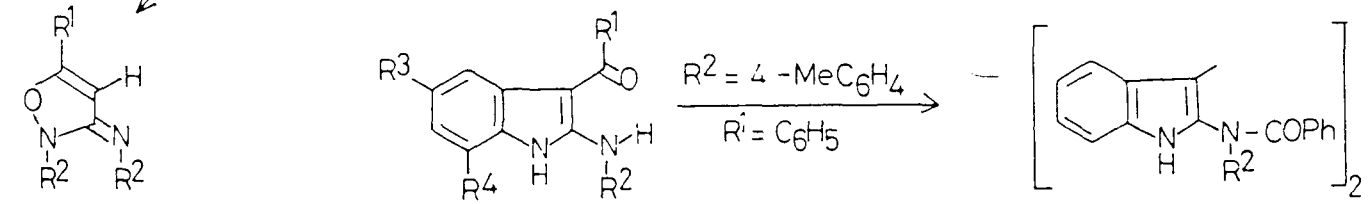


57 71 72 73 74

R = Et, C_6H_5, $C_6H_5CH_2$



56 75 76



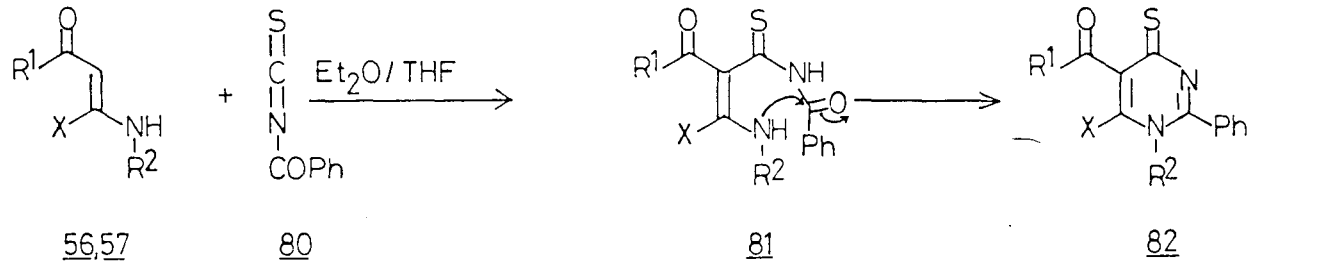
78 77 79

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

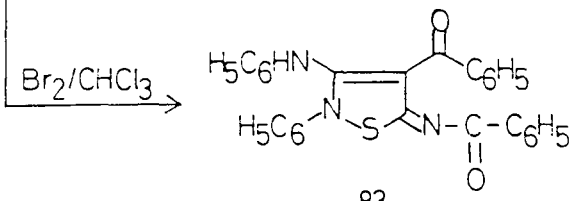
and 73 (Scheme 9) while the corresponding S,N-acetals 57 (R=Et) yielded the iminoacetate 74. The other N,N-acetals 56 afforded 2-aryl-3-arylamino-5-aryl-4-isoxazolines (78) under similar reaction conditions involving oxidative cyclization (Scheme 9). However, the N,N-acetals 56 (R^2=4-MeC_6H_4) yielded, 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

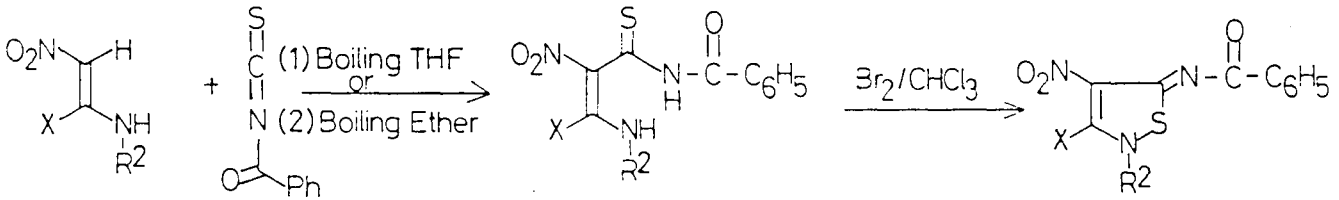


56,57 80 81 82

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



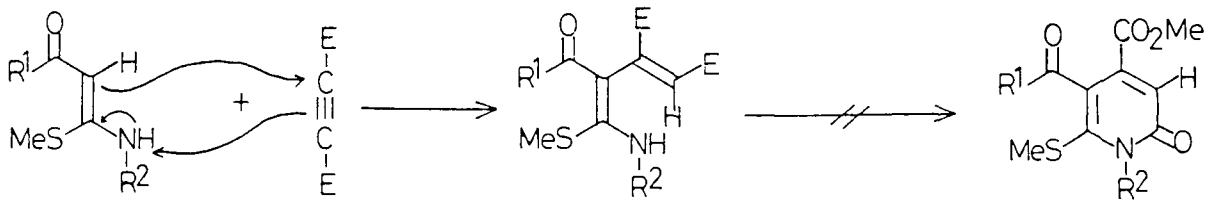
61 80 84 85

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 $CHCl_3$.

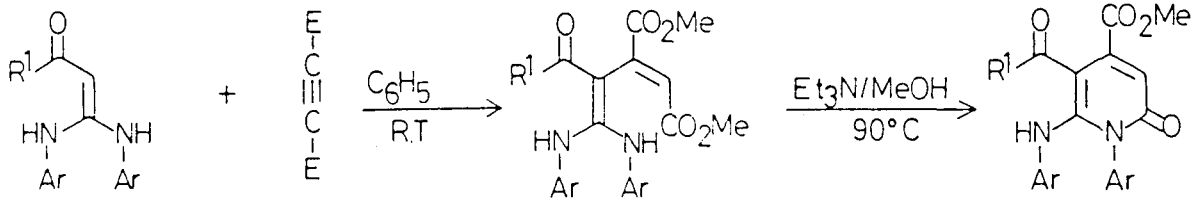
The reaction of α-oxoketene S,N-acetals and N,N-acetals with dimethylacetylenedicarboxylate (DMAD) 86 has been investigated[67] in this laboratory. The S,N-acetal 57 underwent Michael addition to yield the corresponding open chain adducts 87 which failed to undergo intramolecular cyclization to afford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

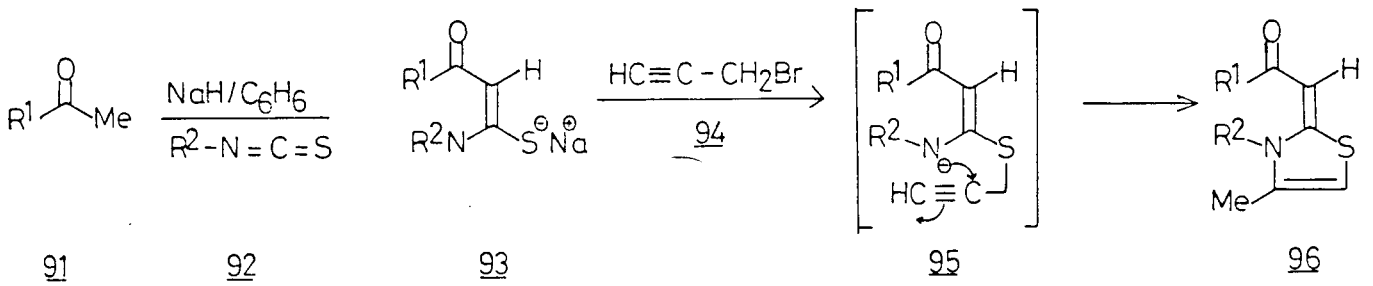
$R^1 = C_6H_5$; $R^2 = C_6H_5$, Et



56 86 89 90

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

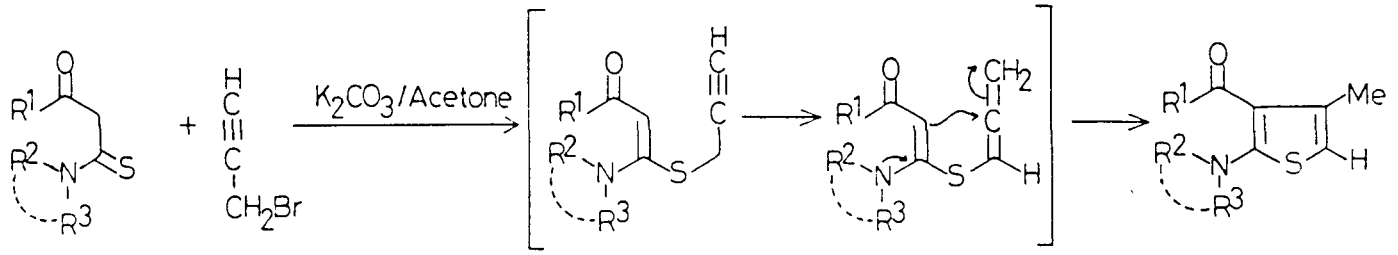
Scheme -11



91 92 93 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

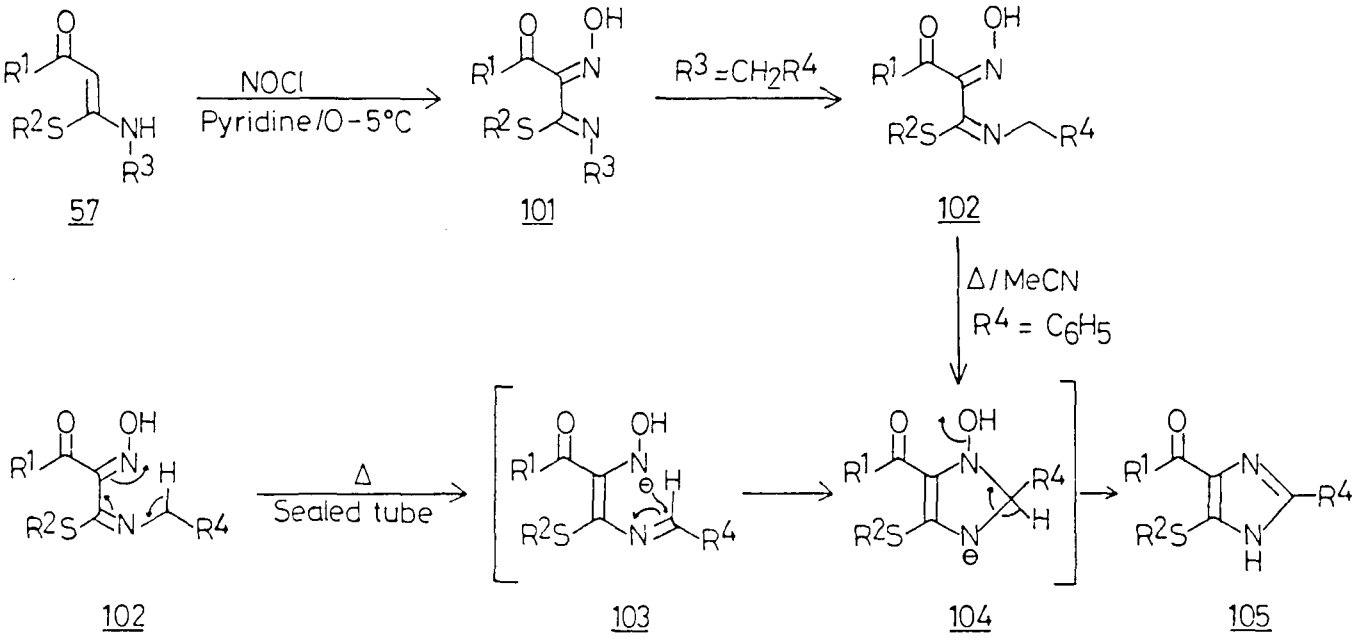
R^2
R^3 >N- = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$

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

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



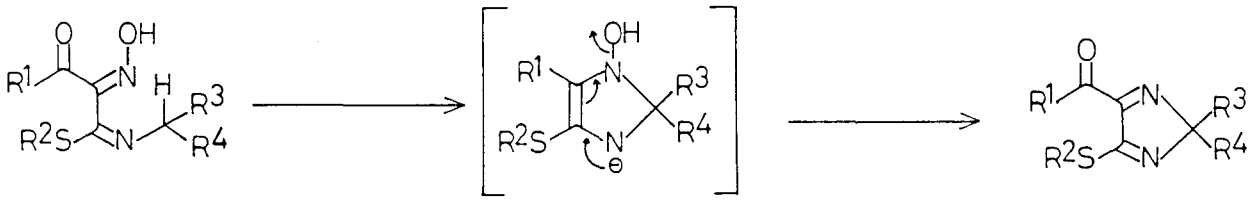
57 101 102 102 103 104 105

R^1 = substituted aryl, Me, CO_2Et

R^2 = Me, Et

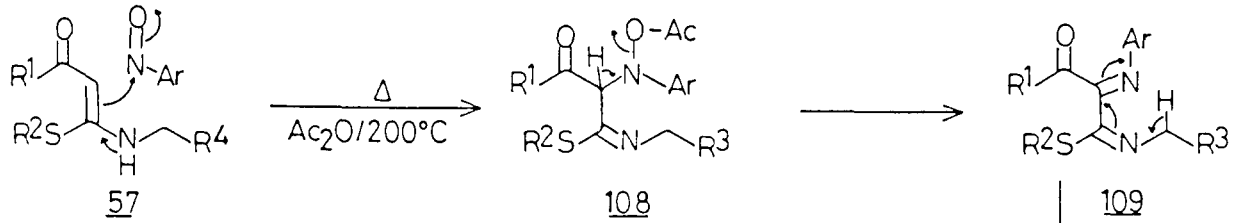
R^4 = H, Me, Et, C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$

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 = $-(CH_2)_5-$



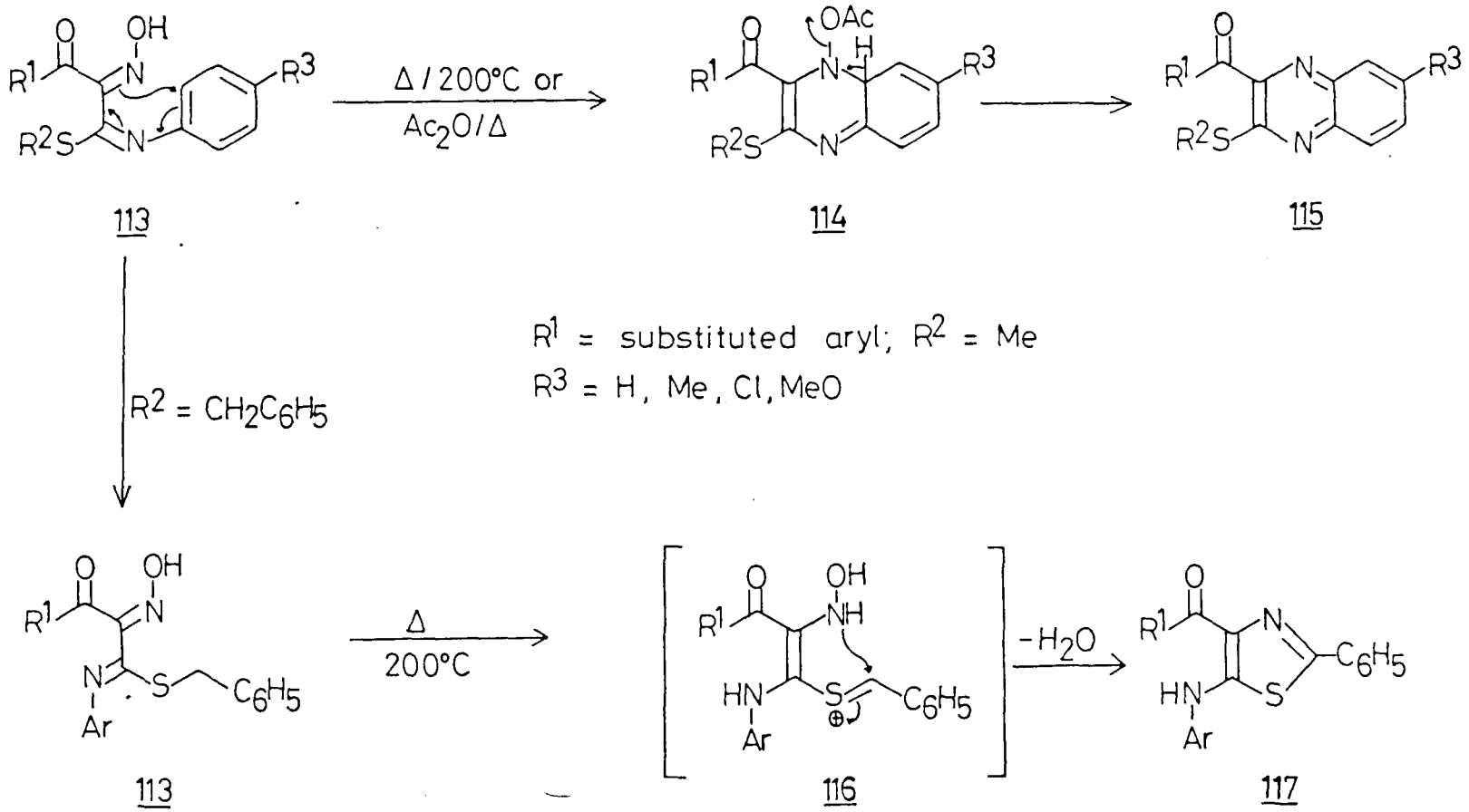
57 108 109 110 111 112

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

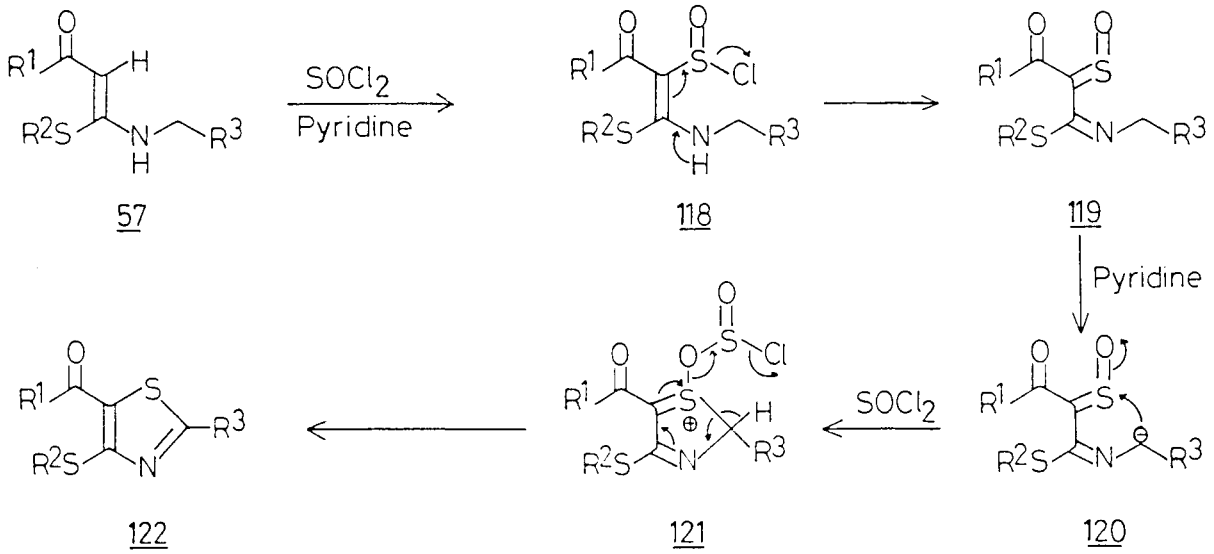
Scheme - 14

(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).


Δ / 200°C or
Ac2O/Δ
R2 = CH2C6H5
R1 = substituted aryl; R2 = Me
R3 = H, Me, Cl, MeO
Δ
200°C
-H2O
113
114
115
113
116
117

SCheme - 15



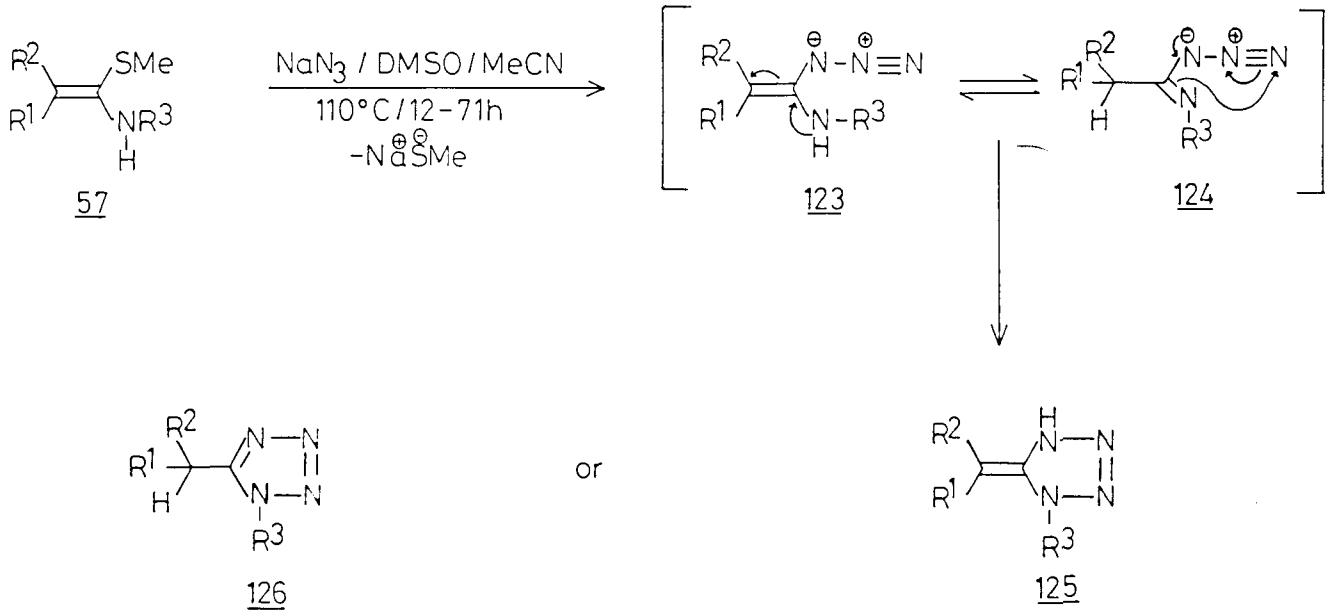
57 118 119 120 121 122

R^1 = substituted cryl, 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



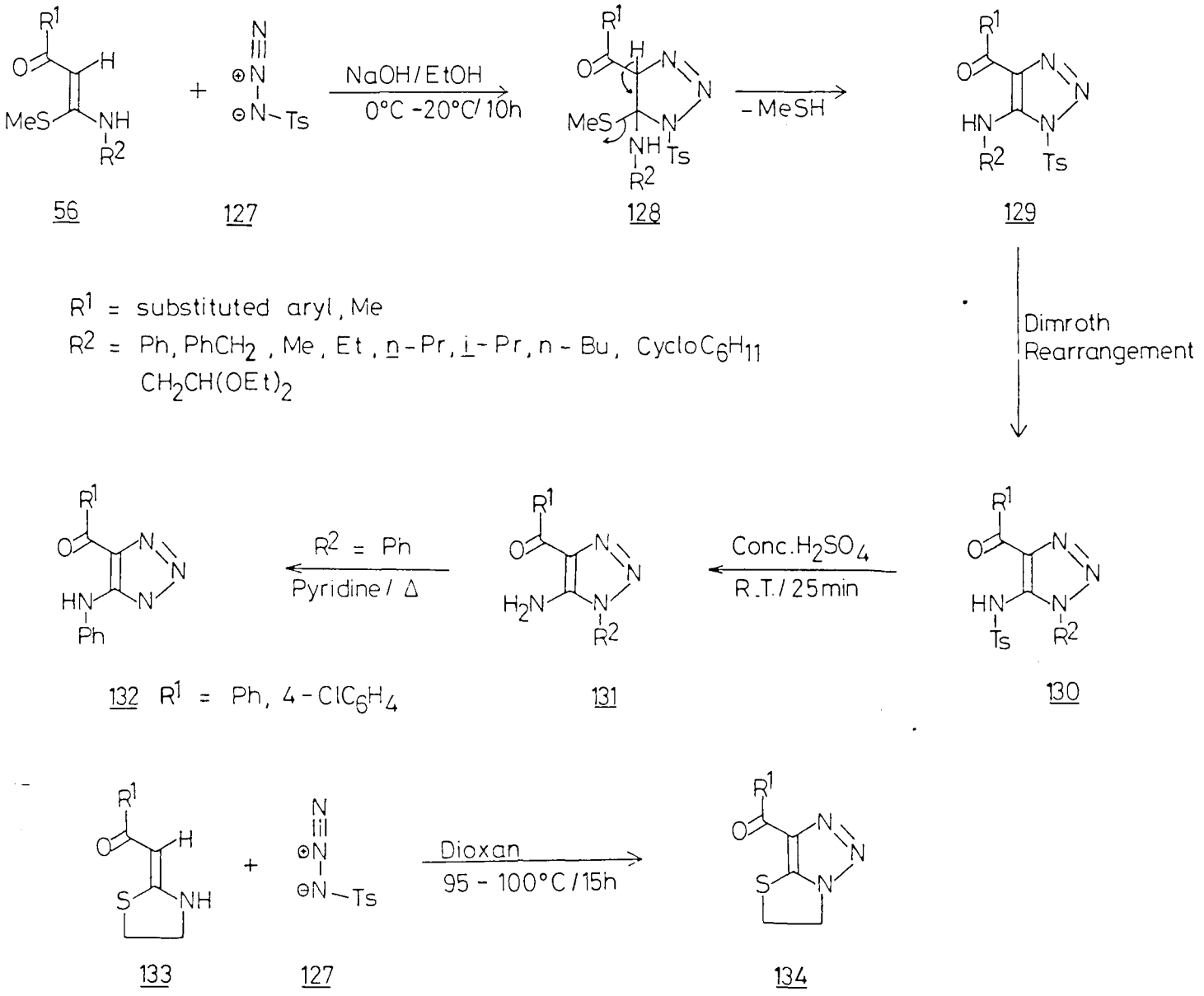
57 123 124 126 125

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, $CycloC_6H_{11}$, $CH_2CH(OEt)_2$

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

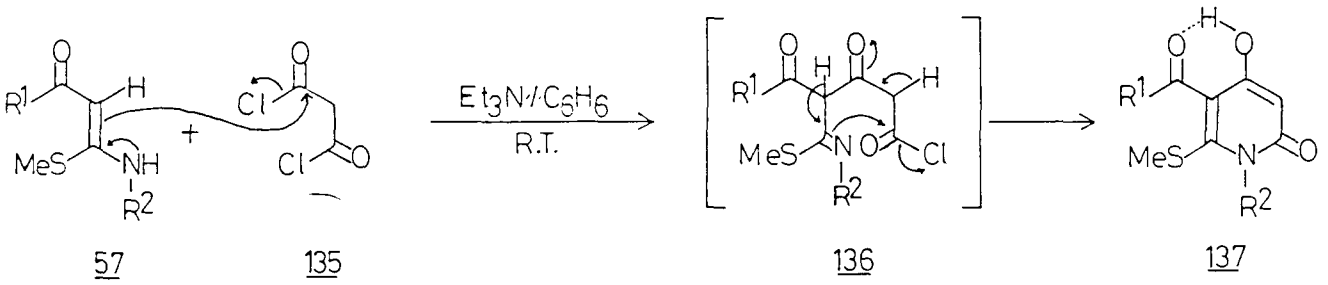
133 127 134

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.

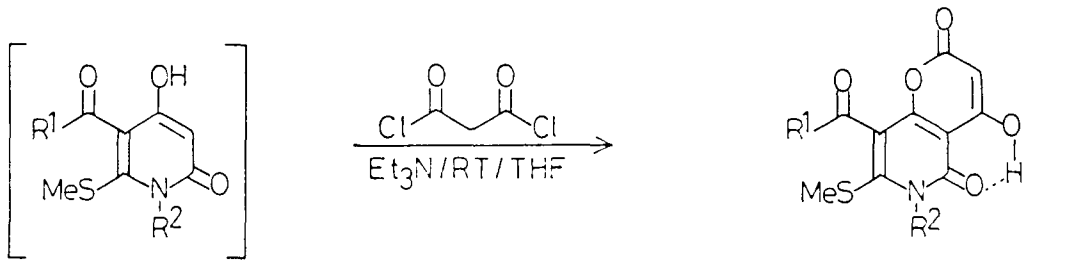
Similarly, the S,N-acetals 57 reacted with oxalyl chloride 140 to give highly unstable pyrrolo-2,3-diones[75] 141 in high yield (Scheme 20). They underwent easy hydrolytic cleavage to yield 5-hydroxy pyrrole diones 142. However, when 141 was reacted with amines the corresponding amino pyrrole-2,3-diones (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

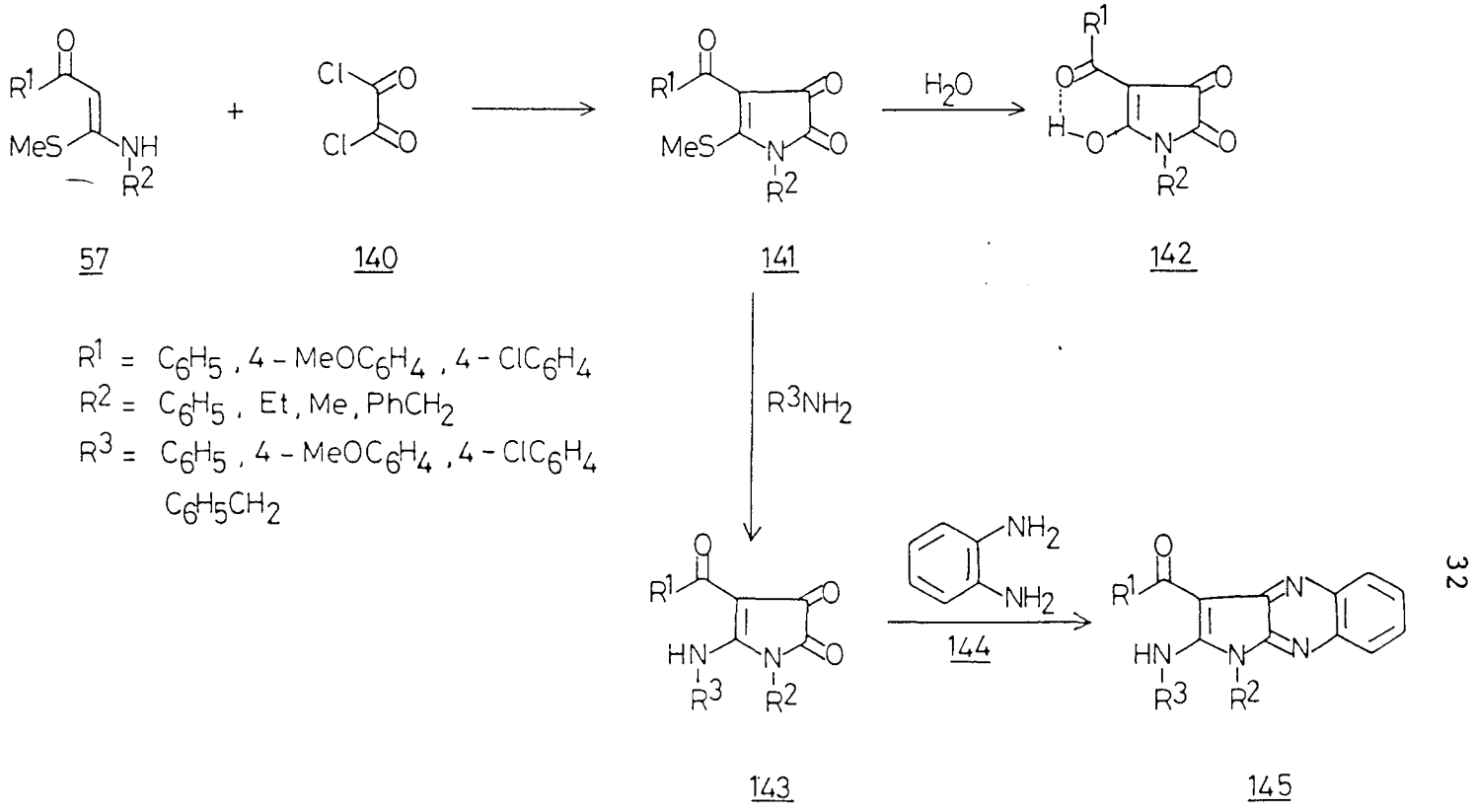


138 139

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
$C_6H_5CH_2$

143 145

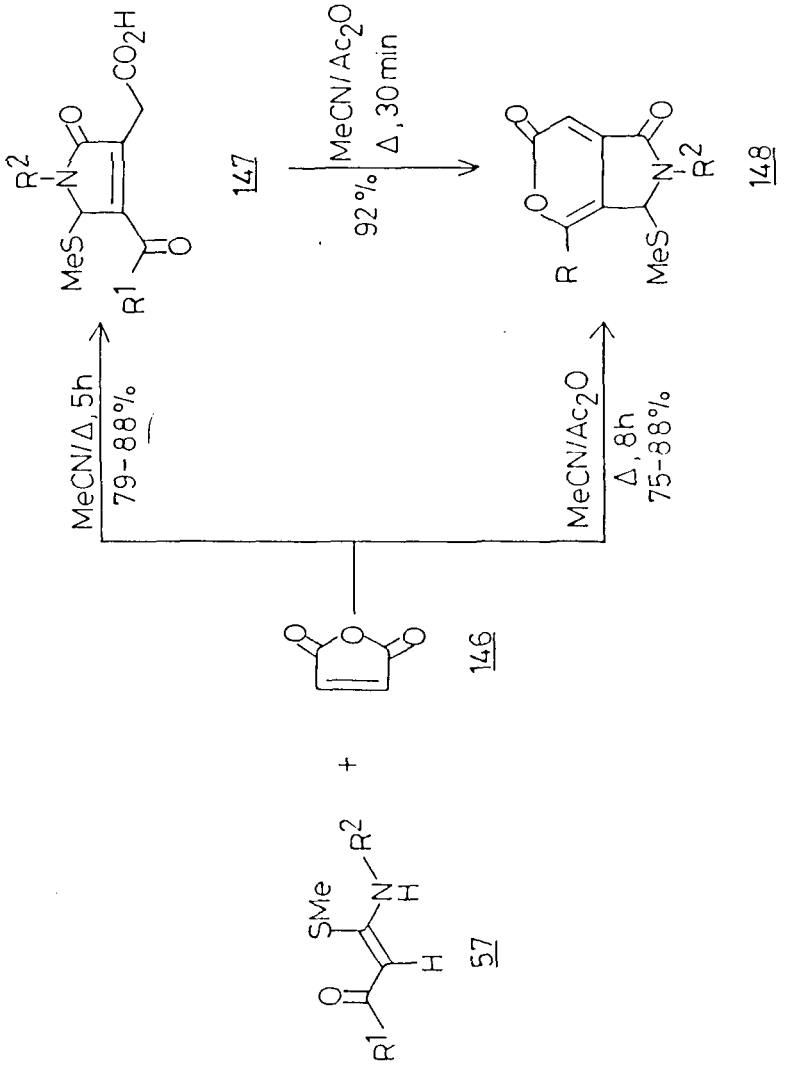
Scheme - 20

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

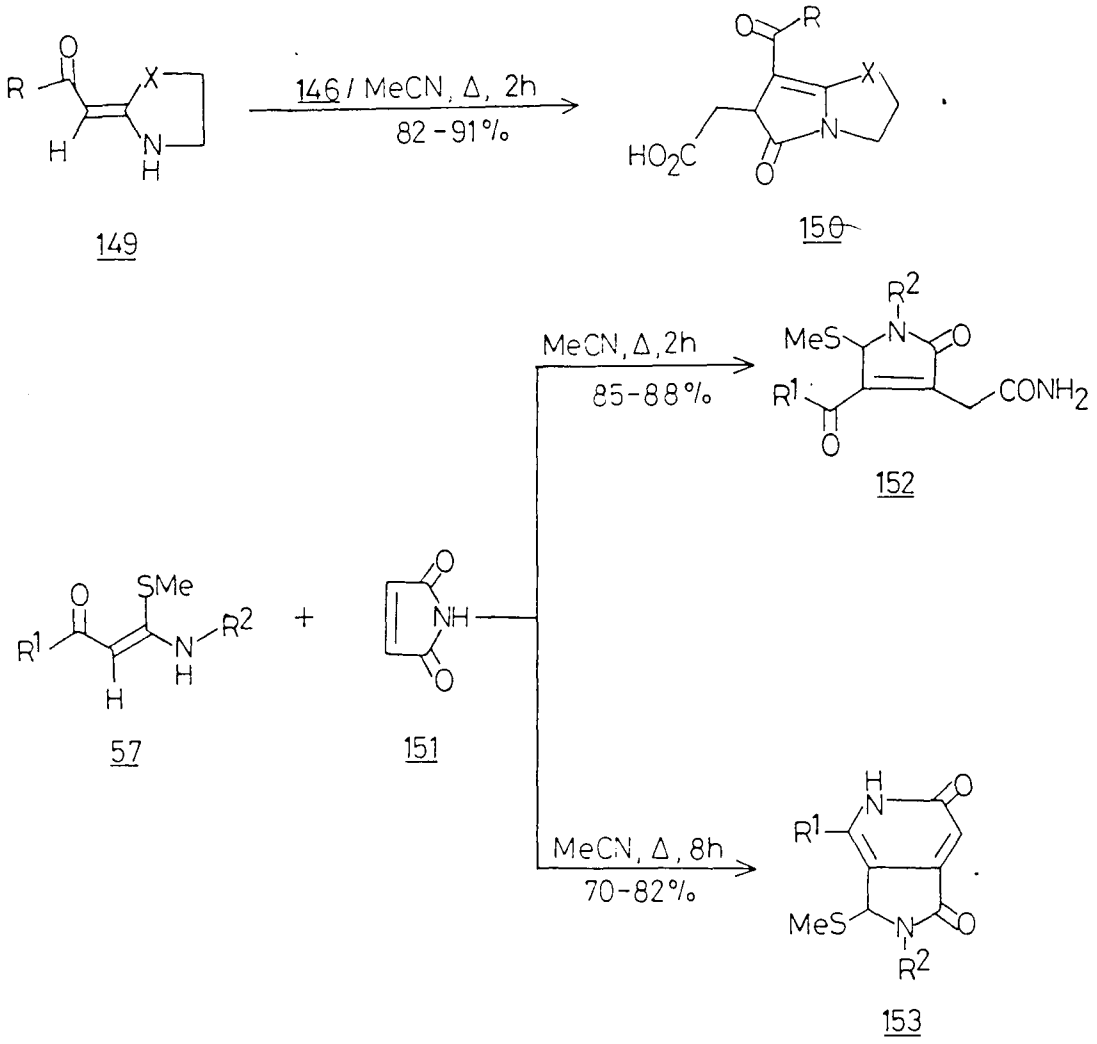
C. The Work Presented in this Thesis:

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.

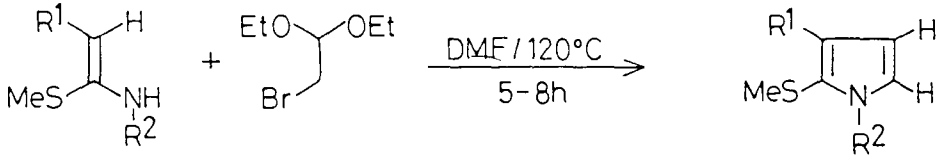
In the third chapter the application of the polarized ketene S,N- and N,N-acetals for the synthesis of various pyrroles[77] is discussed (Scheme 23). This method is superior to the earlier method developed in this laboratory which failed when extended to the synthesis of N-substituted pyrroles. Interestingly,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


MeCN/Δ, 5h
79-88%
MeCN/Ac2O
Δ, 8h
75-88%
MeCN/Ac2O
Δ, 30 min
92 %
147
148
146
57

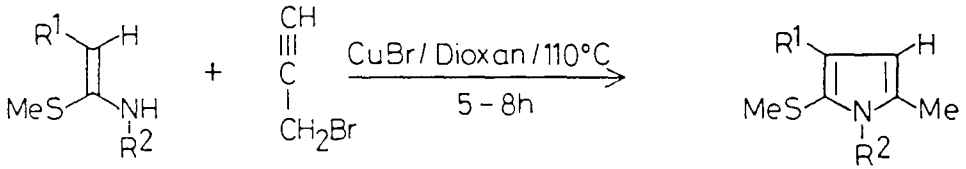
Scheme-21


R
X
H
N
H
O
146 / MeCN, Δ, 2h
82-91%
R
X
HO2C
N
O
O
149
150
MeCN, Δ, 2h
85-88%
R2
MeS
N
O
R1
O
CONH2
152
SMe
R1
O
N
R2
H
H
+
NH
O
O
57
151
MeCN, Δ, 8h
70-82%
H
N
O
R1
MeS
N
O
R2
153

Scheme -22



57 154 155



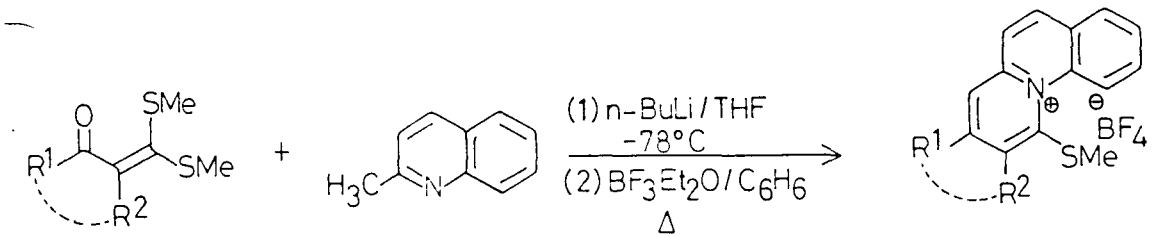
57 94 156

Scheme - 23

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

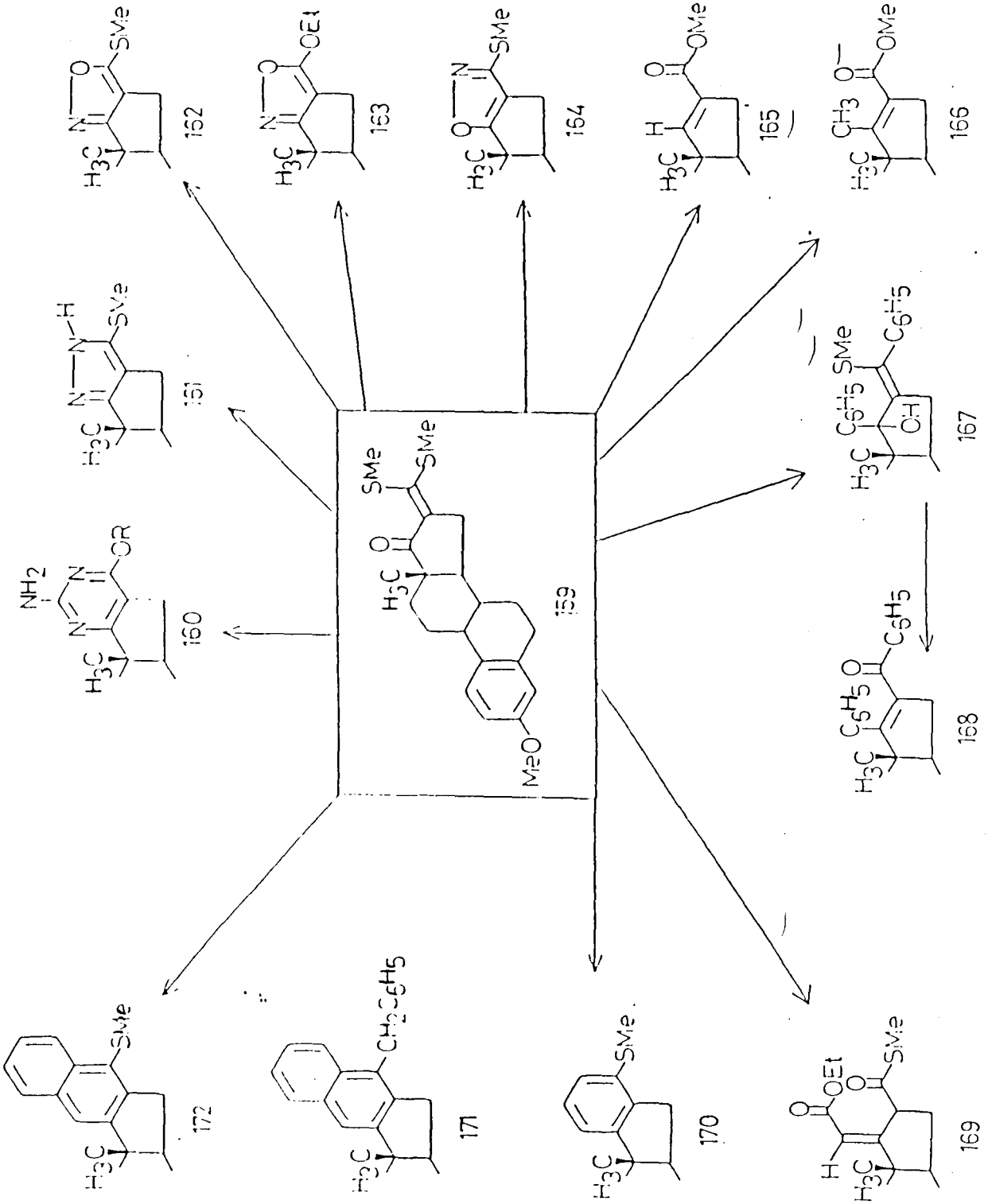
Like S,N-and N,N-acetals, the S,S-acetals also constitute an important class of synthetic intermediates whose synthetic importance has been reviewed briefly in the beginning of this chapter. In continuation of these studies various methods for aromatic and heteroaromatic annelation have been developed 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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CHAPTER - II

REACTION OF α-OXOKETENE S,N- AND N,N-ACETALS WITH MALEIC ANHYDRIDE AND MALEIMIDE: SYNTHESIS OF NOVEL PYRANO [3,4-*c*]PYRROLES, PYRROLO[3,4-*c*]PYRIDINES AND OTHER PYRROLE DERIVATIVES.*

INTRODUCTION

The reaction of 3-aminocrotonates with *p*-benzoquinone in refluxing acetone to afford the corresponding 5-hydroxyindole-3-carboxylates is known as the Nenitzescu reaction[1] discovered in 1929. Ever since extensive work has been done in this area and a large number of 5-hydroxyindoles have been prepared[2-14]. The enamine components used in this reaction were mainly derived from

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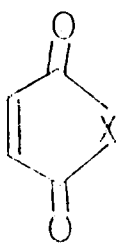
* Akhilesh K. Gupta, H. Ila, H. Junjappa, Synthesis, 284 (1988).

