NEWER SYNTHETIC METHODS FOR NOVEL HETEROCYCLES VIA OXOKETENE- S,S-, S,N- AND N,N-ACETALS

ABSTRACT

By

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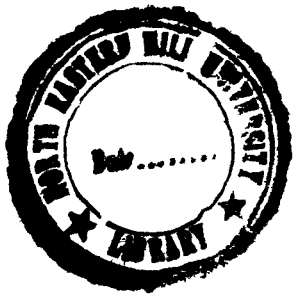

A THESIS
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To

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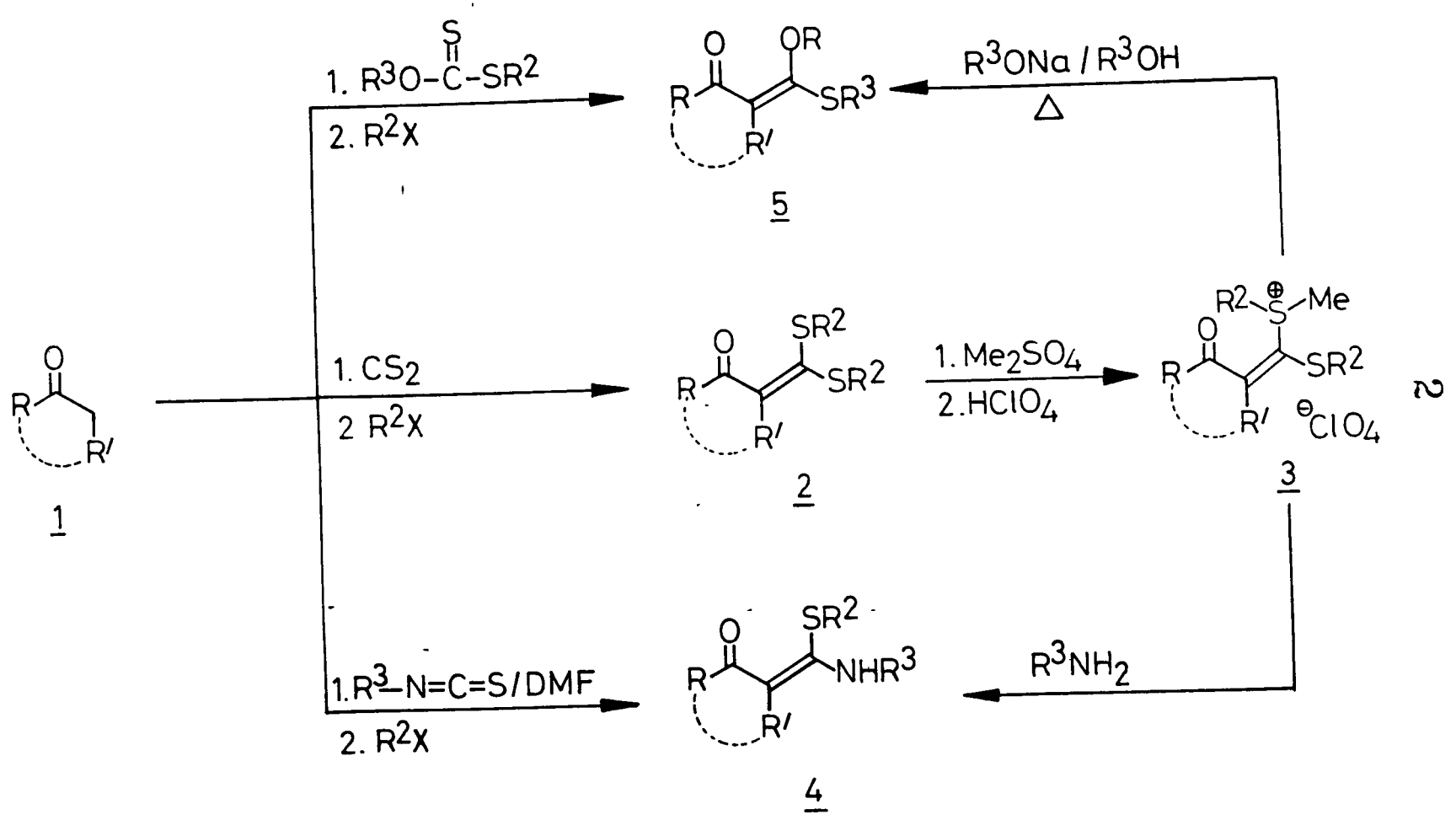
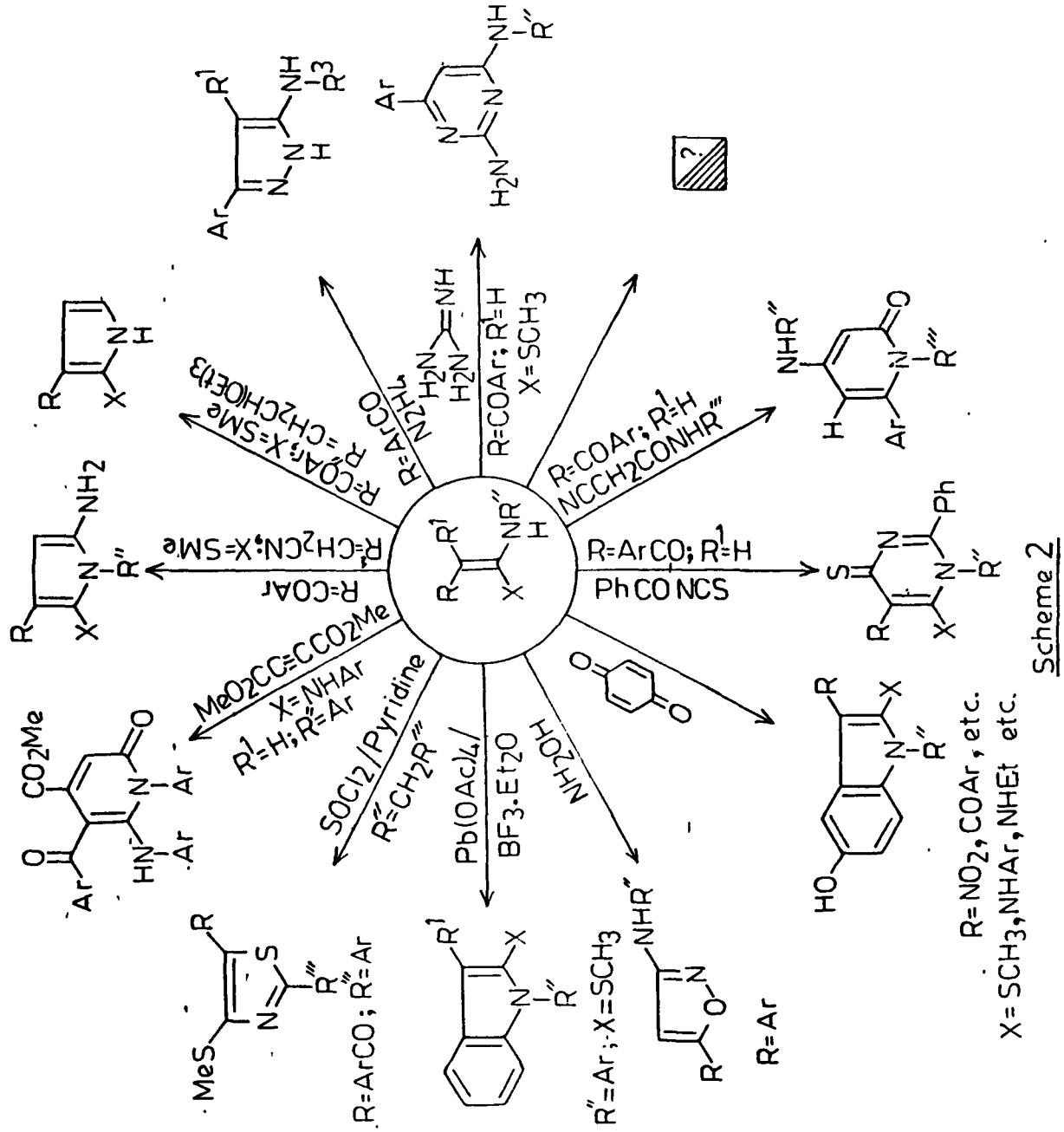
Chem

The synthesis of α-oxoketene dithioacetals of the general formula 2 were first reported in 1910 by Kelber and co-workers[1]. A number of these compounds have been subsequently prepared by reacting active methylene ketones with carbondisulphide, in the presence of suitable base followed by alkylation (Scheme 1). Many experimental variations of this method have been developed[2-4] in order to improve the yields of dithioacetals 2 evolving the overall process to a one pot transformation. It is therefore now possible to prepare large structural variants of 2 from widely occuring active methylene ketones. They can also be converted into the corresponding S,N-4[5] and O,S-5[6] acetals, although there are direct methods for the synthesis of S,N-acetals 4 from active methylene compounds 1 (Scheme 1)[7]. The α-oxoketene S,N-acetals are also shown to be useful three carbon precursors for amino heterocycles, when they are reacted with bifunctional nucleophiles[8]. Their usefulness as novel functionalized enaminones has been manifested in their reactions with several electrophilic species like activated double bands, thionyl chloride, nitrosyl chloride etc., to give a number of novel five and six membered heterocycles[8]. Some of the most important transformations achieved in this laboratory have been formulated in Scheme 2 . These methods have been shown to be general for the construction of the corresponding heterocycles with liberal structural variations. These representative transformations manifest immense synthetic potential of S,N and N,N-acetals to construct heterocycles and their further application in this area

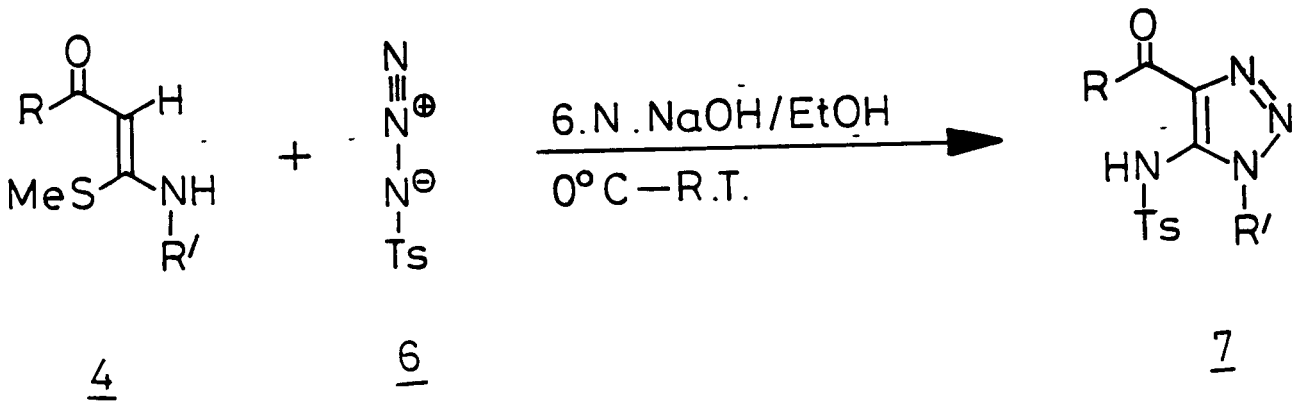

1. $R^3O-C(=S)-SR^2$
2. R^2X
1. CS_2
2 R^2X
1. $R^3-N=C=S$/DMF
2. R^2X
R^3ONa / R^3OH
Δ
1. Me_2SO_4
2. $HClO_4$
R^3NH_2
1
2
3
4
5

Scheme 1

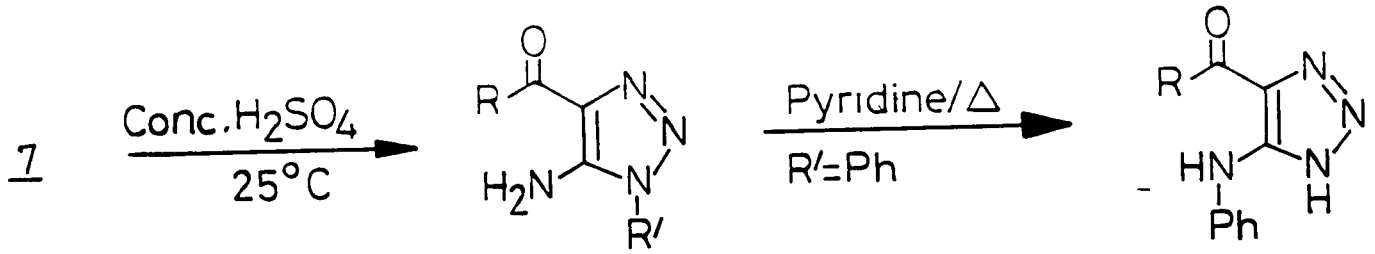

R=ArCO; R¹=H
PhCONCS
R=COAr
R=CH2CN; X=SMe
MeO2CC≡CCO2Me
X=NHAr
R¹=H; R=Ar
SOCl2/Pyridine
R‴=CH2R‴
Pb(OAc)4/
BF3.Et2O
NH2OH
R=ArCO; R=Ar
R″=Ar; X=SCH3
R=Ar
R=NO2, COAr, etc.
X=SCH3, NHAr, NHEt etc.
R=COAr; R¹=H
NCCH2CONHR‴
R=COAr; R¹=H
X=SCH3
R=ArCO
R=COAr; R¹=H
X=SMe
=CH2CH(OEt)2

Scheme 2

is still an ongoing research activity in this laboratory. In continuation of these studies and as a part of the research on polarized ketene S,S-, S,N- and N,N- acetals, it was proposed to study further applications of these synthons for the synthesis of novel heterocycles. Thus, the [3+2] cycloaddition of α-oxoketene S,N-acetal 4 with tosyl azide 6 under alkaline conditions affords a novel regiospecifically substituted 5-tosylamino 1H-1,2,3-triazoles 7 in high yields (Scheme 3)[9]. These 5-tosylamino triazoles 7 are shown to undergo facile detosylation in the presence of concentrated sulphuric acid to give the corresponding 5-amino triazole 8 in excellent yields. The amino triazoles 8 further underwent Dimroth rearrangement in the presence of refluxing pyridine to give the corresponding 5-anilino-1H-1,2,3-triazoles 9 in good yields (Scheme 3)[9]. Similarly the α-oxoketene N,N-acetals 10 have been shown to undergo [3+2] cycloaddition with tosylazide 6 in hot dioxane to yield the corresponding 5-alkyl/aryl-amino 1H-1,2,3-triazoles 11 in excellent yields (Scheme 4)[10]. The cyclic S,N-(X=S) and N,N-(X=NH) acetals 12 did react under identical reaction conditions with tosyl azide 6 to yield the corresponding bicyclic 3-aroyl-5,6-dihydrothiazolo [3,2-c] [1,2,3]-triazoles 13 in good yields (Scheme 4)[9,10]. The α-oxoketene dithioacetals 2 failed to undergo cycloaddition with tosylazide. However, when 2 were reacted with sodium azide 14 in hot dimethylsulfoxide the corresponding 5-methylthio-1H-1,2,3-triazoles 15 were obtained in good yields (Scheme 5)[11]. It is apparent that the method for the synthesis of triazoles is highly versatile, since a large number

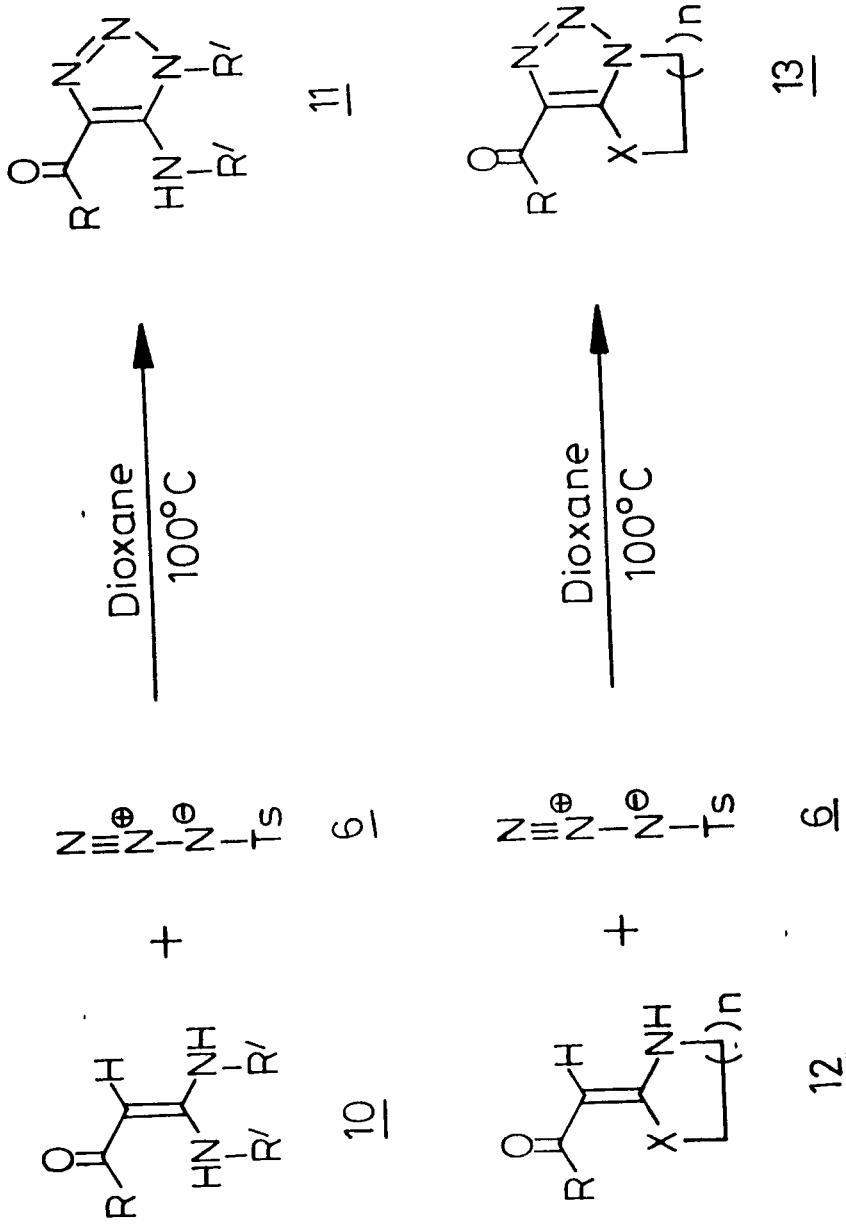


4 6 7

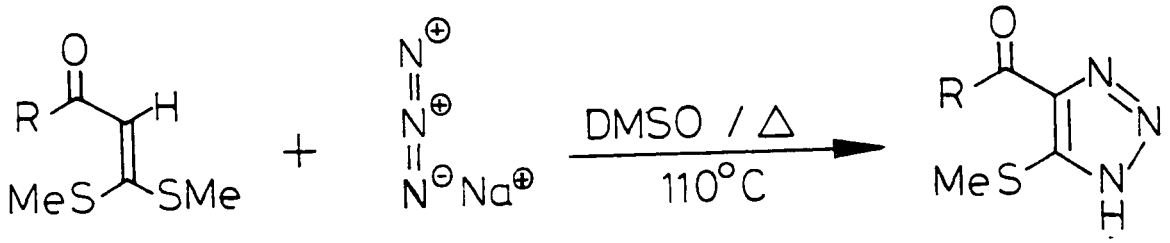


8 9

Scheme 3



Scheme 4



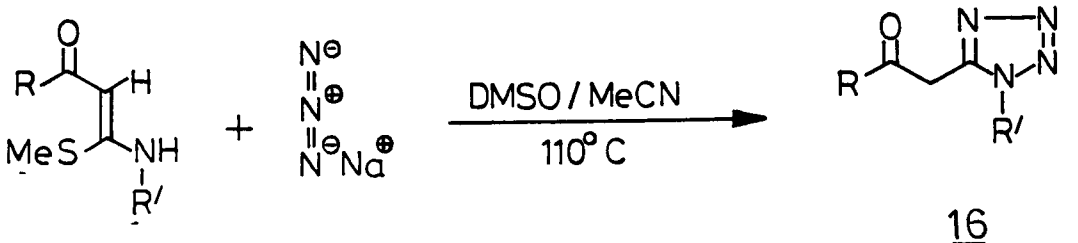
2 14 15

Scheme 5

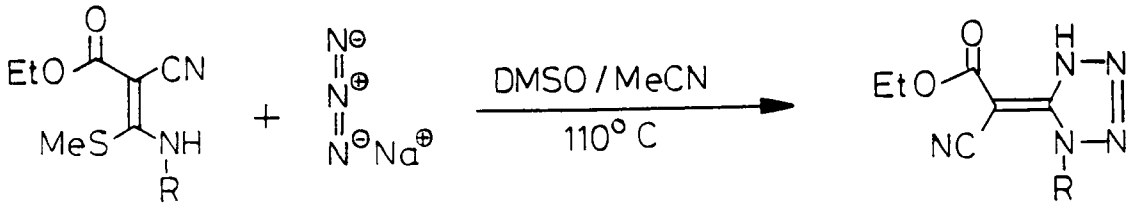
of active methylene ketones can play as primary precursors through the corresponding S,N-acetals. Interestingly, the S,N-acetals 4 did react with sodiumazide 14 through different pathway involving cyclization of initially formed imidoylazide intermediates to give a novel 1,5-substituted tetrazoles 16 instead of the corresponding 5-amino triazoles (Scheme 6)[11]. The method has been extended to many structural variants of S,N-acetals 17 to study the reactivity towards sodiumazide 14. The exception was the S,N-acetal 19 derived from malononitrile, which gave the tetrazole 20 formed by cycloaddition of the azide ion with one of the nitrile groups (Scheme 6)[11]. The scope and limitations of the tetazole synthesis have been critically discussed in Chapter II.

The α-oxoketene S,N-acetals 4 have been reacted with one equivalent of malonyl chloride 21 in the presence of a base to give novel 1,5-substituted 4-hydroxy-6-methylthio-2(1H) pyridones 22 in good yields (Scheme 7)[12]. However, in the presence of excess of malonyl chloride 21 (3 equivalent) the reaction proceeds further to give the corresponding pyrano[3,2-c] pyridones 23 in moderate yields (Scheme 7)[12]. The synthetic approach described for 22 and 23 is one of the simplest routes as compared to the reported methods. The scope and limitations of the methods are discussed in Chapter III.

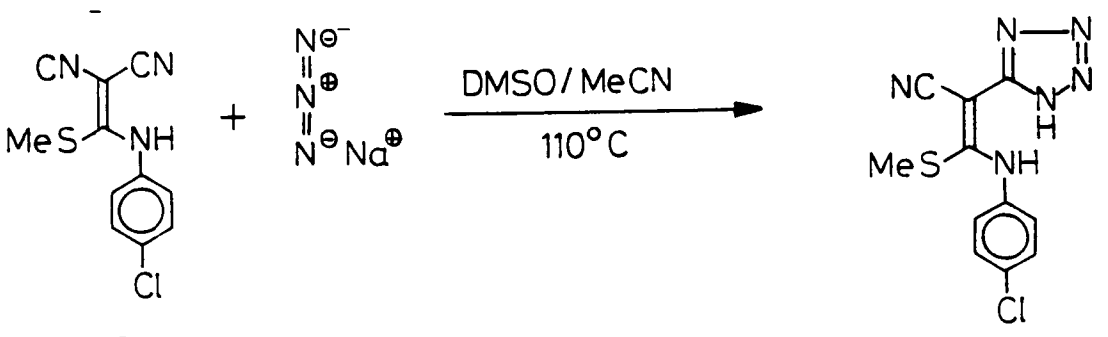
The hydroxyiminoimines 24 were reacted with hydrazine hydrate with a view to develop a new methodology for the 4,5-diaminopyrazoles. Thus, when hydroxyiminoimines 24 reacted with one equivalent of hydrazine hydrate at room temperature, afforded a corresponding 4-nitroso-3(5)-



4 14 16

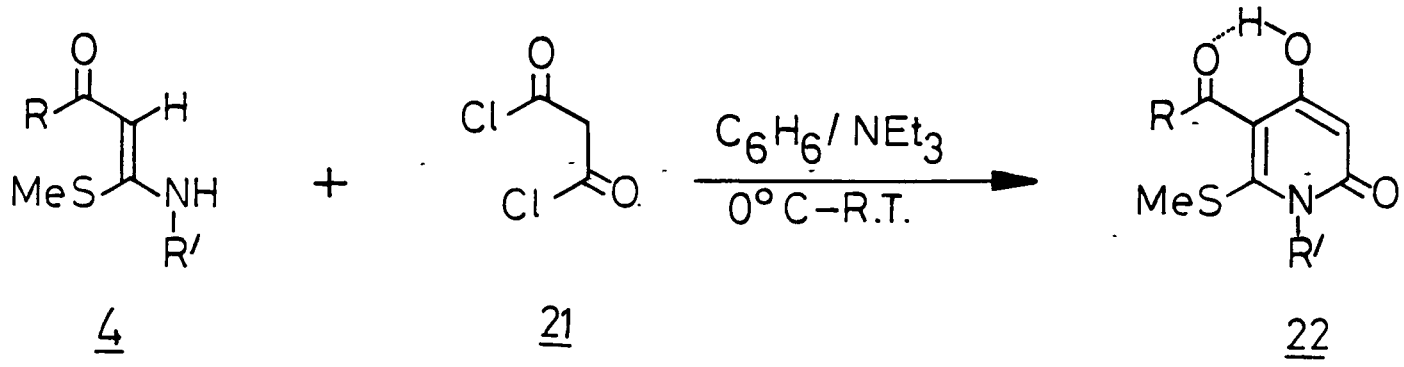


17 25 18

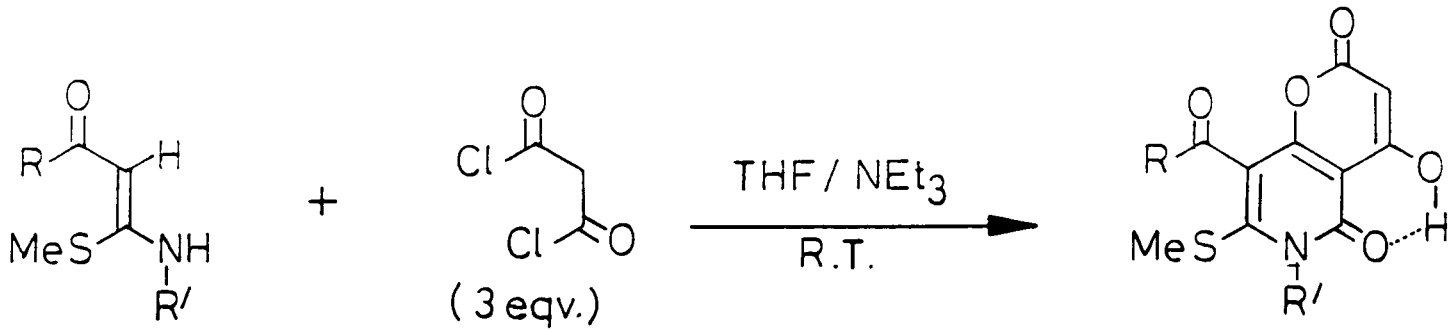


19 25 20

Scheme 6



4 21 22

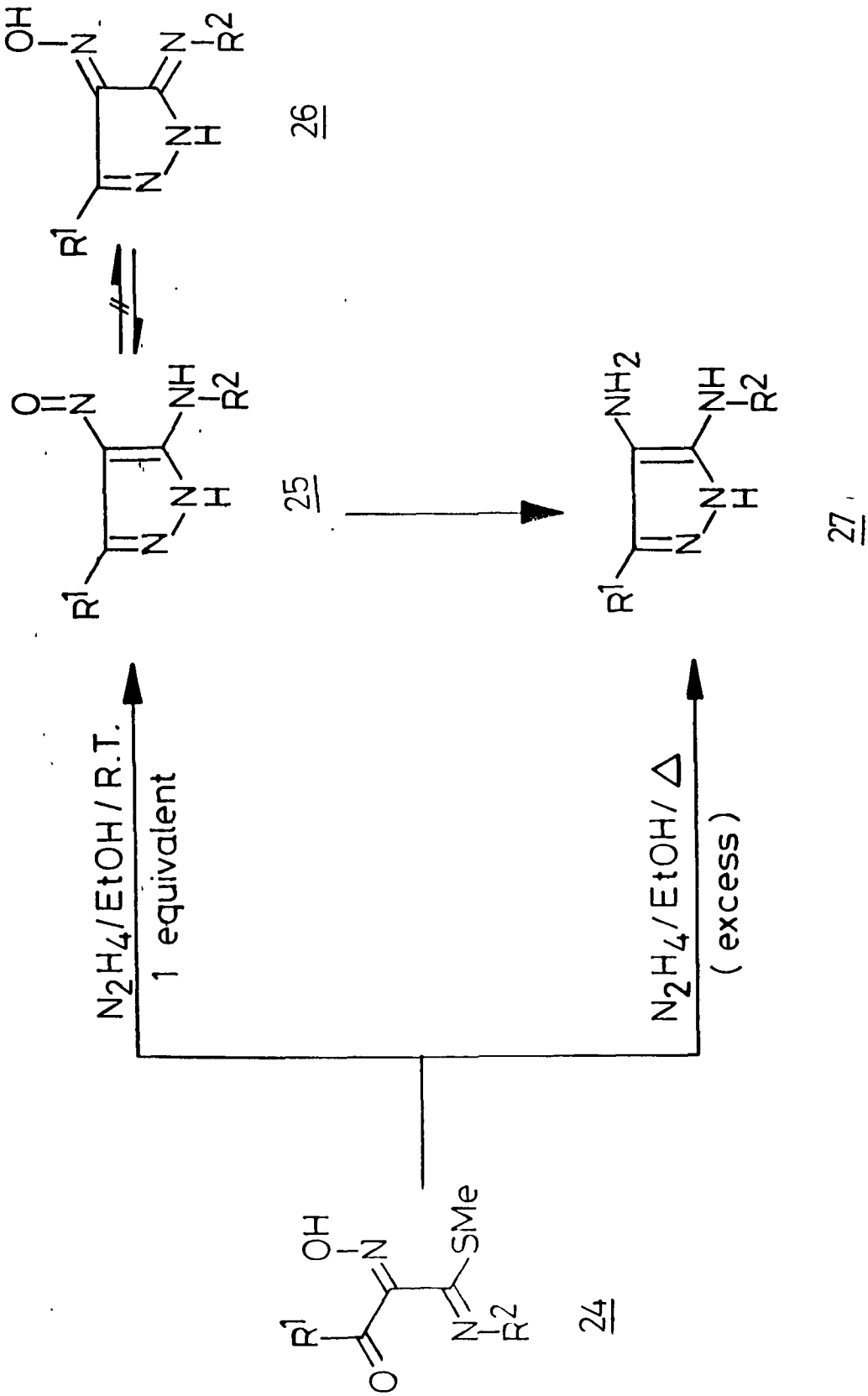


4 (3 eqv.) 21 23

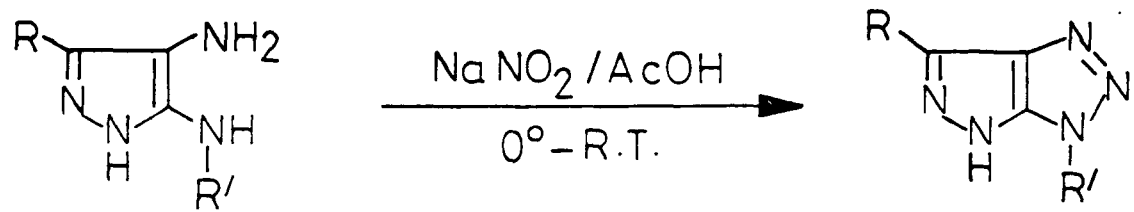
Scheme 7

aryl 5(3)-alkyl/aryl aminopyrazoles 25 in excellent yields (Scheme 8)[13]. However, when excess of hydrazine hydrate was used the 4-nitroso group was reduced to the corresponding amino group and diamino pyrazole 27 were formed in quantitative yields (Scheme 8)[13], which are of synthetic value for the construction of fused heterocycles. Thus, 27 underwent diazotization to yield the intermediate diazo compound which underwent intramolecular ring closure to yield the triazolo[3,4-d] pyrazoles 28 (Scheme 9)[13]. The generality and the scope of the present method is discussed in Chapter IV.

When α-oxoketene dithioacetals 2 were reacted with sodium cyanoborohydride in the presence of boiling acetic acid, underwent facile 1,4-reduction followed by elimination of methylthio group to yield the desired vinylogous thiolesters 29 in good yields (Scheme 10)[14]. The importance of these compounds 29 in organic synthesis, the generality and the scope of the present method is discussed in the Chapter V.

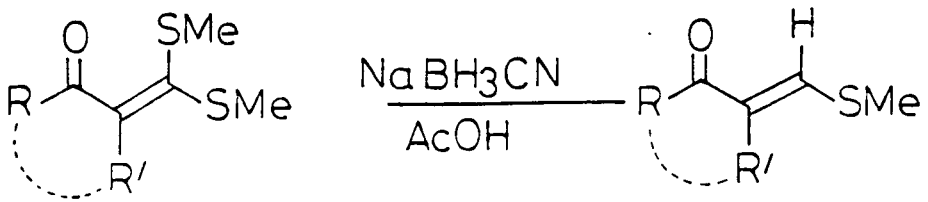


Scheme 8



27 28

Scheme 9



2 29

Scheme 10

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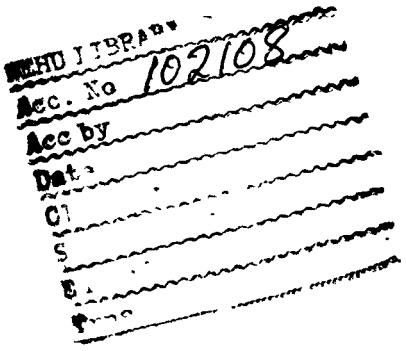

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Thesis

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Professor H. Junjappa
Department of Chemistry

CERTIFICATE

This is to certify that the work described in this thesis has been carried out by Mr. R.T. Chakrasali under my supervision. He has satisfactorily completed the pre-Ph.D. course prescribed and the 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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Head
Department of Chemistry

This is to certify that Mr. R.T. Chakrasali, 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 - 624	Pericyclic reactions
2. Chem - 630	Biosynthesis and Natural Product Chemistry
3. Chem - 631	Medicinal Chemistry
4. SPS - 601	French Language

Head
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I further extend my thanks to Regional Sophisticated Instrumentation Centres at Central Drug Research Institute, Lucknow and North-Eastern Hill University, Shillong for providing the spectral and analytical data of the compounds described in this thesis. Also quite a few spectral and analytical data were obtained from Dr. S. Apparao, Department of Chemistry and Biochemistry, Utah State University, U.S.A. and Dr. A. Rahman, Department of Chemistry, Medizinschem University, Lubeck, West Germany for which I remain grateful. Financial assistance from Department of Science and Technology, New Delhi, is also acknowledged.

I also wish to express my gratitude to my Colleagues, Dr. S. Apparao, Dr. B. Myrboh, Dr. S.S. Bhattacharjee, Dr. A. Rahman, Dr. J.N. Vishwakarma, Dr G. Singh, Dr. L. Warjeet Singh, Dr. Apurba Dutta, Dr. C.V. Asokan, Mr. M.L. Purkayastha, Mr. A. Thomas, Mr. Akhilesh Gupta, Mr. M.P. Balu, Mr. Arun K. Gupta, Miss D. Pooranchand, Mr. B. Deb, Miss Susmita Bhattacharjee, Mrs. M. Chakraborty, Mrs. Nisha Jain,

Mr. Md. Mofizuddin, Ch. Srinivasa Rao, Mr. Laxminarayan Bhat, Mr. M. Chandrasekharam and Mr. Balaram Patro, Mr. Satyanarayan, Mr. K. Raghav Reddy and Mr. K. Mallaih for their cooperation and help. I am also grateful to Mrs. Rajamma K. for her excellent typing of this thesis.

Finally, I would like to express my sincere gratitude to my parents, Uncle and Aunt for their support, patience and encouragement.

Chakrasali 3rd April 89.

R.T. CHAKRASALI

C O N T E N T S

PREFACE

The work described in this thesis is part of an on going research programme in our laboratory since the last ten years. It is aimed at developing newer synthetic methods for both heterocyclic and carbocyclic compounds utilizing polarized ketene dithioacetals as synthetic intermediates. The versatality of these intermediates which are easily available in one pot reaction from any kind of active methylene compounds for the synthesis of heterocyclic and carbocyclic compounds has been already established in the earlier works. In the present investigation, a systematic study was undertaken to further explore the α-oxoketene S,N-acetals as novel functionalized enaminones and useful three carbon fragments for the construction of a variety of important heterocyclic ring systems. These studies have evolved into the new general methods for the synthesis of novel triazoles, tetrazoles, pyridones, amino and nitroso pyrazoles, pyrazolo [3,4-d] 1,2,3-triazoles and methylthioalkenyl ketone derivatives.

In the first Chapter a brief survey of the various synthetic transformations using α-oxoketene S,S-, S,N- and N,N-acetals, achieved in this laboratory, is described.

The reactions of α-oxoketene S,S-, S,N- and N,N-acetals with sodium azide and tosylazide are discussed in Chapter II. The reaction affords a novel class of triazole, tetrazole, thiazolotriazole and imidazolotriazole derivatives. The generality and synthetic limitations of these methods and mechanism of the transformations are discussed.

In the next Chapter (III) a new general method for the synthesis of 1,5-substituted 4-hydroxy-6-methylthio-2(1H)-pyridones and 6,8-substituted 4-hydroxy-7-methylthio-2,5-doxo-5,6-dihydro-2H-pyrano [3,2-c] pyridines have been developed by cyclocondensation of α-oxoketene S,N-acetals with malonylchloride.

The reactions of α-oxoketene S,N-acetals with nitrosyl chloride are discussed in Chapter IV. The reaction affords a novel class of open chain functionalized hydroxy iminomine intermediates in excellent yields, which are shown to be efficient three carbon fragments for the synthesis of novel 3(5)-aryl-4-nitroso 5(3)-aryl/alkylamino pyrazoles and 3(5)-aryl-4-amino 5(3)-aryl/alkylamino pyrazoles and their further transformations to yield pyrazolo [3,4-d] 1,2,3-triazoles.

In the last Chapter, a new general method for the synthesis of alkylthiomethylene ketones by reductive dimethylthiolation of α-oxoketene dithioacetals with sodium cyanoborohydride is described. The method is general and can be extended for the synthesis of a number of alkylthiomethylene ketones with wide structural variations.

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

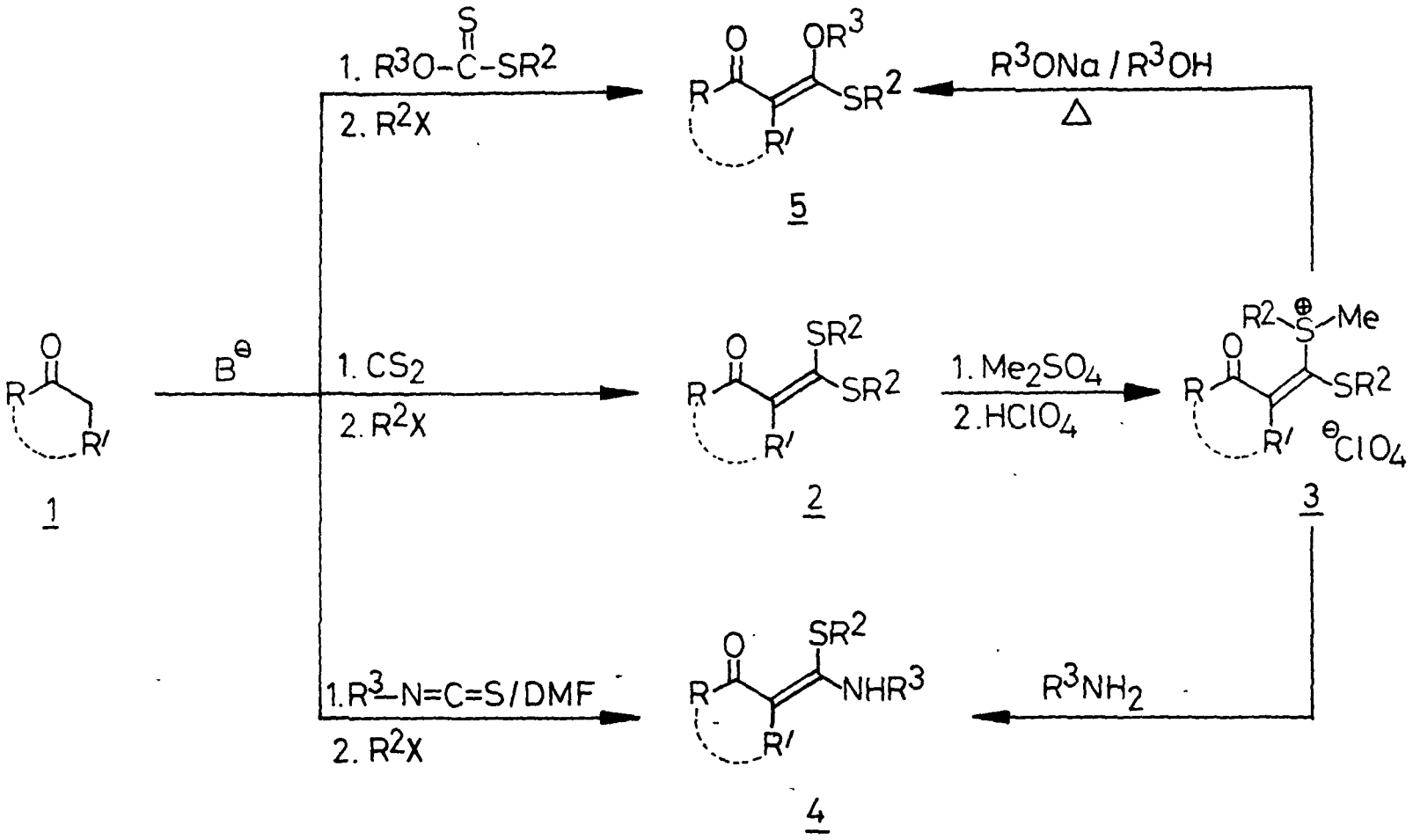
CHAPTER I

INTRODUCTION

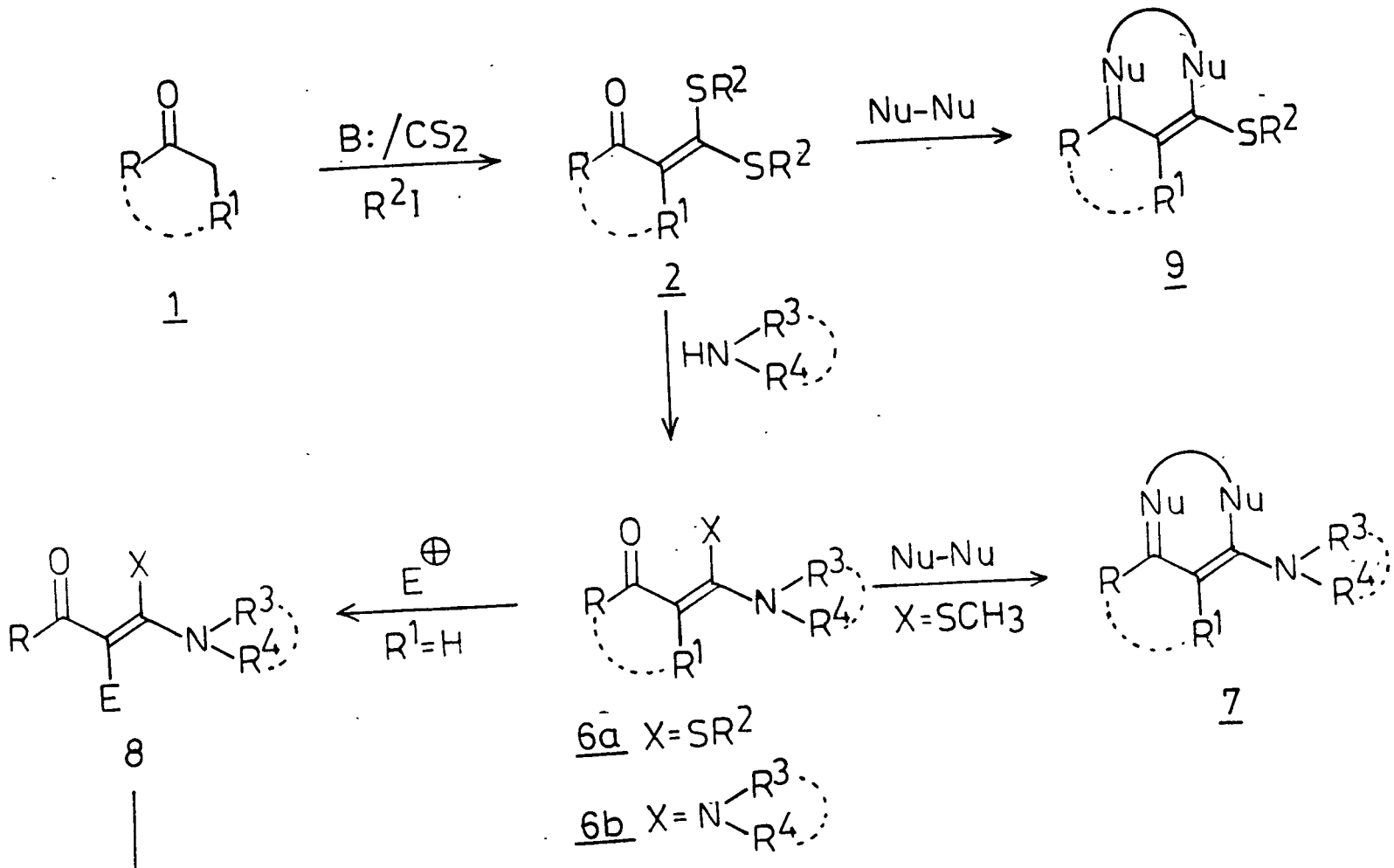
During the last ten years, the α-oxoketene dithioacetals 2[1] have emerged as verstile 1,3-electrophilic three carbon synthons, used in the synthesis of a variety of heterocyclic and carbocyclic compounds. They are among the simplest synthetic intermediates which can be easily prepared[2-9] in one pot reaction, by treating structurally diverse active methylene ketones 1 with two equivalents of base in the presence of carbon disulphide followed by alkylation (Scheme 1). The dithioacetals 2 thus formed exhibit well defined physical properties and can be purified by conventional purification methods. They are stable at room temperature, and can withstand mild acidic and alkaline conditions and can be stored indefinitely without apparent decomposition (Scheme 1). The S,N-acetals 4 can also be prepared[10]

directly in one pot reaction by reacting the enolate anion of 1 with appropriate isothiocyanates followed by alkylation in good to excellent yields (Scheme 1). The corresponding O,S-acetals of the general formula 5 can also be prepared[11] similarly, by reacting the enolate anion of 1 with alkyl xanthates followed by alkylation in good yields (Scheme 1). Alternatively the α-oxoketene dithioacetals 2 can be quaternized to yield the corresponding sulfonium salt 3[12] thereby, activating the methylthio group which can be displaced under very mild conditions either by amines, to yield the corresponding S,N-acetals 4[13] or by oxygen nucleophiles to afford the O,S-ketene acetals 5 (Scheme 1)[12,13].

The α-oxoketene dithioacetals 2 have been extensively explored in this laboratory for the synthesis of a number of five and six membered heterocycles[14-22] by reacting them with bifunctional nucleophiles like guanidine, hydrazine hydrate, hydroxylamine and cyanoacetamide anion etc. Further displacement of alkylthio groups by one or two equivalents of primary or secondary alkyl/aryl amines, yield the corresponding α-oxoketene S,N-6a[23] and N,N-acetals 6b[24], which are also proved to be useful intermediates, for the construction of a variety of heterocyclic ring systems (Scheme 2). The α-oxoketene S,N-acetals are also shown to be useful three carbon precursors for aminoheterocycles[10,25,26] when they are reacted with bifunctional nucleophiles. Their usefulness as novel functionalized enaminones has been manifested in their reactions with several electrophilic species like activated double bonds, heteromultiple bonds, thionyl chloride, nitrosyl chloride and nitrosobenzene to give a number of novel five and six membered heterocycles[27-38] (Scheme 2). All these reactions have been discussed in a recent review[39].


1. R3O-C(=S)-SR2
2. R2X
R3ONa / R3OH
Δ
B⊖
1. CS2
2. R2X
1. Me2SO4
2. HClO4
1. R3-N=C=S / DMF
2. R2X
R3NH2
⊖ClO4
1
2
3
4
5

Scheme 1

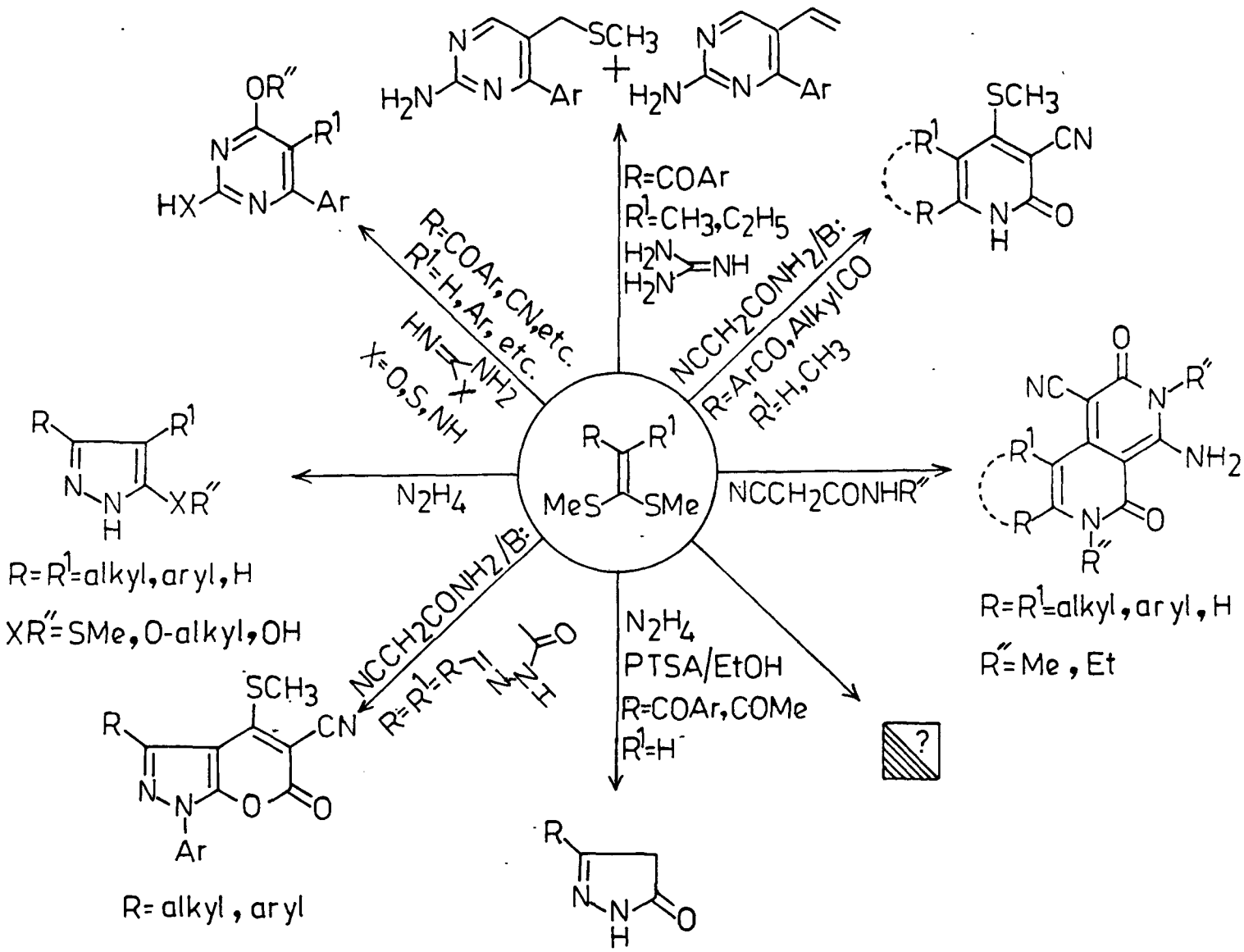

B:/CS2
R21
Nu-Nu
1
2
9
HN
R3
R4
E⊕
R1=H
6a X=SR2
6b X=N
Nu-Nu
X=SCH3
7
8
Heterocycles

Scheme 2

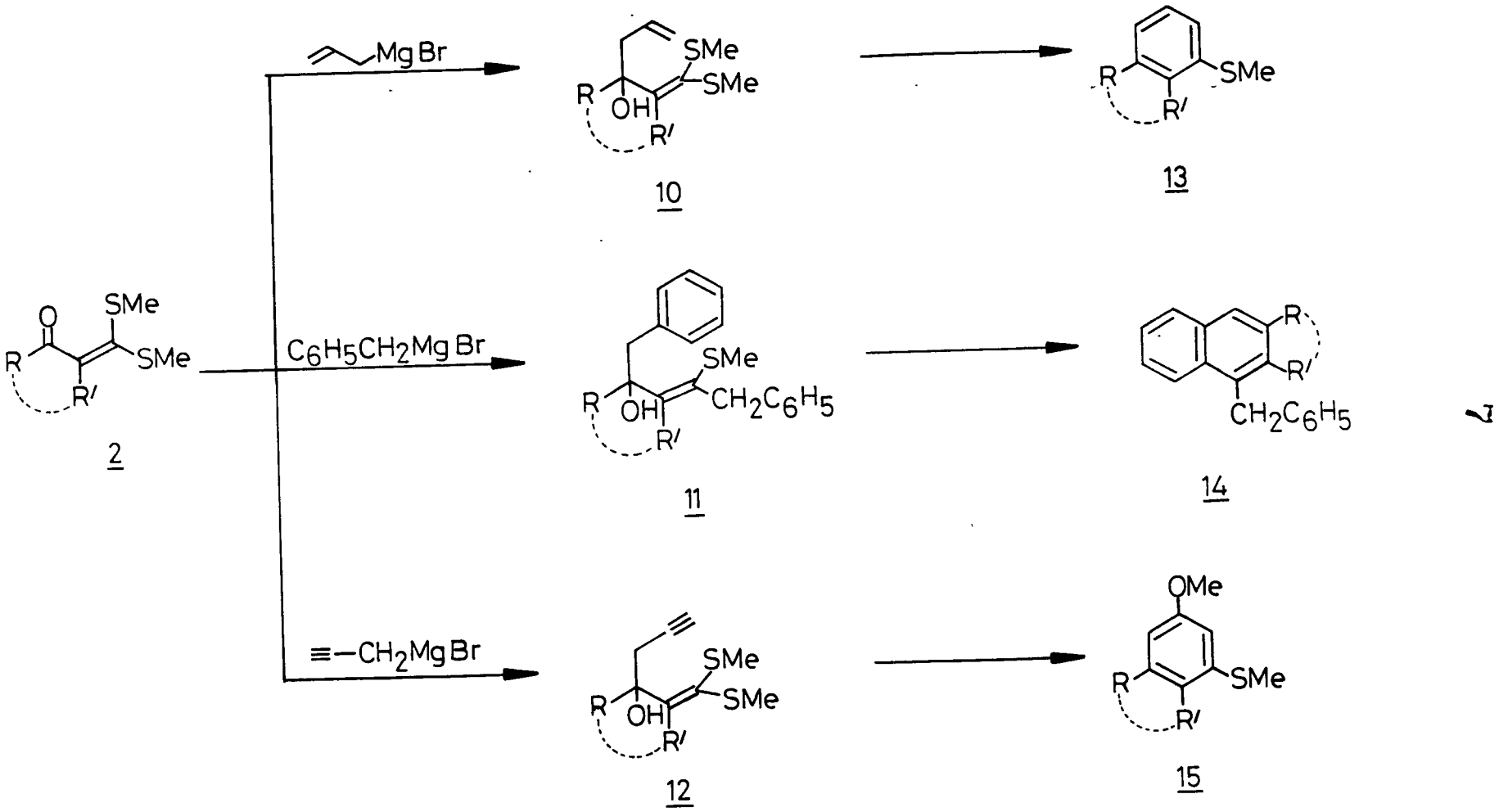
A few of the important synthetic applications of α-oxoketene dithioacetals 2 for the construction of a variety of heterocyclic compounds which are developed in our laboratory are shown in the Scheme 3. The methods thus developed have been shown to be of general synthetic importance, since the choice of the structural varients of active methylene compounds are quite large. The α-oxoketene dithioacetals have also been proved to be attractive three carbon fragments for construction of aromatic ring in their reaction with allyl[40], benzyl[41] and propargyl[42] magnesium halides (Scheme 4). The overall reaction sequence involve either exclusive 1,2 (allyl and propargyl magnesium halides) or sequential 1,4- and 1,2-additions (benzyl magnesium chloride) of the Grignard reagent to give carbinols 10-12 followed by cyclo-aromatization in the presence of borontrifluoride etherate and benzene yielding either benzo(13) and naphthoannulated (14) products or the corresponding thioresorcinol dimethylether derivatives 15 by cyclization of 12 in the presence of BF_3. Et_2O and methanol (Scheme 4).

The S,N- and N,N-acetals derived from α-oxoketene dithioacetals 2 again proved to be synthetically useful substrates for the construction of a variety of heterocyclic rings. Some of the most important transformations achieved in this laboratory have been formulated in Scheme 5. These methods have been shown to be general for the construction of the corresponding heterocycles with liberal structural variations. The generality and the scope of these methods have been well established, choosing appropriate substrates.

