SYNTHETIC STUDIES ON HETEROCYCLIC COMPOUNDS OF BIOLOGICAL INTEREST

BY

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DOCTOR OF PHILOSOPHY

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Dedicated to my Mother

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

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

(H. Junjappa)
Supervisor

Date : April 1993.

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(SANJEEV KUMAR SHARMA)

Date :

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- and N,N-acetals have been extensively explored in this laboratory for the development of several new synthetic methods for a variety of heterocyclic and carbocyclic compounds. The work described in this thesis highlights further new interesting transformations of polarized ketene S,S-, S,N-acetals.

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

Fifth chapter of this thesis describes the synthesis of 7-substituted and 6,7-annulated-5-deazapteridines. Mannich

reaction on α-oxoketene S,N-acetals for the synthesis of substituted and annulated tetrahydropyrimidine and tetrahydrotriazine has been described in the last chapter.

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

C O N T E N T S

CHAPTER I

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

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

have been used in the synthesis of 1-substituted-2-methylthio imidazoles (chapter 4). In the first section a brief survey of polarized ketene S,S-acetals is described and the second section describes a survey of polarized ketene S,N- and N,N-acetals. A brief description of the present work is described at the end of this chapter.

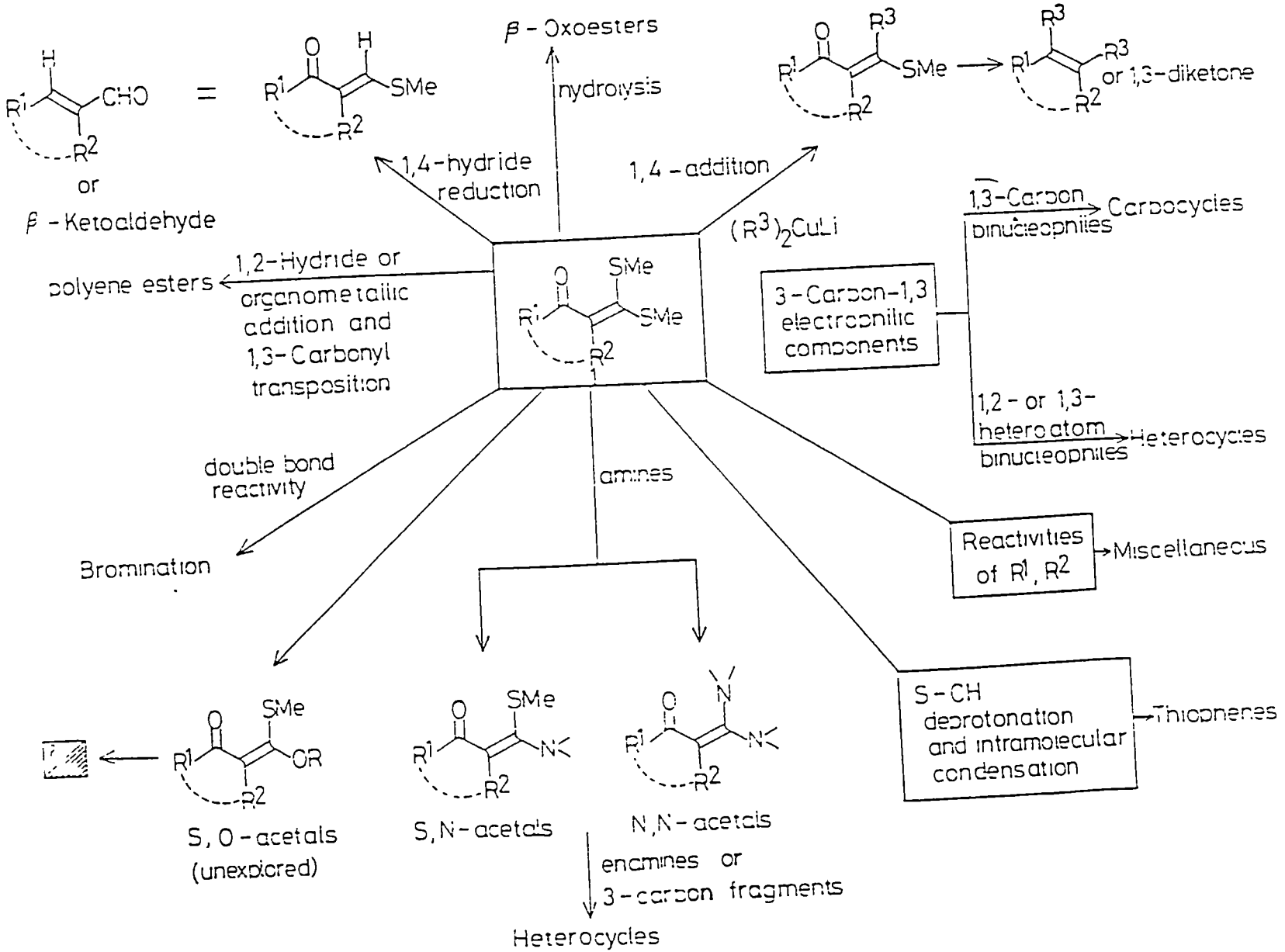
A. The Polarized Ketene S,S-acetals:

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

The oxoketene S,S-acetals generally exhibit well defined physical properties and can be easily purified by

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

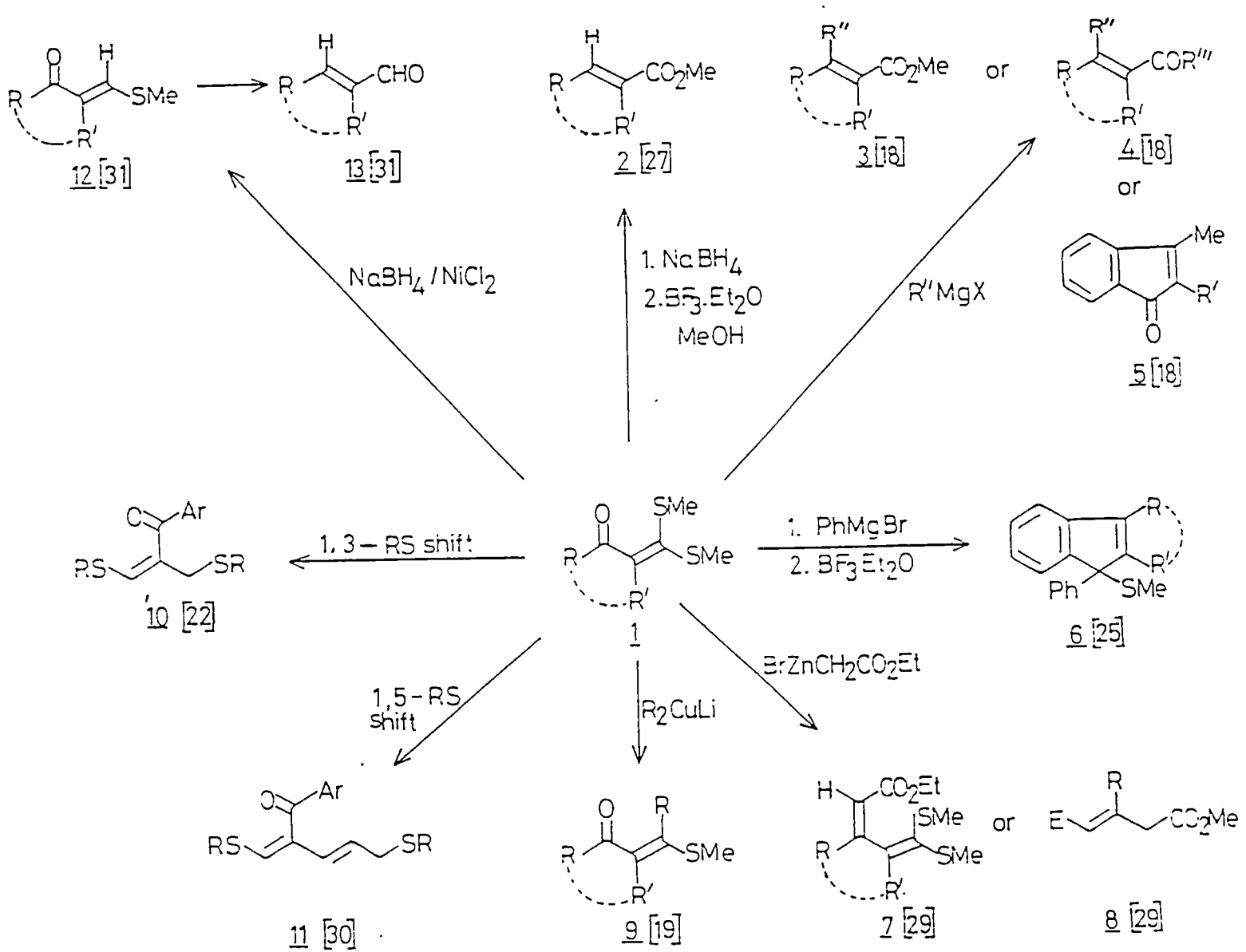
In Scheme 1 various reactivity profiles of α-oxoketene S,S-acetals of the general formula 1 have been outlined. Hydrides and organometallic reagents give 1,2-addition reactions typical of carbonyl function reactivity[18]. These


β - Oxoesters
hydrolysis
1,4-hydride reduction
1,4 - addition
(R3)2CuLi
1,2-Hydride or organometallic addition and 1,3-Carbonyl transposition
polyene esters
3 - Carbon-1,3 electrophilic components
1,3-Carbon binucleophiles
Carbocycles
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
or
β - Ketoaldehyde
or 1,3-diketone
S, O - acetals (unexplored)
S, N - acetals
N, N - acetals
enamines or 3 - carbon fragments
Heterocycles

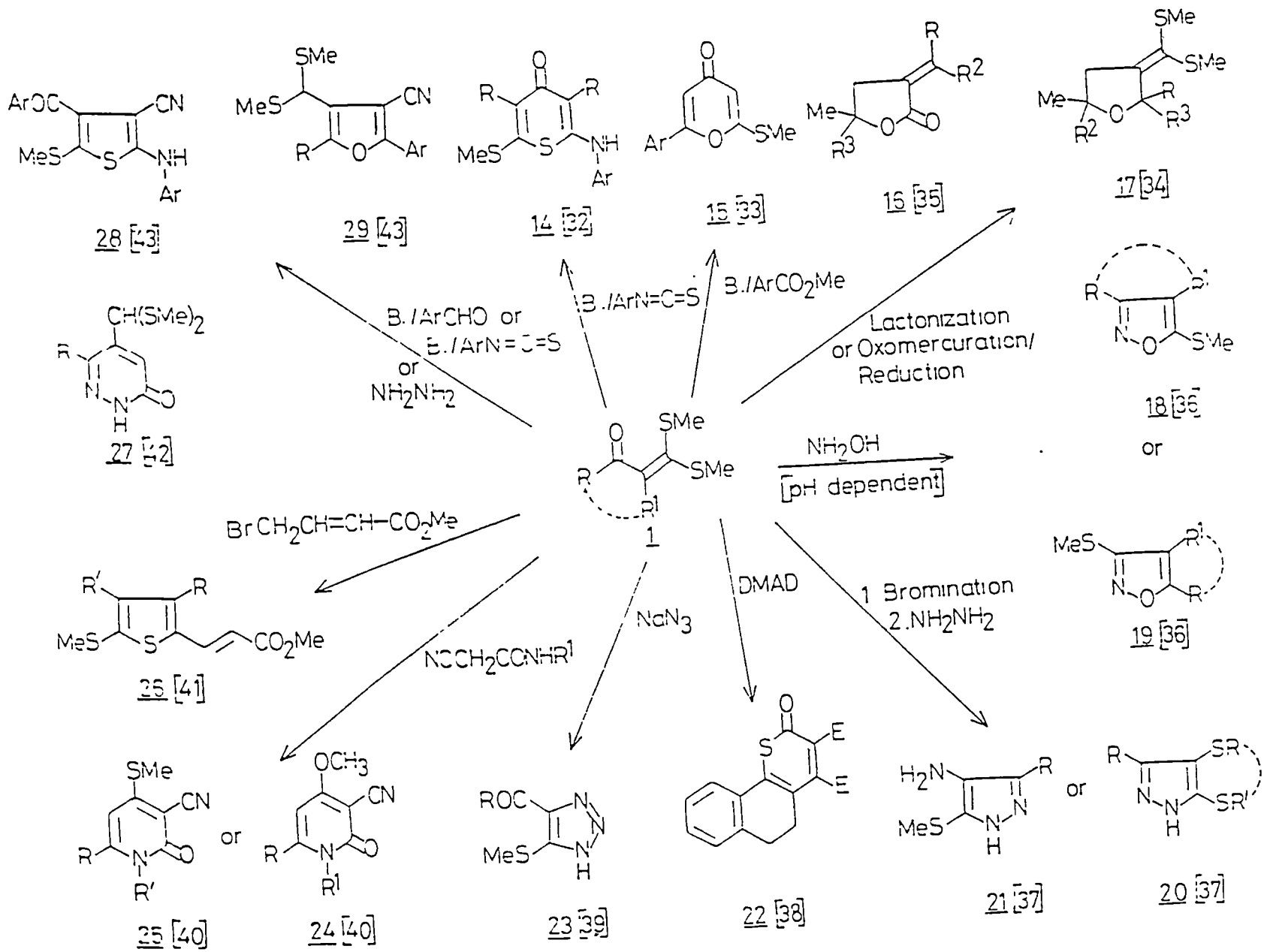
reactions can be directed in 1,4-manner by suitably manipulating the reagent and reaction conditions[18-20]. Further transformations after the initial 1,2- or 1,4-additions are also reported[18]. The α-oxoketene S,S-acetals possess typical 1,3-electrophilic centres and they react with 1,2- and 1,3-heteroatom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

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

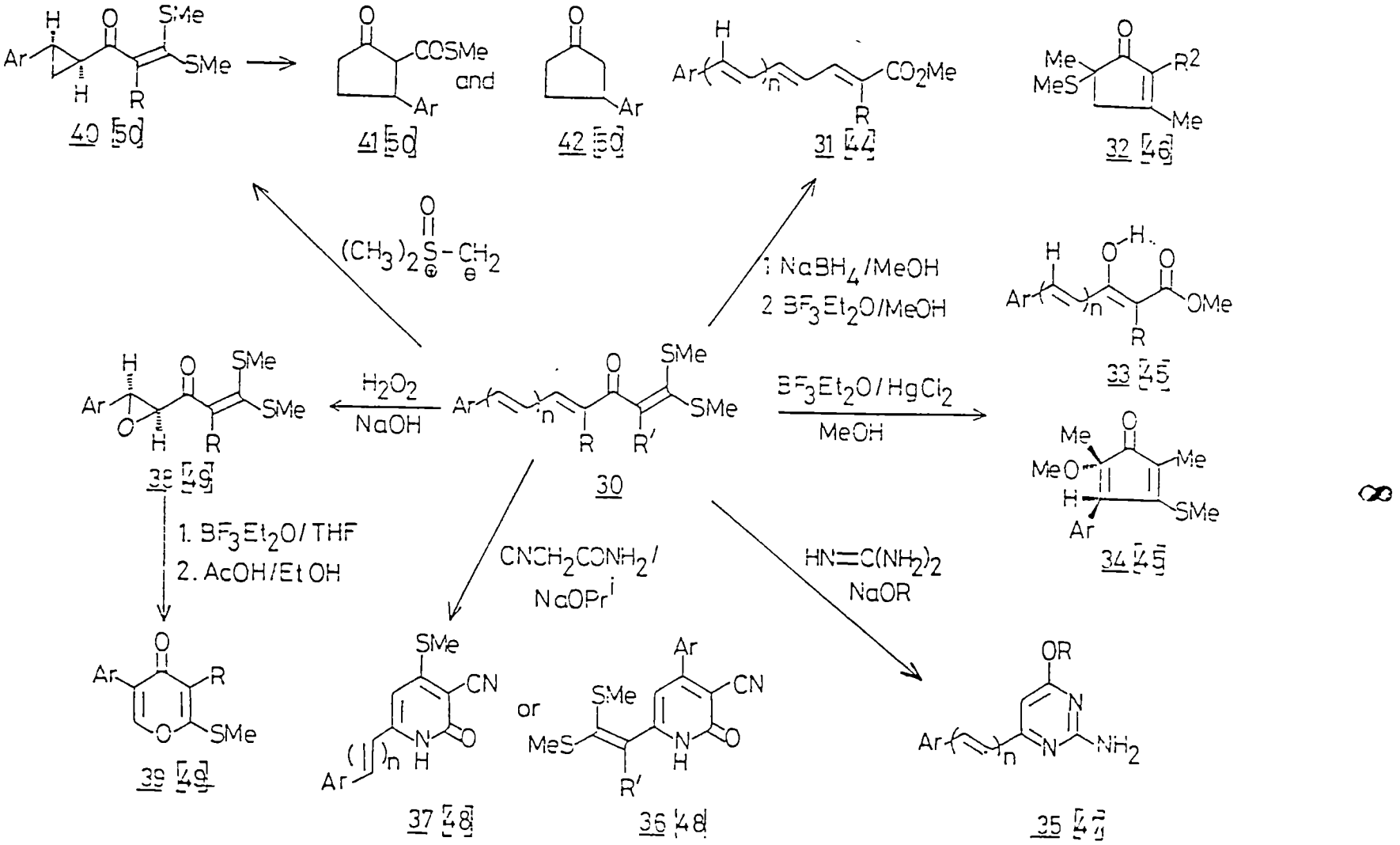
Like oxoketene S,S-acetals, the S,N- and N,N-acetals also possess 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. As stated in the preceding


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

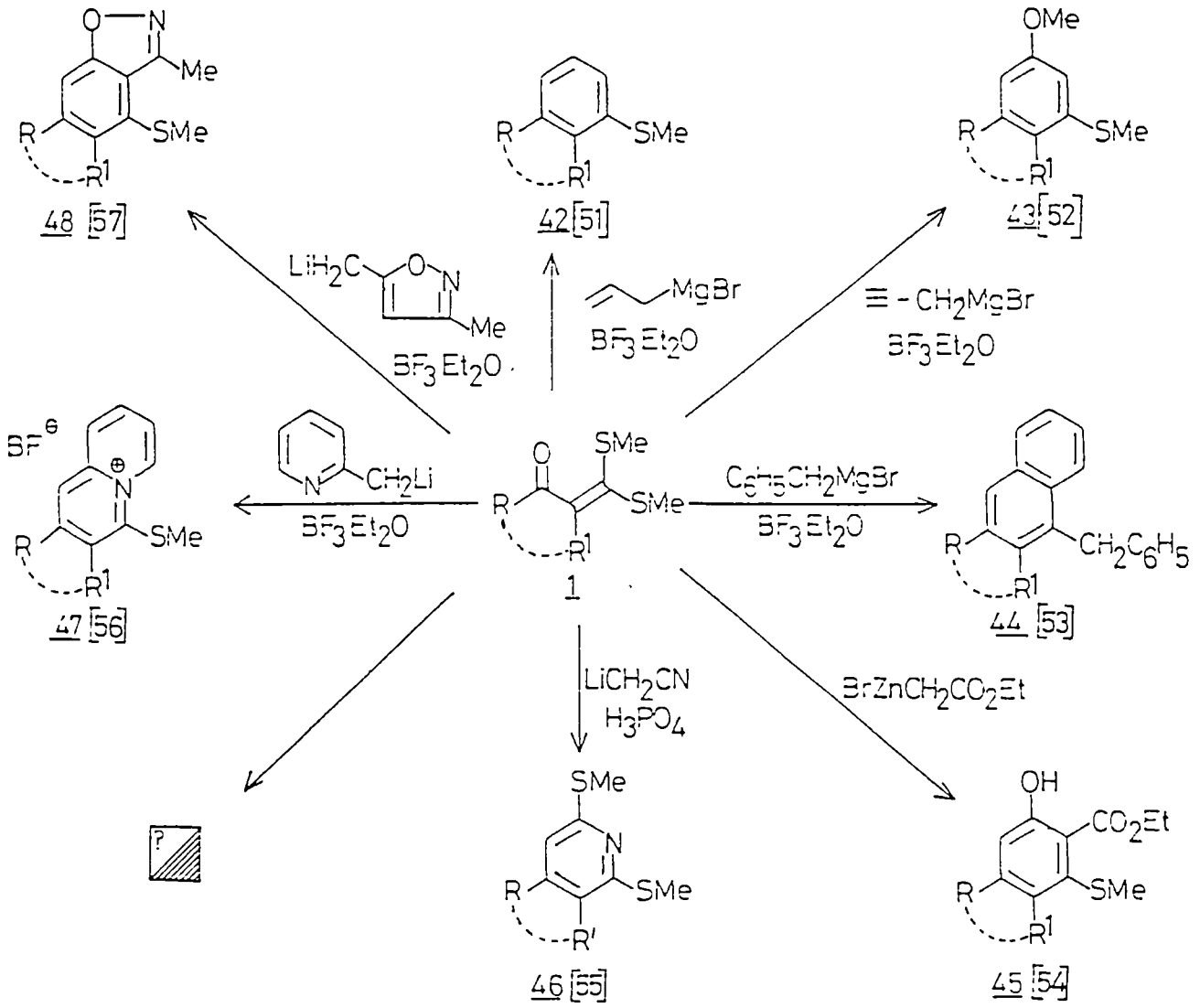
Scheme - 2


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

Scheme - 3


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

Scheme - 4


48 [57]
42 [51]
43 [52]
LiH2C
Me
BF3 Et2O
MgBr
BF3 Et2O
≡ - CH2MgBr
BF3 Et2O
BF4⊖
47 [56]
CH2Li
BF3 Et2O
1
C6H5CH2MgBr
BF3 Et2O
44 [53]
LiCH2CN
H3PO4
BrZnCH2CO2Et
46 [55]
45 [54]

Scheme – 5

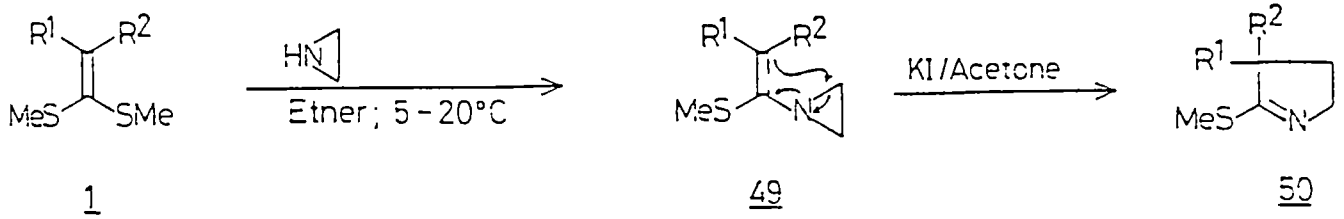
section, they can be prepared by displacement of one or both of the methylthio groups from oxoketene S,S-acetals by suitable amines under different reaction conditions. The S,N-acetals can alternatively be prepared direct from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates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

The α-oxoketene S,N- and N,N-acetals, like oxoketene S,S-acetals, are well defined compounds which can be preserved without apparent decomposition. they can be considered as vinylogous amides if they are derived from ketones and as vinylogous amines if they are derived from other methylene compounds. The chemistry of enamines derived from various ketones and primary or secondary amines is well documented. They have been extensively used as synthetic intermediates to react with various electrophiles making use of the α-carbon. however, these enamines are found to be more sensitive to moisture and readily undergo hydrolytic cleavage to the starting materials. On the other hand, the ketene S,N- and N,N-acetals are more stable and exhibit properties identical to enamines. They can undergo nucleophilic displacement with various binucleophiles[59-61] followed by intramolecular cyclization with α-oxo functionality. Like enamines, the α-carbon in the ketene S,N-and N,N-acetals is nucleophilic enough to react with various electrophilic species so that these reactions can be utilized to construct heterocycles of different structural features[62-75]. The chemistry and synthetic applications of the α-oxoketene S,N- and N,N-acetals have been reviewed[1] and

a number of synthetic methods have been developed in this laboratory which are briefly discussed in the following section.

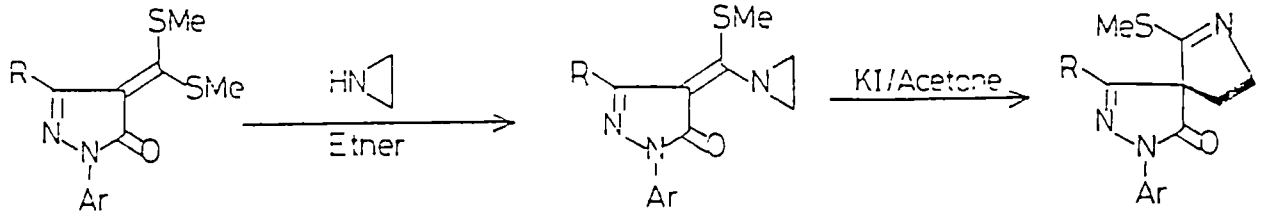
The doubly activated α-oxoketene S,S-acetal 1 underwent smooth displacement reaction at room temperature with aziridinek[62] to give the corresponding S,N-acetal 49 in high yields (Scheme 6). The S,N-acetals 49 can be viewed as N-vinyl aziridine and undergo facile ring expansion to yield the corresponding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

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



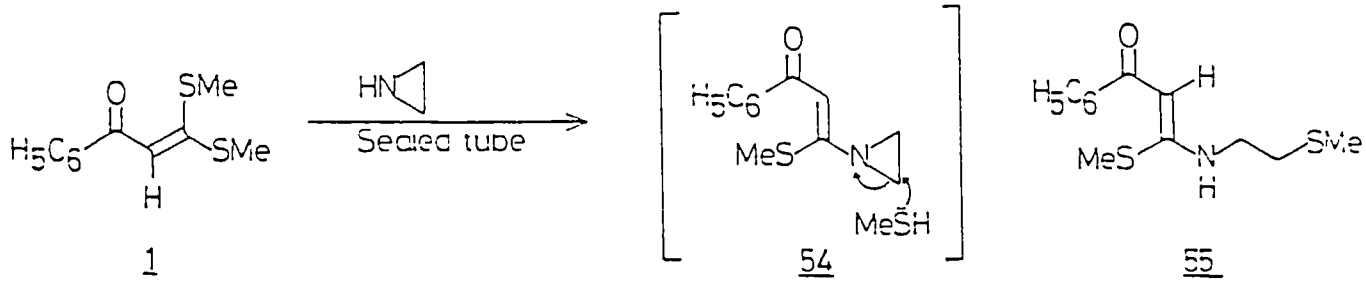
1 49 50

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

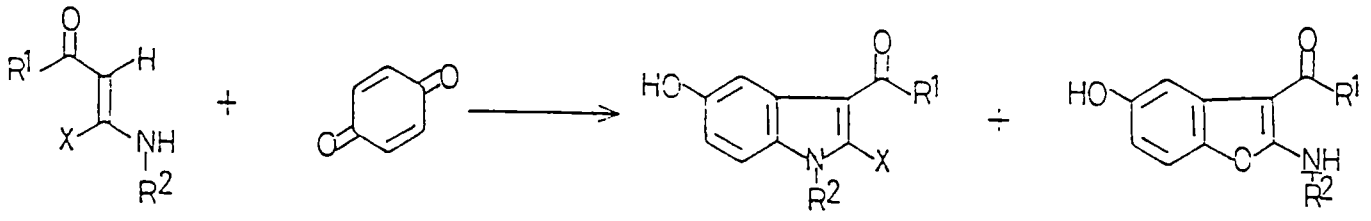


1 54 55

Scheme-6

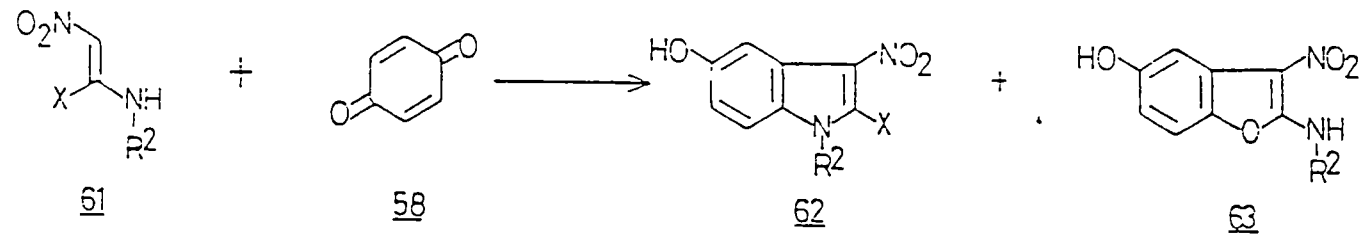
method suffered from limitations since it carried a substituent at 2-position arising from the enamine component. The α-oxoketene S,N- and N,N-acetals were considered as suitable alternatives to these enamine components in the Nenitzescu indole synthesis. Thus, the N,N-acetals 56 underwent smooth reaction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

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

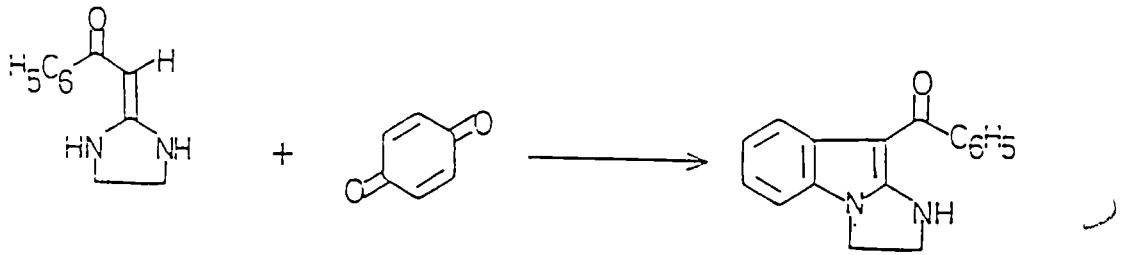


55,57 58 59 60

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

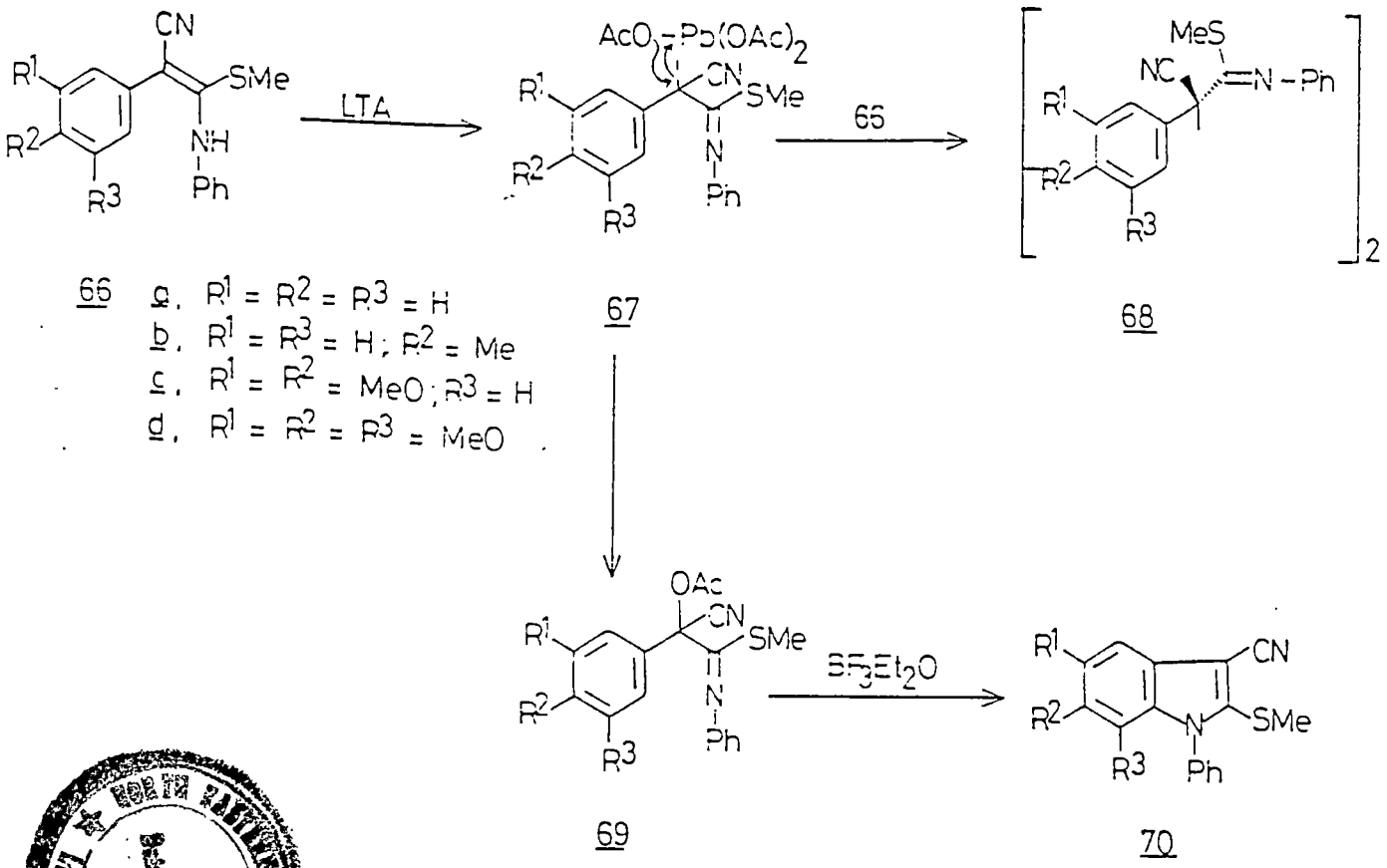


61 58 62 63

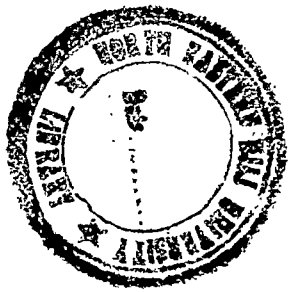


64 58 65

Scheme - 7



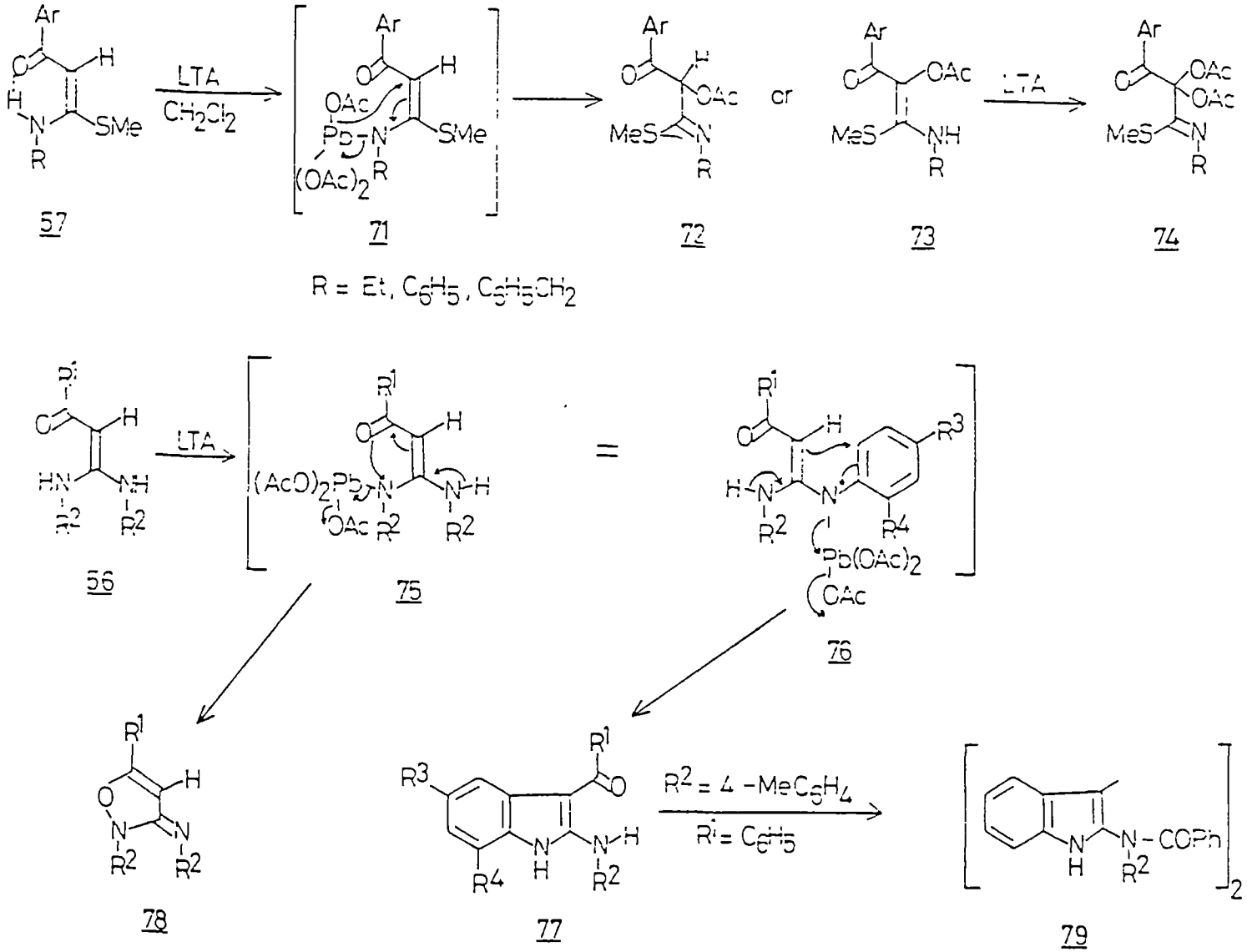
66 a. $R^1 = R^2 = R^3 = H$
b. $R^1 = R^3 = H$; $R^2 = Me$
c. $R^1 = R^2 = MeO$; $R^3 = H$
d. $R^1 = R^2 = R^3 = MeO$



Scheme - 8

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

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



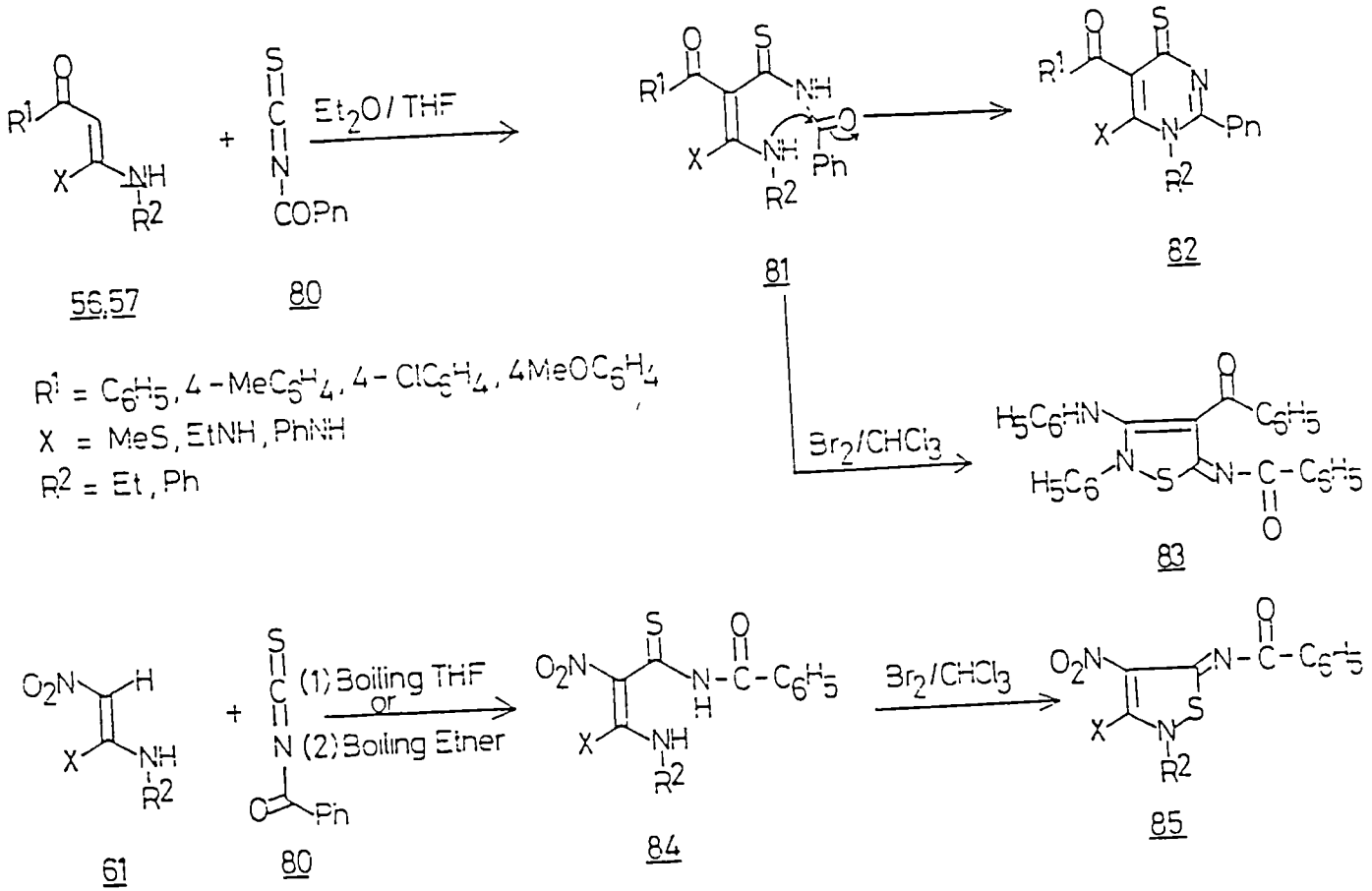
57 71 72 73 74

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

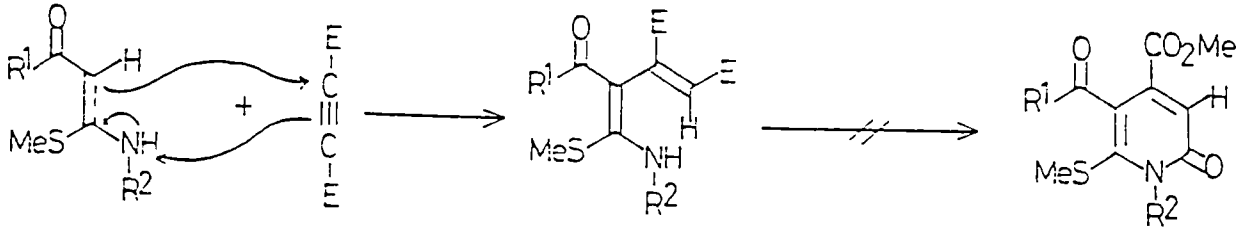

Et2O / THF
56,57
80
81
82
R1 = C6H5, 4-MeC6H4, 4-ClC6H4, 4MeOC6H4
X = MeS, EtNH, PhNH
R2 = Et, Ph
Br2/CHCl3
83
(1) Boiling THF
or
(2) Boiling Ether
61
80
84
Br2/CHCl3
85