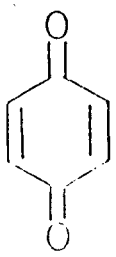
the reaction of ammonia or primary amines with β-ketoesters, 1,3-diketones and cyclic 1,3-diketones. The application of these enamines in Nenitzescu reaction suffered from limitations since the product indoles always contained a substituent at 2-position which could not be easily removed. As a modification, to resolve this problem, Aggarwal, Ila and Junjappa[15] investigated the potential application of α-oxoketene S,N- and N,N-acetals as enamine component and their reaction with *p*-benzoquinone to synthesize various 5-hydroxy-2-methylthioindoles so that the methylthio group at 2-position could be removed under desulfurization conditions. These results have certainly enhanced the scope of Nenitzescu Reaction since the preparation of the ketene S,N-and N,N-acetals from the active methylene ketones provides increased scope for structural variation in the enamine component. Thus, the α-oxoketene S,N-and N,N-acetals were demonstrated as enamines with regard to their reactivity towards *p*-benzoquinone.

Interestingly, there has been considerable literature in the recent years on the parallel reactivity studies of various enamines with fumerates, maleates, maleic anhydride, maleimide, etc. The reaction is considered as analogous to the Nenitzescu reaction though in later cases only the pyrroles or pyrrolopyrroles are formed. The structure of maleic anhydride and its nitrogen and sulfur analogues A could be considered as isosteric with *p*-benzoquinone B and the reactivity of various enamines,

including the α-oxoketene S,N-and N,N-acetals, could yield



A, X=O,NH,S



B

the corresponding five membered heterocycles annelated at 3-and 4-positions and the reaction can be considered as analogous to the Nenitzescu method. A number of reports have appeared in the literature[16,27] on the reaction of various enamines with these activated olefins to yield the corresponding five membered heterocycles. However, the analogous reactivity of the easily accessible α-oxoketene S,N-and N,N-acetals with maleic anhydride and maleimide has not been investigated. Therefore, it was intended to investigate the reaction of various α-oxoketene S,N-and N,N-acetals with maleic anhydride and maleimide.

At this moment it is appropriate to briefly discuss the related reactions of various enamines with maleic anhydride and maleimide.

SOME OF THE RELATED REACTIONS

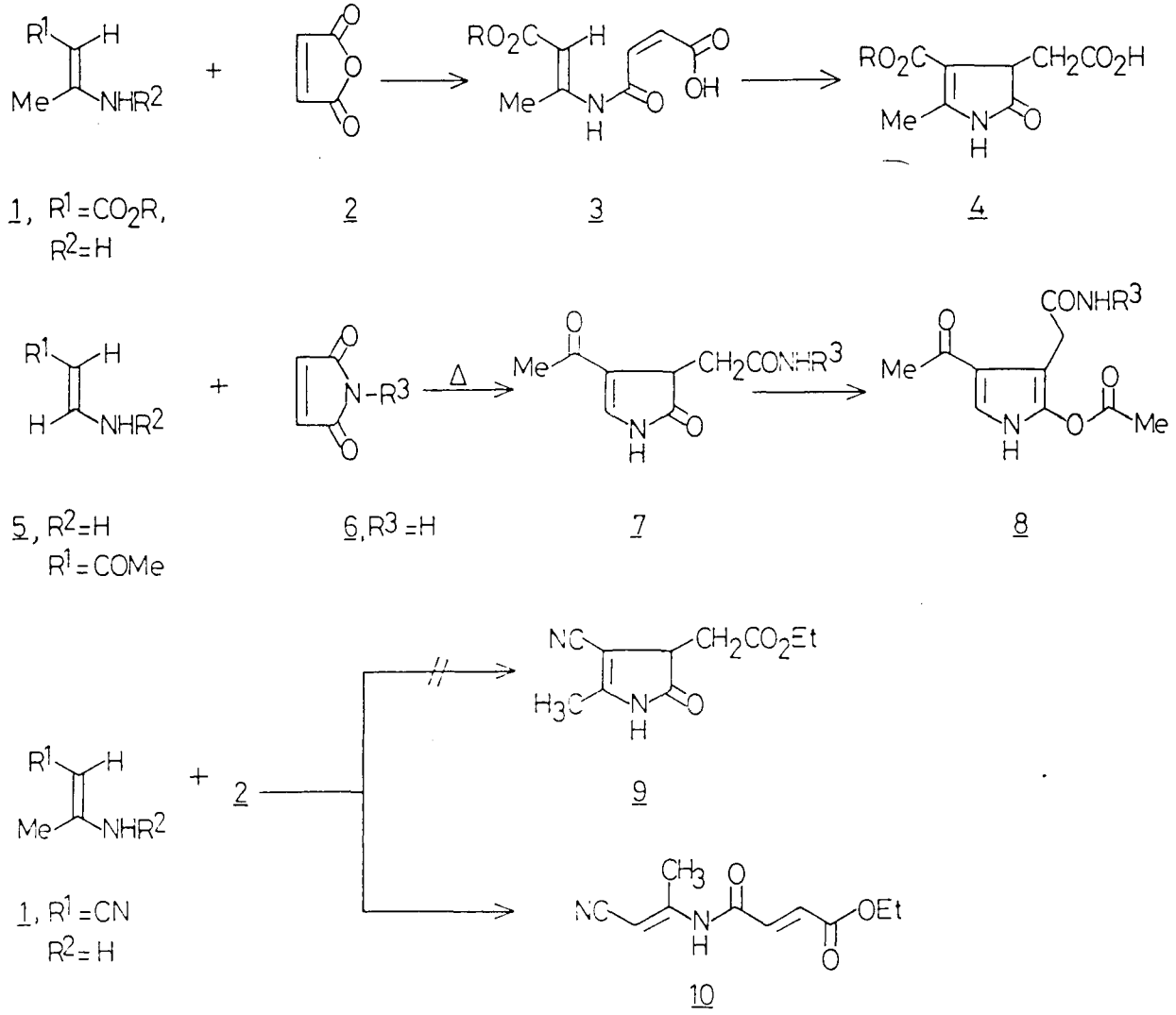
In 1890 Emery[16] reported the synthesis of pyrrolin-2-one 4 by the reaction of the enamine 1 with maleic anhydride 2.

This reaction was reported to proceed via the enamine intermediate 3 followed by intramolecular cyclization (Scheme 1) which is probably the first report on pyrrolin-2-one synthesis. Subsequently, Fischer and Herrmann[17] reported the synthesis of variously substituted pyrrolin-2-ones 7 by using Emery's method, and these hydroxypyrroles were then converted to the stable acetates 8 (Scheme 1).

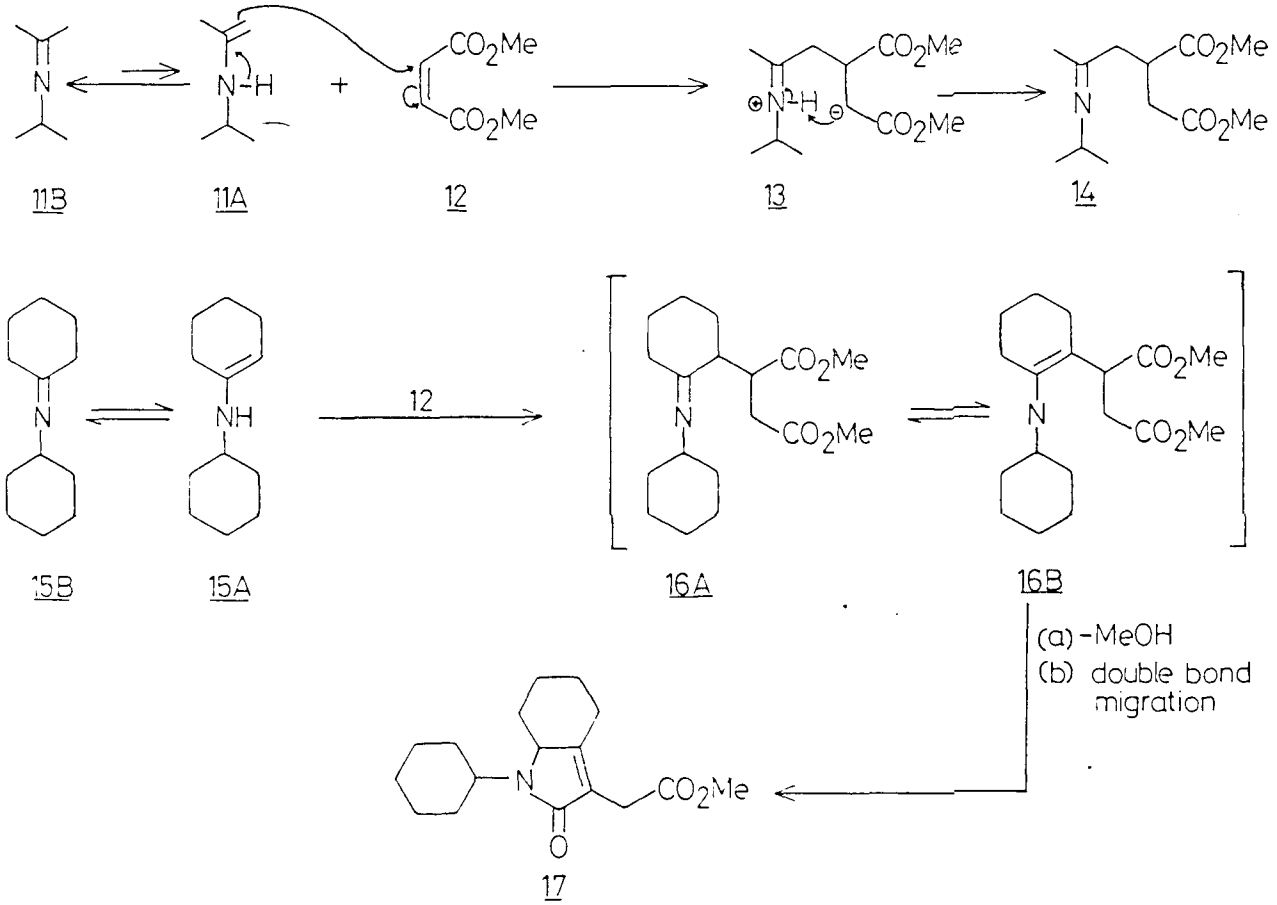
Agbalyan and Nersesyan[18] reported the reaction of ethyl-β-alkylamino crotonates 1 with maleic anhydride to yield the pyrrolin-2-ones 9 (Scheme 1), and the method was also extended to synthesize other pyrrolin-2-ones[19].

Pfau and Ribiere[20] investigated the reaction of enamines derived from acyclic and cyclic ketones with dimethylmaleate 12 and proposed a different mechanism. They observed that the acyclic enamine 11A reacted with 12 by the initial Michael addition to give the intermediate 13 which abstracted a proton to yield the open chain compound 14 (Scheme 2). However, when the cyclic enamine 15A was reacted with 12 under similar reaction conditions, an intermediate 16B, supposed to have been formed, underwent intramolecular cyclization to yield the condensed pyrrolin-2-one 17 (Scheme 2).

Dobeneck et al[21] reported the reaction of the 3-aminocrotonates 1 with maleic anhydride 2 to give the open chain compound 10 instead of the corresponding pyrrolin-2-



Scheme - 1

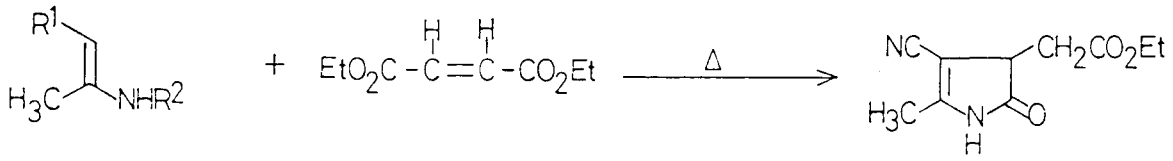

CO2Me
CO2Me
N
N-H
+
11B
11A
12
13
14
NH
12
15B
15A
16A
16B
(a) -MeOH
(b) double bond migration
O
17

Scheme - 2

one 9 (Scheme 1). However, they reported the synthesis of pyrrolin-2-ones 19 and 20 by reacting the crotonates 1 with diethylmaleate 18 and maleic anhydride 2 respectively (Scheme 3).

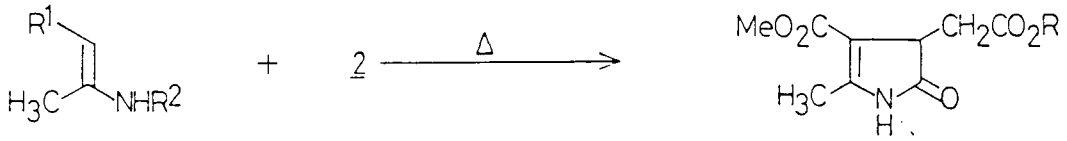
Shah and Blanton, Jr.[22] reinvestigated the reaction of maleimides 6 with ethyl-3-aminocrotonates 1. The structure of the product formed after cyclization of 22 in basic medium was wrongly assigned as the pyrrolo[2,3-*b*]pyrrole 23[23] which was based only on elemental analyses (Scheme 4). Subsequently the correct structure of 23 was assigned as the pyrrolopyridone 30 as shown in Scheme 5. It was proposed that the intermediate pyrrolin-2,5-dione 27 underwent cyclization to yield the corresponding pyrrolo[3,4-c]pyridines 30 which on treatment with acetic anhydride gave the corresponding acetate derivatives 31 and 32 (Scheme 5). The work was further extended to study the scope of the reaction by replacing the 3-aminocrotonates 1 with 2-benzylamino-prop-1-enylmethyl ketone (33) to synthesize the corresponding 1H-pyrrolo[3,4-c] pyridines 36 (Scheme 6).

Giardina et al[24] developed a methodology for the synthesis of pyrrolo[3,4-c]pyran-4-ones 41 (Scheme 7). Thus, the trans-3-hexen-2,5-dione 37 underwent initial Michael addition with the enolate anion of the acetoacetic ester 38 to afford the dihydrofuran 39 which on treatment with ammonia yielded the corresponding pyrrole 40. The 40 on treatment with acetylchloride yielded the corresponding



1 + 18 → 19

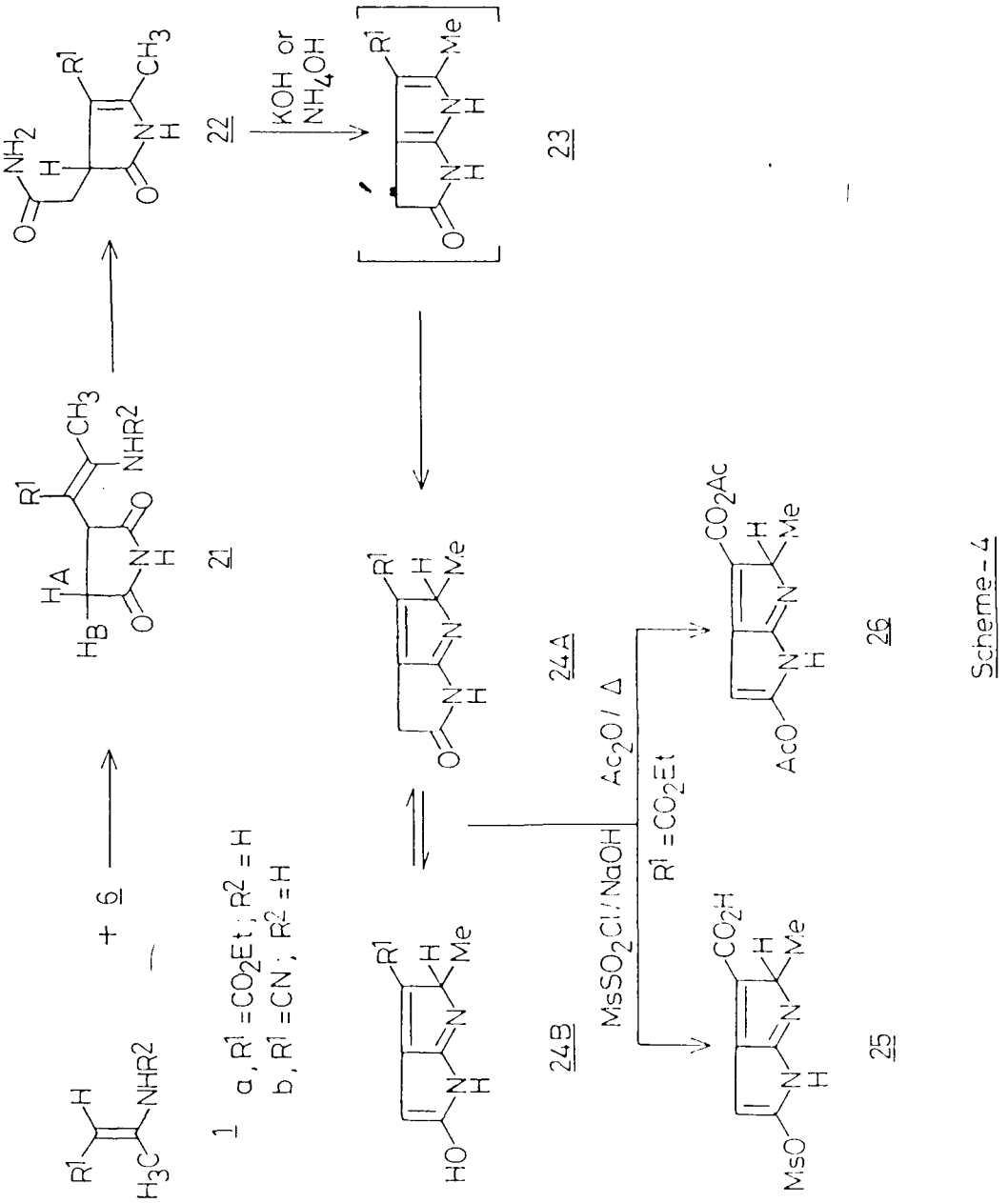
$R^1 = CN$; $R^2 = H$



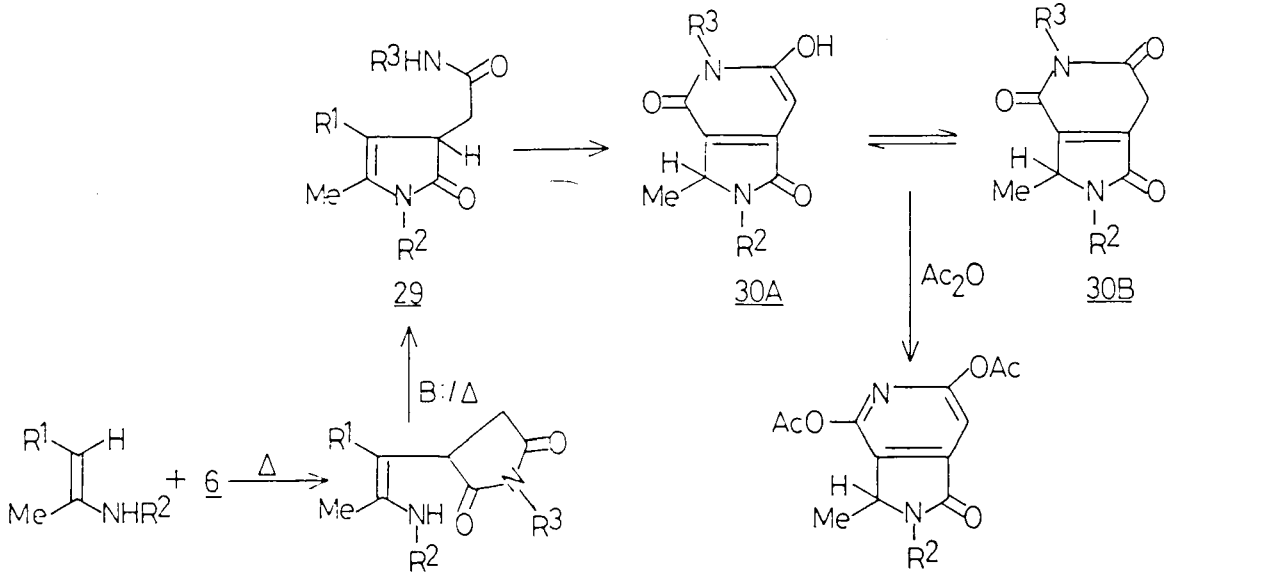
1 + 2 → 20

$R^1 = CO_2Me$; $R^2 = H$; R = H, Me

Scheme – 3

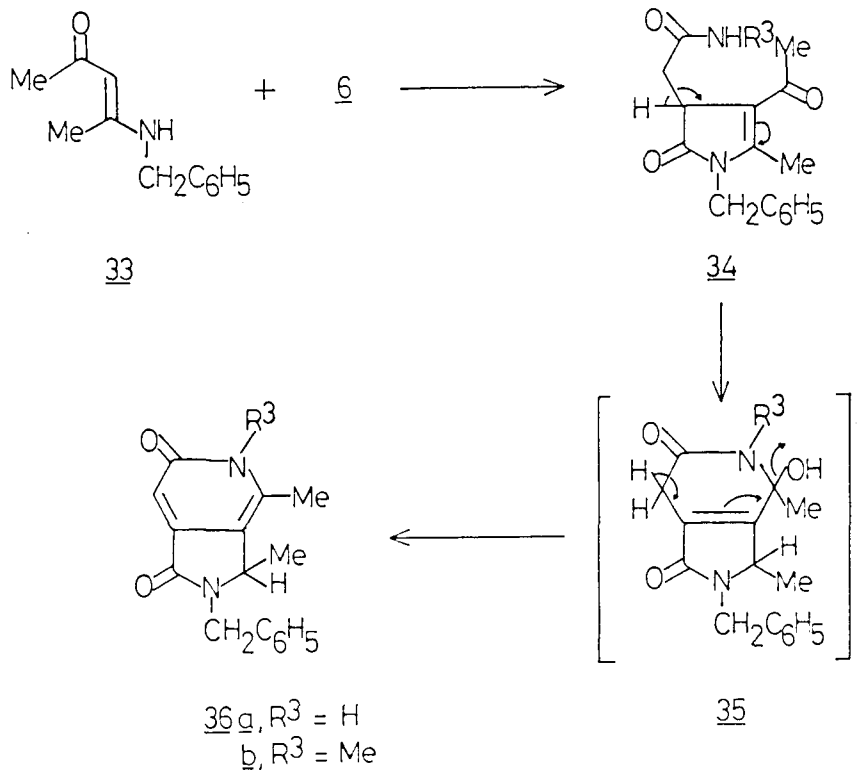

1
a, R1 = CO2Et ; R2 = H
b, R1 = CN ; R2 = H
+ 6
21
22
KOH or NH4OH
23
24A
24B
MsSO2Cl / NaOH
Ac2O / Δ
R1 = CO2Et
25
26

Scheme-4



R^1 = CO_2Et, CN ; R^2 = H, Me, $C_6H_5CH_2$

Scheme -5



33 34 35

36 a, R^3 = H
b, R^3 = Me

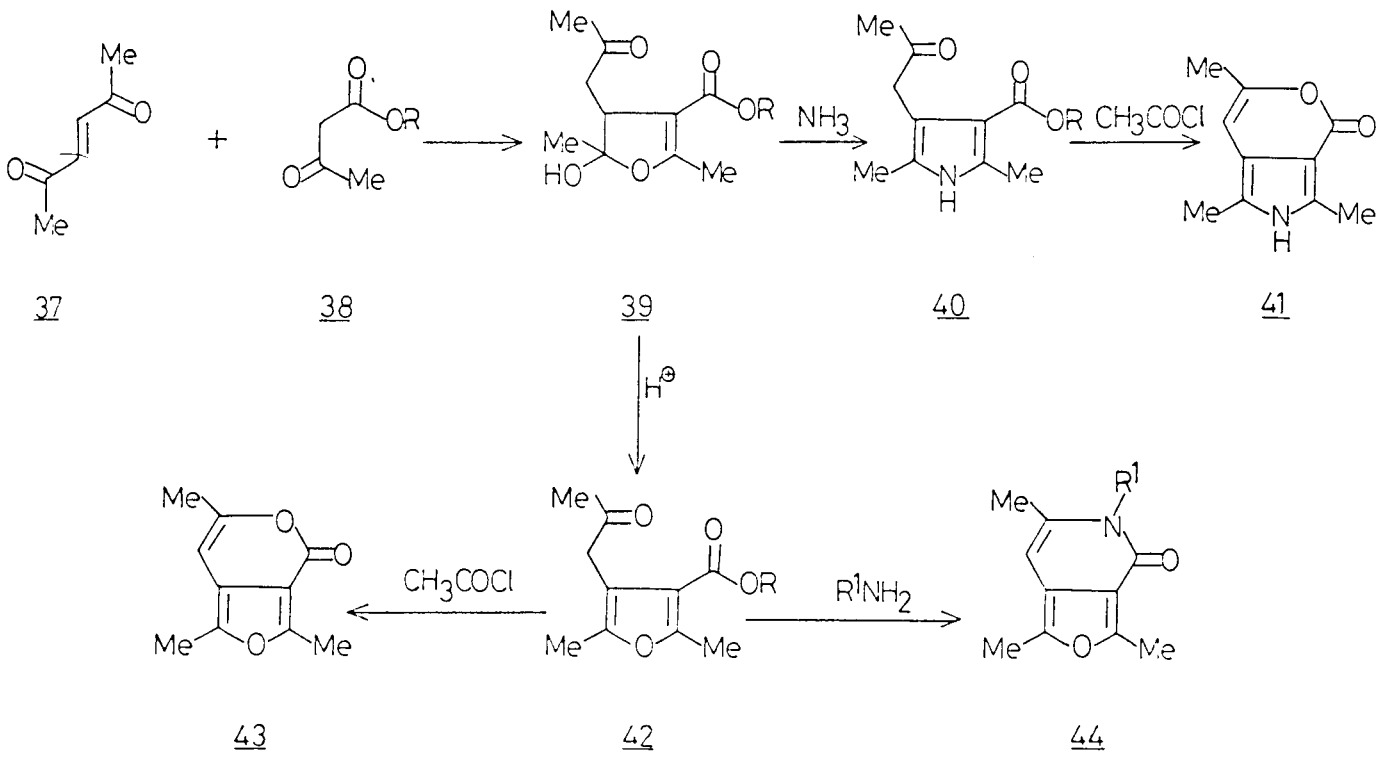
Scheme - 6

pyrrolo[3,4-c]pyran-4-one (41). Also 39 on treatment with acid yielded the furan 42 which was subsequently converted to the corresponding furo[3,4-c]pyran-4-one (43) on treatment with acetyl chloride (Scheme 7). The corresponding furo[3,4-c]pyridin-4-ones (44) were obtained by the reaction of 42 with various amines (Scheme 7).

Davis and Howarth[25] have reported the formation of 3,4-disubstituted pyrroles 47 by subjecting the sodioderivative of Clavulanic acid 45 to methanolysis (Scheme 8). The pyrroles 47 were subsequently cyclized to the corresponding δ-lactones 48. The methodoloxy for 3,4-disubstituted pyrroles 47, developed by these authors, is important since they are similar in structure to Verrucarine. E. (Scheme 9), an antimitotic agent isolated from Myrothecium verrucaria.

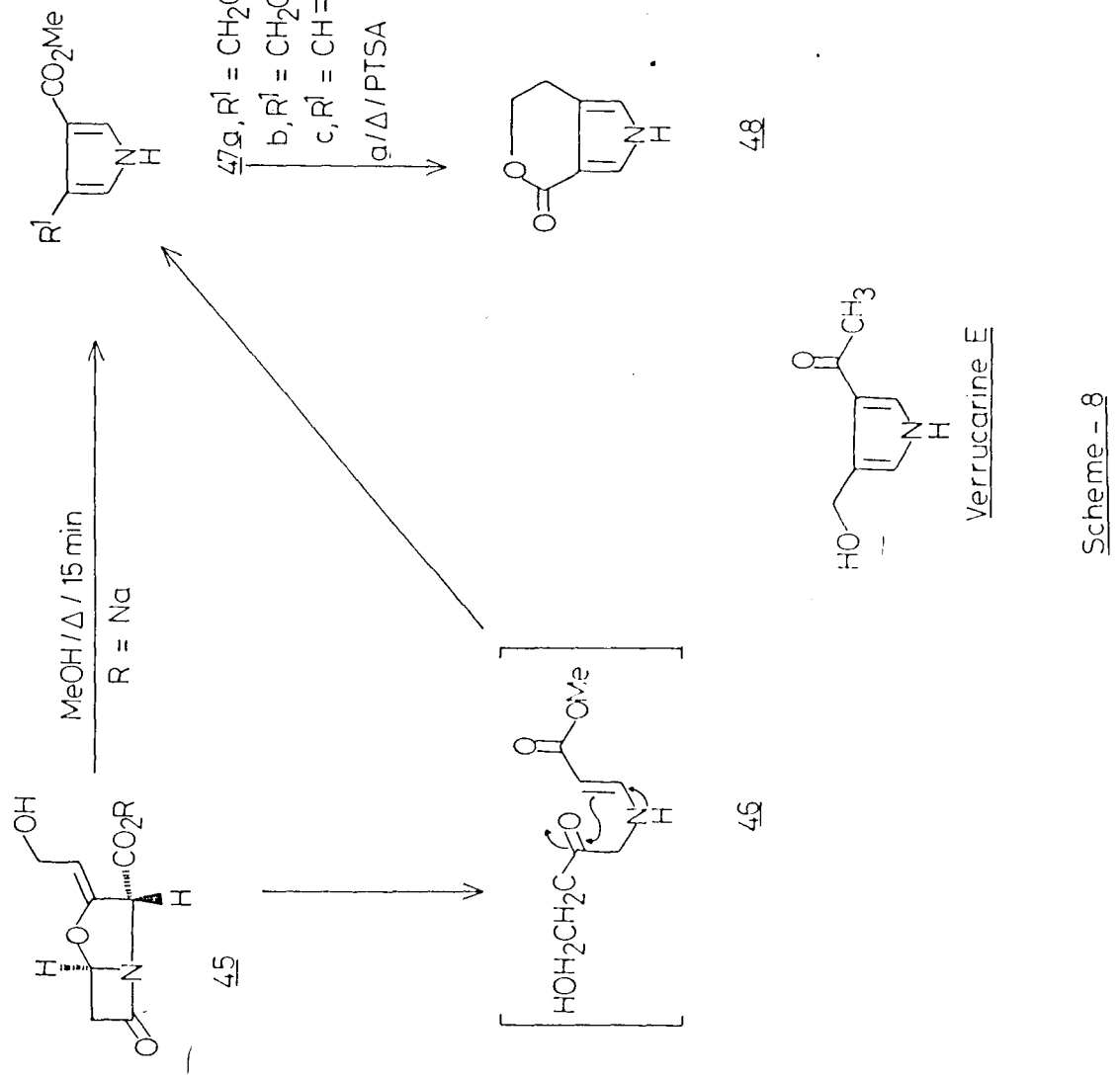
Goldberg et al[26] have reported the synthesis of bicyclic lactones of the general structure 50 from kainic acid 49 (Scheme 9). These lactones are reported to be potential selective antagonists of neuroexcitatory amino acids.

Baldwin et al[27] prepared various γ-lactam analogues of penicillanic acids and carbapenicillanic acids of which the 6-methoxy-3,3-dimethyl-8-oxo-4-thia-1-azabicyclo-[3.3.o] oct-6-ene-2-carboxylic acid 51 (Scheme 9) is of particular importance since it has structural framework similar to those reported in this Chapter. Also, 51 were tested for antibiotic activity (*Bacillus substilis* ATCC 6633 and *Esch ichia Coli*) and β-lactamase inhibition

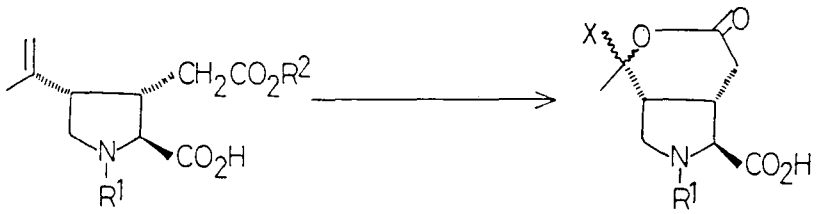


R = t-Bu, Me, H; R^1 = H, Me

Scheme-7

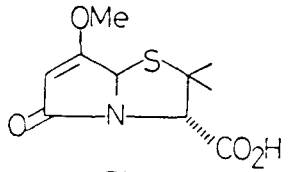

MeOH / Δ / 15 min
R = Na
47a, R1 = CH2CH2OH
b, R1 = CH2CH2OMe
c, R1 = CH=CH2
a/Δ/PTSA
45
46
47
48
Verrucarine E

Scheme - 8



49 a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = Me$

50
$R^1 = H, CO_2Bu^t$
X = H, I, OH, SPh



51

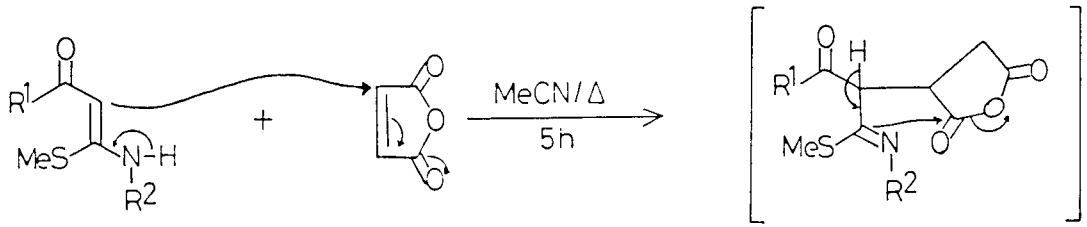
Scheme - 9

(*Bacillus cereus* β-lactamase II and *Klebsiella aerogenes* BRL 1003) and were shown to be inactive.

From the above discussion it is clear that the enamines react with activated double bonds through β-carbon to form the initial Michael adducts which then cyclize to yield the corresponding pyrrolin-2-ones. Some of these structural frames have potential application in the field of medicine. The enamines employed require the β-ketoesters and 1,3-diketones or their equivalents while the α-oxoketene S,N- and N,N-acetals can be derived in high yields from active methylene ketones either by reacting the enolate anion with various isothiocyanates followed by alkylation or by reacting the α-oxoketene S,S-acetals with primary amines[28-30]. Therefore, there is a wide scope for structural variation and a large number of S,N-and N,N-acetals can be prepared. Their behaviour as enamines towards maleic anhydride and maleimide would certainly yield the hitherto unreported novel pyrrolin-2-ones which can further be converted into 3,4-annelated products. Also, there is an additional advantage with the chemistry of S,N- and N,N-acetals as their cyclic analogues could be of particular interest since they could give bicyclic heterocycles of biological interest. The results of these investigations are discussed in this chapter.

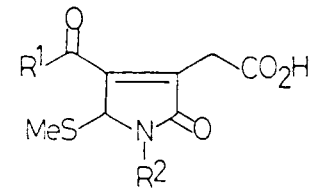
RESULTS AND DISCUSSION

In a typical experiment, when α-oxoketene S,N-acetal 52a was reacted with maleic anhydride 2 for 5 hours in refluxing acetonitrile, the reaction mixture, after work-up and purification, yielded a product which was characterized as 1-ethyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acid 54a (Scheme 10). The structure of 54a was fully established from its spectral and analytical data. Thus, it was analyzed for $C_{16}H_{17}NO_4S$ (319.4). Its mass spectrum exhibited molecular ion peaks at m/z : 319 (M^+,1%), 275 (9%),228(100%). Its I.R.(KBr) spectrum exhibited characteristic stretching vibrations at ν_{max} = 1720 cm^{-1}, 1672 cm^{-1} and 1642 cm^{-1}. The structure of 54a was further confirmed from its ^1H n.m.r.($CDCl_3$) spectrum. Thus, the triplet at δ 1.15 (3H,J=7Hz) was assigned to the CH_3 of N-ethyl group. The singlet at δ 1.67(3H) was due to the methylthio group. The singlet at δ 3.25(2H) was due to the CH_2 of CH_2COOH. The multiplet around δ3.32-4.00(2H) was assigned to the CH_2 of NCH_2CH_3. The ring H-5 methyne proton appeared as a singlet at δ 5.34. The aromatic protons appeared as a multiplet around δ7.33-7.82(5H). The OH of carboxylic group appeared as a singlet at δ 9.29(1H) which was exchangeable with D_2O. Similarly, the other α-oxoketene S,N-acetals 52 b-d were reacted with 2 to yield the corresponding 1-alkyl/aryl-4-acyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acids (54b-d) in 79-88% overall yields (Scheme 10). The structures of

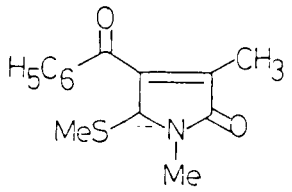


52 2 53

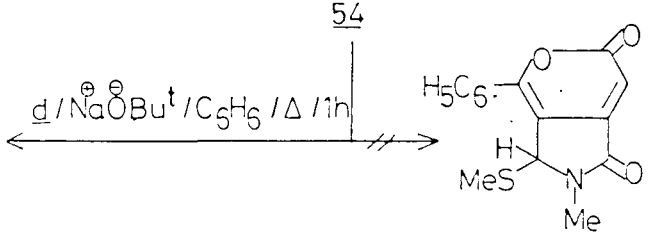
a, $R^1 = C_6H_5$; $R^2 = C_2H_5$
b, $R^1 = C_6H_5$; $R^2 = C_6H_5CH_2$
c, $R^1 = R^2 = C_6H_5$
d, $R^1 = C_6H_5$; $R^2 = CH_3$



54



55



56

Scheme - 10

54b-d were fully established from their spectral and analytical data which are described in the experimental section.

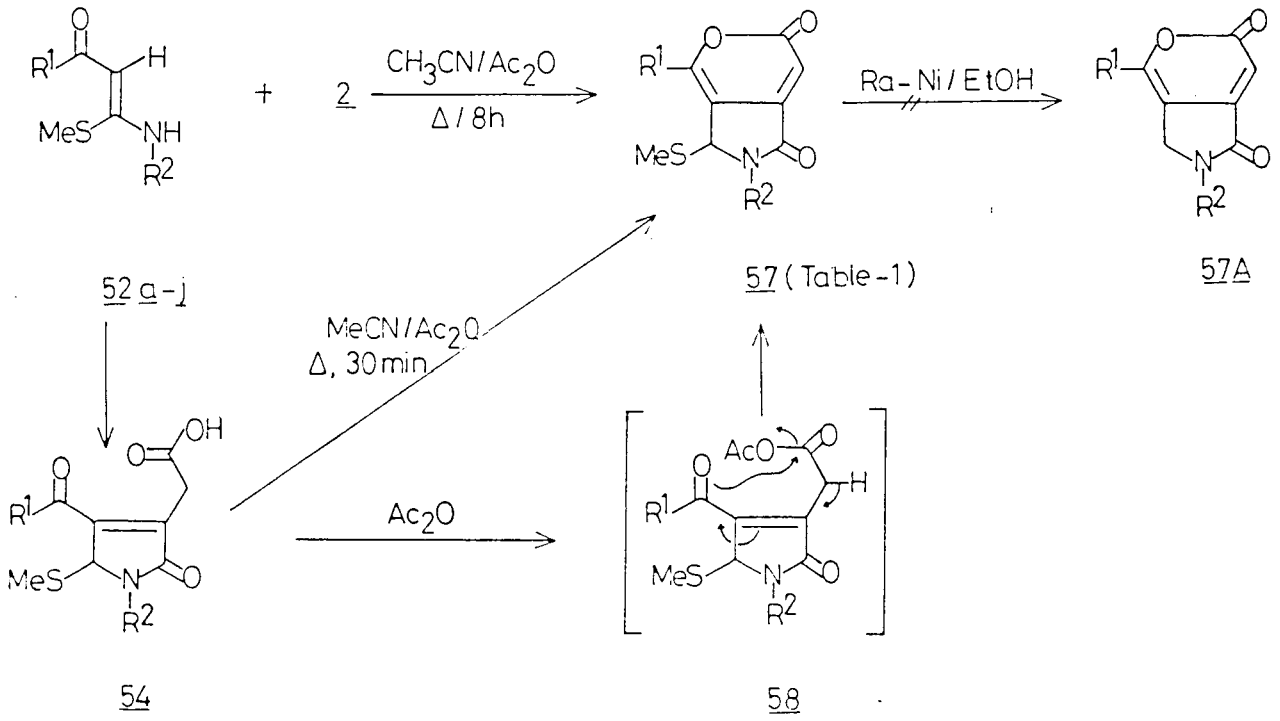
Further, the pyrrolin-3-acetic acid 54a underwent smooth cyclization when heated with acetic anhydride in refluxing acetonitrile for 30 minutes when the reaction mixture, after work-up and purification, afforded a product which was characterized as 2-ethyl-4-phenyl-3-methylthio-1,6-dioxo-2,3-dihydropyrano[3,4-*c*]pyrrole 57a (Scheme 11). The structure of 57a was fully established from its spectral and analytical data. Thus, it was analyzed for $C_{16}H_{15}NO_3S$ (301.4). Its mass spectrum exhibited molecular ion peaks at m/z: 254(M^+-47,100%), 226 (16%). Its I.R. (KBr) spectrum showed absorption peaks at νmax=1727 cm^{-1}, and 1693 cm^{-1}. The structure of 57a was further confirmed from its ^1H n.m.r. (DMSO-d_6) spectrum. Thus, the triplet at δ 1.26 (3H,J=7Hz) was assigned to the CH_3 of NCH_2CH_3. The singlet at δ1.50 (3H) was due to the methylthio group and the methylene protons of N-ethyl group exhibited non-equivalence of chemical shift and appeared as two doublets of quartets at δ3.48 and 3.78 with J=17Hz in each case. The ring H-3 methyne proton appeared as a singlet at δ6.36 and the ring H-7 proton appeared as a singlet at δ6.49. The aromatic protons appeared as two multiplets around δ 7.40-7.45 (3H) and δ7.75-8.12 (2H).

It was subsequently found that it was not necessary to isolate 54 since 57a could be prepared directly in 85%

yield by reacting 52a with 2 in the presence of acetic anhydride in boiling acetonitrile for 8 hours (Scheme 11). Therefore, the other pyrano[3,4-*c*]pyrroles 57b-j were prepared in 70-86% overall yields by reacting 52b-j with 2 in the presence of acetic anhydride in boiling acetonitrile for 8 hours (Table 1). The structures of 57b-j were fully established from their spectral and analytical data which are given in the experimental section.

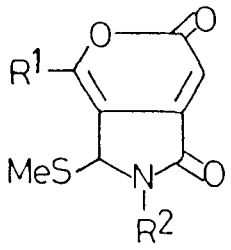
The mechanism of formation of 54 and 57 is shown in Schemes 10 and 11 respectively. Thus, the α-oxoketene S,N-acetals 52 add to the double bond of maleic anhydride 2 through β-carbon to give the intermediate 53 followed by breaking of the anhydride ring and subsequent ring closure to give 54 (Scheme 10). The acetic acid 54 is converted to the mixed anhydride 58 in the presence of acetic anhydride and then undergoes intramolecular cyclization by the elimination of acetic acid to give the corresponding pyrano[3,4-*c*]pyrrole 57 (Scheme 11).

An attempted cyclization of 54d in basic medium afforded the decarboxylated product 55 instead of the expected pyranopyrrole 56 (Scheme 10). Thus, when 54d was treated with potassium-t-butoxide in refluxing benzene for 1 hour, the reaction mixture, after work-up and purification, afforded the pyrrolin-2-one 55. The structure of 55 was fully established from its spectral and analytical data which are given in the experimental section.


R1
MeS
NH
R2
+
2
CH3CN/Ac2O
Δ / 8h
Ra-Ni / EtOH
57 (Table-1)
57A
52 a-j
MeCN/Ac2O
Δ, 30 min
Ac2O
OH
AcO
H
54
58

Scheme - 11

Table -1



57

57	R^1	R^2
a	C_6H_5	C_2H_5
b	C_6H_5	$C_6H_5CH_2$
c	C_6H_5	C_6H_5
d	C_6H_5	CH_3
e	4 - $MeOC_6H_4$	CH_3
f	4 - $MeOC_6H_4$	C_2H_5
g	4 - ClC_6H_4	C_6H_5
h	4 - ClC_6H_4	$C_6H_5CH_2$
i	CH_3	C_2H_5
j	4 - MeC_6H_4	$C_6H_5CH_2$

An attempted desulfurization of 57 in the presence of Raney-Nickel in ethanol failed to give 57A (Scheme 11).