The examples described above, amply demonstrate that the synthetic applications of S,S-acetals and the corresponding S,N- and N,N-acetals could further be extended to develop new synthetic methods for a number of


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

Scheme 3


SMe
O
R
SMe
R′
2
Mg Br
C6H5CH2Mg Br
≡—CH2Mg Br
SMe
SMe
R
OH
R′
10
SMe
R
OH
CH2C6H5
R′
11
SMe
R
OH
R′
12
R
SMe
R′
13
R
R′
CH2C6H5
14
OMe
R
SMe
R′
15

Scheme 4

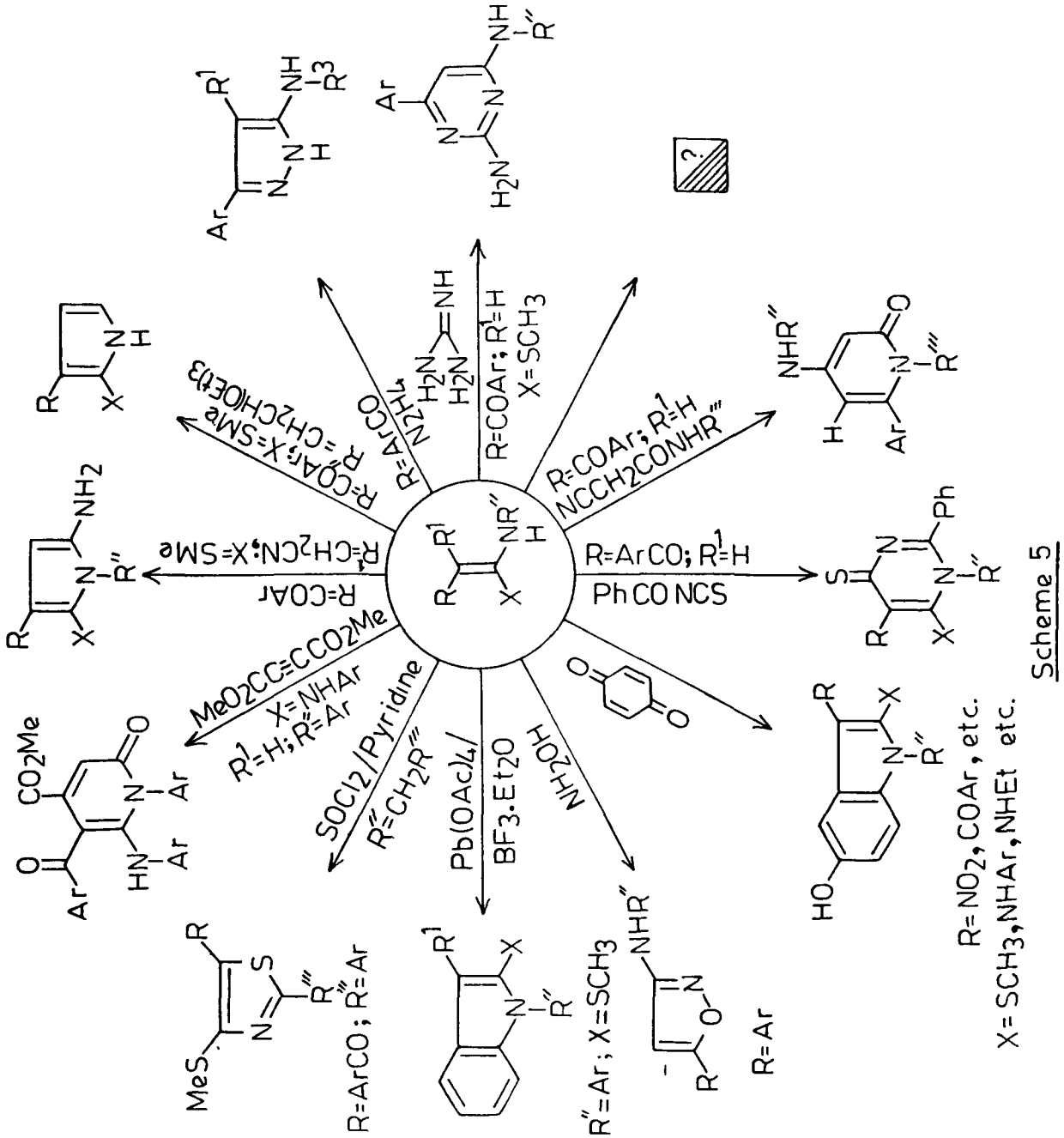
heterocycles to enhance the synthetic utility of this calss of compounds. Some of the methods developed in the present investigation have been briefly discussed.

In Chapter II a new general method for the synthesis of 1,2,3-aminotriazoles 18, 19 and 20 has been developed[43]. Thus, the [3+2] cycloaddition of α-oxoketene S,N-acetals 16 with tosylazide 17 under alkaline conditions affords a novel regiospecifically substituted 5-tosylamino-1H-1,2,3-triazoles 18 in high yields. These 5-tosylamino triazoles 18 are shown to undergo facile detosylation in the presence of concentrated sulphuric acid to give the corresponding 5-aminotriazoles 19 in excellent yields. The amino-triazoles 19 further underwent Dimroth rearrangement in the presence of refluxing pyridine to give the corresponding 5-anilino-1H-1,2,3-triazoles 20 in good yields (Scheme 6).

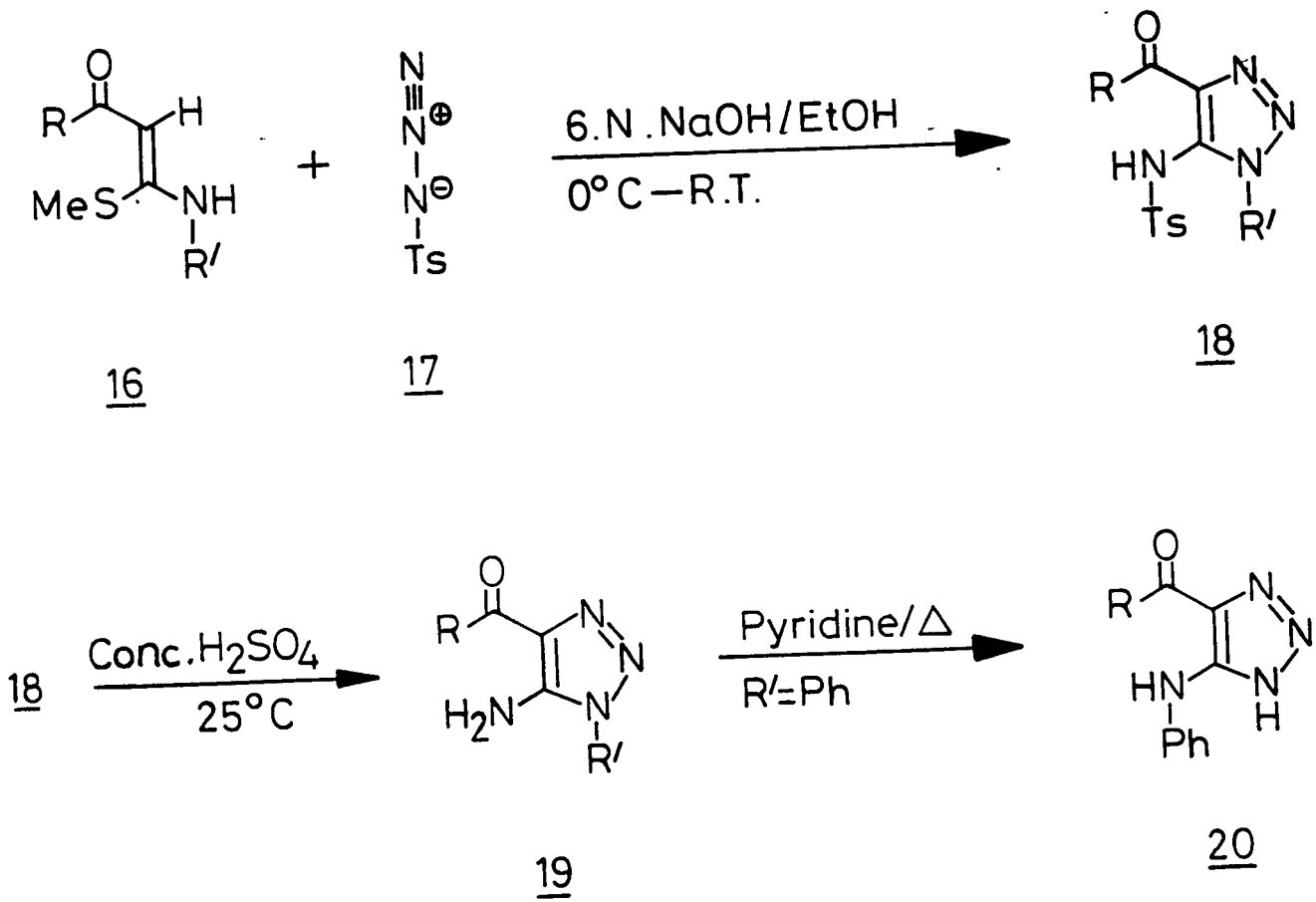
Similarly the α-oxoketene N,N-acetals 21 have been shown to undergo [3+2] cycloaddition with tosylazide 17 in hot dioxane to yield the corresponding 5-alkyl/aryl amino 1H-1,2,3-triazole 22 in excellent yields (Scheme 7)[44].

The cyclic S,N-(X=S) and N,N-(X=NH) acetals 23 did react under identical reaction conditions with tosylazide 17 to yield the corresponding bicyclic 3-aroyl-5,6-dihydro thiazolo [3,2-c] [1,2,3]-triazoles 24 in good yields (Scheme 7)[43,44].

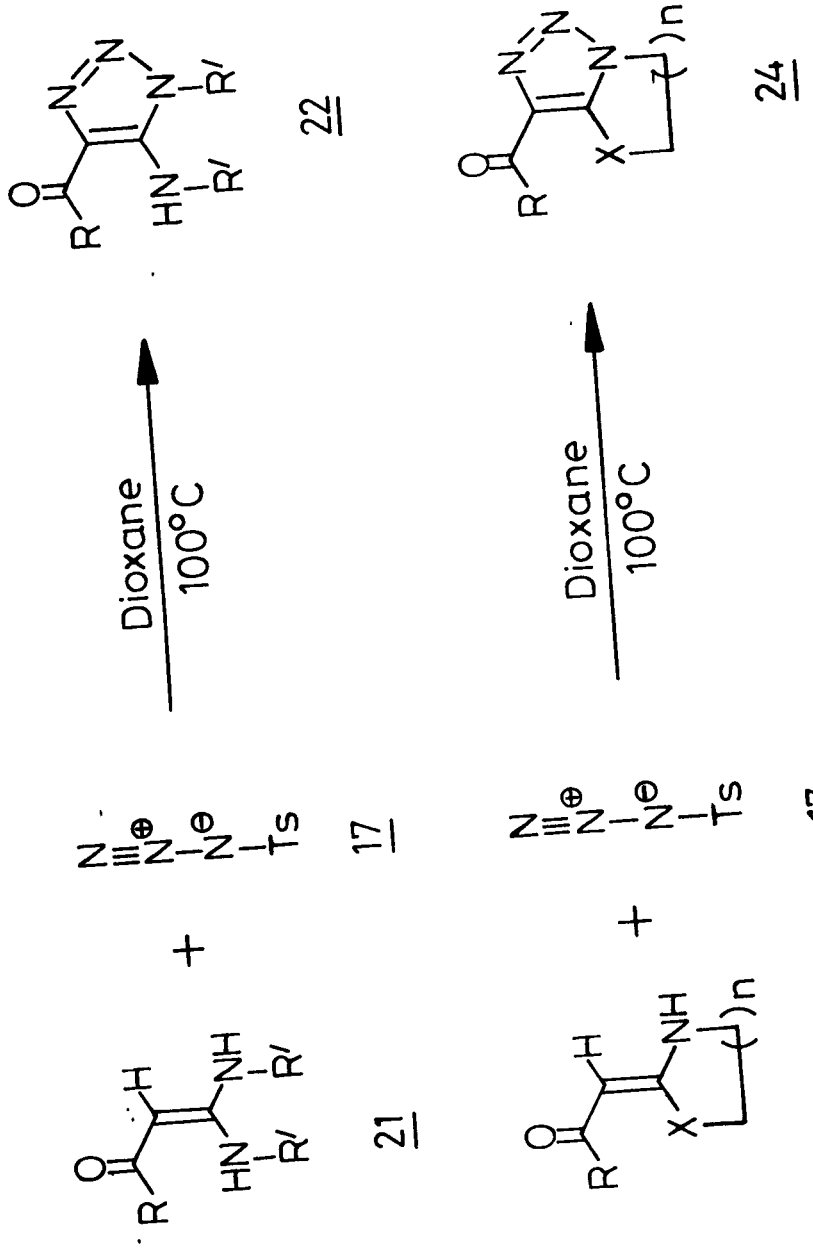
The α-oxoketene dithioacetals 2 failed to undergo cycloaddition with tosyl-azide. However, when 2 were reacted with sodium azide 25 in hot dimethyl sulfoxide the corresponding 5-methylthio-1H-1,2,3-triazoles 26 were obtained in 65-70% overall yields (Scheme 8)[45]. It is apparent that method for the synthesis of triazoles is highly versatile, since a large


R=ArCO; R¹=H
PhCONCS
R=COAr
R=ArCO; R¹=H
NCCH2CONHR‴
R=COAr; R¹=H
X=SCH3
R=ArCO
N2H4
R=COAr; X=SMe
=CH2CH(OEt)3
R=CH2CN; X=SMe
MeO2CC≡CCO2Me
X=NHAr
R¹=H; R=Ar
SOCl2/Pyridine
R‴=CH2R‴
Pb(OAc)4/
BF3.Et2O
NH2OH
R=Ar
R=NO2, COAr, etc.
X=SCH3, NHAr, NHEt etc.
R″=Ar; X=SCH3
R=ArCO; R=Ar
?

Scheme 5


R
H
MeS
NH
R′
16
+
N
N⊕
N⊖
Ts
17
6.N.NaOH/EtOH
0°C—R.T.
O
R
N
N
HN
N
Ts
R′
18
18
Conc.H2SO4
25°C
O
R
N
N
H2N
N
R′
19
Pyridine/Δ
R′=Ph
O
R
N
N
HN
N
H
Ph
20

Scheme 6



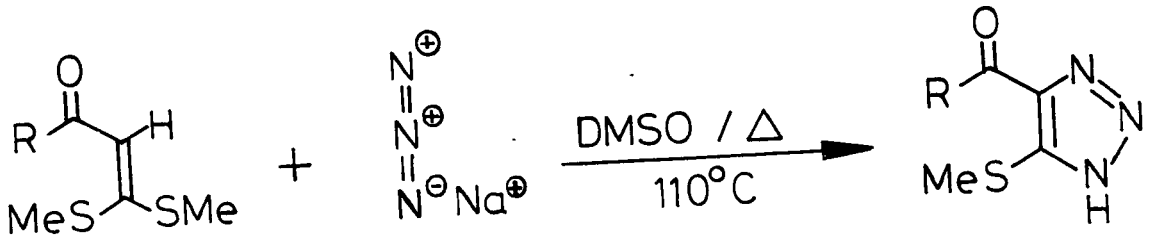
Scheme 7

number of active methylene ketones can play as primary precursors through the corresponding S,N-acetals. The Chemistry and the scope of the method has been highlighted in the Chapter II.

Interestingly, the S,N-acetals 16 did react with sodium azide 25 through different pathway involving cyclization of initially formed imidoyl azide intermediates to give a novel 1,5-disubstituted tetrazoles 27 instead of the corresponding 5-amino triazoles (Scheme 9)[45]. The method has been extended to many structural variants of S,N-acetals 28 and 30 to study the reactivity towards sodium azide 25. The exception was the S,N-acetal 30 derived from the malononitrile, which gave the tetrazole 31 formed by cycloaddition of the azide ion with one of the nitrile groups (Scheme 9)[45]. The scope and the limitations of the tetrazole synthesis have been critically discussed in Chapter II, part II.

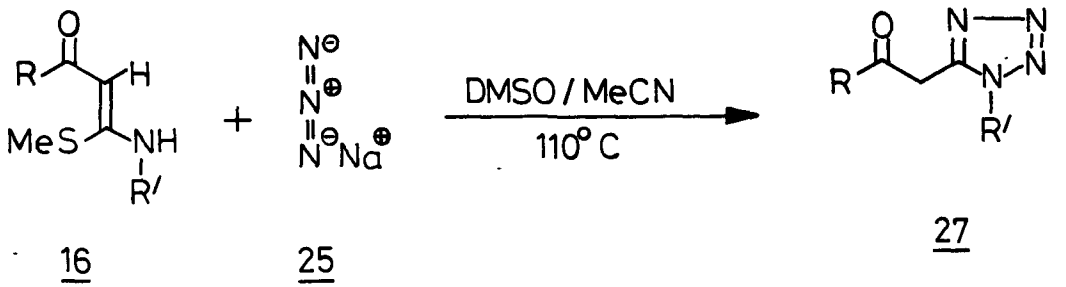
In Chapter III, the α-oxoketene S,N-acetals 16 have been reacted with one equivalent of malonyl chloride 32 in the presence of a base to give novel 1,5-substituted 4-hydroxy-6-methylthio-2(1H) pyridones 33 in good yields. However, in the presence of excess of malonyl chloride (three equivalent) the reaction proceeds further to give the corresponding pyrano [3,2-c] pyridones 34 in moderate yields (Scheme 10)[46]. The synthetic approach described for 33 and 34 is one of the simplest routes as compared to the reported methods. The scope and limitations of the methods are discussed in Chapter III.

In Chapter IV the hydroxyiminoimines 35 were reacted with hydrazine hydrate with a view to developing a new methodology for the 4,5-diaminopyrazoles. Thus, when hydroxyiminoimines 35 reacted with one equivalent of hydrazine

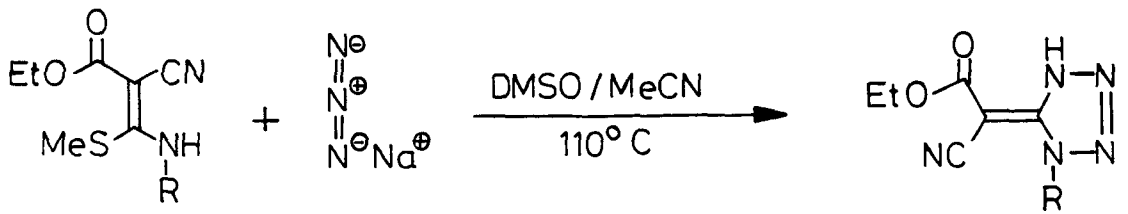


2 25 26

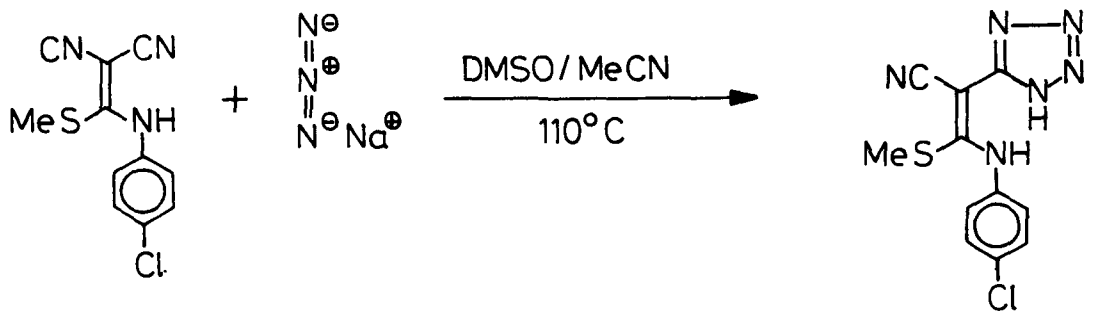
Scheme 8



16 25 27

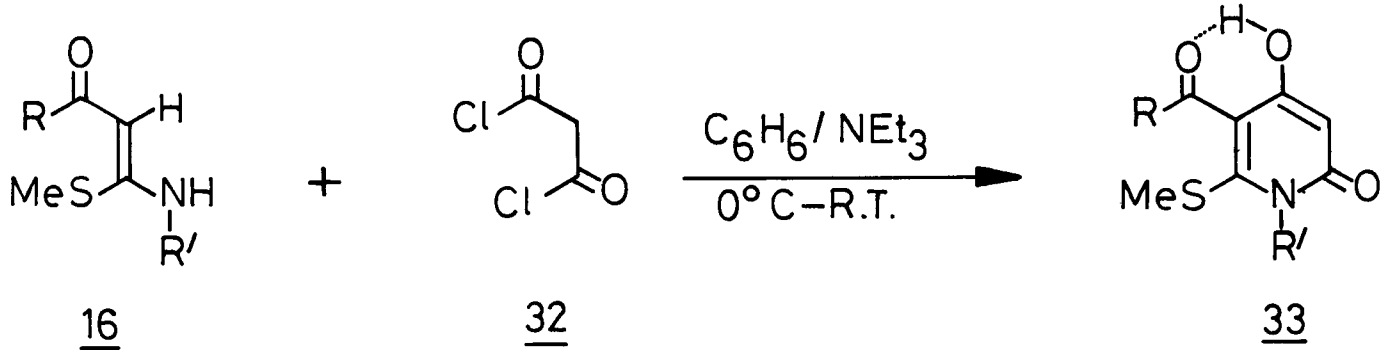


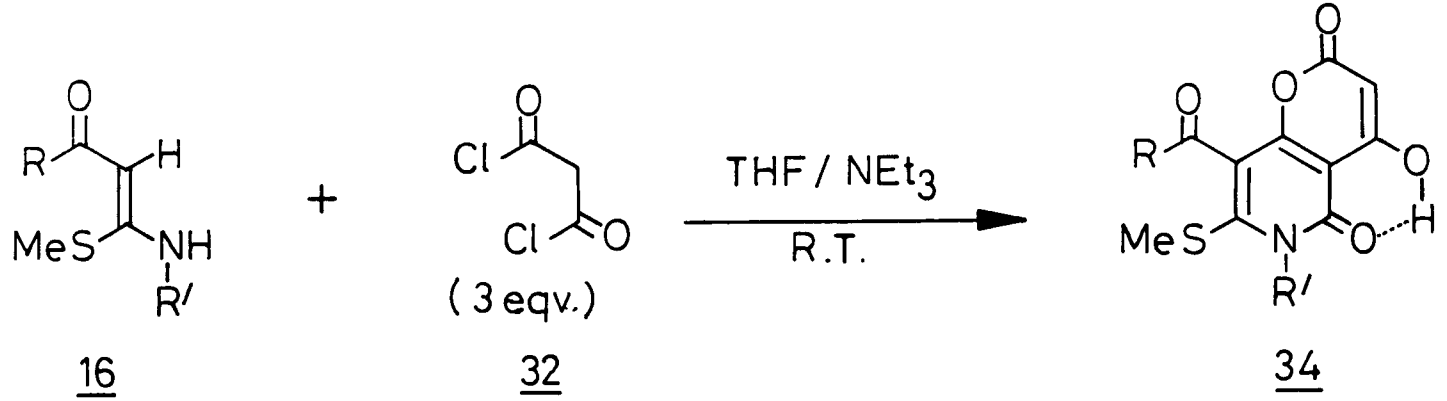
28 25 29



30 25 31

Scheme 9



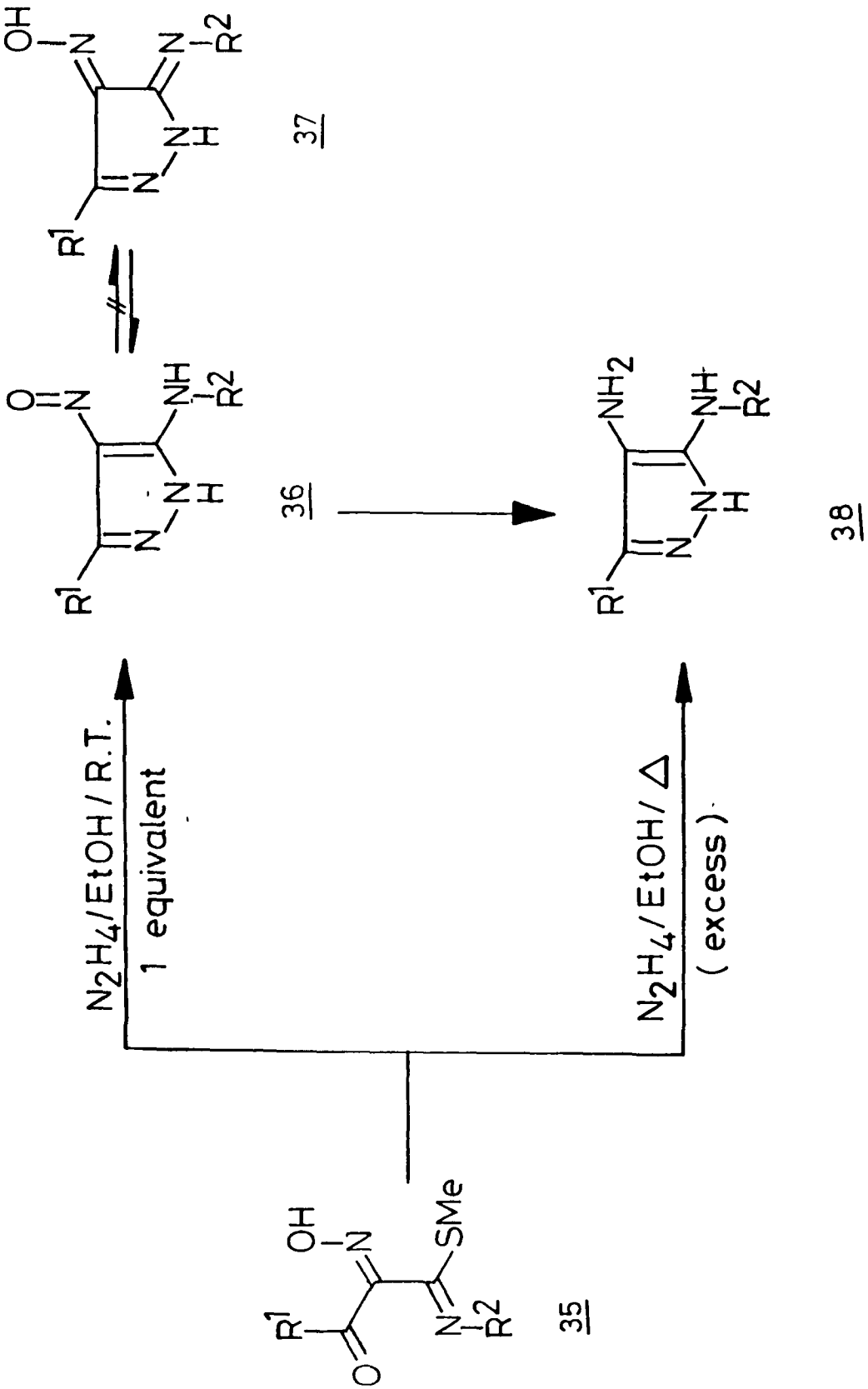


Scheme 10

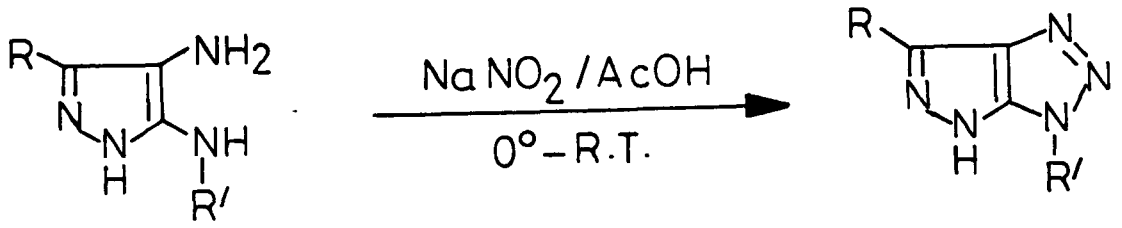
hydrate at room temperature, afforded a corresponding 4-nitroso 3(5)-aryl 5(3)-alkyl/arylamino pyrazoles 36 in excellent yields (Scheme 11)[47]. However, when excess of hydrazine hydrate was used the 4-nitroso group was reduced to the corresponding amino group and diamino pyrazoles 38 were formed in quantitative yields (Scheme 11), which are of synthetic value for the construction of fused heterocycles. Thus, 38 underwent nitrosation to yield the intermediate diazo compound which underwent intramolecular ring closure to yield the triazolo pyrazoles 39 (Scheme 12)[47].

The conversion of 2 to 40 was reported[48] from our laboratory in 1982. When α-oxoketene dithioacetals 2 were reacted with sodium borohydride in the presence of nickel chloride the corresponding alkylthiomethylene ketones 40 were formed in moderate to good yields. The method was found to give inconsistent yields due to extensive adsorption of the product 40 on the surface of the nickel boride. Thus, it was contemplated in the present studies to develop a convenient preparative method for the conversion of 2 to 40 (R'=H). It has been shown that the α-oxoketene dithioacetals 2 undergo facile 1,4-reduction followed by elimination of methylthio group in the presence of refluxing acetic acid and sodium cyanoborohydride to yield the desired alkylthio methylene ketones 40 in good yields (Scheme 13)[49]. The importance of these compounds 40 in organic synthesis, the generality and the scope of the present method is discussed in the Chapter V.

Each chapter is preceded with a short appraisal of the literature related to the area of investigation. The actual work carried out in the present investigation then follows.

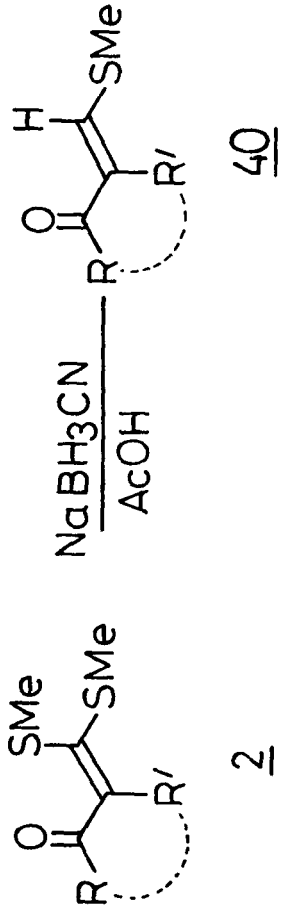

OH
N
N
R2
NH
R1
37
O
NH
R2
36
NH2
38
N2H4/EtOH/R.T.
1 equivalent
N2H4/EtOH/Δ
(excess)
OH
SMe
35

Scheme 11



38 39

Scheme 12



Scheme 13

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CHAPTER II

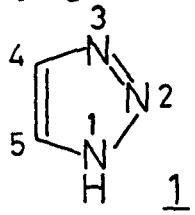
A. CYCLOADDITION OF AROYL/ACYL KETENE S,N-ACETALS WITH TOSYLAZIDE: SYNTHESIS OF NOVEL 4-AROYL/ACYL-5-AMINO 1H-1,2,3-TRIAZOLES AND 3,4-ANNULATED 1,2,3-TRIAZOLES*

CYCLOADDITION OF SODIUM AZIDE TO AROYL KETENE S,S-ACETALS: SYNTHESIS OF NOVEL 4,5-SUBSTITUTED TRIAZOLES**

B. CYCLOADDITION OF SODIUM AZIDE TO POLARIZED KETENE S,N-ACETALS: SYNTHESIS OF NOVEL 1,5-SUBSTITUTED TETRAZOLE DERIVATIVES**

II.1 INTRODUCTION

Chemistry of 1,2,3-triazoles of the general formula 1 represents an overwhelming rapidly developing field in modern heterocyclic Chemistry.



1

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* Chakrasali, R.T., Ila, H., Junjappa, H., Synthesis, 851 (1988).

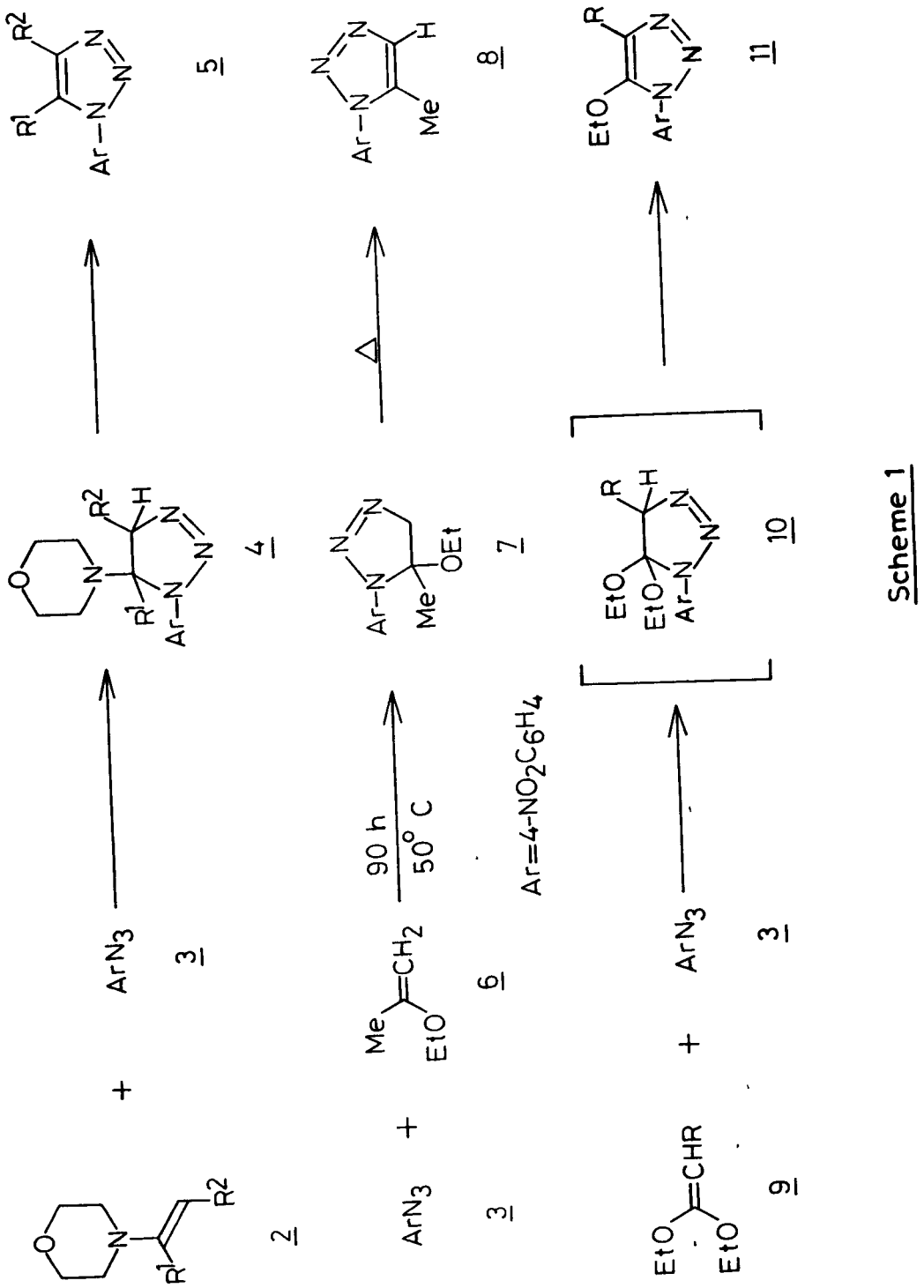
** Chakrasali, R.T., Ila, H., Junjappa, H., Synthesis, 453 (1988).

From the discovery[1] of the first triazole by Hans Von Pechmann in 1888 to the present time, interest in these substances has expanded exponentially, and the subject now commands a vast literature. The 1,2,3-triazoles 1 are of special interest because of their application in industry and agriculture due to extensive biological activity[2,3]. Also, they are useful as reagents in analytical chemistry and as intermediates in dyes[4], photostabilizers[5] and optical brightners[6] etc.

Several reviews have been appeared on various aspects of triazole chemistry[7,8,9,10]. The extensive literature available on the synthesis of a large number of 1,2,3-triazoles is mainly based on classical methods which are well documented in excellent reviews[7,8,9]. These reviews may be divided into two categories(a) those which emphasizing different synthesis and (b) those aiming at different substitution products. Exclusive reviews devoted to formation of 1,2,3-triazoles by the addition of azides to different dipolarophiles have also been appeared[11].

Since well covered reviews are available in the literature on the Chemistry of triazoles, a brief survey, limited to the present investigation, has been discussed in this Chapter.

The reaction of alkyl and aryl substituted azides with electron rich olefins is one of the most commonly employed methods for the synthesis of triazoles. The reaction generally proceeds in [3+2] cycloaddition pathway, normally in concerted fashion, first to the triazolines followed by the formation of the corresponding triazoles either by elimination of one of the leaving groups or through oxidation process[12]. Thus the enamines of the general formula 2 (Scheme 1) react with arylazides 3 in [3+2] cycloaddition path, first to afford the corresponding



Scheme 1

1-aryl-5-amino triazolines 4 generally in high yields. Subsequent elimination of the amines leads to the aromatic triazoles 5 (Scheme 1)[13]. Similarly with open chain enol ethers, triazolines are formed by cycloaddition regiospecifically in high yields. Thus, with 2-ethoxy-1-propene 6 and azide 3, the Δ^2-1,2,3-triazoline 7 is formed in quantitative yield, at 150°C. The ethanol was then eliminated to give the corresponding triazole 8 (Scheme 1)[14]. The cycloaddition of bis enol ethers 9 with arylazide 3 also yielded the 4-alkoxy triazole 11 through the intermediate triazoline 10 (Scheme 1)[15].

From the above examples it is apparent that, the 1,3-dipolar cycloaddition of azides to enamines and enol ethers leads to stereospecific and regiospecific triazolines. The formation of these regiomers can be explained satisfactorily on the basis of MO perturbation treatments provided by Sustmann[16] and Houk[17,18]. Perturbation theory gives a reliable guide to the most stable geometry of approach of two addends in the early stages of a cycloaddition reaction, when the interaction between two addends is small. The resulting interaction between an occupied orbital on the one addend with an unoccupied orbital on the other has been shown to result in a stabilization which is inversely proportional to the difference in energy between interacting orbitals. This means that Frontier orbital interactions should provide the main electronic stabilization of a transition state (minimum energy separation between interacting orbitals) and for two regioisomeric transition states, that, one will be favoured in which the largest coefficients on the HOMO and LUMO of the two addends are united, provided that steric repulsions do not overwhelm the electronic preference for one regioisomer.

HOMO LUMO

12

13

Z = electron withdrawing substituent

14

15

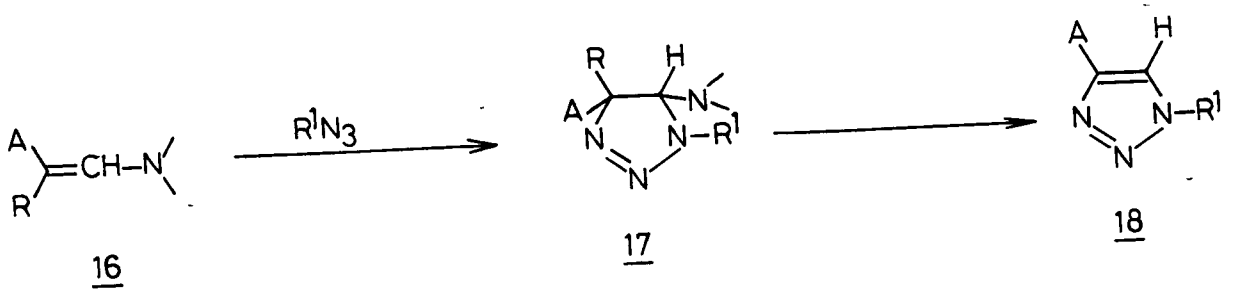
Ẍ = electron donating substituent

Scheme 2

Based on these considerations Sustmann[16] has shown that the reactivity of a dipolarophile towards an azide is determined by (i) the difference between azide HOMO and dipolarophile LUMO energies for electron deficient alkenes 12 (Scheme 2) (ii) the difference between azide LUMO and dipolarophile HOMO energies for electron rich alkenes 14 (Scheme 2). For cycloaddition of azides to electron rich alkenes, the smallest energy gap is that between the HOMO of the electron rich alkenes and LUMO of the azide rather than the HOMO of the azide and LUMO of the electron rich dipolarophiles (Scheme 2).

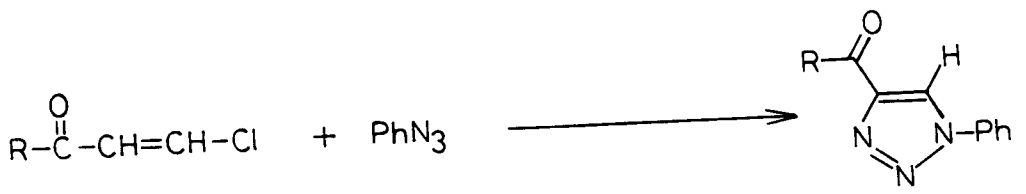
Enamines 16 with β-substituents such as an ester, ketone, cyano group also reacted with azide 3 to afford the corresponding triazoles 18 through intermediate triazolines 17 in case where at least one 4-H is present, only in case of non-availability of 4-H for elimination, reaction stopped at triazoline 17 (Scheme 3)[19]. Kochetkov reported the reaction of arylazides 3 with β-ketovinyl chlorides 19 to yield the corresponding triazoles 20 (Scheme 3)[20]. Aminals 21 react with aryl azides 3 to give 4,5-dihydro 1,2,3-triazoline 22, in general, these [3+2] cycloaddition products are unstable and they undergo deamination to afford 1-aryl-4-substituted triazoles 23 (Scheme 3)[21]. Good yields of 1-aryl-4-nitro triazoles 25 are obtained on cycloaddition of 1-morpholino-2-nitroethylene 24 with aryl azides 3 (Scheme 4)[22].

Of the various polyfunctional 1,2,3-triazoles reported, an overwhelming number contains the sulfonamido group. One of the reasons for this interest lies in the phenomenon of ring open chain tautomerism (Scheme 5). The addition of tosyl azide to an enamine, represents a potentially interesting approach. Thus enamines 26 undergo cycloaddition with tosyl azide 27 under neutral conditions to the corresponding unstable triazoline 28 which rapidly undergoes ring cleavage to diazomethane and tosylamidine

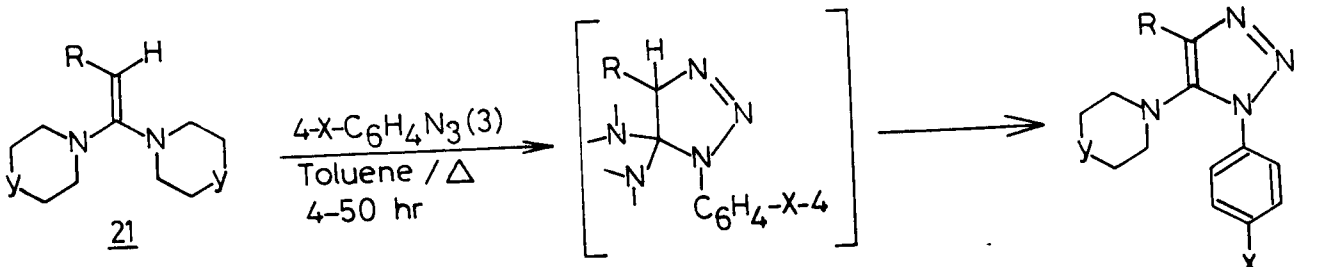


16 17 18

A = CO_2R , COR , CN ; R = H , Me



19 3 20

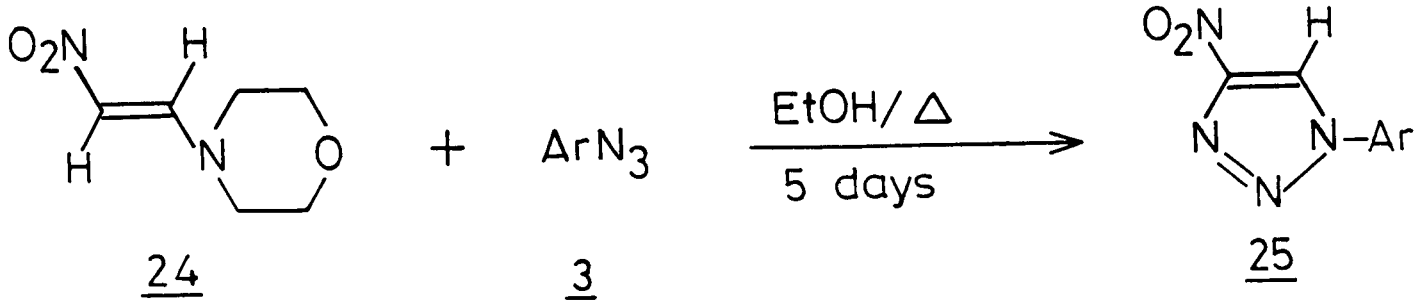


21 22 23

y = O , CH_2 ; X = Cl , NO_2

R = MeCO, PhCO; CO_2Et; CO_2CH_2Ph; 4-$MeC_6H_4SO_2$; NO_2

Scheme 3



24 3 25

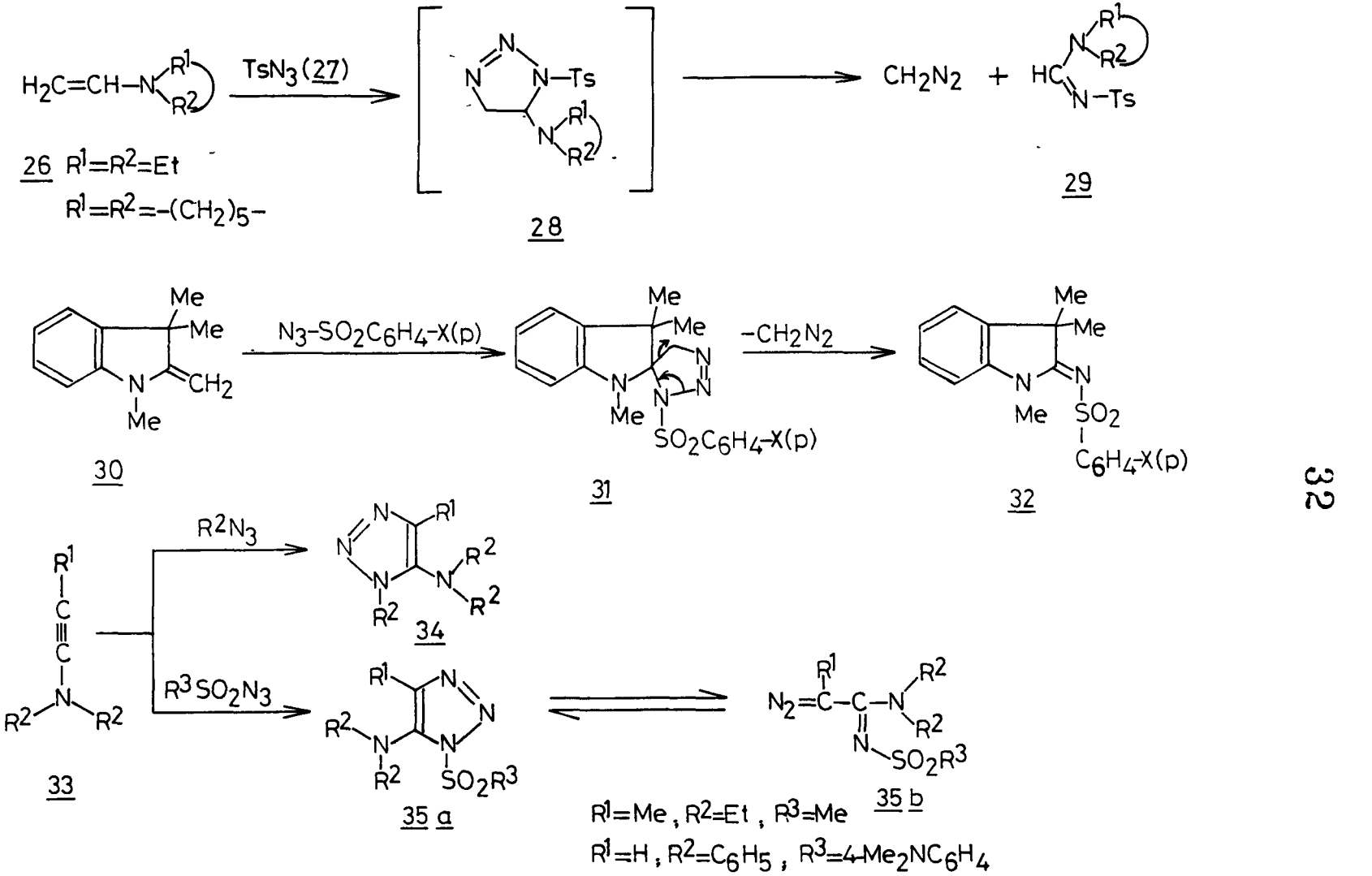
Ar=C_6H_5; 4-$NO_2C_6H_4$

Scheme–4

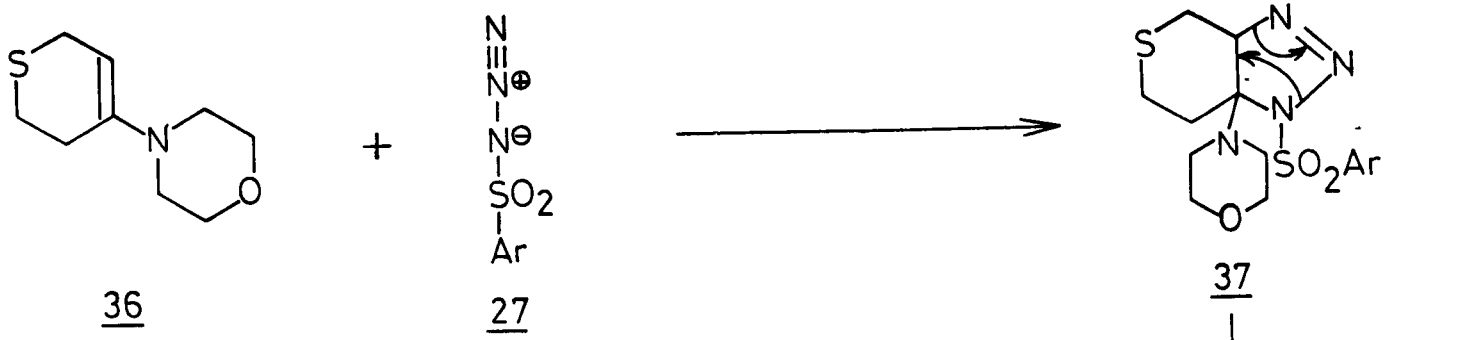
29[23], however, the same reaction under strongly alkaline conditions reported to yield the triazole, possibly due to rapid elimination of the amine group. Similarly indoline 30 reacted with aryl sulphonyl azide 27 to afford an unstable triazoline 31, which underwent cleavage to yield diazomethane and 2-sulfonamido indole 32 (Scheme 5)[23]. The 1,3-dipolar additions of a number of aryl sulphonyl azides 27 to N,N-dialkyl aminoprop-1-yne 33 yielded 1,2,3-triazoles and ∝-diazoamides which, in solution, were shown by n.m.r. and i.r. spectroscopy to exist in a tautomeric equilibrium. Whereas the reaction of aryl/alkyl azides with ynamines 33 afforded the stable triazoles 34 (Scheme 5)[24,25].

The reaction between 3,6-dihydro-4-morpholino-2H-thiopyran 36 and aryl sulphonylazide (Ar=4-$NO_2C_6H_4$) 27 yielded only the sulphonyl amino-enamine 39. The formation of 39 can be rationalized as shown in Scheme 6. Aryl sulphonyl azides are known to react with enamines affording only unstable adducts 37, which rearrange to the sulphonyl amino-enamine 39 through unstable aziridine intermediate 38 (Scheme 6)[26].

The cyanomethylene anion 40 derived from malononitrile, attack on the electrophilic terminal nitrogen atom of the azide 27. This gives an open chain triazene 41, which under neutral or mild basic conditions afforded the diazonitriles 41a instead of triazole 44. This course can be circumvented by carrying out the reaction in water and at a concentration of alkali in excess of 2N. The reaction then proceeds as expected, but with instantaneous Dimroth rearrangement to give 5-tosylaminotriazole 44, which was converted to 4-benzoyl triazole 45 by reacting with phenyl magnesium bromide (Scheme 7)[27]. The 4-benzoyl-5-tosyl amino triazole 45 was detosylated to 5-amino-4-benzoyl triazole 46 by stirring with concentrated sulfuric acid at room temperature for 25 minutes (Scheme 7)[28].


TsN3 (27)
CH2N2 +
26 R1=R2=Et
R1=R2=-(CH2)5-
28
29
N3-SO2C6H4-X(p)
-CH2N2
30
31
32
R2N3
R3SO2N3
33
34
35 a
35 b
R1=Me , R2=Et , R3=Me
R1=H , R2=C6H5 , R3=4-Me2NC6H4

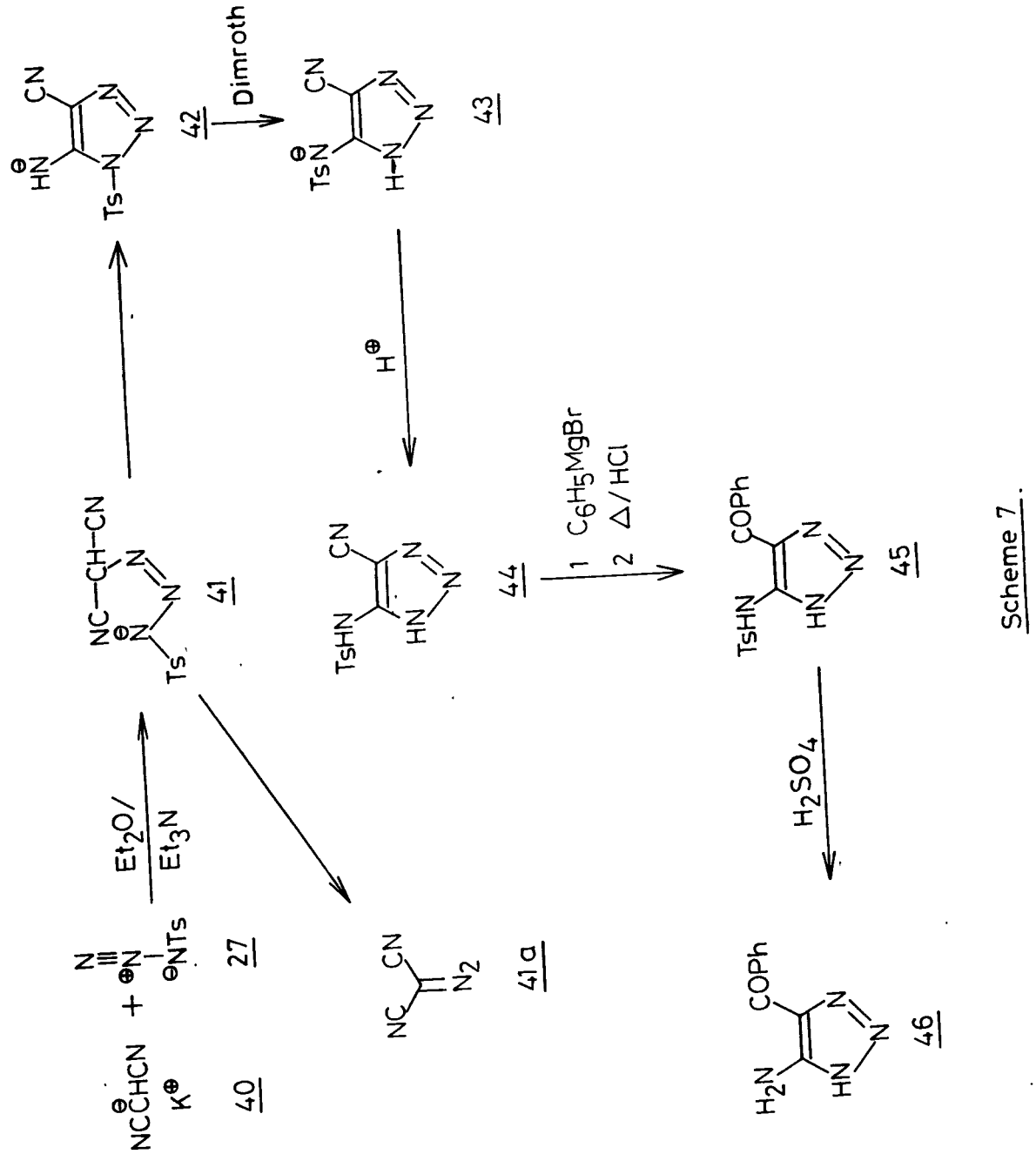
Scheme–5



36 27 37 38 39

Ar = 4-$NO_2C_6H_4$

Scheme–6



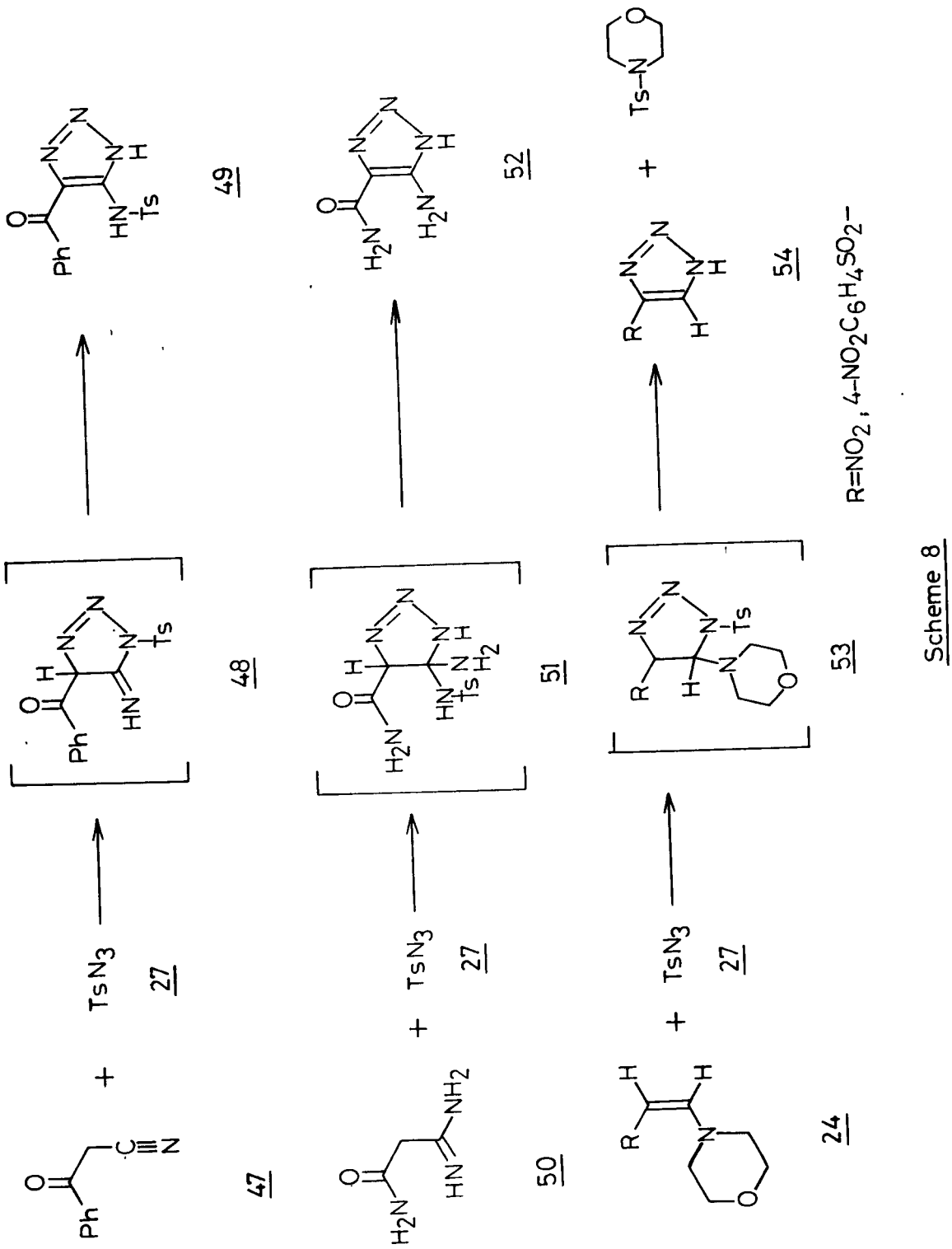
Scheme 7.

