SYNTHETIC STUDIES ON HETEROCYCLES USING OXOKETENE - S,S-, S, N - AND O,S-ACETALS

ABSTRACT

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SCHOOL OF PHYSICAL SCIENCES

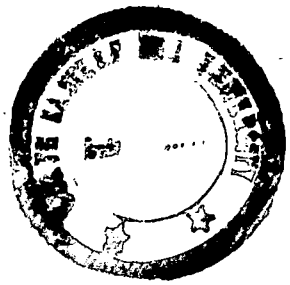
A THESIS

SUBMITTED

IN

FULFILMENT OF THE REQUIREMENT FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY



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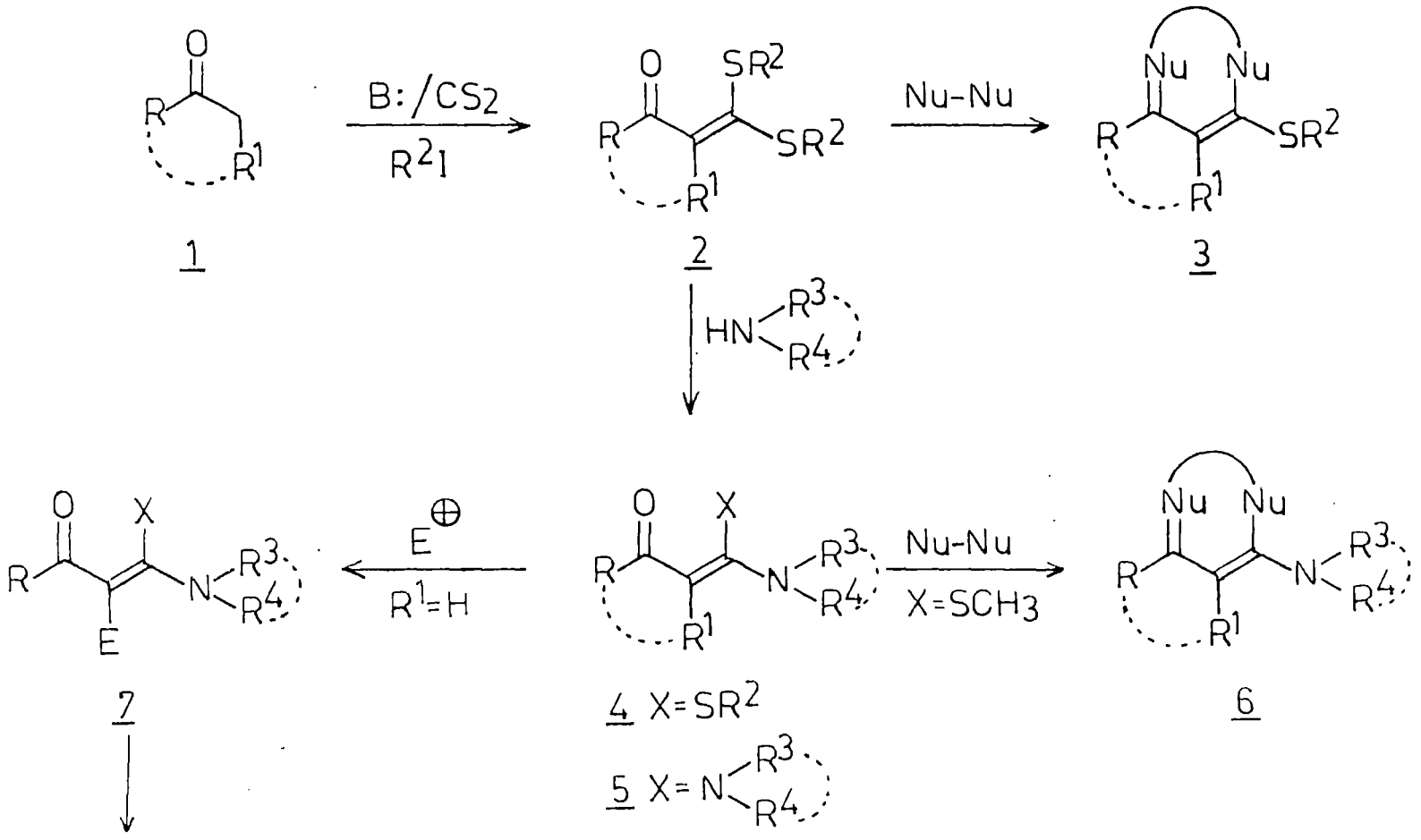
1989

The α-oxoketene dithioacetals of general formula 2 were first reported by Kelber and co-workers[1] in 1910. Improved methods for the synthesis of these compounds have been subsequently developed[2-4], and they can now be prepared, often in one pot reaction by treating the enolate anions with carbon disulphide followed by alkylation. They can also be converted into the corresponding S,N[5], N,N[6]- and O,S-acetals[7] although there are direct methods for the synthesis of S,N-acetals from active methylene compounds[8-11]. The α-oxoketene dithioacetals posses 1,3-electrophilic centres with a discrete dissymmetry in their electrophilic property, which makes these compounds follow regiospecific attack by nucleophiles depending on their nucleophilicity. Their 1,3-electrophilic reactivity has been extensively exploited for the construction of regio-selective new C-C bonds involving either 1,2 or 1,4-nucleophilic addition leading to a diverse product range.

Similarly, the α-oxoketene S,N- and N,N-acetals exhibit 1,3-electrophilicity substantially inversed so that the β-carbon becomes more electrophilic than the oxo carbon. The nucleophilic reagents therefore preferentially add in the 1,4 fashion, in these systems.

The discriminating 1,3-electrophilicity in the α-oxoketene dithioacetals and the S,N-acetals was exploited in the present investigation as a key theme to develop novel routes for the synthesis of heterocycles. Thus, the α-oxoketene dithioacetals 2 when reacted[12] with hydroxylamine hydrochloride in the presence of sodium methoxide (pH=9) the corresponding 5-alkylthio-3-arylisoxazoles 8 were formed exclusively confirming the

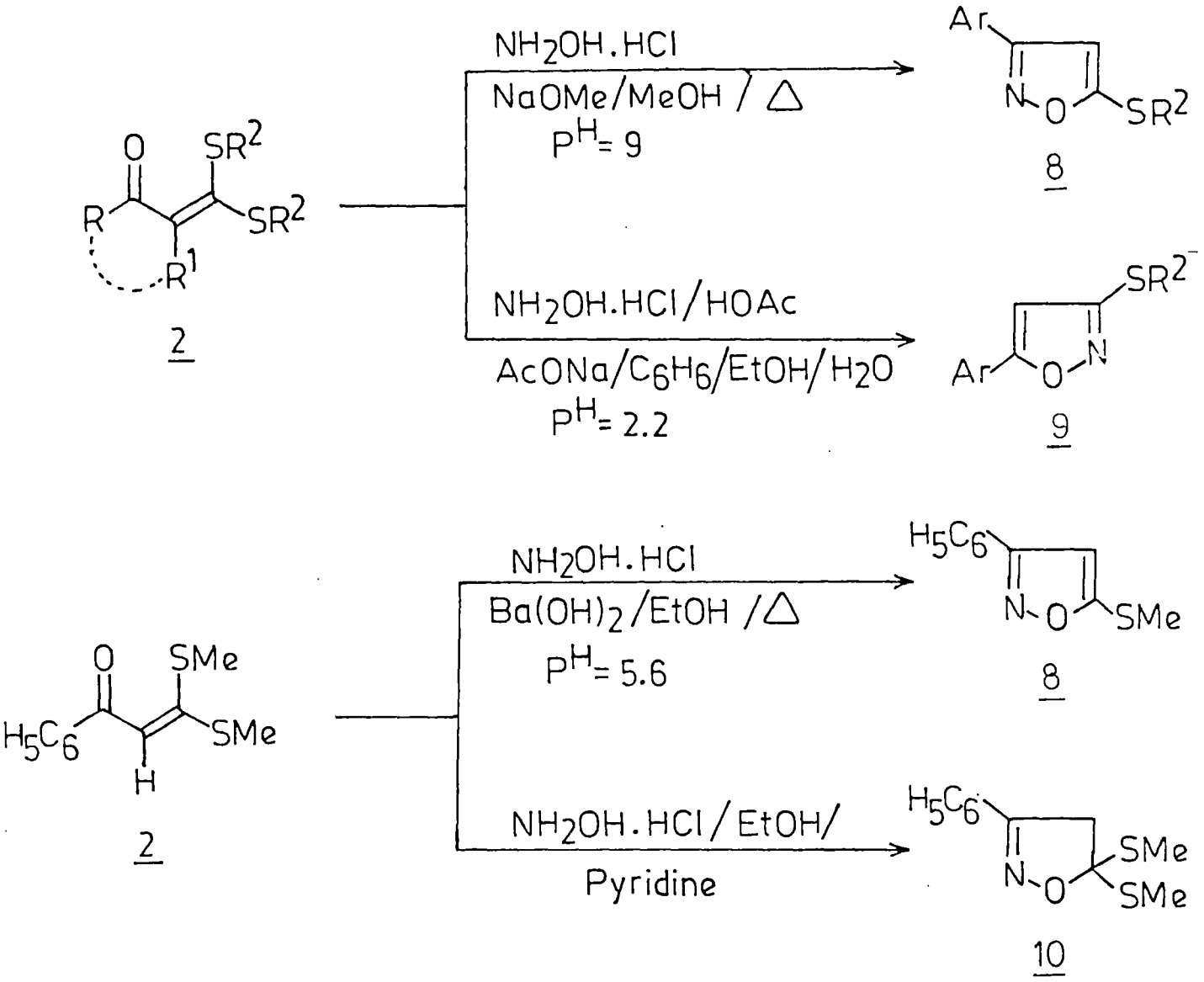


Scheme 1

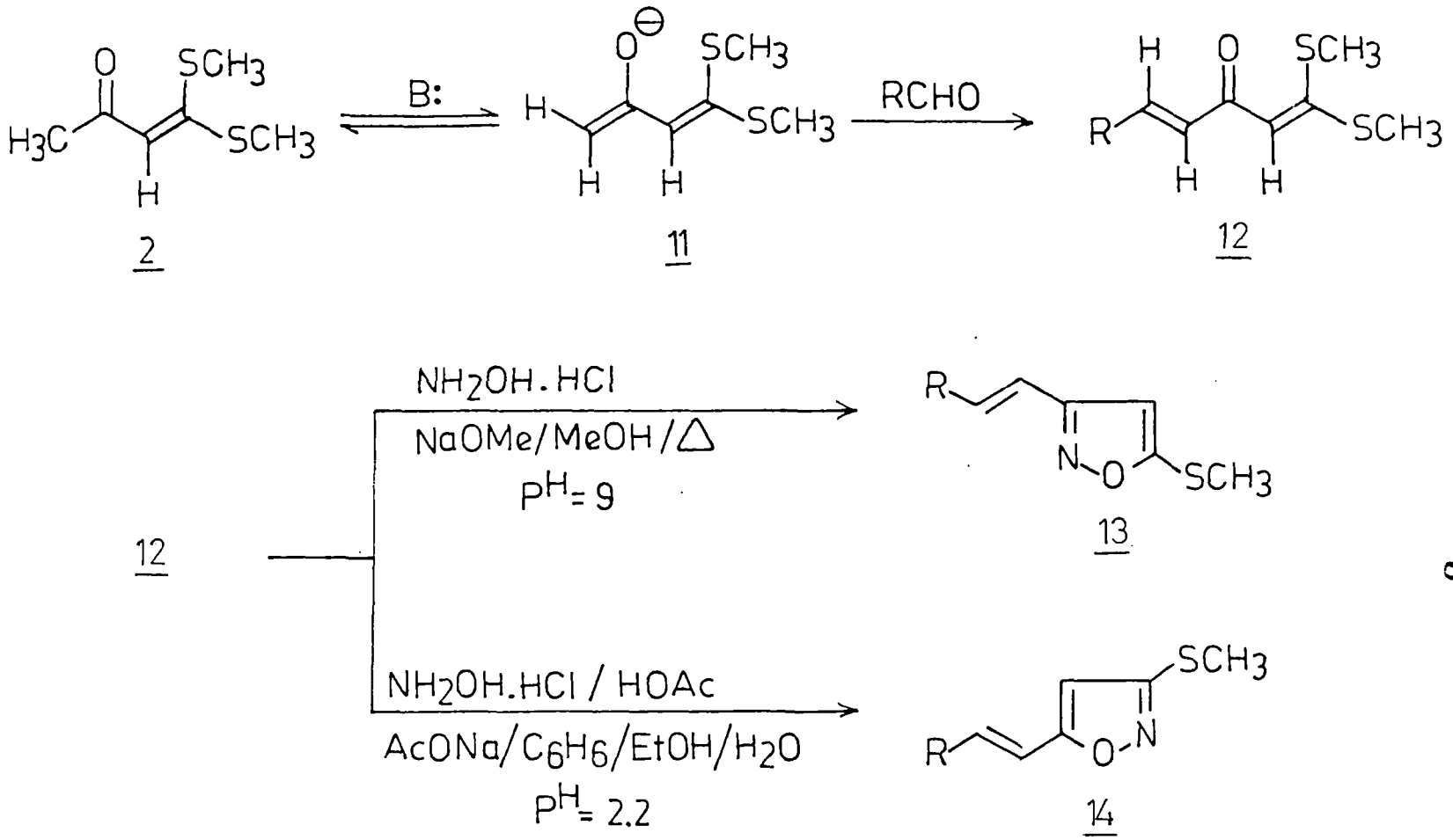
oxime formation as the first step. The high regioselectivity in this case is marked by clear absence of the isomeric isoxazoles 9. Alternatively the α-oxoketene dithioacetals reacted with hydroxylamine hydrochloride under acidic medium (pH=2.2) to yield the corresponding 3-alkylthio-5-arylisoxazoles 9 almost exclusively. The mechanism governing the formation of these regioisomers 8 and 9 is discussed in the thesis. From the experimental evidence it is clearly demonstrated that the α-oxoketene dithioacetals can be made to react with hydroxylamine hydrochloride under different reaction conditions to yield different regioisomers in high yeilds. Thus the method is of considerable synthetic importance since it is applicable to dithioacetals with greater structural flexibility.

The α-oxoketene dithioacetals 2 react with hydroxylamine hydrochloride in the presence of barium hydroxide (pH=5.6) to give 5-thiomethylisoxazole 8 in high yields. However, when 2 was reacted with hydroxylamine hydrochloride in the presence of pyridine the corresponding isoxazoline 10 was isolated (Scheme 2).

The cinnamoyl ketene dithioacetals 12 similarly yielded the regioisomers 13 and 14 (Scheme 3) in high yields. The acetals 12 also reacted with hydrazine hydrate to give a mixture of acetylpyrazoles 16 and acetylpyrazolines 15 involving condensation with carbonyl group followed by cyclisation and Michael addition on the styryl double bond followed by cyclisation respectively. The ambiguity was eliminated when 16 was reacted with hydrazine hydrate in the presence of acetic acid to yield styryl pyrazoles 17 exclusively (Scheme 4).


NH2OH.HCl
NaOMe/MeOH / △
PH= 9
NH2OH.HCl/HOAc
AcONa/C6H6/EtOH/H2O
PH= 2.2
2
8
9
NH2OH.HCl
Ba(OH)2/EtOH /△
PH= 5.6
NH2OH.HCl/EtOH/
Pyridine
10

Scheme 2

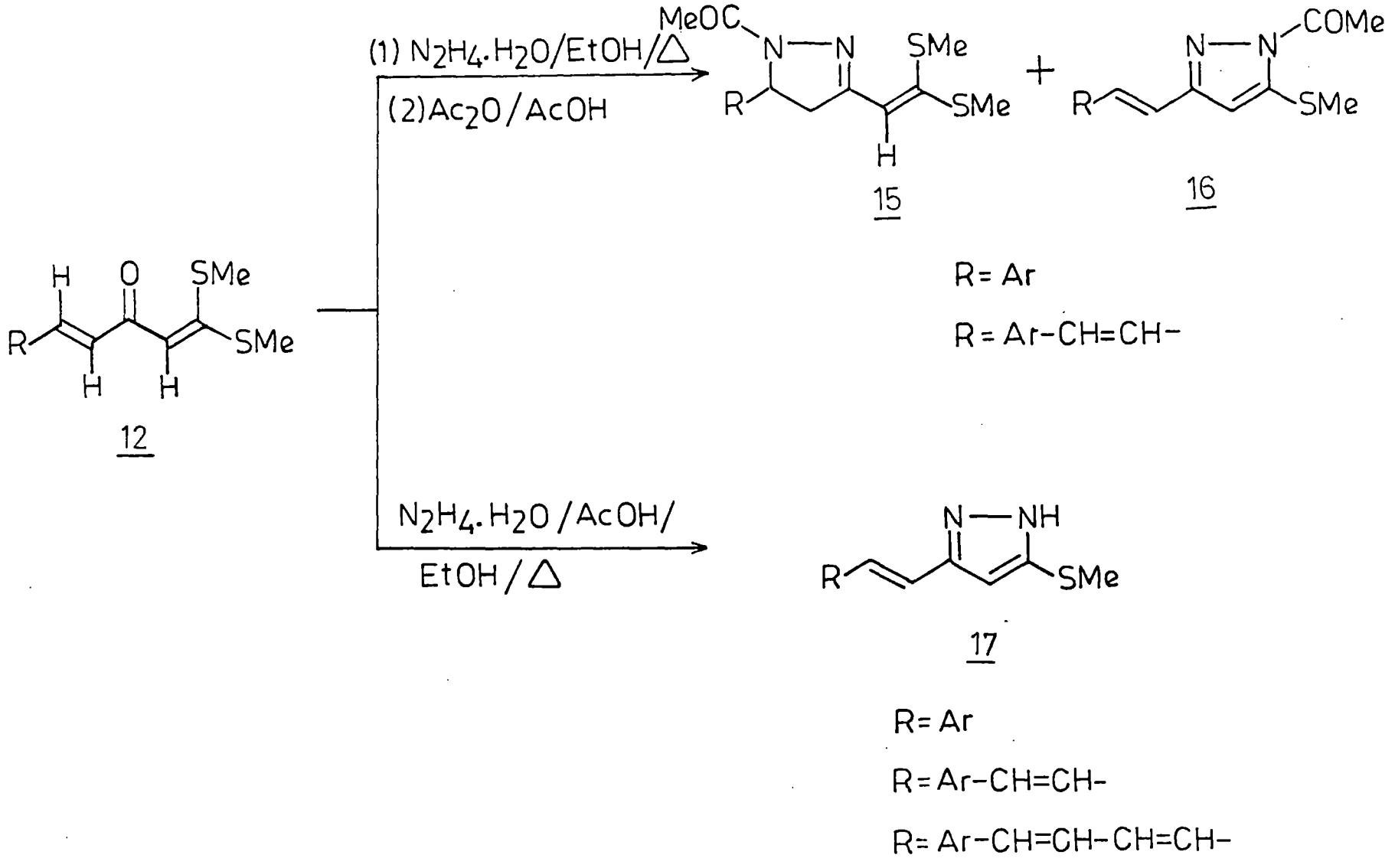


R = Ar

R = Ar-CH=CH-

R = Ar-CH=CH-CH=CH-

Scheme 3


(1) $N_2H_4.H_2O$/EtOH/△
(2)Ac_2O/AcOH
MeOC
N—N
SMe
SMe
R
H
15
+
N—N
COMe
R
SMe
16
R= Ar
R= Ar-CH=CH-
H
O
SMe
R
SMe
H
H
12
$N_2H_4.H_2O$ /AcOH/
EtOH/△
N—NH
R
SMe
17
R= Ar
R= Ar-CH=CH-
R= Ar-CH=CH-CH=CH-

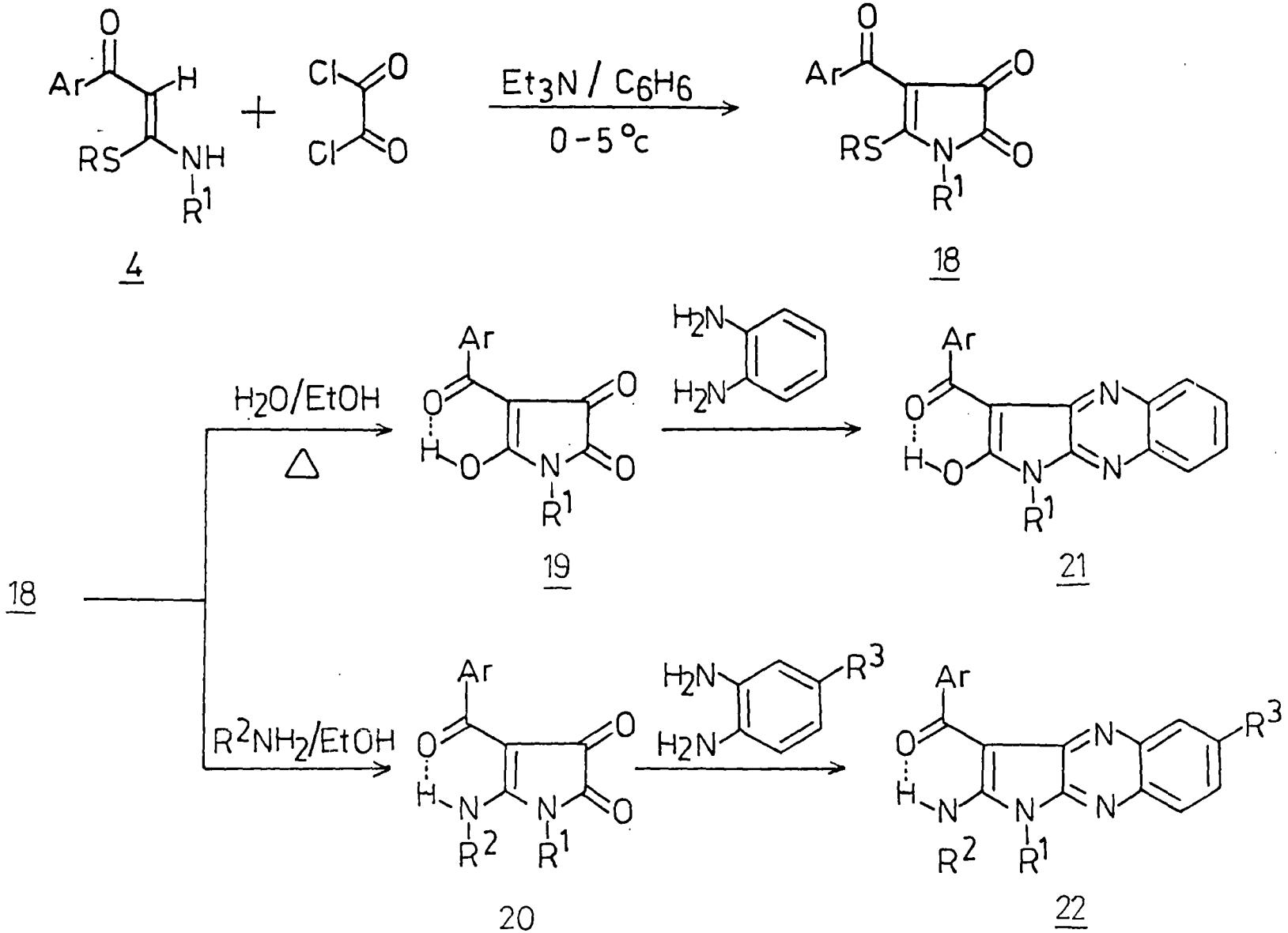
Scheme 4

The S,N-acetals 4 underwent smooth condensation with oxalyl chloride to yield the moisture sensitive 2-thioalkyl-3-aroyl-1-aryl/benzyl/alkylpyrrol-4,5-diones 18 in high yields. They underwent facile hydrolytic cleavage to yield the corresponding 2-hydroxypyrrol-4,5-diones 19. The thiomethyl group in 23 was displaced with various amines to yield 2-aminopyrrole-4,5-diones 20 and were found to be more stable than the corresponding alkylthio compounds 18. The pyrrolediones 19 and 20 were condensed with orthophenylene diamine to yield the corresponding pyrroloquinoxalines 21 and 22 respectively.

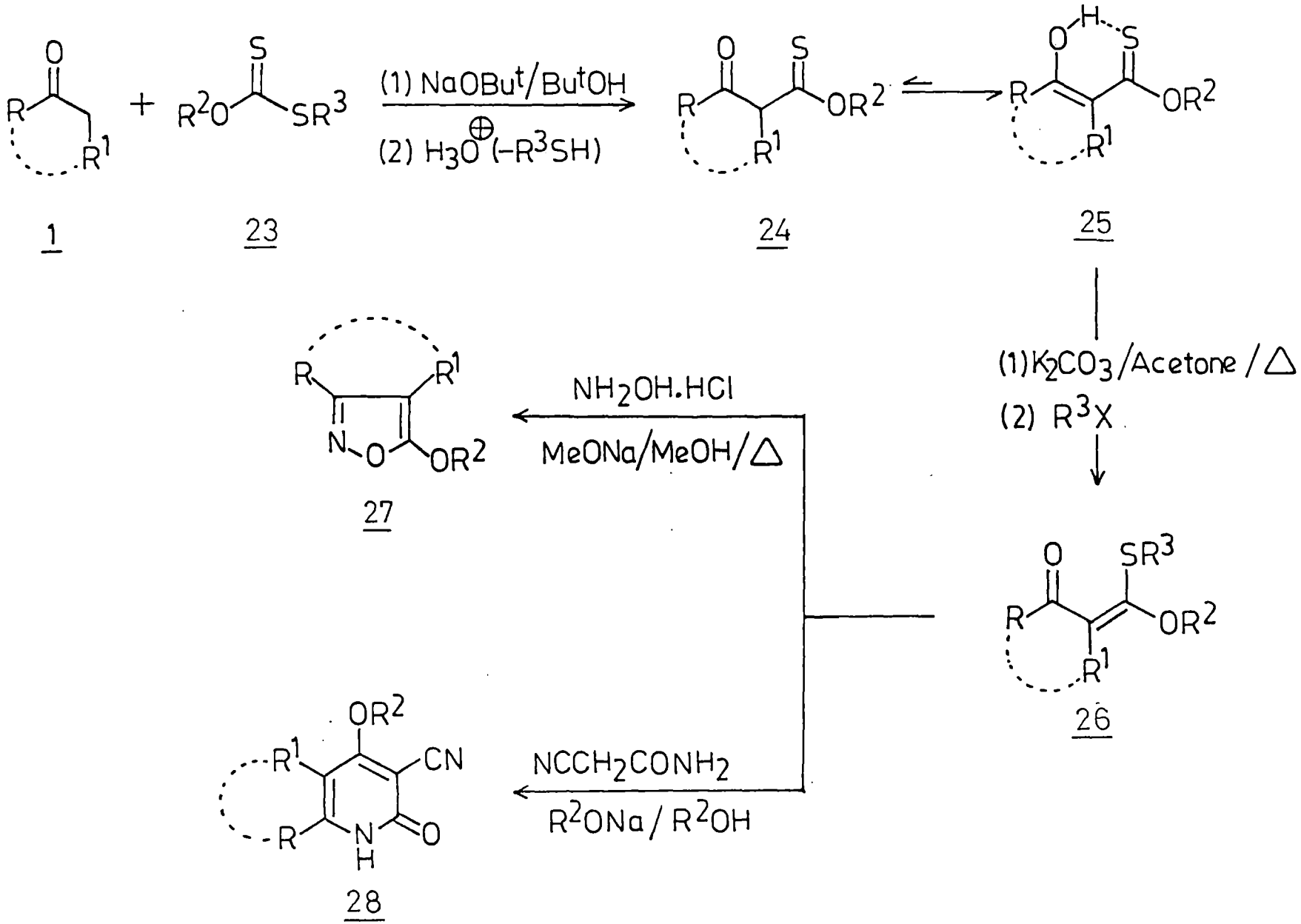
Preliminary investigation for the synthesis of α-oxoketene O,S-acetals directly from active methylene ketones has been initiated. Thus the enolate anions of ketone 1 reacted smoothly with xanthate 23 to yield the corresponding β-oxothionoesters 25 in good yields. These thionoesters are subsequently alkylated to yield the corresponding α-oxoketene O,S-acetals 26. The generality of this approach for the synthesis of 26 is demonstrated by reacting some of the structural variants.

The selected synthetic application of 26 has been initiated by reacting 26 with hydroxylamine in the presence of sodium methoxide to yield the corresponding 5-alkoxy-3-substituted isoxazoles 27. Attempted preparation of the isomeric 3-alkoxy-5-substituted isoxazoles was not successful due to greater acid sensitivity of 26.

The O,S-acetals were also reacted with sodio derivative of cyanoacetamide to yield the corresponding 3-cyano-4-alkoxy-6-substituted pyridin-1H-2(one) 28 in good yields. The importance of this method for which 26 as a necessary starting material makes these compounds strategically important. The advantages and limitations of all these useful transformations are described in the thesis.


Ar
H
RS
NH
R1
Cl
O
Et3N / C6H6
0-5 °c
4
18
H2O/EtOH
△
19
H2N
H2N
21
R2NH2/EtOH
20
R3
22
18

Scheme 5


(1) NaOBut/ButOH
(2) H3O⊕ (-R3SH)
1
23
24
25
(1)K2CO3/Acetone/△
(2) R3X
26
NH2OH.HCl
MeONa/MeOH/△
27
NCCH2CONH2
R2ONa/R2OH
28

Scheme 6

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11. A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 748 (1980).
12. M.L. Purkayastha, H. Ila and H. Junjappa, Synthesis, 000 (1989).

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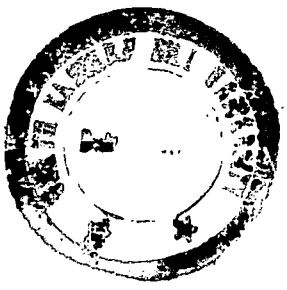

To

NORTH-EASTERN HILL UNIVERSITY

SHILLONG-793 001

INDIA

1989

Thesis

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My
Parents & Teachers

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Department of Chemistry

This is to certify that the work described in this thesis has been carried out by Mr. Makhan Lal Purkayastha under my supervision. He has satisfactorily completed the pre-Ph.D. courses prescribed and the minimum period of two years of investigational work for the award of Ph.D. degree in Chemistry.

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

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This is to certify that Mr. Makhan Lal Purkayastha, a Ph.D. student of the Department of Chemistry has satisfactorily completed the following courses as a part of his Ph.D. course programme.

Course No.	Title
1. Chem - 630	Biosynthesis and Natural Product Chemistry
2. Chem - 640	Chemical Kinetics

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M Purkayastha
31/3/89

Makhan Lal Purkayastha

CONTENTS

PREFACE

Polarized ketene dithioacetals, ketene S,N-acetals and N,N-acetals which are easily derived from a variety of active methylene compounds, are versatile intermediates for the synthesis of novel heterocyclic compounds. In the present investigation, a systematic study was undertaken to further exploit α-oxoketene S,S-, S,N-acetals and O,S-acetals as useful three carbon fragments for the construction of a variety of novel heterocyclic ring systems. These studies have resulted in the development of new general methods for the synthesis of novel isoxazoles, pyrazolines, pyrazoles, dioxopyrroles, quinoxalines and pyridone derivatives.

In the first chapter, a brief survey of the various synthetic transformations using polarized ketene S,S-, S,N- and N,N-acetals derived in this laboratory is described.

In the second chapter, the reaction of α-oxoketene dithioacetals with hydroxylamine and hydrazine hydrate is discussed. The reaction with hydroxylamine affords 3-alkylthio and 5-alkylthio isoxazoles regioselectively in good yield. Reaction of α-styryl oxoketene dithioacetals and their higher enyl homologs with hydrazine hydrate yielded the pyrazolines and pyrazoles in good yields.

In the next chapter(III) annelation of S,N-acetals with oxalyl chloride to give 3-aroyl-2-alkylthio-1-aryl/benzyl/alkylpyrrol-4,5-diones and their further transformations to the corresponding 3-aroyl-2-arylamino/benzylamino/hydroxy-1-aryl/alkylpyrrol-4,5-diones and 3-aroyl-2-

arylamino/hydroxy-1-arylpyrrolo[2,3-b] quinoxalines are described.

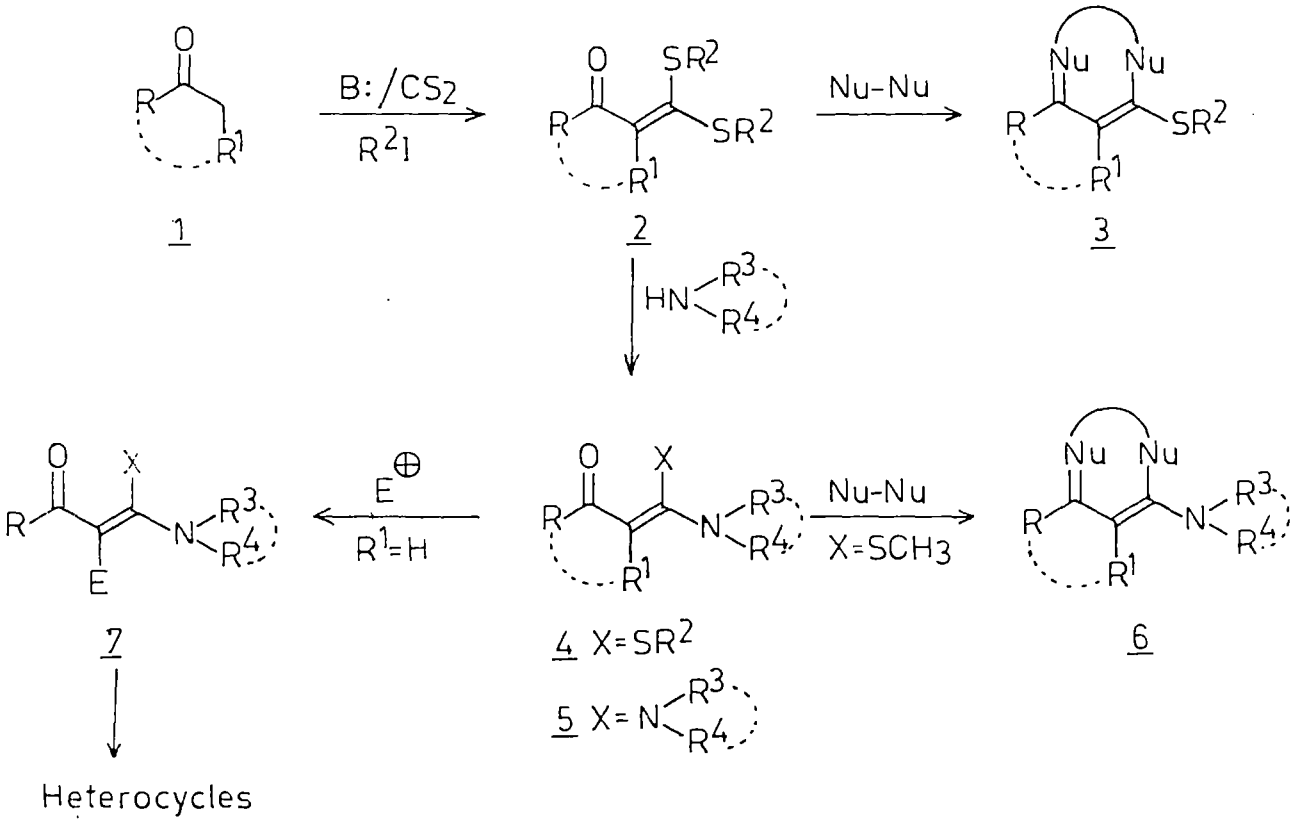
In the fourth chapter, a novel method for the synthesis of β-oxo-thionoesters and α-oxoketene O,S-acetals from active methylene ketones and alkyl xanthates is reported. These α-oxoketene O,S-acetals are converted to the corresponding alkoxy isoxazoles and alkoxypyridones by treatment with hydroxylamine and cyanoacetamide anion respectively.

CHAPTER I

INTRODUCTION

The α-oxoketene dithioacetals[1] 2 and the corresponding S,N-acetals 4 and N,N-acetals 5 (Scheme 1) are among the novel synthetic intermediates which can be prepared from active methylene ketones of the general formula 1. The enolate anions of 1 react with carbon disulphide followed by alkylation to yield 2 in high yields[2-13] often in one pot reaction. A large number of α-oxoketene dithioacetals have now been reported and their chemistry has been reviewed[14]. The oxoketene dithioacetals are either liquids with well defined boiling points or solids with sharp melting points which can be purified by conventional purification

methods. They are stable at room temperature and display stability under mild acidic and alkaline conditions and thus can be stored indefinitely without apparent decomposition. The corresponding O,O-acetals however, cannot be prepared from active methylene ketones using the described method and are prepared by reacting the ketene O,O-acetals with alkyl or aryl acid chlorides in the presence of anhydrous aluminium chloride[15,16]. The α-oxoketene dithioacetals can thus be prepared from a wide variety of active methylene ketones as well as other active methylene compounds. The thiomethyl group in 2 can be easily replaced by various carbon nucleophiles to give the corresponding C-alkyl derivatives[17,18] and the replacement of thiomethyl group by nitrogen nucleophiles results in the formation of S,N[19] and N,N-acetals[20]. The ketene dihalogenides[21,22] are also obtained by chlorinating 2 in high yields. The α-oxoketene dithioacetals can therefore be considered as key intermediates as they serve as starting materials for the preparation of a number of their derivatives which are useful synthetic intermediates. The α-oxoketene dithioacetals 10 (Scheme 2) carrying mixed S-alkyl substituents cannot be prepared directly in two step alkylation process although,such alkylations have been achieved using phase transfer catalysts. They can be conveniently obtained by reacting the enolate anions of 1 with trithiocarbonate first to yield the corresponding dithioesters[23] 9 which could then be converted to the corresponding oxoketene dithioacetals 10 using different alkyl-halides[24]. The dithioesters 9 could be easily converted into the corresponding thioamides 11 which are found to be useful precursors



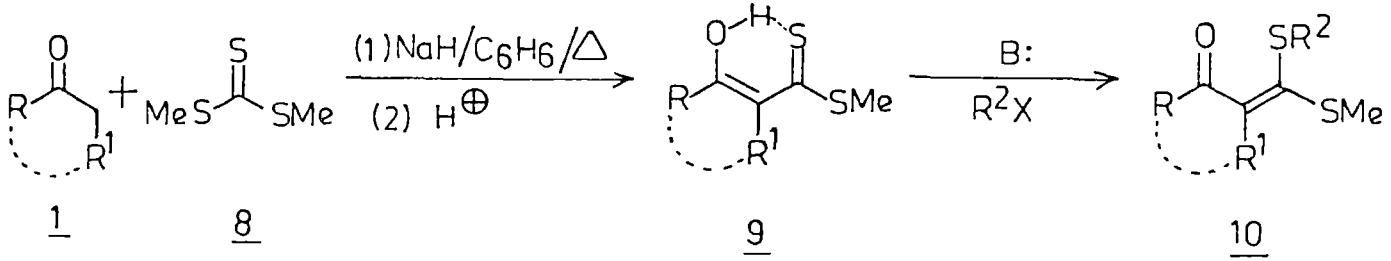
1 2 3

4 X=SR2

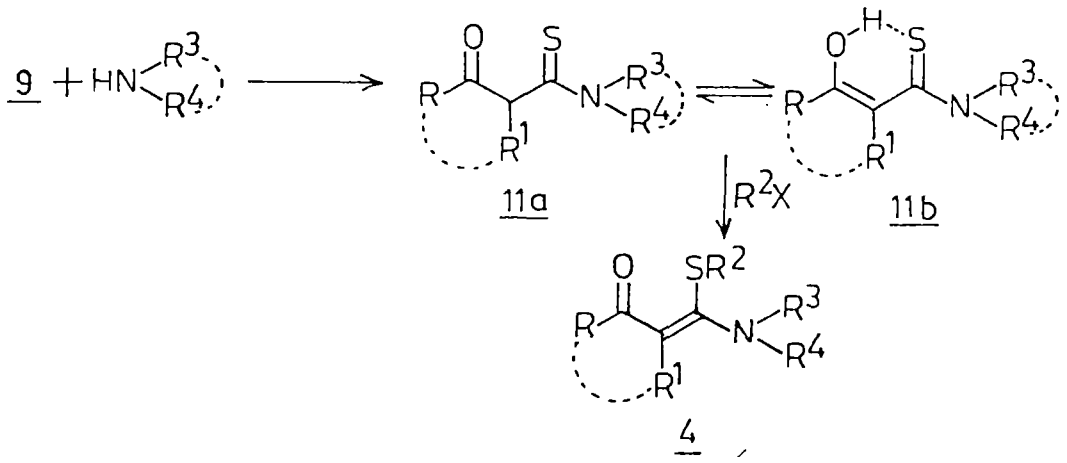
5 X=N

6 7

Scheme 1



1 8 9 10



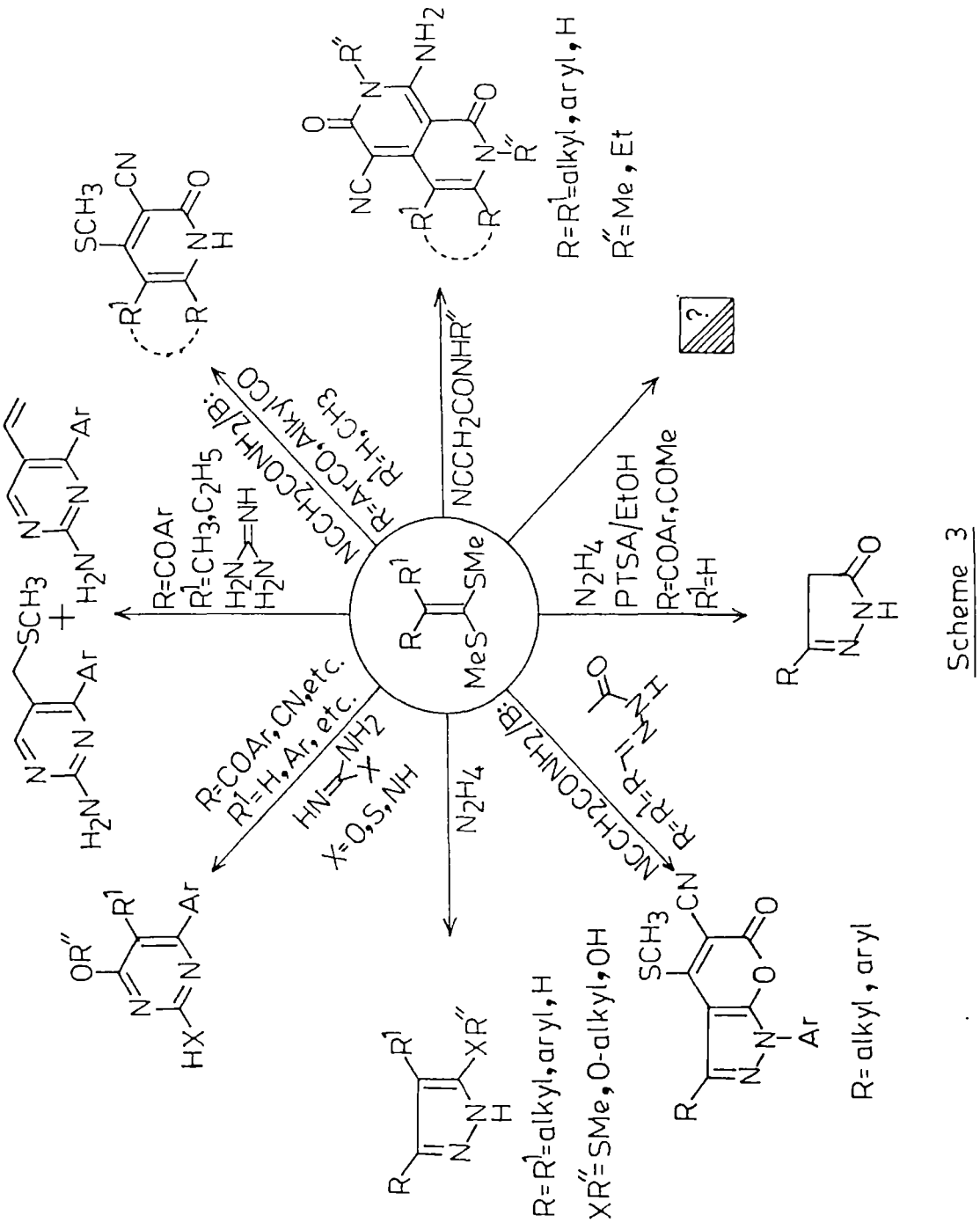
11a 11b 4

Scheme 2

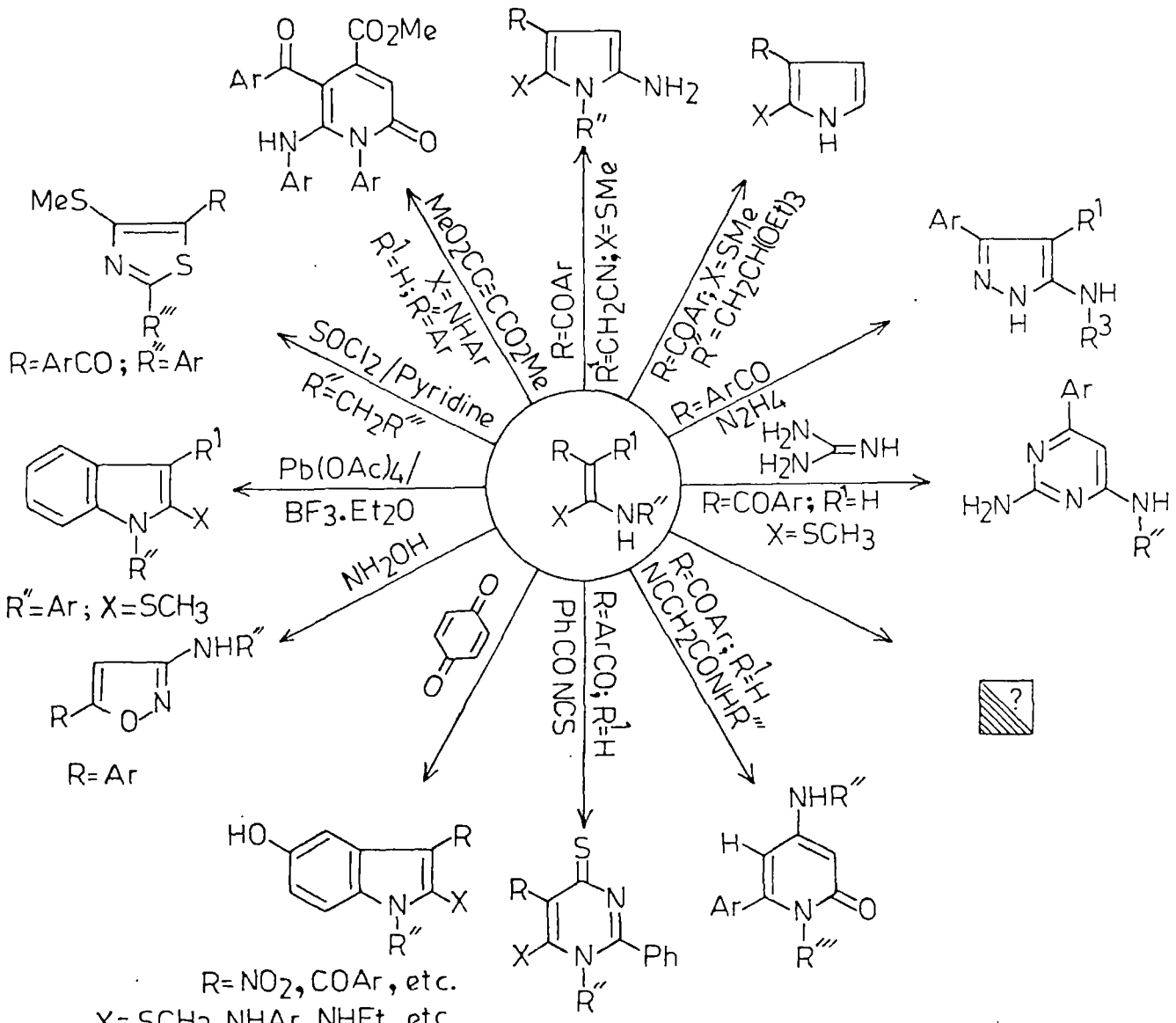
for the synthesis of the corresponding S,N-acetals[25] 4 (Scheme 2).

The α-oxoketene dithioacetals have been shown to be excellent 3-carbon fragments possessing 1,3-electrophilic centers with differing electrophilic properties, suitable for synthetic exploitation. These S,S-acetals, α-oxoketene S,N- and N,N-acetals have been extensively used in this laboratory for developing a number of new synthetic methods, for both heterocyclic and carbocyclic systems[26-58]. They react with guanidine and thiourea to yield alkoxy pyrimidines[26,27,13,35,36,37] and amino pyrimidines[38,51]. They also react with sodiocyanoacetamide to yield the corresponding 2H-pyridones[20.29,32,39] and when N-substituted cyanoacetamide was used the products isolated were the corresponding naphthyridines[33] instead of N-substituted pyridones. The reaction with hydrazine hydrate under different reaction conditions yield the corresponding thiomethyl, alkoxy and aminopyrazoles[28,36,52]. Similarly they react with binucleophiles to yield amino isoxazoles[40], thiazoles[45,46], pyrazolopyrones[30], imidazoles[46,47,53] quinoxalines[46] and aminopyrones[55]. Some of the transformations using α-oxoketene S,S-acetals are depicted in Scheme 3.