Scheme - 10

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

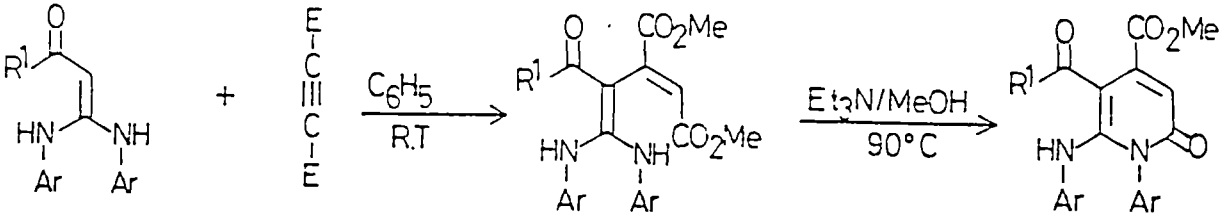
The reaction of α-oxoketene S,N-acetals and N,N-acetals with dimethylacetylenedicarboxylate (DMAD) 86 has been investigated[67] in this laboratory. The S,N-acetal 57 underwent Michael addition to yield the corresponding open chain adducts 87 which failed to undergo intramolecular cyclization to afford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

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



57 86 87 88

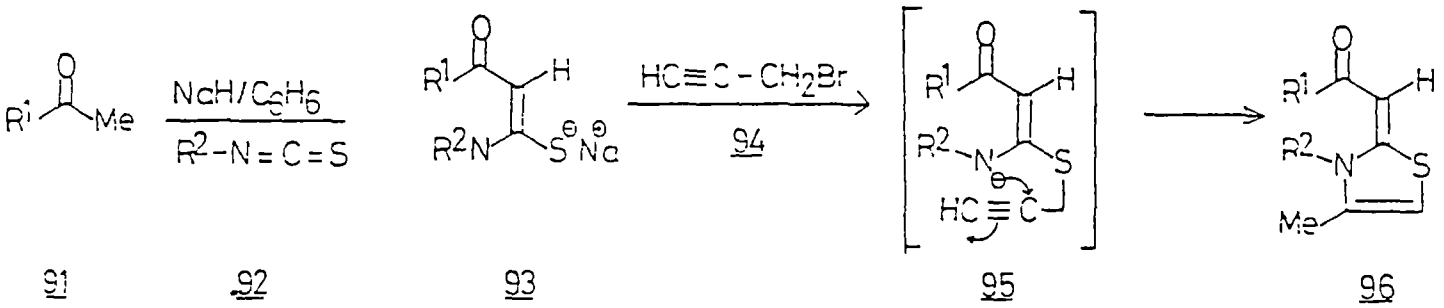
$R^1 = C_6H_5$; $R^2 = C_6H_5$, Et



55 86 89 90

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

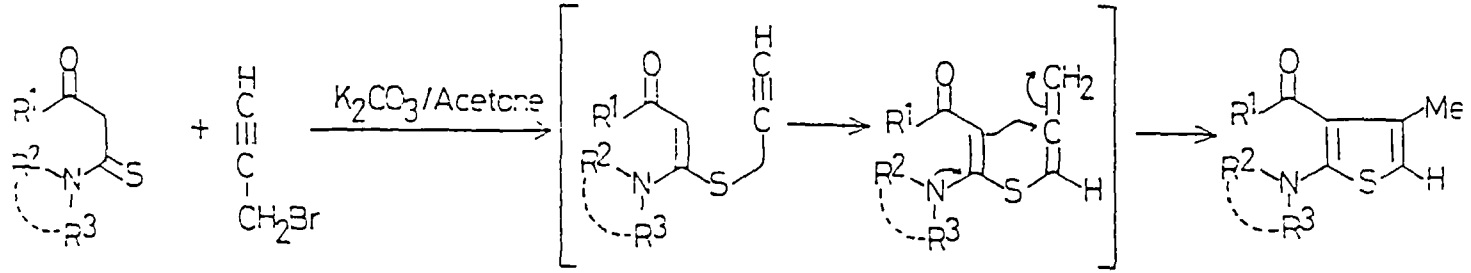
Scheme-11



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

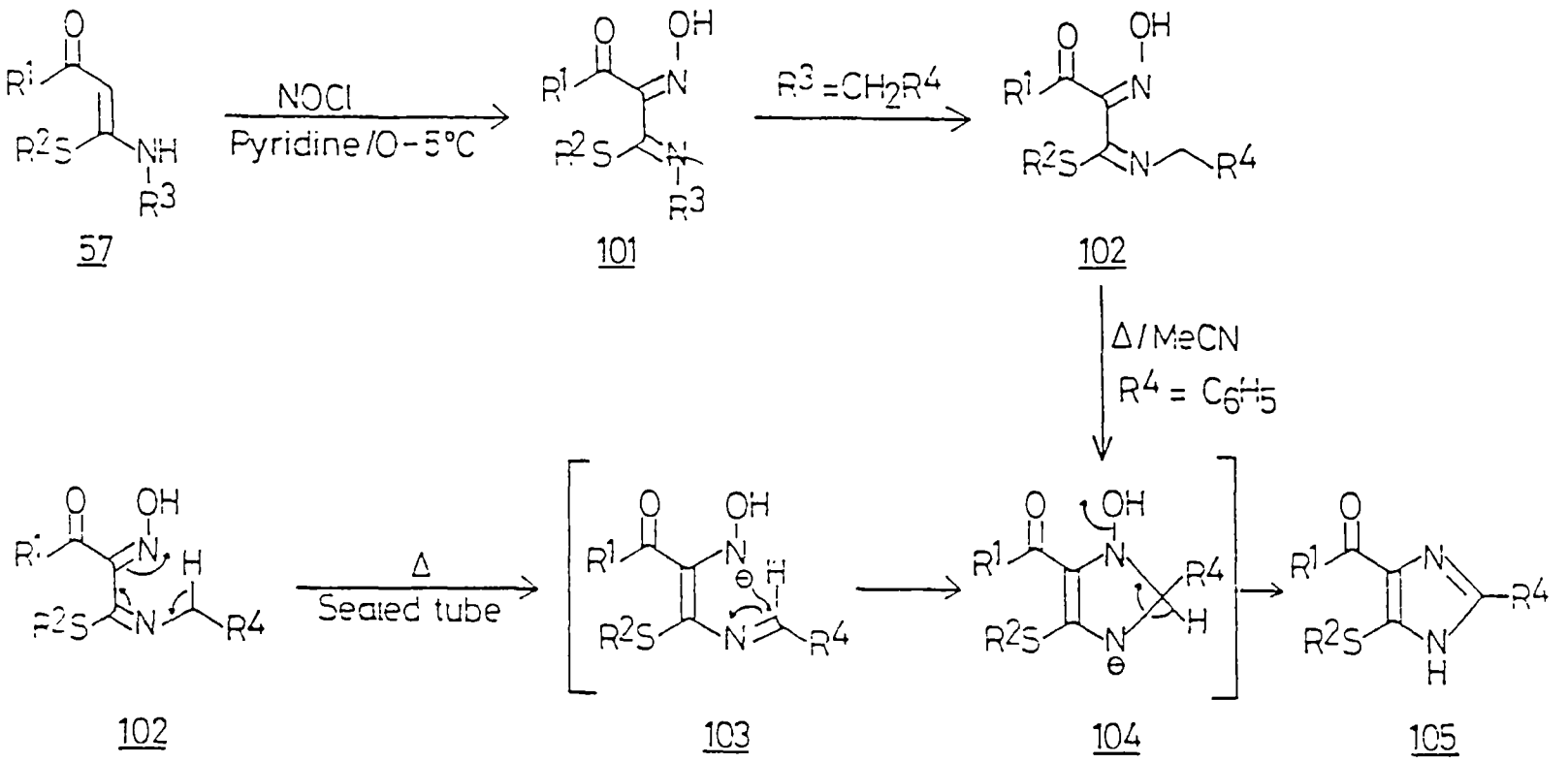
R^2
R^3 >N- = $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2-O-(CH_2)_2-$

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

Scheme -12

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

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



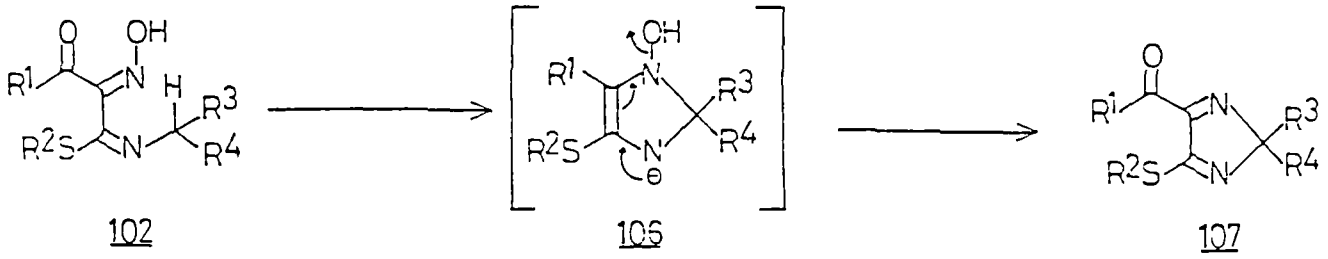
57 101 102 102 103 104 105

R^1 = substituted aryl, Me, CO_2Et

R^2 = Me, Et

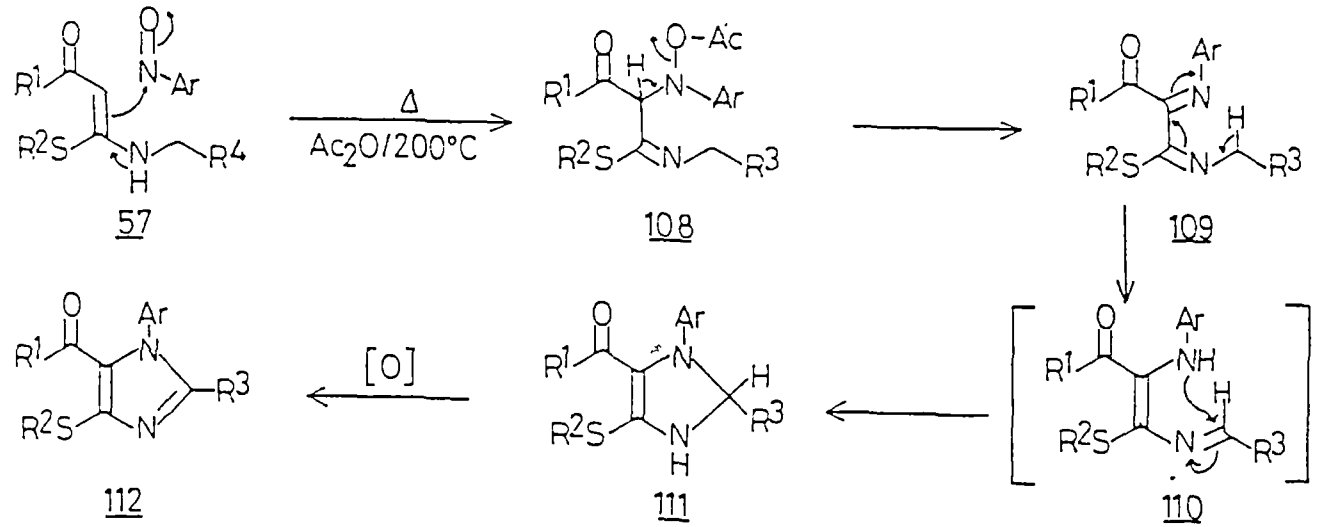
R^4 = H, Me, Et, C_6H_5, 4-ClC_5H_4, 4-$MeOC_6H_4$

Scheme -13



102 105 107

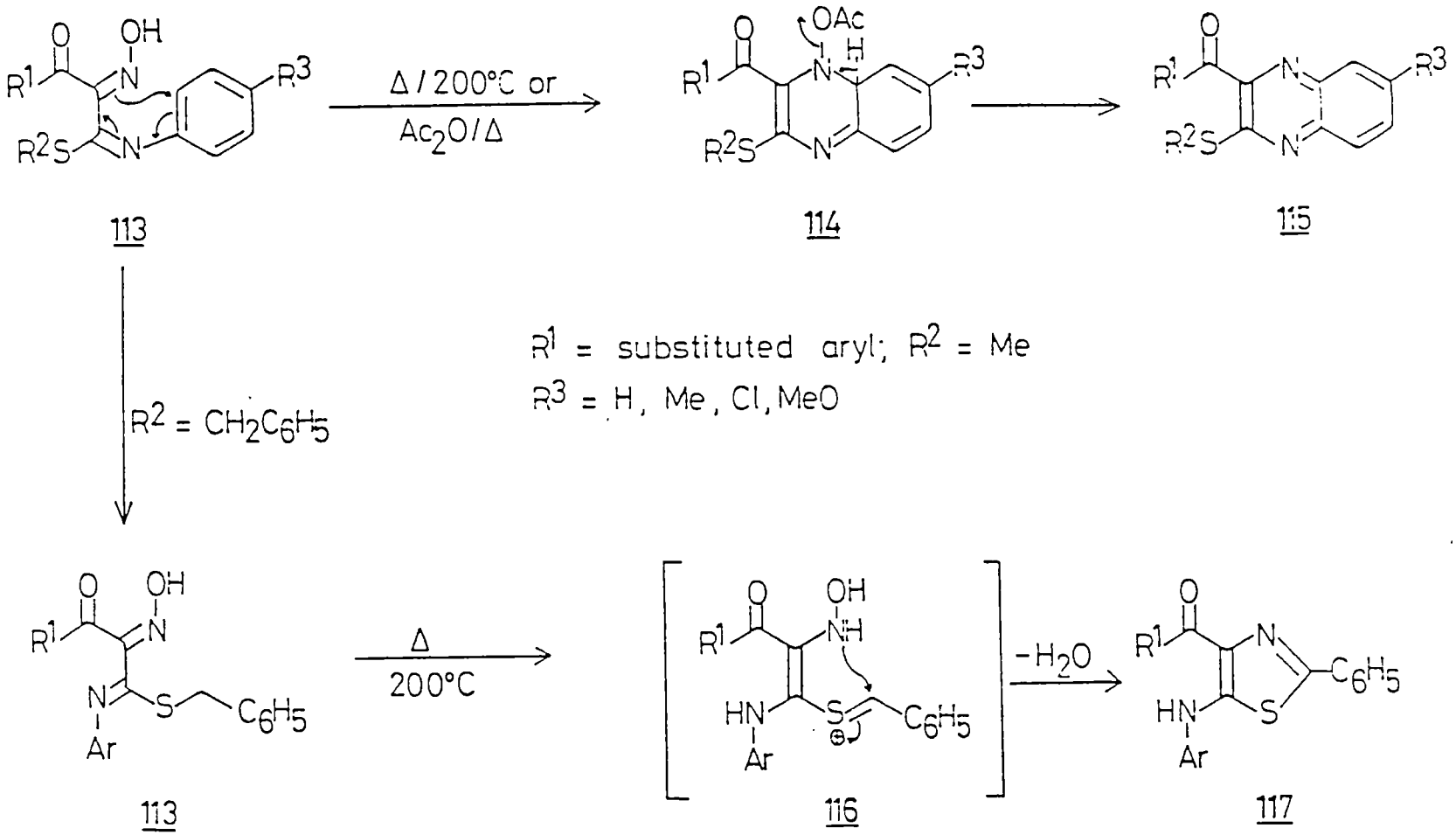
R^1 = substituted aryl; R^2 = Me, Et;
R^3 = R^4 = Me; R^3 = C_6H_5; R^2 = Me; R^3 = R^4 = $-(CH_2)_5-$



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

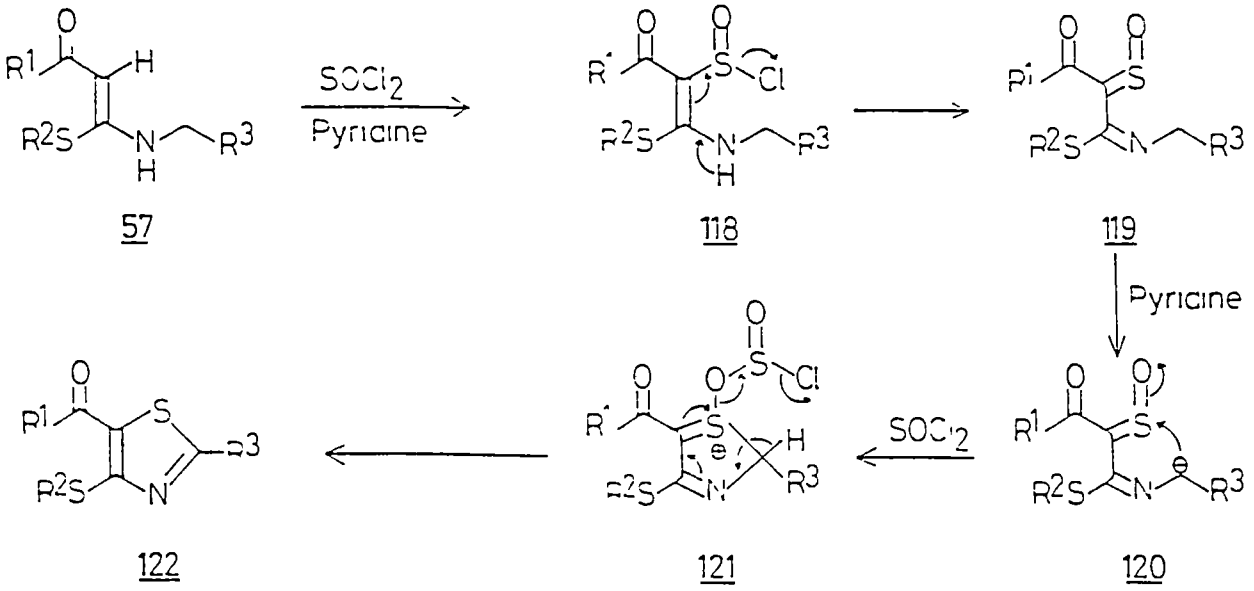
Scheme - 14


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
116
117

SCheme - 15

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

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



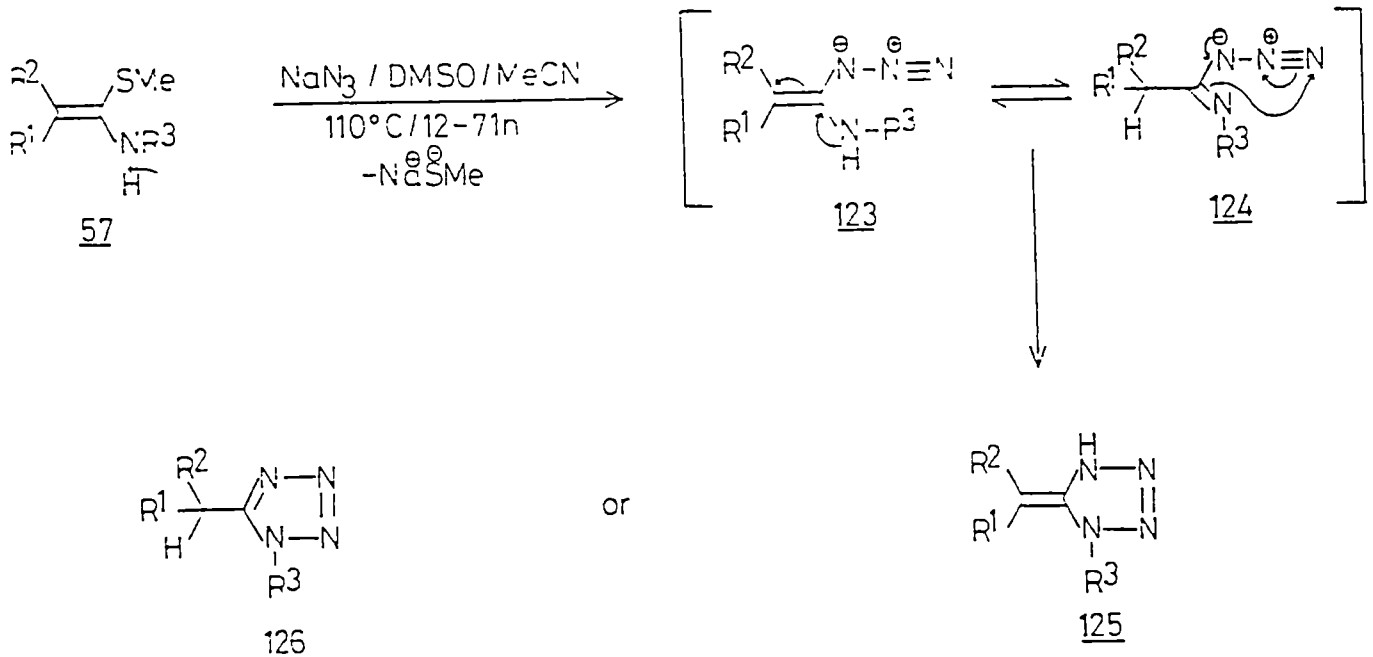
57 118 119 120 121 122

R^1 = substituted aryl, Me

R^2 = Me, Et, $C_6H_5CH_2$

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

Scheme – 15

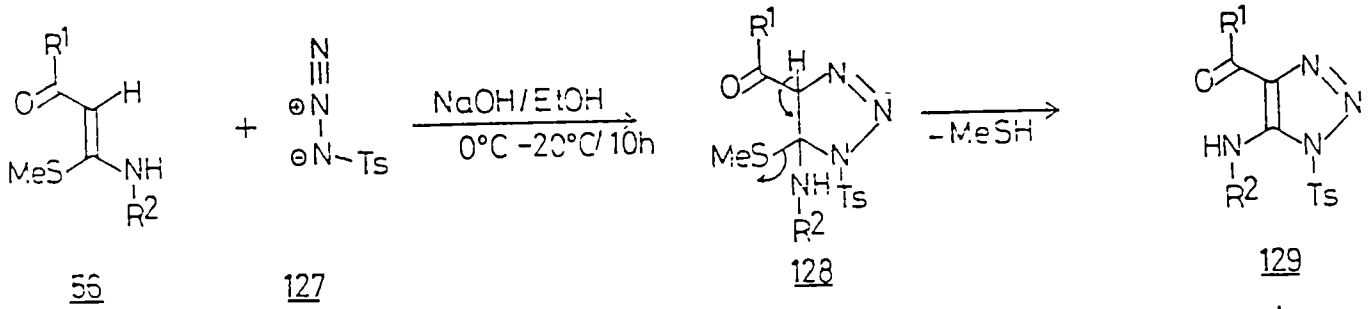


R^1 = ArCO, MeCO ; R^2 = H ; R^3 = Me, Et, n-Pr, i-Pr, C_6H_{11}, C_6H_5, $C_5H_5CH_2$

R^1 = C_6H_5, R^2 = CN,

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

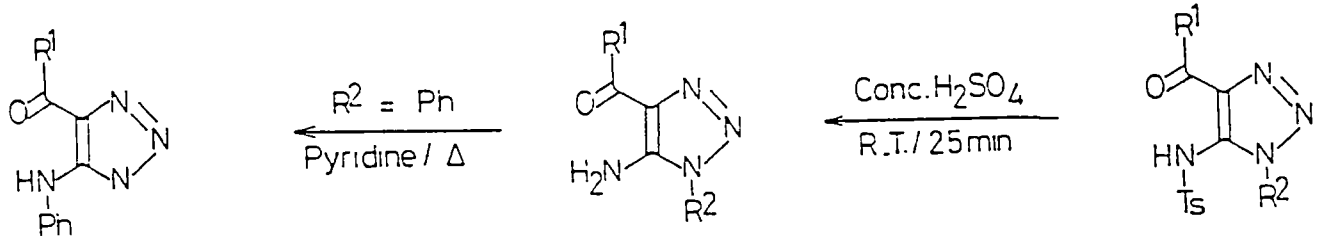
Scheme - 17



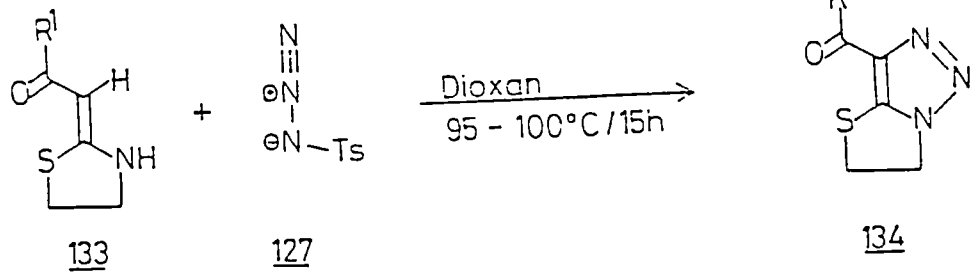
56 127 128 129

R^1 = substituted aryl, Me

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



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



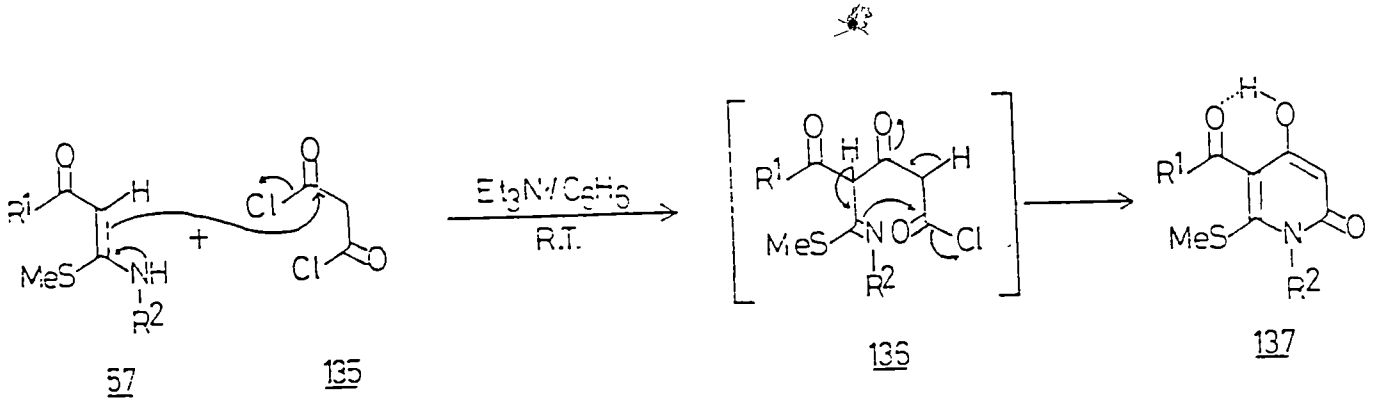
133 127 134

Scheme -18

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

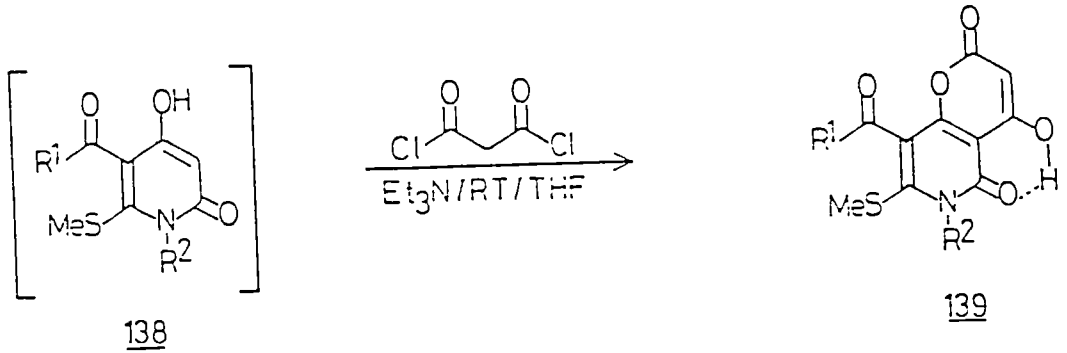
The α-oxoketene S,N-acetals **57** have also been reacted with malonyl chloride **135** leading to a new general methodology for the synthesis of 1,5-disubstituted-4-hydroxy-6-methylthio-2-1H-pyridones[74] **137** in high yields (Scheme 19). Also, when **57** was reacted with excess of **135** (3 equivalents)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

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



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

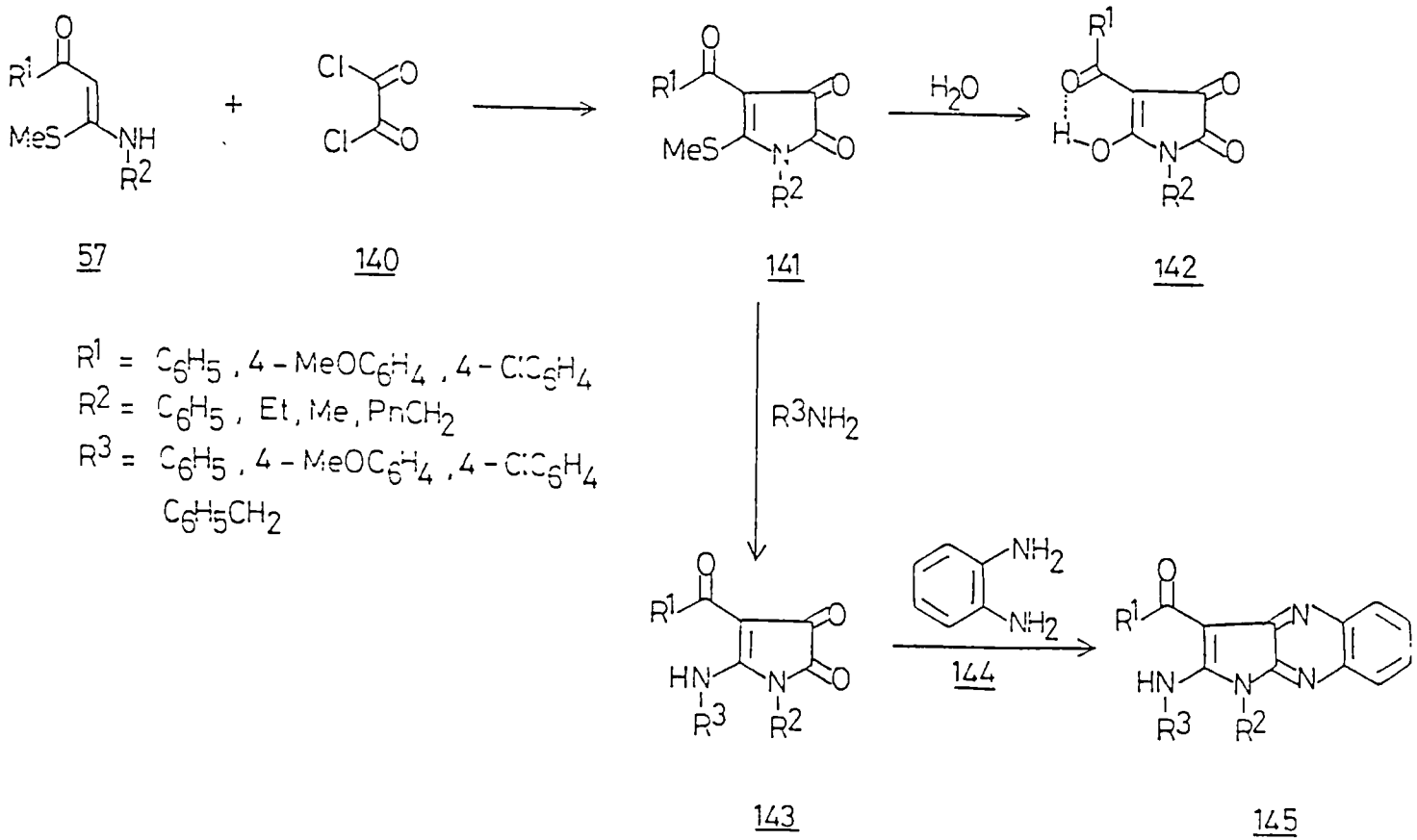
R^2 = Me, Et, n-Pr, $PhCH_2$, Ph , 4 - MeC_6H_4



R^1 = Me , C_6H_5

R^2 = Me , Et , $C_6H_5CH_2$

Scheme -19



57 140 141 142

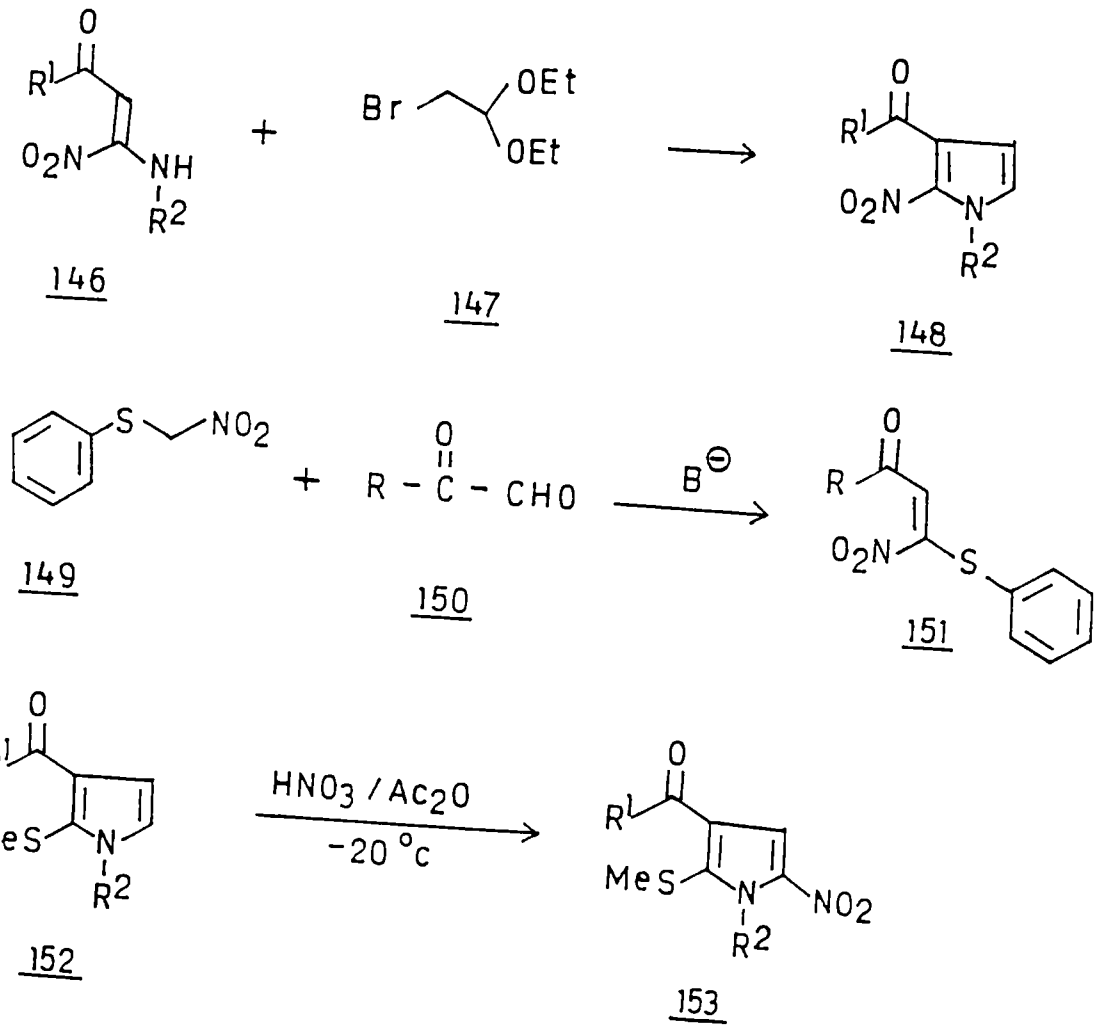
143 145

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

Scheme - 20

The Work Presented in this Thesis:

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


O
R1
O2N
NH
R2
146
+
Br
OEt
OEt
147
O
R1
O2N
N
R2
148
S
NO2
149
+
O
R - C - CHO
150
B⊖
O
R
O2N
S
151
O
R1
MeS
N
R2
152
HNO3 / Ac2O
-20 °c
O
R1
MeS
N
R2
NO2
153