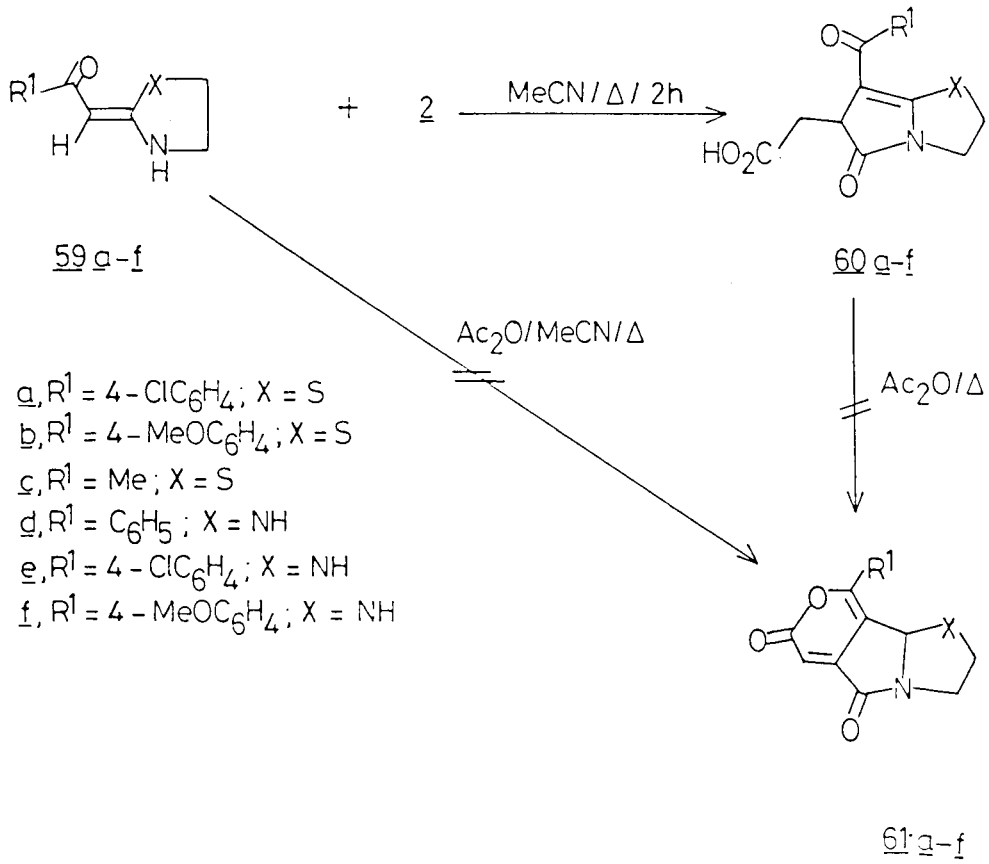
The reaction of the cyclic α-oxoketene S,N-acetals 59a-c and N,N-acetals 59d-f with maleic anhydride was next investigated. Thus, when 59a was reacted with 2 for two hours in the presence of refluxing acetonitrile, the reaction mixture, after work-up and purification, afforded a product which was characterized as 7-(4-chlorobenzoyl)-5-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*]-thiazole-6-acetic acid 60a (Scheme 12) on the basis of its spectral and analytical data. Thus, it was analyzed for $C_{15}H_{12}NO_4SCl$ (337.8). Its mass spectrum showed molecular ion peaks at m/z: 339(8%), 338(M^+,24%), 295(34%), 293(100%). Its I.R.(KBr) spectrum exhibited characteristic absorption bands at ν max=1733 cm^{-1}, 1647 cm^{-1} and 1612 cm^{-1}. The structure of 60a was further confirmed from its ^1H n.m.r. (DMSO-d_6) spectrum. Thus, the multiplet around δ2.07-2.90(2H) was assigned to the methylene protons adjacent to the carboxylic acid group. The ring SCH_2 protons appeared as a multiplet around δ3.00-3.28(2H) and the NCH_2 protons appeared as a multiplet around δ3.55-3.86(2H). The methyne H-6 proton appeared as a multiplet around δ4.29-4.60. The four aromatic protons appeared as a broad singlet at δ7.52. Similarly, the other tetrahydropyrrolo[2,1-*b*]thiazoles 60b and 60c were prepared in high yields and their spectral and analytical data were in full accordance with their structures (experimental section).

Similarly, the cyclic α-oxoketene N,N-acetals 59d-f reacted with maleic anhydride 2 in boiling acetonitrile for 2 hours to afford the corresponding 7-acyl-5-oxo-2,3,5,6-tetrahydropyrrolo[1,2-*b*]imidazole-6-acetic acids (60d-f) in excellent yields (Scheme 12). The structures of 60d-f were in full accordance with their spectral and analytical data which are described in the experimental section.

Interestingly, the acid 60a failed to undergo cyclization in the presence of acetic anhydride to yield the corresponding tricyclo derivative 61 (Scheme 12). Also, efforts to prepare 61 directly by reacting 59a with maleic anhydride in the presence of acetic anhydride in boiling acetonitrile failed (Scheme 12).

In a separate experiment, when the α-oxoketene S,N-acetal 52d was headed with citraconic anhydride 62 in the presence of acetic anhydride in boiling acetonitrile, the desired product 63 was not obtained even after prolonged heating for 20 hours (Scheme 13).

The reaction of the α-oxoketene N,N-acetals 64 with maleic anhydride 2 was next examined. Thus, when 64a was reacted with 2 in refluxing acetonitrile for 2 hours, the reaction mixture, after work-up and purification, afforded the corresponding 1-phenyl-4-benzoyl-2-oxo-5-phenylimino-3-pyrrolidin-3-acetic acid (65a) in 87% yield (Scheme 13). Similarly, 65b was also prepared in 89% yield by reacting 64b and 2 in boiling acetonitrile. The structures of 65a



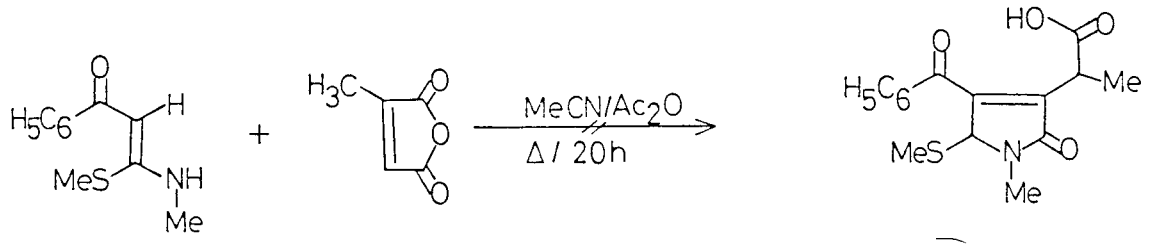
59 a-f

60 a-f

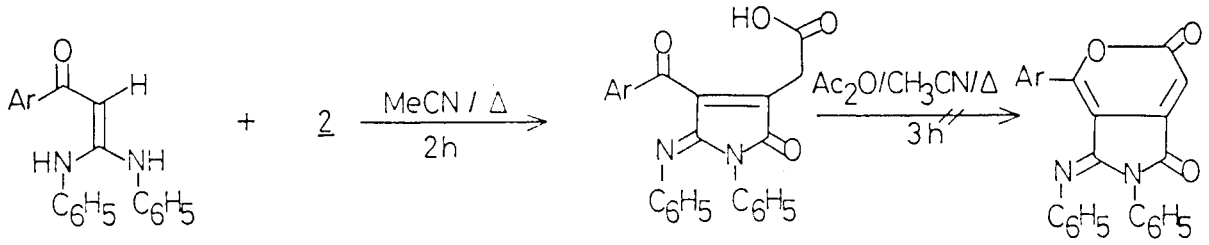
61 a-f

a, R^1 = 4-ClC_6H_4; X = S
b, R^1 = 4-$MeOC_6H_4$; X = S
c, R^1 = Me; X = S
d, R^1 = C_6H_5; X = NH
e, R^1 = 4-ClC_6H_4; X = NH
f, R^1 = 4-$MeOC_6H_4$; X = NH

Scheme - 12



52 d 62 63



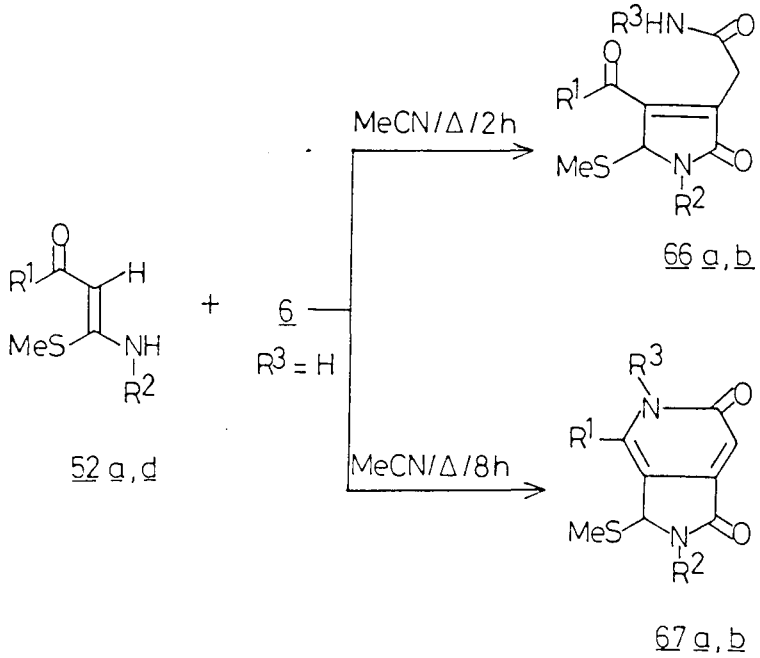
64 a, Ar = C_6H_5
b, Ar = 4-MeC_6H_4

65 a-b 65 A

Scheme - 13

and 65b were fully in accordance with their spectral and analytical data which are described in the experimental section. Both 65a and 65b failed to cyclize in the presence of acetic anhydride in boiling acetonitrile to afford 65A derivatives (Scheme 13).

It was considered to investigate the reaction of a few α-oxoketene S,N-and N,N-acetals with maleimide 6 so that the scope and the generality of this reaction is established. Thus,in a typical experiment,when 52a and 52d were reacted separately with 6 in refluxing acetonitrile for two hours, the reaction mixture,after work-up and purification, afforded the corresponding 1-ethyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin -3-acetamide (66a) and 1-methyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin -3-acetamide (66b) in 85% and 88% yields respectively (Scheme 14). The structures of 66a and 66b were fully established from their spectral and analytical data which are described in the experimental section. Alternatively, when the reaction mixture was allowed to reflux for 8 hours the corresponding 2-ethyl-3-methylthio-4-phenyl-1,6-dioxo-2,3,5,6-tetrahydro-(5H)-pyrrolo [3,4-*c*]pyridine (67a) and its methyl analogue (67b) were obtained in 70% and 82% yields respectively (Scheme 14). The structures of 67a and 67b were fully established from their spectral and analytical data which are described in the experimental section.

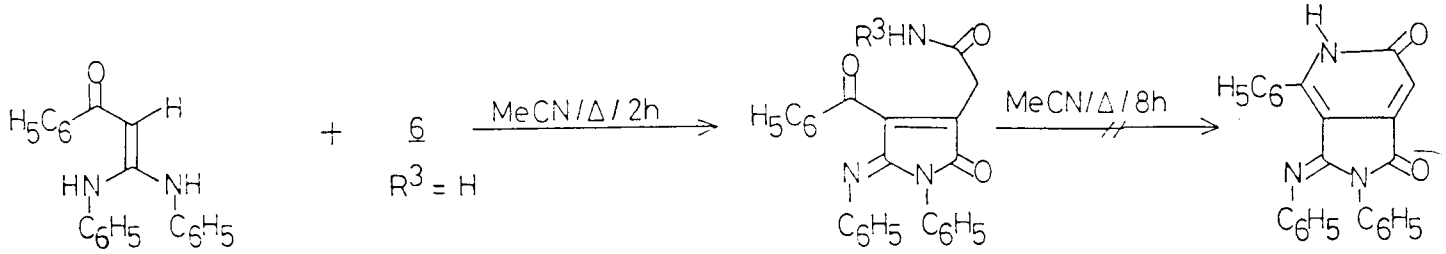

R3HN
O
O
R1
MeS
N
O
R2
MeCN/Δ/2h
66 a, b
R1
H
MeS
NH
R2
52 a, d
+
6
R3 = H
MeCN/Δ/8h
R3
N
O
R1
MeS
N
O
R2
67 a, b

Scheme - 14

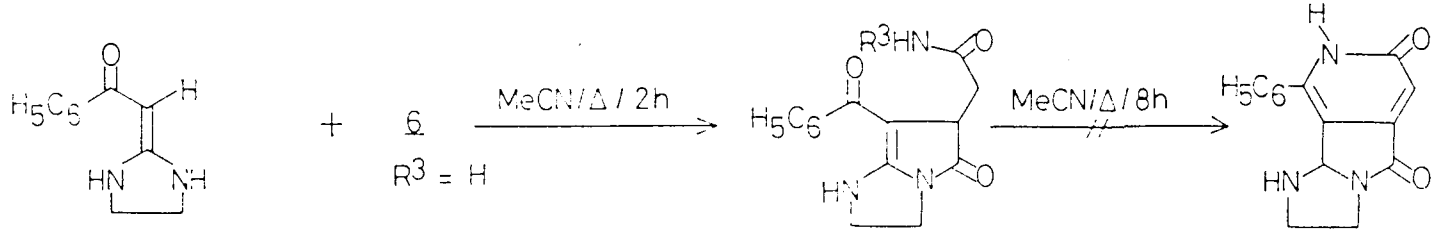
Similarly, the reaction of the α-oxoketene N,N-acetal 64 and the cyclic α-oxoketene N,N-acetal 59d with maleimide afforded the corresponding acetamides 68 and 69 in 79% and 77% yields respectively (Scheme 15). Their structures were fully established by their spectral and analytical data which are given in the experimental section. However, attempts to cyclize 68 and 69 by increasing the refluxing time to prepare their cyclic derivative 68A and 69A failed (Scheme 15).

CONCLUSION

Thus, it may be inferred that the α-oxoketene S,N- and N,N-acetals efficiently function as Michael donors and react with maleic anhydride and maleimide to give the expected pyrrolinones, pyrrolothiazoles, pyrrolopyridines, pyranopyrroles, pyrroloimidazoles, etc. Further, it may be noted that the bicyclic compounds with bridgehead nitrogen can only be obtained from the cyclic α-oxoketene S,N- and N,N-acetals which are otherwise inaccessible by the reported methods which yield only the pyrroline derivatives. Besides, various α-oxoketene S,N-and N,N-acetals used in these experiments are easily accessible in high yields from a large variety of active methylene compounds. Their stability towards mild hydrolytic conditions is also a contributing factor towards the preference for using them in synthetic design.



64 68 68A



59 d 69 69A

Scheme - 15

EXPERIMENTAL

General

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. The I.R. spectra were recorded on a 'Perkin-Elmer-297' spectrometer and frequencies are expressed in cm^{-1}. The ^1H n.m.r. spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using tetramethyl silane (TMS) as internal standard and chemical shifts are expressed as δ(ppm) down field from TMS. The mass spectra were recorded on a Jeol-D 300 spectrometer and relative intensities are expressed in percentage. Carbon, hydrogen and nitrogen elemental analyses were done at Central Drug Research Institute, Lucknow, India.

STARTING MATERIALS

The commercial samples of various acetophenones, acetone, amines, ethanol, acetonitrile, maleic anhydride, acetic anhydride, benzene etc., were purified before use. Phenylisothiocyanate was prepared according to the reported procedure[28]. Commercially available maleimide, potassium iodide and sodium carbonate were used as such.

The known α-oxoketene S,N-acetals 52a-d, 52f-g were prepared according to the reported procedure[29,30] and their analytical and spectral data were found to be similar to those of reported ones. The unknown S,N-acetals 52e and 52h were prepared by extending the

reported procedure[30] and their structures were confirmed by their analytical and spectral data which are given below.

3-Methylthio-3-methylamino-1-(4-methoxyphenyl)-2-propene-1-one (52e) was obtained as a yellow solid ($CHCl_3$); m.p. 57-58°C; yield 89%; IR.(KBr):νmax = 3230,1590 cm^{-1}; ^1H n.m.r. (CCl_4): δ=2.41 (s, 3H,$SC\underline{H}_3$), 3.03 (d,J=6Hz, 3H, $NC\underline{H}_3$), 3.78 (s,3H, $OC\underline{H}_3$), 5.48 (s, 1H,vinylic), 6.81 (d,J=9Hz, A_2B_2, $2H_{arom}$), 7.71 (d,J=9Hz, A_2B_2, $2H_{arom}$), 11.67 (brs, 1H, $N\underline{H}$, exchangeable with D_2O), [Found: C, 60.81; H, 6.41; N, 6.08 calculated for $C_{12}H_{15}O_2NS$ (237.3): C, 60.73; H, 6.37; N, 5.90%].

3-Methylthio-3-benzylamino-1-(4-chlorophenyl)-2-propene-1-one (52h) was obtained as a yellow solid ($CHCl_3$); m.p. 92°C;yield 79%;I.R.(KBr): ν_{max} =3250,1580,1544,1519 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ=2.30 (s,3H,$SC\underline{H}_3$), 4.48 (d, J=6Hz, 2H, $C\underline{H}_2$), 5.55 (s, 1H, vinylic), 7.27 (s,$5H_{arom}$), 7.29 (d,J=7Hz,A_2B_2, $2H_{arom}$), 7.68 (s,$2H_{arom}$) 12.09 (brs, 1H,$N\underline{H}$, exchangeable with D_2O), [Found: C, 64.04; H, 5.28; N, 4.49 calculated for $C_{17}H_{16}NOSCl$ (317.8): C, 64.24; H, 5.08; N, 4.41%].

The cyclic S,N-acetals 59a-c were prepared by the modification of the reported procedure[31]. A solution of aziridine (0.06 mol) in dry ether (50 ml) is added slowly to an ice-cold solution of dithioester (0.05 mol) in dry ether (50 ml) and the reaction mixture is further stirred

at room temperature for five hours (monitored by TLC). The ether layer is evaporated on water bath to dryness. The residue is dissolved in acetone (100 ml) and potassium iodide (0.40 mol) added to the reaction mixture. The reaction mixture is stirred at room temperature for 8 hours (monitored by TLC). The solid potassium iodide is filtered and mother liquor evaporated to dryness. Chloroform (100 ml) is added to the residue and organic layer washed with water (3x50 ml), dried over sodium sulphate and evaporated to give dark coloured residue, which on column chromatography over silica gel using hexane/ethyl acetate (9:1) as eluent afforded pure cyclic S,N-acetals 59a-c. Structures of 59a-c were fully confirmed by their spectral and analytical data which are given below.

4,5-Dihydro-2-(4-chlorobenzoyl)methylenethiazole (59a) was obtained as a yellow solid (DMF/ethanol); yield 71%; m.p. 183-184°C; I.R.(KBr): ν_{max} =3150,1593,1564 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=3.20 (t, 2H, J=6Hz, $SC\underline{H}_2$), 3.77 (t,2H,J=6Hz, $NC\underline{H}_2$), 6.03 (brs, $1H_{vinylic}$), 7.45 (d, J=8Hz, $2H_{arom}$), 7.88 (d,J=8Hz, $2H_{arom}$),[Found: C, 54.88; H, 4.30; N, 6.01 calculated for $C_{11}H_{10}NOSCl$ (239.7): C, 55.07; H, 4.17; N, 5.84%].

4,5-Dihydro-2-(4-methoxybenzoyl)methylene thiazole (59b) was obtained as a yellow crystalline solid (DMF/ethanol); yield 66%; m.p. 152-153°C; I.R.(KBr): ν_{max}=3222,1590,1568 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=3.21 (t,2H,J=6Hz,$SC\underline{H}_2$), 3.78

(s, 3H, $OC\underline{H}_3$), 3.83 (t, 2H, J=6Hz, $NC\underline{H}_2$), 5.92 (brs, $1H_{vinylic}$), 6.03 (d, J=9Hz, $2H_{arom}$), 7.81 (d,J=9Hz, $2H_{arom}$), 9.79 (brs, 1H, $N\underline{H}$, exchangeable with D_2O), [Found: C, 61.34; H, 5.44; N, 6.07 calculated for $C_{12}H_{13}NO_2S$ (235.2): C, 61.22; H, 5.53; N, 5.95%].

4,5-Dihydro-2-acetyl methylene thiazole (59c) was obtained as a yellow crystalline solid (DMF/ethanol); m.p. 96°C; yield, 71%; I.R.(KBr): ν_{max} =3410,1640,1578,1517 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ=2.01 (s,3H,$C\underline{H}_3$), 3.18 (t,J=6Hz,2H, $SC\underline{H}_2$), 3.83 (t,J=6Hz, 2H,$NC\underline{H}_2$), 5.26 (s,$1H_{vinylic}$), 10.10 (brs,1H,$N\underline{H}$, exchangeable with D_2O), [Found: C, 50; H, 6.30; N, 9.90 calculated for C_6H_9NSO (143.2): C, 50.32; H, 6.34; N, 9.78%].

The α-oxoketene N,N-acetals 64a was prepared according to the reported procedure[30] and its structure was fully confirmed from its spectral and analytical data. The unknown α-oxoketene N,N-acetal 64b was prepared by extending the reported procedure[30] and its spectral and analytical data are given below.

3,3-Diphenylimino-1-(4-methylphenyl)-2-propene-1-one (64b) was obtained as a yellow crystalline solid (DMF/ethanol); m.p. 151°C; yield 88%; I.R.(KBr): ν_{max} = 3243,1623,1594,1549 cm^{-1}; ^1H n.m.r. (TFA/CCl_4): δ=2.40 (s,3H,$C\underline{H}_3$), 4.61 (s,2H,$C\underline{H}_2$), 7.23-7.87 (m, $14H_{arom}$), [Found: C, 80.26; H, 6.00; N, 8.57 calculated for $C_{22}H_{20}N_2O$ (328.39): C, 80.46; H, 614; N, 8.53%].

The know cyclic α-oxoketene N,N-acetal 59d was prepared according to the reported procedure[30] and its spectral and analytical data were found to be similar to those of reported one. The unknown α-oxoketene N,N-acetals 59e and 59f were prepared by extending the reported procedure[30] which is described here.

A solution of α-oxoketene S,S-acetal (0.02 mol) and ethylene diamine (0.025 mol) in ethanol (50 ml) is refluxed for 15 hours. After completion of the reaction (monitored by TLC) the solvent was removed and the crude cyclic N,N-acetal, thus obtained, is purified by crystallization from boiling DMF/ethanol (1:4). Structures of 59e and 59f were confirmed by their spectral and analytical data which are given below.

4,5-Dihydro-2-(4-chlorobenzoyl)methylene imidazole (59e) was obtained as a colourless crystalline solid (DMF/ethanol); m.p. 267-268°C; yield 91%; I.R.(KBr): ν_{max} =3312,1604,1549 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ=3.91 (s,4H,$NC\underline{H}_2$), 4.31 (s,2H, $C\underline{H}_2$), 7.32 (d, J=9Hz,A_2B_2, $2H_{arom}$), 7.73 (d,J=9Hz,A_2B_2, $2H_{arom}$), 9.88 (brs, 1H, N$\underline{H}$, exchangeable with D_2O), [Found: C, 59.09; H, 5.13; N, 12.41 calculated for $C_{11}H_{11}N_2OCl$ (222.7): C, 59.27; H, 4.94; N, 12.57%].

4,5-Dihydro-2-(4-methoxybenzoyl)methylene imidazole (59f) was obtained as a colourless solid (DMF/ethanol); m.p. 230-231°C; yield 92%; I.R.(KBr): ν_{max}=3120,1594,1549 cm^{-1}; ^1H n.m.r. ($CDCl_3$/TFA): δ=3.88 (s,3H,$OC\underline{H}_3$), 4.03

(s,4H,NC$\underline{H}_2$), 4.42 (s,2H,C$\underline{H}_2$), 7.00 (d, J=9Hz, A_2B_2,2H$_{arom}$), 7.90 (d, J=9Hz,2H$_{arom}$), 8.58 (brs, 1H, N$\underline{H}$, exchangeable with D_2O), [Found: C, 66.12; H, 6.31; N, 12.94 calculated for $C_{12}H_{14}N_2O_2$ (218.2): C, 65.99;H, 6.42; N,12.83%].

1-Alkyl/aryl-4-aroyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acids (54a-d): General Procedure:

A solution of the α-oxoketene S,N-acetals 52 (20 mmol) and maleic anhydride (20 mmol) in acetonitrile (30 ml) is refluxed for 5 hours (monitored by TLC). The reaction mixture is then cooled, poured into ice water (50 ml) and extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give crude pyrrolines 54a-d which were further purified by column chromatography over silica gel using hexane/ethylacetate (9:1) as eluent. The structures of 54a-d were confirmed by their spectral and analytical data which are given below.

1-Ethyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acid (54a) was obtained as a colourless solid (MeOH); m.p. 138°C; yield, 81%. Its I.R., ^1H n.m.r. and mass spectral data are given in the text. [Found: C, 59.97; H, 5.30; N, 4.15 calculated for $C_{16}H_{17}NO_4S$ (319.4): C, 60.16; H, 5.37; N, 4.38%].

1-Benzyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acid (54b) was obtained as a colurless solid (MeOH); m.p. 154°C; yield 79%; I.R.(KBr): ν_{max} =1705, 1684, 1640 cm^{-1};

^{1}H n.m.r.($CDCl_3$): δ=1.74 (s,3H,$SC\underline{H}_3$), 3.30 (s,2H,$C\underline{H}_2CO_2H$), 4.20 (d,J=17Hz, 1H,H_A of $C\underline{H}_2$), 5.51 (d, J=17Hz, 1H, H_B of $C\underline{H}_2$), 5.16 (s, 1H, $\underline{H}$-5), 7.20 (s, 5H, N-C_6H_5), 7.33-7.80 (m,5$\underline{H}$, $COC_6\underline{H}_5$), 9.13 (brs, 1H, O$\underline{H}$, exchangeable with D_2O); m/z : 337 (M^+-44,4%); 290 (28%)· [Found: C, 66.21; H, 5.20; N, 3.51 calculated for $C_{21}H_{19}NO_4S$ (381.4): C, 66.11; H, 5.02; N, 3.67%].

1-Phenyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acid (54c) was obtained as a colourless solid (MeOH); m.p. 168°C;yield, 82%;I.R.(KBr):ν_{max}=1716,1660,1640 cm^{-1}; ^{1}H n.m.r ($CDCl_3$): δ=1.68 (s, 3H, $SC\underline{H}_3$), 3.39 (s, 2H, $C\underline{H}_2CO_2H$), 5 (s,1H,$\underline{H}$-5).,7.10-7.93 (m, 10H_{arom}), 9.08 (brs, 1H, O$\underline{H}$, exchangeabale with D_2);m/z : 367 M^+,3%), 323(9%),267(83%), [Found: C,65.08; H,4.37;N, 3.95 calculated for $C_{20}H_{17}NO_4S$ (367.4): C,56.38; H,4.66; N,3.81%].

1-Methyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetic acid (54d) was obtained as a colurless solid ($CDCl_3$); m.p. 120 °C;yield 88%; I.R.(KBr):ν_{max}=1720,1670,1642 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ=1.79 (s, 3H, $SC\underline{H}_3$), 3.13 (s, 3H, $NC\underline{H}_3$), 3.46(s,2H,$C\underline{H}CO_2H$),5.49 (s,1H,$\underline{H}$-5),7.61-8.10 (m,5H_{arom}), 8.57 (brs,1H, O$\underline{H}$, exchangeable with D_2O), [Found: C, 58.6; H, 4.71; N,4.37 calculated for $C_{15}H_{15}NO_4$ (306.3): C, 58.81; H, 4.94; N, 4.57%].

1,3-Dimethyl-4-benzoyl-5-methylthio-3-pyrrolin-2-one (55)
Typical Procedure: Sodium t-butoxide (20 mmol) is added to a solution of 54d (20 mmol) in dry benzene (50 ml) and

the mixture is refluxed for 1 hour. The mixture is then cooled, poured into ice water (50 ml), extracted from benzene (3x50 ml), dried over sodium sulphate and evaporated to give crude pyrroline 55 which is further purified by column chromatography over silica gel using hexane/ethylacetate (9:1) as eluent and the structure was confirmed from its analytical and spectral data which are given below.

1,3-Dimethyl-4-benzoyl-5-methylthio-3-pyrrolin -2-one (55) was obtained as a colurless solid ($CHCl_3$); m.p. 120°C; yield 80%; I.R.(KBr): ν_{max}=1686, 1642 cm^{-1}; ^1H n.m.r.(CCl_4): δ=1.75 (s, 3H, $C\underline{H}_3$), 1.89 (s, 3H, $SC\underline{H}_3$), 3.02 (s,3H,$NC\underline{H}_3$), 5.27 (brs,1H,$\underline{H}$-5),7.33-8.00 (m, $5H_{arom}$); m/z : 261 (M^+, 32%), 214 (M^+ -47, 44%), [Found: C,64.21; H, 5.71; N,5.12 calculated for $C_{14}H_{15}NO_2S$ (261.3): C, 64.35; H, 5.7; N, 5.36%].

2-Alkyl/aryl-4-aryl/methyl-3-methylthio-1,6-dioxo-2,3-dihydro-pyrano[3,4-*c*]pyrroles (57a-j): General Procedure: To a solution of the α-oxoketene S,N-acetal 52 (20 mmol) and maleic anhydride (20 mmol) in acetonitrile (30 ml) freshly distilled acetic anhydride (20 mmol) is added and the mixture is refluxed for 8 hours. The mixture is then cooled and poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give crude pyranopyrroles 57 which are purified by column chromatography over silica gel using hexane/ethylacetate (9:1) as eluent and subsequent

crystallization from chloroform.

Cyclization of 54 : Typical Procedure :

To a solution of the pyrroline-2-one 54a (10 mmol) in acetonitrile (20 mmol), freshly distilled acetic anhydride (20 mmol) is added and the mixture is refluxed for 30 minutes. The mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give crude pyranopyrroles 57a which are purified by column chromatography over silica gel using hexane/ethylacetate (9:1) as eluent.

The structures of 57a-j were confirmed by their spectral and analytical data which are described below.

2-Ethyl-3-methylthio-4-phenyl-1,6-dioxo-2,3-dihydropyrano-[3,4-*c*]pyrrole (57a) was obtained as a colurless solid ($CHCl_3$); m.p. 148°C; yield 85%; Its I.R., ^1H n.m.r. and mass spectral data are given in the text. [Found: C, 63.52; H, 4.90; N, 4.40 calculated for $C_{16}H_{15}NO_3S$ (301.4): C,. 63.76; H, 5.02; N, 4.65%].

2-Benzyl-3-methylthio-4-phenyl-1,6-dioxo-2,3-dihydro-pyrano[3,4-*c*]pyrrole (57b) was obtained as a colourless solid ($CHCl_3$); m.p. 134°C; yield 80%; I.R. (KBr): ν_{max}=1719,1710 cm^{-1}; ^1H n.m.r.(TFA): δ=1.60(s,3H,SCH_3)4.56 (d,J=15Hz,1H,H_A of CH_2), 5.38 (d, J=15Hz, 1H,H_B of CH_2), 5.68 (s,1H,H-3), 6.98 (s, 1H, H-7), 7.18-7.84 (m,

$10H_{arom}$); m/z : 316 (M^+-47, 100%), [Found: C, 69.12; H, 4.62; N, 3.67 calculated for $C_{21}H_{17}NO_3S$ (363.4): C, 69.40; H, 4.72; N, 3.85%].

2-Phenyl-3-methylthio-4-phenyl-1,6-dioxo-2,3-dihydro-pyrano[3,4-*c*] pyrrole (57c) was obtained as a colourless solid ($CHCl_3$); m.p. 192°C; yield 86%; I.R.(KBr): ν_{max}=1720,1705 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=1.53 (s, 3H,$SC\underline{H}_3$), 6.65 (s, 1H, $\underline{H}$-3), 7.08 (s, 1H, $\underline{H}$-7), 7.32-7.82 (m,$8H_{arom}$), 7.83-8.00 (m, $2H_{arom}$); m/z : 302 (M^+-47,100%), 247 (10%), [Found: C, 68.53; H, 4.13; N, 3.87 calculated for $C_{20}H_{15}NO_3S$ (349.3): C, 68.75; H, 4.33; N, 4.01%].

2-Methyl-3-methylthio-4-phenyl-1,6-dioxo-2,3-dihydro-pyrano[3,4] pyrrole (57d) was obtained as a colourless solid ($CHCl_3$); m.p. 176°C; yield, 84%; I.R.(KBr): ν_{max}=1721, 1698 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.66 (s, 3H, $SC\underline{H}_3$), 3.14 (s, 3H, $NC\underline{H}_3$), 5.79 (s, 1H,$\underline{H}$-3), 6.60 (s, 1H, $\underline{H}$-7), 7.32-7.65 (m, $3H_{arom}$), 7.65-7.94 (m, $2H_{arom}$); m/z: 240 (M^+ - 47,100%); 212 (18%), [Found: C, 62.52; H, 4.30; N, 4.99 calculated for $C_{15}H_{13}NO_3S$ (287.3): C, 62.70; H, 4.56; N, 4.88%].

2-Methyl-3-methylthio-4-(4-methoxyphenyl)-1,6-dioxo-2,3-dihydropyrano[3,4-*c*]pyrrole (57e) was obtained as colourless solid ($CHCl_3$) ; m.p. 164°C; yield 81%; I.R. (KBr): ν_{max}= 1720, 1685 cm^{-1}; ^1H n.m.r.(TFA) : δ=1.20 (s, 3H, $SC\underline{H}_3$), 2.89 (s, 3H, $NC\underline{H}_3$), 3.53 (s, 3H, $OC\underline{H}_3$), 5.45 (s, 1H, $OC\underline{H}_3$), 6.43 (s, 1H,$\underline{H}$-7), 6.70 (d, J=7Hz,

(M^+-47,100%), 242 (12%), [Found: C, 60.70; H, 4.91; N, 4.60 calculated for $C_{16}H_{15}NO_4S$ (317.3): C, 60.54; H, 4.76; N, 4.41%].

2-Ethyl-3-methylthio-4-(4-methoxyphenyl)-1,6-dioxo-2,3-dihydro-pyrano[3,4-*c*]pyrrole (57f) was obtained as a colourless solid ($CHCl_3$); m.p.158°C; yield 84%; I.R.(KBr):ν_{max} = 1711 cm^{-1}; ^1H n.m.r.(TFA): δ=1.40 (t, J=7Hz, βH, $CH_2C\underline{H}_3$), 1.60 (s, 3H, $SC\underline{H}_3$), 3.50-4.28 (m, 2H, $NC\underline{H}_2$), 3.97 (s, 3H, $OC\underline{H}_3$), 5.97 (s, 1H, $\underline{H}$-3), 6.89 (s, 1H, $\underline{H}$-7), 7.15 (d, J=7Hz, A_2B_2 $2H_{arom}$), 7.87 (d, J=7Hz, $2H_{arom}$); m/z : 284 (M^+-47, 100%); 256(10%), [Found: C, 61.75; H, 5.30; N, 4.46 calculated for $C_{17}H_{17}NO_4S$ (331.38): C, 61.16; H, 5.17; N, 4.23%].

2-Phenyl-3-methylthio-4-(4-chlorophenyl)-1,6-dioxo-2,3-dihydro-pyrano[3,4-*c*]pyrrole (57g) was obtained as a colourless solid ($CHCl_3$); m.p. 218°C; yield 88%; I.R. (KBr):ν_{max} =1727, 1708 cm^{-1}; ^1H n.m.r.(TFA): δ=1.73 (s, 3H, $SC\underline{H}_3$), 6.57 (s,1H,$\underline{H}$-3), 7.18 (s, 1H, $\underline{H}$-7), 7.45-7.80 (m, $7H_{arom}$), 7.81-8.11 (d, J=9Hz,A_2B_2, $2H_{arom}$); m/z : 338 (36%); 336 (M^+-47 100%); 3.08 (8%), [Found: C, 62.30; H, 3.41; N, 3.80 calculated for $C_{20}H_{14}NO_3SCI$ (383.8): C, 62.57; H, 3.68; N, 3.65%].

2-Benzyl-3-methylthio-4-(4-chlorophenyl)-1,6-dioxo-2,3-dihydro-pyrano[3,4-*c*]pyrrole (57h) was obtained as a colourless solid ($CHCl_3$); m.p. 120°C; yield 80%; I.R. (KBr):ν_{max}=1718, 1704 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.58 (s, 3H, $SC\underline{H}_3$), 4.36 (d, J=15Hz, 1H, H_A of $C\underline{H}_2$), 5.33 (d,

J=15Hz, 1H, H_B of $C\underline{H}_2$), 5.48 (s, 1H, $\underline{H}$-3), 6.70 (s, 1H, $\underline{H}$-7), 7.33 (s, $5H_{arom}$), 7.30-7.71 (d, J=9Hz each, $4H_{arom}$); m/z:352 (9%); 350 (M^+-47, 18%), [Found: C, 63.52; H, 4.25; N, 3.72 calculated for $C_{21}H_{16}NO_3SCI$ (397.2): C, 63.39; H, 4.05; N, 3.52%].

2-EThyl-3-methylthio-4-methyl-1,6-dioxo-2,3-dihydropyrano-[3,4-*c*] pyrrole (57i) was obtained as a colourless solid ($CHCl_3$); m.p. 108°C; yield, 79%; I.R.(KBr):ν_{max} = 1728, 1629 cm^{-1}; ^1H n.m.r. (TFA): δ=1.34 (t,J=7Hz, 3H, $CH_2C\underline{H}_3$), 1.74 (s, 3H, $SC\underline{H}_3$), 2.60 (s, 3H, $C\underline{H}_3$), 3.45-4.32 (m, 2H, $C\underline{H}_2CH_3$), 5.73 (s, 1H, $\underline{H}$-3), 6.92 (s, 1H,$\underline{H}$-7); m/z:239 (M^+, 19%), 192 (M^+-47,100%), 164 (30%), [Found: C, 45.24; H, 4.69; N, 4.99 calculated for $C_{11}H_{13}NO_3S$ (239.3): C, 45.04; H, 4.47; N, 4.78%].

2-Benzyl-3-methylthio-4-(4-methylphenyl)-1,6-dioxo-2,3-dihydropyrano[3,4-*c*]pyrrole (57j) was obtained as a colourless solid ($CHCl_3$); m.p. 91°C; yield 75%; I.R. (KBr): ν_{max} = 1715,1700 cm^{-1}; ^1H n.m.r.($CDCl_3$) : δ=1.55 (s,3H, $SC\underline{H}_3$), 2.40 (s, 3H, $C\underline{H}_3$), 4.40 (d,J=15Hz, 1H, H_A of $C\underline{H}_2$), 5.35 (d, J=15Hz, 1H, H_B of $C\underline{H}_2$), 5.58 (s, 1H, $\underline{H}$-3), 6.72 (s, 1H, $\underline{H}$-7), 7.41 (s, $5H_{arom}$), 7.28 (d, J=9Hz, A_2B_2, $2H_{arom}$), 7.64 (d, J=9Hz, A_2B_2, $2H_{arom}$); m/z: 330 (M^+-47, 37%), [Found: C.70.10; H, 5.30; N, 3.90 calculated for $C_{22}H_{19}NO_3S$ (377.4): C, 69.99; H, 5.07; N, 3.71%].

7-Acetyl/aroyl-5-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*]-thiazole-6-acetic acid (60a-c) and 7-Aroyl-5-oxo-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-*a*]imidazole-6-acetic acid(60d-f): General Procedure:

A solution of the cyclic α-oxoketene S,N- 59a-c or N,N-acetal 59d-f (20 mmol) and maleic anhydride (20 mmol) in acetonitrile (30 ml) is refluxed for 2 hours. The reaction mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give crude pyrrolothiazoles 60a-c and pyrroloimidazoles 60d-f which are purified by crystallization from methanol and their structures were confirmed by their analytical and spectral data which are described below.

7-(4-Chlorophenyl)-5-oxo-2,3,5,6-tetrahydropyrrolo[2,1-b]thiazole-6-acetic acid (60a) was obtained as a colourless solid (MeOH); m.p. 220°C; yield, 85%. Its I.R., ^1H n.m.r. and mass spectral data are given in the text. ^{13}C n.m.r. (DMSO-d_6): δ = 27.60 ($\underline{C}H_2CO_2H$); 33.08 (C-2), 39.51 (C-6), 47.22 (C-3), 104.73 (C-7), 128.27 (C-3'; C-5'), 128.97 (C-2', C-6'), 134.99 (C-4'), 138.43 (C-1'), 157.41 (C-7a), 166.28 ($\underline{C}O_2H$), 172.93 (C-5), 190.51 (COC_6H_4), [Found: C, 53.32; H, 3.57; N, 4.16 calculated for $C_{15}H_{12}NO_4SCl$ (337.8): C, 53.33; H, 3.58; N, 4.15%].

7-(4-Methoxyphenyl)-5-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazole-6-acetic acid (60b) was obtained as a colourless solid (MeOH); m.p. 170°C; yield, 87%; I.R.(KBr): ν_{max} =

1722, 1646, 1603 cm^{-1}; ^1H n.m.r. (DMSO-d_6):δ=2.80 (d, J=5.5Hz, 2H, $C\underline{H}_2CO_2H$), 2.97-3.18 (m, 2H, $SC\underline{H}_2$), 3.57-3.97 (m, 2H, $NC\underline{H}_2$), 3.83 (s, 3H, $OC\underline{H}_3$), 4.23-4.68 (m, 1H, $\underline{H}$-6), 6.90 (d, J = 9Hz, A_2B_2, $2H_{arom}$), 7.52 (d, J=9Hz, A_2B_2, $2H_{arom}$); m/z : 333 (M^+-4), 289 (M^+-44,34), [Found: C, 57.65; H, 4.57; N, 4.24 Calculated for $C_{16}H_{15}NO_5S$ (333.3): C, 57.64; H, 4.54; N, 4.20%].

7-(4-Chlorophenyl)-5-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*] thiazole-6-acetic acid (60c) was obtained as a colourless solid (MeOH); m.p. 222°C; yield, 91%; I.R.(KBr):ν_{max} =1720, 1650, 1640 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ = 2.31 (s, 3H, $C\underline{H}_3$), 2.66-2.89 (m, 2H, $C\underline{H}_2CO_2H$), 2.90-3.28 (m, 2H, $SC\underline{H}_2$), 3.44-3.96 (m, 2H, $NC\underline{H}_2$), 4.18-4.50 (m, 1H, $\underline{H}$-6); m/z : 241 (M^+, 4%), 197 (M^+-44, 70%), [Found: C, 49.80; H, 4.58; N, 5.78 calculated for $C_{10}H_{11}NO_4S$ (241.2): C, 49.79;H, 4.60; N, 5.81%].

7-Phenyl-5-oxo-2,3,5,6-tetrahydro-1H-pyrrolo[1,2,-*a*]-imidazole-6-acetic acid (60d) was obtained as a colourlees solid (MeOH); m.p. 198°C; yield, 82%; I.R. (KBr):ν_{max} = 3258, 1718, 1580, 1620 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=2.59-2.80 (m, 2H, $C\underline{H}_2CO_2H$), 3.43-4.-4 [m, 5H, $N(C\underline{H}_2)_2$ and $\underline{H}$-6], 7.35 (s, $5H_{arom}$), 9.55 (brs, 1H, $O\underline{H}$, exchangeable with D_2O); m/z : 268 (M^+-18, 10%), 242 (M^+-44.5%) , [Found: C, 62.70; H, 4.71; N, 9.90 calculated for $C_{15}H_{14}N_2O_4$ (286.2): C, 62.92; H, 4.93; N, 9.78%].

7-(4-Chlorophenyl)-5-oxo-2,3,5,6-tetrahydro-1H-pyrrolo-[1,2-a] imidazole-6-acetic acid (60e) was obtained as a colourless solid (MeOH); m.p. 150°C; yield, 87%; I.R. (KBr): ν_{max} = 3265, 1735, 1712, 1639 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=2.28-2.81 (m, 2H, $C\underline{H}_2CO_2H$), 3.38-4.12 [m,5H, $N(C\underline{H}_2)_2$ and $\underline{H}$-6], 7.23-7.61 (2d, J=Hz, each $4H_{arom}$), 7.97 (brs, 1H, O$\underline{H}$ exchangeable with D_2O); m/z : 304 (1%), 302 (M^+-18.5%), 278 (6%), 276 (M^+-44,2%), [Found: C, 56.30; H, 4.22; N, 8.6 calculated for $C_{15}H_{13}N_2O_4$ (320.7): C, 56.16;H, 4.08; N, 8.74%].

7-(4-Methoxyphenyl)-5-oxo-2,3,5,6-tetrahydro-1H-pyrrolo-[1,2-a] imidazole-6-acetic acid (60f) was obtained as a colourless solid (MeOH); m.p. 168°C; yield, 88%; I.R. (KBr): ν_{max} = 3222, 1708, 1691, 1629 cm^{-1}; ^1H n.m.r.(DMSO-$_6$): δ=2.56-2.78 (m,2H, $C\underline{H}_2CO_2H$), 3.48-4.15 [m, 5H, $N(C\underline{H}_2)_2$ and $\underline{H}$-6], 3.77 (s, 3H, $OC\underline{H}_3$), 6.88 (d, J=9Hz, A_2B_2, $2H_{arom}$), 7.35 (d, J=9Hz, A_2B_2, $2H_{arom}$), 9.50 (brs, 1H, O$\underline{H}$, exchangeable with D_2O); ^{13}C n.m.r. (DMSO-d_6): δ = 34.61 ($\underline{C}H_2CO_2H$), 41.49, 42.43 (C-2, C-3), 48.64 (C-6), 55.05 (OCH_3), 83.95 (C-7), 113.16 (C-3'), C-5'), 128.42 (C-2', C-6'), 134.21 (C-1'), 156.35 (C-7a), 159.86 (C-4') 167.40 (CO_2H), 174.99 (C-5), 189.30 ($COC_6H_4OCH_3$); m/z : 298 (M^+-18,2%), [Found: C, 60.90; H, 5.00; N, 8.98 calculated for $C_{16}H_{16}N_2O_5$ (316.4) : C, 60.75; H, 5.10; N, 8.86%].

1-Phenyl-4-aroyl-2-oxo-5-phenylimino-3-pyrroline-3-acetic acid 65a-b : General Procedure: A solution of the α-oxoketene N,N-acetal 64 (20 mmol) and maleic anhydride

(20 mmol) in acetonitrile (30 ml) is refluxed for 2 hours. The reaction mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give the crude products which are further purified by crystallization from methanol and their structures were confirmed from their spectral and analytical data which are given below.