Important transformations based on α-oxoketene S,N- or N,N-acetals have been depicted in Scheme 4. They undergo lead tetraacetate oxidation to yield the corresponding indole derivative[57,58]. The N,N-acetals were shown to react with acetylene dicarboxylate to yield the corresponding pyridones[44]. When reacted with p-benzoquinone the S,N-acetals yield the corresponding 5-hydroxy indoles[43]. The versatile synthetic applications of the oxoketene S,N- and N,N-acetals are amply demonstrated and hold further potential as synthetic intermediates for many hitherto


R=COAr
R¹=CH3,C2H5
H2N
H2N
NCCH2CONH2/B:
R=ArCO, Alkyl CO
R1=H, CH3
NCCH2CONHR″
R=R¹=alkyl, aryl, H
R″=Me, Et
N2H4
PTSA/EtOH
R=COAr, COMe
R¹=H
?
R=COAr, CN, etc.
R¹=H, Ar, etc.
HN=C(NH2)-X
X=O, S, NH
N2H4
NCCH2CONH2/B:
R=R1=alkyl, aryl, H
XR″=SMe, O-alkyl, OH
R=alkyl, aryl
SMe
MeS

Scheme 3

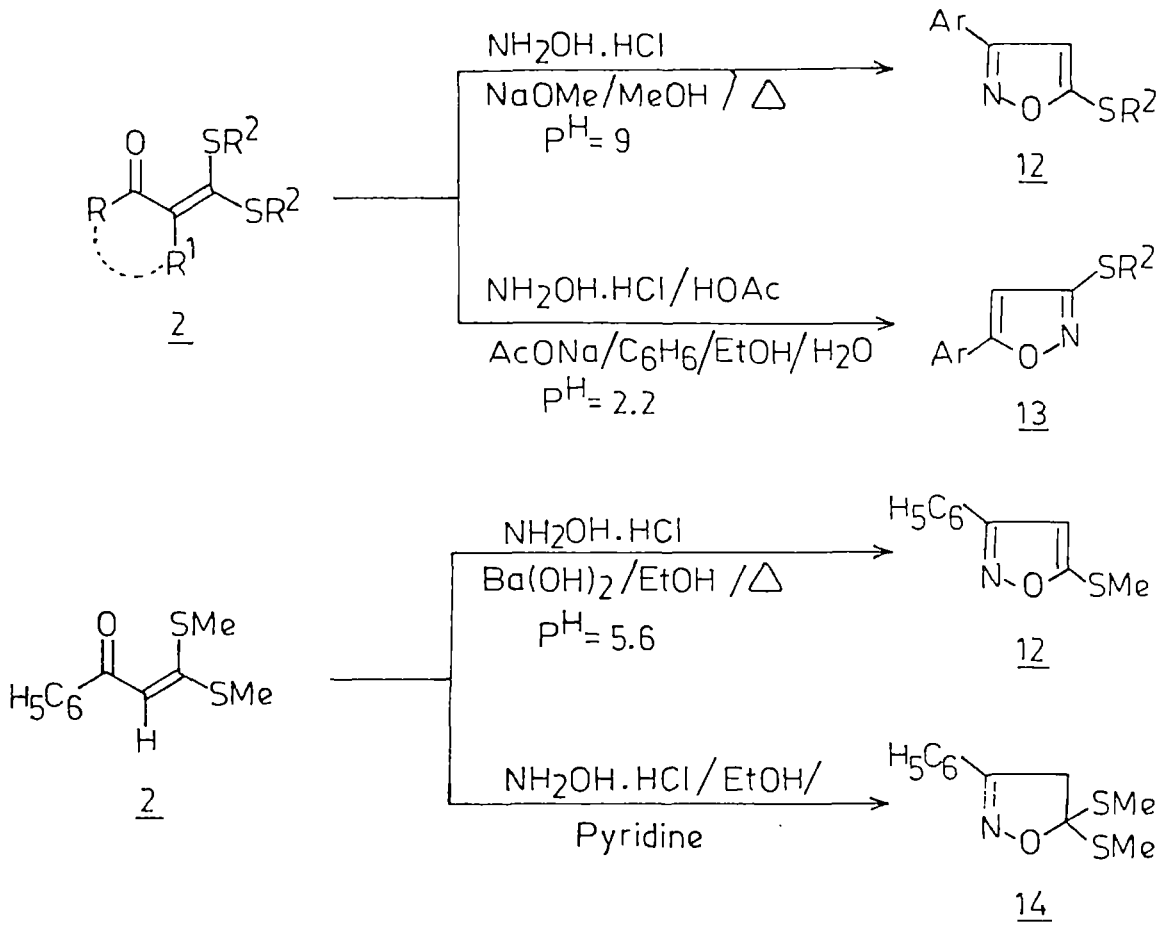

R=ArCO ; R‴=Ar
R″=Ar ; X=SCH3
R=Ar
R=NO2, COAr, etc.
X=SCH3, NHAr, NHEt etc.
Me02CC=CCO2Me
X=NHAr
R1=H; R=Ar
R=COAr
R1=CH2CN; X=SMe
R=COAr; X=SMe
R‴=CH2CH(OEt)3
R=ArCO
N2H4
R=COAr; R1=H
X=SCH3
R=COAr; R1=H
NCCH2CONHR‴
R=ArCO; R1=H
PhCONCS
SOCl2/Pyridine
R″=CH2R‴
Pb(OAc)4/
BF3.Et2O
NH2OH
?

Scheme 4

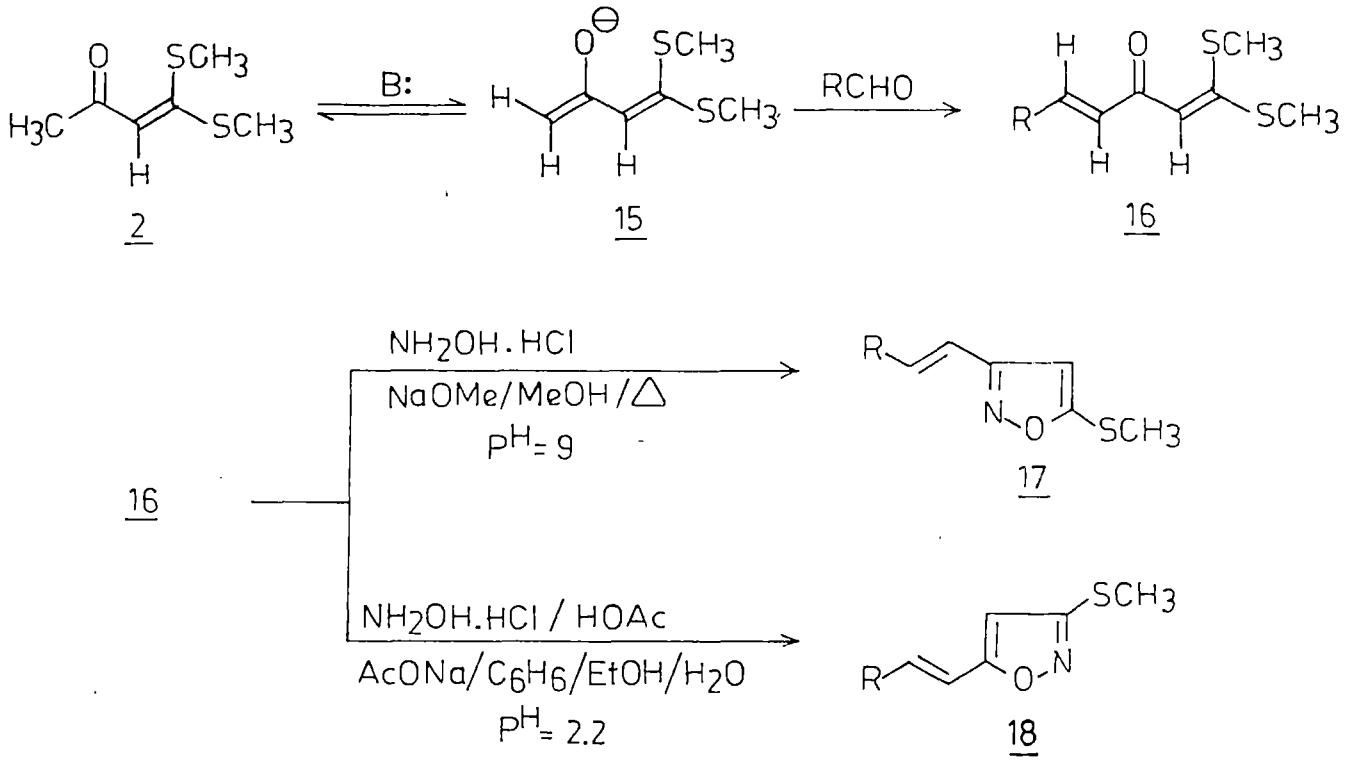
unreported transformations yielding a novel heterocyclic systems.

It was considered of interest in the present investigation to explore the potential of these intermediates 2 for the synthesis of isoxazoles. The extension of 2 for the synthesis of isoxazoles posses certain problems since 2 has two electrophilic centres at 1,3 positions with differing electrophilicity and the binucleophile also has two nucleophilic centres with differing nucleophilicity. Thus the ambivalent nature of both reactants hydroxylamine and the substrate 2 should yield different regioisomers. It has been shown that the α-oxoketene dithioacetals 2 react with hydroxylamine to yield the corresponding 5-alkylthioisoxazoles 12 regioselectively at pH 9, whereas the same reaction at pH 2.2 leads to the formation of 3-alkylthio isoxazoles 13. The mechanism of these regioselective transformations has been proposed in Chapter II. The regioisomers 12 are also obtained using Barium hydroxide as base at pH 5.6 whereas the corresponding isoxazoline 14 was formed when pyridine was used as base (Scheme 5).

The cinnamoyl ketene dithioacetals 16 required in the present investigation were prepared by the reported method as described in Scheme 6. These oxoketene dithioacetals 16 were reacted with hydroxylamine to yield the corresponding regioisomeric isoxazoles 17 and 18 under identical reaction conditions as described above. The enyloxoketene dithioacetals 16 with hydrazine hydrate underwent competitive reaction to yield a mixture of pyrazoline 19 and pyrazole 20. The factors governing the formation of 19 and 20 have been discussed in Chapter II. At low pH however the oxoketene


NH2OH.HCl
NaOMe/MeOH / △
PH= 9
NH2OH.HCl/HOAc
AcONa/C6H6/EtOH/H2O
PH= 2.2
NH2OH.HCl
Ba(OH)2/EtOH /△
PH= 5.6
NH2OH.HCl/EtOH/
Pyridine
2
12
13
14

Scheme 5

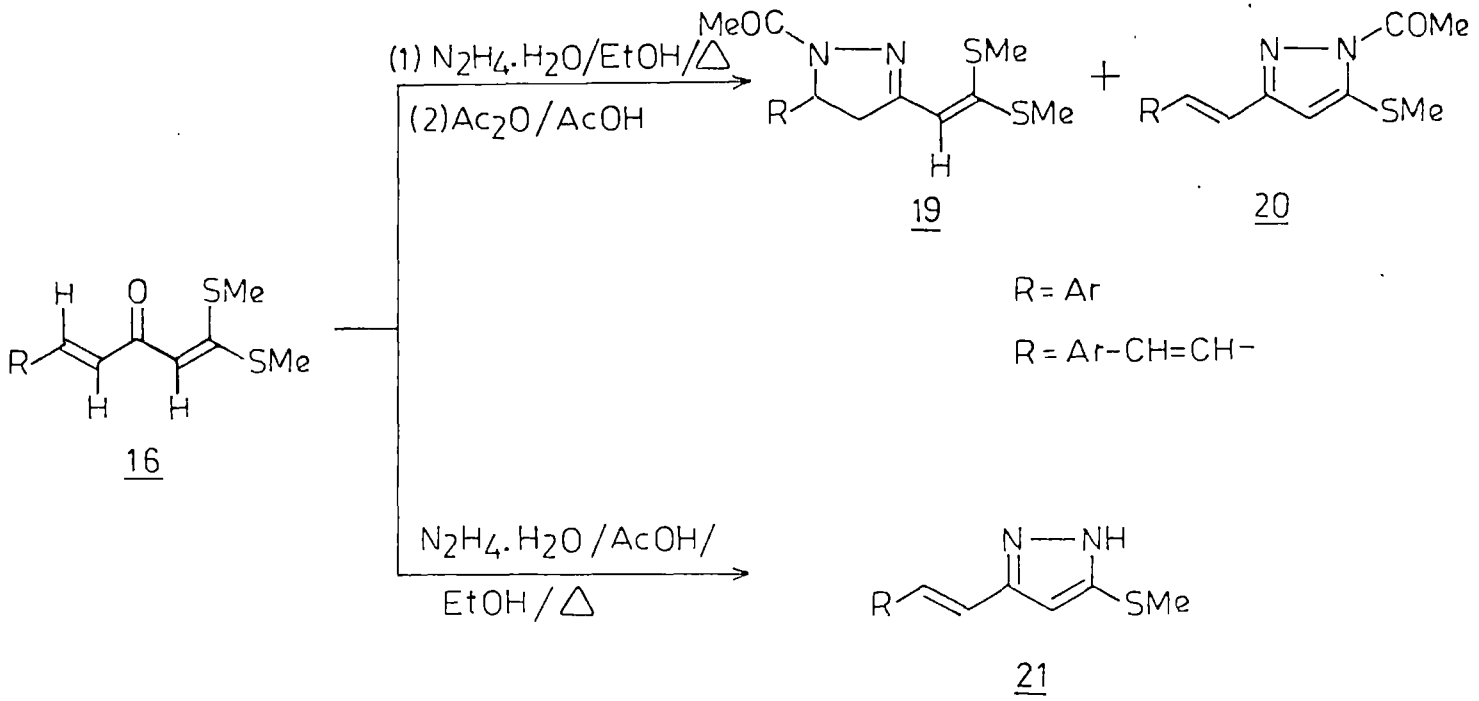


R = Ar

R = Ar-CH=CH-

R = Ar-CH=CH-CH=CH-

Scheme 6

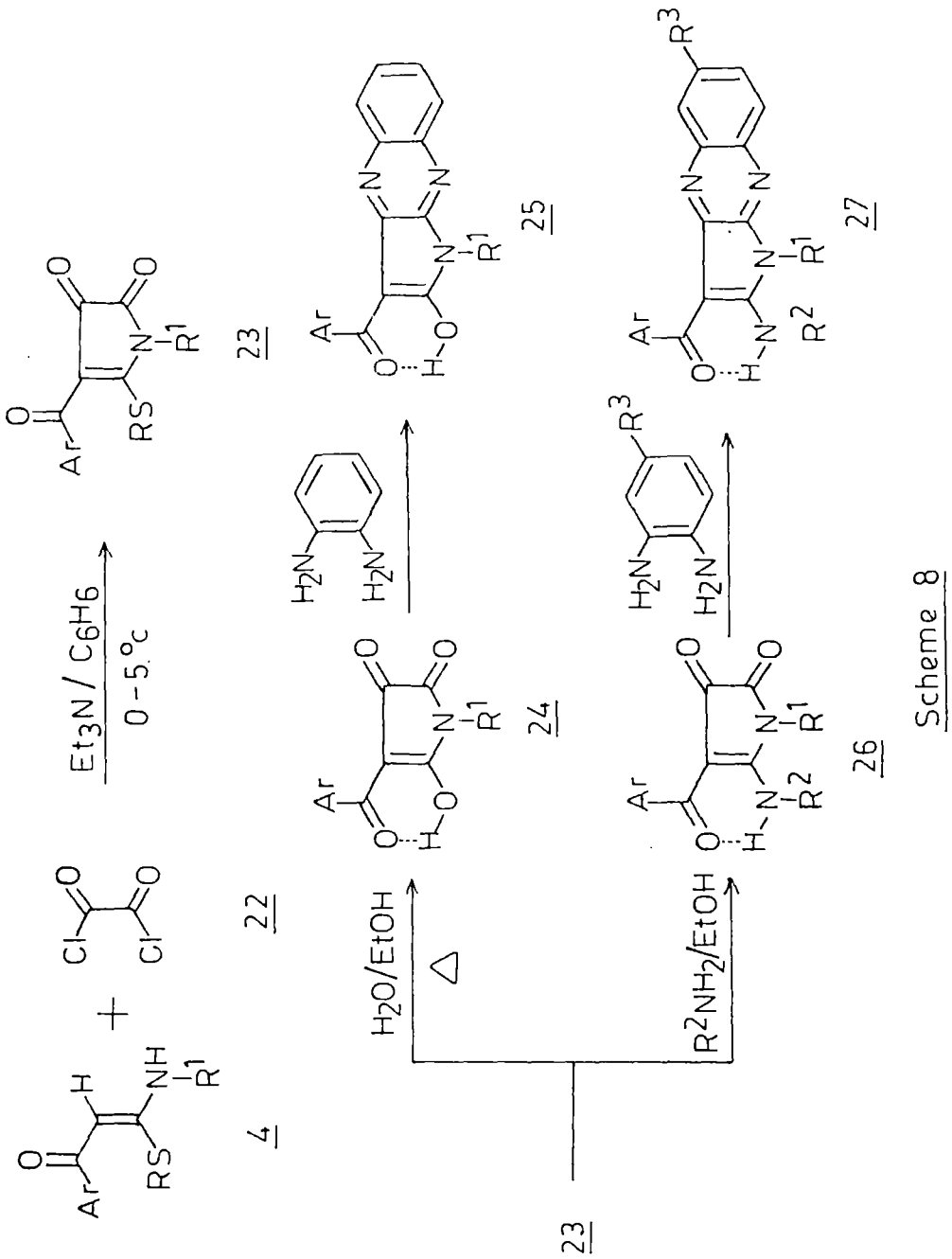

(1) $N_2H_4.H_2O$/EtOH/△
(2)Ac_2O/AcOH
MeOC
N—N
SMe
R
SMe
H
19
+
N—N
COMe
R
SMe
20
R = Ar
R = Ar-CH=CH-
H
O
SMe
R
SMe
H
H
16
$N_2H_4.H_2O$ /AcOH/
EtOH/△
N—NH
R
SMe
21
R = Ar
R = Ar-CH=CH-
R = Ar-CH=CH-CH=CH-

Scheme 7

dithioacetals 16 react with hydrazine hydrate to yield the corresponding enyl pyrazoles 21 exclusively and the reasons for such regioselectivity are discussed (Scheme 7).

In the third chapter the reaction of oxoketene S,N-acetals with oxalyl chloride is investigated. Thus a novel method for the synthesis of 3-aroyl-2-alkylthio-1-phenyl/benzyl/alkyl pyrrol-4,5-diones 23 has been developed. The compounds 23 underwent easy hydrolytic cleavage to yield the corresponding 2-hydroxy pyrrol-4,5-diones 24 which were then shown to undergo facile condensation with o-phenylenediamine to yield the corresponding pyrroloquinoxalines 25 in excellent yields. The thioalkyl group in 23 was easily replaced by amines to yield the corresponding 2-aminopyrrol-4,5-diones 26 which were found to be more stable than the corresponding 2-alkylthiopyrrol-4,5-diones 23. On condensation with o-phenylenediamine the 2-amino-pyrrol-4,5-diones 26 are converted to the corresponding pyrroloquinoxalines 27 (Scheme 8).

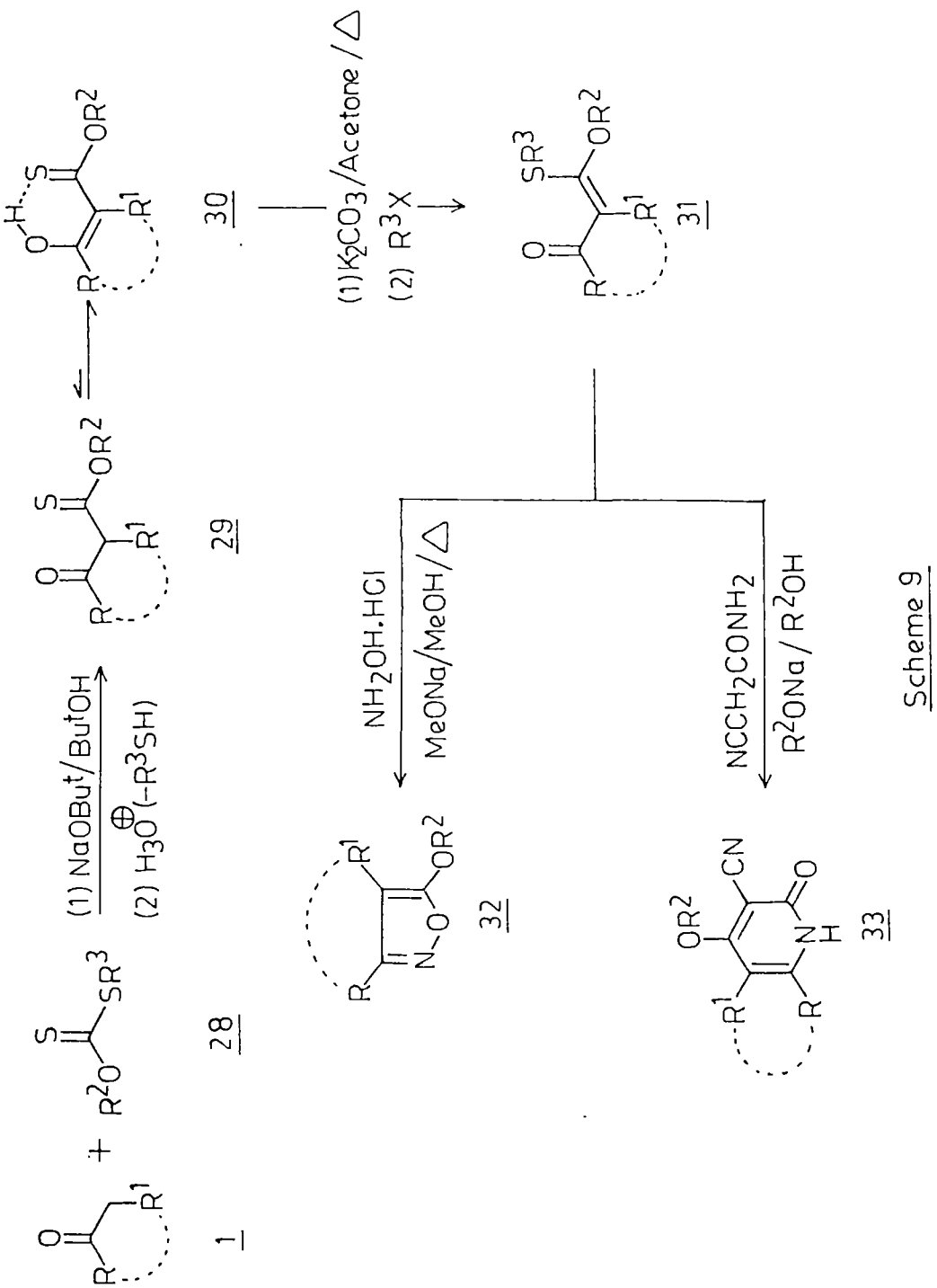
The reaction of active methylene ketones with trithiocarbonate to yield the corresponding dithioesters has been described in Scheme 2. The analogous approach for the synthesis of thionoesters 29 which are important precursors for the synthesis of the corresponding O,S-acetals 31 was considered appropriate. The enolate anions of ketone 1 were reacted with alkyl xanthate 28 to yield the corresponding thionoesters 30 in good yields. These thionoesters were subsequently alkylated to yield the corresponding O,S-acetals 31 in high yields. Attempts to prepare 31 directly in one pot reaction by reacting the enolate anion of 1 with 28 followed by alkylation failed. These details are discussed in Chapter IV (Scheme 9).



Scheme 8

The hitherto unreported α-oxoketene O,S-acetals were fully characterized and were shown to react with binucleophiles to give the corresponding alkoxyheterocycles. Thus, the α-oxoketene O,S-acetals 31 when reacted with hydroxylamine in the presence of sodium methoxide and methanol yielded a highly regioselective 5-alkoxy-3-substituted isoxazoles 32 in moderate yields. The acid sensitivity of 31 was manifested when it was reacted with hydroxylamine at pH 2.2, when the corresponding 3-alkoxyisoxazoles were not formed.

The reaction of α-oxoketene O,S-acetals 31 with sodio derivative of cyanoacetamide is shown to yield the corresponding alkoxypyridones 33 in high yields. It may be noted that the α-oxoketene dithioacetals 2 could not be converted to alkoxypyridones 33. Thus the α-oxoketene O,S-acetals have been shown to hold considerable promise as key intermediates for the synthesis of many alkoxy heterocycles.



Scheme 9

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CHAPTER II

A. REGIOSELECTIVE SYNTHESIS OF 5-ALKYLTHIO- AND 3-ALKYLTHIO ISOXAZOLES FROM α-OXO-KETENE DITHIOACETALS*

B. SYNTHESIS OF 3(5)-STYRYL/(4-ARYL-1,3-BUTADIENYL)/(6-ARYL-1,3,5-HEXATRIENYL)-5(3)-METHYLTHIO PYRAZOLES FROM α-OXO-KETENE DITHIOACETALS.

II.1 INTRODUCTION

The synthesis of isoxazole ring of general formula 1 (Scheme 1) was first reported by Claisen[1] in 1888 by reacting 1,3-diketones with hydroxylamine. They also subsequently reported that the isoxazole ring system possesses typical aromatic properties. Quilico and co-workers[2] made extensive investigation in the mid forties on the

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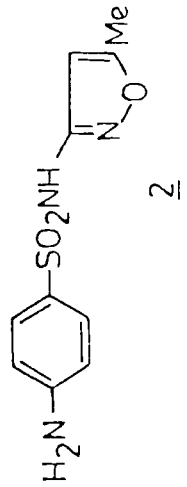
* M.L. Purkayastha, H. Ila and H. Junjappa, Synthesis, 000 (1989).

formation of isoxazoles from nitrile N-oxides and the unsaturated compounds. Subsequent methodologies relating to the synthesis of isoxazoles have largely been developed on the basis of these two approaches. Many variants of these procedures have been widely used by subsequent workers to prepare isoxazoles in large numbers. The development of the chemistry of isoxazoles, due to their characteristic chemical properties as masked enaminones or as 1,3-diketones, have been extensively exploited in the synthesis of many heterocycles and natural products[3]. The 3-unsubstituted isoxazolium salts have also been used as coupling agents in the peptide synthesis[4].

Many isoxazoles have displayed important medicinal properties. They found application inter alia, in agriculture as fungicides, pesticides and pharmacologically important drugs such as antibacterial sulphonamides, namely, sulphamethoxazole 2, sulphisoxazole 3 and semisynthetic penicillin cephalosporin. The isoxazole structure is also found in anabolic steroid danazol 4 (Scheme 1). Various other pharmaceutical applications of isoxazoles and their derivatives have been extensively reviewed[5]. The development of this class of compounds is largely due to their diverse applications in the areas of health-care, agriculture and industry as well.

The general synthetic approaches employed for the construction of isoxazole ring systems constitute the [3+2] routes containing (CCC+NO) and (CNO+CC) components. The major part of the chemistry of isoxazoles, therefore, falls within these two categories, which



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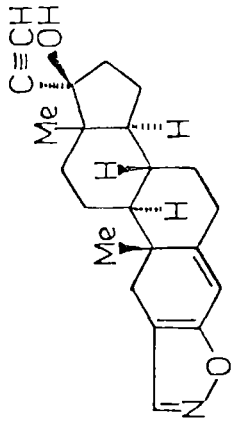

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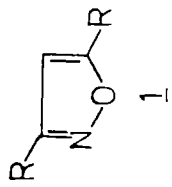
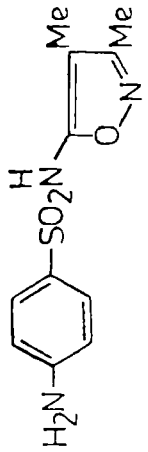


1



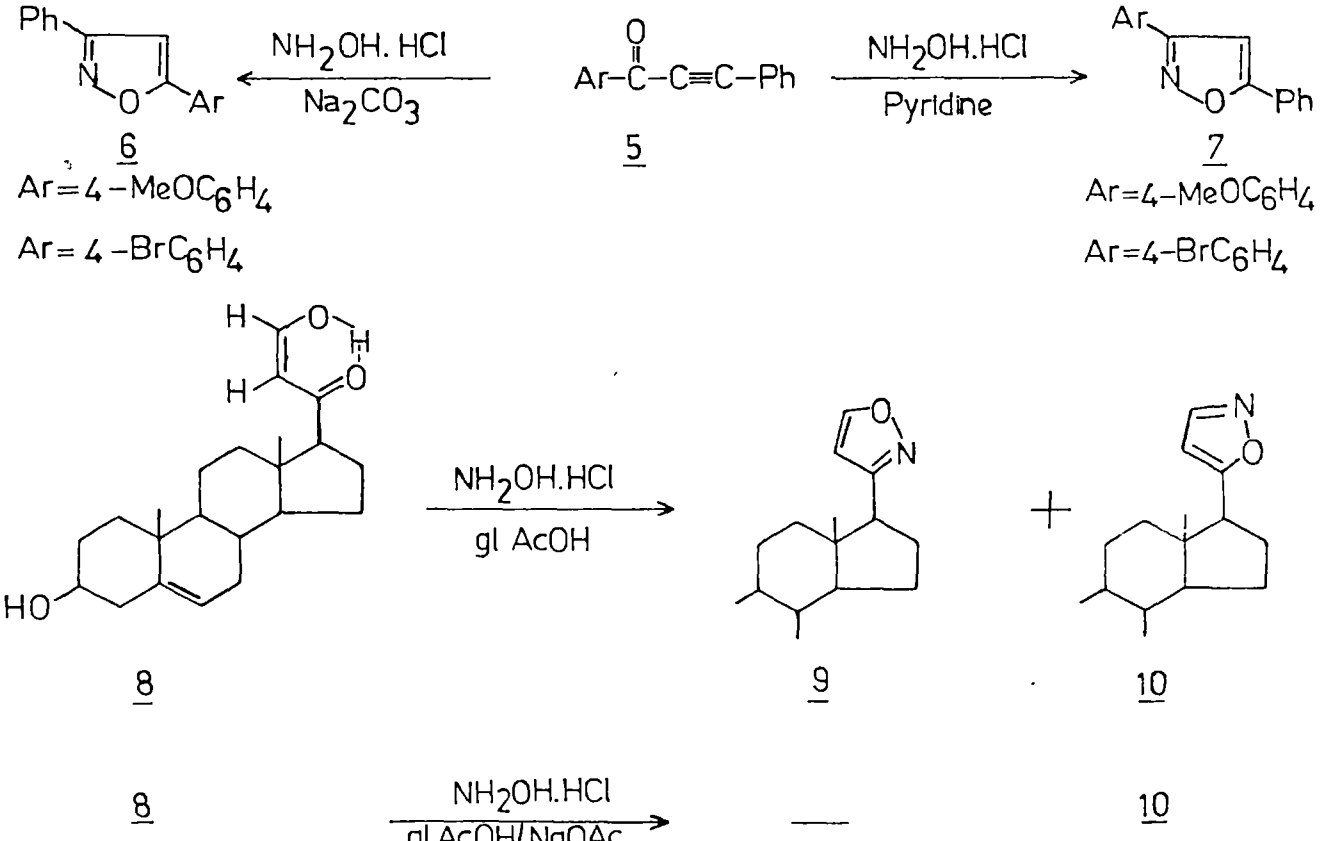
3

Scheme 1

have been extensively reviewed in the recent past[6,7]. A brief resume of the methods pertaining to the synthesis of isoxazoles has been discussed in this Chapter keeping in view of their relevance to the chemistry of isoxazoles based on 1,3-electrophilic synthons.

The α,β-alkynic ketones[8] and esters have been reacted with hydroxylamine hydrochloride in the presence of a suitable base to yield different regioisomers of isoxazoles depending upon the reaction conditions. Thus, the acetylenic ketone 5 when reacted with hydroxylamine hydrochloride in the presence of pyridine yielded 3-aryl-5-phenylisoxazole 7 (Scheme 2). The reaction path apparently involves the initial oxime formation followed by intramolecular Michael addition to yield the isoxazole 7. The acetylenic ketone 5,however, when reacted with hydroxylamine hydrochloride in the presence of sodium carbonate the initial step was the Michael addition on the triple bond carbon followed by intramolecular aldol condensation to yield the corresponding 3-phenyl-5-arylisoxazoles 6 (Scheme 2). It appears that the nucleophilic nitrogen of the free hydroxylamine generated in the presence of sodium carbonate undergoes initial Michael addition whereas, the hydroxylamine which is in equilibrium with its salt in the presence of pyridine, undergoes carbonyl addition followed by cyclization.

The isoxazoles have also been constructed[9] from the corresponding β-ketoaldehyde 8 to introduce β-ketonitrile functionality in steroids. 3-β-Hydroxy-21-formylpregn-5-en-2-one 8 was reacted with hydroxylamine hydrochloride in acetic acid to yield a mixture of 17-β-(3-isoxazolyl)-

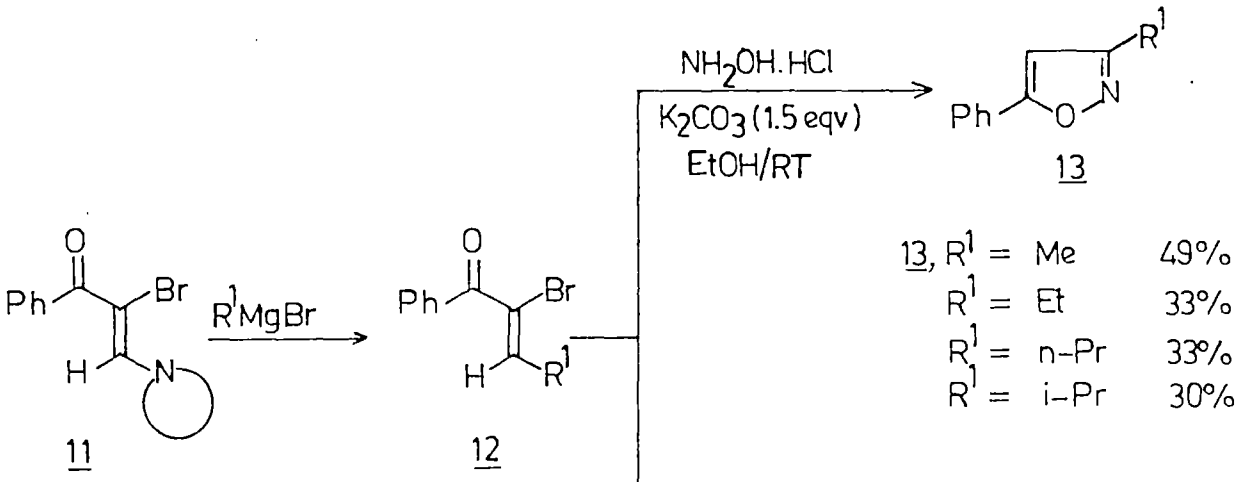

Ph
N
O
Ar
6
Ar=4-MeOC6H4
Ar=4-BrC6H4
NH2OH. HCl
Na2CO3
O
Ar-C-C≡C-Ph
5
NH2OH.HCl
Pyridine
Ar
N
O
Ph
7
Ar=4-MeOC6H4
Ar=4-BrC6H4
H
O
H
O
HO
8
NH2OH.HCl
gl AcOH
O
N
9
N
O
10
8
NH2OH.HCl
gl AcOH/NaOAc
Buffer
—
10

Scheme 2

5-androsten-3-β-ol 9 and 17-β-(5-isoxazolyl)-5-androsten-3-β-ol 10. However, the reaction of 8 with hydroxylamine hydrochloride in sodium acetate buffer gave exclusively 10 (Scheme 2), which could be cleaved under basic conditions to yield the corresponding β-keto-nitrile.

Highly regiospecific 5-aryl isoxazoles are obtained[10] by reacting hydroxylamine hydrochloride with 1-aryl-3-dimethylamino-2-propene-1-one. Thus the enamino ketone functionality constitutes 1,3-dielectrophilic synthons in which the electrophilicity of the β-carbon can be regaraded as hard electrophilic centre which is preferentially attacked by the hard nucleophilic nitrogen of the hydroxylamine to afford exclusively 5-substituted regioisomers. Similarly the α-bromo-enaminones 11 have been reacted[11] first with alkyl Grignard reagents to yield the corresponding α-bromoenones 12 which are then reacted with hydroxylamine hydrochloride in the presence of potassium carbonate, to afford the corresponding isoxazoles 13 formed by the initial Michael addition followed by intramolecular aldol condensation. On the other hand, when the reaction was carried out in the presence of sodium ethoxide the oxime pathway was operative followed by ring closure to afford 5-alkyl substituted isoxazoles 14 in low yields (Scheme 3).

Kashima and co-workers[12] have made detailed investigations regarding the formation of isomeric isoxazoles by controlled reaction of β-substituted enones with hydroxylamine under different basic



11 12 13 14

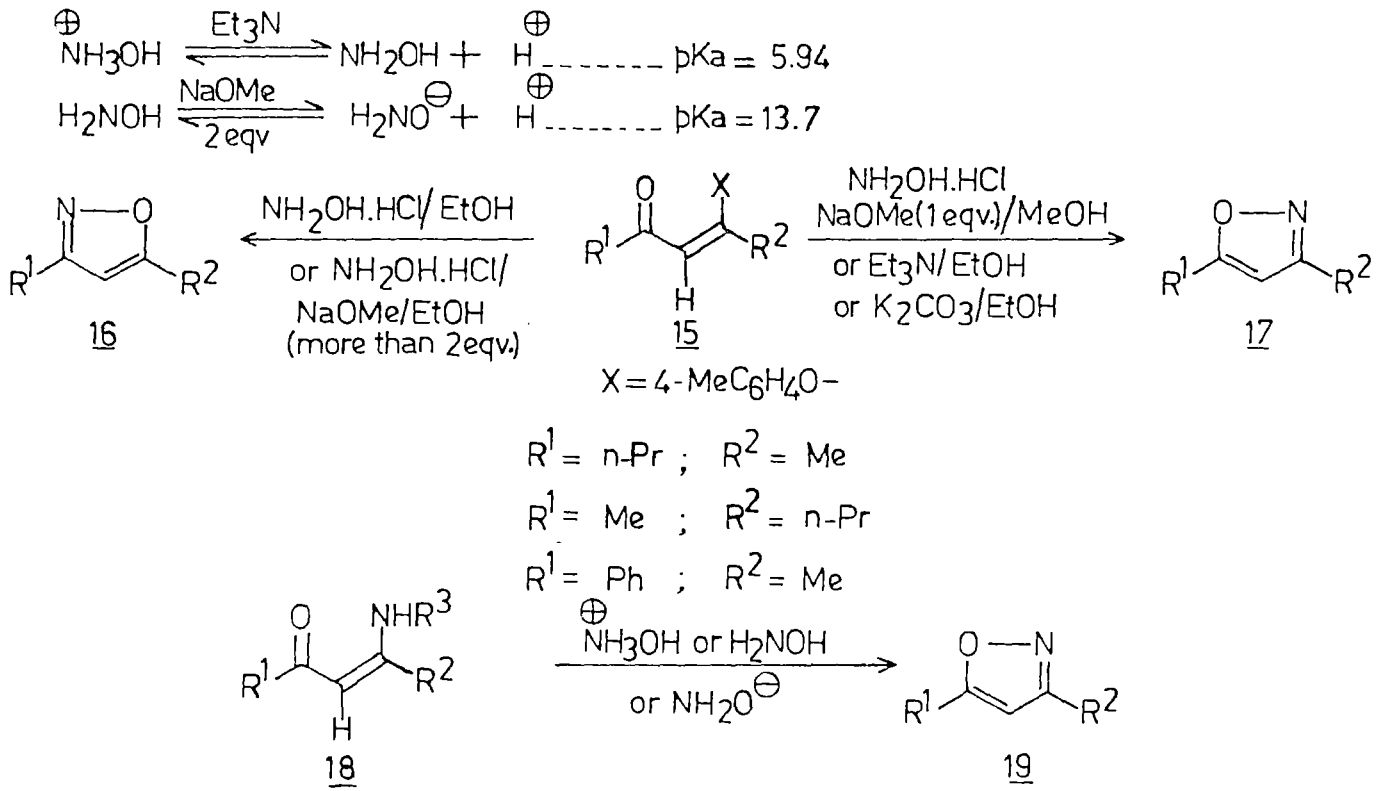
13, R^1 = Me 49%
R^1 = Et 33%
R^1 = n-Pr 33%
R^1 = i-Pr 30%

14, R^1 = Me 33%
R^1 = Et 30%
R^1 = n-Pr 25%
R^1 = i-Pr 25%

Scheme 3

conditions (Scheme 4). Their studies have shown that the hydroxylamine salt exists in equilibrium with free hydroxylamine in the presence of triethylamine and the pK_a of this equilibrium was reported to be 5.94. They have further shown that in the presence of strong base, such as, sodium methoxide the free hydroxylamine undergoes proton abstraction to give the corresponding oxyanion at pK_a value of 13.7. Thus the reaction of this species formed in the presence of various bases like sodium methoxide, triethylamine or potassium carbonate with α,β-unsaturated ketones 15 proceed through 1,4-conjugate addition of hydroxylamine followed by ring closure through intramolecular aldol condensation to afford isoxazoles 17. On the other hand, the α,β-unsaturated ketones 15 reacted with hydroxylamine in the presence of two equivalents of sodium methoxide to give the corresponding isomeric isoxazoles 16, following the oxime pathway.

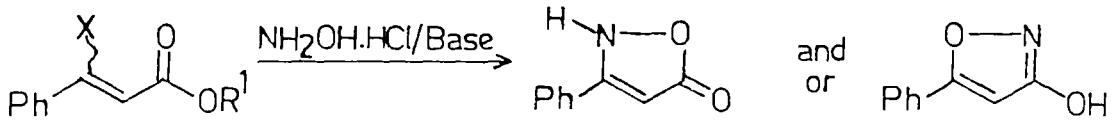
Kashima and co-workers[13] also reported (Scheme 4) that the reaction of enaminones 18 with hydroxylamine hydrochloride under different pH conditions affords only one regioisomer 19 in good yields (Scheme 4). Also the reactivity of hydroxylamine under different reaction conditions[14] with α,β-unsaturated ketones $Me_2C{=}CH{-}\overset{O}{\overset{\|}{C}}{-}CH{=}CMe_2$ in the presence of excess base, involves the attack of oxygen anion following the 1,4-conjugate addition pathway, while in the presence of equivalent amount of base, addition follows the 1,4-fashion through N-nucleophile followed by cyclisation to give respective regioisomers. Thus, enough base is required for the generation of NH_2O^- species so that it can act as a oxygen nucleophile in preference to nitrogen nucleophile.


⊕ NH3OH Et3N NH2OH + ⊕ H ..... pKa = 5.94
H2NOH NaOMe (2 eqv) H2NO⊖ + ⊕ H ..... pKa = 13.7
16
NH2OH.HCl/ EtOH
or NH2OH.HCl/ NaOMe/EtOH (more than 2eqv.)
15
X = 4-MeC6H4O-
NH2OH.HCl NaOMe(1eqv.)/MeOH
or Et3N/EtOH
or K2CO3/EtOH
17
R1 = n-Pr ; R2 = Me
R1 = Me ; R2 = n-Pr
R1 = Ph ; R2 = Me
18
R3 = Ph, Et
⊕ NH3OH or H2NOH
or NH2O⊖
19
R1 = n-Pr ; R2 = Me
R1 = Me ; R2 = n-Pr
R1 = Ph ; R2 = Me

Scheme 4

Kashima and co-workers[15] investigated the reaction of hydroxylamine hydrochloride with β-enaminoesters 20 and observed that the different regioisomers could be obtained using different bases. The reaction in the presence of triethylamine predominantly yielded regioisomer 21. The mechanism involves the nucleophilic nitrogen attack in an addition elimination sequence followed by ring closure to afford 21. On the otherhand regioisomer 22 was formed in the presence of sodium methoxide though the regioselectivity and yields were not very high in these reactions. Apparently, the reaction proceeds through amidation followed by cyclisation to give regioisomer 22 (Scheme 5).

Jacobsen and co-workers[16] have made detailed investigations on the formation of isoxazoles from the reaction of hydroxylamine with β-ketoesters 23 and 1,3-diketones. They observed that the maintenance of strict pH condition is necessary to get the desired regioisomers. In an effort to direct the course of reaction to 3-hydroxyisoxazole 25 in good yields from β-ketoesters they maintained the pH around 10 throughout the reaction and the reaction mixture was quenched with excess mineral acid, which they proposed, is responsible for suppressing the formation of 5-isoxazolone 30 which are otherwise the main products in these reactions. At pH 10, the hydroxylamine is in its neutral form in which the nitrogen atom is the nucleophilic centre,which could either attack to form the oxime 28 through 23a or the amide 24. The amide 24 requires to be treated strictly with excess of strong acid so that an improved yield of 25 is obtained. Otherwise, under slow acid addition conditions generally the yield



20 21 22

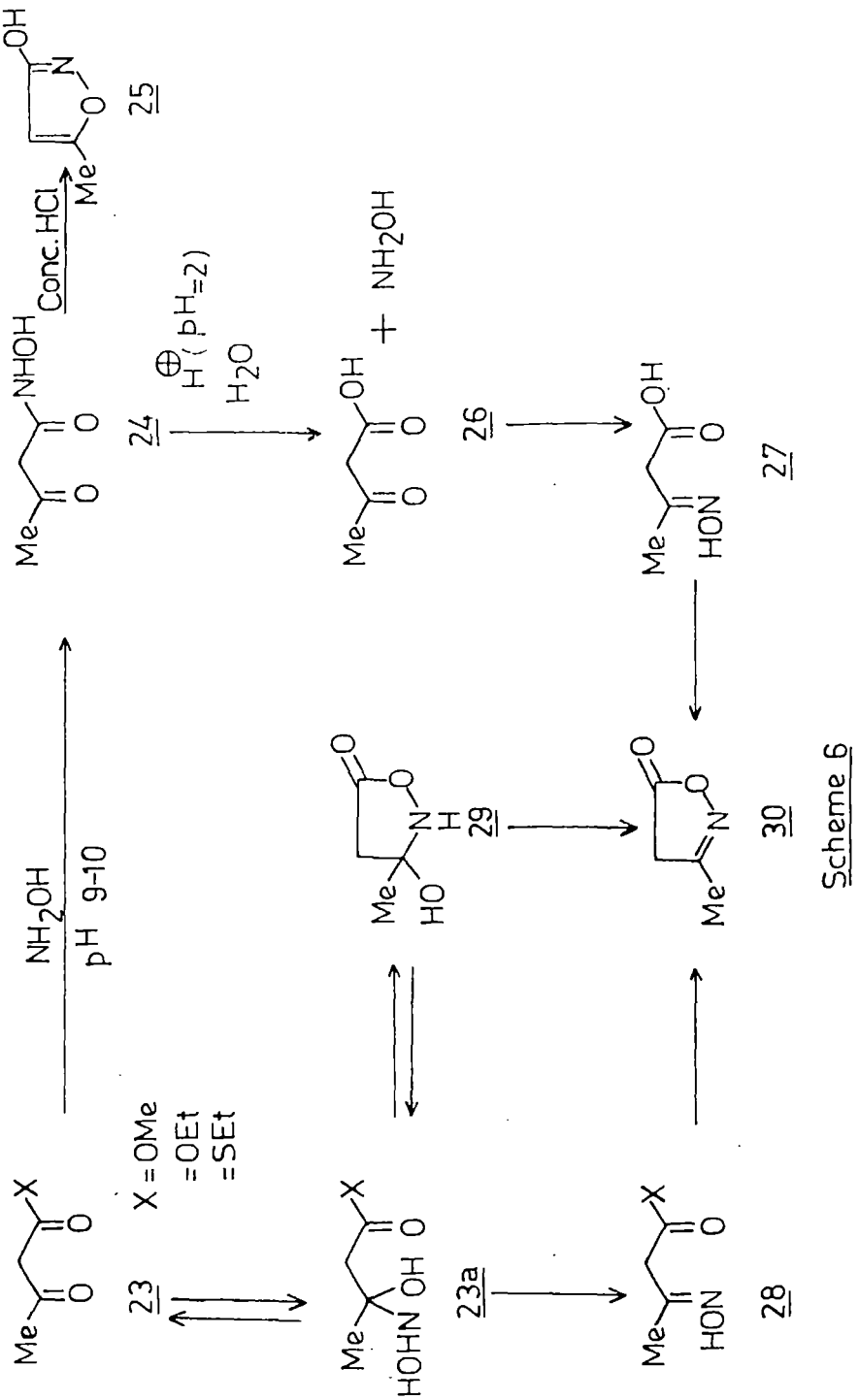
R^1 = Me, Et

	X	Et_3N yield(%)		Sodium methoxide yield(%)	
a	1-imidazolyl	7	97 : 3	60	0 : 100
b	4-nitroanilino	14	100 : 0	42	4 : 96
c	Anilino	80	100 : 0	18	26 : 74
d	4-Toluidino	77	100 : 0	12	12 : 88
e	1-Pyrrolidinyl	89	100 : 0	3	100 : 0

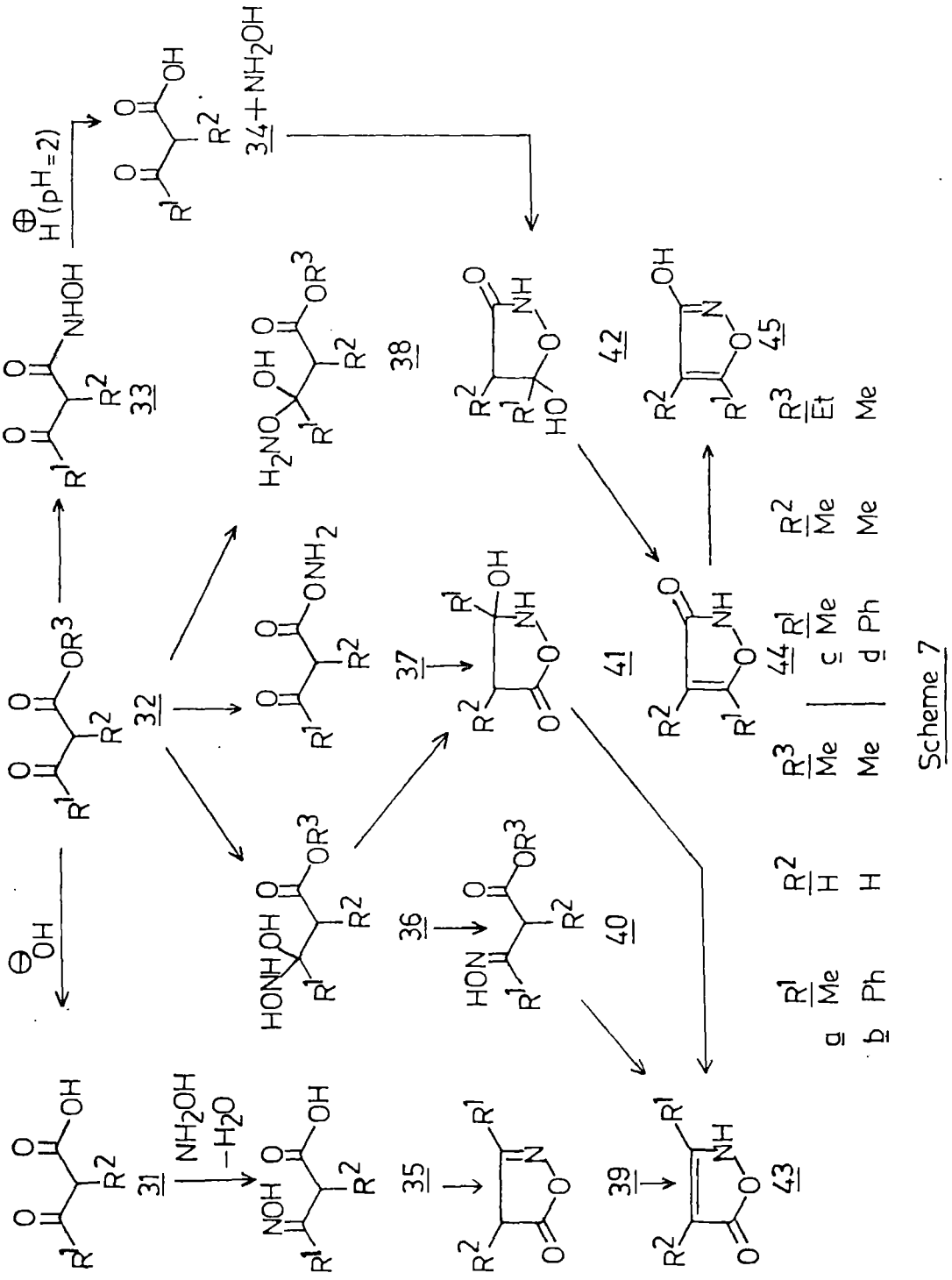
Scheme 5

of 30 becomes predominant (Scheme 6). Subsequently, Katritzky and co-workers[17] made detailed investigations on the reaction of β-keto-esters with hydroxylamine. The reaction of these esters with hydroxyl-amine was also found to be pH dependent. At pH 10-12 a mixture of isoxazolin-5-one 39 and 5-hydroxyisoxazolidin-3-ones 42 are obtained although, the latter isomer predominated on rapid acidifi-cation. Interestingly, they have found that on slow reduction of pH, the hydroxyisoxazolidin-5-one 41 is formed which opens and recloses to give isomeric isoxazolin-5-one 43. In the pH range of 10-12, the pathway 32-36-40-43 is consistant, while the intermediate 42 requires dehydration to form 44 or 45 on rapid acidification (Scheme 7).