Similarly benzoyl acetonitrile 47 and tosylazide 27 vigorously agitated in 6N sodium hydroxide at room temperature for 5 min, produced 4-benzoyl 5-tosylamino 1,2,3-triazole 49 (Scheme 8)[28]. The enolate anions of amidines 50 underwent [3+2] cycloaddition with tosylazide 27 and Dimroth rearrangement of the intermediate 51 to give the corresponding 1,2,3-triazole 52 (Scheme 8)[29]. The triazole 54 was also prepared by reaction of 1-morpholino-2-nitro ethylene 24 with tosylazide 27 (Scheme 8)[22].

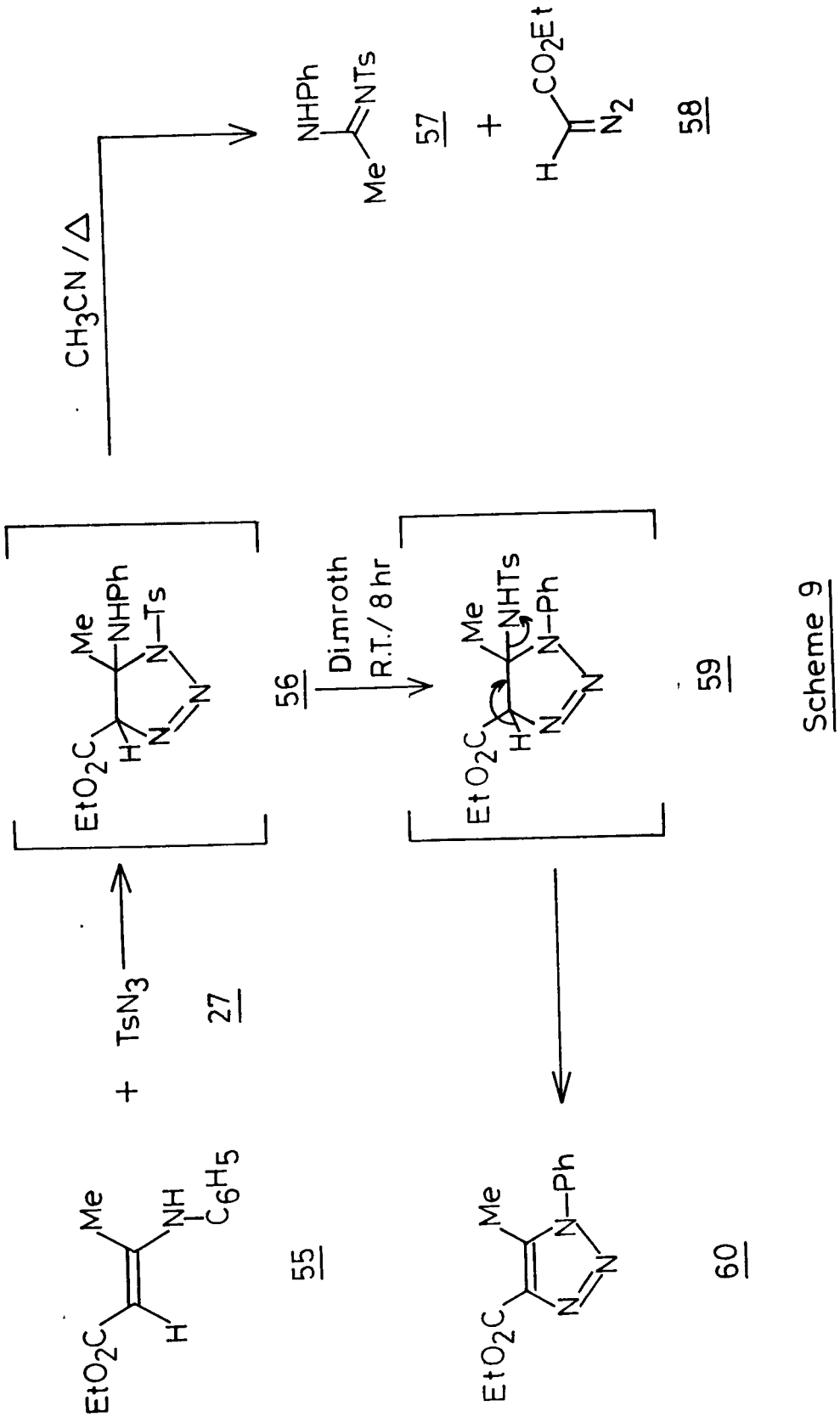
The addition of tosylazide to an enamine represents a potentially interesting approach. The enaminone 55 and tosylazide 27 underwent [3+2] cycloaddition to produce an unstable triazoline 56, which either decomposed on heating in acetonitrile (i.e. neutral condition) to diazoacetate 58 and methyl-amidine 57 or underwent Dimroth rearrangement followed by E2 elimination of anilino group under basic conditions to yield the stable triazole 60 (Scheme 9)[23]. Zbiral and his collaborators have studied a large number of reactions involving the addition of sodium azide 62 to phosphonium salts of type 61 and 65 (Scheme 10) to afford 1,2,3-triazoles 64 and 66 respectively. Although the yields vary from poor to excellent, those methods are of genuine importance in the synthesis of a broad range of acyl 1,2,3-triazoles. The proposed mechanism (Scheme 10)[30,31] involves nucleophilic attack at the α-to the phosphorus, followed by cyclization with displacement of triphenyl phosphine.

The α-chloroenaminone 67 when stirred with sodium azide 62 in acetonitrile, gave one of the rarely encountered 4-H triazoles 68. which on thermolysis gave an aromatic triazole 69 and/or 3-amino-2H-azirines 70, on photolysis only azirines 70 are obtained (Scheme 11)[32].

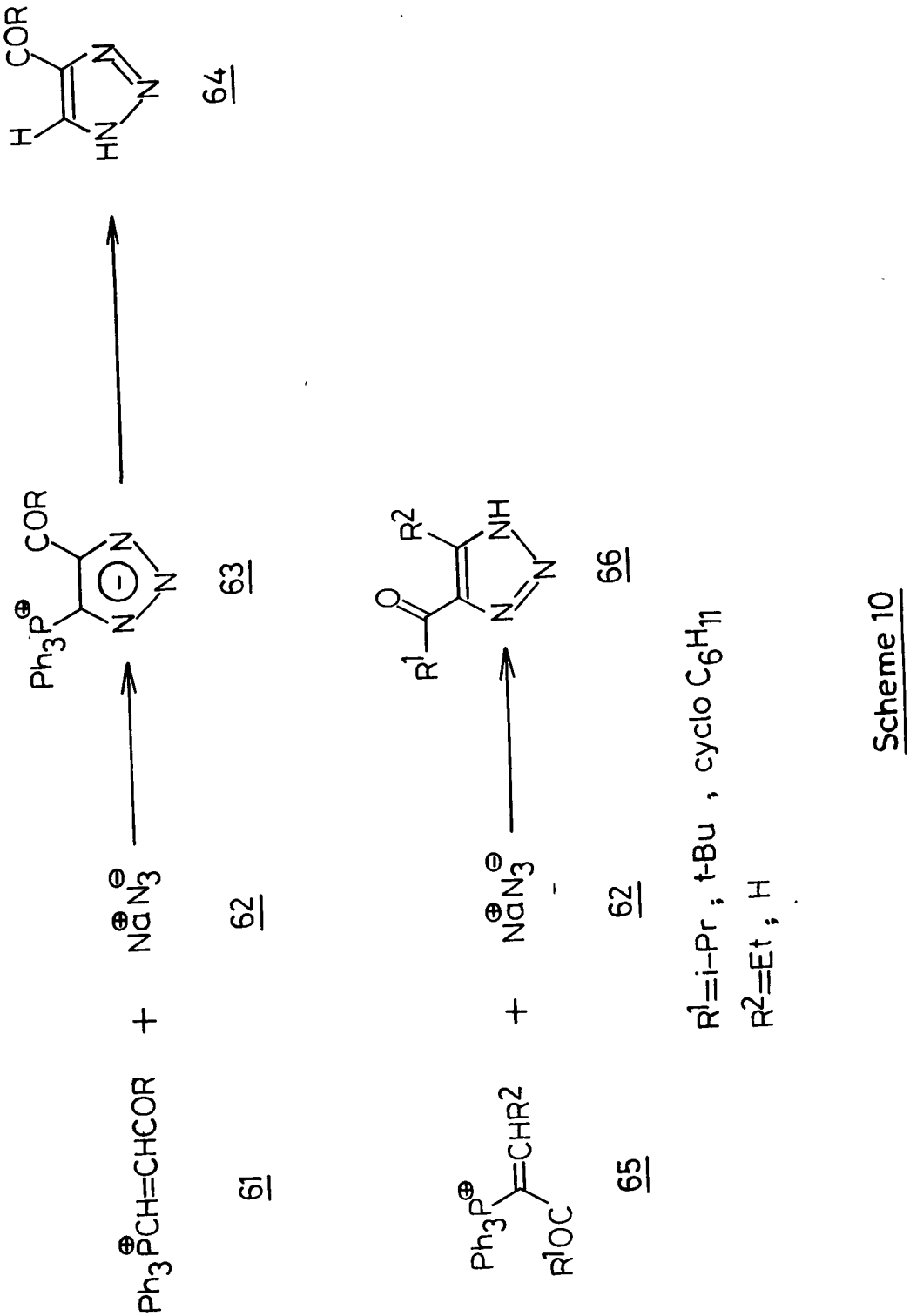
Saalfrank and co-workers have observed an interesting ring closure of vinyl azides 72 derived from 3,3-diazido-2-cyano acrylate 71 with donor



Scheme 8


CH3CN / Δ
NHPh
NTs
Me
57
+
CO2Et
N2
58
Me
NHPh
N—Ts
EtO2C
H
56
Dimroth
R.T./ 8 hr
Me
NHTs
N—Ph
EtO2C
H
59
+ TsN3
27
Me
NH
C6H5
EtO2C
H
55
Me
N—Ph
EtO2C
60

Scheme 9


COR
H
HN
64
COR
Ph3P
63
Ph3PCH=CHCOR
61
+
NaN3
62
R2
NH
O
R1
66
Ph3P
CHR2
R1OC
65
+
NaN3
62
R1=i-Pr ; t-Bu , cyclo C6H11
R2=Et ; H

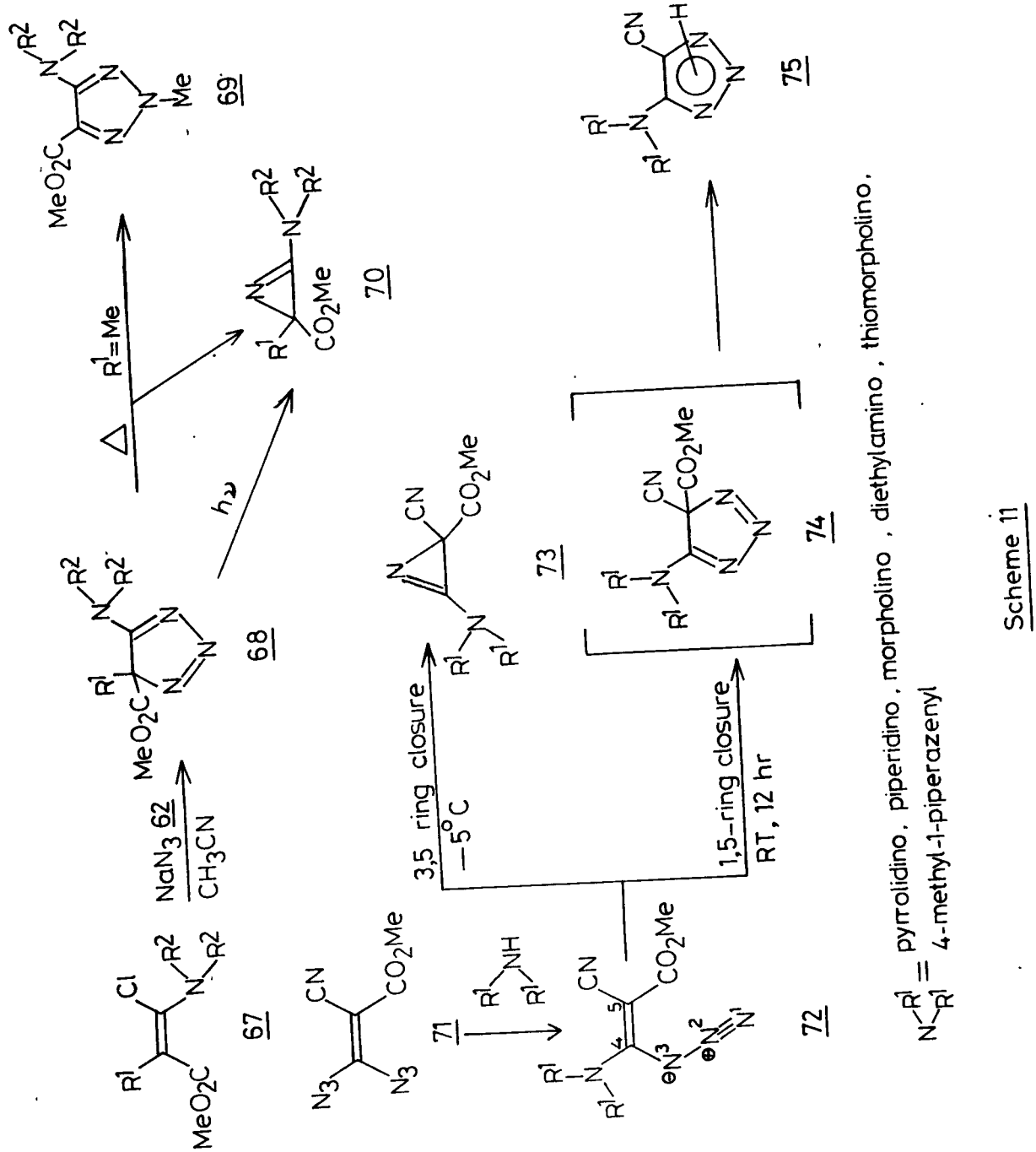
Scheme 10

substituents (e.g. amines) in 4-position. These vinyl azides 72 undergo both 1,5 and 3,5 ring closure reactions. Depending upon the reaction conditions, either stable 1,2,3-triazoles 75 are formed via 4H-1,2,3-triazoles 74, or 2H-azirines 73 are formed with elimination of nitrogen (Scheme 11)[33] whereas thermolysis of vinyl azide 72 exclusively leads to 2H-azirines 73.

In the preceding section, the reactions of azides with various enamines and enol ethers have been surveyed. It may be noted that in all the cases cycloaddition leads to stereospecific and regiospecific triazolines with respect to enamines and enol ethers. Without exception the nitrogen of the azide bearing the substituent bonds with the carbon atom of the dipolarophile (i.e. enamines or enol ethers) bearing the amine or ether moiety. In the light of these observations it was considered of interest to study the reactivities of the α-oxoketene S,N-acetals and S,S-acetals with tosyl and sodium azides respectively and the results of these investigations have been described in this Chapter.

II.2 RESULTS AND DISCUSSION

For the present study, the known α-oxoketene S,N-acetals 76a-h and 76m (Table 1) were prepared according to the reported procedures[34,35]. The structures of all the known S,N-acetals were confirmed by comparison of their spectral and analytical data with those of authentic samples. The hitherto unknown α-oxoketene S,N-acetals 76i-l (Table 1) were also prepared essentially by extending the reported methodology[34]. Thus, the α-oxoketene S,N-acetal 76i was prepared by reacting the corresponding 3,3-bismethylthio-1-(4-chlorophenyl)-2-propene-1-one with one equivalent of n-propylamine in refluxing ethanol in 87% yield.

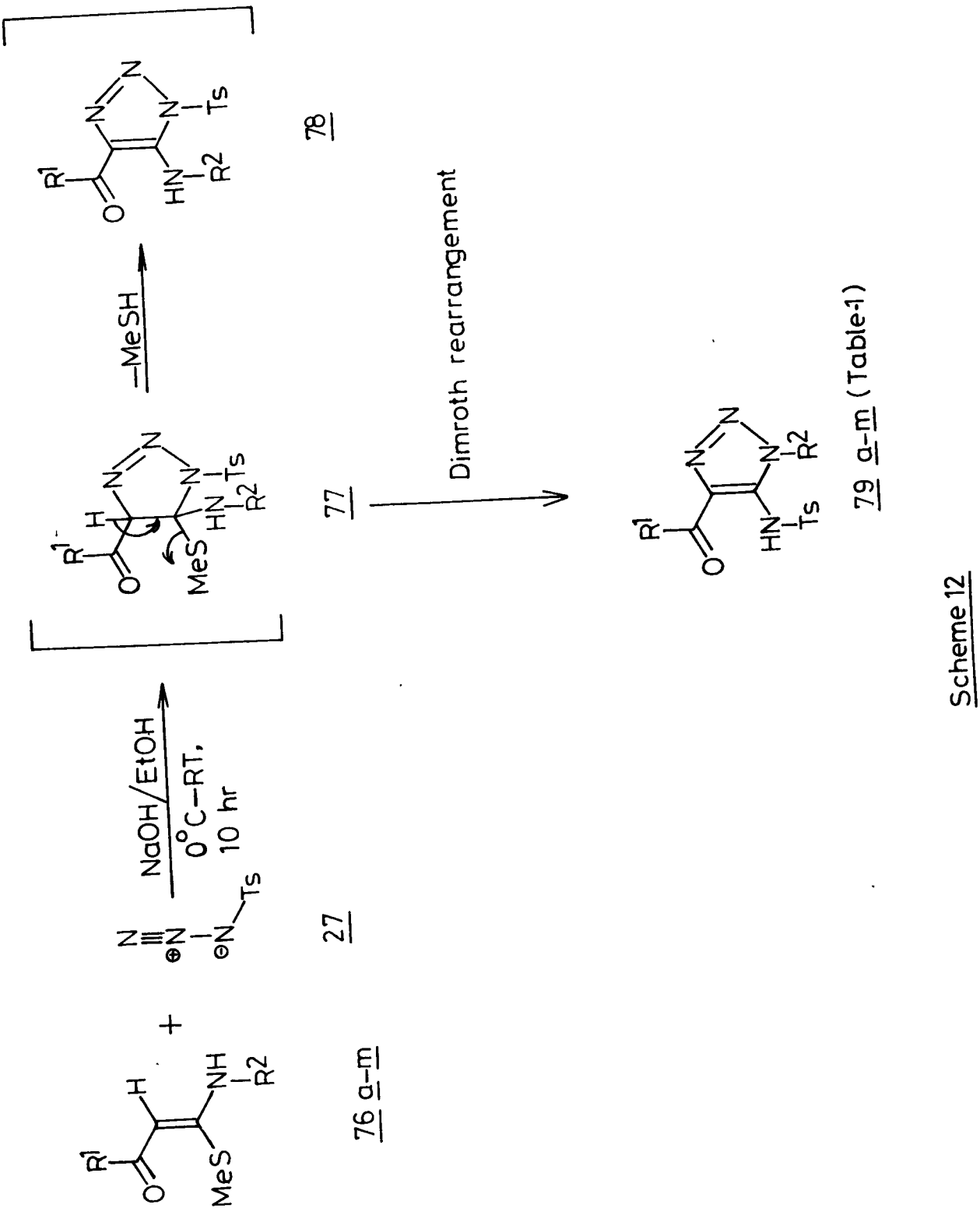

NaN3 62
CH3CN
68
hν
Δ
R1=Me
69
70
3,5 ring closure
−5°C
73
1,5-ring closure
RT, 12 hr
74
75
67
71
72
R1 = pyrrolidino, piperidino, morpholino, diethylamino, thiomorpholino,
4-methyl-1-piperazenyl

Scheme 11

The structure was fully confirmed by its analytical and spectral data which are described in the experimental section. Similarly when S,S-acetal was reacted with n-butylamine in refluxing ethanol the corresponding 3-methylthio-3-n-butylamino-1-(4-methylphenyl)-2-propen-1-one 76k was obtained in 88% yield. The structural confirmation was achieved through its analytical and spectral data which are described in experimental section. The other S,N-acetals 76j and 76l were prepared by reacting the enolate anion of the corresponding acetophenone and 4-chloroacetophenone with isopropyl and cyclohexylisothiocyanates respectively. The thioamide thus obtained were alkylated in situ to yield the corresponding S,N-acetals 76j and 76l in 81% and 91% respectively. The structures of these S,N-acetals were established by analytical and spectral data which are described in experimental section.

II.2.1 REACTION OF α-OXOKETENE S,N-ACETALS WITH TOSYL AZIDE: SYNTHESIS OF NOVEL 4-AROYL/ACYL-5-AMINO-1H-1,2,3-TRIAZOLES

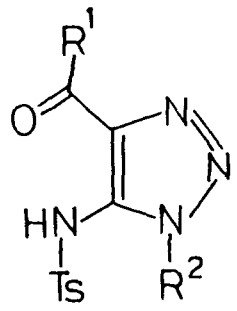
In one of the typical experiments the α-oxoketene S,N-acetal 76a and tosyl azide 27 were refluxed in dioxane, the unreacted starting materials were recovered unchanged. However, when S,N-acetal 76a and tosyl azide 27 reacted smoothly in ethanolic sodium hydroxide to afford a colourless product (m.p. 180-181°C) in 57% yield, which was characterized as 4-benzoyl-1-phenyl-5-tosylamino-1H-1,2,3-triazole 79a. The structural assignment of 79a was established as follows. The triazole 79a was subjected to detosylation in the presence of concentrated sulphuric acid, when the corresponding 1-phenyl-4-benzoyl-5-amino-1H-1,2,3-triazole 80a was obtained in 95% yield. In the structure the exocyclic amino functionality was fully in accordance with its analytical and spectral data. The compound 80a was analysed for $C_{15}H_{12}N_2O$ and its mass spectrum showed the molecular



76 a–m + 27 → 77 → 78 → 79 a–m (Table-1)

Scheme 12

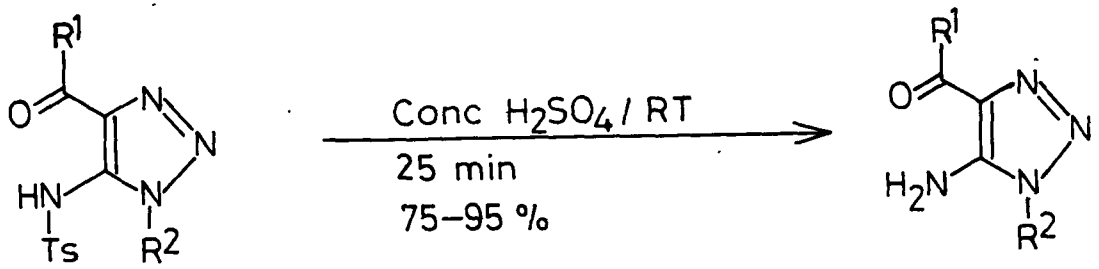
Table 1



79

76,79	R^1	R^2
a	C_6H_5	C_6H_5
b	4-ClC_6H_4	C_6H_5
c	C_6H_5	$C_6H_5CH_2$
d	CH_3	$C_6H_5CH_2$
e	4-MeC_6H_4	$C_6H_5CH_2$
f	C_6H_5	CH_3
g	4-MeC_6H_4	CH_3
h	C_6H_5	C_2H_5
i	4-ClC_6H_4	n-C_3H_7
j	C_6H_5	i-C_3H_7
k	4-MeC_6H_5	n-C_4H_9
l	4-ClC_6H_4	cyclo-C_6H_{11}
m	C_6H_5	$CH_2CH(OEt)_2$

ion peak at m/z 264 (M^+,22%). Its i.r. spectrum (KBr) exhibited sharp peaks at 3390 and 3275 cm^{-1} which were assigned to the primary amino stretching vibrations, the band at 1625 cm^{-1} was assigned to NH_2 out of plane vibrations which confirms the presence of exocyclic primary amino group. The band at 1600 cm^{-1} was assigned to the enamino carbonyl functionality. The structure of 80a was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$). The broad signal at δ 6.03(2H) was assigned to free NH_2 protons, which were exchangeable with D_2O, thus, confirming the exocyclic position of tosylamine functionality. The multiplet between δ7.31-7.71(8H) which could be assigned to five anilino protons and three aryl protons. The two aromatic protons of benzoyl group adjacent to carbonyl appeared between δ 8.40-8.63 as multiplet. The triazole 80a was further subjected to Dimroth rearrangement in the presence of boiling pyridine to yield the corresponding 5-anilino-4-benzoyl-1H-1,2,3-triazole 81a m.p. 160-161°C (ethanol) in 60% yield. Thus, the compound 81a was analysed for $C_{15}H_{12}N_4O$ and its mass spectrum showed the molecular ion peak at m/z 264 (M^+,64%). The i.r. spectrum was very characteristic in comparison to the corresponding aminotriazole 80a. Thus, the i.r. (KBr) band at 3130 cm^{-1} was assigned to the secondary amino stretching vibrations, while the enamino carbonyl function was assigned to 1590 cm^{-1} band. Further confirmation of the structure was done by its ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6). The multiplet between δ 7.17-7.70 was assigned to seven aromatic protons and it was observed by the exchange with D_2O that the NH proton is buried in this aromatic multiplet, thus confirming the multiplet for only six aromatic protons. The other multiplet at δ8.25-8.50(2H) was due to C-2', 6' protons of benzoyl group. The singlet at δ 9.12 accounting for one proton and was exchangeable with D_2O was



79 80

79,80 a $R^1=R^2=C_6H_5$

b $R^1=4\text{-}ClC_6H_4$; $R^2=C_6H_5$

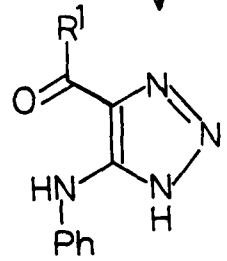
c $R^1=C_6H_5$; $R^2=C_6H_5CH_2$

d $R^1=Me$; $R^2=C_6H_5CH_2$

e $R^1=Ph$; $R^2=CH_3$

g $R^1=Ph$; $R^2=C_2H_5$

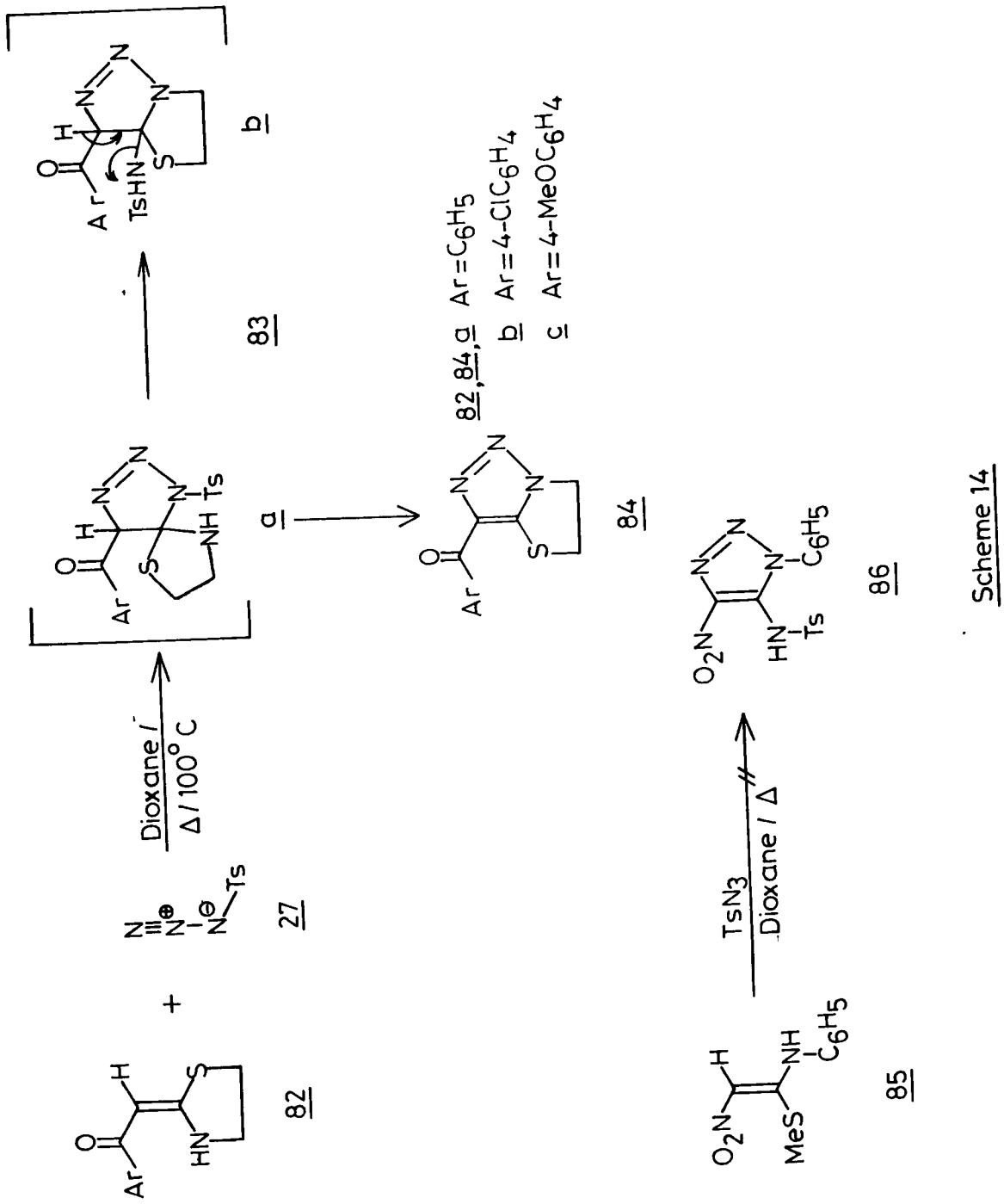
h $R^1=4\text{-}ClC_6H_4$; $R^2=n\text{-}C_3H_7$



81 a $R^1=Ph$

b $R^1=4\text{-}ClC_6H_4$

Scheme-13



Scheme 14

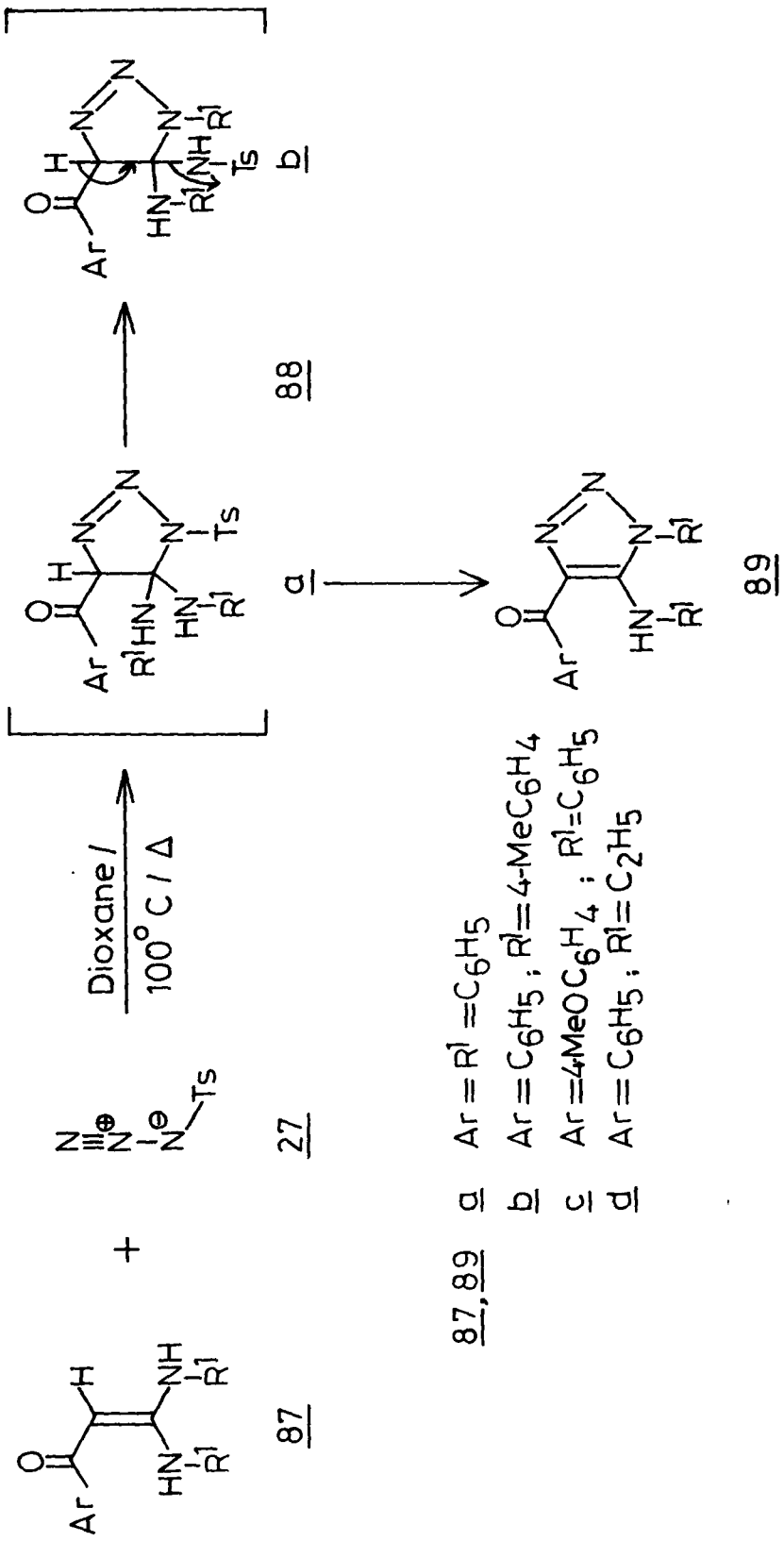
assigned to exocyclic aryl NH proton. The structural confirmation of triazole 79a was thus confirmed through its conversion to the corresponding aminotriazole 80a and its subsequent Dimroth rearrangement to the corresponding anilino triazole 81a. The 5-tosylaminotriazoles 80b-e,g,h were similarly hydrolysed in the presence of concentrated sulphuric acid to yield the corresponding 5-aminotriazoles 81b-e,g,h (Scheme 13) in 84-87% overall yields and the structures of these compounds were fully established by their analytical and spectral data which are described in the experimental section.

Another aminotriazole 80b was also subjected to Dimroth rearrangement in the presence of refluxing pyridine when the rearranged triazole 81b was obtained in 71% yield. The structure of triazole 81b was confirmed by its analytical and spectral data which are described in experimental section.

The other S,N-acetals 76b-m were similarly reacted with tosylazide 27 to give the corresponding triazoles 79b-m in 44-75% overall yields. The analytical and spectral data of these triazoles 79b-m (Scheme 12) are in conformity with their assigned structures and are given in the experimental section.

II.2.2 REACTION OF CYCLIC S,N-ACETALS WITH TOSYL AZIDE: SYNTHESIS OF NOVEL 3-BENZOYL-5,6-DIHYDROTHIAZOLO [3,2-c] [1,2,3] TRIAZOLES.

The reaction of tosyl azide 27 with cyclic S,N-acetals 82a-c was next examined. Thus, when cyclic S,N-acetal 82a was reacted with tosyl azide 27 in ethanolic sodium hydroxide as described above, the reaction mixture resulted in an intractable tar, from which no well defined compound could be isolated. However, in dioxane, at higher temperature, the product isolated was identified as 3-benzoyl-5,6-dihydrothiazolo [3,2-c] [1,2,3]


Dioxane /
100°C / Δ
87
27
88
a
b
89
87,89
a Ar = R¹ = C6H5
b Ar = C6H5 ; R¹ = 4-MeC6H4
c Ar = 4MeOC6H4 ; R¹ = C6H5
d Ar = C6H5 ; R¹ = C2H5

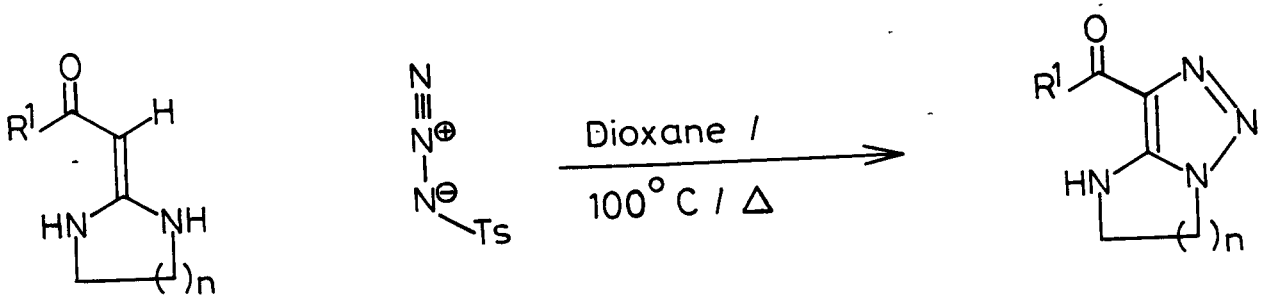
Scheme 15

triazole 84a in 69% yield. The structure of 84a was confirmed by its analytical and spectral data. Thus it was analysed for $C_{11}H_{11}N_3OS$ and showed the molecular ion peak at m/z 324 (M^+,13%) in its mass spectrum. Its i.r. spectrum (KBr) showed a band at 1632 cm^{-1} due to the carbonyl group, apart from other bands which are described in the experimental section, the band at 920 cm^{-1} was assigned to the characteristic 4-benzoyl triazole ring systems. The structure was further confirmed from its ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6). The signal at δ 5.20 distorted triplet accounting for two protons and the signal at δ 4.70 distorted triplet for two protons were assigned to the ring methylene protons. The multiplet between δ 7.20-7.70(3H) was assigned to 3'4'5'-protons of benzoyl group, while the multiplet between δ 8.20-8.54 accounting for two protons was assigned to the 2'6'-benzoyl protons. Similarly the cyclic S,N-acetals 82b-c were reacted with tosylazide 27 to yield the corresponding thiazolotriazoles 84b-c in 60-65% overall yields (Scheme 14). The analytical and spectral data for these compounds are given in the experimental section. The mechanism of the transformation of 82-84 is depicted in the Scheme 14, which involves the intermediate 83a as initial [3+2] cycloadduct undergoing Dimroth rearrangement in situ to 83b followed by elimination of tosylamino group to yield finally the thiazolotriazoles 84.

The notable exception in this investigation was the reaction of tosyl azide 27 with α-nitroketene S,N-acetal 85, which did not give the expected triazole 86 and the reaction resulted in an intractable tar from which no well defined compound could be isolated.

II.2.3 REACTION OF N,N-ACETALS WITH TOSYLAZIDE

a. SYNTHESIS OF NOVEL 5-ARYL/ACYLAMINO 1,2,3-TRIAZOLES



90 a–j 27 91 a–j

90 91 a $R^1 = C_6H_5$, n = 1

b $R^1 = 4\text{-}MeC_6H_4$, n = 1

c $R^1 = 4\text{-}MeOC_6H_4$, n = 1

d $R^1 = 4\text{-}ClC_6H_4$, n = 1

e R^1 = 2-Thienyl , n = 1

f $R^1 = C_6H_5$, n = 2

g $R^1 = 4\text{-}ClC_6H_4$, n = 2

h $R^1 = 4\text{-}MeOC_6H_4$, n = 2

i R^1 = 2-Furyl , n = 2

j R^1 = 2-Naphthyl , n = 2

Scheme 16

b. SYNTHESIS OF IMIDAZOLO TRIAZOLES

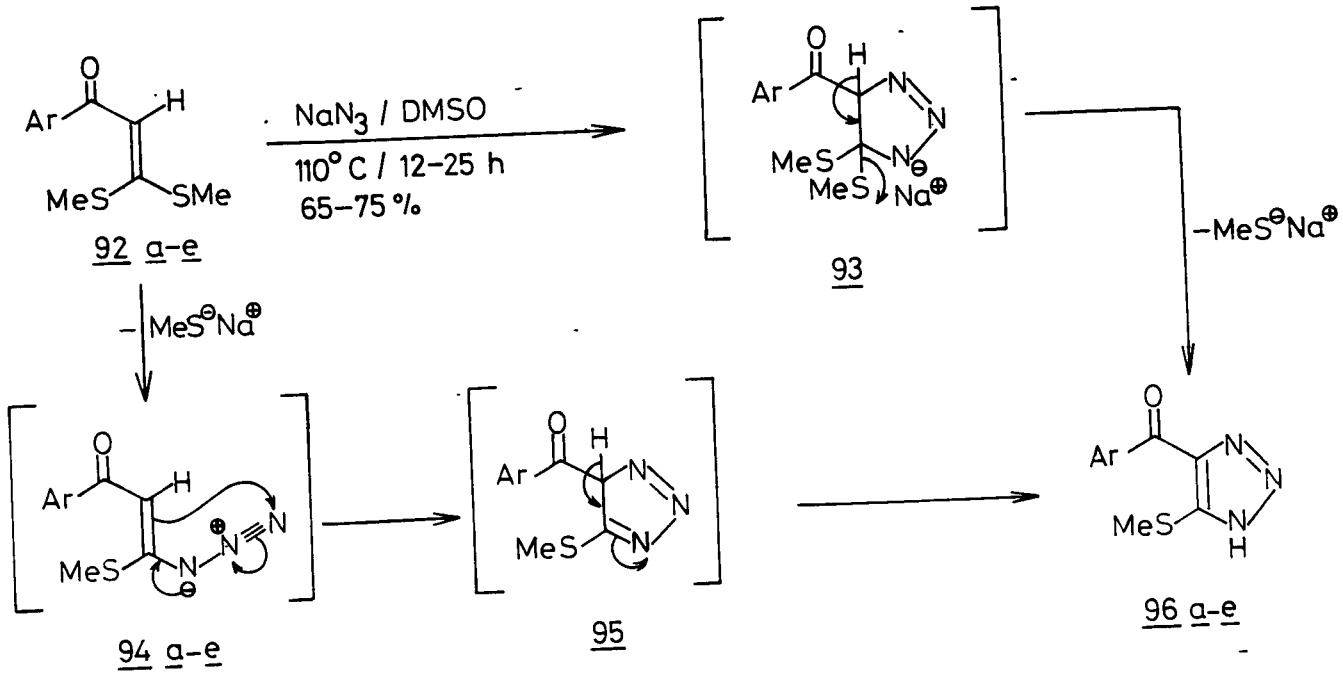
c. SYNTHESIS OF PYRIMIDO TRIAZOLES

In the preceding section, the reactions of tosyl azide with ∝-oxoketene S,N-acetals were investigated which gave high yields of triazoles. The reaction was further extended to the ∝-oxoketene N,N-acetals and these results are described in this section.

The required ∝-oxoketene N,N-acetals 87a-d were prepared as per reported methods[35]. The structures of all the N,N-acetals 87a-d were confirmed by comparison of their analytical and spectral data with those of authentic samples.

When the ∝-oxoketene N,N-acetals 87a and tosyl azide 27 were heated in dioxane at 95-100°C for 15 hrs, work-up of the reaction mixture afforded a white crystalline solid (m.p. 131-132°C) in 83% yield which was characterised as 1-phenyl-4-benzoyl-5-anilino 1H-1,2,3-triazole 89a (Scheme 15) on the basis of its analytical and spectral data which are described in the experimental section. Other triazoles 89b-d were similarly prepared from the corresponding 87b-d in 62-94% overall yields (Scheme 15). The mechanism of the formation of triazoles 89 can be explained on the identical pathway described in the preceding section (Scheme 14). Initial cycloadduct 88a undergoes Dimroth rearrangement in situ followed by the elimination of the tosylamino group to yield the corresponding triazole 89 (Scheme 15).

The known cyclic N,N-acetal 90a (Scheme 16) was prepared according to the reported procedure[35], while the hitherto unknown cyclic N,N-acetals 90b-e (Scheme 16) were prepared by reacting ∝-oxoketene dithioacetals with ethylene diamine in refluxing ethanol. The structures of unknown N,N-acetals



92, 96 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 = 3,4-Cl_2 C_6H_3

Scheme-17

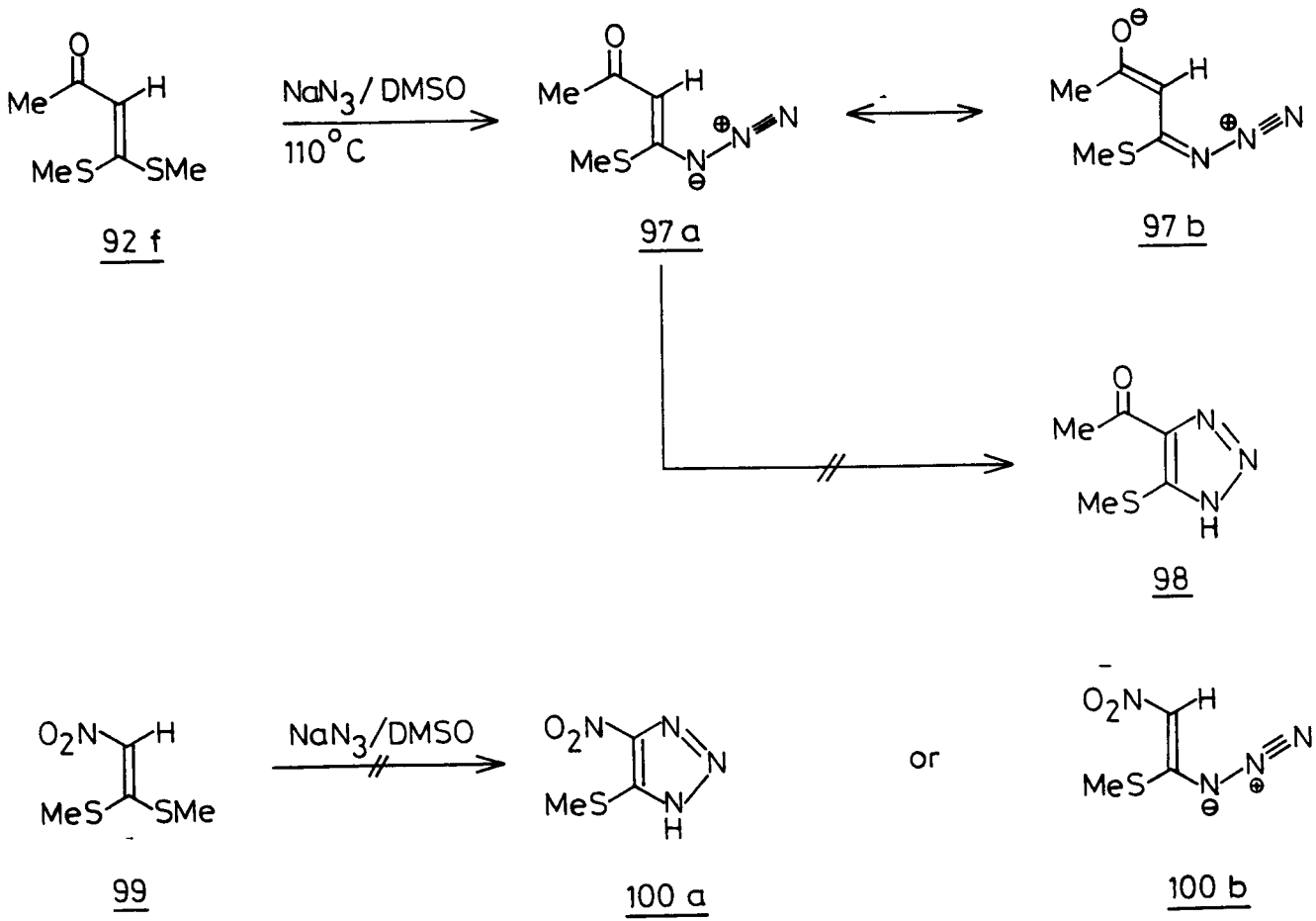
90b-e were confirmed by their spectral and analytical data which are described in the experimental section.

Similarly, the α-oxoketene dithioacetals were refluxed with propylene diamine in ethanol, when the corresponding cyclic N,N-acetals 90f-j were obtained in 91-94% overall yields (Scheme 16). The structures of these compounds were also fully established by analytical and spectral data which are described in the experimental section.

In a typical reaction the cyclic N,N-acetal 90a was reacted with tosyl azide 27 in refluxing dioxane to afford the corresponding 3-benzoyl-5,6-dihydroimidazolo [3,2-c] [1,2,3] triazole 91a in 94% yield. Thus, 91a was analysed for $C_{11}H_{10}N_4O$ and its mass spectrum showed a molecular ion peak at m/z 214 (M^+,40). Its i.r. spectrum (KBr) exhibited sharp peaks at 3200 and 1605 cm^{-1} due to arylamino and carbonyl functions respectively. The ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6) showed a multiplet between δ 4.20-4.59(4H) which was assigned to the four methylene protons of imidazoline ring. The singlet at δ 7.30 was assigned to NH, which was exchangeable with D_2O while the aromatic protons, appeared as a multiplet between δ7.40-7.61. The other multiplet between δ 8.27-8.49 was assigned for the remaining two aryl protons. Similarly, the annulated triazoles 91b-j were obtained in 87-95% overall yields from the corresponding N,N-acetals 90b-j and tosyl azide 27 under the described conditions. The structural assignment of all the triazoles 91b-j (Scheme 16) was confirmed from their analytical and spectral data which are described in the experimental section.

II.2.4 REACTION OF SODIUM AZIDE WITH α-OXOKETENE DITHIOACETALS: SYNTHESIS OF NOVEL SUBSTITUTED 4-AROYL-5-METHYLTHIO 1H-1,2,3-TRIAZOLES:

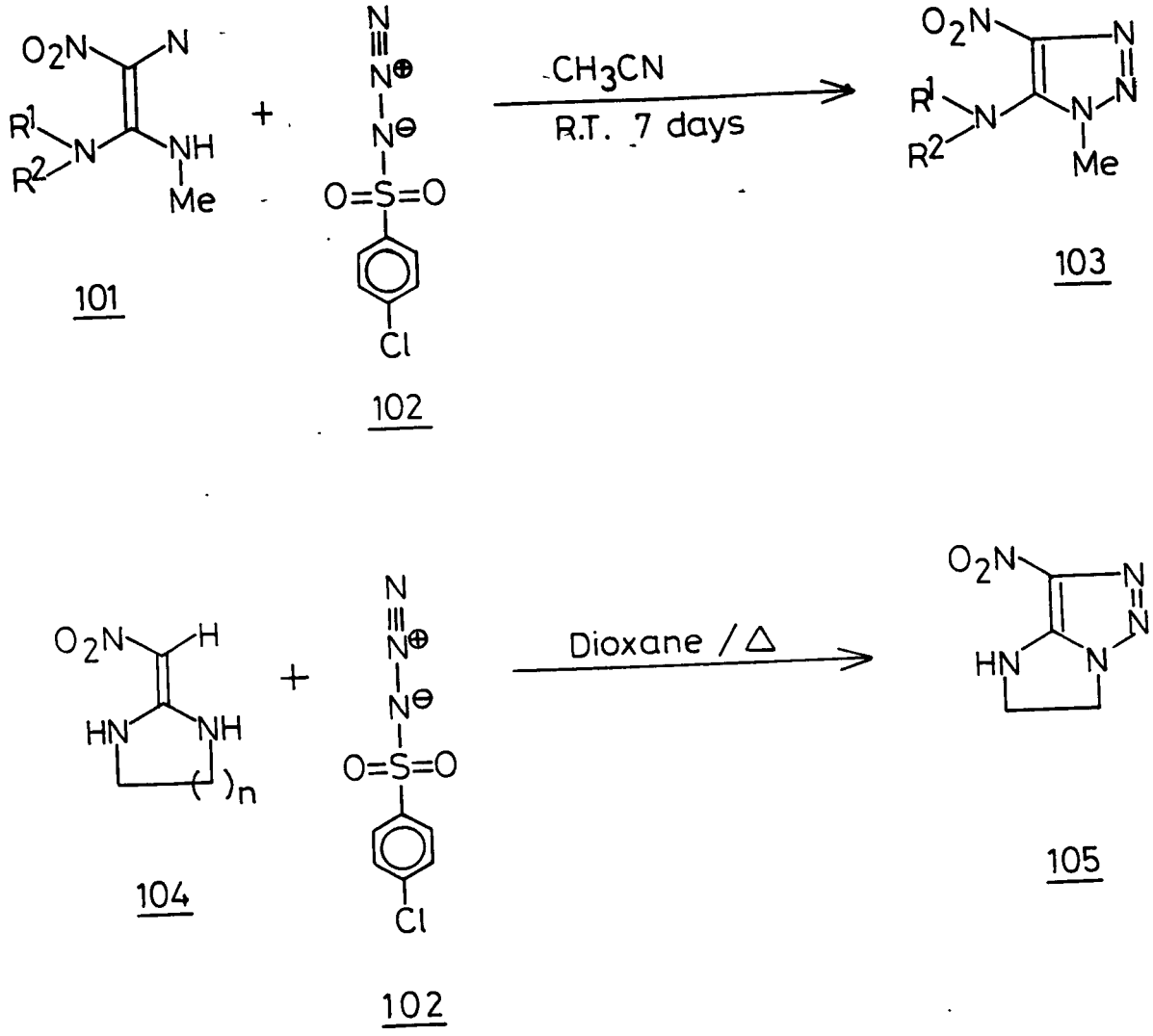
Besides the reactivity of enamines with azides, only the enol ethers and


Me
H
MeS
SMe
92 f
NaN3 / DMSO
110°C
97 a
97 b
98
O2N
99
NaN3/DMSO
100 a
or
100 b

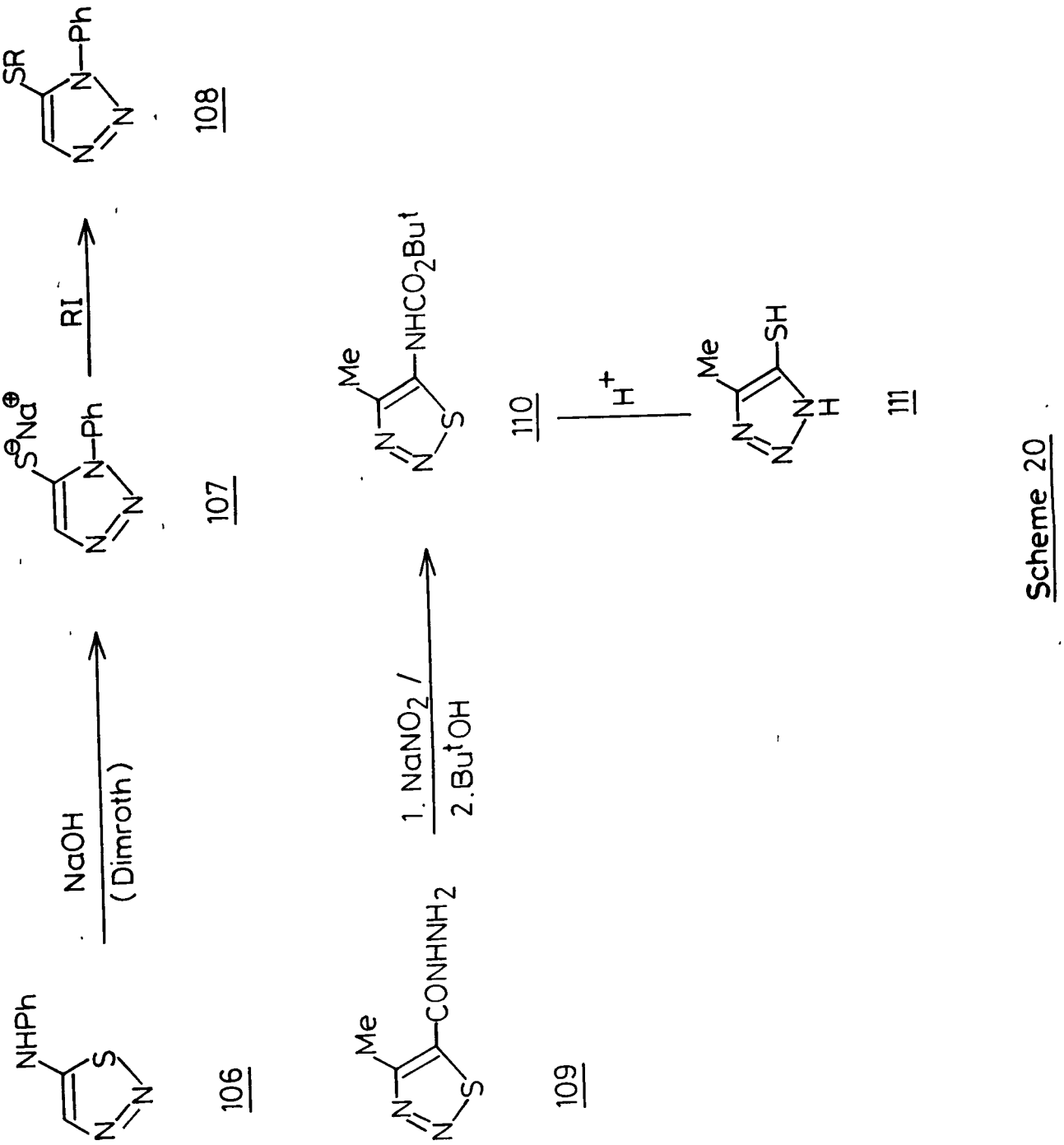
Scheme 18

vinyl chlorides have been known to undergo [3+2] cycloaddition to yield triazoles. In the course of the present investigation the reaction of tosylazide with various S,N- and N,N-acetals were investigated and the reaction was generally facile to yield the corresponding aminotriazoles. However, in the light of reactions of sodium azide with the enol ethers, the reaction of sodium azide 62 with α-oxoketene dithioacetals 92 was contemplated, where the double bond of α-oxoketene dithioacetal should serve as a good dipolarophile. The present section deals with these results.

The α-oxoketene dithioacetals 92a-e required for this investigation were prepared according to the reported procedures[36]. The structures of these compounds were confirmed by comparing the analytical and spectral data with the reported ones. When the dithioacetal 92a was reacted with sodium azide 62 at 110°C in dimethyl sulfoxide, the product isolated was identified as 4-benzoyl-5-methylthio-1H-1,2,3-triazole 96a (m.p. 123-124°C) in 72% yield. The compound was confirmed by its analytical and spectral data. The elemental analysis of 96a agreed with the molecular formula $C_{10}H_9N_3OS$, while its mass spectrum exhibited molecular ion peak at m/z 219 (M^+,100%). Its i.r. spectrum (KBr) showed a broad peak at 3170 cm^{-1} which was due to ring NH. It showed another strong peak at 1615 cm^{-1} which was assigned to carbonyl function. The ^1H n.m.r. spectrum ($CDCl_3$/ DMSO-d_6) showed a singlet at δ 2.63(3H) which was assigned to SMe protons, while the aromatic protons appeared as two multiplets at δ 7.31-7.75(3H) and δ 7.23-8.44(2H). Further confirmation of its structure was obtained from its ^{13}C n.m.r. spectrum which is described in experimental section. The reaction of other α-oxoketene dithioacetals 92b-e with sodium azide 62 similarly yielded the corresponding 4-aroyl-5-methylthio 1H-1,2,3-triazoles 96b-e in 65-75% overall yields. The structures of all the new


O2N
N
R1
N
R2
NH
Me
101
+
N
N⊕
N⊖
O=S=O
Cl
102
CH3CN
R.T. 7 days
O2N
N
R1
N
R2
N
N
Me
103
O2N
H
HN
NH
( )n
104
+
N
N⊕
N⊖
O=S=O
Cl
102
Dioxane / Δ
O2N
N
HN
N
105

Scheme 19


NHPh
106
NaOH
(Dimroth)
SNa⊕
N–Ph
107
RI
SR
N–Ph
108
CONHNH2
Me
109
1. NaNO2 /
2. But OH
NHCO2But
Me
110
H+
SH
Me
111

Scheme 20

triazoles 96b-e were confirmed with the help of analytical and spectral data, which are given in the experimental section.