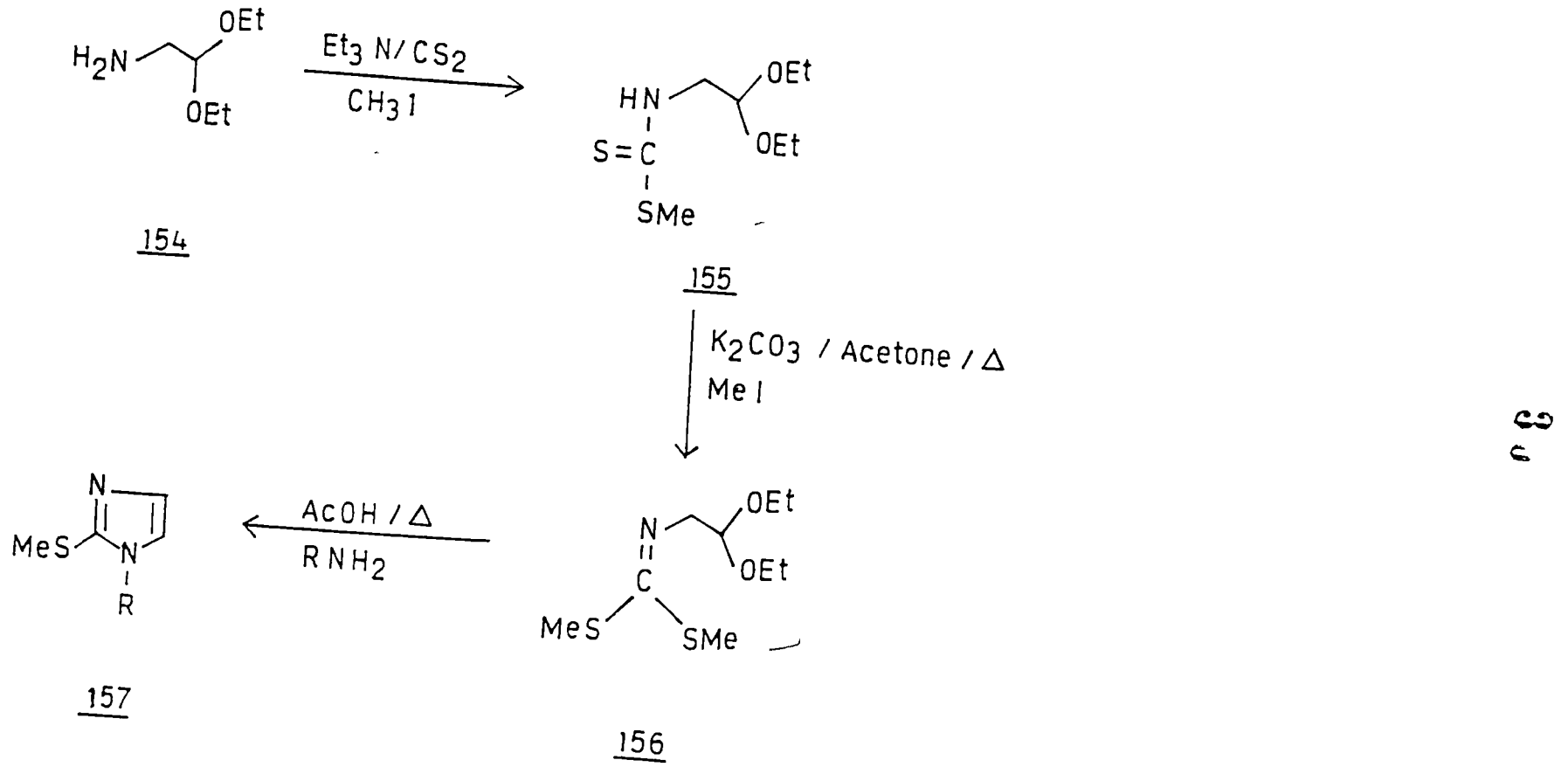
Scheme – 21

FG

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

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

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



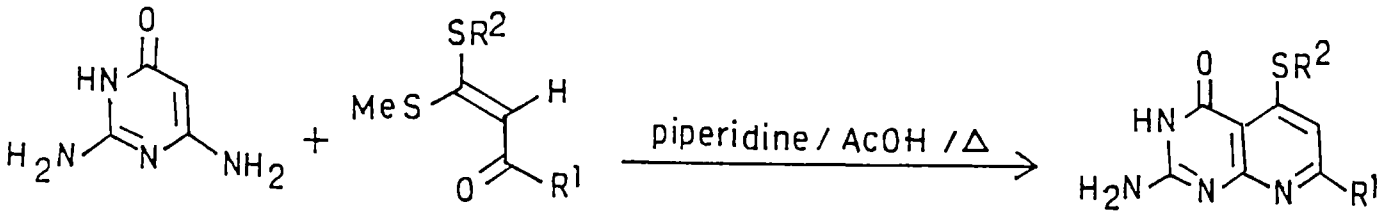
154

155

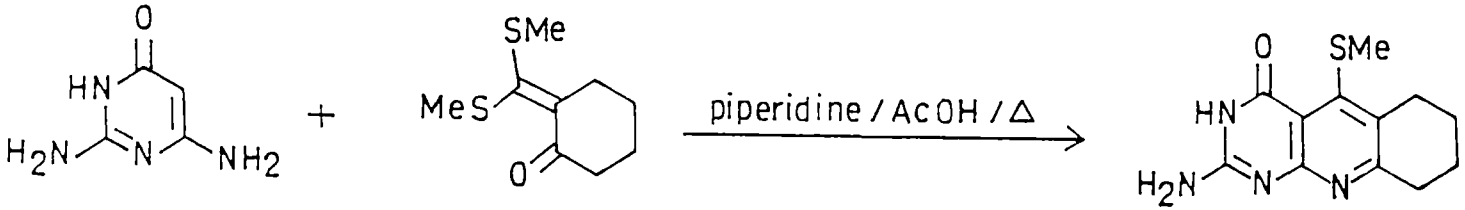
156

157

Scheme – 22

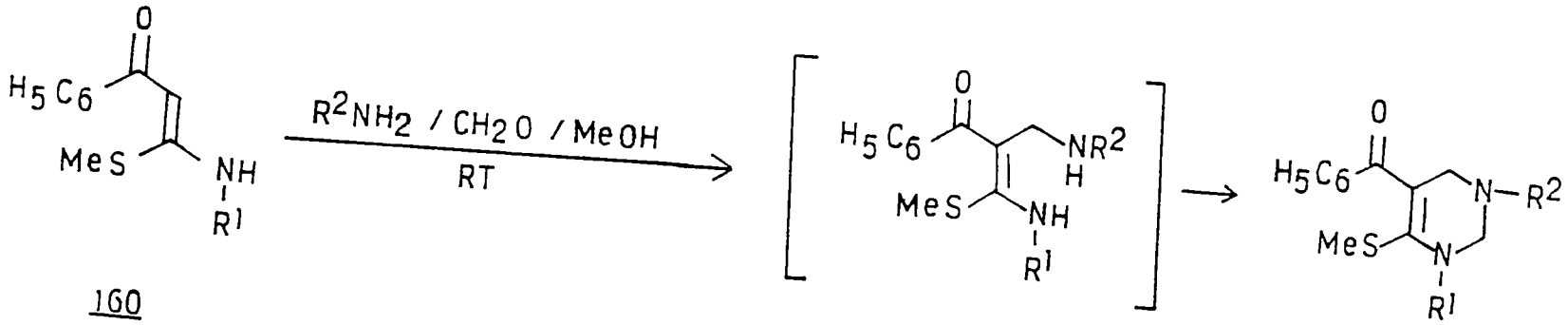


158 159

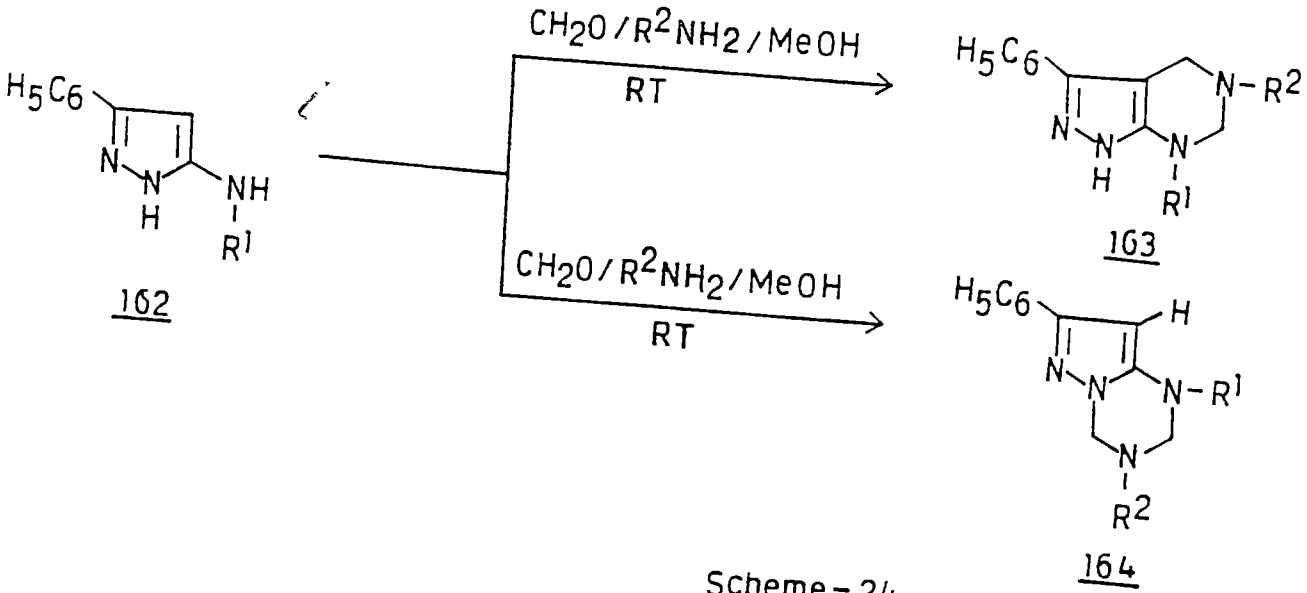


158 159 a

Scheme - 23



160 161



162 163 164

Scheme – 24

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

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

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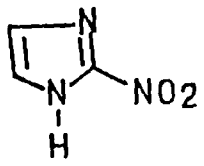
CHAPTER II

USE OF 5-NITRO HETEROCYCLES AS ANTIPARASITIC AGENTS : A BRIEF REVIEW

Ever since the discovery of antitrichomonas activity of azomycin 1 (2-nitro-1H-imidazole), from fermentation of a strain of Nocardia mesenterica[1,2], in 1956, efforts have been made to develop many nitro heterocycles with a view to developing more potent biologically active compounds.



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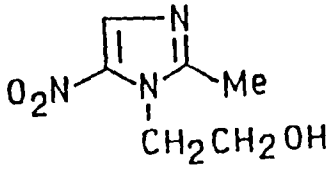

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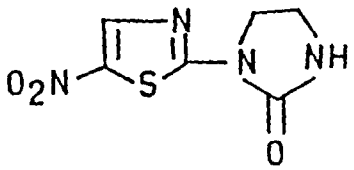
Extensive synthetic work was subsequently undertaken to make a variety of nitro imidazoles to screen them as possible antiprotozoal drugs. Consequently a group of compounds were described in a patent literature with the aim of finding

drugs with antitrichomonas activity[3]. Metronidazole 2 was one of those described in the list.

Subsequent studies revealed that the 5-nitro imidazole derivatives have better antiprotozoal activity than the corresponding 2 and 4-nitroimidazoles[4]. The Metronidazole 2 was selected for further biological activity particularly to treat infections due to *Trichomonas vaginalis*. The desired compound was prepared by alkylation of 2-methyl-4(5)-nitroimidazole with either 2-chloroethanol[5] or ethylene oxide[6]. Surprisingly it was found to be active on *E.histolytica* in vitro at concentrations of 10 µg/ml and exhibited marked activity against intestinal amebiasis in rats and against hepatic amebiasis in hamsters[7,8]. In its clinical studies, three times treatment per day for 5 to 10 days cured 96 of 105 patients with confirmed amebic liver abscess[9]. In contrast to niridazole 3, the metronidazole exhibited no significant electrocardiographic changes or neuropsychiatric disturbances. It was therefore considered that the Metronidazole 2 was found to be unique drug as a



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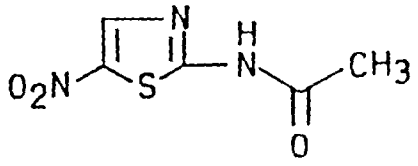

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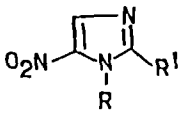
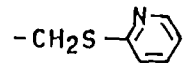
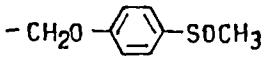
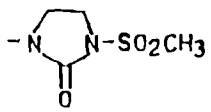
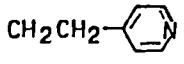
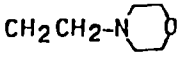
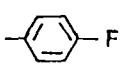
single direct acting amebicide effective in the bowel and the liver, without significant toxicity. The drug was also found to be active for the treatment of *giardiasis*[10], *Crohn's disease*[11], and *anaerobic bacterial infections*[12].

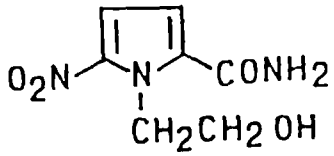
Since then a number of 5-nitro imidazoles have been prepared and evaluated for therapeutic and prophylactic applications[13]. List of these nitro derivatives, which have received clinical acceptance is described in the Table. Among others, tinidazole, (2) (Table) has displayed higher cure rates than (1) (Table) in the treatment of intestinal amebiasis[14]. similarly the other drugs (3-14) (Table) have displayed varying degrees of antiamebic properties sometimes with improved biological profile. Apparently structural modifications at 1 and 2 positions of 5-nitro imidazoles could provide drugs with improved protozoal activities.

The five membered heterocycles with an appropriately substituted nitro group have also been used in the clinical practice. Thus the 2-acetamido-5-nitro thiazole 4 has displayed potential intestinal antiamebiasis in rats and dogs at well-tolerated doses[15]. Another thiazole derivative niridazole 3 has also displayed strong therapeutic effects against amebiasis and schistosomiasis[16]. It also strongly suppresses amebic liver abscess in hamsters following daily doses of 60-120 mg/kg for 7 days. Despite its higher antiamebic activity against both intestinal and hepatic amebiasis, frequent electrocardiographic changes and occasional neuropsychic episodes,have been encountered[17,18].

TABLE



COMPOUND No.	R	R^1	GENETIC NAME
1	CH_2CH_2OH	Me	Metronidazole
2	$CH_2CH_2SO_2Et$	Me	Tinidazole
3	Me	Me	Dimitridazole
4	Me	CH_2OCONH_2	Ronidazole
5	Me		Ipronidazole
6	Me		Pirinidazole
7	Me		Fexinidazole
8	Me		C10213 - Go (Satronidazole)
9	$CH_2CH_2NHCSOCH_3$	Me	Carnidazole
10	$CH_2\underset{\underset{OH}{\vert}}{CH}-CH_2Cl$	Me	Ornidazole
11	$CH_2-\underset{\underset{OH}{\vert}}{CH}-CH_3$	Me	Secnidazole
12		Me	Panidazole
13		H	Nimorazole
14	CH_2CH_2OH		Flunidazole



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In addition to nitro imidazoles and nitro thiazoles many nitro heterocyclic compounds possess anti amebic activity including nitro pyrroles[19,20], which have displayed potential antiamebic activity both intestinal and hepatic. Among them 1-(2-hydroxyethyl)-5-nitro pyrrole-2-carboxamide 5 has exhibited activity against intestinal amebiasis in rats and hepatic amebiasis in hamsters[19]. Similarly combination of nitro pyrrazoles[21] and nitro furans[22,23] has displayed marked antiamebic activity.

Generally the synthesis of nitro heterocycles involves nitration in a preconstructed ring system and extensive nitration studies are described in the literature. Apparently there is a wide scope for the study of 5-membered nitro heterocycles as potential area of development of new drugs for treatment of protozoal disease. It was considered of interest to undertake some studies involving the preparation of nitro heterocycles and screen them for antiprotozoal activity.

In the following chapter the synthesis and anti amebic screening of 1-substituted-2-methylthio-3-acyl-5-nitro

pyrroles have been described. The antiamebic activity was carried out in Organon Research Centre, Saturday Club Building, 7-Wood Street, P.B. No. 9070, Calcutta at their laboratory. We express our gratitude for their efficient screening methodology. The results are presented at the end of the next chapter.

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CHAPTER III

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

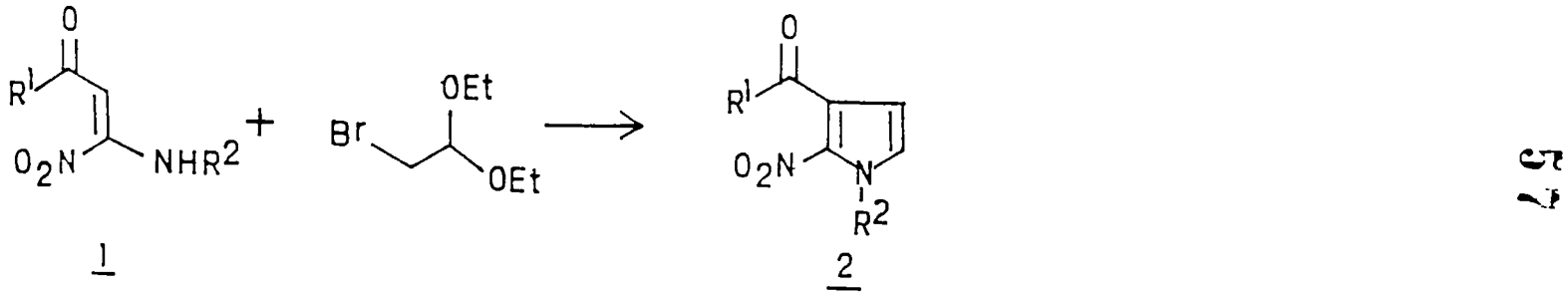
B. NITRATION OF 1-SUBSTITUTED-2-METHYLTHIO-3-ACYL PYRROLES: SYNTHESIS OF 1-SUBSTITUTED-2-METHYLTHIO-3-ACYL-5-NITRO PYRROLES.

C. RESULTS OF ANTIPROTOZOAL SCREENING.

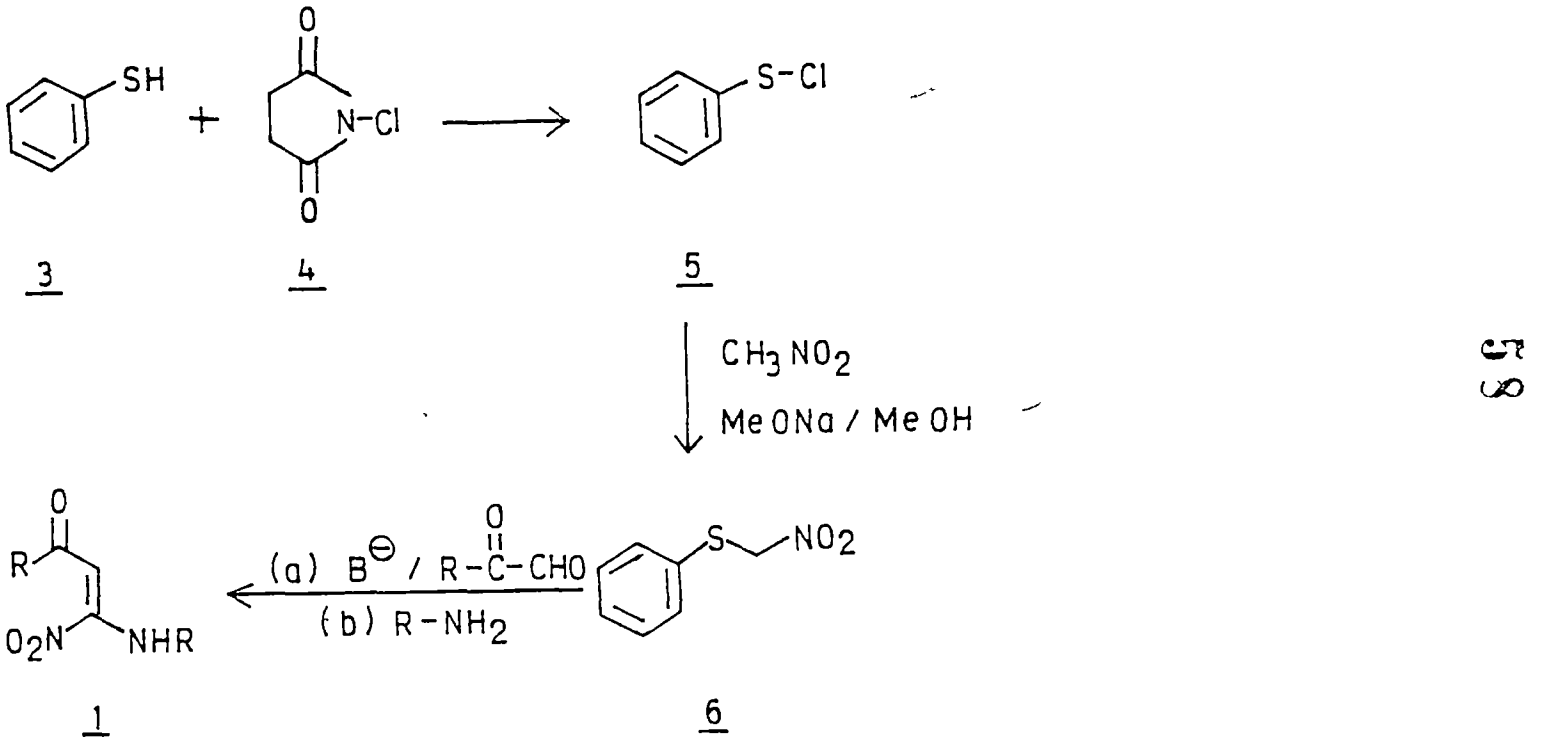
INTRODUCTION

In the preceding chapter it has been shown that the 5-nitro pyrroles have displayed marked antiamebic activity. The nitro pyrroles also displayed activity against hepatic infections in hamsters. It is therefore presumed that the 5-nitro pyrroles could serve as a potential source of antiparasitic drugs. Extensive work in the area of synthetic chemistry of pyrroles has been reported only in the later part of this century. Much work has been done in the recent

past and the chemistry of these pyrroles has been reviewed[1-14]. A number of methods have been reported for the synthesis of pyrroles but the methods for 3-nitro substituted pyrroles from acyclic precursors have been few in number. Most of the nitro pyrroles have thus been obtained by nitration after the basic pyrrole ring is constructed. Generally the pyrrole ring is sensitive to strong acidic conditions and results in intractable product mixture. Yet there have been extensive experimental reports on the nitration of pyrroles[15-23]. However to construct 5-nitro pyrroles from the open chain precursors we need the 3 carbon 1,3-electrophilic fragment 1 which, in principle, should react with Bromo acetaldehyde diethyl acetal to provide the corresponding pyrroles 2 (Scheme 1) which are important derivatives for screening against protozoal infections. However the preparation of 1 has not been possible though efforts are being made to develop reasonably plausible route as described in Scheme 2. The previously reported thiophenyl nitro methane was prepared by reacting sulphenyl chloride 5 with nitromethano- enolate developed in methanolic sodium methoxide. The nitro compounds 6 however did not undergo satisfactory condensations with aryl ketoaldehydes in the presence of base. The reaction conditions are still being investigated. An alternative approach for the synthesis of nitro pyrroles was attempted by directly nitrating 2-methylthio-1-substituted-3-acyl pyrroles. The methodology for these pyrroles was developed in this laboratory [24] and it was decided to prepare a number of pyrroles by this



Scheme – 1


SH
+
O
N-Cl
O
S-Cl
3
4
5
CH_3NO_2
MeONa / MeOH
R
O
O_2N
NHR
(a) $B^{\ominus}$ / R-C(=O)-CHO
(b) $R-NH_2$
S
NO_2
1
6

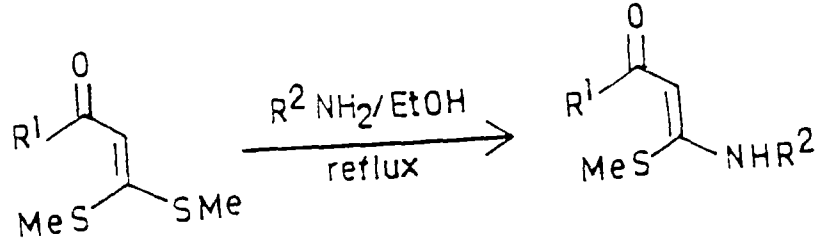
Scheme-2

method and subject them for nitration so that the corresponding nitro pyrroles are available for screening.

A total no of 33 nitro pyrroles with a wide variety of structural features have been prepared, of which 28 pyrroles are new and which are not described in the literature. Also the corresponding S,N-acetals have been prepared of which 13 are new and not reported in the literature.

RESULTS AND DISCUSSION:

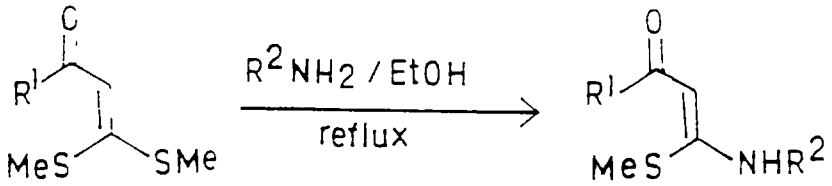
A total no. of 33 α-oxoketene S,N-acetals, 8a-t (Table 1) were prepared as per the reported procedure[27,28], the remaining unknown S,N- acetals **10a-m** (Table 2) were prepared essentially by extending the earlier methods which were used in the present work. Thus in a typical experiment the α-oxoketene dithioacetal **9a** was treated with octyl amine in refluxing ethanol and the reaction mixture, after work-up and purification, afforded a compound which was characterized as 3-octylamino-3-methylthio-1-phenyl-2-propen-1-one in 78% yield. The structure of 10a was fully established from its spectral and analytical data. Thus, it was analyzed for $C_{18}H_{27}NOS$ and analysis was in accordance with its molecular weight 305.4. Its I.R. (Neat) spectrum showed bands at ν max = 2937, 1579 cm^{-1}. Its structure was further confirmed from its ^1H n.m.r. (CCl_4) spectrum. The broad singlet at δ 0.85 (3H) was assigned to the methyl protons of N-octyl group. The broad singlet at δ 1.30 (12H) was due to the methylene protons. The thiomethyl protons



7a-e

8a-t

Scheme - 3



9a-c

10a-m

Scheme - 4

TABLE 1

S.No.	Starting Compound 7	Product 8	R^1	R^2
1	a	a	Me	Et
2	a	b	Me	Cyclo C_6H_{11}
3	b	c	Ph	Me
4	b	d	Ph	Et
5	b	e	Ph	n-Bu
6	b	f	Ph	$PhCH_2$
7	b	g	Ph	Cyclo C_6H_{11}
8	c	h	4-ClC_6H_4	Me
9	c	i	4-ClC_6H_4	Et
10	c	j	4-ClC_6H_4	n-Bu
11	c	k	4-ClC_6H_4	$PhCH_2$
12	c	l	4-ClC_6H_4	Cyclo C_6H_{11}
13	d	m	4-$OMeC_6H_4$	Me
14	d	n	4-$OMeC_6H_4$	Et
15	d	o	4-$OMeC_6H_4$	n-Bu
16	d	p	4-$OMeC_6H_4$	$PhCH_2$
17	d	q	4-$OMeC_6H_4$	Cyclo C_6H_{11}
18	e	r	4-MeC_6H_4	n-Bu
19	e	s	4-MeC_6H_4	$PhCH_2$
20	e	t	4-MeC_6H_4	Cyclo C_6H_{11}

TABLE 2

S.No.	Starting Compound 9	Product 10	R^1	R^2
1	a	a	Ph	Octyl
2	a	b	Ph	Dodecyl
3	a	c	Ph	Cetyl
4	b	d	4-$OMeC_6H_4$	Heptyl
5	c	e	2,4-$Cl_2C_6H_3$	n-Bu
6	c	f	2,4-$Cl_2C_6H_3$	$PhCH_2$
7	c	g	2,4-$Cl_2C_6H_3$	Cyclo C_6H_{11}
8	d	h	3,4-$Cl_2C_6H_3$	n-Bu
9	d	i	3,4-$Cl_2C_6H_3$	$PhCH_2$
10	d	j	3,4-$Cl_2C_6H_3$	Cyclo C_6H_{11}
11	d	k	3,4-$Cl_2C_6H_3$	Octyl
12	d	l	3,4-$Cl_2C_6H_3$	Dodecyl
13	d	m	3,4-$Cl_2C_6H_3$	Cetyl

appeared as a singlet at δ 2.46 (3H). The quartet at δ 3.36 (2H, J = 7Hz) was assigned to the NCH_2 protons. The vinylic proton appeared as a singlet at δ 5.62 (1H). The multiplet around δ 7.36 - 7.62 (3H) and another multiplet around δ7.82-8.06 (2H) was due to the aromatic protons. The NH proton appeared as a broad singlet at δ 11.50 (1H) exchangeable with D_2O. Similarly **10b** and **10c** were prepared by reacting **9a** with dodecyl amine and cetylamine as described above to afford the corresponding S,N- acetals **10b** and **10c** in 82% and 81% yields respectively. The 4-methoxy benzoyl ketene dithioacetal[9b] was reacted with heptyl amine to obtain the corresponding S,N-acetal **10d** in 72% yield. The analytical and spectral data of these compounds were in accordance with the structural assignment. Similarly 2,4-dicholoro acetophenone prepared as reported in the literature[25] was converted into α-oxoketene dithioacetal and reacted with butyl, benzyl and cyclohexyl amines to afford the corresponding S,N-acetals **10e-g** in 83-85% overall yields. The 3,4-dichloro acetophenone[25] was also converted into α-oxoketene dithioacetal **9d** which was further reacted with butyl, benzyl, cyclohexyl, octyl, dodecyl and cetyl amines to afford the corresponding S,N- acetals **10h-m** in 81-85% overall yields. The hitherto unreported S,N-acetals **10a-m** thus prepared were fully established from their spectral and analytical data which are described in the experimental section.

In the preceding chapter the importance of 5-nitro pyrroles **5** (Chapter 2) as potential antiamebic drugs active both in

intestine as well as liver has been described. The molecules as potential antiamebic drug with duel advantage of being active both in intestine and hepatic models should possess structural features such that the drug possibly should partially transport to the liver as well as remain in the gut. The metronidazole has this duel advantage over other drugs, and it is therefore necessary to keep appropriately substituted lipophilic and hydrophilic functional groups which could balance the transport process, fulfilling the required drug distribution profile.

With this in view it was considered of interest to undertake the synthesis of a series of pyrroles as reported from this laboratory[24]. Besides a number of hitherto unreported pyrroles were also prepared by extending the above method. The pyrroles thus, obtained were subsequently nitrated in the presence of fuming nitric acid and acetic anhydride, to obtain the target nitro pyrroles in varying yields. The nitro pyrroles thus obtained were screened for the antiamebic activity and the results are presented at the end of this chapter.

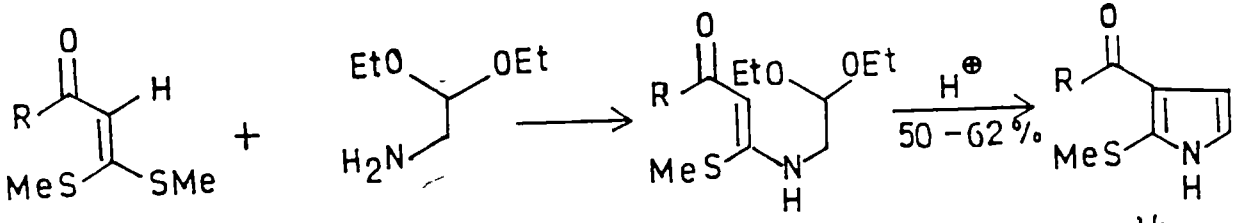
A. Reaction of polarized ketene S,N-acetals with bromoacetaldehyde diethylacetal:

In one of the earlier communications[26] a general method for the synthesis of 2-methylthio-3-acyl pyrroles **14** by reacting the α-oxoketene S,S-acetals **11** with aminoacetaldehyde diethyl acetal **12** to yield the

corresponding S,N-acetals 13 followed by cyclization in the presence of ethereal hydrochloric acid was developed in this laboratory (Scheme 5). It may be noted that the nitroketene S,S-acetal 15 also underwent a similar sequence of reactions to afford the corresponding nitro pyrrole 17 in 55% yield. This is one of the few methods that a pyrrole ring is constructed with a nitro group carried from the open chain precursors. The reported methods generally adopt the nitration procedure after the pyrrole ring is constructured. However this methodology could not be extended for the synthesis of 2- or 5-nitro pyrroles which requires the 3 carbon 1,3-electrophilic fragment 1 as described earlier.

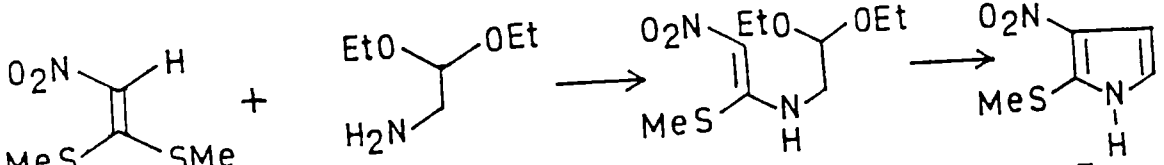
The synthesis of 1 however could not be standardised and therefore decided to construct the pyrrole ring first and then subject for nitration to get the target nitro pyrroles for screening.

When the above pyrrole synthesis was extended to N-substituted pyrroles it was required to react the α-oxoketene S,S- acetal 11 with appropriate N-substituted aminoacetaldehyde diethyl acetal 18 to get the corresponding S,N-acetal 19 which however could not be obtained in desirable yield. The reduced basicity of acetal 18 coupled with steric factors due to substituents, the reaction of 18 with 11 was not satisfactory. Thus, the methodology suffered from limitations that it could be used only for the synthesis of unsubstituted pyrroles. The alternative approach for the synthesis of N-alkyl/aryl-2-methylthio-3-

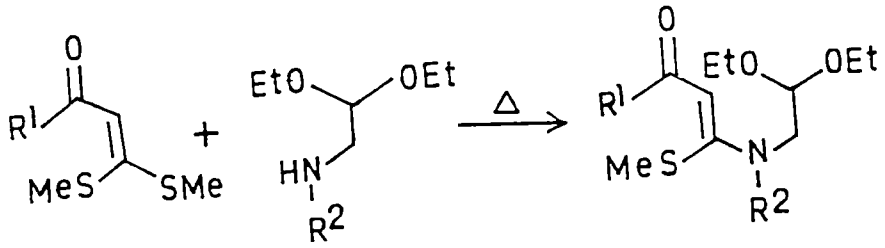


11 12 13 14

R = C_6H_5, 4-Me C_6H_4, 4-MeO C_6H_4, 4-EtO C_6H_4
4-Cl C_6H_4, 4-Br C_6H_4, Me



15 12 16 17



11 18 19

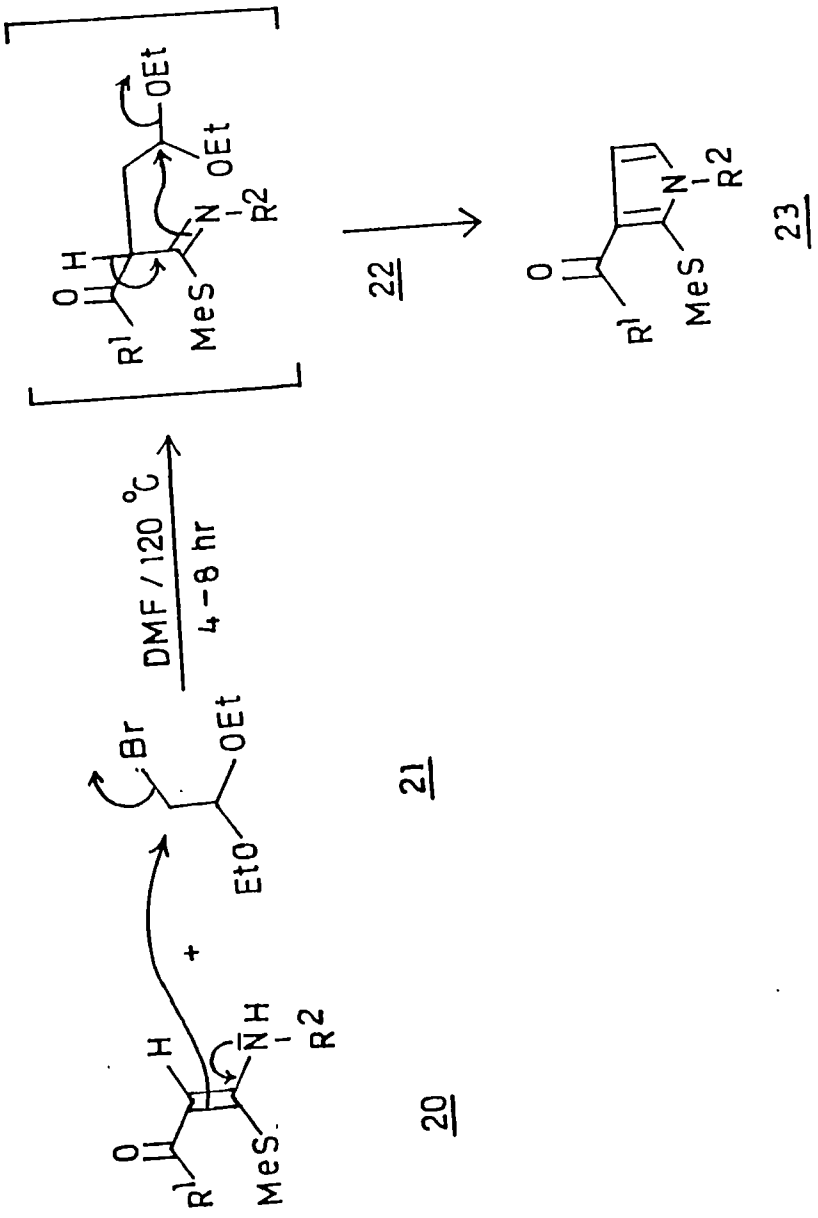
R^2 = Me, Et, C_6H_5

Scheme - 5

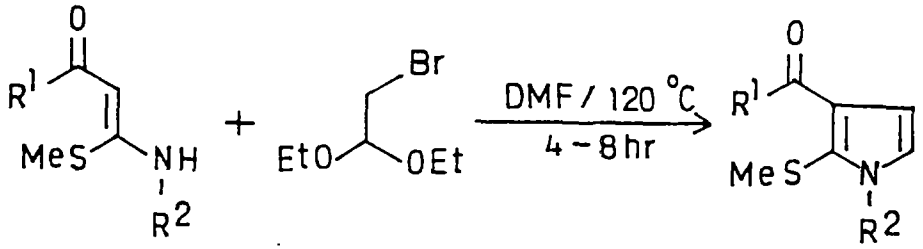
acyl pyrroles through the reaction of easily accessible α-oxoketene S,N-acetals 20 with bromoacetaldehyde diethyl acetal 21 was used. The methodology was very successful and a number of pyrroles carrying various substituents in 1 position were prepared.

In the present work this method was used to prepare various pyrroles required for screening.

The reported pyrroles 25a-e (Scheme 7) were prepared and remaining hitherto unreported pyrroles 28a-z, 28aa and 28bb (Scheme 8) (Table 3) were prepared for the first time. When the α-oxoketene S,N-acetal 27a was reacted with bromoacetaldehydediethyl acetal 21 in dimethyl formamide (DMF) at 120°C for 4 hours, the reaction mixture, after work-up and purification gave the corresponding 1-cyclohexyl-2-methylthio-3-aroyl pyrrole 28a in 79% yield. The structure of 28a was fully established from its spectral and analytical data. Thus, it was analyzed for $C_{18}H_{21}NOS$ and the mass spectral analysis was in accordance with its molecular weight 299.4. Its I.R. (KBr) spectrum showed a strong absorption band at ν_{max} = 1645 cm^{-1}. Its structure was further confirmed from its ^{1}H n.m.r ($CDCl_3$) spectrum. The multiplet around δ 1.15 - 2.15 (10 H) was due to ring CH_2 protons. The singlet at δ 2.42 (3H) was assigned to the thiomethyl group. The broad singlet at δ 4.60 (1H) was due to CH proton of the ring. The doublets at δ 6.52 (1 H, J = 3Hz) and δ 6.73 (1H,J = 3Hz) were due to H-4 and H-5 protons respectively. The aromatic protons appeared as two



Scheme-6



24 a–e 21 25 a–e

24, 25	R^1	R^2
a	Me	Et
b	Ph	Me
c	Ph	Et
d	Ph	n-Bu
e	Ph	Ph CH_2

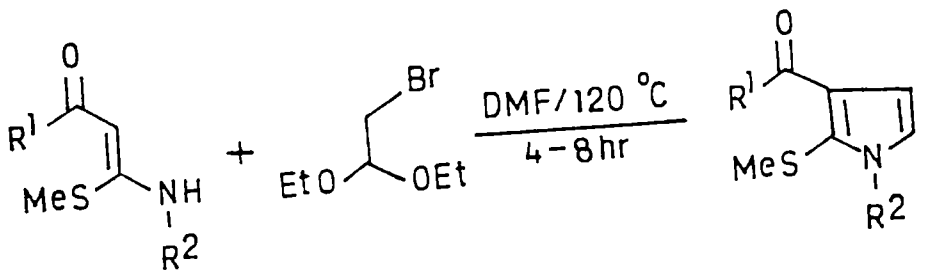
Scheme – 7

multiplets at δ 7.36-7.66 (3H) and δ 7.75 - 8.09 (2H) respectively. Similarly, the other α-oxoketene S,N-acetals 27b-d also reacted with 21 to afford the corresponding 1-substituted-2-methylthio-3-acyl pyrroles 28b-d in 72-86% overall yields (Scheme 8). The structures of pyrroles thus obtained were fully established from their spectral and analytical data which are described in the experimental section.

Similarly, the α-oxoketene S,N-acetals derived from 4-chloroacetophenone reacted with 21 to afford the corresponding pyrroles 28e-i in 62-88% overall yields (Scheme 8). The structures of 28e-i were fully established from the spectral and analytical data which are described in the experimental section.

It was also decided to react the S,N-acetals 27j-n and 27aa derived from 4-methoxy acetophenone with 21 to examine the effect of electron donating group on the biological activity of the corresponding nitro pyrroles 29j-n. The structures of pyrroles thus obtained 28j-n and 28aa in 62-73% overall yields, were fully established from their spectral and analytical data, which are described in the experimental section.

Thus S,N-acetals 27o-q derived from 4-methyl acetophenone were similarly reacted with 21 to afford the corresponding pyrroles 28o-q in 71-78% overall yields. The spectral and analytical data of these compounds are described in the experimental section.



27a-z 21 28a-z

Scheme-8

TABLE 3

27,28	R^1	R^2
a	Ph	Cyclo C_6H_{11}
b	Ph	Octyl
c	Ph	Dodecyl
d	Ph	Cetyl
e	4-ClC_6H_4	Me
f	4-ClC_6H_4	Et
g	4-ClC_6H_4	n-Bu
h	4-ClC_6H_4	$PhCH_2$
i	4-ClC_6H_4	Cyclo C_6H_{11}
j	4-$OMeC_6H_4$	Me
k	4-$OMeC_6H_4$	Et
l	4-$OMeC_6H_4$	$PhCH_2$
m	4-$OMeC_6H_4$	Cyclo C_6H_{11}
n	4-$OMeC_6H_4$	Heptyl
o	4-MeC_6H_4	n-Bu
p	4-MeC_6H_4	$PhCH_2$
q	4-MeC_6H_4	Cyclo C_6H_{11}
r	2,4-$Cl_2C_6H_3$	n-Bu
s	2,4-$Cl_2C_6H_3$	$PhCH_2$
t	2,4-$Cl_2C_6H_3$	Cycloc $_6H_{11}$
u	3,4-$Cl_2C_6H_3$	n-Bu

Table 3 (Contd.)

v	3,4-$Cl_2C_6H_3$	$PhCH_2$
w	3,4-$Cl_2C_6H_3$	Cyclo C_6H_{11}
x	3,4-$Cl_2C_6H_3$	Octyl
y	3,4-$Cl_2C_6H_3$	Dodecyl
z	3,4-$Cl_2C_6H_3$	Cetyl
aa	4-$OMeC_6H_4$	n-Bu
bb	Me	Cyclo C_6H_{11}

The S,N-acetals 27r-z derived from 2,4-dichloro and 3,4-dichloro acetophenones were reacted with 21 to afford the corresponding pyrroles 28r-z in 82-86% overall yields. The structures of 28r-z were fully established from the spectral and analytical data (Experimental).