1-Phenyl-4-benzoyl-2-oxo-5-phenyliminopyrrolidin-3-acetic acid (65a) was obtained as a colourless crystalline solid (MeOH); m.p. 210°C; yield, 89%; I.R. (KBr):ν_{max} = 1738, 1720, 1660, 1635, 1590 cm^{-1}; ^1H n.m.r.(DMSO-d_6): δ = 2.70-3.08 (m, 3H, C<u>H</u>C<u>H</u>$_2$), 4.89 (d, J=3Hz, 1H, C<u>H</u>), 5.60 (brs, 1H, O<u>H</u> exchangeable with D_2O), 6.38-6.58 (m, 15H_{arom}); m/z : 412 (M^+, 36%), 307 (M^+-105,30%), [Found: C, 72.65; H, 4.71; N, 6.69 calculated for $C_{25}H_{20}N_2O_4$ (412.4): C, 72.80; H, 4.89; N, 6.79%].

1-Phenyl-4-(4-methylbenzoyl)-2-oxo-5-phenyliminopyrrolidin-3-acetic acid (65b) was obtained as a colourless crystalline solid (MeOH); m.p. 203°C; yield, 87%; I.R.(KBr):ν_{max} = 3432, 1766, 1739, 1668, 1642, 1593 cm^{-1}; ^1H n.m.r. (DMSO-d_6) : δ = 2.32 (s, 3H, C<u>H</u>$_3$), 2.86 (d, J=6Hz, 2H, C<u>H</u>$_2$), 3.20 (m, 1H, C<u>H</u>CH$_2$), 5.50 (d, J=3Hz, 1H, C<u>H</u>CO), 6.44-7.55 (m, 15H_{arom}); ^{13}C n.m.r. (DMSO-d_6); δ = 20.93 (<u>C</u>H$_3$), 34.34 (<u>C</u>H$_2$CO$_2$H), 120.59 (C-3), 122.87 (C-4), 127.54, 127.94, 128.19, 128.44, 128.67, 128.75 (aromatic CH carbons), 132.79 (C-1' of $COC_6H_4CH_3$), 134.14 (2C-1' of

N-phenyl), 143.85 (2C-4' of N-phenyl), 147.82 (C-4' of $COC_6H_4OCH_3$), 157.96 (C-5), 172.05 (CO_2H), 175.93 (C-2), 196.22 ($COC_6H_4OCH_3$); m/z : 426 (M^+, 47%), 307 (37%), [Found: C, 73.21; H, 5.10; N, 6.47 calculated for $C_{26}H_{22}N_2O_4$ (426.5): C, 73.21; H, 5.20; N, 6.57%].

1-Alkyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin -3-acetamides 66a-b: General Procedure:

A solution of the α-oxoketene S,N-acetal 52 (20 mmol) and maleimide 6 (20 mmol) in acetonitrile (30 ml) is refluxed for 2 hours. The reaction mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give the crude acetamides 66 which are further purified by column chromatography over silica gel using hexane/ethylacetate (9:1) as eluent and their structures were confirmed from their spectral analytical data which are given below.

1-Ethyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetamide (66a) was obtained as a colourless solid (MeOH); m.p. 158°C; yield, 85%; I.R.(KBr):ν_{max} = 3168, 1678, 1650, 1625 cm^{-1}, ^1H n.m.r. (DMSO-d_6): δ = 1.20 (t, J=3Hz, $CH_2C\underline{H}_3$), 1.71 (s, 3H, $SC\underline{H}_3$), 3.23 (s, 2H, $C\underline{H}_2CO$), 3.15-3.63 (dq, J=17, 7Hz, 1H, H_A of $C\underline{H}_2CH_3$), 5.56 (s, 1H, $\underline{H}$-5), 6.60, 7.22 (2 brs, 1H each, $N\underline{H}_2$ exchangeable with D_2O), 7.38-8.13 (m, $5H_{arom}$); m/z : 318 (M^+, 11%), 228 (M^+-90,100%), [Found: C, 60.15; H, 4.85; N, 8.60 calculated for $C_{16}H_{18}N_2O_3S$ (318.4): C, 60.35; H, 4.93; N, 8.80%].

1-Methyl-4-benzoyl-5-methylthio-2-oxo-3-pyrrolin-3-acetamide (66b) was obtained as a colourless solid (MeOH); m.p. 156°C; yield, 88%; I.R.(KBr): ν_{max} = 3360, 3170, 1680, 1650, 1624 cm^{-1}; ^1H n.m.r.(DMSO-d_6): δ=1.73 (s, 3H, $SC\underline{H}_3$), 3.03 (s, 3H, $NC\underline{H}_3$), 3.33 (s, 2H, $C\underline{H}_2$), 5.37 (s, 1H, $\underline{H}$-5), 6.00, 6.80 (2brs, 1H, each $N\underline{H}_2$ exchangeable with D_2O), 7.37-7.68 (m, $3H_{arom}$), 7.84-8.03 (m, $2H_{arom}$); m/z : 304 (M^+, 9%), 257 (19%), 214 (100%), [Found: C, 59.00; H, 5.20; N, 9.00 calculated for $C_{15}H_{16}N_2O_3S$ (304.4): C, 59.18; H, 5.30; N, 9.20%].

2-Alkyl-3-methylthio-4-phenyl-6-dioxo-2,3,5,6-tetrahydro-5H-pyrrolo [3,4-*c*] pyridines 67a-b; General Procedure:

A solution of the α-oxoketene S,N-acetal 52 (20 mmol) and maleimide 6 (20 mmol) in acetonitrile (30 ml) is refluxed for 8 hours. The reaction mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give crude pyrrolopyridines 67 which were further purified by crystallization from methanol and their structures were confirmed from their spectral and analytical data which are given below.

2-Ethyl-3-methylthio-4-phenyl-2,6-dioxo-2,3,6-tetrahydro-5H-pyrrolo[3,4-*c*]pyridine (67a) was obtained as a colourless solid (MeOH); m.p. 218°C; yield, 82%; I.R. (KBr): ν_{max} = 1684, 1660, 1625 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ =1.24 (t, 3H, J=7Hz, $CH_2C\underline{H}_3$), 1.38 (s, 3H, $SC\underline{H}_3$), 3.41

(dq, J=17,7Hz, H_A of $C\underline{H}_2$), 3.90 (dq, J=17, 7Hz, H_B of $C\underline{H}_2$), 5.70 (s, 1H, $\underline{H}$-3), 6.85 (s, 1H, $\underline{H}$-7), 7.58 (brs, $5H_{arom}$); m/z : 253 (M^+-47, 100%), 225 (26%), [Found: C, 63.97; H, 5.31; N, 9.01 Calculated for $C_{16}H_{16}N_2O_2S$ (300.4): C, 63.97; H, 5.37; N,. 9.35%].

2-Methyl-3-methylthio-4-phenyl-1,6-dioxo-2,3,5,6-tetrahydro-5H-pyrrolo[3,4-*c*]pyridine (67b) was obtained as a colourless crystalline solid (MeOH); m.p. 249°C; yield, 70%; I.R. (KBr):ν_{max} = 1685, 1660, 1623 cm^{-1}; ^1H n.m.r.(DMSO-d_6): δ = 1.33 (s, 3H, $SC\underline{H}_3$), 3.04 (s, 3H, $C\underline{H}_3$), 6.07 (s, 1H, $\underline{H}$-3), 6.63 (s, 1H, $\underline{H}$-7), 7.38-7.78 (m, $5H_{arom}$), 11.88 (brs, 1H, N$\underline{H}$ exchangeable with D_2O); m/z : 239 (M^+-47, 100%), [Found: C, 62.93; H, 4.92; N, 9.81 calculated for $C_{15}H_{14}N_2O_2S$ (286.4): C, 62.90; H, 4.93; N, 9.78%].

1-Phenyl-4-benzoyl-2-oxo-5-phenylamino-4-pyrrolin-3-acetamide (68): Typical Procedure:

A solution of the α-oxoketene N,N-acetal 64 (20 mmol) and maleimide (20 mmol) in acetonitrile (30 ml) is refluxed for 2 hours. The reaction mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give the crude product which is purified by crystallization from methanol and its structure was confirmed from its spectral and analytical data which are given below.

The 68 was obtained as a colourless crystalline solid (MeOH); m.p. 261°C; yield, 88%; I.R.(KBr): ν_{max} = 3315, 1751, 1658, 1594 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ = 2.40 (d, J=3Hz, 2H, $C\underline{H}_2$), 2.65 (m, 1H, $C\underline{H}CH_2$), 5.03 (d, J=6Hz, 1H, $C\underline{H}CO$), 6.36-7.53 (m, $15H_{arom}$); m/z : 411 (M^+, 25%), 306 (M^+-105, 11%), [Found: C, 72.98; H, 5.15; N, 10.20 calculated for $C_{25}H_{21}N_3O_3$ (411.4): C, 72.98; H, 5.15; N, 10.21%].

7-Benzoyl-5-oxo-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-*a*]imidazole-6-acetamide (69) : Typical Procedure:

A solution of the cyclic α-oxoketene N,N-acetal 59d (20 mmol) and maleimide (20 mmol) in acetonitrile (30 ml) is refluxed for 2 hours. The reaction mixture is then cooled, poured into ice water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate, evaporated to give the crude product which is purified by crystallization from methanol and its structure was confirmed by its spectral and analytical data which are given below.

The 69 was obtained as a colourless crystalline solid (MeOH); m.p. 201°C; yield, 87%; I.R.(KBr) = ν_{max} = 1682, 1670, 1629 cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ = 2.33-2.67 (m, 3H, $C\underline{H}CH_2$), 3.01-3.72 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 6.73 (brs, 1H, $N\underline{H}$, exchangeable with D_2O), 7.27 (s, $5H_{arom}$); m/z : 285 (M^+, 3%), 241 (M^+-44,11%), [Found: C, 63.00; H, 5.35; N, 14.62 calculated for $C_{15}H_{15}N_3O_3$ (285.3): C, 63.14; H, 5.30; N, 14.73%].

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CHAPTER III

A. REACTION OF POLARIZED KETENE S,N-ACETALS WITH BROMOACETALDEHYDE DIETHYLACETAL: SYNTHESIS OF NOVEL 3-ACYL/NITRO-2-METHYLTHIO-1-SUBSTITUTED AND 1,2-ANNELATED PYRROLES.*

B. REACTION OF POLARIZED KETENE S,N-ACETALS WITH PROPARGYL BROMIDE: SYNTHESIS OF NOVEL 3-ACYL/NITRO-2-METHYLTHIO-5-METHYL-1-SUBSTITUTED AND 1,2-ANNELATED PYRROLES.

INTRODUCTION

The presence of pyrrole ring in haem and chlorophyll was known as early as 1868[1]. This finding created immense interest in the isolation of pyrrole and its derivatives

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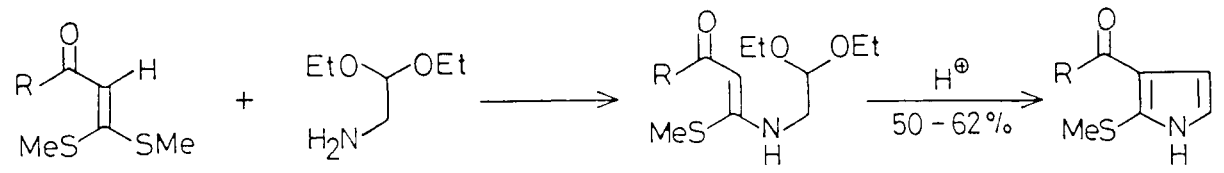
from many natural sources. Interest in the synthetic aspects of pyrrole gained importance only in the later part of this century. Much work has been done in the recent past, and the chemistry of these compounds has been reviewed[3-16]. A number of methods have been reported for the synthesis of pyrroles but the methods for 3-nitro-substituted pyrroles from acyclic precurssors have been few in number. Most of these derivatives of pyrrole have been synthesized by electrophilic substituion which require drastic reaction conditions often leading to a mixture of isomers or polysubstituted pyrroles. As a part of our programmed studies on polarized α-oxoketene S,N-acetals it was considered of interest to explore the possibilities to synthesize novel heterocycles by reacting the S,N-acetals with various 1,2- and 1,3-electrophilic species. Some of the important applications of these synthons have been discussed in the first chapter. In the second chapter, a novel method for the synthesis of various heterocycles has been developed. We now report a new route to synthesize various pyrroles by reacting the polarized ketene S,N-acetals with bromoacetaldehyde diethyl acetal and propargyl bromide. This method will certainly be a potential synthetic tool to prepare substituted pyrroles from open chain precurssors.

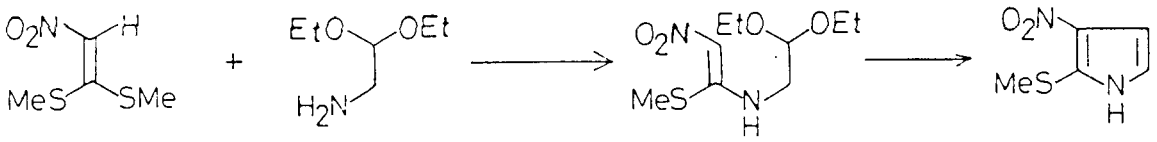
A. Reaction of the polarised ketene S,N-acetals with bromoacetaldehyde diethylacetal:

In our earlier communication[17] a general method was developed for the synthesis of 2-methylthio-3-acylpyrroles

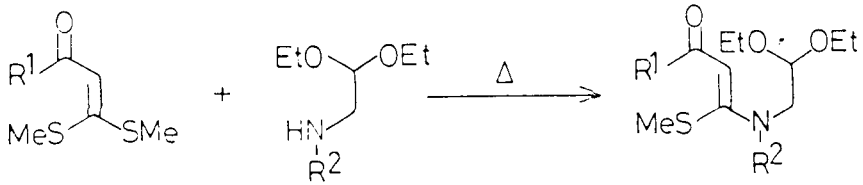


1 2 3 4

R = C_6H_5 , 4-MeC_6H_4 , 4-$MeOC_6H_4$, 4-$EtOC_6H_4$, 4-ClC_6H_4 , 4-BrC_6H_4 ; Me



5 2 6 7



1 8 9

R^2 = Me , Et , C_6H_5

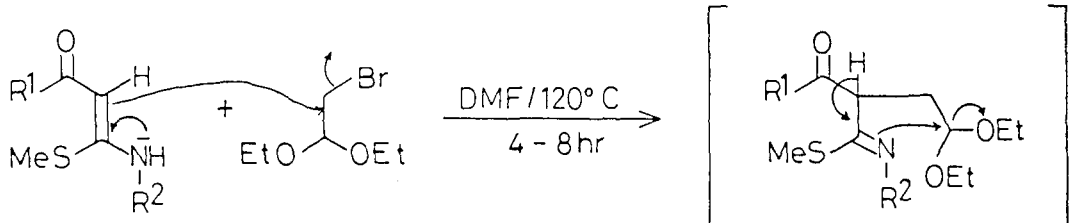
Scheme - 1

4 by reacting α-oxoketene S,S-acetals 1 with aminoacetaldehyde diethylacetal 2 to yield the corresponding S,N-acetal 3 followed by cyclization in the presence of ethereal hydrochloric acid (Scheme 1). Similarly, the nitroketene S,S-acetal 5 was reacted with 2 to afford the corresponding S,N-acetal 6 in 62% yield which underwent cyclization in the presence of the ethereal hydrochloric acid to afford the corresponding 3-nitro-2-methylthiopyrrole 7 in 55% yield (Scheme 1). This method was of particular use for the synthesis of 3-acyl/nitropyrroles since the acylation or nitration of pyrrole generally affords a mixture of isomeric nitropyrroles and polynitropyrroles. Further, when this method was extended to synthesize the corresponding N-substituted pyrroles by reacting the polarized ketene S,S-acetals with appropriately N-substituted aminoacetaldehyde diethylacetals 8, the corresponding S,N-acetals 9 were obtained consistently in poor yields particularly when the substituents on nitrogen were higher alkyl and aryl groups (Scheme 1). This may have been due to steric reasons as well as reduced basicity of the amino group. Thus, the methodology suffered from limitations when extended to the synthesis of N-substituted pyrroles. Thus, an alternative approach for the synthesis of N-alkyl/aryl-2-methylthio-3-acylpyrroles 13 through the reaction of easily accessible polarized ketene S,N-acetals 10 and bromoacetaldehyde diethylacetal 11 was considered appropriate to overcome the above mentioned limitations encountered in the earlier

communication. The results of these investigations have been described in the following section.

RESULTS AND DISCUSSION

In a typical experiment, when the α-oxoketene S,N-acetal 10a derived from acetone and ethylamine was reacted with bromoacetaldehyde diethylacetal 11 in dimethylformamide (DMF) at 120°C for 4 hours, the reaction mixture, after work-up and purification, afforded a compound which was characterized as 3-acetyl-1-ethyl-2-methylthiopyrrole 13a in 71% yield (Scheme 2). The structure of 13a was fully established from its spectral and analytical data. Thus, it was analyzed for $C_9H_{13}NOS$ (183.3). Its mass spectrum exhibited molecular ion peaks at m/z : 183 (M^+, 94%), 168(93%), 150(100%). Its I.R. (Neat) spectrum showed a strong absorption band at ν_{max} = 1669 cm^{-1}. Its structure was further confirmed from its ^1H n.m.r. ($CDCl_3$) spectrum. The triplet at δ 1.37 (3H, J=7Hz) was assigned to the methyl protons of the N-ethyl group. The singlet at δ2.37 (3H) was due to the thiomethyl group. The acetyl protons appeared as a singlet at δ2.43 (3H). The quartet at δ 4.13 (2H, J=7Hz) was assigned to the methylene protons of N-ethyl group. The doublets at δ 6.53 (1H, J=3Hz) and 6.67 (1H, J=3Hz) were due to H-4 and H-5 protons respectively. Similarly, the other α-oxoketene S,N-acetals 10b-i also reacted with 11 to afford the corresponding 3-acyl-2-methylthio-1-alkyl/arylpyrroles



10 a-i 11 12

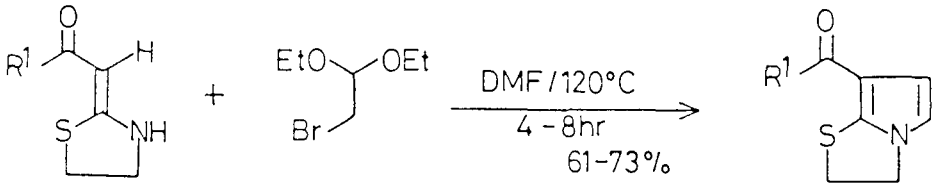
10	R^1	R^2		R^1	R^2
a	Me	Et	f	4-ClC_6H_4	i-Pr
b	Me	$PhCH_2$	g	Ph	n-Bu
c	Ph	Me	h	Ph	Ph
d	Ph	Et	i	Ph	$PhCH_2$
e	Ph	n-Pr			

13 a-i

Scheme - 2

13b-i in 62-85% overall yields (Scheme 2). The structures of 13b-i were fully established from their spectral and analytical data which are described in the experimental section.

The cyclic α-oxoketene S,N-acetals 14a-c were considered of interest since they could yield the corresponding 1,2-annelated pyrroles 15. Thus, when 14a was reacted with 11 in DMF at 120°C for 6 hours, the reaction mixture, after work-up and purification, afforded a compound which was characterized as 7-acetyl-2,3-dihydropyrrolo[2,1-*b*]-thiazole 15a (Scheme 3). The structure of 15a was fully established from its spectral and analytical data. Thus it was analyzed for C_8H_9NOS (167.2). Its mass spectrum showed molecular ion peaks at m/z : 129 (42%), 109(58%), 43(64%). Its I.R. (KBr) spectrum showed absorption bands at ν_{max} = 1708, 1615, 1593 cm^{-1}. Its structure was further confirmed from its ^1H n.m.r. ($CDCl_3$) spectrum. The singlet at δ 2.48 (3H) was assigned to the acetyl protons. The triplet at δ 3.20 (2H, J=7.5Hz) was assigned to the SCH_2 protons and the triplet at δ 4.22 (2H, J=7.5Hz) was due to the NCH_2 protons. The doublets at δ 6.48 (1H, J=3Hz) and 7.13 (1H, J=3Hz) were assigned to the H-6 and H-5 protons respectively. Similarly, the other cyclic S,N-acetals 14b-c were reacted with 11 under identical reaction conditions to afford the corresponding 7-acetyl-2,3-dihydropyrrolo[2,1-*b*]thiazoles 15b-c in 64-73% overall yields. The structures of 15b and 15c were fully established from their spectral and analytical data which



14 a-c 11 15 a-c

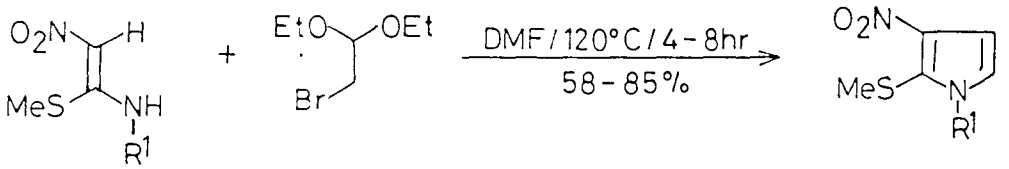
a, R^1 = Me
b, R^1 = 4-ClC_6H_4
c, R^1 = Ph

Scheme-3

are given in the experimental section.

The reaction of nitroketene S,N-acetals 16a-c with 11 was next investigated. Thus, when 16a was reacted with 11 in DMF at 120°C for 4 hours, the reaction mixture, after work-up and purification, afforded a compound which was characterized as 1-ethyl-2-methylthio-3-nitropyrrole 17a in 58% yield (Scheme 4) on the basis of its spectral and analytical data. Thus it was analyzed for $C_7H_{10}N_2O_2S$ (186.2). Its mass spectrum showed molecular ion peaks at m/z : 186 (M^+, 100%), 139 (71%), 110 (22%). Its I.R.(KBr) spectrum exhibited bands at ν_{max} = 1600 and 1540 cm^{-1}. The structure of 17a was further confirmed from its ^1H n.m.r.($CDCl_3$) spectrum. The triplet at δ 1.35 (3H, J=7Hz) was assigned to the methyl of N-ethyl group. The singlet at δ6.79 (2H) was due to the H-4 and H-5 protons. The other nitropyrroles 17b-c were similarly obtained in 63-77% overall yields by reacting the corresponding S,N-acetals 16b-c with 11 (Scheme 4). The structures of 17b-c were fully in accordance with their spectral and analytical data which are given in the experimental section.

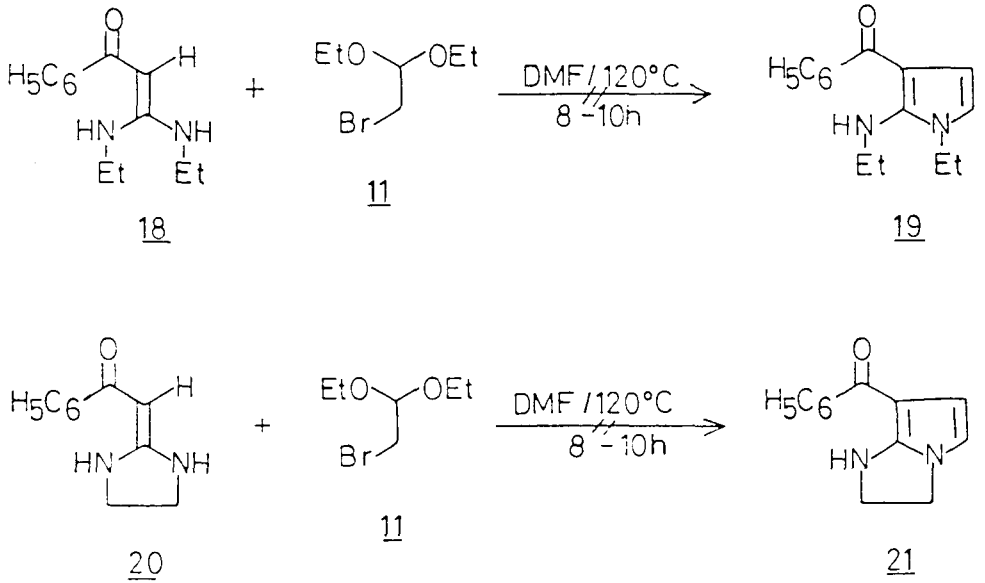
However, the α-oxoketene N,N-acetal 18 and the cyclic α-oxoketene N,N-acetal 20 did not yield the corresponding pyrroles 19 and 21 (Scheme 5). Similarly, the cyclic nitroketene S,N-acetal 22, cyclic nitroketene N,N-acetal 24 and the nitroketene N,N-acetal 26 also did not react



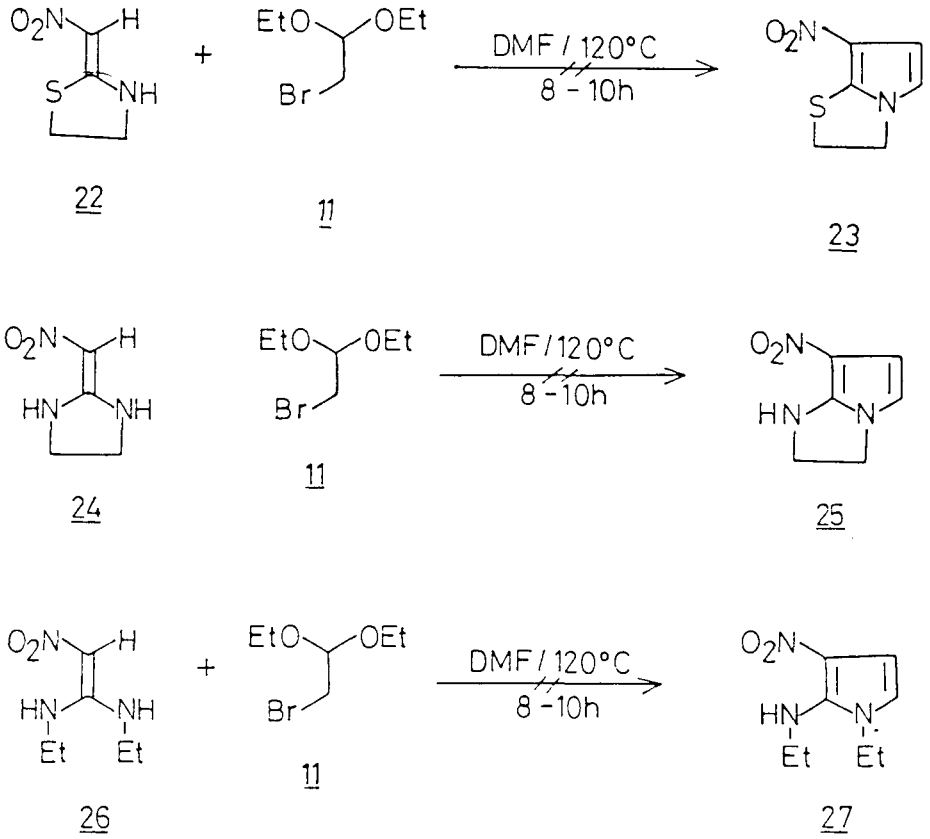
16 a-c 11 17 a-c

a, R^1 = Et
b, R^1 = $PhCH_2$
c, R^1 = Ph

Scheme - 4


O
H5C6
H
HN
NH
Et
Et
18
+
EtO
OEt
Br
11
DMF/120°C
8 -10h
O
H5C6
HN
N
Et
Et
19
O
H5C6
H
HN
NH
20
+
EtO
OEt
Br
11
DMF /120°C
8 -10h
O
H5C6
HN
N
21

Scheme - 5



Scheme - 6

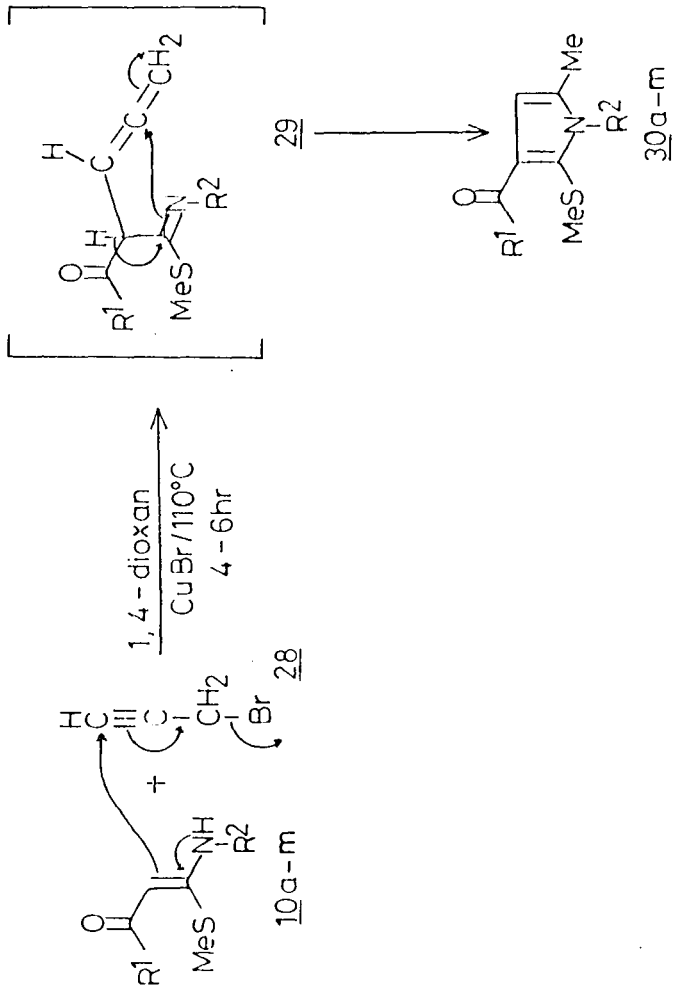
with 11 to yield the corresponding pyrroles 23, 25 or 27 (Scheme 6).

B. Reaction of the polarized ketene S,N-acetals with propargyl bromide:

It has been shown in the previous section that bromoacetaldehyde diethylacetal behaves as two carbon fragment in the synthesis of pyrroles. It was therefore considered to explore the potential of propargyl bromide as two carbon fragment for the synthesis of pyrroles from the corresponding S,N-acetals. These investigations have been discussed in the following section.

RESULTS AND DISCUSSION

In a typical experiment, when the α-oxoketene S,N-acetal 10c was reacted with propargyl bromide 28 in the presence of Cu(I)Br in 1,4-dioxane at 110°C for 6 hours, the reaction mixture, after work-up and purification, afforded a compound which was characterized as 1,5-dimethyl-3-benzoyl-2-methylthiopyrrole 30c (Scheme 7). The structure of 30c was fully established from its spectral and analytical data. Thus, it was analyzed for $C_{14}H_{15}NOS$ (245.3). Its mass spectrum showed molecular ion peaks at m/z : 245 (M^+, 100%), 230 (41%), 212 (65%). Its I.R.(neat) spectrum showed band at ν_{max} = 1638 cm^{-1}. Its structure was further confirmed from its ^1H n.m.r.($CDCl_3$) spectrum. Thus the singlet at δ 2.20 (3H) was assigned to the 5-methyl group. The singlet at δ 2.20 (3H) was due to



Scheme – 7

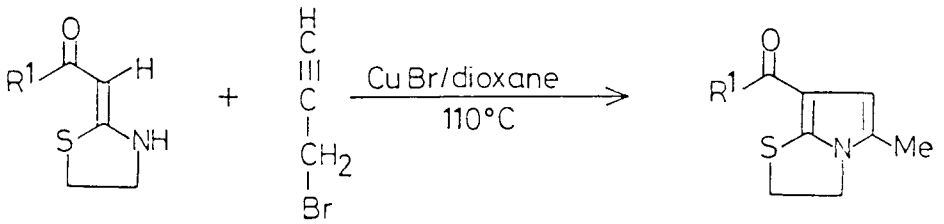
TABLE

10	R^1	R^2
a	R^1 = Me	R^2 = Et
b	R^1 = Me	R^2 = $PhCH_2$
c	R^1 = Ph	R^2 = Me
d	R^1 = Ph	R^2 = Et
e	R^1 = Ph	R^2 = n-Pr
f	R^1 = 4-ClC_6H_4	R^2 = i-Pr
g	R^1 = Ph	R^2 = n-Bu
h	R^1 = Ph	R^2 = Ph
j	R^1 = 4-MeC_6H_4	R^2 = Me
k	R^1 = 4-ClC_6H_4	R^2 = Et
l	R^1 = 4-MeC_6H_4	R^2 = $PhCH_2$
m	R^1 = Ph-	R^2 = $CyClOC_6H_{11}$

the thiomethyl group. Another singlet at δ 3.62 (3H) was due to the N-methyl group. The singlet at δ 6.03 (1H) was assigned to H-4 proton. The multiplet around δ 7.30-7.47 (3H) was due to the aromatic protons and another multiplet around δ 7.67-7.83 (2H) was due to the remaining aromatic protons. The other pyrroles 30a-b and 30d-m were similarly prepared by reacting the corresponding α-oxoketene S,N-acetals 10a-b and 10d-m with 28 in identical reaction conditions (Scheme 7). The structures of all these pyrroles were fully established from their spectral and analytical data which are given in the experimental section. The cyclic α-oxoketene S,N-acetals 14a-c also reacted with 28 under identical conditions to afford the corresponding 2,3-dihydropyrrolo[2,1-*b*]thiazoles 31a-c in 57-65% overall yields (Scheme 8). Their structures were fully established from their spectral and analytical data which are given in the experimental section.

The reaction of the nitroketene S,N-acetals 16 with 28 was next investigated. Thus, when 16a and 16b were reacted with 28 under identical conditions the corresponding 3-nitropyrroles 32a and 32b were obtained in 57 and 81% yields respectively (Scheme 9). The structures of the 32a and 32b were fully established from their spectral and analytical data which are given in the experimental section.

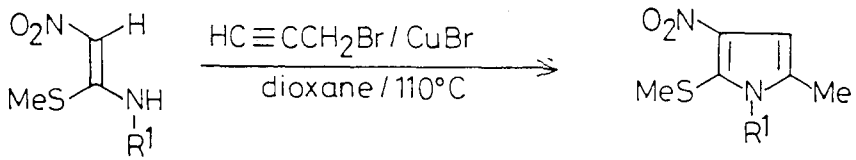
Interestingly, the α-oxoketene N,N-acetal 18 and the corresponding cyclic N,N-acetal 20 did not yield the



14 a-c 28 31 a-c

a, R^1 = Me
b, R^1 = Ph
c, R^1 = 4-ClC_6H_4

Scheme-8



16 a-b

a, R^1 = Et
b, R^1 = $PhCH_2$

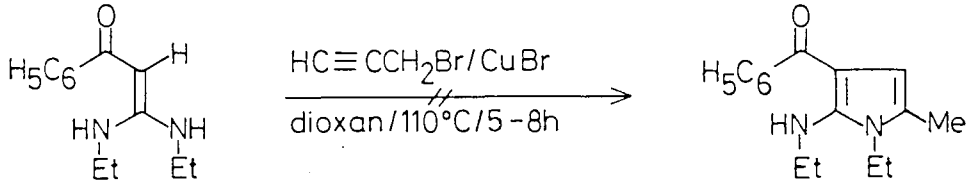
32 a-b

Scheme - 9

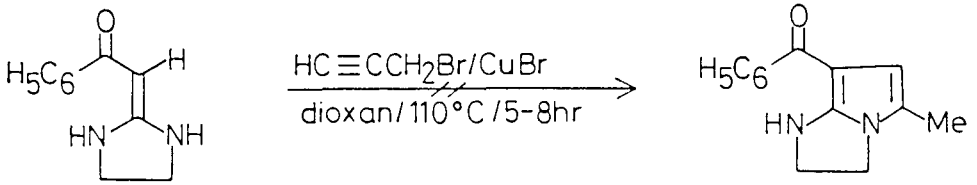
corresponding pyrroles 33 and 34 (Scheme 10). Similarly, the nitroketene S,N-acetal 22, N,N-acetal 24 and acyclic N,N-acetal 26 did not react with 28 to yield the corresponding nitropyrroles 35, 36 and 37 (Scheme 11).

Mechanistic Aspect

The mechanisms governing the reaction of the polarized ketene S,N-acetals with bromoacetaldehyde diethylacetal and propargyl bromide are in accordance with the reactivity pattern of enamines with electrophilic species. Thus, the polarized ketene S,N-acetals first undergo C-alkylation to give the intermediate 12 with bromoacetaldehyde diethylacetal followed by intramolecular cyclization as shown in scheme 2 with simultaneous elimination of ethanol to give the product pyrroles. The enamine behaviour of the polarized ketene S,N-acetals is best manifested in their reaction with propargyl bromide. The various possible paths are shown in scheme 12. Path-A and Path-B are ruled out since they would yield the pyrroles 39 which have a methyl group at 4 position. Path-C looks less probable because the intermediate 41, thus formed, will be less stable than the other intermediate 29 formed by Path-D since the allenic functionality is known to form from the rearrangement of the propargyl functionality. Moreover, Cu(I)Br (a Lewis acid) complexes with the electrons of the triple bond making C-1 carbon of propargyl bromide more electrophilic. Thus, Path-D appears to be the most probable one. Therefore, the

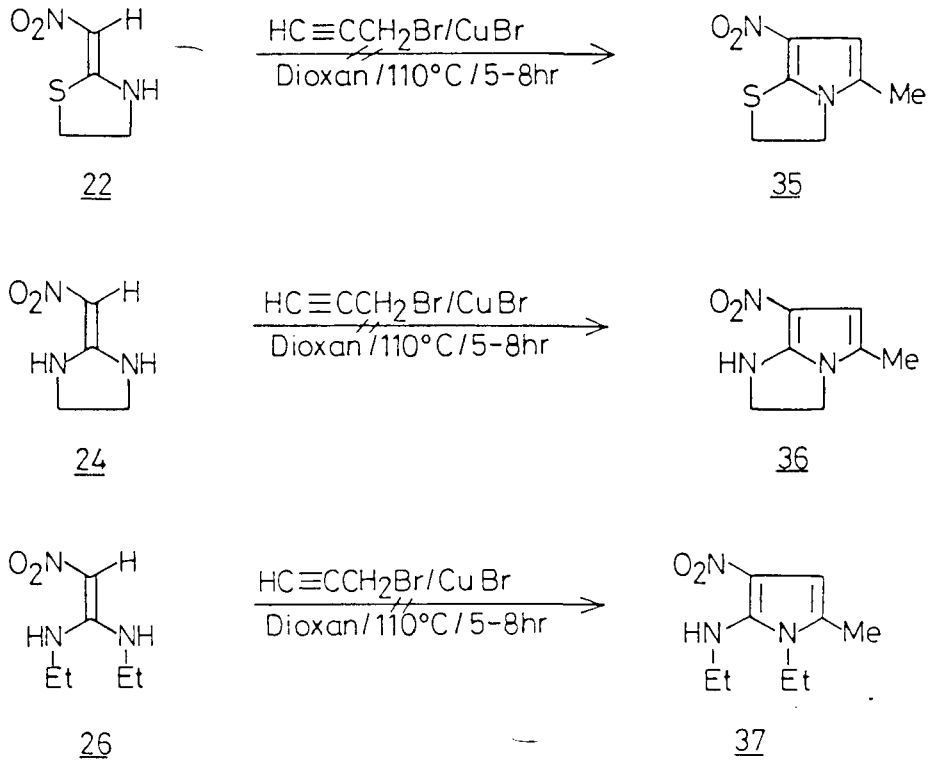


18 33

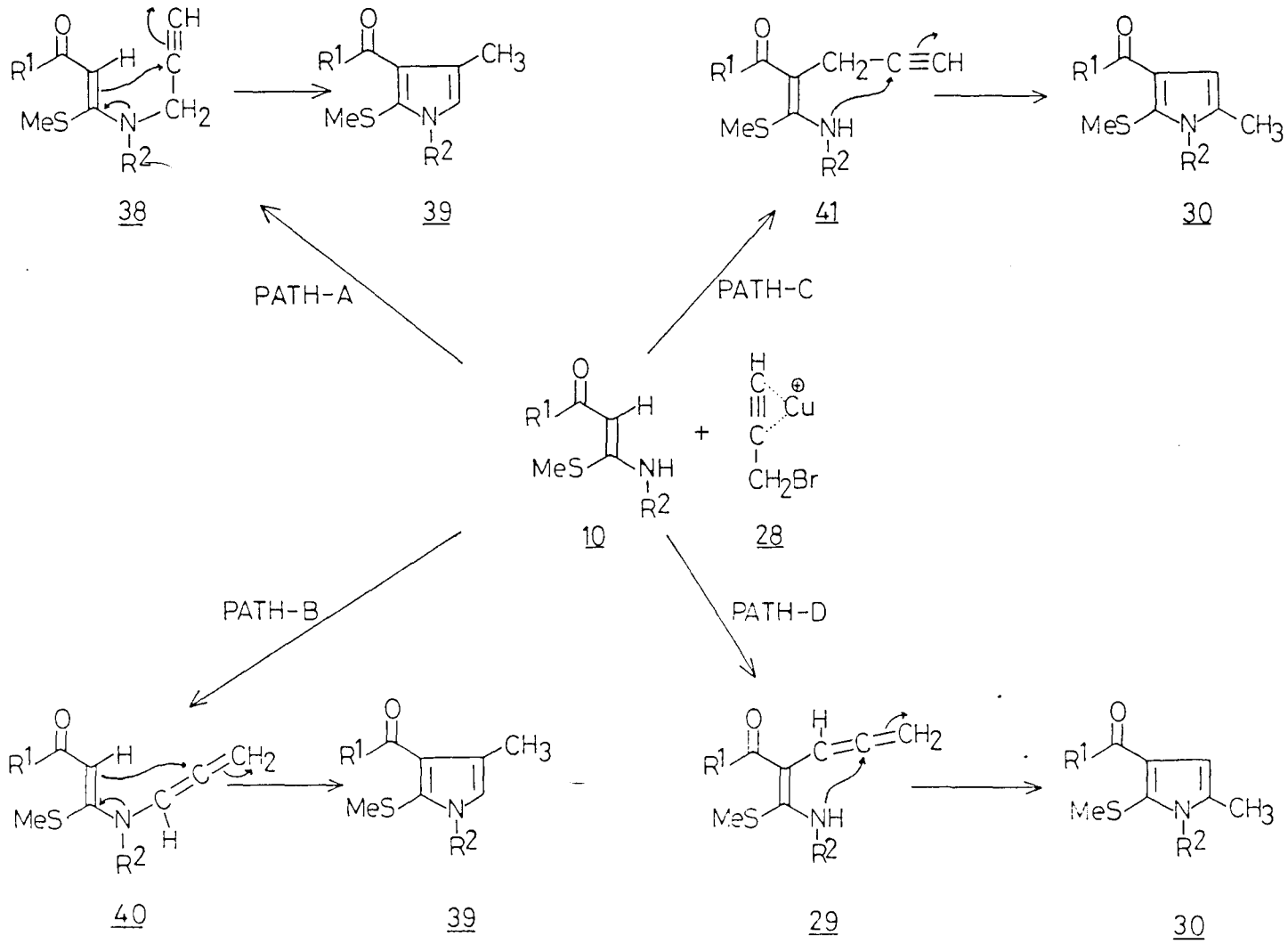


20 34

Scheme-10


O2N
H
S
NH
HC≡CCH2Br/CuBr
Dioxan/110°C/5-8hr
Me
HN
Et
22
35
24
36
26
37

Scheme -11



Scheme - 12

enamine behaviour of the S,N-acetals is in accord with their reactivity. The position of the methyl group in 30 was ascertained by the comparison of the chemical shift values of the methyl group and H-4 proton[12,13] with those reported for the similar systems.

CONCLUSION

It is apparent that the method is found to be very useful for the synthesis of N-substituted pyrroles in improved yields. Moreover, the synthesis of 1,2-annelated pyrroles is very important since easily accessible starting materials and simple reaction conditions have been employed. Most important is the synthesis of the 3-nitro and 3-acyl pyrroles since electrophilic substitutions on pyrroles are less compatible to introduce substituents at 3-& 4-positions unless 2-and 5-positions are blocked[14-16]. The 3-nitropyrroles may find use in the field of medicine as many nitropyrroles are used as antiviral and antibacterial agents.

EXPERIMENTAL

General: Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The I.R. spectra were recorded on a Perkin Elmer -297 spectrometer and frequencies are expressed in cm^{-1}. The ^{1}H n.m.r. spectra were recorded on a Varian EM 390 (90 MHz) spectrometer using tetramethylsilane as

internal standard and the chemical shifts are expressed as δ(ppm) down field from TMS. The mass spectra were recorded on a Jeol D-300 spectrometer and relative intensities are expressed in percentage. Carbon, Hydrogen and Nitrogen elemental analyses were done on Heraeus CHN-O-RAPID instrument.

STARTING MATERIALS:

The commercial samples of various acetophenones, acetone, amines, aziridine, dioxane, ethanol, DMF etc., were purified before use. Phenylisothiocyanate, isopropyl-isothiocyanate and cyclohexylisothiocyanate were prepared according to the reported procedure[18,19]. Commercially available bromoacetaldehyde diethylacetal (ALDRICH), propargyl bromide (ALDRICH) and cuprous bromide [Cu(I)Br] were used as such.

The known α-oxoketene S,N-acetals 10a-d and 10h-l were prepared according to the reported procedure[20,21] and their spectral and analytical data were found to be similar to the reported ones. The unknown α-oxoketene S,N-acetals 10e-g, 10m were prepared by extending the reported procedure[20] and their structures were fully established from their spectral and analytical data which are given below.

3-Methylthio-3-propylamino-1-phenyl-2-propene-1-one (10e) was obtained as a red oil; yield 92%; I.R. (Neat): ν_{max} = 1588, 1567, 1495 cm^{-1}; ^1H n.m.r. (CCl_4): δ =1.00 (t, J =

6Hz, 3H, $C\underline{H}_3$), 1.68 (distorted sext., J=6Hz, 2H, $NCH_2C\underline{H}_2CH_3$), 2.35 (s, 3H, $SC\underline{H}_3$), 3.27 (t, J = 6Hz, 2H, $NC\underline{H}_2$), 5.57 (s, 1H, vinylic), 7.23-7.43 (m, $3H_{arom}$), 7.73-8.00 (m, $2H_{arom}$), 11.83 (brs, 1H, $N\underline{H}$, exchangeable with D_2O), [Found: C, 66.21; H, 7.35; N, 6.05 calculated for $C_{13}H_{17}NOS$ (235.3): C, 66.43; H, 7.28; N, 5.95%].