The limitation of the method was experienced when the reaction of sodium azide 62 with 1-acetyl-2,2-bismethylthio ethylene 92f failed to afford the corresponding triazoles 96f. The product isolated in 52% yield, was characterized as 1-azido-1-methylthio-1-butene-3-one 97 (Scheme 18). This is probably due to greater electron-acceptor ability of the acetyl group in comparison to an aroyl group, thus resulting in a nucleophilic addition of azide ion at C-2 of 92f, rather than cycloaddition to give azido compound 97 after elimination of methylthiolate (Scheme 18). Similarly 1-nitro-2,2-bis(methylthio)ethylene 99 neither gave nitrotriazole 100a nor open chain azido compound 100b under the described conditions.

A related 4-nitro 5-amino-1,2,3-triazoles 103 and 3-nitro 5,6-dihydro-imidazolo [3,2-c] [1,2,3] triazoles 105 are reported in literature[37] which have been synthesized by cycloaddition of nitroketene aminals 101 and 104 carrying at least one NH with p-chlorobenzene sulphonyl azide 102. Cycloaddition seems to be followed by Dimroth rearrangement and elimination of p-chlorobenzene sulphonamide, to give finally triazoles (Scheme 19).

The Scant literature on the 5-methylthio triazoles appears to be due to non-availability of suitable precursors. The reported method for the synthesis of 1-phenyl-5-alkylthio triazole 108 involves Dimroth rearrangement of the corresponding 5-anilino thiadiazole 106 to intermediate 107 which was followed by alkylation[38]. Similarly 4-methyl-5-mercapto triazole 111 has been obtained by the Dimroth rearrangement followed by hydrolysis of thiadiazole 110 (Scheme 20)[39].

II.3 CONCLUSION

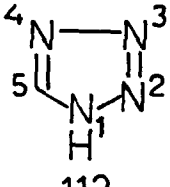
In conclusion it may be summarized: (1) A method of preparative importance for the synthesis of 5-aminotriazoles 79, 80 and 81 is formulated from the easily available ketones via α-oxoketene S,N-acetals 76. (2) A novel general approach for 3-benzoyl-5,6-dihydrothiazolo [3,2-c] [1,2,3] triazole 84 and 3-benzoyl 5,6-dihydro imidazolo [3,2-c] [1,2,3] triazole 91 has been developed by reaction of the corresponding cyclic S,N-82 and N,N-acetals 90 with tosylazide 27. The reaction yields the thiazolotriazole 84 and imidazole 91 under simpler reaction conditions from easily available cyclic S,N- and N,N-acetals in excellent yields. (3) The oxoketene dithioacetals 92 provide facile entry to novel substituted 5-methylthio triazoles 96.

II.4 CYCLOADDITION OF SODIUM AZIDE TO POLARIZED KETENE S,N-ACETALS: SYNTHESIS OF NOVEL SUBSTITUTED TETRAZOLE DERIVATIVES

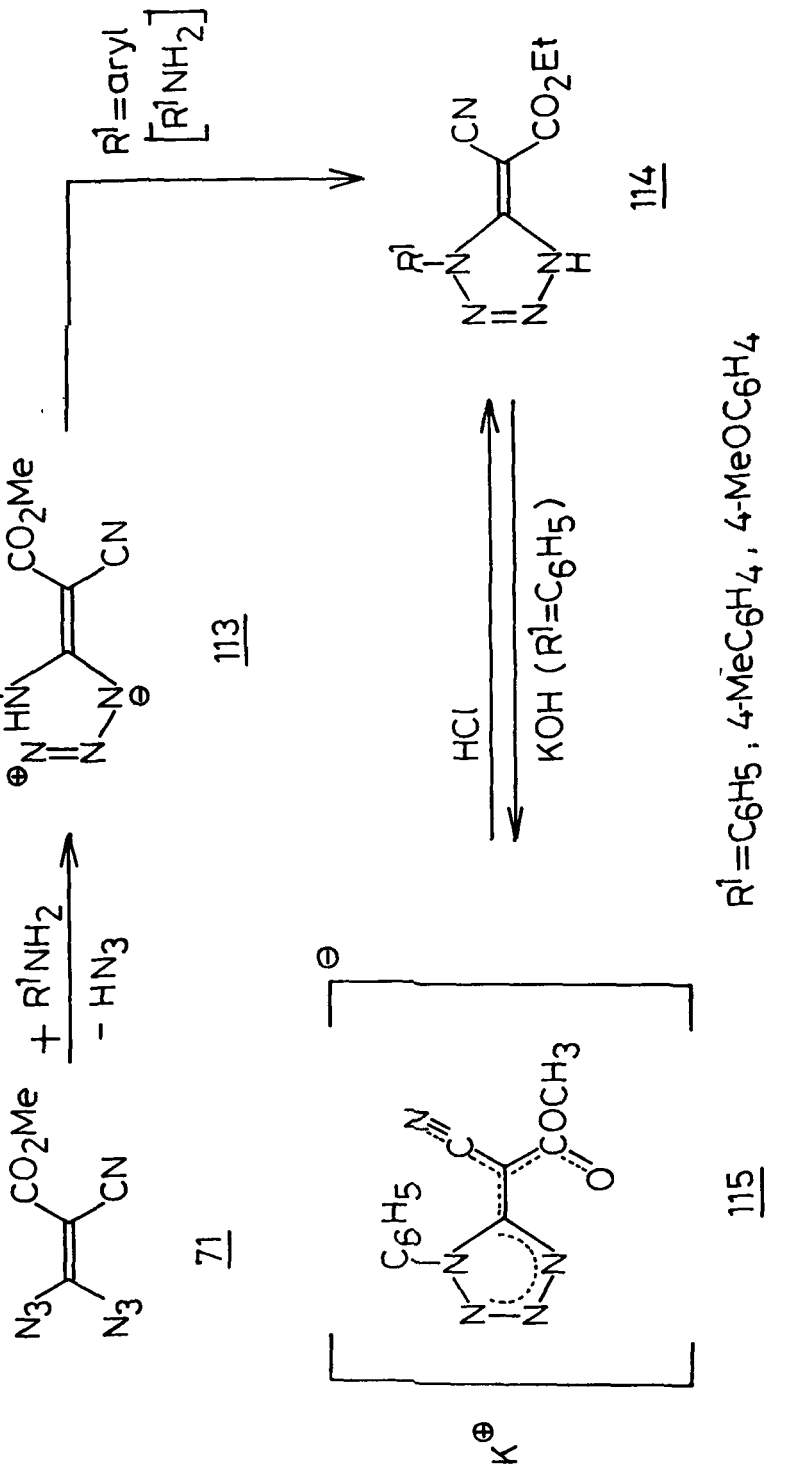
II.4.1 INTRODUCTION

In the preceding section, the reaction of sodium azide with α-oxoketene dithioacetals is described. It was further considered of interest to examine the reactivity of α-oxoketene S,N-acetals towards sodium azide. These results are presented in this section.

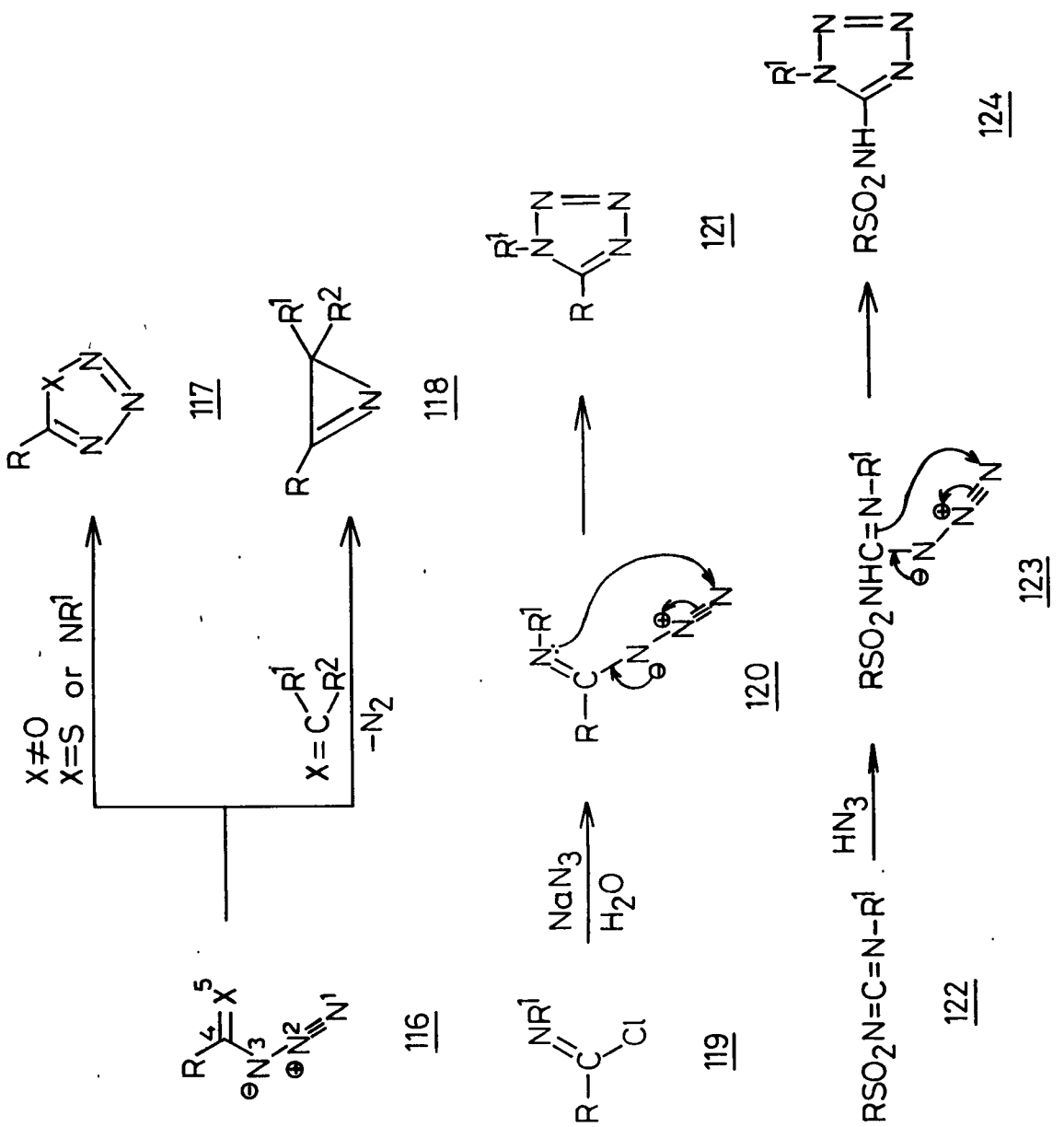
The first tetrazole derivative of the general formula 112 was reported[40] almost a century ago. Like other higher azoles this class of compounds received little attention. By the late forties the potential of the higher azoles in the fields of explosives[41], photography[42] and agriculture[43] had been realized and this led to renewed interest in these compounds.



112


R¹=aryl [R¹NH₂]
+ R¹NH₂
- HN₃
HCl
KOH (R¹=C₆H₅)
R¹=C₆H₅ ; 4-MeC₆H₄ , 4-MeOC₆H₄
71
113
114
115

Scheme 21



Scheme 22

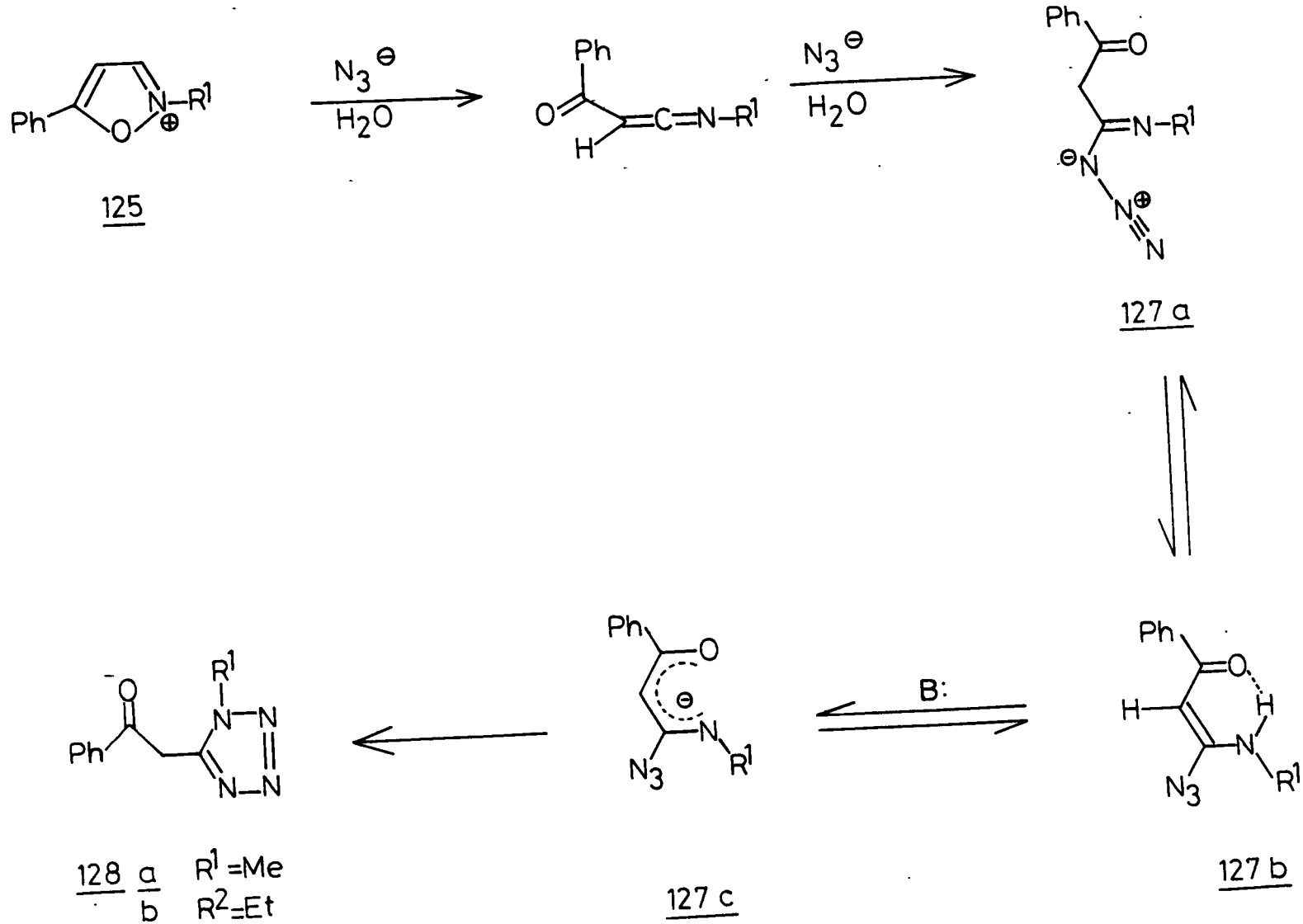
The subsequent discovery of the pharmacological[44] and biochemical[45] properties of tetrazole derivatives has resulted in an enormous development over the past 20 years.

There are extensive reviews on the Chemistry of tetrazoles in the literature[46,47,48]. A brief survey of some of the current methods for the synthesis of tetrazoles is presented here.

Saalfrank and co-workers have reported[49] that the reaction of methyl 3,3-diazido-2-cyano acrylate 71 with primary arylamines leads to donor substituted vinyl azides 113, which undergo base catalysed isomerization in dichloromethane to afford the tetrazole derivatives 114 (Scheme 21). The compounds 114 forms potassium salt 115 as it dissolves in aqueous potassium hydroxide, which can be reversed back into tetrazole 114 by acidification with hydrochloric acid (Scheme 21).

Molecules with an azide group bonded to a doubly bound carbon may exist in acyclic 116 or cyclic form 117 (Scheme 22). When X is an oxygen atom, the molecule exists in the acyclic form 116 and when X is sulfur atom, the cyclic form 117 predominates. When X is N-R' moiety, an equillibrium of both forms may be present or either form may predominatae (Scheme 22)[48]. Thus the synthesis and cyclization of imidoyl azides 120 from imidoyl chloride 119 is a principal route to 1,5-disubstituted tetrazoles 121 (Scheme 22)[50].

The cyclization of imidoyl azides 120 usually occurs spontaneously. In the cyclization the formation of the activated complex entails a movement of the imino lone pair towards the terminal azido nitrogen at the same time as a lone pair being formed on the central azido nitrogen at the expense of the azido terminal π-bond. The cyclization is an example


Ph
N–R1
O
125
N3 ⊖
H2O
Ph
O
C=N–R1
H
N3 ⊖
H2O
Ph
O
N–R1
⊖N
N⊕
N
127 a
Ph
O
H
N
N3
R1
127 b
B:
Ph
O
⊖
N
N3
R1
127 c
R1
N–N
N–N
Ph
O
128 a R1 =Me
b R2=Et

Scheme 23

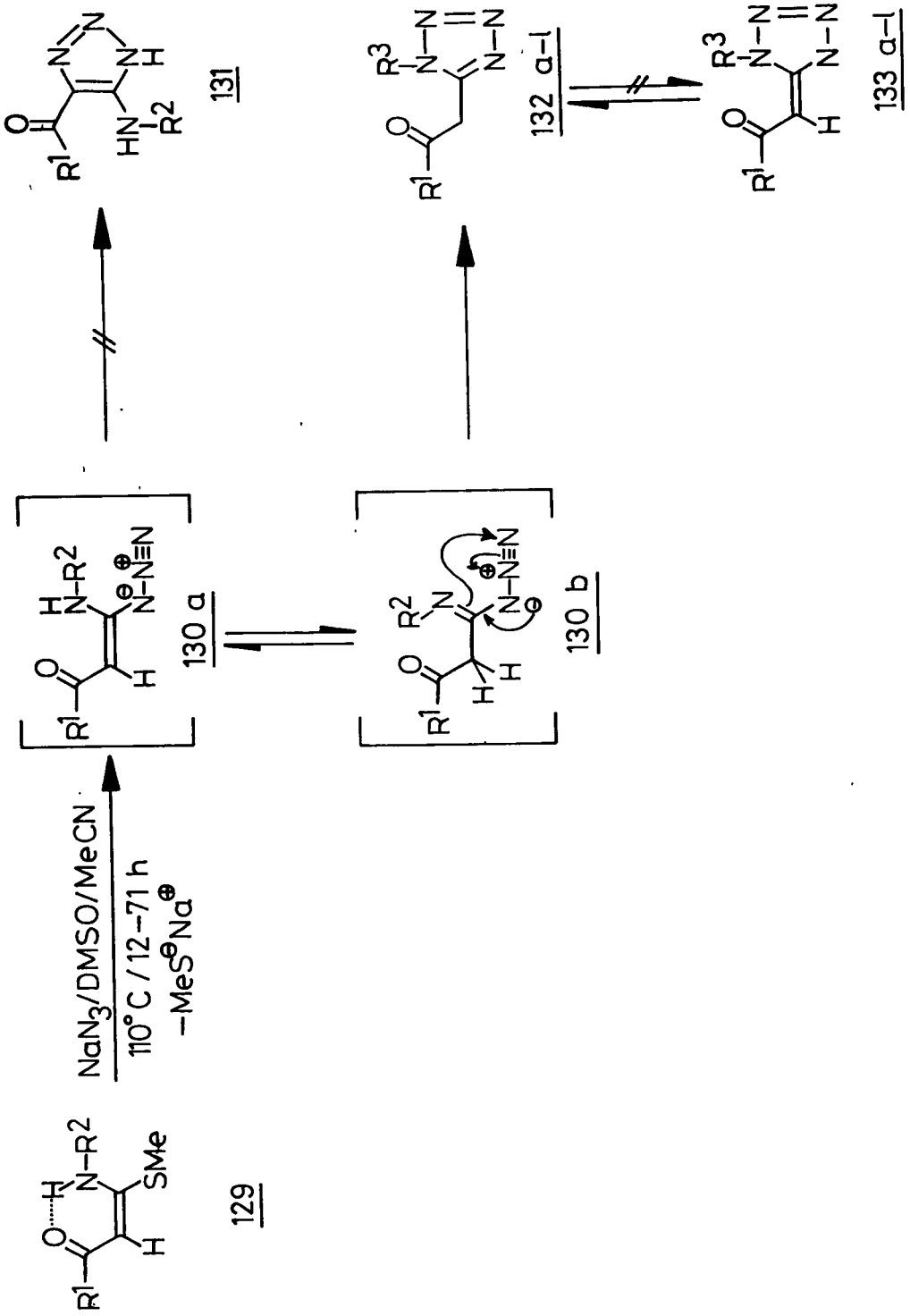
of a 1,5-heteroelectrocyclization operating in conformation with the principle of conservation of orbital symmetry (Scheme 22)[51].

Treatment of the sulfonyl carbodiimides 122 with hydrazoic acid yielded the 1-substituted-5-sulfonyl aminotetrazoles 124 via an iminoazide 123 (Scheme 22)[52].

Woodward and co-workers developed a novel method for 1,5-disubstituted tetrazoles 128. Thus, 5-phenyl-isoxazolium methyl sulfate 125 reacted with sodium azide 62 to give an open chain intermediate imino azide 127 which underwent smooth ring closure to afford the tetrazole 128 in boiling ethanol (Scheme 23)[53]. There are two main structural constraints on the cyclization of imidoyl azides 127a-c, one of these is a stereoelectronic effect which arises from the required cis orientation of the imino lone pair and the azido group. The other arises from the electronic effects of substituents on the imino moiety. Imidoyl azides in which the azido group and the imino lone pair are in a trans arrangement do not cyclize without prior inversion in accordance with the requirements of the transition state (Scheme 23)[54]. In compound 127b, interestingly, the azido form is stablized by an intramolecular hydrogen bond. The open chain imino azides 127 readily converted into tetrazoles 128 through a series of geometrical configurations of which 127a leads to 128.

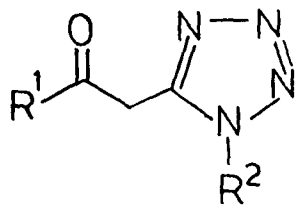
II.4.2 RESULTS AND DISCUSSION

All the ketene S,N-acetals 129a-g required for the present investigation were prepared according to the reported procedures[34,35]. And the unreported 129h and i were prepared as described in the preceding section. When S,N-acetal 129a was reacted with sodium azide at 110°C in 1:2 Dimethyl sulfoxide/acetonitrile, the product isolated was characterized as 1-phenyl-5-(p-toluolyl) methyl tetrazole 132a (m.p. 85-86°C) in 72% yield,


NaN3/DMSO/MeCN
110°C / 12–71 h
–MeS⊖Na⊕
129
130 a
130 b
131
132 a–l
133 a–l

Scheme 24

Table 2

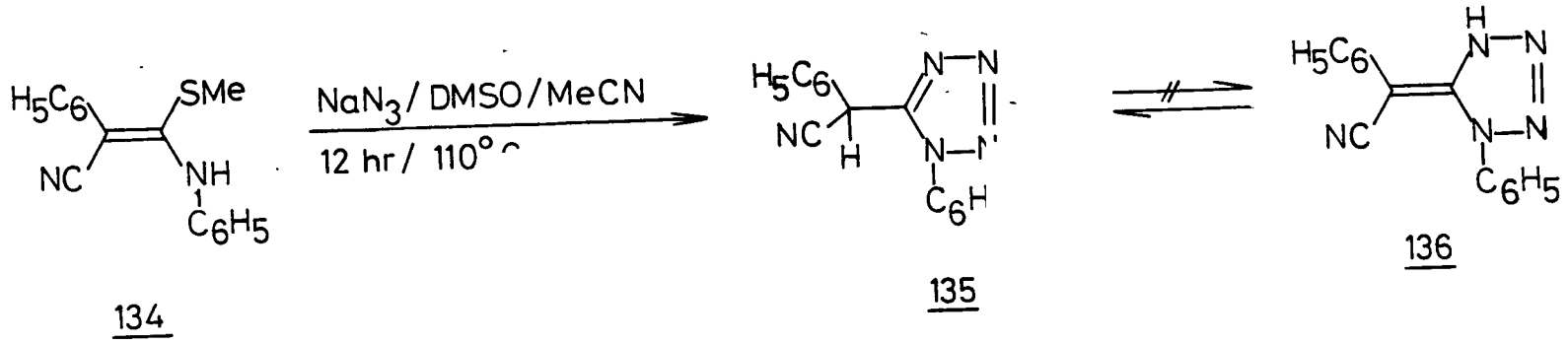


132

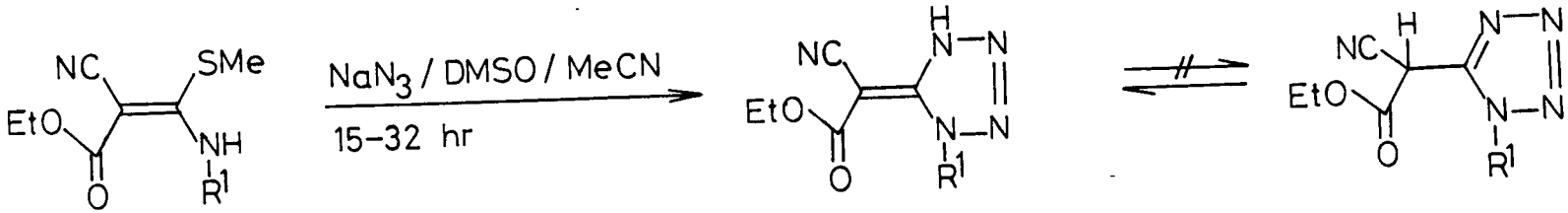
129, 132	R^1	R^2
a	4-MeC_6H_4	C_6H_5
b	4-ClC_6H_4	C_6H_5
c	C_6H_5	$C_6H_5CH_2$
d	4-$MeOC_6H_4$	$C_6H_5CH_2$
e	C_6H_5	CH_3
f	C_6H_5	C_2H_5
g	C_6H_5	n-C_3H_7
h	C_6H_5	i-C_3H_7
i	C_6H_5	cyclo-C_6H_{11}
j	Me	C_2H_5

instead of the corresponding 5-anilinotriazole 131. The structure of tetrazole 132a was confirmed from its analytical and spectral data. Thus tetrazole 132a showed molecular ion peak at m/z 272 (M^+,5) and another peak at m/z 250(M^+-28,23) due to loss of nitrogen from molecular ion which is characteristic of tetrazoles. Its i.r. spectrum (KBr) exhibited sharp peaks at 1678 and 1599 cm^{-1} due to carbonyl and C=N stretching frequencies respectively. The ^1H n.m.r. spectrum of tetrazole 132a showed a signal at δ 2.36 (s,3H) which was assigned to methyl protons. The singlet at δ 4.65(2H) was assigned to methylene protons, which establishes the tautomeric form 132a rather than 133a, while the aromatic protons appeared as a doublet at δ 7.24(2H) and 7.50(2H). Similarly the other α-oxoketene S,N-acetals 129b-j were reacted with sodium azide 62 under identical conditions to yield the corresponding tetrazoles 132b-j in 63-79% overall yields. All the tetrazoles 132b-j were confirmed by their analytical and spectral data and found to exist in phenacyl form rather than 133. These data are described in the experimental section. Similarly the α-cyanobenzyl ketene S,N-acetal 134 derived from phenyl acetonitrile reacted with sodium azide 62 in dimethyl sulfoxide/acetonitrile mixture to yield the expected tetrazole 135. From its analytical and spectral data (experimental section) it was concluded that it exists as 135 rather than 136(Scheme 25).

Interestingly the S,N-acetals 137a derived from ethyl cyanoacetate reacted with sodium azide 62 under similar reaction condition to yield the tetrazole 138a, which from its ^1H n.m.r. spectrum ($CDCl_3$) established that it exists as 5-(ethoxy carbonyl cyano)-methylene- Δ^2-tetrazoline tautomeric form 138a not as 139a. The band at 3160 cm^{-1} due to NH which was absent in all tetrazoles was indicative of its structural deviation, also the signal at δ 12.05 exchangeable with D_2O confirms the existence of ring



134 135 136

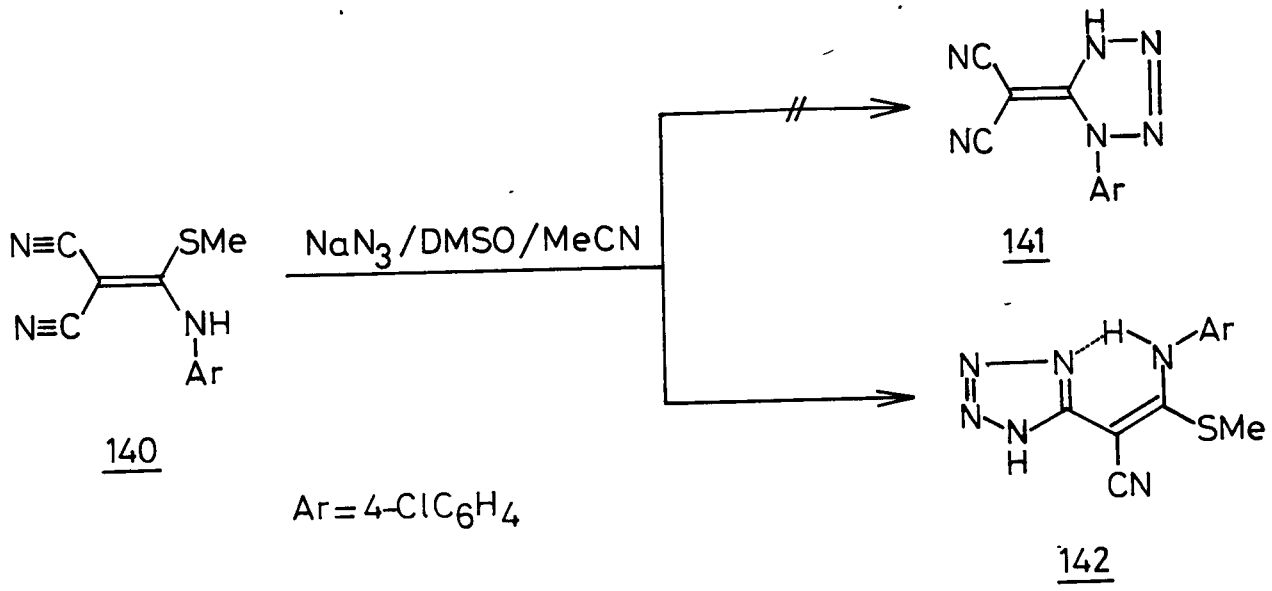


137 138 a-b 139 a-b

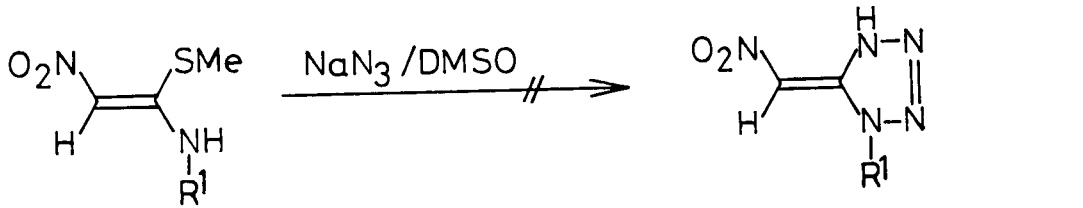
137–139 a $R^1=C_6H_5$

b $R^1=C_6H_5CH_2$

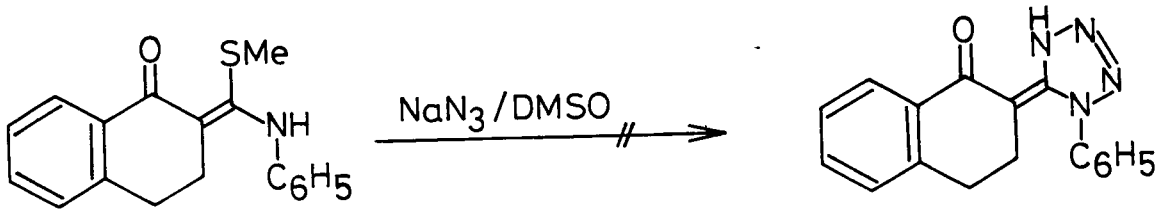
Scheme 25



140 141 142



143 144 a $R^1 = C_6H_5$ b $R^1 = C_6H_5CH_2$



145 146

Scheme 26

NH proton. The analytical and spectral data of 138a is described in the experimental section. Similarly tetrazole 138b was also found to exist in the 5-(ethoxy carbonyl cyano) methylene form in accordance with its analytical and spectral data which are described in the experimental section. It may be noted that among a large number of tetrazoles described above, only the tetrazoles 138a and 138b exhibit the exocyclic methylene double bond as an exclusive tautomer. It appears that the two electron withdrawing groups renders this hydrogen too acidic and consequently makes the tautomer 139 unstable (Scheme 25).

On the otherhand, the S,N-acetal 140 obtained from malononitrile reacted with sodium azide 62 under the identical conditions. The azide 62 added to one of the nitrile groups to yield the corresponding tetrazole 142 (Scheme 26). The difference in behaviour of 137a-b and 140 can be rationalized in terms of greater delocalization of non bonding electrons of amino nitrogen over the more polar nitrile group in 137a-b than over the ester group. The presence of two nitrile groups in S,N-acetal 140 facilitates the addition to one of the cyano groups. The structure of 142 was confirmed by its analytical and spectral data which are described in experimental section.

The S,N-acetals 143 and 145 derived from nitromethane and tetralone respectively did not yield the expected tetrazoles 144 and 146 respectively (Scheme 26).

II.5 EXPERIMENTAL

General

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. The i.r. spectra were recorded on a 'Perkin-Elmer 297' spectrometer and frequencies are expressed in cm^{-1}. The ^{1}H n.m.r. spectra

were recorded on a Varian EM 390, 90MHz spectrometer using tetramethyl silane (TMS) as internal standard and chemical shifts values are expressed as δ (ppm). The mass spectra were recorded on a Jeol-D 300 spectrometer and relative intensities are expressed in percentage. ^{13}C n.m.r.spectra were recorded on a Brucker WH-270 spectrometer. Carbon, hydrogen, nitrogen elemental analysis were done at Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of various acetophenones, amines, acetonitrile, ethanol, dimethylsulfoxide, dioxane, pyridine were purified before use. Phenylisothiocyanate, and isopropylisothiocyanate and cyclohexyl isothiocyanate were prepared according to reported procedure[55,56]. Commercially available sodium azide was used as such. Tosyl azide was prepared according to reported procedure[57].

The required α-oxoketene dithioacetals 92a-f were prepared according to reported procedure[36]. The known ketene S,N-acetals 76a-h were prepared according to the reported procedure[34,35] and their analytical and spectral data were found to be similar to that of reported ones. The unknown α-oxoketene S,N-acetals 76i-l were prepared by extending the reported procedures[34] and the structures were confirmed by their analytical and spectral data which are given below.

3-Methylthio-3-n-propylamino-1-(4-chlorophenyl)-2-propen-1-one (76i) was obtained as pale yellow solid (benzene/hexane); yield 87%; m.p. 65-66°C; i.r.(KBr): ν_{max} = 1575, 1535, 1466 cm^{-1}; ^1H n.m.r. (CCl_4): δ 1.02(t,3H, J=7Hz,$CH_3CH_2CH_2$); 1.70(sext,2H,J=7Hz,$CH_3CH_2CH_2$); 2.37(s,3H,SCH_3); 3.24 (q,2H,J=7Hz,$HN-CH_2CH_2CH_3$); 5.42(s,$1H_{olefin}$); 7.23(d,J=9Hz,$2H_{arom}$);

7.72(d,J=7Hz,$2H_{arom}$); 11.90(brs,1H,NH, exchangeable with D_2O). (Found: C,58.06; H,6.15; N,5.37. Calc. for $C_{13}H_{16}ClNOS$(269.7): C,57.88; H,5.94; N,5.19%). m/z 271(M^+,20); 269(M^+,45).

3-Isopropylamino-3-methylthio-1-phenyl-2-propen-1-one (76j) was obtained as viscous liquid (TLC single spot); yield 91%; i.r.(KBr): ν_{max} = 3240, 1623, 1542 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.30[d,6H,J=7Hz,$(CH_3)_2CH$]; 2.35(s,3H, SCH_3); 3.82[sept,1H,J=7Hz,$(CH_3)_2CH$]; 5.60(s,$1H_{olefin}$); 7.04-7.41(m,$3H_{arom}$); 7.80-7.85(m,$2H_{arom}$); 11.90(brs,1H,NH,exchangeable with D_2O). (Found: C,66.01; H,7.44; N,6.16. Calc. for $C_{13}H_{17}NOS$(235.2): C,66.33; H,7.23; N,5.95%).

3-n-Butylamino-3-methylthio-1-(4-methylphenyl)-2-propen-1-one (76k) was obtained as yellow solid (benzene/hexane); yield 88%; m.p. 47-48°C; i.r.(KBr): ν_{max} = 3415, 1568, 1470 cm^{-1}; ^1H n.m.r.(CCl_4): δ 0.98(t,3H, J=6Hz,$CH_3CH_2CH_2CH_2$); 1.22-1.71(m,4H,$CH_3CH_2CH_2CH_2$); 2.31(s,3H,CH_3); 2.34 (s,3H,SCH_3); 3.29(q,2H,J=6Hz,$HN-CH_2CH_2CH_2CH_3$); 5.50(s,$1H_{olefin}$); 7.05 (d,J=7.5Hz,$2H_{arom}$); 7.68(d,J=7.5Hz,$2H_{arom}$); 11.92(brt,1H,exchangeable with D_2O). (Found: C,68.21; H,8.19; N,5.16: Calc. for $C_{15}H_{21}NOS$(263.2): C,68.39; H,7.98; N,5.32%).m/z 263(M^+,43).

3-Cyclohexylamino-3-methylthio-1-(4-chlorophenyl)-2-propen-1-one (76l) was obtained as pale yellow solid (benzene/hexane); yield 81%; m.p. 74-75°C; i.r.(KBr): ν_{max} = 1562, 1468 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.81-2.21(m,10H, ring CH_2); 2.43(s,3H,SCH_3); 3.61(quint,1H,CH); 5.38(s,$1H_{olefin}$); 7.39(d,J=9Hz,$2H_{arom}$); 7.84(d,J=9Hz,$2H_{arom}$); 11.98(brs,1H,NH,exchangeable with D_2O). (Found: C,62.29; H,6.24; N,4.70. Calc. for $C_{16}H_{20}ClNOS$(309.7): C,62.00; H,6.46; N,4.52%). m/z 311(17); 309(M^+,45).

3-Cyclohexylamino-3-methylthio-1-phenyl-2-propen-1-one (129i) was was obtained as yellow solid (benzene/hexane); yield 83%; m.p. 79-80°C; i.r.(KBr): ν_{max} = 3400, 1540, 1470 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.15-2.15 (m,10H, ring CH_2); 2.45(s,3H,SCH_3); 3.60(quint,1H,J=6.5Hz,CH); 5.51 (s,$1H_{olefin}$); 7.21-7.47(m,$3H_{arom}$); 7.68-7.90(m,$2H_{arom}$); 10.05(brs,1H, NH,exchangeable with D_2O). (Found: C,69.51; H,7.83; N,4.97. Calc. for $C_{16}H_{21}NOS$(275.3): C,69.80; H,7.63; N,5.09%). m/z 275(M^+,25).

Cyclic S,N-acetals 82a-c were prepared by the modification of reported procedure[58]. A solution of aziridine (0.06 mole) in dry ether (50 ml) was added slowly to an ice cooled and stirred solution of dithioester (0.05 mole) in dry ether (100 ml) and the reaction mixture was further stirred at r.t. for 5 hrs. (monitored by TLC). The ether layer was evaporated on water bath to dryness. The residue dissolved in acetone (100 ml) and potassium iodide (KI) (0.4 mole) added to the reaction mixture. The reaction mixture was stirred at r.t. for 8 hrs. (monitored by TLC). The solid potassium iodide was filtered and mother liquor evaporated to dryness. Chloroform was added (100 ml) to the residue and organic layer washed with water (3x50 ml) and dried over sodium sulfate and evaporated to give dark coloured residue, which on column *chromatography over silica gel using hexane/ethylacetate (9:1) as eluent* affords pure cyclic S,N-acetals 82a-c. Structures were confirmed by their spectral and analytical data which are given below.

4,5-Dihydro-2-benzoylmethylene thiazole (82a) was obtained as yellow crystalline solid (DMF/Ethanol);yield 68%; m.p. 159-160°C; i.r.(KBr): ν_{max} = 3190, 1586, 1564 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6);δ3.27(t,2H,J=6Hz, S-CH_2CH_2); 3.95(t,2H,J=6Hz,N-CH_2CH_2); 5.94(s,$1H_{olefin}$); 7.29-7.54(m,

$3H_{arom}$); 7.73-7.96(m,$2H_{arom}$). (Found: C,64.08; H,5.49; N,6.71. Calc. for $C_{11}H_{11}NOS$(205.2): C,64.39; H,5.37; N,6.83%).

4,5-Dihydro-2-(4-chlorobenzoyl)methylene thiazole (82b) was obtained as yellow crystalline solid (DMF/Ethanol); yield 71%; m.p. 183-184°C; i.r.(KBr):ν_{max} = 3150, 1593, 1564 cm^{-1}; ^1H n.m.r.(DMSO-d_6):δ3.20(t, 2H,J=6Hz,SCH_2CH_2); 3.77(t,2H,J=6Hz,NCH_2CH_2); 6.03(brs,$1H_{olefin}$); 7.45 (d,J=8Hz,$2H_{arom}$); 7.88(d,J=8Hz,$2H_{arom}$). (Found: C,54.88; H,4.30; N,6.01. Calc. for $C_{11}H_{10}ClNOS$(239.7): C,55.07; H,4.17; N,5.84%).

4,5-Dihydro-2-(4-methoxybenzoyl)methylene thiazole (82c) was obtained as yellow crystalline solid (DMF/Ethanol); yield 66%; m.p. 152-153°C; i.r.(KBr):ν_{max} = 3222, 1590, 1568 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 3.21(t, 2H,J=6Hz,SCH_2CH_2); 3.78(s,3H,OCH_3); 3.83(t,2H,J=6Hz,N-CH_2CH_2); 5.92 (brs,$1H_{olefin}$); 6.30(d,J=9Hz,$2H_{arom}$); 7.81(d,J=9Hz,$2H_{arom}$); 9.79(brs, 1H,NH,exchangeable with D_2O). (Found: C,61.34; H,5.44; N,6.07. Calc. for $C_{12}H_{13}NO_2S$(235.2): C,61.22; H,5.53; N,5.95%).

The unknown cyclic N,N-acetals 90b-j were prepared by extending the following reported procedure[35]. A solution of α-oxoketene dithioacetals (0.02 mol) and appropriate amine (0.025 mol) in ethanol (50 ml) was refluxed for 15 hrs. After completion of the reaction (monitored by TLC), the solvent was removed and the crude cyclic N,N-acetals thus obtained were purified by crystallization from boiling ethanol/DMF (4:1). Structures of all the compounds were confirmed by their analytical and spectral data which are given below.

4,5-Dihydro-2-(4-methylbenzoyl)methylene imidazole (90b) was obtained as a white crystalline solid (DMF/ethanol); yield 93%; m.p. 268°C; i.r. (KBr):ν_{max} = 3332, 1600, 1575 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ2.48(s,3H,CH_3);

4.06(s,4H,N-$\underline{CH_2}\underline{CH_2}$-N); 4.43(s,2H,$\underline{CH_2}$); 7.30(d,J=9Hz,$2H_{arom}$); 7.82(d, J=9Hz,$2H_{arom}$); 8.60(brs,1H,NH). (Found: C,71.03; H,7.05; N,13.98. Calc. for $C_{12}H_{14}N_2O$(202.2): C,71.22; H,6.92; N,13.85%).

4,5-Dihydro-2-(4-chlorobenzoyl)methylene imidazole (90c) was obtained as a white crystalline solid (DMF/ethanol); yield 91%; m.p. 267-268°C; i.r. (KBr):ν_{max} = 3312, 1604, 1549 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA):δ3.91 (s,4H,N-$\underline{CH_2}\underline{CH_2}$N); 4.31(s,2H, $\underline{CH_2}$); 7.32(d,J=9Hz,$2H_{arom}$); 7.73(d,J=9Hz, $2H_{arom}$); 9.88(brs,1H,NH). (Found: C,59.09; H,5.13; N,12.41. Calc. for $C_{11}H_{11}ClN_2O$(222.7): C,59.27; H,4.94; N,12.57%).

4,5-Dihydro-2-(4-methoxybenzoyl)methylene imidazole(90d) was obtained as white crystalline solid (DMF/ethanol); yield 92%; m.p. 230-231°C; i.r.(KBr):ν_{max} = 3120, 1594, 1549 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA):δ 3.88 (s,3H,O$\underline{CH_3}$); 4.03(s,4H,N-$\underline{CH_2}\underline{CH_2}$); 4.42(s,2H,$\underline{CH_2}$); 7.00(d,J=9Hz,$2H_{arom}$); 7.90(d, J=9Hz,$2H_{arom}$); 8.58(s,1H,NH). (Found: C,66.12; H,6.31; N,12.94. Calc. for $C_{12}H_{14}N_2O_2$(218.2): C,65.99; H,6.42; N,12.83%).

4,5-Dihydro-2-(2-thienyl)methylene imidazole (90e) was obtained as yellow crystalline solid (ethanol); yield 89%; m.p. 204-205°C; i.r.(KBr):ν_{max} = 3120, 1607, 1545 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA);δ4.12(s,4H,N-$\underline{CH_2}\underline{CH_2}$-N); 4.40(s,2H,$\underline{CH_2}$); 7.30(t,1H,H-4'); 7.98(d,2H,H-3'5'); 8.60(brs,1H,NH). (Found: C,55.73; H,5.28; N,14.33. Calc. for $C_9H_{10}N_2OS$(194.2); C,55.61; H,5.15; N,14.42%).

2-Benzoylmethylene hexahydropyrimidine (90f) was obtained as white crystalline solid (DMF/ethanol); yield 93%; m.p. 204-205°C; i.r.(KBr):ν_{max}= 3241, 3192, 1618, 1597 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ1.84(quint,2H, J=6Hz,CH_2 $\underline{CH_2}CH_2$); 3.09-3.48(m,4H,N$\underline{CH_2}$-CH_2-$\underline{CH_2}$-N); 5.05(s,$1H_{olefin}$); 7.27-7.49(m,$3H_{arom}$); 7.58-7.80(m,$2H_{arom}$). (Found: C,71.36; H,7.04;

N,14.01. Calc. for $C_{12}H_{14}N_2O$(202.2): C,71.22; H,6.92; N,13.85%).

2-(4-Chlorobenzoyl)methylene hexahydropyrimidine (90g) was obtained as white crystalline solid (DMF/ethanol); yield 91%; m.p. 235-237°C; i.r. (KBr): ν_{max} = 3250, 3195, 1621, 1597 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.85(quint,2H,J=6Hz,CH_2-$\underline{CH_2}$-CH_2):3.20(t,4H,J=6Hz,N-$\underline{CH_2}CH_2\underline{CH_2}$-N); 5.05(s,1$H_{olefin}$); 7.28(d,J=9Hz,2$H_{arom}$); 7.62(d,J=9Hz,2$H_{arom}$). (Found: C,61.02; H,5.31; N,11.76. Calc. for $C_{12}H_{13}ClN_2O$ (236.7): C,60.84; H,5.49; N,11.83%).

2-(4-Methoxybenzoyl)methylene hexahydropyrimidine (90h) was obtained as white crystalline solid (DMF/ethanol); yield 88%; m.p. 210-211°C; i.r.(KBr): ν_{max} = 3270, 3200, 1631, 1596 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ 3.32(brt,4H,N$\underline{CH_2}$-$CH_2\underline{CH_2}$); 3.82(s,3H,O$\underline{CH_3}$); 4.21(s,2H,$\underline{CH_2}$); 6.82(d, J=9Hz,2H_{arom})7.75(d,J=9Hz,2H_{arom}); 9.61(brs,1H,NH). (Found: C,66.99; H,6.93; N,11.89. Calc. for $C_{13}H_{16}N_2O_2$(232.2): C,67.18; H,6.89; N,12.05%).

2-(2-Furyl)methylene hexahydropyrimidine (90i) was obtained as pale yellow crystalline solid (DMF/ethanol); yield 83%; m.p. 122-123°C; i.r.(KBr): ν_{max} = 3100, 1611 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.83(quint,2H,J=6Hz,$CH_2\underline{CH_2}CH_2$); 3.21(t,4H,J=6Hz,N-$\underline{CH_2}$-CH_2-$\underline{CH_2}$); 5.20(s,1H_{olefin}); 6.29-6.42(m,1H,H-4'); 6.72(d,1H,H-3'); 7.32(s,1H,H-5'). (Found: C,62.29; H,6.31; N,14.71. Calc. for $C_{10}H_{12}N_2O_2$(192.2): C,62.43; H,6.24; N,14.57%). m/z 192(M^+,48).

2-(Naphthyl)methylene hexahydropyrimidine (90j) was obtained as yellow crystalline solid (DMF/ethanol); yield 86%; m.p. 223-224°C; i.r.(KBr): ν_{max} = 3243, 3190, 1618, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ 1.98(quint, 2H,J=6Hz,CH_2-$\underline{CH_2}CH_2$); 3.42(brt,4H,N-$\underline{CH_2}CH_2\underline{CH_2}$); 4.35(s,2H,$\underline{CH_2}$); 7.32-7.95 (m,6$H_{arom}$); 8.31(s,1$H_{arom}$); 8.70(brs,2H,NH+NH). (Found: C,75.96; H,6.21;N,10.97. Calc. for $C_{16}H_{16}N_2O$(252.3): C,76.09; H,6.34; N,11.10%).

1-Aryl/alkyl-4-aroyl/acyl-5-tosylamino-1H-1,2,3-triazoles 79a-m;

General Procedure:

A solution of sodium hydroxide (4.80g, 0.012 mol) in ethanol (10 ml) was added slowly during 5 min. to an ice-cooled and stirred suspension of respective S,N-acetals 76 (0.01 mol) and tosyl azide 27 (2.36g,0.012 mol) in ethanol (10 ml), and the reaction mixture was further stirred at room temperature for 10 hrs. It was then poured over crushed ice (150g), acidified with 20% acetic acid (30 ml), and extracted with chloroform (3x50 ml). The organic extract was washed with water (3x50 ml), dried over sodium sulfate and evaporated to give crude triazoles 79a-m which were further purified by recrystallization from boiling ethanol.

4-Benzoyl-1-phenyl-5-tosylamino-1H-1,2,3-triazole (79a) obtained as white crystalline solid (ethanol); yield 57%; m.p. 180-181°C; i.r. (KBr): ν_{max} = 3185, 1639, 1595, 1398, 1162, 920 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.06(s,3H,CH_3); 6.98(d,J=8Hz,2H$_{arom}$); 7.21-7.82(m,10H$_{arom}$); 8.22(dd, J=8Hz,2H$_{arom}$); 8.15(s,1H,NH, exchangeable with D_2O). (Found: C,62.90; H,4.63; N,13.11. Calc. for $C_{22}H_{18}N_4O_3S$(418.5): C,63.14; H,4.33; N,13.39%). m/z 418(M^+,1); 353(11); 325(14).

4-(4-Chlorobenzoyl)-1-phenyl-5-tosylamino-1H-1,2,3-triazole (79b) was obtained as white solid (ethanol); yield 65%; m.p. 182-183°C; i.r.(KBr): ν_{max} = 3158, 1625, 1575, 1400, 1160, 917 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.09(s,3H,CH_3); 6.93(d,2H,J=8Hz$_{arom}$); 7.21-8.82(m,9H$_{arom}$); 8.21(d, 2H,J=8Hz$_{arom}$); 8.48(s,1H,NH,exchangeable with D_2O). (Found: C,58.61; H,3.51; N,12.59. Calc. for $C_{22}H_{17}ClN_4O_3S$(452.9): C,58.34; H,3.78; N,12.37%). m/z 452(M^+,2); 389(4); 387(8); 361(5); 359(11).

1-Benzyl-4-benzoyl-5-tosylamino-1H-1,2,3-triazole (79c) was obtained as white crystalline solid (ethanol); yield 47%; m.p. 205-206°C; i.r. (KBr): ν_{max} = 3175, 1640, 1595, 1408, 1162, 920 cm^{-1}; ^1H n.m.r.(DMSO-d_6/$CDCl_3$): δ 2.01(s,3H,CH_3); 5.72(s,2H,$C_6H_5CH_2$); 6.93(d,J=8Hz,$2H_{arom}$); 7.20-7.55(m,$10H_{arom}$); 7.91(dd,J=8Hz,$2H_{arom}$). (Found: C,64.05; H,4.97; N,13.16. Calc. for $C_{23}H_{20}N_4O_3S$(432.5): C,63.87; H,4.66; N,12.95%). m/z 432 (M^+,36).

4-Acetoyl-1-benzyl-5-tosylamino-1H-1,2,3-triazole (79d) was obtained as white crystalline solid (ethanol); yield 54%; m.p. 143-144°C; i.r.(KBr): ν_{max} = 3243, 1673, 1560, 1398, 115, 952 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.26 (s,3H,CH_3); 2.38(s,3H,CH_3); 5.82(s,2H,$C_6H_5CH_2$); 7.10-7.62(m,$9H_{arom}$); 7.80(s,1H,NH,exchangeable with D_2O). (Found: C,58.66; H,5.19; N,14.95. Calc. for $C_{18}H_{18}N_4O_3S$(370.4): C,58.66; H,5.11; N,15.13%). m/z 370(M^+,3); 277(4).

1-Benzyl-4-(4-methylbenzoyl)-5-tosylamino-1H-1,2,3-triazole (79e) was obtained as white crystalline solid (ethanol); yield 51%; m.p. 180-181°C; i.r.(KBr): ν_{max} = 3150, 1625, 1600, 1160, 919 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.01(s,3H,CH_3); 2.40(s,3H,CH_3); 5.90(s,2H,CH_2); 6.98(d,J=9Hz,$2H_{arom}$); 7.12-7.57(m,$4H_{arom}$); 8.05(d,J=9Hz,$2H_{arom}$); 8.10(s,1H,NH,exchangeable with D_2O). (Found: C,64.61; H,5.07; N,12.37. Calc. for $C_{24}H_{22}N_4O_3S$(446.4): C,64.57; H,4.93; N,12.56%). m/z 446(M^+,5).

4-Benzoyl-1-methyl-5-tosylamino-1H-1,2,3-triazole (79f) was obtained as white crystalline solid (ethanol); yield 61%; m.p. 184-185°C; i.r.(KBr): ν_{max} = 3160, 1643, 1595, 1397, 1172, 917 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.03(s,3H,CH_3); 4.25(s,3H,NCH_3); 6.96(d,J=8Hz,$2H_{arom}$); 7.25-7.73(m, $5H_{arom}$); 8.10(dd,J=8Hz,$2H_{arom}$); 8.15(s,1H,NH,exchangeable with D_2O).

(Found: C,57.55; H,4.80; N,15.93. Calc. for $C_{17}H_{16}N_4O_3S$(356.4): C,57.29; H,4.53; N,15.72%). m/z 356(M^+,48); 263(26).

1-Methyl-4-(4-methylbenzoyl)-5-tosylamino-1H-1,2,3-triazole (79g) was obtained as white crystalline solid (ethanol); yield 54%; m.p. 180-181°C; i.r.(KBr):ν_{max} = 3160, 1638, 1598, 1384, 1165, 915 cm^{-1}; ^1H n.m.r. ($CDCl_3$):δ 2.00(s,3H,CH_3): 2.38(s,3H,CH_3); 4.24(s,3H,N-CH_3); 6.92(d, J=8Hz,2H_{arom}); 7.03-7.45(dd,A_2B_2,4H_{arom}); 7.98(d,J=8Hz,2H_{arom}); 8.12 (s,1H,NH,exchangeable with D_2O). (Found: C,58.11; H,5.17; N,15.30. Calc. for $C_{18}H_{18}N_4O_3S$(370.4): C,58.36; H,4.90; N,15.13%). m/z 370(M^+,44); 277(18).

4-Benzoyl-1-ethyl-5-tosylamino-1H-1,2,3-triazole (79h) was obtained as white crystalline solid (ethanol); yield 68%; m.p. 160-161°C; i.r.(KBr): ν_{max} = 3190, 1640, 1595, 1400, 1181, 920 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.68(t,3H,J=7Hz,CH_3CH_2); 1.98(s,3H,CH_3): 4.65(q,2H,J=7Hz,NCH_2CH_3); 6.91(d,J=8Hz,2H_{arom}); 7.25-7.61(m,5H_{arom}); 8.03(dd,J=8Hz,2H_{arom}); 8.12 (s,1H,NH,exchangeable with D_2O). (Found: C,58.13; H,5.21; N,14.99. Calc. for $C_{18}H_{18}N_4O_3S$(370.4): C,58.36; H,4.90; N,15.13%). m/z 370 (M^+,32); 277(18).

4-(4-Chlorobenzoyl)-1-n-propyl-5-tosylamino-1H-1,2,3-triazole (79i) was obtained as white crystalline solid (ethanol); yield 75%; m.p. 160°C; i.r.(KBr):ν_{max} = 3195, 1640, 1585, 1405, 1162, 921 cm^{-1}; ^1H n.m.r. ($CDCl_3$):δ 1.00(t,3H,J=7Hz,$CH_3CH_2CH_2$); 2.05(s,3H,CH_3); 2.13(sext,2H, J=7Hz,$CH_3CH_2CH_2$); 4.56(t,2H,J=7Hz,N-$CH_2CH_2CH_3$); 6.97(d,J=8Hz,2H_{arom}); 7.40(d,J=8Hz,2H_{arom}); 8.01(s,1H,NH,exchangeable with D_2O); 8.09(d,J=8Hz, 2H_{arom}). (Found: C, 54.72; H,4.86; N,13.50. Calc. for $C_{19}H_{19}ClN_4O_3S$ (418.9): C,54.47; H,4.54; N,13.38%). m/z NO M^+,327(5); 325(100).