Similarly the α-oxoketene S,N-acetal 27bb derived from acetone was reacted with 21 to afford the corresponding pyrrole 28bb in 68% yield. The structure of 28bb was fully established from its spectral and analytical data (Experimental).

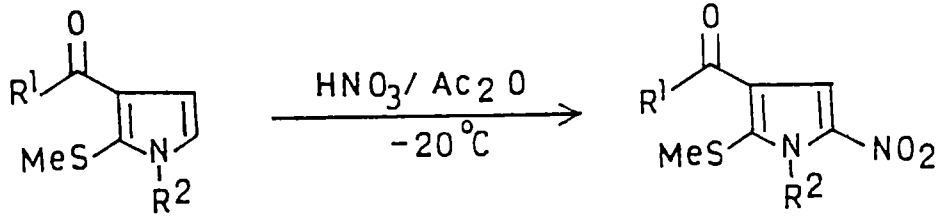
B. Nitration of 1-substituted-2-methylthio-3-acyl pyrroles: Extensive studies on the nitration of pyrroles and their derivatives have been reported in the literature[15-23]. The pyrrole ring being 6π electron 5-membered ring, displays very high reactivity towards electrophilic substitution. The reaction often results in intractable tar and consequently careful controlled mild reaction conditions are to be employed to achieve the desired substitution. The nitration reactions have been generally carried out under very mild conditions over a wide range of temperatures. The use of sulphuric acid as dehydrating agent in nitration is generally avoided since pyrroles under these conditions undergo extensive polymerization. Thus a mixture of fuming nitric acid (d,1.5) and acetic anhydride at ambient temperature is found to be suitable for nitration. It has been proved that acetyl nitrate is a nitrating agent. Even under these conditions the pyrroles generally yield

undesirable resinous substances resulting in reduced yield of the desired nitrated products. The nitration generally takes place at 2(5)-positions depending upon the temperature, while some authors have reported 3-nitro pyrroles as one of the by products. At -10°C Rinks[15] obtained 2-nitro pyrrole as the only homogenous product but under similar conditions Anderson[17], Fournari and Tirouflet[19] and Morgan and Morrey[20] subsequently also detected the presence of 3-nitro isomer. Under this preparative condition the nitro pyrroles were obtained around 70% yield after a reaction period of 90 min. Other attempts to replace acetic anhydride by solvents such as acetic acid, acetonitrile, nitromethane and tetrahydrofuran at 0°C yielded unreacted pyrroles. Prolonged treatment of pyrrole with nitric acid in the presence of acetic acid resulted in total tar formation and neither unreacted pyrroles nor nitrated products could be detected from the reaction mixture. The successful experiment of nitration gave 2-nitro pyrrole in 33.5% yield, when carried out at -10°C in nitromethane as solvent. Further improvement in the yield was not possible.

The electron withdrawing groups on the pyrrole ring should make it resistant to acid assisted polymerization. The present studies on 3-acyl pyrroles should serve as electron withdrawing substituents so that the nitration as described above,should yield the expected nitro pyrroles in improved yields. The details of the nitration are described in the

present chapter. The nitration of pyrroles 25a-e and 28a-z was carried out in the presence of fuming nitric acid and acetic anhydride at -20°C and efforts were not made to optimize the yields. In some cases unreacted pyrroles were recovered and the remaining resinous mass was discarded.

In a typical experiment the pyrrole 25a was dissolved in acetic anhydride and the reaction mixture was cooled to -20°C to which was added dropwise a mixture of nitric acid and acetic anhydride following the progress of the reaction by T.L.C. After 10 min. reaction mixture was allowed to warm to room temperature; poured into icecold water, extracted with dichloromethane, dried (Na_2SO_4) and the solvent distilled off to yield the crude product 26a which was further purified by passing through silica gel column using hexane/ ethyl acetate (19:1) as solvent and purified product was characterized as 1-ethyl-3-acetyl-2-methylthio-5-nitro pyrrole as colorless needles in 35% yield, m.p. 120-121°C. It was analyzed for $C_9H_{12}N_2O_3S$ and it displayed a peak in its mass spectrum at m/z 228 (M^+, 8%). Its I.R. (KBr) spectrum showed strong absorption bands at ν_{max} = 1700 (carbonyl), 1560, 1325 cm^{-1} (Nitro group). Its structure was further confirmed from its ^{1}H n.m.r. spectrum. The triplet at δ 1.56 (3H, J = 7 Hz) was assigned to the methyl protons of the N-ethyl group. The singlet at δ 3.23 (3H) was due to methyl thio group. Another singlet at δ2.54 (3H) was due to acetyl methyl protons. The quartet at δ5.23 (2H, J = 7Hz) was assigned to the methylene protons of N-ethyl group. The ring proton (H-4) of pyrrole appeared as a singlet at



25a-e

26a-e

25,26	R^1	R^2	Reaction time	Yield (%)	M.P. (°C)
a	Me	Et	10 min.	35	120-121
b	Ph	Me	10 min.	42	135-136
c	Ph	Et	20 min.	38	131-132
d	Ph	n-Bu	20 min.	43	97-98
e	Ph	Ph CH	20 min.	42	134-135

Scheme-9

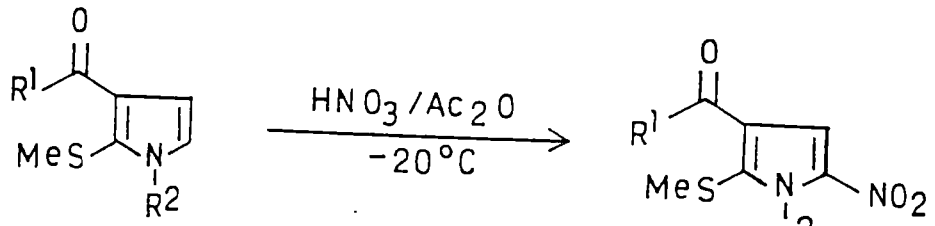
δ7.46 (1H) which proves unequivocally the position of nitro group in the ring. similarly the other known pyrroles **25b-e** were nitrated to afford the corresponding nitro pyrroles **26b-e** in 35-43% overall yields (Scheme 9). The nitration time and yields of the nitro compounds of the pyrroles investigated are described in the Table (Scheme 9). The other hitherto unknown pyrroles prepared in the present investigation were similarly nitrated to afford the corresponding nitro compounds 29a-z (Scheme 10) in 35-55% overall yields (Table 4).

CONCLUSION

The target nitro pyrroles were thus realised by the steps described in the text. The construction of pyrroles was necessary for the subsequent nitration to obtain the desired nitro pyrroles. These nitro pyrroles were fully characterised and subjected to antiamebic screening and the results of biological screening are discussed here.

C. Results of antiprotozoal screening:

From the screening chart it is apparent that compound **26d**, **29k**, **291**, **29m**, **29n**. **29q** and **29v** showed activity at 3.13 µg/ml with variation in time for complete inhibition. However all these compounds did not show similar activity in their *invivo* test. Only compound **29n** showed some moderate acctivity in both intestinal and hepatic model. On the other hand compounds **26e**, **29a**, **29g** and **29h** showed activity at 12 µg/ml and the *invivo* activity was not significant.



28 a-z

29 a-z

Scheme-10

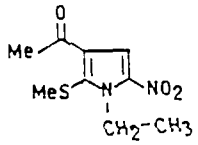
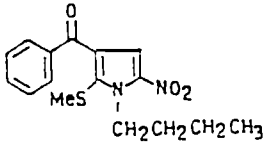
TABLE 4

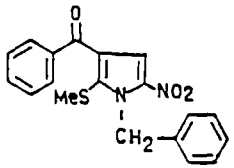
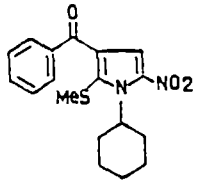
28,29	R^1	R^2	Reaction time	Yield (%)	M.P. (°C)
a	Ph	Cyclo C_6H_{11}	20 min.	41	129-130
b	Ph	Octyl	25 min.	45	64-65
c	Ph	Dodecyl	25 min.	54	61-62
d	Ph	Cetyl	30 min.	55	56-57
e	4-ClC_6H_4	Me	10 min.	44	201-202
f	4-ClC_6H_4	Et	10 min.	41	155-156
g	4-ClC_6H_4	n-Bu	5 min.	44	79-80
h	4-ClC_6H_4	$PhCH_2$	15 min.	40	164-165
i	4-ClC_6H_4	Cyclo C_6H_{11}	15 min.	43	154-155
j	4-$OMeC_6H_4$	Me	10 min.	35	123-124
k	4-$OMeC_6H_4$	Et	20 min.	35	119-120
l	4-$OMeC_6H_4$	$PhCH_2$	20 min.	38	119-120
m	4-$OMeC_6H_4$	Cyclo C_6H_{11}	20 min.	37	137-138
n	4-$OMeC_6H_4$	Heptyl	20 min.	37	115-116
o	4-MeC_6H_4	n-Bu	10 min.	43	125-126
p	4-MeC_6H_4	$PhCH_2$	25 min.	41	162-163
q	4-MeC_6H_4	Cyclo C_6H_{11}	25 min.	43	154-155
r	2,4-$Cl_2C_6H_3$	n-Bu	20 min.	52	87-88
s	2,4-$Cl_2C_6H_3$	$PhCH_2$	20 min.	51	94-95
t	2,4-$Cl_2C_6H_3$	Cyclo C_6H_{11}	20 min.	54	169-170
u	3,4-$Cl_2C_6H_3$	n-Bu	25 min.	53	95-96

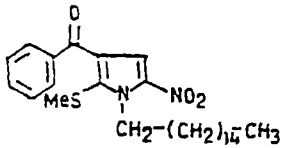
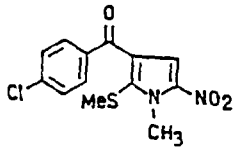
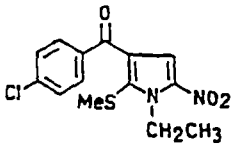
Table 4 (Contd.)

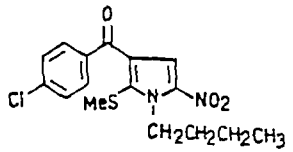
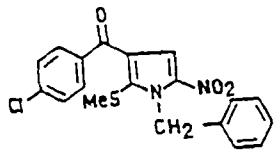
v	3,4-$Cl_2C_6H_3$	$PhCH_2$	25 min.	51	113-114
w	3,4-$Cl_2C_6H_3$	Cyclo C_6H_{11}	30 min.	52	154-155
x	3,4-$Cl_2C_6H_3$	Octyl	20 min.	55	64-65
y	3,4-$Cl_2C_6H_3$	Dodecyl	20 min.	54	75-76
z	3,4-$Cl_2C_6H_3$	Cetyl	30 min.	55	76-77

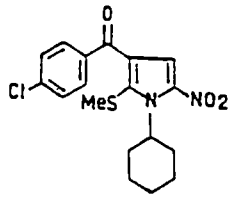
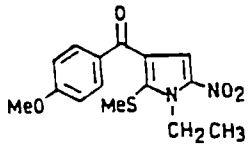
Similarly compounds **26a**, **29o**, **29s** and **29t** were active at 25 µg/ml while their *invivo* activity was negligible. Compounds **29p**, **29e**, **29f** and **29w** showed *invitro* marginal activity at 100 µg/ml and were inactive in their *invivo* test. The compounds **29d**, **29y** and **29z** were found to be inactive in both *invitro* and *invivo* test.

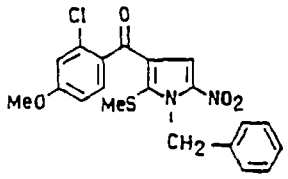
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
26a		Active (100)24h Active (25)24h Inactive (12.5)72h	(25) 48% N					
26d		Active (100)24h (25)24h (12.5)24h Partially active (6.25)48h (3.13)48h		Partially active (150x5) CI=85.7% VI=70% C/T=3/5 Inactive 150x5 CI=21% VI=95% C/T=0/5			AC:I (100)	

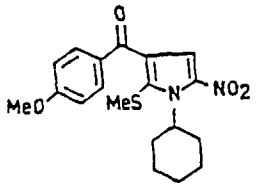
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
26e		Active (100)24h (25)24h (12.5)24h Inactive (6.25)72h	(25) 58% N			Inactive (150x4)0/3	AC:I (100) Nd:I (100)	
29a		Active (100)24h (25)24h Inactive (6.25)72h	(25) 17% N	Partially active (150x5) CI=50% (VI=70%) C/T=2/5 Inactive (150x5) CI=1.6 VI=91 C/T=0/3	Exhausted	Inactive (150x4)	AC:I (100) Nd:I (100)	

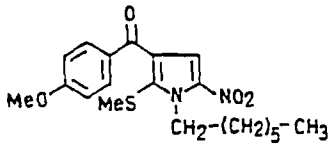
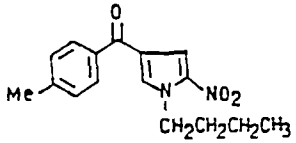
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29d		Inactive (100)72h						
29e		Partially active (100) 24h	(25) 0% N					
29f		Partially active (100) 24h	(25) 0% N					

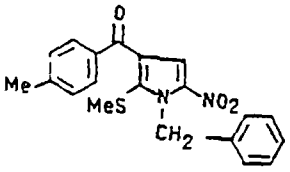
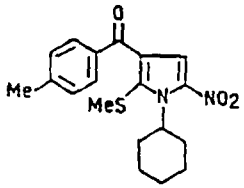
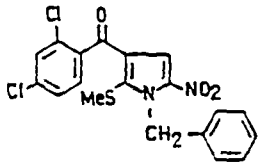
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29g		Active (100)24h Active (12.5)24h Inactive (6.25)72h	(25) 57% N			150x4.I (0/3)	AC;I (100) Nd:I (100)	
29h		Active (100)24h Active (25) 24h Active (12.5)48h	(25) 0% N					

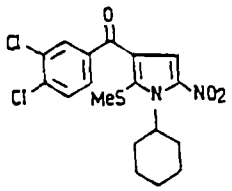
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29i		Active (100)24h Inactive (25)72h	(25) 34% N					
29k		Active (100)24h (25)24h (12.5)24h (6.25)24h (3.13)24h					Nd:I (100) AC:I (100)	

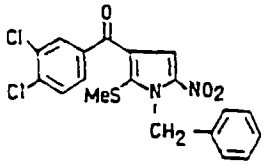
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
291		Active (100)24h (25)24h (12.5)48h (6.25)48h (3.13)48h	(25) 67%Ab.N				AC:I (100) Nd:I (100)	
				Inactive (150x5) CI=10% (VI=100%)	(150x5) CI=36% (VI=39%) C/T=0/6			

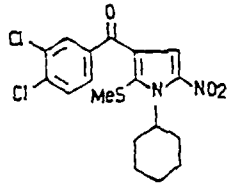
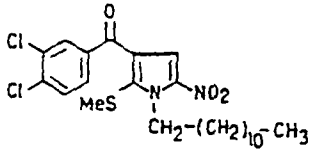
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg. x day;P.O.)
29m		Active (100)24h (25)24h (6.25)24h (3.13)24h	(25) 67%Ab.N				AC:I (100) Nd:I	
		Inactive (150x5) CI=42% (VI=100% C/T=0/3		Inactive (150x5) CI=54.5% (VI=39%) C/T=2/7				
		Inactive (50x5 IP) CI=19% (VI=100%) C/T=0/4		Inactive (150x5) CI:78% VI:45% C/T:0/5				
		Inactive (150x5) CI=40% VI=100% C/T=0/3		Inactive CI=36% (VI=39%) C/T=1/7				

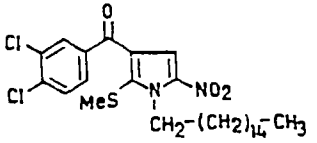
Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29n		Active (100)24h Active (25)24h Active (12.5)24h Inactive (3.13)72h		Partially active (150x5)				
29o		Active (100)24h Partially active (25)24h						

Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29p		Active (100)24h Inactive (25)72h						
29q		Active (100)24h Active (25)24h Active (12.5)24h Active (6.25)24h Active (3.1372h		Inactive (150x5)				
29s		Active (100)24h (25)24h Inactive (12.5)72h						

Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29t		Active (100)24h (25)24h Inactive (12.5)72h	(25) 55%Ab.N					
				Inactive (150x5) CI=30% (VI=62.5%) Inactive (150x5) CI=12.5% (VI=100%)	(150x5) CI=37% (VI=39%) C/T=0/6			

Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29v		Active (100)24h (25)24h (12.5)24h (6.25)24h (3.13)24h					AC:T (100) Nd:I (100)	
				Inactive (150x5) CI=20% (VI=62.5%)	(150x5) CI=63% (VI=39%) C/T=3/6			

Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29w		Active (100)24h Inactive (25)24h						
				Inactive CI=0% (VI=100%)			AC:I (100) Nd:I (100)	
			(25) 30% N	Inactive (150x5) CI=36% (VI=62.5) C/T=2/5	(150x5) CI=31% (VI=39%) C/T=0/6			
29y		Inactive (100)72h						

Sl. No	Structures	Antiamebic				Antitrichomonas	Anthelmintic	
		In vitro		In vivo		in vivo	in vitro	in vivo
		Cydal (Conc. in µg/ml)	LaI(%) Conc. in µg/ml)	Hepatic (mg/kg x day;P.O.)	Intestinal (mg/kg x day; P.O)	(mg/kg x day;P.O.)	(Conc.in µg/ml)	(mg/kg x day;P.O.)
29z		Inactive (100)72h						

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 analysis were done on Heraus CHN-O-RAPID instrument.

STARTING MATERIALS:

The commercial samples of various acetophenones, acetone, amines, ethanol, DMF etc. were purified before use. Commercially available bromoacetaldehyde diethyl acetal (ALDRICH) and acetic anhydride were used as such. Fuming HNO_3 was prepared according to the reported procedure. The known α-oxokeene, S,N-acetals 8a-t were prepared according to the reported procedure[27,28] and their spectral and analytical data were found to be similar to the reported ones. The unknown α-oxoketene S,N-acetals 10a-m were prepared by extending the reported procedure[27] and their structures were fully established from their spectral and analytical data which are given below.

3-Octylamino-3-methylthio-1-phenyl-2-propen-1-one [10a] was obtained as viscous oil; yield, 78%; I.R. (Neat): ν_{max} = 2937, 1579 cm^{-1}; ^1H n.m.r. (CCl_4): δ=0.85 (brs, 3H, $-CH_2(CH_2)_6CH_3$); 1.30 (brs,12H, $-CH_2(CH_2)_6CH_3$), 2.46 (s, 3H, SCH_3), 3.36 (q, J=7Hz, 2H, $-CH_2(CH_2)_6CH_3$), 5.62 (s, $1H_{olefin}$), 7.36-7.62 (m, $3H_{arom}$), 7.82-8.06 (m, $2H_{arom}$), 11.85 (brs, 1H, NH). [Found: C, 70.64; H, 8.78; N, 4.37 calculated for $C_{18}H_{27}NOS$ (305.4): C, 70.78; H, 8.91; N, 4.58%]

3-Dodecylamino-3-methylthio-1-phenyl-2-propen-1-one [10b] was obtained as a colourless solid; m.p. 38-39°C; yield, 82%; I.R. (KBr):ν_{max} = 2919, 1563 cm^{-1}; ^1H n.m.r. (CCl_4), δ = 0.89 (brs, 3H, $-CH_2(CH_2)_{10}CH_3$), 1.30 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$), 2.39 (s, 3H, SCH_3), 3.36 (brs, 2H, $-CH_2(CH_2)_{10}CH_3$), 5.59 (s, $1H_{olefin}$), 7.33-7.56 (m, $3H_{arom}$), 7.79-8.0 (m, $2H_{arom}$), 11.82 (brs, 1H, NH). [Found: C, 73.22; H, 9.89; N, 3.61 calculated for $C_{22}H_{35}NOS$ (361.5): C, 73.08; H, 9.75; N, 3.87%].

3-Cetylamino-3-methylthio-1-phenyl-2-propen-1-one [10c] was obtained as a colourless solid; m.p. 55-56°C; yield, 81%; I.R. (KBr): ν_{max} = 2939, 1569 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.89 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.30 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 2.46 (s, 3H, SCH_3), 3.33 (brs, 2H, $-CH_2(CH_2)_{14}CH_3$), 5.66 (s, $1H_{olefin}$); 7.39-7.56 (m, $3H_{arom}$), 7.82-8.03 (m, $2H_{arom}$), 11.85 (brs, 1H, NH). [Found : C, 74.51; H, 10.09; N, 3.63 calculated for $C_{26}H_{43}NOS$ (417.6); C, 74.77; H, 10.37; N, 3.35%].

3-Heptylamino-3-methylthio-1-(4-methoxyphenyl)-2-propen-1-one [10d] was obtained as viscous oil; yield, 72%; I.R. (KBr): ν_{max} = 2913, 1567 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.89 (brs, 3H, $CH_2(CH_2)_5CH_3$), 1.30 (brs, 10H, $-CH_2(CH_2)_5CH_3$), 2.42 (s, 3H, SCH_3), 3.36 (q, J = 7Hz, 2H, $-CH_2(CH_2)_5CH_3$), 5.62 (s, $1H_{olefin}$); 6.95 (d, J = 9Hz, $2H_{arom}$), 7.89 (d, J = 9Hz, $2H_{arom}$), 11.85 (brs, 1H, NH). [Found: c, 67.04, H, 8.27; N, 4.11 calculated for $C_{18}H_{27}NO_2S$ (321.4): C, 67.26; H, 8.46; N, 4.35%].

3-Butylamino-3-methylthio-1-(2,4-dichlorophenyl)-2-propen-1-one [10e] was obtained as viscous oil; yield, 85%; I.r. (Neat) :ν_{max} = 2921, 1587 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 0.95 (t, 3H, $-CH_2(CH_2)_2CH_3$), 1.13-1.79 (m, 4H, $-CH_2(CH_2)_2CH_3$), 2.36 (s, 3H, SCH_3), 3.33 (q, J = 7Hz, 2H, $-CH_2(CH_2)_2CH_3$), 5.29 (s, $1H_{olefin}$), 7.13-7.56 (m, $3H_{arom}$), 11.65 (brs, 1H, NH). [Found : C, 52.71; H, 5.24; N, 4.24 calculated for $C_{14}H_{17}NOSCl_2$ (318.2): C, 52.84; H, 5.38; N, 4.40%].

3-Benzylamino-3-methylthio-1-(2,4-dichlorophenyl)-2-propen-1-one [10f] was obtained as a colourless solid, m.p. 85-86°C; yield, 83%; I.R. (KBr): ν_{max} = 1569 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.40 (s, 3H, SCH_3), 4.69 (d, J = 7Hz, 2H, $-CH_2C_6H_5$), 5.49 (s, $1H_{olefin}$), 7.33-7.66 (m, $8H_{arom}$); 11.68 (brs, 1H, NH). [Found: C, 58.21; H, 4.06; N, 3.73 calculated for $C_{17}H_{15}NOSCl_2$ (352.2): C, 57.96; H, 4.29; N, 3.97%].

3-Cyclohexylamino-3-methylthio-1-(2,4-dichlorophenyl)-2-propen-1-one [10g] was obtained as a colourless solid, m.p.

69-70°C; yield, 85%; I.R. (KBr): ν_{max} = 2948, 1557 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.06-2.23 (m, 10H, ring CH_2), 2.36 (s, 3H, SCH_3), 3.69 (brs, 1H, CH), 5.36 (s, $1H_{olefin}$), 7.30-7.69 (m, $3H_{arom}$), 11.47 (brs, 1H, NH). [Found, C, 55.69; H, 5.43; N, 3.81 calculated for $C_{16}H_{19}NOSCl_2$ (344.2): C, 55.82; H, 5.56; N, 4.06%].

3-Butylamino-3-methylthio-1-(3,4-dichlorophenyl)-2-propen-1-one [10h] was obtained as viscous oil; yield 84%; IR (Neat): ν_{max} = 2925, 1592 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.95 (t, J = 7Hz, 3H, $-CH_2(CH_2)_2CH_3$), 1.13-1.79 (m, 4H, $-CH_2(CH_2)_2CH_3$), 2.46 (s, 3H, SCH_3), 3.33 (q, J = 7Hz, 2H, $-CH_2(CH_2)_2CH_3$), 5.56 (s, $1H_{olefin}$), 7.39-7.82 (m, $2H_{arom}$), 8.00 (d, J = 2Hz, $1H_{arom}$), 11.89 (brs, 1H, NH). [Found : C, 52.59; H, 5.56; N, 4.59 calculated for $C_{14}H_{17}NOSCl_2$ (318.2): C, 52.84; H, 5.38; N, 4.40%].

3-Benzylamino-3-methylthio-1-(3,4-dichlorophenyl-2-propen-1-one [10i] was obtained as a colourless solid; m.p. 70-71°C; yield, 82%; I.R. (KBr): ν_{max} = 1563 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.49 (s, 3H, SCH_3), 4.69 (d, J = 7Hz, 2H, $-CH_2C_6H_5$), 5.66 (s, $1H_{olefin}$), 7.42-7.92 (m, $7H_{arom}$), 8.13 (d, J = 2Hz, $1H_{arom}$), 11.95 (brs, 1H, NH). [Found : C, 57.71; H, 4.49; N, 4.11 calculated for $C_{17}H_{15}NOSCl_2$ (352.2): C, 57.96; H, 4.29; N, 3.97%].

3-Cyclohexylamino-3-methylthio-1-(3,4-dichlorophenyl)-2-propen-1-one [10j] was obtained as a colourless solid m.p. 55-56°C; yield 85%; I.R. (KBr): ν_{max} = 2953, 1559 cm^{-1}; ^1H

n.m.r. ($CDCl_3$): δ = 1.03 - 2.23 (m, 10H, ring CH_2), 2.56 (s, 3H, SCH_3), 3.75 (brs, 1H, CH), 5.69 (s, $1H_{olefin}$), 7.52-8.00 (m, $2H_{arom}$), 8.16 (d, J = 2Hz, $1H_{arom}$), 11.95 (brs, 1H, NH). [Found : C, 55.96; H, 5.73; N, 3.88 calculated for $C_{16}H_{19}NOSCl_2$ (344.2); C, 55.82; H, 5.56; N, 4.06%].

3-Octylamino-3-methylthio-1-(3,4-dichlorophenyl)-2-propen-1-one [10k] was obtained as viscous oil; yield, 81%; I.R. (Neat) : ν_{max} = 2926, 1535 cm^{-1}; ^1H n.m.r.(CCl_4): δ = 0.85 (brs, 3H, $-CH_2(CH_2)_6CH_3$), 1.26 (brs, 12H, $-CH_2(CH_2)_6CH_3$), 1.39 (s, 3H, SCH_3), 3.19 (brs,2H, $CH_2(CH_2)_6CH_3$); 5.39 (s, $1H_{olefin}$), 7.36-7.69 (m, $2H_{arom}$), 7.85 (d, J = 2Hz, $1H_{arom}$), 11.85 (brs, 1H, NH). [Found : C, 57.61; H, 6.94; N, 3.87 calculated for $C_{18}H_{25}NOSCl_2$ (374.3), C, 57.75, H, 6.73; N, 3.74%].

3-Dodecylamino-3-methylthio-1-(3,4-dichlorophenyl)-2-propen-1-one [10l] was obtained as a colourless solid, m.p. 36-37°C; Yield, 83%; I.R. (KBr): ν_{max} = 2918, 1565 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 0.89 (brs, 3H, $-CH_2(CH_2)_{10}CH_3$), 1.30 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$), 2.46 (s, 3H, SCH_3), 3.36 (brs, 2H, $-CH_2(CH_2)_{10}CH_3$), 5.57 (s, $1H_{olefin}$) 7.49-7.89 (m, $2H_{arom}$), 8.03 (d, J = 2Hz, $1H_{arom}$), 11.85 (brs, 1H, NH). [Found: C, 61.17; H, 7.97; N, 3.09 calculated for $C_{22}H_{33}NOSCl_2$ (430.4) : c, 61.38; H, 7.72; N, 3.25%].

3-Cetylamino-3-methylthio-1-(3,4-dichlorophenyl)-2-propen-1-one [10m] was obtained as a colourless solid, m.p. 53-54°C; yield, 83%; I.R. 2919, 1565 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 1.85 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.29 (brs, 28H, -

$CH_2(CH_2)_{14}CH_3$) 2.46 (s, 3H, SCH_3), 3.39 (brs, 2H, -$CH_2(CH_2)_{14}CH_3$), 5.62 (s, $1H_{olefin}$), 7.26-7.79 (m, $2H_{arom}$), 8.03 (d, J = 2Hz, $1H_{arom}$), 11.83 (brs, 1H, NH). [Found : C, 64.04; H, 8.31; N, 2.66 calculated for $C_{26}H_{41}NOSCl_2$ (486.5): C, 64.18; H, 8.49; N, 2.87%].

The known 3-acyl-2-methylthio-1-alkyl pyrroles 25a-e were prepared according to the reported procedure[24] and their spectral and analytical data were found to be similar to the reported ones. The unknown 3-acyl-2-methylthio-1-alkyl pyrroles 28a-z and 28aa-bb were prepared by extending the reported procedure[24] and their structures were fully established from their spectral and analytical data which are given below.

1-Cyclohexyl-3-benzoyl-2-methylthio pyrrole [28a] was obtained as a colourless solid; m.p. 71-72°C: yield, 79%; I.R. (KBr): ν_{max} = 1645 cm^{-1}: ^1H n.m.r. ($CDCl_3$): δ = 1.15 - 2.15 (m, 10H, ring CH_2), 2.42 (s, 3H, SCH_3), 4.60 (brs, 1H, CH), 6.52 (d, J = 3Hz, 1H, H-4), 6.73 (d, J = 3Hz, 1H, H-5), 7.36-7.66 (m, $3H_{arom}$), 7.75-8.09 (m, $2H_{arom}$). [Found: C, 72.33; H, 6.91; N, 4.49 calculated for $C_{18}H_{21}NOS$ (299.4): C, 72.20; H, 7.07; N, 4.67%].

1-Octyl-3-benzoyl-2-methylthio pyrrole [28b] was obtained as a red viscous oil; yield 72%;I.R.(Neat):ν_{max} = 1656 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.92 (brs, 3H, -$CH_2(CH_2)_6CH_3$), 1.36 (brs, 12H, -CH_2 (CH_2)$_6CH_3$), 2.46 (s, 3H, SCH_3), 4.13 (t, J = 7Hz, 2H, -$CH_2(CH_2)_6CH_3$), 6.39 (d, J = 3Hz, 1H, H-4), 6.69 (d, J =

3Hz, 1H, H-5), 7.26-7.59 (m, $3H_{arom}$); 7.69-7.95 (m, $2H_{arom}$). [Found: C, 72.76; H, 8.42; N, 4.07 calculated for $C_{20}H_{27}NOS$ (329.4): C, 72.90; H, 8.26; N, 4.25%].

1-Dodecyl-3-benzoyl-2-methylthio pyrrole [28c] was obtained as a colourless solid; m.p. 39-40°C; yield, 81%; I.R. (KBr): ν_{max} = 1647 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.95 (brs, 3H, $-CH_2(CH_2)_{10}CH_3$), 1.36 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$) 2.56 (s, 3H, SCH_3), 6.56 (d, J = 3Hz, 1H, H-4), 6.89 (d, J = 3Hz,1H, H-5), 7.42-7.75 (m, $3H_{arom}$), 7.85-8.16 (m, $2H_{arom}$). [Found: C, 74.88; H, 9.30; N, 3.74 calculated for $C_{24}H_{35}NOS$ (385.5): C, 74.75; H, 9.14; N, 3.63%].

1-Cetyl-3-benzoyl-2-methylthio pyrrole [28d] was obtained as a colourless solid; m.p. 41-42°C; yield, 86%; I.R. (KBr): ν_{max} = 1647 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.85 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.26 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 2.46 (s, 3H, SCH_3), 4.09 (t, J = 2Hz, 2H, $-CH_2(CH_2)_{14}CH_3$), 6.36 (d, J = 3Hz, 1H, H-4), 6.66 (d, J = 3Hz, 1H, H-5), 7.36-7.56 (m, $3H_{arom}$), 7.69-7.85 (m, $2H_{arom}$). [Found : C, 76.29; H, 9.62; N, 3.02 calculated for $C_{28}H_{43}NOS$ (441.6): C, 76.13; H, 9.81; N, 3.17%].

1-Methyl-3-(4-chlorobenzoyl)-2-methylthio pyrrole [28e] was obtained as a colourless solid; m.p. 69-70°C; yield, 88%; I.R. (KBr): ν_{max} = 1645 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.39 (s, 3H, SCH_3), 3.75 (s, 3H, NCH_3), 6.35 (d, J = 3Hz, 1H, H=4), 6.67 (d, J = 3Hz, 1H, H-5), 7.35 (d, J = 9Hz, $2H_{arom}$), 7.67 (d, J = 9Hz, $2H_{arom}$). [Found: C, 58.59; H, 4.31; N,

5.41 calculated for $C_{13}H_{12}NOSCl$ (265.7): C, 58.75, H, 4.75, N, 5.27%].

1-Ethyl-3-(4-chlorobenzoyl)-2-methylthio pyrrole [28f] was obtained as a colourless solid; m.p. 61-62°C; yield 79%; I.R. (KBr) ν_{max} = 1669 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.4 (t, 7Hz, 3H, $-CH_2CH_3$), 2.43 (s, 3H, SCH_3), 4.2 (q, J = 7Hz, 2H, $-CH_2CH_3$), 6.46 (d, J = 3Hz, 1H, H-4), 6.82 (d, 3Hz, 1H, H-5), 7.42 (d, J = 9Hz, $2H_{arom}$), 7.86 (d, J = 9Hz, $2H_{arom}$). [Found: C, 60.23; H, 5.19; N, 5.16 calculated for $C_{14}H_{14}NOSCl$ (279.7): C, 60.09; H, 5.04; N, 5.00%].

1-Butyl-3-(4-chlorobenzoyl)-2-methylthio pyrrole [28g] was obtained as a red viscous oil; yield 62%; I.R. (Neat) ν_{max} = 1641 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.96 (t, J = 7Hz, 3H, $CH_2CH_2CH_2CH_3$), 1.35 (distorted sext., J = 7 Hz, 2H,-$CH_2CH_2CH_2CH_3$), 1.77 (distorted quint., J = 7 Hz, 2H,-$CH_2CH_2CH_2CH_3$), 2.43 (s, 3H, SCH_3), 4.16 (t, J = 7Hz, 2H, -$CH_2CH_2CH_2CH_3$), 6.42 (d, J = 3Hz, 1H, H-4), 6.79 (d, J = 3Hz, 1H, H-5), 7.49 (d, J = 9Hz, $2H_{arom}$), 7.85 (d, J = 9Hz, $2H_{arom}$). [Found: C, 62.58; H, 5.98; N, 4.78 calculated for $C_{16}H_{18}NOSCl$ (307.8): C, 62.42; H, 5.89; N, 4.55%].

1-Benzyl-3-(4-chlorobenzoyl)-2-methylthio pyrrole [28h] was obtained as a colourless solid; m.p. 75-76°C; yield, 78%; I.R. (KBr): ν_{max} = 1629, 1718 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.26 (s, 3H, SCH_3), 5.36 (s, 2H, NCH_2), 6.49 (d, J = 3Hz, 1H, H-4), 6.82 (d, J = 3Hz, 1H, H-5), 7.03-7.56 (m, $7H_{arom}$), 7.69-8.03 (m, $2H_{arom}$). [Found: C, 66.87; H, 4.88; N, 4.23

calculated for $C_{19}H_{16}NOSCl$ (341.8): C, 66.75; H, 4.71; N, 4.09%].

1-Cyclohexyl-3-(4-chlorobenzoyl)-2-methylthio pyrrole [28i] was obtained as a colourless solid: m.p. 119-120°C; yield, 75%; I.R. (KBr): ν_{max} = 1647 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.15-2.15 (m, 10H, ring CH_2), 2.42 (s, 3H, SCH_3), 4.60 (brs, 1H, CH), 6.46 (d, J = 3Hz, 1H, H-4), 6.85 (d, J = 3Hz, 1H, H-5), 7.42 (d, J = 9Hz, $2H_{arom}$), 7.82 (d, J = 9Hz, $2H_{arom}$). [Found : C, 64.91; H, 6.24; N, 4.37 calculated for $C_{18}H_{20}NOSCl$ (333.8): C, 64.75; H, 6.03; N, 4.19%].

1-Methyl-3-(4-methoxybenzoyl)-2-methylthio pyrrole [28j] was obtained as a colourless solid; m.p. 64-65°C; yield, 73%; I.R. (KBr): ν_{max} = 1625 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ = 2.39 (s, 3H, SCH_3), 3.79 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 6.42 (d, J = 3Hz, 1H, H-4), 6.75 (d, J = 3Hz, 1H,H-5), 6.96 (d, J = 9Hz, $2H_{arom}$), 7.92 (d, J = 9Hz, $2H_{arom}$). [Found: C, 64.52; H, 5.49; N, 5.24 calculated for $C_{14}H_{15}NO_2S$ (261.3): C, 64.34; H, 5.78; N, 5.36%].

1-Ethyl-3-(4-methoxybenzoyl)-2-methylthio pyrrole [28k] was obtained as a colourless solid; m.p. 69-70°C; yield, 71% I.R. (KBr): ν_{max} = 1629 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.46 (t, J = 7Hz, 3H, $-CH_2CH_3$), 2.49 (s, 3H, SCH_3), 6.95 (s, 3H, OCH_3), 4.29 (q, J = 7Hz, 2H, $-CH_2CH_3$), 6.59 (d, J = 3Hz, 1H, H-4), 6.95 (d, J = 3Hz, 1H, H-5), 7.09 (d, J = 9Hz, $2H_{arom}$), 8.06 (d, J = 9Hz, $2H_{arom}$). [Found: C, 65.61; H, 6.38; N, 5.29 calculated for $C_{15}H_{17}NO_2S$ (275.3): C, 65.42; H, 6.22; N, 5.08%].

1-Benzyl-3-(4-methoxybenzoyl)-2-methylthio pyrrole [28l] was obtained as a colourless solid; m.p. 67-68°C; yield, 65%; I.R. (KBr): ν_{max} = 1625 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 2.97 (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 5.39 (s, 2H, NCH_2), 6.52 (d, J = 3Hz, 1H, H-4), 6.82 (d, J = 3Hz, 1H, H-5); 6.89-7.52 (m, $7H_{arom}$), 6.95 (d, J = 9Hz, $2H_{arom}$). [Found: C, 71.31; H, 6.26; N, 4.32 calculated for $C_{20}H_{19}NO_2S$ (337.4): C, 71.18; H, 6.08; N, 4.15%].

1-Cyclohexyl-3-(4-methoxybenzoyl)-2-methylthio pyrrole [28m] was obtained as a colourless solid; m.p. 90-91°C; yield, 67%; I.R. (KBr): ν_{max} = 1610 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.15-2.15 (m, 10H, ring CH_2), 2.42 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3), 4.66 (brs, 1H, CH), 6.49 (d, J = 3Hz, 1H, H-4), 6.82-7.13 (m, 3H, $2H_{arom}$, & H-5), 7.95 (d, J = 9Hz, $2H_{arom}$). [Found: C, 69.38; H, 7.16; N, 8.18 calculated for $C_{19}H_{23}NOS$ (329.4): C, 69.26; H, 7.03; N, 8.50%].

1-Heptyl-3-(4-methoxybenzoyl)-2-methylthio pyrrole [28n] was obtained as a viscous red oil; yield, 67%; I.R. (Neat) : ν_{max} = 1625 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 0.95 (brs, 3H,-$CH_2(CH_2)_5CH_3$), 1.09 (brs, 10H, -$CH_2(CH_2)_5CH_3$)2.23 (s, 3H, SCH_3), 3.95 (s, 3H, OCH_3) 4.06 (t, J = 7Hz, 2H, -$CH_2(CH_2)_5CH_3$), 6.33 (d, J = 3Hz, 1H, H-4), 6.72 (d, J = 3Hz, 1H, H-5), 6.89 (d, J = 9Hz, $2H_{arom}$), 7.95 (d, J = 9Hz, $2H_{arom}$). [Found : C, 69.67; H, 7.64; N, 3.87 calculated for $C_{20}H_{27}NO_2S$ (345.4) : C, 69.52; H, 7.87; N, 4.05%].