3-Methylthio-3-isopropylamino-1-(4-chlorophenyl)-2-propene-1-one (10f) was obtained as a red oil ; yield, 82%; I.R.(Neat): ν_{max} = 1711, 1585, 1563, 1536 cm^{-1}; ^1H n.m.r. (CCl_4): δ= 1.30 (d, J= 6Hz, 6H, $CH(C\underline{H}_3)_2$, 2.38 (s, 3H, $SC\underline{H}_3$), 3.85 (distorted hept. J = 6Hz, 1H, $C\underline{H}$), 5.39 (s, 1H, vinylic), 7.30 (d, J=7Hz, A_2B_2, $2H_{arom}$), 11.97 (brs, 1H, $N\underline{H}$, exchangeable with D_2O), [Found: C,57.99; H, 6.10; N, 5.30 Calculated for $C_{13}H_{16}NOSCl$ (269.7): C,57.87; H, 5.98; N, 5.19%].

3-Methylthio-3-butylamino-1-phenyl-2-propene-1-one (10g) was obtained as a yellow solid (benzene/hexane); m.p. 45-46°C; yield 89%; I.R.(KBr): ν_{max} = 3415, 1568, 1470 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.98 (t, J = 6Hz, 3H, $C\underline{H}_3CH_2CH_2CH_2$),1.22-1.71 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2CH_2N$), 2.34 (s, 3H, $SC\underline{H}_3$), 3.29 (q, J=6Hz, 2H, $NC\underline{H}_2$), 5.50 (s, 1H, vinylic), 7.00-7.70 (m, $5H_{arom}$), 11.91 (brt, 1H, $N\underline{H}$, exchangeable with D_2O), [Found: C,68.05; H, 7.91; N, 5.72 calculated for $C_{14}H_{19}NOS$(247.3): C, 67.98; H, 7.74; N, 5.66%].

3-Methylthio-3-cyclohexylamino-1-phenyl-2-propene-1-one (10m) was obtained as a yellow solid (benzene/hexane); m.p. 79-80°C; yield, 83%; I.R.(KBr): ν_{max} = 3400, 1540, 1470 cm^{-1}; ^1H n.m.r. (CCl_4): δ=1.15-2.15 (m, 10H, ring $C\underline{H}_2$), 2.45 (s, 3H, $SC\underline{H}_3$), 3.60 (quint., J = 6.5Hz, 1H, C<u>H</u>), 5.51 (s, 1H, vinylic), 7.21-7.47 (m, $3H_{arom}$), 7.68-7.90 (m, $2H_{arom}$), 10.05 (brs, 1H, N<u>H</u>, exchangeable with D_2O); m/z : 275 (M^+, 25%), [Found: C, 69.51; H, 7.83; N, 4.97 Calculated for $C_{16}H_{21}NOS$ (275.4): C, 69.77; H, 7.69; N, 5.09%].

The cyclic α-oxoketene S,N-acetals <u>14a-c</u> were prepared by the modification of reported procedure[22] (given in the previous chapter). The structures of <u>14a</u> and <u>14b</u> were confirmed from their spectral and analytical data which are described in the previous chapter. The spectral and analytical data of <u>14c</u> are given below.

4,5-Dihydro-2-benzoylmethylene thiazole (14c) was obtained as a yellow crystalline solid (DMF/Ethanol); m.p. 159-160°C; yield 68%; I.R.(KBr): ν_{max} = 3190, 1568, 1564 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6): δ=3.27 (t, J = 6Hz, 2H, $SC\underline{H}_2$), 3.95 (t, J = 6Hz, 2H, $NC\underline{H}_2$), 5.94 (s, 1H, vinylic), 7.29-7.54 (m, $3H_{arom}$), 7.73-7.96 (m, $2H_{arom}$), [Found: C, 64.08; H, 5.49; N, 6.71 calculated for $C_{11}H_{11}NOS$ (205.2): C, 64.39; H, 5.37; N, 6.83%].

The α-oxoketene N,N-acetal <u>18</u> was prepared according to the reported procedure [21] and its spectral and analytical data are given below.

1-Phenyl-3,3-bis(N-ethylamino)-1-oxo-2-propene-1-one (18) was obtained as a yellow solid (benzene/hexane); m.p. 76-77°C; yield 77%; I.R.(KBr): ν_{max} = 3400, 3260, 1590 cm^{-1}; ^1H n.m.r. (TFA): δ= 1.23 (t, J = 6Hz, 6H, $NCH_2\underline{CH}_3$), 3.16 (q, J = 6Hz,4H, $NC\underline{H}_2$), 5.10 (s, 1H, vinylic), 6.40 (brs, 1H, N<u>H</u>, exchangeable with D_2O), 7.16-7.43 (m, $3H_{arom}$), 7.56-7.83 (m, $2H_{arom}$), 11.55 (brs, 1H, N<u>H</u>, exchangeable with D_2O), [Found: C, 71.73; H, 7.99; N, 12.58 calculated for $C_{13}H_{18}N_2O$ (218.2) : C, 71.55; H, 8.25; N, 12.84%].

The unknown cyclic α-oxoketene N,N-acetal <u>20</u> was prepared according to the reported procedure and its spectral and analytical data were found to be in conformity with those of the reported ones.

The nitroketene S,N-acetals <u>16a-c</u> were prepared according to the reported procedure[21] and their structures were fully established from their spectral and analytical data which are given below.

1-Nitro-2-methylthio-2-ethylamino-1-ethylene (16a) was obtained as a yellow solid (benzene/hexane); m.p. 61-62°C; yield, 64%; I.R.(Nujol) : ν_{max} = 3170,1560 cm^{-1}; ^1H n.m.r. (CCl_4): δ=1.40 (t, J = 6Hz,3H, $C\underline{H}_3$), 2.52 (s, 3H, $SC\underline{H}_3$), 3.52 (q, J = 6Hz,2H, $C\underline{H}_2$), 6.44 (s, 1H, <u>H</u>-2), 10.73 (brs, 1H, N<u>H</u>, exchangeable with D_2O), [Found: C, 36.72; H, 6.32; N, 17.09 calculated for $C_{15}H_{10}N_2O_2S$ (162.0): C, 37.03; H, 6.17; N, 17.28%].

1-Nitro-2-methylthio-1-ethylene (16b) was obtained as yellow solid (benzene/hexane); m.p. 105-107°C; yield, 89%; I.R. (KBr): ν_{max} = 1460 cm^{-1}; ^1H n.m.r. (CCl_4): δ= 2.43 (s, 3H, $SC\underline{H}_3$), 4.56 (d, J=7Hz, 2H, $NC\underline{H}_2$), 6.33 (s, 1H, vinylic), 7.26 (brs, $5H_{arom}$), 13.25 (brs, 1H, N<u>H</u>, exchangeable with D_2O), [Found: C, 53.10; H, 5.56; N, 12.19 calculated for $C_{10}H_{12}N_2O_2S$ (224.0): C, 53.57; H, 5.36; N, 12.50%].

1-Nitro-2-methylthio-2-anilino-1-ethylene (16c) was obtained as a yellow solid (benzene/hexane); m.p. 147-148°C; yield, 92%; I.R.(KBr): ν_{max} = 1525 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ= 2.35 (s, 3H, $SC\underline{H}_3$), 6.73 (s, 1H, <u>H</u>-2), 7.38 (brs, $5H_{arom}$), 11.80 (brs, 1H, N<u>H</u>, exchangeable with D_2O), [Found: C,55.93; H, 5.30; N, 14.60 Calculated for $C_9H_{10}N_2OS$ (194.2): C, 55.64; H, 5.19; N, 14.42%].

The cyclic nitroketene S,N-acetal <u>22</u>, cyclic N,N-acetal <u>24</u> and acyclic N,N-acetal <u>26</u> were prepared according to the reported procedure and their spectral and analytical data were in conformity with their structures.

Synthesis of 3-acyl/nitro-2-methylthio-1-alkyl/aryl pyrroles <u>13a-i</u>,<u>17a-c</u> and 7-acyl-2,3-dihydropyrrolo [2,1-*b*]-thizoles <u>15a-c</u>:

General Procedure:

A solution of the polarized ketene S,N-acetal <u>10</u>, <u>14</u> or <u>16</u> (10 mmol) and bromoacetaldehyde diethylacetal <u>11</u> (10 mmol) in dry DMF (10 ml) is heated at 120°C for 4-8 hours

(monitored by TLC). The reaction mixture is then cooled, poured into ice cold water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give the crude products 13,15 and 17 which are further purified by column chromatography over silica gel using hexane/ethylacetate (20:1) as eluent. The structures of 13a-i, 15a-c and 17a-c were fully established from their spectral and analytical data which are given below.

1-Ethyl-3-acetyl-2-methylthiopyrrole (13a) was obtained as a viscous red oil; yield, 71%. Its I.R., ^{1}H n.m.r. and mass spectral data are given in the text. [Found: C, 58.71; H, 7.00; N, 7.51 Calculated for $C_9H_{13}NOS$ (183.3): C, 58.97; H, 7.15; N, 7.64%].

1-Benzyl-3-acetayl-2-methylthio pyrrole (13b) was obtained as a viscous red oil; yield, 73%; I.R.(Neat): ν_{max} = 1660 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 2.13 (s, 3H,$COCH_3$), 2.34 (s, 3H, SCH_3), 5.30 (s, 2H, NCH_2), 6.57 (d, J=3Hz, 1H, H-4), 6.76 (d, J=3Hz, 1H, H-5), 6.90-7.35 (m, $5H_{arom}$); m/z : 245 (M^+, 84%), 212 (94%), [Found: C, 58.32; H, 6.35; N, 5.99 calculated for $C_{14}H_{15}NOS$ (245.3): C, 58.54; H, 6.16; N, 5.71%].

1-Methyl-3-benzoyl-2-methylthio pyrrole (13c) was obtained as a colourless solid; m.p. 55-56°C; yield, 80%; I.R. (KBr): ν_{max} = 1625 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ= 2.32 (s, 3H, SCH_3), 3.67 (s, 3H, NCH_3), 6.28 (d, J = 3Hz,1H, H-4), 6.62 (d, J = 3Hz, 1H, H-5), 7.25-7.48 (m, $3H_{arom}$), 7.62-7.83

(m, $2H_{arom}$); m/z : 231(M^+, 83%), 198 (100%), [Found: C, 67.21; H, 5.47; N, 5.85 calculated for $C_{13}H_{13}NOS$ (231.3): C, 67.50; H, 5.66; N, 6.06%].

1-Ethyl-3-benzoyl-2-methylthio pyrrole (13d) was obtained as a colourless solid; m.p. 75-76°C; yield, 71%; I.R.(KBr): ν_{max} = 1629 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 1.38 (t, J=7Hz, 3H, $CH_2C\underline{H}_3$), 2.43 (s, 3H, $SC\underline{H}_3$), 4.16 (q, J = 7Hz, 2H, $C\underline{H}_2CH_3$), 6.32 (d, J = 3Hz, 1H, $\underline{H}$-4), 6.69 (d, J = 3Hz, 1H, $\underline{H}$-5), 7.20-7.45 (m, $3H_{arom}$), 7.60-7.91 (m, $2H_{arom}$); m/z : 245 (M^+,94%), 212 (100%), [Found: C, 58.71; H,6.01; N, 5.98 calculated for $C_{14}H_{15}NOS$ (245.3): C, 58.54; H, 6.16; N, 5.71%].

1-Propyl-3-benzoyl-2-methylthio pyrrole (13e) was obtained as a red viscous oil; yield, 69%; I.R.(Neat): ν_{max} = 1649 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 0.89 (t, J = 7Hz, 3H, $CH_2C\underline{H}_3$), 1.69 (distorted sext., J = 7Hz, 2H, $C\underline{H}_2CH_3$), 2.40 (s, 3H, $SC\underline{H}_3$), 4.03 (t, J = 7Hz, 2H, $C\underline{H}_2CH_2CH_3$), 6.30 (d, J=3Hz, 1H, $\underline{H}$-4), 6.70 (d, J=3Hz, 1H, $\underline{H}$-5), 7.10-7.45 (m, $3H_{arom}$), 7.58-7.87 (m, $2H_{arom}$); m/z : 259 (M^+, 100%), 226 (100%), [Found: C, 69.68; H, 6.75; N, 5.61 calculated for $C_{15}H_{17}NOS$ (259.4): C, 69.45; H, 6.61; N, 5.40%].

1-Isopropyl-3-(4-chlorophenyl)-2-methylthio pyrrole (13f) was obtained as a colourless solid; m.p. 87-88°C; yield, 85%; I.R.(KBr): ν_{max} = 1647 cm^{-1}; ^{1}Hn.m.r.($CDCl_3$) :δ= 1.41 [d, J = 7Hz, 6H, $CH(C\underline{H}_3)_2$], 6.31 (d, J = 3Hz, 1H, $\underline{H}$-4), 6.80 (d, J = 3Hz, 1H, $\underline{H}$-5), 7.35 (d, J = 9Hz, $2H_{arom}$),

7.77 (d, J = 9Hz, $2H_{arom}$); m/z : 295 (37%), 293 (M^+-2, 100%), 279 (20%), 277 (25%), [Found: C, 61.39; H, 5.68; N, 4.91 calculated for $C_{15}H_{16}NOSCl$ (293.8): C, 61.32; H, 5.49; N, 4.77%].

1-Butyl-3-benzoyl-2-methylthio-pyrrole (13g) was obtained as a viscous red oil; yield , 62%; I.R. (Neat): ν_{max} = 1647 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$):δ = 0.96 (t, J=7Hz, 3H, $CH_2C\underline{H}_3$), 1.35 (distorted sext., J = 7Hz, 2H, $C\underline{H}_2CH_3$), 1.77 (distorted quint., J = 7Hz, 2H, $C\underline{H}_2CH_2CH_3$), 2.43 (s, 3H, $SC\underline{H}_3$), 4.08 (t, J = 7Hz, 2H, $NC\underline{H}_2$), 6.29 (d, J = 3Hz, 1H, $\underline{H}$-4), 6.62 (d, J = 3Hz, 1H, $\underline{H}$-5), 7.17-7.45 (m, $3H_{arom}$), 7.63-7.82 (m, $2H_{arom}$); m/z : 273 (M^+-91%), 240 (86%), [Found: C, 70.09; H, 7.21; N, 5.38 calculated for $C_{16}H_{19}NOS$ (273.4): C, 70.29; H, 7.00; N, 5.12%].

1-Benzyl-3-benzoyl-2-methylthio pyrrole (13h) was obtained as a colourless solid; m.p. 76-77°C; yield, 74%; I.R.(KBr):ν_{max} = 1628 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$): δ= 2.24 (s, 3H, $SC\underline{H}_3$), 5.25 (s, 2H, $NC\underline{H}_2$), 6.33 (d, J = 3Hz,1H, $\underline{H}$-4), 6.70 (d, J = 7Hz, 1H, $\underline{H}$-5), 6.92-7.43 (d, J = 3Hz, $8H_{arom}$), 7.67-9.00 (m, $2H_{arom}$); m/z : 307 (M^+, 72%), 274 (28%), [Found: C, 74.46; H, 5.72; N, 4.68 Calculated for $C_{19}H_{17}NOS$ (307.4) : C, 74.23; H, 5.58; N, 4.56%].

1-Phenyl-3-benzoyl-2-methylthio pyrrole (13i) was obtained as a colourless solid; m.p. 111-112°C; yield, 77%; I.R.(KBr): ν_{max} = 1636 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ = 2.20 (s, 3H, $SC\underline{H}_3$); 6.47 (d, J = 3Hz, 1H, $\underline{H}$-4), 6.83 (d, J = 3Hz, 1H, $\underline{H}$-5), 7.20-7.60 (m, $8H_{arom}$); m/z : 293 (M^+,

100%), 260 (97%), [Found: C, 7.73; H, 5.30; N, 4.97 calculated for $C_{18}H_{15}NOS$ (293.4): C, 73.68; H, 5.15; N, 4.77%].

7-Acetyl-2,3-dihydropyrrole [2,1-*b*] thiazole (15a) was obtained as a viscous oil; yield, 61%. Its I.R., ^1H n.m.r. and mass spectral data are given in the text. [Found: C, 57.30; H, 5.21; N, 8.21 calculated for C_8H_9NOS (167.2): C, 57.46; H, 5.42; N, 8.38%].

7-Benzoyl-2,3-dihydropyrrolo [2,1-*b*] thizole (15b) was obtained as a viscous oil; yield, 64%; I.R. (Neat): ν_{max} = 1620 cm^{-1}; ^1Hn.m.r. ($CDCl_3$): δ= 3.26 (t, J = 7Hz, 2H, $SC\underline{H}_2$), 4.35 (t, J = 7Hz, 2H, $NC\underline{H}_2$), 6.70 (d, J = 3Hz, 1H, $\underline{H}$-6), 7.28 (d, J = 3Hz, 1H, $\underline{H}$-5), 7.20-7.41 (m, $3H_{arom}$), 7.73-8.05 (m, $2H_{arom}$); m/z : 229 (M^+, 21%), 228 (100%), 169(41%), [Found: C, 68.39; H, 4.64; N, 6.31 calculated for $C_{13}H_{11}NOS$ (229.3): C, 68.09; H, 4.84; N, 6.11%].

7-(4-Chlorobenzoyl)-2,3-dihydropyrrolo[2,1-*b*] thiazole (15c) was obtained as a colourless solid; m.p. 128-129°C; yield 73%; I.R.(KBr): ν_{max} = 1600 cm^{-1}; ^1Hn.m.r. ($CDCl_3$): δ= 3.70 (t, J=7.5Hz, 2H, $SC\underline{H}_2$), 4.18 (t, J=7.5Hz, 2H, $NC\underline{H}_2$),6.46 (d, J = 3Hz,1H,$\underline{H}$-6), 6.58 (d, J = 3Hz,1H,$\underline{H}$-5), 7.40 (d, J = 9Hz, $2H_{arom}$), 7.76 (d, J = 9Hz,$2H_{arom}$); m/z : 263 (1%), 264 (3%), 263 (M^+, 10%), 262 (49%), [Found: C, 59.01; H, 3.99; N, 5.05 calculated for $C_{13}H_{10}NOSCl$ (263.7): C, 59.20; H, 3.82; N, 5.31%].

1-Ethyl-3-nitro-2-methylthio pyrrole (17a) was obtained as

a yellow solid; m.p. 69-70°C; yield, 58%. Its I.R., ^{1}Hn.m.r. and mass spectral data are given in the text. [Found: C, 45.23; H, 5.59; N, 15.31 calculated for $C_7H_{10}N_2O_2S$ (186.2): C, 45.15; H, 5.41; N, 15.04%].

1-Benzoyl-3-nitro-2-methylthio pyrrole (17b) was obtained as a yellow solid; m.p. 75-76°C; yield, 63%; I.R.(KBr): ν_{max} = 1600, 1540 cm^{-1}; ^{1}Hn.m.r.($CDCl_3$): δ= 2.30 (s, 3H, $SC\underline{H}_3$), 5.31 (s,2H, $NC\underline{H}_2$), 6.73 (d, J = 3Hz, 1H, H-4), 6.90 (d, J = 3Hz, 1H, H-5), 7.03-7.40 (m, $5H_{arom}$); m/z : 248 (M^+, 23%), 201 (12%), [Found: C, 58.24; H, 4.98; N, 11.38 calculated for $C_{12}H_{12}N_2O_2S$ (248.3): C, 58.04; H, 4.87; N, 11.28%].

1-Phenyl-3-nitro-2-methylthio pyrrole (17c) was obtained as a yellow solid; m.p. 140-141°C; yield, 77%; I.R.(KBr): ν_{max} = 1594, 1548 cm^{-1}; ^{1}Hn.m.r.($CDCl_3$): δ= 2.30 (s, 3H, $SC\underline{H}_3$), 6.83 (d, J = 3Hz, 1H, H-4), 7.00 (d, J = 3H, J = 3Hz, 1H, H-5), 7.28-7.63 (m, $5H_{arom}$); m/z : 234 (M^+, 100%), 187 (63%), [Found: C, 56.21; H, 4.45; N, 11.71 calculated for $C_{11}H_{10}N_2O_2S$ (234.3): C, 56.38; H, 4.30; N, 11.96%].

Reaction of α-oxoketene S,N-acetals 10a-h, 10j-m, the nitro ketene S,N-acetals 16a and 16b and the cyclic S,N-acetals 14a-c with propargyl bromide 28:

General Procedure:

Propargyl bromide 28 (10 mmol) is dissolved in dry 1,4-dioxane (30 ml) and Cu(I)Br (mmol) is added to the above solution and stirred for 30 minutes at room temperature.

The 14 or 16 (10 mmol) is added to the above solution and the reaction mixture is heated at 110°C for 4-6 hours. The reaction mixture is then cooled, poured into ice-cold water (50 ml), extracted with chloroform (2x50 ml), dried over sodium sulphate and evaporated to give the crude pyrroles which are purified by column chromatography over silica gel using hexane/ethyl acetate (20:1) as eluent. The structures of 30a-m, 31a-c, 32a and 32b were fully confirmed from their spectral and analytical data which are given below.

1-Ethyl-3-acetyl-2-methylthio-5-methyl pyrrole (30a) was obtained as a viscous oil; yield, 52%; I.R.(Neat): ν_{max} = 1660 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 1.23 (t, J = 7Hz,3H, $CH_2C\underline{H}_3$), 2.20 (s, 3H, $SC\underline{H}_3$), 2.30 (s, 3H, $C\underline{H}_3CO$), 2.35 (s, 3H, $SC\underline{H}_3$), 4.05 (q, J = 7Hz, 2H, $C\underline{H}_2CH_3$), 6.20 (s, 1H, H-4); m/z : 197 (M^+, 100%), 182 (61%), 164 (63%), [Found: C, 60.65; H, 7.47; N, 7.31 calculated for $C_{30}H_{15}NOS$ (197.2): C, 60.87; H, 7.66; N, 7.10%].

1-Benzyl-3-acetyl-2-methylthio-5-methyl pyrrole (30b) was obtained as a viscous oil; yield, 54%; I.R.(Neat): ν_{max} = 1663^{-1}; ^{1}H n.m.r. ($CDCl_3$): δ= 2.10 (s, 3H, $C\underline{H}_3$), 2.17 (s, 3H, $COC\underline{H}_3$), 2.43 (s, 3H, $SC\underline{H}_3$), 5.32 (brs, 2H, $C\underline{H}_2$), 6.35 (s, 1H, H-4), 6.80-6.97 (m,$2H_{arom}$), 7.16-7.33 (m, $3H_{arom}$); m/z : 259 (M^+, 59%), 226 (11%), [Found: C, 69.21; H, 6.47; N, 5.25 calculated for $C_{15}H_{17}NOS$ (259.3): C, 69.46; H, 6.61; N, 5.40%].

1,5-Dimethyl-3-benzoyl-2-methylthio pyrrole (30c) was obtained as a viscous oil; yield, 63%. Its I.R., ^{1}H n.m.r. and mass spectral data are given in the text. ^{13}C n.m.r.($CDCl_3$):δ=12.42 ($\underline{C}H_3$),19.73 ($S\underline{C}H_3$), 38.37 ($N\underline{C}H_3$), 110.58, 128.89, 130.88 ($\underline{C}H$, C-4, C-2', C-3', C-4', C-5'and C-6'), 125.97, 127.37, 130.65, 139.66, 190.80 (C-2, C-3, C-5, C-1'and carbonyl carbon), [Found: C, 68.50; H, 6.15; N, 5.69 calculated for $C_{14}H_{15}NOS$ (245.3): C, 68.54; H, 6.16; N, 5.71%].

1-Ethyl-3-benzoyl-2-methylthio-5-methyl pyrrole (30d) was obtained as a viscous oil; yield, 59%; I.R.(Neat): ν_{max} = 1638 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 1.28 (t, J=7Hz, 3H, $CH_2C\underline{H}_3$), 2.23 (s, 3H, $C\underline{H}_3$), 2.42 (s, 3H, $SC\underline{H}_3$), 4.11 (q, J = 7Hz,2H, $C\underline{H}_2CH_3$), 6.05 (s, 1H, $\underline{H}$-4), 7.30-7.50 (m, $3H_{arom}$), 7.70-7.87 (m, $2H_{arom}$), [Found: C, 69.21; H, 6.47; N, 5.25 calculated for $C_{15}H_{17}NOS$ (259.3): C, 69.46; H, 6.61; N, 5.40%].

1-Propyl-3-benzoyl-2-methylthio-5-methyl pyrrole (30e) was obtained as a viscous oil; yield, 49%; I.R. (Neat): ν_{max} = 1638 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 0.99 (t, J = 7Hz, 3H, $CH_2C\underline{H}_3$), 1.67 (distorted sext., J = 7Hz, 2H, $C\underline{H}_2CH_3$),2.18 (s, 3H, $C\underline{H}_3$), 2.36 (s, 3H, $SC\underline{H}_3$), 3.96 (t, J = 7Hz, 2H, $NC\underline{H}_2$), 6.00 (s, 1H, $\underline{H}$-4), 7.27-7.60 (m, $3H_{arom}$), 7.70-7.87 (m, $2H_{arom}$); m/z : 273 (M^+, 100%), 258 (33%), 240 (72%), [Found: C, 7.31; H, 7.20; N, 5.30 calculated for $C_{16}H_{19}NOS$ (273.3): C, 70.29; H, 7.00; N, 5.12%].

1-Isopropyl-3-(4-chlorobenzoyl)-2-methylthio-5-methyl pyrrole (30f) was obtained as a viscous oil; yield, 79%; I.R.(Neat):ν_{max} = 1647 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 1.53 [d, J = 7Hz, 6H, $CH(C\underline{H}_3)_2$], 2.30 (s, 3H, $C\underline{H}_3$), 2.35 (s, 3H, $SC\underline{H}_3$), 5.14 [distorted sext., J = 7Hz, 1H, $C\underline{H}(CH_3)_2$], 6.00 (s, 1H, $\underline{H}$-4), 7.32 (d, J = 9Hz, $2H_{arom}$), 7.72 (d, J = 9Hz, $2H_{arom}$); m/z : 308 (M^+, 25%), 307 (M^+, 100%), 292 (22%), 274 (38%), [Found: C, 62.23; H, 5.71; N, 4.71 calculated for $C_{16}H_{18}NOSCI$ (307.8): C, 62.43; H, 5.89; N, 4.55%].

1-Butyl-3-benzoyl-2-methylthio-5-methyl pyrrole (30g) was obtained as a viscous oil; yield, 51%; I.R.(Neat):ν_{max} = 1642 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 0.97 (t, J = 7Hz, 3H, $C\underline{H}_3CH_2$) 1.20-1.67 (distorted quint., J = 7Hz, 4H, $CH_2(C\underline{H}_2)CH_3$), 2.20 (s, 3H, $C\underline{H}_3$), 2.39 (s, 3H, $SC\underline{H}_3$), 4.09 (t, J = 7Hz, 2H, $NC\underline{H}_2$), 6.13 (s, 1H, $\underline{H}$-4), 7.40-7.57 (m, $3H_{arom}$), 7.77-7.90 (m, $2H_{arom}$); m/z : 287 (M^+, 47%), 272 (14%), 253 (34%), [Found: C, 71.00; H, 7.35; N, 4.88 calculated for $C_{17}H_{21}NOS$ (287.4): C, 71.04; H, 7.36; N, 4.87%].

1-Phenyl-3-benzoyl-2-methylthio-5-methyl pyrrole (30h) was obtained as a colourless solid; m.p. 118°C; yield, 54%; I.R.(KBr):ν_{max} = 1638 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 2.05 (s, 3H, $C\underline{H}_3$), 2.20 (s, 3H, $SC\underline{H}_3$), 6.20 (s, 1H, $\underline{H}$-4), 7.13-7.33 (m,$3H_{arom}$), 7.34-7.57 (m, $5H_{arom}$), 7.73-7.93 (m, $2H_{arom}$); m/z : 307 (M^+, 100%), 292 (31%); 274 (70%), [Found: C, 74.01; H, 5.34; N, 4.79 calculated for $C_{19}H_{17}NOS$ (307.4): C, 74.23; H, 5.58; N, 4.56%].

1,5-Dimethyl-3-(4-methylbenzoyl)-2-methylthio pyrrole (30j) was obtained as colourless solid; m.p. 95°C; yield, 68%; I.R.(KBr): ν_{max} = 1630 cm^{-1}; ^{1}Hn.m.r.($CDCl_3$):δ= 2.20 (s, 3H, $C\underline{H}_3$), 2.30 (s, 3H, 5-methyl), 2.35 (s, 3H, $SC\underline{H}_3$), 3.60 (s, 3H, $NC\underline{H}_3$), 6.03 (s, 1H, $\underline{H}$-4), 7.13 (d, J = 9Hz, $2H_{arom}$), 7.60 (d, J = 9Hz, $2H_{arom}$); m/z : 259 (M^+, 100%), 244 (41%), 226(75%), [Found: C, 69.25; H, 6.53; N, 5.25 calculated for $C_{15}H_{15}NOS$ (259.3): C, 69.46; H, 6.61; N, 5.40%].

1-Ethyl-3-(4-chlorobenzoyl)-2-methylthio-5-methyl pyrrole (30k) was obtained as a viscous oil; yield, 62%; I.R.(Neat): ν_{max}=1622 cm^{-1}; ^{1}Hn.m.r.($CDCl_3$):δ= 1.30 (t,J = 7Hz,3H, $CH_2C\underline{H}_3$), 2.25 (s, 3H, $C\underline{H}_3$), 2.40 (s, 3H, $SC\underline{H}_3$), 4.13 (q, J = 7Hz, 2H, $C\underline{H}_2CH_3$), 6.03 (s, 1H, $\underline{H}$-4), 7.35 (d, J = 9Hz, $2H_{arom}$), 7.73 (d, J = 9Hz, $2H_{arom}$); m/z : 295 (M^+, 36%), 293 (100%), 278(46%), 260(64%), [Found: C, 61.26; H, 5.42; N, 4.89 calculated for $C_{15}H_{16}NOSCI$ (293.8): C, 61.32; H, 5.49; N, 4.77%].

1-Benzyl-3-(4-methylbenzoyl)-2-methylthio-5-methyl pyrrole (30l) was obtained as a viscous oil; yield, 64%; I.R.(Neat): ν_{max} = 1638 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 2.10 (s, 3H, $C\underline{H}_3$), 2.24 (s, 3H, $C\underline{H}_3$), 2.39 (s, 3H, $SC\underline{H}_3$), 5.38 (s, 2H, $NC\underline{H}_2$), 6.17 (s, 1H, $\underline{H}$-4), 6.80-7.00 (d, J = 9Hz, $2H_{arom}$), 7.00-7.30 (m, $5H_{arom}$), 7.61-7.80 (d, J = 9Hz, $2H_{arom}$); m/z : 335 (M^+, 52%), 302 (19%), [Found: C, 75.10; H, 6.21; N, 4.36 calculated for $C_{21}H_{21}NOS$ (335.4): C, 75.19; H, 6.31; N, 4.18%].

1-Cyclohexyl-3-benzoyl-2-methylthio-5-methyl pyrrole (30m) was obtained as a viscous oil; yield, 57%;I.R.(Neat): ν_{max}= 1638 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 1.07-1.50 (m, 6H, $CHCH_2CH_2CH_2CH_2$), 1.70-2.00 (m, 4H, $CHCH_2CH_2CH_2CH_2CH_2$), 2.27 (s, 3H, CH_3), 2.31 (s, 3H, SCH_3), 3.33-3.57 (distorted quint. , J=7Hz, 1H, NCH), 5.95 (s, 1H, H-4), 7.20-7.38 (m, $3H_{arom}$), 7.60-7.77 (m, $2H_{arom}$); m/z : 312 (M^+, 68%), 298 (9%), 280 (20%), [Found: C, 72.83; H, 7.43; N, 4.50 calculated for $C_{19}H_{22}NOS$ (313.4): C, 72.80; H, 7.40; N, 4.47%].

7-Acetyl-5-methyl-2,3-dihydropyrrolo [2,1-*b*] thiazole (31a) was obtained as a viscous oil; yield, 57%; I.R.(Neat): ν_{max} = 1615 cm^{-1}: ^{1}Hn.m.r ($CDCl_3$): δ=2.21 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 3.21 (t, J = 7Hz, 2H, SCH_2), 4.25 (t, J = 7Hz, 2H, NCH_2), 6.07 (s, 1H, H-4); m/z : 181 (M^+, 100%), [Found: C, 59.44; H, 6.00; N, 7.99 calculated for $C_9H_{11}NOS$ (181.2): C, 59.64; H, 6.12; N, 7.73%].

7-Benzoyl-5-methyl-2,3-dihydropyrrolo[2,1-*b*] thiazole (31b) was obtained as a viscous oil; yield, 63%; I.R.(Neat): ν_{max} = 1600 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 2.38 (s, 3H, CH_3), 3.24 (t, J = 7Hz, 2H SCH_2), 4.33 (t, J = 7Hz, 2H NCH_2), 6.27 (s, 1H, H-4), 7.21-7.35 (m, $3H_{arom}$), 7.80-7.97 (m, $2H_{arom}$); m/z : 243 (M^+, 68%), 209 (77%), [Found: C, 69.00; H, 5.31; N, 5.46 calculated for $C_{14}H_{13}NOS$ (243.3): C, 69.11; H, 5.38; N, 5.76%].

7-(4-Chlorobenzoyl)-5-methyl-2,3-dihydropyrrolo[2,1-*b*] thiazole (31c) was obtained as a viscous oil; yield, 65%; I.R.(Neat):ν_{max} = 1615 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$) δ= 2.35 (s, 3H, $C\underline{H}_3$), 3.23 (t, J = 7Hz, 2H, $SC\underline{H}_2$), 4.33 (t, J = 7Hz, 2H, $NC\underline{H}_2$), 6.26 (s, 1H, $\underline{H}$-4), 7.29 (d, J = 9Hz, $2H_{arom}$), 7.97 (d, J = 9Hz, $2H_{arom}$); m/z : 278 (M^+, 39%), 276 (100%), 243(6%), [Found: C, 60.35; H, 4.65; N, 5.34 calculated for $C_{14}H_{12}NOSCI$ (277.7) : C, 60.53; H, 4.36; N, 5.04%].

1-Ethyl-3-nitro-2-methylthio-5-methyl pyrrole (32a) was obtained as a viscous oil; yield, 57%; I.R.(Neat):ν_{max} = 1560, 1500 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ=1.29 (t, J = 7Hz, 3H, $CH_2C\underline{H}_3$), 2.24 (s, 3H, $C\underline{H}_3$), 2.39 (s, 3H, $SC\underline{H}_3$), 4.13 (q, J = 7Hz, 2H, $C\underline{H}_2CH_3$), 6.43 (s, 1H, $\underline{H}$-4); m/z : 200 (M^+, 100%), 167(88%), [Found: C, 47.79; H, 6.15; N, 14.02 calculated for $C_8H_{12}N_2O_2S$ (200.2): C, 47.98; H, 6.04; N, 13.99%].

1-Benzoyl-3-nitro-2-methylthio-5-methyl pyrrole (32b) was obtained as a viscous oil; yield, 81%; I.R. (Neat):ν_{max} = 1540, 1505 cm^{-1}; ^{1}Hn.m.r. ($CDCl_3$): δ= 2.13 (s, 3H, $C\underline{H}_3$), 2.28 (s, 3H, $SC\underline{H}_3$), 5.33 (s, 2H, $NC\underline{H}_2$), 6.55 (s, 1H, $\underline{H}$-4), 6.80-7.00 (m, $2H_{arom}$), 7.13-7.33 (m, $3H_{arom}$); m/z : 262 (M^+, 52%), [Found: C, 59.32; H, 5.28; N, 10.79 calculated for $C_{13}H_{14}N_2O_2S$ (262.3): C, 59.52; H, 5.38; N, 10.68%].

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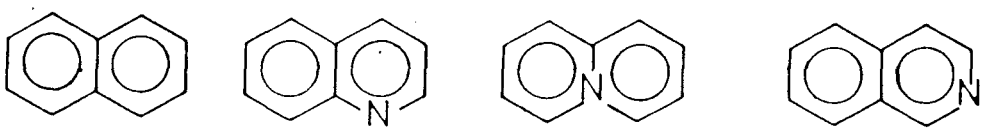
CHAPTER - IV

REACTION OF α-OXOKETENE S,S-ACETALS WITH 2-METHYLQUINOLINE AND 2,4-DIMETHYL-6-METHOXYQUINOLINE: A NOVEL SYNTHESIS OF BENZO[C]QUINOLIZINIUM AND CONDENSED QUINOLIZINIUM DERIVATIVES.

INTRODUCTION

The occurrence of aromatic compounds formally related to the classical aromatic hydrocarbons by the replacement of a CH by N has long been recognized. The structural relationship of quinoline (B) to naphthalene (A) was understood nearly 100 years ago[1] while the relationship of



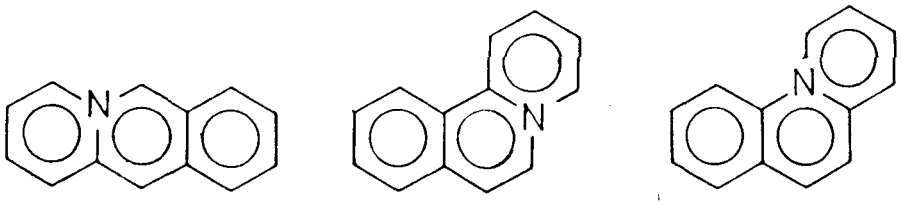
A B C D

isoquinoline[2] (D) was recognized a few years later. Despite the continuing attention devoted to aromatic systems, the first synthesis of the dehydroquinolizinium ion (C), in which the carbon at 4a position of naphthalene nucleus is replaced by a quaternary nitrogen, was not announced until 1954[3] and this date may be regarded as the beginning of the systematic study of the quinolizinium ion and its benzologs. In contrast to quinoline and isoquinoline, the other two simple nitrogen analogs of naphthalene, the chemistry of quinolizinium ion has been little studied and knowledge regarding this ion has been gained almost entirely from investigations of alkaloids containing this nucleus as a part of fairly complex structure. For example, the quinolizinium ion (C) is the parent structure for the various berberine alkaloids[4-7], palmatine[8], columbamine[9], jatrorrhizine[10], coptisine[11], worenine[12], dehydrocorydaline[13] and dehydrothialic-trifoline[14].

Actually, the occurrence, among alkaloids, of the fully unsaturated quinolizinium ion was first recognized when Woodward and Witkop proposed that sempervirine contained this nucleus[15]. This was immediately confirmed by Woodward and McLamore's synthesis of sempervirine methochloride[16].

Ever since the appearance of this work in this area, there are various reports of the synthesis of benzologs of quinolizinium ions. There are only three simple

monobenzologs of the quinolizinium ion: one linear and two angular.



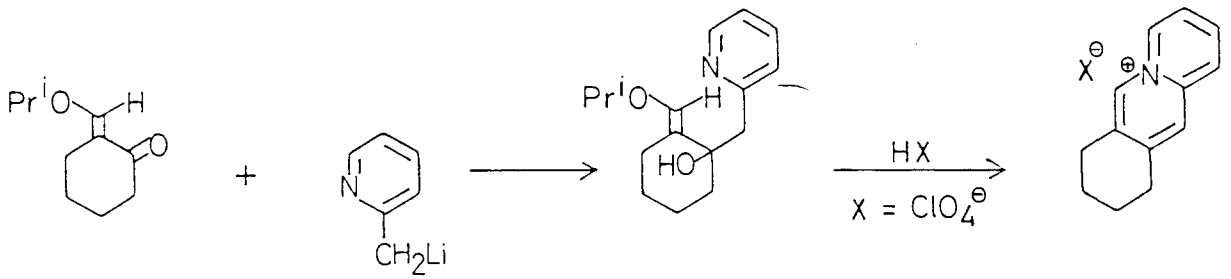
Benzolog:	Benzo[b]quinolizinium ion	Benzo[a]quinolizinium ion	Benzo[c]-quinolizinium ion
Trival Name :	Acridizinium ion	Phenanthridizinium ion	

A brief survey of the reported literature on the synthesis of various quinolizinium ions and their benzologs is presented in the following section.

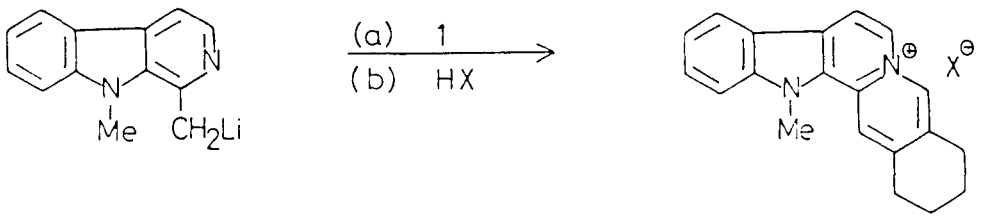
SURVEY OF THE LITERATURE

Woodward and McLamore[16] were the first to synthesize sempervirine methochloride. They condensed the lithium derivative of α-picoline 2 with β-*iso*propoxymethylene cyclohexanone 1 to yield the carbinol acetal 3 followed by its treatment with acid to afford the quinolizinium cation 4 in 51% yield (Scheme 1). They subsequently extended this reaction to synthesize methylsempervirinium cation 6 by reacting the lithium derivative of N-methylharman 5 with 1 (Scheme 1).

The preparation of the necessary starting material, the



1 2 3 4



5 6

Scheme - 1

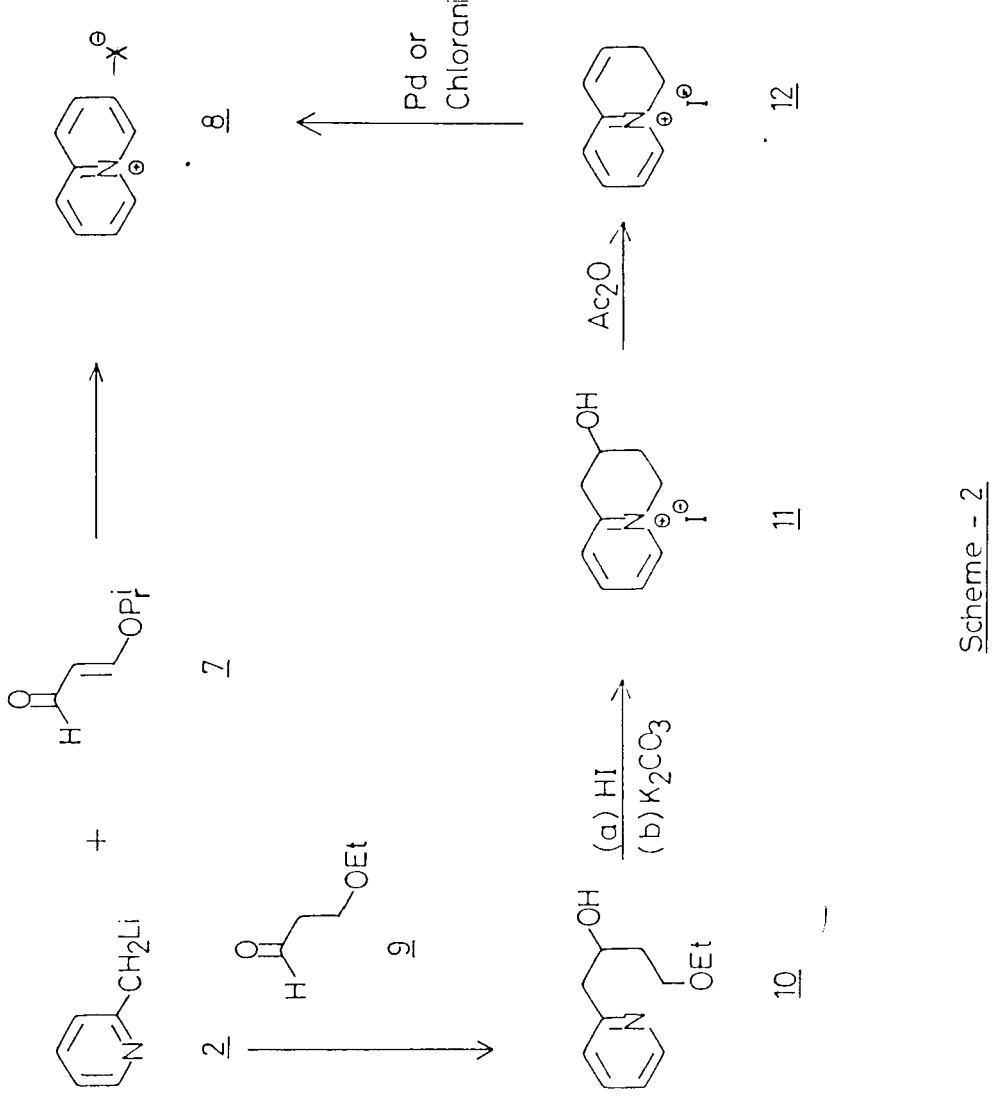
β-*iso*propoxyacrolein[15] 7, is tedius and proceeds in very poor yield. This approach was modified by Boekelheide and Gall[3]. These authors reacted 2-picolyllithium 2 with β-ethoxypropionaldehyde 9 to afford the corresponding carbinol 10 followed by treatment with hydroiodic acid and subsequent neutralization by potassium carbonate to yield the cyclic ammonium iodide 11 which on treatment with acetic anhydride gave the dihydroquinolizinium iodide 12 in high yields. The aromatization of 12 was achieved by treating with chloranil (Scheme 2).

Subsequently, Bradsher et al. published a series of papers[16-29,31] developing new strategies for the synthesis of several quinolizinium and condensed quinolizinium compounds. Their work can be divided into three main units:

(1) Synthesis of Acridizinium Ion 17.
(2) Synthesis of Phenanthridizinium Ion 19.
(3) Synthesis of Benzo[c]quinolizinium Ion 22.