4-Benzoyl-1-isopropyl-5-tosylamino-1H-1,2,3-triazole (79j) was obtained as white solid (ethanol); yield 45%; m.p. 187-188°C; i.r.(KBr): ν_{max} = 3173, 1639, 1593, 1400, 1162, 921 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.70[d,6H, J=7Hz,$(CH_3)_2CH$]; 1.98(s,3H,CH_3); 5.25[sept,1H,J=7Hz,$(CH_3)_2CH$]; 6.91(d, J=8Hz,$2H_{arom}$): 7.92(s,1H,NH,exchangeable with D_2O); 7.28-7.61(m,$4H_{arom}$); 8.04(dd,J=8Hz,$2H_{arom}$). (Found: C,59.66; H,5.53; N,14.31. Calc. for $C_{19}H_{20}N_4O_3S$(384.4): C,59.36; H,5.25; N,14.58%). m/z 384(M^+,16); 291(4).

1-n-Butyl-4-(4-methylbenzoyl)-5-tosylamino-1H-1,2,3-triazole (79k) was obtained as white crystalline solid (ethanol); yield 70%; m.p. 148-149°C; i.r.(KBr): ν_{max} = 3193, 1635, 1600, 1400, 1165, 919 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 0.98[t,3H,J=7Hz,$CH_3(CH_2)_3$]; 1.38(sext,2H,J=7Hz,$CH_2CH_2CH_2$); 1.98(quint,2H,J=2Hz,$CH_3CH_2CH_2CH_2$); 2.00(s,3H,CH_3); 2.39(s,3H,CH_3); 4.60[t,2H,J=7Hz,$NCH_2(CH_2)_2CH_3$];6.92(d,J=8Hz,$2H_{arom}$); 7.10-7.49(dd,$4H_{arom}$); 8.00(d,J=8Hz,$2H_{arom}$); 8.06(s,1H,NH,exchangeable with D_2O). (Found: C,60.93; H,6.13; N,13.77. Calc. for $C_{21}H_{24}N_4O_3S$(412.5); C,61.14; H,5.86; N,13.58%). m/z 412 (M^+,4); 357(5); 319(2).

4-(4-Chlorobenzoyl)-1-cyclohexyl-5-tosylamino-1H-1,2,3-triazole (79l) was obtained as white crystalline solid (ethanol); yield 44%; m.p. 216-217°C; i.r.(KBr): ν_{max} = 3200, 1640, 1583, 1410, 1160, 925 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 1.09-2.25(brm,10H,ring CH_2); 2.04(s,3H,CH_3); 4.72 (brm,1H,-CH-N); 6.93(d,J=8Hz,$2H_{arom}$); 7.21-7.43(m,$4H_{arom}$); 7.86(brs, 1H,NH,exchangeable with D_2O); 8.10(d,J=8Hz,$2H_{arom}$). (Found: C,57.84; H,5.32; N,12.49. Calc. for $C_{22}H_{23}ClN_4O_3S$(458.9); C,57.58; H,5.05; N,12.21%). m/z 460(0.4); 458(M^+,1); 380(11); 379(17); 378(24); 377(38).

1-Acetaldehyde diethylacetal-4-benzoyl-5-tosylamino-1H-1,2,3-triazole(79m) was obtained as white crystalline solid (ethanol); yield 56%; m.p. 118°-119°C; i.r.(KBr): ν_{max} = 3180, 1636, 1592, 1410, 1167, 921 cm^{-1};

^{1}H n.m.r.($CDCl_3$):δ 1.15(t,J=7Hz,6H,$\underline{CH_3}CH_2O$); 2.00(s,3H,$\underline{CH_3}$); 3.83-3.90(m,4H,$CH_3\underline{CH_2}O$); 4.70(d,2H,J=6Hz,$N\underline{CH_2}$); 5.17(t,1H,J=6Hz,$NCH_2\underline{CH}$); 6.95(d,J=8Hz,2H$_{arom}$); 7.27-7.63(m,5H$_{arom}$); 8.06(d,J=8Hz,2H$_{arom}$); 8.10(s,1H,NH,exchangeable with D_2O). (Found: C,57.90; H,5.93; N,12.01. Calc. for $C_{22}H_{26}N_4O_5S$(458.5): C,57.63;H,5.72; N,12.22%). m/z NO M^+,413 ($M^+-OC_2H_5$,4).

1-Aryl/alkyl-4-aroyl-5-amino-1H-1,2,3-triazoles 80a-e,g,h; General Procedure:

A solution of appropriate triazole (79a-e,g,h, 3 mmol) in concentrated sulfuric acid (10 ml) was stirred at room temperature for 25 min. The reaction mixture was poured over crushed ice (350g), and the triazoles 80 are separated as colourless solids, which were filtered and recrystallized from ethanol.

5-Amino-4-benzoyl-1-phenyl-1H-1,2,3-triazole (80a) was obtained as white crystalline solid (ethanol); yield 95%; m.p. 140-141°C; i.r.(KBr): ν_{max} = 3390, 3275, 1625, 1600, 1510, 1390, 920 cm^{-1}; ^{1}H n.m.r.($CDCl_3$):δ 6.03(brs,2H,NH_2,exchangeable with D_2O); 7.31-7.77(m,8H$_{arom}$); 8.40-8.63 (m,2H$_{arom}$). (Found: 68.45; H,4.88; N,21.59. Calc. for $C_{15}H_{12}N_4O$(264.3): C,68.16; H,4.58; N,21.20%). m/z 264(M^+,22); 236(16); 235(21); 208(23).

5-Amino-4-(4-chlorobenzoyl)-1-phenyl-1H-1,2,3-triazole (80b) was obtained as white crystalline solid (ethanol); yield 87%; m.p. 180-181°C; i.r. (KBr):ν_{max} = 3465, 3335, 1625, 1605, 1510, 928 cm^{-1}; ^{1}H n.m.r.($CDCl_3$):δ 5.98(brs,2H,NH_2,exchangeable with D_2O); 7.41-7.72(m,7H$_{arom}$); 8.45-8.68 (d,J=9Hz,2H$_{arom}$). (Found: C,60.58; H,3.98; N,18.51. Calc. for $C_{15}H_{11}ClN_4O$ (298.7): C,60.31; H,3.71; N,18.76%). m/z 300(12); 298(M^+,36); 270(12); 272(10); 269(20).

5-Amino-1-benzyl-4-benzoyl-1H-1,2,3-triazole (80c) was obtained as white crystalline solid (ethanol); yield 89%; m.p. 150-151°C; i.r. (KBr):ν_{max} = 3380, 3280, 1638, 1620, 1510, 938 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 5.40(s,2H,$C_6H_5\underline{CH_2}$); 6.31(brs,2H,NH_2,exchangeable with D_2O); 7.15-7.57 (m,8H_{arom}); 8.30-8.54(m,2H_{arom}). (Found: C,69.33; H,5.34; N,20.34. Calc. for $C_{16}H_{14}N_4O$(278.3): C,69.05; H,5.07; N,20.13%). m/z 278(M^+,2); 250(21).

4-Acetoyl-5-amino-1-benzoyl-1H-1,2,3-triazole (80d) was obtained as white crystalline solid(ethanol); yield 84%; m.p. 185-186°C; i.r.(KBr):ν_{max} = 3385, 3280, 1658, 1639, 1508, 952 cm^{-1}; ^1H n.m.r($CDCl_3$/DMSO-d_4);δ 2.52 (s,3H,$\underline{CH_3}$); 5.40(s,2H,$C_6H_5\underline{CH_2}$); 6.49(brs,2H,NH_2,exchangeable with D_2O); 7.26(s,5H_{arom}). (Found: C,60.99; H,5.88; N,26.14. Calc. for $C_{11}H_{12}N_4O$ (216.2): C,61.10; H,5.60; N,25.91%). m/z 216(M^+,28); 188(M^+-28,5); 187 (23).

5-Amino-4-benzoyl-1-methyl-1H-1,2,3-triazole (80e) was obtained as crystalline solid (ethanol); yield 75%; m.p. 131-132°C; i.r.(KBr):ν_{max} = 3440, 3280, 1639, 1605, 1521, 916 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ3.75(s,3H, $N\underline{CH_3}$); 6.92(brs,2H,NH_2,exchangeable with D_2O); 7.31-7.65(m,3H_{arom}); 8.30-8.49(m,2H_{arom}). (Found: C,59.67; H,5.27; N,27.99. Calc. for $C_{10}H_{10}N_4O$(202.2): C,59.40; H,4.99; N,27.71%). m/z 202(M^+,35); 173(16); 167(37).

5-Amino-4-benzoyl-1-ethyl-1H-1,2,3-triazole (80g) was obtained as white crystalline solid (ethanol); yield 82%; m.p. 96-97°C; i.r.(KBr):ν_{max}= 3400, 3310, 1630, 1618, 1505, 921 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.27(t, 3H,J=7Hz,$\underline{CH_3}CH_2$); 4.00(q,2H,J=7Hz,$N\underline{CH_2}CH_3$); 6.00(brs,2H,NH_2,exchangeable with D_2O); 7.32-7.57(m,3H_{arom}); 8.24-8.43(m,2H_{arom}). (Found: C,60.89; H,5.88; N,26.04. Calc. for $C_{11}H_{12}N_4O$(216.2): C,61.10;H,5.60; N,25.91%).

m/z 216(M^+,32); 187(15); 160(28).

5-Amino-4-(4-Chlorobenzoyl)-1-propyl-1H-1,2,3-triazole (80h) was obtained as white crystalline solid (ethanol); yield 80%; m.p. 138-139°C; i.r. (KBr):ν_{max} = 3405, 3300, 1622, 1608, 1500, 920 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.00(t,3H,J=7Hz,$CH_3CH_2CH_2$); 1.88(sext,2H,J=7Hz,$CH_3CH_2CH_2$); 4.12(t,2H, J=7Hz,$NCH_2CH_2CH_3$); 5.70(brs,2H,NH_2,exchangeable with D_2O); 7.43(d,J=8Hz, $2H_{arom}$); 8.50(d,J=8Hz,$2H_{arom}$). (Found: C,54.17; H,4.72; N,21.45. Calc. for $C_{12}H_{13}ClN_4O$(264.7): C,54.45; H,4.95; N,21.17%. m/z 266(13); 264(M^+,50).

5-Anilino-4-aroyl-1H-1,2,3-triazoles 81a-b; General Procedure:

A solution of triazoles 80a or 80b (2 mmol) in pyridine (5 mL) was refluxed for 36 h. The pyridine was removed under reduced pressure, and the residue was poured over crushed ice (100g) to give triazoles 81a or 81b as bright yellow solids, which are filtered and recrystallized from ethanol.

5-Anilino-4-benzoyl-1H-1,2,3-triazole (81a) was obtained as bright yellow crystalline solid (ethanol); yield 60%; m.p. 160-161°C; i.r.(KBr):ν_{max}= 3130, 1590, 1560, 931 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 6.81-7.08(m, $2H_{arom}$); 7.17-7.70(m,$7H_{arom+NH}$); 8.28-8.50(m,$2H_{arom}$); 9.12(s,1H,NH, exchangeable with D_2O). (Found: C,68.43; H,4.29; N,21.49. Calc. for $C_{15}H_{12}N_4O$(264.3): C,68.16; H,4.58; N,21.20%). m/z 264(M^+,54); 235(19); 208(20).

5-Anilino-4-(4-chlorobenzoyl)-1H-1,2,3-triazole (81b) was obtained as bright yellow solid(ethanol); yield 71%; m.p. 180-181°C; i.r.(KBr): ν_{max} = 3126, 1600, 1580, 928 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 6.18-7.10 (m,$2H_{arom}$): 7.10-7.65(m,$6H_{arom+NH}$); 8.20-8.47(m,$2H_{arom}$); 8.98(s,1H,NH,

exchangeable with D_2O). (Found: C,60.60; H,3.98; N,18.55. Calc. for $C_{15}H_{11}ClNO_4O$(298.7); C,60.31; H,3.71; N,18.76%). m/z 300(12); 298(M^+,29); 272(5); 270(16).

3-Aroyl-5,6-dihydrothiazolo [3,2-c] triazoles 84a-c; General Procedure: A solution of cyclic S,N-acetals 82 (0.01 mol) and tosylazide(27; 2.36g, 0.012 mol) in dioxane (25 ml) was heated with stirring at 90-100°C for 15 h. monitored by TLC (silica gel-G, 75%,Acmes). Dioxane was removed under reduced pressure, the residue was poured over crushed ice (100g), and the products 84 were separated as colourless solids, which were filtered and recrystallized from ethanol.

3-Benzoyl-5,6-dihydrothiazolo [3,2-c] [1,2,3] triazole (84a) was obtained as colourless crystalline solid (ethanol); yield 69%; m.p. 154-155°C; i.r.(KBr):ν_{max} = 1632, 1500, 1482, 1240, 920 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 4.20(distorted t,2H,CH_2); 4.70(distorted t,2H,CH_2); 7.25-7.70(m,3H_{arom}); 8.20-8.53(m,2H_{arom}). (Found: C,56.84; H,4.13; N,17.98. Calc. for $C_{11}H_9N_3OS$(231.3): C,57.12; H,3.92; N,18.17%). m/z 231(M^+,36); 203(33).

3-(4-Chlorobenzoyl)-5,6-dihydrothiazolo [3,2-c] [1,2,3] triazole (84b) was obtained as colourless crystalline solid (ethanol); yield 60%; m.p. 175-176°C; i.r.(KBr):ν_{max} = 1620, 1582, 1480, 1240, 918 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 4.20(distorted t,2H,CH_2); 4.68(distorted t,2H,CH_2); 7.50(d,J=9Hz,2H_{arom}); 8.40(d,J=9Hz,2H_{arom}). (Found: C,49.99; H,3.25; N,16.03. Calc. for $C_{11}H_8ClN_3OS$(265.7): C,49.72; H,3.04; N,15.81%); m/z 267(13); 265(M^+,34); 239(18); 238(38); 237(48); 236(87).

3-(4-Methoxybenzoyl)-5,6-dihydrothiazolo [3,2-c] [1,2,3] triazole (84c) was obtained as colourless crystalline solid (ethanol); yield 65%; m.p. 154-155°C; i.r.(KBr):ν_{max} = 1608, 1595, 1488, 1232, 1222, 1172, 919 cm^{-1};

^{1}H n.m.r.($CDCl_3$): 3.85(s,3H,OCH_3); 4.10(distorted t,2H,CH_2); 4.60 (distorted t,2H,CH_2); 6.97(d,J=8Hz,2H_{arom}); 8.60(d,J=8Hz,2H_{arom}). (Found: C,54.97; H,3.98; N,16.31. Calc. for $C_{12}H_{11}N_3O_2S$(261.3): C,55.15; H,4.24; N,16.08%). m/z 261(M^+,62); 233(26); 232(86).

5-Aryl/alkylamino-4-aroyl-1-aryl/alkyl-1H-1',2,3-triazoles(89a-d);

General Procedure:

A solution of N,N-acetals 87 (0.01 mol) and tosylazide (27; 2.36g, 0.012 mol) in dioxane (25 mL) were heated with stirring at 90-100°C for 15 h. monitored by TLC. Dioxane was removed under reduced pressure, the residue was poured over crushed ice (100g) and the products 89a-d were separated as pale yellow solids, which are filtered and recrystallized from ethanol.

5-Anilino-4-benzoyl-1-phenyl-1H-1,2,3-triazole (89a) was obtained as colourless crystalline solid (ethanol); yield 83%; m.p. 131-132°C; i.r. (KBr):ν_{max} = 3270, 1621, 1563, 931 cm^{-1}; ^{1}H n.m.r.($CDCl_3$):δ 6.63-7.68 (m,13H_{arom}); 8.47-8.63(m,2H_{arom}); 9.38(s,1H,NH,exchangeable with D_2O). (Found: C,73.91; H,5.03;N,16.30. Calc. for $C_{21}H_{16}N_4O$(340.4): C,74.09; H,4.74; N,16.46%). m/z 340(M^+,25); 312(M^+-28,19).

4-Benzoyl-1-(4-methylphenyl)-5-toluidino-1H-1,2,3-triazole (89b) was obtained as colourless solid (ethanol); yield 94%; m.p. 134-135°C; i.r. (KBr):ν_{max} = 3320, 1618, 1603, 925 cm^{-1}; ^{1}H n.m.r.($CDCl_3$):δ 2.10(s,3H, CH_3); 2.21(s,3H,CH_3); 6.41-7.61(m,11H_{arom}); 8.39-8.58(m,2H_{arom}); 9.28 (s,1H,NH,exchangeable with D_2O). (Found: C,75.21; H,5.29; N,15.01. Calc. for $C_{23}H_{20}N_4O$(368.4): C,74.98; H,5.47; N,15.21%). m/z 368(M^+,91); 340(M^+-28,35).

5-Anilino-4-(4-methoxybenzoyl)-1-phenyl-1H-1,2,3-triazole (89c) was obtained as pale yellow crystalline solid (DMF/ethanol, 1:5); yield 76%;

m.p. 163-164°C; i.r.(KBr):ν_{max} = 3303, 1620, 1587, 929 cm^{-1}; ^1H n.m.r. ($CDCl_3$):δ 3.85(s,3H,OCH_3); 6.61-7.48(m,12H_{arom}); 8.68(d,J=9Hz,2H_{arom}); 9.40(s,1H,NH,exchangeable with D_2O). (Found: C,71.50; H,5.17; N,14.98. Calc. for $C_{22}H_{18}N_4O_2$(370.4): C,71.33; H,4.90; N,15.13%).m/z 370(M^+,11); 342(M^+-28,37).

4-Benzoyl-1-ethyl-5-ethylamino-1H-1,2,3-triazole (89d) was obtained as thick viscous liquid (TLC single spot); yield 62%; i.r.(neat):ν_{max} = 3415, 1631, 1580 cm^{-1}; ^1H n.m.r.(CCl_4):δ 1.03-1.68(m,6H,CH_2CH_3); 3.89-4.53(m,4H,CH_2CH_3); 7.15-7.58(m,3H_{arom}); 8.38-8.61(m,2H_{arom}). (Found: C,64.02; H,6.51; N,23.06. Calc. for $C_{13}H_{16}N_4O$(244.3): C,63.91;H,6.60; N,22.93%). m/z 244(M^+,89).

3-Aroyl 5,6-dihydroimidazolo [3,2-c] [1,2,3] triazoles 91a-e and 3-Aroyl 4,5,6,7-tetrahydropyrimidine [1,5a] [1,2,3] triazoles 91f-j; General Procedure:

A solution of cyclic N,N-acetals 90a-j (0.01 mol) and tosylazide 27 (2.36g, 0.012 mol) in dioxane (25 ml) was heated with stirring at 90-100°C for 15 h. monitored by TLC. Dioxane was removed under reduced pressure, the residue was poured over crushed ice (100g) and the products 91a-j were separated as pale yellow crystalline solids, which are filtered and recrystallized from thanol.

3-Benzoyl 5,6-dihydroimidazolo [3,2-c] [1,2,3] triazole (91a) was obtained as colourless crystalline solid (ethanol); yield 94%; m.p. 193-194°C; i.r.(KBr):ν_{max} = 3200, 1605, 1590, 922 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6); δ 4.35(distorted t, 4H,CH_2-CH_2); 7.30(s,1H,NH,exchangeable with D_2O); 7.40-7.61(m,3H_{arom}); 8.27-8.49(m,2H_{arom}). (Found: C,61.73; H,4.57; N,25.97. Calc. for $C_{11}H_{10}N_4O$(214.2): C,61.68; H,4.71; N,26.16%). m/z 214(M^+,40); 186(M^+,28,75).

3-(4-Methylbenzoyl)-5,6-dihydroimidazolo [3,2-c] [1,2,3] triazole (91b)

was obtained as colourless crystalline solid (DMF/ethanol 1:5): yield 87%; m.p. 231-232°C; i.r.(KBr):ν_{max} = 3319, 1621, 1603, 928 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 2.35(s,3H,CH_3); 4.37(distorted t,4H,CH_2CH_2); 7.25(d,J=9Hz,3H$_{arom+NH}$); 8.27(d,J=9Hz,2H$_{arom}$). (Found: C,62.96; H,5.51; N,24.42. Calc. for $C_{12}H_{12}N_4O$(228.3): C,63.13; H,5.30; N,24,54%). m/z 228(M^+,25); 200(M^+-28,39).

3-(4-Methoxybenzoyl) 5,6-dihydroimidazolo [3,2-c] [1,2,3] triazole(91c)

was obtained as colourless crystalline solid (DMF/ethanol 1:5); yield 95%; m.p. 209°C; i.r.(KBr):ν_{max} = 3315, 1617, 1598, 925 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 3.80(s,3H,OCH_3); 4.32(distorted t,4H,CH_2-CH_2); 6.90 (d,J=9Hz,3H$_{arom+NH}$); 8.38(d,J=9Hz,2H$_{arom}$). Found: C,59.19; H,4.84; N,23.17. Calc. for $C_{12}H_{12}N_4O_2$(244.3): C,58.99; H,4.95; N,22.93%). m/z 244(M^+,27); 216(M^+-28,13).

3-(4-Chlorobenzoyl) 5,6-dihydroimidazolo [3,2-c] [1,2,3] triazole (91d)

was obtained as colourless crystalline solid (DMF/ethanol 1:5); yield 88%; m.p. 214-215°C; i.r.(KBr):ν_{max} = 3321, 1625, 1587, 929 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 4.38(distorted t,4H,CH_2CH_2); 7.53(d,J=9Hz, 3H$_{arom+NH}$); 8.40(d,J=9Hz,2H$_{arom}$). (Found: C,52.91; H,3.76; N,22.34. Calc. for $C_{11}H_9N_4OCL$(248.7): C,53.12; H,3.65; N,22.53%). m/z 250(13); 248(M^+,29); 222(37); 220(M^+-28,92).

3-(2-Thienyl) 5,6-dihydroimidazolo [3,2-c] [1,2,3] triazole (91e) was obtained as colourless crystalline solid (ethanol); yield 89%; m.p. 214-215°C; i.r.(KBr):ν_{max} = 3310, 1619, 1565 cm^{-1}; ^1H n.m.r.($CDCl_3$/TFA): δ 4.04(s,4H,CH_2CH_2); 7.05-7.35(m,1H,H-4'); 7.70(d,1H,J=6Hz,H-5'); 7.85 (d,1H,J=6Hz,H-3'); 8.80(brs,1H,NH). (Found: C,48.95; H,3.81; N,25.31.

Calc. for $C_9H_8N_4OS$(220.2): C,49.05; H,3.63; N,25.43%).

3-Benzoyl, 4,5,6,7-tetrahydropyrimidine [1,5a] [1,2,3] triazole (91f) was obtained as colourless crystalline solid (ethanol); yield 93%; m.p. 152-153°C; i.r.(KBr):ν_{max} = 3394, 1630, 1600, 1563, 920 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.08(quint,2H,J=7Hz,CH_2-$CH_2$$CH_2$); 3.39(distorted t, 2H, -CH_2-CH_2-CH_2-NH); 4.25(t,2H,J=7Hz,N-CH_2-CH_2-CH_2); 6.82(s,1H, NH,exchangeable with D_2O); 7.36-7.51(m,3H_{arom}); 8.37-8.59(m,2H_{arom}). (Found: C,62.97; H,5.54; N,24.33. Calc. for $C_{12}H_{12}N_4O$(228.3): C,63.13; H,5.30; N,24.54%). m/z 228(M^+,100); 199(66).

3-(4-Chlorobenzoyl) 4,5,6,7-tetrahydropyrimidine [1,5a] [1,2,3] triazole (91g) was obtained as colourless crystalline solid (ethanol); yield 91%; m.p. 182-183°C; i.r.(KBr):ν_{max} = 3297, 1638, 1592, 910 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.17(quint, 2H,J=7Hz,CH_2-CH_2-CH_2); 3.51(distorted t,2H,-CH_2-CH_2 -CH_2); 4.32(t,3H,J=7Hz,N-CH_2-CH_2-CH_2); 6.80(brs,1H,NH, exchangeable with D_2O); 7.49(d,J=9Hz,2H_{arom}); 8.52(d,J=9Hz,2H_{arom}). (Found: 55.13; H,4.03; N,21.47. Calc. for $C_{12}H_{11}ClN_4O$(262.7): C,54.86; H,4.22; N,21.33%). m/z 264(33); 262(M^+,100).

3-(4-Methoxybenzoyl) 4,5,6,7-tetrahydropyrimidine [1,5a] [1,2,3] triazole (91h) was obtained as colourless crystalline solid (ethanol); yield 94%; m.p. 166-167°C; i.r.(KBr):ν_{max} = 3325, 1640, 1604, 915 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.12(quint, 2H,J=6.5Hz,CH_2-CH_2-CH_2); 3.42(distorted t,2H,CH_2-CH_2-CH_2); 3.88(s,3H,OCH_3); 4.30(t,3H,J=6.5Hz,CH_2-CH_2-CH_2); 6.72(brs,1H,NH,exchangeable with D_2O); 7.00(d,J=7Hz,2H_{arom}): 8.58(d,J=7Hz, 2H_{arom}). (Found: C,60.31; H,5.53; N,21.73. Calc. for $C_{13}H_{14}N_4O$(258.3): C,60.45; H,5.46; N,21.69%). m/z 258(M^+-28,11).

3-(2-Furyl)-4,5,6,7-tetrahydropyrimidine [1,5a] [1,2,3] triazole (91i)

was obtained as yellow crystalline solid (ethanol); yield 88%; m.p. 149-150°C; i.r.(KBr):ν_{max} = 3350, 1628, 1595, 918 cm^{-1}; ^1H n.m.r. ($CDCl_3$):δ 2.21(quint,2H,J=6.5Hz,CH_2-CH_2-CH_2); 3.53(distorted t,2H, CH_2-CH_2-CH_2); 4.37(t,2H,J=6.5Hz,N-CH_2-CH_2-CH_2); 6.60-6.72(m,1H,C-3'); 6.80(brs,1H,NH,exchangeable with D_2O); 7.75(d,1H,J=3Hz,C-4'); 8.15(d, 1H,J=3Hz,C-5'). (Found: C,54.91; H,4.78; N,25.51; Calc. for $C_{10}H_{10}N_4O_2$ (218.2): C,55.04; H,4.59; N,25.68%). m/z 218(M^+,100); 190(M^+-28,32).

3-(2-Naphthyl)-4,5,6,7-tetrahydropyrimidine [1,5a] [1,2,3] triazole (91j)

was obtained as yellow crystalline solid (ethanol); yield 87%; m.p. 150-151°C; i.r.(KBr):ν_{max} = 3365, 1615, 1578, 908 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.09(quint,2H,J=6.5Hz,CH_2-CH_2-CH_2); 3.41(distorted t,2H,CH_2-CH_2); 4.28(t,2H,N-CH_2-CH_2-CH_2); 6.79(brs,1H,NH,exchangeable with D_2O); 7.45-7.72(m,2H_{arom}); 7.80-8.16(m,3H_{arom}); 8.36-8.55(m,1H_{arom}); 9.28(s,1H_{arom}). (Found: C,68.92; H,5.21; N,19.98. Calc. for $C_{16}H_{14}N_4O$(278.3): C,69.05; H,5.07; N,20.13%). m/z 278(M^+,100%).

4-Aroyl-5-methylthio-1H-1,2,3-triazoles 96a-e and 1-Azido-1-methylthio-1-buten-3-one 97; General Procedure:

To a stirred solution of S,S-acetals 92 (10 mmol) in DMSO (15 ml), a solution of sodium azide (0.65g, 10 mmol) in DMSO (15 ml) was added during 10 min. and the reaction mixture was heated at 110°C with stirring for 12-25 h. (monitored by TLC). The mixture was then cooled to room temperature, poured into crushed ice (150g), acidified with 20% acetic acid (10 ml), and extracted with chloroform (3x50 ml). The organic layer was washed with water (3x100 ml), dried over sodium sulfate, and evaporated to give dark coloured residies, which were

column chromatographed on silica gel using ethyl acetate/hexane (3:1) as eluent to give pure triazoles 96a-e, crystallized from chloroform/hexane. The product 97 was obtained as yellow viscous liquid, which decompes on keeping two days.

4-Benzoyl-5-methylthio-1H-1,2,3-triazole (96a) was obtained as pale yellow crystalline solid (chloroform/hexane); yield 73%; m.p.123-124°C; i.r.(KBr):ν_{max} = 3170, 1675, 1570, 910 cm^{-1}; ^1H n.m.r($CDCl_3$/DMSO-d_6): δ 2.36(s,3H,SCH_3): 7.31-7.75(m,3H$_{arom}$); 8.23-8.44(m,2H$_{arom}$); 12.28 (brs,1H,NH,exchangeable with D_2O). ^{13}C n.m.r.($CDCl_3$):δ 14.67(SCH_3); 128.38; 130.24; 133.24(CH_{arom}); 133.56(C-1' aryl); 136.52(C-4); 141.13 (C-5); 185.95(CO).

4-(4-Methylbenzoyl)-5-methylthio-1H-1,2,3-triazole (96b) was obtained as pale yellow crystalline solid (chloroform/hexane); yield 72%; m,p. 160-161°C; i.r.(KBr):ν_{max} = 3120, 1605, 1590, 900 cm^{-1}; ^1H n.m.r. $CDCl_3$/DMSO-d_6):δ 2.41(s,3H,CH_3); 2.59(s,3H,SCH_3); 7.30(d,J=9Hz,2H$_{arom}$); 8.22(d,A_2B_2,J=9Hz.,2H$_{arom}$); 12.47(brs,1H,NH,exchangeable with D_2O). (Found: C,56.29; H,5.01; N,17.74. Calc. for $C_{11}H_{11}N_3OS$(233.2): C,56.60; H,4.72; N,18.01%). m/z 233(M^+,34).

4-(4-Chlorobenzoyl)-5-methylthio-1H-1,2,3-triazole (96c) was obtained as pale yellow crystalline solid (chloroform/hexane); yield 75%; m.p. 157-158°C; i.r.(KBr):ν_{max} = 3160, 1600, 1580, 900 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 2.55(s,3H,SCH_3); 7.50(d,A_2B_2,J=9Hz,2H$_{arom}$); 8.31(d, J=9Hz,2H$_{arom}$); 12.47(brs,1H,NH,exchangeable with D_2O). ^{13}C n.m.r. (DMSO-d_6):δ 19.22(SCH_3): 128.50(C-2', 6'); 131.52(C-3'5'); 135.21(C-1'); 137.95(C-4'); 141.13(C-5); 147.67(C-4); 183.63(CO). (Found: C,47.01; H,2.92; N,16.82. Calc. for $C_{10}H_8ClN_3OS$(253.7): C,47.30; H,3.15; N,16.55%). m/z 253(M^+,100).

4-(4-Methoxybenzoyl)-5-methylthio-1H-1,2,3-triazole (96d) was obtained as pale yellow crystalline solid (chloroform/hexane); yield 65%; m.p. 184-185°C; i.r.(KBr):ν_{max} = 3120, 1609, 1584, 909 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 2.61(s,3H,SCH_3); 3.88(s,3H,OCH_3); 6.98(d,J=9Hz,$2H_{arom}$); 8.37(d,A_2B_2,J=9Hz,$2H_{arom}$); 12.35(brs,1H,NH,exchangeable with D_2O). (Found: C,53.26; H,4.62; N,17.01. Calc. for $C_{11}H_{11}N_3O_2S$(249.2): C,52.97; H,4.41; N,16.85%). m/z 249(M^+,40).

4-(3,4-Dichlorobenzoyl)-5-methylthio-1H-1,2,3-triazole (96c) was obtained as pale yellow crystalline solid (chloroform/hexane); yield 75%; m.p. 208-209°C; i.r.(KBr):ν_{max} = 3200, 1608, 1581, 903 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 2.50(s,3H,SCH_3); 7.45(d,1H,J=8Hz,5'-H); 7.70(dd,1H, J=8Hz,2,6'-4); 7.90(d,1H,J=2Hz,2'-H); 12.59(brs,1H,NH, exchangeable with D_2O). (Found: C,41.33; H,2.71; N,14.29. Calc. for $C_{10}H_7Cl_2N_3OS$(288.3): C,41.62; H,2.42; N,14.45%). m/z 287(M^+-1,14).

1-Azido-1-methylthio-1-buten-3-one (97) was isolated as viscous liquid; yield 52%; i.r.(KBr):ν_{max} = 2200, 1596 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.25 (s,3H,CH_3); 2.54(s,3H,SCH_3); 7.40(s,$1H_{olefin}$). (Found: unstable.calc. for $C_5H_7N_3OS$(157.2): C,38.16; H,4.45; N,26.72%).

5-Substituted-1-Alkyl/aryl tetrazoles 132a-j, 1-phenyl-5-phenylacetonitrile tetrazole 135; 1-Benzyl/phenyl-5-[cyano(ethoxycarbonyl)-methylene] -Δ^2-tetrazoline 138a-b; 5-[1-cyano-2-(4-chlorophenylamino)-2-methylthio ethenyl] tetrazole(142); General Procedure:

To a stirred solution of S,N-acetals 129 (10 mmol) in acetonitrile (30 mL), a solution of sodium azide 62 (0.65g, 10 mmol) in dimethylsulfoxide (15 mL) was added during 10 min. and the reaction mixture was heated at 110°C with stirring for 12-71 h. (monitored by TLC

silica gel: solvent system; ethyl acetate/hexane 1:20). The reaction mixture was cooled to room temperature, poured into crushed ice (150g) acidified with 20% acetic acid (10 mL), and extracted with chloroform (3x50 mL). The organic layer was washed with water (3x100 mL), dried with sodium sulfate, and evaporated to give crude tetrazoles, which were purified either by crystallization 132a-f, 135 and 138a-b, 142 from ethanol or by column chromatography 132g-j on silica gel (Acme 60-120 Mesh) column using chloroform/hexane (1:3) as eluent.

5-(p-toluoyl)methyl-1-phenyltetrazole (132a) was obtained as white solid (chloroform/hexane); yield 72%; m.p. 85-86°C; i.r.(KBr):ν_{max} = 1678, 1599 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 2.36(s,3H,$\underline{CH}_3$); 4.65(s,2H,$\underline{CH}_2$); 7.24(d, A_2B_2,J=9Hz,$2H_{arom}$); 7.50(s,$5H_{arom}$); 7.84(d,A_2B_2,J=9Hz,$2H_{arom}$). (Found: C,69.27; H,4.82; N,19.87. Calc. for $C_{16}H_{14}N_4O$(278.3): C,68.99; H,5.03; N,20.12%).m/z 278(M^+,5); 250(M^+-28,23).

5-(4-Chlorobenzoyl)methyl-1-phenyl tetrazole (132b) was obtained as white crystalline solid (ethanol); yield 67%;m.p. 86-87°C; i.r.(KBr): ν_{max} = 1682, 1592 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 4.58(s,2H,$\underline{CH}_2$): 7.18-7.63 (m,$7H_{arom}$); 7.80(d,J=8Hz,$2H_{arom}$). (Found: C,60.56; H,3.96; N,19.04. Calc. for $C_{15}H_{11}ClN_4O$(298.7): C,60.26; H,3.68; N,18.74%). m/z 300(3); 298(M^+,12); 272(12); 270(M^+-28,11).

1-Benzyl-5-(benzoyl)methyl tetrazole (132c) was obtained as white crystalline solid (ethanol); yield 63%; m.p. 120°C; i.r.(KBr):ν_{max} = 1680, 1595 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 4.43(s,2H,$\underline{CH}_2$); 5.48(s,2H,$C_6H_5\underline{CH}_2$); 7.00-7.61(m,$8H_{arom}$); 7.72-7.92(m,$2H_{arom}$); ^{13}C n.m.r.($CDCl_3$): 34.17 ($\underline{CH}_2$); 51.46(Ar$\underline{CH}_2$N); 127.80,128.31; 128.44; 128.83, 129.05, 134.25 (CH_{arom}); 132.62, 134.82(C-1'$_{arom}$); 149.75(C-5); 191.97(CO). (Found:

C,68.68; H,5.30; N,20.39. Calc. for $C_{16}H_{14}N_4O$(278.3); C,68.99); H,5.03; N,20.12%). m/z 278(M^+,2); 250(M^+-28,5).

1-Benzyl-5-(4-methoxybenzoyl) methyltetrazole (132d) was obtained as white crystalline solid (ethanol); yield 64%; m.p. 104°C; i.r.(KBr): ν_{max} = 1665, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 3.90(s,3H,OCH_3); 4.34(s,2H, CH_2); 5.63(s,2H,$CH_2C_6H_5$); 6.97(d,J=8Hz,$2H_{arom}$); 7.25-7.30(m,$5H_{arom}$); 7.98(d,J=8Hz,$2H_{arom}$). (Found: C,65.84; H,4.93; N,17.89. Calc. for $C_{17}H_{16}N_4O_2$(308.3): C,66.16; H,5.19; N,18.18%). m/z 308(M^+,11); 280(M^+-28,5).

1-Methyl-5-(benzoylmethyltetrazole (132e) was obtained as white crystalline solid (ethanol); yield 79%; m.p. 156-157°C; i.r.(KBr):ν_{max} = 1678, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 4.02(s,3H,$NCCH_3$); 4.77(s,2H,CH_2); 7.40-7.70(m,$3H_{arom}$); 7.97-8.11(m,$2H_{arom}$). (Found: C,59.09; H,5.22; N,27.40. Calc. for $C_{10}H_{10}N_4O$(202.2); C,59.35; H,4.94; N,27.70%).m/z 202(M^+,21); 174(M^+-28,100).

1-Ethyl-5-(benzoyl)methyltetrazole (132f) was obtained as whte crystalline solid (chloroform/hexane); yield 65%; m.p. 80-81°C; i.r.(KBr):ν_{max} =1675, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6);δ 1.49(t,3H,J=7Hz,CH_2CH_3); 4.28(q, 2H,J=7Hz,CH_3CH_2); 4.88(s,2H,CH_2); 7.34-7.76(m,$3H_{arom}$); 7.90-8.18(m, $2H_{arom}$); ^{13}C n.m.r.($CDCl_3$/DMSO-d_6):δ 14.44(CH_3); 33.63(CH_2); 42.06 (CH_3CH_2N-); 128.46; 128.75; 133.91(CH_{arom}); 135.44 (C-1'$_{arom}$); 150.15 (C-5); 193.65(CO). (Found: C,60.80; H,5.76; N,26.19. Calc. for $C_{11}H_{12}N_4O$(216.2): C,61.05; H,5.55; N,25.90%). m/z 216(M^+,6); 188(M^+-28,35).

5-(Benzoyl)methyl-1-propyl tetrazole (132g) was isolated as yellow viscous oil; yield 74%; i.r.(KBr):ν_{max} = 1682, 1645 cm^{-1}; ^1H n.m.r. ($CDCl_3$);δ0.90(t,3H,J=7Hz,CH_3); 1.94(sext,2H,J=7Hz,CH_3CH_2); 4.20(t,2H, J=7Hz,$CH_3CH_2CH_2$); 4.74(s,2H,CH_2); 7.80-7.65(m,$3H_{arom}$); 7.73-8.12(m,$2H_{arom}$).

(Found: C,62.84; H,6.35; N,24.64. Calc. for $C_{12}H_{14}N_4O$(230.3): C,62.52; H,6.08; N,24.33%). m/z 230(M^+,11); 202(M^+-28,42).

1-Isopropyl 5-(benzoyl)methyl tetrazole (132h) was isolated as white crystalline solid (chloroform/hexane); yield 60%; m.p. 104-105°C; i.r. (KBr):ν_{max} = 1680, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.61(d,6H,J=7Hz,CH_3); 4.56(sept,1H,J=7Hz,$(CH_3)_2CH$); 4.66(s,2H,CH_2); 7.35-7.68(m,3H_{arom}); 7.95-8.15(m,2H_{arom}). (Found: C,62.24; H,5.83; N,24.03. Calc. for $C_{12}H_{14}N_4O$(230.3): C,62.52; H,6.08; N,24.33%). m/z 230(M^+,11); 202 (M^+-28,63).

1-Cyclohexyl-5-(benzoy)methyl tetrazole(132i) was isolated as white crystalline solid (chloroform/hexane); yield 67%; m.p. 89-90°C; i.r. (KBr):ν_{max} = 1673, 1590 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.05-2.23(m,10H,ring CH_2); 4.15(quint, 1H,J=6Hz,CH); 4.70(s,2H,CH_2); 7.38-7.73(m,3H_{arom}); 7.99-8.20(m,2H_{arom}). (Found:C,66.32; H,6.91; N,21.00. Calc. for $C_{15}H_{18}N_4O$(270.2): C,66.62; H,6.66; N,20.72%). m/z 270(M^+,1); 242(M^+-28,6).

1-Ethyl-5-(acetoly)methyl tetrazole (132j) was isolted as yellow viscous oil; yield 64%; i.r.(KBr):ν_{max} = 1718, 1605 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 1.54(t,3H,J=7Hz,CH_3); 2.32(s,3H,CH_3); 4.14(s,2H,CH_2); 4.21(q,2H, J=7Hz,CH_3CH_2). (Found: C,47.01; H,6.76; N,36.01. Calc. for $C_6H_{10}N_4O$ (154.2): C,46.69; H,6.48; N,36.32%). m/z 154(M^+,7); 112(100).

1-Phenyl-5-phenylacetonitrile tetrazole (135) was obtained as white crystalline solid (ethanol); yield 76%; m.p. 99-100°C; i.r.(KBr): ν_{max} = 2220, 1590, 1487 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ 5.62(s,1H,-CHCN); 7.05-7.62(m,10H_{arom}). (Found: C,69.17; H,3.92; N,27.04. Calc. for $C_{15}H_{11}N_3$(261.2): C,68.88; H,4.20; N,26.79%). m/z 261(M^+,6); 233(M^+-28,6).

5-(Ethoxycarbonylcyano)-methylene-1-phenyl- Δ^2-tetrazoline (138a) was obtained as white crystalline solid (ethanol); yield 77%; m.p. 190-191°C; i.r.(KBr): ν_{max} = 3165, 2197, 1647, 1570 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.22(t,3H,J=7Hz,$CH_2\underline{CH_3}$); 4.20(q,2H,J=7Hz,$CH_3\underline{CH_2}$); 7.64(s,$5H_{arom}$); 12.50(brs,1H,NH,exchangeable with D_2O). ^{13}C n.m.r.(DMSO-d_6);δ14.35 (CH_3); 59.77($O\underline{CH_2}$); 115.76(CN); 127.18; 128.18, 130.92, 131.07, (=$\underline{C}$(O)CN,CH_{arom}); 132.96(C-1'$_{arom}$); 148.97(C-5); 165.81($\underline{CO_2}$Et).(Found: C,56.23; H.4.00; N,26.94. Calc. for $C_{12}H_{11}N_5O_2$(257.2): C,55.98; H,4.28; N,27.22%) m/z 257(M^+,9); 156(79); 157(58).

1-Benzyl-5-(ethoxy carbonylcyano)-methylene- Δ^2-tetrazoline (138b) was obtained as white crystalline solid (ethanol); yield 73%; m.p. 151-152°C; i.r.(KBr): ν_{max} = 3160, 2195, 1645, 1580 cm^{-1}; ^1H n.m.r.($CDCl_3$):δ1.31 (t,3H,J=7Hz,$\underline{CH_3}$); 4.32(q,2H,J=7Hz,$CH_3\underline{CH_2}$); 5.76(s,2H,$C_6H_5\underline{CH_2}$); 7.21-7.57(m,$5H_{arom}$); 13.32(brs,1H,NH,exchangeable with D_2O); ^{13}C n.m.r.($CDCl_3$): δ 14.37($\underline{CH_3}$); 51.44(Ar$\underline{CH_2}$N); 61.40($O\underline{CH_2}$); 117.04(CH); 128.30; 128.43; 129.05, 129.09 (=$\underline{C}$(CO)CN, CH_{arom}): 132.54(C-1'$_{arom}$); 148.41(C-5); 168.70($\underline{CO_2}$Et). (Found: C,57.22; H,5.02; N,26.09. Calc. for $C_{13}H_{13}N_5O_2$ (271.3): C,57.52; H,4.74; N,25.81%). m/z 271(M^+,21); 242(29); 170(30).

5-[1-cyano-2-(4-chlorophenylamino)-2-methylthio ethenyl] tetrazole (142) was obtained as white crystalline solid (ethanol); yield 65%; m.p. 220°C; i.e. (KBr): ν_{max} = 3130, 3039, 2200, 1622, 1560 cm^{-1}; ^1H n.m.r.($CDCl_3$/ DMSO-d_6):δ 2.26(s,3H,$S\underline{CH_3}$); 7.38(s,$4H_{arom}$); 10.78(brs,1H,NH,exchangeable with D_2O). (Found: C,44.83; H,43.35; N,29.00. Calc. for $C_{11}H_9ClN_6S$(292.8): C,45.10; H,3.07; N,28.70%). m/z 292(M^+,29); 245(49).

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CHAPTER III

REACTION OF ACYLKETENE S,N-ACETALS WITH MALONYL CHLORIDE: SYNTHESIS OF NOVEL 1,5-SUBSTITUTED 4-HYDROXY-6-METHYLTHIO-2(1H)-PYRIDONES AND 6,8-SUBSTITUTED 4-HYDROXY-7-METHYLTHIO-2,5-DIOXO-5,6-DIHYDRO-2H-PYRANO [3,2-c] PYRIDINES*

III.1 INTRODUCTION

Preparation and properties of α-oxoketene S,N-, N,N-, and α-nitroketene S,N-acetals of general formula 2, 8 and 5 respectively have been extensively investigated[1,2,3]. They can easily be prepared in excellent yields by displacement of one of the methylthio groups in α-oxoketene dithioacetals with either primary or secondary amines[4,5,6]. They can also be prepared from active methylene ketones by reacting their enolate anions with appropriate isothiocyanates followed by alkylation[4,7-10,11]. Thus a large number of active methylene ketones can be considered as primary precursors

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* Chakrasali, R.T., Ila, H., Junjappa, H. Synthesis, 87 (1988).

for the synthesis of these compounds. They are stable crystalline compounds and are comparitively less susceptible to hydrolytic conditions than the corresponding enamines. The Chemistry of these compounds has been extensively investigated and their applications as three carbon fragments exploiting the 1,3-electrophilic centres has led to the synthesis of a variety of amino heterocycles[1,3,12]. On the other hand by virtue of amino functionality in the β-position, these compounds can display pronounced enamine properties and increased electrophilicity at β-carbon. Also these class of compounds can function as enamines by participating as two carbon fragments in the reaction with Michael acceptors as well as 1,3-electrophilic components to yield many heterocycles[13,14,15,16].

A number of examples of synthetic applications of these enamines to prepare a variety of important heterocyclic systems have been reported[13,14,15,16]. Some of these selected applications of α-oxoketene S,N-2 and N,N-acetals 8 as enamines have been briefly described in the following section.

III.1.2 α-OXOKETENE-S,N-AND N,N-ACETALS AS ENAMINES IN NENITZESCU INDOLE SYNTHESIS[14]:

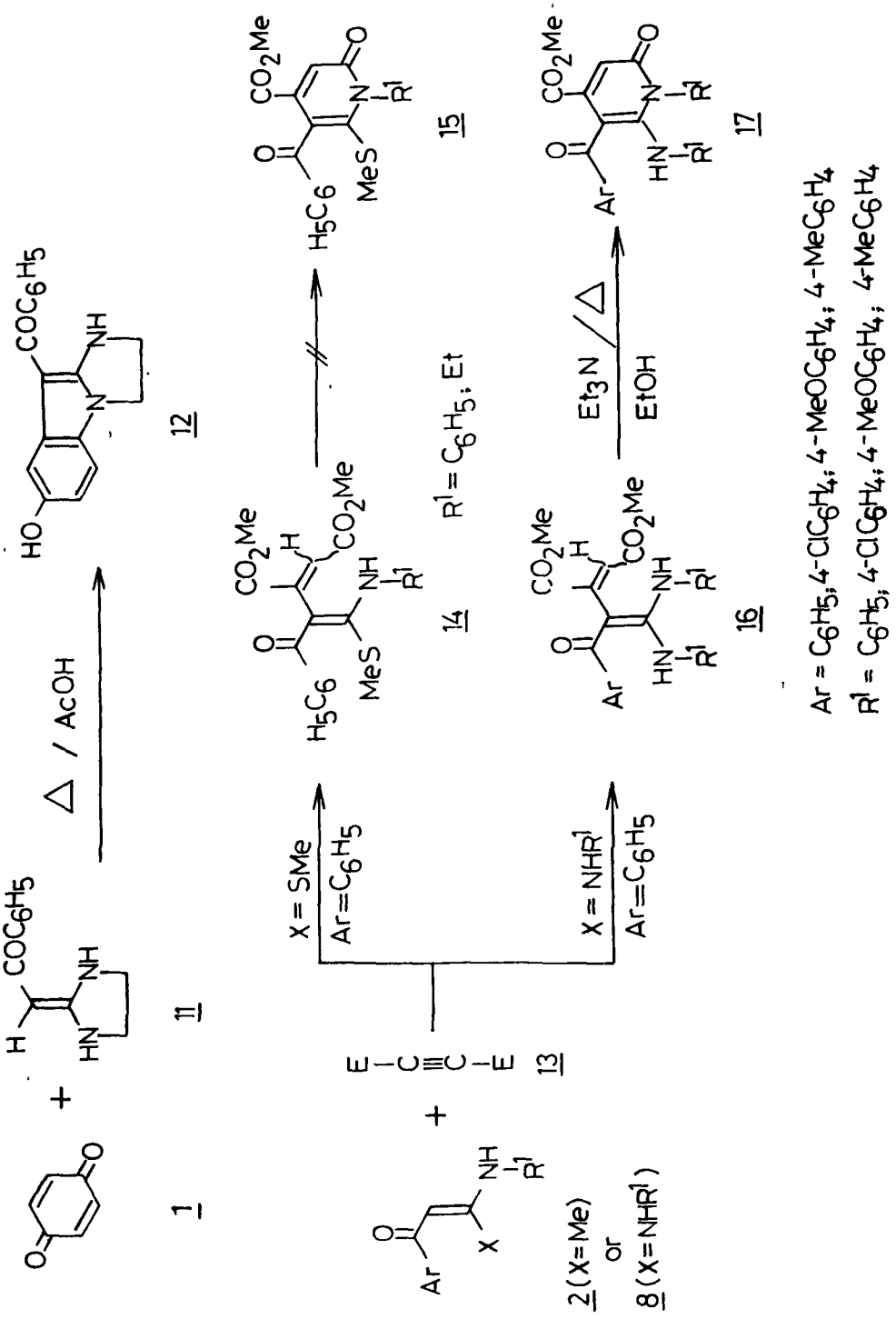
The reaction of p-benzoquinone with ethyl 3-amino crotonate in refluxing acetone to yield ethyl 5-hydroxy-2-methylindole-3-carboxylate was discovered by Nenitzescu[17] in 1929. This method was reinvestigated in the seventies and a number of structural variants in enamine components were introduced to make the method more versatile[18]. However, the Chemistry of enamines employed in these developments remained within the traditional methods.

Scheme 1

Subsequently Junjappa, Ila and co-workers introduced the α-oxoketene S,N- 2 , α-nitro S,N- 5 and N,N-acetals 8 (Scheme 1) as new class of enamines for the synthesis of 5-hydroxy indoles[14]. Thus p-benzoquinone 1 was reacted with α-oxoketene S,N-acetals 2 in acetic acid to yield the corresponding 2-amino-3-aroyl-5-hydroxybenzofuran 3 (Scheme 1) along with hydrolysed Michael adduct 4. However, when the nitroketene S,N-acetals 5 were reacted with 1 in refluxing acetic acid, the expected 1-aryl/alkyl 2-methylthio-3-nitro-5-hydroxy indole 6, and the corresponding 2-methylthio-3-nitro-5-hydroxybenzofuran 7a or 2-anilino-3-nitro-5-hydroxybenzofuran 7b were formed (Scheme 1). Similarly the N,N-acetals 8 reacted with p-benzoquinone 1 to yield a mixture of the corresponding 5-hydroxyindole 9 and the benzofurans 10 (Scheme 1). The cyclic N,N-acetals 11 also reacted with p-benzoquinone 1 to yield the tricyclic indole 12 (Scheme 2). The α-oxoketene S,N- and N,N-acetals therefore have synthetic potential as functionalized enamines.

III.1.3 REACTION OF α-OXOKETENE S,N- AND N,N-ACETALS WITH DIMETHYLACETYLENE DICARBOXYLATE[15]

The α-oxoketene S,N-acetals 2 were reacted with dimethylacetylene dicarboxylate 13 to exploit the nucleophilic α-carbon reactivity towards Michael acceptors. Thus when S,N-acetal 2 was reacted with DMAD 13, indeed the first Michael adducts 14 were formed in high yields. However, on further heating the adducts 14 failed to undergo cyclization to the corresponding pyridones 15 (Scheme 2)[15]. Apparently the electron withdrawing carboethoxy group and nucleophilic the amino group preferentially occupy the trans position, which prohibits the intramolecular condensation to yield the corresponding pyridones 15 (Scheme 2). This limitation of geometrical barrier was circumvented when the α-oxoketene N,N-acetals


Δ / AcOH
X = SMe
Ar = C6H5
X = NHR1
Ar = C6H5
Et3N / Δ
EtOH
R1 = C6H5; Et
Ar = C6H5; 4-ClC6H4; 4-MeOC6H4; 4-MeC6H4
R1 = C6H5; 4-ClC6H4; 4-MeOC6H4; 4-MeC6H4

Scheme 2

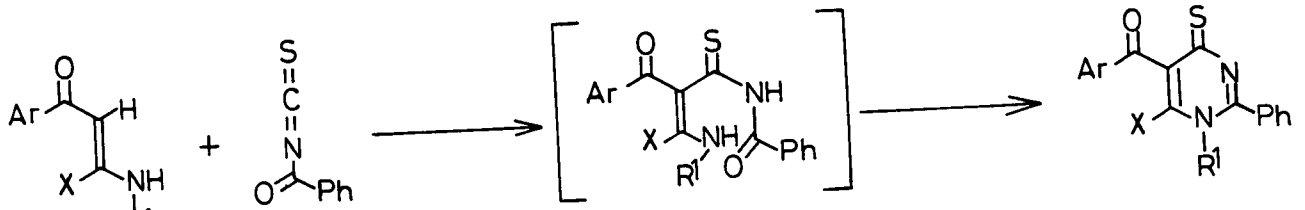
8 (X=NHR[1]) were reacted with DMAD 13, which underwent facile intramolecular condensation to give the corresponding pyridones 17 (Scheme 2). The α-carbon in the N,N-acetals 8 is apparently more nucleophilic than that in the corresponding S,N-acetals 2 due to the presence of two amino groups at the β-carbon.

III.1.4 REACTION OF α-OXOKETENE S,N- AND N,N-ACETALS WITH BENZOYL ISOTHIOCYANATE[13]

The enamine like properties of S,N-acetals 2 which can be considered as enaminones were further exploited in this laboratory by reacting them with aroyl isothiocyanates 18 to give the corresponding thiopyrimidines 20 in high yields (Scheme 3)[13]. The nitroketene S,N-5 and N,N-acetals 8 (X=PhNH) though condensed with aroyl isothiocyanates through α-carbon to yield the corresponding adducts 19 (X=PhNH) and 22 failed to cyclize intramolecularly to yield the corresponding nitropyrimidines 23 (Scheme 3). However, under oxidative conditions with bromine, 5 and 8 yielded the corresponding isothiozolines 24 in good yields (Scheme 3).

III.1.5 CYCLOCONDENSATION OF α-OXOKETENE S,N- AND N,N-ACETALS WITH MALEIC ANHYDRIDE AND MALEIMIDE[19]

The synthetic applications of the α-oxoketene S,N- and N,N-acetals as enaminones were further exploited in this laboratory by reacting them with maleic anhydride 25. Thus the S,N-acetals 2 in refluxing acetonitrile reacted with maleic anhydride 25 to give the corresponding pyrrolinone acetic acids 26 (Scheme 4)[19]. These pyrrolinones 26 underwent smooth cyclization in the presence of acetic anhydride, when the corresponding 2,4-substituted-3-methylthio-1,6-dioxo-2,3-dihydropyrano [3,4-c] pyrroles 27 were formed in high yields (Scheme 4).



