INVESTIGATIONS *ON* HETEROCYCLIC SYNTHESIS *VIA* OXOKETEN-S,S; S,N AND N,N-ACETALS

Abstract

By

JAI NARAIN VISHWAKARMA

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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

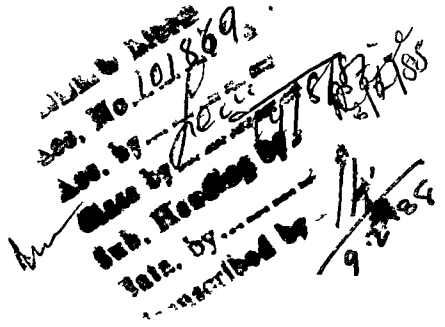
DOCTOR OF PHILOSOPHY

To

NORTH EASTERN HILL UNIVERSITY
SHILLONG-793 001
MEGHALAYA (INDIA)

DECEMBER, 1984

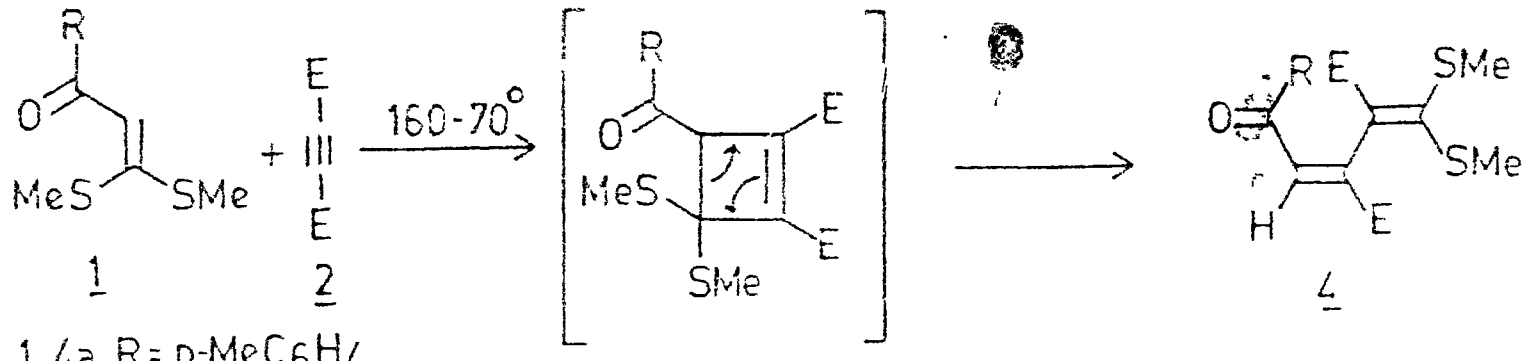
chem.



S U M M A R Y

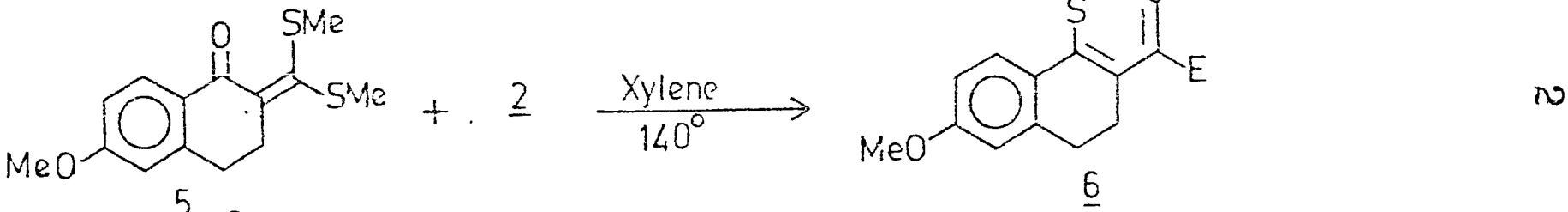
The chemistry and synthetic application of polarized keten-dithioacetals 1 (Scheme 1), which are derived from a wide variety of active methylene compounds and carbon disulphide in the presence of two eq. of base followed by alkylation in one pot reaction is well documented. They have been shown to be versatile three carbon fragments towards binucleophiles yielding a wide variety of heterocyclic ring systems.[1-4] It was considered to undertake further investigation on hitherto unreported transformation of the polarized keten S,S- and S,N-acetals. The results of these investigations are described in the thesis under three different chapters while a brief introduction is described in the first chapter.