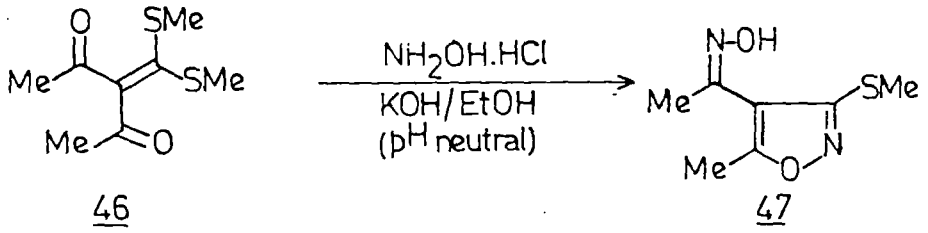
The doubly activated oxoketenedithioacetal 46 has been reacted with hydroxylamine hydrochloride at neutral pH by Darnow and Dehmer[18] to afford the oxime of the corresponding 3-thiomethyl-4-acetyl-5-methylisoxazoles in good yields (Scheme 8). Similarly, Rudorf and co-workers[19] reacted α-cyanooxoketene dithioacetals 48 with hydroxyl-amine hydrochloride in the presence of calcium hydroxide to yield the corresponding 3-methylthio-4-cyano-5-substituted isoxazoles 49 in high yields. It is important to note that the double activation of ketene S,S-acetals either by addition of acetyl, cyano or any other electron withdrawing groups, renders the β-carbon highly electrophilic so that the nitrogen of NH_2OH is the operative nucleo-phile which attacks the highly electrophilic β-carbon to afford single regioisomers 47 and 49 in high yields (Scheme 8). Similarly, Gompper[20] and co-workers reacted doubly activated ketene dithioacetals



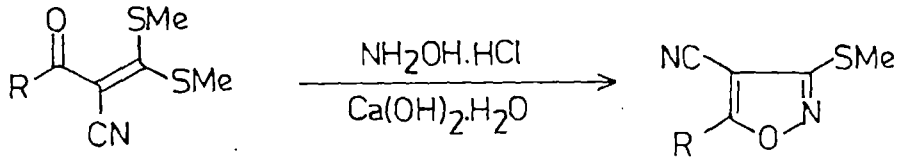
Scheme 6



Scheme 7



46 47



48 49

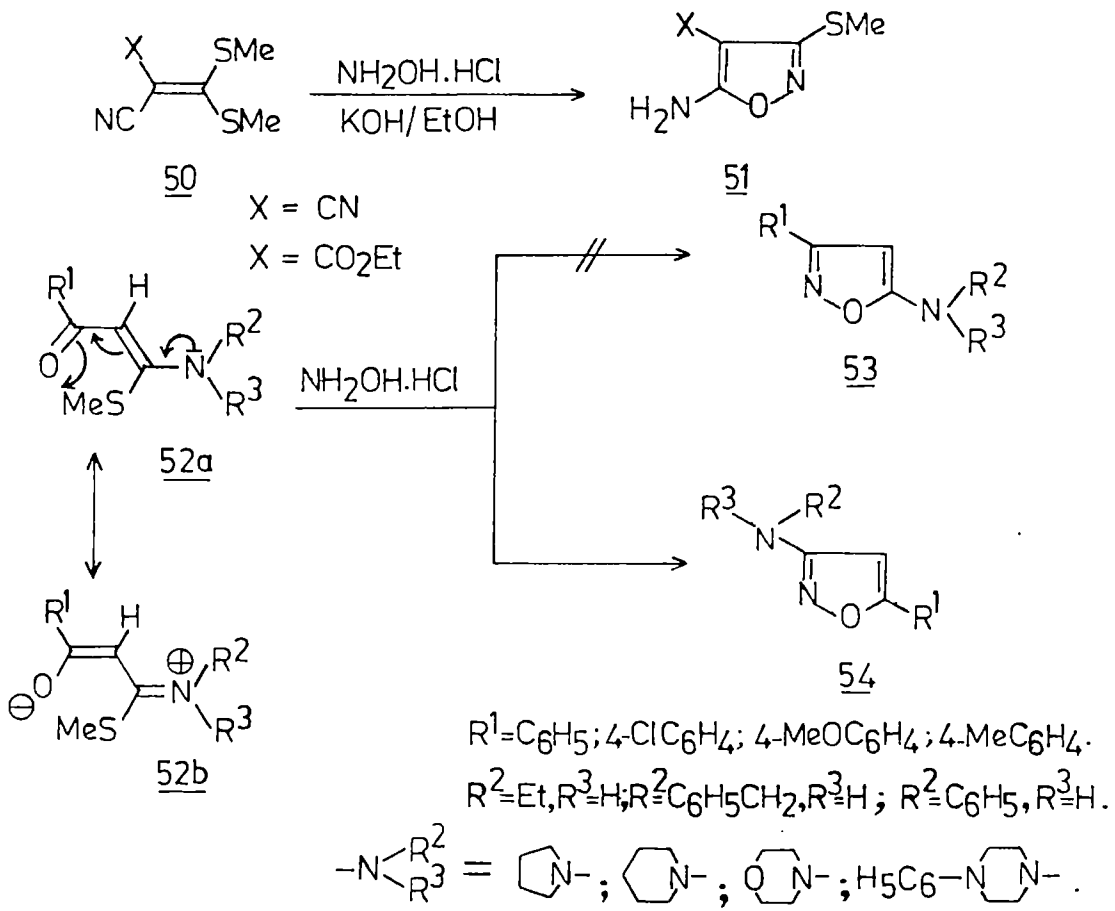
R	% yield
C_6H_5	70
4-ClC_6H_4	45
2-Furyl	68

Scheme 8

50 with hydroxylamine in the presence of potassium hydroxide in ethanol to afford 3-thiomethylisomers 51 exclusively (Scheme 9).

In our laboratory, Rahman, Ila and Junjappa[21] when reacted oxoketene S,N-acetals 52 with hydroxylamine hydrochloride in the presence of base, obtained exclusively one regioisomer, i.e. 3-aminoisoxazoles 54 in high yields. No trace of other isomeric isoxazole 53 was detected in the reaction mixture. The reactivity can be explained on the hard-soft dissymmetry inversion inducted by displacing one of the thiomethyl groups by the amino functionality and the enaminones thus exist predominantly in the resonance form 52b, where the β-carbon displays pronounced electrophilicity over that of carbonyl carbon to afford only the regioisomer 54 (Scheme 9).

The α-oxoketene dithioacetals having 1,3-discriminating electrophilic centres, can serve as versatile 3-carbon synthons in reactions with binucleophiles to yield the corresponding fully aromatised 5-membered heterocyclic systems. Their reaction with hydroxylamine has only been studied with doubly activated systems and α-oxoketene S,N-acetals where in both the cases the β-carbon is more strongly electrophilic than the carbonyl carbon yielding only a single 3-methylthio isomer while the corresponding 5-methylthio isomers were not detected in the reaction mixture (Scheme 8 and 9). In the light of pH dependent reactions of hydroxylamine with β-ketoesters , β-diketones and other 1,3-electrophilic compounds it is pertinent to investigate the reaction of hydroxylamine with α-oxoketene dithioacetals under different pH conditions with a view to elucidate the optimum reaction



R^1=C_6H_5; 4-ClC_6H_4; 4-MeOC_6H_4; 4-MeC_6H_4.

R^2=Et, R^3=H; R^2=$C_6H_5CH_2$, R^3=H; R^2=C_6H_5, R^3=H.

$-N\begin{matrix}R^2\\R^3\end{matrix}$ =

Scheme 9

path requirements for the synthesis of both the regioisomers. These investigations have been described in this Chapter.

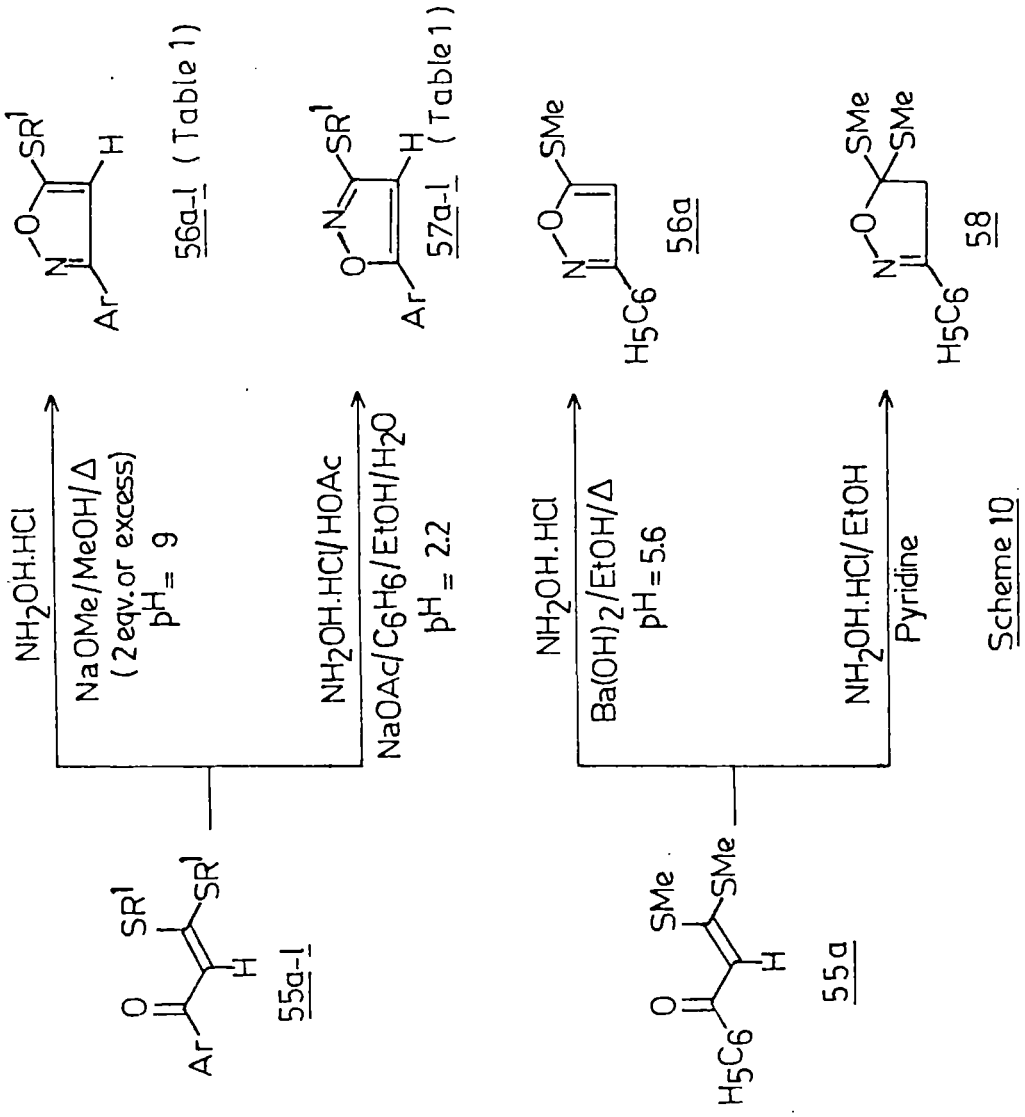
II.2 RESULTS AND DISCUSSION

When α-oxoketene dithioacetal 55a (Ar=C_6H_5; R^1=Me) was reacted with hydroxylamine hydrochloride in the presence of excess sodium methoxide in refluxing methanol, after work-up, the reaction mixture yielded a pale yellow solid m.p. 40°C; in 78% yield which was characterised as 5-methylthio-3-phenylisoxazole 56a (Table 1) on the basis of spectral and analytical data. Thus, 56a showed molecular ion peak at m/z 191 (M^+ 42%) and it was analysed for $C_{10}H_9NOS$. Its i.r. spectrum (KBr) exhibited bands at 1540, 1500, 1450, 1400 cm^{-1} of which 1540 band appears to be due to C=N system. The structural assignment was further confirmed by its ^1H n.m.r. signals ($CDCl_3$). Thus, a singlet at δ 2.56(3H) was assigned to SCH_3 protons and the other singlet at δ 6.33 was assigned to H-4 proton. The multiplet between δ 7.33-7.61 (3H) were assigned to 3 aromatic protons and the remaining two protons exhibited signals between δ 7.71-8.15. The structural assignment was further confirmed by its ^{13}C n.m.r. spectral data. A signal at δ_C 15.46 was assigned to SCH_3 carbon and the other signal at δ 100.07 was assigned to C-4. The signals at δ 126.74, 128.90, 130.09 were assigned to CH phenyl, 128.95(C-1' phenyl) and the signal at 162.99 was assigned to C-3 while the signal at 168.05 was assigned to C-5).

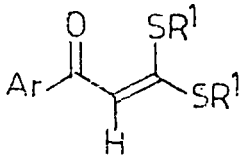
Apparently from the structural assignment of 56a and its comparison with the data of the reported[22] compound confirms the position of the thiomethyl group at C-5. The position of the thiomethyl group

was further confirmed by its mass fragmentation, where a clear distinction of the 5-alkylthio and 3-alkylthio regioisomers could be made by means of their characteristic fragmentation pattern. The isoxazole 56a showed characteristic peaks at m/z 144(100%) and 116(29%) due to loss of SCH_3 and $COSCH_3$ fragments (M^+-47 and M^+-75) respectively suggesting that the thiomethyl group is adjacent to ring oxygen atom. The synthesis of 56a was also achieved regioselectively employing barium hydroxide as base. It is interesting to note that isoxazoline 58 was formed when pyridine was used as base (Scheme 10).

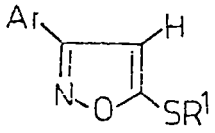
When the α-oxoketene dithioacetal 55a was reacted with hydroxylamine hydrochloride in the presence of sodium acetate in a refluxing mixture of acetic acid, benzene, water and ethanol (pH = 2.2) the product isolated in 65% yield; m.p. 65°C was characterised as 3-methylthio-5-phenyl isoxazole 57a on the basis of spectral and analytical data. Thus, 57a showed molecular ion peak at m/z 191 (M^+,62%)and it was analysed for $C_{10}H_9NOS$. Its i.r. spectrum (KBr) exhibited bands at 1600, 1580, 1560, 1482, 1440, 1402 cm^{-1}. The structure was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$). The signal at δ 2.58(3H) was assigned to $S\underline{CH}_3$ protons and the singlet at δ6.27 integrating for 1 proton was assigned to H-4 proton. The multiplet between δ 7.17-7.45 was assigned to three aromatic protons whereas the other multiplets between 7.49-7.79 was assigned to the remaining two aromatic protons. The structure was also confirmed from its ^{13}C n.m.r. spectral data which showed signals at δ_C13.90($S\underline{CH}_3$); 99.07(C-4); 125.79 128.91, 130.27(CH, phenyl), 127.18(C-1',phenyl), 160.89(C-3) and


NH2OH.HCl
NaOMe/MeOH/Δ
(2eqv.or excess)
pH= 9
NH2OH.HCl/HOAc
NaOAc/C6H6/EtOH/H2O
pH= 2.2
55a-1
56a-1 (Table 1)
57a-1 (Table 1)
NH2OH.HCl
Ba(OH)2/EtOH/Δ
pH=5.6
NH2OH.HCl/EtOH
Pyridine
55a
56a
58

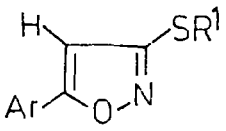
Scheme 10



55



56



57

55,56,57	Ar	R^1
a	C_6H_5	CH_3
b	C_6H_5	C_2H_5
c	C_6H_5	$n\text{-}C_3H_7$
d	$4\text{-}MeC_6H_4$	CH_3
e	$4\text{-}ClC_6H_4$	CH_3
f	$4\text{-}MeOC_6H_4$	CH_3
g	$4\text{-}BrC_6H_4$	CH_3
h	$2,4\text{-}Cl_2C_6H_3$	CH_3
i	$4\text{-}EtOC_6H_4$	CH_3
j	2-naphthyl	CH_3
k	2-pyridyl	CH_3
l	2-furyl	CH_3

Table 1

169.89(C-5) respectively. The structural confirmation was further carried out from its mass spectral fragmentation pattern. The 3-methylthio isoxazole 57a exhibits low intensity peak at m/z 144(10%) for the (M^+-47) fragment whereas, the base peak corresponds to C_6H_5CO group (m/z = 105) at m/z 105(100%) confirming that the phenyl group is adjacent to neighbouring oxygen atom. Therefore, the crucial mass fragmentation pattern distinguishing between 56a and 57a is the benzoyl cation which is not formed in case of 56a.

Thus, it is feasible to prepare 5-methylthio-3-phenylisoxazole 56a and 3-methylthio-5-phenylisoxazole 57a from the same α-oxoketene dithioacetal 55a using appropriate reaction conditions. The regioselective 56a is formed by using both sodium methoxide and barium hydroxide either in equivalent or excess amounts in the pH range of 5.6-9. The predominant species upto pH=10 has been shown to be neutral hydroxylamine molecule which proves that the role of base in these reactions is limited only to the release of free NH_2OH from its salt. It, therefore, does not exert any observable effect on the substrate α-oxoketene dithioacetal which undergoes oxime 69a formation as a first step followed by ring closure to form isoxazole 56 (Scheme 12). On the otherhand, in the presence of sodium acetate acetic acid medium (pH=2.2), the dominant species is the hydroxylammonium ion with only a small amount of free NH_2OH, which adds regioselectively to more electrophilic C-3 of 65b in the rate determining step followed by intramolecular ring closure to yield 3-alkylthio isoxazole 57 (Scheme 12). It is interesting to note that the formation

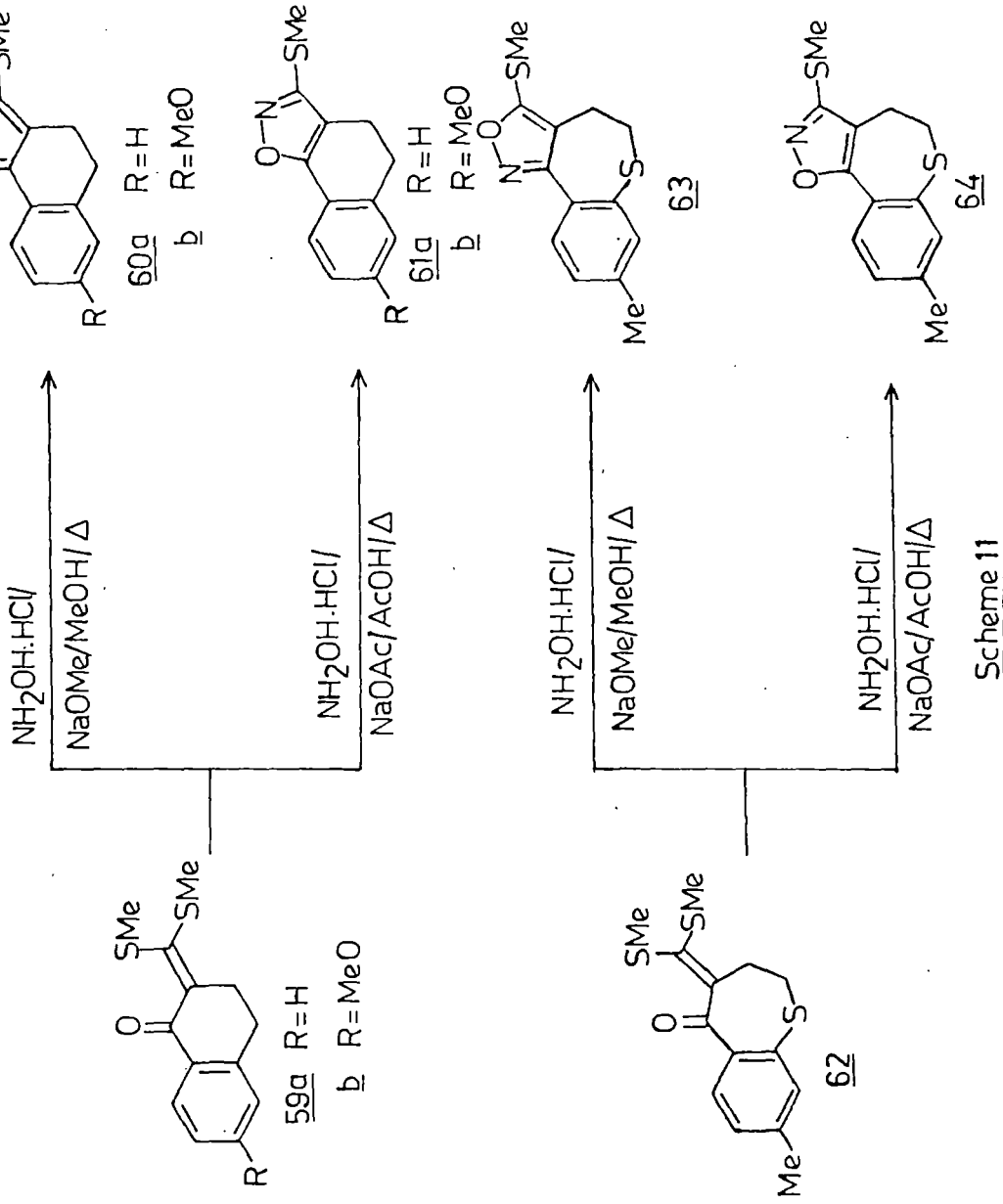
of highly regioselective isoxazoles under different pH conditions reveals a clear case of inversion of 1,3-electrophilicity in 55. In the acidic medium the hard base oxygen undergoes protonation to give the corresponding protonated species 65a and 65b which can be termed as hard soft dissymmetry inversion or hard soft affinity inversion where the β-carbon is rendered more electrophilic. The hydroxylamine N-nucleophile from the equilibrium mixture, therefore, attacks the β-carbon to give intermediate 67 through 66 followed by cyclisation to yield isoxazole 57 (Scheme 12).

After establishing the exact reaction condition to make appropriate regioisomers of isoxazoles, it became necessary to study the generality of the reaction to demonstrate the synthetic usefulness of the method. Thus the α-oxoketene dithioacetals 55b-l were reacted with hydroxylamine under basic conditions (Method A) when the corresponding 5-alkylthioisoxazoles 56b-l were obtained in 58-77% overall yields and in all the cases only one regioisomer was formed. Similarly when the oxoketene dithioacetals 55b-l were reacted with hydroxylamine hydrochloride in the presence of sodium acetate and acetic acid at pH 2.2, (Method B) when the corresponding 3-alkylthioisoxazoles 57b-l were formed in 51-68% overall yields (Scheme 10 and Table 1). However in the case of 57b and 57c the reaction mixture was found to be contaminated with about 5% of the other regioisomers. The structural assignment of these isoxazoles was confirmed by their analytical and spectral data which were fully in agreement with the assigned structure. The details of these are described in the experimental section.

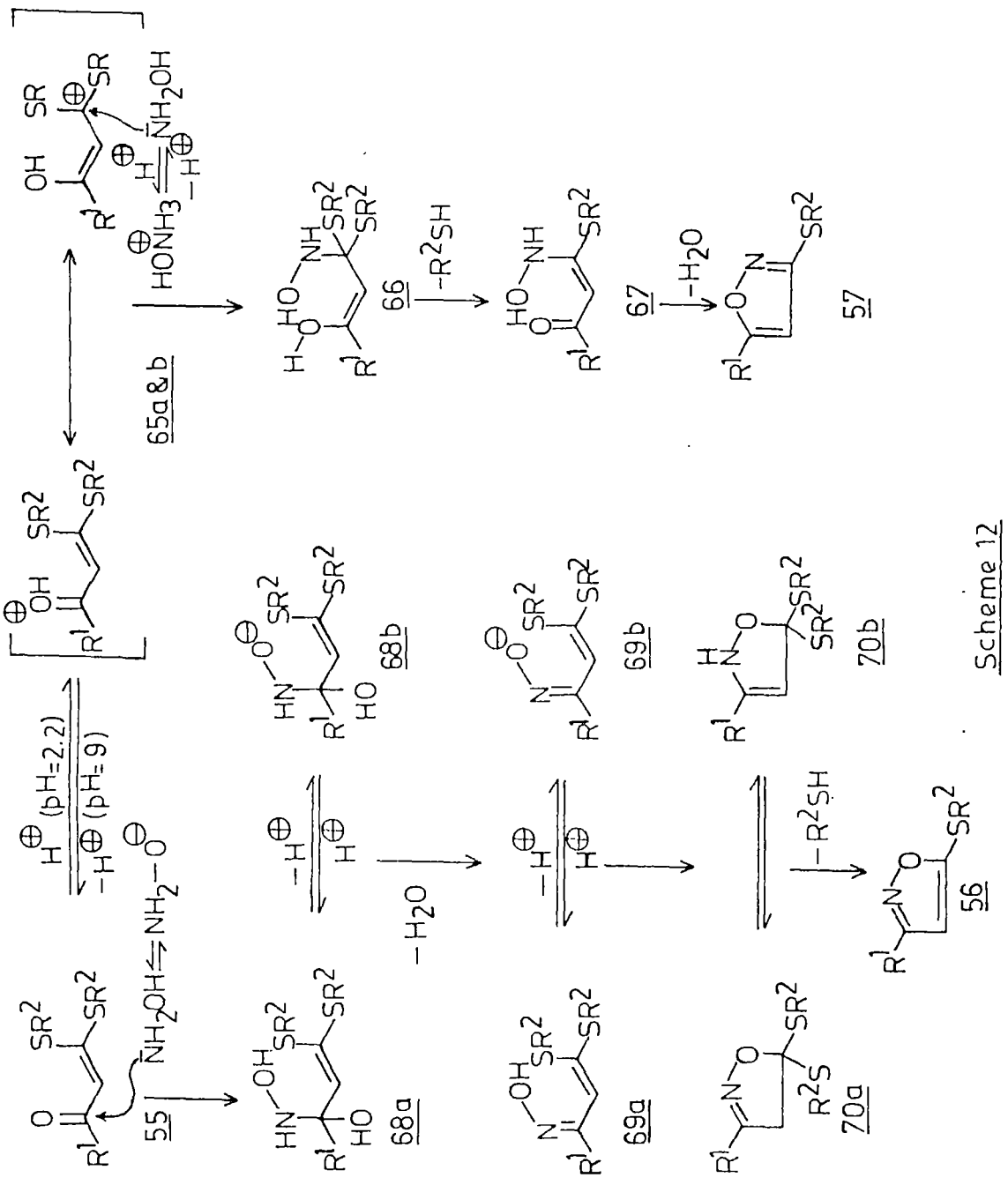
The regioisomeric isoxazoles 56 and 57 were distinguished with the help of their mass spectral fragmentation pattern (Scheme 13). Thus all 5-alkylthio isoxazoles showed characteristic peak due to loss of $COSR^1$ group (M^+-COSR^1) showing that alkylthio group is adjacent to oxygen while the presence of base peak due to $ArCO^+$ ion in the mass spectra of 3-alkylthioisoxazoles confirmed the presence of aryl group at 5-position of isoxazoles in this series (Scheme 13).

The cyclic α-oxoketene dithioacetals 59a and 59b were similarly reacted with hydroxylamine under both the described reaction conditions when the corresponding 5-methylthio isoxazoles 60a (78%), 60b (57%) and the corresponding 3-methylthio isoxazoles 61a (64%), 61b (53%) were obtained (Scheme 11). The method was also found to be general with α-oxoketene dithioacetal 62 which yielded the corresponding 3,4-annelated-5-methylthio isoxazole 63 and 4,5-annelated 3-thiomethylisoxazoles 64 in 78% and 53% yields respectively (Scheme 11). The analytical and spectral data of these compounds were in confirmity with their assigned structures which are described in experimental section.

It is pertinent to note that very few alkylthio isoxazoles are reported in the literature. The reported synthesis of 5-alkylthio isoxazoles 56a and 56b involves the reaction of isoxazolone 81 with phosphorous oxychloride in presence of triethylamine, to yield 5-chloroisoxazole 82 which is subsequently heated with sodium alkylthiolates to yield 5-alkylthioisoxazoles (Scheme 14)[22]. The 3-alkylthioisoxazoles 57a-c have been obtained by the reaction of 3-chloroisoxazolium chloride 84


NH2OH.HCl/
NaOMe/MeOH/Δ
NH2OH.HCl/
NaOAc/AcOH/Δ
59a R=H
b R=MeO
60a R=H
b R=MeO
61a R=H
b R=MeO
62
63
64

Scheme 11

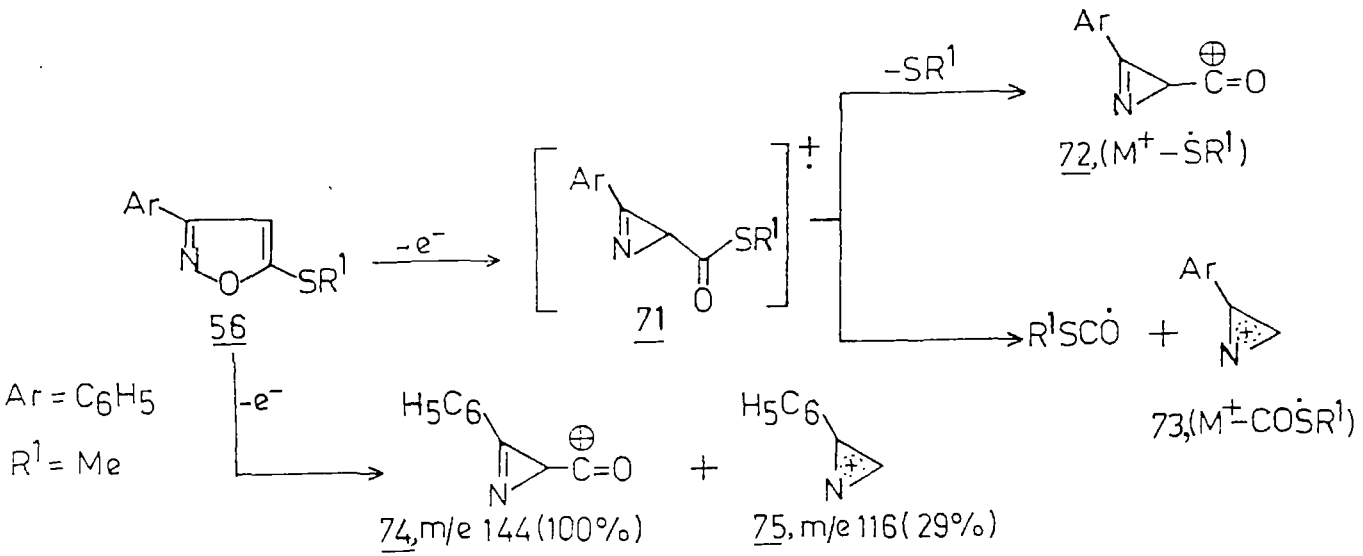


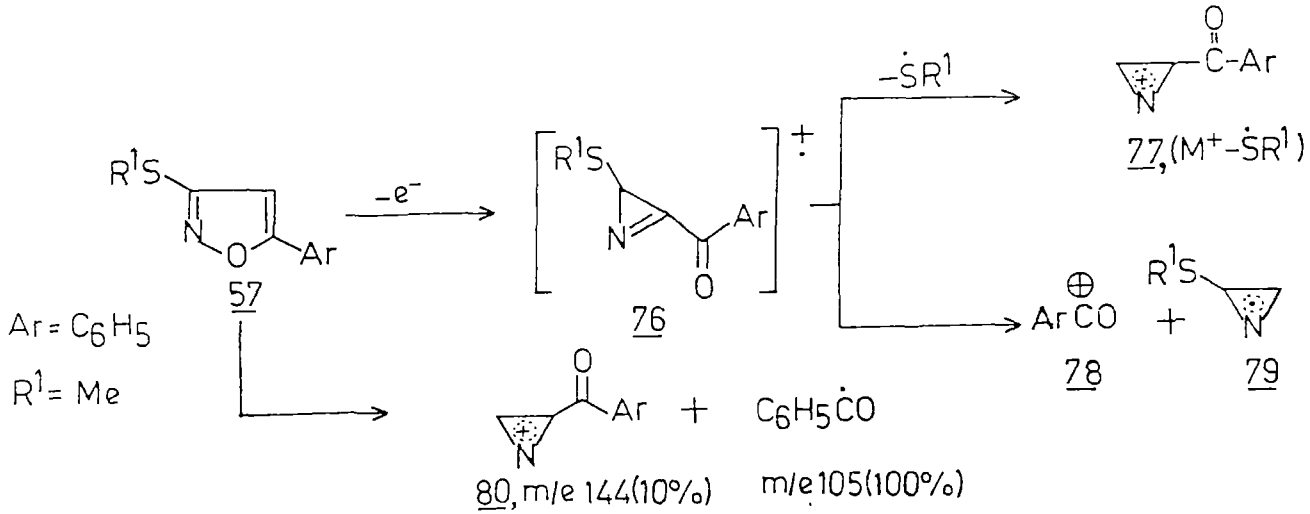
Scheme 12

with sodium hydrogen sulfide or thiourea to yield 2-benzyl-4-isoxazolin-3-thione 87, which on treatment with excess of alkyl-halide and subsequent heating yielded the corresponding 3-alkylthio isoxazoles (Scheme 15)[23]. The methodology has also been extended to 3-phenylthio 86 and 3-carboxymethylthio isoxazoles 89 also (Scheme 15). The 3-ethylthioisoxazole 57b has also been synthesized by reaction of 3-hydroxy-5-phenyl isoxazole 91 with thiophosphite (Scheme 16)[24]. Similarly the 5-ethylthio isoxazoles 56b has also been obtained by the reaction of benzonitrile N-oxide 94b with ketene dithioacetal 93 (Scheme 16)[25].

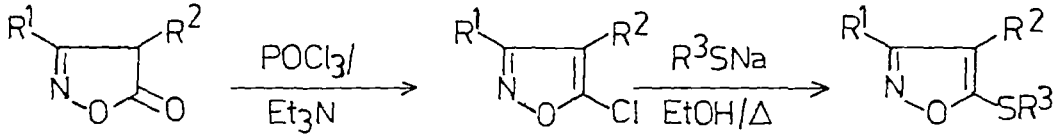
Some of the 5-alkylthio-3-arylisoxazoles 56 have been found to exhibit anthelmintic activity[26,27].

The α-enyl oxoketene dithioacetals were of particular interest structurally, since the carbonyl functionality is flanked between double bonds from both sides and they are of interest as substrates for the synthesis of enyl isoxazoles under the described reaction conditions. On survey of literature it was revealed that they were prepared by condensing α-acetyl ketene dithioacetals with aldehydes in presence of a base. Thuillier and co-workers[28] have reported the synthesis of a number of these enyl oxoketene dithioacetals which were prepared in this laboratory in addition to some of the acetals which were unreported earlier. Thus the dithioacetal 98o-98q which were not reported earlier were prepared as a part of the present investigation by condensing 96 with 5-aryl-2,4-pentadienals in high yields. The structures of 98o-98q were established by its


Ar
SR1
56
-e⁻
71
-SR1
72,(M+ - ṠR1)
R1SCȮ
73,(M± COṠR1)
Ar = C6H5
R1 = Me
H5C6
C=O
74, m/e 144 (100%)
75, m/e 116 (29%)


R1S
Ar
57
-e⁻
76
-ṠR1
77,(M+ - ṠR1)
ArCO
78
79
Ar = C6H5
R1 = Me
80, m/e 144 (10%)
C6H5ĊO
m/e 105 (100%)

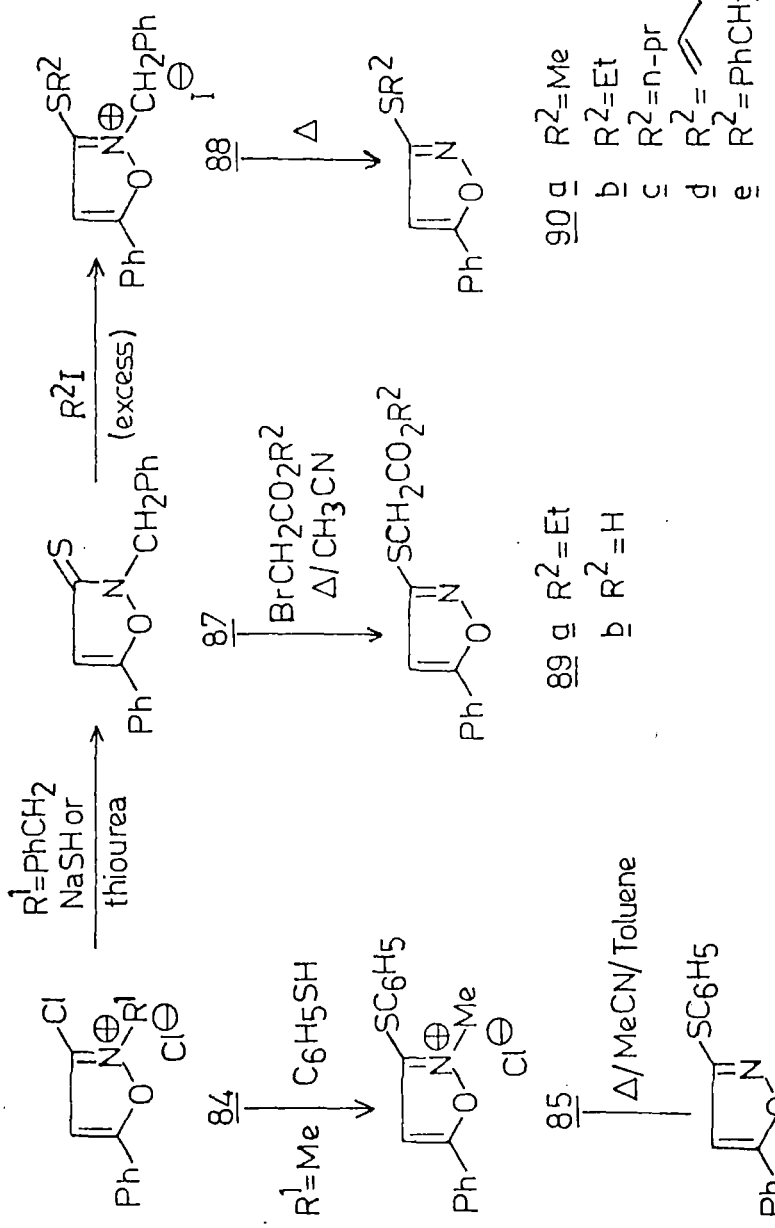
Scheme 13



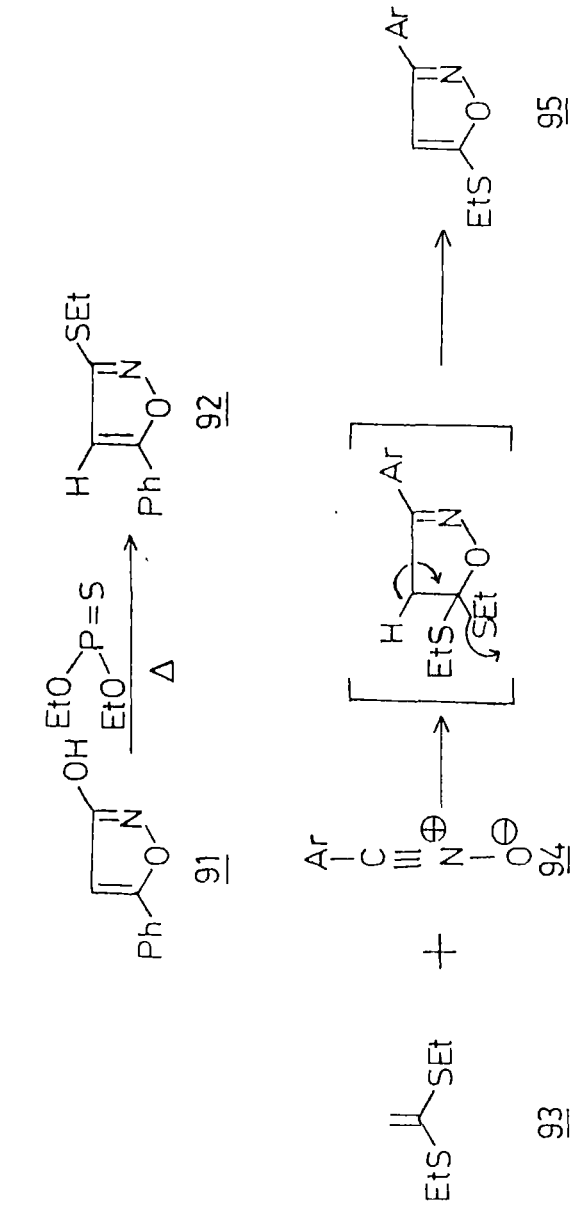
81 82 83

81, 82, 83 a $R^1 = C_6H_5$; $R^2 = H$; $R^3 = Me$
b $R^1 = C_6H_5$; $R^2 = H$; $R^3 = Et$
c $R^1 = C_6H_5$; $R^2 = H$; $R^3 = n\text{-}Bu$
d $R^1 = C_6H_5$; $R^2 = Me$; $R^3 = Et$
e $R^1 = 4\,MeOC_6H_4$ $R^2 = H$; $R^3 = Me$

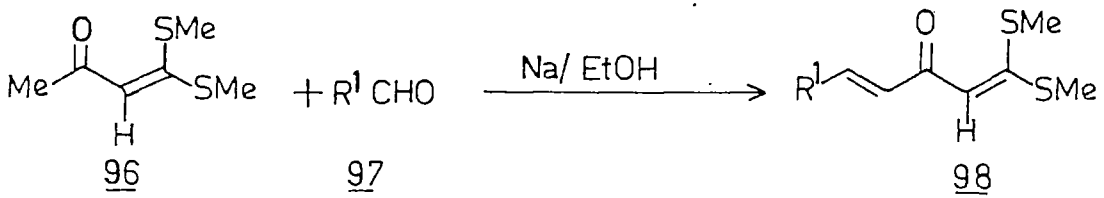
Scheme 14


R1=PhCH2
NaSH or
thiourea
R2I
(excess)
84
R1=Me
C6H5SH
87
BrCH2CO2R2
Δ/CH3CN
88
Δ
85
Δ/MeCN/Toluene
86
89 a R2=Et
b R2=H
90 a R2=Me
b R2=Et
c R2=n-pr
d R2=
e R2=PhCH2

Scheme 15


OH
EtO
EtO
P=S
Ph
N
O
91
Δ
SEt
H
Ph
92
Ar
C
N
O
94
+
EtS
SEt
93
H
Ar
EtS
SEt
Ar
N
O
95
a Ar = 4-ClC6H4 45%
b Ar = C6H5 53%
c Ar = 4-MeC6H4 50%

Scheme 16



96 97 98

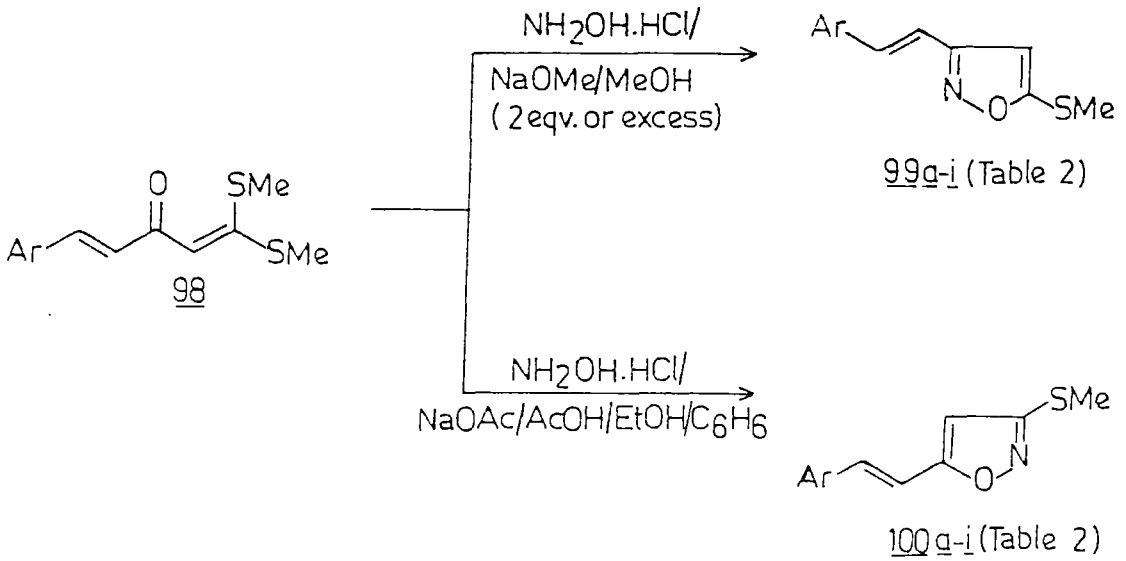
a	$R^1 = C_6H_5$	j	$R^1 = 3,4\text{-}(MeO)_2C_6H_3$
b	$R^1 = 4\text{-}MeC_6H_4$	k	$R^1 = 3,4,5\text{-}(MeO)_3C_6H_2$
c	$R^1 = 4\text{-}ClC_6H_4$	l	$R^1 = C_6H_5CH{=}CH\text{-}$
d	$R^1 = 4\text{-}MeOC_6H_4$	m	$R^1 = 4\text{-}MeOC_6H_4CH{=}CH\text{-}$
e	$R^1 = 4\text{-}Me_2NC_6H_4$	n	$R^1 = 3,4\text{-methylenedioxy}\,C_6H_3CH{=}CH\text{-}$
f	$R^1 = 2\text{-}ClC_6H_4$	o	$R^1 = C_6H_5\text{-}CH{=}CH\text{-}CH{=}CH\text{-}$
g	$R^1 = 2,6\text{-}Cl_2C_6H_3$	p	$R^1 = 4\text{-}MeOC_6H_4\text{-}CH{=}CH\text{-}CH{=}CH\text{-}$
h	$R^1 = 2,4\text{-}Cl_2C_6H_3$	q	$R^1 = 3,4\text{-methylenedioxy}\,C_6H_3CH{=}CH\text{-}CH{=}CH\text{-}$
i	$R^1 = 3,4\text{-methylenedioxy}\,C_6H_3$		

Scheme 17

analytical and spectral data which are described in the experimental section. When 98a, in a typical reaction was treated with hydroxylamine hydrochloride in the presence of sodium methoxide the expected regioisomer 5-methylthio-3-styrlisoxazole 99a was obtained in moderate yield (37%). The structure of 99a was fully confirmed by its analytical and spectral data and those are duly described in the experimental section.Similarly,other 3-enylisoxazoles 99b-i were prepared respectively from 98b-i and hydroxylamine in 35-49% overall yields. The analytical and spectral data of these compounds have been described in the relevant portion of the experimental section.

Likewise it was decided to study the reactivity of the dienyl 98l-n and trienyl 98o-q oxoketene dithioacetals whether the olefinic double bonds could be retained without participating in the ring formation process. When 98l-n were reacted with hydroxylamine hydrochloride with 2 equivalents of sodium methoxide the corresponding 3-(4-aryl-1,3-butadienyl-5-methylthioisoxazoles 101a-c were obtained in 41-44% overall yields. The analytical and spectral data were in conformity with the assigned structures and the results are described in the experimental section. Similarly 3-(6-aryl-1,3,5-hexatrienyl)-5-methylthioisoxazoles 103a-c were prepared under the condition described for 101a-c in 38-44% overall yields.

The corresponding 3-methylthio regioisomers were also prepared by extending the present methodology. Thus, 98a was reacted with hydroxylamine hydrochloride and sodium acetate in refluxing mixture of acetic acid, benzene, water and ethanol (pH 2.2) to afford the

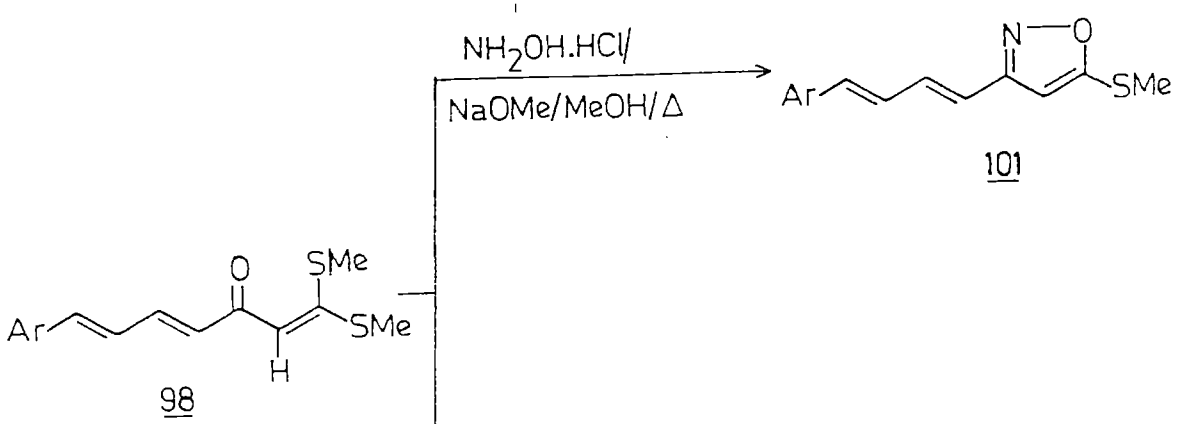


98, 99, 100 a Ar = C_6H_5
b Ar = 4-MeC_6H_4
c Ar = 4-ClC_6H_4
d Ar = 4-$MeOC_6H_4$
e Ar = 4-$Me_2NC_6H_4$
f Ar = 2-ClC_6H_4
g Ar = 2,6-$Cl_2C_6H_3$
h Ar = 2,4-$Cl_2C_6H_3$
i Ar = 3,4-methylenedioxy C_6H_3

Scheme 18

corresponding 3-methylthio-5-styryl isoxazole 100a in moderate yield (56%). The structure was fully confirmed by its analytical and spectral data which are described in experimental section. Similarly, the other oxoketene dithioacetals 98b-i were reacted with hydroxylamine hydrochloride to afford the corresponding 5-styryl-3-methylthioisoxazoles 100b-i in 35-65% overall yields. The analytical and spectral data of these compounds are described in the experimental section. The isomeric 3-methylthio-5-(4-aryl-1,3-butadienyl)102a-c and 3-methylthio-5-(6-aryl-1,3,5-hexatrienyl) isoxazoles 104a-c were prepared from the appropriate oxoketene dithioacetals respectively. The analytical and spectral data of 100b-i, 102a-c and 104a-c are fully in conformity with the assigned structures and they are described in the experimental section.