1-Butyl-3-(4-methylbenzoyl)-2-methylthio pyrrole [28o] was obtained as a colourless solid; m.p. 64-65°C yield, 71%; I.R. (KBr): ν_{max} = 1645 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.96 (t, J = 7Hz, 3H,-$CH_2CH_2CH_2CH_3$), 1.35 (distorted sext., J = 7Hz, 2H, -$CH_2CH_2CH_2CH_3$), 1.77 (distorted quint., J = 7Hz, 2H, -$CH_2CH_2CH_2CH_3$), 2.43 (s, 3H, SCH_3), 4.16 (t, J = 7Hz, 2H, -$CH_2CH_2CH_2CH_3$), 6.52 (d, J = 3Hz, 1H, H-4), 6.82 (d, J = 3Hz, 1H, H-5), 7.36 (d, J = 9Hz, $2H_{arom}$), 7.89 (d, J = 9Hz, $2H_{arom}$). [Found: C, 71.28; H, 7.52; N, 4.98 calculated for $C_{17}H_{21}NOS$ (287.4): C, 71.03; H, 7.36; N, 4.87%].

1-Benzyl-3-(4-methylbenzoyl)-2-methylthiopyrrole [28p] was obtained as a colourless solid; m.p. 69-70°C; yield 75%; I.R. (KBr): ν_{max} = 1625 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 2.29 (s, 3H, SCH_3), 2.39(s, 3H, CH_3), 5.34 (s, 2H, NCH_2), 6.59 (d, J = 3Hz, 1H, H-4), 6.89 (d, J = 3Hz, 1H, H-5), 7.06-7.59 (m, $7H_{arom}$), 7.92 (d, J = 9Hz, $2H_{arom}$). [Found: C, 74.88; H, 5.82; N, 4.48 calculated for $C_{20}H_{19}NOS$ (321.4): C, 74.73; H, 5.95; N, 4.35%].

1-Cyclohexyl-3-(4-methylbenzoyl)-2-methylthio pyrrole [28q] was obtained as a colourless solid; m.p. 89-90°C; yield, 78%; I.R. (KBr): ν_{max} = 1625 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.15-2.15 (m, 10H, ring CH_2), 2.42 (s, 6H, CH_3 & SCH_3), 4.60 (brs, 1H, CH), 6.49 (d, J = 3Hz, 1H, H-4), 6.89 (d, J = 3Hz, 1H, $2H_{arom}$), 7.29 (d, J = 9Hz, $2H_{arom}$). [Found: C, 72.98; H, 7.61, N, 4.62 calculated for $C_{19}H_{23}NOS$ (313.4): C, 72.80; H, 7.39, N, 4.46%].

1-Butyl-3-(2,4-dichlorobenzoyl)-2-methylthiopyrrole [28r] was obtained as a viscous red oil; yield, 85%; I.R. (Neat): ν_{max} = 1610, 1669 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.96 (t, J = 7Hz, 3H, $-CH_2CH_2CH_2CH_3$), 1.33 (distorted sext., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 1.72 (distorted quint., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 2.36 (s, 3H, SCH_3), 4.13 (t, J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 6.26 (d, J = 3Hz, 1H, H-4) 6.75 (d, J = 3Hz, 1H, H-5), 7.36 (s, $2H_{arom}$), 7.49 (s, $1H_{arom}$). [Found: C, 56.27; H, 5.23; N, 4.31 calculated for $C_{16}H_{17}NOSCl_2$ (342.2): C, 56.14; H, 5.00; N, 4.09%].

1-Benzyl-3-(2,4-dichlorobenzoyl)-2-methylthio pyrrole [28s] was obtainted as a colourless solid; m.p. 73-74°C; yield, 85%; I.R. (KBr): ν_{max} = 1629 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.26 (s, 3H, SCH_3), 5.46 (s, 2H, NCH_2), 6.56 (d, J = 3Hz, 1H, H-4), 6.92 (d, J = 3Hz, 1H, H-5), 7.19-7.66 (m, $8H_{arom}$). [Found : C, 60.82; H, 4.19; N, 3.56 calculated for $C_{19}H_{15}NOSCl_2$ (376.2): C, 60.64, H, 4.01; N, 3.72%].

1-Cyclohexyl-3-(2,4-dichlorobenzoyl)-2-methylthio pyrrole [28t] was obtained as a colourless solid; m.p. 95-96°C; yield, 85%; I.R. (KBr): ν_{max} = 1669 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.15-2.15 (m, 10H, ring CH_2), 2.36 (s, 3H, SCH_3), 3.62 (brs, 1H, CH), 6.39 (d, J = 3Hz, 1H, H-4), 6.85 (d, J = 3Hz, 1H, H-5), 7.36 (s, $2H_{arom}$) 7.49 (s, $1H_{arom}$). [Found: C, 58.79; H, 5.35; N, 3.64 calculated for $C_{18}H_{19}NOSCl_2$ (368.3): C, 58.68; H, 5.19; N, 3.80%].

1-Butyl-3-(3,4-dichlorobenzoyl)-2-methylthio pyrrole [28u] was obtained as a viscous red oil; yield, 85%; I.R. (Neat) : ν_{max} = 1669 cm^{-1} ; ^1H n.m.r. (CCl_4) : δ = 0.96 (t, J = 7Hz, 3H, $-CH_2CH_2CH_2CH_3$), 1.35 (distorted sext., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 1.75 (distorted quint., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 2.43 (s, 3H, SCH_3), 4.16 (t, J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 6.46 (d, J = 3Hz, 1H, H-4), 6.82 (d, J = 3Hz, 1H, H-5), 7.52-7.82 (m, $2H_{arom}$), 8.00 (d, J =2Hz $1H_{arom}$). [Found : C, 56.32; H, 5.16; N, 4.24 calculated for $C_{16}H_{17}NOSCl_2$ (342.2): C, 56.14; H, 5.00; N, 4.09%].

1-Benzyl-3-(3,4-dichlorobenzoyl)-2-methylthio pyrrole [28v] was obtained as a colourless solid, m.p. 57-58°C; yield, 83%; I.R. (KBr): ν_{max} = 1645 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.97 (s, 3H, SCH_3), 5.39 (s, 2H, NCH_2), 6.52 (d, J = 3Hz, 1H, H-4), 6.89 (d, J = 3Hz, 1H, H-5), 7.16-7.89 (m, $7H_{arom}$), 8.06 (d, J = 2Hz, $1H_{arom}$). [Found: C, 60.79; H, 4.19; N, 3.58 calculated for $C_{19}H_{15}NOSCl_2$ (376.2): C, 60.64; H, 4.01; N, 3.72%].

1-Cyclohexyl-3-(3,4-dichlorobenzoyl)-2-methylthio pyrrole [28w] was obtainted as a colourless solid; m.p. 112-113°C; yield, 85%; I.R. (KBr): ν_{max} = 1647 cm^{-1}; ^1H n.m.r. ($CDCl_3$); δ = 1.15-2.15 (m, 10H, ring CH_2), 2.39 (s, 3H, SCH_3), 4.66 (brs, 1H, CH), 6.49 (d, J = 3Hz, 1H, H-4), 6.89 (d, J = 3Hz, 1H, H-5), 7.49-7.82 (m, $2H_{arom}$), 7.95 (d, J = 2Hz, $1H_{arom}$). [Found: C, 59.28; H, 5.32; N, 3.69 calculated for $C_{18}H_{19}NOSCl_2$ (365.3): C, 59.17; H, 5.24; N, 3.83%].

1-Octyl-3-(3,4-dichlorobenzoyl)-2-methylthio pyrrole [28x] was obtained as a red viscous oil yield, 82%; I.R. (Neat): ν_{max} = 1659 cm^{-1}; ^1H n.m.r. (CCl_4) δ = 0.89 (brs, 3H, $-CH_2(CH_2)_6CH_3$), 1.33 (brs, 12H, $-CH_2(CH_2)_6CH_3$ 2.46 (s, 3H, SCH_3), 4.19 (t, J = 7Hz, 2H, $-CH_2(CH_2)_6CH_3$), 6.42 (d, J = 3Hz, 1H, H-4), 6.82 (d, J = 3Hz, 1H, H-5), 7.16-7.82 (m, $2H_{arom}$), 8.03 (d, J = 2Hz, $1H_{arom}$). [Found: C, 60.12; H, 6.18; N, 3.72 calculated for $C_{20}H_{25}NOSCl_2$ (398.3): C, 60.29; H, 6.32; N, 3.51%].

1-Dodecyl-3-(3,4-dichlorobenzoyl)-2-methylthiopyrrole [28y] was obtained as red viscous oil; yield, 85%; I.R. (Neat): ν_{max} = 1659 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.89 (brs, 3H, $-CH_2(CH_2)_{10}CH_3$), 1.26 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$), 2.46 (s, 3H, SCH_3) 4.16 (t, J = 7Hz, 2H, $-CH_2(CH_2)_{10}CH_3$), 6.36 (d, J = 3Hz, 1H, H-4), 6.82 (d, J = 3Hz, 1H, H-5), 7.49-7.85 (m, $2H_{arom}$), 8.03 (d, J = 2Hz, $1H_{arom}$). [Found: C, 63.28; H, 7.43; N, 3.26 calculated for $C_{24}H_{33}NOSCl_2$ (454.4): C, 63.42; H, 7.32; N, 3.08%].

1-Cetyl-3-(3,4-dichlorobenzoyl)-2-methylthio pyrrole [28z] was obtained as a colourless solid; m.p. 39-40°C; yield, 86%; I.R. (KBr)ν_{max} = 1647 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.92 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.29 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 2.46 (s, 3H, SCH_3), 4.16 (t, J = 7Hz, 2H, $-CH_2(CH_2)_{14}CH_3$), 6.36 (d, J = 3Hz, 1H, H-4), 6.72 (d, J = 3Hz, 1H, H-5), 7.46-7.79 (m, $2H_{arom}$), 7.92 (d, J = 2Hz, $1H_{arom}$). [Found: C, 65.64; H, 7.87; N, 2.56 calculated for $C_{28}H_{41}NOSCl_2$ (510.5): C, 65.86; H, 8.09; N, 2.74%].

1-Butyl-3-(4-methoxybenzoyl)-2-methylthio pyrrole [28aa] was obtained as a red viscous oil; yield, 62%: I.R. (Neat) ν_{max} = 1625 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 0.96 (t, J = 7Hz, 3H, $-CH_2CH_2CH_2CH_3$), 1.29 (distorted sext., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$) 1.69 (distorted quint., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 2.42 (s, 3H, SCH_3) 3.82 (s, 3H, OCH_3), 4.13 (t, J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 6.39 (d, J = 3Hz, 1H, H-4), 6.72 (d, J = 3Hz, 1H, H-5), 6.95 (d, J = 9Hz, $2H_{arom}$), 7.92 (d, J = 9Hz, $2H_{arom}$). [Found: C, 67.4; H, 6.78; N, 4.84 calculated for $C_{17}H_{21}NO_2S$ (303.4): C, 67.29: H, 6.97; N, 4.61%].

1-Cyclohexyl-3-acetyl-2-methylthio pyrrole [28bb] was obtained as a viscous red oil; yield, 68%: I.R. (Neat): ν_{max} = 1669 cm^{-1}; ^1H n.m.r. (CCl_4): δ = 1.15-2.15 (m, 10H, ring CH_2), 2.42 (s, 3H, $COCH_3$), 2.59 (s, 3H, SCH_3), 4.63 (brs, 1H, CH), 6.82 (d, J = 3Hz, 1H, H-4), 6.95 (d, J = 3Hz, 1H, H-5). [Found: C, 65.64; H, 7.90; N, 6.01 calculated for $C_{13}H_{19}NOS$ (237.3): C, 65.79; H, 8.06; N, 5.90%].

Synthesis of 1-substituted-3-acyl-2-methylthio-5-nitro pyrroles 26a-e and 29a-z; General Procedure:

A solution of pyrrole 25a (10 mmol) in 7 ml acetic anhydride is treated with a cold solution of fuming nitric acid (20 mmol) in acetic anhydride (3 ml). After 5-30 minutes at -20°C (monitored by TLC) the reaction mixture is allowed to warm to room temperature poured into ice cold water (50 ml), extracted with dichloromethane (3x50 ml), dried over sodium

sulphate and evaporated to give the crude product 26a which is further purified by column chromatography over silica gel using hexane/ethyl acetate (19:1) as eluent. The structurers of 26a-e and 29a-z were fully established from their spectral and analytical data which are given below.

1-Ethyl-3-acetyl-2-methylthio-5-nitro pyrrole [26a] was obtained as a colourless solid; m.p. 120-121°C; yield, 35%; I.R. (KBr): ν_{max} = 1700, 1560, 1325 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.56(t, J = 7Hz, 3H, $-CH_2CH_3$), 2.56 (s, 3H, $COCH_3$), 3.23 (s, 3H, SCH_3), 5.23 (q, J = 7Hz, 2H, $-CH_2CH_3$), 7.46 (s, 1H, H-4).[Found: C, 47.52; H,5.13; N, 12.46 calculated for $C_9H_{12}N_2O_3S$ (228.2): C, 47.35; H, 5.29; N, 12.27%].

1-Methyl-3-benzoyl-2-methylthio-5-nitro pyrrole [26b] was obtained as a colourless soid; m.p. 135-136°C; yield, 42%; I.R. (KBr): ν_{max} = 1659, 1505, 1307 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 3.33 (s, 3H, SCH_3), 4.59 (s, 3H, $-CH_3$), 7.42-7.82 (m, 4H, H-4 and $3H_{arom}$), 7.89-8.06 (m, $2H_{arom}$). [Found: C, 56.68; H, 4.52; N, 10.25 calculated for $C_{13}H_{12}N_2O_3S$ (276.3): C, 56.50; H, 4.37; N, 10.13%].

1-Ethyl-3-benzoyl-2-methylthio-5-nitro pyrrole [26c] was obtained as a colourless solid; m.p. 131-132°C; yield, 38%; I.R. (KBr): ν_{max} = 1659, 1500, 1350 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.59 (t, J = 7Hz, 3H, $-CH_2CH_3$), 3.33 (s, 3H, SCH_3), 5.13 (q, J = 7Hz, 2H, $-CH_2CH_3$), 7.42-7.79 (m, 4H, H-4 and $3H_{arom}$), 7.82-8.03 (m, $2H_{arom}$). [Found: C, 57.76; H, 4.98; N, 9.48 calculated for C, 57.91; H, 4.86; N, 9.64%].

1-Butyl-3-benzoyl-2-methylthio-5-nitro pyrrole [26d] was obtained as a colourless solid; m.p. 97-98°C; yield, 43%; I.R. (KBr): ν_{max} = 1660, 1529, 1305 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.00 (t, J = 7Hz, 3H, $-CH_2CH_2CH_2CH_3$), 1.49 (distorted sext., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 1.92 (distorted quint., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 3.33 (s, 3H, SCH_3), 5.16 (t, J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 7.42-7.79 (m, 4H, H-4 and $3H_{arom}$), 7.82-8.13 (m, $2H_{arom}$). [Found: C, 60.46; H, 5.54; N, 8.96 calculated for $C_{16}H_{18}N_2O_3S$ (318.3): C, 60.35; H, 5.69; N, 8.79%].

1-Benzyl-3-benzoyl-2-methylthio-5-nitro pyrrole [26e] was obtained as a colourless solid; m.p. 134-135°C; yield, 42%; I.R. (KBr): ν_{max} = 1647, 1545, 1320 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ = 2.96 (s, 3H, SCH_3), 6.46 (dd, J = 9, 15Hz, 2H, $CH_2C_6H_5$) 7.06-7.23 (m, $2H_{arom}$), 7.29-7.46 (m, $3H_{arom}$), 7.56-7.72 (m, 4H, H-4 and $3H_{arom}$), 7.25-8.03 (m, $2H_{arom}$), m/z: 304 (1%), 262 (33%): [Found: C,64.56; H, 4.41; N, 7.78 calculated for $C_{19}H_{16}N_2O_3S$ (352.4): C, 64.75; H, 4.57; N, 7.94%].

1-Cyclohexyl-3-benzoyl-2-methylthio-5-nitro pyrrole [29a] was obtained as a colourless solid: m.p. 129-130°C; yield, 41%; I.R. (KBr): ν_{max} = 1657, 1540, 1304 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.19-2.72 (m, 10H, ring CH_2), 3.33 (s, 3H, SCH_3), 5.69 (brs, 1H, CH), 7.39-7.75 (m, 4H, H-4 and $3H_{arom}$) 7.82-8.00 (m, $2H_{arom}$), m/z : 344 (M^+, 9%), 262 (28%). [Found: C, 62.57; H, 5.59; N, 7.92 calculated for $C_{18}H_{20}N_2O_3S$ (344.4): C, 62.76; H, 5.85; N, 8.13%].

1-Octyl-3-benzoyl-2-methylthio-5-nitro pyrrole [29b] was obtained as a colourless solid; m.p. 64-65°C; yield, 45%; I.R. (KBr): ν_{max} = 1669, 1550, 1323 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ =0.56 (brs, 3H, $-CH_2(CH_2)_6CH_3$), 1.29 (brs, 12H, $-CH_2(CH_2)_6CH_3$), 3.29 (s, 3H, SCH_3), 5.06 (t, J = 7Hz, 2H, $-CH_2(CH_2)_6CH_3$), 7.42-7.72 (m, 4H, H-4 and $3H_{arom}$), 7.79-8.06 (m, $2H_{arom}$). [Found: C, 64.29; H, 7.21; N, 7.67 calculated for $C_{20}H_{26}N_2O_3S$ (374.4): C, 64.13; H, 6.99; N, 7.48%].

1-Dodecyl-3-benzoyl-2-methylthio-5-nitro pyrrole [29c] was obtained as a colourless solid; m.p. 61-62°C; yield, 54%; I.R. (KBr): ν_{max} = 1649, 1528, 1307 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.56 (brs, 3H, $-CH_2(CH_2)_{10}CH_3$), 1.29 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$), 3.33 (s, 3H, SCH_3), 5.09 (t, 2H, J = 7Hz, $-CH_2(CH_2)_{10}CH_3$), 7.56-7.79 (m, 4H, H-4 and $3H_{arom}$), 7.89-8.09 (m, $2H_{arom}$). [Found: C, 67.14; H, 7.82; N, 6.61 calculated for $C_{24}H_{34}N_2O_3S$ (430.5): C, 66.94; H, 7.95; N, 6.50%].

1-Cetyl-3-benzoyl-2-methylthio-5-nitro pyrrole [29d] was obtained as a colourless solid; m.p. 56-57°C, yield 55%; I.R. (KBr): ν_{max} = 1657, 1540, 1312 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.56 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.29 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 3.29 (s, 3H, SCH_3), 5.06 (brs, 2H, $-CH_2(CH_2)_{14}CH_3$), 7.39-7.66 (m, 4H, H-4 and $3H_{arom}$), 7.79-8.03 (m, $2H_{arom}$). [Found: C, 69.21; H, 8.49; N,5.58 calculated for $C_{28}H_{42}N_2O_3S$ (486.7): C, 69.09; H, 8.69; N, 5.75%].

1-Methyl-3-(4-chlorobenzoyl)-2-methylthio-5-nitro pyrrole [29e] was obtained as a colourless solid; m.p. 69-70°C;

yield, 44%; I.R. (KBr): ν_{max} = 1660, 1550, 1500, 1310 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 3.26 (s, 3H, SCH_3), 4.52 (s, 3H, $-CH_3$), 7.39-7.69 (m, 3H, H-4 and $3H_{arom}$), 7.89 (d, J = 9Hz, $2H_{arom}$). [Found: C, 50.11; H, 3.38; N, 9.17 calculated for $C_{13}H_{11}N_2O_3SCl$ (310.7): C, 50.24; H, 3.56; N, 9.01%].

1-Ethyl-3-(4-chlorobenzoyl)-2-methylthio-5-nitro pyrrole [29f] was obtained as a colourless solid; m.p. 155-156°C; yield; 41%; I.R. (KBr): ν_{max} = 1679, 1555, 1325 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.56 (t, J = 7Hz, 3H, $-CH_2CH_3$), 3.29 (s, 3H, SCH_3), 5.16 (q, J = 7Hz, 2H, $-CH_2CH_3$), 7.59 (d, J = 9Hz, 3H, H-4 and $2H_{arom}$), 7.89 (d, J = 9Hz, $2H_{arom}$). [Found: C, 51.96; H, 4.15; N, 8.49 calculated for $C_{14}H_{13}O_3N_2SCl$ (324.7): C, 51.77; H, 4.03; N, 8.62%].

1-Butyl-3-(4-chlorobenzoyl)-2-methylthio-5-nitro pyrrole [29g] was obtained as a colourless solid; m.p. 79-80°C; yield, 44%; I.R. (KBr): ν_{max} = 1637, 1529, 1304 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 1.00 (t, J = 7Hz, 3H, $-CH_2CH_2CH_2CH_3$), 1.49 (distorted sext., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 1.92 (distorted quint., J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 3.36 (s, 3H, SCH_3), 5.16 (t, J = 7Hz, 2H, $-CH_2CH_2CH_2CH_3$), 6.66 (d, J = 9Hz, 3H, H-4 and $2H_{arom}$), 7.95 (d, J = 7Hz, $2H_{arom}$). [Found: C, 54.32; H, 4.67; N, 8.14 calculated for $C_{16}H_{17}N_2O_3SCl$ (352.8): C, 54.46; H, 4.85; N, 7.93%].

1-Benzyl-3-(4-chlorobenzoyl)-2-methylthio-5-nitro pyrrole [29h] was obtained as a colourless solid; m.p. 75-76°C; yield; 40%; I.R. (KBr): ν_{max} = 1660, 1545, 1318 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.96 (s, 3H, SCH_3), 6.46 (dd, J = 9,

15Hz, 2H,-CH_2C$_6$H$_5$), 7.06-7.23 (m, 2H$_{arom}$), 7.29-7.46 (m, 3H$_{arom}$), 7.49-7.66 (m, 3H, H-4 and 2H$_{arom}$), 7.89 (d, J = 9Hz, 2H$_{arom}$). m/z 338, 339 (M^+,10%), 296(27%). [Found: C, 58.77; H, 3.69; N, 7.08 calculated for $C_{19}H_{15}N_2O_3SCl$ (386.8): C, 58.98; H, 3.90; N, 7.24%].

1-Cyclohexyl-3-(4-chlorobenzoyl)-2-methylthio-5-nitropyrrole [29i] was obtained as a colourless solid; m.p. 154-155°C; yield, 43%; I.R. (KBr) : ν_{max} = 1657, 1545, 1328 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.16-2.72 (m, 10H, ring CH_2), 3.29 (s, 3H, SCH_3), 5.69 (brs, 1H, C*H*), 7.49 (d, J = 9Hz, 2H$_{arom}$), 7.62 (s, 1H, H-4), 7.92 (d, J = 9Hz, 2H$_{arom}$). [Found : C, 57.21; H, 4.89; N, 7.57 calculated for $C_{18}H_{19}N_2O_3SCl$ (378.8): C, 57.05; H, 5.05; N, 7.39%].

1-Methyl-3-(4-methoxybenzoyl)-2-methylthio-5-nitro pyrrole [29j] was obtained as a colourless solid; m.p. 64-65°C; yield, 35%; I.R. (KBr): ν_{max} = 1625, 1305 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.29 (s, 3H, SCH_3) 3.95 (s, 3H, OCH_3), 4.56 (s, 3H, NCH_3), 7.09 (d, J = 9Hz, 2H$_{arom}$), 7.49 (s, 1H, H-4), 7.95 (d, J = 9Hz, 2H$_{arom}$). [Found: C, 54.97; H, 4.44; N, 9.27 calculated for $C_{14}H_{14}O_4N_2S$ (306.3): C, 54.88; H, 4.60; N, 9.14%].

1-Ethyl-3-(4-methoxybenzoyl)-2-methylthio-5-nitro pyrrole [29k] was obtained as a colourless solid; m.p. 119-120°C; yield, 35%; I.R. (KBr): ν_{max} = 1625, 1500, 1320 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.59 (t, J = 7Hz, 3H, -CH_2CH_3); 3.36 (s, 3H, SCH_3), 4.33 (s, 3H, OCH_3), 5.19 (brq. J = 3Hz, 2H,

CH_2CH_3), 7.13 (d, J = 9Hz, $2H_{arom}$), 7.59 (s, 1H, H-4), 8.03 (d, J = 9Hz, $2H_{arom}$). [Found: C, 56.42; H, 4.84; N, 8.57 calculated for $C_{15}H_{16}N_2O_4S$ (320.3): C, 56.23; H, 5.03; N, 8.74%].

1-Benzyl-3-(4-methoxybenzoyl)-2-methylthio-5-nitro pyrrole [29l] was obtained as a colourless solid; m.p. 119-120°C; yield, 38%; I.R. (KBr); ν_{max} = 1625, 1518, 1300 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 3.00 (s, 3H, SCH_3), 4.00 (s, 3H, OCH_3), 6.52 (dd, J = 9, 15Hz, 2H, $-CH_2C_6H_5$), 7.06-7.33 (m, $4H_{arom}$), 7.39-7.56 (m, $3H_{arom}$), 7.69 (s, 1H, H-4), 8.06 (d, J = 9Hz, $2H_{arom}$). [Found: C, 62.98; H, 4.57; N, 7.46 calculated for $C_{20}H_{18}N_2O_4S$ (382.4): C, 62.80; H, 4.74; N, 7.32%].

1-Cyclohexyl-3-(4-Methoxybenzoyl)-2-methylthio-5-nitro pyrrole [29m] was obtained as a colourless solid; m.p. 137-138°C; yield, 37%: I.R. (KBr): ν_{max} = 1625, 1520, 1300 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.06-2.66 (m, 10H, ring CH_2) 3.29 (s,3H, SCH_3), 3.92 (s, 3H, OCH_3); 5.66 (brs, 1H, CH), 7.03 (d, J = 9Hz, $2H_{arom}$), 7.46 (s, 1H, H-4), 7.92 (d, J = 9Hz, $2H_{arom}$). [Found: C, 60.74; H, 6.14; N, 7.66 calculated for $C_{10}H_{22}N_2O_4S$ (374.4): C, 60.93; H, 5.92; N, 7.48%].

1-Heptyl-3-(4-methoxybenzoyl)-2-methylthio-5-nitro pyrrole [29n] was obtained as a colourless solid; m.p. 115-116°C; yield, 37%; I.,R. (KBr): ν_{max} = 1618, 1530, 1305 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.56 (t, J = 7Hz, 3H, $-CH_2(CH_2)_5CH_3$), 1.03 (brs, 10H, $-CH_2(CH_2)_5CH_3$), 3.00 (s, 3H, SCH_3), 3.66 (s, 3H, OCH_3), 4.75 (t, J = 7Hz, 2H, $-CH_2(CH_2)_5CH_3$), 6.79 (d, J = 9Hz, $2H_{arom}$), 7.26 (s, 1H, H-4), 7.69 (d, J = 9Hz,

$2H_{arom}$). [Found: C, 61.77; H, 6.49; N, 6.89 calculated for $C_{20}H_{26}N_2O_4S$ (390.4): C, 61.51; H, 6.71; N, 7.17%].

1-Butyl-3-(4-methylbenzoyl)-2-methylthio-5-nitro pyrrole [29o] was obtained as a colourless solid; m.p. 125-126°C; yield, 43%; I.R. (KBr): ν_{max} = 1625, 1520, 1300 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.00 (t, J = 7Hz, 3H, $-CH_2(CH_2)_2CH_3$), 1.19-2.19 (m, 4H, $-CH_2(CH_2)_2CH_3$), 2.42 (s, 3H, CH_3), 3.26 (s, 3H, SCH_3), 4.92 (t, J = 7Hz, 2H, $-CH_2(CH_2)_2CH_3$), 7.06-7.39 (m, 3H, H-4 and $2H_{arom}$), 7.62 (d, J = 9Hz, $2H_{arom}$). [Found: C, 61.27; H, 5.88; N, 8.55 calculated for $C_{17}H_{20}N_2O_3S$ (332.4): C, 61.42; H, 6.06; N, 8.42%].

1-Benzyl-3-(4-methylbenzoyl)-2-methylthio-5-nitro pyrrole [29p] was obtained as a colourless solid; m.p. 162-163°C; yield; 41%; I.R. (KBr): ν_{max} = 1630, 1522, 1300 cm^{-1}; ^1H n.m.r. ($CDCl_3$); δ = 2.46 (s, 3H, $-CH_3$), 2.96 (s, 3H, SCH_3), 6.46 (dd, J = 9, 15Hz, 2H, $-CH_2C_6H_5$), 7.13-7.29 (m, $2H_{arom}$), 7.36-7.59 (m, $5H_{arom}$), 7.66 (s, 1H, H-4), 7.92 (d, J = 9Hz, $2H_{arom}$). [Found: C, 65.74; H, 4.78; N, 7.49 calculated for $C_{20}H_{18}O_3N_2S$ (366.4): C, 65.55; H, 4.95; N, 7.64%].

1-Cyclohexyl-3-(4-methylbenzoyl)-2-methylthio-5-nitro pyrrole [29q] was obtained as a colourless solid; m.p. 154-155°C; yield, 43%; I.r. (KBr): ν_{max} = 1634, 1518, 1308 cm^{-1}; ^1H n.m.r. ($CDCl_3$); δ = 1.03-2.19 (m, 10H, ring CH_2); 2.39 (s, 3H, CH_3), 3.23 (s, 3H, SCH_3), 5.59 (brs, 1H, CH), 7.13-7.36 (m, 3H, H-4 and $2H_{arom}$), 7.69 (d, J = 9Hz, $2H_{arom}$). [Found: C, 63.82; H, 6.39; N, 7.98 calculated for

$C_{19}H_{22}O_3N_2S$ (358.4): C, 63.65; H, 6.18; N, 7.18%].

1-Butyl-3-(2,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29r] was obtained as a colourless solid; m.p. 87-88°C; yield, 52%; I.R. (KBr): ν_{max} = 1677, 1527, 1307 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 1.00 (t, J = 7Hz, 3H, $-CH_2(CH_2)_2CH_3$), 1.19-2.19 (m, 4H, $-CH_2(CH_2)_2CH_3$), 5.06 (t, J = 7Hz, 2H, $-CH_2(CH_2)_2CH_3$); 7.23 (s, 1H, H-4), 7.46 (brs, $2H_{arom}$), 7.92 (brs, $1H_{arom}$). [Found: C, 49.77; H, 4.02; N, 7.08 calculated for $C_{16}H_{16}N_2O_3SCl_2$ (387.2): C, 49.61; H, 4.16; N, 7.23%].

1-Benzyl-3-(2,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29s] was obtained as a colourless solid; m.p. 94-95°C; yield, 51%; I.R. (KBr): ν_{max} = 1660, 1542, 1318 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 2.96 (s, 3H, SCH_3), 6.46 (dd, J = 9, 15Hz, 2H, $-CH_2C_6H_5$), 7.00-7.23 (m, $2H_{arom}$), 7.29-7.56 (m, $6H_{arom}$), 7.62 (s, H-4). [Found: C, 54.34; H, 3.52; N, 6.48 calculated for $C_{19}H_{14}N_2O_3SCl_2$ (421.2): C, 54.16; H, 3.34; N, 6.64%].

1-Cyclohexyl-3-(2,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29t] was obtained as a colourless solid; m.p. 169-170°C; yield, 54%; I.R. (KBr); ν_{max} = 1605, 1517, 1318 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.06-2.62 (m, 10H, ring CH_2), 3.29 (s, 3H, SCH_3), 5.69 (brs, 1H, CH), 7.23 (s, 1H, H-4), 7.46 (brs, $2H_{arom}$), 7.62 (s, $1H_{arom}$). [Found: C, 52.47; H, 4.56; N, 6.98 calculated for $C_{18}H_{18}N_2O_3SCl_2$ (413.3): C, 52.30; H, 4.38; N, 6.77%].

1-Butyl-3-(3,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29u] was obtained as a colourless solid; m.p. 95-96°C; yield, 53%; I.R. (KBr): ν_{max} = 1641, 1527, 1300 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.00 (t, J = 7Hz, 3H, $-CH_2(CH_2)_2CH_3$); 1.19-2.19 (m, 4H, $-CH_2(CH_2)_2CH_3$), 3.33 (s, 3H, SCH_3), 5.09 (t, J = 7Hz, 2H, $-CH_2(CH_2)_2CH_3$), 7.39-8.00 (m, 3H, H-4 and $2H_{arom}$); 8.09 (brs, $1H_{arom}$). [Found: C, 49.76; H, 4.30; N, 7.11 calculated for $C_{16}H_{16}N_2O_3SCl_2$ (387.2): C, 49.61; H, 4.16; N, 7.23%].

1-Benzyl-3-(3,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29v] was obtained as a colourless solid; m.p. 113-114°C; yield, 51%; I.R. (KBr): ν_{max} = 1657, 1545, 1310 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 2.96 (s, 3H, SCH_3), 6.52 (dd, J = 9, 15Hz, 2H, $-CH_2C_6H_5$), 7.09-7.29 (m, $2H_{arom}$), 7.33-7.52 (m, $3H_{arom}$), 7.62 (s, 1H, H-4), 7.72-7.95 (m, $2H_{arom}$), 8.00 (brs, $1H_{arom}$). [Found: C, 54.33; H, 3.57; N, 6.49 calculated for $C_{19}H_{14}N_2O_3SCl_2$ (421.2): C, 54.16; H, 3.34; N, 6.64%].

1-Cyclohexyl-3-(3,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29w] was obtained as a colourless solid; m.p. 154-155°C; yield, 52%; I.R. (KBr): ν_{max} = 1647, 1536, 1306 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.13-1.92 (m, 10H, ring CH_2), 3.33 (s, 3H, SCH_3), 5.66 (brs, 1H, CH), 7.42 (s, 1H, H-4), 7.69 (brs, $2H_{arom}$), 8.00 (brs, $1H_{arom}$). [Found: C, 52.11; H, 4.56; 6.65 calculated for $C_{18}H_{18}N_2O_3SCl_2$ (413.3): C, 52.30; H, 4.38; N, 6.77%].

1-Octyl-3-(3,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29x] was obtained as a colourless solid; m.p. 64-65°C;

yield, 55%; I.R. (KBr): ν_{max} = 1667, 1543, 1312 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 0.56 (brs, 3H, $-CH_2(CH_2)_6CH_3$), 1.33 (brs, 12H, $-CH_2(CH_2)_6CH_3$), 3.33 (s, 3H, SCH_3), 5.06 (t, J = 9Hz, 2H, $-CH_2(CH_2)_6CH_3$), 7.56 (s, 1H, H-4), 7.79 (brs, $2H_{arom}$), 8.03 (brs, $1H_{arom}$). [Found: C, 54.38; H, 5.29; N, 6.12 calculated for $C_{20}H_{24}N_2O_3SCl_2$ (443.3): C, 54.17; H, 5.45; N, 6.31%].

1-Dodecyl-3-(3,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29y] was obtained as a colourless solid; m.p. 75-76°C; yield, 54%; I.R. (KBr): ν_{max} = 1660, 1542, 1310 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.56 (brs, 3H, $-CH_2(CH)_{10}CH_3$), 1.33 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$), 3.33 (s, 3H, SCH_3), 5.09 (t, J = 7Hz, 2H, $-CH_2(CH_2)_{10}CH_3$), 7.92 (s, 1H, H-4), 7.82 (brs, $2H_{arom}$), 8.13 (d, J = 2Hz, $1H_{arom}$). [Found: C, 57.86; H, 6.59; N, 5.77 calculated for $C_{24}H_{32}N_2O_3SCl_2$ (499.4): C, 57.70, H, 6.45; N, 5.60%].

1-Cetyl-3-(3,4-dichlorobenzoyl)-2-methylthio-5-nitro pyrrole [29z] was obtained as a colourless solid; m.p. 76-77°C; yield, 55%; I.R. (KBr): ν_{max} = 1641, 1529, 1300 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 0.56 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.29 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 3.23 (s, 3H, SCH_3), 5.00 (brs, 2H, $-CH_2(CH_2)_{14}CH_3$), 7.46 (s, 1H, H-4), 7.69 (brs, $2H_{arom}$), 7.97 (brs, $1H_{arom}$). [Found: C, 60.71; H, 7.49; N, 5.27 calculated for $C_{28}H_{40}N_2O_3SCl_2$ (555.5): C, 60.52; H, 7.25; N, 5.04%].

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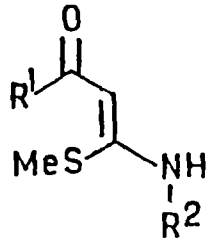
CHAPTER IV

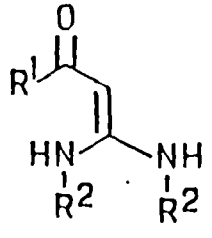
REACTION OF DIMETHYL N(2,2-DIETHOXY ETHYL)-IMINODITHIOCARBONATE WITH PRIMARY AMINES: A NEW GENERAL APPROACH FOR 1-SUBSTITUTED-2-METHYLTHIO IMIDAZOLES :

INTRODUCTION

The synthetic applications of various α-oxoketene S,N-and N,N-acetals as versatile intermediates for the construction of various heterocyclic systems are well documented in the literature[1-8]. They are versatile three carbon fragments 1 and 2 which are shown to be active with various bifunctional



1

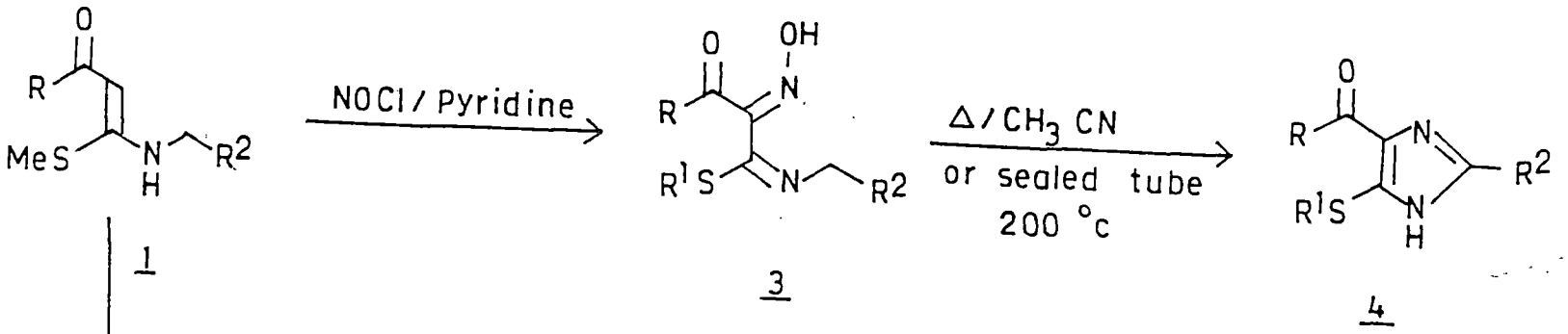


2

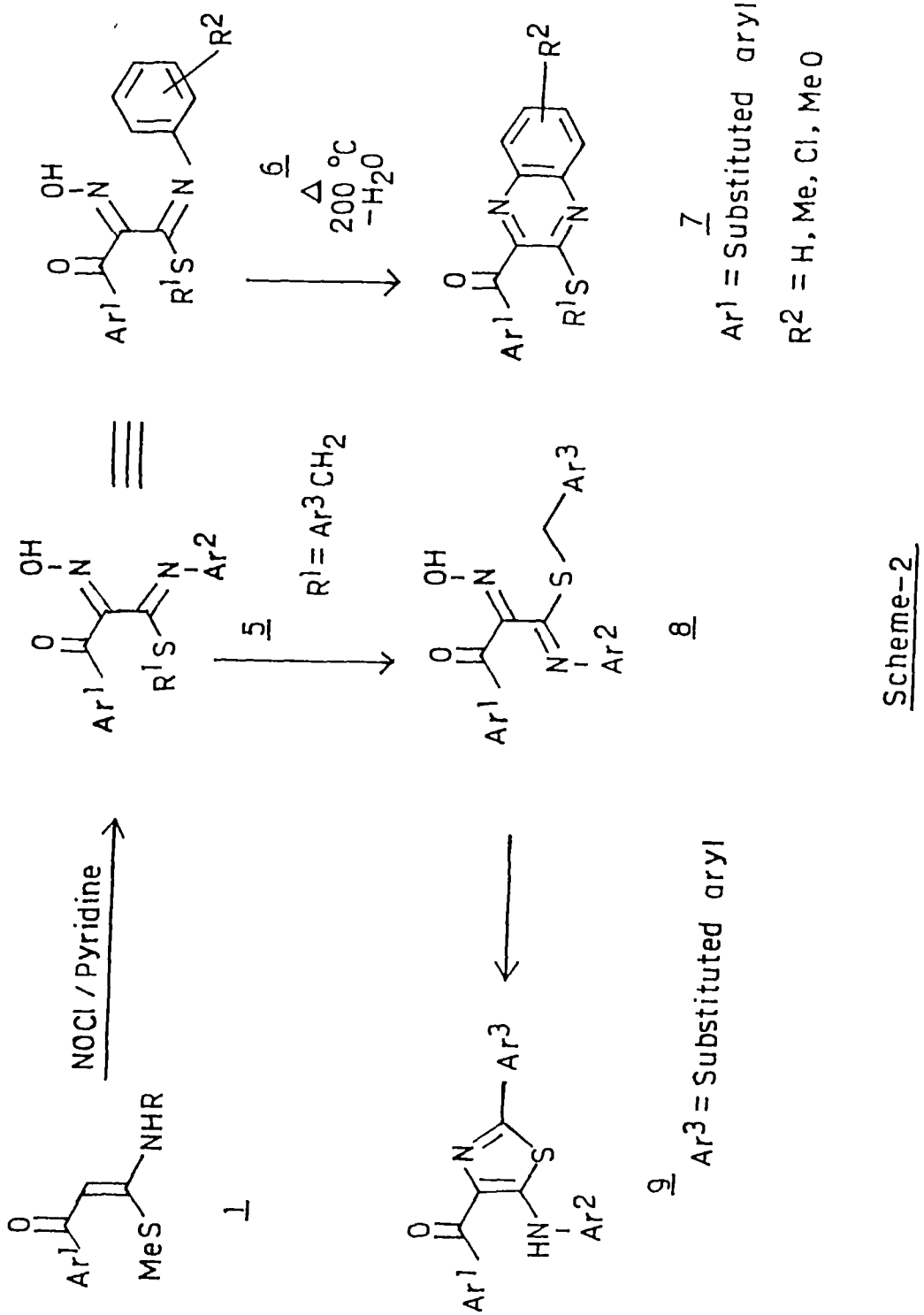
nucleophiles to afford the corresponding heterocycles with wide structural variations.