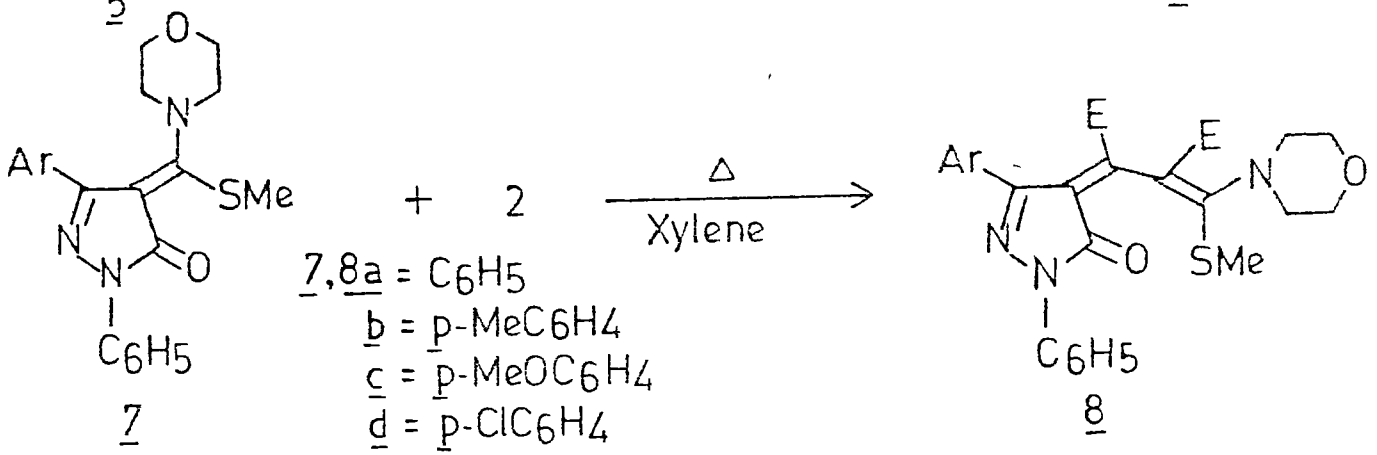
In chapter II the reactions of polarized keten-S,S- and S,N-acetals with dimethylacetylenedicarboxylate (DMAD) have been described.[5] While the reaction of thioacylketendithioacetals with DMAD is reported to yield the corresponding Diels-Alder adducts, the oxoketendithioacetals (1) react with 2 only at elevated temperatures to give 1:1 adducts 4 (Scheme 1). Apparently 1 undergoes [2+2] cycloaddition with 2 to give an unstable cyclobutene derivative 3 followed by its cleavage to give the corresponding diene 4. The method has consistence with all the examples 1(a-e). The oxoketen-dithioacetal derived from cyclohexanone which was considered to be