The characteristic mass fragmentation pattern of both the regioisomers could easily be understood as an index of recognizing the individual regioisomers. Thus, 5-methylthioisoxazole 99a on first ionisation followed by loss of methylmercaptan yields the cation 106 (m/z 170 (60%) which, with the loss of carbon monoxide goes to mass fragment. 107 m/z 142 (35%) styrylazirinium ion. The mass fragment corresponding to 107 (M^+-COSMe) in all the isoxazoles 99a-i confirming the presence of methylthio group in 5-position of isoxazole. On the otherhand, 3-methylthio-5-styrylisoxazole 100a underwent cleavage to give the first fragment 110 which breaks down to styryl cation radical 111 [m/z 103 (51%)] and formylazirinium cation 112 [m/z 113 (33%)]. The present procedure utilising easily accessible oxoketene dithioacetals 98 with built-in styryl moiety provides a simple route



l , Ar = C_6H_5

m , Ar = 4-$MeOC_6H_4$

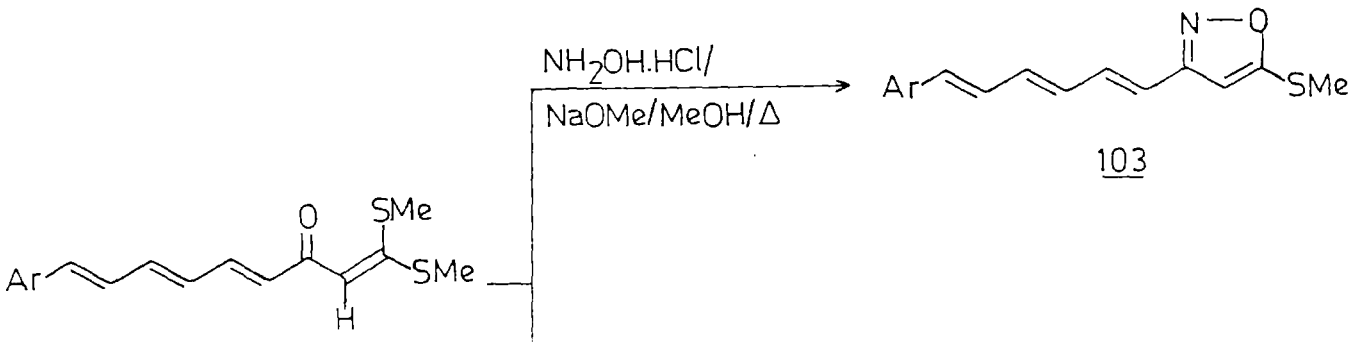
n , Ar = 3,4-methylenedioxy C_6H_3

101 , 102 a , Ar = C_6H_5

b , Ar = 4-$MeOC_6H_4$

c , Ar = 3,4-methylenedioxy C_6H_3

Scheme 19



o, Ar = C_6H_5

p, Ar = 4-$MeOC_6H_4$

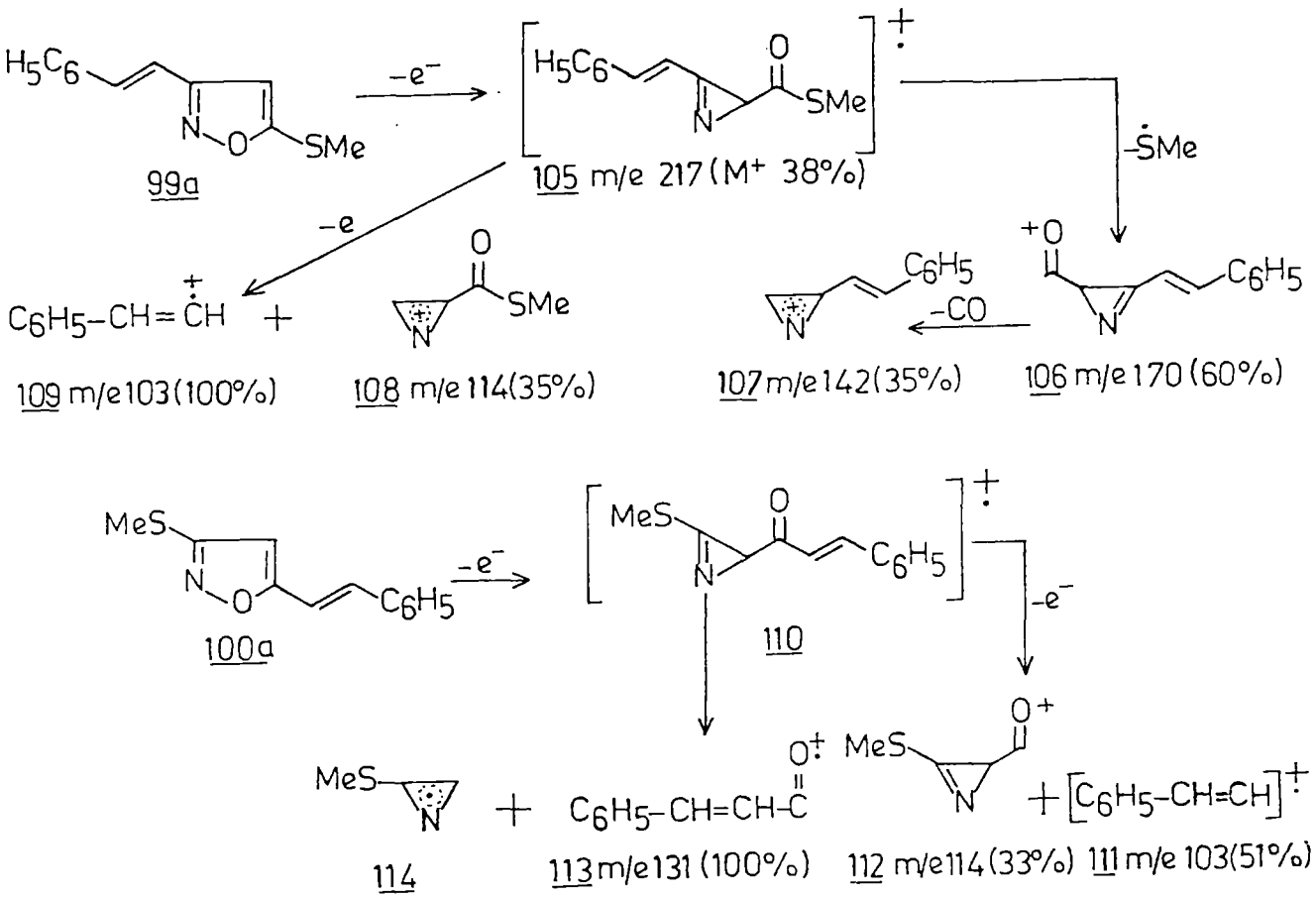
q, Ar = 3,4-methylenedioxy C_6H_3

103,104 a, Ar = C_6H_5

b, Ar = 4-$MeOC_6H_4$

c, Ar = 3,4-methylenedioxy C_6H_3

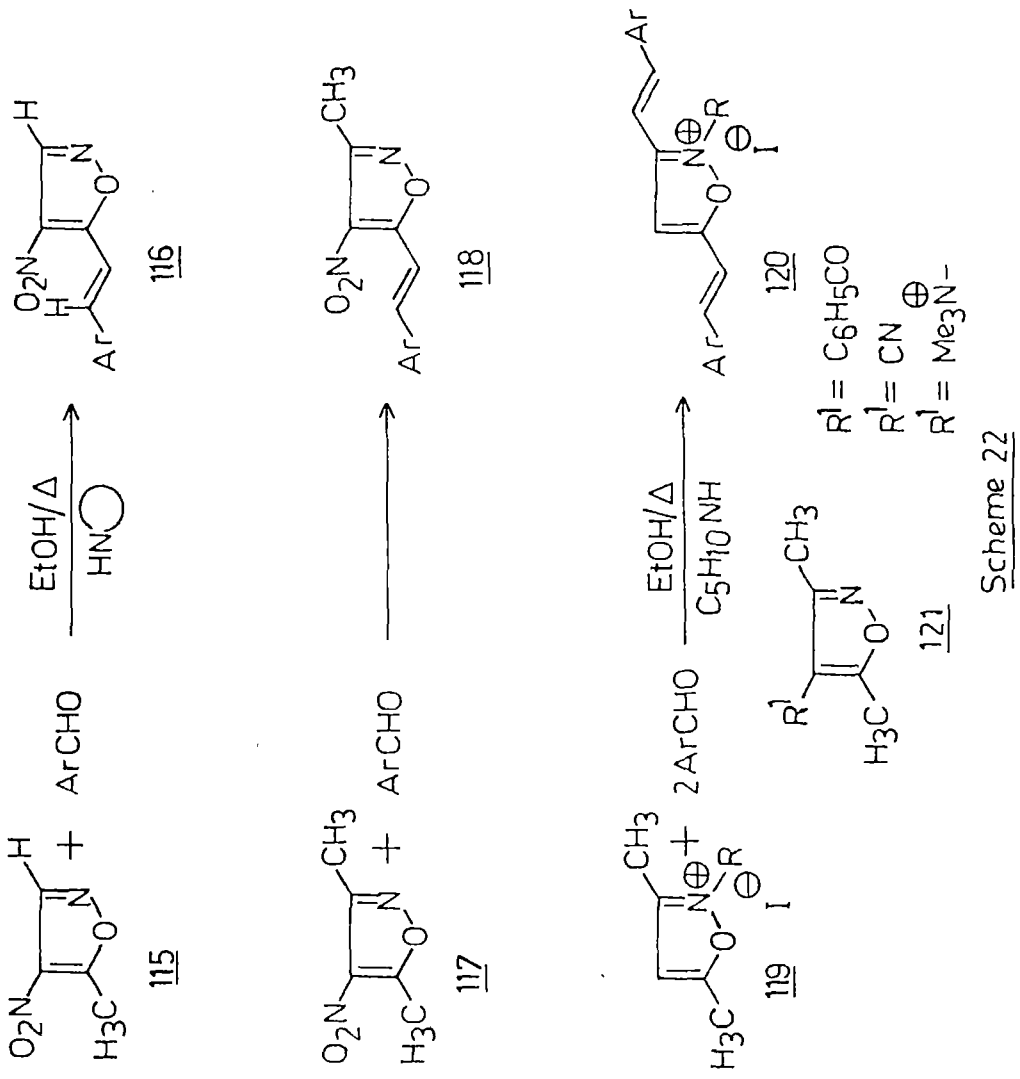
Scheme 20


H5C6
SMe
99a
-e⁻
105 m/e 217 (M+ 38%)
-e
-ṠMe
C6H5-CH=ĊH
109 m/e103(100%)
108 m/e 114(35%)
107 m/e142(35%)
-CO
106 m/e 170 (60%)
MeS
100a
-e⁻
110
-e⁻
114
C6H5-CH=CH-C
113 m/e131 (100%)
112 m/e114(33%)
111 m/e 103(51%)

Scheme 21

for both the regioisomers in moderate to good yields. Only a few 5-styrylisoxazoles have been reported in the literature. The 4-nitro-5-styrylisoxazole 116 is obtained by base catalyzed condensation of 4-nitro-5-methylisoxazole 115 with aromatic aldehydes (Scheme 22). Similarly the 3,5-dimethyl-4-nitroisoxazole 117 yielded[30] 3-methyl-4-nitro-5-styrylisoxazole 118 (Scheme 22). The presence of 4-nitro group is apparently necessary for the activation of 5-methyl group. The 5-methyl group in isoxazole 121 is also activated by the presence of electron withdrawing groups like C_6H_5CO, CN, $Me_3\overset{+}{N}$-at 4 position of the isoxazole ring and undergoes condensation with aromatic aldehydes to give 5-styryl isoxazole (Scheme 22)[29,30]. When the quaternary alkyl iodide of 3,5-dimethyl isoxazole 119 was condensed with two equivalents of aromatic aldehydes in the presence of piperidine, both the methyl groups participated in the condensation to afford 3,5-distyryl isoxazolium salt 120 (Scheme 22)[31]. These are the only references that are available from the literature on the styrylisoxazoles whereas, the methodology for the dienyl and trienylisoxazoles have not been reported so far. The present method has an advantage to prepare the isoxazoles with the side chain either at 3 or at 5-position by merely changing the reaction condition starting from the same open chain appropriate dithioacetals.

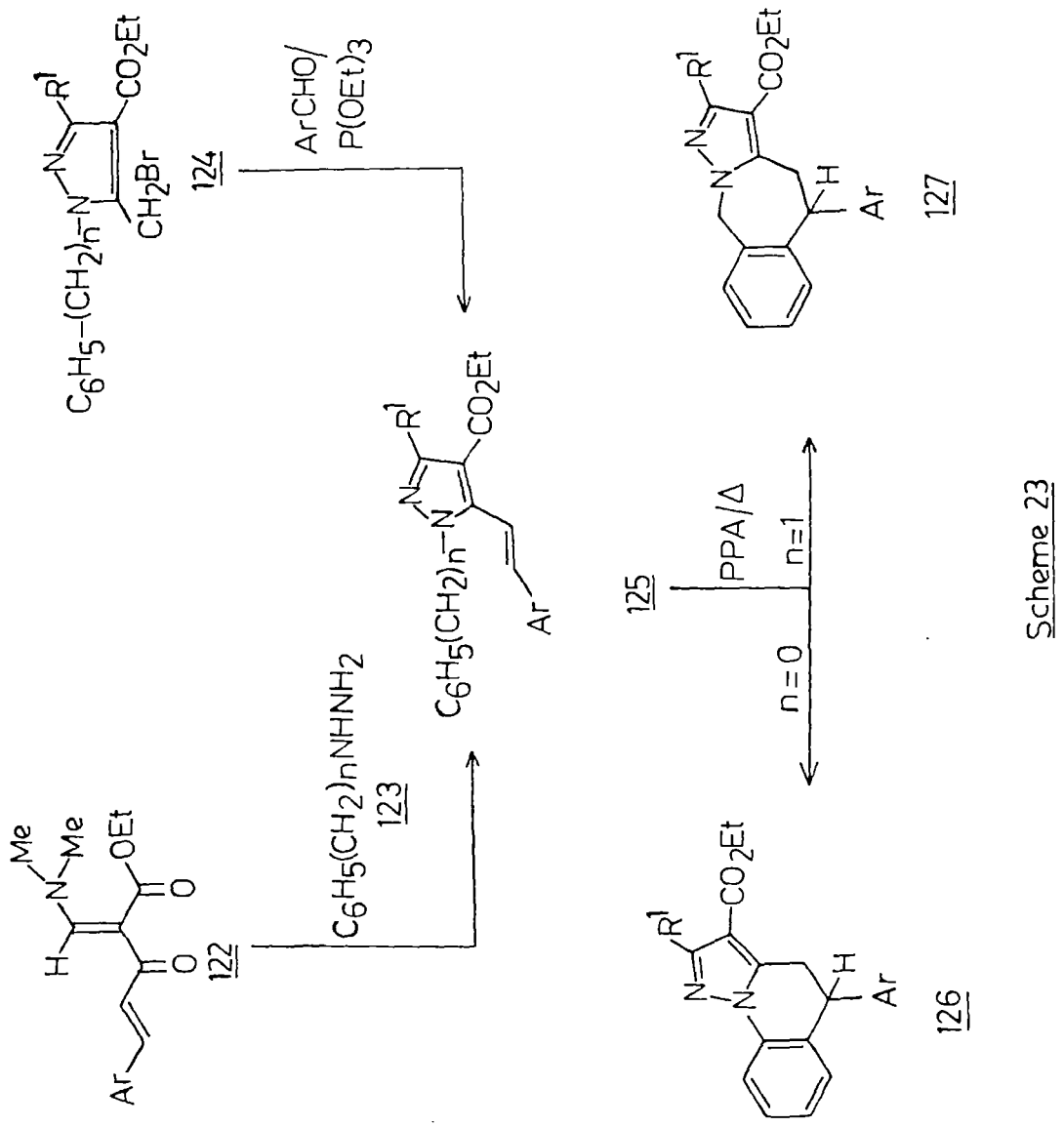
In general, the oxoketene dithioacetals and their structural variants could be efficiently used to prepare highly regioselective isoxazoles by maintaining appropriate pH of the reaction medium. This new general method described therefore should be of considerable synthetic importance.


115
ArCHO
EtOH/Δ
HN
116
117
ArCHO
118
119
2ArCHO
EtOH/Δ
C5H10NH
120
121
R1 = C6H5CO
R1 = CN
R1 = Me3N-

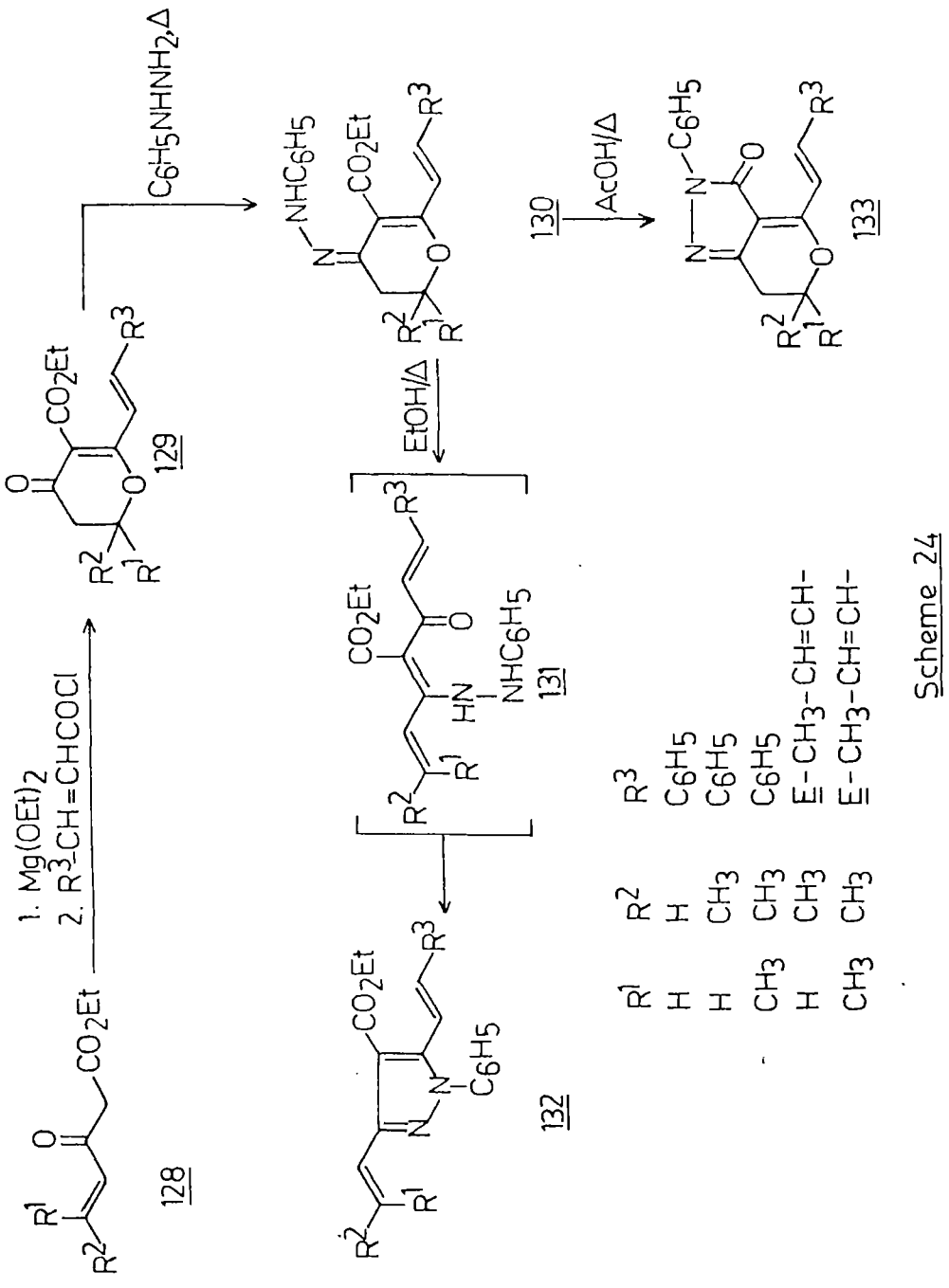
Scheme 22

II.3 SYNTHESIS OF 3-(5)-STYRYLPYRAZOLES AND THEIR HIGHER ENYL HOMOLOGS FROM OXOKETENE DITHIOACETALS:

The reactivity of enyl oxoketene dithioacetals towards hydrazine and its derivatives could be of interest since carbonyl functionality is flanked by two 1,3-electrophilic centres. It is likely that the hydrazine could react with these systems either by first adding to mercapto functionality followed by intramolecular cyclocondensation to afford the appropriate styryl or enyl pyrazoles or the reaction might proceed by adding in Michael fashion followed by cycloconden-sation to afford respective pyrazolines. It was with this interest the literature was surveyed to see whether the conceived pyrazoles or pyrazolines were reported. The known methods of styryl pyrazoles are briefly summarised in this section. In one of these methods β-ketoenaminones 122 are reacted with substituted hydrazines 123 to yield[32] the corresponding 5-styryl pyrazole 125 which was also alternatively been prepared (Scheme 23)[33] from 5-bromomethyl pyrazoles 124 by Wittig-Horner method. The styrylpyrazoles 125 were then cyclized in the presence of polyphosphoric acid to give corresponding fused heterocycles. Similarly the β-enoyl esters 128 reacted with crotonylchloride in the presence of magnesium ethoxide to give dihydropyran-4-ones 129 which were converted first into its hydrazones 130 and then cyclized to the corresponding pyrazolone 133 while the ethanol solution of hydrazone 130 on heating underwent ring cleavage and then cyclisation to yield the corresponding 3,5-distyryl pyrazole 132 (Scheme 24)[34]. Preparation of 5-styrylpyrazole-3-carboxylate by the condensation of ethyl 2,4-dioxo-6-phenyl-hex-5-enoates with various hydrazines is also reported[35].



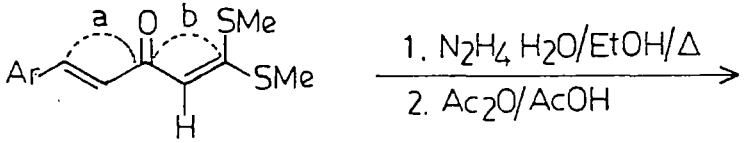
Scheme 23



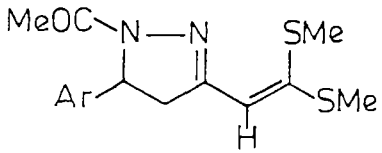
R^1	R^2	R^3
H	H	C_6H_5
H	CH_3	C_6H_5
CH_3	CH_3	C_6H_5
H	CH_3	E-CH_3-CH=CH-
CH_3	CH_3	E-CH_3-CH=CH-

Scheme 24

Apparently the literature on the synthesis of styrylpyrazoles is scanty. Thus it was contemplated to examine the reaction of hydrazine hydrate with various cinnamoyl and their homologous oxoketene dithioacetals. The styryl oxoketene dithioacetal 98a when reacted with hydrazine hydrate in refluxing aqueous ethanol after work-up the reaction mixture turned into intractable tar from which no well defined compound could be isolated. In an another experiment the worked-up reaction mixture was immediately treated with acetic anhydride and acetic acid to yield two different compounds (Scheme 25), which on TLC [silica gel, ethylacetate/benzene (1:20) as mobile phase] showed two spots (R_f 0.75 and 0.25) and were separated using column chromatography. The first fraction obtained as white crystalline solid m.p. 124°C in 18% yield was characterised as 1(2)-acetyl-3(5)-styryl-5(3)-methylthiopyrazole 135a on the basis of spectral and analytical data. Thus 135a showed molecular ion peak at m/z 258 (M^+,54%) and it was analysed for $C_{14}H_{14}N_2OS$. Its i.r. spectrum (KBr) exhibited bands at 1730, 1518 and 1420 cm^{-1}. Further proof for its structure was obtained from its n.m.r. spectrum ($CDCl_3$), which showed a signal at δ 2.46(s,3H), which was assigned to $S\underline{CH}_3$ proton. The singlet at δ 2.66 integrating for three protons was assigned to $\underline{CH}_3CO$ protons and the singlet at δ 6.23 was assigned to H-4 proton, while a singlet at δ 7.06(2H) was assigned to two olefinic protons and the multiplet between 7.23-8.14 was assigned to five aromatic protons. Further elution with 1:1 mixture of ethylacetate and hexane gave the second compound as pale yellow solid m.p. 50°C in 65% yield, which was characterised as 1-acetyl-3-[bis(methylthiomethylene) methyl]-5-phenyl-2-pyrazoline 134a on

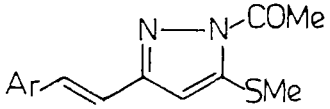


98



134

+



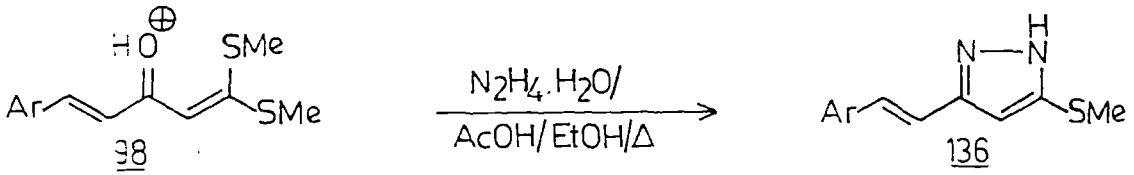
135

98 a, 134 a, 135 a, Ar = C_6H_5
b, b, b, Ar = 4-MeC_6H_4
d, c, c, Ar = 4-$MeOC_6H_4$
g, d, d, Ar = 2,6-$Cl_2C_6H_3$
l, e, e, Ar = $C_6H_5CH{=}CH$-

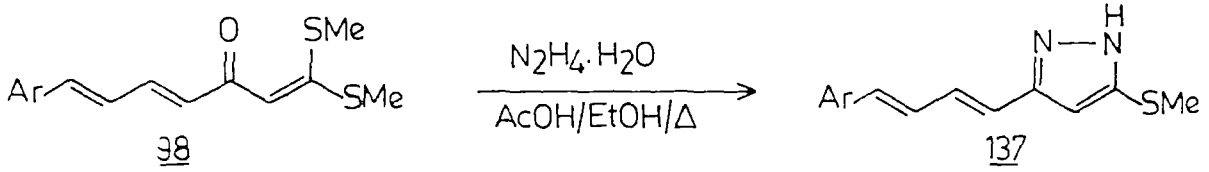
Scheme 25

the basis of spectral and analytical data. Thus 134a showed molecular ion peak at m/z 306(M^+,100%) and it was analyzed for $C_{15}H_{18}N_2OS_2$. Its i.r. spectrum(KBr) exhibited bands at 1650 and 1413 cm^{-1}. The assigned structure was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$), which showed a signal at δ 2.30(s,3H) which was assigned to SCH_3 protons and the signal at δ 2.40(s,6H) was assigned to SCH_3 and CH_3CO protons. The signals at δ 3.20(dd,1H, J=18 and 6Hz) were assigned to H_A-4 proton and the signals 3.51-3.96 (dd,H,J=18 and 12Hz) were assigned to H_B-4) proton, while the signal at δ 5.45(dd,1H,J=12,6Hz) was assigned to H_X-5. The signal at δ 6.31 (s,1H) was assigned to olefinic proton, while the broad singlet at δ 7.25 integrating for five protons was assigned to five aromatic protons. It is interesting to note that the pyrazoline could only be isolated as its acetyl derivative and the attempts to isolate the free pyrazoline resulted only in intractable tar. The mechanism governing the formation of 134a and 135a can be explained involving competitive Michael addition either on the styryl β-carbon or on the bismethylthio carbon leading to a mixture of 134a and 135a respectively. Under neutral reaction conditions,the Michael addition on the styryl double bond predominates, though the formation of 3-styryl pyrazole by addition and elimination sequence is 18% only. Oxoketene dithioacetals 98b, 98d, 98g, 98l were reacted with hydrazine hydrate under similar reaction conditions to yield pyrazoline 134b-e in 54-61% and pyrazole 135b-e in 13-21% overall yields. However it was considered of interest that the reaction of 98a with hydrazine hydrate in the presence of acetic acid should afford 136a which can be explained

through the attack of hydrazine on protonated 98a at the β-carbon which is stabilized by bis(methylthio) group. Therefore, the hydrazine hydrate reaction with 98a in the presence of acetic acid should yield only one regioisomer. Indeed, 3-styrylpyrazole 136a was isolated in this reaction as the sole product (Scheme 26). The structure of 136a was fully confirmed by its analytical and spectral data which are described in the experimental section. Thus the reaction is regioselective when it is carried out in acidic medium. Similarly 98c-g and 98i-k were reacted with hydrazine hydrate in the presence of acetic acid to afford the corresponding pyrazole 136b-i in 63-80% overall yields. Similarly the reaction was found to be regioselective under the same reaction conditions when the dienyl oxoketene dithioacetal 98l-n reacted with hydrazine hydrate in the presence of acetic acid to afford 137a-c in 74-77% overall yields. The analytical and spectral data of all these compounds are in conformity with the assigned structures and are described in the experimental section. The trienyl oxoketene dithioacetals 98o-q when reacted with hydrazine under identical conditions afford the corresponding trienyl pyrazoles 138a-c in 71-75% overall yields. The analytical and spectral data of these compounds are in conformity with the assigned structures and are described in the experimental section. The highly regioselective synthesis of 3-styryl,3-(4-aryl-1,3-butadienyl) and 3-(6-aryl-1,3,5-hexatrienyl) pyrazoles is of practical utility since introduction of such enyl side chains on the pre-constructed pyrazole is not possible.

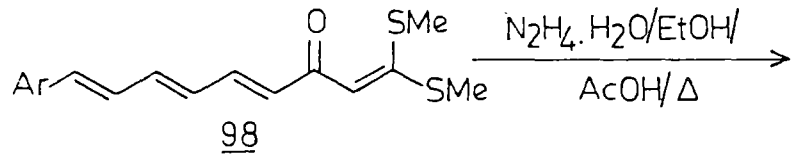


98 a, 136 a, Ar = C_6H_5
98 g, 136 f, Ar = 2,6-$Cl_2C_6H_3$
c, b, Ar = 4-ClC_6H_4
i, g, Ar = 3,4-methylenedioxy C_6H_3
d, c, Ar = 4-$MeOC_6H_4$
j, h, Ar = 3,4-$(MeO)_2C_6H_3$
e, d, Ar = 4-$Me_2NC_6H_4$
k, i, Ar = 3,4,5-$(MeO)_3C_6H_2$
f, e, Ar = 2-ClC_6H_4

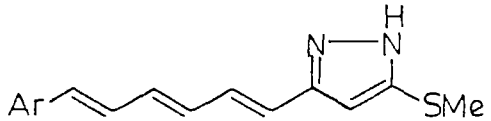


98 l, 137 a, Ar = C_6H_5
m, b, Ar = 4-$MeOC_6H_4$
n, c, Ar = 3,4-methylenedioxy C_6H_3

Scheme 26



98



138

98 o, 138 a, Ar= C_6H_5
p, b, Ar= 4-$MeOC_6H_4$
q, c, Ar= 3,4-methylenedioxy C_6H_3

Scheme 27

II.4 EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point (capillary method) apparatus and are uncorrected. ^{1}H n.m.r. spectra were recorded on a Varian EM 390, 90MHz spectrometer and the chemical shift values are expressed as δ(ppm) downfield from Me_4Si as internal standard. ^{13}C n.m.r. spectra were recorded on a Bruker WP-80-DS (20.15 MHz)spectrometer. I.r. and mass spectra were recorded on a Perkin-Elmer 297 spectrometer and a Jeol-D 300 mass spectrometer respectively. Carbon, hydrogen, nitrogen elemental analysis were done at R.S.I.C. Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of acetophenone, 4-methylacetophenone, 4-chloroacetophenone, 4-methoxyacetophenone, 4-bromoacetophenone, 2,4-dichloroacetophenone, 4-ethoxyacetophenone, 2-acetylnaphthalene, 4-acetylpyridine, 2-acetylfuran, 6-methoxy-1-tetralone, acetone, benzaldehyde, 4-tolualdehyde, 4-chlorobenzaldehyde, anisaldehyde, 4,N,N-dimethylamino benzaldehyde, 2-chlorobenzaldehyde, 2,6-dichlorobenzaldehyde, 2,4-dichlorobenzaldehyde, piperonal, 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxybenzaldehyde, cinnamaldehyde were purified before use, while 1-tetralone, b.p. 140-150°C (10 mm)[36], benzthiepenone, m.p. 68°C[37], 4-methoxycinnamaldehyde, 3,4-methylenedioxycinnamaldehyde, 5-phenyl-2,4-pentadienal, 5-(4-methoxyphenyl)-2,4-pentadienal, 5-(3,4-methylenedioxyphenyl)-2,4-pentadienal were prepared according to the reported procedure[38], ketene S,S-acetal (55a-o) and 4,4-bis(methylthio)-3-buten-2-one 96, m.p. 66-67°C[28] were prepared as given below.

General method for the preparation of α-oxoketene dithioacetals (55a-o and 96) using sodium t-butoxide:

A mixture of ketone (0.2 mol) and carbon disulphide (0.02 mol) was added dropwise to an ice cold and well stirred suspension of sodium t-butoxide (0.04 mol) in dry benzene (100 ml) and the reaction mixture was allowed to stir at room temperature for 5-6 hrs, appropriate alkyl halide (0.4 mol) [methyliodide or ethylbromide or 1-bromopropane], then gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 6-10 hr at room temperature with occasional shaking and poured over ice water (200 ml). The benzene layer was separated and the aqueous portion was extracted with benzene (3x50 ml), the combined extract were washed with water (3x100 ml), dried (Na_2SO_4) and concentrated to give crude dithioacetals 55 and 96 which were further purified by crystallisation.

5-Aryl,1-1-bis(methylthio)-1,4-pentadiene-3-ones 98a-k, 1,1-bis (methylthio)-7-aryl-1,4,6-heptatriene-3-ones 98l-n and 1,1-bis (methylthio)-9-aryl-1,4,6,8-nonatetraene-3-one 98o-g; General Procedure:

Sodium (0.06 mol) was dissolved with cooling in 30 ml of 95% ethanol. A solution of -oxoketene dithioacetal 96 (0.03 mol) and benzaldehyde/ cinnamaldehyde (0.03 mol)/5-aryl-2,4-pentadienal (0.03 mol) in 25 ml of 95% ethanol was added dropwise to the sodium ethoxide solution and the reaction mixture was stirred at room temperature for 4-5 hrs. It was then diluted with cold water (200 ml), the solid separated was filtered, washed with water (3x25 ml) and dried and was used as such in the subsequent reaction.

1,1-Bis(methylthio)-9-phenyl-1,4,6,8-nonatetraene-3-one (98o) was isolated as brown solid (methanol), yield 82%; m.p. 142-143°C; i.r. (KBr): ν_{max} = 1619, 1550, 1458 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,6H, SCH_3); 6.10(s,1H,H-2); 6.27(d,J=16Hz,1H,H-4); 6.39-7.90(m,$5H_{olefin}$); 7.16-7.53(m,$5H_{arom}$). (Found: C,67.26; H,6.11. Calc. for $C_{17}H_{18}OS_2$ (302.4): C,67.51; H,6.00%).

1,1-Bis(methylthio)-9(4-methoxyphenyl)-1,4,6,8-nonatetraene-3-one (98p) was isolated as brown solid (methanol); yield 86%; m.p. 135°C; i.r.(KBr): ν_{max}= 1661, 1599, 1560, 1473 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.47 (s,6H,SCH_3); 3.79(s,3H,OCH_3); 6.12(s,1H,H-2); 6.27(d,J=16Hz,1H,H-4); 6.55-6.98(m,$6H_{arom+olefin}$); 7.17-7.50(m,$3H_{arom+olefin}$). (Found: C,64.86; H,6.31. Calc. for $C_{18}H_{20}O_2S_2$(332.5): C,65.02; H,6.06%). m/z 332(M^+ 6%).

1,1-Bis(methylthio)-9(3,4-methylenedioxy)-1,4,6,8-nonatetraene-3-one (98q) was isolated as brown solid (methanol); yield 85%; m.p. 133-135°C; i.r.(KBr): ν_{max} = 1610, 1594, 1512 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,6H,SCH_3); 5.97(s,2H,-O-CH_2-O-); 6.23(d,J=16Hz,1H,H-4); 6.13 (s,1H,H-2); 6.60-7.03(m,$6H_{arom+olefin}$); 7.15-7.49(m,$2H_{arom}$). (Found: C,62.38; H,5.19. Calc. for $C_{18}H_{18}O_3S_2$(346.4): C,62.40; H,5.24%).

5-Alkylthio-3-arylisoxazoles 56a-l, 5-methylthio-3,4-annelated isoxazoles 60a, 60b, 63, 5-methylthio-3-styrylisoxazoles 99a-i, 5-methylthio-3-(4-aryl-1,3-butadienyl)isoxazoles 101a-c and 5-methylthio-3[6-aryl-(1,3,5-hexatrienyl)] isoxazoles 103a-c; General Procedure: Method A

Hydroxylamine hydrochloride (2.80g, 0.04 mol) was added to a stirred

suspension of sodium methoxide [prepared by dissolving Na(1.38g, 0.06 mol) in absolute methanol (30 ml)] and stirring was continued for 10 min. The respective oxoketene dithioacetal (0.01 mol) was added and the reaction mixture was refluxed with stirring for 4 hrs, in case of 98a-q and in case of 55a-l, 59a, 59b and 62 for 15 hrs. Methanol was removed under reduced pressure and the residue was poured into ice-cold water (200 ml). In most cases, the isoxazoles separated as pale-coloured solids which were isolated by suction and were recrystallized from chloroform/hexane. In case of isoxazole 56b and 56c, the mixture obtained after pouring the reaction mixture into ice-cold water was extracted with chloroform(2x50 ml) and organic layer is washed with water (1x100 ml) dried (Na_2SO_4), and evaporated to give 56b or 56c respectively as orange viscous liquids which were passed through a small column of neutral alumina using carbontetra-chloride as eluent to give pure product 56b or 56c.

5-Methylthio-3-phenylisoxazole (56a); Typical procedure using barium hydroxide as base:

Hydroxylamine hydrochloride (2.80g, 0.04 mol) was added to a stirred suspension of barium hydroxide (10.30g, 0.06 mol) in 95% ethanol (30 ml) followed by addition of α-oxoketene dithioacetal (55a; 2.24g, 0.01 mol). The mixture was refluxed with stirring for 4 hrs, ethanol was then removed under reduced pressure, the residue was poured into ice-cold water (200 ml), and this mixture was acidified with dilute acetic acid (5%, 15 ml). The isoxazole 56a thus obtained was isolated by suction and passed through a neutral alumina column using carbon tetrachloride as eluent yield; 1.30g (70%).

5-Methylthio-3-phenylisoxazole (56a) was isolated as pale yellow solid ($CHCl_3$/hexane); yield 78%; m.p. 40°C (reported m.p. 39-40°C); i.r.(KBr): ν_{max} = 1540, 1500, 1450, 1400 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.56(s,3H,$SC\underline{H}_3$); 6.33(s,1H,$\underline{H}$-4); 7.33-7.61(m,$3H_{arom}$); 7.71-8.15 (m,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 15.46(SCH_3); 100.07($\underline{C}$-4); 126.74, 128.90, 130.09($\underline{C}$H phenyl); 128.95 (C-1' phenyl); 162.99($\underline{C}$-3); 168.05 ($\underline{C}$-5). (Found: C,62.61; H,4.98; N,7.17. Calc. for $C_{10}H_9NOS$(191.3): C,62.82; H,4.71; N,7.32%). m/z 191(M^+,42); 144(100); 116(29); 77(70%).

5-Ethylthio-3-phenylisoxazole (56b) was isolated as colourless viscous liquid yield 58% (reported b.p. 96-98°C/0.05 Torr); i.r.(neat): ν_{max} = 1540, 1500, 1460, 1400 cm^{-1}; ^1H n.m.r.($CDCl_3$): 1.36(t,3H, J=7Hz,$C\underline{H}_3CH_2$); 3.03(q,2H,J=7Hz,$SC\underline{H}_2CH_3$); 6.33(s,1H,$\underline{H}$-4); 7.25-7.46 (m,$3H_{arom}$); 7.53-7.82(m,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 15.14(CH_3); 27.79(SCH_2); 102.18($\underline{C}$-4); 126.70, 128.90, 130.08(CH phenyl); 128.95 (C-1' phenyl); 162.95($\underline{C}$-3); 166.85($\underline{C}$-5). (Found: C,64.27; H,5.58; N,6.56. Calc. $C_{11}H_{11}NOS$(205.3): C,64.39; H,5.36; N,6.82%).m/z 205 (M^+,28); 144(100); 116(24), 77(53%).

5-(1-Propylthio)-3-phenylisoxazole (56c) was isolated as colourless viscous liquid; yield 61%; i.r.(neat): ν_{max} = 1540, 1500, 1455, 1392 cm^{-1}; ^1H n.m.r.($CDCl_3$):0.98(t,3H,J=7Hz,$C\underline{H}_3$); 1.67(sext,2H, J=7Hz,$SCH_2C\underline{H}_2CH_3$); 2.97(t,2H,J=7Hz,$SC\underline{H}_2CH_2CH_3$); 6.36(s,1H,$\underline{H}$-4); 7.25-7.58(m,$3H_{arom}$); 7.60-7.86(m,$2H_{arom}$). (Found: C,65.88; H,6.09; N,6.58. Calc. for $C_{12}H_{13}NOS$(219.3): C,65.75; H,5.93; N,6.39%). m/z 219(M^+,39); 144(100); 116(21%).

5-Methylthio-3-(4-methylphenyl)isoxazole (56d) was isolated as pale yellow solid ($CHCl_3$/hexane); yield 77%; m.p. 51°C; i.r.(KBr): ν_{max} = 1610, 1540, 1510, 1438, 1420 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.32(s,3H,$C\underline{H}_3$); 2.50(s,3H,$SC\underline{H}_3$); 6.22(s,1H,$\underline{H}$-4); 7.14(d,J=8Hz,$2H_{arom}$); 7.58(d,J=8Hz, $2H_{arom}$). (Found: C,64.53; H,5.59; N,6.70. Calc. for $C_{11}H_{11}NOS$(205.3): C,64.39; H,5.36; N,6.82%). m/z 205(M^+,10); 158(100); 130(38); 91(39%).

5-Methylthio-3-(4-chlorophenyl)isoxazole (56e) was isolated as white solid ($CHCl_3$/hexane); yield 71%; m.p. 61°C; i.r.(KBr): ν_{max} = 1614, 1541, 1505, 1440, 1420 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,$SC\underline{H}_3$); 6.23(s,1H,$\underline{H}$-4); 7.35(d,J=8Hz,$2H_{arom}$); 7.66(d,J=8Hz,$2H_{arom}$); ^{13}C n.m.r. ($CDCl_3$): δ_C 15.40(SCH_3); 99.79($\underline{C}$ 4); 128.00, 129.18(CH_{arom}); 127.23, 136.11(C-1', C-4' phenyl); 162.01($\underline{C}$-3); 168.48($\underline{C}$-5). (Found: C,52.96; H,3.81; N,6.40. Calc. for $C_{10}H_8ClNOS$(225.7): C,53.21; H,3.54; N,6.20%). m/z 227(12); 225(M^+,31); 180(36); 178(100); 152(16); 150(50); 113(9); 111(22%).

5-Methylthio-3-(4-methoxyphenyl)isoxazole (56f) was isolated as white solid ($CHCl_3$/hexane); yield 72%; m.p.64°C; i.r.(KBr): ν_{max} = 1620, 1522, 1446 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.52(s,3H,$SC\underline{H}_3$); 3.72(s,3H,$OC\underline{H}_3$); 6.18(s,1H,$\underline{H}$-4); 6.84(d,J=8.5Hz,$2H_{arom}$); 7.59(d,J=8.5Hz,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 15.44(SCH_3); 55.32($OC\underline{H}_3$); 99.86($\underline{C}$-4); 114.27, 128.12(CH_{arom}); 121.20, 161.03(C-1' phenyl, C-4' phenyl); 162.59 ($\underline{C}$-3); 167.67($\underline{C}$-5). (Found: C,59.94; H,5.17; N,6.39. Calc. for $C_{11}H_{11}NO_2S$(221.3): C,59.72; H,5.17; N,6.39%). m/z 221(M^+,37); 174(100); 146(86%).

5-Methylthio-3-(4-bromophenyl)isoxazole (56g) was isolated as white solid ($CHCl_3$/hexane); yield 71%; m.p. 95°C; i.r.(KBr): ν_{max} = 1595, 1535, 1490, 1430, 1418 cm^{-1}; ^1H n.m.r.($CDCl_3$); 2.61(s,3H,$SC\underline{H}_3$); 6.28(s,1H,$\underline{H}$-4); 7.58(s,$4H_{arom}$). (Found: C,44.17; H,3.27; N,5.37. Calc. for $C_{10}H_8BrNOS$(270.1): C,44.44; H,2.96; N,5.18%). m/z 271(30); 269(M^+,28); 224(98); 222(100); 196(41); 194(44); 157(21); 155(22%).

5-Methylthio-3-(2,4-dichlorophenyl)isoxazole (56h) was isolated as white solid ($CHCl_3$/hexane); yield 70%; m.p. 48°C; i.r.(KBr): ν_{max} = 1590, 1532, 1488, 1438 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.62(s,3H,$SC\underline{H}_3$); 6.26(s,1H,$\underline{H}$-4); 7.32(dd,1H,J=7Hz,2Hz,$\underline{H}$-5'); 7.48(d,1H,J=2Hz,$\underline{H}$-3'); 7.73(d,1H,J=7Hz,$\underline{H}$-6'). (Found: C,45.88; H,2.93; N,5.51. Calc. for $C_{10}H_7Cl_2NOS$(260.1): C,46.15; H,2.69; N,5.38%). m/z 261(19); 259(M^+,26); 214(73); 212(100); 186(30); 184(53%).

5-Methylthio-3-(4-ethoxyphenyl)isoxazole (56i) was isolated as white solid (chloroform/hexane); yield 76%; m.p. 54-55°C; i.r.(KBr): ν_{max} = 1620, 1525, 1446, 1418, 1394 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 1.42(t,3H,J=7Hz, $OCH_2C\underline{H}_3$); 2.60(s,3H,$SC\underline{H}_3$); 4.06(q,2H,J=7Hz,$OC\underline{H}_2CH_3$); 6.22(s,1H,$\underline{H}$-4); 6.85(d,J=9Hz,$2H_{arom}$); 7.69(d,J=9Hz,$2H_{arom}$). (Found: C,61.49; H,5.72; N,6.08. Calc. for $C_{12}H_{13}NO_2S$(235.3): C,61.27; H,5.53; N,5.95%). m/z 235(M^+,33); 188(100); 160(29); 132(70%).

5-Methylthio-3-(2-naphthyl)isoxazole (56j) was isolated as light yellow solid (chloroform/hexane); yield 68%; m.p. 79°C; i.r.(KBr): ν_{max} = 1602, 1542, 1440, 1398 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.62(s,3H, $SC\underline{H}_3$); 6.41(s,1H,$\underline{H}$-4); 7.33-8.16(m,$7H_{arom}$). (Found: C,69.98; H,4.84; N,6.07. Calc. for $C_{14}H_{11}NOS$(241.3): C,69.70; H,4.56; N,5.80%).m/z 241(M^+,37); 194(100); 166(43); 127(91%).

5-Methylthio-3-(4-pyridinyl)isoxazole (56k) was isolated as light yellow solid (chloroform/hexane); yield 68%; m.p. 99°C; i.r.(KBr): ν_{max} = 1600, 1530, 1520, 1437, 1394 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.56 (s,3H,SCH_3); 6.33(s,1H,H-4); 7.60(d,J=8Hz,2H pyridyl); 6.73(d,J=8Hz, 2H pyridyl). (Found: C,55.98; H,4.43; N,14.41. Calc. for $C_9H_8N_2OS$ (192.2): C,56.25; H,4.16; N,14.58%. m/z 192(M^+,100); 145(100); 117 (29); 79(90%).

5-Methylthio-3-(2-furyl)isoxazole (56l) was isolated as white solid (chloroform/hexane); yield 63%; m.p. 83°C; i.r.(KBr): ν_{max} = 1611, 1528, 1438 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.62(s,3H,SCH_3); 6.32(s,1H,H-4); 6.55(dd,1H,J=3, 1.4Hz,H-4' furyl); 6.91(d,1H,J=3Hz,H-3' furyl); 7.56(d,1H,J=1.4Hz,H-5' furyl). (Found: C,52.91; H,3.98; N,7.58. Calc. for $C_8H_7NO_2S$(181.2): C,53.03; H,3.86; N,7.73%). m/z 181 (M^+,96); 134(100); 106(74%).

3-Methylthio-4,5-dihydronaphth [1,2-c] isoxazole 60a was obtained as light yellow solid; yield 78%; m.p. 46°C; i.r. (KBr): ν_{max} = 1606, 1420, 1378 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.53(s,3H,SCH_3); 2.50-3.05(m,A_2B_2, 4H,-CH_2-); 7.16-7.45(m,$3H_{arom}$); 7.75-7.96(m,$1H_{arom}$). (Found: C,66.61; H,5.29; N,6.53. Calc. for $C_{12}H_{11}NOS$(217.3): C,66.35; H,5.06; N,6.43%). m/z 217(M^+,100); 170(24); 142(55); 115(62%).

3-Methylthio-7-methoxy-4,5-dihydronaphth [1,2-c] isoxazole (60b) was obtained as white crystalline solid; yield 57%; m.p. 44°C; i.r.(KBr): ν_{max} = 1604, 1448, 1388 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.56(s,3H,SCH_3); 2.52-2.95(m,A_2B_2,4H,CH_2); 3.79(s,3H,OCH_3); 6.63-6.83(m,$2H_{arom}$);

7.78(d,J=8Hz,1H_{arom}). (Found: C,63.36; H,5.49; N,5.92. Calc. for $C_{13}H_{13}NO_2S$(247.3): C,63.15; H,5.26; N,5.66%). m/z 247(M^+,100); 202(11); 172(39%).

3-Methylthio-8-methyl-4,5-dihydro[1]benzothiepino[1,2-c] isoxazole (63) was isolated as white crystalline solid (chloroform/hexane); yield 78%; m.p. 98°C; i.r.(KBr): ν_{max} = 1600, 1658, 1417, 1410 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.33(s,3H,$C\underline{H}_3$); 2.60(s,3H,$SC\underline{H}_3$); 2.83-3.16(m,A_2B_2,4H,$-CH_2-$); 7.10(dd,J=8,2Hz,1H_{arom}); 7.32(d,J=2Hz,1H_{arom}); 7.85(d,J=8Hz,1H_{arom}); ^{13}C n.m.r.($CDCl_3$): δ_C 15.25($S\underline{C}H_3$); 21.02($\underline{C}H_3$); 25.82($\underline{C}H_2$); 33.99 ($S\underline{C}H_2$); 114.59($-\underline{C}=\langle^{O}_{SCH_3}$); 128.99; 129.61; 133.90($\underline{C}H$ arom.); 129.17, 136.28, 140.03(quaternary carbon); 162.15($-\underline{C}$=N-O); 162.66($=\underline{C}\langle^{O}_{SCH_3}$). (Found: C,59.11; H,5.13; N,5.36. Calc. for $C_{13}H_{13}NOS_2$(263.4): C,59.31; H,4.94; N,5.32%). m/z 263(M^+,60); 216(17); 188(100%).