SYNTHESIS OF ACRIDIZINIUM ION

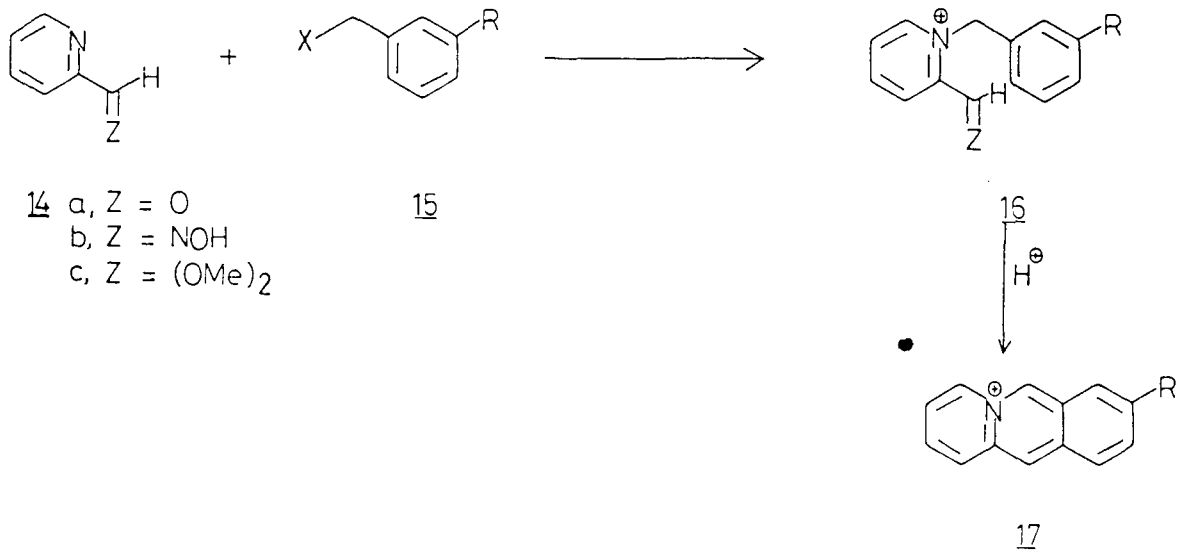
The synthesis of acridizinium ion or benzo[b]quinolizinium ion was achieved in good yields by treating appropriately substituted benzyl halides 15 with 2-pyridine-carboxaldehyde or its derivative 14 to get the salt 16 which on acid catalyzed cyclization yielded 17 (Scheme 3). The yields of 17 were higher when the oxime 14a was used as the starting material.



2 9 10 11 12

7 8

Scheme - 2



14 a, Z = O
b, Z = NOH
c, Z = $(OMe)_2$

15

16

17

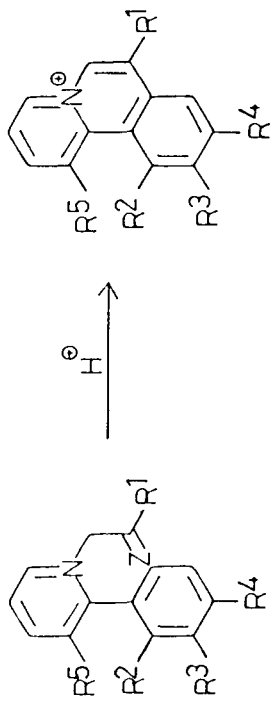
Scheme - 3

SYNTHESIS OF PHENANTHRIDIZINIUM ION

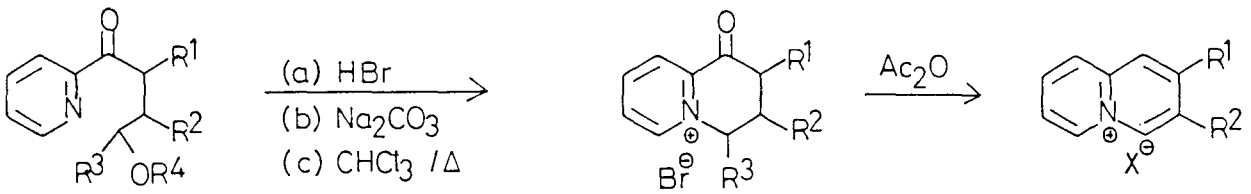
The first general method[30] for the synthesis of simple phenanthridizinium ion or benzo[a]quinolizinium ion involved the quaternization of 2-phenylpyridine or a derivative with α-halo carbonyl derivatives to yield the corresponding salts 18 which were cyclized in boiling hydrobromic acid (Scheme 4).

Simultaneously, Glover and Jones[32] reported the synthesis of alkyl and aryl quinolizinium salts 22 by reacting the pyridylketones 20 with hydrobromic acid to yield the oxoquinolizinium bromides 21 which underwent aromatization on treatment with acetic anhydride to give the corresponding quinolizinium salts 22 in good yields (Scheme 5). These authors further extended this reaction for the synthesis of various benzologs of quinolizinium salts 25, 28 and 31 by reacting the corresponding 2-quinolyl 23, 1-isoquinolyl 26 and 3-isoquinolyl 29 ketones with hydrobromic acid followed by aromatization as shown in Scheme 5. In a separate communication[33] they have also reported the synthesis of some indolo[2,3-a]quinolizine 33 and benz[g]indolo[2,3-a]quinolizine derivatives 35 by treating 21 and 30 with phenyl hydrazine followed by indolization. However, they could not get 35 by catalytic dehydrogenation of 34 (Scheme 6).

Another route to the phenanthridizinium ion was reported by Bradsher et al[19,25,34] by ring contraction of



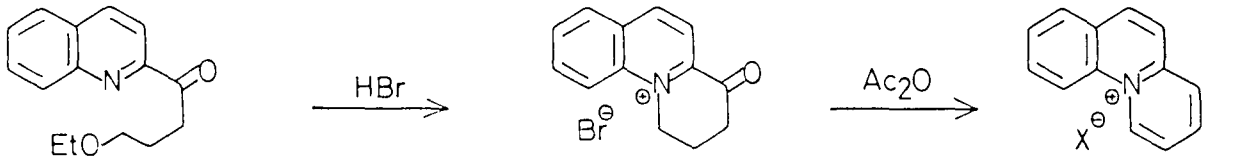
Scheme - 4



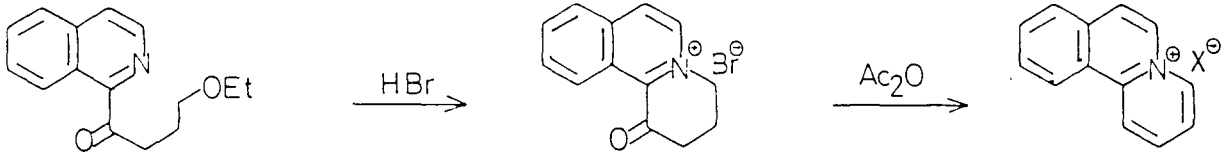
20 21 22

R^1 = Me; R^2 = R^3 = H; R^4 = Et ;
R^1 = R^3 = H; R^2 = Me; R^4 = Me ;

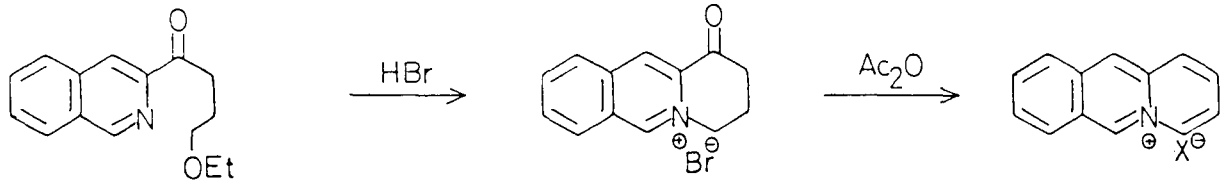
R^1 = Ph; R^2 = R^3 = H; R^4 = Et
R^1 = R^2 = H; R^3 = Me; R^4 = Et



23 24 25

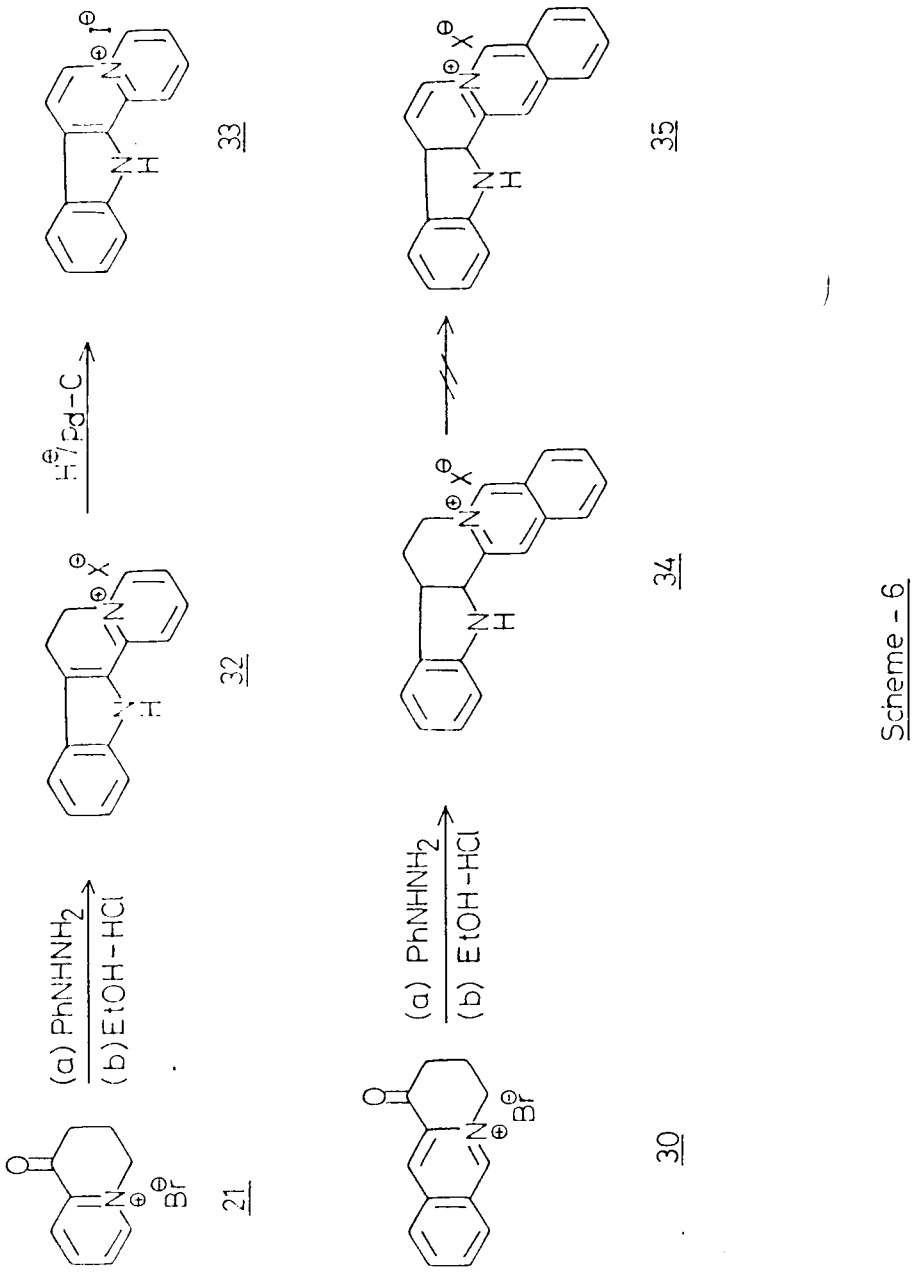


26 27 28



29 30 31

Scheme - 5



Scheme - 6

pyrido[2,1-b] benzo[f][1,3]thiazepinium perchlorates 36 to afford 37 in 24-45% overall yields (Scheme 7).

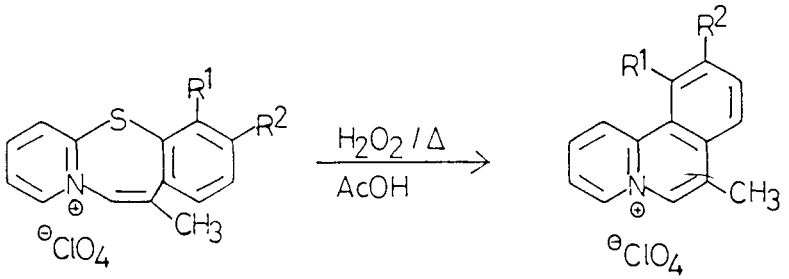
The most recent method reported[27,35] involves the UV irradiation of 1-styrylpyridinium salts 38 to afford the phenanthridizinium salts 39 in 50% average yields (Scheme 7).

SYNTHEIS OF BENZO[C]QUINOLIZINIUM ION

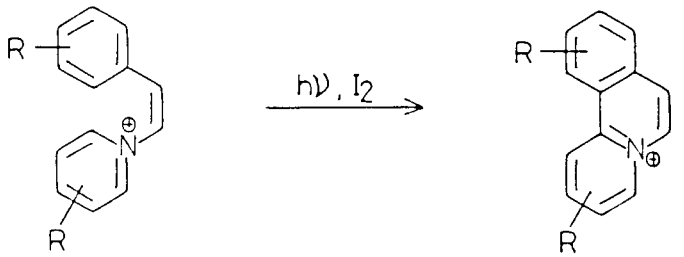
The first synthesis of the benzo[c]quinolizinium ion was accomplished by Glover and Jones[32] using their general method for the synthesis of the quinolizinium ion and its benzologs. This method has been explained earlier (Scheme 5).

A new general method[22,26] has been reported which makes the benzo[c]quinolizinium ion nearly as accessible as the benzo[b]analogues. Thus, the stilbazoles 40 formed by the condensation of o-chlorobenzaldehyde with α-picoline or its derivative were irradiated to afford, largely, the *cis*-isomer 41. This mixture was either heated at 170°C for 1 hour or irradiated with UV light for 48 hours to afford the corresponding salts 42 in 66% average yields (Scheme 8).

In continuation of the synthesis of quinolizinium salts, Richards and Stevens[36,37] have reported the synthesis of these homologues by a more effective process by using the method of Woodward and McLamore. They converted the

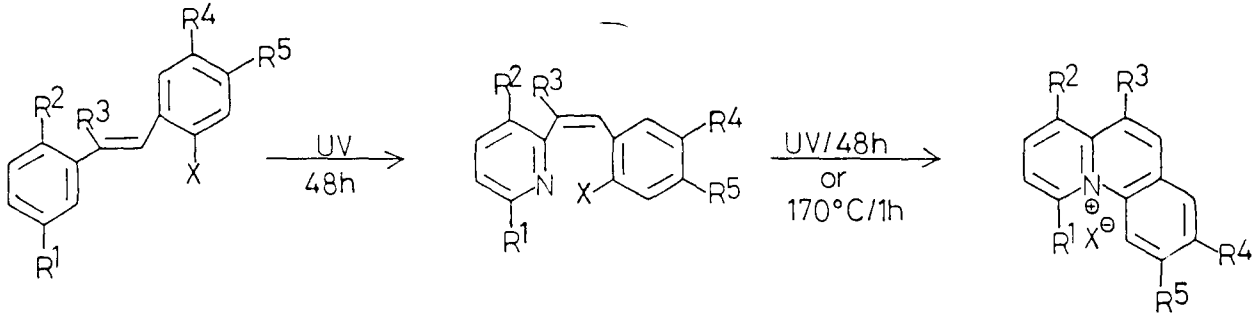


36 37



38 39

Scheme - 7



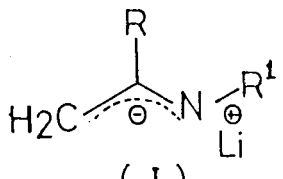
40 41 42

Scheme - 8

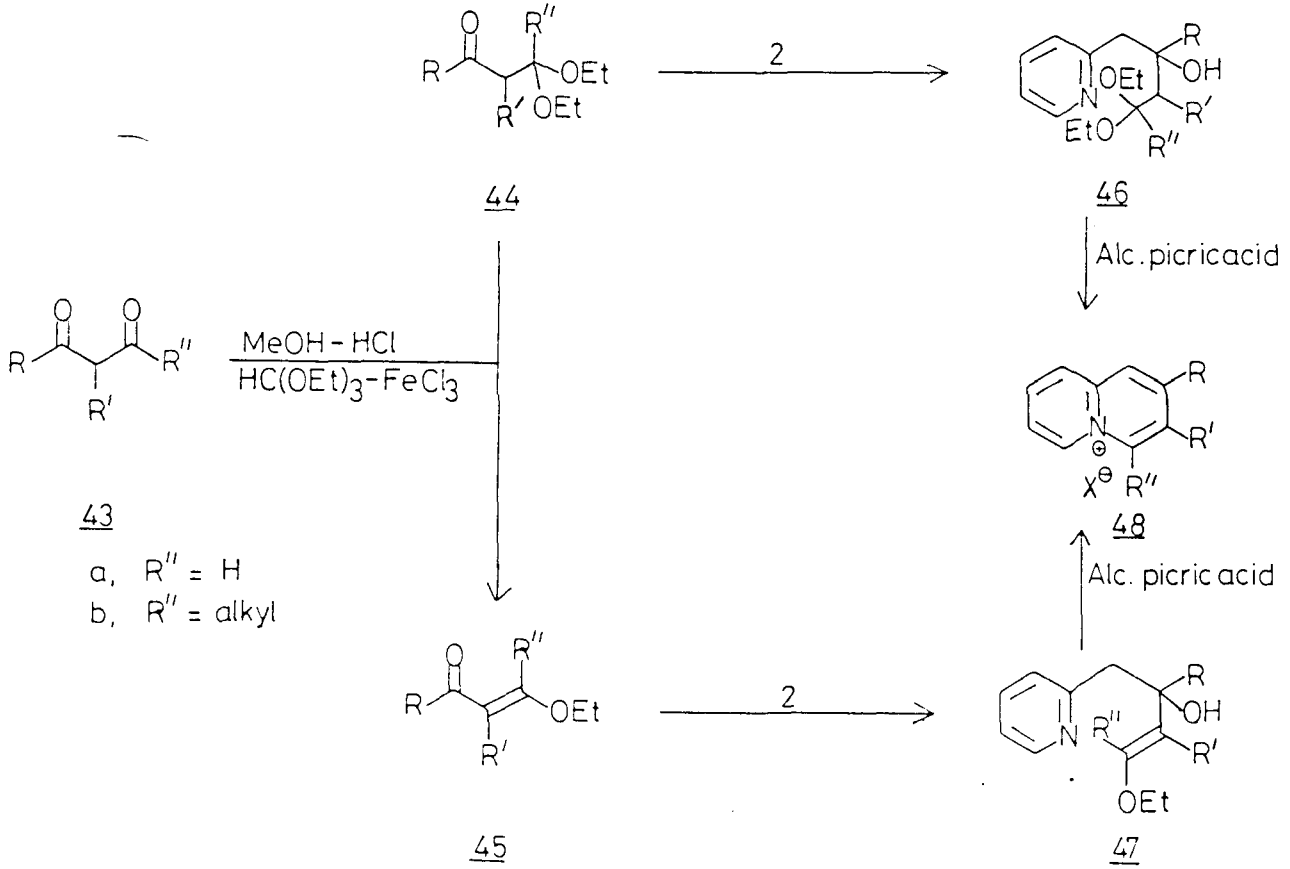
β-oxoaldehyde 43a or ketone 43b into the monoacetal 44 or the *enol* ether 45 and then reacted with 2-picolyllithium to get the carbinol acetals 46 or 47 which were cyclized by alcoholic picric acid to afford the corresponding salts 48 (Scheme 9).

From the above discussion it is clear that the quinolizinium ion and its condensed derivatives have attracted prime attention from the synthetic organic chemists and a number of methods for their synthesis have been developed due to their importance in alkaloid chemistry. It is also clear that most of these methods have employed starting materials which are either very difficult to prepare or are very costly. Some methods consist of various steps thereby reducing the overall yields of the final products.

As a part of our programmed studies on the synthetic utilization of α-oxoketene S,S-acetals, various methods for heterocyclic and aromatic annelation have been reported from this laboratory. These methods have been briefly reviewed in the first chapter. It was considered of interest to extend this new methodology to construct heteroaromatic systems analogous to the quinolizinium ions and their benzologs by reacting the α-oxoketene S,S-acetals with appropriate lithio-3-azaallyl systems[38] (I).



(I)



43

a, R'' = H
b, R'' = alkyl

44 45 46 47 48

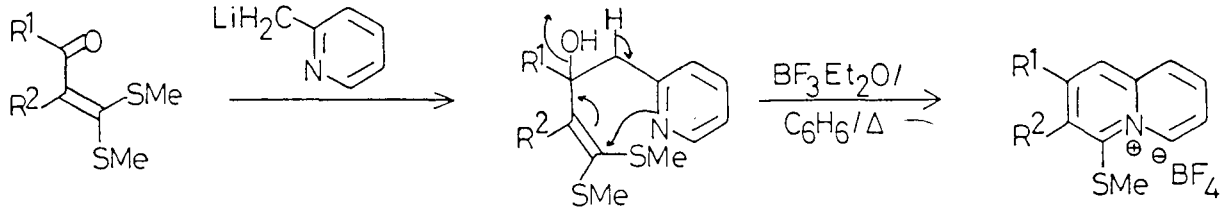
Scheme - 9

Thus, an efficient method for the synthesis of various substituted and fused quinolizinium ions was developed[38a] by reacting 2-picolyllithium 2 with α-oxoketene S,S-acetals 49 to yield the carbinol acetal 50 through 1,2-addition which on treatment with borontrifluoride etherate in refluxing benzene yielded the corresponding quinolizinium salts 51 in high yields (Scheme 10). This methodology was further extended to various other α-oxoketene S,S-acetals 52, 54 and 56 to yield 53, 55 and 57 respectively (Schemes 10 & 11).

In the present investigation it was considered appropriate to employ 2-methylquinoline system as a model to study its heteroaromatic annelation which could be extended for the synthesis of many natural products. Thus, the reaction of 2-methylquinoline and 2,4-dimethyl-6-methoxyquinoline with α-oxoketene S,S-acetals was examined and the results are described in the next section.

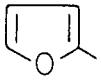
RESULTS AND DISCUSSION

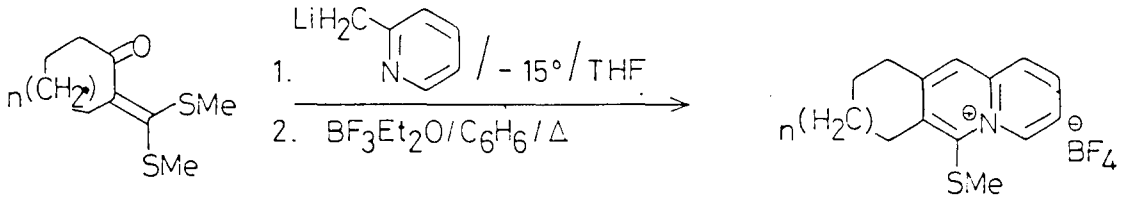
In an optimized condition, when 2-methylquinolyllithium 58 was reacted with α-oxoketene S,S-acetal 49a derived from acetophenone, the corresponding carbinol acetal 59a was formed in quantitative yield. The carbinol acetal was then directly subjected to borontrifluoride etherate assisted cycloaromatization in refluxing benzene. The reaction mixture, after work-up and purification, yielded the corresponding yellow crystalline salt 61a which was



49 50 51

R^1 = C_6H_5 ; 4 - MeC_6H_4 ; 4 - $MeOC_6H_4$; 4 - ClC_6H_4 ; 2 - naphthyl ; R^2 = H

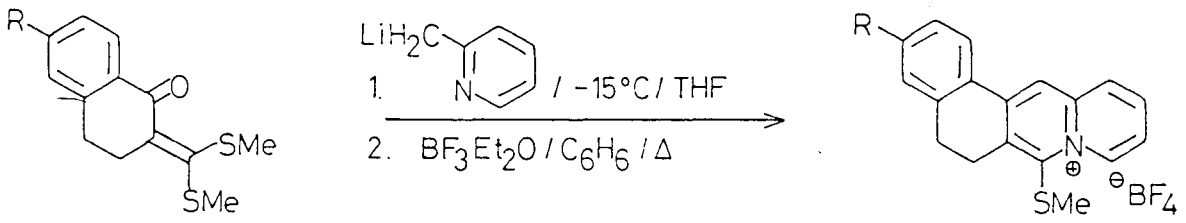
R^1 =  ,  ; R^2 = H



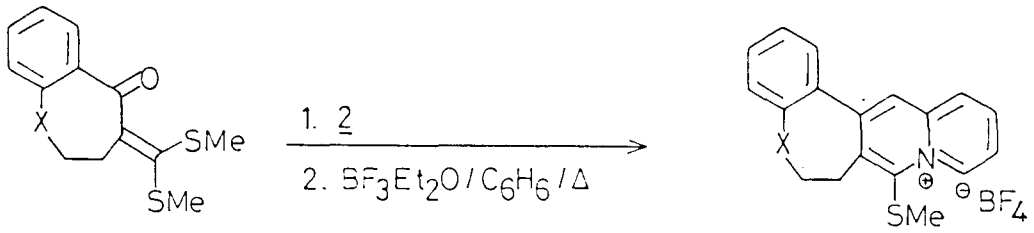
52 53

n = 1
n = 2

Scheme - 10



54 R = H , Me , MeO 55

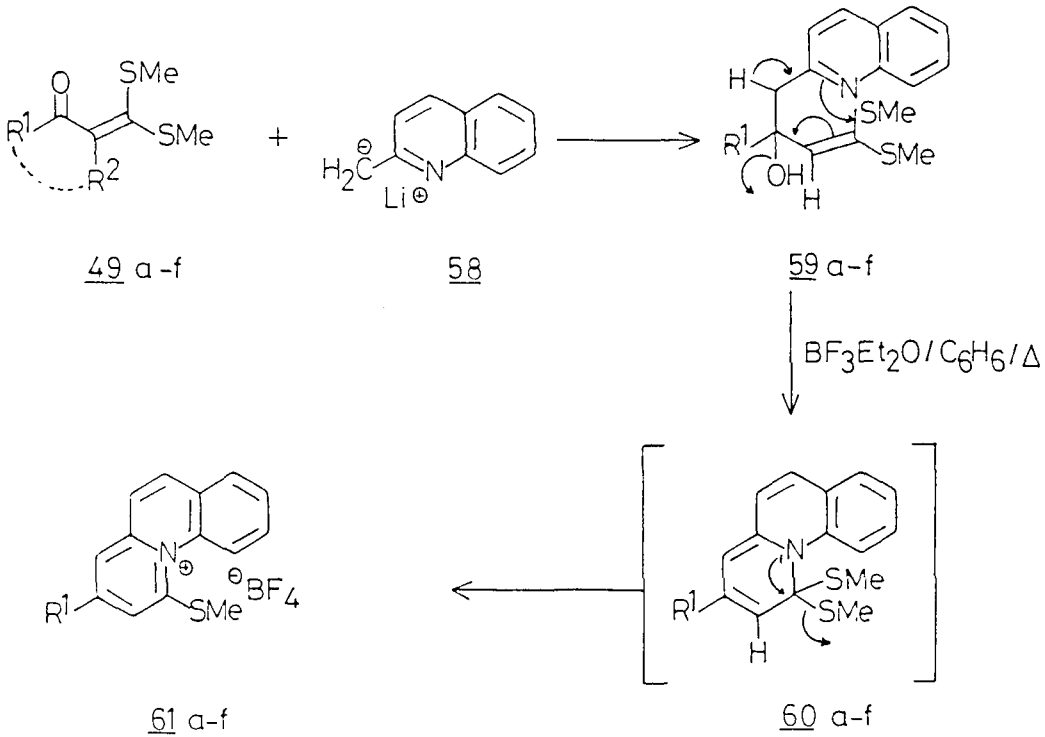


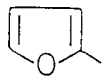
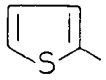
56 X = S
X = O
57

Scheme - 11

characterized as 3-phenyl-1-methylthiobenzo[c]quinolizinium tetrafluoroborate (Scheme 12). The structure of 61a was fully established from its spectral and analytical data. Thus, it was analyzed for $C_{20}H_{16}NSBF_4$ (389.2). Its mass spectrum showed molecular ion peaks at m/z = 353 (M^+-47,100%) and 335(32%). Its I.R.(KBr) spectrum showed bands at ν_{max} = 1603,1542 cm^{-1} and the characteristic tetrafluoroborate cation absorption band around 1030-1122 cm^{-1}. Its structure was further confirmed from ^{1}H.n.m.r. (DMSO-d_6) spectrum. The singlet at δ 2.93 (3H) was assigned to the methylthio group. The aromatic protons appeared at δ 7.63-7.73 (m,3H,arom), 7.93-8.07 (m,2H arom), 8.13-8.33 (m,5H,H-6,H-7,H-8,H=9 and H-10),. 8.55 (s,1H,H-2), and 8.71-8.86 (m,2H,H-5,H-4). Similarly, 58 reacted with other α-oxoketene S,S-acetals 49b-f to give the corresponding carbinol acetals 59b-f in high yields, which underwent smooth cycloaromatization in the presence of $BF_3.Et_2O$ in refluxing benzene to give the corresponding fused quinolizinium salts 61b-f in 49-82% overall yields (Scheme 12). The structures of 61b-f were fully established on the basis of their spectral and analytical data which are given in the experimental section.

The reaction of the cyclic α-oxoketene S,S-acetals with 58 was next examined. Thus, 49g and 49h derived from cyclohexanone and cycloheptanone respectively reacted smoothly with 58 to give the corresponding carbinol



a, R^1 = C_6H_5 ; R^2 = H
b, R^1 = 4-$MeOC_6H_4$; R^2 = H
c, R^1 = 4-MeC_6H_4 ; R^2 = H
d, R^1 = 2-naphthyl ; R^2 = H
e, R^1 =  R^2 = H
f, R^1 =  R^2 = H

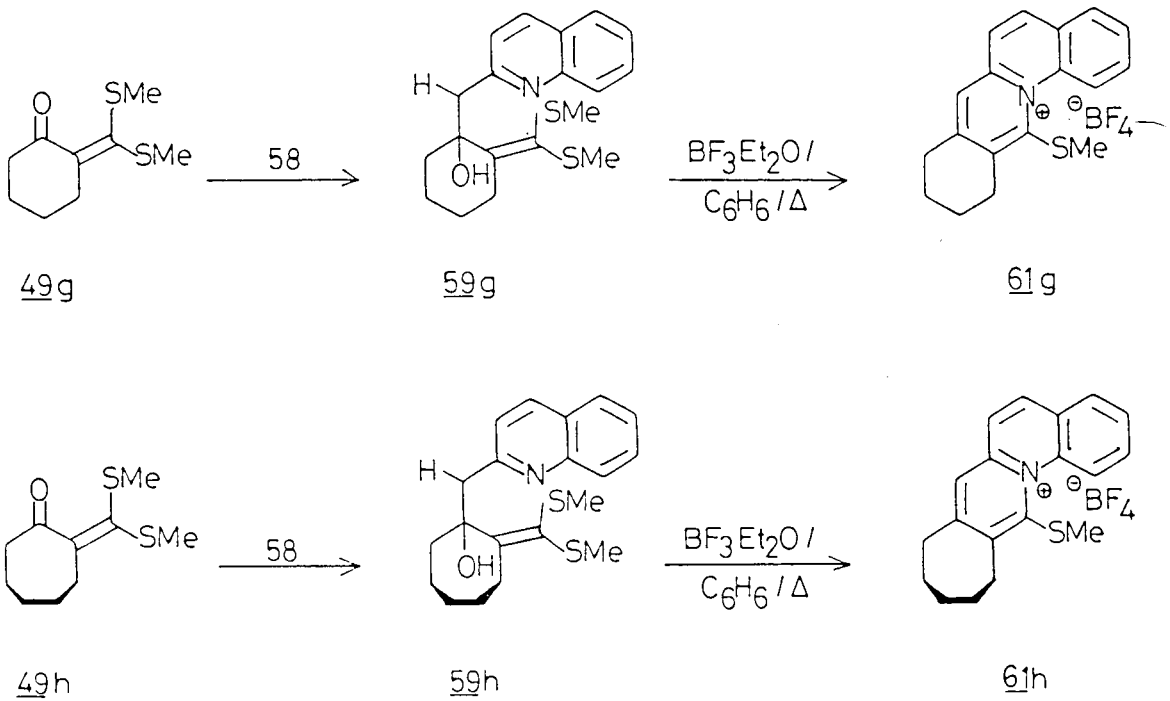
Scheme - 12

acetals 59g and 59h in quantitative yields. These carbinol acetals underwent cycloaromatization in the presence of $BF_3.Et_2O$ in refluxing benzene to yield the quinolizinium salts 61g and 61h in high yields (Scheme 13). The structures of 61g and 61h were confirmed from their spectral and analytical data which are given in the experimental section.

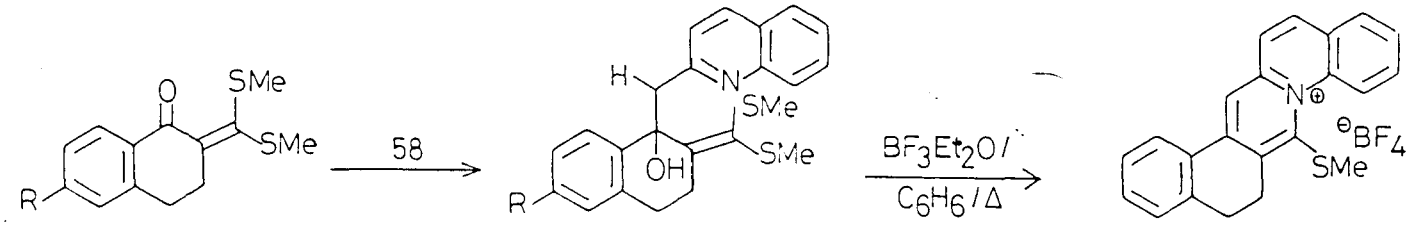
In the same manner, the α-oxoketone S,S-acetals 49i-l derived from α-tetralones, benzosuberanone and benzothiepinone yielded the carbinol acetals 59i-l in high yields followed by subsequent $BF_3.Et_2O$ assisted cycloaromatization to yield the quinolizinium salts 61i-l in excellent yields (Schemes 14 & 15). The structures of 61i-l were confirmed from their spectral and analytical data which are given in the experimental section.

However, the α-oxoketene S,S-acetal 49m derived from cyclopentanone did not give the corresponding quinolizinium salt 61m although the intermediate carbinol acetal 59m was obtained in high yields (Scheme 16). Similarly, 49n derived from indanone, though reacted smoothly with 58 to give the carbinol acetal 59n, but failed to give the corresponding salt 61n (Scheme 16) on treatment with $BF_3.Et_2O$ in refluxing benzene.

The cinnamoylketenedithioacetal 49o also reacted with 58 to yield the carbinol acetal 58o in high yields but failed to yield the corresponding quinolizinium salt 61o (Scheme 16).


SMe
O
SMe
58
H
N
SMe
OH
SMe
BF_3Et_2O /
C_6H_6 / Δ
N⊕
⊖BF_4
SMe
49g
59g
61g
SMe
O
SMe
58
H
N
SMe
OH
SMe
BF_3Et_2O /
C_6H_6 / Δ
N⊕
⊖BF_4
SMe
49h
59h
61h

Scheme - 13

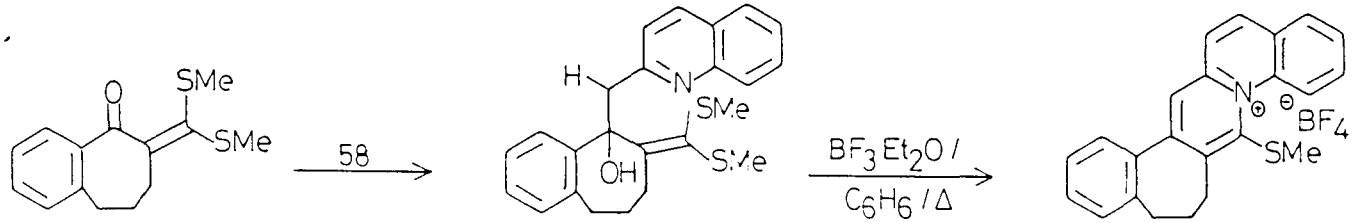


49 i-j

59 i-j

61 i-j

i, R = H ; j, R = OMe

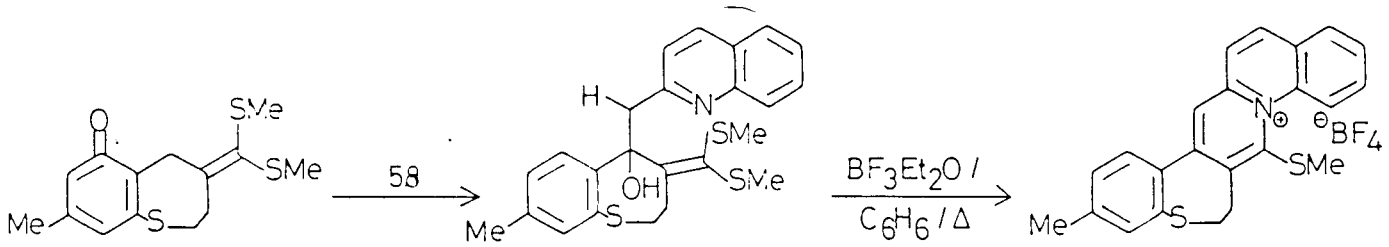


49 k

59 k

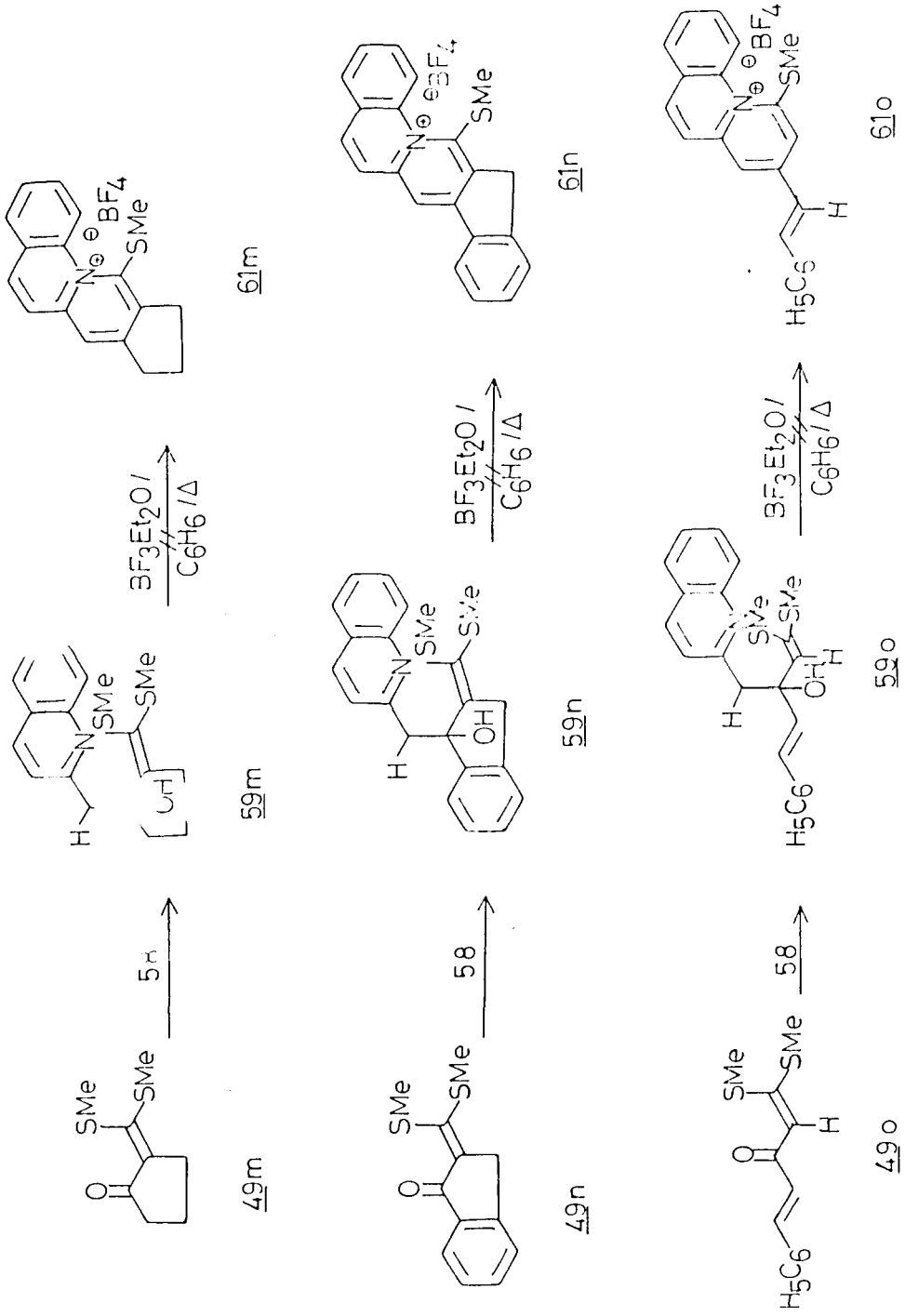
61 k

Scheme - 14



491 591 611

Scheme - 15

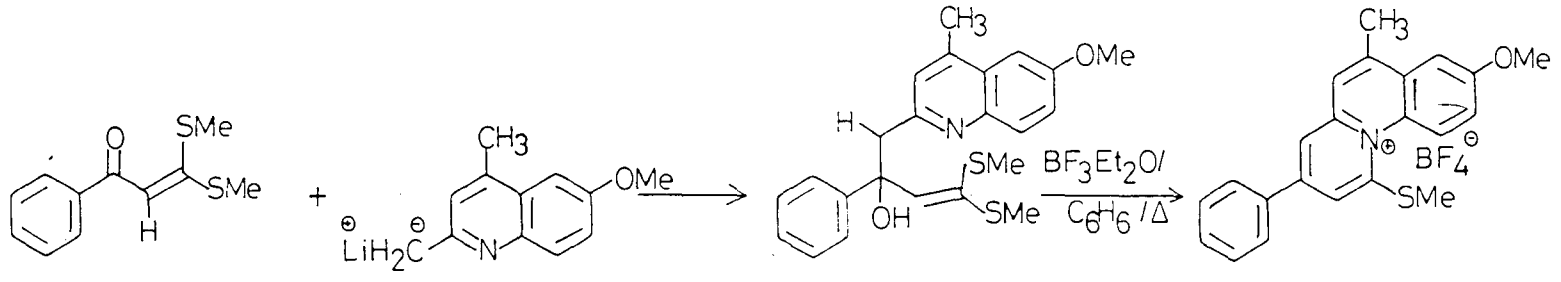


Scheme - 15

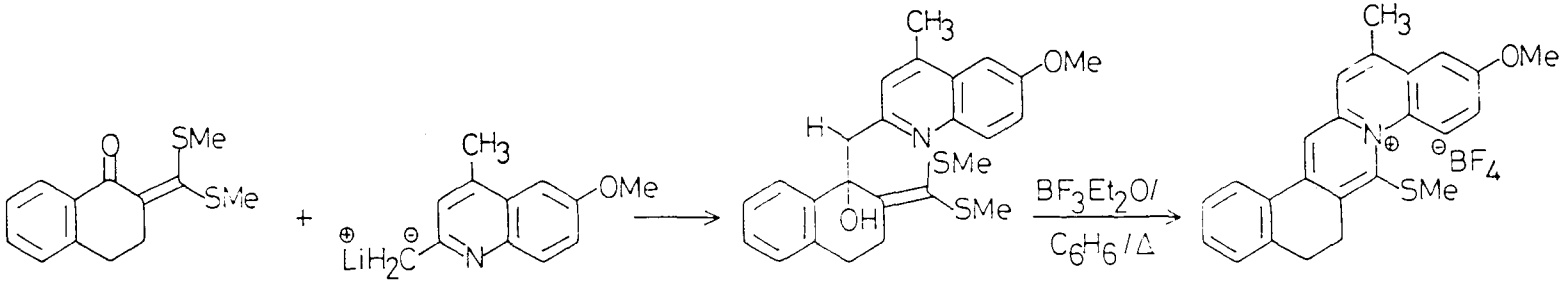
The reaction of 2,4-dimethyl-6-methoxyquinolyllithium 62 with α-oxoketene S,S-acetals was next investigated. Due to the difficulty in obtaining 2,4-dimethyl-6-methoxyquinoline in anhydrous state, only two α-oxoketene S,S-acetals 49a and 49i were reacted with 62 (Scheme 17). Thus, 49a reacted with 62 to yield the corresponding carbinol acetal 63 in high yields which underwent smooth cycloaromatization in the presence of $BF_3.Et_2O$ in refluxing benzene to afford the quinolizinium salt 64 in high yields. Similarly, 49i reacted with 62 to yield the corresponding carbinol acetal 65 and then the quinolizinium salt 66 in high yield (Scheme 17). The structures of 64 and 66 were fully established from their spectral and analytical data which are given in the experimental section.

CONCLUSION

Thus, it is clear that a general methodology is developed for the synthesis of various benzo[c]quinolizinium ions and its benzologs via α-oxoketene S,S-acetals. This methodology is of considerable synthetic importance since a large number of azaallyl anions could be reacted with α-oxoketene S,S-acetals to construct various heteroaromatic compounds. Also, the Woodward's approach to alkaloid synthesis could be efficiently extended for a large number of naturally occurring isoquinoline and indole alkaloids which are under progress in our laboratory.



49 a 62 63 64



49 i 62 65 66

Scheme - 17

EXPERIMENTAL

General : Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. I.R. spectra were recorded on a Perkin Elmer 297 spectrometer. ^{1}H.n.m.r. spectra were recorded at 90 MHz on a Varian EM-390 spectrometer with tetramethylsilane (TMS) as internal standard, and chemical shifts are given in δ(ppm) units down field from TMS. Mass spectra were obtained on a Jeol JMS D-300 spectrometer. ^{13}C.n.m.r were recorded on a Brucker WM-400 spectrometer. Elemental analyses were done on a Heraeus CHN-O-RAPID instrument.