The S,N-acetal 1 and N,N-acetal 2 display properties of typical enaminone moity and react with electrophiles through the β-carbon atom as shown in scheme 1 (Chapter I) and this type of reactivity has been extensively exploited to construct a large number of heterocyclics from this laboratory. A typical reaction involves treatment of 1 and 2 with nitrosyl chloride to yield the corresponding nitroso derivatives in high yields. These nitroso compounds have been shown to exist in their oximino tautomeric form 3 (Scheme 1). They are shown to undergo thermal cyclocondensation to yield the corresponding 1H-imidazoles 4 (Scheme 1) in good yields[9]. The method was subsequently shown to be generally applicable for the synthesis of imidazoles with wide structural variations. Analogously the method was extended to thiazoles 9 and quinoxalines 7 as described in Scheme 2. Also subsequently the alkyl group in the aminofunctionality 1 was modified to carry (R = isopropyl, cyclohexyl and α-phenyl ethyl group etc.) alkyl and cyclo alkylchain followed by their nitrosation and thermal condensation to yield the corresponding 2,2-disubstituted 4-aroyl-5-alkylthio-2H-imidazoles[10] as described in Scheme 3.

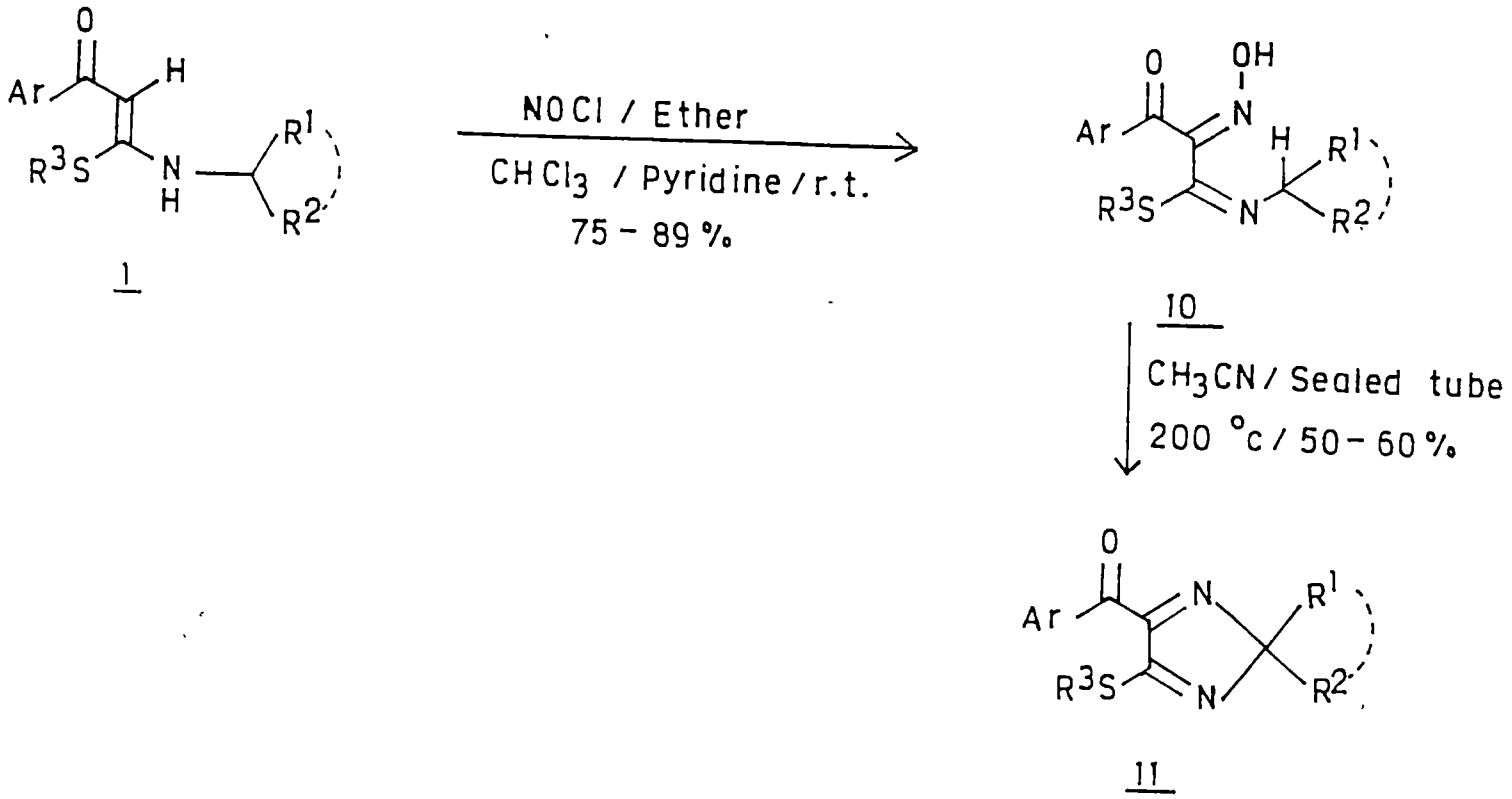
In an another approach a novel methodology for the sythesis of substituted imidazoles was developed in this laboratory[11] which appears to be a method of general synthetic importance. The reaction involves the preparation of dimethyl N-aryl/alkyl iminodithiocarbonate[12-15] and their


NOCl / Pyridine
Δ / CH3 CN
or sealed tube
200 °c
NOCl / Pyridine / Δ
R2 = aryl
55 - 87%
1
3
4
4
1,3,4, R = Substituted aryl ; Me ; Et
R1 = Me ; Et, C6H5 CH2
R2 = H, Me, Et, Substituted aryl, CO2 Et

Scheme - 1


NOCl / Pyridine
1
MeS
NHR
Ar1
O
Ar1
O
OH
N
N
Ar2
R1S
5
R1 = Ar3CH2
Ar1
O
OH
N
S
Ar3
N
Ar2
8
9
Ar3 = Substituted aryl
Ar1
O
Ar3
N
S
HN
Ar2
6
Δ
200 °C
-H2O
R2
7
Ar1 = Substituted aryl
R2 = H, Me, Cl, MeO

Scheme-2


O
Ar
H
R3S
N
H
R1
R2
NOCl / Ether
CHCl3 / Pyridine / r.t.
75 - 89 %
OH
10
CH3CN / Sealed tube
200 °c / 50 - 60 %
11

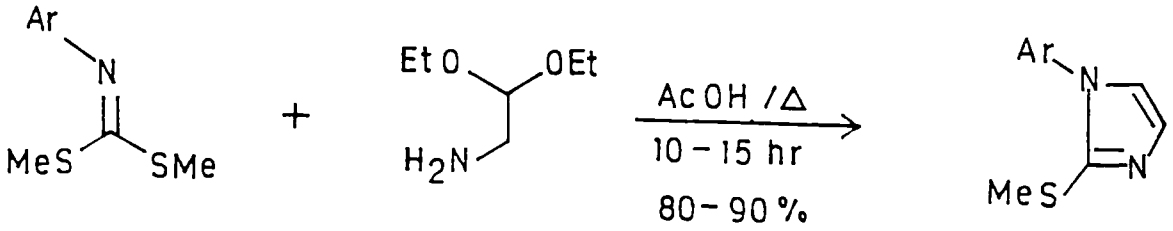
Scheme - 3

reactions with aminoacetaldehyde diethyl acetal. The iminodithiocarbonate12 which was prepared by the reported method[12] was treated with aminoacetaldehyde diethyl acetal 13 in refluxing acetic acid to yield the corresponding 1-aryl-2-methylthio imidazole 14 in consistently high yields and the method was found to be of general application and a better method for the synthesis of N-aryl/alkyl imidazols in 80-90% overall yields.

The above method utilizes 3 atom + 2 atom approach to construct 5-membered heterocyclics particularly imidazoles with possible applications to wide structural variations. Interestingly iminodithiocarbonate functionality can be created from aminoacetaldehyde diethyl acetal itself by converting this fragment into 4 atom fragment 16 for the construction of imidazole ring. This approach has been examined in the present investigation as a useful synthon for the construction of 1-substituted 2-methylthio imidazole. The results are described as follows:

RESULTS AND DISCUSSION

The required iminodithiocarbonate 16 was not described earlier in the literature. However the reaction of amino acetaldehyde diethyl acetal 13 with carbondisulphide followed by alkylation is reported to yield the corresponding methyl dithiocarbamate 15a, 15b. Direct one pot reaction of 16 from 13 was not successful and only the partially alkylated dithiocarbamate 15 was obtained despite the use of excess methyl iodide. The alkylation step of 15

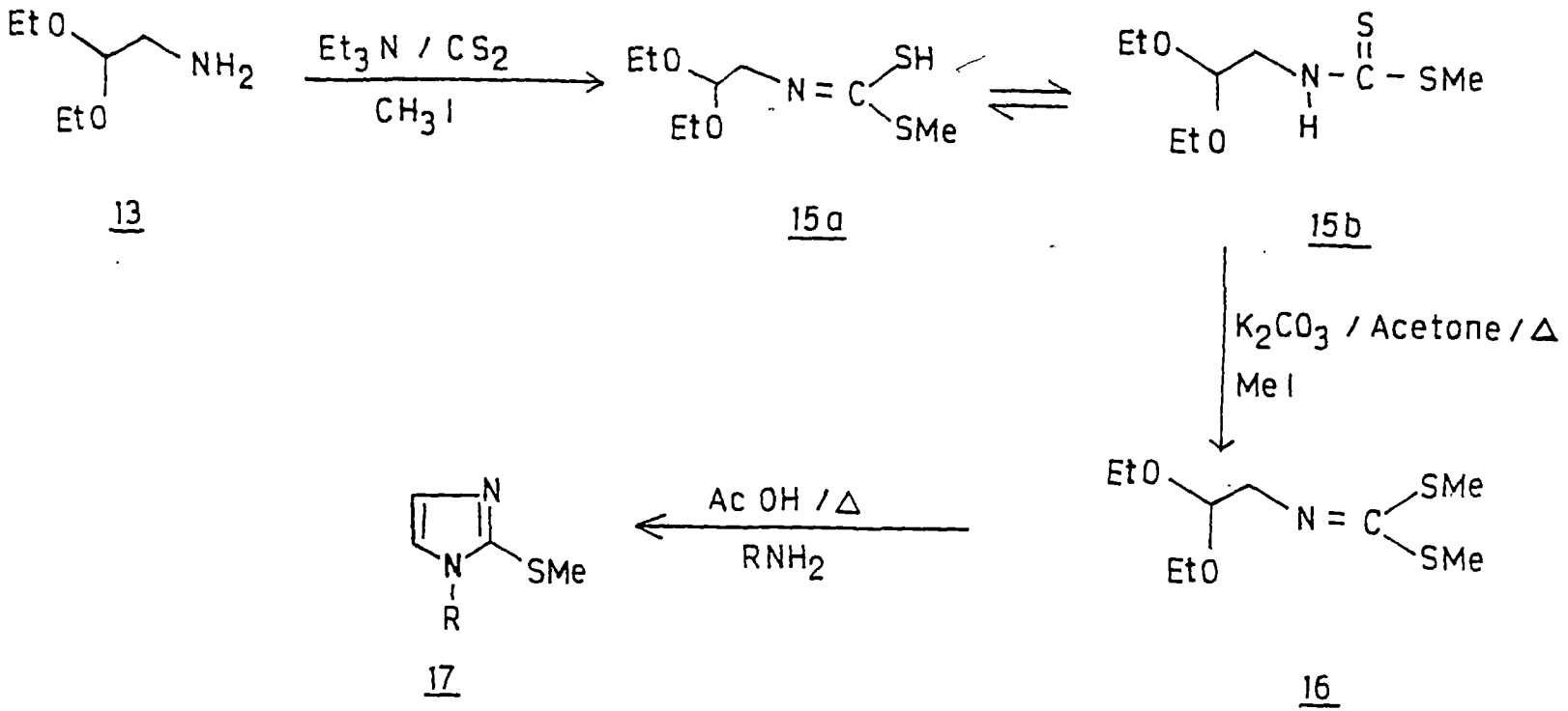


12 13 14

Scheme – 4

to obtain hitherto unreported 16 was separately carried out. Thus 15 was refluxed with anhydrous potassium carbonate in acetone for 3 hr followed by dropwise addition of methyl iodide at 0°C and further stirring for 5-6 hr at room temperature until the starting material 15 disappeared from the reaction mixture (monitored by TLC). After work-up the desired dimethyl N(2,2-diethoxy ethyl) iminodithiocarbonate 16 was obtained in 87% yield. The structure of 16 was confirmed by its spectral and analytical data. Thus, it was analysed for $C_9H_{19}NO_2S_2$ and analysis was in accordance with its m.w. 237.3. Its I.R. spectrum showed band at ν_{max} = 3355 cm^{-1}. Its structure was further confirmed from its ^1H n.m.r. (CCl_4) spectrum. The triplet at δ 1.19 (6H, J = 7Hz) was assigned to the methyl of O-ethyl group. The singlet at δ 2.36 (3H) was due to thiomethyl group. Another singlet at δ 2.56 (3H) was due to adjacent thiomethyl group. The multiplet around δ 3.36-3.72 (6H) was assigned to the methylene protons. The CH proton appeared as a triplet at δ 4.72 (1H, J = 7Hz).

The dithioate 16 is a hitherto unreported versatile 4 atom unit involving 1,4-electrophilic carbon atoms with nitrogen in a suitable position. The 4-atom unit 16 should react with primary amines which should serve as one atom unit under suitable reaction conditions possibly resulting in the formation of corresponding imidazoles. It was indeed a very successful reaction and a number of amines did react with 16 to give the corresponding imidazoles. Here we describe a new



17a, R = C_6H_5

b, R = Me

c, R = Et

d, R = Bu

e, R = $CH_2C_6H_5$

f, R = Cyclo C_6H_{11}

17g, R = $CH_2(CH_2)_6\ CH_3$

h, R = $CH_2(CH_2)_{10}\ CH_3$

i, R = $CH_2(CH_2)_{14}\ CH_3$

j, R = $CH_2CH_2\ C_6H_5$

k, R = CH_2 

l, R =

Scheme – 5

method for the synthesis of N-substituted imidazoles starting from primary amines as 1 atom unit and a iminodithiocarbonate as 4 atom unit.

The equimolar amounts of iminodithiocarbonate 16 and aniline were dissolved in acetic acid and reaction mixture was refluxed for 6 hours, concentrated after distilling of excess acetic acid, diluted with ice cold water and worked-up as usual to yield the crude 1-phenyl-2-methylthio imidazole 17a (Scheme 5) in 88% yield. The imidazole was found to be identical with that reported earlier[11,16] M.P., M.M.P. superimposable I.R. and n.m.r. spectral data (see experimental section).

The method for the synthesis of 1-phenyl imidazole appeared to be the most efficient one as other methods involve more steps than those employed in the present method (see review at the end). Similarly the imidazole 17b to 17e reported earlier[11] by other methods were also prepared by extending our method in an average of more than 80% yield. The properties of all these compounds were in accordance with that of the reported ones in the literature[16-21].

The imidazole 17f hitherto unreported was prepared by heating cyclohexyl amine under similar reaction conditions in 86% yield. The compound was fully in agreement with its analytical and spectral data which are described in the experimental section. Similarly 17g to 17l were prepared in 81-87% overall yields. The analytical and spectral data of all these imidazoles are in accordance with the assigned

structures and are described in the experimental section.

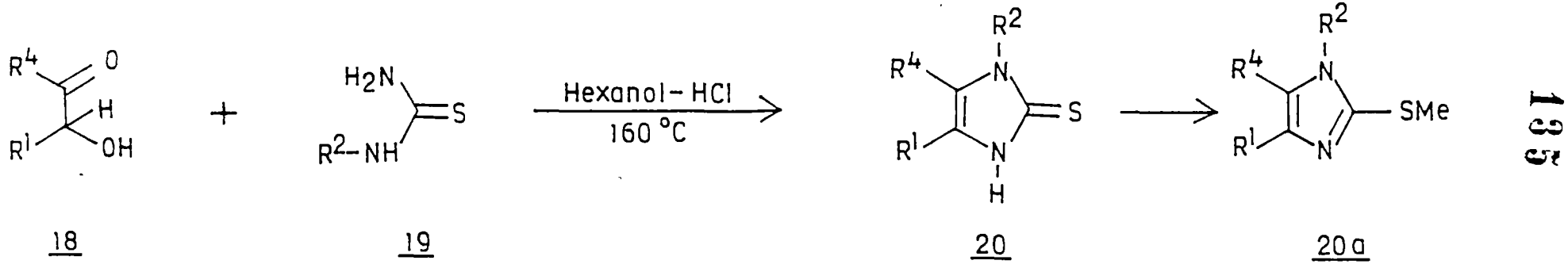
Following is a brief account on the synthesis of analogous imidazoles. The phenyl-1 4 imidazolinethiones-2 20 (Scheme 6) have been reported in the literature[22-29] which are nearest precursors of 2-methylthio imidazoles 20a. The required thiones-2 20 were prepared by reacting O-hydroxy aldehyde and ketones with thioureas (Scheme 6).

Subsequently another eligant method was discovered by A. Wohl and coworkers.

The isothiocyanate 21 (Scheme 7) was derived from aminoacetaldehyde diethyl acetal in 50% yield[30,31]. The isothiocyanate was then reacted with various primary amines to afford the corresponding thioureas 22 which on subsequent cyclization yielded the corresponding thiones-2 24. The 2-methylthio imidazole 25 were then obtained from 24 as shown in scheme 7.

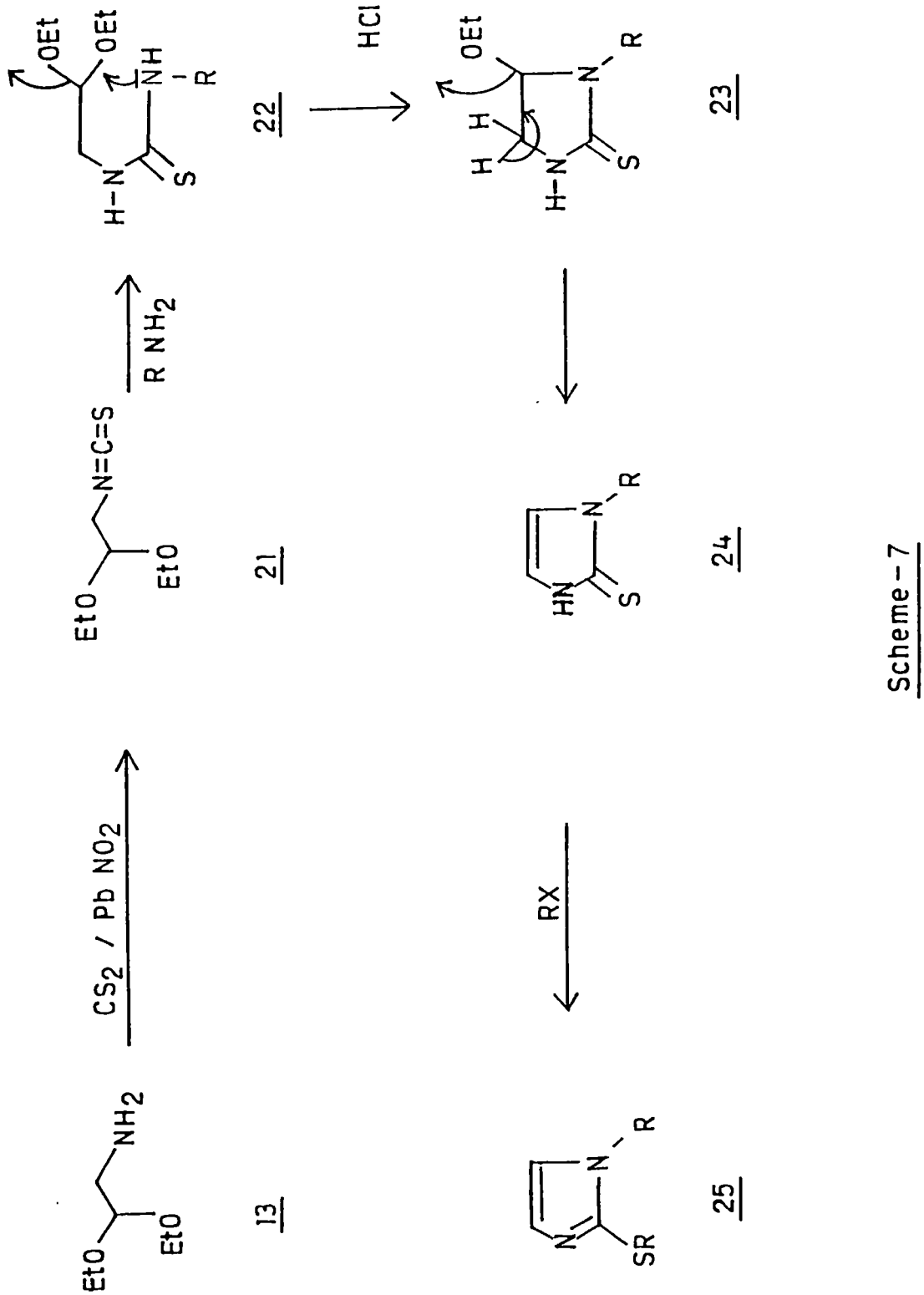
These methods by and large have been used for the corresponding thiourea intermediate such as 22 (Scheme 7) to obtain the corresponding imidazoline thiones-2. The thiones in a seperate step are alkylated to afford the corresponding methylthio-imidazole[32,33] 25.

In the present method the intermediate 16 by heating with various aliphatic as well as aromatic amines yielded 1-alkyl/aryl-2-methylthio imidazoles in over all high yields. It is certainly more efficient than those described in the



18 19 20 20a

Scheme – 6


OEt
OEt
NH
R
H-N
S
22
HCl
OEt
R
N
H
H
H-N
S
23
N=C=S
EtO
EtO
21
R NH2
R
N
HN
S
24
NH2
EtO
EtO
13
CS2 / Pb NO2
RX
R
N
N
SR
25

Scheme-7

literature in overall yields as well as number of steps. The present method is likely to be popular for the synthesis of imidazoles of wide structural diversity at 1 and 2 positions.

EXPERIMENTAL

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 tetramethyl silane 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 analysis were done on Heraeus CHN-O-RAPID instrument.

STARTING MATERIALS:

The commercial samples of various amines and acetone were purified before use. N-(2,2-diethoxyethyl)dithio carbamic acid methyl ester was prepared according to the reported procedure[34]. Commercially available anhydrous potassium carbonate, acetic acid and methyl iodide were used as such.

General method for the preparation of dimethyl N(2,2-diethoxy ethyl) iminodithiocarbonate [16].

To a solution of N-(2,2-diethoxy ethyl)dithiocarbamic acid

methyl ester (100 mmol) in 75 ml acetone, was added anhydrous potassium carbonate (200 mmol) and refluxed for 6-7 hr. The reaction mixture was cooled (ice-bath) and methyliodide (100 mmol) was added dropwise with constant stirring. Stirring was continued for 1 hr at 0°C and for 5-6 hr at room temperature (monitored by TLC). The reaction mixture was filtered, the residue was washed twice with acetone (2x25 ml), concentrated on water bath. The residue was diluted with chloroform (100 ml), washed with water (3x100 ml), dried (Na_2SO_4) and evaporated. The crude product 16 was purified by passing through a short silica gel column using hexane/ethylacetate (99:1) as an eluent.

Dimethyl N(2,2-diethoxyethyl)iminodithiocarbonate [16] oil; yield 87%; IR (Neat); ν_{max} = 2914, 1579, cm^{-1}; ^1H n.m.r. (CCl_4); δ = 1.19 (t, J = 7Hz, 6H, $-CH_2CH_3$), 2.36 (s, 3H, SCH_3), 2.56 (s, 3H, $-SCH_3$), 3.36-3.72 (m, 6H, $-CH_2$), 4.72 (t, J = 7Hz, 1H, CH). [Found : C, 45.32; H, 7.91; N, 6.13 calculated for $C_9H_{19}NO_2S_2$ (237.3) : C, 45.54; H, 8.06; N, 5.90%].

General method for the preparation of 1-aryl/alkyl-2-methylthio imidazoles (1a-l)

Dimethyl N(2,2-diethoxyethyl)iminodithiocarbonate (15 mmol) and primary amine (10 mmol) was refluxed in acetic acid for 6-11 hrs. Then acetic acid was removed under vaccum and the residue was dissolved in chloroform (50 ml). This solution was washed with water (3x30 ml), dried over sodium sulphate and evaporated to give the crude product 17a which was

purified by column chromatography on silica gel using EtOAc/Hexane (1:19) as eluent.

1-Phenyl-2-methylthio imidazole [17a]; white solid, reaction time 6 hr; yield, 83%; m.p. 54-55°C; lit. m.p. 53-54°C; IR (KBr) : ν_{max} = 3120, 2900, 1609, 1510, 1442 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 2.66 (s, 3H, SCH_3), 7.23 (brs, 2H, H-4 and H-5) 7.59 (brs, 5H, C_6H_5). [Found : C, 62.91; H, 5.03; N, 14.79. Calculated for $C_{10}H_{10}N_2S$ (190.2) ; C, 63.14; H, 5.24; N, 14.57%].

1-Methyl-2-methylthio imidazole [17b]; oil; reaction time 7 hrs yield, 82%; IR (Neat) : ν_{max} = 3100,3051,1487, 1425 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 2.49 (s, 3H, SCH_3), 3.26 (s, 3H, NCH_3), 6.88 (brs, 2H, H-4 and H-5). [Found : C, 46.63; H, 6.07; N, 22.09 calculated for $C_5H_8N_2S$ (128.1) : C, 46.87; H, 6.29; N, 21.87%].

1-Ethyl-2-methylthio imidazole [17c]; oil; reaction time 2 hr yield, 82%; IR(Neat) : ν_{max} = 3109, 3024, 1490, 1450 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 1.16 (t, J = 7Hz, 3H, $-CH_2CH_3$), 2.59 (s, 3H, SCH_3), 3.19-3.66 (m, 2H,$-CH_2CH_3$), 7.00 (brs, 2H, H-4 and H-5). [Found : C, 50.43; H, 7.31; N, 19.46 calculated for $C_6H_{10}N_2S$ (142.2) : C, 50.67; H, 7.08; N, 19.70%].

1-Butyl-2-methylthio imidazole [17d]; oil; reaction time 8hrs, yield 85%; IR (Neat) : ν_{max} = 3102, 3049, 1509, 1490 cm^{-1}; ^1H n.m.r. (CCl_3) : δ = 1.00 (t, J = 7Hz, 3H, $-CH_2(CH_2)_2CH_3$), 1.13-1.89 (m, 4H, $-CH_2(CH_2)_2CH_3$) 2.59 (s, 3H,

SCH_3) 3.82 (t, J = 7Hz, 2H, $-CH_2(CH_2)_2CH_3$), 6.82 (s, 1H, H-4), 6.89 (s, 1H, H-5). [Found : C, 56.19; H, 8.07; N, 16.73 calculated for $C_8H_{14}N_2S$ (170.2) : C, 56.45; H, 8.29; N, 16.46%].

1-Benzyl-2-methylthio imidazole [17e]; oil; reaction time 11 hrs; yield, 86%; IR (Neat) : ν_{max} = 3100, 3058, 1492, 1450, 1425 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 2.56 (s, 3H, SCH_3), 5.13 (s, 2H, $-CH_2C_6H_5$), 6.95 (s, 1H, H-4). 7.13 (s, 1H, H-5), 7.13-7.52 (m, $5H_{arom}$). [Found : C, 64.94; H, 6.17; N, 13.98. Calculated for $C_{11}H_{12}N_2S$ (204.2) : C, 64.69; H, 5.93; N, 13.72%].

1-Cyclohexyl-2-methylthio imidazole [17f]; oil; reaction time 8 hrs; yield, 86%; IR (Neat): ν_{max} = 3058, 2925, 1481, 1440 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 1.03-2.13 (m, 10H, ring CH_2), 2.59 (s, 3H, SCH_3), 3.85 (brs, 1H, CH), 6.85 (brs, 2H, H-4 and H-5); m/z : 196 (M^+, 8%), 127(100%), 114(28%). [Found : C, 60.94; H, 8.03; N, 14.48 calculated for $C_{10}H_{10}N_2S$ (196.3); C, 61.18; H, 8.21; N, 14.27%].

1-Octyl-2-methylthio imidazole [17g]; oill; reaction time 7 hrs; yield, 84%; IR (Neat) : ν_{max} = 3047, 2900, 1487, 1444 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 0.89 (brs, 3H, $-CH_2$ $(CH_2)_6CH_3$), 1.30 (brs, 12H, $-CH_2(CH_2)_6CH_3$), 2.62 (s, 3H, SCH_3), 3.89 (t, J = 7 Hz, 2H, $-CH_2$ $(CH_2)_6CH_3$), 6.95 (s, 1H, H-4), 7.06 (s, 1H, H-5). [Found : C, 63.45; H, 9.59; N, 12.56 calculated for $C_{12}H_{22}N_2S$ (226.3): C, 63.69; H, 9.80; N, 12.38%].

1-Dodecyl-2-methylthio imidazole [17h]; oil; reaction time, 9 hrs; yield , 87%; IR (Neat) : ν_{max} = 2900, 1441 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 0.89 (brs, 3H, $-CH_2(CH_2)_{10}CH_3$); 1.30 (brs, 20H, $-CH_2(CH_2)_{10}CH_3$), 2.60 (s, 3H, SCH_3), 3.85 (t, J=7Hz, 2H, $-CH_2(CH_2)_{10}CH_3$), 6.89 (s, 1H, H-4), 6.95 (s, 1H, H-5), m/z : 282 (M^+, 100%); 235 (M^+-47, 88%). [Found : C, 68.29; H, 10.47; N, 10.18 calculated for $C_{10}H_{30}N_2S$ (282.4) : C, 68.04; H, 10.70; N, 9.92%].

1-Cetyl-2-methylthio imidazole [17i]; oil; reaction time 9 hrs; yield, 87%; IR(Neat): ν_{max} = 2900, 1441 cm^{-1}; ^1H n.m.r. (CCl_4) :δ=0.89 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.30 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 2.92 (s, 3H, SCH_3), 3.82 (t, J = 7Hz, 2H, $-CH_2(CH_2)_{14}CH_3$), 6.82 (s, 1H, H-4), 6.92 (s, 1H, H-5). m/z : 338 (M^+, 98.8%); 291 (M^+-47, 44.8%). [Found : C, 71.21; H, 11.07; N, 8.51 calculated for $C_{20}H_{38}N_2S$ (338.5): C, 70.96; H, 11.31; N, 8.27%].

1(2-Phenylethyl)-2-methylthio imidazole [17j]; oil; reaction time, 8hr; yield, 83%; IR (Neat) : ν_{max} = 3120, 1447 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 2.46 (s, 3H, SCH_3), 2.89 (t, J = 7Hz, 2H, $-CH_2CH_2C_6H_5$), 4.03 (t, J = 7Hz, 2H, $-CH_2CH_2C_6H_5$), 6.69 (s, 1H, H-4), 6.89 (s, 1H, H-5), 6.95-7.33 (m, $5H_{arom}$). m/z : 218 (M^+, 91.2%); 171(6%), 114 (100%). [Found : C, 66.27; H, 6.29; N, 12.59 calculated for $C_{12}H_{14}N_2S$ (218.3) : C, 66.01; H, 6.46; N, 12.83%].

1(2-Furylmethyl)-2-methylthio imidazole [17k]; oil; reaction time 6 hr; yield, 81%; IR (Neat):ν_{max} = 3160, 1440 cm^{-1}; ^1H

n.m.r. (CCl_4) : δ = 2.52 (s, 3H, SCH_3), 5.00 (s, 2H, $-CH_2$), 6.30 (brs, 2H, H-4 and H-5), 6.95 (brs, 2H, 3,4 furyl), 7.42 (brs, 1H, furyl). m/z : 194 (M^+, 81.6), 81 (100%). [Found : C, 55.49; H, 5.02; N, 14.17 calculated for $C_9H_{10}N_2OS$ (194.2) : C, 55.65; H, 5.19; N, 14.42%].

1-Cyclopropyl-2-methylthio imidazole [171]; oil, reaction time 6 hr; yield, 81%; IR (Neat) : ν_{max} = 3150, 1492, 1425 cm^{-1}; ^1H n.m.r. (CCl_4) : δ = 0.89 (brs, 4H, cyclopropyl CH_2); 2.56 (s, 3H, SCH_3), 3.09 (m, 1H, CH), 6.82 (brs, 2H, H-4 and H-5). m/z : 154 (M^+, 100%), 107 (23%). [Found : C, 56.71; H, 6.29; N, 18.41 calculated for $C_7H_{10}N_2S$ (154.2): C, 56.46; H, 6.53, N, 18.17%].

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CHAPTER V

CYCLOCONDENSATION OF 2,4-DIAMINO-6(1H)-PYRIMIDINONE WITH α-OXOKETENE DITHIOACETALS: SYNTHESIS OF 5-ALKYLTHIO-7-SUBSTITUTED AND 6,7-ANNULATED-5-DEAZAPTERIDINE DERIVATIVES*

INTRODUCTION

Methotrexate (MTX) 1,[1] Aminopterine 2[2] and dichloromethotrexate 3[3] are among the earliest clinically accepted anti cancer agents as powerful dihydrofolate reductase and thymidylate synthetase inhibitors[4-8]. All these compounds are 4-amino analogs of folic acid and only MTX 1 has been extensively investigated although 2 and 3 are equally active.

MTX has been found to be highly toxic and is toxic towards most forms of human cancer. Its selectivity depends on other considerations such as differences between growth rates of

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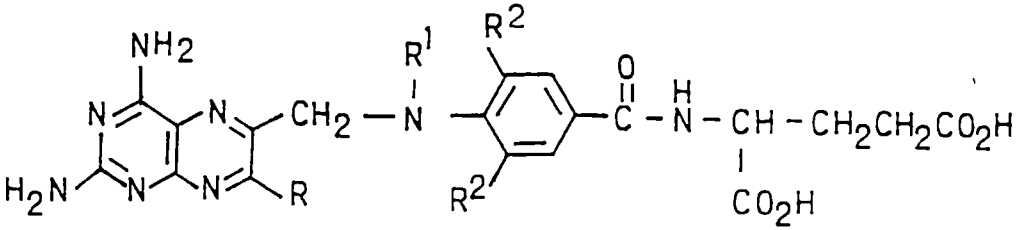
* Sharma, S.K.; Chakrasali, R.T.; Ila, H.; Junjappa, H., *Ind. J. Chem.* 000 (1993).



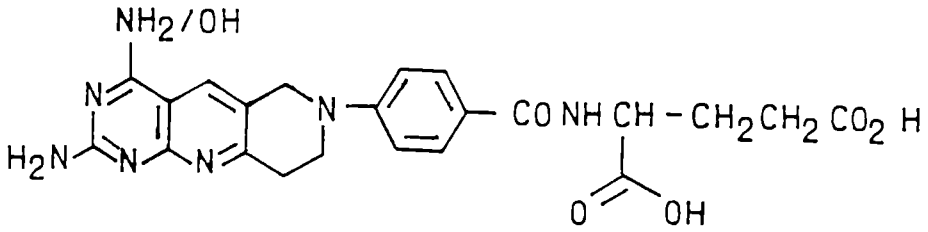
1, R = H ; R^1 = Me ; R^2 = H Methotrexate

2, R = R^1 = R^2 = H Aminopterine

3, R = H ; R^1 = Me ; R^2 = Cl Dichloromethotrexate

4, R = OH ; R^1 = R^2 = H

5, R = Me ; R^1 = R^2 = H



6

Scheme-1

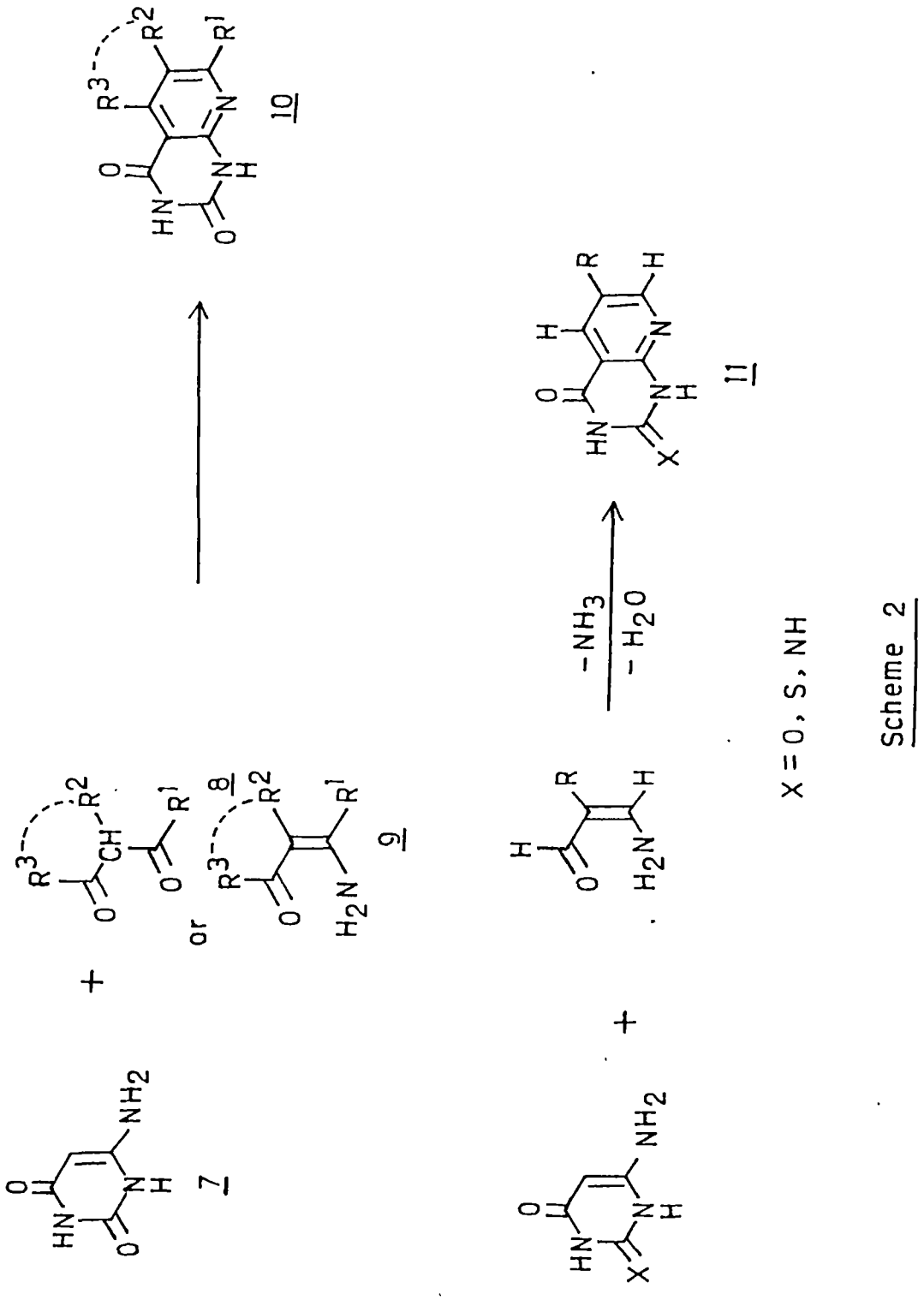
normal and cancer cells, folate enzyme pools, levels of dihydrofolate reductase and its transport to active site. MTX is known to develop drug resistance, besides being found to be ineffective against tumor of central nervous system as well as malarial parasites[9-11]. A major pathway for methotrexate metabolism is oxidation at C-7 to give extremely insoluble 7-oxo derivative 4. In an attempt to block this metabolic inactivation path way for methotrexate, the 7-methyl derivative 5 was prepared and was found to be inactive against L_{1210} cells[12].