5-Methylthio-3-styrylisoxazole (99a) was isoalted as white solid (chloroform/hexane); yield 37%; m.p.91°C; i.r.(KBr): ν_{max} = 1640, 1528, 1422 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,$SC\underline{H}_3$); 6.20(s,1H,$\underline{H}$-4); 6.98(s,2H_{olefin}); 7.15-7.58(m,5H_{arom}). (Found: C,66.48; H,5.22; N,6.71. Calc. for $C_{12}H_{11}NOS$(217.3): C,66.36; H,5.06; N,6.45%). m/z 217(M^+,37); 170(59); 142(32); 114(30); 103(100%).

5-Methylthio-3-(4-methylstyryl)isoxazole (99b) was isolated as white solid (chloroform/hexane); yield 35%; m.p. 93-94°C; i.r.(KBr): ν_{max} = 1640, 1534, 1422 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.33(s,3H,$C\underline{H}_3$); 2.52(s,3H, $SC\underline{H}_3$); 8.15(s,1H,$\underline{H}$-4); 6.92(s,2H_{olefin}); 7.00-7.40(m,4H_{arom}); ^{13}C n.m.r. ($CDCl_3$): $_C$ 15.42($S\underline{C}H_3$); 21.33($\underline{C}H_3$); 99.04($\underline{C}$-4); 126.93-129.54($\underline{C}H_{arom}$); 114.66, 136.02($\underline{C}H_{arom}$); 139.11(C-1' arom); 132.94(C-4' arom); 162.41,

167.35(C-3, C-5). (Found: C,67.31; H,5.81; N,5.93. Calc. for $C_{13}H_{13}NOS$ (231.3): C,67.53; H,5.62; N,6.06%). m/z 231(M^+,99); 184(98); 156(98); 128(89); 117(98%).

5-Methylthio-3-(4-chlorostyryl)isoxazole (99c) was isolated as white solid (chloroform/hexane); yield 40%; m.p. 133°C; i.r.(KBr): ν_{max} = 1640, 1532, 1422 cm^{-1}; ^1H n.m.r.($CDCl_3$):2.59(s,3H,SCH_3); 6.18(s,1H, H-4); 7.00(s,$2H_{olefin}$); 7.21-7.50(m,$4H_{arom}$). (Found: C,57.41; H,4.15; N,5.68. Calc. for $C_{12}H_{10}ClNOS$(251.7): C,57.25; H,3.97; N,5.56%). m/z 253(29); 251(M^+,59); 206, 204(33,94); 178, 176(14,38); 150, 148 (10,39); 137-135(100,18%).

5-Methylthio-3-(4-methoxystyryl)isoxazole (99d) was isolated as white solid (chloroform/hexane); yield 49%; m.p. 96°C; i.r.(KBr): ν_{max} = 1600, 1540, 1508, 1422 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.53(s,3H,SCH_3); 3.78(s,3H,OCH_3); 6.15(s,1H,H-4); 6.71-6.92(m,$2H_{arom}$+ $2H_{olefin}$); 7.39(d,J=10Hz,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 15.44(SCH_3); 55.34(OCH_3); 99.00(C-4); 114.28, 128.39(CH, arom); 113.42, 135.62(CH,olefin); 128.48(C-1' arom); 160.32(C-4' arom); 162.52, 167.24(C-3, C-5). (Found: C,62.93; H,5.36; N, 5.38. Calc. for $C_{13}H_{13}NO_2S$(247.3): C,63.15; H,5.26; N,5.66%). m/z 247(M^+,100); 200(85); 172(78); 144(38); 133(79%).

5-Methylthio-3-(4,N,N-dimethylaminostyryl)isoxazole (99e) was prepared as pale yellow solid (chloroform/hexane); yield 46%; m.p. 124°C; i.r. (KBr): ν_{max} = 1600, 1528, 1418 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.55(s,3H,SCH_3); 2.95[s,6H,$N(CH_3)_2$]; 6.15(s,1H,H-4); 6.44-6.9 (m,$2H_{arom}$+ $2H_{olefin}$); 7.25(d,J=9Hz,$2H_{arom}$). (Found: C,64.48; H,6.28; N,10.92. Calc. for

$C_{14}H_{16}N_2OS$(260.3): C,64.61; H,6.15; N,10.76%). m/z 260(M^+,100); 213(39); 185(57); 158(19); 146(20%).

5-Methylthio-3-(2-chlorostyryl)isoxazole (99f) was prepared as white solid (chloroform/hexane); yield 40%; m.p. 69°C; i.r.(KBr): ν_{max} = 1532, 1422 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.55(s,3H,SCH_3); 6.28(s,1H,H-4); 6.98(d,J=18Hz,$1H_{olefin}$); 7.13-7.84(m,$4H_{arom}$+ $1H_{olefin}$). (Found: C,57.31; H,4.20; N,5.72. Calc. for $C_{12}H_{10}ClNOS$(251.7): C,57.25; H,3.97; N,5.56%). m/z 253(16); 251(M^+,46); 206, 204(13,41); 137(100%).

5-Methylthio-3-(2,6-dichlorostyryl)isoxazole (99g) was isolated as white solid (chloroform/hexane); yield 42%; m.p. 94°C; i.r.(KBr): ν_{max} = 1532, 1425 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH_3); 6.28 (s,1H,H-4); 7.09-7.50(m,$3H_{arom}$+ $2H_{olefin}$). (Found: C,50.61; H,3.28; N,5.11. Calc. for $C_{12}H_9Cl_2NOS$(286.2): C,50.34; H,3.14; N,4.89%). m/z 289(4); 285(M^+,38); 242, 238(5,38); 222(73%).

5-Methylthio-3-(2,4-dichlorostyryl)isoxazole (99h) was isolated as white solid (chloroform/hexane); yield 43%; m.p. 111°C; i.r.(KBr): ν_{max} = 1582, 1539, 1475, 1430 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.56(s,3H, SCH_3); 6.23(s,1H,H-4); 6.92(d,J=18Hz,$1H_{olefin}$); 7.11-7.63(m,$3H_{arom}$+$1H_{olefin}$) (Found: C,50.17; H,3.34; N,4.73. Calc. for $C_{12}H_9Cl_2NOS$(286.2): C,50.34; H,3.14; N,4.89%). m/z 289(6); 285(M^+,41); 238(33); 222(100%).

5-Methylthio-3-(3,4-methylenedioxystyryl)isoxazole (99i) was isolated as white solid (chloroform/hexane); yield 46%; m.p. 128°C; i.r.(KBr): ν_{max} = 1640, 1540, 1500, 1426 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.58(s,3H,SCH_3); 5.95(s,2H,-O-CH_2-O-); 6.19(s,1H,H-4); 6.68-7.04(m,$3H_{arom}$+$2H_{olefin}$).

(Found: C,60.01; H,4.38; N, 5.20. Calc. for $C_{13}H_{11}NO_3S$(261.3): C,59.77; H,4.21; N,5.36%). m/z 261(M^+,42); 214(100); 186(40); 156(54%).

5-Methylthio-3-(4-phenyl-1,3-butadienyl)isoxazole (101a) was isolated as white solid (chloroform/hexane); yield 41%; m.p. 102°C; i.r.(KBr): ν_{max} = 1625, 1537, 1423 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH_3); 6.19(s,1H,H-4); 6.40-6.86(m,$4H_{olefin}$); 7.13-7.48(m,$5H_{arom}$); ^{13}C n.m.r. ($CDCl_3$): δ_C 15.42(SCH_3); 99.06(C-4); 126.76, 127.69, 128.74(CH,arom); 119.01, 128.37, 136.22, 136.34(CH,olefin); 136.45(C-1',arom); 162.20, 167.34(C-3, and C-5). (Found: C,69.30; H,5.54; N,5.83. Calc. for $C_{14}H_{13}NOS$(243.3): C,69.13; H,5.34; N,5.76%). m/z 243(M^+,71); 196(98); 168(77); 140(5); 129(8%).

5-Methylthio-3-[4-(4-methoxyphenyl)1,3-butadienyl] isoxazole (101b) was isolated as pale yellow solid (chloroform/hexane); yield 44%; m.p. 112°C; i.r.(KBr): ν_{max} = 1600, 1530, 1500, 1420 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.58(s,3H,SCH_3); 3.79(s,3H,OCH_3); 6.13(s,1H,H-4); 6.40-6.91 (m,$2H_{arom}$+ $4H_{olefin}$); 7.34(d,J=8Hz,$2H_{arom}$). (Found: C,65.88; H,5.68; N,4.96. Calc. for $C_{15}H_{15}NO_2S$(273.3); C,65.93; H,5.49; N,5.12%). m/z 273(M^+,19); 226(26); 198(14%).

5-Methylthio-3-[4-(3,4-methylenedioxyphenyl) 1,3-butadienyl]isoxazole (101c) was isolated as pale yellow solid (chloroform/hexane); yield 41%; m.p. 118°C; i.r.(KBr): ν_{max} = 1625, 1525, 1498, 1420 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH_3); 5.82(s,2H,-O-CH_2-O); 6.11(s,1H, H-4); 6.40-7.08(m,$3H_{arom}$+ $4H_{olefin}$). (Found: C,62.87; H,4.67; N,5.12. Calc. for $C_{15}H_{13}NO_3S$(287.3): C,62.71; H,4.52; N,4.87%). m/z 287(M^+,84); 240(80); 212(67%).

5-Methylthio-3-(6-phenyl-1,3,5-hexatrienyl)isoxazole (103a) was isolated as yellow solid (chloroform/hexane); yield 44%; m.p.133-134°C; i.r.(KBr): ν_{max} = 1600, 1530, 1425 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.57(s,3H, SCH_3); 6.14(s,1H,H-4); 6.33-6.88(m,$6H_{olefin}$); 7.18-7.50(m,$5H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 15.41(SCH_3); 99.08(C-4); 126.58, 128.35, 128.70(CH arom); 11.8.73, 128.02, 131.81, 134.76, 136.15, 136.75(CH olefin); 136.88(C-1' arom); 162.33, 167.29(C-3 and C-5). (Found: C,71.18; H,5.48; N,4.98. Calc. for $C_{16}H_{15}NOS$(269.3): C,71.37; H,5.57; N,5.20%). m/z 269(M^+,36); 222(100); 194(8%).

5-Methylthio-3-[6-(4-methoxyphenyl)-1,3,5-hexatrienyl]isoxazole (103b) was isolated as yellow solid (chloroform/hexane); yield 40%; m.p. 135°C; i.r.(KBr): ν_{max} = 1600, 1538, 1510, 1428 cm^{-1}; ^1H n.m.r.($CDCl_3$); 2.57(s,3H,SCH_3); 3.80(s,3H,OCH_3); 6.18(s,1H,H-4); 6.33-6.74(m,$6H_{olefin}$); 6.87(d,J=8Hz,$2H_{arom}$); 7.50(d,J=8Hz,$2H_{arom}$). (Found: C,67.98; H,5.72; N,4.81. Calc. for $C_{17}H_{17}NO_2S$(299.3): C,68.22; H,5.68; N,4.68%). m/z 299(M^+,15); 251(100); 224(59); 185(25%).

5-Methylthio-3-[6-(3,4-methylenedioxyphenyl)-1,3,5-hexatrienyl] isoxazole (103c) was isolated as yellow solid (chloroform/hexane); yield 38%; m.p. 150°C; i.r.(KBr): ν_{max} = 1605, 1500, 1440, 1420 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH_3); 5.96(s,2H,-O-CH_2-O); 6.21(s,1H,H-4); 6.38-7.00(m,$3H_{arom}$+ $6H_{olefin}$). (Found: C,65.33; H,4.86; N,4.13. Calc. for $C_{17}H_{15}NO_3S$(313.3): C,65.17; H,4.79; N,4.47%). m/z 313(M^+,79); 266(100); 238(69); 210(5%).

3-Alkylthio-5-arylisoxazoles 57a-l, 3-methylthio-4,5-annelated isoxazoles 61a, 61b, 64, 3-methylthio-5-styrylisoxazoles 100a-i 3-methylthio-5-(4-aryl-1,3-butadienyl) isoxazoles 102a-c and 3-methylthio-5-(6-aryl-1,3,5-hexatrienyl)isoxazoles 104a-c ;

General Procedure:

Method B

To a stirred solution of the respective oxoketene dithioacetal (0.01 mol) in benzene (100 ml) and acetic acid (100 ml), a solution of sodium acetate (2.80g, 0.034 mol) and hydroxylaminehydrochloride (2.80g, 0.04 mol) in water (10 ml) was added. The mixture was made homogeneous by addition of ethanol (55 ml) and refluxed for 8-10 hrs. It was then evaporated to dryness under reduced pressure, and extracted with chloroform (2x50 ml). The chloroform layer was washed with water (2x100 ml), dried (Na_2SO_4), and evaporated to give a dark brown residue. The brown residue is filtered through a small neutral alumina column using ethylacetate/hexane (1:20) as eluent to give isoxazoles.

3-Methylthio-5-phenylisoxazole (57a) was isolated as white solid (chloroform/hexane); yield 65%; m.p. 56-57°C (reported m.p. 56-57°C); i.r.(KBr): ν_{max} = 1600, 1580, 1560, 1482, 1440, 1402, 1340 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH_3); 6.27(s,1H,H-4); 7.17-7.45(m,$3H_{arom}$); 7.49-7.79(m,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 13.90(SCH_3); 99.07(C-4); 125.79, 128.91, 130.27(CH phenyl); 127.18(C-1' phenyl); 160.89(C-5); 169.89(C-3). (Found: C,63.07; H,4.96; N,7.60. Calc. for $C_{10}H_9NOS$(191.3): C,62.82; H,4.71; N,7.32%). m/z 191(M^+,62); 144(10); 105(100%).

3-Ethylthio-5-phenylisoxazole (57b) was isolated as white solid (chloroform/hexane); yield 63%; m.p. 50-51°C (reported m.p. 51-52°C); i.r.(KBr): ν_{max} = 1600, 1581, 1562, 1482, 1440, 1400 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 1.44(t,3H,J=7Hz,$C\underline{H}_3CH_2$); 3.10(q,2H,J=7Hz($SC\underline{H}_2CH_3$); 6.30 (s,1H,$\underline{H}$-4); 7.30-7.60(m,$3H_{arom}$); 7.68-7.80(m,$2H_{arom}$); ^{13}C n.m.r. ($CDCl_3$): δ_C 14.73($\underline{C}H_3CH_2$); 25.86($S\underline{C}H_2CH_3$); 102.22($\underline{C}$-4); 125.80, 128.96, 130.30(*CH* phenyl); 127.16(*C*-1' phenyl); 160.16($\underline{C}$-5); 169.71($\underline{C}$-3). (Found: C,64.11; H,5.65; N,7.02. Calc. for $C_{11}H_{11}NOS$(205.3): C,64.39; H,5.36; N,6.82%). m/z 205(M^+,100); 144(50); 105(100%).

3-(1-Propylthio)-5-phenylisoxazole (57c) was isolated as white solid (chloroform/hexane); yield 64%; m.p.41-42°C (reported m.p. 41-42°C; i.r.(KBr): ν_{max} = 1600, 1580, 1561, 1480, 1440, 1340 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 1.03(t,3H,J=7Hz,$C\underline{H}_3CH_2CH_2$); 1.78(sext,2H,J=7Hz,$CH_3C\underline{H}_2CH_2$); 3.07(t,2H,J=7Hz,$SC\underline{H}_2CH_2CH_3$); 6.28(s,1H,$\underline{H}$-4); 7.24-7.52(m,$3H_{arom}$); 7.52-7.80(m,$2H_{arom}$). (Found: C,66.03; H,6.22; N,6.11. Calc. for $C_{12}H_{13}NOS$(219.3): C,65.75; H,5.93; N,6.39%). m/z 219(M^+,16); 144(24); 105(100%).

3-Methylthio-5-(4-methylphenyl)isoxazole (57d) was isolated as white solid (chloroform/hexane); yield 68%; m.p.64-65°C; i.r.(KBr): ν_{max}= 1600, 1583, 1560, 1498, 1403, 1342 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.36(s, 3H,$C\underline{H}_3$); 2.58(s,3H,$SC\underline{H}_3$); 6.22(s,1H,$\underline{H}$-4); 7.19(d,J=8.5Hz,A_2B_2,$2H_{arom}$); 7.60(d,J=8.5Hz,$2H_{arom}$). (Found: C,64.68; H,5.64; N,7.02. Calc. for $C_{11}H_{11}NOS$(205.3): C,64.39; H,5.36; N,6.82%). m/z 205(M^+,38); 158(7); 119(100%).

3-Methylthio-5-(4-chlorophenyl)isoxazole (57e) was isolated as white solid (chloroform/hexane); yield 62%; m.p. 107-108°C; i.r.(KBr): ν_{max}= 1600, 1578, 1479, 1403, 1339 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.59(s, 3H,$SC\underline{H}_3$); 6.28(s,1H,$\underline{H}$-4); 7.46(d,J=8Hz,$2H_{arom}$); 7.72(d,J=8Hz,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 13.86($S\underline{C}H_3$); 99.31($\underline{C}$-4); 127.01, 129.24(CH arom); 126.97, 136.34(C-1' phenyl, C-4' phenyl);161.04($\underline{C}$-5); 168.68($\underline{C}$-3). (Found: C,53.46; H,3.82; N,5.95. Calc. for $C_{10}H_8ClNOS$(225.7): C,53.21; H,3.54; N,6.20%). m/z 227(29); 225(M^+,79); 180(2); 178(5); 141(65); 139(100%).

3-Methylthio-5-(4-methoxyphenyl)isoxazole (57f) was isolated as white solid (chloroform/hexane); yield 63%; m.p. 74-75°C; i.r.(KBr): ν_{max} = 1611, 1598, 1500, 1419, 1348 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,3H,$C\underline{H}_3$); 3.82(s,3H,$OC\underline{H}_3$); 6.19(s,1H,$\underline{H}$-4); 6.83(d,J=9Hz,$2H_{arom}$); 7.70(d,J=9Hz, $2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 13.91($S\underline{C}H_3$); 55.39($O\underline{C}H_3$); 97.71($\underline{C}$-4); 114.37, 127.44(CH arom); 119.96(C-1' phenyl); 160.83(C-4' phenyl); 161.20($\underline{C}$-5); 169.91($\underline{C}$-3). (Found: C,59.99; H,5.25; N,6.55. Calc. for $C_{11}H_{11}NO_2S$(221.3): C,59.72; H,4.97; N,6.33%). m/z 221(M^+,42); 174(10); 135(100%).

3-Methylthio-5-(4-bromophenyl)isoxazole (57g) was isolated as white solid (chloroform/hexane); yield 63%; m.p.120-121°C; i.r.(KBr): ν_{max}= 1600, 1476, 1398, 1340 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,$SC\underline{H}_3$); 6.28(s,1H,$\underline{H}$-4); 7.56(s,$4H_{arom}$). (Found: C,44.21; H,3.26; N,4.90. Calc. for $C_{10}H_8BrNOS$(270.1): C,44.44; H,2.96; N,5.18%). m/z 271(48); 269(M^+,48); 224(11); 222(9); 185(100); 183(100%).

3-Methylthio-5-(2,4-dichlorophenyl)isoxazole (57h) was isolated as white solid (chloroform/hexane); yield 58%; m.p. 110-111°C; i.r.(KBr): ν_{max} = 1601, 1476, 1399, 1339 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.62(s,3H,$SC\underline{H}_3$); 6.76(s,1H,$\underline{H}$-4); 7.37(dd,1H,J=8Hz,2Hz,H-5'); 7.52(d,1H,J=2Hz,H-3'); 7.90(d,1H,J=8Hz,H-6'). (Found: C,66.39; H,2.96; N,5.56. Calc. for $C_{10}H_7Cl_2NOS$(260.1): C,46.15; H,2.69; N,5.38%); m/z 261(28); 259(M^+,41); 226(11); 224(28); 175(90); 173(100%).

3-Methylthio-5-(4-ethoxyphenyl)isoxazole (57i) was isolated as white solid (chloroform/hexane); yield 60%; m.p. 78-79°C; i.r.(KBr): ν_{max}= 1600, 1500, 1402, 1321 cm^{-1}; ^1H n.m.r.($CDCl_3$): 1.40(t,3H,J=7Hz,$OCH_2C\underline{H}_3$); 2.57(s,3H,$SC\underline{H}_3$); 4.02(q,2H,J=7Hz,$OC\underline{H}_2CH_3$); 6.15(s,1H,$\underline{H}$-4); 6.85(d, J=8Hz,A_2B_2,$2H_{arom}$); 7.59(d,J=8Hz,A_2B_2,$2H_{arom}$). (Found: C,60.99; H,5.78; N,6.10. Calc. for $C_{12}H_{13}NO_2S$(235.3): C,61.27; H,5.53; N,5.95%). m/z 235(M^+,56); 188(4); 149(100%).

3-Methylthio-5-(2-naphthyl)isoxazole (57j) was isolated as pale yellow solid (chloroform/hexane); yield 66%; m.p. 110-111°C; i.r. (KBr): ν_{max} = 1600, 1578, 1569, 1400, 1360, 1320 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.60(s,3H,$SC\underline{H}_3$); 6.36(s,1H,$\underline{H}$-4); 7.23-8.35(m,$7H_{arom}$). (Found: C,69.52; H,4.85; N,5.99. Calc. for $C_{14}H_{11}NOS$(241.3): C,69.70; H,4.56; N,5.80%). m/z 241(M^+,53); 194(8); 155(100%).

3-Methylthio-5-(4-pyridinyl)isoxazole (57k) was isolated as pale yellow solid (chloroform/hexane); yield 51%; m.p. 96-97°C; i.r.(KBr): ν_{max} = 1598, 1540, 1388, 1350 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.61(s,3H, $SC\underline{H}_3$); 6.46(s,1H,$\underline{H}$-4); 7.53(d,2H pyridyl); 8.67(d,2H pyridyl).

(Found: C,56.41; H,4.46; N,14.41. Calc. for $C_9H_8N_2OS$(192.2): C,56.25; H,4.16; N,14.58%). m/z 192(M^+,74); 145(19); 106(100%).

3-Methylthio-5-(2-furyl)isoxazole (57l) was isolated as white solid (chloroform/hexane); yield 68%; m.p. 56-57°C; i.r.(KBr): ν_{max} = 1617, 1549, 1410, 1378, 1342 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.60(s,3H,SCH_3); 6.25(s,1H,H-4); 6.51(dd,1H,J=3, 1.4Hz,H-4' furyl); 6.87(d,1H, J=3Hz,H-3' furyl); 7.51(d,1H,J=1.4Hz,H-5' furyl). (Found: C,53.31; H,4.15; N,7.90. Calc. for $C_8H_7NO_2S$(181.2): C,53.03; H,3.86; N,7.73%). m/z 181(M^+,40); 134(30); 95(42%).

3 methylthio-4,5-dihydro-naphth[2,1-d]isoxazole (61a) was obtained as viscous liquid; yield 64%; i.r.(neat): ν_{max} = 1630, 1590, 1540, 1480 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.59(s,3H,SCH_3); 2.48-3.12(m,A_2B_2,4H, CH_2); 7.13-7.33(m,3H_{arom}); 7.50-7.70(m,1H_{arom}). (Found: C,66.60; H,5.33; N,6.62. Calc. for $C_{12}H_{11}NOS$(217.3): C,66.35; H,5.06; N,6.45%). m/z 217(M^+,100); 202(39); 170(19); 118(40); 114(50%).

3-Methylthio-7-methoxy-4,5-dihydro-naphth[2,1-d]isoxazole (61b) was obtained as white crystalline solid (chloroform/hexane); yield 53%; m.p. 82-83°C; i.r.(KBr): ν_{max} = 1635, 1600, 1560, 1500, 1429 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH_3); 2.45-3.11(m,A_2B_2,4H,$-CH_2-$); 3.78 (s,3H,OCH_3); 6.64-6.78(m,2H_{arom}); 7.50(d,J=8Hz,1H_{arom}). (Found: C,62.86; H,5.55; N,5.89. Calc. for $C_{13}H_{13}NO_2S$(247.3): C,63.15; H,5.26; N,5.66%). m/z 247(M^+,100); 200(27); 172(86); 147(67%).

3-Methylthio-8-methyl-4,5-dihydro[1]benzothiepino[2,1-d]isoxazole (64) was obtained as white crystalline solid (chloroform/hexane); yield 53%; m,p. 107-108°C; i.r.(KBr): ν_{max} = 1618, 1592, 1480, 1420, 1391,

1305 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.35(s,3H,$C\underline{H}_3$); 2.64(s,3H,$SC\underline{H}_3$); 2.58-3.28(m,A_2B_2,4H,$C\underline{H}_2$); 7.10(dd,J=8,2Hz,$1H_{arom}$); 7.28(d,J=2Hz,$1H_{arom}$); 7.87(d,J=8Hz,$1H_{arom}$); ^{13}C n.m.r.($CDCl_3$: δ_C 13.50($S\underline{C}H_3$); 20.99($\underline{C}H_3$); 27.56($\underline{C}H_2$); 31,50($S\underline{C}H_2$): 113.91($\underline{C}$-$\overset{N}{\underset{SCH_3}{\diagup\!\!\diagdown}}$); 128.39, 128.66, 132.66 ($\underline{C}H$ arom); 126.85; 136.20, 139.48(quaternary $\underline{C}$,arom); 161.34(=$\underline{C}$'-O); 162.95(-$\underline{C}\overset{N}{\underset{SCH_3}{\diagup\!\!\diagdown}}$). (Found: C,59.56; H,5.22; N.5.56. Calc. for $C_{13}H_{13}NOS_2$ (263.4): C,59.31; H,4.94; N,5.32%). m/z 263(M^+,100); 216(72); 188(46%).

3-Methylthio-5- styrylisoxazole (100a) was isolated as white solid ($CHCl_3$/hexane); yield 56%; m.p. 78°C; i.r.(KBr): ν_{max} = 1638, 1578, 1550, 1410, 1360 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.57(s,3H,$SC\underline{H}_3$); 6.00(s,1H, $\underline{H}$-4); 6.72(d,J=18Hz,$1H_{olefin}$); 7.13-7.48(m,$5H_{arom}$+ $1H_{olefin}$). (Found: C,66.28; H,5.24; N,6.32. Calc. for $C_{12}H_{11}NOS$(217.3): C,66.36; H,5.06; N,6.45%). m/z 217(M^+,42); 170(8); 131(78); 103(50); 77(46%).

3-Methylthio-5-(4-methylstyryl)isoxazole (100b) was isolated as white solid ($CHCl_3$/hexane); yield 60%; m.p. 98°C; i.r.(KBr): ν_{max} = 1640, 1600, 1568, 1545, 1410 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.33(s,3H,$C\underline{H}_3$); 2.56(s,3H,$SC\underline{H}_3$); 5.97(s,1H,$\underline{H}$-4); 6.75(d,J=18Hz,$1H_{olefin}$); 6.93-7.48 (m,$4H_{arom}$+ $1H_{olefin}$); ^{13}C n.m.r.($CDCl_3$): δ_C 13.92($S\underline{C}H_3$); 21.44($\underline{C}H_3$); 100.69($\underline{C}$-4); 127.15; 129.64($\underline{C}H$ arom); 111.84, 135.27($\underline{C}H$ olefin); 139.51 (C-1' arom); 132.69(C-4' arom); 168.70, 160.66($\underline{C}$3, $\underline{C}$5). (Found: C,67.80; H,5.81; N,6.34. Calc. for $C_{13}H_{13}NOS$(231.3): C,67.53; H,5.62; N,6.06%). m/z 231(M^+,50); 184(12); 145(100); 117(18); 91(12%).

3-Methylthio-5-(4-chlorostyryl)isoxazole (100c) was isolated as white crystalline solid (chloroform/hexane); yield 64%; m.p. 133°C; i.r. (KBr): ν_{max} = 1600, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,$SC\underline{H}_3$);

6.00(s,1H,H-4); 6.82(d,J=18Hz,1H$_{olefin}$); 7.09-7.58(m,4H$_{arom}$+ 1H$_{olefin}$). (Found: C,57.51; H,4.16; N, 5.39. calc. for $C_{12}H_{10}ClNOS$(251.7): C,57.25; H,3.97; N,5.56%). m/z 253(24): 251(M^+,52); 204(6%).

3-Methylthio-5-(4-methoxystyryl)isoxazole (100d) was isolated as white crystalline solid (chloroform/hexane); yield 65%; m.p. 84°C; i.r.(KBr): ν_{max} = 1600, 1568, 1508 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.56(s, 3H,SCH$_3$); 3.81(s,3H,OCH$_3$); 5.95(s,1H,H-4); 6.64(d,J=18Hz,1H$_{olefin}$); 6.79(d,J=10Hz,2H$_{arom}$); 7.18(d,J=18Hz,1H,olefin); 7.37(d,J=10Hz,2H$_{arom}$); ^{13}C n.m.r.($CDCl_3$): δ_C 13.88(SCH$_3$);55.35(OCH$_3$); 100.26(C-4); 114.30, 128.61(CH arom); 110.60, 134.85(CH, olefin); 128.17(C-1' arom); 160.50 (C-4' arom); 168.83, 160.51(C-3 and C-5).(Found: C,63.01; H,5.41; N,5.60. Calc. for $C_{13}H_{13}NO_2S$(247.3): C,63.15; H,5.26; N,5.66%). m/z 247(M^+,49); 200(6); 161(100); 133(30); 107(8%).

3-Methylthio-5-(4-N,N-dimethylaminostyryl)isoxazole (100e) was isolated as pale yellow solid (chloroform/hexane); yield 62%; m.p. 108°C; i.r.(KBr): ν_{max} = 1600, 1560, 1358 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.56(s,3H,SCH$_3$); 3.00[s,6H,N(CH$_3$)$_2$]; 5.90(s,1H,H-4); 6.43-6.66(m, 2H$_{arom}$+ 2H$_{olefin}$); 7.43(d,J=10Hz,2H$_{arom}$). (Found: C,64.38; H,6.38; N,10.81. Calc. for $C_{14}H_{16}N_2OS$(260.3): C,64.61; H,6.15; N,10.76%). m/z 260(M^+,63); 202(100); 174(22); 146(38%).

3-Methylthio-5-(2-chlorostyryl)isoxazole (100f)was isolated as white solid (chloroform/hexane); yield 56%; m.p. 70°C; i.r.(KBr): ν_{max} = 1640, 1567, 1550, 1468, 1428 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.58(s,3H,SCH$_3$); 6.10(s,1H,H-4): 6.81(d,J=18Hz,1H$_{olefin}$); 7.12-7.50(m,4H$_{arom}$); 7.78 (d,J=18Hz,1H$_{olefin}$). (Found: C,60.00; H,4.31; N,5.16. Calc. for

$C_{12}H_{10}ClNOS$(251.7): C,57.25; H,3.97; N,5.56%). m/z 253(19); 251 (M^+56); 204(5); 165(100); 137(40%).

3-Methylthio-5-(2,6-dichlorostyryl)isoxazole (100g) was isolated as white crystalline solid (chloroform/hexane); yield 63%; m.p. 62°C; i.r.(KBr): ν_{max} = 1546, 1420, 1358 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.60(s, 3H,SCH_3); 6.15(s,1H,H-4); 6.9-7.49(m,$3H_{arom}$+ $2H_{olefin}$). (Found: C,50.61; H,3.26; N,4.68. Calc. for $C_{12}H_9Cl_2NOS$ (286.2): C,50.34; H,3.14; N,4.89%). m/z 289(5); 285(M^+,17); 203, 199(14,45%).

3-Methylthio-5-(2,4-dichlorostyryl)isoxazole (100h) was isolated as white crystralline solid (chloroform/hexane); yield 35%; m.p. 115°C; i.r.(KBr): ν_{max} = 1565, 1460, 1400, 1346 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.60(s,3H,SCH_3); 6.12(s,1H,H-4); 6.80(d,J=18Hz,$1H_{olefin}$); 7.12-7.78 (m,$3H_{arom}$+ $1H_{olefin}$). (Found: C,50.41; H, 3.31; N,4.71. Calc. for $C_{12}H_9Cl_2NOS$(286.2): C,50.34; H,3.14; N,4.89%). m/z 289(7): 285(M^+,44); 203, 199(29,100%).

3-Methylthio-5-(3,4-methylenedioxystyryl)isoxazole (100i) was isolated as white crystalline solid (chloroform/hexane); yield 62%; m.p. 120°C; i.r.(KBr): ν_{max} = 1600, 1570, 1500, 1490, 1448 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.57(s,3H,SCH_3); 5.92(s,3H,-O-CH_2-O- & H-4); 6.33-7.30(s,$3H_{arom}$ + $2H_{olefin}$). (Found: C,60.00; H,4.31; N,5.16. Calc. for $C_{13}H_{11}NO_3S$(261.3): C,59.77); H,4.21; N,5.36%). m/z 261(M^+,87); 214(22); 175(100); 147(60%).

3-Methylthio-5-(4-phenyl-1,3-butadienyl)isoxazole (102a) was isolated as pale yellow crystalline solid (chloroform/hexane); yield 66%; m.p. 90°C; i.r.(KBr): ν_{max} = 1630, 1565, 1546, 1410 cm^{-1}; ^1H n.m.r.($CDCl_3$):

2.57(s,3H,SC$\underline{H}_3$); 5.93(s,1H,$\underline{H}$-4); 6.33(d,J=8Hz,1H_{olefin}); 6.66-6.98 (m,3H_{olefin}); 7.10-7.48(m,5H_{arom}); ^{13}C n.m.r.($CDCl_3$): δ_C 13.98(S$\underline{C}H_3$); 100.91($\underline{C}$-4); 126.93, 127.46, 128.86($\underline{C}$H arom); 116.05, 128.61, 135.66, 137.38($\underline{C}$H olefin); 136.50($\underline{C}$-1' arom); 168.49, 160.68($\underline{C}$-3 and $\underline{C}$-5). (Found: C,69.01; H,5.48; N,5.87. Calc. for $C_{14}H_{13}NOS$(243.3): C,69.13; H,5.34; N,5.76%). m/z 243(M^+,94); 196(73); 157(100%).

3-Methylthio-5-[4-(4-methoxyphenyl) 1,3-butadienyl]isoxazole (102b) was isolated as pale yellow crystalline solid (chloroform/hexane); yield 58%; m.p. 102°C; i.r. (KBr): ν_{max} = 1597, 1571, 1547, 1507, 1462 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): 2.6(s,3H,SC$\underline{H}_3$); 3.81(s,3H,OC$\underline{H}_3$); 6.00 (s,1H,$\underline{H}$-4); 6.25(d,J=18Hz,1H_{olefin}); 6.63-7.00(m,2H_{arom}+ 3H_{olefin}); 7.34(d,J=8Hz,2H_{arom}). (Found: C,65.80; H,5.61; N,5.32. Calc. for $C_{15}H_{15}NO_2S$(273.3): C, 65.93; H,5.49; N,5.12%). m/z 273(M^+,39); 226(21); 187(20%).

3-Methylthio-5-[4-(3,4-methylenedioxyphenyl)-1,3-butadienyl] isoxazole (102c) was isolated as pale yellow crystalline solid (chloroform/hexane); yield 63%; m.p. 108°C; i.r.(KBr): ν_{max} = 1627, 1599, 1536, 1499, 1484 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): 2.6 (s,3H,SC$\underline{H}_3$); 5.93(s,3H,-O-C$\underline{H}_3$-O- and $\underline{H}$-4); 6.35(d,J=18Hz,1H_{olefin}); 6.61-7.30 (m,3H_{arom}+ 3H_{olefin}). (Found: C,62.56; H,4.58; N,5.01. Calc. for $C_{15}H_{13}NO_3S$(287.3): C,62.71; H,4.52; N,4.87%. m/z 287(M^+,100); 240(39); 201(32); 173(24%).

3-Methylthio-5-(6-phenyl-1,3,5-hexatrienyl)isoxazole (104a) was isolated as yellow crystalline solid (chloroform/hexane); yield 59%; m.p. 123°C; i.r.(KBr): ν_{max} = 1627, 1597, 1530, 1440 cm^{-1}; ^{1}H n.m.r.($CDCl_3$)

2.58(s,3H,SC$\underline{H}_3$); 5.92(s,1H,$\underline{H}$-4); 6.31(d,J=18Hz,1H_{olefin}); 6.42-6.89 (m,5H_{olefin}); 7.1-7.48(m,5H_{arom}); ^{13}C n.m.r.($CDCl_3$): δ_C 13.87(S$\underline{C}H_3$): 100.76($\underline{C}$-4); 126.64, 128.28, 128.70($\underline{C}$H arom); 115.58, 128.11, 131.46, 135.25, 135.37, 137.83($\underline{C}$H olefin); 136.83(C-1' arom); 168.43, 160.50 (C-3 and $\underline{C}$-5). (Found: C,71.53; H,5.81; N,5.36. Calc. for $C_{16}H_{15}NOS$ (269.3): C,71.37; H,5.57; N,5.20%). m/z 269(M^+,100); 222(27); 155(30%).

3-Methylthio-5-[6-(4-methoxyphenyl)-1,3,5-hexatrienyl]isoxazole (104b)

was prepared as yellow solid (chloroform/hexane); yield 47%; m.p. 139°C; i.r.(KBr): ν_{max} = 1605, 1585, 1508 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): 2.57(s,3H,SC$\underline{H}_3$); 3.80(s,3H,OC$\underline{H}_3$); 6.00(s,1H,$\underline{H}$-4); 6.11-6.92(m, 2H_{arom}+ 6H_{olefin}); 7.31(d,J=8Hz,2H_{arom}). (Found: C,68.08; H,5.86; N,4.91. Calc. for $C_{17}H_{17}NO_2S$(299.3): C,68.22; H,5.68; N,4.68%). m/z 299(M^+,19); 252(27); 224(18); 185(25%).

Methylthio-5-[6-(3,4-methylenedioxyphenyl)-1,3,5-hexatrienyl] isoxazole (104c) was prepared as yellow solid (chloroform/hexane); yield 51%; m.p. 144°C; i.r.(KBr): ν_{max} = 1600, 1578, 1485, 1440, 1355 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): 2.58(s,3H,SC$\underline{H}_3$); 5.95(s,2H,-O-CH_2-O); 6.03(s,1H,$\underline{H}$-4); 6.18-7.13(m,3H_{arom} + 6H_{olefin}). (Found: C,65.26; H,4.91; N,4.36. Calc. for $C_{17}H_{15}NO_3S$(313.3): C,65.17; H,4.79; N,4.47%). m/z 313(M^+,100); 266(20); 238(15); 208(17%).

1-Acetyl-3[bis(methylthiomethylene)methyl]-5-aryl/styryl-2-pyrazoline 134a-e and 1(2)-acetyl-3(5)styryl/4-aryl-1,3-butadienyl)-5(3)-methyl-thiopyrazole 135a-e; General Procedure:

To a solution of S,S-acetal 98 (10 mmol) in ethanol (30 ml), hydrazine

hydrate (2g) was added and the reaction mixture was refluxed for 6 hrs. Ethanol was removed under reduced pressure and the residue dissolved in chloroform (300 ml) washed with water (2x200 ml), dried (Na_2SO_4) and concentrated to a volume of 100 ml. To this chloroform extract, acetic anhydride (5 ml) and acetic acid (5 ml) were added and the reaction mixture was stirred at room temperature for 12 hrs. It was then poured over ice cold water (200 ml) and the chloroform layer separated, washed with saturated sodium bicarbonate solution (200 ml), water (200 ml), dried (Na_2SO_4) and evaporated to give crude residue which was subjected to column chromatography over silica gel. Elution with ethyl acetate:hexane (1:10) gives pyrazole 135. Further elution with ethyl acetate:hexane (1:1) affords the pyrazoline 134 as pale yellow solid.

1(2)-Acetyl-3(5)-styryl-5(3)-methylthiopyrazole (135a) was obtained as white solid; yield 18%; m.p. 124°C; i.r.(KBr): ν_{max} = 1730, 1518, 1420 cm^{-1}; ^1H n.m.r.(CCl_4): 2.46(s,3H,$SC\underline{H}_3$);2.66(s,3H,$C\underline{H}_3CO$); 6.23 (s,1H,$\underline{H}$-4); 7.06(s,$2H_{olefin}$); 7.23-8.14(m,$5H_{arom}$). (Found: C,64.87; H,5.66; N,10.78. Calc. for $C_{14}H_{14}N_2OS$(258.3): C,65.11; H,5.42; N,10.85%). m/z 258(M^+,54%).

1(2)-Acetyl-3(5)-(4-methylstyryl)-5(3)-methylthiopyrazole (135b) was obtained as white solid; yield 15%; m.p. 115°C; i.r.(KBr): ν_{max} = 1722, 1510, 1415 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.39(s,3H,$C\underline{H}_3$): 2.48(s,3H, $SC\underline{H}_3$); 2.70(s,3H,$C\underline{H}_3CO$); 6.36(s,1H,$\underline{H}$-4); 7.10-7.36(m,$4H_{arom}$+ $2H_{olefin}$); 7.50(d,J=8Hz,$2H_{arom}$). (Found: C,66.44; H,5.99; N,10.01. Calc. for $C_{15}H_{16}N_2OS$(272.4): C,66.17; H,5.88; N,10.29%). m/z 274(M^++2,34%).

1(2)-Acetyl-3(5)-(4-methoxystyryl)-5(3)-methylthiopyrazole (135c)

was obtained as white solid yield 21%; m.p. 134°C; i.r.(KBr): ν_{max}= 1720, 1600, 1518 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,3H,$SC\underline{H}_3$); 2.67(s, 3H,$C\underline{H}_3CO$); 3.84(s,3H,$C\underline{H}_3O$); 6.35(s,1H,$\underline{H}$-4); 6.80-7.15(m,$2H_{arom}$+ $2H_{olefin}$); 7.50(d,J=8Hz,$2H_{arom}$). (Found: C,62.71; H,5.61; N,9.56. Calc. for $C_{15}H_{16}N_2O_2S$ (288.4): C,62.50; H,5.55; N,9.72%). m/z 288(M^+,93%),

1-(2)-Acetyl-3(5)-(2,6-dichlorostyryl)-5(3)-methylthiopyrazole (135d)

was obtained as white solid; yield 13%; m.p. 159-160°C; i.r.(KBr): ν_{max} = 1720, 1503, 1420 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.50(s,3H,$SC\underline{H}_3$); 2.69(s,3H,$C\underline{H}_3CO$); 6.38(s,1H,$\underline{H}$-4); 6.93-7.49(m,$3H_{arom}$ + $2H_{olefin}$). (Found: C,51.55; H,3.48; N,8.68. Calc. for $C_{14}H_{12}Cl_2N_2OS$(327.2): C,51.37; H,3.66; N,8.56%). m/z 330(8); 326(M^+,27%).

1-(2)-Acetyl-3(5)-(4-phenyl-1,3-butadienyl)-5(3)-methylthiopyrazole (135e) was obtained as white solid; yield 17%; m.p. 141°C; i.r.(KBr): ν_{max} = 1724, 1500, 1420 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,3H,$SC\underline{H}_3$): 2.68(s,3H,$C\underline{H}_3CO$); 6.25(s,1H,$\underline{H}$-4); 6.60-6.99(m,$4H_{olefin}$); 7.23-7.62(m,$5H_{arom}$). (Found: C,67.44; H,5.81; N,9.67. Calc. for $C_{16}H_{16}N_2OS$(284.4): C,67.60; H,5.63; N,9.85%). m/z 284(M^+,63%).

1-Acetyl-3[bis(methylthiomethylene)methyl]-5-phenyl-2-pyrazoline (134a)

was obtained as off white solid; yield 65%; m.p. 50°C; i.r.(KBr): ν_{max} = 1650, 1413 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.30(s,3H,$SC\underline{H}_3$); 2.40 (s,6H,$SC\underline{H}_3$ and $C\underline{H}_3CO$); 3.20(dd,1H,J=18,6Hz,H_A-4); 3.51-3.96(dd,1H, J=18,12Hz,H_B-4); 5.45(dd,1H,J=12,6Hz,H_X-5); 6.31(s,$1H_{olefin}$); 7.25 (brs,$5H_{arom}$). (Found: C,58.72; H,6.03; N,9.33. Calc. for $C_{15}H_{18}N_2OS_2$ (306.4): C,58.82; H,5.88; N,9.15%). m/z 306(M^+,100 %).

1-Acetyl-3[bis(methylthiomethylene)methyl]-5-(4-methylphenyl)-2-pyrazoline (134b) was obtained as off white solid; yield 58%; m.p. 98°C; i.r.(KBr): ν_{max} = 1658, 1520 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.30(s, 3H,$C\underline{H}_3$); 2.32(s,3H,$SC\underline{H}_3$); 2.42(s,6H,$SC\underline{H}_3$) and $C\underline{H}_3CO$); 3.21(dd,1H, J=18,6Hz,H_A-4); 3.52-3.88(dd,1H,J=18,12Hz,H_B-4); 5.40(dd,1H,J=12, 6Hz,H_X-5); 6.33(s,$1H_{olefin}$); 7.12(s,$4H_{arom}$). (Found: C,59.86; H,6.31; N,8.60. Calc. for $C_{16}H_{20}N_2OS_2$(320.5): C,60.00; H,6.25; N,8.75%). m/z 320(M^+,100 %).

1-Acetyl-3[bis(methylthiomethylene)methyl]-5-(4-methoxyphenyl)-2-pyrazoline (134c) was obtained as off white solid; yield 61%; m.p. 102°C; i.r.(KBr): ν_{max} = 1650, 1405 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.13(s, 3H,$SC\underline{H}_3$); 2.36(s,3H,$SC\underline{H}_3$); 2.40(s,3H,$C\underline{H}_3CO$); 3.21(dd,1H,J=18,6Hz, H_A-4); 3.73(s,3H,$C\underline{H}_3O$); 3.52-3.91(dd,1H,merged with $C\underline{H}_3O$ signal, J=18,12Hz,H_B-4); 5.38(dd,1H,J=12,6Hz,H_X-5); 6.32(s,$1H_{olefin}$); 6.85 (d,J=8Hz,$2H_{arom}$); 7.20(d,J=8Hz,$2H_{arom}$). (Found: C, 56.88; H,6.12; N, 8.41.. Calc. for $C_{16}H_{20}N_2O_2S_2$ (336.5): C,57.14; H,5.95; N,8.33%). m/z 336(M^+,100%).

1-Acetyl-3[bis(methylthiomethylene)methyl] 5-(2,6-dichlorophenyl)-2-pyrazoline (134d) was obtained as off white solid; yield 59%; m.p. 142°C; i.r.(KBr): ν_{max} = 1658, 1558 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.25(s,3H,$SC\underline{H}_3$); 2.43(s,6H,$SC\underline{H}_3$ and $C\underline{H}_3CO$); 3.33(dd,1H,J=18,6Hz, H_A-4); 3.53-5.00(dd,1H,J=18,12Hz,H_B-4); 6.10(dd,1H,J=12,6Hz,H_X-5); 6.40(s,$1H_{olefin}$); 6.96-7.47(m,$3H_{arom}$). (Found: C,48.21; H,4.38; N,7.61. Calc. for $C_{15}H_{16}Cl_2N_2OS_2$(375.3): C,48.00; H,4.26; N,7.46%). m/z 378(17); 374(M^+,100%).

1-Acetyl-3[bis(methylthiomethylene)methyl]-5-styryl-2-pyrazoline (134e) was obtained as viscous liquid; yield 54%; i.r.(neat): ν_{max} = 1650, 1520 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.33(s,3H,SCH_3); 2.40(s,3H,SCH_3); 2.46(s,3H,CH_3CO); 3.19(dd,J=18,6Hz,H_A-4); 3.52(dd,J=18,12Hz,H_B-4); 4.95-5.26(m,1H,H_X-5); 5.98-6.33(m,$2H_{olefin}$); 6.54(d,J=16Hz,$1H_{olefin}$); 7.13-7.54(m,$5H_{arom}$). (Found: C,61.61; H,5.88; N,8.25. Calc. for $C_{17}H_{20}N_2OS_2$(332.5): C,61.44; H,6.02; N,8.43%). m/z 332(M^+,100%).

3(5(-Styryl-5(3)-methylthiopyrazoles 136a-i; 3(5-(4-aryl-1,3-butadienyl)-5(3)-methylthiopyrazoles 137a-e and 3(5)-(6-aryl-1,3,5-hexatrienyl)-5(3)-methylthiopyrazoles 138a-c; General Procedure:

To a solution of S,S-acetal 98 (10 mmol) in ethanol (40 ml) and acetic acid (40 ml), was added hydrazine hydrate (2g) and the reaction mixture was refluxed (110°C) for 20 hrs. The solvent was removed under reduced pressure and the residue was poured over ice cold water (100g), the crude pyrazoles separated as light yellow solids are filtered, dried and recrystallized from chloroform/hexane. The pyrazole 136a is obtained as viscous oil after pouring the residue over water. It was extracted with chloroform(2x2 ml), evaporated, dried (Na_2SO_4) and residue passed through small column of silica gel using hexane as eluent to give 136a as pale yellow viscous liquids.

3(5)-Styryl-5(3)-methylthiopyrazole (136a) was obtained as pale yellow viscous liquid; yield 79%; i.r.(neat): ν_{max} = 3320, 1638, 1430 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.45(s,3H,SCH_3); 6.39(s,1H,H-4); 7.08(s,$2H_{olefin}$); 7.23-7.62(m,$5H_{arom}$); 11.10(brs,1H,exchangeable with D_2O, NH). (Found: C,66.39; H,5.81; N,12.73. Calc. for $C_{12}H_{12}N_2S$(216.3): C,66.66; H,5.55; N,12.96%). m/z 216(M^+,100); 215(71); 183(49); 119(35%).

3(5)-(4-Chlorostyryl-5(3)-methylthiopyrazole (136b) was obtained as white solid (chloroform/hexane) yield 72%; m.p. 142-143°C; i.r. IKBr): ν_{max} = 3150, 1540, 1480 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,3H, SCH_3); 6.44(s,1H,H-4); 7.00(s,$2H_{olefin}$); 7.17-7.50(m,$4H_{arom}$); 8.94(brs, 1H,exchangeable with D_2O, NH). (Found: C,57.21; H,4.66; N,10.90. Calc. for $C_{12}H_{11}ClN_2S$(250.7): C,57.48; H,4.39; N,11.17%). m/z 252(37); 250(M^+,100); 249(75); 217(41%).

3(5)-(4-Methoxystyryl)-5(3)-methylthiopyrazole (136c) was obtained as white solid (chloroform/hexane) yield 73%; m.p.112-113°C; i.r. (KBr): ν_{max} = 3100, 1600, 1400 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,3H, SCH_3); 3.78(s,3H,OCH_3); 6.40(s,1H,H-4); 6.82(d,J=8Hz,$2H_{arom}$); 6.98 (s,$2H_{olefin}$); 7.40(d,J=8Hz,$2H_{arom}$); 10.00(brs,1H,exchangeable with D_2O,NH). (Found: C,63.70; H,5.99; N,11.63. Calc. for $C_{13}H_{14}N_2OS$ (246.3): C,63.41; H,5.69; N,11.38%). m/z 246(M^+,100); 245(43); 213(30); 198(16%).