1, 4a, R = p-MeC6H4
b, R = C6H5
c, R = p-MeOC6H4
d, R = p-BrC6H4
e, R = Me

E = CO2Me



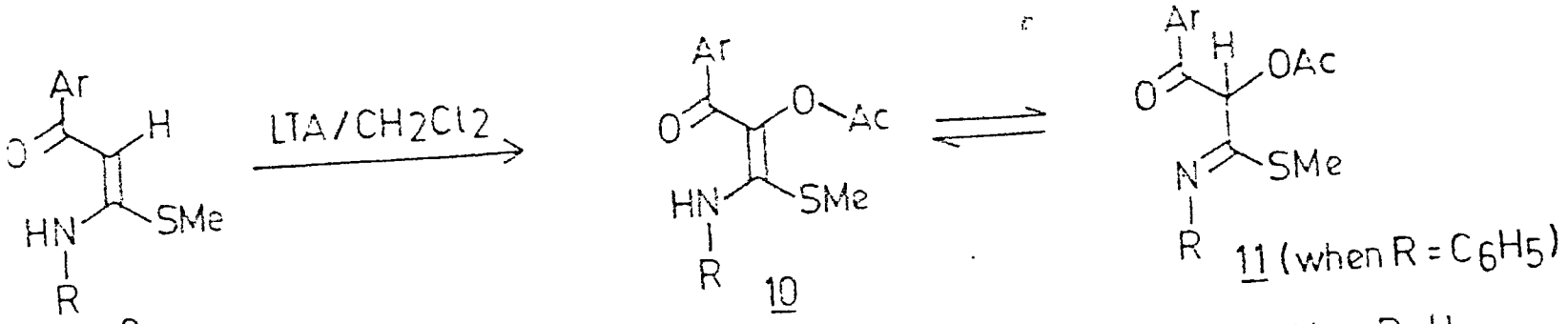


7, 8a = C6H5
b = p-MeC6H4
c = p-MeOC6H4
d = p-ClC6H4
e = p-BrC6H4

Scheme 1

suitable candidate for possible 4+2 cycloaddition with 2, however, did not yield any identifiable product under varying conditions. On the other hand acetal 5 and 2 were found to react when heated in sealed tube to give 6 in low yields whose structure has been supported by its structural data. A mechanism governing the formation of 6 has been discussed. Similarly the S,N-morpholine acetals 7a-e were reacted with 2 in refluxing xylene when the corresponding dienes 8 were formed (Scheme 1). The structure of all the compounds described in this chapter has been thoroughly established by their spectral and analytical data.

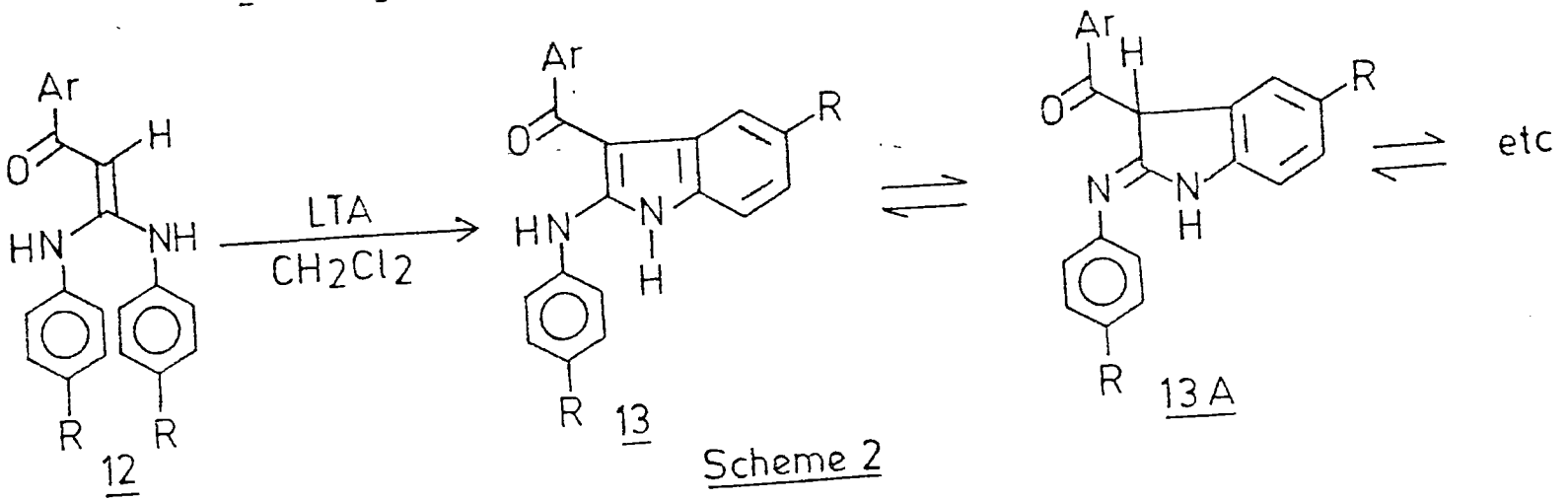
In chapter III the results on LTA oxidation of polarized keten-S,N- and N,N-acetals are described.[6] When 9(a-f) were oxidised with LTA in CH_2Cl_2 after work up the corresponding acetoxy S,N-acetals 10 were obtained in about 50 to 55% yields (Scheme 2). While the other possible products such as dimers and the corresponding pyrrole derivatives were not found to be formed. Similarly N,N-acetals 12 (Scheme 2) underwent cyclisation in the presence of LTA in CH_2Cl_2 to give the corresponding 2-anilino-3-aroyl-5-substituted indoles in 50, 60 and 25% yields. The S,N-acetal (15) derived from phenylacetonitrile underwent oxidation in the presence of lead-tetraacetate (LTA) in CH_2Cl_2 to give the iminoacetate (16) in 50% yield along with an unidentifiable viscous semisolid. When 16 was refluxed with BF_3Et_2O in order to get the indole (19) (Scheme 3), it remained unchanged but under drastic conditions it gave the