There is considerable interest therefore to construct structural analogs of folic acid which would exhibit enhanced binding to dihydrofolate reductase or thymidylate synthetase and thus greater selectivity for a broader range of human tumors[13]. A number of annulated 5-deazapteridines (pyrido[2,3-*d*]-pyrimidines) have been synthesized as potential dihydrofolate reductase and thymidylate synthetase inhibitors[14]. Thus the 5,10-dideaza 6,7,8,9-tetrahydroaminopterin 6 an extremely potent inhibitor of L_{1210} Leukemia has been recently synthesized.

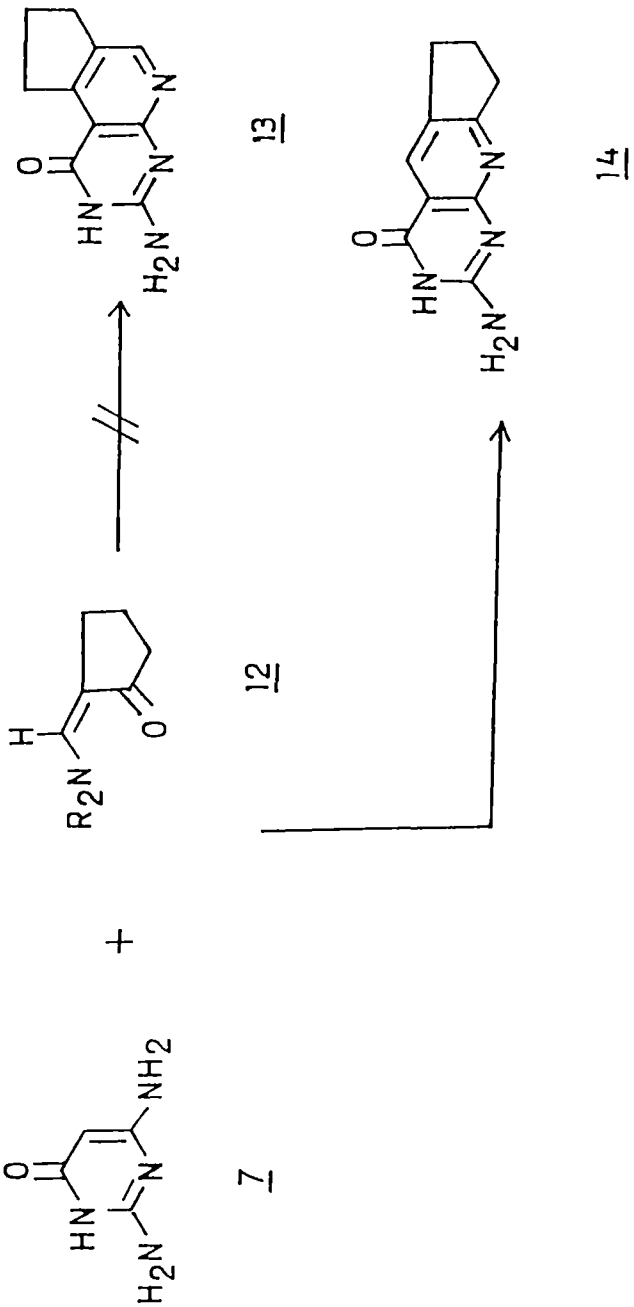
These observations prompted us to synthesize new substituted and 6,7-annulated-5-deazapteridines through condensation of 2,4-diamino-6(1H)pyrimidinone with α-oxoketene dithioacetal and the results are reported in this chapter.

RESULTS AND DISCUSSION

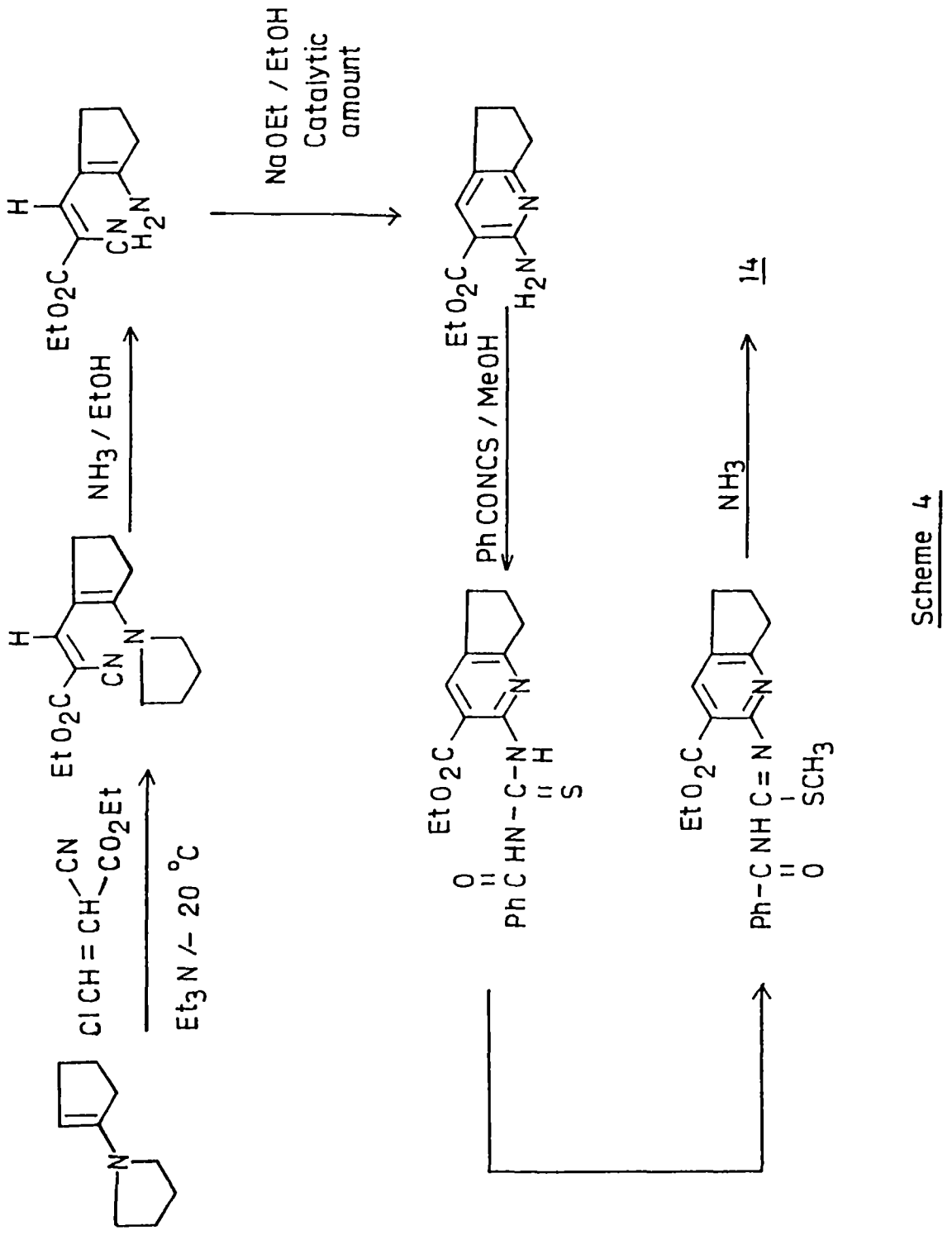
Breitmaier and co-workers[15] have reported simple synthesis of several 7-alkyl and 5,6-cycloalkeno-5-deazapteridines by cyclization of 4-amino uracil (X=O,S, NH) with N,N-unsubstituted β-enaminocarbonyl compounds such as 3-aminoacroleins and 2-aminomethylene cycloalkanones (Scheme 2). However it could not be decided by these authors whether the product possessed the 5,6-annulated structure 13. Subsequently Taylor and co-workers[14] investigated the structure of the product arising from the condensation of 2,4-diamino-6(1H) pyrimidinone with 2-dimethylaminomethylene cyclopentanone 12 which was described earlier by Breitmaier and co-workers. The product was shown to possess 6,7-annulated structurer 14 instead of 5,6-annulated frame work 13 as suggested by Breitmaier and co-workers (Scheme 3). The structure of 14 was further confirmed by Taylor through an independant and unequivocal synthesis (Scheme 4)[14]. Similarly the dimethylaminomethylene derivative 15 from 3-oxopyrrolidine was subjected to cyclization with 2,4-diamino-6(1H)pyrimidinone 7 to give 6,7 fused-5-deazapteridine 16 which was subsequently converted to 7,10-methano-5-deazapteroic acids 17 and 18 whose structures were confirmed by unambiguous synthesis[13]. Authors however did not report biological activity of any of these products 14,17 and 18.



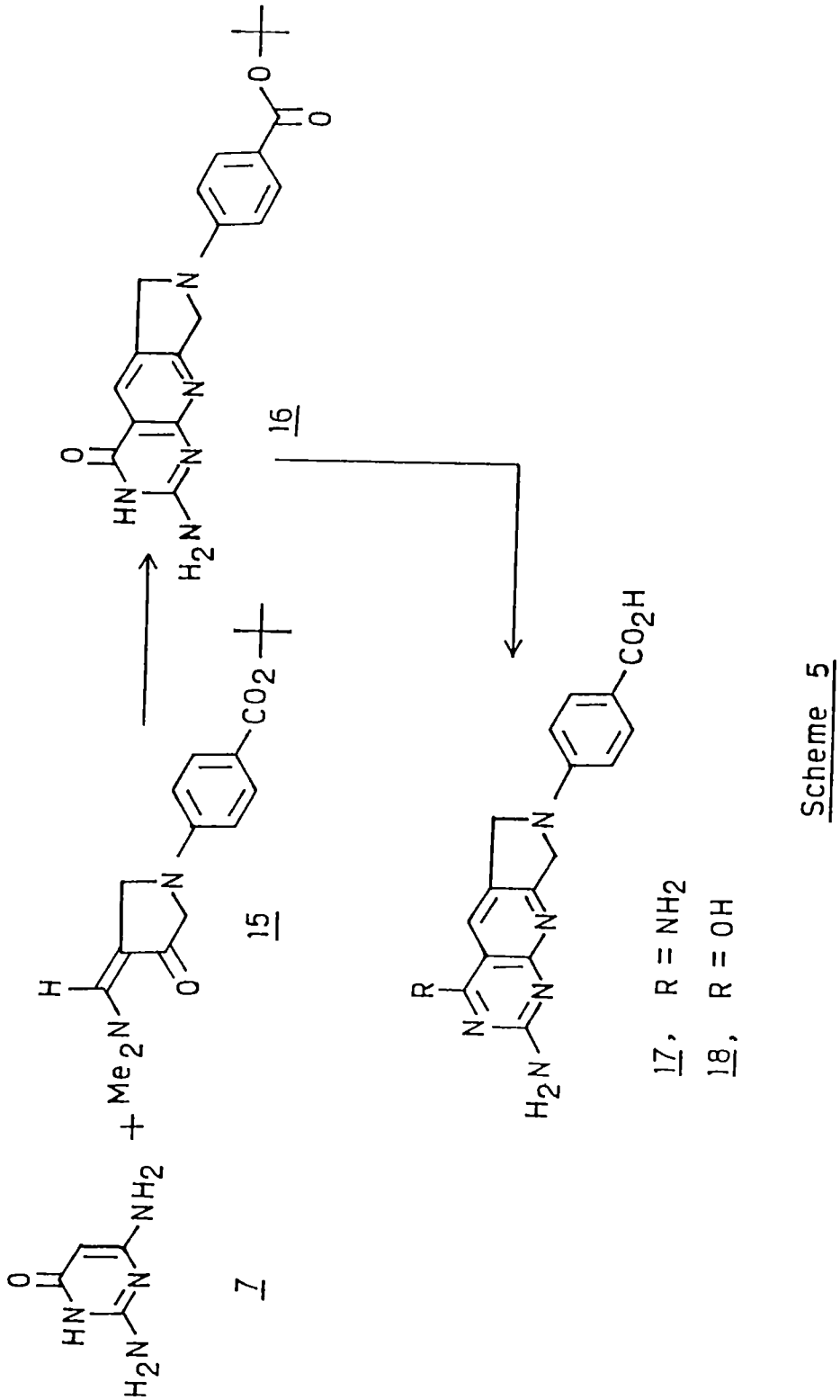
Scheme 2



Scheme 3


Et3N /– 20 °C
NH3 / EtOH
NaOEt / EtOH
Catalytic amount
PhCONCS / MeOH
NH3
14

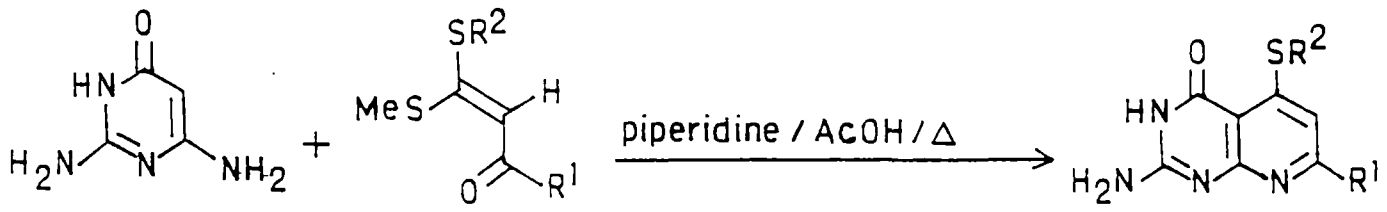
Scheme 4



Scheme 5

Earlier work from this laboratory has established that the α-oxoketene dithioacetals are useful 3-carbon fragments for construction of 5 and 6 membered carbocyclic compounds. Many of the bifunctional heteronucleophiles like hydrazine hydrate, hydroxylamine, guanidines, cyanoacetamide and acetonitrile anions react with these dithioacetals which are easily prepared from acyclic and cyclic active methylene ketones to afford regiospecifically substituted and annulated[7] heterocycles like pyrazoles[16,17], isoxazoles[18], pyrimidines[19], pyridones[21] and pyridines[21] etc. These studies have been covered in a recent review article[22].

In a typical experiment, when equimolar mixture of 7 and 19a were refluxed in dilute acetic acid in the presence of catalytic amount of piperidine, work up of the reaction mixture afforded a pale yellow solid (81%) which was characterized as 5-methylthio-7-phenyl-5-deazapteridine 20a on the basis of spectral and analytical data. Thus the mass spectrum of **20a** showed molecular ion peak (M^+) at m/e 284 (91%), however its elemental data indicated incorporation of one mole of acetic acid during crystallization. This was evident from the ^1H n.m.r. spectrum (TFA) of 20a also. The three proton singlet at δ2.60 (3H) was assigned to methylthio protons, whereas another singlet at δ 2.10 (3H) was due to acetic acid methyl protons. The H-6 proton signal appeared as singlet at δ 7.20 (1H) while aromatic protons resonance appeared as multiplet at δ 7.50 - 8.10 (5H). In DMSO-d_6 solvent, the aromatic multiplet was



7 19 20

19,20 a, $R^1 = C_6H_5$; R^2 = Me

b, R^1 = 4-Me C_6H_4; R^2 = Me

c, R^1 = 4-Me O C_6H_4; R^2 = Me

d, R^1 = 4-cl C_6H_4; R^2 = Me

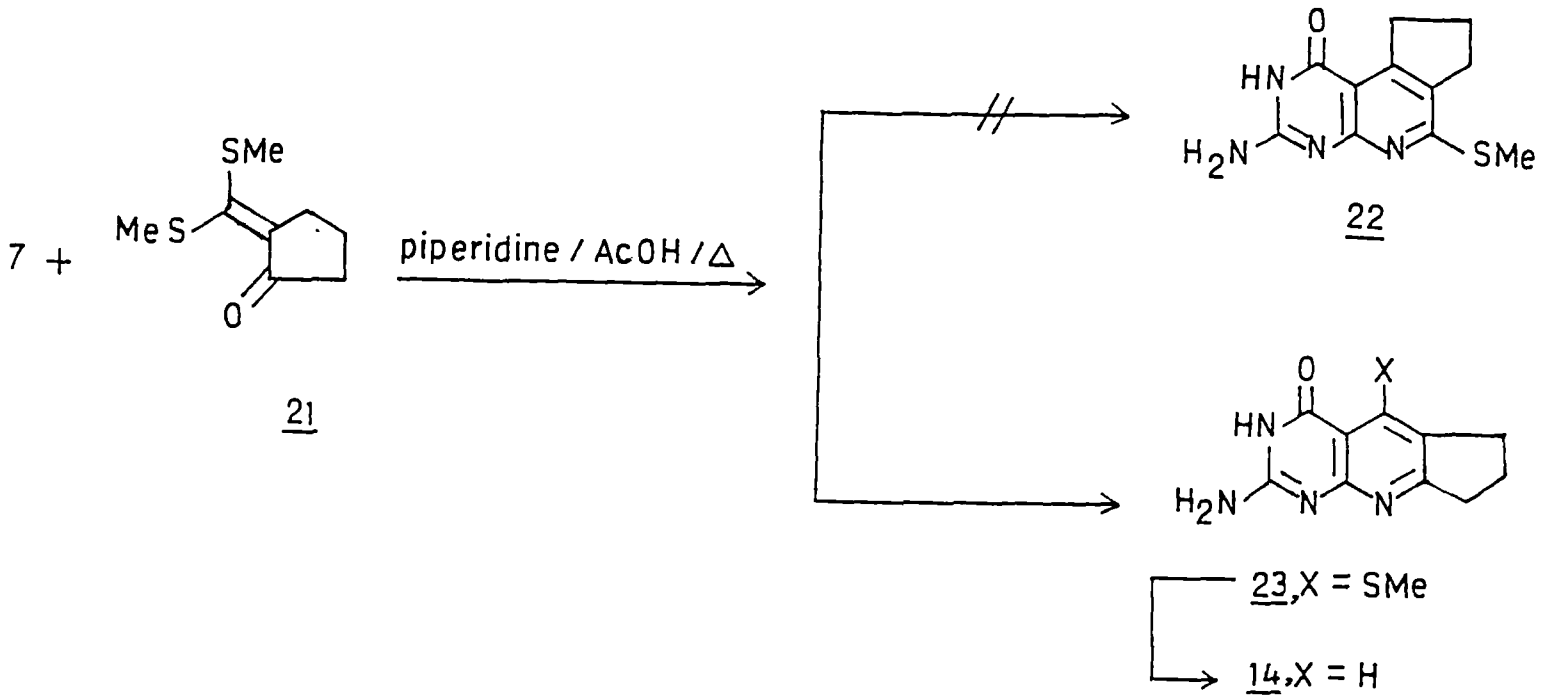
e, $R^1 = R^2$ = Me

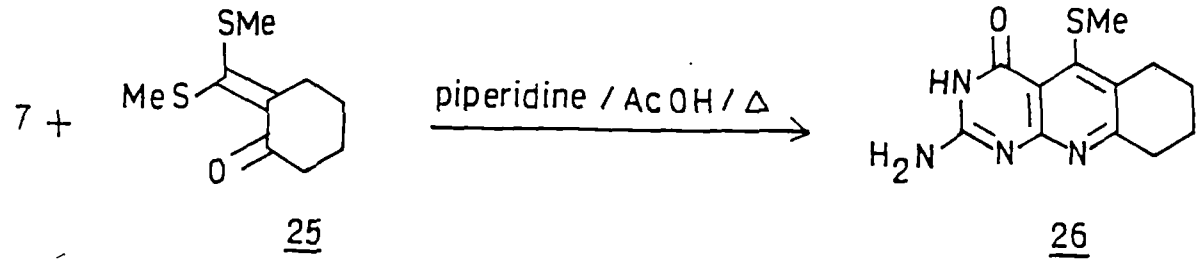
f, $R^1 = C_6H_5$; R^2 = n-Pr

Scheme 6

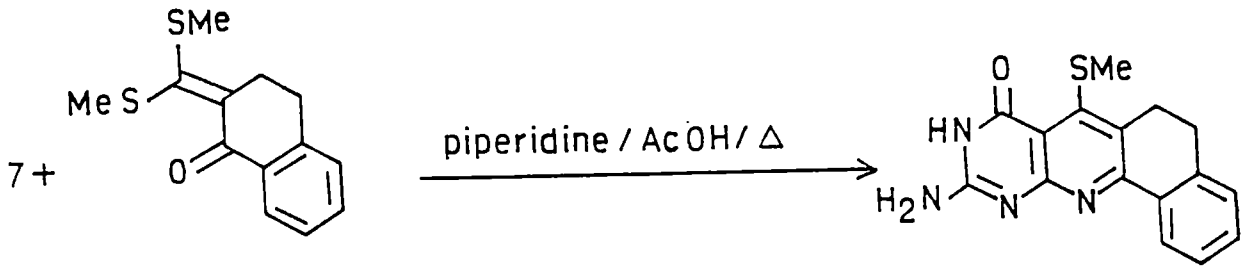
resolved in two multiplets at δ 7.58 (3H) and δ 8.16 (2H) respectively. The two NH protons appeared at δ 6.7 as broad singlet (2H) in DMSO-d_6 solvent. The infra red spectrum (KBr) of 20a also exhibited free and bonded NH vibrations at 3306 and 3162 cm^{-1}. The other 7-aryl/methyl substituted 5-deazapteridines 20b-f (Scheme 6) were similarly prepared in 50-78% overall yields. The spectral and analytical data for 20b-f was found to be in conformity with the assigned structures.

The reaction was next investigated for the synthesis of 6,7-annulated 5-deazapteridines. The cyclization of dithioacetal 21 (derived from cyclopentanone) with 7 under the reported conditions yielded 6,7-cyclopentano-5-deazapteridine 23 in 42% yield. The alternative 5,6-annulated regiomeric structure 22 was ruled out by dethiomethylation of 23 with Raney Nickel to afford 5-unsubstituted product 14 in 41% yield. The product 14 was found to be identical (superimposable IR and n.m.r. spectra) with that prepared by Taylor by condensation of 7 with 2-N,N-dimethylaminomethylene cyclopentanone 12 (Scheme 3)[14]. The dithioacetal 25 from cyclohexanone similarly reacted with 7 under the described conditions to afford 6,7-tetramethylene compound in 45% yield (Scheme 7). The tetracyclic 6,7-annulated 5-deazapteridine 28 was also obtained in 47% yield by cyclization of 7 with tetralone derived α-oxoketene dithioacetal 27 (Scheme 8). The spectral and analytical data of the products 26 and 28 were


7 +
SMe
Me S
O
piperidine / AcOH / Δ
O
HN
H2N
N
N
SMe
22
O
X
HN
H2N
N
N
23, X = SMe
14, X = H
21

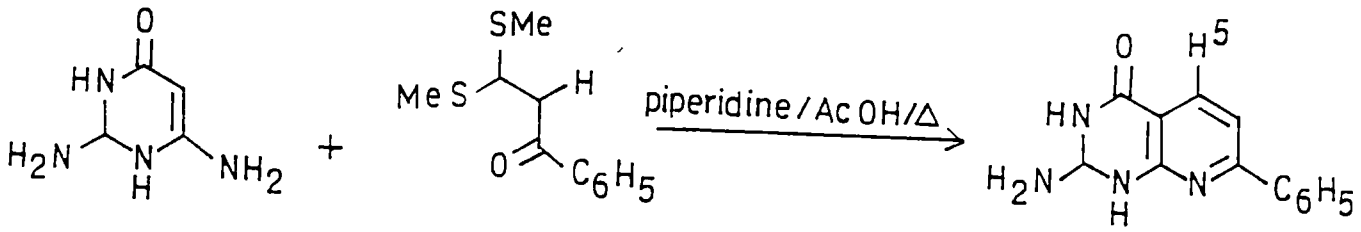

7 +
SMe
Me S
O
piperidine / AcOH / Δ
O
SMe
HN
H2N
N
N
25
26

Scheme 7



27 28

Scheme 8



7 29 30

Scheme 9

in conformity with the assigned structures.

Reaction of 7 with β-oxodithioacetal 29 under described conditions yielded 7-aryl 5-unsubstituted-5-deazapteridine 30 in 50% yield (Scheme 9). The product 30 showed a characteristic low field doublet (J = 8 Hz) at δ 9.15 due to H-5 proton in its ^{1}H n.m.r. spectrum.

EXPERIMENTAL

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-983 spectrophotometer 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 tetramethyl silane 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, cyclopentanone, cyclohexanone, acetone, ethyl cyanoacetate, piperidine, ethanol etc. were purified before use. 2,4-diamino-6(1H)pyrimidinone was prepared according to the reported procedure[23]. Commercially available acetic acid and

guanidine hydrochloride were used as such.

Synthesis of 2-amino-5-alkylthio-7-substituted/6,7-annulated-4(3H)-pyrido[2,3-*d*]-pyrimidinones 20a-f, 23, 26 and 28: General Procedure:

A suspension of dithioacetal **19** (15 mmol) and **7** (15 mmol) in glacial acetic acid (45 ml) and water (30 ml) in the presence of catalytic amount of piperidine (2 drops) were refluxed with stirring for 8-20 hr. All the reactants dissolved completely under refluxing conditions. The reaction mixture was cooled and few of the pyrido[2,3-d] pyrimidinones **20a-f** separated as yellow amorphous solids which were filtered. In the case of 6,7-annulated compounds **23,26,28**, the reaction mixture was concentrated to half the volume under reduced pressure and the residue poured over water to give **23**, **26**, **28** as yellow amorphous solids which were filtered, washed with water and methanol, acetone mixture and dried at 100°C for 1 hr. All the products **20a-f**, **23**, **26**, **28** thus obtained were crystallized from glacial acetic acid. Microanalytical and ^{1}H n.m.r. spectral data of **20a-d** showed presence of 1 mole of acetic acid as solvent of crystallization.

Reductive Dethiomethylation of 23 : Synthesis of 14

A suspension of **23** (1.0g, 4 mmol) in acetic acid (15 ml) and W-2 Raney Nickel (20g) was refluxed with stirring for 5 hr. The reaction mixture was filtered hot, washed with acetic acid, the filtrate concentrated under reduced pressure and

poured over cold water. The solid separated was filtered, dried and crystallized from acetic acid to give **14** as colourless solid, yield 0.65 gm (80%); m.p. 265-266°C (lit.[14] m.p. > 250°C, I.R. and ^{1}H n.m.r. spectra were superimposable)

Synthesis of 2-amino-7-aryl-4(3H)-pyrido[2,3-*d*]-pyrimidinone 30 : General Procedure :

A suspension of dithioacetal **29** (15 mmol) and **7** (15 mmol) in glacial acetic acid (45 ml) and water (30 ml) in the presence of catalytic amount of piperidine (2 drops) were refluxed with stirring for 18 hr. All the reactants dissolved completely under refluxing condition. The reaction mixture was concentrated to half the volume under reduced pressure and the residue poured over water to give **30** as yellow amorphous solid which was filtered, washed with water and methanol, acetone mixture and dried at 100°C for 1 hr. The product **30** thus obtained was crystallized from glacial acetic acid.

^{1}H n.m.r. spectra of **20a-d** showed a peak at δ 2.10 (s, 3H) which is found to be due to incorporation of 1 mole of acetic acid. This was also supported by elemental analysis of these compounds. However, the nature of association of acetic acid with these compounds is uncertain. The structure of **20a-f**, **23**, **26**, **28** and **30** were fully established from their spectral and analytical data which are given below.

2-Amino-5-methylthio-7-phenyl-4(3H)-pyrido[2,3-*d*]pyrimidinone [20a] was obtained as a yellow amorphous solid m.p. > 360°C,

reaction time 8hr, yield, 81%. Its I.R., ^{1}H n.m.r. and mass spectral data are given in the text. [Found : C, 55.61; H, 4.47; N, 16.49 calculated for $C_{16}H_{16}N_4O_3S$ (344.37): C, 55.80; H, 4.68; N, 16.27%].

2-Amino-5-methylthio-7-(4-methylphenyl)-4(3H)-pyrido[2,3-*d*]-pyrimidinone (20b) was obtained as a yellow amorphous solid; m.p. > 360°C; reaction time 8hr., yield, 78%, I.R. (Nujol) : ν_{max} = 3309, 3158, 1709, 1689, 1658 cm^{-1}; ^{1}H n.m.r. (TFA/$CDCl_3$) : δ = 2.40 (s, 3H, CH_3), 2.58 (s, 3H, SCH_3), 7.15 (s, 1H, H-6); 7.32 (d, J = 9Hz, $2H_{arom}$); 7.68 (d, J = 9Hz, $2H_{arom}$); m/z : 298 (M^+, 100%). [Found : C, 56.71; H, 5.23; N, 15.48 calculated for $C_{17}H_{18}N_4O_3S$ (358.4): C, 56.96; H, 5.06; N, 15.63%].

2-Amino-5-methylthio-7-(4-methoxyphenyl)-4(3H)-pyrido(2,3-*d*) pyrimidinone (20c) was obtained as a yellow amorphous solid; m.p. > 360°C; reaction time 8hr., yield, 75%; I.R. (Nujol) : ν_{max} = 3306, 3162, 1709, 1690, 1658 cm^{-1}; ^{1}H n.m.r. (TFA/$CDCl_3$): δ = 2.48 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3), 7.05 (d, J = 9Hz, $2H_{arom}$), 7.15 (s, 1H, H-6), 7.70 (d, J = 9Hz, $2H_{arom}$); m/z : 314 (M^+, 35%). [Found : C, 54.57; H, 4.89; N, 15.11 calculated for $C_{17}H_{19}N_4O_4S$ (375.4) : C, 54.38; H, 5.10; N, 14.92%].

2-Amino-5-methylthio-7-(4-chlorophenyl)-4(3H)-pyrido[2,3-*d*]pyrimidinone (20d) was obtained as a yellow amorphous solid; m.p. > 360°C; reaction time 8hr., yield, 76%; I.R. (Nujol); ν_{max} = 3303, 3158, 1709, 1689, 1679 cm^{-1}; ^{1}H n.m.r.

(DMSO-d_6) δ = 2.50 (s, 3H, SCH_3), 6.86 (s, 1H, H-6), 7.56 (d, J = 8Hz, $2H_{arom}$), 7.98 (d, J = 8Hz, $2H_{arom}$); m/z : 318 (20%). [Found : C, 50.61; H, 4.23; N, 14.98 calculated for $C_{16}H_{15}ClN_4O_3S$ (378.8): C, 50.72; H, 3.99; N, 14.79%].

2-Amino-5-methylthio-7-methyl-4(3H)pyrido[2,3-*d*]pyrimidinone (20e) was obtained as a yellow amorphous solid; m.p. > 360°C; reaction time 10hr., yield, 50%; IR (Nujol) : ν_{max} = 3418, 3078, 1709, 1691, 1664 cm^{-1}; ^1H nmr (TFA/$CDCl_3$) δ=2.50 (s, 3H, SCH_3), 2.55 (s, 3H, CH_3); 7.10 (s, 1H, H-6): m/z : 222 (M^+, 100%). [Found : C, 48.39; H, 4.41; N, 25.03 calculated for $C_9H_{10}N_4OS$ (222.2): C, 48.64; H, 4.53; N, 25.21%].

2-Amino-5-(n-propylthio)-7-phenyl-4(3H)-pyrido[2,3-*d*]-pyrimidinone (20f) was obtained as a yellow amorphous solid; m.p. > 360°C ; reaction time 20hr., yield, 60%; I.R. (Nujol) : ν_{max} = 3308, 3162, 1696, 1666 cm^{-1}; ^1H n.m.r. (TFA/$CDCl_3$) : δ = 0.98 (t, J = 7Hz, 3H, $SCH_2CH_2CH_3$), 1.80 (sext. J = 7Hz, 2H, $SCH_2CH_2CH_3$), 3.15 (t, J = 7Hz, 2H, $SCH_2CH_2CH_3$), 7.35 (s, 1H, H-6), 7.10-7.85 (m, $5H_{arom}$); m/z : 312 (M^+, 62%). [Found : C, 61.27; H, 4.93; N, 20.11 calculated for $C_{16}H_{16}N_4OS$ (312.3) : C, 61.53; H, 5.16; N, 19.94%].

2-Amino-5-methylthio-6,7-trimethylene-4(3H)-pyrido[2,3-*d*]-pyrimidinone (23) was obtained as a yellow amorphous solid; m.p. 303-304°C (d); reaction time 15hr., yield, 42%; I.R. (Nujol) : ν_{max} 3417, 3158, 1711, 1660, 1650 cm^{-1}; ^1H n.m.r. (TFA/$CDCl_3$) : δ = 2.0-2.31 (m, 2H, CH_2), 2.72 (s, 3H, SCH_3), 2.90-3.34 (t, 4H, CH_2); m/z : 248 (M^+, 68%). [Found : C,

53.46; H, 4.59; N, 22.41 calculated for $C_{11}H_{12}N_4OS$ (248.3) : C, 53.20; H, 4.87; N, 22.56%].

2-Amino-5-methylthio-6,7-methylene-4(3H)-pyrido[2,3-*d*]-pyrimidinone (26) was obtained as a yellow amorphous solid ; m.p. 310-311°C (d); reaction time 15hr., yield, 45%; I.R. (Nujol) : ν_{max} 3319, 3138, 1710, 1659, 1630 cm^{-1}; ^1H n.m.r. (TFA/$CDCl_3$) : δ = 1.10 - 1.90 (m, 4H, CH_2), 2.20 (s, 3H, SCH_3), 2.30-2.75 (m, 4H, CH_2); m/z : 262 (M^+, 62%). [Found : C, 55.13; H, 5.11; N, 21.55 calculated for $C_{12}H_{14}N_4OS$ (262.3): C, 54.94; H, 5.37; N, 21.36%].

2-Amino-5-methylthio-6,7(1',2'-dihydronapthalene)-4(3H)-pyrido [2,3-*d*]-pyrimidinone (28) was obtained as a yellow amorphous solid; m.p. > 360°C; reaction time 15hr., yield, 47%; I.R. (Nujol) : ν_{max} = 3379, 3295, 1659, 1650, 1643 cm^{-1}; ^1H n.m.r. (TFA/$CDCl_3$) : 2.65 (s, 3H, SCH_3), 2.50-3.25 (m, 4H, $(CH_2)_2$), 6.95-8.05 (m, $4H_{arom}$); m/z : 312 (M^+, 18%). [Found : C, 61.67; H, 4.26; N, 17.81 calculated for $C_{16}H_{14}N_4OS$ (310.3) : C, 61.92; H, 4.54; N, 18.05%].

2-Amino-7-phenyl-4(3H)pyrido [2,3-*d*] pyrimidinone [30] was obtained as a yellow amorphous solid; m.p. > 360°C; reaction time 18hr., yield, 52%; I.R. (Nujol) : ν_{max} = 3408, 3147, 1715, 1657 cm^{-1}; ^1H n.m.r. (TFA/$CDCl_3$) : 7.46-8.06 (m, 6H, $5H_{arom}$ & H-6), 9.03 (d, J = 9Hz, 1H, H-5). [Found : C, 65.31; H, 4.51; N, 23.76 calculated for $C_{13}H_{10}N_4O$ (238.2) : C, 65.54; H, 4.23; N, 23.52%].