STARTING MATERIALS

The commercial samples of various acetophenones, cyclopentanone, cyclohexanone, cycloheptanone and 6-methoxy-1-tetralone were used as such. 1-Tetralone, b.p.140-150°C (10 mm)[39], indanone, m.p. 39-40°C[40], 3,4-dihydro-8-methyl-1-benzothiepin-5(2H)-one, b.p.138-142°C (0.7 mm)[41] and benzosuberanone, b.p. 90-93°C (1 mm)[42] were prepared according to the reported procedures. Lithium ingot (Aldrich) were cut into pieces and washed twice with dry ether. n-Butyllithium was prepared according to the reported procedures[43]. The α-oxoketene S,S-acetals (49a-n) used in this study were prepared either according to the reported procedure[44-46] which is given in the following section or by slight modification of this procedure (indicated against the name of the compound).

Preparation of α-oxoketene S,S-acetals 49a-n.

General Procedure :

A mixture of the appropriate ketone (0.5 mol) and carbon disulfide (0.5 mol) in dry benzene (100 ml) is added dropwise to an ice-cold and well stirred suspension of sodium t-butoxide (1.0 mol) in dry benzene (200 ml) and the reaction mixture is stirred for 6 hours. Methyliodide (1.1 mol) or dimethylsulfate (0.55 mol) is then gradually added with cooling (ice) and the reaction mixture is further stirred for 6 hours and then refluxed for 1 hour, cooled, poured into ice-cold water (250 ml). The benzene layer is separated and the aqueous phase extracted with benzene (100 ml), the combined extracts are washed with water (200 ml), dried over sodium sulfate (Na_2SO_4) and evaporated to give the crude α-oxoketene S,S-acetals 49 which are further purified either by crystallization (benzene/hexane) or by distillation under reduced pressure.

The following α-oxoketene S,S-acetals were thus prepared: 3,3-bismethylthio-1-phenyl-2-propen-1-one 49a, m.p. 93°C[44]; 3,3-bismethylthio-1-(4-methoxyphenyl)-2-propen-1-one 49b, m.p. 100°C[44]; 3,3-bismethylthio-1-(4-methylphenyl)-2-propen-1-one 49c, m.p. 102°C[44]; 3,3-bismethylthio-1-(2-naphthyl)-2-propen-1-one 49d, m.p. 87°C[44]; 3,3-bismethylthio-1-(2-furyl)-2-propen-1-one 49e, m.p. 91°C[44]; 2-bismethylthiomethylene cyclohexanone 49f, b.p. 118°C (1mm)[44]; 2-bismethylthiomethylene cycloheptanone

49h, m.p. 104°C[44]; 2-bismethylthiomethylene-1-tetralone 49i, m.p. 58°C[46]; 2-bismethylthiomethylene-6-methoxy-1-tetralone 49j, m.p. 78°C[47]; 2-bismethylthiomethylene-1-benzosuberanone 49k, m.p. 75 °C[47]; 4-bismethylthiomethylene-3,4-dihydro-8-methyl-1-benzothiepin-5-(2H)-one 491, m.p. 136°C[48]; 2-bismethylthiomethylene cyclopentanone 49m[47], 2-bismethylthiomethylene-1-indanone 49n, m.p. 70-71°C[49].

The structures of these α-oxoketene S,S-acetals were fully established from the comparison of their spectral and analytical data with those reported.

The cinnamoylketene S,S-acetal 49o was prepared by the reported procedure[50,51] which is given below.

Condensation of α-acetylketene S,S-acetal with benzaldehyde: Preparation of 49o :

To a cooled and stirring solution of sodium ethoxide (6 mmol) in ethanol, a solution of the α-acetylketene S,S-acetal (3 mmol) and benzaldehyde (3 mmol) in minimum quantity of ethanol (10 ml) is added dropwise over a period of 5 min. and stirred for 3 hours. The reaction mixture is then diluted with water (50 ml) and the solid separated is filtered, washed with water (4x20 ml), dried, and recrystallized from ethanol/water. The structure of 49o was confirmed by comparison of its spectral and analytical data with those reported.

The 2-methylquinoline and 2,4-dimethyl-6-methoxyquinoline

were prepared according to the reported procedure[52].

Reaction of 2-methylquinoline and 2,4-dimethyl-6-methoxyquinoline with α-oxoketene S,S-acetals: General Procedure for Carbinol Acetals 59,63 & 65:

A solution of α-oxoketene S,S-acetal 49 (10 mmol) in dry tetrahydrofuran (25 ml) is added to a solution of 2-methylquinolyllithium 58 or 2,4-dimethyl-6-methylquinolyl-lithium 62 [(15 mmol), prepared from 2-methylquinoline (15 mmol) or 2,4-dimethyl-6-methoxy quinoline (15 mmol) and n-BuLi (15 mmol) in THF (25 ml)] at -78°C under N_2 atmosphere. The reaction mixture is further stirred at room temperature for 2 hours, poured into saturated aqueous ammonium chloride (NH_4Cl) solution (50 ml) and extracted with ether (2x50 ml). The combined ether extracts are washed with water (2x50 ml), dried over sodium sulfate (Na_2SO_4) and evaporated to give the crude carbinol acetals 59a-l, 63 and 65 in quantitative yields, which decomposed on attempted purification and therefore, are used as such in the cycloaromatization step.

Cycloaromatization of the Carbinol Acetals: General Procedure for the Synthesis of Quinolizinium Salts 61a-l, 64 and 66:

To a solution of crude carbinol acetals (Ca. 10 mmol), obtained from above reaction, in dry benzene (50 ml), borontrifluoride etherate (3 ml) is added and the reaction mixture is refluxed with stirring for 1 hour. The

reaction mixture is then cooled, benzene layer is removed by decantation. The remaining residue is dissolved in minimum amount of acetone, neutralized with saturated sodium bicarbonate ($NaHCO_3$) solution (20 ml) and the solid separated is collected by filtration, washed with water (3x50 ml) and then with ether (2x10 ml). Analytically pure products are obtained by recrystallization from glacial acetic acid . The structures of 61a-l, 64 and 66 were fully established from their spectral and analytical data which are given below.

1-Methylthio-3-phenylbenzo[c]quinolizinium tetrafluoroborate (61a) was obtained as a yellow solid (AcOH); m.p. 286°C; yield 58%. Its I.R.(KBr), ^{1}H.n.m.r.(DMSO-d_6) and mass spectral data are given in the text. [Found: C,62.02; H,4.46; N,3.47 calculated for $C_{20}H_{16}NSBF_4$ (389.2): C,61.71; H,4.14; N,3.60%].

1-Methylthio-3-(4-methoxyphenyl)benzo[c]quinolizinium tetrafluoroborate (61b) was obtained as a yellow solid (AcOH); m.p. 248°C; yield 79%; I.R.(KBr): ν_{max} = 1625, 1596, 1565 and 1023-1083 (BF_4) cm^{-1}; ^{1}H.n.m.r.(TFA): δ = 2.88 (s,3H,SC$\underline{H}_3$), 4.02 (s,3H,OC$\underline{H}_3$), 7.28 (d,J=9 Hz, A_2B_2, 2H arom), 7.97 (m,3H,$\underline{H}$-7,$\underline{H}$-8,$\underline{H}$-9), 7.99 (d, J=9Hz, A_2B_2, 2H arom), 8.09-8.29 (m,4H,$\underline{H}$-10,$\underline{H}$-6,$\underline{H}$-2,$\underline{H}$-5), 8.77-8.93 (m,1H,$\underline{H}$-4); m/z : 317 (M^+-102,39%), 301(69%), 273(81%) and 258(44%), [Found: C,60.34; H,4.36; N,3.10 calculated for $C_{21}H_{18}NOSBF_4$ (419.2): C,60.16; H, 4.33; N,3.34%].

1-Methylthio-3-(4-methylphenyl)benzo[c]quinolizinium tetrafluoroborate (61c) was obtained as a yellow solid (AcOH); m.p. 268°C; yield, 54%; I.R.(KBr): ν_{max} = 1623,1599,1567 and 1030-1070 (BF_4) cm^{-1}; ^{1}H.n.m.r. (DMSO-d_6): δ=2.46 (s,3H,C<u>H</u>$_3$), 2.94 (s,3H,SC<u>H</u>$_3$), 7.53 (d,J=7.5Hz, A_2B_2, 2H arom), 7.99-8.05 (m,2H,<u>H</u>-5 and <u>H</u>-6), 8.17-8.21 (m,3H,A_2B_2 and <u>H</u>-2) 8.32-8.35 (m,1H,<u>H</u>-8) 8.57-8.61 (m,2H,<u>H</u>-4, <u>H</u>-7); 8.74-8.77 (m,1H,<u>H</u>-9) 8.88-8.89 (m,1H,<u>H</u>-10); ^{13}C.n.m.r (DMSO-d_6): δ=21.02 (<u>C</u>H$_3$), 21.10 (S<u>C</u>H$_3$), 119.29, 121.90, 123.34, 123.81, 128.12, 129.05, 129.14, 130.27, 130.58, 135.73,(<u>C</u>H; C-2, C-4, C-5, C-6, C-7,C-8, C-9, C-10 and 4 aromatic carbons), 130.41, 132.63, 135.74, 142.56, 146.03, 148.43, 155.89 (C-1, C-3, C-4a, C-6a, C-10a, C-1' and C-4'); m/z : 317 (M^+-BF_4, 23%), 301(28%), and 285(25%), [Found: C, 62.37; H,4.65; N,3.69 calculated for $C_{21}H_{18}NSBF_4$ (403.2): C, 62.55; H, 4.50; N, 3.47%].

1-Methylthio-4-(2-naphthyl)benzo[c]quinolizinium tetrafluoroborate (61d) was obtained as a yellow solid (AcOH); m.p. 265°C; yield, 61%; I.R.(KBr): ν_{max} = 1620, 1600, 1570 and 1030-1080 (BF_4) cm^{-1}; ^{1}H n.m.r. (TFA): δ = 2.87 (s, 3H, SC<u>H</u>$_3$), 7.68-7.72 (m,2H$_{naphthyl}$), 7.93-8.37 (m, 8H, 4H$_{naphthyl}$, <u>H</u>-7, <u>H</u>-8, <u>H</u>-9, <u>H</u>-10), 8.39-8.68 (m,4H,<u>H</u>-6,<u>H</u>-2,<u>H</u>-5,<u>H</u>-1' naphthyl), 8.83-9.33 (m,1H, <u>H</u>-4); m/z : 337 (M^+-1-2, 20%) and 294 (29%), [Found: C,65.81; H,4.29; N,3.30 calculated for $C_{24}H_{18}NSBF_4$ (439.2): C, 65.62; H,4.13; N,3.19%].

1-Methylthio-3-(2-furyl)benzo[c]quinolizinium tetrafluoroborate (61e) was obtained as a yellow solid (AcOH); m.p. 243°C; yield, 49%; I.R.(KBr):ν_{max} = 1623, 1600, 1565 and 1039-1117 (BF_4) cm^{-1}; ^1H n.m.r (DMSO-d_6): δ=2.89 (s, 3H,SCH_3), 6.97-6.99 (dd,J=3.5 and 1.5Hz; 1H, H-4' furyl), 7.98-8.01 (m, 3H, H-10, H-3' and H-5' furyl), 8.22 (d, J = 9Hz,1H,H-5), 8.27-8.32 (m,2H, H-8,H-9), 8.44 (d, J=2Hz, 1H, H-7), 8.56 (d, J=9Hz, 1H, H-6), 8.62 (1H, H-4) 8.67-8.70 (m, 1H,H-2);^{13}C n.m.r (DMSO-d_6): δ=22.10 (SCH_3), 115.13, 116.39, 118.14, 120.10, 124.25, 124.65, 128.81, 129.84, 130.00, 131.29, 133.29, 133.71, 136.68, 138.47, 147.37, 149.79, 156.56 (C-1, C-2, C-3, C-4, C-4a, C-5, C-6, C-6a, C-7, C-8, C-9, C-10, C-10a, C-2', C-3', C-4' and C-5'); m/z : 276 (M^+-102,100%); 247 (23%), 233(28%) and 204(30%), [Found: C, 57.28; H, 3.79; N, 3.65 calculated for $C_{18}H_{14}NOSBF_4$ (379.1): C, 57.02; H, 3.72; N, 3.69%].

1-Methylthio-3-(2-thiophenyl)benzo[c]quinolizinium tetrafluoroborate (61f) was obtained as a green solid (AcOH); m.p. 241°C; yield, 59%; I.R.(KBr):ν_{max} = 1618,1599,1568 and 1032-1100 (BF_4) cm^{-1}; ^1H n.m.r.(TFA): δ=2.87 (s,3H,SCH_3), 7.37 (dd, J=3.5Hz, 1H, H-4' thiophenyl), 7.79-8.30 (m,9H, H-7,H-8, H-9, H-10, H-3' and H-5' thiophenyl, H-6, H-2, H-5), 8.73-8.97 (m,1H, H-4); m/z : 308 (M^+-BF_4, 11%), 293(39%), 292(100%) and 249(31%), [Found: C,54.47; H,3.69; N,3.35 calculated for $C_{18}H_{14}NS_2BF_4$ (395.2): C,54.70; H,3.57; N,3.54%].

12-Methylthio-2,3,4,5-tetrahydrobenz[g]benzo[c]quinolizinium tetrafluoroborate (61g) was obtained as a yellow solid (AcOH); m.p. 170°C; yield, 81% I.R.(KBr):ν_{max} =1620, 1593, 1564 and 1036-1122 (BF_4) cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=1.86-2.03 (m, 4H, 2H-9 and 2H-10), 2.13 (s,3H,SCH_3), 3.12-3.24 (m,4H, 2H-8 and 2H-11), 7.88-7.98 (m,2H, H-2, H-3), 8.08-8.13 (m,1H,H-6) 8.27-8.35 (m,2H,H-7 and H-5), 8.55 (d, J=6Hz, 1H, H-4) 8.84 (d, J=6Hz, 1H, H-1); ^{13}C n.m.r. (DMSO-d_6): δ=19.55 (SCH_3), 20.60, 21.65 (CH_2, C-9, C-10), 28.45, 29.42 (CH_2, C-8, C-11, 122.87, 124.00, 125.02, 128.86, 128.90, 130.17, 135.29(CH, C-1, C-2, C-3, C-4, C-5, C-6, C-7), 127.85, 133.80, 141.43, 144.00, 150.51, 152.72 (C-4a, C-6a, C-7a, C-11a, C-12, C-13a); m/z : 280 (M^+-BF_4, 16%), [Found: C, 58.68; H, 5.02; N, 3.73 Calculated for $C_{18}H_{18}NSBF_4$ (367.2): C, 58.87; H, 4.94; N, 3.81%].

1-Methylthio-cycloheptan[g]benzo[c]quinolizinium tetrafluoroborate (61h) was obtained as a yellow solid (AcOH); m.p. 168°C, yield, 82%; I.R.(KBr):ν_{max} =1620, 1595, 1568 and1040-1115 (BF_4) cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=1.67-2.03 (m,6H,2H-9, 2H-10 and 2H-11), 2.19 (s, 3H, SCH_3), 3.33-3.45 (m, 2H, 2H -8), 3.50-3.67 (m,2H, 2H-12), 7.97 (d, J=9Hz, 2H, H-1, H-4), 8.20 (d, J=9Hz,2H, H-5, H-6), 8.39 (s, 1H, H-7), 8.62 (t, J=9Hz, 2H, H-1, H-4), 8.20 (d, J=9Hz, 2H, H-5, H-6), 8.39 (s, 1H, H-7), 8.62 (t, J=9Hz, 2H, H-2, H-3);^{13}C n.m.r. (DMSO-d_6): δ=22.82 (SCH_3), 27.44, 27.94, 31.58 (CH_2, C-9, C-10 and C-11), 34.47, 36.51 (CH_2,

C-8, C-12), 123.45, 126.08, 126.17, 128.76, 129.49, 129.86, 131.05, 134.78, 137.14, 145.30, 147.89, 149.81, 158.55 (C-1, C-2, C-3, C-4, C-4a, C-5, C-6, C-6a, C-7, C-7a, C-12a, C-13 and C-13b); m/z : 297 (M^+-102, 24%), 278(100%), 246(33%), 217(27%), [Found: C, 59.73; H, 5.49; N, 3.45 calculated for $C_{19}H_{20}NSBF_4$ (381.2): C, 59.86; H, 5.29; N, 3.67%].

8-Methylthio-9,10-dihydronaphth[1,2-b]benzo[f]quinoliznium tetrafluoroborate (61i) was obtained as a yellow solid (AcOH); m.p. 270°C; yield, 49%; I.R.(KBr): ν_{max} =1619, 1593, 1562 and 1038-1115 (BF_4) cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=2.30 (s, 3H, $SC\underline{H}_3$), 3.03-3.27 (m, 4H, 2H-5 and 2H-6), 7.53-7.67 (m, 3H, H-2, H-3, H-4), 7.93-8.10 (d, J=3Hz, 2H, H-12, H-13), 8.27-8.45 (m, 3H, H-1, H-10, H-11), 8.52-8.70 (m, 2H, H-9, H-12), 9.11 (m, 1H, H-15); ^{13}C n.m.r. (DMSO-d_6): δ=21.07 ($S\underline{C}H_3$), 27.11, 28.50 ($\underline{C}H_2$, C-5, C-6), 119.15, 123.44, 125.20, 126.52, 128.12, 128.75, 128.96, 129.20, 130.37, 132.68, 136.06 (CH, C-1, C-2, C-3, C-4, C-9, C-10, C-11, C-12, C-13, C-14, C-15), 127.99, 133.60, 139.72, 144.47, 145.23, 149.63 (C-4a, C-6a, C-7, C-8a, C-12a, C-14a, C-15a, C-15b); m/z : 313 (M^+-102, 100%) and 281(31%), [Found: C, 63.51; H,4.47; N,3.19 calculated for $C_{22}H_{18}NSBF_4$ (415.2): C, 63.63; H,4.37; N, 3.37%].

8-Methylthio-12-methoxy-9,10-dihydronaphth[1,2-b]benzo[f]-quinolizinium tetrafluoroborate (61j) was obtained as a yellow solid (AcOH); m.p. 196°C; yield, 68%; I.R.(KBr): ν_{max} =1660,1604, 1554 and 1038-1140 (BF_4) cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=2.23 (s, 3H, $SC\underline{H}_3$), 2.93-3.18 (m,4H, 2H-5 and

2H-6), 3.89 (s, 3H, OCH_3), 6.83-7.19 (m, 2H, H-2, H-4), 7.82-8.07 (m, 3H, H-10, H-11, H-1), 8.19-8.33 (m,2H, H-13, H-14), 8.37-8.60 (m, 2H, H-9, H-12), 8.80-8.90 (m, 1H, H-15); m/z : 343 (M^+-102,48%) and 342(100%), [Found: C, 62.08; H, 4.59; N, 2.94 Calculated for $C_{23}H_{20}NOSBF_4$ (445.2): C, 62.04; H,4.53; N,3.15%].

8-Methylthio-9,10-dihydro-11(2H)benzosuberan[1,2-b]benzo-[f]quinolizinium tetrafluoroborate (61k) was obtained as a yellow solid (AcOH); m.p. 241°C; yield, 70%; I.R.(KBr): ν_{max} =1618, 1596, 1589, 1562 and 1040-1105 (BF_4) cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=2.25 (s, 3H, SCH_3), 2.51-2.90 (m, 6H, 2H-5, 2H-6 and 2H-7), 7.50-7.76 (m, 3H, H-2, H-3, H-4), 7.83-8.13 (m, 3H, H-11, H-12, H-1), 8.26-8.47 (m, 2H, H-14, H-15), 8.58-8.75 (m, 2H, H-10, H-13), 8.97-9.17 (m, 1H, H-16); m/z : 327 (M^+-102,100%), 311(15%) and 299(28%), [Found: C, 64.17; H, 4.72; N, 2.98 Calculated for $C_{23}H_{20}NSBF_4$ (429.2): C, 64.35; H, 4.70; N, 3.26%].

8-Methylthio-13-methyl-9,10-dihydro[11]benzothiepin[4,5-b]benzo[f]quinolizinium tetrafluoroborate (61l) was obtained as a yellow solid (AcOH); m.p. 210°C; yield, 80%; I.R.(KBr):ν_{max} =1621, 1600, 1568 and 1035-1084 (BF_4) cm^{-1}; ^1H n.m.r. (DMSO-d_6): δ=2.10 (s, 3H, CH_3), 2.45 (s, 3H, SCH_3), 3.34 (s, 2H, 2H-14), 3.60 (distorted t, J=4Hz, 2H, 2H-13), 7.63 (m, 2H, H-11 and H-4), 7.73-8.11 (m, 3H, H-1, H-2, H-3), 8.27-8.43 (m, 2H, H-8, H-9), 8.78 (d, J=9Hz, 2H, H-6, H-7), 9.17-9.36 (m, 1H, H-5); ^{13}C n.m.r. (DMSO-d_6): δ=20.92 (CH_3), 21.50 (SCH_3), 31.68, 38.50 (CH_2, C-13,

C-14), 124.44, 125.09, 125.93, 129.10, 129.92, 130.08, 131.09, 131.33, 131.43, 131.73, 135.39, 136.61, 137.61, 138.52, 142.89, 143.21, 146.38, 149.34, 153.15 (C-1, C-2, C-3, C-4, C-4a, C-5, C-6, C-6a, C-7, C-7a, C-7b, C-8, C-9, C-10, C-11, C-15, C-15b); m/z : 359 (M^+-102,55%), 358(100%) and 326(26%), [Found:C, 59.67; H, 4.49; N, 3.00 Calculated for $C_{23}H_{20}NS_2BF_4$ (461.3): C, 59.88; H, 4.37; N, 3.04%].

1-Methylthio-3-phenyl-6methyl-8-methoxybenzo[c]quinolizinium tetrafluoroborate (64) was obtained as a yellow solid (AcOH); m.p. 210°C; yield, 47%; I.R.(KBr):ν_{max}=1624, 1613, 1570 and 1030-1082 (BF_4) cm^{-1}; ^1H n.m.r. (TFA): δ=2.84 (s, 3H, $C\underline{H}_3$), 2.89 (s, 3H, $SC\underline{H}_3$), 4.13 (s, 3H, $OC\underline{H}_3$), 7.48-7.61 (m, 1H, <u>H</u>-7), 7.65-7.81 (m, 4H, <u>H</u>-2, <u>H</u>-4, <u>H</u>-5, <u>H</u>-8), 7.82-8.05 (m,3H arom), 8.18 (dd, J=6 and 3Hz,2H, <u>H</u>-3' and <u>H</u>-5'), 887 (d, J=9Hz, 1H, <u>H</u>-10); ^{13}C n.m.r. (DMSO-d_6): δ=19.69 ($\underline{C}H_3$), 22.17 ($S\underline{C}H_3$), 57.13 ($O\underline{C}H_3$), 107.75, 117.94, 119.88, 122.71, 124.11, 126.11, 127.56, 128.87, 130.45, 131.08, 132.43, 134.62, 139.08, 145.22, 145.39, 148.39, 154.89, 160.90, 175.63 (C-1, C-2, C-3, C-4, C-4a, C-5, C-6, C-6a, C-7, C-8, C-9, C-10 and C-10a); m/z : 340 (M^+-93,84%), [Found: C,61.19; H, 4.75; N, 3.20 Calculated for $C_{22}H_{20}NOSBF_4$ (433.2): C, 60.98; H, 4.65; N, 3.23%].

8-Methylthio-4-methoxy-2-methyl-9,10-dihydronaphth[1,2-b]benzo[f]quinoliznium tetrafluoroborate (66) was obtained as a yellow solid (AcOH); m.p. 140°C; Yield, 61%; I.R.(KBr):ν_{max} =1622, 1614, 1568 and 1040-1085 (BF_4) cm^{-1};

^{1}H n.m.r. (DMSO-d_6): δ=2.22 (s, 3H, $C\underline{H}_3$), 2.84 (s, 3H, $SC\underline{H}_3$), 3.10 (distorted t, J=7Hz,2H, 2H-5), 3.90 (distorted t, J=7Hz, 2H, 2H-6), 4.03 (s, 3H, $OC\underline{H}_3$), 7.42-7.62 (m,5H, H-1,H-2, H-3, H-4, H-12), 8.05 (s,1H, H-14), 8.17-8.47 (m, 2H, H-9, H-10), 8.82 (s, 1H, H-15); m/z : 372 (M^+-BF_4,12%) and 357(18%), [Found: C, 62.61; H, 4.93; N, 2.85 Calculated for $C_{24}H_{22}NOSBF_4$ (459.3):C, 62.76; H, 4.83; N, 3.05%].

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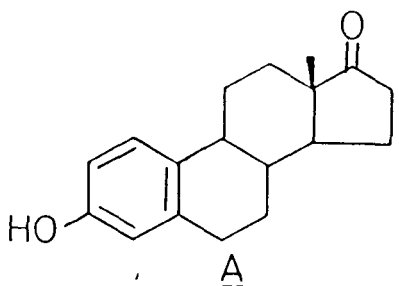
CHAPTER - V

REACTION OF 3-METHOXY-16-BISMETHYL-THIOMETHYLENE ESTRONE WITH VARIOUS BINUCLEOPHILES AND ALLYL ANIONS : A GENERAL METHOD FOR THE CONSTRUCTION OF HETEROCYCLIC AND AROMATIC RING SYSTEMS ON D-RING.

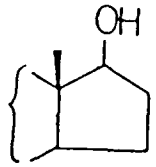
INTRODUCTION

The estrone (A) is the parent nucleus of female sex hormones which are known to influence the reproductive organs of mammals. They are responsible for the growth, development and maintenance of the female reproductive tract and secondary sex organs. The parent estrone molecule has been greatly modified[1] chemically to



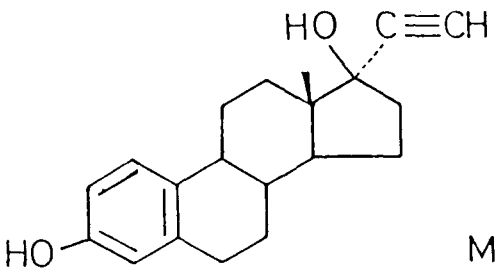
A

develop new compounds to increase their hormonal activities. The estradiol (B) is a potent estrogen containing 17 β-hydroxy group

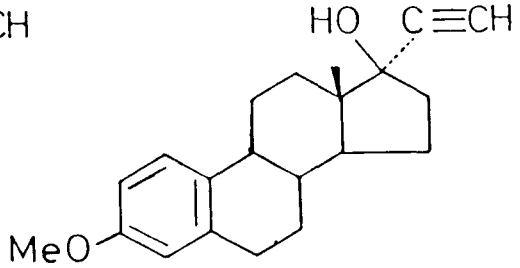


B

which is obtained by the stereospecific Lithium Aluminium Hydride (LAH) reduction[2] on the 17-carbonyl group of estrone. This attack is preferred since the reducing agent attacks from the sterically less hindered side. Some of these derivatives have been administered either as a mixture with progestin or sequentially to animals and humans to control birth. In addition to estradiol, the 17 α-ethynylestra-1,3,5(10)-triene-3,17β-diol (C) (estranol) and its 3-methyl ether (D) (mestranol) have been used



C



D

with various progestins in the available contraceptive preparations. A large number of estrogens have been prepared in an effort to evolve more potent compounds[3].

The antifertility activity of various estrogens often parallels their estrogenic properties and consequently the latter properties become prominent and manifest their characteristic physiological effects in accord with the *corresponding increase in dosage administered to prevent* conception. Therefore, many attempts have been made in recent past to obtain compounds where a distinct separation between estrogenic and antifertility properties could be recognized[4]. Compounds which possess potent antifertility properties and minimal estrogenic properties may act by a mechanism that does not involve hypothalamic axis, thus allowing the normal menstrual cycle. Though some success has been achieved to separate estrogenicity and antifertility effects,the problem remains unsolved to a large extent.

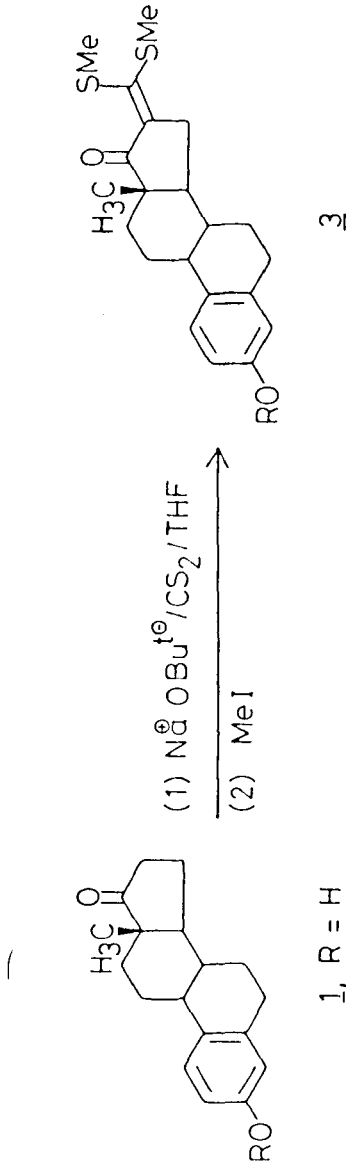
The chemical modification of estrone (A) has been generally achieved by addition of carbon nucleophiles which have been shown to attack from the α-side to yield the corresponding 17β-hydroxy compounds. However, no efforts have been made to alter the structure of estrone (A), by constructing both heterocyclic and carbocyclic rings over the D-ring. The physiological activities of these compounds may be of potential importance since these compounds are unknown in the literature.

As a part of our interest in the chemistry of α-oxoketene S,S-acetals it was proposed to prepare the S,S-acetal of estrone so that an efficient 3-carbon 1,3-electrophilic

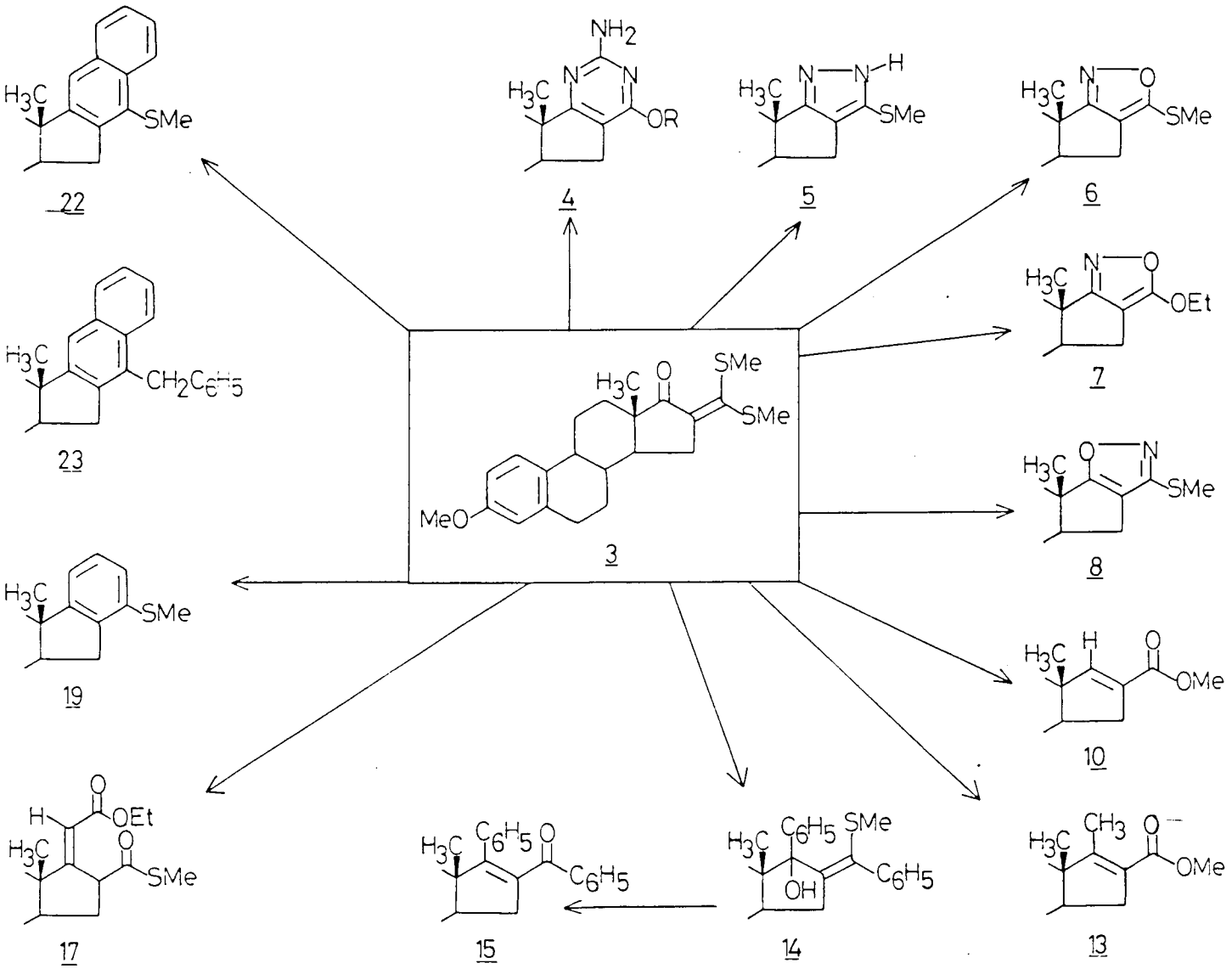
structural frame is available for further elaboration to construct rings, both heterocyclic and carbocyclic, in addition to open chain derivatives. In the present chapter, it was, therefore, undertaken to prepare the hitherto unreported 3-methoxy-16-bismethylthiomethylene estrone (3) in 65% yield (Scheme 1). The structure of 3 was fully established from the characteristic ^{1}H n.m.r. signal for the bismethylthio protons at δ2.43. The other spectral and analytical data of 3 are described in the experimental section.

Various transformations achieved in the present investigation have been briefly described in Scheme 2. Thus, when 3 was reacted with guanidine nitrate in the presence of sodium methoxide in refluxing methanol, the reaction mixture afforded a compound in 81% yield which was characterized as estr-3,4'-dimethoxy-2'-amino[17,16-*d*]pyrimidine (Scheme 3) on the basis of its spectral and analytical data which are described in the experimental section. The formation of alkoxy group in pyrimidine ring has already been achieved in this laboratory[5,6]. Similarly, the ethoxy and n-propoxy pyrimidines 4b and 4c were prepared by using appropriate alcohol in the reaction mixture. The spectral and analytical data for 4b and 4c are described in the experimental section.

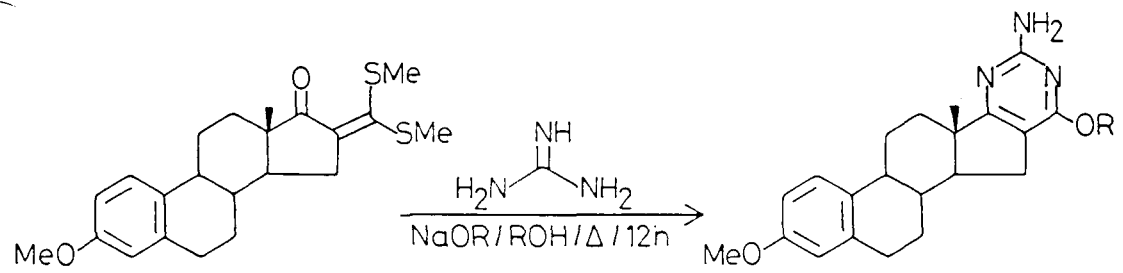
When 3 was refluxed with hydrazine hydrate in ethanol, the corresponding 2'H-estr-3-methoxy-5'-methlthio-16-eno [17,



Scheme-1



Scheme - 2



3

4, a, R = Me
b, R = Et
c, R = n-Pr

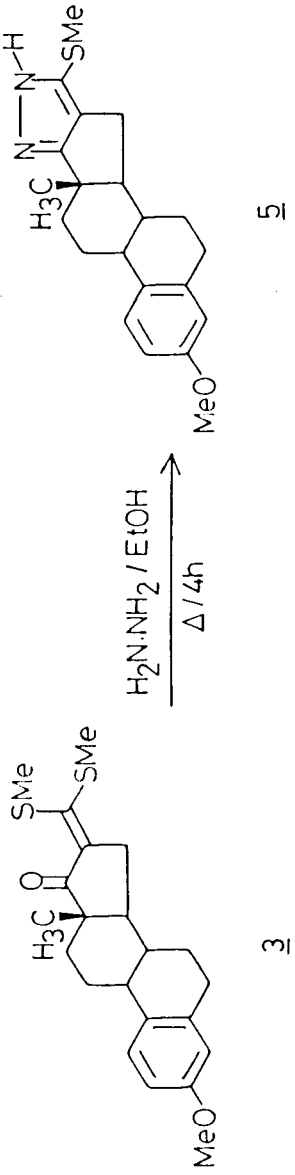
Scheme-3

16-*c*]pyrazole (5) was obtained in 79% yield (Scheme 4). The structure of 5 was fully in accordance with its spectral and analytical data which are described in the experimental section.

Three different isoxazoles 6,7 and 8 were prepared by reacting 3 with hydroxylamine hydrochloride in different reaction conditions. Thus, when, 3 was reacted with hydroxylamine hydrochloride in the presence of sodium ethoxide, the reaction mixture, after 24 hours of refluxing,afforded estr-3-methoxy-5'-methylthio [16,17-*c*] isoxazole (6) in 69% yield (Scheme 5). However, when the refluxing time was increased to 36 hours, the corresponding 5-ethoxyisoxazole 7 was obtained in 73% yield (Scheme 5). The structures of 6 and 7 were fully established from their spectral and analytical data which are given in the experimental section.

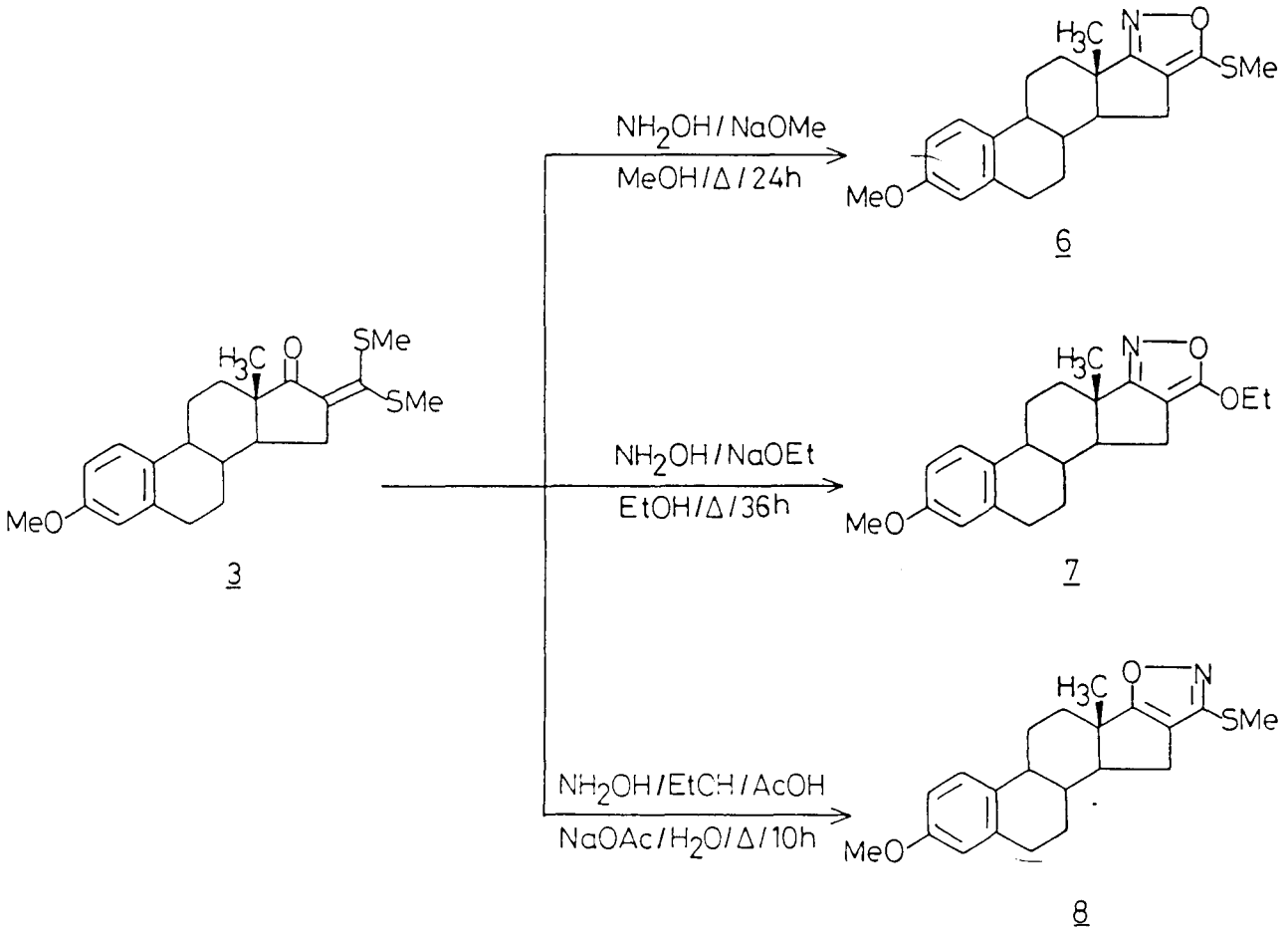
The other regioisomer 8 was obtained when 3 was reacted with hydroxylamine hydrochloride at a lower pH of 2.2. The compound was characterized as estr-3-methoxy-3'-methylthio-16-eno[17,16-*d*]isoxazole 8 (Scheme 5) on the basis of its spectral and analytical data which are given in the experimental section. The mechanism governing the formation of the regioisomers has been discussed in our earlier communication[7].

The 3 was converted to the corresponding ene-ester 10 in 67% yield following the sequence of reactions shown in scheme 6. Thus, when, 3 was subjected to sodium



3 5

Scheme - 4

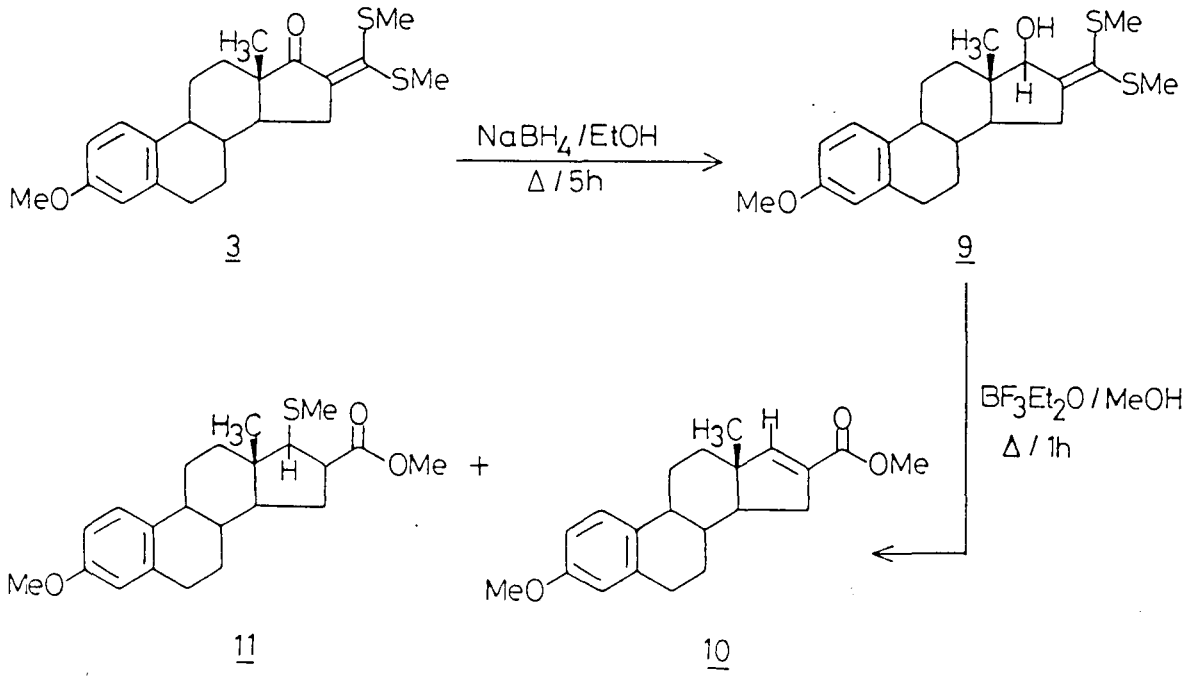

NH2OH / NaOMe
MeOH / Δ / 24h
NH2OH / NaOEt
EtOH / Δ / 36h
NH2OH / EtCH / AcOH
NaOAc / H2O / Δ / 10h
H3C
O
SMe
SMe
MeO
N
O
OEt
SMe
3
6
7
8

Scheme -5

borohydride reduction, the corresponding carbinol acetal 9 was obtained in quantitative yield which was directly subjected to methanolysis in the presence of borontrifluoride etherate in methanol to give the ene ester 10 alongwith an addition product 11 which is supposed to have been formed by the attack of methylmercaptan on the hydroxy carbon followed by solvolysis. The compounds 10 and 11 were fully characterized on the basis of their spectral and analytical data which are described in the experimental section.