9 10 11 (when R = C6H5)

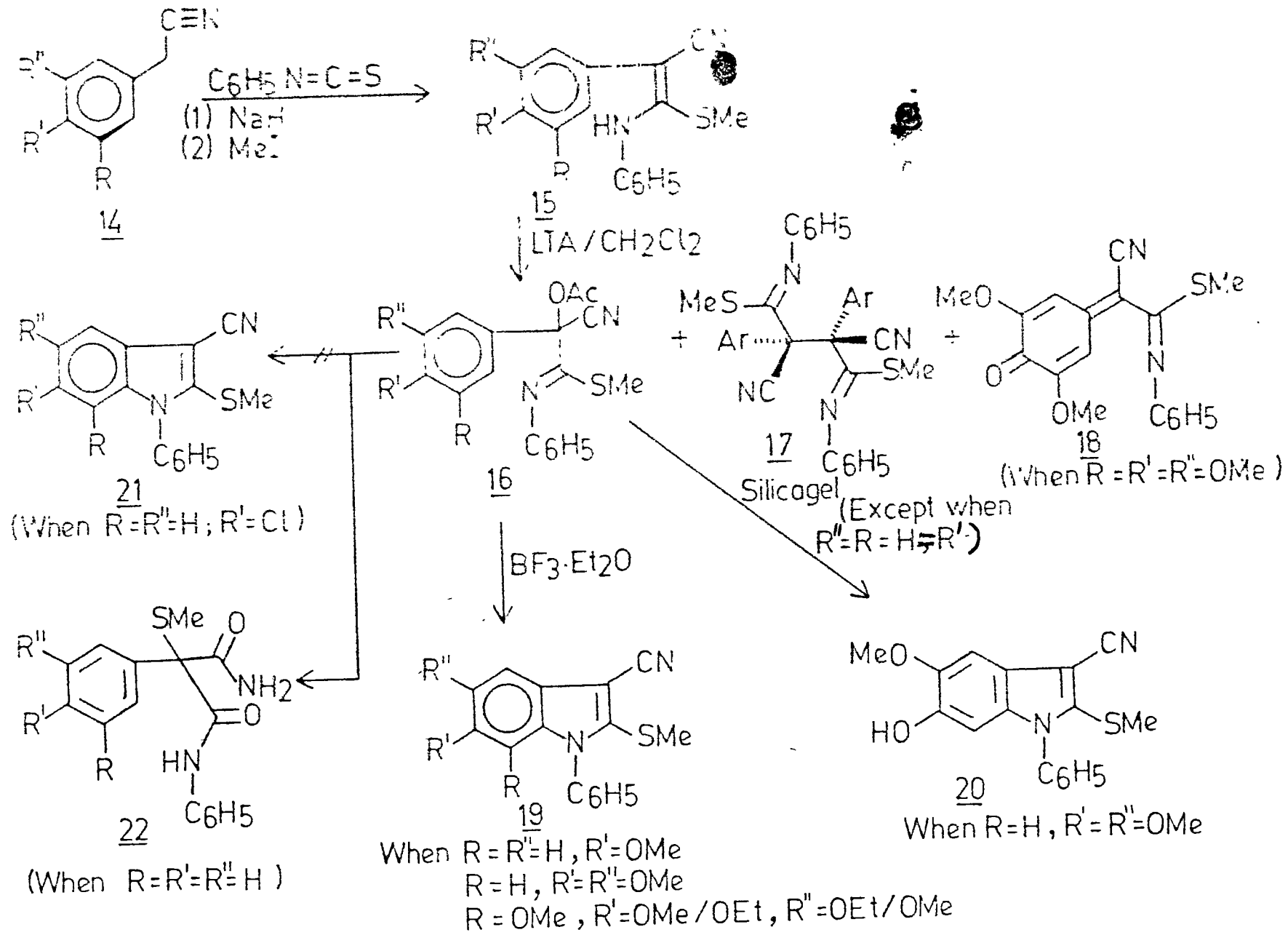
9, 10, 11 a, Ar = C6H5 ; R = Et
b, Ar = C6H5 ; R = C6H5CH2
c, Ar = p-MeC6H4, R = C6H5CH2
d, Ar = p-MeC6H4, R = C6H5
e, Ar = R = C6H5
f, Ar = p-ClC6H4, R = C6H5