3(5)-(4-N,N-Dimethylaminostyryl)-5(3)-methylthiopyrazole (136d) was obtained as white solid (chloroform/hexane) yield 69%; m.p. 149-150°C; i.r.(KBr):ν_{max} = 3180, 1600, 1440 cm^{-1}; ^1H n.m.r.($CDCl_3$):

2.46(s,3H,SC$\underline{H}_3$): 2.93[s,6H,N(CH_3)$_2$]; 6.48(s,1H,$\underline{H}$-4); 6.68(d,J=8Hz, $2H_{arom}$); 6.82(d,J=6Hz,$2H_{olefin}$); 7.30(d,J=8Hz,$2H_{arom}$); 10.10(brs, 1H,exchangeable with D_2O,NH). (Found: C,65.11; H,6.79; N,16.06. Calc. for $C_{14}H_{17}N_3S$(259.3): C,64.86; H,6.56; N,16.21%). m/z 259 (M^+,100); 258(28); 211(14%).

3(5)-(2-Chlorostyryl)-5(3)-methylthiopyrazole (136e) was obtained as white solid (chloroform/hexane) yield 64%; m.p. 101-102°C; i.r. (KBr): ν_{max} = 3100, 1540, 1460 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.40(s,3H, SC$\underline{H}_3$); 6.42(s,1H,$\underline{H}$-4); 6.82-7.62(m,$4H_{arom}$+ $2H_{olefin}$); 10.80(s,1H, exchangeable with D_2O, NH). (Found: C,57.26; H,4.67; N,11.44. Calc. for $C_{12}H_{11}ClN_2S$(250.7): C,57.48; H,4.39; N,11.17%).m/z 252(19); 250(M^+,49%).

3(5)-(2,6-Dichlorostyryl)-5(3)-methylthiopyrazole (136f) was obtained as white solid (chloroform/hexane) yield 63%; m.p. 110°C; i.r.(KBr): ν_{max} = 1546, 1420, 1350 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.47(s,3H,SC$\underline{H}_3$); 6.45(s,1H,$\underline{H}$-4); 7.14(s,$2H_{olefin}$); 6.95-7.35(m,$3H_{arom}$); 9.40(brs, 1H,exchangeable with D_2O,NH). (Found: C,50.23; H,3.78; N,9.62. Calc. for $C_{12}H_{10}Cl_2N_2S$(285.2): C,50.52; H,3.50; N,9.82%). m/z 284 (M^+,28); 249(100); 202(46%).

3(5)-(3,4-Methylenedioxystyryl)-5(3)-methylthiopyrazole (136g) was obtained as white solid (chloroform/hexane) yield 69%; m.p. 143°C; i.r.(KBr): ν_{max} = 3250, 1600, 1540, 1500, 1480, 1419 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.43(s,3H,SC$\underline{H}_3$): 5.92(s,2H,-O-CH_2-O-); 6.38(s,1H,$\underline{H}$-4); 6.65-7.18(m,$3H_{arom}$+ $2H_{olefin}$); 10.10(brs,1H,exchangeable with D_2O, N$\underline{H}$). (Found: C,60.23; H,4.90; N,11.01. Calc. for $C_{13}H_{12}N_2O_2S$(260.3): C,60.00; H,4.62; N,10.76%). m/z 260(M^+,100); 259(43); 232(22); 227(23%).

3(5)-(3,4-Dimethoxystyryl)-5(3)-methylthiopyrazole (136h) was obtained as white solid (chloroform/hexane) yield 80%; m.p. 90°C; i.r.(KBr): ν_{max}= 3220, 1582, 1510, 1455 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.50 (s,3H,SCH_3); 3.90(s,6H,OCH_3); 6.45(s,1H,H-4); 6.72-7.32(m,$3H_{arom}$+$2H_{olefin}$); 8.93(brs,1H,exchangeable with D_2O,NH); ^{13}C n.m.r.($CDCl_3$): δ_C 17.42 (SCH_3); 55.66; 55.73(OCH_3); 103.08(CH-4); 108.41; 110.93; 131.18 (CH arom); 114.42, 131.18(CH olefin); 129.38(C-1'arom); 148.92, 149.13(C-3 and C-5); 157.83, 157.95(C-3', C-4' arom). (Found:C,61.11; H,6.07; N,9.93. Calc. for $C_{14}H_{16}N_2O_2S$(276.3): C,60.86; H,5.79; N,10.14%). m/z 276(M^+,100); 275(40%).

3(5)-(3,4,5-Trimethoxystyryl)-5(3)-methylthiopyrazole (136i) was obtained as white solid (chloroform/hexane) yield 78%; m.p. 150°C; i.r.(KBr): ν_{max} = 3310, 1589, 1551, 1503, 1462, 1420 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.48(s,3H,SCH_3): 3.86(s,9H,OCH_3); 6.47(s,1H,H-4); 6.82(s, $2H_{olefin}$); 7.07(s,$2H_{arom}$); 11.07(brs,1H,exchangeable with D_2O,NH). (Found: C,59.01; H,6.11; N,9.33. Calc. for $C_{15}H_{18}N_2O_3S$(306.4): C,58.82; H,5.88; N,9.15%). m/z 306(M^+,45); 305(13); 231(5%).

3(5)-(4-phenyl-1,3-butadienyl)-5(3)-methylthiopyrazole (137a) was obtained as off white solid (chloroform/hexane) yield 74%; m.p.119°C; i.r.(KBr): ν_{max} = 3260, 1622, 1525, 1422 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.42(s,3H,SCH_3); 6.33(s,1H,H-4); 6.50-6.88(m,$4H_{olefin}$); 7.13-7.50 (m,$5H_{arom}$); 11.20(brs,1H,exchangeable with D_2O,NH). (Found: C,69.63; H,5.93; N,11.78. Calc. for $C_{14}H_{14}N_2S$(242.3): C,69.42; H,5.78; N,11.57%). m/z 242(M^+,100); 241(33); 195(31); 165(90%).

3(5)-[4-(4-methoxyphenyl)-1,3-butadienyl]-5(3)-methylthiopyrazole (137b) was obtained as off white solid (chloroform/hexane) yield 74%; m.p. 105°C; i.r.(KBr): ν_{max} = 3190, 1590, 1500, 1438 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.52(s,3H,SCH_3); 3.87(s,3H,OCH_3); 6.40(s,1H,H-4); 6.49-6.80 (m,$4H_{olefin}$); 6.91(d,J=8Hz,$2H_{arom}$); 7.32(d,J=8Hz,$2H_{arom}$); 10.51(brs, 1H,exchangeable with D_2O,NH); ^{13}C n.m.r.($CDCl_3$/DMSO-d_6);δ_c15.80 SCH_3); 53.83(OCH_3); 101.47(CH-4); 112.79, 126.34(CH arom); 125.18, 126.25, 129.70, 131.71(CH olefinic); 128.30(C-1' arom); 147.11, 148.92(C-3, C-5); 157.92(C-4' arom). (Found: C,65.99; H,6.16;N,10.47. Calc. for $C_{15}H_{16}N_2OS$(272.3): C,66.17; H,5.88; N,10.29%). m/z 272 (M^+,100); 271(28); 225(14%).

3(5)-[4-(3,4-Methylenedioxyphenyl)-1,3-butadienyl]-5(3)-methylthiopyrazole (137c) was obtained as pale yellow solid (chloroform/hexane) yield 77%; m.p. 131°C; i.r.(KBr): ν_{max} = 3265, 1540, 1498, 1480, 1440 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.47(s,3H,SCH_3); 5.90(s,2H,-O-CH_2-O-); 6.30 (s,1H,H-4); 6.50-7.11(m,$3H_{arom}$+$4H_{olefin}$); 10.20(brs,1H,exchangeable with D_2O,NH). (Found: C,63.11; H,5.18; N,10.07. Calc. for $C_{15}H_{14}N_2O_2S$ (286.3): C,62.93; H,4.89; N,9.97%). m/z 286(M^+,29); 285(8%).

3(5)-[6-Phenyl-1,3,5- hexatrienyl]-5(3)-methylthiopyrazole (138a) was obtained as pale yellow solid (chloroform/hexane) yield 75%; m.p. 140°C; i.r.(KBr): ν_{max} = 3275, 1530, 1440, 1360 cm^{-1}; ^1H n.m.r. ($CDCl_3$): 2.50(s,3H,SCH_3); 6.34(s,1H,H-4); 6.41-7.01(m,$6H_{olefin}$); 7.15-7.53(m,$5H_{arom}$); 10.20(brs,1H,exchangeable with D_2O, NH); ^{13}C n.m.r.($CDCl_3$/DMSO-d_6);δ_c15.92(SCH_3); 102.43(CH-4); 125.42, 127.73, 132.04(CH arom); 125.50, 126.79, 127.82, 128.02, 129.78, 133.31

(CH olefine); 136.25(C-1' arom); 146.23, 149.20(C-3 and C-5). (Found: C,71.93; H,6.28; N,10.59. Calc. for $C_{16}H_{16}N_2S$(268.3); C,71.64; H,5.97; N,10.44%). m/z 268(M^+,100); 267(39); 221(21%).

3(5)-[6-(4-Methoxyphenyl)-1,3,5-hexatrienyl]-5(3)-methylthiopyrazole (138b) was obtained as pale yellow solid (chloroform/hexane) yield 74%; m.p. 158°C; i.r.(KBr): ν_{max} = 3180, 1595, 1510, 1442 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.50(s,3H,SCH_3); 3.79(s,3H,OCH_3); 6.28(s,1H,H-4); 6.20-6.81(m,$6H_{olefin}$); 6.85(d,J=8.5Hz,$2H_{arom}$); 7.30(d,J=8.5Hz,$2H_{arom}$); 11.00(brs,1H,exchangeable with D_2O,NH). (Found: C,68.66; H,6.32; N,9.60. Calc. for $C_{17}H_{18}N_2OS$(298.4): C,68.45; H,6.04; N,9.39%). m/z 298(M^+,100); 297(33%).

3(5)-[6-(3,4-Methylenedioxyphenyl)-1,3,5-hexatrienyl]-5(3)-methylthiopyrazole (138c) was obtained as yellow solid (chloroform/hexane) yield 71%; m.p. 162°C; i.r.(KBr): ν_{max} = 3220, 1593, 1550, 1450 cm^{-1}; ^1H n.m.r.($CDCl_3$): 2.48(s,3H,SCH_3); 5.92(s,2H,-O-CH_2-O); 6.30(s, 1H,H-4); 6.31-6.93(m,$3H_{arom}$+ $6H_{olefin}$); 9.50(brs,1H,exchangeable with D_2O, NH). (Found: C,65.16; H,5.39; N,9.16. Calc. for $C_{17}H_{16}N_2O_2S$(312.4): C,65.38; H,5.12; N,8.97%. m/z 312(M^+,100); 311(36); 265(12%).

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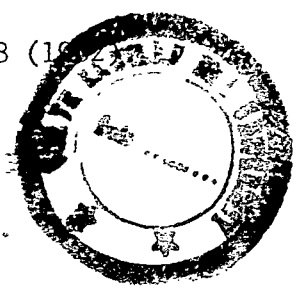

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CHAPTER III

REACTION OF α-OXOKETENE S,N-ACETALS WITH OXALYL CHLORIDE: A FACILE ROUTE FOR THE SYNTHESIS OF 3-AROYL-2-ALKYLTHIO-1-ARYL/BENZYL/ALKYL PYRROL-4,5-DIONE.

III.I INTRODUCTION

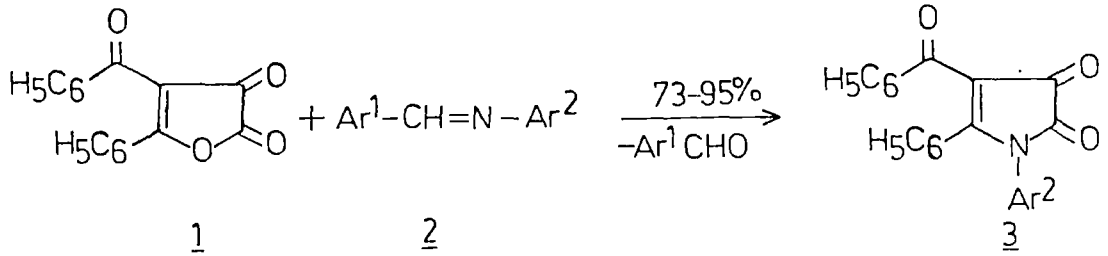
Unlike oxoketene dithioacetals, the corresponding S,N-acetals in addition to their reactivity as 1,3-electrophilic 3-carbon fragments behave like enamines participating with electrophiles through α-carbon atom. They differ from oxoketene dithioacetals in their enamine reactivity profile providing C-C-N component in the product heterocycles. In utilising this reactivity profile a number of reactions has been reported from this and other laboratories for the construction of different heterocyclic compounds. They have been shown to be important precursors for the synthesis of pyrroles[1], indoles[2], pyridones[3], pyrimidines[4], imidazoles[5,6], thiazoles[7] etc.

In most of the cases the enamine nitrogen and the two carbon atoms essentially become part of the heterocyclic ring. Thus the oxoketene S,N-acetals have special advantage as important precursors for the synthesis of heterocycles. In the present investigation it is considered of interest to exploit the oxoketene S,N-acetals to develop a novel and convenient methodology for the synthesis of 4,5-dioxopyrroles.

A brief survey of the methods for the synthesis of 4,5-dioxopyrroles and related compounds is described.

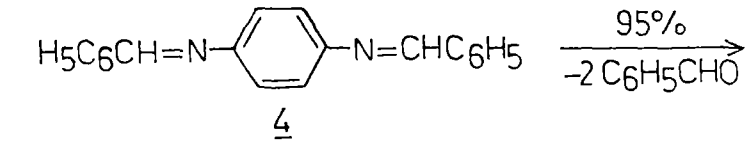
The furan-4,5-diones of the general formula 1 have been reacted with Schiff's bases 2 to yield the corresponding 1-aryl-2-phenyl-3-benzoyl-pyrrol-4,5-diones 3 in good yields. Similarly when Schiff's base 4 derived from 4-phenylenediamine and benzaldehyde reacted with furandione 1 the corresponding bispyrroledione 5 was obtained in 95% yield (Scheme 1)[8]. The mechanism of the formation of compound 3 is depicted in Scheme 2. The furandione 1 is cleaved by the Schiff's base to give the corresponding open chain betaine 6 which undergoes ring closure to give 7 followed by ring contraction with the elimination of benzaldehyde to give high yields of 3 (Scheme 2)[9].

Furandione 1 is also reported to undergo 4+2 cycloaddition with carbodiimide to give an unstable adduct 9 which undergoes fragmentation with the elimination of alkylisocyanate to give the corresponding 2-phenyl-3-alkyliminobenzoyl-furan-4,5-dione 10. The intermediate 10 presumably on rearrangement through 11 affords the corresponding pyrrol -4,5-dione 3 (Scheme 3)[10].



1 2 3

$Ar^1 = C_6H_5$; 4-ClC_6H_4; $Ar^2 = C_6H_5$; 4-MeC_6H_4;
4-$MeOC_6H_4$; 4-$NO_2C_6H_4$;



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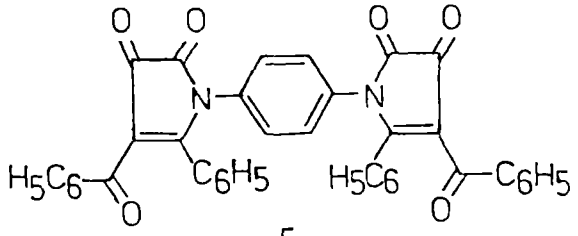

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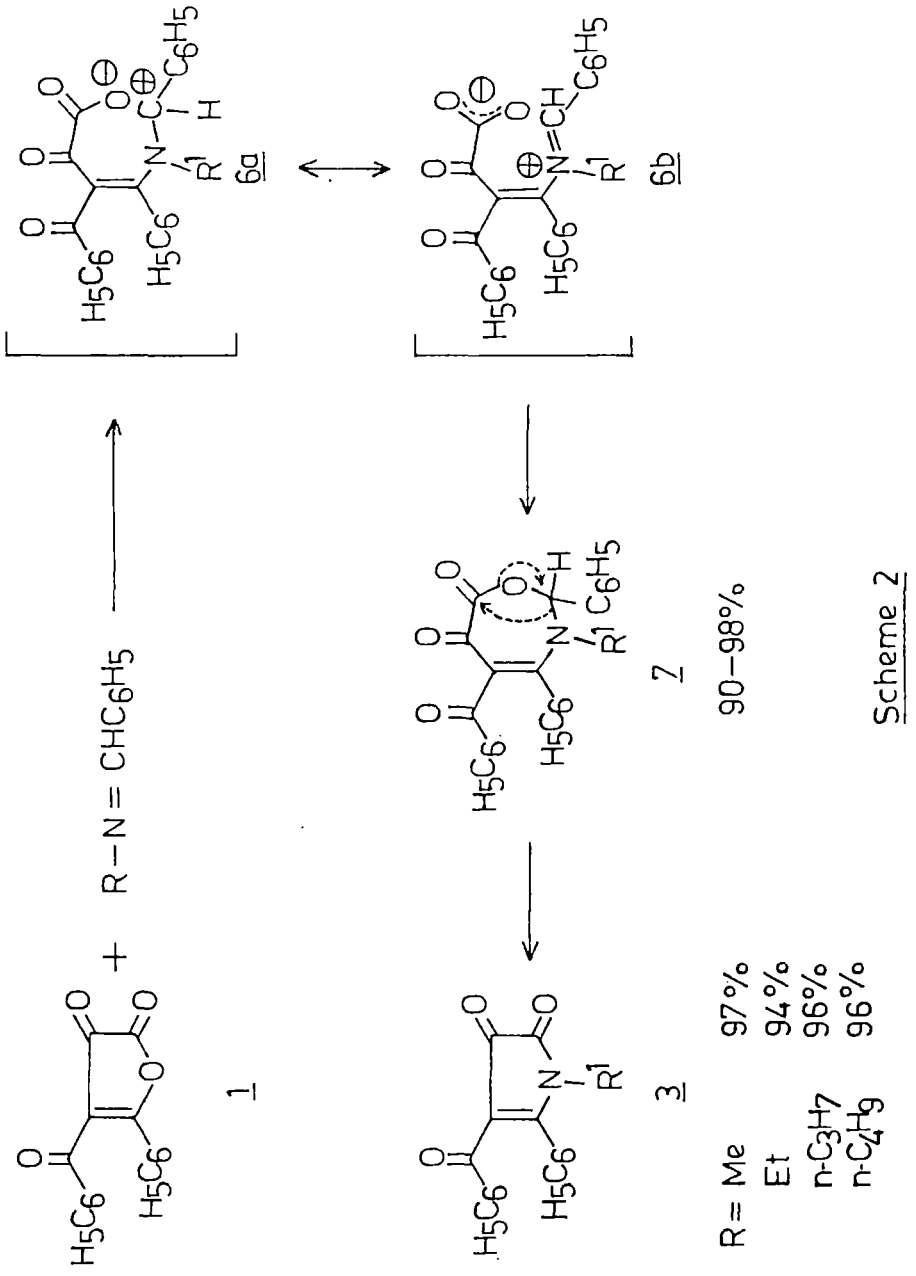
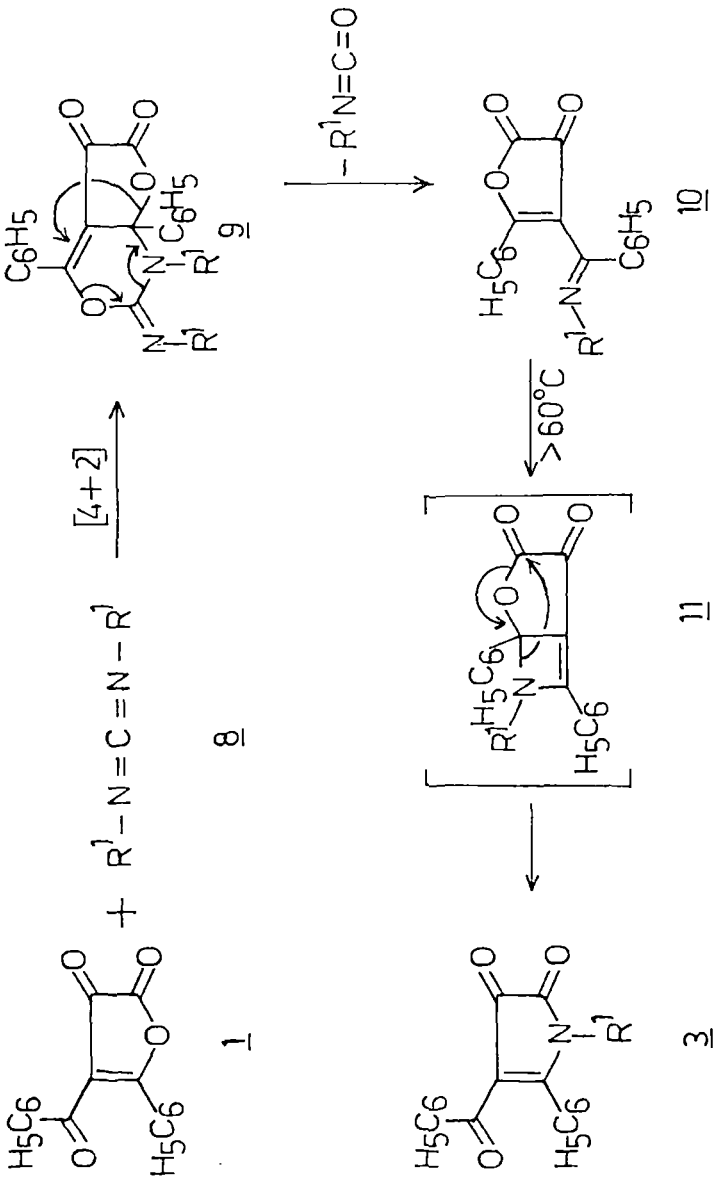
Scheme 1



Scheme 2



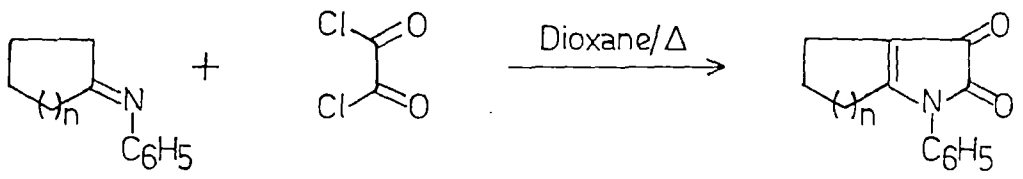
Scheme 3

2,3-Dioxo-4,5-annelated pyrroles 14 have also been obtained[11] by reacting a number of anils 12 derived from cycloalkanones with oxalyl chloride 13 in refluxing dioxane (Scheme 4). Similar approach has been extended to the synthesis of dioxopyrrolidine 18. Thus the methylimino compound 15 formed by reacting methylamine with 4-methoxy-benzaldehyde was condensed with β-ketoester 16 to yield the corresponding dioxopyrrolidine 18 involving the sequence of reaction described in the Scheme 5 [12].

Mumm and Hornhardt[13] have developed a novel synthesis of 2-phenyl-pyrrol -4,5-dione 23 through isoxazolium ring transformation. Generally it requires 3-unsubstituted isoxazoles and the sequence of reaction involves the attack of the cyanide ion at electrophilic C-3 of the intermediate 19 followed by ring opening to yield 21 which underwent acid catalysed cyclisation to the corresponding 4-methylimino-2-phenyl-pyrroline-5-one 22. The 2-phenyl-pyrrol -4,5-dione 23 was obtained by the hydrolysis of 22 (Scheme 6).

The enaminones 24 have been reported to react with oxalyl chloride to yield the corresponding pyrrol -4,5-dione 25. The enamines 24 are also reacted with malonyl chloride to yield the corresponding 5-benzoyl-1,6-diphenyl-4-hydroxy-2-oxo-1,2-dihydropyridine 27 (Scheme 7)[14].

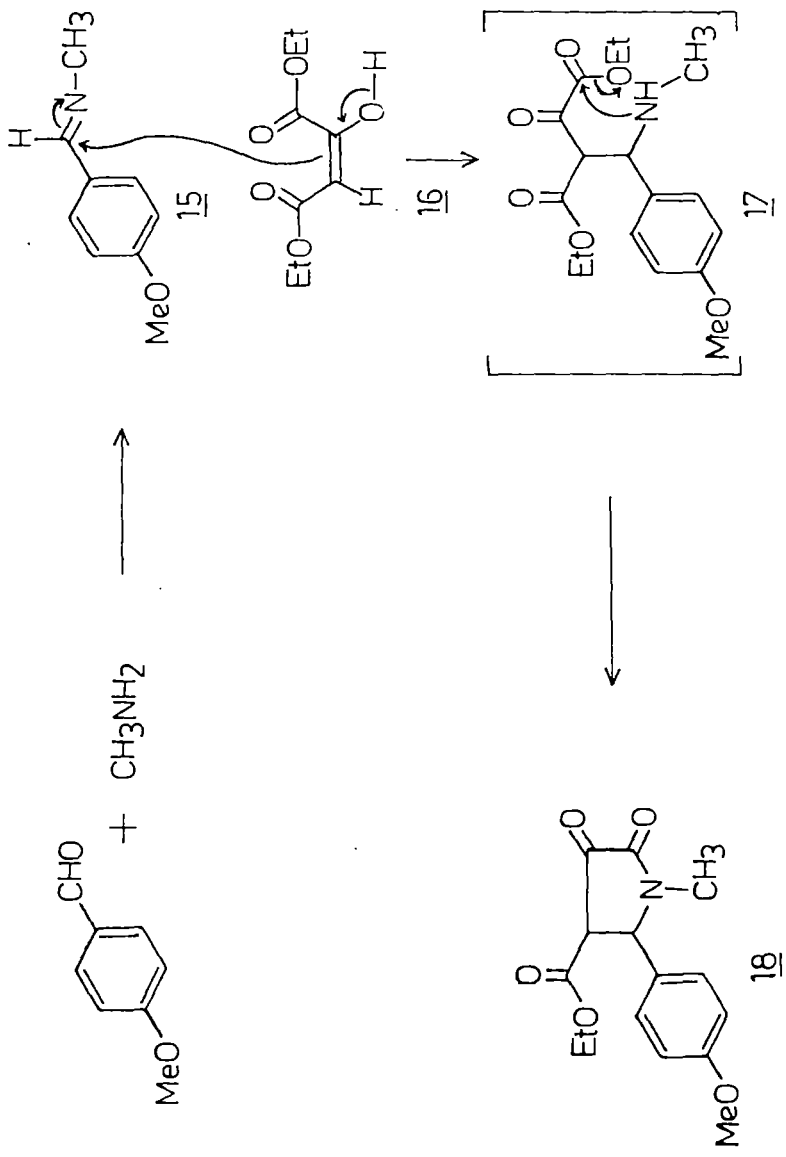
In the course of the present investigation, it was considered to react the oxoketene S,N-acetals with oxalyl chloride and from the literature survey, it was found that the reaction of nitroketene S,N-acetals 28 with oxalyl chloride was reported to yield the



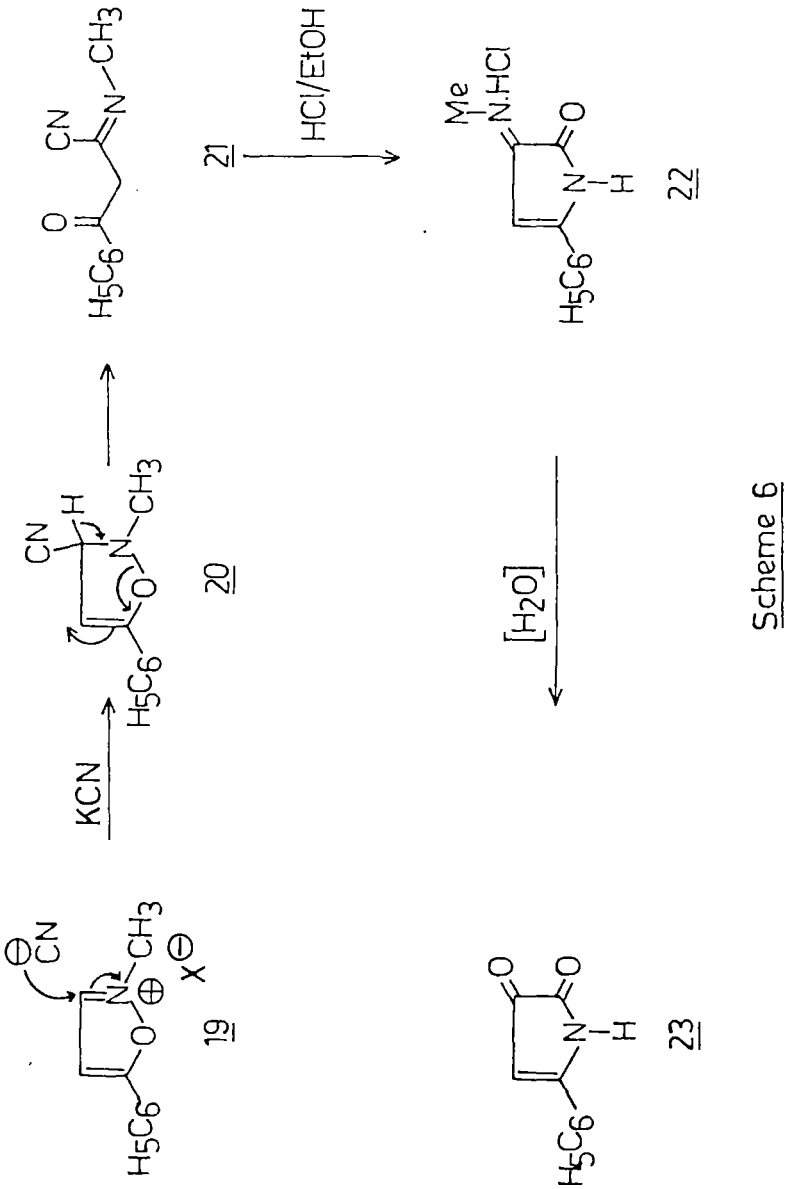
12 13 14

n = 1,2,3 and 4

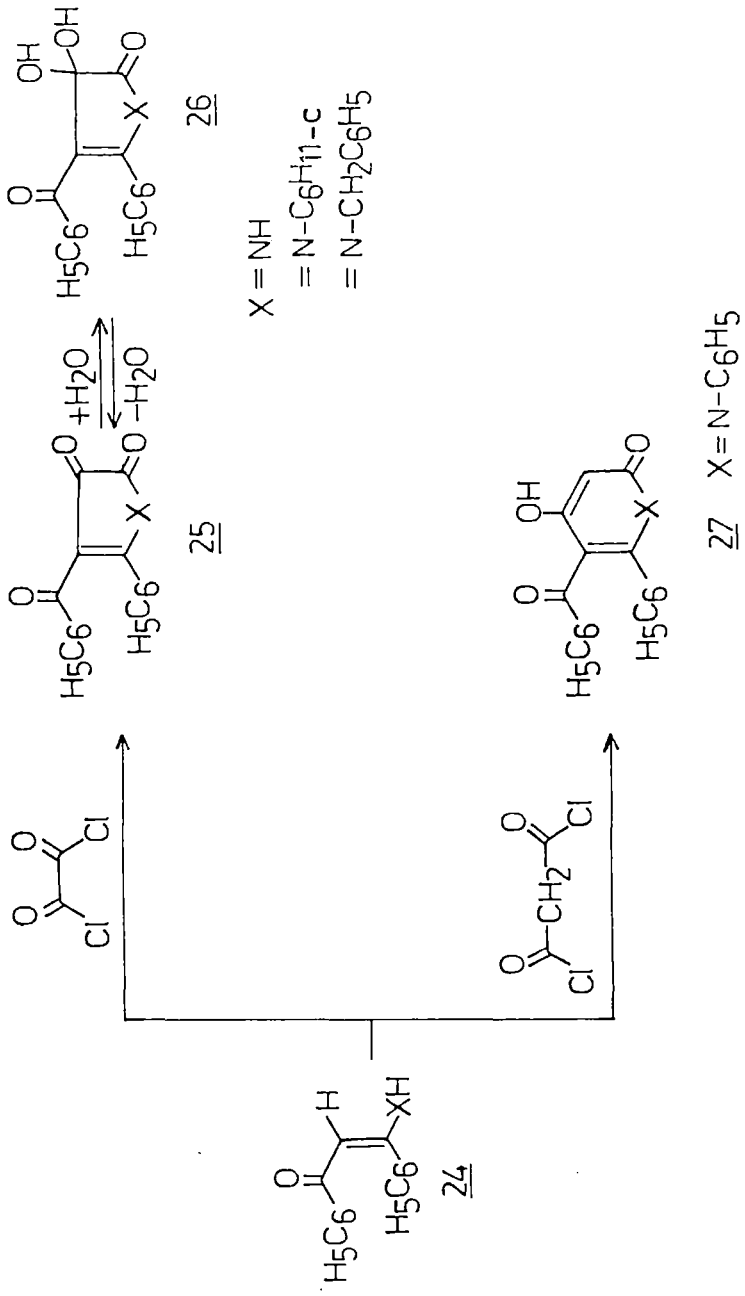
Scheme 4



Scheme 5



Scheme 6

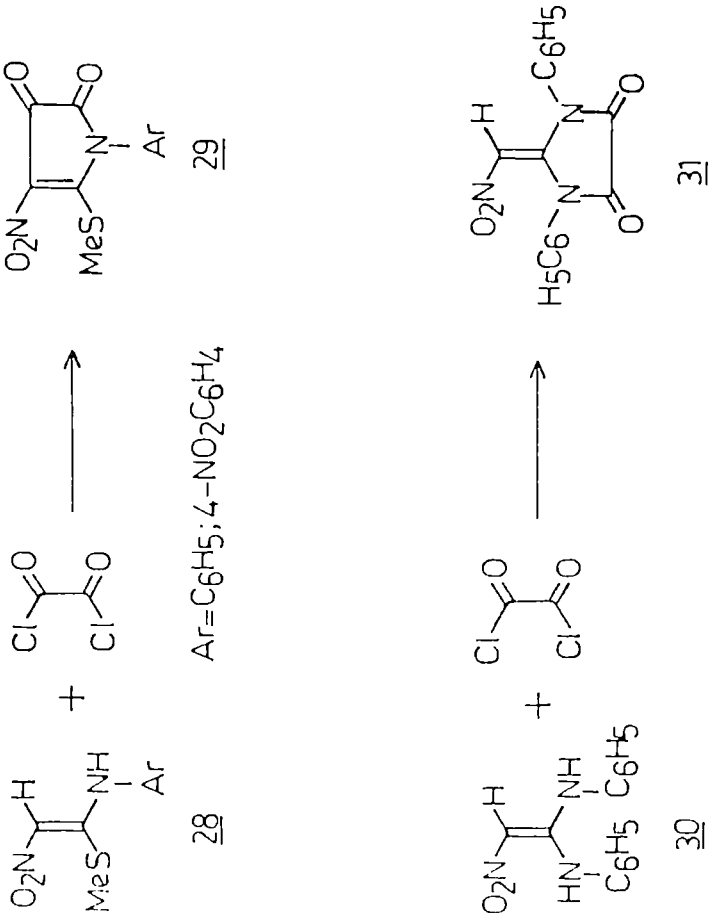

OH
OH
O
X
O
H5C6
H5C6
26
X = NH
= N-C6H11-c
= N-CH2C6H5
+H2O
−H2O
O
O
X
O
H5C6
H5C6
25
O
Cl
O
Cl
O
Cl
O
CH2
Cl
O
H
XH
O
H5C6
H5C6
24
OH
O
X
O
H5C6
H5C6
27 X = N-C6H5

Scheme 7

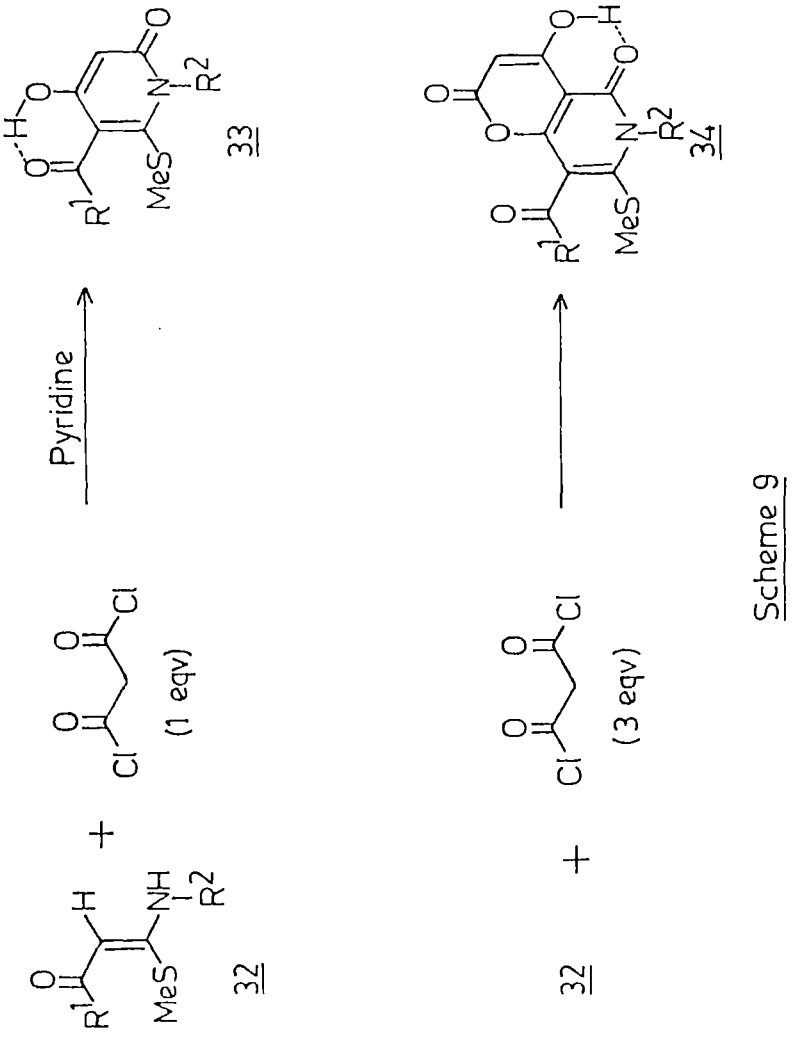
corresponding 3-nitro-2-methylthio-1-phenylpyrrol-4,5-dione 29 in 48% yield. The same authors also reacted the corresponding N,N-acetals 30 with oxalyl chloride to yield the corresponding 2-nitromethyleneimidazole-4,5-diones 31 in moderate yields (Scheme 8)[15].

Junjappa, Ila and Chakrasali have reported[16] the reaction of equimolar quantities of malonyl chloride and α-oxoketene S,N-acetals 32 to give the corresponding 5-aroyl-4-hydroxy-6-methylthio-1-N-aryl/benzyl/alkyl-2(1H)-pyridones 33 in high yields. Alternatively use of three equivalents of malonyl chloride resulted in the formation of pyrano-[3,2-c]-pyridines 34 in moderate yields (Scheme 9).

From the above discussion, it is apparent that some approaches have been developed for the synthesis of 4,5-dioxopyrroles though many of them use more difficult starting precursors to achieve the synthesis of the title compounds. Indeed, the oxalyl chloride reaction with nitroketene S,N-acetals was observed to yield the corresponding 4,5-dioxopyrroles in moderate yields. In the present investigation, the α-oxoketene S,N-acetals were used as primary precursors to react with oxalyl chloride to yield the corresponding 3-aroyl-2-methylthio-4,5-dioxopyrroles so that the product dioxopyrroles can act as important precursor either as 1,2 dielectrophilic centres through dioxofunctionalities or as 3-carbon fragments with 1,3-electrophilic centres through exocyclic carbonyl functionality which could further react with binucleophiles to yield the corresponding annelated heterocycles. It was, therefore, considered of interest



Scheme 8



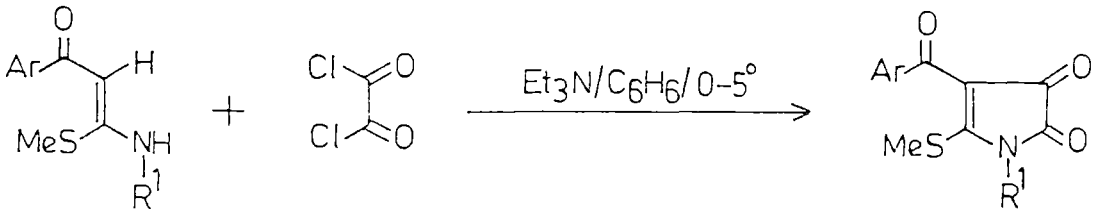
Scheme 9

to study the reaction of oxalyl chloride with α-oxoketene S,N-acetals.

III.2 RESULTS AND DISCUSSION

The α-oxoketene S,N-acetals 32a-l (Table 1) required in the present investigation were prepared as per the reported methods and the structures of all these S,N-acetals were fully confirmed before they were used in the reaction.

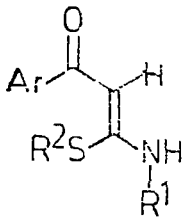
In a typical experiment, the α-oxoketene S,N-acetal 32a was reacted (Scheme 10) with oxalyl chloride in the presence of triethylamine at 0-5°C for 30 min, work-up of the reaction mixture yielded an orange yellow crystalline solid (88%) m.p. 115°C, which was characterised as 3-benzoyl-2-methylthio-1-phenylpyrrol-4,5-dione 35a on the basis of its analytical and spectral data. Thus the product 35a showed molecular ion peak at m/z 323 (M^+) and analyzed for $C_{18}H_{13}NO_3S$. Its infrared spectrum (KBr) exhibited strong intensity peaks at 1760 and 1700 cm^{-1} which were assigned to 4-carbonyl and 5-carbonyl stretching vibrations respectively while, the strong intensity peak at 1620 cm^{-1} was assigned to exocyclic aroyl carbonyl stretching vibration which is in conjugation with the nitrogen lone pair. Its ^1H n.m.r. spectrum showed signal due to MeS group protons at δ 2.37 (s,3H), while aromatic protons appeared as two multiplets. The multiplet between δ 7.23-7.78(8H) was assigned to 5-protons of N-phenyl and 3-protons of the aroyl group while the other multiplet between δ 7.84-8.00 (2H) was assigned two protons adjacent to carbonyl function of the aroyl group which were in conformity with the assigned structure. The other pyrrol-4,5-diones 35b-l were



32 a-l (Table-1)

35 a-l (Table-1)

Scheme 10



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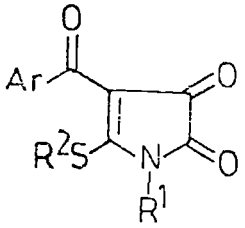


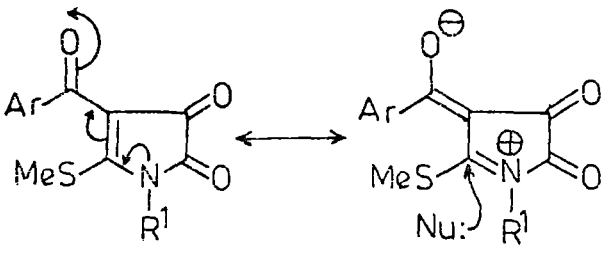
35

	Ar	R^1	R^2
32, 35a	C_6H_5	C_6H_5	CH_3
b	4-$MeOC_6H_4$	C_6H_5	CH_3
c	C_6H_5	4-ClC_6H_4	CH_3
d	4-MeC_6H_4	C_6H_5	CH_3
e	C_6H_5	C_6H_5	C_2H_5
f	4-BrC_6H_4	C_6H_5	CH_3
g	C_6H_5	4-MeC_6H_4	CH_3
h	4-ClC_6H_4	C_6H_5	CH_3
i	C_6H_5	$C_6H_5CH_2$	CH_3
j	4-ClC_6H_4	$C_6H_5CH_2$	CH_3
k	4-$MeOC_6H_4$	$C_6H_5CH_2$	CH_3
l	C_6H_5	C_2H_5	CH_3

Table 1

similarly prepared in 21-87% overall yields. The spectral and analytical data of 35b-l were in conformity with the assigned structures and are described in the experimental section.

The pyrrol-4,5-diones 35 were found to be moisture sensitive and underwent facile hydrolysis to yield the corresponding 1-substituted-2-hydroxy-3-aroylpyrrol-4,5-diones. The hydrolysis was particularly facile when R^1 was an alkyl group. 3-Benzoyl-2-methylthio-1-methyl-pyrrol-4,5-dione cleaved during work-up to yield the corresponding 2-hydroxypyrrol-4,5-dione 36f (Table 2). The yield of 1-ethyl-pyrroldione 351 was only 21% which was comparatively more stable than the corresponding N-methylpyrroldione. The low yield of 351 was therefore attributed to its partial hydrolysis. The corresponding hydrolyzed product 36e (Scheme 11 and Table 2) was isolated and characterised separately. However, the 1-aryl-pyrrol-4,5-diones 35b-h are obtained in the range of overall high yields indicating that these compounds are more stable to hydrolytic conditions. Similarly N-benzylpyrroldiones 35i-k were obtained in the range of 41-43% overall yields presumably due to resonance participation of the lone pair of electrons of the ring nitrogen with phenyl ring.

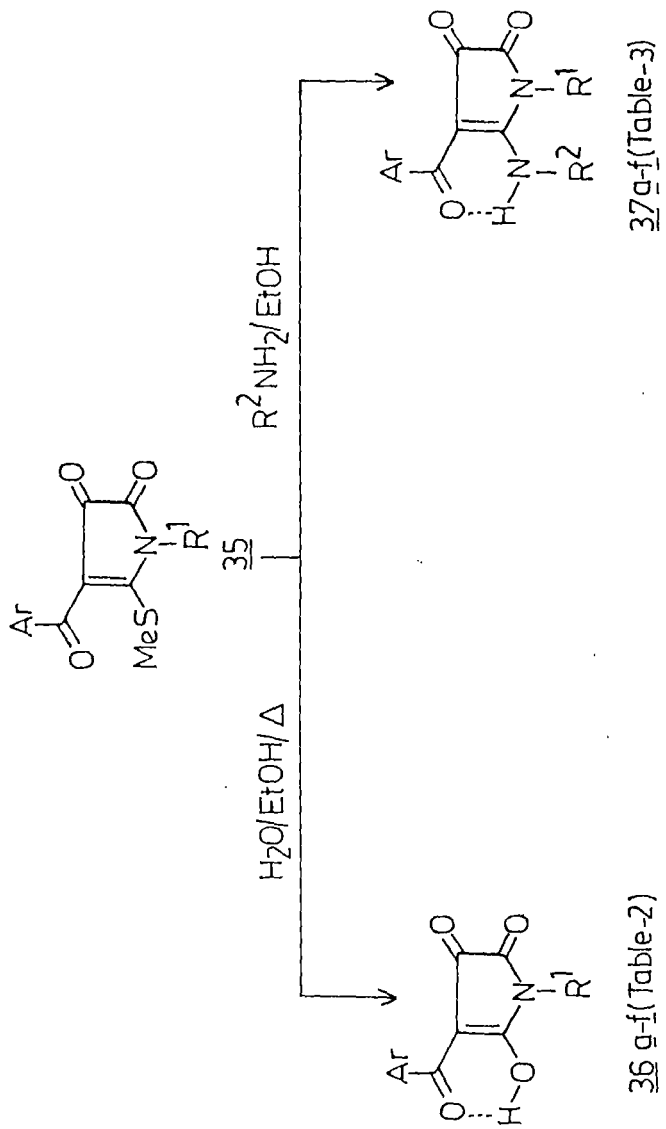


A B

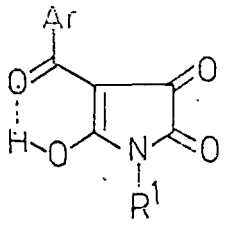
In the case of alkyl substituted products therefore the lone pair experiences resonance (A↔B) with exocyclic carbonyl group through ring double bond making the 2-carbon atom highly electrophilic which becomes more susceptible to hydrolytic conditions.

The methylthio-1-aryl/benzyl/alkylpyrroldiones 35a-c, 35j and 35l (Table 2) when refluxed with a mixture of ethanol and water are converted readily to the corresponding 2-hydroxy-pyrroldiones 36a-e respectively in 86-92% overall yields (Scheme 11).

The structure of 3-benzoyl-2-hydroxy-1-phenylpyrrol-4,5-dione 36a was confirmed from its analytical and spectral data. Thus the product 36a showed molecular ion peak at m/z 293 (M^+) and was analyzed for $C_{17}H_{11}NO_4$. Its i.r. spectrum (KBr) exhibited peak at 3425 cm^{-1} which was assigned to strongly hydrogen bonded stretching vibration of the hydroxyl group. Strong intensity peak at 1773 and 1734 cm^{-1} were assigned to 4-carbonyl and 5-amido stretching vibrations respectively where as the other strong peak at 1650 cm^{-1} was assigned to exocyclic aroyl carbonyl stretching vibrations. In its ^1H n.m.r. spectrum ($CDCl_3$) the multiplet between δ7.24-7.77(8H) were assigned to 5 protons of N-phenyl and 3 protons of aroyl group while the other multiplet between δ8.18-8.38 (2H) were assigned to two aromatic protons of the aroyl group adjacent to carbonyl function. The structure of hydroxy pyrroldiones 36a-e and 36f were fully confirmed by their analytical and spectral data which are described in the experimental section. It is pertinent to note that the preparation of 3-benzoyl-2-hydroxy-1-methylpyrrol-4,5-dione in its


Ar
MeS
N
R1
35
R2NH2/EtOH
H2O/EtOH/Δ
Ar
N
R1
R2
H
O
37a-f(Table-3)
Ar
N
R1
H
O
36 a-f(Table-2)

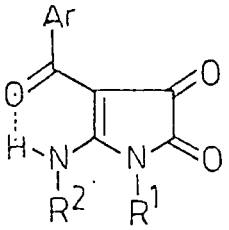
Scheme 11



36

	Ar	R^1
36a	C_6H_5	C_6H_5
b	4-$MeOC_6H_4$	C_6H_5
c	C_6H_5	4-ClC_6H_4
d	4-ClC_6H_4	$C_6H_5CH_2$
e	C_6H_5	C_2H_5
f	C_6H_5	CH_3

Table 2



37

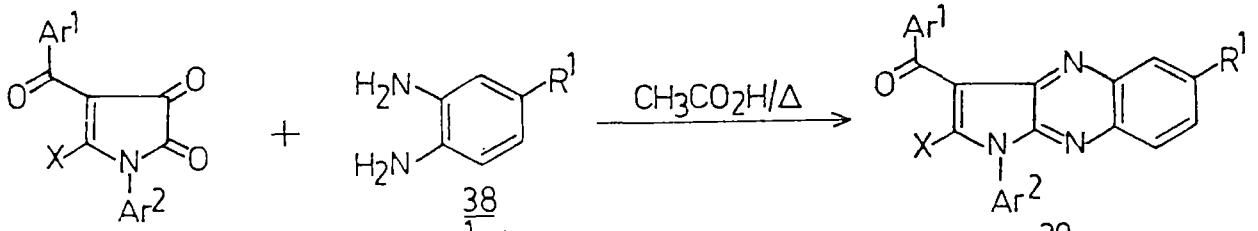
	Ar	R^1	R^2
37a	C_6H_5	C_6H_5	C_6H_5
b	C_6H_5	C_6H_5	$4\text{-}MeC_6H_4$
c	C_6H_5	C_6H_5	$4\text{-}BrC_6H_4$
d	$4\text{-}MeOC_6H_4$	C_6H_5	C_6H_5
e	C_6H_5	$4\text{-}MeC_6H_4$	$4\text{-}ClC_6H_4$
f	C_6H_5	C_6H_5	$C_6H_5CH_2$

Table 3

keto form was reported by Howard[17] which involves reaction of N-methylbenzoyl-acetamide with ethyl oxalate in the presence of sodium ethoxide. Preparation of the same compound is also reported by Mumm and co-workers[18,19].