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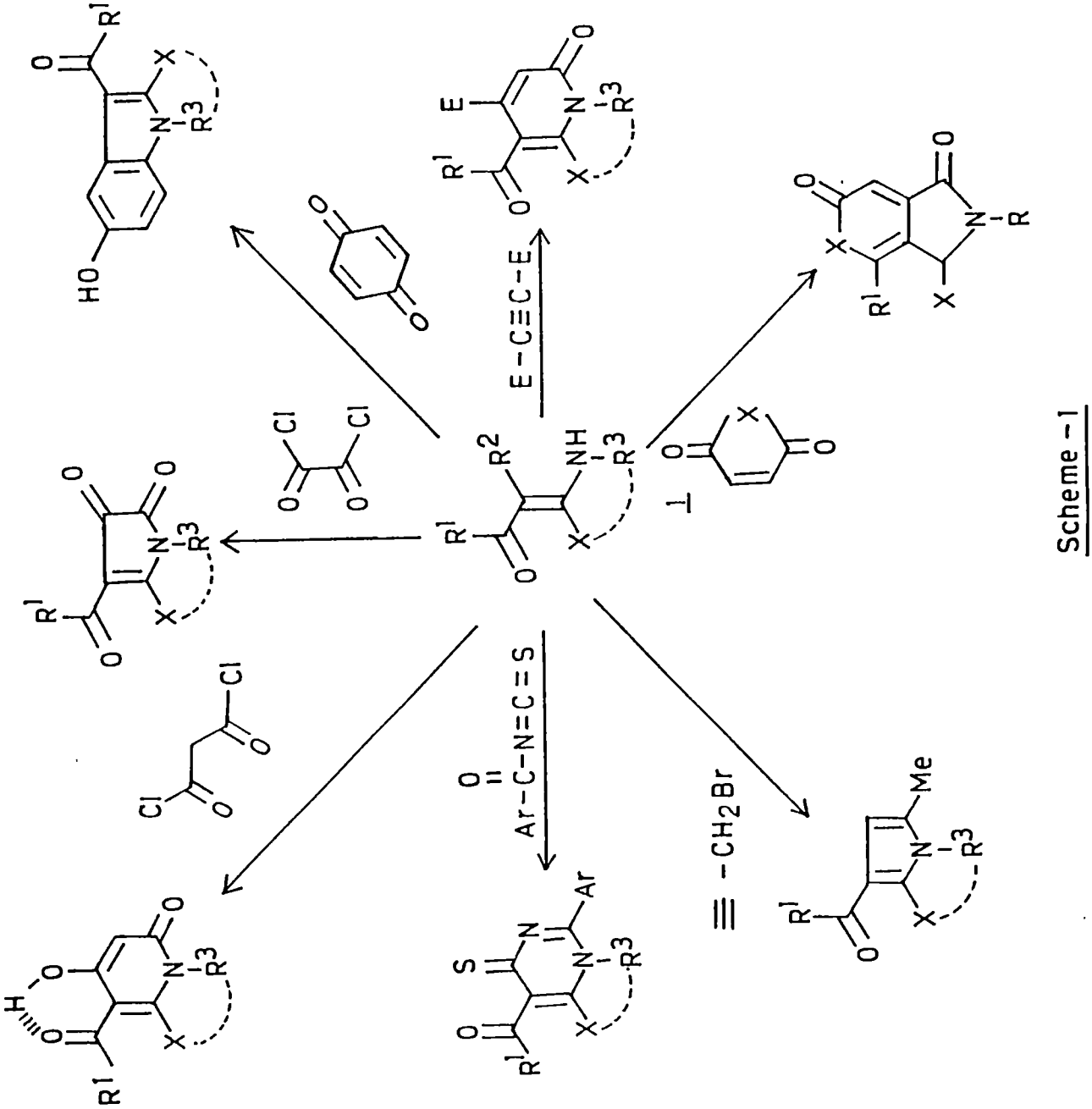
CHAPTER - VI

SYNTHESIS OF 5-AROYL-6-METHYLTHIO 1,2,3,4-TETRAHYDROPYRIMIDINES, PYRAZOLO [3,4-*d*]-4,5,6,7-TETRAHYDROPYRMIDINES AND PYRAZOLO[1,5-*a*]-1,2,3,4-TETRAHYDRO TRIAZINE DERIVATIVES

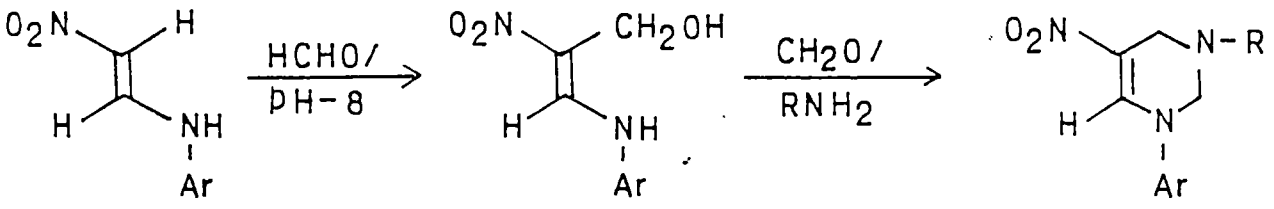
INTRODUCTION

Earlier work from this laboratory has demonstrated[1] α-oxoketene S,N- and N,N-acetals as useful functionalized enaminones which are easily prepared either from the corresponding S,S-acetals or directly from active methylene ketones. These S,N- and N,N-acetals are shown to react with various ambident electrophilic species to afford a variety of heterocyclic compounds. Thus a number of new general routes have been developed for the synthesis of heterocyclic compounds like indoles[2], pyrroles[3], pyrrole 2,3-diones[4], pyridones[5,6] pyrimidines[7], imidazoles[8,9,10], thiazoles[11] and condensed heterocycles like pyrrolopyrones[12] (Scheme 1) by cyclocondensation of S,N- and N,N-acetals with varies electrophiles like p-quinone, propargyl bromide, oxalyl chloride, acetylenic ester, malonyl chloride, acyl isothiocyanate, nitrosyl chloride, nitrosobenzene, thionyl chlroide and maleic anhydride respectively. We further



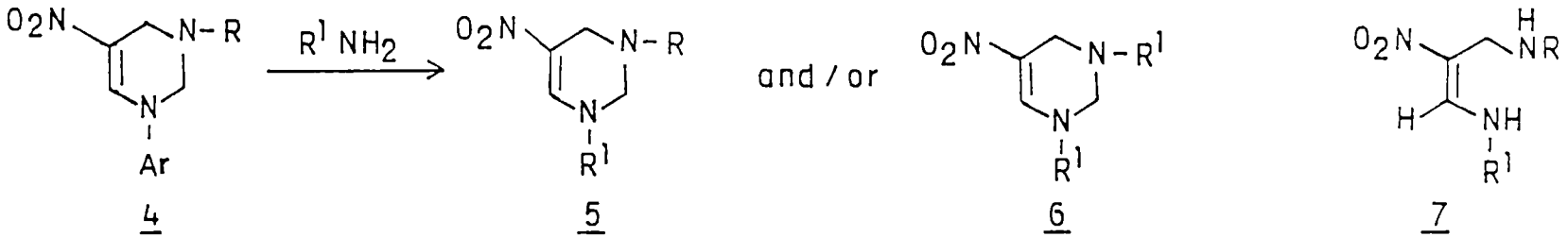
Scheme - 1

considered of interest to react these intermediates with formaldehyde and amines to afford 5-aroyl-6-methylthio-1,2,3,4-tetrahydro-pyrimidine derivatives 11 (Scheme V). Our main interest in compounds like 11 was to further exploit these compounds for the synthesis of tetrahydropyrimidine annulated heterocycles by reaction with bifunctional nucleophiles like hydrazine hydrate, hydroxylamine and guanidine etc (Scheme VI). Many of the condensed pyrimidine derivatives like pyrazolo[3,4-*d*]-pyrimidines and their mercapto analogs are known to possess biological activity[13-17]. However, the synthesis of the corresponding 4,5,6,7-tetrahydro derivatives has not been attempted and hence their biological activity has not been investigated. Our literature survey at this stage revealed that a few of the 5-nitro-1,3-disubstituted 1,2,3,4-tetrahydropyrimidine derivatives 4 have been prepared by reaction of nitroenamines with formaldehyde and primary amines (Scheme II)[18]. These reactions may be of the Mannich type or they may involve formation of carbinol 3 depending on the ratio of 2, formalin and primary amines (1:2:2). With the amounts of amine larger than two moles, transamination products 5,6,7 were formed in addition to 4 (Scheme II). Thus 2 with formaldehyde and benzylamine in boiling ethanol gave both 4 (Ar=4-ClC_6H_4; R=$CH_2C_6H_5$) and 5 (R=R^1=$C_6H_5CH_2$). Trans amination also accurs on preformed 5-nitro tetrahydropyrimidine 4 ——>5 or 6 on treatment with various amines especially benzylamine. A probable mechanism involving (1) ring opening of the pyrimidine 4 with loss of



2 3 4

Ar = 4-Cl C_6H_4 ; R = Me, Et, CH_2Ph ; 4-Cl C_6H_4



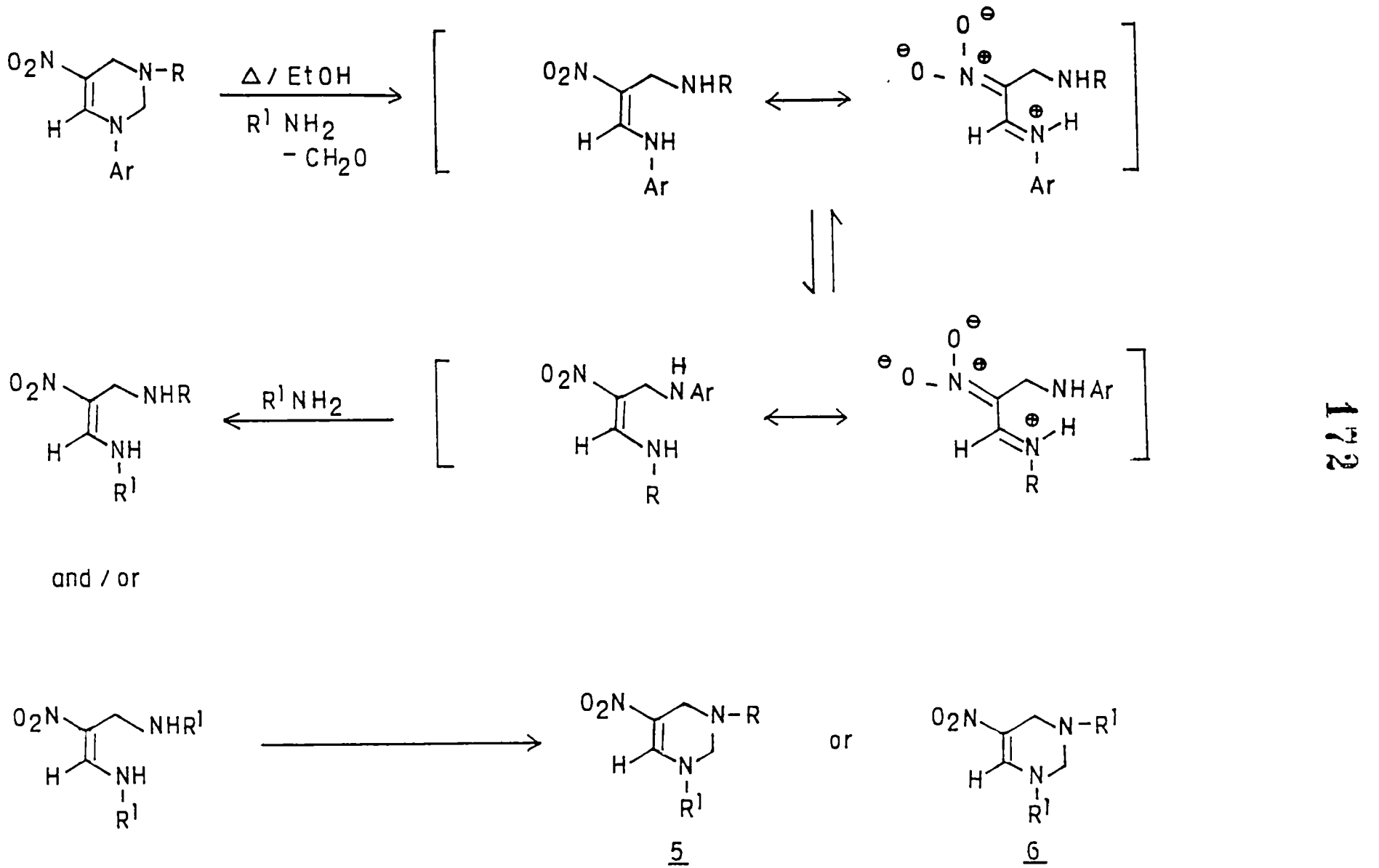
4 5 6 7

Ar = 4-Cl C_6H_4

R = Me, $CH_2C_6H_5$

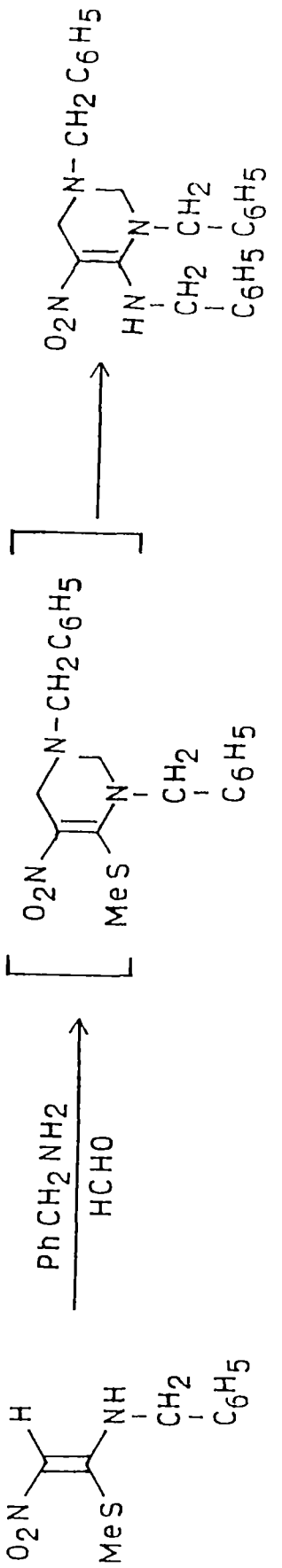
R^1 = Me or $C_6H_5CH_2$

Scheme II



5 or 6

Scheme III



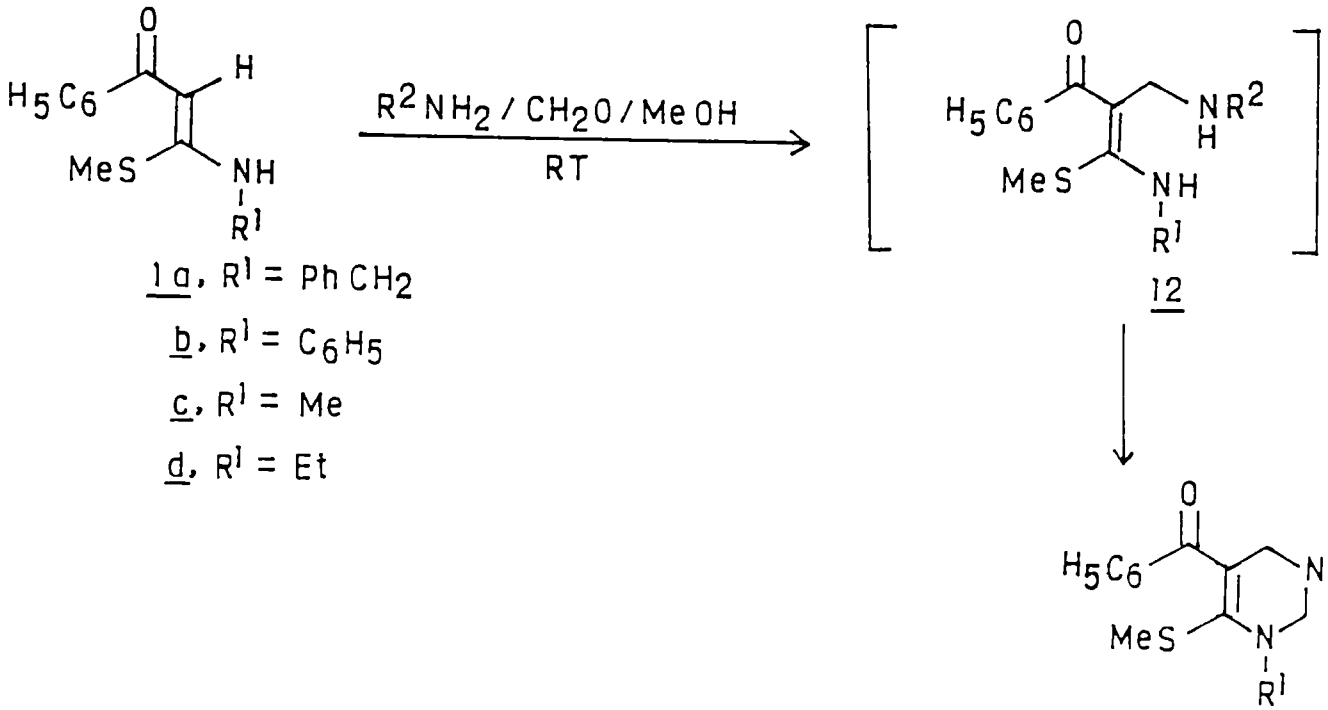
Scheme IV

a mole of formaldehyde to form a Schiff's base zwitter ion (2) replacement of the amine forming the Schiff's base and (3) reclosure of the ring by formaldehyde was suggested for this novel transamination reactions (Scheme III). In an another isolated report[19], nitroketene S,N-acetals 8 is reported to give 1,3-dibenzyl-5-nitro-6-benzylamino-1,2,3,4-tetrahydro pyrimidine 10 when reacted with excess benzylamine and formaldehyde. Apparently the initially formed 6-methylthiopyrimidine 9 undergoes facile displacement with benzylamine to give the observed product 10 (Scheme IV). However no extensive study or generalization of this reaction has been carried out by the authors. We therefore studied the reaction of α-oxoketene S,N-acetals with formaldehyde and primary amines to give 5-aroyl-6-methylthio-1,2,3,4-tetrahydropyrimidines 11 (Scheme V). A few of the aminopyrazoles have also been reacted with formaldehyde and primary amines to afford tetrahydropyrimidine annulated pyrazoles (Scheme VII). The results of these studies have been reported in this chapter.

RESULTS AND DISCUSSION

Synthesis of 5-Aroyl-6-Methylthio-1,2,3,4,-Tetrahydro pyrimidines

A few selected S,N-acetals 1a-d derived from aliphatic and aromatic amines were prepared according to our earlier reported procedure[20]. When 1a, formaldehyde and benzylamine were stirred at room temperature in methanol, work-up of the



1a, R^1 = $PhCH_2$

b, R^1 = C_6H_5

c, R^1 = Me

d, R^1 = Et

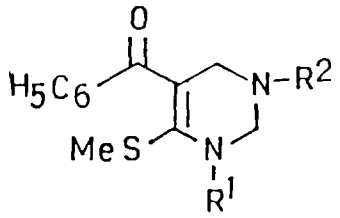
11a-g (Table 1)

Scheme V

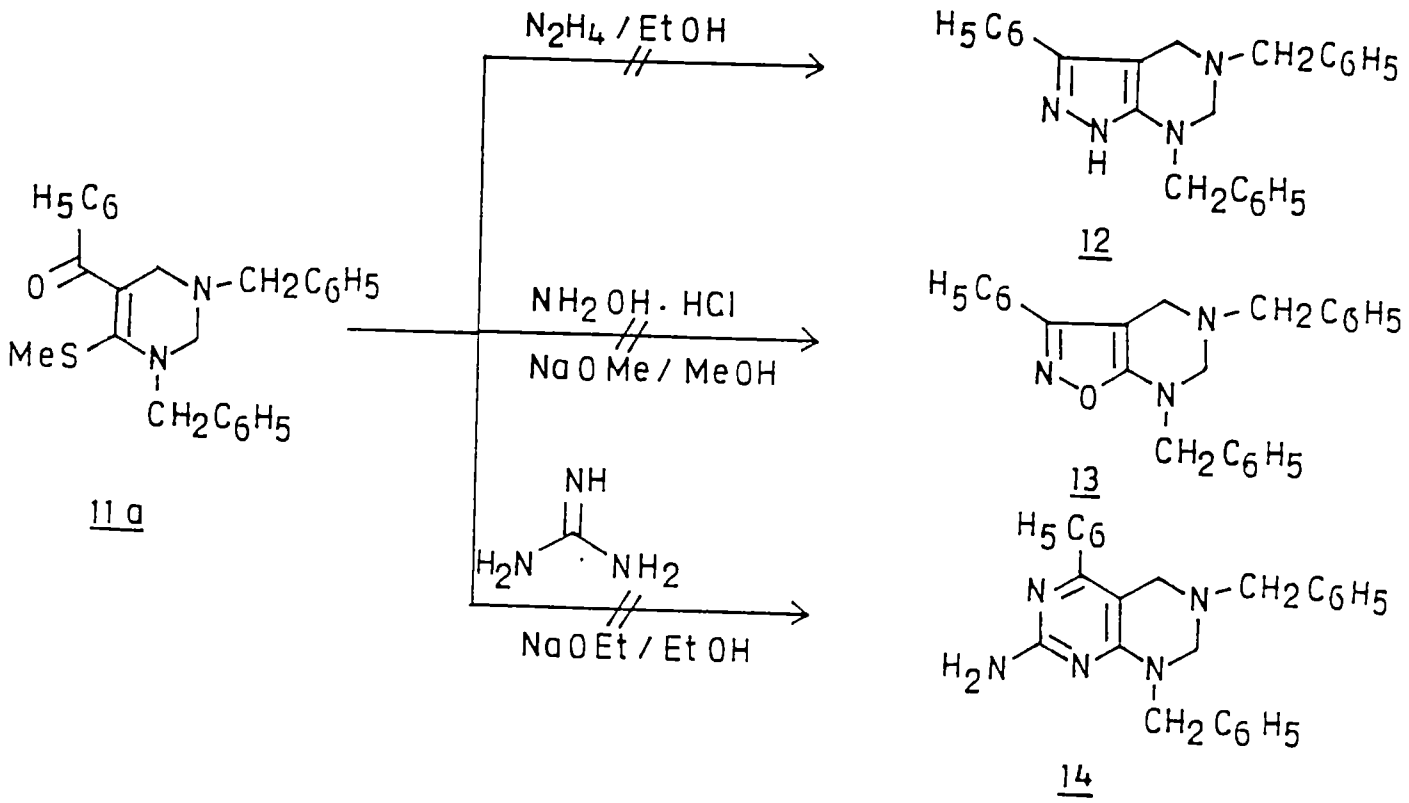
Table

1,3-Disubstituted-5-benzoyl-6-methylthio

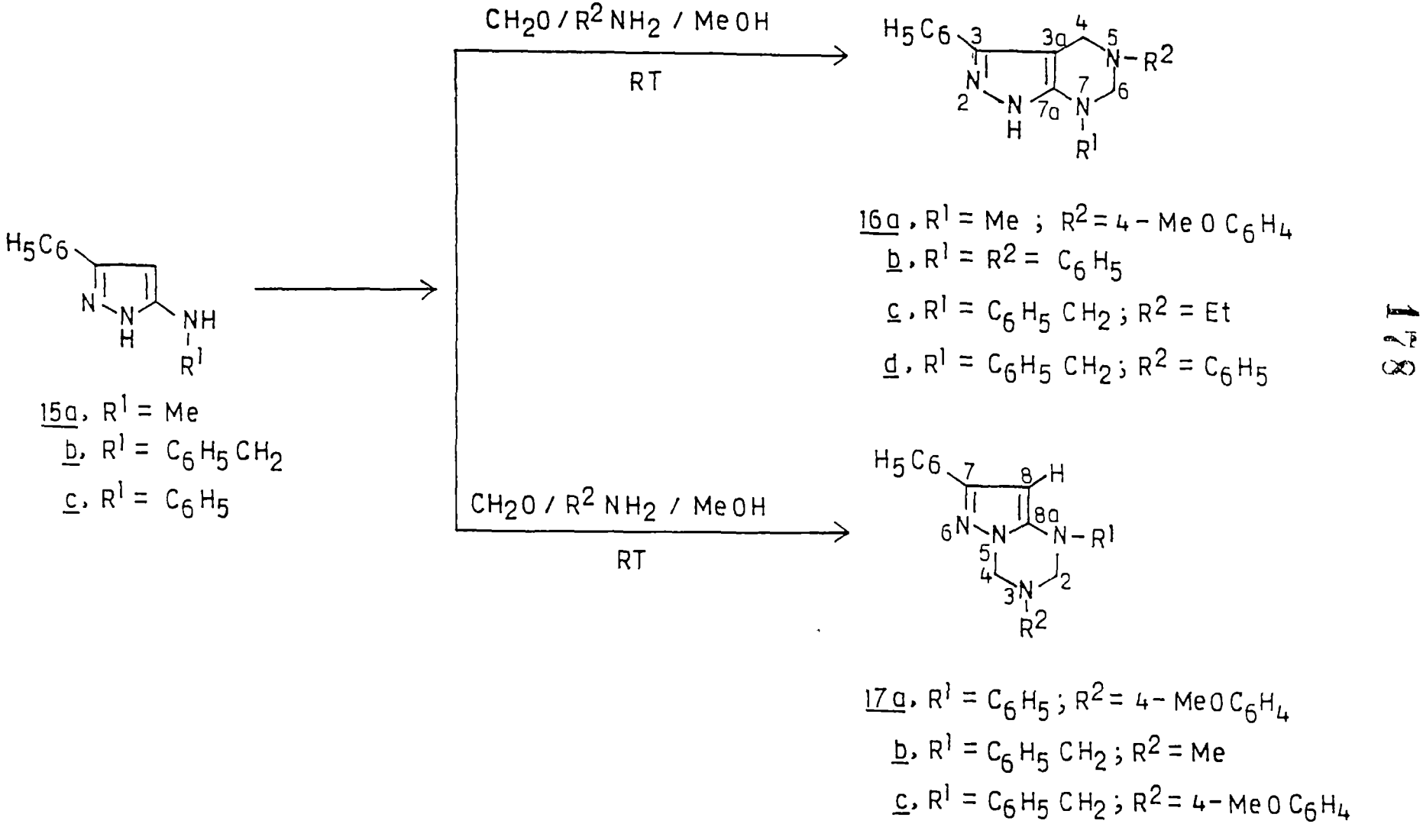
1,2,3,4-tetrahydropyrimidines 11a-g prepared



11	R^1	R^2	% yield
11a	Ph CH_2	Ph CH_2	77
11b	Ph CH_2	Ph	70
11c	Ph CH_2	4-Cl C_6H_4	75
11d	Ph	Ph CH_2	75
11e	Ph	Ph	72
11f	Me	Ph CH_2	61
11g	Et	Ph CH_2	65


N2H4 / EtOH
NH2OH · HCl
NaOMe / MeOH
NaOEt / EtOH
H5C6
O
MeS
N-CH2C6H5
CH2C6H5
11a
12
13
14

Scheme VI



15a, R^1 = Me
b, R^1 = $C_6H_5CH_2$
c, R^1 = C_6H_5

16a, R^1 = Me ; R^2 = 4-MeOC_6H_4
b, R^1 = R^2 = C_6H_5
c, R^1 = $C_6H_5CH_2$; R^2 = Et
d, R^1 = $C_6H_5CH_2$; R^2 = C_6H_5

17a, R^1 = C_6H_5 ; R^2 = 4-MeOC_6H_4
b, R^1 = $C_6H_5CH_2$; R^2 = Me
c, R^1 = $C_6H_5CH_2$; R^2 = 4-MeOC_6H_4

Scheme VII

reaction mixture yielded (85%) a colourless crystalline solid which was characterized as 1,3-dibenzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidine **11a** on the basis of spectral and analytical data. Thus **11a** analyzed for $C_{26}H_{26}N_2OS$ and its mass spectrum exhibited very weak molecular ion peak (M^+,414,2%) while the base peak was present at M/z 399 ($^+$-15,17%). The infra-red spectrum of **11a** showed strong peaks at 1580 and 1630 cm^{-1} due to highly delocalized double bond and carbonyl group stretching frequencies of enaminone functionality. The structure of **11a** was finally confirmed by its ^1H n.m.r. spectrum (CCl_4) which showed a singlet (3H) due to methylthio group at δ 2.0 while the four singlet peaks at δ 3.47 (2H), 3.55 (2H), 3.60 (2H) and 4.39 (2H) were assigned to two benzylic methylene protons, 4-CH_2 and NCH_2N methylene resonance respectively. The other tetrahydro-pyrimidines **11b-g** were similary obtained in 70-88% overall yields by reacting the respective S,N-acetals with formaldehyde and various amines under identical conditions. The spectral and analytical data of the products 11b-g were in conformity with the assigned structures (Experimental). The pyrimidines **11a-g** were found to be stable and could be crystallyzed from chloroform/hexane. However the pyrimidines **11f** and **11g** gave complex mixture of products on prolonged refluxing in either methanol or ethanol. Attempted synthesis of tetrahydropyrimidine annulated heterocycles **12-14** by reacting **11a** with either hydrazinehydrate or hydroxylamine hydrochloride or guanidine was not successful which resulted

in the formation of only intractable reaction mixtures. This is probably due to cleavage of the fragile tetrahydropyrimidine ring in the presence of these nucleophilic species under experimental conditions.

Synthesis of Pyrazolo[3,4-*d*]-4,5,6,7-Tetrahydropyrimidines and pyrazolo[1,5-*a*] 1,2,3,4-Tetrahydrotriazine Derivatives

From the earlier work from this laboratory[21] a few of the previously prepared 3(5)-alkyl/arylaminopyrazoles were employed as bifunctional nucleophiles in tetrahydropyrimidine annulation with formaldehyde and amines to give either pyrazolo[3,4-*d*]pyrimidines 16 or pyrazolo[1,5-*a*] traizine 17 in good yields (Scheme VII). We have now extended this reaction and synthesized some new pyrazolo pyrimidines 16 and pyrazolotriazines 17 bearing different substituents with a view to screening for their biological activity and examine the various factors responsible for the formation of either 16 or 17 (Scheme VII). When the 3(5)-methylaminopyrazole 15a was reacted with formaldehyde and 4-methoxyaniline in methanol, the corresponding pyrazolo [3,4-*d*]pyrimidine 16a was obtained in 75% yield. In the previous work[21] 3(5)-arylaminopyrazoles 15c were reported to give only pyrazolotriazine derivatives 17 when reacted with various amines under these conditions and the corresponding 7-aryl pyrazolo pyrimidines 16 could not be synthesized. Thus anilinopyrazole 15c afforded 1,3-diaryl pyrazolotriazine 17a exclusively when reacted with formalin and 4-methoxyaniline (1:2:1) under identical

conditions (Scheme VII) (15 hr). However when a solution of formalin and aniline in methanol was added slowly to a solution of anilinopyrazole **15c** in methanol for prolonged time (48 hr), the corresponding 5,7-diphenyl pyrazolo [3,4-*d*] pyrimidine **16b** was obtained as an exclusive product (80%). Similarly the corresponding 1-alkyl (or arylalkyl)pyrazolo[1,5-*a*]triazines **17** could not be obtained from the corresponding 3(5)-alkylamino-pyrazole which afforded only pyrazolo[3,4-*d*]pyrimidines **16** when reacted with various amines under the above described conditions. Thus 3(5)-benzylaminopyrazole **15b** gave the respective pyrazolopyrimidines **16c** and **16d** exclusively on treatment with formalin, ethylamine or aniline (1:2:1) in methanol (12 hr). However when **15b** was reacted with formalin and excess of methylamine or 4-methoxyaniline (1:2:2), the corresponding 1-benzyl pyrazolo[1,5-*a*]triazines **17b** and **17c** were formed exclusively (Scheme VII) under similar condition for prolonged time (40 hr).

Thus by changing the reaction conditions and ratio of formalin and amines it was possible to obtain either pyrazolo[3,4-*d*]-pyrimidine **16** or pyrazolo[1,5-*a*]triazine **17** from either 3(5)-arylamino- or 3(5)-alkylaminopyrazoles. The products **16** were distinguished from **17** by the presence of signal due to H-8 proton between δ 5-6 (s,1H) in their ^{1}H n.m.r. spectra. Besides, the band due to NH stretching frequency present between 3100-3250 cm^{-1} in the I.R. spectra of **16a-d** was clearly absent in those of **17a-c**. The condensed pyrazoles **16a-d** and **17a-c** were tested for xanthine oxidase

inhibition and herbicidal activity, however they were found to be inactive.

EXPERIMENTAL

Melting points were determined on Thomas Hoover capillary melting point apparatus and are uncorrected. The reactions were monitored by TLC on silica gel. The I.R. spectra were recorded on a Perkin Elmer-297 spectrophotometer and frequencies are expressed in cm^{-1} and the ^{1}H n.m.r. spectra on a Varian EM-390 (90 MHz) spectrometer using TMS as internal standard and the chemical shifts are expressed as δ (PPM) down field from TMS. The mass spectra were obtained on Jeol D-300 mass spectrometer and relative intensities are expressed in percentage. The microanalysis were obtained on Heraeus CHN-O-RAPID instrument.

STARTING MATERIALS

The S,N-acetals 1a-d were prepared according to the procedure reported in chapter 3. Where as 3(5)-Alkyl/arylaminopyrazoles 15a-c were prepared by reacting the respective oxoketene S,N-acetals with hydrazine hydrate in refluxing ethanol as reported in the previously published paper.[22]

Reaction of α-oxoketene S,N-acetals 1a-d or 3(5)-Alkylamino/arylamino-5(3)-phenylpyrazoles 15a-c with Primary amines and Formaldehyde; synthesis of 5-Aroyl-6-methylthio-1,2,3,4-Tetrahydropyrimidines 11a-g, 5,7-disubstituted tetrahydropyrazolo [3,4-*d*]pyrimidines 16a-d and ,3-disubstituted tetrahydropyrazolo [1,5-*a*]triazines 17a-c; General Procedure :

A solution of S,N-acetal 1a-d (10 mmole) or pyrazole 15a-c (10 mmol) in methanol (30 ml) was added to a stirred solution of formaldehyde (20 mmol, 40% solution) and amines (10 mmol) in methanol (25 ml) and the reaction mixture was stirred at room temperature for 12-48 hr (monitored by TLC). In most of the cases, the products 11,16 and 17 separated out as colourless solids, which were filtered, washed with methanol (2x3 ml), dried and crystallyzed from chloroform/hexane to give pure products 11a-g, 16a-d and 17a-c.

In the case of pyrazolopyrimidines 16a-b and the triazine 17b, the solid did not separate out and the reaction mixture was worked up by removing methanol under reduced pressure. The residue was poured over ice-water (100 ml), extracted with chloroform (2x50 ml), dried (sodium sulfate) and the chloroform was removed on water bath to give either 16 or 17 which were further purified by crystallization from chloroform/hexane.

For the preparation of pyrazolopyrimidine 16b, reverse addition was followed ie a solution of formalin and aniline was added slowly to the solution of anilinopyrazole. Similarly for the preparation of pyrazolotiazines 7b-c, the ratio of pyrazole : formalin : amine was taken as 1:2:2 (in moles). Spectral and analytical data for the compounds 11a-g, 16a-d and 17a-c were found to be in conformity with the assigned structures which are given below.

1,3-Dibenzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydro-pyrimidine [11a] was obtained as a colourless crystalline solid; m.p. 105-106°C; reaction time 12hr., yield, 77%; I.R. (KBr): ν_{max}=1630, 1580 cm^{-1}; ^1H n.m.r ($CDCl_3$): δ = 2.00 (s, 3H, SCH_3), 3.48 (s, 2H, CH_2), 3.55 (s, 2H, CH_2), 3.60 (s, 2H, CH_2) 4.40 (s, 2H, NCH_2N), 6.80-7.49 (m, $13H_{arom}$), 7.56-7.90 (m, $2H_{arom}$), m/z 399 (M^+-15,17%); 248 (11%). [Found : C, 75.49; H, 6.17; N, 6.49 calculated for $C_{26}H_{26}N_2OS$ (414.5): C, 75.33; H, 6.32; N, 6.75%].

1-Benzyl-3-phenyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydro-pyrimidine [11b] was obtained as a colourless crystalline solid; m.p. 96-97°C; reaction time 12 hr., yield 70%; I.R. (KBr): ν_{max} = 1582, 1550, 1520, 1465 cm^{-1}; ^1H n.m.r ($CDCl_3$) : δ=2.35 (s, 3H, SCH_3), 4.45 (s, 2H, CH_2), 4.52 (s, 2H, CH_2), 5.51 (s, 2H, NCH_2N), 7.10-7.42 (m, $13H_{arom}$), 7.50-7.82 (m, $2H_{arom}$). [Found : C, 74.68; H, 5.81; N, 6.72 Calculated for $C_{25}H_{24}N_2OS$ (400.5): C, 74.96; H, 6.04; N, 6.99%].

1-Benzyl-3-(4-Chlorophenyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidine [11c] was obtained as a colourless crystalline solid; m.p. 129-130°C; reaction time 12 hr., yield, 76%; I.R. (KBr): ν_{max} = 1580, 1540, 1518, 1460 cm^{-1}; ^1H n.m.r ($CDCl_3$): δ = 2.40 (s, 3H, SCH_3); 4.45 (s, 2H, CH_2), 4.50 (s, 2H, CH_2) 5.52 (s, 2H, NCH_2N), 7.08-7.33 (m, $12H_{arom}$), 7.65-7.50 (m, $2H_{arom}$). [Found : C, 69.29; H, 5.07; N, 6.65 calculated for $C_{25}H_{23}ClN_2OS$ (434.9): C, 69.03; H, 5.32; N, 6.44%].

1-Phenyl-3-benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydro-pyrimidine [11d] was obtained as a colourless crystalline solid; m.p. 155-156°C; reaction time 12hr., yield, 75%; I.R. (KBr) : ν_{max} = 1620, 1550 cm^{-1}; ^1H n.m.r ($CDCl_3$) : δ = 2.65 (s, 3H, SCH_3), 3.65 (s, 2H, CH_2), 3.71 (s, 2H, CH_2), 4.31 (s, 2H, NCH_2N), 6.85-7.58 (m, $13H_{arom}$), 7.60-7.95 (m, $2H_{arom}$) m/z 385 (M^+-15, 17%) 281 (1%) 234 (98%). [Found : C, 74.72; H, 6.29; N, 7.27 calculated for $C_{25}H_{24}N_2OS$ (400.5): C, 74.96; H, 6.03; N, 6.99%].

1,3-Diphenyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydro-pyrimidine [11e] was obtained as a colourless crystalline solid; m.p. 166-167°C; reaction time 12hr., yield, 72%; I.R. (KBr):ν_{max} = 1620, 1550 cm^{-1}; ^1H nmr ($CDCl_3$) : δ = 1.70 (s, 3H, SCH_3), 4.14 (s, 2H, CH_2), 4.55 (s, 2H, NCH_2N) 6.34-7.46 (m, $13H_{arom}$), 7.50-7.90 (m, $2H_{arom}$),m/z 374 (M^+-15,37%), 234 (98%). [Found : C, 74.27; H, 5.49; N, 7.51 calculated for $C_{24}H_{22}N_2OS$ (386.5): C, 74.50; H, 5.73; N, 7.24%].

1-Methyl-3-benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydro-pyrimidine [11f] was obtained as a colourless solid; m.p. 129-130°C; reaction time 12hr., yield, 69%; I.R. (KBr): ν_{max} = 1605, 1590, 1550 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 1.91 (s, 3H, SCH_3): 2.89 (s, 3H, NCH_3), 3.45 (s, 2H, CH_2), 3.68 (s, 4H, NCH_2N, NCH_2Ph), 7.05-7.48 (m, $8H_{arom}$), 7.50-7.85 (m, $2H_{arom}$), m/z 338 (M^+,2%), 323 (M^+15, 79%), 172 (100%). [Found : C, 71.23; H, 6.41; N, 8.01 calculated for $C_{20}H_{22}N_2OS$ (338.4): C, 70.98; H, 6.55; N, 8.28].

1-Ethyl-3-benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidine [11g] was obtained as a colurless solid; m.p. 135-136°C; reaction time 12hr., yield, 65%; I.R.(KBr) : ν_{max} = 1600, 1592, 1530 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ = 1.04 (t, J = 7 Hz, 3H, CH_2CH_3), 1.91 (s, 3H, SCH_3), 3.31 (q, J = 7Hz, 2H, CH_2), 3.42 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 3.70 (s, 2H, NCH_2N), 6.92-7.41 (m, $8H_{arom}$), 7.45-7.75 (m, $2H_{arom}$), m/z 337 (M^+-15,34%), 186 (52%). [Found : C, 71.72; H, 7.11; N, 7.68 calculated for $C_{21}H_{24}N_2OS$ (352.4): C, 71.56; H, 6.86; N, 7.95%].

3-Phenyl-5-(4-methoxyphenyl)-7-methyl pyrazolo [3,4-*d*]-4,5,6,7-tetrahydropyrimidine [16a] was obtained as a colourless solid; m.p. 194-196°C; reaction time 12hr., yield, 82%; I.R. (KBr) : ν_{max} = 3225, 1595, 1565, 1505 cm^{-1}; ^1H n.m.r. ($CDCl_3$); δ = 2.66 (s, 3H, N-CH_3), 3.21 (s, 3H, OCH_3) 4.28 (s, 2H, CH_2), 4.49 (s, 2H, NCH_2N), 6.78-7.65 (m, $9H_{arom}$), 8.95 (s, 1H, NH), m/z 320 (m^+, 100%). [Found : C, 71.01; H, 6.57; N, 17.32 calculated for $C_{19}H_{20}N_4O$ (320.3): C, 71.24; H, 6.29; N, 17.49%].

3,5,7-Triphenyl pyrazolo[3,4-*d*]-4,5,6,7-tetrahydropyrimidine [16b] was obtained as a colourless solid; m.p. 223-224°C; reaction time 48hr., yield, 76%; I.R. (KBr) : ν_{max} = 3250, 1598, 1518, 1494 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 4.61 (s, 2H, CH_2), 5.08 (s, 2H, NCH_2N), 6.41-7.78 (m, $15H_{arom}$), 8.11 (s, 1H, NH), m/z 352 (M^+, 21%), 247 (100%). [Found : C, 78.09; H, 5.89; N, 15.62 calculated for $C_{23}H_{20}N_4$ (352.4); C, 78.38; H, 5.72; N, 15.89%].

3-Phenyl-5-ethyl-7-benzyl pyrazolo[3,4-*d*]-4,5,6,7-tetrahydropyrimidine [16c] was obtained as a colourless solid, m.p. 156-157°C; reaction time 12 hr., yield, 90%; I.R. (KBr): ν_{max} = 3225, 1590, 1560, 1538 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 0.95 (t, 7Hz, 3H, CH_2CH_3), 2.55 (q, J = 7Hz, 2H, CH_2CH_3); 3.70 (s, 2H, CH_2), 3.85 (s, 2H, CH_2), 4.33 (s, 2H, NCH_2N), 7.00 - 7.75 (m, $10H_{arom}$), 8.06 (s, 1H, NH),. [Found : C, 75.19; H, 6.82; N, 17.79 calculated for $C_{20}H_{22}N_4$ (318.4) : C, 75.43; H, 6.96; N, 17.59%].

3,5-Diphenyl-7-benzylpyrazolo [3,4-*d*]-4,5,6,7-tetrahydropyrimidine [16d] was obtained as a colourless solid ; m.p. 170-171°C; reaction time 12 hr., yield, 85%; I.R. (KBr) : ν_{max} = 3202, 1590, 1563, 1544 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 4.35 (s, 4H, CH_2), 4.45 (s, 2H, NCH_2N), 6.70-7.85 (m, $15H_{arom}$), 8.35 (s, 1H, NH), m/z 366 (M^+, 70%) 365 (49%), 261 (69%), 260(100%). [Found : C, 78.82; H, 6.26; N, 15.03 calculated for $C_{24}H_{22}N_4$ (366.4): C, 78.66; H, 6.05; N, 15.29%].

1,7-Diphenyl-3-(4-methoxyphenyl)pyrazolo[1,5-*a*]-1,2,3,4-tetrahydrotriazine [17a] was obtained as a colourless solid; m.p. 152-153°C; reaction time 15 hr., yield, 95%; I.R. (KBr): ν_{max} = 1580, 1550, 1510 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 3.60 (s, 3H, OCH_3), 4.95 (s, 2H, CH_2), 5.50 (s, 2H, CH_2), 5.85 (s, 1H, H-8), 6.60-7.82 (m, $14H_{arom}$), m/z 382 (M^+, 37%), 247 (100%), 246 (62%). [Found : C, 75.53; H, 5.59; N, 14.86 calculated for $C_{24}H_{22}N_4O$ (382.4) : C, 75.37; H, 5.80; N, 14.65%].

1-Benzyl-3-methyl-7-phenyl-pyrazolo[1,5-*a*]-1,2,3,4-tetrahydrotriazine [17b] was obtained as a colourless solid; m.p. 110-111°C; reaction time 40 hr., yield, 90%; I.R. (KBr): ν_{max} = 1582, 1570 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 2.60 (s, 3H, NCH_3), 3.85 (s, 2H, CH_2), 4.20 (s, 2H, CH_2) 4.83 (s, 2H, CH_2), 5.51 (s, 1H, H-8), 6.80-7.65 (m, $10H_{arom}$); m/z 304 (M^+, 12%), 261 (11%). [Found : C, 74.69; H, 6.81; N, 18.68 calculated for $C_{19}H_{20}N_4$ (304.3): C, 74.98; H, 6.62; N, 18.41%].

1-Benzyl-3-(4-methoxyphenyl)-7-phenylpyrazolo [1,5-*a*]-1,2,3,4-tetrahydrotriazine [17c] was obtained as a colourless solid; m.p. 205-206°C; reaction time 40 hr., yield, 90%; I.R. (KBr) : ν_{max} = 1560, 1505 cm^{-1}; ^1H n.m.r. ($CDCl_3$) : δ = 3.69 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 5.63 (s, 1H, H-8),6.35-7.70 (m, $9H_{arom}$). m/z 430 (M^+, 11%), 432 (4%). [Found : C, 75.58; H, 5.89; N, 14.39 calculated for $C_{25}H_{24}N_4O$ (396.4) : C, 75.74; H, 6.10; N, 14.13%].

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