2 (X=SMe) or 8 (X=NHR^1)

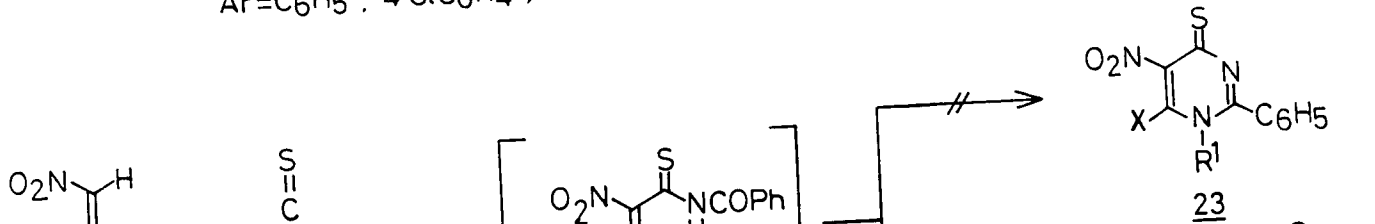
18

19

20

Ar=C_6H_5 , 4-MeC_6H_4 , 4-MeOC_6H_4 4-ClC_6H_4 , R^1=C_6H_5, Et, X=SMe

Ar=C_6H_5 , 4 ClC_6H_4 , 4 MeOC_6H_4 , R^1=Et , X=EtNH



5 X=SMe or 21 X=NHR^1

18

22

23

24

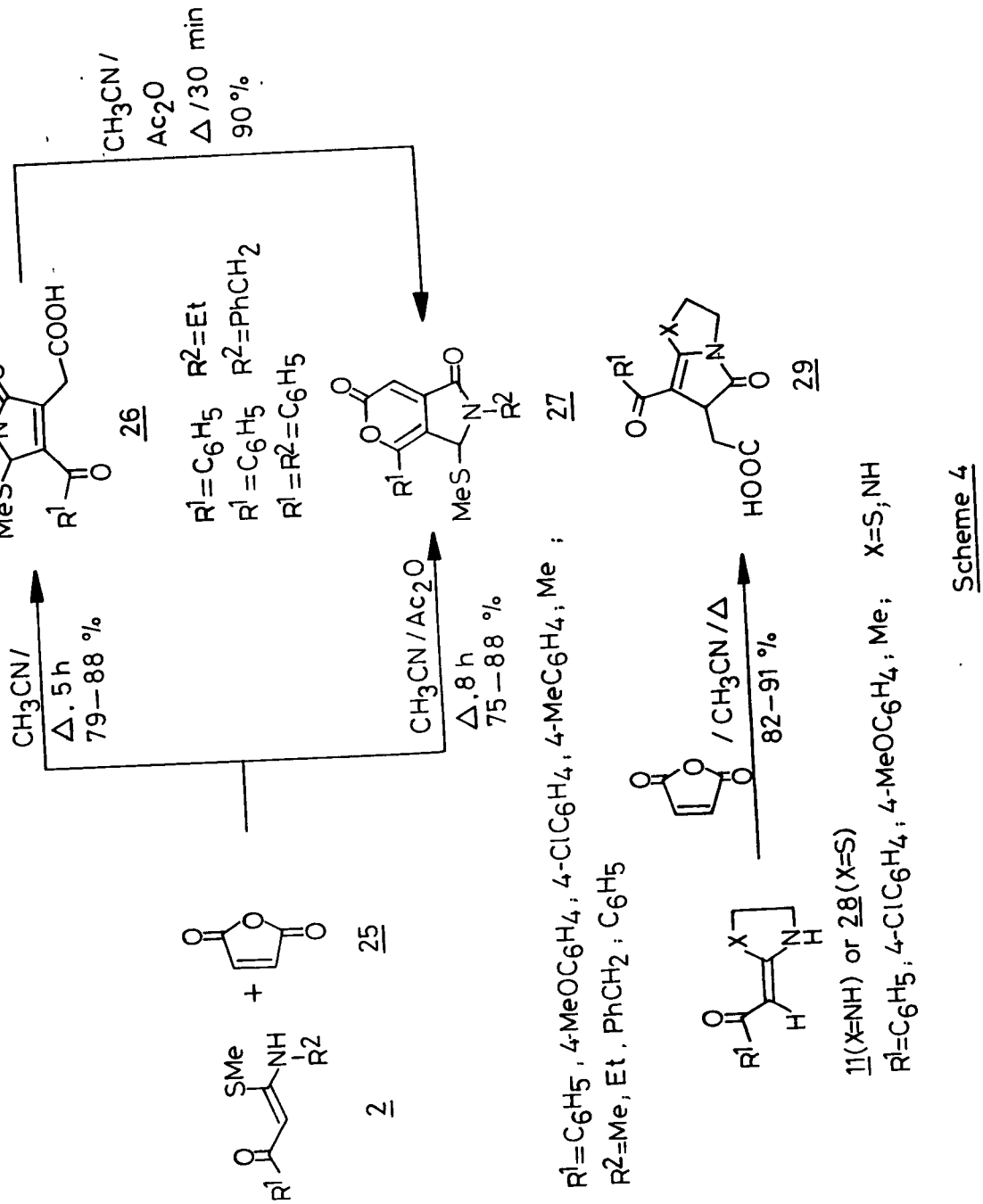
R^1=Ph X=SMe

R^1=Et X=SMe

R^1=Ph X=NHPh

R^1=Et X=EtNH

Scheme 3

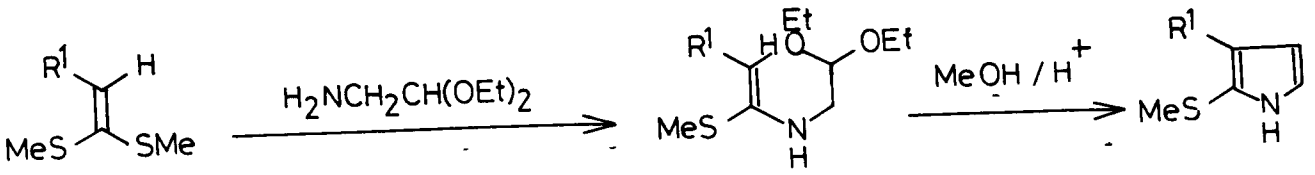

CH3CN/
Δ. 5 h
79–88 %
CH3CN/Ac2O
Δ. 8 h
75–88 %
CH3CN/
Ac2O
Δ/30 min
90 %
/CH3CN/Δ
82–91 %
R1=C6H5; R2=Et
R1=C6H5; R2=PhCH2
R1=R2=C6H5
R1=C6H5, 4-MeOC6H4, 4-ClC6H4, 4-MeC6H4, Me;
R2=Me, Et, PhCH2, C6H5
11(X=NH) or 28(X=S)
R1=C6H5, 4-ClC6H4, 4-MeOC6H4, Me; X=S, NH

Scheme 4

In an alternative experiment, condensation of S,N-acetals 2 and maleic anhydride 25 in the presence of acetic anhydride directly afforded the corresponding 2-substituted-3-methylthio-4-aryl-1,6-dioxo-2,3-dihydro-pyrano [3,4-c] pyrroles 27 in excellent yields (Scheme 4). Similarly, the reaction of cyclic S,N-acetals 28 (X=S) and N,N 11 acetals (X=NH) with maleic anhydride 25 in refluxing acetonitrile gave the corresponding pyrrolo [2,1-b] thiazoles 29 (X=S) and pyrrolo [1,2-a] imidazoles 29 (X=NH) respectively in good yields.

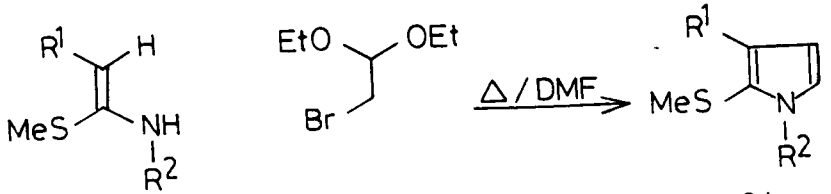
III.1.6 REACTIONS OF α-OXOKETENE DITHIOACETALS WITH AMINOACETALDEHYDE DIETHYLACETAL AND α-OXOKETENE S,N-ACETALS WITH BROMOACETALDEHYDE DIETHYLACETAL[20,21]

The α-oxo and α-nitro ketene dithioacetals 30 react with aminoacetaldehyde diethylacetal to yield the functionalized enamines 31. Such S,N-acetals 31 were shown to undergo facile acid catalysed ring closure to the corresponding 2-methylthio-3-substituted pyrroles 32 in good yields (Scheme 5)[20]. It may be noted here that the nucleophilic α-carbon of S,N-acetals 31 attacks the electrophilic carbon (diacetal carbon) intramolecularly to give 32 (Scheme 5), when the method was extended to the corresponding N-substituted pyrroles 34 the yields of the S,N-acetals were apparently poor due to reduced basicity of the amino group. Thus, an alternative approach was developed through the reaction of α-oxo 2 and α-nitro 5 ketene S,N-acetals and bromoacetaldehyde diethylacetal 33 in hot DMF to yield the desired N-substituted pyrroles 34 (Scheme 5)[21]. The method was equally facile when the cyclic S,N-acetals 28 were reacted with 33 under similar reaction conditions to yield the annulated pyrroles 35 (Scheme 5).



30 31 32

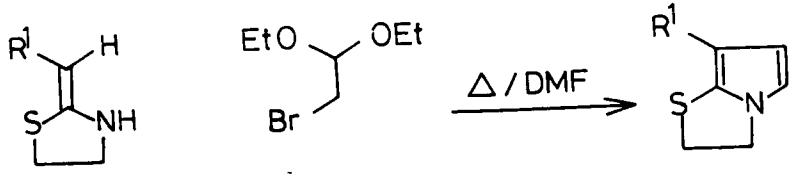
R^1 = MeCO , substituted ArCO , NO_2



2 33 34

R^1 = MeCO , substituted ArCO , NO_2

R^2 = Me , Et , n-Pr , n-Bu , Cyclo-C_6H_{11}



28 33 35

R^1 = MeCO , substituted ArCO , NO_2

Scheme 5

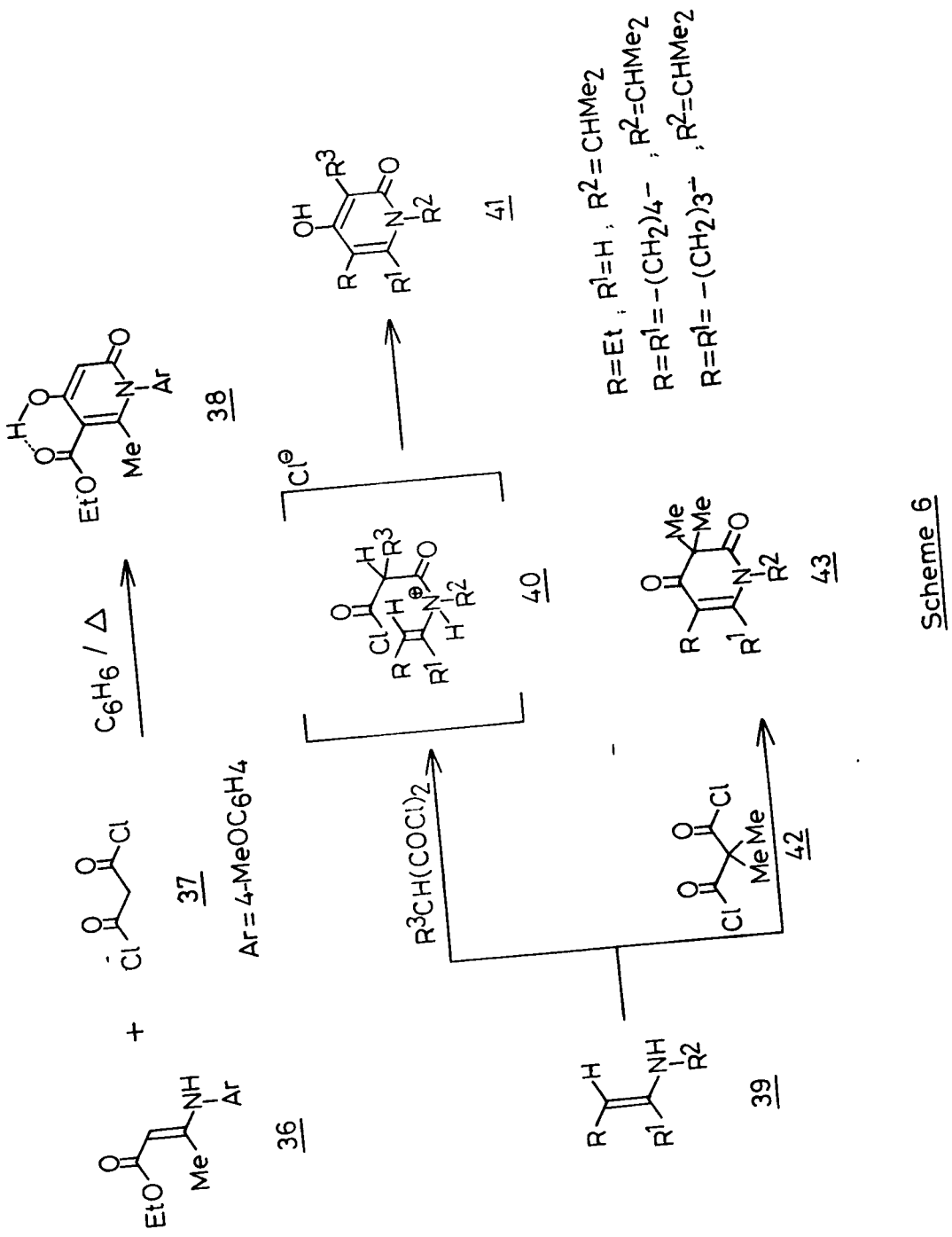
III.1.7 REACTION OF ENAMINONES AND ENAMINES WITH MALONYL CHLORIDE[22,23]

The enaminones 36 derived from β-ketoesters have been reacted with malonyl chloride 37 to yield the corresponding 4-hydroxy pyridones 38 in high yields (Scheme 6)[22]. The method is extended to substituted malonyl chloride 42 as well to yield the corresponding pyridones 41 and 43 (Scheme 6)[23]. Interestingly in these systems, initially the carbonyl carbon of acid chloride is attacked by the lone pair of the nitrogen 40 followed by cyclization through nucleophilic α-carbon.

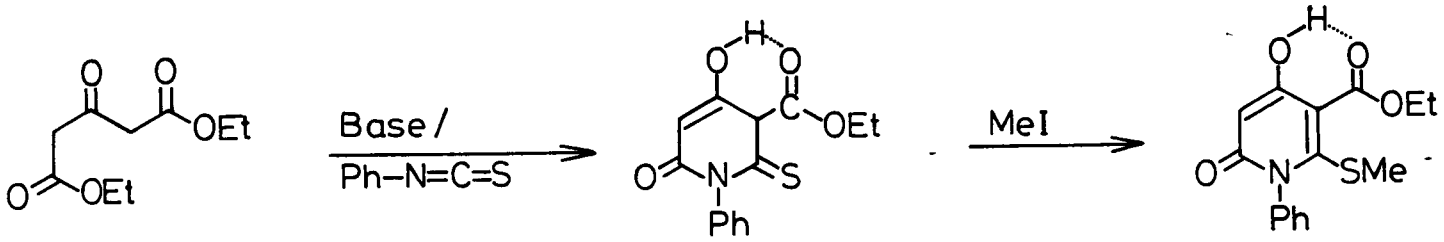
Becher and co-workers have reported[25] the reaction of ethyl acetone dicarboxylates 44 with arylisothiocyanates in the presence of sodium ethoxide and Dimethyl Sulfoxide to afford the intermediate pyridones 45, which were S-methylated to give the thiomethyl pyridone 46 (Scheme 7).

In a series of papers Becher et al reported[24,25] that the enolates of penten-1,5-diones 48 as well as those of glutanaldehyde in a general reaction with organic isothiocyanates yielded 3-acyl or 3-formyl 2(1H) pyridinethiones 49 (Scheme 7).

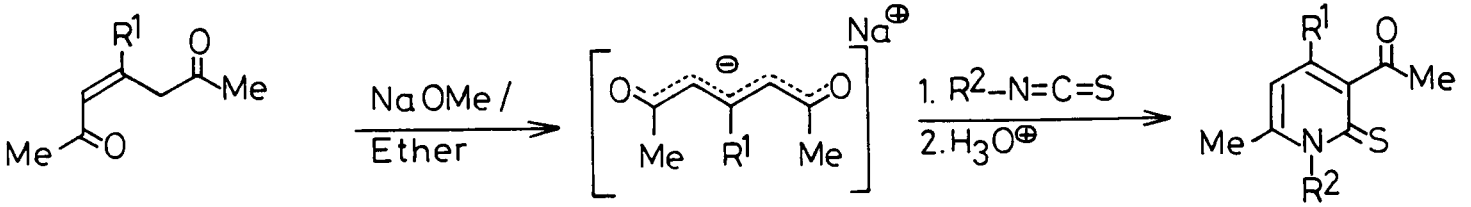
In the preceding section a brief account of the Chemistry of α-oxoketene S,N-acetals 2 which display the properties of enamines has been discussed. It is therefore, possible to exploit these acetals to construct many important and highly functionalized heterocycles. Our literature survey revealed that the existing methods available for the synthesis of pyridones are not satisfactory particularly when the structural diversity is considered. Thus, the synthesis of pyridones 38, from the classical enamine components 36 derived from β-ketoesters, suffer from one of the serious limitations involving the product formation with alkyl


C6H6 / Δ
Ar = 4-MeOC6H4
R3CH(COCl)2
Cl⊖
R = Et ; R1 = H ; R2 = CHMe2
R = R1 = -(CH2)4- ; R2 = CHMe2
R = R1 = -(CH2)3- ; R2 = CHMe2

Scheme 6



44 45 46



47 48 49

48, 49	R^1	R^2
	Me	Ar
	MeO	Ar
	SMe	Ar

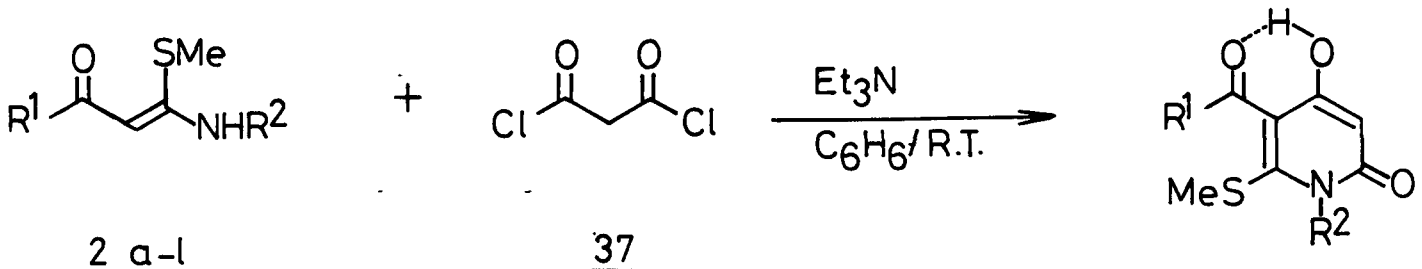
Scheme 7

group at the 6-position of the ring making it unsuitable for subsequent structural elaboration for the fused ring construction[22]. Thus, it was contemplated that the reaction of α-oxoketene S,N-acetals 2 with malonyl chloride 37 would lead to the formation of hitherto inaccessible heterocycles which are suitable for further ring elaboration. The results of these studies are described in this Chapter.

III.2 RESULTS AND DISCUSSION

In the present study, the known α-oxoketene S,N-acetals 2a-k (Scheme 8) were prepared according to the reported procedures[1,5], while hitherto unknown S,N-acetal 21 (Scheme 8) was prepared by reacting the α-oxoketene dithioacetal derived from acetone, with methylamine in boiling ethanol. The structures of all the S,N-acetals 2a-l were fully confirmed with the help of analytical and spectral data before they were used as starting materials.

In one of the experiments, the α-oxoketene S,N-acetal 2a was reacted with one equivalent of malonyl chloride 37 in the presence of triethylamine in benzene and work-up of the reaction mixture yielded a white crystalline solid (m.p. 267-268°C) in 89% yield, which was characterized as 5-benzoyl-4-hydroxy-6-methylthio-1-N-phenyl-2(1H)-pyridone 50a (Scheme 8) on the basis of its analytical and spectral data. Thus, pyridone 50a was analysed for $C_{19}H_{15}NO_3S$ and its mass spectrum showed the molecular ion peak at m/z 337(11%). Its i.r. spectrum (KBr) exhibited sharp peaks at 1660 cm^{-1} and 1635 cm^{-1}, which could be assigned to amide carbonyl and benzoyl carbonyl respectively. Its structure was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6). Thus, the singlet at δ 1.82(3H) was assigned to three protons of the methylthio group, while the other singlet at δ 5.84(1H) was assigned to the ring H-3 proton. The multiplet



2 a-l 37 50 a-l

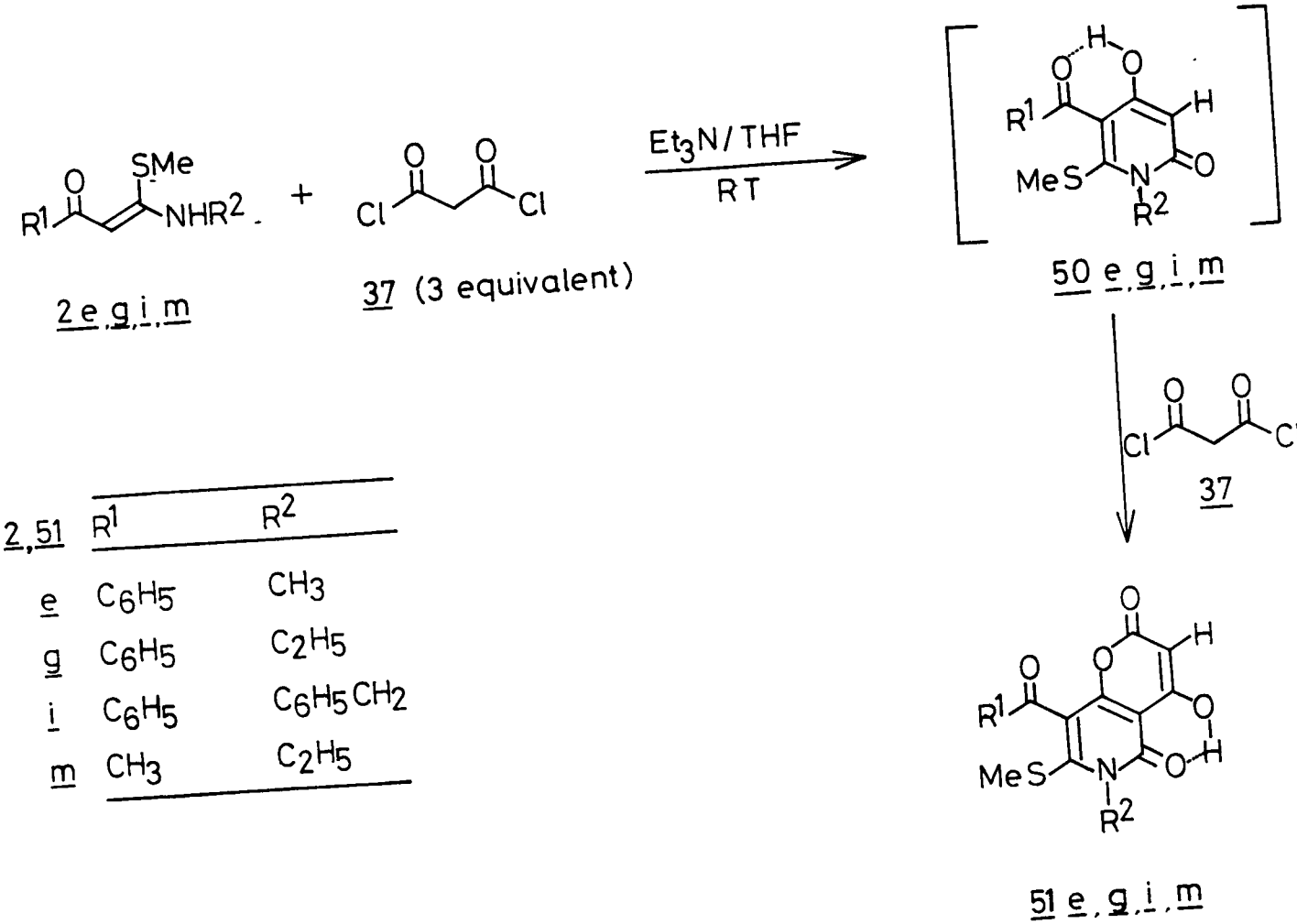
2,50	R^1	R^2		R^1	R^2
a	C_6H_5	C_6H_5	g	C_6H_5	C_2H_5
b	4-ClC_6H_4	C_6H_5	h	4-ClC_6H_4	C_2H_5
c	4-$MeOC_6H_4$	C_6H_5	i	C_6H_5	$C_6H_5CH_2$
d	C_6H_5	4-MeC_6H_4	j	4-$MeOC_6H_4$	$C_6H_5CH_2$
e	C_6H_5	CH_3	k	C_6H_5	n-C_3H_7
f	4-ClC_6H_4	CH_3	l	CH_3	CH_3

Scheme 8

around δ 7.15-7.70(8H) was assigned to the eight aromatic protons, the other multiplet between δ 7.83-8.03(2H) was assigned to two aromatic protons. Under similar reaction conditions the other α-oxoketene S,N-acetals 2b-1 underwent smooth cyclization with one equivalent of malonyl chloride 37 to yield the corresponding pyridones 50b-1 in 71-91% overall yields. The analytical and spectral data of these compounds are in confirmity with their assigned structures and are given in the experimental section.

Since pyridones 50 can easily be converted to their enolates and could be reacted further with another mole of malonyl chloride 37 to yield the corresponding pyrano [3,2-c] pyridones 51 (Scheme 9) attempts were made to react 2 with excess of 37.

Thus when α-oxoketene S,N-acetal 2e was reacted with three equivalent of malonyl chloride 37 in the presence of triethylamine in tetrahydrofuran, after work-up the reaction mixture yielded a white crystalline solid (m.p. 202-203°C) different from pyridone 50e in 36% yield (Scheme 9) which was characterized as 8-benzoyl-4-hydroxy-6-methyl-7-methylthio-2,5-dioxo-5,6-dihydro 2H-pyrano [3,2-c] pyridine 51e (Scheme 9) on the basis of its analytical and spectral data. Thus 51e was analysed for $C_{17}H_{13}NO_5S$ and its mass spectrum showed the molecular ion peak at m/z 343 (38%). Its i.r. spectrum (KBr) exhibited peaks at 1735 cm^{-1} which was assigned to pyrano ring carbonyl whereas broad band at 1670 cm^{-1} was assigned to both benzoyl carbonyl as well as amide carbonyl stretching vibrations. Further structural proof for 51e was obtained from its ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6) which showed two singlets at δ 2.26(3H) and δ 3.88(3H) which were attributed to the methylthio protons



2 e, g, i, m

37 (3 equivalent)

50 e, g, i, m

37

51 e, g, i, m

2, 51	R^1	R^2
e	C_6H_5	CH_3
g	C_6H_5	C_2H_5
i	C_6H_5	$C_6H_5CH_2$
m	CH_3	C_2H_5

Scheme 9

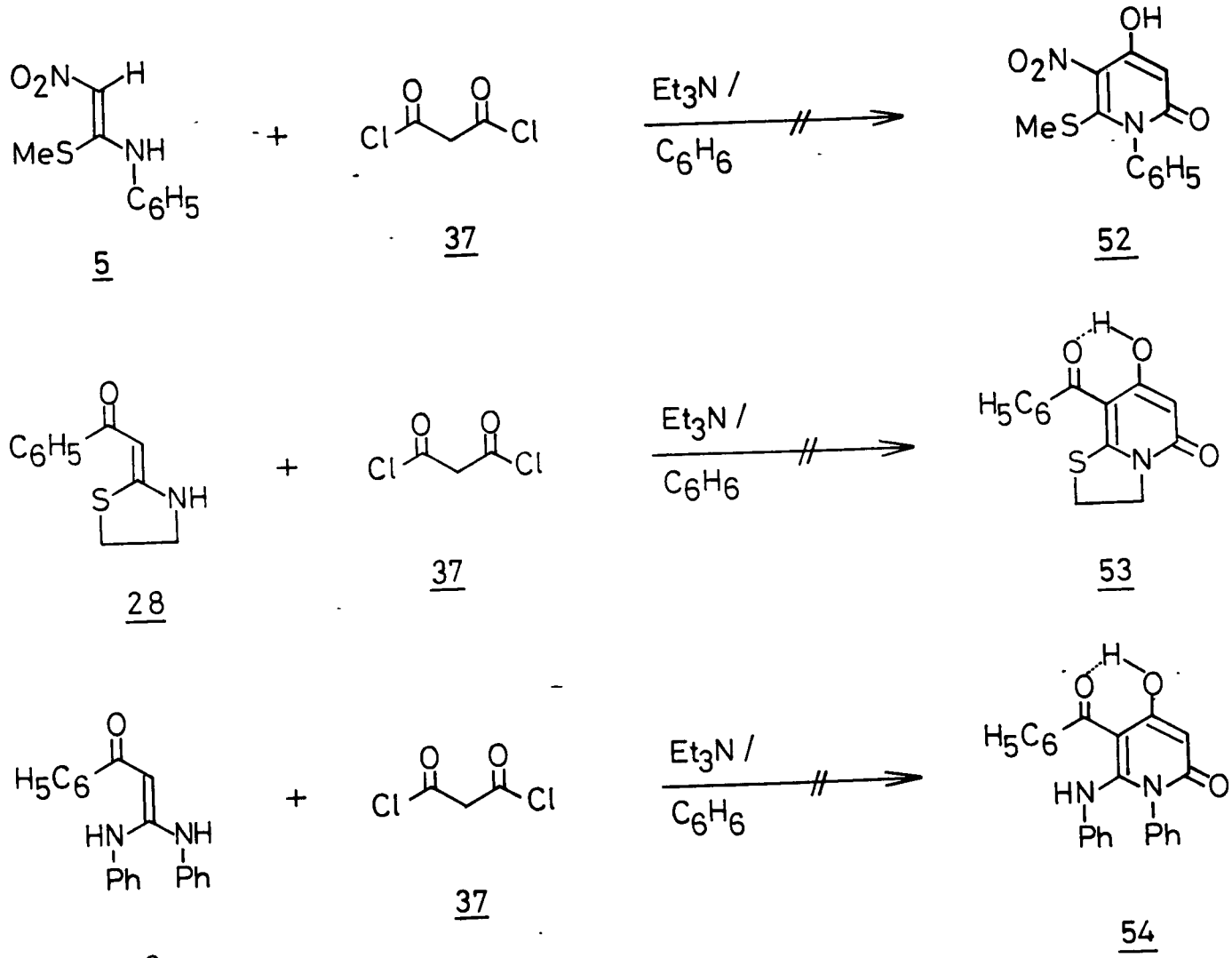
respectively. The H-3 proton of the pyranoring appeared as another singlet at δ 5.45(1H). The multiplets between δ 7.48-7.85(3H) and between δ 7.97-8.17(2H) were assigned to the aromatic protons.

The other α-oxoketene S,N-acetals 2g, l, m, similarly reacted with excess of malonyl chloride 37 in the presence of triethylamine in tetrahydrofuran to yield the corresponding pyrano [3,2-c] pyridines 51g, i, m (Scheme 9) in 38-44% overall yields. The structures of all the products were confirmed by their analytical and spectral data, which are described in the experimental section.

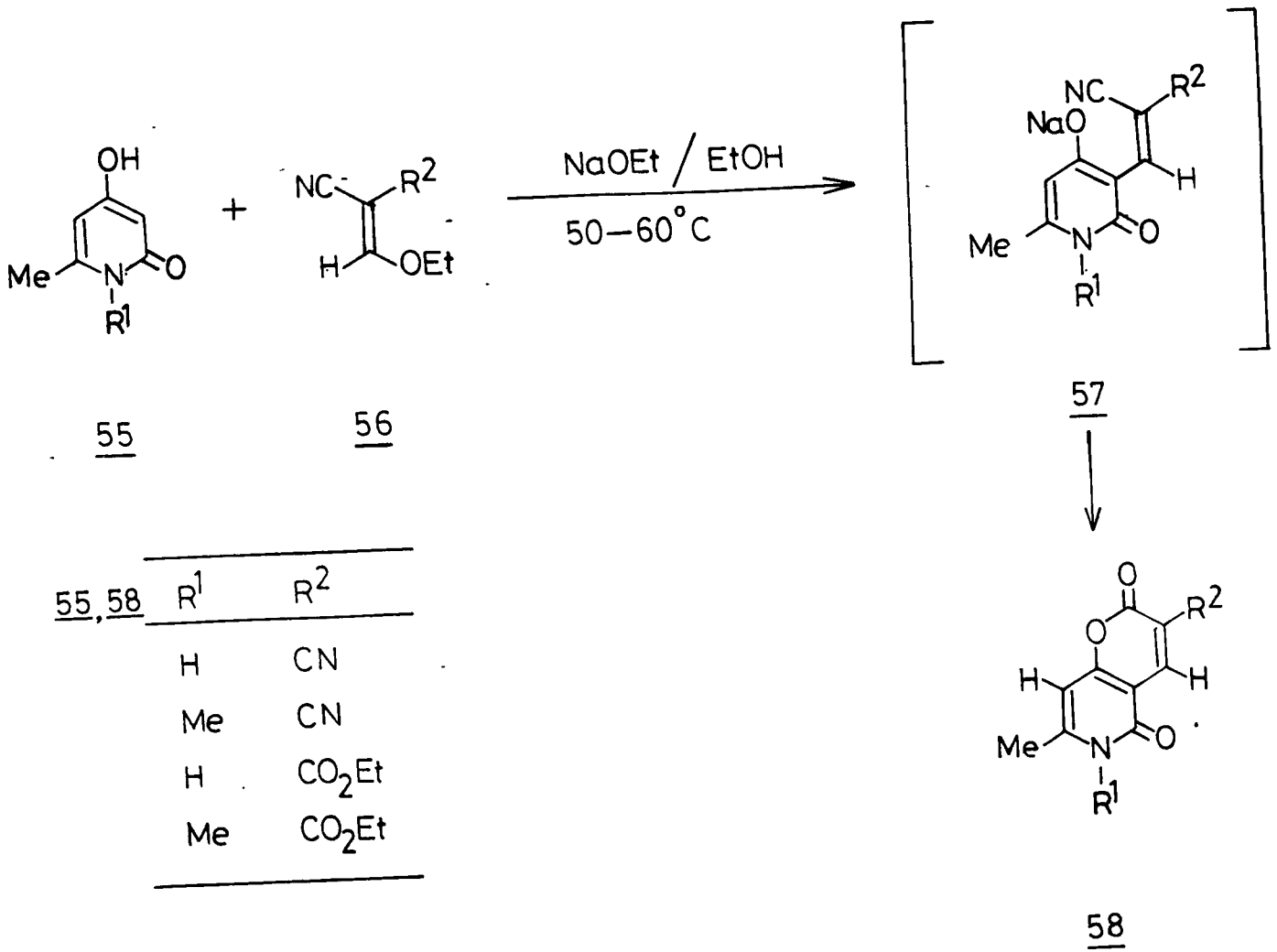
The S,N-acetals 5, cyclic S,N-acetals 28 derived from nitromethane and acetophenone respectively did not yield the expected pyridones 52 and 53 respectively (Scheme 10). Also the reaction of N,N-acetal 8 with malonyl chloride 37 did not afford any identifiable products (Scheme 10).

It may be noted that the overall yields of annulated pyridines 51 are modest. However, reports on the synthesis of the annulated pyridines with these structural features are very scanty in the literature. The only reference that could be traced out was reported by Schmidt and co-workers in 1978[26]. The strategy of the synthesis was based on the reaction of pre-constructed 4-hydroxy pyridones 55 with ethoxymethylene malononitrile 56 in the presence of a base. Moderate to good yields of pyranopyridines 58 (Scheme 11) were obtained when the reaction was carried out in ethanol at 50-60°C using NaOEt as the base.

The reaction provides a simple method for the synthesis of hitherto unreported pyranopyridones from readily accessible starting materials. In the absence of satisfactory routes for the synthesis of these class of compounds the present method could be considered as an important


O2N
H
MeS
NH
C6H5
5
+
Cl
O
O
Cl
37
Et3N /
C6H6
OH
O2N
MeS
N
O
C6H5
52
C6H5
O
S
NH
28
+
37
Et3N /
C6H6
H
O
H5C6
S
N
O
53
H5C6
HN
NH
Ph
Ph
8
+
37
Et3N /
C6H6
H5C6
HN
N
O
Ph
Ph
54

Scheme 10



55 56 57 58

55,58	R^1	R^2
	H	CN
	Me	CN
	H	CO_2Et
	Me	CO_2Et

Scheme 11

addition despite the moderate yields, though the optimization of yields has not been studied.

III.3 EXPERIMENTAL

General

Melting points were determined on Thomas Hoover apparatus and are uncorrected. The i.r. spectra were recorded on a 'Perkin-Elmer, 297' Spectrophotometer and the ^{1}H n.m.r. spectra were recorded on a Varian EM-390, 90 MHz Spectrometer using tetramethyl silane (TMS) as internal standard and chemical shifts values are expressed in δ(ppm). ^{13}C n.m.r. spectra were recorded on a Brucker WH-270 spectrometer. The mass spectra were recorded on a Jeol D-300 mass spectrometer and carbon, hydrogen, nitrogen analysis were done at Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial samples of the various acetophenones and benzene, tetrahydrofuran, triethylamine were purified before use. Malonyl chloride was prepared by the reported procedure[27]. Of the various α-oxoketene S,N-acetals used 2a-k were prepared by the reported procedure[1,5] and their structures were confirmed by comparing their analytical and spectral data with the reported ones. The unknown α-oxoketene S,N-acetal 2i was prepared by extending the reported procedure[5], and structure was confirmed by the spectral and analytical data which is given below.

3-Methylamino-3-methylthio-1-methyl-2-propen-1-one (2i) was obtained as viscous oil (TLC single spot); yield 76%; i.r. (CCl_4): ν_{max} = 3435, 1757 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.98(s,3H,CH_3); 2.37(s,3H,SCH_3); 3.05(d, 3H,$NHCH_3$); 4.75(s,1H$_{olefin}$); 11.30(brs,1H,NH). (Found: C,49.51; H,7.63; N,9.58; Calc. for $C_6H_{11}NOS$(145.1): C,49.62; H,7.58; N,9.65%).

1-Alkyl/aryl-5-aroyl/acyl-4-hydroxy-6-methylthio(2H)-pyridones (50a-l);

General Procedure:

To a well stirred and ice cooled solution of S,N-acetal 2 (10 mmol) and dry triethylamine (2.02g, 20 mmol) in dry benzene (30 ml), a solution of malonyl chloride (1.41g, 10 mmol) in benzene (15 ml) was added slowly during 15 min. and the reaction mixture was further stirred for 3 h. The reaction mixture was poured into crushed ice (150g), neutralized with solid $NaHCO_3$(10g), and it was allowed to warm up to room temperature. The light brown solid separated was collected by suction filteration and recrystallized from boiling ethanol to give pure pyridones 50a-l as white crystalline solids.

5-Benzoyl-4-hydroxy-6-methylthio-1-phenyl-2-pyridone (50a) was obtained as white crystalline solid (ethanol); yield 89%; m.p. 267-268°C; i.r. (KBr): ν_{max} = 1660, 1635 cm^{-1}; ^1H n.m.r($CDCl_3$/DMSO-d_6):δ 1.82(s,3H, SCH_3); 5.84(s,1H,H-3); 7.15-7.70(m,8H_{arom}); 7.83-8.03(m,2H_{arom}). (Found: C,67.35; H,4.43; N,4.13; Calc. for $C_{19}H_{15}NO_3$(337.4): C,67.65; H,4.45; N,4.15%). m/z 337(M^+,11); 209(12).

5-(4-Chlorobenzoyl)-4-hydroxy-6-methylthio-1-phenyl-2-pyridone (50b) was obtained as white crystalline solid (ethanol); yield 81%; m.p.211-212°C; i.r.(KBr): ν_{max} = 1660, 1638 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.85(s,3H,SCH_3); 5.93(s,1H,H-3); 7.14-7.60(m,7H_{arom}); 7.78-8.13(m, 2H_{arom}). (Found: C,61.13; H, 3.74: N, 3.75; Calc. for $C_{19}H_{14}ClNO_3$(371.8): C,61.37; H,3.76; N,3.76%). m/z 371(M^+,12).

4-Hydroxy-5-(4-methoxybenzoyl)-6-methylthio-1-phenyl-2-pyridone (50c) was obtained as white crystalline solid (ethanol); yield 83%; m.p. 270°C; i.r.(KBr): ν_{max} = 1665, 1640 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):

δ1.85(s,3H,SCH_3); 3.83(s,3H,OCH_3); 5.95(s,1H,H-3); 6.80-7.70(m,$7H_{arom}$); 7.70-8.15(m,$2H_{arom}$). (Found: C,65.12; H,4.61; N,3.80; Calc. for $C_{20}H_{17}NO_3S$(367.4): C,65.39; H,4.63; N,3.81%). m/z 367 (M^+,9).

5-Benzoyl-4-hydroxy-6-methylthio-1-(4-methylphenyl)-2-pyridone (50d) was obtained as white crystalline solid (ethanol); yield 91%; m.p. 286-287°C; i.r.(KBr): ν_{max} = 1660, 1640 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.82(s,3H,SCH_3); 2.37(s,3H,CH_3); 5.97(s,1H,H-3); 7.00-7.70(m,$7H_{arom}$); 7.82-8.10(m,$2H_{arom}$). (Found: C,68.09; H,4.83; N,3.97. Calc. for $C_{20}H_{17}NO_3S$(351.4): C,68.37; H,4.84; N,3.98%). m/z 351 (M^+,14).

5-Benzoyl-4-hydroxy-1-methyl-6-methylthio-2-pyridone (50e) was isolated as white crystalline solid (ethanol); yield 73%; m.p. 270-271°C; i.r. (KBr): ν_{max} = 1660, 1635 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 2.20(s,3H, SCH_3); 3.60(s,3H,NCH_3); 5.77(s,1H,H-3); 7.40-7.60(m,$3H_{arom}$); 7.72-7.92 (m,$2H_{arom}$). (Found: C,60.87; H,4.71; N,5.06. Calc. for $C_{14}H_{13}NO_3S$(275.3): C,61.09; H,4.72; N,5.09%). m/z 275(M^+,30).

5-(4-Chlorobenzoyl)-4-hydroxy-1-methyl-6-methylthio-2-pyridone (50f) was obtained as white crystalline solid (ethanol); yield 71%; m.p. 229-230°C; i.r.(KBr): ν_{max} = 1670, 1650 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 2.26(s,3H,SCH_3); 3.70(s,3H,NCH_3); 6.01(s,1H,H-3); 7.35-7.86(m,A_2B_2, $4H_{arom}$). (Found: C,54.01; H,3.85; N,4.50. Calc. for $C_{14}H_{12}ClNO_3S$(309.8): C,54.28; H,3.87; N,4.52%). m/z 309(M^+,27).

5-Benzoyl-1-ethyl-4-hydroxy-6-methylthio-2-pyridone (50g) was obtained as white crystalline solid (ethanol); yield 76%; m.p. 279-280°C; i.r. (KBr): ν_{max} = 1660, 1640 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.22(t,3H, J=7Hz,CH_3CH_2); 2.30(s,3H,SCH_3); 4.23(q,2H,J=7Hz,CH_3CH_2); 6.85(s,1H,H-3); 7.40-7.95(m,$5H_{arom}$). (Found: C,62.06; H,5.17; N,4.82. Calc. for

$C_{15}H_{15}NO_3S$(289.3): C,62.28; H,5.19; N,4.84%). m/z 289(M^+,19).

5-(4-Chlorobenzoyl)-1-ethyl-4-hydroxy-6-methylthio-2-pyridones (50h)

was obtained as white crystalline solid (ethanol); yield 74% m.p. 264-265°C; i.r.(KBr): ν_{max} = 1670, 1640 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.22(t,3H,J=7Hz,$C\underline{H}_3CH_2$); 2.30(s,3H,$SC\underline{H}_3$); 4.22(q,2H,J=7Hz,$CH_3C\underline{H}_2$); 5.82(s,1H,$\underline{H}$-3); 7.35-7.98(m,A_2B_2,$4H_{arom}$). (Found: C,55.38; H,4.30; N,4.29. Calc. for $C_{15}H_{14}ClNO_3S$(323.8): C,55.64; H,4.32; N,4.32%). m/z 323(M^+,16).

1-Benzyl-5-benzoyl-4-hydroxy-6-methylthio-2-pyridone (50i) was obtained as white crystalline solid (ethanol); yield 77%; m.p. 211-212°C; i.r. (KBr): ν_{max} = 1660, 1630 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 2.02(s,3H, $SC\underline{H}_3$); 5.48(s,2H,$C_6H_5C\underline{H}_2$); 5.98(s,1H,$\underline{H}$-3); 7.10-8.05(m,$10H_{arom}$). (Found: C,68.18; H,4.82; N,3.97. Calc. for $C_{20}H_{17}NO_3S$(351.4): C,68.37; H,4.84; N,3.98%). m/z 351(M^+,29).

1-Benzyl-4-hydroxy-5-(methoxybenzoyl)-6-methylthio-2-pyridones (50j)

was obtained as white crystalline solid (ethanol); yield 78%; m.p. 208-209°C; i.r.(KBr): ν_{max} = 1660, 1640, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ2.00(s,3H,$SC\underline{H}_3$); 3.83(s,3H,$OC\underline{H}_3$): 5.50(s,2H,$C_6H_5C\underline{H}_2$); 5.98(s,1H,$\underline{H}$3); 6.84-7.45(m,$7H_{arom}$); 7.76-7.92(m,A_2B_2,$2H_{arom}$). (Found: C,65.87; H,4.97 N,3.66. Calc. for $C_{21}H_{19}NO_4S$(381.4): C,66.14; H,4.98; N,3.67%). m/z 381 (M^+,10).

5-Benzoyl-4-hydroxy-6-methylthio-1-n-propyl-2-pyridone (50k) was obtained as white crystalline solid (ethanol); yield 76%; m.p. 230-231°C; i.r. (KBr): ν_{max} = 1667, 1640 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 0.90(t,3H, J=6.5Hz,$C\underline{H}_3CH_2CH_2$); 1.66(sext,2H,J=6.5Hz,$CH_3C\underline{H}_2CH_2$); 2.27 (s,3H,$SC\underline{H}_3$); 4.11(t,2H,J=6.5Hz,$CH_3CH_2C\underline{H}_2$); 5.84(s,1H,$\underline{H}$-3); 7.37-7.90

(m,5H$_{arom}$). (Found: C,63.15; H,5.59; N,4.60. Calc. for $C_{16}H_{17}NO_3S$(303.4): C,63.36; H,5.61; N,4.62%. m/z 303(M^+,10).

5-Acetyl-4-hydroxy-1-methyl-6-methylthio-2-pyridone (501)was obtained as colorless crystalline solid (ethanol); yield 75%; m.p. 224-225°C; i.r.(KBr): ν_{max} = 1700, 1640, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 2.32(s,3H,SCH_3); 2.40(s,3H,CH_3); 3.60(s,3H,NCH_3); 5.87(s,1H,H-3). (Found: C,50.47; H,5.14; N,6.54. Calc. for $C_9H_{11}NO_3S$(213.25): C,50.64; H,5.16; N,6.56%). m/z 213(M^+,55).

6-Alkyl/Benzyl-8-benzoyl/acetyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro 2H-pyrano [3,2-c] pyridines (51e,g,i,m); General Procedure:

To a well stirred solution of S,N-acetal 2 (10 mmol) and dry triethylamine (6.06g, 60 mmol) in dry tetrahydrofuran (15 ml), malonyl chloride (4.23g, 30 mmol) was added slowly during 15 min. and the mixture was further stirred for 25 hr. at room temperature. The mixture was poured onto crushed ice (150g), neutralized with solid sodium bicarbonate(10g), extracted with chloroform (3x100 ml) washed with water (3x100 ml), dried over sodium sulfate and evaporated to give a dark colored viscous residue, which on column chromatography on silica gel (chloroform/hexane 1:3 eluent) gave pure pyrano pyridones 51e,g,i,m as pale colored solids (ethanol).

8-Benzoyl-4-hydroxy-6-methyl-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-c] pyridine (51e) was obtained as pale yellow crystalline solid (ethanol); yield 36%; m.p. 202-203°C; i.r.(KBr): ν_{max} = 1735, 1670(br) cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 2.36(s,3H,SCH_3); 3.88(s,3H, NCH_3); 5.45(s,1H,H-3); 7.48-7.85(m,3H$_{arom}$); 7.90-8.17(m,2H$_{arom}$). (Found: 59.30; H,3.77; N,4.06. Calc. for $C_{17}H_{13}NO_5S$(343.5): C,59.41; H,3.79; N,4.08%). m/z 343(M^+,38).

8-Benzoyl-6-ethyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-c] pyridine (50g) was obtained as pale yellow crystalline solid (ethanol); yield 44%; m.p. 202-203°C; i.r.(KBr): ν_{max} = 1740, 1675(br) cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6); δ 1.35(t,3H,J=7Hz,$\underline{CH_3}CH_2$); 2.38(s,3H,$SC\underline{H_3}$); 4.45(q,2H,J=7Hz,$CH_3C\underline{H_2}N$); 4.56(s,1H,H-3); 7.40-7.75 (m,$3H_{arom}$); 7.85-8.08(m,$2H_{arom}$): ^{13}C n.m.r.(DMSO-d_6; 100 MHz); 13.70 ($\underline{C}H_3CH_2$); 20.50(CH_3S); 41.69($CH_3\underline{C}H_2$); 89.35(C-3); 101.73(C-8); 119.85 (C-4a); 129.06, 129.55, 134.55(CH aromatic); 136.03(C-1' of phenyl); 145.21(C-4); 158.62(C-8a); 159.77(C-7); 163.01(O=C-N); 167.9(C=O); 188.56(Ar-C=O). (Found: C,60.56; H,4.24; N,4.01. Calc. for $C_{18}H_{15}NO_5S$ (357.4): C,60.44; H,4.19; N,3.91%). m/z 357(M^+,100).

6-Benzyl-8-benzoyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-c] pyridines (51i) was obtained as pale yellow solid(ethanol); yield 38%; m.p.200°C; i.r.(KBr): ν_{max} = 1732, 1660(br)cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6): δ 2.11(s,3H,$SC\underline{H_3}$); 5.45(s,1H,H-3); 5.65(s,2H,$C_6H_5C\underline{H_2}$); 7.01-8.02(m,$10H_{arom}$). (Found: C,66.03; H,3.97; N,3.39. Calc. for $C_{23}H_{17}NO_5S$(419.4): C,65.80; H,4.05; N,3.34%). m/z 419(M^+,57).

8-Acetyl-6-ethyl-4-hydroxy-7-methylthio-2,5-dioxo-5,6-dihydro-2H-pyrano [3,2-c] pyridine(51m) was obtained as pale yellow crystalline solid (ethanol); yield 35%; m.p. 165-166°C; i.r.(KBr): ν_{max} = 1740, 1705, 1665 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6); δ 1.33(t,3H,J=7.5Hz,$\underline{CH_3}CH_2$); 2.54 (s,3H,$SC\underline{H_3}$); 2.60(s,3H,$\underline{CH_3}$); 4.44(q,2H,J=7.5Hz,$CH_3C\underline{H_2}N$); 5.47(s,1H, H-3). (Found: C,53.02; H,4.48; N,4.67. Calc. for $C_{13}H_{13}NO_5S$(295.3): C,52.82; H,4.40; N,4.74%). m/z 295(M^+,79).

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CHAPTER IV

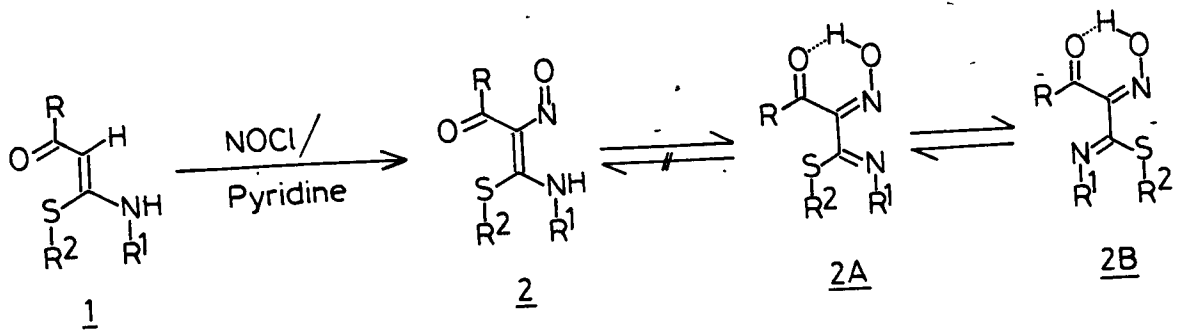
REACTION OF HYDROXYIMINOIMINES WITH HYDRAZINE HYDRATE: SYNTHESIS OF 3(5)-ARYL-5(3)-ALKYL/ARYLAMINO 4-NITROSO PYRAZOLES, 3(5)-ARYL-5(3)-ALKYL/ARYLAMINO-4-AMINO PYRAZOLES AND 1,4-SUBSTITUTED PYRAZOLO [3,4-d] [1,2,3] TRIAZOLES.

IV.1 INTRODUCTION

In the preceding chapter it has been demonstrated that the α-oxoketene S,N-acetals function as versatile enaminones, which react with electrophiles through the nucleophilic α-carbon to yield α-substituted enaminones. The advantage of these properties of S,N-acetals has been demonstrated for the synthesis of several important heterocycles. Earlier work from this laboratory has

shown that the α-oxoketene S,N-acetals undergo facile electrophilic nitrosation with nitrosyl chloride to afford the corresponding hydroxyiminoimines[1]. These intermediates are of particular synthetic importance, since they can further undergo an intramolecular cyclization with one of the carbon atoms on the β-amino group[1]. Indeed 6-amino-5-nitrosopyrimidine derivatives have been converted into purines[2,3], alloxazines[4,5] and flavins[6]. Similar syntnetic approach based on open chain nitroso enaminones (α-hydroxyimino-imines) to afford imidazoles, quinoxalines, thiazoles have been successfully accomplished[1] in this laboratory.

α-Oxoketene S,N-acetals of general formula 1 are shown to be highly reactive towards electrophilic substitution at α-position. Thus, nitrosation of α-oxoketene S,N-acetals 1 with nitrosyl chloride in ether yields the corresponding hydroxyiminoimines 2 in excellent yields (Scheme 1)[1] which are proved to be ubiquitous intermediates for the synthesis of imidazoles, quinoxalines, thiazoles and other fused heterocycles[1]. The 2-aryl imidazoles 3 could be prepared directly in one step in 70-82% yield by refluxing a mixture of S,N-acetal 1 ($R^1=CH_2C_6H_5$) and nitrosyl chloride in pyridine for 3 hrs. (Scheme 1)[7]. The reaction was found to be a general and the method thus provides a direct entry to 2-aryl imidazoles 3 without the need for isolation of the corresponding hydroxy imino-imine intermediates. Similarly the S,N-acetal 1 ($R^1=CH_2CO_2Et$) derived from ethyl glycinate was reacted with nitrosyl chloride in refluxing pyridine to afford the corresponding 2-carboethoxy imidazole 4 in excellent yield (Scheme 2)[7].

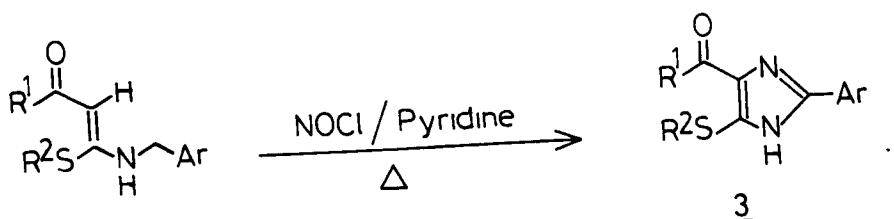


1 2 2A 2B

R = Me, C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$

R^1 = Me, Et, $C_6H_5CH_2$, C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, CH_2CO_2Et

R^2 = Me, Et, $C_6H_5CH_2$



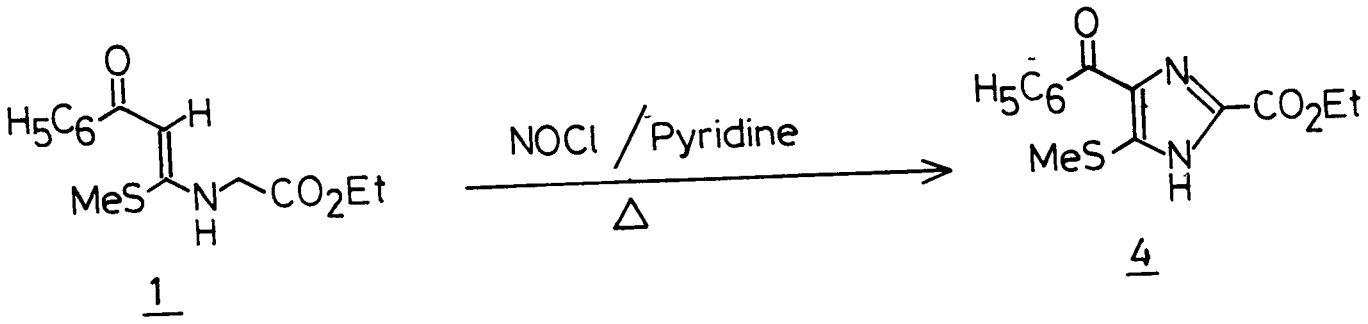
1 3

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

R^2 = Me, Et

Ar = C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4

Scheme 1



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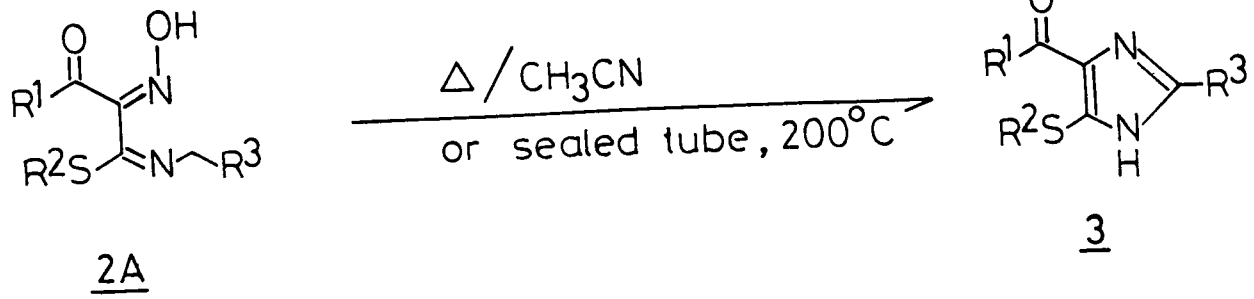


2A

R^1 = Me ; C_6H_5 ; 4-MeC_6H_4 ; 4-ClC_6H_4

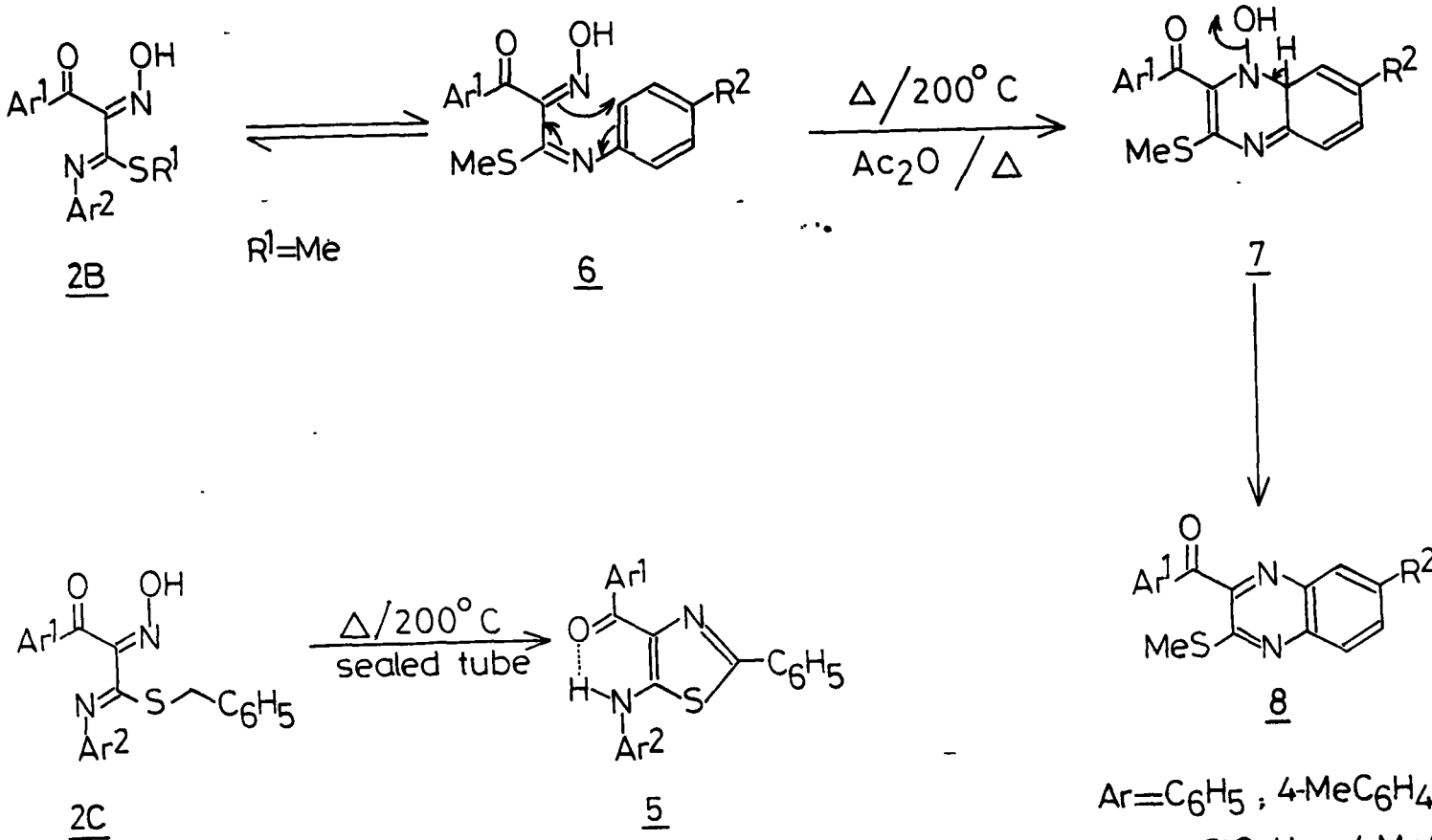
R^2 = Me ; $C_6H_5CH_2$

R^3 = H, Me ; C_6H_5

Scheme 2

The hydroxyiminoimine derivatives 2 carrying CH_2 or CH_3 substituents on the β-amino group undergo facile thermal cyclodehydration to substituted imidazole derivatives 3 (Scheme 2). It is interesting to note that the methylene group need not be activated, thus the hydroxyiminoimine derivative 2 (R^3=H) undergoes facile intramolecular condensation to give the 2-unsubstituted imidazole 3 when heated in a steel bomb at 200°C in acetonitrile. The thermal cyclodehydration of the corresponding N-aryl hydroxyiminoimines 2 (R^1=Ar) in sealed tube (200°C) afforded quinoxaline derivatives 8 in good yields (Scheme 3)[1]. However, cyclodehydration of the corresponding benzylthio hydroxyiminoimines 2 (R^2=$CH_2C_6H_5$) took a different course and the corresponding 5-anilino thiazoles 5 were obtained in good yields (Scheme 3)[1]. Thus the method provides a novel approach for the synthesis of quinoxaline derivatives 8 and 5-anilino thiazoles 5 (Scheme 3).