12 13 a, Ar = p-MeC6H4 ; R = H
b, Ar = C6H5 ; R = H
c, Ar = C6H5 ; R = Me



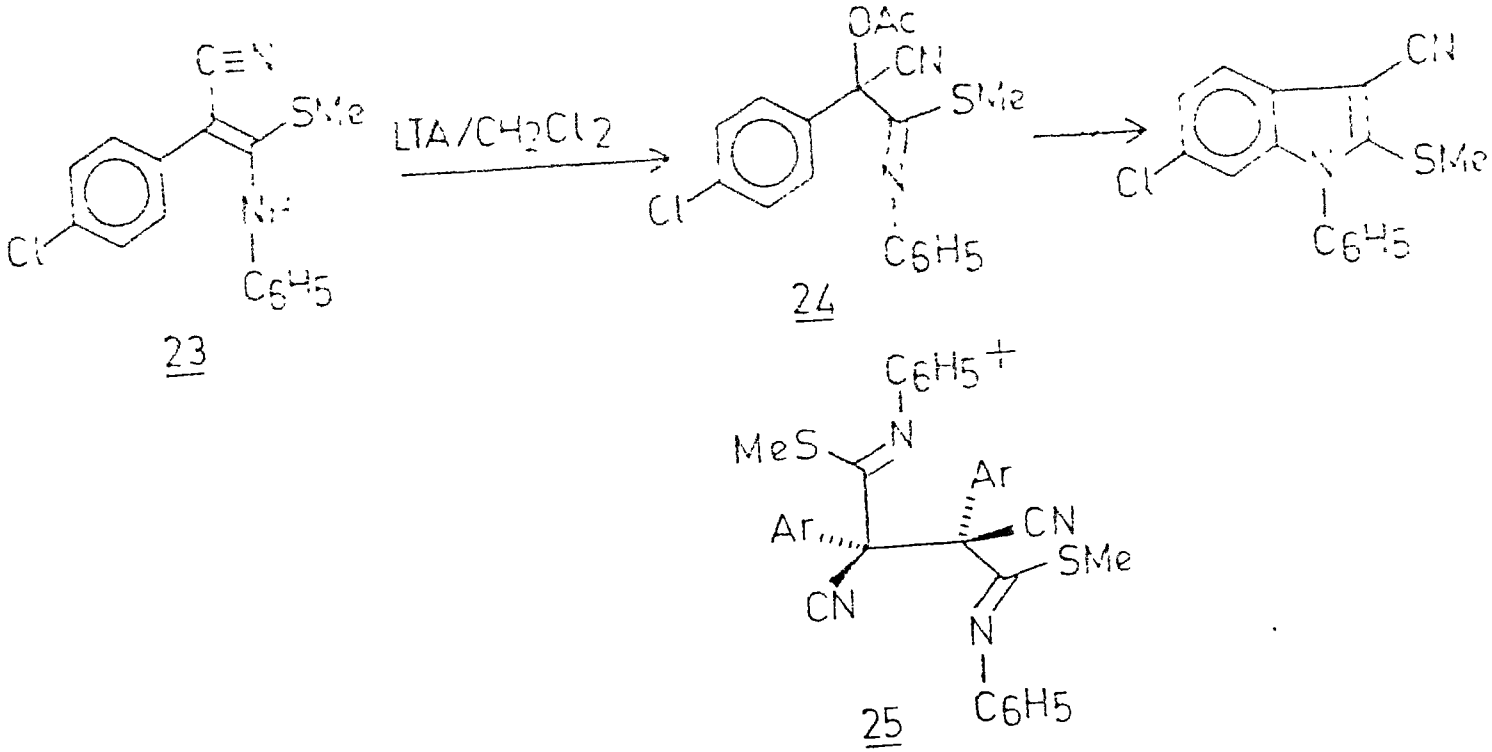
12 13 13A

Scheme 2


C≡N
C6H5N=C=S
(1) NaH
(2) MeI
14
15
LTA/CH2Cl2
16
BF3·Et2O
Silicagel
(Except when R''=R=H≠R')
17
18
(When R=R'=R''=OMe)
21
(When R=R''=H; R'=Cl)
22
(When R=R'=R''=H)
19
When R=R''=H, R'=OMe
R=H, R'=R''=OMe
R=OMe, R'=OMe/OEt, R''=OEt/OMe
20
When R=H, R'=R''=OMe

Scheme 3

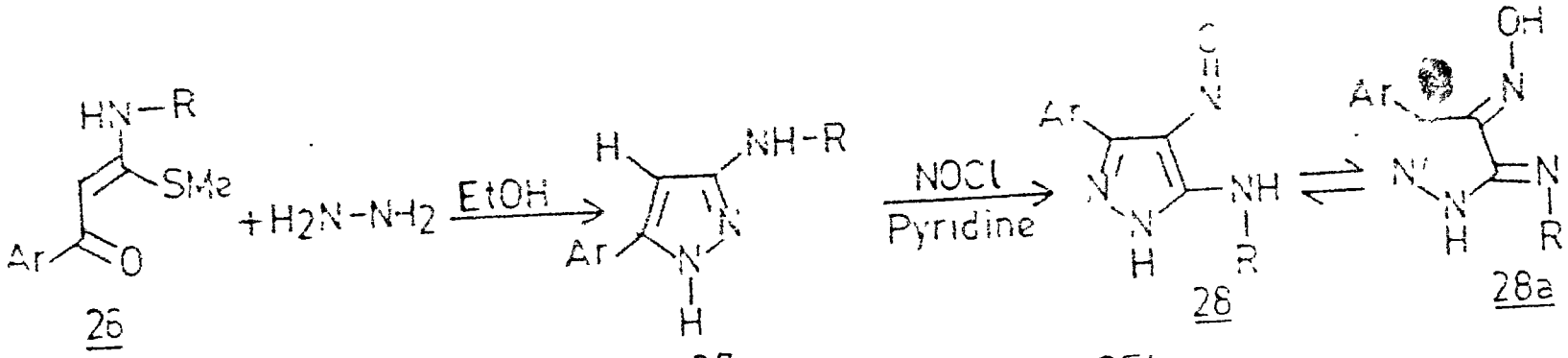
hydrolysed amide 22 in 70% yield. After unsuccessful attempts to achieve the indole 19, oxidation of S,N-acetal derived from 3,4-dimethoxyphenylacetonitrile was undertaken which under identical conditions gave the corresponding dimer (17) in 52% yield and the mother liquor content was found to contain the iminoacetate (16). The crude 16 when refluxed with BF_3Et_2O yielded the desired indole (19) in 95% yield (based on 16). Interestingly when crude 16 was passed through silica gel column, it gave 1-N-phenyl-2-methylthio-3-cyano-5-methoxy-6-hydroxyindole (20). The oxidation of S,N-acetal derived from p-methoxyphenylacetonitrile by LTA followed the same course of reaction giving the corresponding dimer (17) and the indole (19). The S,N-acetal derived from trimethoxyphenylaceto-nitrile underwent oxidation under similar conditions to yield the corresponding dimeric product (17) in low yields. The mother liquor contained two products which on column chromatographic separation gave the quinone derivative (18). On the other hand when t the same mother liquor content was treated with $BF_3.Et_2O$, work up and column chromatographic separation yielded the quinone 18 and the corresponding indole 19 in which one of the methoxy groups was replaced by an ethoxy group. The mechanism of the oxidation of these acetals is described in this thesis. The S,N-acetal derived from p-chlorophenylacetonitrile failed to give the corresponding indole (Scheme 4). It gave only the dimer (25) and the imino-acetate (24).