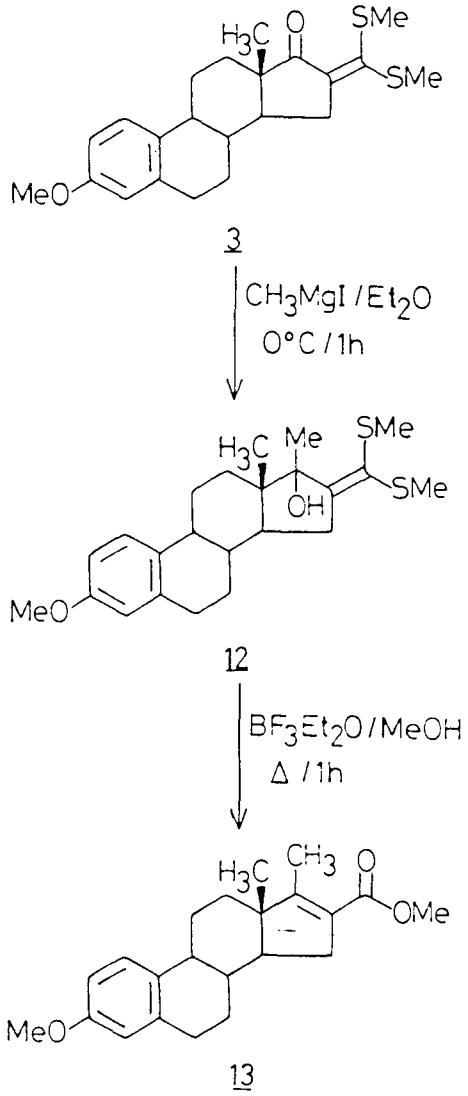
Similarly, the 3 was reacted with methyl magnesium iodide to afford the corresponding carbinol acetal 12 in quantitative yield. The carbinol acetal 12 was directly subjected to borontrifluoride etherate assisted methanolysis to afford the corresponding ene ester 13 in 83% yield (Scheme 7), which was characterized as 3-methoxy-13,17-dimethyl-16-carbmethoxy-16-eno-6, 7, 8, 9, 11, 12-hexahydrocyclopenta[a]phenanthrene on the basis of its spectral and analytical data which are given in the experimental section.

However, phenyl magnesium bromide underwent sequential 1,4-followed by 1,2-addition on 3 to yield the corresponding carbinol acetal 14 in 93% yield (Scheme 8). The structure of 14 was fully established from its spectral and analytical data which are described in the experimental section. The carbinol acetal 14 was



3 9 11 10

Scheme - 6

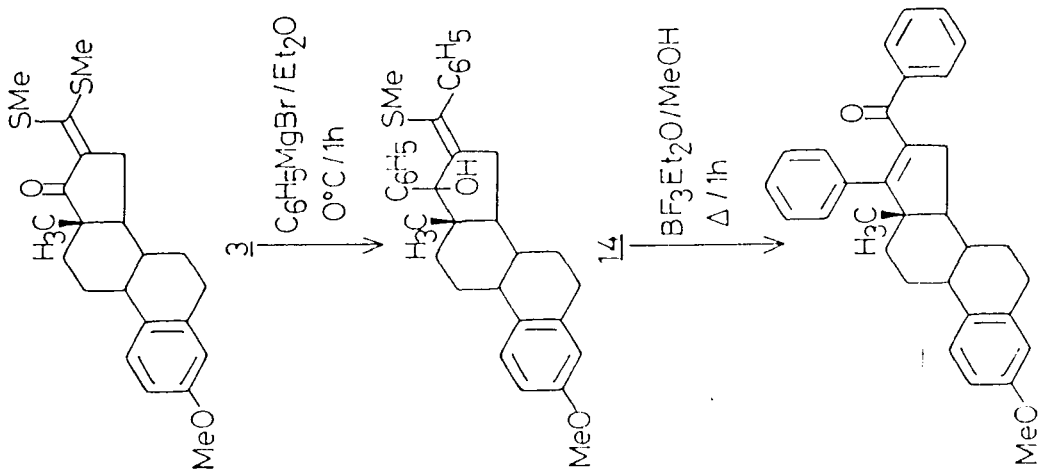

H3C
O
SMe
SMe
MeO
3
CH3MgI / Et2O
0°C / 1h
H3C
Me
SMe
OH
SMe
MeO
12
BF3Et2O / MeOH
Δ / 1h
H3C
CH3
O
OMe
MeO
13

Scheme -7

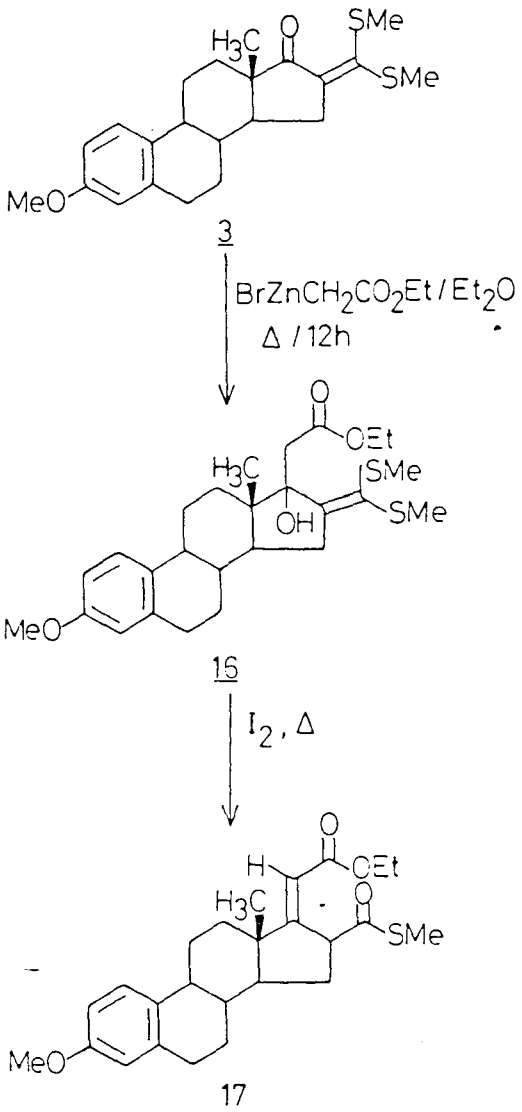
conveniently solvolyzed in the presence of boron-trifluoride etherate in dry benzene to yield the corresponding ketone 15 in 89% yield (Scheme 8). The 15 was characterized as 3-methoxy-13-methyl-16-benzoyl-17-phenyl-16-eno-6,7,8,9,11, 12-hexahydrocyclopenta[a]phenanthrene on the basis of its spectral and analytical data which are described in the experimental section.

The reactivity of 3 was then examined with Reformatsky reagent. Thus, when ethylbromozinc acetate was reacted with 3, the corresponding carbinol acetal 16 was obtained in quantitative yield (monitored by tlc) which was directly dehydrated in the presence of iodine followed by hydrolysis by dilute sulfuric acid to yield the corresponding exocyclic ene ester 17 in 63% yield (scheme 9) which was characterized as 3-methoxy-13-methyl-16-carbthiomethyl-17-carbethoxymethylene-6,7,8,9,11,12-hexahydrocyclopenta[a]phenanthrene on the basis of the characteristic ^{1}H n.m.r. signal at δ 5.31 due to the vinylic proton. The other spectral and analytical data in support of the structure of 17 are given in the experimental section.

It was considered of interest to construct aromatic and condensed aromatic ring over the D-ring of estrone. Thus, when 3 was reacted with allylmagnesium bromide, the corresponding carbinol acetal 18, was obtained in high yield. The carbinol acetal 18 was directly subjected to cycloaromatization in the presence of borontrifluoride


SMe
SMe
O
H3C
MeO
3
C6H5MgBr / Et2O
0°C / 1h
C6H5
SMe
C6H5
OH
H3C
MeO
14
BF3Et2O/MeOH
Δ / 1h
O
H3C
MeO
15

Scheme - 8


H3C
O
SMe
SMe
MeO
3
BrZnCH2CO2Et / Et2O
Δ / 12h
O
OEt
H3C
SMe
OH
SMe
MeO
16
I2 , Δ
O
H
OEt
H3C
O
SMe
MeO
17

Scheme - 9

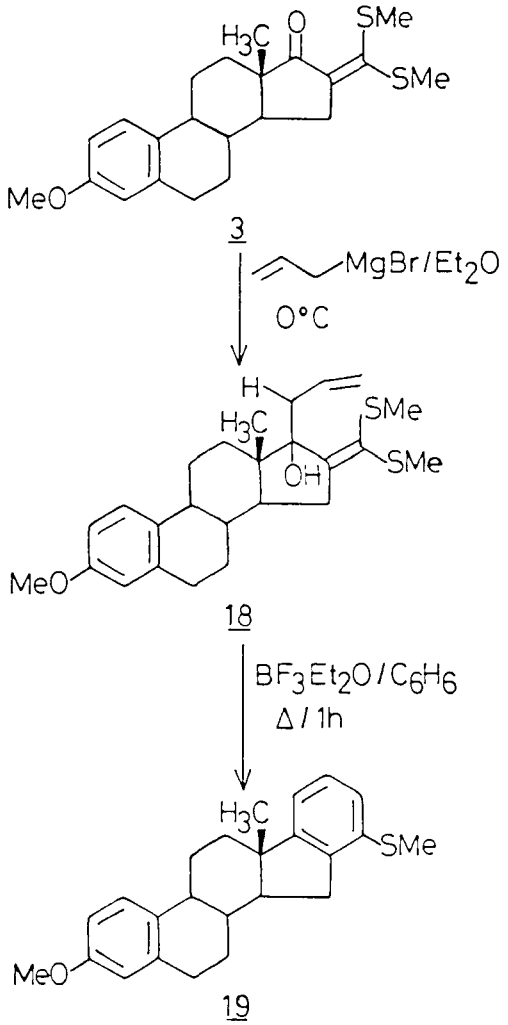
etherate in refluxing benzene to yield the corresponding indane 19 in 87% yield (Scheme 10). The 19 was characterized as 3-methoxy-13-methyl-21-methylthio-6,7,8,9,11,12,14-heptahydro-15H-naphtho[1,2-*c*]fluorene on the basis of its spectral and analytical data which are given in the experimental section. Benzylmagnesium bromide, however, reacted with 3 to yield a mixture of two products 22 and 23 in 31% and 59% yields respectively (Scheme 11). The formation of 22 and 23 demonstrates that benzylmagnesium bromide, in addition to the sequential 1,4-followed by 1,2-addition, also gives the 1,2-addition product. The structures of 22 and 23 were fully estrablished from their spectral and analytical data which are given in the experimental section.

CONCLUSION

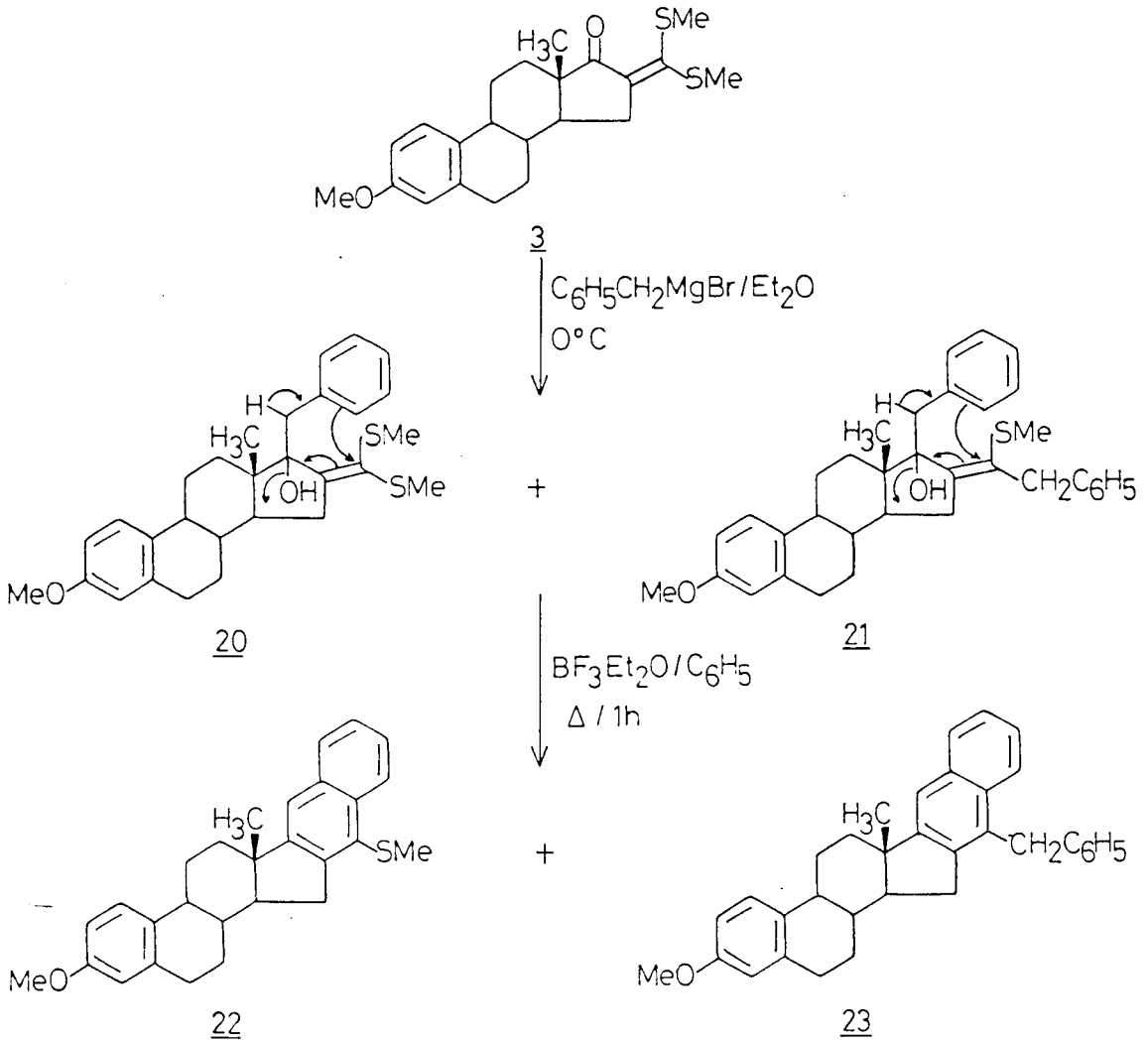
In conclusion, it has been possible to prepare a number of interesting and hitherto unknown derivatives of estrone by extending the methods developed in this laboratory. These compounds could be potential antifertility agent and have been submitted for biological screening to M/s. Organon International.

EXPERIMENTAL

General : Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. I.R. spectra were recorded on a Perkin Elmer-297 spectrometer. ^{1}H n.m.r. spectra were recorded on a Varian EM-390 (90MHz) spectrometer using tetramethyl


H3C
O
SMe
SMe
MeO
3
MgBr/Et2O
0°C
H
H3C
SMe
SMe
OH
MeO
18
BF3Et2O/C6H6
Δ / 1h
H3C
SMe
MeO
19

Scheme -10


H3C
O
SMe
SMe
MeO
3
C6H5CH2MgBr / Et2O
0° C
H
H3C
SMe
OH
SMe
MeO
20
+
H
H3C
SMe
OH
CH2C6H5
MeO
21
BF3Et2O / C6H5
Δ / 1h
H3C
SMe
MeO
22
+
H3C
CH2C6H5
MeO
23

Scheme -11

silane (TMS) as internal standard and the chemical shift values are expressed as δ(ppm) down field from TMS. Mass spectra were recorded on a Jeol JMS D-300 spectrometer. Elemental analyses were done on a Heraeus CHN-O-RAPID instrument.

STARTING MATERIALS:

The pure estrone was obtained from M/s. Organon Research Centre, Calcutta, India. Commercially available samples of carbon disulfide (SD's), methyliodide (SISCO), t-butanol (SD's), sodium, zinc powder, sodium borohydride, guanidine nitrate, hydroxylamine hydrochloride, hydrazine hydrate, acetone, potassium carbonate, magnesium, acetic acid, etc., were used as such. Benzene, ether, alcohol, bromobenzene, allylbromide, benzyl bromide, ethylbromoacetate, etc., were purified before use.

Preparation of 3-methoxy estrone (2):

The estrone 1 (10 mmol) is dissolved in acetone (100 ml) and anhydrous potassium carbonate (14 mmol) is added to the reaction mixture. The reaction mixture is refluxed with stirring for 10 hours and then cooled in an ice-bath and methyl iodide (20 mmol) added dropwise. The reaction mixture is stirred for 6 hours (monitored by tlc). The solid potassium carbonate is filtered at suction and the solvent is removed from the filtrate to give the crude product. The residue, thus, obtained, is dissolved in chloroform (100 ml) and washed thrice with water (50 ml),

dried over sodium sulfate and evaporated to give the pure product which was characterized completely on the basis of its spectral and analytical data which are given below.

The 2 was obtained as a colourless solid (chloroform/ hexane); m.p. 170°C; yield, 89%; I.R.(KBr): ν_{max} = 3432, 1738 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=0.90 (s, 3H, $C\underline{H}_3$), 1.37-1.60 (m, 6H, methylene protons), 1.90-2.47 (m, 6H, methylene and methyne protons), 2.80-2.93 (m, 3H benzylic), 3.77 (s, 3H, $OC\underline{H}_3$), 6.63 (s, 1H arom), 6.67 (d, J=7Hz, 1H arom), 7.18 (d, J=7Hz,1H arom), [Found: C, 80.34; H, 8.41 calculated for $C_{19}H_{24}O_2$ (284.3): C, 80.24; H, 8.51%].

Preparation of 3-methoxy-16-bismethylthiomethylene estrone (3):

The 3 was prepared by slight modification of the reported procedure[8-15]. The 3-methoxy estrone 2 (100 mmol) is dissolved in dry tetrahydrofuran (150 ml) and added to a cooled and stirred mixture of carbon disulfide (100 mmol) and sodium t-butoxide (200 mmol) in dry THF (150 ml). The reaction mixture is stirred for 8 hours. Methyl iodide (250 mmol) is added dropwise to the above precooled reaction mixture and stirred for further 8 hours (monitored by tlc). The reaction mixture is poured into a saturated aqueous ammonium chloride solution (150 ml), extracted from chloroform (3x50 ml), dried over sodium sulfate and evaporated to give the crude product which is purified by column chromatography over silica gel using

heaxane/ethylacetate (19:1) as eluent. The product, thus, obtained was fully characterized on the basis of its spectral and analytical data which are given below.

The 3 was obtained as a light yellow solid ($CHCl_3$/hexane); yield, 65% (based on recovered starting material); m.p. 135°C; I.R.(KBr): ν_{max} = 1700 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=0.93 (s, 3H, $C\underline{H}_3$), 1.37-1.67 (m, 5H, methylene and methyne protons), 1.90-2.07 (m, 5H, methylene and methyne protons), 2.43 (s, 6H, $SC\underline{H}_3$), 6.60 (s, 1H arom), 6.61 (d, J=7Hz, 1H arom), 7.14 (d, J=7Hz,1H arom); m/z : 388 (M^+, 37%), 373 (M^+-15,23%), 357 (M^+-31,4%), [Found: C, 68.24; H, 7.01 calculated for $C_{22}H_{28}S_2O_2$ (388.5): C, 68.00; H, 7.26%].

Preparation of estr-3-methoxy-4'-alkoxy-2'-amino[17,16-*d*]-pyrimidines (4a-c): General Procedure:

The pyrimidines 4a-c were prepared according to the reported procedure[5,6] which is given below. Guanidine nitrate (6 mmol) is added to a stirred suspension of appropriate sodium alkoxide (11 mmol) in corresponding dry alcohol (15 ml) and the reaction mixture is stirred for 30 minutes. A solution of the S,S-acetal 3 (6 mmol) in dry alcohol (10 ml) is added to the reaction mixture. The reaction mixture is refluxed for 24 hours (monitored by tlc). The alcohol is removed under vacuo and ice-cold water (15 ml) is added to the residue. The crude products, thus obtained, are filtered at pump and are further

purified by column chromatography over silica gel using hexane/ethyl acetate (19:1) as eluent. The structures of 4a-c were fully established from their spectral and analytical data which are given below.

Estr-3,4'-dimethoxy-2'-amino[17,16-*d*]pyrimidine (4a) was obtained as a colourless solid ($CHCl_3$/hexane); yield, 81%; m.p. 235°C; I.R.(KBr):ν_{max} = 3452, 1629, 1567 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=0.93 (s, 3H, $C\underline{H}_3$), 1.33-1.80 (m, 5H, methylene and methyne protons), 2.07-2.35 (m, 5H, methylene and methyne protons), 2.73-2.90 (m, 3H benzylic), 3.75 (s, 3H, $OC\underline{H}_3$), 3.87 (s, 3H, $OC\underline{H}_3$), 5.13 (brs, 2H, $N\underline{H}_2$, exchangeable with D_2O), 6.60 (s, 1H arom), 6.68 (d, J=7Hz, 1H arom), 7.18 (d, J=9Hz, 1H arom); m/z : 365 (M^+, 100%), 350 (M^+-15,32%), [Found: C, 72.31; H, 7.48; N, 11.52 Calculated for $C_{22}H_{27}N_3O_2$ (365.4): C, 72.30; H, 7.45; N, 11.50%]..

Estr-3-methoxy-4'-ethoxy-2'-amino[17,16-*d*]pyrimidine (4b) was obtained as a colourless solid ($CHCl_3$/hexane); yield , 83%, m.p. 198°C; I.R. (KBr):ν_{max} 3468, 3362, 2914, 1632, 1598, 1567 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ=0.93 (s, 3H, $C\underline{H}_3$), 1.37 (t, J=7.5Hz, 3H, CH_3 of $OCH_2C\underline{H}_3$); 1.56-1.85 (m, 5H, methylene and methyne protons), 2.05-2.55 (m, 5H, methylene and methyne protons), 2.78-3.03 (m, 3H benzylic), 3.85 (s, 3H, $OC\underline{H}_3$), 4.41 (q, J=7.5Hz, 2H, $OC\underline{H}_2$), 5.41 (brs, 2H, $N\underline{H}_2$, exchangeable with D_2O), 6.77 (s, 1H arom), 6.82 (d, J=9Hz, 1H arom), 7.35 (d, J=9Hz,1H arom); m/z : 379 (M^+, 100%), 365 (M^+-15,42%), 349 (M^+-

31,5%), [Found:C, 72.59; H, 7.91; N, 11.14 calculated for $C_{23}H_{29}N_3O_2$ (379.4): C, 72.79; H, 7.70; N, 11.07%].

Estr-3-methoxy-4'-n-propoxy-2'-amino[17,16-*d*]pyrimidine (4c) was obtained as a colourless solid ($CHCl_3$/hexane); yield, 85%; m.p. 242°C; I.R.(Br):ν_{max} = 3380, 3312, 2922, 1634, 1598, 1558 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=0.98 (s, 3H, $C\underline{H}_3$), 1.05 (t, J=7.5Hz, 3H, CH_3 of $OCH_2CH_2C\underline{H}_3$), 1.53-2.10 (m, 8H, methylene, methyne and $C\underline{H}_2C\underline{H}_3$), 2.17-2.73 (m, 5H, methylene and methyne protons), 2.83-3.17 (m, 3H benzylic), 3.97 (s, 3H, $OC\underline{H}_3$), 4.43 (t, J=7Hz, 2H, $OC\underline{H}_2$), 5.13 (brs, 2H, $N\underline{H}_2$, exchangeable with D_2O), 6.91 (s, 1H arom), 6.97 (d, J=9Hz, 1H arom), 7.51 (d, J=9Hz, 1H arom); m/z : 393 (M^+, 100%), 378 (M^+-15,19%), 351 (28%), [Found: C, 73.26; H, 7.98; N, 10.69 calculated for $C_{24}H_{31}N_3O_2$ (393.5): C, 73.25; H, 7.94; N, 10.68%].

Preparation of 2'-H-estr-3-methoxy-5'-methylthio-16-eno[17,16-*d*]pyrazole (5):

The pyrazole 5 was prepared according to the reported procedure[16] which is given below.

The hydrazine hydrate (6 mmol) is added to a solution of the S,S-acetal 3 (5 mmol) in distilled ethanol (20 ml) and the reaction mixture is refluxed for 3 hours (monitored by tlc). The solvent is removed under vacuo and ice-cold water (50 ml) is added to residue. The crude product thus obtained is filtered at pump and is further purified by column chromatography over silica gel using

hexane/ethylacetate (19:1) as eluent. The structure of 5 was fully established from its spectral and analytical data which are given below.

The 5 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 79%; m.p. 194°C; I.R. (KBr): ν_{max} = 3193, 2903, 1611, 1571 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.03 (s, 3H, $C\underline{H}_3$), 1.31-1.93 (m, 5H, methylene and methyne protons), 1.97-2.53 (m, 5H, methylene and methyne protons), 2.43 (s, 3H, $SC\underline{H}_3$), 2.77-3.00 (m, 3H benzylic), 3.73 (s, 3H, $OC\underline{H}_3$), 6.57 (s, 1H arom), 6.61 (d, J=7Hz, 1H arom), 7.07 (d, J=7Hz, 1H arom), 8.77 (brs, 1H, N$\underline{H}$, exchangeable with D_2O); m/z : 354 (M^+, 100%), 339 (M^+-15,39%), 307 (M^+-47,3%), [Found: C, 71.00; H, 7.09; N, 7.70 calculated for $C_{21}H_{26}N_2OS$ (354.5): C, 71.14; H, 7.39; N, 7.90%].

Preparation of estr-3-methoxy-5'-methylthio[16,17-*c*]-isoxazole (6):

The 6 was prepared according to the reported procedure[7] which is given below.

Hydroxylamine hydrochloride (2.5 mmol) is added to a suspension of sodium ethoxide (5 mmol) in dry ethanol (20 ml) and the solution of the S,S-acetal 3 (2.5 mmol) in ethanol (10 ml) is added to the reaction mixture and refluxed for 12 hours (monitored by tlc). The solvent is removed under vacuo and ice-cold water (20 ml) added to the residue, extracted from $CHCl_3$ (3x50 ml), dried over sodium sulfate, evaporated to give the crude product which

was further purified by column chromatography over neutral alumina using carbontetrachloride as eluent. The structure of 6 was fully established from its spectral and analytical data which are given below.

The 6 was obtained as a colourless solid (CCl_4); yield, 69%; m.p. 177°C; I.R. (KBr):ν_{max} = 1599, 1490 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.95 (s, 3H, $C\underline{H}_3$), 1.27-1.73 (m,5H, methylene and methyne protons), 1.83-2.40 (m, 5H, methylene and methyne protons), 2.10 (s, 3H, $SC\underline{H}_3$), 2.73-2.97 (m, 3H benzylic), 3.73 (s, 3H, $OC\underline{H}_3$), 6.53 (s, 1H arom), 6.60 (d, J=9Hz, 1H arom), 7.13 (d, J=9Hz, 1H arom); [Found: C,70.75; H,7.00; N,3.70 ; Calculated for $C_{21}H_{25}NO_2S$ (355.4): C, 70.95 ;H, 7.09; N, 3.94%].

Preparation of estr-3-methoxy-5'-ethoxy[16,17-*c*]isoxazole (7):

The 7 was prepared by the above procedure[7] by extending the refluxing time from 24 to 36 hours. Its structure was fully established from its spectral and analytical data which are given below.

The 7 was obtained as a colourless solid($CHCl_3$); yield, 73%; m.p. 197°C; I.R.(KBr):ν_{max} =1608, 1497 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=0.98 (s, 3H, $C\underline{H}_3$), 1.20 (t, J=6Hz, 3H, $OCH_2C\underline{H}_3$), 1.33-2.60 (m, 10H, methylene and methyne protons), 2.73-3.00 (m, 3H benzylic), 3.48 (q, J=6Hz, 2H, $OC\underline{H}_2CH_3$), 3.77 (s, 3H, $OC\underline{H}_3$) 6.67 (s, 1H arom), 6.75 (d, J=9Hz, 1H arom), 7.25 (d, J=9Hz, 1H arom), [Found:

C,74.60; H,7.80; N, 3.99 calculated for $C_{22}H_{27}NO_3$ (353.4): C, 74.76; H, 7.70; N, 3.96%].

Preparation of estr-3-methoxy-3'-methylthio-16-eno[17,16-*d*] isoxazole (8):

The 8 was prepared according to the reported procedure[7] which is given below.

To a solution of the S,S-acetal 3 (2.5 mmol) in distilled benzene (40 ml) is added glacial acetic acid (24 ml) followed by a solution of hydroxylamine hydrochloride (10 mmol) and sodium acetate (9 mmol) in water (2 ml). The pH of the reaction mixture is thus maintained at 2.2. The reaction mixture is made homogeneous by the addition of distilled ethanol (14 ml). The reaction mixture is then refluxed for 10 hours (monitored by tlc). The solvent is then removed under vacuo. The residue is dissolved in $CHCl_3$ (50 ml) and the solution is washed with water (3x50 ml), dried over sodium sulfate, and evaporated to give the crude product which is further purified by column chromatography over neutral alumina using CCl_4 as eluent. The structure of 8 was fully established from its spectral and analytical data which are given below.

The 8 was obtained as a colourless solid (CCl_4); yield, 75%; m.p. 145°C; I.R. (KBr): ν_{max} = 1608, 1498 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.03 (s, 3H, $C\underline{H}_3$), 1.67-2.47 (m, 10H, methylene and methyne protons), 2.57 (s, 3H, $SC\underline{H}_3$), 2.60-3.07 (m, 3H benzylic), 3.80 (s, 3H, $OC\underline{H}_3$), 6.70 (s, 1H

arom), 6.75 (d, J=9Hz, 1H arom), 7.28 (d, J=9Hz, 1H arom); m/z : 3.55 (M^+, 15%), 173 (100%), 160(47%), [Found: C, 70.75; H, 7.00; N, 3.70 calculated for $C_{21}H_{25}NO_2S$ (355.4) C, 70.95; H, 7.09; N, 3.94%].

Preparation of 3-methoxy-13-methyl-16-carbmethoxy-16-eno-6,7,8,9,11,12-hexahydrocyclopent[a]phenanthrene (10):

The 10 was prepared according to the reported procedure[17], which is given below.

The S,S-acetal 3 (2.5 mmol) is added to a suspension of sodium borohydride (20 mmol) in dry ethanol (25 ml) and the reaction mixture is refluxed for 3 hours. The reaction mixture is cooled and poured into water (100 ml), extracted from $CHCl_3$ (3x50ml), dried over sodium sulfate and evaporated to give the crude carbinol acetal 9 in quantitative yield. The carbinol acetal 9 is dissolved in dry methanol (20 ml). Borontrifluoride etherate (1 ml) is added to the reaction mixture and is refluxed for 36 hours (monitored by tlc). The reaction mixture is cooled and poured into saturated aqueous solution (100 ml) of sodium bicarbonate, extracted from $CHCl_3$ (3x50 ml), dried over sodium sulfate and evaporated to give a mixture of two products 10 and 11 which are separated and purified by column chromatography over silica gel using hexane as eluent. The structure of 10 and 11 were fully established from their spectral and analytical data which are given below.

The 10 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 67%; m.p. 129°C; I.R.(KBr):ν_{max} = 1707, 1610, 1600, 1500 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.90 (s, 3H, CH_3), 1.33-2.43 (m, 10H, methylene and methyne protons), 2.73-3.00 (m, 3H benzylic), 3.67 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.50 (s, 1H arom) 6.51 (d, J=9Hz, 1H arom) 6.80 (s, 1H vinylic), 7.05 (d, J=9Hz,1H arom); m/z : 326 (M^+, 100%), 311 (M^+-15,6%), 295 (M^+-31,5%), 267 (M^+-59,8%), [Found:C, 77.16; H, 8.00 calculated for $C_{21}H_{26}O_3$ (326.4) : C, 77.26; H, 8.03%].

3-Methoxy-13-methyl-17-methylthio-16-carbmethoxy-6,7,8,9,11,12-hexahydrocyclopenta[a]phenanthrene (11) was obtained as a colourless solid ($CHCl_3$/hexane); yield, 28%; m.p. 92°C; I.R.(KBr):ν_{max} = 3000, 2910, 1718, 1598, 1488 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.88 (s, 3H, CH_3), 1.23-2.43 (m,11H,methylene and methyne protons), 2.10 (s, 3H, SCH_3), 2.67-3.00 (m, 3H benzylic), 3.15 (d, J=3Hz, 1H, 17-H), 3.67 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.60 (s, 1H arom), 6.68 (d, J=9Hz, 1H arom), 7.15 (d, J=9Hz,1H arom); m/z : 374 (M^+,72%), 359 (M^+-15,45%), 327 (M^+-47,83%), [Found: C,70.34; H, 8.27 calculated for $C_{22}H_{30}O_3S$ (374.5): C, 70.55; H, 8.07%].

Preparation of 3-methoxy-13,17-dimethyl-16-carbmethoxy-6,7,8,9,11,12-hexahydrocyclopent-16-eno[a]phenanthrene (13):

The 13 was prepared according to the reported procedure[18], which is given below.

Methyliodide (5 mmol) is added dropwise to a cooled and stirred suspension of magnesium (8 mmol) and iodine (1,2-crystals) in dry ether (25 ml). The reaction mixture is further stirred for 30 minutes. A solution of the S,S-acetal 3 (2.5 mmol) in dry benzene (20 ml) is added dropwise to the ice-cold reaction mixture. The reaction mixture is further stirred for 90 minutes (monitored by tlc); poured into an aqueous saturated solution (100 ml) of ammonium chloride, extracted from ether (3x50 ml), dried over sodium sulfate, and evaporated to give the crude carbinol acetal 12 in quantitative yield. The carbinol acetal 12 is directly dissolved in dry benzene (20 ml) followed by addition of borontrifluoride etherate (1 ml). The reaction mixture is refluxed for 36 hours (monitored by tlc). The reaction mixture is cooled and poured into an aqueous saturated solution (100 ml) of sodium bicarbonate, extracted from $CHCl_3$ (3x50 ml), dried over sodium sulfate and evaporated to give the crude product 13 which is further purified by column chromatography over silica gel using hexane as eluent. The structure of 13 was fully characterized on the basis of its spectral and analytical data which are given below.

The 13 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 83%; m.p. 107°C; I.R.(KBr):ν_{max} =2938, 2920, 2898, 1705, 1606, 1500 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.83 (s, 3H, $C\underline{H}_3$), 1.33-1.67 (m, 5H, methylene and methyne protons), 1.83-2.40 (m, 6H, methylene and methyne protons), 2.03 (s,

3H, $C\underline{H}_3$), 2.73-2.97 (m, 2H benzylic), 3.67 (s, 3H, $OC\underline{H}_3$), 3.73 (s, 3H, $OC\underline{H}_3$), 6.50 (s, 1H arom), 6.55 (d, J=9Hz, 1H arom), 7.07 (d, J=9Hz, 1H arom); m/z : 340 (M^+,100%), 325 (M^+-15,23%), 309 (M^+-31,8%), 293 (M^+-47,10%), 265 (M^+-75,8%), [Found: C, 77.45; H, 8.08 calculated for $C_{12}H_{28}O_3$ (340.4): C, 77.61; H, 8.29%].

Preparation of 3-methoxy-13-methyl-16-(phenyl methylthio)-methylene-17-phenyl-17-hydroxy-6,7,8,9,11,12-hexahydro-cyclopenta[a]phenanthrene (14):

The 14 was prepared according to the reported procedure[19] which is given below.

Bromobenzene (6 mmol) is added dropwise to a cooled and stirred suspension of magnesium (9 mmol) and iodine (1.2-crystals) in dry ether (25 ml). the reaction mixture is stirred for 60 minutes. A solution of the S,S-acetal 3 (2.5 mmol) in dry benzene (20 ml) is added dropwise to the ice-cold reaction mixture. The reaction mixture is stirred for 90 minutes (monitored by tlc), poured into an aqueous saturated solution (100 ml) of ammonium chloride, extracted from ether (3x50 ml), dried over sodium sulfate, and evaporated to give the crude product which is further purified by column chromatography over neutral alumina using hexane as eluent. The structure of 14 was fully confirmed from its spectral and anlaytical data which are given below.

The 14 was obtained as a colourless solid ($CHCl_4$/hexane); yield, 93%; m.p. 186°C; I.R. (KBr):ν_{max} = 3400, 1605, 1587, 1494, 1420 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.20 (s, 3H, $C\underline{H}_3$), 1.30-1.72 (m, 5H, methylene and methyne protons), 1.79 (s, 3H, $SC\underline{H}_3$); 1.92-2.50 (m, 5H, methylene and methyne protons), 2.67-2.89 (m,3H benzylic), 3.75 (s, 3H, $OC\underline{H}_3$), 5.23 (brs, 1H, O<u>H</u>, exchangeable with D_2O), 6.67 (s, 1H arom), 6.70 (d, J=9Hz, 1H arom), 7.18 (d, J=9Hz, 1H arom), 7.47 (s, 5H arom), 7.50 (s, 5H arom); m/z : 496 (M^+,10%), 481 (M^+-15,29%), 449 (M^+-47,25%), 419 (M^+-47,13%), [Found: C, 79.91; H, 7.35 calculated for $C_{33}H_{36}O_2S$ (496.6): C, 79.80; H, 7.30%].

Preparation of 3-methoxy-13-methyl-16-benzoyl-17-phenyl-6,7,8,9,11,12-hexahydrocyclopent-16-eno[a]phenanthrene (15):

The 15 was prepared according to the reported procedure[19] which is given below.

The crude carbinol acetal 14, obtained in the above reaction, is directly dissolved in dry benzene (20 ml) and borontrifluoride etherate (1 ml) is added. The reaction mixture is refluxed for 1 hour (monitored by tlc), cooled, poured into an aqueous saturated solution (100 ml) of sodium bicarbonate, extracted from $CHCl_3$ (3x50 ml), dried over sodium sulfate and evaporated to give the crude product which was purified by column chromatography over silica gel using hexane as eluent. The structure of 15 was

fully confirmed from its spectral and analytical data which are given below.

The 15 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 89%; m.p. 204°C; I.R. (KBr):ν_{max} = 1640,1610, 1598, 1497 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.05 (s, 3H, CH_3), 1.50-2.05 (m, 7H, methylene and methyne protons), 2.25-2.56 (m, 3H, methylene and methyne protons), 2.70-2.89 (m, 3H benzylic), 3.80 (s, 3H, OCH_3), 6.70 (s, 1H arom), 6.75 (d, J=9Hz, 1H arom), 7.13 (d, J=9Hz,1H arom), 7.15 (s, 5H arom), 7.23-7.30 (m, 3H arom), 7.60-7.73 (m, 2H arom); m/z : 448 (M^+, 20%), 433 (M^+-15,13%), 105 (M^+-343,7%), [Found: C, 85.69; H, 7.24 calculated for $C_{32}H_{32}O_2$ (448.5): C, 85.67; H, 7.19%].

Preparation of 3-methoxy-13-methyl-16-carbthiomethyl-17-carbmethoxy methylene cyclopenta[a]phenanthrene (17):

The 17 was prepared according to the reported procedure[20] which is given below.

To a suspension of zinc (10 mmol, preheated at 110°C for 1 hour) and a few crystals of iodine in dry ether (20 ml), ethylbromoacetate (5 mmol) in dry ether (10 ml) is added dropwise (10 min.) with stirring and the reaction mixture is refluxed for 30 minutes. A solution of the S,S-acetal 3 (2.5 mmol) in dry benzene (25 ml) is then added dropwise (30 min.) and refluxing is continued for another 2-3 hours. Then few crystals of iodine are added and the reaction mixture is refluxed for another 4-5 hours

(monitored by tlc). The reaction mixture is then cooled and poured into ice-cooled 20% sulphuric acid (100 ml), extracted from ether (3x50 ml), dried over sodium sulphate and evaporated to give the crude product which is purified by column chromatography over silica gel using hexane/ethylacetate (9:1) as eluent. The structure of 17 was fully confirmed from its spectral and analytical data which are given below.

The 17 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 63%; m.p. 203°C; I.R. (KBr): ν_{max}=1692, 1618 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ=1.07 (s, 3H, $C\underline{H}_3$), 1.35 (t, J=6Hz, 3H, $OCH_2C\underline{H}_3$), 1.38-2.40 (m, 11H, methylene and methyne protons), 2.53 (s, 3H, $SC\underline{H}_3$), 2.85-2.97 (m, 3H benzylic), 3.80 (s, 3H, $OC\underline{H}_3$), 4.31 (q, J=6Hz, 2H, $OC\underline{H}_2CH_3$), 5.31 (s, 1H vinylic), 6.70 (s, 1 H arom), 6.73 (d, J=9Hz, 1H arom), 7.23 (d, J=9Hz, 1H arom); m/z : 428 (M^+, 6%), 397 (M^+-31,4%), 381 (M^+-47,20%), [Found: C, 70.00, H, 7.03 calculated for $C_{25}H_{32}D_4S$ (427.5): C, 70.22; H, 7.31%].

Preparation of 3-methoxy-13-methyl-6,7,8,9,11,12-hexahydro 21-methylthioindano[2,1-*a*]phenanthrene (19):

The 19 was prepared according to the reported procedure[21] which is given below.

To an ice-cooled solution of allyl magnesium bromide [5 mmol, prepared from magnesium turnings (2 mmol) and allyl bromide (10 mmol)] in dry ether (60 ml), 3 (125 mmol) in dry benzene (10 ml) is added dropwise and after stirring

for 45 minutes, the reaction mixture is poured into saturated aqueous solution (50 ml) of ammonium chloride and then extracted from ether (3x50 ml). The combined ether extracts are washed with water (50 ml), dried over sodium sulfate and evaporated to give crude carbinol acetal 18 in nearly quantitative yield. The carbinol acetal 18 is directly dissolved in dry benzene (60 ml) and borontrifluoride etherate (1 ml) is added and the reaction mixture is refluxed for 45 minutes. It is then cooled, poured into saturated sodium bicarbonate solution (50 ml), extracted from $CHCl_3$ (3x50 ml), washed with water (50 ml), dried over sodium sulfate and evaporated to give the crude product which is further purified by column chromatography over silica gel using hexane as eluent. The structure of 19 was fully established from its spectral and analytical data which are given below.

The 19 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 87%; m.p. 112°C; I.R. (KBr): ν_{max} = 2910, 1610, 1572, 1500 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.93 (s, 3H, $C\underline{H}_3$), 1.20-1.73 (m, 5H, methylene and methyne protons), 1.93-2.50 (m, 5H, methylene and methyne protons), 2.40 (s, 3H, $C\underline{H}_3$), 2.63-2.93 (m, 3H benzylic), 3.70 (s, 3H, $OC\underline{H}_3$), 6.33-6.60 (m, 2H arom), 6.73-7.13 (m, 4H arom); m/z : 364 (M^+, 88%), 349 (M^+-15, 18%, [Found: C, 79.00; H, 7.54 calculated for $C_{24}H_{28}Os$ (364.5): C, 79.07; H, 7.74%].

Preparation of 3-methoxy-13-methyl-25-benzyl-6,7,8,9,11, 12-hexahydrocyclopent[a]naphtho[2,3-*c*]phenanthrene (23):

The 23 was prepared according to the reported procedure[22] which is given below.

To an ice-cooled solution of benzyl magnesium bromide [5 mmol, prepared from magnesium turnings (10 mmol) and benzyl bromide (50 mmol)] in dry ether (20 ml), S,S-acetal 3 (2.5 mmol) in dry benzene (20 ml) is added dropwise (2-3 min.) under an efficient atmosphere of nitrogen. The reaction mixture after stirring for 45 minutes, is decomposed by pouring into saturated aqueous solution (50 ml) of ammonium chloride and then extracted from ether (3x50 ml). The combined ether layer is washed with water (100 ml), dried over sodium sulphate and evaporated to give the crude carbinol acetals 20 and 21 in high yields. This mixture of crude carbinol acetals was used directly for the cycloaromatization step which is given below.

To a solution of the carbinol acetals 20 and 21 in dry benzene (50 ml), borontrifluoride etherate (1 ml) is added and the reaction mixture is refluxed for 45 minutes. It is then cooled and poured into saturated aqueous sodium bicarbonate solution (50 ml), extracted from $CHCl_3$ (3x50 ml), dried over sodium sulphate and evaporated to give the crude products 22 and 23 which are separated and purified by column chromatography over silica gel using hexane as eluent. The structures of 22 and 23 were fully confirmed

from their spectral and analytical data which are given below.

The 22 was characterized as **3-methoxy-13-methyl-25-methylthio-6,7,8,9,11,12-hexahydrocyclopent[a]naphtho-[2,3-*c*]phenanthrene.** It was obtained as a colourless solid ($CHCl_3$/hexane); yield, 31%; m.p.79°C; I.R.(KBr):ν_{max} =1612, 1560, 1517 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.98 (s, 3H, $C\underline{H}_3$), 1.50-2.47 (m, 8H, methylene and methyne protons), 2.33 (s, 3H, $SC\underline{H}_3$), 2.60-3.00 (m, 4H, benzylic), 3.17-3.27 (m, 1H benzylic), 3.70 (s, 3H, $OC\underline{H}_3$), 6.53 (s, 1H arom), 6.55 (d, J=9Hz, 1H arom), 7.06 (d, J=9Hz, 1H arom), 7.33-7.47 (m, 1H arom), 7.70-7.80 (m, 1H arom), 8.47-8.53 (m, 1H arom); m/z : 414 (M^+, 100%), 399 (M^+-15,20%), 352 (M^+-62,3%), [Found:C,81.00; H, 7.00 calculated for $C_{28}H_{30}OS$ (414.5): C, 81.11; H, 7.29%].

The 23 was obtained as a colourless solid ($CHCl_3$/hexane); yield, 59%; m.p. 144°C; I.R. (KBr):ν_{max}=1611, 1587, 1499, 1496 cm^{1-}; ^1H n.m.r. ($CDCl_3$): δ=1.03 (s, 3H, $C\underline{H}_3$), 1.67-1.97 (m, 4H, methylene and methyne protons), 2.27-2.60 (m, 4H, methylene and methyne protons), 2.77-3.00 (m, 5H benzylic), 3.73 (s, 3H, $OC\underline{H}_3$), 4.45 (s, 2H benzylic), 6.60 (s, 1H arom), 6.67 (d, J=9Hz, 1H arom), 7.00-7.33 (m, 8H arom), 7.47 (s, 1H naphthyl), 7.73-7.93 (m, 2H arom); m/z : 458 (M^+, 58%), 443 (M^+-15,34%), [Found: C, 89.00; H, 7.49 calculated for $C_{34}H_{34}O$ (458.6): C, 89.04; H, 7.47%].

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C O R R I G E N D U M

	Page No.	Line	Incorrect	Correct
CHAPTER I :	19	19	thizolines	thiazolines
	25	20	trizoles	triazoles

CHAPTER II: 77 EXPERIMENTAL, GENERAL;

"^{13}C n.m.r. spectra were recorded on a BRUCKER WM-400 spectrometer" is not printed.

CHAPTER III: 122 EXPERIMENTAL, GENERAL;

"^{13}C n.m.r. spectra were recorded on a BRUCKER WM-400 spectrometer" is not printed.