The pyrroldione 35a when reacted (Scheme 11) with aniline yielded a yellow crystalline solid (91%) m.p. 224°C, which was characterised as 3-benzoyl-2-anilino-1-phenylpyrrol-4,5-dione 37a on the basis of analytical and spectral data. Thus, 37a showed molecular ion peak at m/z 368 (M^+) and was analysed for $C_{23}H_{16}N_2O_3$. Its i.r. spectrum (KBr) exhibited strong intensity peak at 1780 and 1694 cm^{-1} which were assigned to 4-carbonyl and 5-amido carbonyl stretching vibrations respectively. Strong peak for exocyclic carbonyl stretching vibration appeared at 1606 cm^{-1} apparently due to the presence of anilino nitrogen which is also in conjugation with exocyclic carbonyl group. Its ^1H n.m.r. spectrum ($CDCl_3$) showed a multiplet between δ6.83-7.23(10H) which were assigned to aromatic protons while other 5 aromatic protons of the aroyl group appeared as multiplet between δ 7.33-7.68(3H) and 7.84-8.04(2H). The NH proton appeared as broad singlet at δ13.26(1H) which was exchangeable with D_2O. The other 2-arylamino compounds 37b-e and 2-benzylamino compound 37f (Scheme 11 and Table 3) were similarly obtained from the corresponding alkylthio compounds 35 in 87-93% overall yields. The spectral and analytical data of 37b-f were in conformity with the assigned structures and are described in the experimental section.

Some of the pyrrol-4,5-diones 37a-e and 36c were selected for further reaction with o-phenylene diamine 38a and 38b to afford the corresponding pyrroloquinoxaline 39a-f. In a typical experiment 3-benzoyl-2-anilino-1-phenylpyrrol-4,5-dione 37a was heated with o-phenylene diamine 38a in acetic acid for 2 hrs, and work-up of the reaction mixture yield a bright yellow solid (89%) m.p. 184°C, which was characterised as 3-benzoyl-2-anilino-1-phenylpyrrolo-[2,3-b]-quinoxaline 39a on the basis of analytical and spectral data. Thus the product 39a showed molecular ion peak at m/z 440(M^+,8%) and was analysed for $C_{29}H_{20}N_4O$. In its i.r. spectrum(KBr) 39a showed clearly the absence of both characteristic bands due to the oxo and amido carbonyl groups. Strong intensity peaks at 1630 and 1662 cm^{-1} were assigned to C=N stretching vibrations while the band at 1597 cm^{-1} was assigned to exocyclic C=O stretching vibrations. The compound 39a however in its ^1H n.m.r. spectrum showed all its aromatic protons as multiplets (19H) between 6.53-8,26. The other substituted 3-aroyl-2-arylamino/hydroxy-1-arylpyrrolo [2,3-b] quinoxalines 39b-f were similarly prepared in 79-91% overall yields. The spectral and analytical data of all these quinoxalines were in conformity with the assigned structures and are described in the experimental section.



36c

37a-f

38

a R^1 = H

b R^1 = Cl

39

		Ar^1	Ar^2	X	R^1
37a	39a	C_6H_5	C_6H_5	C_6H_5NH	H
b	b	C_6H_5	C_6H_5	$4\text{-}CH_3C_6H_4NH$	H
c	c	C_6H_5	C_6H_5	$4\text{-}BrC_6H_4NH$	H
d	d	$4\text{-}CH_3OC_6H_4$	C_6H_5	C_6H_5NH	H
d	e	$4\text{-}CH_3OC_6H_4$	C_6H_5	C_6H_5NH	Cl
36c	f	C_6H_5	$4\text{-}ClC_6H_4$	OH	H

Scheme 12

III.3 EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point (Capillary method) apparatus and are uncorrected. The i.r. spectra were recorded on Perkin-Elmer 297 Spectrophotometer. The n.m.r. spectra were recorded on Varian EM-390 Spectrometer using TMS as internal standard and the values are expressed in δ (ppm). Mass spectra were recorded on a Jeol-D 300 Mass Spectrometer.

Starting Materials

The commercial sample of acetophenone, 4-methylacetophenone, 4-chloroacetophenone, 4-methoxyacetophenone, 4-bromoacetophenone, benzylamine, 4-methylaniline, aniline, 2-phenylene diamine, 4-chloroaniline, ethylamine, methylamine, oxalyl chloride and triethyl amine were purified before use.

Phenylisothiocyanate, 4-chlorophenyl isothiocyanate, 4-methyl phenylisothiocyanate were prepared by the reported[20] methods.

The ketene S,S-acetals 3,3-bis(methylthio)-1-phenyl-2-propen-1-one, m.p. 93°C, 3,3-bis(methylthio)-1-(4-methoxyphenyl)-2-propen-1-one, m.p. 100-101°C and 3,3-bis(methylthio)-1-(4-chlorophenyl)-2-propen-1-one, m.p. 109-110°C were prepared by the reported method[21] and are described in Chapter II.

Preparation of Ketene S,N-acetals

Method A: Displacement method[22-24]; General Procedure:

A solution of ketene S,S-acetal (0.02 mol) and the appropriate amine (0.025-0.09 mol) (or 40% solution of methylamine/ethylamine or benzylamine) in ethanol (50 ml) was refluxed for 5-25 hrs. After completion

of the reaction (monitored by TLC), solvent was removed and the reaction mixture was diluted with water, extracted with ethylacetate, dried (Na_2SO_4) and evaporated to give crude S,N-acetals 32i-l which were purified by crystallisation using benzene/hexane mixture and all of them are reported[23].

Method B: By the reaction of active methylene compounds with aryl-isothiocyanates[25-29]; General Procedure:

To an ice cooled and well stirred suspension of sodium hydride (3.6g, 0.15 mol) (washed 2-3 times with dry benzene) in dry dimethylformamide (DMF) (50 ml), a solution of active methylene compounds (0.05 mol) in dry DMF (15 ml) was added dropwise during 0.5 hr. A solution of arylisothiocyanate (0.05 mol) in dry DMF (25 ml) was then added and reaction mixture was further stirred for 1.5-2 hr, followed by subsequent addition of alkylhalide (0.05 mol) in DMF (15 ml). After further stirring for 2 hrs, the reaction mixture was poured over crushed ice, neutralized with 20% acetic acid, extracted with chloroform (3x75 ml). The chloroform layer was washed with water (3x200 ml), dried (Na_2SO_4) and concentrated to give crude S,N-acetals 32a-h (Table 1), which were purified either by crystallisation from benzene/hexane (1:1) or by passing through silica gel column using hexane/benzene (4:1) as eluent. The reported[30] S,N-acetals 32a-h were prepared by this method.

General Method for the preparation of 3-aroyl-2-methylthio/ethylthio-1-aryl/ethyl/benzyl-pyrrol-4,5-diones 35a-l

To a well stirred and ice-cooled solution of S,N-acetal (10 mmol) and dry triethylamine (2.02g, 20 mmol) in dry benzene (40 ml), a solution

of oxalyl chloride (1.27g, 10 mmol) in benzene (5 ml) was added slowly (15 min) and the reaction mixture was further stirred for 20 minutes. The mixture was poured onto crushed ice (100g) and neutralised with a saturated solution of sodium bicarbonate (100 ml), and the mixture was allowed to warm upto room temperature. It was then extracted with benzene (2x100 ml), washed with water (2x100 ml), dried (Na_2SO_4) and evaporated to give orange yellow solid, which was purified by crystallisation using benzene, hexane mixture.

3-Benzoyl-2-methylthio-1-phenylpyrrol-4,5-dione (35a); orange yellow crystals (benzene/hexane); yield 88%; m.p. 115°C; i.r. (KBr): ν_{max}= 1760, 1700, 1620 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.37(s,3H,SCH_3); 7.23-7.78 (m,8H_{arom}); 7.84-8.00(m,2H_{arom}). (Found: C,66.67; H,3.89; N,4.41. Calc. for $C_{18}H_{13}NO_3S$(323.4): C,66.87; H,4.02; N,4.33%). m/z 323(M^+,2%).

3-(4-Methoxybenzoyl)-2-methylthio-1-phenylpyrrol-4,5-dione (35b); orange yellow crystals (benzene/hexane); yield 87%; m.p. 164°C; i.r. (KBr): ν_{max} = 1760, 1688, 1620, 1600 cm^{-1}; ^1H n.mr.($CDCl_3$): δ 2.36 (s,3H,SCH_3); 3.85(s,3H,OCH_3); 7.00(d,J=8Hz,2H_{arom}); 7.26-7.81(m, 5H_{arom}); 7.95(d,J=8Hz,2H_{arom}). (Found: C,64.61; H,4.31; N,3.88; Calc. for $C_{19}H_{15}NO_4S$(353.4): C,64.58; H,4.24; N,3.96%). m/z 353 (M^+,2%).

3-Benzoyl-2-methylthio-1-(4-chlorophenyl)pyrrol-4,5-dione (35c); orange yellow crystals (benzene/hexane); yield 78%; m.p. 170°C; i.r.(KBr): ν_{max} = 1746, 1684, 1630 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.36 (s,3H,SCH_3); 7.15-7.68(m,7H_{arom}); 7.94(d,J=8Hz,2H_{arom}). (Found: C,60.32; H,3.51; N,3.78. Calc. for $C_{18}H_{12}ClNO_3S$(357.8): C,60.41; H,3.35; N,3.91%). m/z 357(M^+,2%).

3-(4-Methylbenzoyl)-2-methylthio-1-phenylpyrrol-4,5-dione (35d); orange yellow crystals (benzene/hexane); yield 79%; m.p. 105°C; i.r.(KBr): ν_{max} = 1746, 1692, 1625, 1600 cm^{-1}; ^1H n.m.r.(TFA/CCl_4): δ 2.53(s,6H,SCH_3 and CH_3); 7.23-7.96(m,9H_{arom}). (Found: C,67.81; H,4.61; N,3.98. Calc. for $C_{19}H_{15}NO_3S$(337.4): C,67.65; H,4.45; N,4.15%).

3-Benzoyl-2-ethylthio-1-phenylpyrrol-4,5-dione (35e); orange yellow crystals (benzene/hexane); yield 80%; m.p. 151°C; i.r.(KBr): ν_{max} = 1774, 1700, 1625 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.12(t,J=8Hz,3H,CH_2CH_3); 2.94(q,J=8Hz,2H,S-CH_2CH_3); 7.03-7.74(m,8H_{arom}); 7.82-8.04(m,2H_{arom}). (Found: C,67.84; H,4.31; N,4.28. Calc. for $C_{19}H_{15}NO_3S$(337.4): C,67.65; H, 4.45; N,4.15%). m/z 337(M^+,4%).

3-(4-Bromobenzoyl)-2-methylthio-1-phenylpyrrol-4,5-dione (35f); orange yellow crystals (benzene/hexane); yield 86%; m.p. 158°C; i.r.(KBr): ν_{max} = 1757, 1696, 1640, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.36(s,3H, SCH_3); 7.22-7.80(m,7H_{arom}); 8.19(d,J=6Hz,2H_{arom}). (Found: C,53.93; H,3.12; N,3.59. Calc. for $C_{18}H_{12}BrNO_3S$(402.3): C,53.73; H,2.98; N,3.48%). m/z 403(2); 402(M^+,2%).

3-Benzoyl-2-methylthio-1-(4-methylphenyl)-pyrrol-4,5-dione (35g); orange yellow crystals (benzene/hexane); yield 81%; m.p. 134°C; i.r. (KBr): ν_{max} = 1748, 1693, 1628 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.33(s,3H, CH_3); 2.39(s,3H,SCH_3); 7.06-7.69(m,7H_{arom}); 7.80-7.95(m,2H_{arom}). (Found: C,67.41; H,4.52; N,4.31. Calc. for $C_{19}H_{15}NO_3S$(337.4): C,67.65; H,4.45; N,4.15%). m/z 337(M^+,3%).

3-(4-Chlorobenzoyl)-2-methylthio-1-phenylpyrrol-4,5-dione (35h); orange yellow crystals (benzene/hexane); yield 83%; m.p. 160°C; i.r.(KBr): ν_{max} = 1760, 1695, 1640, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.35(s,3H,SCH_3); 7.18-7.64(m,7H_{arom}); 7.82(d,J=8Hz,2H_{arom}). (Found: C,60.64; H,3.48; N,3.78. Calc. for $C_{18}H_{12}ClNO_3S$(357.8): C,60.41; H,3.35; N,3.91%). m/z 357(M^+,5%).

3-Benzoyl-2-methylthio-1-benzylpyrrol-4,5-dione (35i); orange yellow crystals (benzene/hexane); yield 41%; m.p. 110°C; i.r.(KBr): ν_{max} = 1760, 1690, 1630 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.48(s,3H,SCH_3); 4.95 (s,2H,N-CH_2); 7.03-7.61(m,8H_{arom}); 7.85(d,J=8Hz,2H_{arom}). (Found: C,67.42; H,4.38; N,4.28. Calc. for $C_{19}H_{15}NO_3S$(337.4): C,67.65; H,4.45; N,4.15%).

3-(4-Chlorobenzoyl)-2-methylthio-1-benzylpyrrol-4,5-dione (35j); orange yellow crystals (benzene/hexane); yield 40%; m.p. 131°C; i.r.(KBr): ν_{max} = 1748, 1690, 1626 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.52 (s,3H,SCH_3); 4.98(s,2H,N-CH_2); 7.26-8.00(m,9H_{arom}). (Found: C,61.52; H,4.01; N,3.93. Calc. for $C_{19}H_{14}ClNO_3S$(371.8): C,61.37; H,3.76; N,3.76%). m/z 373(3); 371(M^+,7%).

3-(4-Methoxybenzoyl)-2-methylthio-1-benzylpyrrol-4,5-dione (35k); orange yellow crystals (benzene/hexane); yield 43%; m.p.181-182°C; i.r.(KBr): ν_{max} = 1750, 1688, 1621, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.48(s,3H,SCH_3); 3.84(s,3H,OCH_3); 4.95(s,2H,N-CH_2); 6.94(d,J=8Hz, 2H_{arom}); 7.13-7.53(m,5H_{arom}); 7.89(d,J=8Hz,2H_{arom}). (Found: C,65.28; H,4.82; N,3.67. Calc. for $C_{20}H_{17}NO_4S$(367.4): C,65.39; H,4.63; N,3.81%). m/z 367(M^+,12%).

3-Benzoyl-2-methylthio-1-ethylpyrrol-4,5-dione (351); orange yellow crystals (benzene/hexane); yield 21%; m.p. 161°C; i.r.(KBr): ν_{max} = 1753, 1690, 1627 cm^{-1}; ^1H n.m.r ($CDCl_3$): δ 1.27(t,J=8Hz,3H,$CH_2\underline{CH_3}$); 2.53(s,3H,$S\underline{CH_3}$); 3.83(q,J=8Hz,2H,N-$\underline{CH_2}CH_3$); 7.23-7.54(m,$3H_{arom}$); 7.68-7.90(m,$2H_{arom}$). (Found: C,60.88; H,4.67; N,5.21. Calc. for $C_{14}H_{13}NO_3S$(275.3): C,61.09; H,4.72; N,5.09%). m/z 275(M^+,6%).

Reaction of aqueous ethanol with 2-alkylthio-pyrrol-4,5-dione 35: General method for the preparation of 3-aroyl-2-hydroxyl-1-aryl/alkyl/benzylpyrrol-4,5-dione 36a-f:

A solution of 35 (10 mmol) in ethanol (30 ml) and water (5 ml) was refluxed for 20 hrs. Ethanol was then removed under reduced pressure and the reaction mixture was diluted with water (100 ml), the solid separated was filtered, washed with water (3x30 ml) and dried. The solid thus obtained was purified by crystallisation using benzene/hexane mixture.

3-Benzoyl-2-hydroxy-1-phenylpyrrol-4,5-dione (36a) off white solid; yield 90%; m.p. 183°C; i.r.(KBr): ν_{max} = 3425, 1773, 1734, 1650,1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 7.24-7.77(m,$8H_{arom}$); 8.18-8.38(m,$2H_{arom}$). (Found: C,69.41; H,3.92; N,4.84. Calc. for $C_{17}H_{11}NO_4$(293.3): C,69.62; H,3.75; N,4.77%). m/z 293(M^+,16%).

3-(4-Methoxybenzoyl)-2-hydroxy -1-phenylpyrrol-4,5-dione (36b); yellow solid; yield 91%; m.p. 157°C; i.r.(KBr): ν_{max} = 3400, 1760, 1700, 1657, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 3.93(s,3H,$O\underline{CH_3}$); 7.06(d,J=9Hz,$2H_{arom}$); 7.48(s,$5H_{arom}$); 8.50(d,J=9Hz,$2H_{arom}$). (Found: C,66.58; H,4.23; N,4.46. Calc. for $C_{18}H_{13}NO_5$(323.3): C,66.87; H,4.02; N,4.33%). m/z 323(M^+,21%).

3-Benzoyl-2-hydroxy-1(4-chlorophenyl)-pyrrol-4,5-dione (36c); off white solid; yield 86%; m.p. 211-212°C; i.r.(KBr): ν_{max} = 3430, 1774, 1730, 1650 , 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 7.41-7.74(m, $7H_{arom}$); 8.10-8.33(m,$2H_{arom}$). (Found: C,62.41; H,2.87; N,4.41. Calc. for $C_{17}H_{10}ClNO_4$(327.7): C,62.29; H,3.05; N,4.27%). m/z 329(22); 327(M^+,54%).

3-(4-Chlorobenzoyl)-2-hydroxy -1-benzylpyrrol-4,5-dione (36d); off white solid; yield 92%; m.p. 169-170°C; i.r.(KBr): ν_{max} = 3410, 1778, 1715, 1650, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 4.86(s,2H,N-CH_2); 7.20-7.63(m,$7H_{arom}$); 8.20(d,J=8Hz,$2H_{arom}$). (Found: C,63.11; H,3.68; N,3.89. Calc. for $C_{18}H_{12}ClNO_4$(341.7): C,63.25; H,3.51; N,4.09%). m/z 343(2); 341(M^+,43%).

3-Benzoyl-2-hydroxy-1-ethylpyrrol-4,5-dione (36e); off white solid; yield 88%; m.p. 83°C; i.r.(KBr): ν_{max} = 3410, 1760, 1720, 1658, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.31(t,J=8Hz,3H,CH_2CH_3); 3.76(q, J=8Hz,2H,N-CH_2CH_3); 7.40-7.73(m,$3H_{arom}$); 8.16-8.36(m,$2H_{arom}$). (Found: C,63.51; H,4.57; N,5.47. Calc. for $C_{13}H_{11}NO_4$(245.2): C,63.67; H,4.48; N,5.71%). m/z 245(M^+,36%).

3-Benzoyl-2-hydroxy-1-methylpyrrol-4,5-dione (36f); off white solid 89%; m.p.105-106°C; i.r.(KBr): ν_{max} = 3440, 1775, 1728, 1665 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 3.33(s,3H,N-CH_3); 7.06-7.76(m,$5H_{arom}$). (Found: C,62.18; H,4.11; N,6.28. Calc. for $C_{12}H_9NO_4$(231.2): C,62.33; H,3.89; N,6.06%). m/z 231(M^+,46%).

Reaction of amines with 2-alkylthio-pyrrol-4,5-dione 35:

General method for the preparation of 3-aroyl-2-arylamino/benzylamino-1-arylpyrrol-4,5-dione 37a-f:

To a well stirred solution of 35 (10 mmol) in ethanol (30 ml) corresponding amines (11 mmol) were added and stirred at room temperature for 10 min. Ethanol was then removed under reduced pressure and the content was diluted with cold water (200 ml), the solid separated was filtered, washed with water (100 ml) and dried. The solid thus obtained was purified by crystallisation using chloroform and hexane mixture.

3-Benzoyl-2-anilino-1-phenylpyrrol-4,5-dione (37a); yellow crystal (chloroform/hexane); yield 91%; m.p. 224°C; i.r.(KBr): ν_{max} = 3430, 1780, 1694, 1606 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 6.83-7.23(m,10H_{arom}); 7.33-7.68(m,3H_{arom}); 7.84-8.04(m,2H_{arom}); 13.26(brs,1H,N$\underline{H}$ exchangeable with D_2O). (Found: C,74.88; H,4.51; N,7.81. Calc. for $C_{23}H_{16}N_2O_3$ (368.4): C,75.00; H,4.34; N,7.60%). m/z 368 (M^+,22%).

3-Benzoyl-2-(4-methylanilino)-1-phenylpyrrol-4,5-dione (37b); yellow crystal (chloroform/hexane); yield 91%; m.p. 181°C; i.r.(KBr): ν_{max}= 3440, 1770, 1687, 1620 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.14(s,3H,$C\underline{H}_3$); 6.73(s,4H_{arom}); 6.83-7.20(m,5H_{arom}); 7.33-7.60(m,3H_{arom}): 7.80-7.96 (m,2H_{arom}); 13.40(brs,1H,N$\underline{H}$ exchangeable with D_2O). (Found: C,75.26; H,4.66; N,7.21. Calc. for $C_{24}H_{18}N_2O_3$(382.4): C,75.39; H.4.71; N,7.32%). m/z 382(M^+,23%).

3-Benzoyl-2(4-bromoanilino)-1-phenylpyrrol-4,5-dione (37c); yellow crystals (chloroform/hexane); yield 93%; m.p. 253°C; i.r.(KBr): ν_{max} = 3438, 1775, 1685, 1618 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 6.63-7.19 (m,9H$_{arom}$); 7.41-7.58(m,3H$_{arom}$); 7.81-7.96(m,2H$_{arom}$); 13.56(brs, 1H,NH exchangeable with D_2O). (Found: C,61.97; H,3.16; N,6.13. Calc. for $C_{23}H_{15}BrN_2O_3$(447.3): C,61.74; H,3.35; N,6.26%). m/z 448(14); 446(M^+,15%).

3-(4-Methoxybenzoyl)-2-anilino-1-phenylpyrrol-4,5-dione (37d); yellow crystals (chloroform/hexane); yield 88%); m.p. 204°C; i.r. (KBr): ν_{max} = 3440, 1780, 1686, 1605 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 3.83(s,3H,OCH$_3$); 6.76-7.16(m,12H$_{arom}$); 8.00(d,J=8Hz,2H$_{arom}$); 13.65(brs,1H,NH exchangeable with D_2O). (Found: C,72.17; H,4.61; N,6.88. Calc. for $C_{24}H_{18}N_2O_4$(398.4): C,72.36; H,4.52; N,7.03%). m/z 398(M^+,17%).

3-Benzoyl-2-(4-chloroanilino)-1-(4-methylphenyl)-pyrrol-4,5-dione (37e) yellow crystals (chloroform/hexane); yield 87%; m.p. 204°C; i.r.(KBr): ν_{max} = 3436, 1766, 1695, 1603 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.20(s,3H,CH$_3$); 6.66-7.00(m,8H$_{arom}$); 7.34-7.50(m,3H$_{arom}$); 7.76-7.96(m,2H$_{arom}$); 13.41(brs,1H,NH exchangeable with D_2O). (Found: C,69.02; H,4.31; N,6.58. Calc. for $C_{24}H_{17}ClN_2O_3$(416.9): C,69.14; H,4.08; N,6.72%). m/z 416(M^+,8%).

3-Benzoyl-2-benzylamino-1-phenylpyrrol-4,5-dione (37f); yellow crystals (chloroform/hexane); yield 92%; m.p. 180°C; i.r.(KBr): ν_{max} = 3440, 1777, 1693, 1615 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 4.05(d, J=5Hz,N-CH$_2$); 6.66-7.59(m,13H$_{arom}$); 7.67-7.96(m,2H$_{arom}$); 12.10 (brs,1H,NH exchangeable with D_2O). (Found: C,75.62; H,4.68; N,7.18·

Calc. for $C_{24}H_{18}N_2O_3$(382.4): C,75.39; H,4.71; N,7.32%). m/z 382 (M^+,38%).

Reaction of 2-phenylenediamine with pyrrol-4,5-dione 36 and 37: General method for the preparation of 3-aroyl-2-arylamino/hydroxy-1-arylpyrrolo [2,3-b] quinoxaline 39a-f:

To a mixture of 2-phenylenediamine (6 mmol) and pyrrol-4,5-dione 36 or 37 (5 mmol) was added 15 ml of water and 5 ml of acetic acid and refluxed for 2 hrs. After cooling the reaction mixture was poured on ice water (200 ml), the solid separated was filtered, washed with water and dried. The solid thus obtained was crystallised from acetic acid water mixture.

3-Benzoyl-2-anilino-1-phenylpyrrolo [2,3-b] quinoxaline (39a); bright yellow solid; yield 89%; m.p. 184°C; i.r.(KBr): ν_{max} = 1662, 1630, 1597 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ 6.53-8.26(m,19H_{arom}). (Found: C,79.31; H, 4.48; N,12.60. Calc. for $C_{29}H_{20}N_4O$(440.5): C,79.09; H,4.54; N,12.72%). m/z 440(M^+,8%).

3-Benzoyl-2-(4-methylanilino)-1-phenylpyrrolo [2,3-b] quinoxaline (39b); bright yellow solid; yield 91%; m.p. 197°C; i.r.(KBr): ν_{max}= 3420, 1660, 1622, 1595 cm^{-1}; ^1H n.m.r.(DMSO-d_6): δ 2.09(s,3H,CH_3); 6.61-7.88(m,18H_{arom}). (Found: C,79.08; H,4.77; N,12.49. Calc. for $C_{30}H_{22}N_4O$(454.5): C,79.29; H,4.84; N,12.33%). m/z 454(M^+,8%).

3-Benzoyl-2-(4-bromoanilino)-1-phenylpyrrolo [2,3-b] quinoxaline (39c); bright yellow solid; yield 81%; m.p. 195°C; i.r.(KBr): ν_{max}= 3430, 1658, 1622, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA); δ 6.47(d,J=8Hz, 2H_{arom}); 6.80-7.86(m,16H_{arom}). (Found: C,66.88; H,3.79; N,10.91.

Calc. for $C_{29}H_{19}BrN_4O$(519.37): C,67.05; H,3.66; N,10.79%). m/z 519(M^+,3%).

3-(4-Methoxybenzoyl)-2-anilino-1-phenylpyrrolo [2,3-b] quinoxaline (39d); bright yellow solid; yield 85%; m.p. 192-193°C; i.r.(KBr): ν_{max} = 3440, 1655, 1595, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ 3.96 (s,3H,OCH_3); 6.44-6.56(m,$2H_{arom}$); 6.77-7.72(m,$16H_{arom}$). (Found: C,76.81; H,4.56; N,11.76. Calc. for $C_{30}H_{22}N_4O_2$(470.5): C,76.59; H,4.68; N,11.91%). m/z 470(M^+ 1%).

6-Chloro-3(4-methoxybenzoyl)-2-anilino-1-phenylpyrrolo [2,3-b] quinoxaline (39e); bright yellow solid; yield 76%; m.p. 207-208°C; i.r.(KBR): ν_{max} = 3450, 1658, 1628, 1599 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ 4.01(s,3H,OCH_3); 6.55-6.82(m,$2H_{arom}$); 6.96-7.82(m,$15H_{arom}$). (Found: C,71.51; H,4.44; N,11.31. Calc. for $C_{30}H_{21}ClN_4O_2$(505): C,71.36; H,4.16; N,11.10%). m/z 505(M^+ 1%).

3-Benzoyl-2-hydroxy-1(4-chlorophenyl)-pyrrolo [2,3-b] quinoxaline (39f); bright yellow solid; yield 86%; m.p. 246-247°C; i.r.(KBr): ν_{max} = 1710, 1640, 1613 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 7.17-8.31 ($13H_{arom}$). (Found: C,69.31; H,3.66; N,10.68. Calc. for $C_{23}H_{14}ClN_3O_2$(399.8): C, 69.08; H,3.50; N,10.51%). m/z 399(M^+,74%).

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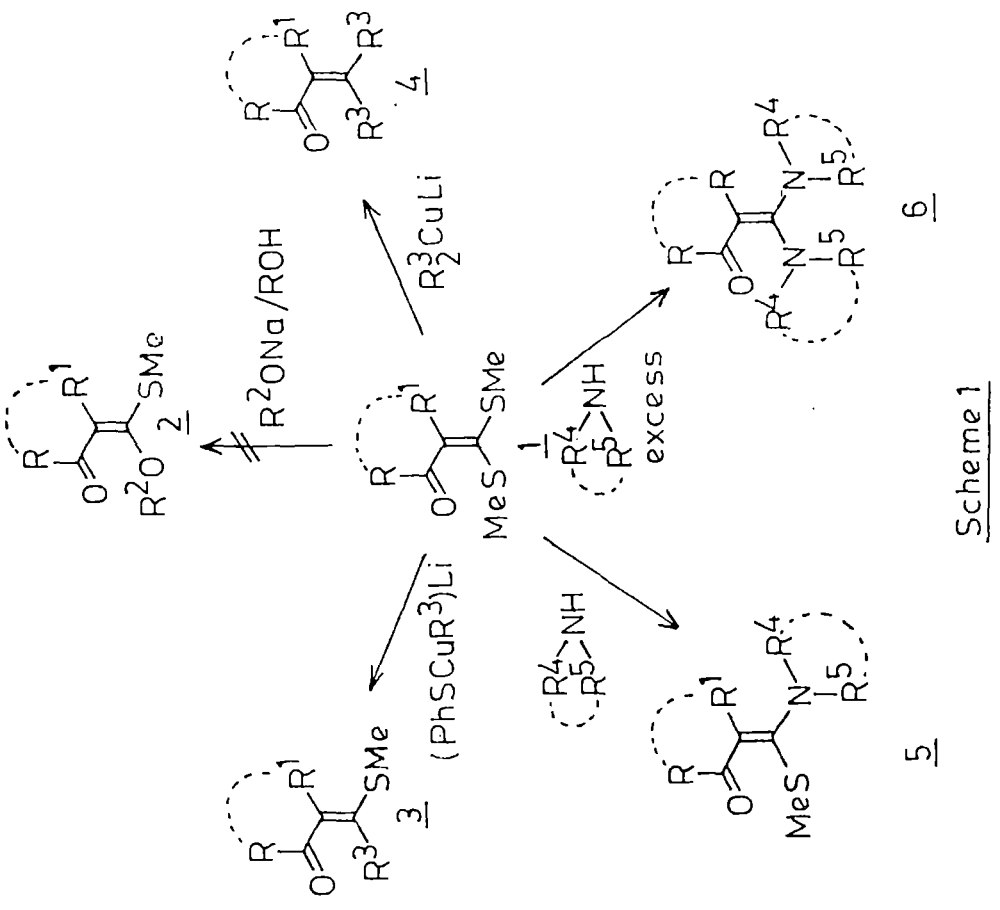
CHAPTER IV

REACTION OF ENOLATE ANIONS WITH ALKYL XANTHATES: A NOVEL METHOD FOR β-OXOTHIONO ESTERS AND α-OXOKETENE O,S-ACETALS.

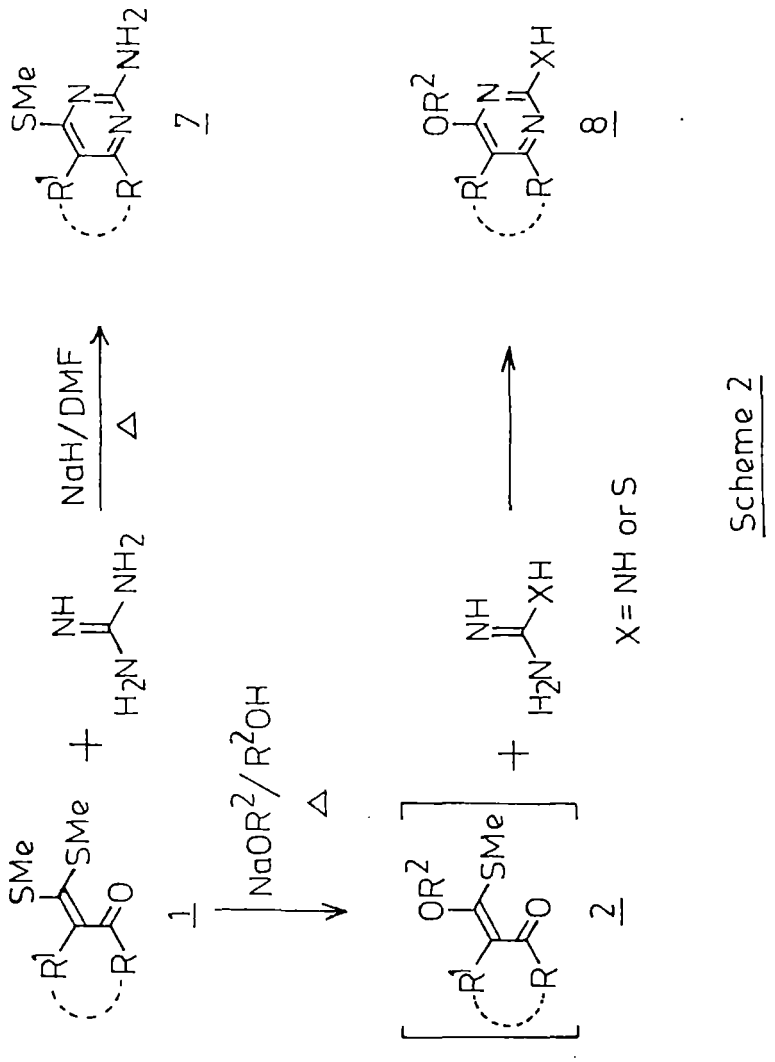
IV.1 INTRODUCTION

The α-oxoketene dithioacetals 1 have been reported to undergo facile displacement reaction with both nitrogen and carbon nucleophiles. The doubly activated oxoketene dithioacetals 1 (R'=CHO, CO_2Et,CN etc.) undergo facile displacement by primary and secondary amines to yield[1-3] the corresponding S,N-acetals 5 in high yields (Scheme 1). However, when R^1=H or neutral group the displacement by amines requires more vigorous reaction conditions. Invariably, in these reactions the N,N-acetals 6 are formed while the control for the preparation of the corresponding S,N-acetals is not always

practicable. Thus, the alternative method for the preparation of 5 by reacting the corresponding enolate anions with isothiocyanates[4-8] followed by alkylation is employed. The S,N-acetals are also obtained[4,8,9] by converting dithioesters to the corresponding thioamides followed by S-alkylation. Similarly carbon nucleophiles, particularly the stabilized enolate anions also displace the thiomethyl group in an addition elimination sequence to give the corresponding β-alkyl thiol acetals 3. The organo cuprates have also been shown to undergo 1,4-addition elimination sequence to yield the corresponding 3[10,11]. Further, the reaction can be regulated to displace both thiomethyl groups to yield the corresponding β-dialkylenones and enoates 4[12]. Despite extensive studies involving displacement of β-thiomethyl groups by both nitrogen and carbon nucleophiles, the corresponding O,S-acetals 2 (Scheme 1) have not been successfully isolated by direct displacement of thiomethyl group by the corresponding alkoxides though the intermediacy of the O,S-acetals has been reported in the course of their investigation by Junjappa and Chauhan[13,14]. Thus the oxoketene dithioacetals 1 have been reacted with guanidine and thiourea in the presence of sodium alkoxide and the corresponding alcohol to yield the alkoxypyrimidine 8 in high yields. In all these reactions the corresponding thiomethyl pyrimidines 7 were not detected although the reaction of 1 in the presence of aprotic solvent and sodium hydride yielded the corresponding 4-thiomethylpyrimidines 7 in comparatively lower yields[15] (Scheme 2). The thiomethylpyrimidines 7 also undergo nucleophilic displacement by RO^- ions to yield the corresponding



Scheme 1

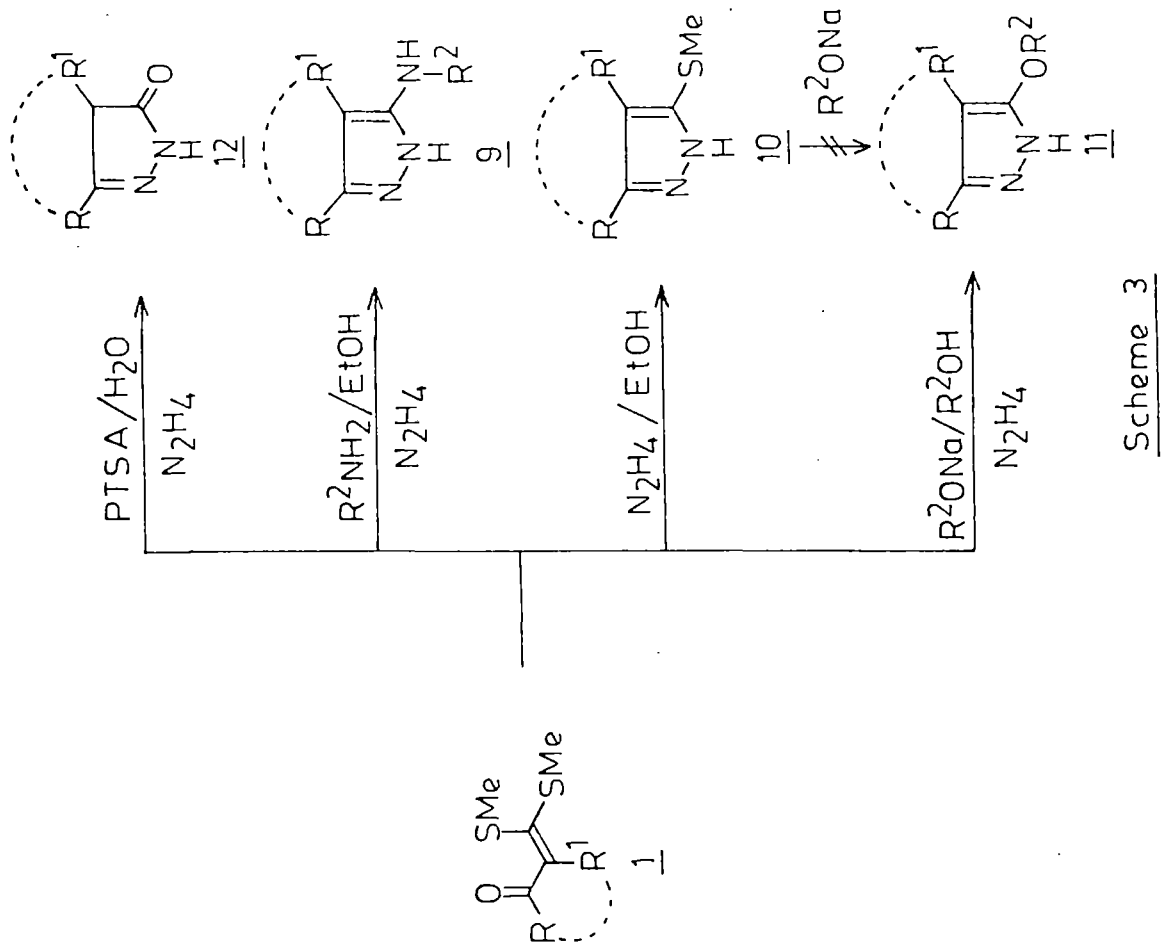

SMe
SMe
R1
R
O
1
NaOR2/R2OH
Δ
OR2
SMe
R1
R
O
2
NH
H2N
XH
X= NH or S
NH
H2N
NH2
NaH/DMF
Δ
SMe
N
R1
R
N
NH2
7
OR2
N
R1
R
N
XH
8

Scheme 2

alkoxypyrimidines 8. Therefore, it became necessary to prove whether the formation of 8 occurs through the initial formation of O,S-acetals 2 or by displacement of thiomethyl group of the pre-constructed pyrimidine ring 7.

The intermediacy of the O,S-acetals was proved by Junjappa and Chauhan[16] by monitoring the reaction under the described conditions to afford the corresponding alkoxypyrazoles (Scheme 3) where the displacement of thiomethyl group from 5(3)-thiomethyl pyrazole 10 is not possible. The reaction of α-oxoketene dithioacetals with sodium alkoxide prior to the dropwise addition of hydrazine hydrate afforded the corresponding 5(3)-alkoxypyrazoles 11. However, the 5(3)-thiomethyl pyrazoles 10 which were obtained by merely treating 1 with hydrazine hydrate in refluxing alcohol did not undergo displacement to yield the corresponding alkoxy pyrazoles even after prolonged heating with sodium alkoxide. Thus the intermediacy of the O,S-acetals during the synthesis of alkoxy pyrimidines was fully established. Similarly, by treating the S,S-acetals 1 with amines followed by dropwise addition of hydrazine hydrate, the corresponding 5(3)-aminopyrazoles 9 (Scheme 3) were formed in high yields. The pyrazolones 12 were also similarly obtained by reacting the S,S-acetals 1 with hydrazine hydrate under hydrolytic conditions. The intermediacy of the O,S-acetals in these reactions was therefore fully established though attempts to isolate them by reacting the S,S-acetals 1 with alkoxides could not be achieved successfully.

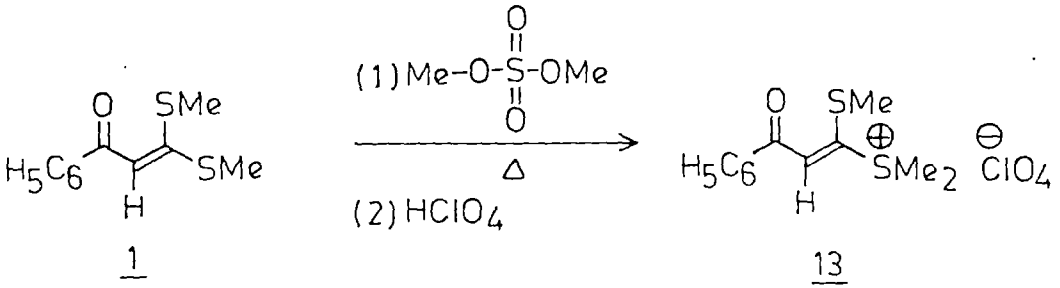
In an interesting example of conversion of S,S-acetal to the corresponding O,S-acetals, Schroth and co-workers[17], reacted the α-oxoketene


PTSA/H2O
N2H4
R2NH2/EtOH
N2H4
N2H4 / EtOH
R2ONa/R2OH
N2H4
R2ONa
12
9
10
11
1

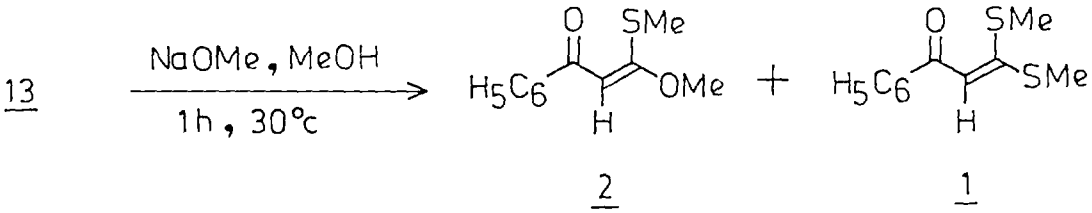
Scheme 3

dithioacetals 1 with dimethylsulphate to yield the corresponding dimethylsulphonium-S-methyl-acetals 13 (Scheme 4) in high yields and showed that these activated sulphonium acetals underwent smooth displacement with methanol in the presence of catalytic amount of sodium methoxide to yield a mixture of the corresponding O,S-acetals (72%) and S,S-acetals (4%). The O,S-acetals 2 thus isolated were not unstable as was originally considered and found to be stable enough for isolation and characterization.

The chemistry of α-oxoketene dithioacetals has been extensively investigated to construct a variety of carbocycles and heterocycles. In all these cases the final product carries the thioalkyl group as one of the substituents and similarly the corresponding S,N-acetals lead to the product with amino substitution. It was therefore, considered of interest to investigate the reactivity of α-oxoketene O,S-acetals with various binucleophiles to afford the corresponding alkoxy substituted end products. Such synthetic operation will certainly widen the synthetic scope of α-oxoketene acetals in general. Alternatively it was considered of interest to develop a direct synthetic method for α-oxoketene O,S-acetals from active methylene ketones. One of the most general approaches employed for the synthesis of dithioesters involves the reaction of enolate anions with trithiocarbonate[18]. These dithioesters have been used as intermediates in the synthesis of the corresponding α-oxoketene dithioacetals[19] and S,N-acetals[9]. It was therefore, considered of interest to extend this approach for the synthesis of thionoesters by reacting enolate anions with alkyl xanthates. These thionoesters



1 13



2 1

Scheme 4

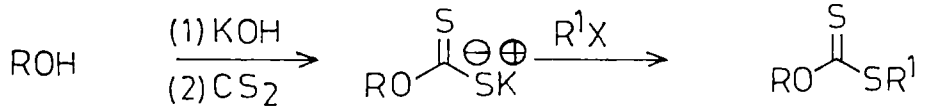
could well be important precursors for the synthesis of α-oxoketene O,S-acetals.

A new general method for the synthesis of α-oxoketene O,S-acetals has thus been developed and the results are presented as follows.

IV.2 RESULTS AND DISCUSSION

The xanthates 16a-c (Scheme 5) prepared for the use in the present investigation were obtained by alkylation of the corresponding potassium xanthate 15 and were purified by distillation. The structural assignment of these xanthates was confirmed by their analytical and spectral data before they were used.

In a typical experiment, the acetophenone 17a was treated with sodium t-butoxide and t-butanol (Scheme 6) and the methyl xanthate 16a was added dropwise and the reaction mixture was directly alkylated with methyl iodide. After work-up it was found that oxoketene O,S-acetals was formed (65%) alongwith corresponding S,S-acetals (15%). Subsequent efforts to find the appropriate conditions, monitoring the reaction conditions in one pot reaction to yield only the corresponding O,S-acetals were not successful. The formation of S,S-acetals though in small quantities alongwith O,S-acetal in one pot reaction created practical difficulties for their removal by column chromatography since they have close R_f values with those of the corresponding O,S-acetals. Further modifications in the experimental conditions were therefore considered necessary and thus it was decided to isolate the corresponding thionoesters 20 first and characterize, which should in principle undergo facile



14 15 16

a , R = Me ; R^1 = Me

b , R = Et ; R^1 = Et

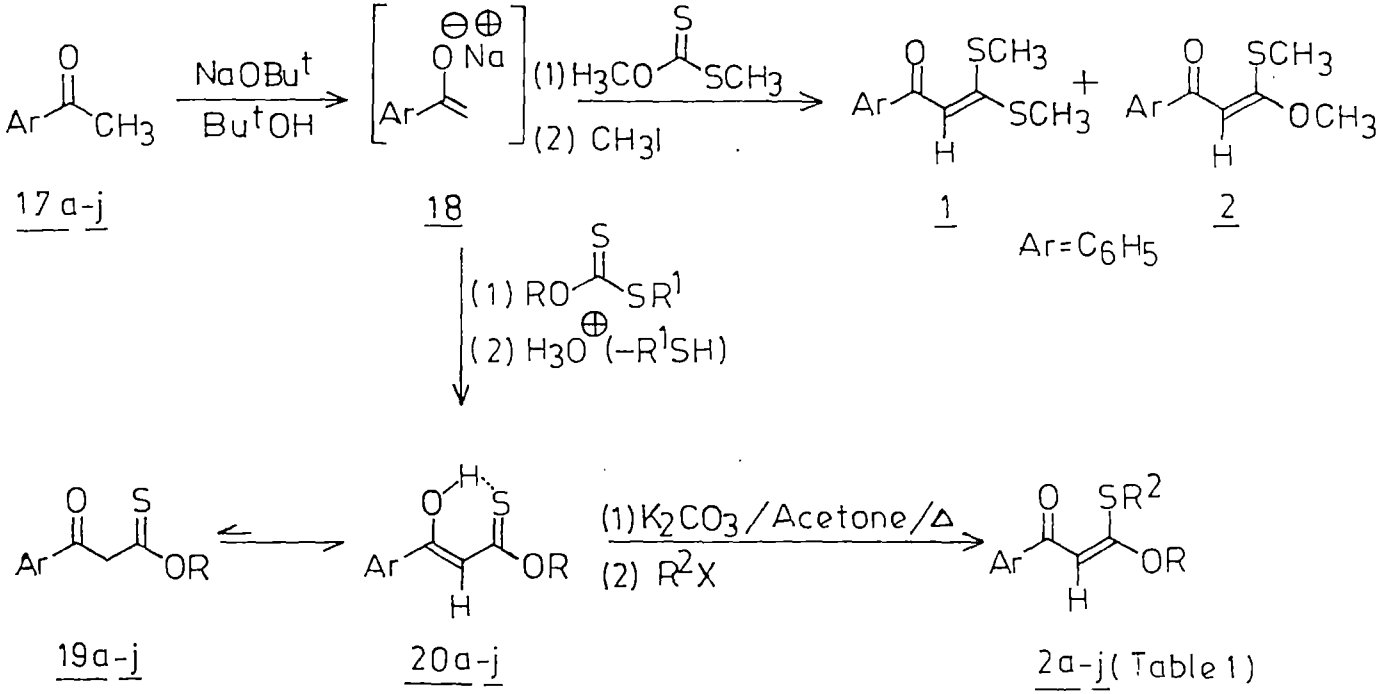
c , R = n-Pr; R^1 = Me

Scheme 5

alkylation in the presence of a weak base to yield the corresponding O,S-acetals.

Thus, the reaction mixture after the addition of xanthate was treated with aqueous acid, extracted with benzene to yield, after column chromatography, a yellow solid m.p. 44°C; in 71% yield, which was characterized as O-methyl-β-hydroxy-thiocinnamate 20a on the basis of its analytical and spectral data. Thus 20a showed molecular ion peak at m/z 194(M^+,45%) and was analyzed for $C_{10}H_{10}O_2S$. Its i.r. spectrum exhibited bands at 1608, 1578, 1495, 1455, 1403 cm^{-1} as major peaks. The intramolecular H-bonding in 20 is manifested in the low frequency of the carbonyl group. The structural assignment was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$). Thus the singlet at δ 4.00(3H) was assigned to OCH_3 protons and the vinylic proton due to tautomerism appeared as a singlet at δ6.36 integrating for one proton thereby fully confirming its existence in the enol form 20. The multiplets between δ 7.25-7.50 and between δ7.63-7.94 were assigned to aromatic [3+2] protons, and the hydroxyl proton appeared as singlet at δ 14.15 which was exchangeable with D_2O.