23 24 25

Scheme 4

In chapter IV the reactions of polarized keten S,N-acetals with hydrazine have been investigated.[7] When oxoketen S,S-acetals derived from acetophenones were reacted with hydrazine hydrate in the presence of aniline, the corresponding 5(3)-anilino-3(5)aryl-pyrazoles were obtained in low yields alongwith the corresponding N,N-acetals.[8] Under these conditions N,N-acetals were recovered unreacted with hydrazine hydrate. Thus the S,N-acetals 26a was prepared by reacting acetophenone with phenylisothiocyanate followed by alkylation which underwent smooth condensation with hydrazine hydrate to give aminopyrazole 27a in high yields. Similarly 27b-f were prepared in 89-97%. Overall yields (Scheme 5). The S,N-alkylacetals 26g-t obtained by direct displacement of the thiomethyl group by appropriate amine of the oxoketen S,S-acetals were also condensed with hydrazine hydrate to give the corresponding amino-pyrazoles 27g-t in excellent yields. Interestingly the pyrazoles 27o-t failed to undergo cyclisation under mild acidic conditions to yield the pyrrolopyrazoles 29 and 30 while the unreacted pyrazoles were recovered. Also the 4-nitrosopyrazoles 28 which were prepared in high yields by reacting 27 (Scheme 5) with nitrosyl chloride in pyridine when the corresponding nitroso compounds 28 were presumed to be formed. On the basis of the absence of proton signal of the 4-position the entry of nitroso group is assigned as in 28.



26

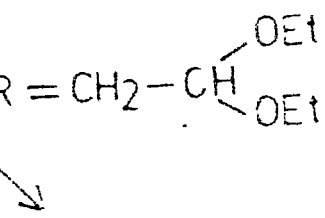
27

28

28a

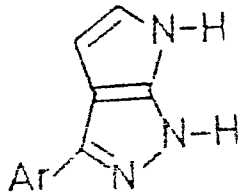
26, 27a, Ar = R = C_6H_5

b, Ar = p-MeC_6H_4 ; R = C_6H_5
c, Ar = p-ClC_6H_4 , R = C_6H_5
d, Ar = C_6H_5 ; R = p-MeC_6H_4
e, Ar = p-$EtOC_6H_4$, R = p-MeC_6H_4
f, Ar = p-ClC_6H_4 ; R = p-MeC_6H_4
g, Ar = C_6H_5 ; R = Me
h, Ar = p-ClC_6H_4 ; R = Me
i, Ar = p-$MeOC_6H_4$; Me
j, Ar = C_6H_5 ; R = Et
k, Ar = p-Cl-C_6H_4 ; R = Et
l, Ar = p-$MeOC_6H_4$; R = Et
m, Ar = C_6H_5 ; R = $C_6H_5CH_2$
n, Ar = p-MeC_6H_4 ; R = $C_6H_5CH_2$
o, Ar = C_6H_5