The new method of imidazole synthesis was further extended for the synthesis of 2H imidazoles. Thus, the S,N-acetals 9 derived from isopropylamine and cycloalkyl amines underwent smooth nitrosation with nitrosyl chloride in the presence of chloroform and pyridine to yield the corresponding hydroxyiminoimine derivatives 10 in excellent yields (Scheme 4)[8]. When hydroxyiminoimines 10 were heated at 200°C in a sealed tube underwent smooth cyclodehydration to afford the 2H imidazoles 11 in good yields (Scheme 4). The attempts to rearrange imidazoles 11 to 1-N-alkyl/aryl-1H-imidazoles either thermally or in boiling acetic acid were not



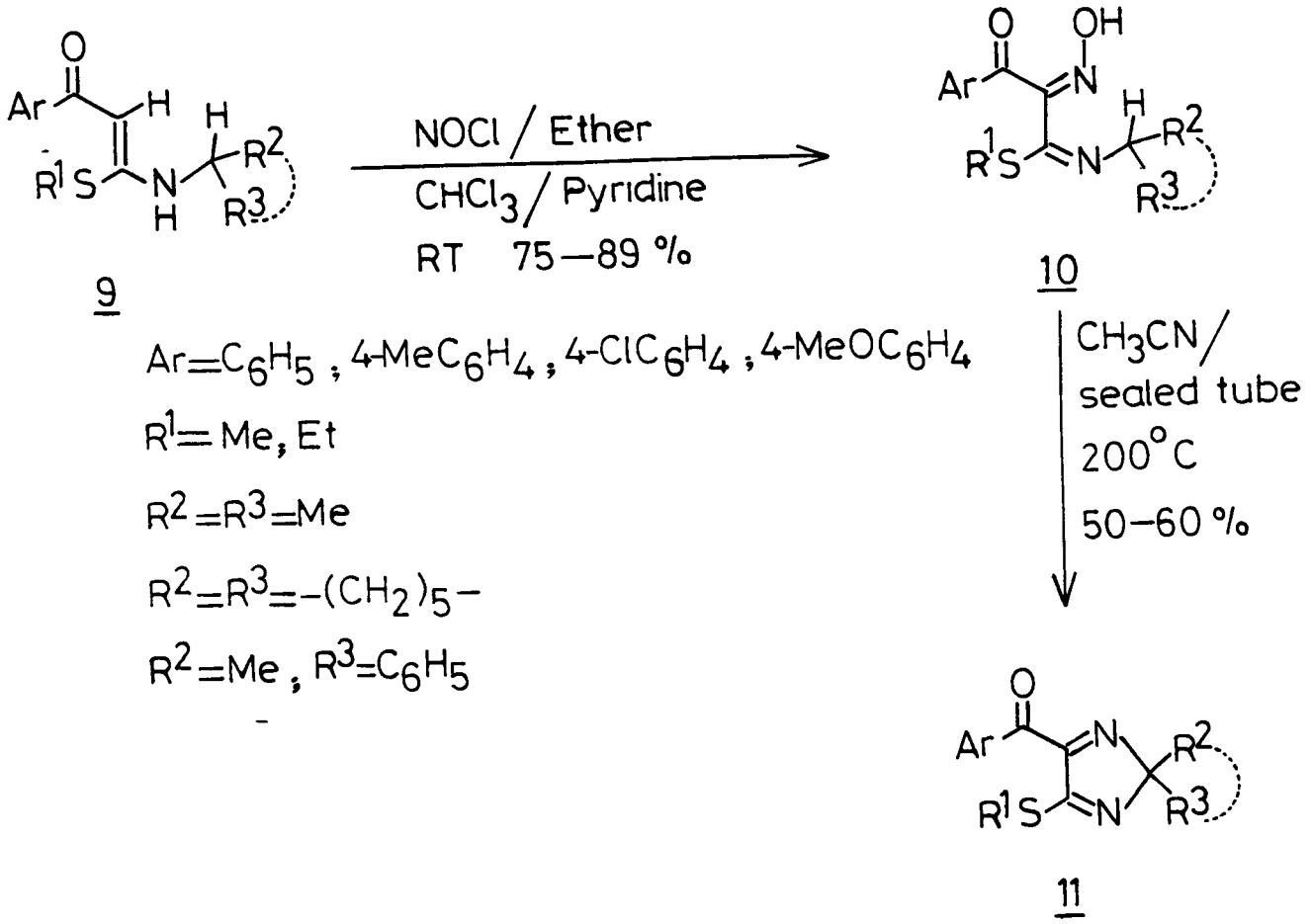
$Ar^1 = C_6H_5$; 4-MeC_6H_4 ; 4-ClC_6H_4 ; 4-$MeOC_6H_4$

$Ar^2 = C_6H_5$, 4-MeC_6H_4 ; 4-ClC_6H_4

Ar = C_6H_5 ; 4-MeC_6H_4
4-ClC_6H_4 ; 4-$MeOC_6H_4$

R^2 = H , Me , Cl , MeO

Scheme 3


NOCl / Ether
CHCl3 / Pyridine
RT 75—89 %
9
10
11
CH3CN/
sealed tube
200°C
50–60 %
Ar=C6H5 ; 4-MeC6H4 ; 4-ClC6H4 ; 4-MeOC6H4
R1= Me, Et
R2=R3=Me
R2=R3=-(CH2)5-
R2=Me , R3=C6H5

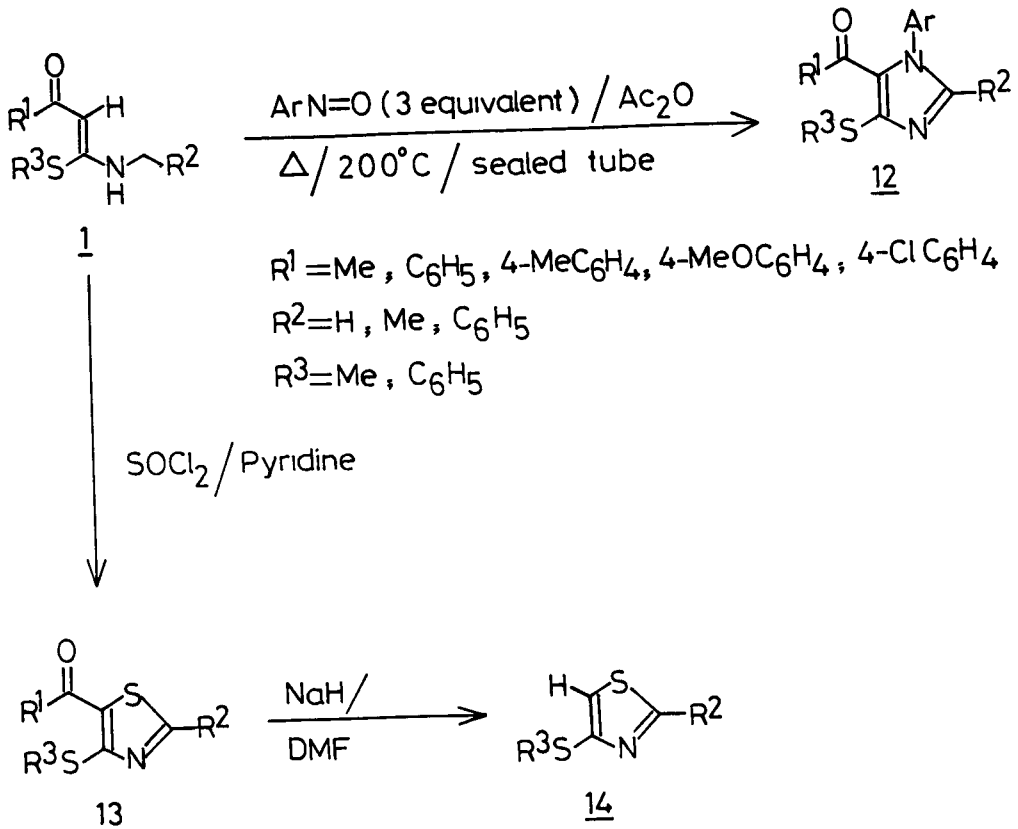
Scheme 4

successful (Scheme 4)[8]. Electrophilic nitrosation and cyclization of α-oxoketene S,N-acetals 1 has also been achieved with nitrosobenzene at 200°C (sealed tube) in the presence of acetic anhydride which affords N-arylimidazole derivatives 12 in excellent yields (Scheme 5)[9]. Alternatively the S,N-acetals 1 were also reacted with excess of thionyl chloride in the presence of pyridine at 0°C to yield the corresponding thiazoles 13 in good yields. Some of the thiazoles were subjected to debenzoylation in the presence of sodium hydride and hot dimethyl formamide to afford the 5-unsubstituted thiazoles 14 in good yields (Scheme 5)[10]. Thus the hydroxyiminoimines are shown to be versatile synthons for imidazoles, quinoxalines and thiazoles.

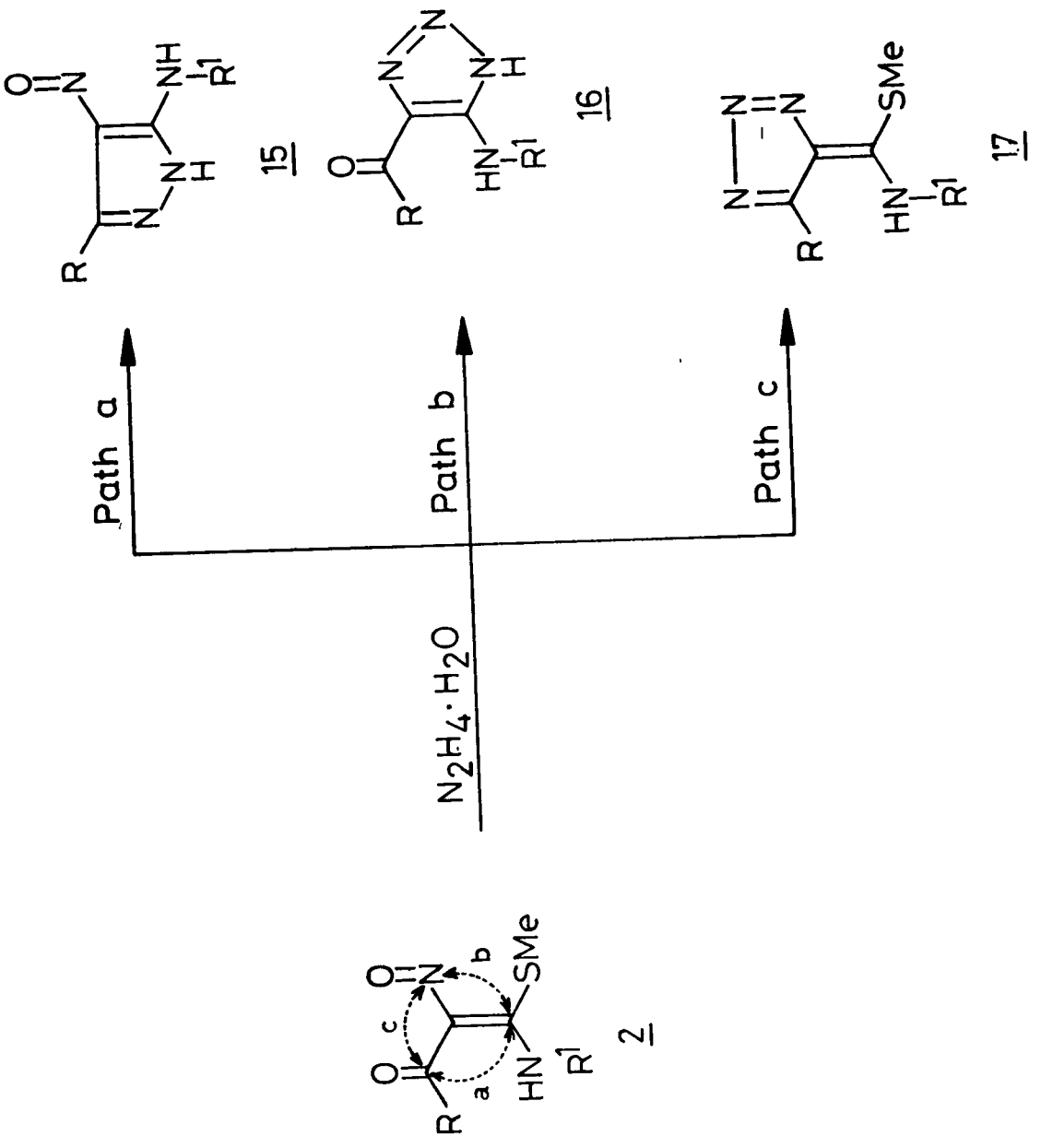
During the course of these investigations it was planned to extend these studies to hydroxyiminoimines 2 with bifunctional nucleophiles (Scheme 6). The hydroxyiminoimines 2 possessing three electrophilic centres could undergo cyclocondensation with bifunctional nucleophiles through different routes (a,b and c) leading to either 4-nitroso pyrazoles 15 or 1,2,3-triazoles 16 and 1,2,3-triazolidines 17 respectively. We have studied the reaction of 2 with hydrazine hydrate and the results are reported here.

IV.2 RESULTS AND DISCUSSION

For the present study, the known hydroxyiminoimines 2a-c and 2f-j (Scheme 7, Table 1) were prepared according to the reported procedures[1,7]. The structures of all the known hydroxyiminoimines were confirmed by the comparison of their spectral and analytical data with those of


ArN=O (3 equivalent) / Ac2O
Δ / 200°C / sealed tube
1
12
R1 =Me , C6H5 , 4-MeC6H4, 4-MeOC6H4 , 4-Cl C6H4
R2=H , Me , C6H5
R3=Me , C6H5
SOCl2 / Pyridine
NaH/
DMF
13
14
R1=Me , Substituted aryl
R2=C6H5 , 4-ClC6H4, 4-MeOC6H4 , CO2Et
R3=Me, Et , C6H5CH2
R2=C6H5 ; 4-ClC6H4 ; 4-MeOC6H4, R3=Me , Et

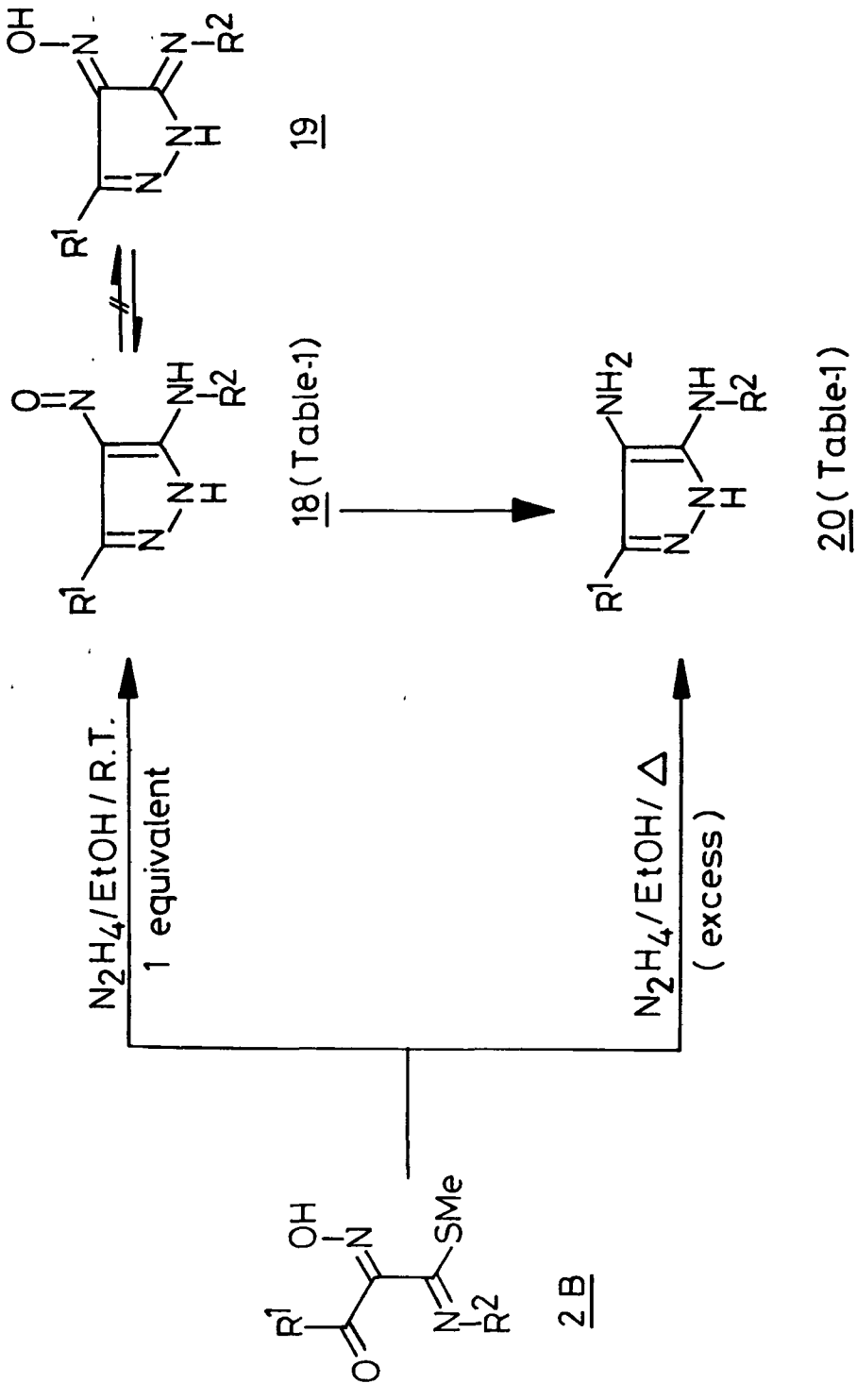
Scheme 5



Scheme 6

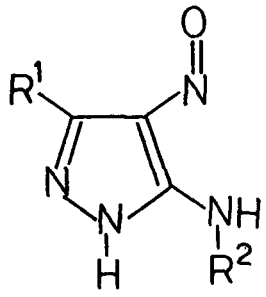
authentic samples. The hitherto unknown hydroxyiminoimines 2d-e (Scheme 7, Table 1) were also prepared essentially by extending the reported methodology. Thus, the hydroxyiminoimine 2d was prepared by reacting the corresponding 3-methylthio-3-n-propylamino-1-phenyl-2-propen-1-one with nitrosyl chloride in presence of ether and pyridine in 83% yield. The structure of the compound was fully confirmed by its analytical and spectral data which are described in the experimental section. Similarly, when 3-butylamino-3-methylthio-1-phenyl-2-propen-1-one was reacted with nitrosyl chloride in presence of ether and pyridine the corresponding hydroxyiminoimine 2e was obtained in 88% yield. The structural confirmation was achieved through its analytical and spectral data which are described in experimental section.

In one of the typical experiments, the hydroxyiminoimine 2a was reacted with one equivalent of hydrazine hydrate in the presence of ethanol at room temperature, work-up of the reaction mixture afforded an orange coloured crystalline solid (ethanol) m.p. 260-261°C, in 95% yield, which was characterised as 5(3)-ethylamino-4-nitroso 3(5) phenyl pyrazole 18a (Scheme 7) on the basis of its analytical and spectral data. The elemental analysis of 18a agreed with the molecular formula $C_{11}H_{12}N_4O$, while its mass spectrum exhibited molecular ion peak at m/z 216 (M^+,100%). Its i.r. spectrum (KBr) showed a peak at 3040 cm^{-1} due to secondary amine stretching vibration, while the band at 1655 cm^{-1} was assigned to nitroso group rather than C=N functionality. The structure was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$/DMSO-d_6). Thus, the

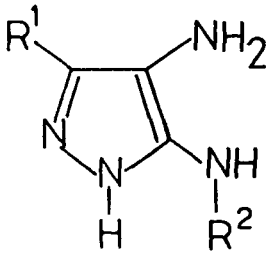

OH
N
N
R2
NH
N
R1
19
O
N
NH
R2
N
H
N
R1
18 (Table-1)
NH2
NH
R2
N
H
N
R1
20 (Table-1)
N2H4/EtOH/R.T.
1 equivalent
N2H4/EtOH/Δ
(excess)
OH
N
SMe
R1
N
R2
O
2B

Scheme 7

Table 1



18

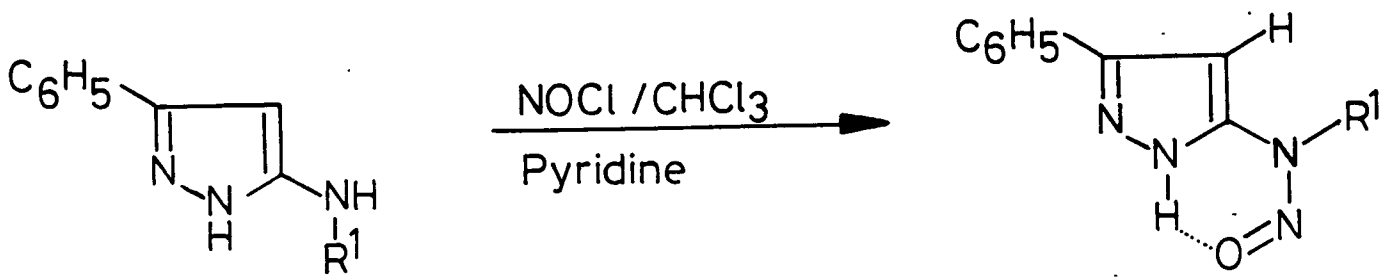


20

2,18,20	R^1	R^2
a	C_6H_5	C_2H_5
b	$4\text{-}MeC_6H_4$	C_2H_5
c	C_6H_5	CH_3
d	C_6H_5	$n\text{-}C_3H_7$
e	C_6H_5	$n\text{-}C_4H_9$
f	C_6H_5	$C_6H_5CH_2$
g	C_6H_5	C_6H_5
h	$4\text{-}ClC_6H_4$	C_6H_5
i	$4\text{-}MeOC_6H_4$	C_6H_5
j	C_6H_5	$4\text{-}ClC_6H_4$

triplet at δ 1.19(3H) was assigned to methyl group with coupling constant 7Hz. The quartet at δ 3.31(2H) was attributed to methylene protons of ethyl group with coupling constant of 7Hz. The multiplet between δ 7.29-7.58 was assigned to the three aromatic protons. Where as the multiplet between δ 8.10-8.36 was due to the other two aromatic protons. The broad singlet at δ 9.41(1H) was assigned to NH proton, confirming the assignment of the 1655 cm^{-1} band to nitroso group. Thus, unlike in open chain precursors the 5(3)-alkyl/aryl amino-4-nitroso-3(5)-aryl pyrazoles 16a-j exists in the nitroso form rather than the oximino tautomer. Probably the tautomerism in favour of oximino form is restricted by the barrier of the pyrazole ring aromaticity, that forces the structure to exist in the nitrosoform. Under similar reaction conditions the other hydroxyiminoimines 2b-j underwent smooth cyclocondensation with one equivalent of hydrazine hydrate at room temperature to yield the corresponding pyrazoles 18b-j in 89-97% overall yields. The analytical and spectral data of these compounds are in confirmity with their structures and are given in experimental section. In an another experiment, when excess of hydrazine hydrate was reacted with hydroxyiminoimine 2a in refluxing ethanol, work-up of the reaction mixture yielded a white crystalline compound (ethanol) m.p. 177°C in 92% yield (Scheme 7) which was characterized as 4-amino 5(3)-ethylamino-3(5)-phenyl pyrazole 20a on the basis of its analytical and spectral data. Thus 20a was analysed for $C_{11}H_{14}N_4$ and its mass spectrum showed a molecular ion peak at m/z 202(M^+,100%). Its i.r. spectrum (KBr) exhibited peaks at 3340 cm^{-1} which was

assigned to primary amino group where as the band at 3160 cm^{-1} was assigned to secondary amino group. Further structural proof for 20a was obtained from its ^1H n.m.r.spectrum ($CDCl_3$/DMSO-d_6) which showed the triplet at δ 1.20(3H) was assigned to methyl protons of ethyl group with coupling constant of 7Hz. The quartet at δ 3.18(3H,J=7Hz) was assigned to methylene protons of ethyl group. The broad singlet at δ 5.41(4H) was assigned to the both secondary and primary NH_2 protons. The multiplet between δ 7.10-7.49(3H) was assigned to aromatic protons. While the other two aromatic protons appeared as multiplet between δ 7.61-7.84. The other hydroxyiminoimines 2b-j were similarly reacted with excess of hydrazine hydrate in the presence of boiling ethanol to yield the corresponding 4-amino pyrazoles 20b-j in 84-96% overall yields. The structures of all the products were confirmed by their analytical and spectral data which are described in experimental section. The structure of 20a was further confirmed by reacting the 5(3)-ethylamino-4-nitroso 3(5)-phenyl pyrazole 18a with excess of hydrazine hydrate in refluxing ethanol, and the white crystalline compound obtained was exactly identical (i.r., n.m.r., m.m.p.) with the pyrazole 20a obtained by reacting excess of hydrazine hydrate with hydroxyiminoimine 2a. It was considered of interest to attempt direct nitrosation of the 5(3)-amino pyrazoles to examine whether the nitrosation goes to 4-position to yield the same 4-nitroso pyrazoles obtained by reacting one equivalent of hydrazine hydrate with hydroxyiminoimines. Thus, when 3(5) phenyl 5(3)-ethylamino pyrazole 21a was subjected to nitrosation with nitrosyl chloride in the presence of chloroform



21

22 a–c

21, 22, a $R^1 = Et$

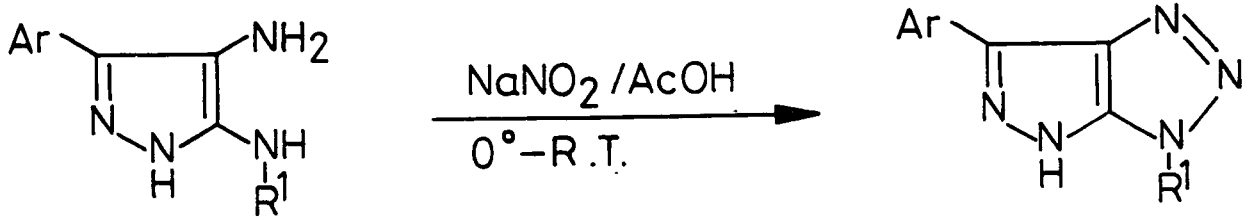
b $R^1 = C_6H_5CH_2$

c $R^1 = C_6H_5$

Scheme 8

and pyridine, work-up of the reaction mixture afforded a grey coloured crystalline compound (ethanol) m.p. 167°C in 90% yield, which was characterized as 5(3)-(N-nitroso) ethylamino-3(5 phenyl pyrazole 22a on the basis of its analytical and spectral data (Scheme 8). Thus 22a showed molecular ion peak at m/z 186 (M^+-30,100%) due to loss of nitroso group from molecular ion, and was analysed for $C_{11}H_{12}N_4O$. Its i.r. spectrum (KBr) showed a peak at 3205 cm^{-1} was assigned to the ring NH stretching vibration which is associated with intramolecular hydrogen bonding with oxygen of nitroso group. The other peak at 1568 cm^{-1} was due to N-nitroso group. The structure was further confirmed by its ^1H n.m.r. spectrum ($CDCl_3$/ DMSO-d_6). Thus, the triplet atδ1.13 (3H,J=7Hz) was assigned to the methyl group protons, while the quartet at δ 4.20(2H,J=7Hz) was attributed to the methylene protons of the ethyl group. The most characteristic singlet at δ 6.91 was assigned to the H-4 proton, which rules out the nitrosation at 4-position of the pyrazole ring. The aromatic protons appeared as broad multiplet at δ 7.29-7.61(3H) and 7.70-7.98(2H). Similarly the other pyrazoles 21b-c reacted with nitrosyl chloride under identical conditions to give the corresponding N-nitroso pyrazoles 22b-c in 87-91% overall yields (Scheme 8). The analytical and spectral data of these compounds are in confirmity with their assigned structures and are given in the experimental section.

After having developed a convenient method for the synthesis of diaminopyrazoles 20, it was considered of interest to examine some



20 23

20,23 a Ar = 4-MeC_6H_4 , R^1 = Et

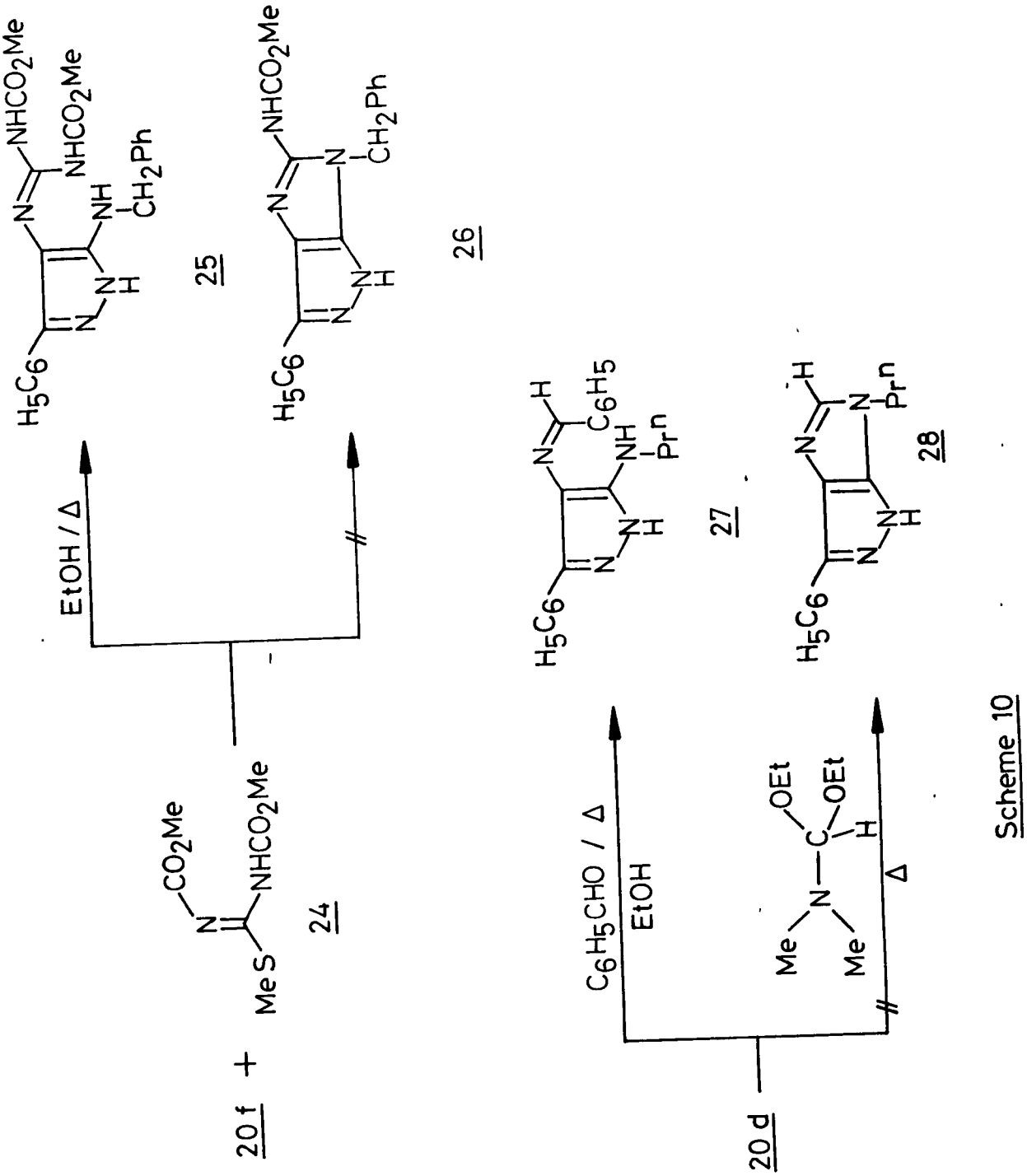
b Ar = C_6H_5 , R^1 = $C_6H_5CH_2$

c Ar = 4-$MeOC_6H_4$, R^1 = C_6H_5

Scheme 9

of the selected reactions of diamino pyrazoles. Thus, when diamino pyrazole 20a was diazotized with sodium nitrite in presence of acetic acid at 0°C, work-up of the reaction mixture afforded a yellow crystalline solid (ethanol) m.p. 206-207°C in 63%, which was characterized as 1-ethyl-4-phenyl pyrazolo [3,4-d] [1.2,3] triazole 23a on the basis of its analytical and spectral data (Scheme 9). The elemental analysis of 23a agreed with the molecular formula $C_{12}H_{13}N_5$. Its i.r. spectrum (KBr) showed bands at 3225(NH), 1623(C=N) and 1540 cm^{-1} (N=N). The ^1H n.m.r. ($CDCl_3$/DMSO-d_6) spectrum of 23a exhibited a triplet at δ 1.19(3H, J=7Hz) due to methyl group and singlet at δ 2.40(3H) due to Ar-CH_3 protons. The quartet at δ 4.25(2H,J=7Hz) was assigned to methylene protons while the aromatic protons appeared as two doublets at δ 7.30(2H) and δ 7.68(2H). The reaction of other diamino pyrazoles 20b-c with sodium nitrite similarly yielded the corresponding pyrazolo triazoles 23b-c in 78-84% yields (Scheme 9). All these pyrazolo triazoles 23b-c were characterized with the help of spectral and analytical data.

However, the attempts to construct imidazolo pyrazole ring 26 by reacting diamino pyrazole (20f) with methyl methoxy carbonyl imino-(methylthio)methyl carbonate 24 in refluxing ethanol, resulted only in the open chain compound 25 instead of corresponding imidazolo pyrazole 26 (Scheme 10). The structure of 25 was confirmed with the help of spectral and analytical data. The elemental analysis of 25 agreed with the molecular formula $C_{21}H_{22}N_6O_4$.


20 f
24
MeS
CO2Me
NHCO2Me
EtOH / Δ
25
26
NHCO2Me
NHCO2Me
CH2Ph
H5C6
20 d
C6H5CHO / Δ
EtOH
27
28
C6H5
Prn
OEt
OEt
Me
Me
Δ

Scheme 10

Its i.r. spectrum (KBr) showed bands at 3375 and 3285 cm^{-1} due to NH, while the band at 1738 cm^{-1} was assigned to amido carbonyl stretching vibration. The band at 1641 and 1612 cm^{-1} were assigned to C=N and C=C respectively. Its structure was further confirmed by its ^1H n.m.r. spectrum (DMSO-d_6). The characteristic free amino proton signal present in the n.m.r. spectrum of 20f, at δ 5.10(brs, 2H) was absent in the n.m.r. spectrum of 25, thus indicating that NH_2 group is involved in the condensation with 24. The signals due to OCH_3 protons were present at δ 3.48(3H) and δ 3.73(3H) and the benzylic protons appeared at δ 4.30(2H). The broad signal at δ 5.45(2H) was due to two NH protons, while the aromatic protons were appeared as multiplet at δ 7.13-7.68(5H). The pyrazolo NH proton appeared as broad singlet at δ 9.32(1H). Also the diamino-pyrazole 20d was reacted with benzaldehyde in boiling ethanol, when the corresponding open chain Schiff base was formed in 72% yield which was confirmed by its analyticaland spectral data, which are described in experimental section. Similarly, the reaction of 20d with N,N-dimethyl formamide diethyl acetal in boiling ethanol gave neither open chain adduct nor pyrazolo imidazole 28 (Scheme 10).

IV.3 EXPERIMENTAL

Melting points were determined on Thomas Hoover apparatus and are uncorrected. The i.r. spectra were recorded on a 'Perkin-Elmer 297' spectrophotometer and the ^1H n.m.r. spectra were recorded on a Varian EM-390, 90MHz spectrometer using tetramethyl silane (TMS) as internal standard and chemical shifts are expressed in δ(ppm).

^{13}C n.m.r. spectra were recorded on a Burcker-WP-80 DS spectrometer. The mass spectra were recorded on Jeol-D 300 mass spectrometer and carbon, hydrogen, nitrogen analysis were done at Central Drug Research Institute, Lucknow, India.

Starting Materials

The commercial ethanol was purified before use. The commercially available hydrazine hydrate used as such. Of the various N-aryl/alkyl hydroxyiminoimines used 2a-c and 2f-j were prepared by the reported procedure[1,7] and their structures were confirmed by comparing their analytical and spectral data with the reported ones. The unknown hydroxy iminoimines 2d-e were prepared by extending the following reported procedure[1,7].

To an ice cooled and well stirred solution of S,N-acetal (0.01 mole) in dry pyridine (2 ml) and dry ether (25 ml), nitrosyl chloride (0.12 mole in 5 ml ether) was added and the reaction mixture was further stirred for 10-15 min. It was then diluted with ice cold water (50 ml), extracted with chloroform (3x50 ml). The chloroform layer was washed with water (3x100 ml) to remove excess of pyridine, dried (Na_2SO_4) and evaporated to give crude solid hydroxyiminoimines 2d-e (Table 1), which were purified by crystallization using benzene/hexane. Spectral and analytical data are given below.

3-Methylthio-2-nitroso-3-n-propylamino-1-phenyl-2-propen-1-one (2d)

was obtained as yellow solid (benzene/hexane); yield 82%; m.p. 103-104°C; i.r.(KBr): ν_{max} = 3460(br,OH); 1655, 1590 cm^{-1}; ^1H n.m.r.

($CDCl_3$/DMSO-d_6): δ 0.91(distorted t,3H,J=7Hz,$CH_2CH_2\underline{CH_3}$); 1.32-1.81 (m,2H,N-$CH_2\underline{CH_2}CH_3$); 2.31 and 2.40(two singlets, 3H,2:1 ratio,$SC\underline{H_3}$); 3.08-3.40(m,2H,N-$\underline{CH_2}CH_2CH_3$); 7.18-7.62(m,$3H_{arom}$); 7.73-8.03(m, $2H_{arom}$). (Found: C,58.92; H,6.21; N,10.71. Calc. for $C_{13}H_{16}N_2O_2S$ (264.2): C,59.05; H,6.06; N,10.60%).

3-n-Butylamino-3-methylthio-2-nitroso-1-phenyl-2-propen-1one (2e) was obtained as yellow crystalline solid (benzene/hexane); yield 84%; m.p. 105-106°C; i.r.(KBr): ν_{max} = 3435 (br,OH); 1658, 1600 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 0.70-1.02[m,3H$(CH_2)_3\underline{CH_3}$]; 1.20-2.00(m,4H, N-CH_2-$\underline{CH_2}CH_2CH_3$); 2.18 and 2.22(two singlets, 3H,1:2 ratio,$SC\underline{H_3}$); 3.05-3.70(m,2H,N-$\underline{CH_2}$); 7.03-7.61(m,$3H_{arom}$); 7.78-8.13(m,$2H_{arom}$). (Found: C,60.24; H,6.53; N,9.97. Calc. for $C_{14}H_{18}N_2O_2S$ (278.3): C,60.37; H,6.47; N,10.06%).

General procedure for the synthesis of 3(5)-aryl-4-nitroso-5(3)-aryl/alkyl/benzylamino pyrazoles (18a-j):

To a well stirred and ice cooled solution of N-aryl/alkyl/benzyl hydroxyiminoimine 2 (10 mmol) in ethanol (10 ml) was added slowly during 5 min. and the mixture was further stirred for 3 hr (monitored by TLC, silica gel, solvent systems ethylacetate:benzene 1:10). The solvent was removed under reduced pressure, and the residue was poured over ice cooled water, the maroon coloured solid in case of N-aryl and orange coloured solid in case of N-alkyl/benzyl separated was collected by suction filtration and recrystallized from boiling ethanol to afford pure pyrazoles 18.

5(3)-Ethylamino-4-nitroso 3(5)-phenyl pyrazole (18a) was obtained as orange coloured solid (ethanol); yield 95%; m.p. 260-261°C; i.r.(KBr): ν_{max} = 3040, 1655, 1510 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.19(t,J=7Hz,3H,$CH_2\underline{CH_3}$); 3.31(q,J=7Hz,2H,$\underline{CH_2}CH_3$); 7.29-7.58(m, $3H_{arom}$); 8.10-8.36(m,$2H_{arom}$); 9.41(brs,1H,NH). (Found: C,60.96; H,5.46; N,25.78. Calc. for $C_{11}H_{12}N_4O$ (216.2): C,61.11; H,5.55; N,25.92%). m/z 216(M^+,100); 200(20); 199(54).

5(3)-Ethylamino-3(5)-(4-methylphenyl)-4-nitrosopyrazole (18b) was obtained as orange crystalline solid (ethanol); yield 95%; m.p. 200-201°C; i.r.(KBr): ν_{max} = 3390, 1670, 1512 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6): δ 1.20(t,J=7Hz,3H,$CH_2\underline{CH_3}$): 2.37(s,3H,$\underline{CH_3}$); 3.28(q,J=7Hz,2H,$\underline{CH_2}CH_3$);7.31(d,J=9Hz,$2H_{arom}$); 8.21(d,J=9Hz,$2H_{arom}$); 9.49(brs,1H,NH); 12.65(brs,1H,NH). (Found: C,65.62; H,5.97; N,24.21. Calc. for $C_{12}H_{14}N_4O$(216.2): C,65.53; H,6.08; N,24.33%). m/z 230(M^+,100); 215(13);214(17).

5(3)-Methylamino-4-nitroso-3(5)-phenylpyrazole (18c) was obtained as orange crystalline solid (ethanol); yield 94%; m.p. 235-236°C; i.r.(KBr): ν_{max} = 3170, 3055, 1660, 1500 cm^{-1}; ^1H n.m.r.($CDCl_3$/ DMSO-d_6): δ 2.98(d,J=6Hz,3H,N-$\underline{CH_3}$); 7.30-7.65(m,$3H_{arom}$); 8.12-8.15 (m,$2H_{arom}$); 9.31(brq,J=7Hz,1H,NH); 12.40(brs,1H,NH). (Found: C,59.49; H,5.03; N,27.83. Calc. for $C_{10}H_{10}N_4O$(202.2): C,59.35; H,4.95; N,27.70%). m/z 202(M^+,22); 185(10).

4-Nitriso-3(5)-phenyl-5(3)-n-propylaminopyrazole (18d) was obtained as orange crystalline solid (ethanol); yield 91%; m.p. 230-231°C; i.r.(KBr): ν_{max} = 3220, 1640, 1495 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):

δ 0.91(t,J=7Hz,3H,$CH_2CH_2\underline{CH}_3$); 1.60(sext,J=7Hz,2H,$CH_2\underline{CH}_2CH_3$); 3.20(q,J=7Hz,2H,N-$\underline{CH}_2CH_2CH_3$); 7.19-8.42(m,5H_{arom}); ^{13}C n.m.r. (DMSO-d_6): 10.84(CH_3); 21.70[(CH_2 $\underline{CH}_2CH_3$]; 43.71(N-CH_2); 127.76, 128.38, 129.08(CH aromatic); 131.33(C' arom); 139.03 (<u>C</u>-4); 148.96[<u>C</u>-5(3)]; 149.90[<u>C</u>-3(5)]. (Found: C,62.63; H,6.24; N,24.17. Calc. for $C_{12}H_{14}N_4O$(230.2): C,62.55; H,6.08; N,24.32%). m/z 230(M^+,88); 213(75).

<u>5(3)-n-Butylamino-4-nitroso 3(5)-phenylpyrazole (18e)</u> was obtained as orange crystalline solid (ethanol); yield 89%; m.p.233-234°C; i.r.(KBr): ν_{max} = 3210, 1642, 1496 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 0.92[t,J=7Hz,3H,$(CH_2)_3CH_3$]; 1.15-1.80(m,4H,$CH_2CH_2\underline{CH}_2CH_3$); 3.23 [q,J=7Hz,2H,NH-$\underline{CH}_2(CH_2)_2CH_3$]; 7.30-7.65(m,3$H_{arom}$); 8.20-8.50(m, 2$H_{arom}$); 9.50(brt,1H,NH). (Found: C,63.94; H,6.41; N,23.03. Calc. for $C_{13}H_{16}N_4O$ (244.3): C,63.86; H,6.55; N,22.92%). m/z 244(M^+,100); 228(23); 227(99).

<u>5(3)-Benzylamino-4-nitroso-3(5)-phenyl pyrazole (18f)</u> was obtained as orange crystalline solid (ethanol); yield 94%; m.p. 240-241°C; i.r.(KBr): ν_{max} = 3250, 1655, 1495 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 4.49(d,J=6Hz,2H,N-$\underline{CH}_2C_6H_5$); 7.20-7.60(m,3H_{arom}); 8.15-8.45(m, 2H_{arom}); 9.88(brs,1H,NH); 12.80(brs,1H,NH). (Found: C,69.13; H,5.27; N,19.98. Calc. for $C_{16}H_{14}N_4O$(278.3): C,68.99; H,5.03; N,20.12%). m/z 278(M^+,28); 262(20); 261(38).

<u>5(3)-Anilino-4-nitroso-3(5)-phenyl pyrazole (18g)</u> was obtained as maroon coloured crystalline solid (ethanol); yield 97%; m.p.235°C; i.r.(KBr): ν_{max} = 3050, 1639, 1598, 1560 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):

δ 6.90-7.70(m,8H$_{arom}$); 8.11-8.38(m,2H$_{arom}$); ^{13}C n.m.r.(DMSO-d$_6$): δ 119.61; 122.79; 127.58; 128.49; 128.84; 128.94(CH aromatic); 130.52(C-1' arom); 137.90(C-1' anilino); 138.69(C-4); 147.54 [C-5(3)]; 150.57[C-3(5)]. (Found: C,67.98; H,4.61; N,21.02. Calc. for $C_{15}H_{12}N_4O$ (264.2): C,68.13; H,4.54; N,21.20%). m/z 264(M^+,65); 243(25); 247(100).

5(3)-Anilino-4-nitroso-3(5)-(4-chlorophenyl)pyrazole (18h) was obtained as maroon coloured crystalline solid (ethanol); yield 93%; m.p. 247-248°C; i.r.(KBr): ν_{max} = 3160, 1639, 1598, 1570 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$/DMSO-d$_6$):δ 7.00-7.70(m,7H$_{arom}$); 8.26-8.45(m,2H$_{arom}$). (Found: C,60.07; H,3.81; N,18.53. Calc. for $C_{15}H_{11}ClN_4O$(298.7): C,60.26; H,3.68; N,18.75%). m/z 298(M^+,70); 283(40); 281(100).

5(3)-Anilino-4-nitroso-3(5)-(4-methoxyphenyl)pyrazole (18i) was obtained as maroon coloured crystalline solid (ethanol); yield 95%; m.p. 241-242°C; i.r.(KBr): ν_{max} = 3160, 1592, 1568, 1547 cm^{-1}; ^{1}H n.m.r. (CDCl$_3$/DMSO-d$_6$):δ 3.83(s,3H,OCH$_3$); 6.92-7.50(m,5H$_{arom}$); 7.74(d,J=9Hz,2H$_{arom}$); 8.29(d,J=7Hz,2H$_{arom}$); 10.00(brs,1H,NH); 13.65(brs,1H,NH). (Found: C,65.38; H,4.66; N,18.97. Calc. for $C_{16}H_{14}N_4O_2$(294.3): C,65.24; H,4.76; N,19.03%). m/z 294(M^+,80); 278(28); 277(100).

5(3)-(4-Chloroanilino)-4-nitroso-3(5)-phenylpyrazole (18j) was obtained as maroon coloured crystalline solid (ethanol); yield 93%; m.p. 238-239°C; i.r.(KBr): ν_{max} = 3180, 1641, 1600, 1577 cm^{-1}; ^{1}H n.m.r.(CDCl$_3$/DMSO-d$_6$):δ 6.97-8.02(m,7H$_{arom}$); 8.34(d,J=9Hz,2H$_{arom}$). (Found: C,60.34; H,3.71; N,18.86. Calc. for $C_{15}H_{11}ClN_4O$(298.7): C,60.26; H,3.68; N,18.75%). m/z 300(M^+,25); 299(19); 298(72); 281(100).

General procedure for the synthesis of 4-amino-3(5)-aryl-5(3)-aryl/alkyl/benzylamino pyrazoles (20a-j):

Method A:

A solution of respective N-aryl/alkyl/benzyl hydroxyiminoimines 2 (10 mmol) and hydrazine hydrate (4g, 80 mmol) in 30 ml of ethanol was refluxed for 75 min.(monitored by TLC, silica gel, solvent system; ethylacetate/benzene (1:10). The solvent was removed on water bath and residue was poured over ice cooled water, white solid separated was collected by suction filtration and recrystallized from boiling ethanol to give pure 4-amino pyrazoles 20.

Method B:

A solution of 4-nitrosopyrazoles 18 (10 mmol) and hydrazine hydrate (4g, 80 mmol) in 30 ml of ethanol was refluxed for 3 hr (monitored by TLC). The solvent was removed on water bath and the residue poured over ice cooled water, white solid separated was collected by suction filtration and recrystallized from boiling ethanol to give pure 4-aminopyrazoles 20.

4-Amino-5(3)-ethylamino-3(5)-phenyl pyrazole (20a) was obtained as white crystalline solid (ethanol); yield; Method A-92%; Method B-86%; m.p. 177°C; i.r.(KBr): ν_{max} = 3340, 3160, 1600, 1540 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6);δ 1.20(t,J=8Hz,3H,$CH_2\underline{CH_3}$); 3.18(q,J=8Hz, 2H,$\underline{CH_2}CH_3$); 5.42(brs,4H,2NH+NH_2); 7.10-7.48(m,3H_{arom}); 7.61-7.87 (m,2H_{arom}). (Found: C,65.05; H,7.11; N,27.83. Calc. for $C_{11}H_{14}N_4$(202.2): C,65.35; H,6.93; N,27.72%). m/z 202(M^+,100).

4-Amino-5(3)-ethylamino-3(5)-(4-methylphenyl) pyrazole (20b) was obtained as white crystalline solid (ethanol) by Method A; yield 92%; m.p. 200°C; i.r.(KBr): ν_{max} = 3345, 3180, 1605, 1540 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.19(t,J=8Hz,3H,$CH_2\underline{CH_3}$); 2.32(s,3H,$\underline{CH_3}$); 3.15(q,J=8Hz,2H,$\underline{CH_2}CH_3$); 4.33(brs,4H,2NH+NH_2); 7.20(d,A_2B_2,2H_{arom}); 7.61(d,A_2B_2,2H_{arom}). (Found: C,66.50; H,7.51; N,26.06. Calc. for $C_{12}H_{16}N_4$(216.2): C,66.66; H,7.40; N,25.93%). m/z 216(M^+,100).

4-Amino-5(3)-methylamino-3(5)-phenyl pyrazole (20c) was obtained as white crystalline solid (ethanol) by Method A; yield 83%; m.p. 98-99°C; i.r.(KBr): ν_{max} = 3347, 3157, 1600, 1540 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 2.75(d,J=6Hz,2H,N-$\underline{CH_3}$); 5.40(brs,4H, 2NH+NH_2); 7.30-7.65(m,3H_{arom}); 8.12-8.15(m,2H_{arom}). (Found: C,63.51; H,6.47; N,29.88. Calc. for $C_{10}H_{12}N_4$(188.2): C,63.76; H,6.38; N,29.76%).

4-Amino-3(5)-phenyl-5(3)-n-propylamino pyrazole (20d) was obtained as white crystalline solid (ethanol) by Method A; yield 90%; m.p. 170°C; i.r.(KBr): ν_{max} = 3338, 3160, 1595, 1540 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6): δ 0.98(t,J=8Hz,3H,$CH_2CH_2\underline{CH_3}$); 1.60(sext,J=8Hz,2H, $CH_2\underline{CH_2}CH_3$); 3.10(t,J=8Hz,3H,$\underline{CH_2}CH_2CH_3$); 5.20(brs,4H,2NH+NH_2); 7.10-7.52(m,3H_{arom}); 7.60-7.88(m,2H_{arom}). (Found: C,66.58; H,7.31; N,26.04. Calc. for $C_{12}H_{16}N_4$(216.2): C,66.66; H,7.40; N,25.93%). m/z 216(M^+,75).

4-Amino-5(3)-n-butylamino-3(5)-phenylpyrazole (20e) was obtained as white crystalline solid (ethanol) by Method A; yield 84%; m.p. 168°C; i.r.(KBr): ν_{max} = 3320, 3173, 1540 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6): δ 0.90[t,J=7Hz,3H,$(CH_2)_3\underline{CH_3}$]; 1.26-1.82(m,4H,

$CH_2\underline{CH_2}CH_3$); 3.15[t,J=7Hz,2H,$\underline{CH_2}(CH_2)_2CH_3$]; 4.83(brs,4H,2NH+$NH_2$); 7.12-7.58(m,3$H_{arom}$): 7.70-7.92(m,2$H_{arom}$); ^{13}C n.m.r.(DMSO-$d_6$): δ 13.81($\underline{CH_3}$); 19.19($CH_2CH_2\underline{CH_2}CH_3$); 31.90($CH_2\underline{CH_2}CH_3$); 43.66(N-$CH_2$); 112.4[$\underline{C}$-5(3)]; 125.03, 126.10, 128.40(CH aromatic); 131.53(C-1' arom); 149.77[$\underline{C}$-3(5)]. (Found: C,67.94; H,7.71; N,24.41. Calc. for $C_{13}H_{18}N_4$(230.2): C,67.83; H,7.83; N,24.36%). m/z 230(M^+,92); 188(17); 187(100).

4-Amino-5(3)-benzylamino-3(5)-phenylpyrazole (20f) was obtained obtained as white crystalline solid (ethanol); yield Method A - 94%; Method B-89%; m.p. 169-170°C; i.r.(KBr): ν_{max} = 3340, 3180, 1603, 1539 cm^{-1}; ^{1}H *n.m.r.*($CDCl_3$/DMSO-d_6):δ 4.32(s,2H,$\underline{CH_2}C_6H_5$); 5.10(brs,2H,NH_2); 7.03-7.47(m,3H_{arom}); 7.58-7.87(m,2H_{arom}). (Found: C,72.61; H,5.92; N,21.16. Calc. for $C_{16}H_{16}N_4$(264.2): C,72.72; H,6.06; N,21.21%). m/z 264(M^+,100).

4-Amino-5(3)-anilino-3(5)-phenylpyrazole (20g) was obtained as white crystalline solid (ethanol); yield Method A 96%; Method B - 82%; m.p. 214°C; i.r.(KBr): ν_{max} = 3320, 3160, 1598, 1542, 1480cm^{-1}; ^{1}H n.m.r.($CDCl_3$/DMSO-d_6);δ 3.73(brs,4H,2NH+NH_2); 6.60-7.82(m,10H_{arom}); ^{13}C n.m.r.(DMSO-d_6): 114.31($\underline{C}$-4); 116.09(CH arom); 117.49(C-1' anilino); 124.85, 126.30, 127.94, 128.51 (CH arom); 130.61(C-1' arom); 143.39[$\underline{C}$-5(3)]; 144.63[$\underline{C}$-3(5)]. (Found: C,71.92; H,5.81; N,22.35. Calc. for $C_{15}H_{14}N_4$(250.2): C,72.00; H,5.60; N,22.40%). m/z 250(M^+,100).

4-Amino-5(3)-anilino-3(5)-(4-chlorophenyl)pyrazole (20h) was obtained as white crystalline solid (ethanol) by Method A; yield 95%; m.p. 194-195°C; i.r.(KBr): ν_{max} = 3330, 3150, 1600, 1542,

1498 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): 4.00(brs,2NH+NH_2);6.60-7.93(m,9H_{arom}). (Found: C,63.11; H,4.47; N,19.71. Calc. for $C_{15}H_{13}ClN_4$(284.7): C,63.26; H,4.56; N,19.68%). m/z 286(M^+,30); 284(M^+,96).

4-Amino-5(3)-anilino-3(5)-(4-methoxyphenyl)pyrazoles (20i) was obtained as white crystalline solid (ethanol) by Method A; yield 95%; m.p. 203°C; i.r.(KBr): ν_{max} = 3175, 1595, 1525 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 3.52(brs,2H,NH_2); 3.78(s,3H,OCH_3); 6.48-7.32 (m,7H_{arom}); 7.50-7.70 (m,2H_{arom}). (Found: C,68.67; H,5.83; N,19.89. Calc. for $C_{16}H_{16}N_4O$(280.3): C,68.57): H,5.71; N,20.00%). m/z 280 (M^+,100).

4-Amino-5(3)-(4-chloroanilino)-3(5)-phenyl pyrazole (20j) was obtained as white crystalline solid (ethanol) by Method A; yield 92%; m.p. 174-175°C; i.r.(KBr): ν_{max} = 3270, 1605, 1560, 1510 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 4.00(brs,2H,NH_2); 6.85-7.90(m,9H_{arom}). (Found: C,63.40; H,4.33; N,19.51. Calc. for $C_{15}H_{13}N_4$(284.7): C,63.27; H,4.57; N,19.68%). m/z 286(M^+,32); 284(M^+,100).