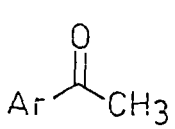
The other thionoesters 20b-j (Table 1) were similarly prepared in 61-73% overall yields. The spectral and analytical data are described in the Table 2 and 6 respectively. The thionoesters 22a-d and 25 derived from the corresponding cyclic ketones were also prepared under the described conditions in 51-67% overall yields. Some thionoesters were found to exist in equilibrium with the corresponding tautomeric keto form 19 (Scheme 6). The spectral and analytical data of these thionoesters are described in the Table 2 and 6 respectively.



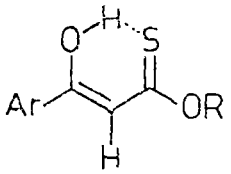
17 a-j 18 1 2

19a-j 20a-j 2a-j (Table 1)

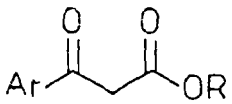
Scheme 6



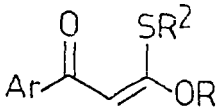
17



20



19



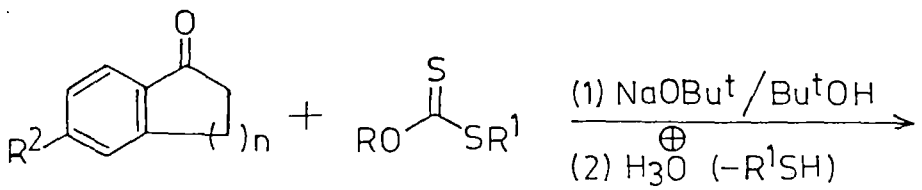
2

	Ar	R	R^2
2,17,19,20a	C_6H_5	CH_3	CH_3
b	C_6H_5	CH_3CH_2	CH_3CH_2
c	C_6H_5	n-C_3H_7	CH_3
d	4-$CH_3OC_6H_4$	CH_3	CH_3
e	4-$CH_3OC_6H_4$	n-C_3H_7	CH_3
f	4-ClC_6H_4	CH_3	CH_3
g	2,4-$Cl_2C_6H_3$	CH_3	CH_3
h	2-naphthyl	CH_3	CH_3
i	2-furyl	CH_3	CH_3
j	2-thienyl	CH_3	CH_3

Table 1

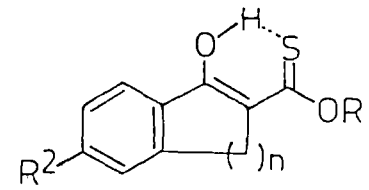
The thionoester 20a was first converted into the corresponding potassium salt by refluxing it in the presence of anhydrous potassium carbonate and acetone and the reaction mixture was brought to room temperature followed by addition of methyl iodide with cooling to afford a white crystalline solid m.p. 61-62°C in 95% yield. The compound thus obtained was characterised as 3-methoxy-3-methylthio-1-phenyl-prop-2-ene-1 one 2a on the basis of its analytical and spectral data. Thus 2a was analyzed for $C_{11}H_{12}O_2S$ and its mass spectrum showed molecular ion peak at m/z 208(M^+,28%). Its infrared spectrum (KBr) exhibited strong bands at 1625 (C=O), 1611, 1592, 1570 cm^{-1}. Further structural proof for 2a was obtained from its ^1H n.m.r. spectrum ($CDCl_3$) which showed a singlet at δ 2.28(3H) which was assigned to SCH_3 protons whereas the other singlet at δ3.92(3H) was assigned to OCH_3 protons. The singlet at δ 6.39(1H) was assigned to olefinic proton. The multiplet between δ 7.31-7.52(3H) was assigned to three aromatic protons and the remaining two protons exhibited signals between δ 7.80-8.03 (2H). The other O,S-acetals 2b-j were similarly obtained in 88-95% overall yields from the corresponding thionoester 20b-j under similar reaction conditions. All these O,S-acetals were fully characterized with the help of their analytical and spectral data which are described in the Table 3 and 7. Similarly the other O,S-acetals 23a-d and 26 (Scheme 7) were obtained in 87-93% overall yields from thionoesters 22a-d and 25 derived from cyclic ketones and their spectral and analytical data are given in the Table 3 and 7.

The α-oxoketene O,S-acetals should in principle exist either as E or Z geometrical isomer or as a mixture of both. In most cases



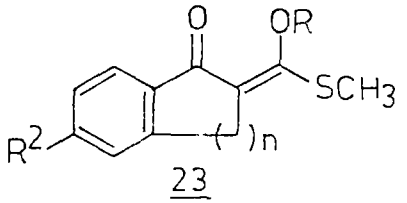
21 + 16a, R^1 = Me; b, R = Et → 22

	n	R	R^2
16-23 a,	1	Me	H
b,	2	Me	H
c,	2	Et	H
d,	2	Me	OMe

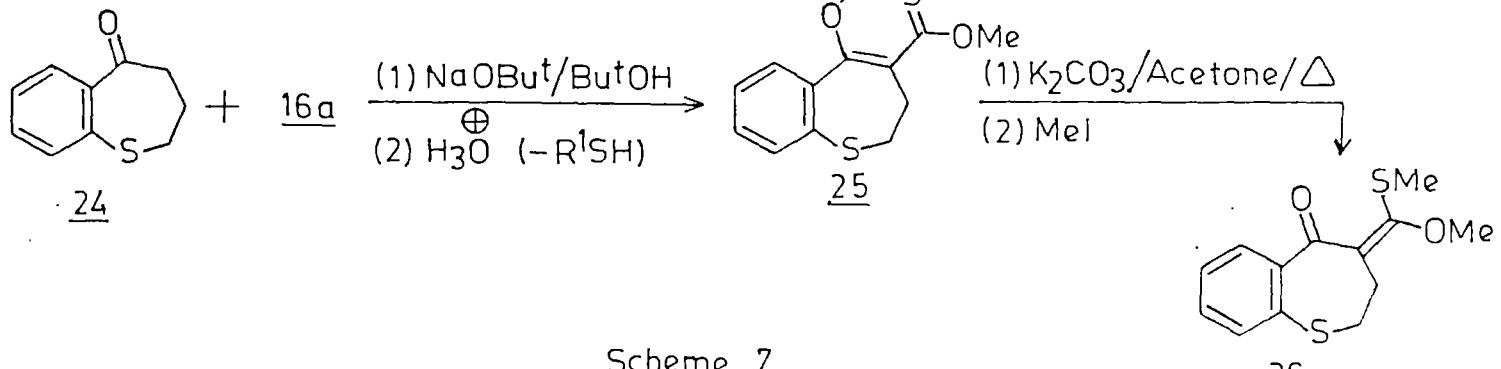


22

(1) K_2CO_3/Acetone/△
(2) MeI



23



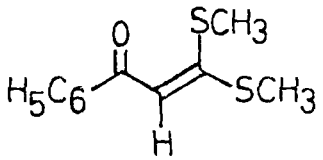
24 + 16a → 25 → 26

(1) NaOBu^t/Bu^{t}OH
(2) $H_3O^{\oplus}$ (−R^1SH)

(1) K_2CO_3/Acetone/△
(2) MeI

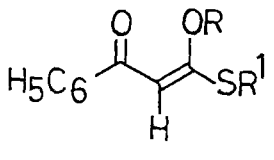
Scheme 7

the α-oxoketene O,S-acetals 2a-g, 2i-2j, 23b-d and 26 exhibit in ^{1}H n.m.r. a single isomer which was assigned Z geometry by comparison of the chemical shift value of the vinylic proton in O,S-acetals with the corresponding S,S-acetals 1. The vinylic

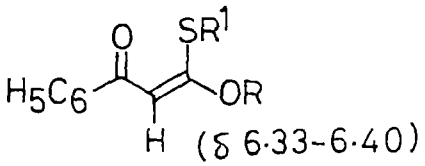


1

proton in 1 appears at δ6.67 whereas in 2a the chemical shift value for vinylic proton is δ6.39. The chemical shift values of the vinylic proton does not change appreciably with higher O-alkyl substituent (2b and 2c) showing that in O,S-acetals the alkoxy group is cis to the vinylic proton.



E

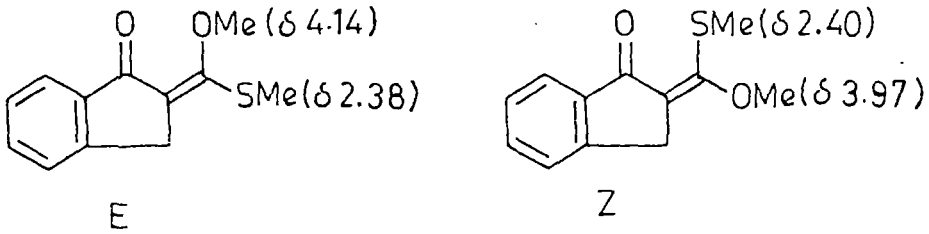


Z

	R	R^1
2a	CH_3	CH_3
b	CH_3CH_2	CH_3CH_2
c	n-C_3H_7	CH_3

However, in case of 2h derived from 2-acetyl naphthalene and 23a, derived from indanone clearly displayed a mixture of both the geometrical isomers as observed from their ^{1}H n.m.r. spectrum.

Thus the thiomethyl signal which appeared as two singlets closely separated, and similarly the other two singlets for OCH_3 protons were attributed due to the existence of E and Z isomers of 23a. The thiomethyl signal which appeared at lower field (δ 2.40) was assigned the Z geometry since it is cis to carbonyl group. Similarly when the methoxy group is cis to carbonyl function the low field signal at δ 4.14 was attributed to the OCH_3 protons of the E isomer.

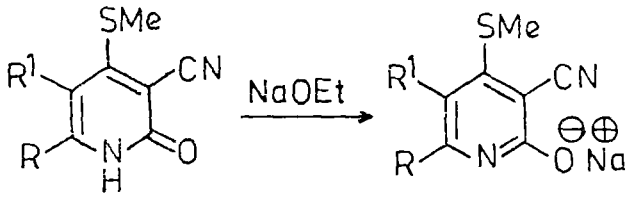


In principle all the reactions exploited with the α-oxoketene S,S-acetals can be extended to the corresponding α-oxoketene O,S-acetals and a few selected reactions investigated in the present study are described as follows.

IV.3 REACTION OF α-OXOKETENE O,S-ACETALS WITH CYANOACETAMIDE: A NOVEL GENERAL METHOD FOR THE SYNTHESIS OF 3-CYANO-4-ALKOXY-6-SUBSTITUTED AND 5,6-ANNELATED PYRIDIN-2-(1H)-ONE:

It was reported[20,21] earlier from this laboratory, that the α-oxoketene dithioacetals react with cyanoacetamide in the presence of sodium ethoxide and ethanol mixture to yield an inseparable mixture of the

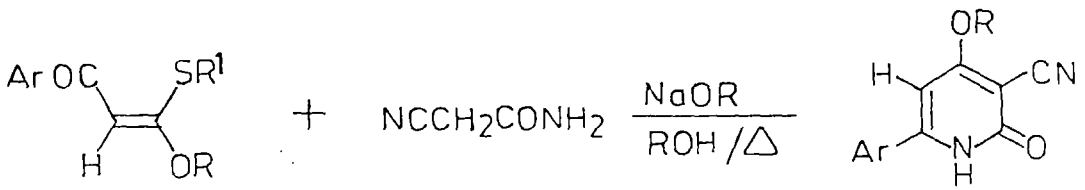
corresponding 4-thiomethyl and 4-ethoxypyridones in the ratio of 9:1. Prolonged reaction time did not alter the ratio of this mixture. The 4-thiomethyl pyridone also failed to yield the corresponding alkoxy pyridone by treating A with alkoxide ions in a separate experiment probably due to the formation of an anion B where the thiomethyl group cannot undergo displacement under the described conditions. The alkoxypyridones formed in low yield in these reactions also could not be separated because of their



A B

overlapping R_f values with those of the 4-thiomethylpyridones. The method was thus improved to give only the 4-thiomethyl pyridones using sodium isopropoxide as base where the 4-alkoxypyridones were not formed. However, the method could not be extended for the synthesis of alkoxypyridones using the corresponding α-oxoketene dithioacetals. It is therefore now possible to synthesise the alkoxy pyridones in high yields in pure form from the corresponding O,S-acetals.

In a typical experiment 2a was reacted with cyanoacetamide in methanolic sodium methoxide, to yield a colourless solid, m.p. 275°C in 81% yield and was characterized as 3-cyano-4-methoxy-6-phenyl-2-(1H)



2 27 28

		Ar	R	R^1
2a, 28a,		C_6H_5	Me	Me
b	b,	C_6H_5	Et	Et
c	c,	C_6H_5	n C_3H_7	Me
d	d,	4-$MeOC_6H_4$	Me	Me
f	e,	4-ClC_6H_4	Me	Me
g	f,	2,4-$Cl_2C_6H_3$	Me	Me

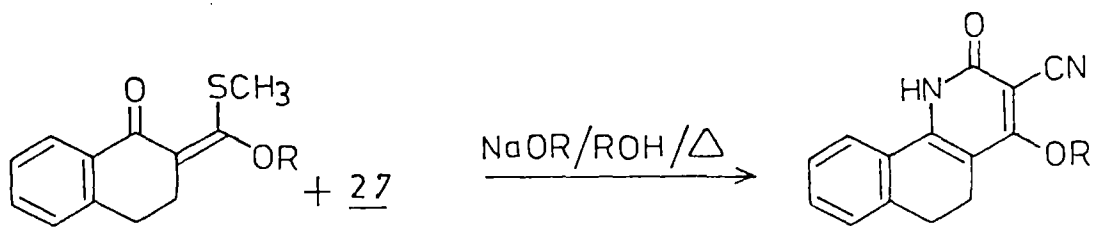
Scheme 8

pyridone 28a on the basis of its analytical and spectral data. Thus 28a was analysed for $C_{13}H_{10}N_2O_2$ and its mass spectrum showed molecular ion peak at m/z 226(M^+,100%). In its i.r. spectrum (KBr) the peak at 2221 cm^{-1} was assigned to C≡N stretching vibrations. The amide band was assigned to 1660 cm^{-1} peak and other bands are described in the Table 4. The structure was further confirmed by its ^1H n.m.r. spectrum (DMSO-d_6). The singlet at δ 4.06(3H) was assigned to three OCH_3 protons. The signal at δ 6.63(1H) was assigned to ring 5H proton whereas the multiplet between δ 7.33-8.03 (5H) was assigned to aromatic protons. The other pyridones 28b-f were similarly prepared from the corresponding O,S-acetals 2b-d, 2f and 2g under similar reaction conditions in 74-83% overall yields.

The cyclic oxoketene O,S-acetals 23b, 23c and 26 were similarly condensed (Scheme 9) to yield the corresponding 5,6-annelated pyridones 29a, 29b and 30 respectively in 68-76% overall yields. The structural assignment of all these pyridones was confirmed by their spectral and analytical data which are described in the Table 4 and 8.

IV.4 REACTION OF α-OXOKETENE O,S-ACETALS WITH HYDROXYLAMINE: A FACILE METHOD FOR 5-ALKOXY-3-SUBSTITUTED AND 3,4-ANNELATED ISOXAZOLES:

In the second chapter it has been extensively discussed[22] on the different pathways of reactivity of α-oxoketene dithioacetals with hydroxylamine to afford the corresponding highly regioselective 5- and 3-alkylthioisoxazoles. It was considered of interest to react the α-oxoketene O,S-acetals with hydroxylamine under similar reaction

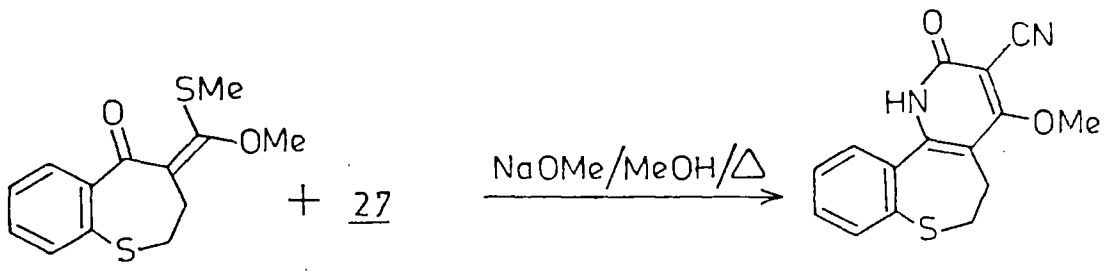


23 b; R = Me

c; R = Et

29 a; R = Me

b; R = Et



26

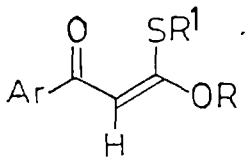
30

Scheme 9

conditions to afford 5-alkoxy and 3-alkoxyisoxazoles.

In a typical experiment when 2a was reacted with hydroxylamine in the presence of sodium methoxide and methanol, after work-up of the reaction mixture, a colourless solid m.p. 77°C was obtained in 48% yield, which was characterized as 5-methoxy-3-phenyl isoxazole 31a on the basis of its analytical and spectral data. Thus 31a was analyzed for $C_{10}H_9NO_2$ and its mass spectrum showed molecular ion peak at 175 (M^+,54). The compound exhibited in its infrared spectrum (KBr) bands at 1615 (C=N), 1575, 1480 cm^{-1}. Its structure was further confirmed by its ^1H n.m.r.($CDCl_3$) spectrum. It showed a signal at δ4.01(3H) which was assigned to the $O\underline{CH}_3$ protons and the singlet at δ5.51 was assigned to H-4 proton. The multiplet between 7.33-7.60(3H) was assigned to three aromatic protons and other two appeared as multiplet between δ 7.67-7.97(2H). Isoxazole 31a showed a characteristic peak at m/z 144(100%) and 116(40%) due to loss of OCH_3 and $COOCH_3$ fragments (M^+-OCH_3 and $M^+-COOCH_3$) respectively suggesting that the methoxy group is adjacent to ring oxygen atom.

The other 5-alkoxyisoxazoles 31b-f were obtained in 41-53% overall yields from the respective O,S-acetals 2a-b, 2d-f, 2h. The 3,4-annelated isoxazoles 33 and 34 were also prepared from the respective O,S-acetals 23c and 26 in 40 and 46% yields respectively. The structural assignment of all these isoxazoles are confirmed by their spectral and analytical data which are described in the Table 5 and 9. All 5-alkoxy isoxazoles showed characteristic peak



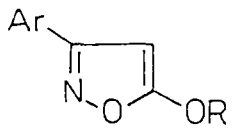
2

$NH_2OH.HCl$

NaOMe/MeOH / △

(1 eqv.)

$p^H = 7$

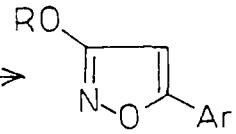


31

$NH_2OH.HCl$ / HOAc

NaOAc/C_6H_6/EtOH/△

$p^H = 2.2$



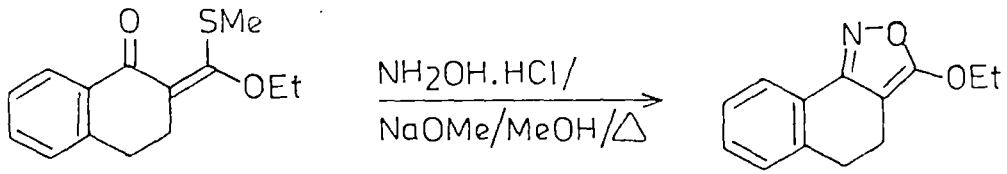
32

Ar = C_6H_5

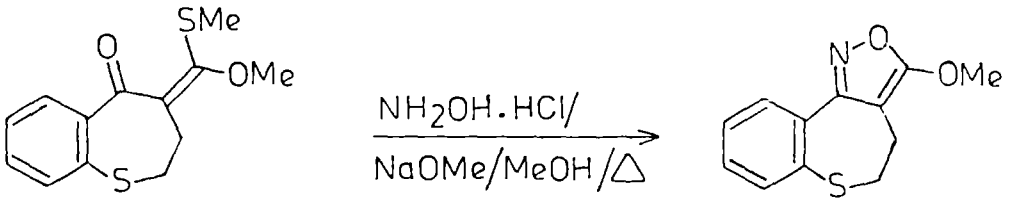
R = Me

		Ar	R	R^1
2a,	31a,	C_6H_5	Me	Me
b	b,	C_6H_5	Et	Et
d	c,	4-$MeOC_6H_4$	Me	Me
e	d,	4-$MeOC_6H_4$	n-C_3H_7	Me
f	e,	4-ClC_6H_4	Me	Me
h	f,	2-Naphthyl	Me	Me

Scheme 10



23c 33



26 34

Scheme 11

due to loss of COOR group (M^+-COOR) showing that alkoxy group is adjacent to oxygen atom of the isoxazole ring.

Further attempts to react the α-oxoketene O,S-acetals 2 with hydroxylamine at pH 2.2 to yield the corresponding 3-alkoxy-5-aryl isoxazoles were not successful. The O,S-acetals underwent hydrolytic cleavage under these reaction conditions. Further investigation is under progress to develop a suitable Lewis acid that could polarize 2 leading to the formation of isomeric isoxazoles 32.

IV.5 EXPERIMENTAL

Melting points were determined on a Thomas Hoover (Capillary method) apparatus and are uncorrected. The i.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer. The ^1H n.m.r. spectra were recorded on a Varian EM-390, 90MHz spectrometer using TMS as internal standard and the chemical shift are expressed as δ(ppm). The mass spectra were recorded on a Jeol-D 300 Mass Spectrometer.

Starting Materials

The commercial samples of acetophenone, 4-methoxyacetophenone, 4-chloroacetophenone, 2,4-dichloroacetophenone, 6-methoxy-1-tetralone, 2-acetylnaphthalene, 2-acetylfuran, 2-acetylthiophene, hydroxylamine hydrochloride, cyanoacetamide were purified before use.

The cyclic ketones 1-tetralone, b.p. 140-150°C(10 mm)[23], 1-indanone, m.p. 39-40°C[24], and benzthiepenone[25] were prepared according to the reported procedure. Methyl xanthate, ethyl xanthate and propyl xanthate were prepared by the reported[26] method and were purified by distillation before use.

General Method for the preparation of β-oxothionoesters 20a-j, 22a-d, 25:

A mixture of ketone (0.2 mol) and alkyl xanthate (0.2 mol) was added dropwise to an ice cold and well stirred suspension of sodium t-butoxide (0.4 mol) in t-butanol (150 ml) and the reaction mixture was allowed to stir at room temperature for 4 hrs. The reaction mixture was then

poured over ice water (500 ml) and acidified with 50% hydrochloric acid (100 ml). It was then extracted with benzene (3x100 ml), the combined extracts were washed with water (3x150 ml), dried (Na_2SO_4) and concentrated to give crude thionoesters, which were further column chromatographed (hexane eluent).

General Method for the preparation of α-oxoketene O,S-acetals 2a-j, 23a-d and 26:

A suspension of thionoester 20 or 22 or 25 (0.04 mol) and potassium carbonate (0.06 mol) in acetone (50 ml) was refluxed for 3 hr. The solution was cooled and appropriate alkyl halide (0.05 mol) was added with stirring and the reaction mixture was further stirred at room temperature for 2 hr. It was then poured over crushed ice, acidified with 10% acetic acid, extracted with chloroform, dried (Na_2SO_4) and solvent evaporated to give the corresponding O,S-acetals, which are either purified by crystallisation from chloroform/hexane 2a-j, 23a, 23b, 23d, 26 or by passing through a silica gel column using ethylacetate/hexane (1:10) eluent 23c.

General Method for the preparation of 3-cyano-4-alkoxy-2(1H) pyridones and 5,6-annelated-2(1H) pyridones 28a-f, 29a and 29b:

To a solution of sodium alkoxide (prepared by dissolving sodium 0,46 gm, 0.02 mol, in 70 ml of methyl/ethyl/1-propyl alcohol), cyanoacetamide (1.68g, 0.02 mol) was added and the mixture was shaken for 5-10 minutes. The appropriate ketene O,S-acetal (0.02 mol) was then added and the reaction mixture was refluxed for 12 hrs. Bright

coloured sodium salt of pyridone, obtained after evaporation of the solvent from the reaction mixture, was diluted with 30-40 ml water and then acidified with dil. acetic acid (10%) to give respective pyridones, which were filtered a purified by crystallisation from acetic acid.

General Method for the preparation of alkoxyisoxazoles 31a-f,33,34:

Hydroxylamine hydrochloride (0.04 mol) was added to a stirred suspension of sodium methoxide (prepared by dissolving 1.38g, 0.06 mol of sodium in 30 ml of absolute methanol) and the reaction mixture was further stirred for 10 min. The respective ketene O,S-acetals (2, 23, 26) was added and the reaction mixture was refluxed with stirring for 10 hrs. Methanol was removed under reduced pressure and the residue poured over ice-cooled water (200 ml), extracted with chloroform(2x50 ml). The chloroform layer was washed with water (2x100 ml), dried (Na_2SO_4) and evaporated to give brown residues. The brown residues are filtered through a small neutral alumina column using ethylacetate/hexane (1:20) as eluent to give pure isoxazoles.

Table 2: Spectral data of thionoesters 20a-j, 23a-d, 25:

Product	I.R. ν_{max} (cm^{-1})	^1H n.m.r. δ(ppm)	M.S. M/e (M^+)
20a	1608, 1578, 1495, 1455, 1403[a]	4.00(s,3H,OC<u>H</u>$_3$); 6.36(s,1H$_{olefin}$); 7.25-7.50(m,3H$_{arom}$); 7.63-7.94(m, 2H$_{arom}$); 14.15(s,1H,O<u>H</u>,exchangeable with D_2O)[c]	194(45%)
20b	1600, 1570, 1450, 1400[b]	1.33(t,J=8Hz,3H,C<u>H</u>$_3$CH$_2$); 4.45(q,J=8Hz, 2H,OC<u>H</u>$_2$); 6.33(s,1H$_{olefin}$); 6.80-7.50 (m,3H$_{arom}$); 7.66-8.00(m,2H$_{arom}$); 14.16(s,1H,O<u>H</u>,exchangeable with D_2O)[c]	
20c	1605, 1572, 1450, 1400[b]	1.03(t,J=8Hz,3H,C<u>H</u>$_3$); 1.80(sext, J=8Hz,2H,OCH$_2$C<u>H</u>$_2$CH$_3$); 4.40(q,J=8Hz, 2H,OC<u>H</u>$_2$CH$_3$); 6.33(s,1H$_{olefin}$); 7.20-7.56(m,3H$_{arom}$); 7.76-8.07(m, 2H$_{arom}$); 14.06(s,1H,O<u>H</u>,exchangeable with D_2O)[d]	

Table 2: Contd...

20d	1605, 1578, 1540, 1495, 1420[a]	3.83(s,3H,$OC\underline{H}_3$); 4.02(s,3H,$OC\underline{H}_3$); 6.23(s,1H$_{olefin}$); 6.86(d,J=9Hz,2H$_{arom}$); 7.75(d,J=9Hz,2H$_{arom}$); 14.03(s,1H, $O\underline{H}$, exchangeable with D_2O)[d]
20e	1600, 1568, 1507, 1430[b]	1.03(t,J=7Hz,3H,$C\underline{H}_3$); 1.80(sext,J=7Hz, 2H,$OCH_2C\underline{H}_2CH_3$); 3.79(s,3H,$OC\underline{H}_3$); 4.36 (t,J=7Hz,2H,$OC\underline{H}_2CH_2CH_3$); 6.24(s,1H$_{olefin}$); 6.85(d,J=9Hz,2H$_{arom}$); 7.77(d,J=9Hz,2H$_{arom}$); 14.11(s,1H,$O\underline{H}$,exchangeable with D_2O)[d]
20f	1600, 1550, 1485, 1440[a]	4.06(s,3H,$OC\underline{H}_3$); 6.20(s,1H$_{olefin}$); 7.30 (d,J=8Hz,2H$_{arom}$); 7.66(d,J=8Hz,2H$_{arom}$); 13.96(s,1H,$O\underline{H}$,exchangeable with D_2O)[c]
20g	1620, 1480, 1420[a]	4.05(s,3H,$OC\underline{H}_3$); 6.08(s,1H$_{olefin}$); 7.12-7.61(m,3H$_{arom}$); 13.95(s,1H,$O\underline{H}$, exchangeable with D_2O)[c]
20h	1618, 1600, 1580, 1458, 1418[a]	4.08(s,3H,$OC\underline{H}_3$); 6.50(s,1H$_{olefin}$); 7.20-7.63(m,2H$_{arom}$); 7.70-8.03(m, 4H$_{arom}$); 8.40(brs,1H$_{arom}$); 14.16, 1H,$O\underline{H}$,exchangeable with D_2O)[c]

Table 2: Contd...

20i	1622, 1544, 1470[b]	4.01(s,3H,$OC\underline{H}_3$); 6.26(s,$1H_{olefin}$); 6.40-6.56(m,1H,H-4'$_{furyl}$); 7.01 (d,J=3Hz,1H,H-3'$_{furyl}$); 7.49(d, J=3Hz,1H,H-5'$_{furyl}$); 13.64(s,1H, $O\underline{H}$,exchangeable with D_2O)[d]
20j	1595, 1505, 1410[a]	4.03(s); 4.06(s,3H,$OC\underline{H}_3$); 4.25(s,0.5Hz, $C\underline{H}_2$); 6.22(s,$0.75H_{olefin}$); 6.93-7.13 (m,1H,H-4'$_{thienyl}$); 7.26-7.87 (m,2H,H-3' and H-5'$_{thienyl}$); 13.97(s,0.75H,$O\underline{H}$,exchangeable with D_2O)[d]
22a	1615, 1532, 1470, 1458[a]	3.58(s,2H,$C\underline{H}_2$): 4.11(s,3H,$OC\underline{H}_3$); 7.21-7.45(m,$3H_{arom}$); 7.59-7.82 (m,$1H_{arom}$); 12.86(s,1H,$O\underline{H}$,exchangeable with D_2O)[d]
22b	1605, 1587,1545, 1445	2.71(s,4H,$C\underline{H}_2$); 4.05(s,3H,$OC\underline{H}_3$); 7.00-7.36(m,$3H_{arom}$); 7.86-8.03(m, $1H_{arom}$);14.30(s,1H,$O\underline{H}$,exchangeable with D_2O)[d]

Table:2Contd..

22c	1608, 1590, 1548, 1450, 1420[a]	1.36(t,J=7Hz,3H,C<u>H</u>$_3$); 2.70(s,4H,C<u>H</u>$_2$); 4.46(q, J=7Hz,2H,OC<u>H</u>$_2$CH$_3$); 7.03-7.41 (m,3H$_{arom}$); 7.83-8.01(m,1H$_{arom}$); 14.51(s,1H,O<u>H</u>,exchangeable with D_2O)[c]
22d	1628, 1593, 1507, 1403[a]	2.70(s,4H,C<u>H</u>$_2$); 3.80(s,3H,OC<u>H</u>$_3$); 4.06(s,3H,OC<u>H</u>$_3$); 6.63-6.90(m,2H$_{arom}$); 7.88(d,J=9Hz,1H$_{arom}$); 14.53(s,1H,O<u>H</u>, exchangeable with D_2O)[c]
25	1592, 1570, 1545, 1407[a]	2.53(t,J=6Hz,2H,C<u>H</u>$_2$); 3.30(t,J=6Hz, 2H,S-C<u>H</u>$_2$); 4.10(s,3H,OC<u>H</u>$_3$); 7.23-7.76(m,4H$_{arom}$); 14.38(s,1H,O<u>H</u>, exchangeable with D_2O)[c]

[a] in KBr; [b] in CCl_4; [c] in $CDCl_3$; [d] in CCl_4

Table 3: Spectral data of O,S-acetals 2a-j; 23a-d and 26:

Product	I.R. $\nu_{max}(cm^{-1})$	^1H N.M.R. ($CDCl_3$) δ(ppm)	M.S. M/e (M^+)
2a	1625, 1611, 1592, 1570[a]	2.28(s,3H,SCH_3); 3.92(s,3H,OCH_3); 6.39(s,$1H_{olefin}$); 7.31-7.52(m,$3H_{arom}$); 7.80-8.03(m,$2H_{arom}$)	208 (27%)
2b	1625, 1595, 1572, 1468[a]	1.05-1.53(m,6H,SCH_2CH_3 and OCH_2CH_3); 2.83(q,J=7Hz,2H,SCH_2CH_3); 4.08(q,J=7Hz,2H, OCH_2CH_3); 6.33(s,$1H_{olefin}$); 7.20-7.48(m,$3H_{arom}$); 7.76-7.98(m,$2H_{arom}$)	236 (18%)
2c	1623, 1573, 1515[a]	1.03(t,J=8Hz,3H,CH_3); 1.83(sext, J=8Hz,2H,$OCH_2CH_2CH_3$); 2.31(s,3H,SCH_3); 4.06(t,J=8Hz,2H,$OCH_2CH_2CH_3$); 6.40(s, $1H_{olefin}$); 7.28-7.63(m,$3H_{arom}$); 7.87-8.10(m,$2H_{arom}$)	236 (5%)
2d	1622, 1604, 1575, 1502, 1436[a]	2.28(s,3H,SCH_3); 3.82(s,3H,OCH_3); 3.95(s,3H,OCH_3); 6.39(s,$1H_{olefin}$); 6.95(d,J=8Hz,$2H_{arom}$); 7.95(d,J=8Hz,$2H_{arom}$)	238 (18%)

Table 3: Contd...

2e	1620, 1600, 1570[a]	1.03(t,J=5Hz,3H,$C\underline{H}_3$); 1.87(sext,J=5Hz, 2H,$OCH_2\underline{CH}_2CH_3$); 2.30(s,3H,$SC\underline{H}_3$); 3.83 (s,3H,$OC\underline{H}_3$); 4.05(t,J=5Hz,2H,$OC\underline{H}_2CH_2CH_3$); 6.38(s,$1H_{olefin}$); 6.94(d,J=8Hz,$2H_{arom}$); 7.94(d,J=8Hz,$2H_{arom}$)	266 (10%)
2f	1622, 1590, 1569, 1440[a]	2.28(s,3H,$SC\underline{H}_3$); 3.94(s,3H,$OC\underline{H}_3$); 6.33 (s,$1H_{olefin}$); 7.36(d,J=8Hz,$2H_{arom}$); 7.82 (d,J=8Hz,$2H_{arom}$)	242 (19%)
2g	1639, 1590, 1520[a]	2.31(s,3H,$SC\underline{H}_3$); 3.92(s,3H,$OC\underline{H}_3$); 6.14 (s,$1H_{olefin}$); 7.18-7.59(m,$3H_{arom}$)	276 (23%)
2h	1618, 1598, 1571, 1502[a]	2.27(s,3H,$SC\underline{H}_3$); 3.78(s.1H,$OC\underline{H}_3$); 3.90(s,3H,$OC\underline{H}_3$); 6.11(s,$0.33H_{olefin}$); 6.53(s,$0.67H_{olefin}$); 7.27-7.60(m, $2H_{arom}$); 7.66-8.03(m,$4H_{arom}$); 8.47 (brs,$1H_{arom}$)	258 (51%)
2i	1613, 1571, 1510, 1430[a]	2.30(s,3H,$SC\underline{H}_3$); 3.93(s,3H,$OC\underline{H}_3$); 6.38 (s,$1H_{olefin}$); 6.41-6.57(m,H-4'$_{furyl}$); 7.14(d,J=3Hz,1H,H-3'$_{furyl}$); 7.51(brs, 1H,H-5' furyl)	198(56%)

Table 3: Contd..

2j	1603, 1517, 1432, 1415[a]	2.27(s,3H,SCH_3); 3.94(s,3H,OCH_3); 6.28 (s,1H$_{olefin}$); 6.98-7.18(m,1H,H-4'$_{thienyl}$); 7.48-7.80(m,2H,H-3' and H-5'$_{thienyl}$)	214(16%)
23a	1652, 1610, 1529 1428[a]	2.38(s), 2.40(s,3H,SCH_3); 3.61(s,0.9H,CH_2); 3.82(s,1.1H,CH_2); 3.97(s,1.35H,OCH_3); 4.14(s,1.65H,OCH_3); 7.25-7.60(m,3H$_{arom}$); 7.73-7.91(m,1H$_{arom}$)	220 (5%)
23b	1605, 1551, 1498[a]	2.27(s,3H,SCH_3); 2.88(s,4H,$-CH_2-$); 3.74(s,3H,OCH_3); 7.10-7.50(m,3H$_{arom}$); 8.00-8.18(m,1H$_{arom}$)	234(45%)
23c	1742, 1650, 1604[b]	1.37(t,J=7Hz,3H,CH_3); 2.28(s,3H,SCH_3); 2.86(s,4H,$-CH_2-$); 3.95(q,J=7Hz, $O-CH_2CH_3$); 7.07-7.48(m,3H$_{arom}$); 8.01-8.20(m,1H$_{arom}$)	248(3%)
23d	1645, 1610, 1580, 1525[a]	2.27(s,3H,SCH_3); 2.87(s,4H,$-CH_2-$); 3.73 (s,3H,OCH_3); 3.81(s,3H,OCH_3); 6.60-6.93 (m,2H$_{arom}$); 8.05(d,J=9Hz,1H$_{arom}$)	

Table 3: Contd...

26	1622, 1589, 1500[a]	2.27(s,3H,SCH_3); 2.63(t,J=6Hz,2H,$-CH_2-$); 3.03(t,J=6Hz,2H,$-CH_2-$); 3.78(s,3H,OCH_3); 7.22-7.45(m,$3H_{arom}$); 7.56-7.76(m,$1H_{arom}$)	266(83%)

[a] in KBr; [b] in CCl_4

Table 4: Spectral data of alkoxy pyridones 28a-f, 29a, 29b and 30:

Products	I.R.(KBr): $\nu_{max}(cm^{-1})$	^1H n.m.r. δ(ppm)	M.S. M/e (M^+)
28a	2221, 1660, 1612, 1580, 1503	4.06(s,3H,OCH_3); 6.63(s,1H,H-5);7.33-7.70(m,3H$_{arom}$); 7.74-8.03(m,2H$_{arom}$)[a]	226 (100%)
28b	2220, 1630, 1575, 1548, 1500	1.64(t,J=6Hz,3H,CH_3); 4.56(q,J=6Hz,2H, OCH_2CH_3); 6.86(s,1H,H-5); 7.40-7.93 (m,5H$_{arom}$)[b]	240 (16%)
28c	2207, 1645, 1608, 1575	1.18(t,J=6Hz,3H,CH_3); 2.05(sext,J=6Hz, 2H,$OCH_2CH_2CH_3$); 4.44(t,J=6Hz,2H, $OCH_2CH_2CH_3$); 6.89(s,1H,H-5); 7.70(brs, 5H$_{arom}$)[b]	
28d	2210, 1625, 1605, 1570, 1515	4.09(s,3H,OCH_3); 4.31(s,3H,OCH_3); 6.91 (s,1H,H-5); 7.25(d,J=8Hz,2H$_{arom}$); 7.83 (d,J=8Hz,2H$_{arom}$)[b]	256 (21%)
28e	2218, 1660, 1607, 1497	4.23(s,3H,OCH_3); 6.81(s,1H,H-5); 7.26-7.85 (m,4H$_{arom}$)[b]	260 (100%)

Table 4: Contd..

28f	2250, 1660, 1617, 1500	4.23(s,3H,OCH_3); 6.83(s,1H,H-5); 7.50 (s,$2H_{arom}$); 7.78(s,$1H_{arom}$)[b]	
29a	2248, 1640, 1560, 1441	2.79-3.13(m,4H,$-CH_2-$); 4.61(s,3H,OCH_3); 7.13-7.64(m,$3H_{arom}$); 7.76-8.00(m,$1H_{arom}$)[b]	252(100%)
29b	2210, 1640, 1548, 1500, 1428	1.60(t,J=7Hz,3H,CH_3); 2.73-3.13(m,4H,$-CH_2-$); 4.90(q,J=7Hz,2H,OCH_2CH_3); 7.16-7.50(m, $3H_{arom}$); 7.62-7.90(m,$1H_{arom}$)[b]	266(72%)
30	2208, 1635, 1464	3.20-3.78(m,4H,$-CH_2-$); 4.57(s,3H,OCH_3); 7.46-7.97(m,$4H_{arom}$)	

[a] in DMSO-d_6 [b] in TFA/$CDCl_3$

Table 5: Spectral data of alkoxy isoxazoles 31a-f, 33, and 34

Product	I.R.(KBr): $\nu_{max}(cm^{-1})$	^1H n.m.r.($CDCl_3$) δ(ppm)	M.S. m/z (%)
31a	1615, 1575, 1480	4.01(s,3H,$OC\underline{H}_3$); 5.51(s,1H,$\underline{H}$-4); 7.33-7.60(m,3H$_{arom}$); 7.67-7.93(m,2H$_{arom}$)	175(M^+,54); 144(100); 116(40)
31b	1610, 1583, 1484	1.46(t,J=8Hz,3H,$OCH_2C\underline{H}_3$); 4.25(q,J=8Hz, 2H,$OC\underline{H}_2CH_3$); 5.50(s,1H,$\underline{H}$-4); 7.28-7.53 (m,3H$_{arom}$); 7.64-7.94(m,2H$_{arom}$)	189(M^+,55); 144(70); 117(100)
31c	1618, 1600, 1542, 1500	3.83(s,3H,$OC\underline{H}_3$): 3.97(s,3H,$OC\underline{H}_3$); 5.43 (s,1H,$\underline{H}$-4); 6.95(d,J=8Hz,2H$_{arom}$); 7.69 (d,J=8Hz,2H$_{arom}$)	
31d	1602, 1572, 1528, 1448	1.03(t,J=7Hz,3H,$C\underline{H}_3$); 1.85(sext,J=7Hz,2H, $OCH_2C\underline{H}_2CH_3$); 3.83(s,3H,$OC\underline{H}_3$); 4.15(t,J=7Hz, $-OC\underline{H}_2CH_2CH_3$); 5.43(s,1H,$\underline{H}$-4); 6.95(d,J=8Hz, 2H$_{arom}$); 7.71(d,J=8Hz,2H$_{arom}$)	233(M^+,52); 191(54); 163(17)
31e	1617, 1570, 1475, 1437	4.03(s,3H,$OC\underline{H}_3$); 5.49(s,1H,$\underline{H}$-4); 7.42(d, J=8Hz,2H$_{arom}$); 7.70(d,J=8Hz,2H$_{arom}$)	209(M^+,53); 178(100);150(52)

Table 5: Contd...

31f	1615, 1572, 1468	4.05(s,3H,$OC\underline{H}_3$); 5.65(s,1H,$\underline{H}$-4); 7.40-7.63 (m,$2H_{arom}$); 7.79-8.02(m,$4H_{arom}$); 8.19(brs, $1H_{arom}$)	225(M^+,61); 194(29); 166(31)
33	1644, 1605, 1570, 1475	1.43(t,J=7Hz,3H,$C\underline{H}_3$); 2.61(t,J=5Hz,2H,$-CH_2-$); 2.88(t,J=5Hz,2H,$-CH_2$); 4.43(q,J=7Hz,2H, $OC\underline{H}_2CH_3$); 7.16-7.44(m,$3H_{arom}$); 7.70-8.03 (m,$1H_{arom}$)	215(M^+,56); 169(33)
34	1628, 1587, 1560,	2.70-3.18(m,4H,$-CH_2-$); 4.08(s,3H,$OC\underline{H}_3$); 7.13-7.46(m,$3H_{arom}$); 7.79-8.02(m,$1H_{arom}$)	233(M^+,100); 201(12); 173(90)

Table 6: Physical and analytical data of the thionoesters 20a-j, 23a-d and 25:

Product	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	Analysis (%) H
20a	71	44	$C_{10}H_{10}O_2S$ (194.2)		61.85 62.11	5.15 5.03
20b	69	Liquid	$C_{11}H_{12}O_2S$ (208.3)		63.46 63.33	5.76 6.01
20c	72	Liquid	$C_{12}H_{14}O_2S$ (222.3)		64.86 64.58	6.30 6.18
20d	73	79	$C_{11}H_{12}O_3S$ (224.3)		58.92 58.78	5.35 5.16
20e	70	Liquid	$C_{13}H_{16}O_3S$ (252.3)		61.90 61.88	6.34 6.51
20f	68	86-87	$C_{10}H_9ClO_2S$ (228.7)		52.51 52.78	3.93 3.64
20g	72	86	$C_{10}H_8Cl_2O_2S$ (263.1)		45.62 45.48	3.04 3.18
20h	67	85	$C_{14}H_{12}O_2S$ (244.3)		68.85 68.64	4.91 4.88

Table 6: Contd..

20i	61	Liquid	$C_8H_8O_3S$ (184.2)	52.17 52.41	4.34 4.51
20j	62	Liquid	$C_8H_8O_2S_2$ (200.3)	48.00 47.88	4.00 3.88
22a	51	96	$C_{11}H_{10}O_2S$ (206.3)	64.08 64.31	4.85 4.80
22b	67	56	$C_{12}H_{12}O_2S$ (220.3)	65.45 65.43	5.45 5.64
22c	63	69-70	$C_{13}H_{14}O_2S$ (234.3)	66.66 66.39	5.98 5.86
22d	61	74	$C_{13}H_{14}O_3S$ (250.3)	62.40 62.12	5.60 5.51
25	65	82	$C_{12}H_{12}O_2S_2$ (252.3)	57.14 56.88	4.76 4.91

Table 7: Physical and analytical data of the O,S-acetals 2a-j, 23a-d and 26

Product	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	Analysis (%) H
2a	95	61-62	$C_{11}H_{12}O_2S$ (208.3)		63.46 63.71	5.76 5.83
2b	95	46	$C_{13}H_{16}O_2S$ (236.3)		66.10 65.88	6.77 6.89
2c	89	89	$C_{13}H_{16}O_2S$ (236.6)		66.10 68.28	6.77 6.44
2d	91	94	$C_{12}H_{14}O_3S$ (238.3)		60.50 60.71	5.88 5.59
2e	89	77	$C_{14}H_{18}O_3S$ (266.3)		63.15 62.97	6.76 6.90
2f	93	131	$C_{11}H_{11}ClO_2S$ (242.7)		54.43 54.31	4.53 4.49
2g	94	110	$C_{11}H_{10}Cl_2O_2S$ (277.2)		47.65 47.57	3.61 3.83
2h	90	64	$C_{15}H_{14}O_2S$ (258.3)		69.76 69.88	5.42 5.55

Table 7: Contd..

2i	87	69-70	$C_9H_{10}O_3S$ (198.2)	54.54 54.71	5.05 5.06
2j	88	56	$C_9H_{10}O_2S_2$ (214.3)	50.46 50.38	4.67 4.81
23a	87	49	$C_{12}H_{12}O_2S$ (220.3)	65.45 65.38	5.45 5.17
23b	88	65	$C_{13}H_{14}O_2S$ (234.3)	66.66 66.39	5.98 5.87
23c	91	Liquid	$C_{14}H_{16}O_2S$ (248.3)	67.74 67.54	6.45 6.42
23d	89	82	$C_{14}H_{16}O_3S$ (264.3)	63.63 63.38	6.06 6.31
26	93	88	$C_{13}H_{14}O_2S_2$ (266.4)	58.64 58.50	5.26 5.41

Crystallisation solvent chloroform/hexane

Table 8: Physical and analytical data of the alkoxy pyridones 28a-f, 29a, 29b and 30:

Product	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
28a	81	275	$C_{13}H_{10}N_2O_2$ (226.2)		69.02 68.88	4.42 4.33	12.39 12.31
28b	74	270	$C_{14}H_{12}N_2O_2$ (240.3)		70.00 70.11	5.00 5.16	11.66 11.47
28c	82	250	$C_{15}H_{14}N_2O_2$ (254.3)		70.87 70.89	5.51 5.41	11.02 10.88
28d	83	250	$C_{14}H_{12}N_2O_3$ (256.3)		65.62 65.49	4.69 4.71	10.93 10.78
28e	78	274	$C_{13}H_9ClN_2O_2$ (260.7)		59.88 59.67	3.45 3.61	10.74 10.83
28f	80	266	$C_{13}H_8Cl_2N_2O_2$ (295.1)		52.88 52.66	2.71 2.94	9.49 9.36
29a	68	245	$C_{15}H_{12}N_2O_2$ (252.3)		71.42 71.70	4.76 4.82	11.11 10.97
29b	61	272	$C_{16}H_{14}N_2O_2$ (266.3)		72.18 72.40	5.26 5.41	10.52 10.47

Table 8: Contd...

30	76	255	$C_{15}H_{12}N_2O_2S$ (284.3)	63.38 63.39	4.22 4.12	9.85 9.66

Crystallisation solvent acetic acid/water

Table 9: Physical and analytical data of the alkoxy isoxazoles 31a-f, 33, and 34:

Products	Yield (%)	m.p. (°C)	Molecular formula	Calc. Found	Analysis (%) C	H	N
31a	48	77	$C_{10}H_9NO_2$ (175.2)		68.57 68.78	5.14 4.93	8.00 7.84
31b	46	72	$C_{11}H_{11}NO_2$ (189.2)		69.84 69.66	5.82 5.91	7.40 7.18
31c	51	80-81	$C_{11}H_{11}NO_3$ (205.2)		64.39 64.61	5.36 5.41	6.82 6.66
31d	50	78	$C_{13}H_{15}NO_3$ (233.3)		66.95 66.81	6.43 6.60	6.00 5.88
31e	53	96	$C_{10}H_8ClNO_2$ (209.6)		57.27 57.41	3.81 4.03	6.68 6.81
31f	41	128-129	$C_{14}H_{11}NO_2$ (225.2)		74.66 74.58	4.88 5.01	6.22 6.39
33	40	84	$C_{13}H_{13}NO_2$ (215.2)		72.55 72.62	6.04 6.12	6.51 6.43
34	46	135-136	$C_{12}H_{11}NO_2S$ (233.3)		61.80 61.58	4.72 4.58	6.00 6.21

Crystallisation solvent chloroform/hexane

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Table 4: Contd..

28f	2250, 1660, 1617, 1500	4.23(s,3H,$OC\underline{H}_3$); 6.83(s,1H,$\underline{H}$-5); 7.50 (s,$2H_{arom}$); 7.78(s,$1H_{arom}$)[b]	
29a	2248, 1640, 1560, 1441	2.79-3.13(m,4H,$-CH_2-$); 4.61(s,3H,$OC\underline{H}_3$); 7.13-7.64(m,$3H_{arom}$); 7.76-8.00(m,$1H_{arom}$)[b]	252(100%)
29b	2210, 1640, 1548, 1500, 1428	1.60(t,J=7Hz,3H,$C\underline{H}_3$); 2.73-3.13(m,4H,$-CH_2-$); 4.90(q,J=7Hz,2H,$OC\underline{H}_2CH_3$); 7.16-7.50(m, $3H_{arom}$); 7.62-7.90(m,$1H_{arom}$)[b]	266(72%)
30	2208, 1635, 1464	3.20-3.78(m,4H,$-CH_2-$); 4.57(s,3H,$OC\underline{H}_3$); 7.46-7.97(m,$4H_{arom}$)	

[a] in DMSO-d_6 [b] in TFA/$CDCl_3$