3(5)-Aryl-5(3)-(N-nitroso)-alkyl/arylamino pyrazoles (22a-c); General Procedure:

To an ice cooled and well stirred solution of 5(3)-aminopyrazoles (0.01 mole) 21 in dry pyridine (2 ml) and dry chloroform(25 ml), nitrosyl chloride (0.012 mol in 5 ml ether) was added and the reaction mixture was further stirred for 10-15 min. It was then diluted with ice cold water (50 ml), extracted with chloroform(3x50 ml).

The chloroform layer was washed with water (3x100 ml) to remove excess of pyridine, dried (Na_2SO_4) and evaporated to give crude solid N-nitrosopyrazoles 22, which were purified by crystallization using boiling ethanol. Spectral and analytical data of 22a-c are given below.

5(3)-(N-nitroso)ethylamino-3(5)-phenylpyrazole (22a) was obtained as grey crystalline solid (ethanol); yield 90%; m.p. 167-168°C; i.r.(KBr): ν_{max} = 3205, 1568, 1500 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 1.13(t,J=7Hz,3H,$CH_2\underline{CH}_3$); 4.20(q,J=7Hz,2H,$\underline{CH}_2CH_3$); 6.94(s,1H, $\underline{H}$-4); 7.29-7.61(m,3H_{arom}); 7.70-7.98(m,2H_{arom}); 13.50(s,1H,NH). (Found: C,60.97; H,5.68; N,26.07. Calc. for $C_{11}H_{12}N_4O$(216.2): C,61.11; H,5.55; N,25.92%). m/z NO M^+; 186(M^+-30,100).

5(3)-(N-nitroso)benzylamino-3(5)-phenylpyrazole (22b) was obtained as pink crystalline solid (ethanol); yield 91%; m.p. 177-178°C; i.r.(KBr): ν_{max} = 3200, 1565, 1500 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 5.29(s,2H,$\underline{CH}_2C_6H_5$); 6.29(s,1H,$\underline{H}$-4); 7.20-7.52(m,8H_{arom}); 7.67-7.83(m,2H_{arom}); 13.50(s,1H,NH). (Found: C,69.09; H,5.17; N,19.98. Calc. for $C_{16}H_{14}NO$(278.3): C,68.99; H,5.03; N,20.12%). m/z NO,M^+; 248(M^+-30,83%).

5(3)-(N-nitroso)anilino-3(5)-phenylpyrazole (22c) was obtained as maroon crystalline solid (ethanol); yield 87%; m.p. 215°C; i.r. (KBr): ν_{max} = 3400, 1639, 1595 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6): δ 6.90-7.79(m,8H_{arom}); 8.21-8.58(m,3H_{arom}); 10.29(brs,1H,NH). (Found: C,68.27; H,4.63; N,21.31. Calc. for $C_{15}H_{12}N_4O$(264.2): C,68.13; H,4.54; N,21.20%). m/z 264(M^+,76%).

1,4-Substituted pyrazolo [3,4-d] [1,2,3] triazoles 23a-c;

General Procedure:

To an ice cooled and stirred solution of diaminopyrazole 20 (0.005 mol) in acetic acid (10 ml), 0.04g(0.006 mol) of sodium nitrate in 3 ml water was added dropwise and reaction mixture was stirred for 3 hr. at room temperature. The reaction mixture was then poured over water, the yellow solid separated was collected by suction filtration and recrystallized from boiling ethanol to afford pure pyrazolo triazoles 23a-c. The analytical and spectral data are given below.

1-Ethyl-4-(4-methylphenyl)pyrazolo [3,4-d] [1,2,3] triazole (23a) was obtained as yellow solid (ethanol); yield 63%; m.p. 206-207°C; i.r.(KBr): ν_{max} = 3225(NH), 1623, 1540 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 1.19(t,J=7Hz,3H,N-$CH_2\underline{CH_3}$); 2.40(s,3H,$\underline{CH_3}$); 4.25(q, J=7Hz,2H,N-$\underline{CH_2}CH_3$); 7.30(d,J=9Hz,$2H_{arom}$); 7.68(d,J=9Hz,$2H_{arom}$). (Found: C,63.21; H,5.91; N,30.73. Calc. for $C_{12}H_{13}N_5$(227.2): C,63.38; H,5.72; N,30.80%).

1-Benzyl-4-phenylpyrazolo [3,4-d[[1,2,3] triazole (23b) was obtained as yellow crystalline solid (ethanol); yield 80%; m.p. 138-139°C; i.r.(KBr): ν_{max} = 3271(NH), 1625, 1543 cm^{-1}; ^1H n.m.r. ($CDCl_3$/TFA):δ 5.28(s,2H,N-$\underline{CH_2}C_6H_5$); 7.34(s,$5H_{arom}$); 7.72(s,$5H_{arom}$). (Found: C,69.83; H,4.59; N,25.61. Calc. for $C_{16}H_{13}N_5$(275.3): C,69.74; H,4.72; N,25.42%).

4-(4-Methoxyphenyl)-1-phenylpyrazolo [3,4-d] [1,2,3] triazole(23c) was obtained as crystalline solid (ethanol); yield 72%; m.p. 233-234°C;

i.r. (KBr): ν_{max} = 3225(NH); 1623, 1540 cm^{-1}; ^1H n.m.r.($CDCl_3$/DMSO-d_6):δ 3.88(s,3H,OCH_3); 7.10(d,J=9Hz,2H_{arom}); 7.37-7.73(m, 4H_{arom}); 8.02-8.21(m,3H_{arom}). (Found: C,66.07; H,4.37; N,23.96. Calc. for $C_{16}H_{13}N_5O$(291.3): C,65.93; H,4.46; N,24.03%).

Condensation of 20f with methyl methoxy carbonylimino(methylthio) methyl carbonate (24)

A solution of 20f (0.53g, 2 mmol) and 24 (0.51g, 2.5 mmol) was refluxed in ethanol (20 ml) for 25 hr. The reaction mixture was then concentrated and the residue poured over water, solid separated was collected by suction filtration and recrystallized from boiling ethanol to afford pure 25. Yield 84%; m.p. 206-207°C; i.r.(KBr): ν_{max} = 3375, 3285, 1738 cm^{-1}; ^1H n.m.r.(DMSO-d_6); δ 3.13(brs,1H,NH); 3.48(s,3H,OCH_3); 3.78(s,3H,OCH_3); 4.30(s,2H, $CH_2C_6H_5$); 5.45(brs,2H,N+NH); 7.13-7.68(m,5H_{arom}); 9.32(s,1H,NH). (Found: C,59.74; H,4.99; N,20.07. Calc. for $C_{21}H_{22}N_6O_4$(422.4): C,59.66; H,5.21; N,19.28%).

Condensation of 22d with benzaldehyde:

A solution of 20d (0.43g, 2 mmol) and benzaldehyde (0.3g, 2.5 mmol) was refluxed in ethanol (20 ml) for 30 hr. The reaction mixture was concentrated, and the residue, on filtration through a small column of silica gel afforded 27 as a yellow solid, yield 72%; m.p. 155-156°C; i.r.(KBr): ν_{max} = 3180, 1610, 1528 cm^{-1}; ^1H n.m.r. ($CDCl_3$/DMSO-d_6):δ 1.00(t,J=7Hz,3H,$CH_2CH_2CH_3$); 1.73(sext,J=7Hz,2H, N-$CH_2CH_2CH_3$); 3.23(t,J=7Hz,2H,N-$CH_2CH_2CH_3$); 7.18-7.60(m,6H_{arom}); 7.71-8.18(m,4H_{arom}); 8.78(s,1H_{olefin}). (Found: C,75.03; H,6.71; N,18.29. Calc. for $C_{19}H_{20}N_4$(304.3): C,74.92; H,6.57; N,18.40%). m/z 304(M^+,80%).

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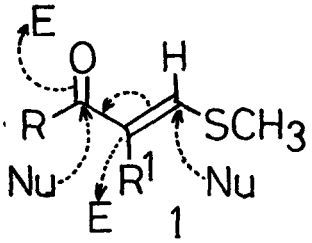
CHAPTER V

REDUCTIVE DETHIOMETHYLATION OF α-OXOKETENE DITHIOACETALS WITH SODIUM CYANOBOROHYDRIDE: A NEW GENERAL METHOD FOR 2-METHYLTHIO-1-ALKENYL KETONES.

V.I INTRODUCTION

The vinylogous thiolesters 1 belong to an interesting class of three carbon fragments with 1,3-electrophilic centres (as shown by the broken arrows) of which the terminal thioalkyl carbon can be considered as masked aldehyde functionality.



1

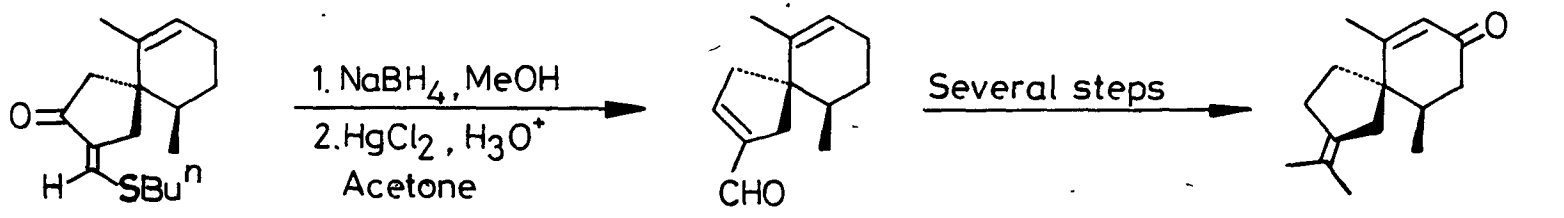
It could be cleaved under mild hydrolytic conditions when desired and the α-carbon in these compounds is activated by the electron withdrawing substituants at the β-position and can thus undergo facile displacement

the thiomethyl group with a wide variety of nucleophiles to further diversify the product range. The vinylogous thiolesters 1 are useful synthetic intermediates in organic synthesis[1-9] and they provide unique opportunities for devising new reactions leading to the synthesis of many natural products. There have been many reports in recent years concerning their synthetic utility rather than the methods of their preparation.

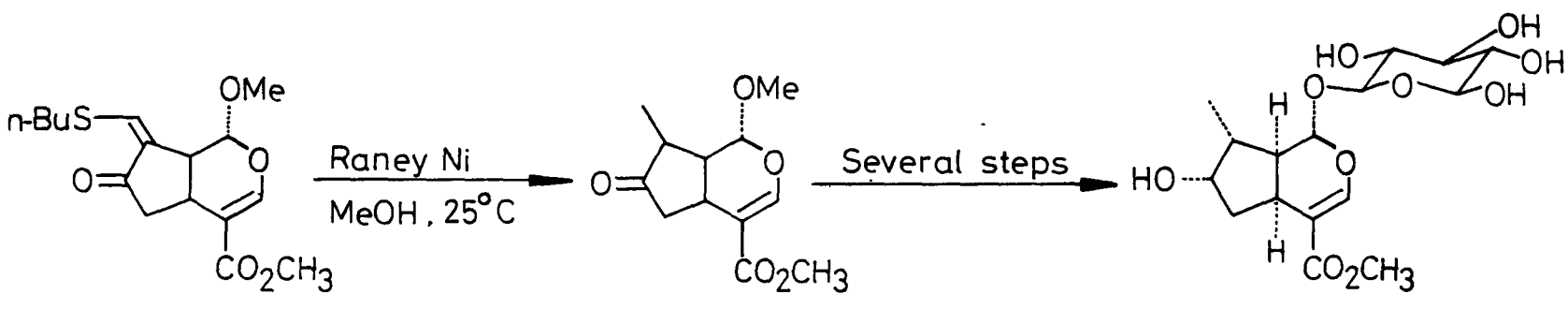
A brief survey of some important synthetic applications of vinylogous thiolesters is described as follows. Thus in a synthesis of β-vetivone 4 the 2-(n-butylthiomethylene) ketone 2 was subjected to a 1,2-reduction with sodium borohydride followed by the mercuric chloride catalyzed hydrolysis to afford the key intermediate enealdehyde 3 (Scheme 1)[10].

The alkylthiomethylene group has also been used to introduce regiospecific methyl substituent involving reductive desulfurization with W-2 Raney Nickel or sodium in liquid ammonia in the synthesis of (±) loganin 7 (Scheme 1)[11].

The vinylogous thiolesters have been useful intermediates in the construction of stereoselective polyene side chains starting from appropriate aldehydes. Thus a synthesis of isorenieraten 13 has been reported involving an efficient use of this intermediates. Thus 2,3,6-trimethyl benzaldehyde 8 was condensed with 4-(t-butylthio)-buten-2-one 9 to yield the corresponding dienone 10 in high yields. On subsequent alkylative carbonyl transposition the dienal 11 was obtained, which could be further used to lengthen the side chain by repeating the aldol condesnation and carbonyl transposition sequence to obtain the next higher tetraene aldehyde 12. The aldehyde 12 treatment with $TiCl_3/LiAlH_4$ yielded the

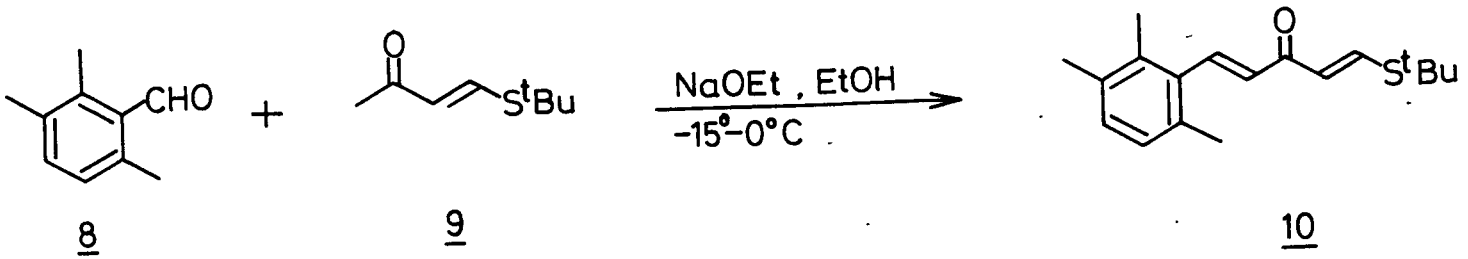


2 3 4

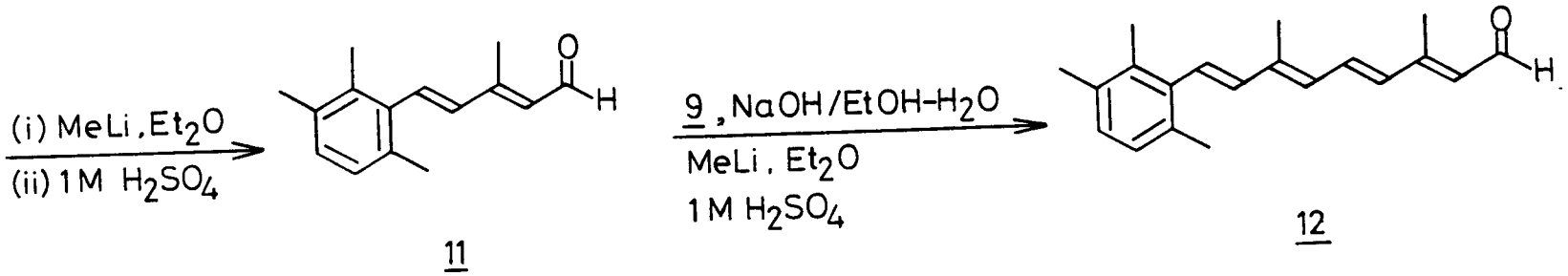


5 6 7

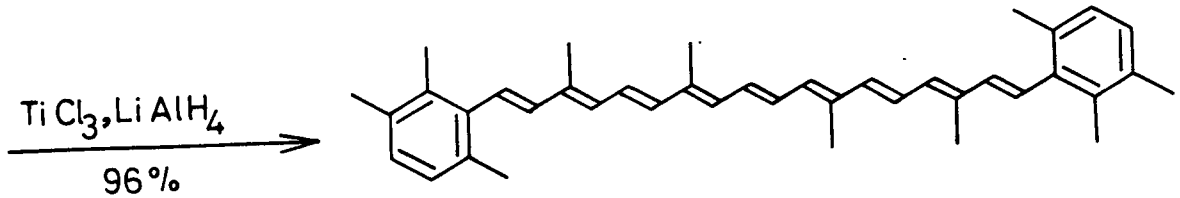
Scheme 1



8 9 10



11 12

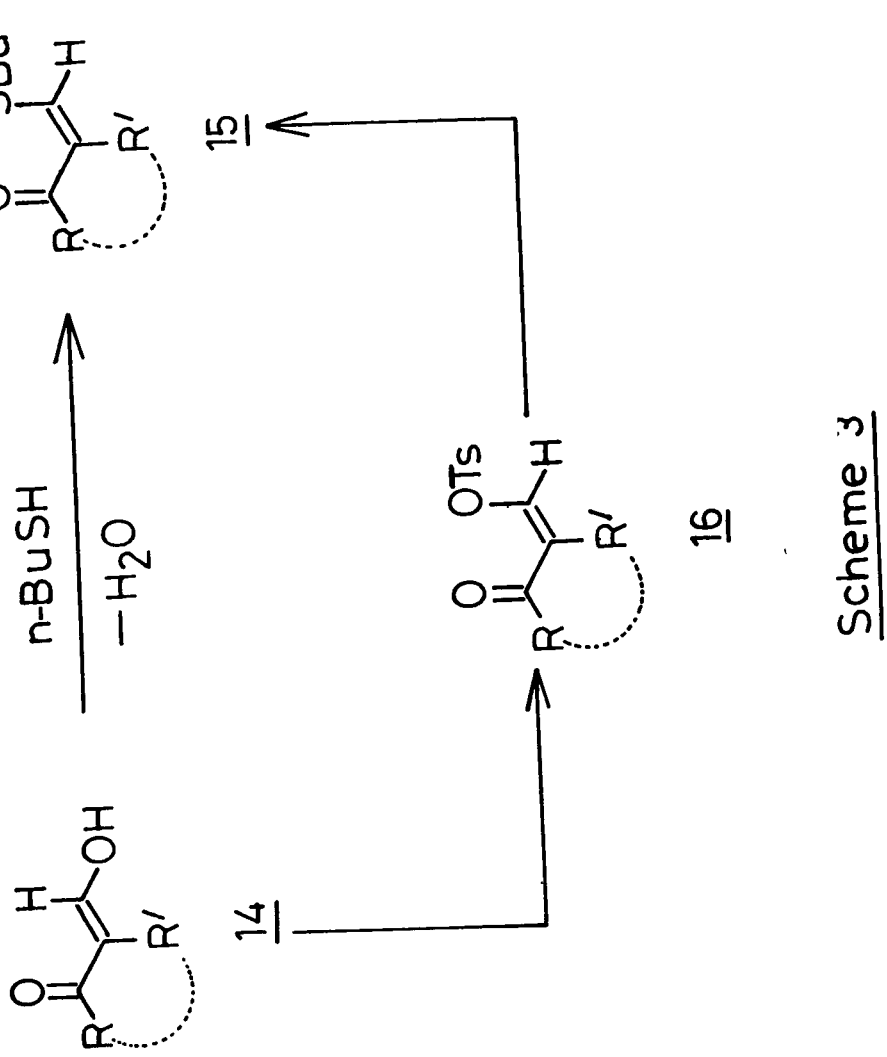


13 isorenieratene

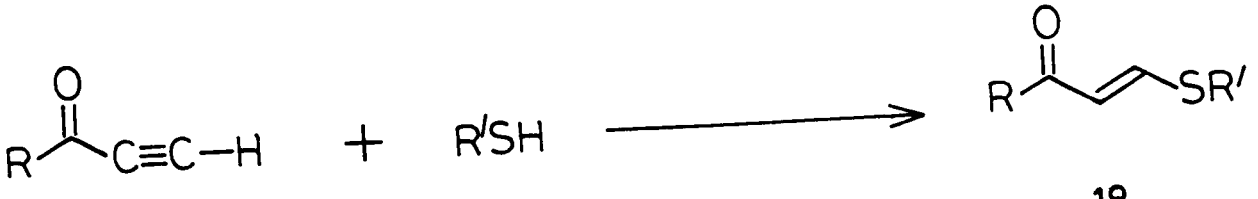
Scheme 2

naturally occuring isorenieraten 13 (Scheme 2)[7].

In the course of our studies on α-oxoketene dithioacetals, we aimed at developing a method for its conversion to vinylogous thiolesters 1 by devising a route involving displacement of one of the thiomethyl groups by hydrogen. Such a method would provide a convenient synthetic entry to the alkylthio enones 1 from a wide variety of easily available active methylene compounds. The reported methods for the preparation of these compounds are briefly discussed here. Ireland and co-workers have prepared[1,10,12] the vinylogous thiolesters 15 by reacting the active methylene ketones with ethyl formate to yield the corresponding formyl derivatives 14 which were subsequently converted into the corresponding alkylthio enones 15 either directly by reaction with n-butyl mercaptan or through their tosylates 16 (Scheme 3). This method has been used by these authors for the subsequent conversion of butyl thioenones 15 to the corresponding α,β-unsaturated aldehydes. The β-aroyl/acyl acetylenes 17 undergo Michael addition with aryl/alkyl mercaptans in the presence of a mild base like Triton B (Scheme 4) to give the corresponding β-alkyl/arylthioenones 18 in excellent yields[13-17]. The method requires polarized triple bonded structural moiety and thus cannot be applied to the cyclic systems. The β-chlorovinyl ketones 19 are perhaps more versatile intermediates, which can undergo displacement with aryl mercaptans to give the β-arylthio enones 18 in fairly good yields. However, when alkyl mercaptans were used the reaction further proceeded to yield the β-dithioacetals 20 (Scheme 5)[18]. Recently Akiyama and co-workers have reported[13] the preparation of β-t-butylthioenone 18a (R=Me; R'=t-Bu) by displacement reaction of 19 with t-butyl mercaptan (Scheme 5).



Scheme 3

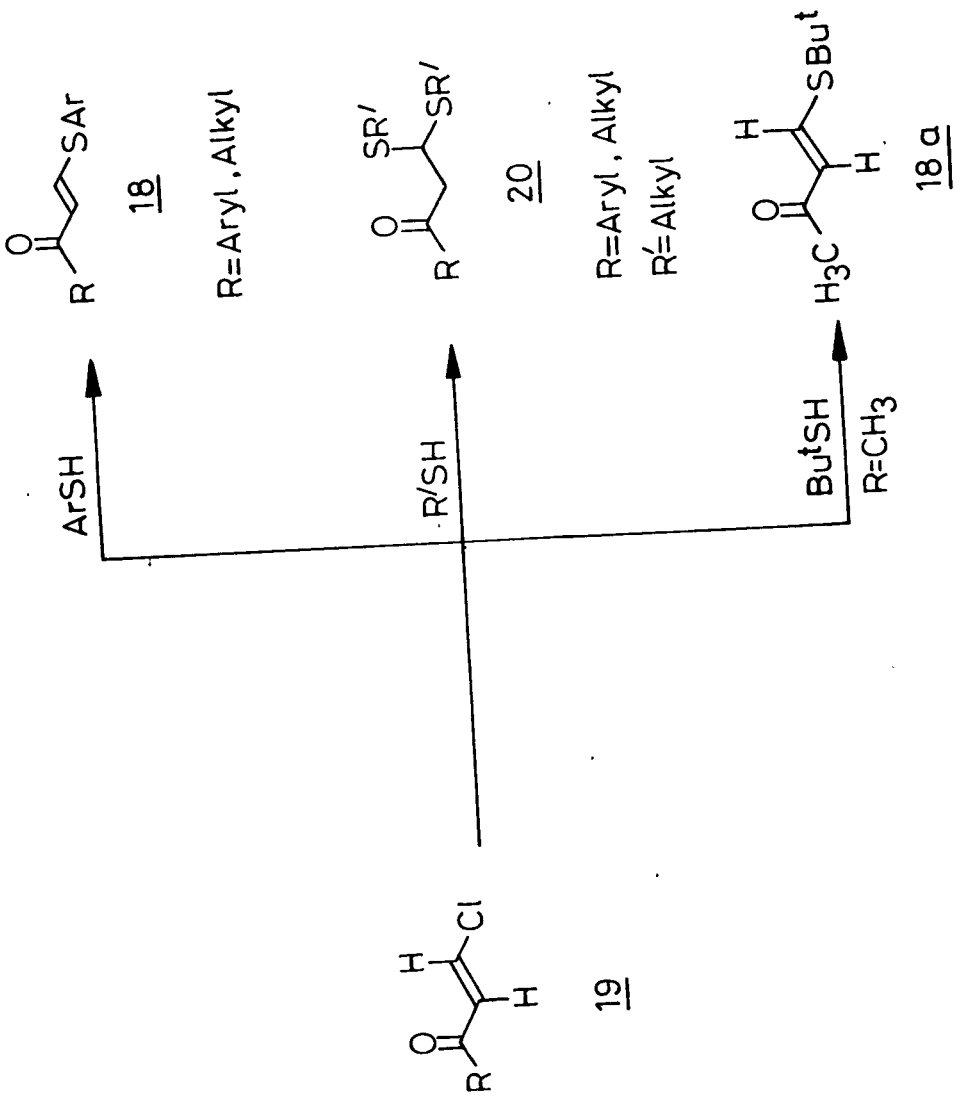


17 18

R=Alkyl or Aryl

R'=Alkyl or Aryl

Scheme-4


ArSH
R/SH
ButSH
R=CH3
18
R=Aryl, Alkyl
20
R=Aryl, Alkyl
R'=Alkyl
18 a
19

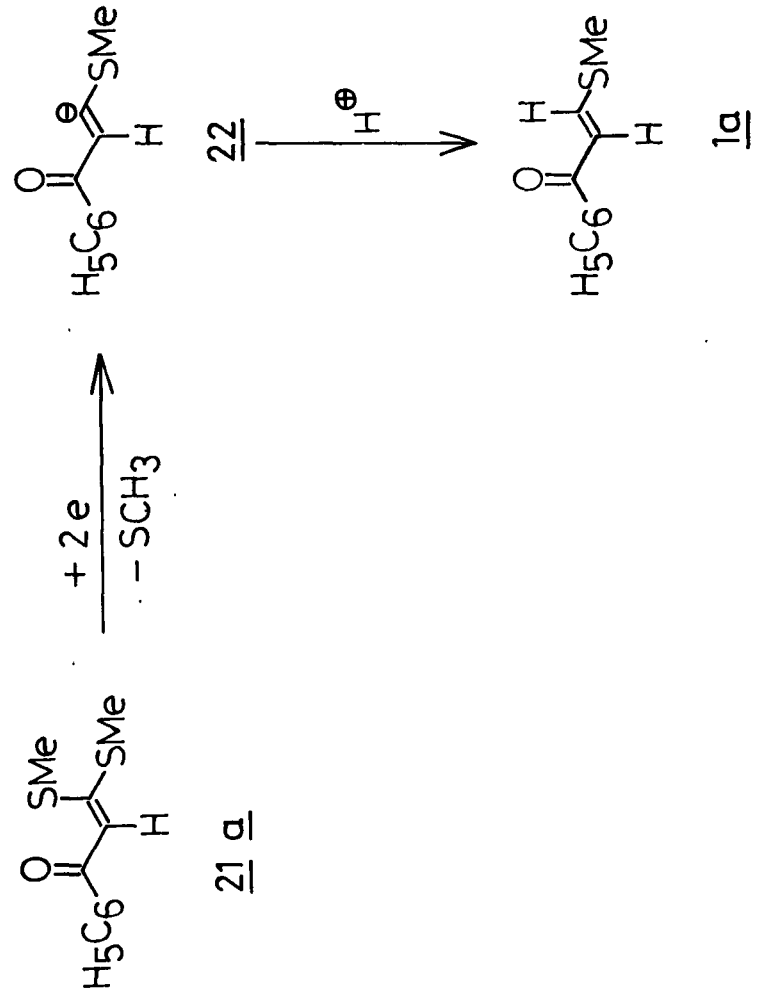
Scheme 5

Rudorf and co-workers have reported[19] the partial cleavage of the thiomethyl group under electrolytic reduction of α-oxoketene dithioacetal 21a when the corresponding methylthioenone 1a was formed in 64% yield (Scheme 6) through protonation of the intermediate carbanian 22. However, the authors have not studied the generality of the reaction. The vinylogous thiolesters underwent further reduction to give the corresponding saturated ketone as well as the saturated dithioacetal through Michael addition of the methyl mercaptan on 1a (Scheme 6).

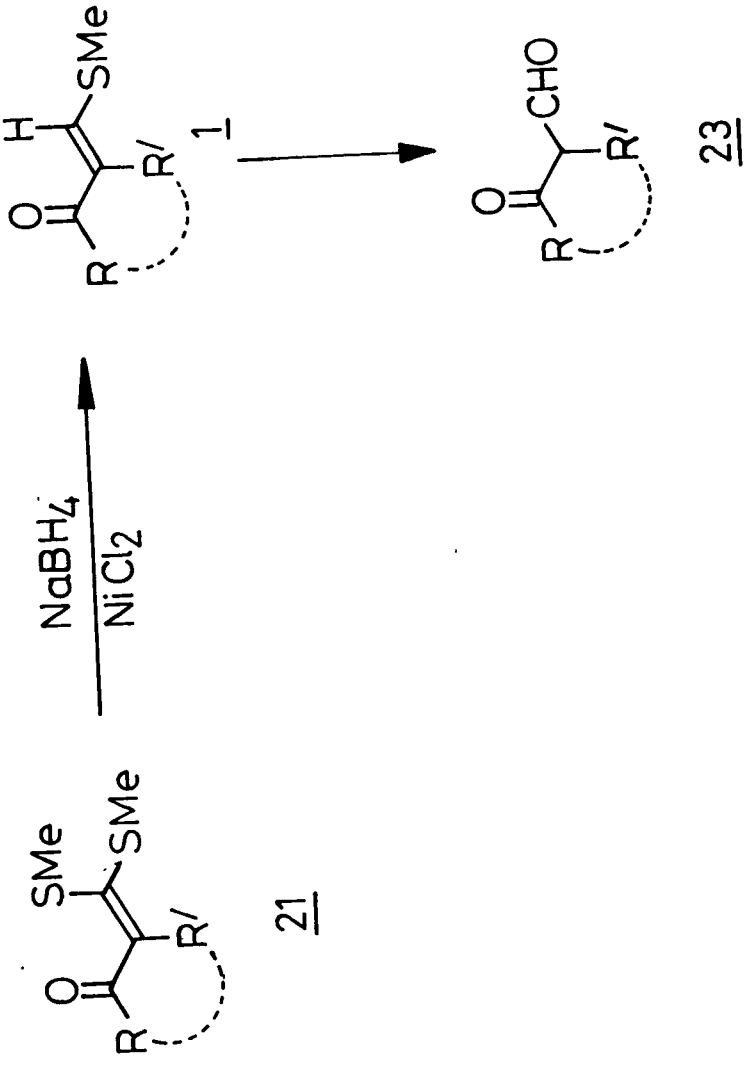
Junjappa, Ila and Myrboh[20] have developed an efficient method for the partial dethiomethylation of α-oxoketene dithioacetals 21 in the presence of sodium borohydride and Nickel chloride (Nickel boride), to afford the vinylogous thiolesters 1 in moderate to good yields (Scheme 7). However, the method suffers from limitations (Scheme 7), due to increased adsorption on Nickel boride. The synthesis of β-alkyl substituted vinylogous thiolesters from an unsymmetrical β-diketones entails problems of regioselectivity and the best approach to these compounds involves the chemo- and stereoselective reaction of organocuprates with α-oxoketene dithioacetals 21 (Scheme 8)[21,22]. The substitution reaction generally affords the E-stereoisomer in a highly stereoselective fashion.

In the present investigation it was considered of interest to develop more efficient methodology that can be applied to wide structural varients of α-oxoketene dithioacetals under simple reaction conditions with improved yields.

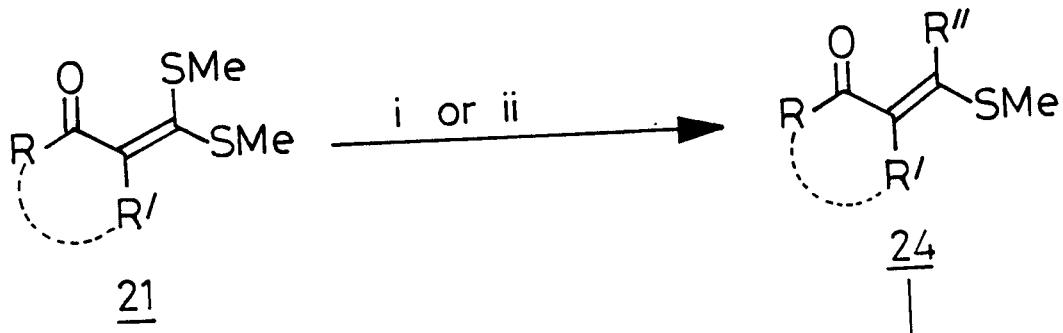
From the literature retrieval it is found that the sodium cyanoborohydride is an extremely non-aggressive reducing agent[23]. Normally, even sensitive groups such as aldehydes and ketones are reduced only when the electrophilicity



Scheme-6



Scheme 7



21 24 25

(i)=R″CuX R″=Aryl,Alkyl

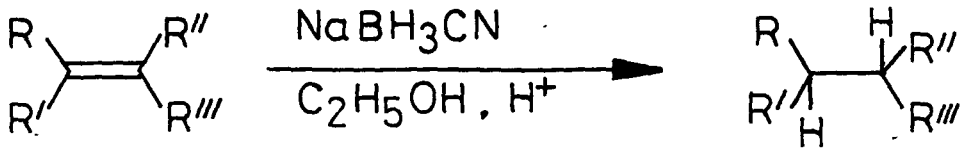
(ii)=Enolate anions

Scheme 8

of the carbonyl group is increased by protonation[24]. However, even under acidic conditions, other carbonyl derivatives, including esters, acids and amides remain uneffected[25]. The following examples prove the argument for the potential use of sodium cyanoborohydride as a chemoselective 1,4-reducing agent on α-oxoketene dithioacetals. Thus when the alkenes 26 with electron withdrawing substituents such as ester, nitrile etc. were reacted with sodium cyanoborohydride, reducing the double bond without affecting the other functional groups. The general procedure utilized was mild and convenient (Scheme 9)[25]. Interestingly the sodium cyanoborohydride in methanolic hydrochloric acid cleaved the C-O bond of acetals 28, 30, 32 and ketals 34 to yield the corresponding methylethers 29, 31, 33 and 35 respectively. The reaction conditions are simple and efficient (Scheme 10)[26]. Similarly enaminones 36 are rapidly reduced to saturated amines 37 by sodium cyanoborohydride at an initial pH of 4 in 15:1 tetrahydrofuran/methanol solvent mixture (Scheme 11)[24]. The reduction of aldoximes 38 with sodium cyanoborohydride provides the corresponding amine ethers 39 (Scheme 11)[27]. It is therefore apparent that the sodium cyanoborohydride is much more efficient, selective and safe as compared to other reducing agents and should be a suitable choice as a reagent in the study of selective dethiomethylation of α-oxoketene dithioacetals where such selectivity can be used to the advantage.

V.2 RESULTS AND DISCUSSION

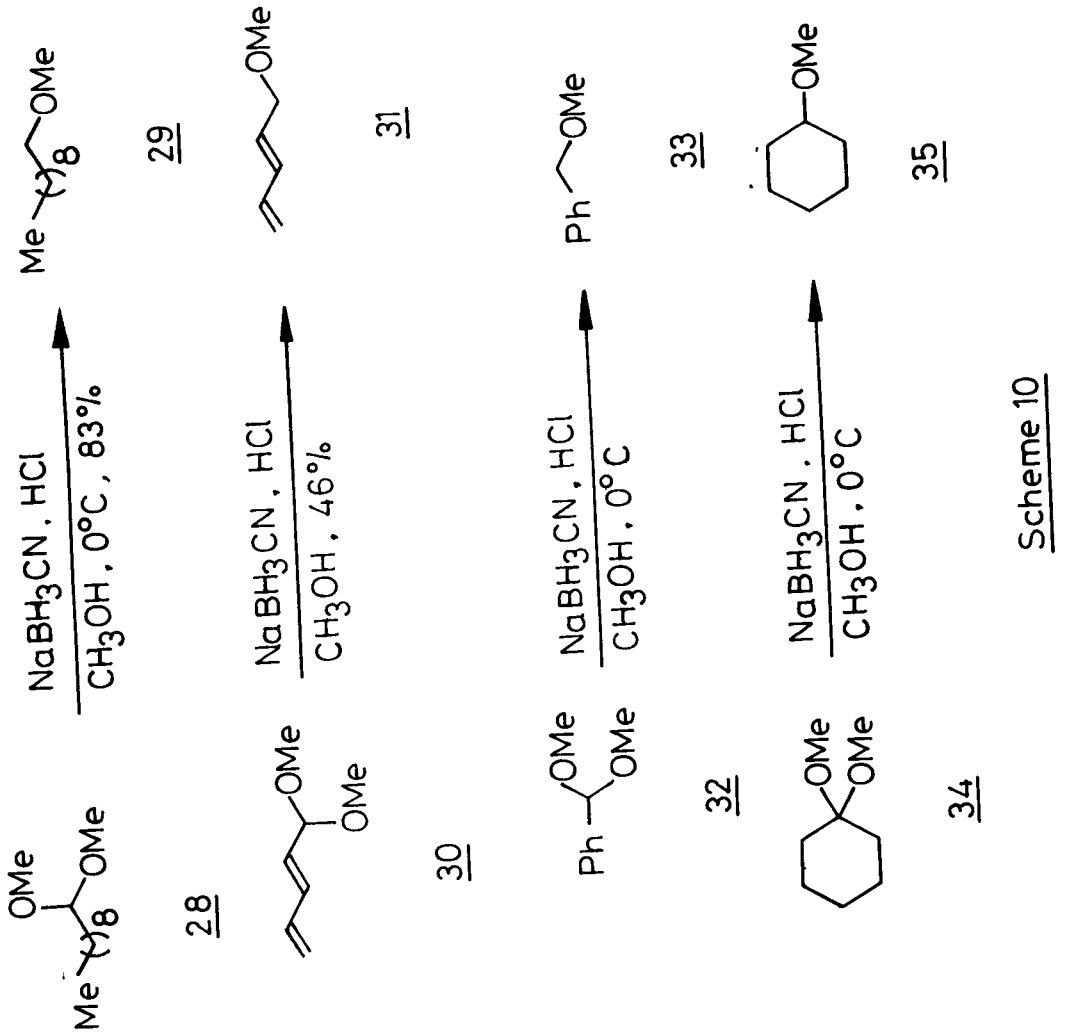
In principle, a large variety of α-oxoketene dithioacetals can be used to demonstrate the efficacy of the sodium cyanoborohydride. A selected number of α-oxoketene dithioacetals were studied only to establish the



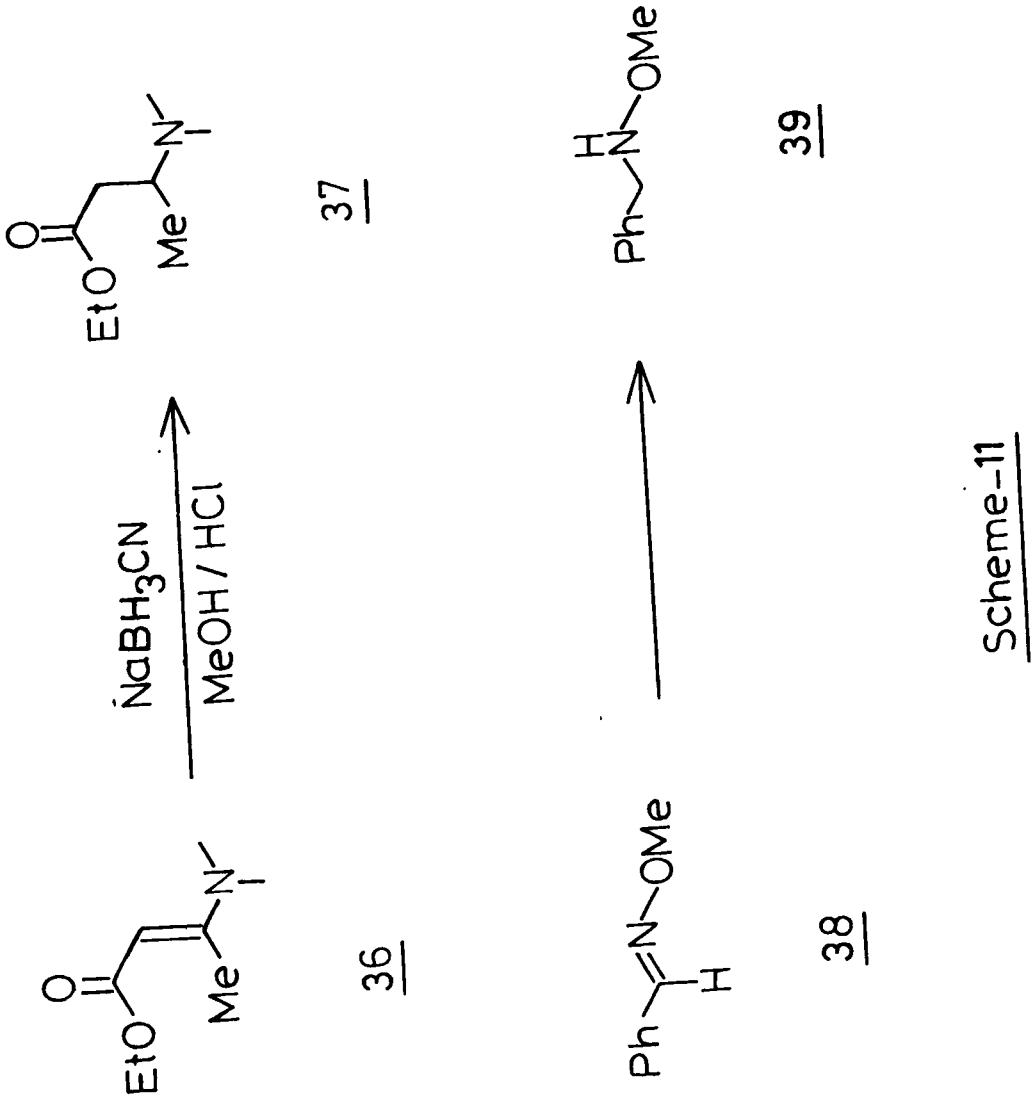
26 27

R	R′	R″	R‴
C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$
o-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$
C_6H_5	H	$CO_2C_2H_5$	CN
CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$
C_6H_5	H	H	$CO_2C_2H_5$

Scheme 9


OMe
Me
OMe
8
28
NaBH3CN, HCl
CH3OH, 0°C, 83%
Me
OMe
8
29
OMe
OMe
30
NaBH3CN, HCl
CH3OH, 46%
OMe
31
OMe
Ph
OMe
32
NaBH3CN, HCl
CH3OH, 0°C
Ph
OMe
33
OMe
OMe
34
NaBH3CN, HCl
CH3OH, 0°C
OMe
35

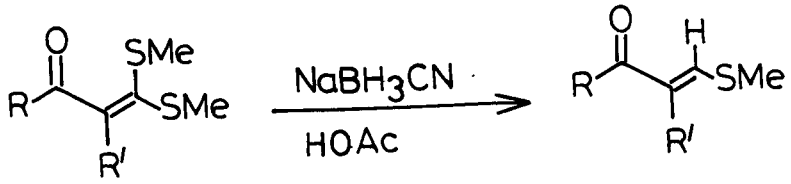
Scheme 10



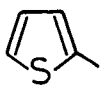
Scheme-11

scope and generality of the methodology. All the α-oxoketene dithioacetals employed in this study were prepared as per the reported methods[28-35]. They were fully characterized by analytical and spectroscopic data for their structural authenticity. After carrying out the reaction with different acids to maintain the pH, it was found out that the acetic acid (pH 0.9)was found to be the most satisfactory medium.

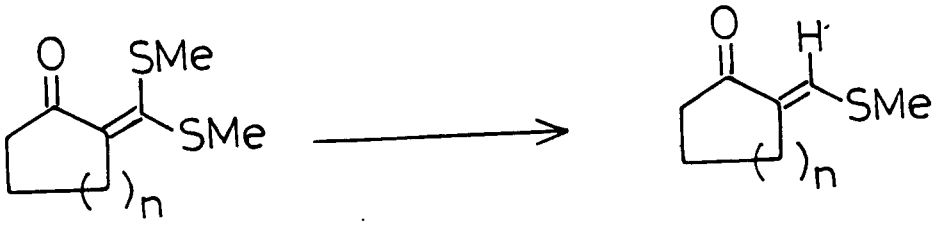
Thus in one of the typical experiments when the α-oxoketene dithioacetal 21a (R=C_6H_5,R'=H) was treated with sodium cyanoborohydride in presence of refluxing acetic acid for 12 hours, the reaction mixture after work-up and purification gave a liquid in 76% yield,which was characterized as 3-methylthio-1-phenyl-2-propen-1-one 1a. The spectral and analytical data were compared with that of the reported compound and were found identical (superimposable i.r. and n.m.r.). The geometry of 1a was assigned as E- on the basis of the coupling constant (15 Hz) of vinylic protons. Thus the compound 1a is exactly identical and obtained in much higher yield 76% against the 62% of Nickel boride reaction. Similarly, under identical reaction conditions the S,S-acetals 21b-g (Scheme 12) derived from the corresponding active methylene ketones gave the respective methylthioenones 1b-g in 60-73% overall yields. The analytical and spectral data of these compounds were in confirmity with their structures. The geometry of the thioenones 1b-e and g was found to be E and only in case of 1f a mixture of cis (46%) and trans (54%) isomers was obtained. Also, the acetal 21h gave the corresponding thiomethylene ketone 1h (Scheme 12) exclusively as E-isomer (i.r., n.m.r.) in 40% yield. The analogous compound 18a (Scheme 5) which is used in polyene synthesis[7,13] was previously prepared by the Michael addition of t-butyl mercaptan with acetylacetylene as a mixture of cis and trans-isomers[13]. The



21 1

21	1	R	R'
	a	C_6H_5	H
	b	p ClC_6H_4	H
	c	p $MeOC_6H_4$	H
	d	p MeC_6H_4	H
	e	C_6H_5	CH_3
	f		H
	g		H
	h	CH_3	H

Scheme-12



21 1

21, 1 i n=1,

j n=2

Scheme–13

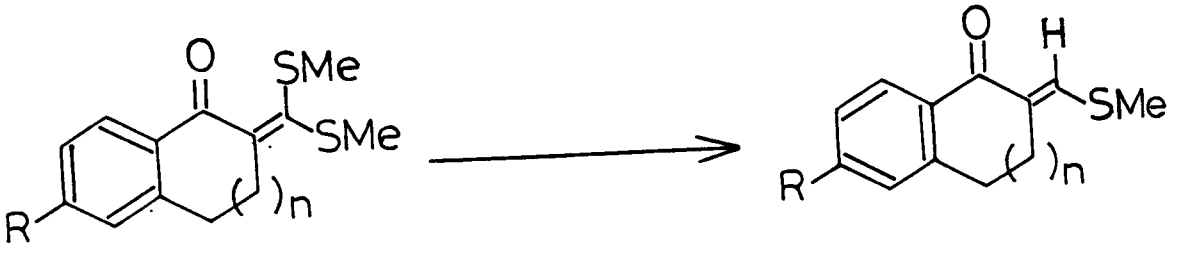
vinyl chloride method, although gave exclusively the trans isomer, the preparation of the acetyl vinyl chloride itself is not easy as for the preparation of 21h. The compound 1h being an important intermediate in olefinic synthesis, the present approach of its preparation should be the method of choice.

When the method was extended to the cyclic ketene dithioacetals 21i-j derived from the respective cyclopentanone and cyclohexanone, the corresponding vinylogous thiolesters 1i and 1j were obtained in 69% and 68% yields respectively (Scheme 13). The analytical and spectral data are in confirmity with the assigned trans structure. Similarly the tetralone, 6-methoxytetralone and benzsuberone acetals 21k-m gave the corresponding methylthioenones 1k-m (Scheme 14) exclusively as E-isomers in 82%, 69% and 78% yields respectively. Their analytical and spectral data are described in the experimental section.

The geometry of all the compounds were assigned on the basis of the n.m.r. coupling constants of the vinyl protons as described in the experimental section.

V.3 CONCLUSION

In conclusion, it may be summarised: A new route for the preparation of vinylogous thiolesters 1 has been formulated from the easily available ketones via the α-oxoketene dithiaocetals 21. The method is shown to be applicable with liberal structural variations. The method is also suitable for the synthesis of both thiomethyl and its higher homologs, whereas the existing methods use only high boiling mercaptans, since the methyl mercaptan is a gas.



21 1

21, 1, k R=H, n=1

l R=OMe, n=1

m R=H, n=2

Scheme 14

V.4 EXPERIMENTAL

General Methods

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

Starting Materials

The commercial samples of acetophenone, p-methylacetophenone, p-chloro-acetophenone, p-methoxyacetophenone, propiophenione, acetone, tetralone, cyclopentanone and cyclohexanone were purified before use. Commercially available sodium cyanoborohydride was purified according to reported procedure[24] before use.

Benzsuberone b.p. 138-39°C (12mm) was prepared according to the reported procedures[36].

The previously reported[28-35] α-oxoketene dithioacetals were prepared by the general method described below.

General method for the preparation of α-oxoketene dithioacetals using sodium t-butoxide:

A mixture of ketone (0.02 mol) and carbondisulphide (0.2 mol) was added to a well stirred suspension of sodium t-butoxide (0.4 mol) in dry benzene (170 ml) and the reaction mixture was allowed to stand at room temperature for 5-6 hr. Dimethylsulfate (neutral) (0.2 mol) was gradually added with stirring and external cooling (exothermic reaction)

and the reaction mixture was allowed to stand (5 hr) at room temperature with occasional shaking and then refluxed on a water bath for 0.5-1 hr. The mixture was poured on crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and the combined extract was washed with water, dried over sodium sulfide and concentrated. The products thus obtained were purified by crystallization or by column chromatography.

General method for the preparation of 2-methylthio-1-alkenyl ketones (1a-m).

To a well stirred solution of α-oxoketene dithioacetals 21 (0.01 mol) in acetic acid (30 ml), excess of sodium cyanoborohydride (1.95,0.03 mol) was added in small portions during 5 min. and the reaction mixture was stirred at room temperature for two hrs. Then the reaction mixture was refluxed for 6-10 hrs.(monitored by TLC). The mixture was then cooled to room temperature, poured into crushed ice (150g), and extracted with chloroform (3x50 ml). The organic layer washed with bicarbonate solution, then with water (3x100 ml), dried over sodium-sulfate and evaporated to give crude methylthioenones(1a-m), which are column chromatographed on silica gel using ethylacetate/hexane (1:9) as eluent to give pure 1a-m.

The data of these compounds are given below.

E-3-Methylthio-1-phenyl-2-propen-1-one (1a) was obtained as yellow viscous oil; yield 76%; i.r.(CCl_4): ν_{max} = 1643 cm^{-1}; ^1H n.m.r.(CCl_4): δ 2.32(s,3H,SCH_3); 6.70(d,1H,J=15Hz$_{olefin}$); 7.19-7.47(m,3H$_{arom}$); 7.89-7.98(m,3H$_{arom+olefin}$). (Found: C,67.70; H,5.92. Calc. for $C_{10}H_{10}OS$ (178.2): C,67.41; H,5.62%).

E-3-Methylthio-1-(4-chlorophenyl)-2-propen-1-one(1b) was obtained as pale yellow solid; yield 69%; m.p. 69-70°C; i.r.(KBr): ν_{max} = 1640 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.42(s,3H,SCH_3); 6.65(d,1H,J=15Hz$_{olefin}$); 7.32(d, J=9Hz,2H$_{arom}$); 7.70-8.05(m,3H$_{arom+olefin}$). (Found: C,56.75; H,4.54. Calc. for $C_{10}H_9ClOS$(212.7): C,56.47; H,4.23%).

E-3-Methylthio-1-(4-methoxyphenyl)-2-propen-1-one (1c) was obtained as yellow viscous oil; yield 68%; i.r.(CCl_4): ν_{max} = 1650 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 2.29(s,3H,SCH_3); 3.70(s,3H,OCH_3); 6.70-7.05(m,3H$_{arom+olefin}$); 7.78-8.03(m,3H$_{arom+olefin}$). (Found: C,63.31; H,5.70. Calc. for $C_{11}H_{12}O_2S$(208.3): C,68.42; H,5.81%).

E-3-Methylthio-1-(4-methylphenyl)-2-propen-1-one (1d) was obtained as pale yellow solid; yield 72%; m.p. 120-121°C; i.r.(CCl_4): ν_{max} = 1645 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.32(s,3H,CH_3); 2.35(s,3H,SCH_3); 6.75 (d,1H,J=15Hz$_{olefin}$); 7.19(d,J=9Hz,2H$_{arom}$); 7.81(d,J=9Hz,2H$_{arom}$); 8.91 (d,1H,J=15H$_{olefin}$). (Found: C,68.97; H,6.50. Calc. for $C_{11}H_{12}OS$(192.2): C,68.75; H, 6.25%).

E-3-Methylthio-2-methyl-1-phenyl-2-propen-1-one(1e) was obtained as yellow viscous oil; yield 60%; i.r.(CCl_4): ν_{max} = 1639 cm^{-1}; ^1H n.m.r. ($CDCl_3$): δ 1.89(s,3H,SCH_3); 2.28(s,3H,CH_3); 6.98(s,1H$_{olefin}$). 7.21-7.62(m,5H$_{arom}$). (Found: C,68.81; H,6.17. Calc. for $C_{11}H_{12}OS$(192.3): C,68.64, H,6.24%).

E and Z-3-methylthio-1-thienyl-2-propene-1-one (1f) was obtained as yellow crystalline solid; yield 73%; m.p. 128-129°C; i.r.(KBr): ν_{max} = 1612 cm^{-1}; ^1H n.m.r. (CCl_4): δ 2.40(s,3H,SCH_3); 2.45(s,3H,SCH_3); 6.60 (d,1H,J=15Hz$_{olefin}$); 6.80(d,1H,J=9Hz$_{olefin}$); 6.98-7.13(m,1H,H-4);

7.19(d,1H,J=9Hz$_{olefin}$); 7.42-7.71(m,2H,H-3',5'); 7.33(d,1H,J=15Hz$_{olefin}$). (Found: C,51.98; H,4.47. Calc. for $C_8H_8OS_2$(184.2): C,52.12; H,4.34%).

E-3-Methylthio-1-naphthyl-2-propen-1-one (1g) was obtained as viscous oil; yield 71 %; i.r.(CCl_4): ν_{max} = 1643 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 2.32 (s,3H,SC$\underline{H}_3$); 6.81(d,1H,J=15Hz$_{olefin}$); 7.08-8.31(m,8H$_{arom+olefin}$). (Found: C,73.52; H,5.41. Calc. for $C_{14}H_{12}OS$(228.3): C,73.65; H,5.30%).

E-4-Methylthio-3-buten-2-one (1h) was obtained as yellow viscous oil; yield 40%; i.r.(CCl_4): ν_{max} = 1670 cm^{-1}; ^{1}H n.m.r.($CDCl_3$): δ 2.21(s,3H, C$\underline{H}_3$); 2.35(s,3H,SC$\underline{H}_3$); 6.05(d,1H,J=15Hz$_{olefin}$); 7.70(d,1H,J=15Hz$_{olefin}$). (Found: C,51.43; H, 6.45. Calc. for C_5H_8OS(116.2): C,51.63); H,6.88%). The viscous oil solidifies on cooling m.p. 22°C.

E-2-(Methylthiomethylene) cylcopentanone (1i) was isolated as pale yellow solid; yield 69%; m.p. 47-48°C; i.r.(CCl_4): ν_{max} = 1701 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.79-2.38[m,6H,(C$\underline{H}_2$)$_3$]; 2.45(s,3H,SC$\underline{H}_3$); 7.10 (t,1H, J=1.5Hz$_{olefin}$). (Found: C,58.96; H,7.54. Calc. for $C_7H_{10}OS$(142.2): C,59.07; H,7.30%).

E-2-(Methylthiomethylene) cyclohexanone (1j) was obtained as pale yellow oil; yield 68%; i.r.(CCl_4): ν_{max} = 1712 cm^{-1}; ^{1}H n.m.r.(CCl_4): δ 1.50-2.00[m,4H-(C$\underline{H}_2$)$_2$-]; 2.00-2.60[m,4H,-(C$\underline{H}_2$)$_2$-]; 2.45(s,3H,SC$\underline{H}_3$); 7.25(t,1H,J=1.5Hz$_{olefin}$).(Found: C,61.71; H,7.92. Calc. for $C_8H_{12}OS$ (156.2): C,61.60; H,7.68%).

E-2-(Methylthiomethylene)tetralone (1k) was isolated as pale yellow solid; yield 82%; m.p. 68-69°C; i.r.(KBr): ν_{max} = 1660 cm^{-1}; ^{1}H n.m.r. (CCl_4): δ 2.43(s,3H,SC$\underline{H}_3$); 2.79[A_2B_2,q,4H,-(C$\underline{H}_2$)$_2$-]; 7.00-7.40(m,3H$_{arom}$); 7.51(s,1H$_{olefin}$); 7.90-8.05(m,1H$_{arom}$). (Found: C,70.72; H,5.91. Calc. for $C_{12}H_{12}OS$(204.3): C,70.48; H, 5.87%).

E-2-(Methylthiomethylene)6-Methoxytetralone (11) was isolated as pale yellow solid; yield 69%; m.p. 92-96°C; i.r.(KBr): ν_{max} = 1640, 1595 cm^{-1}; ^1H n.m.r.($CDCl_3$): δ 2.50(s,3H,SCH_3); 2.63-3.05[m,4H,-$(CH_2)_2$-]; 3.78(s, 3H,OCH_3); 6.51-6.88(m,$2H_{arom}$); 7.61(s,$1H_{olefin}$); 7.98(d,J=9Hz,$1H_{arom}$). (Found: C,66.51; H,5.97; Calc. for $C_{14}H_{12}OS$(228.3): C,68.64; H,6.02%).

E-2-(Methylthiomethylene)benzosuberone (1m) was isolated as yellow liquid; yield 78%; i.r.(KBr): ν_{max} = 1650 cm^{-1}; ^1H n.m.r.(CCl_4): δ 1.88[A_2B_2,q,-$(CH_2)_2$-]; 2.25[t,2H,-$(CH_2)_2$-]; 2.40(s,3H,SCH_3); 2.71 [t,2H,-(CH_2)-]; 6.90-7.60(m,$5H_{arom+olefin}$). (Found: C,71.33; H,6.53. Calc. for $C_{13}H_{14}OS$(218.2): C,71.49; H,6.45%).

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