29

or



30

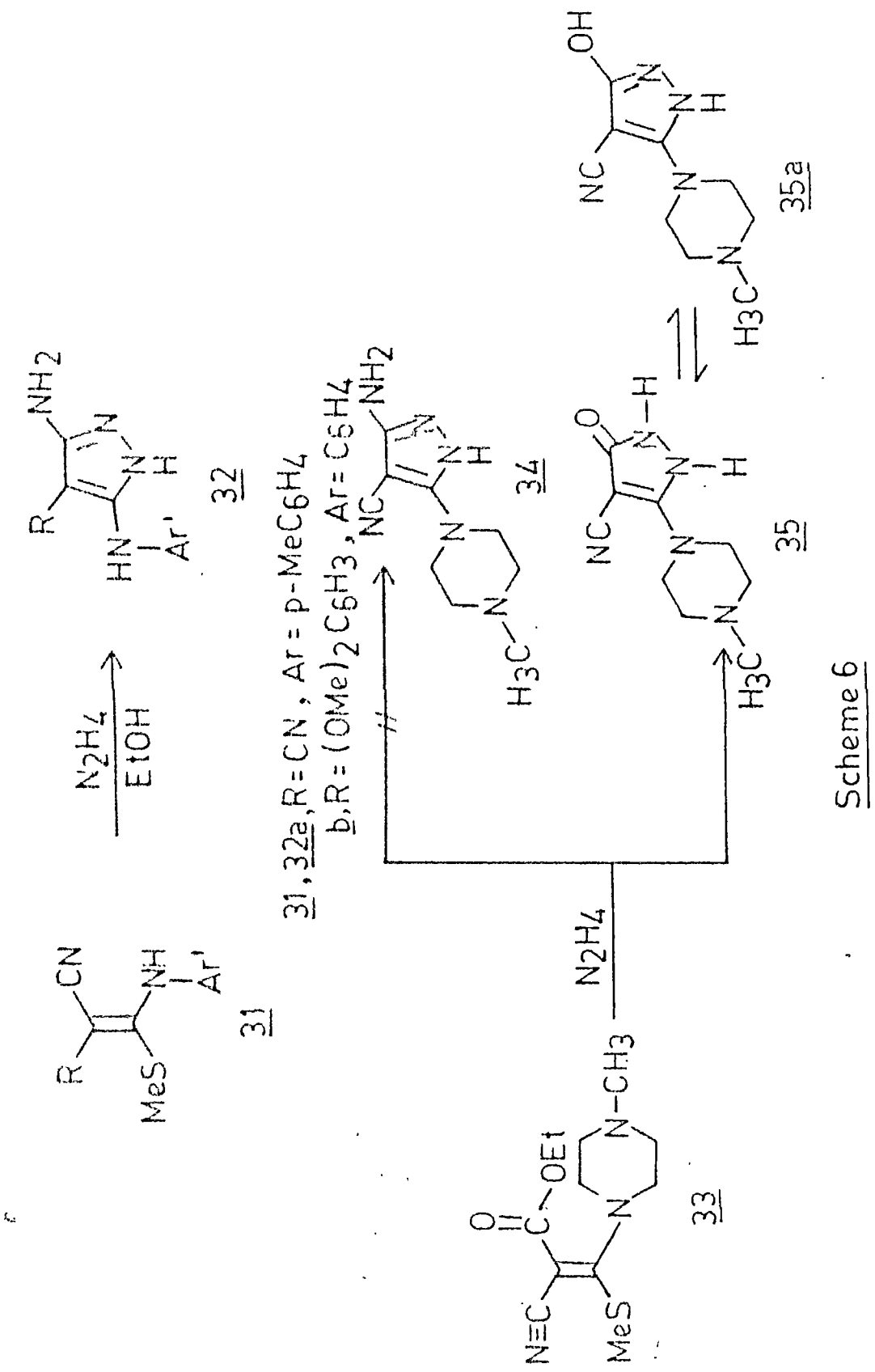
p, Ar = p-MeC_6H_4
q, Ar = p-$MeOC_6H_4$
r, Ar = p-$EtOC_6H_4$
s, Ar = p-ClC_6H_4
t, Ar = p-BrC_6H_4

Scheme 5

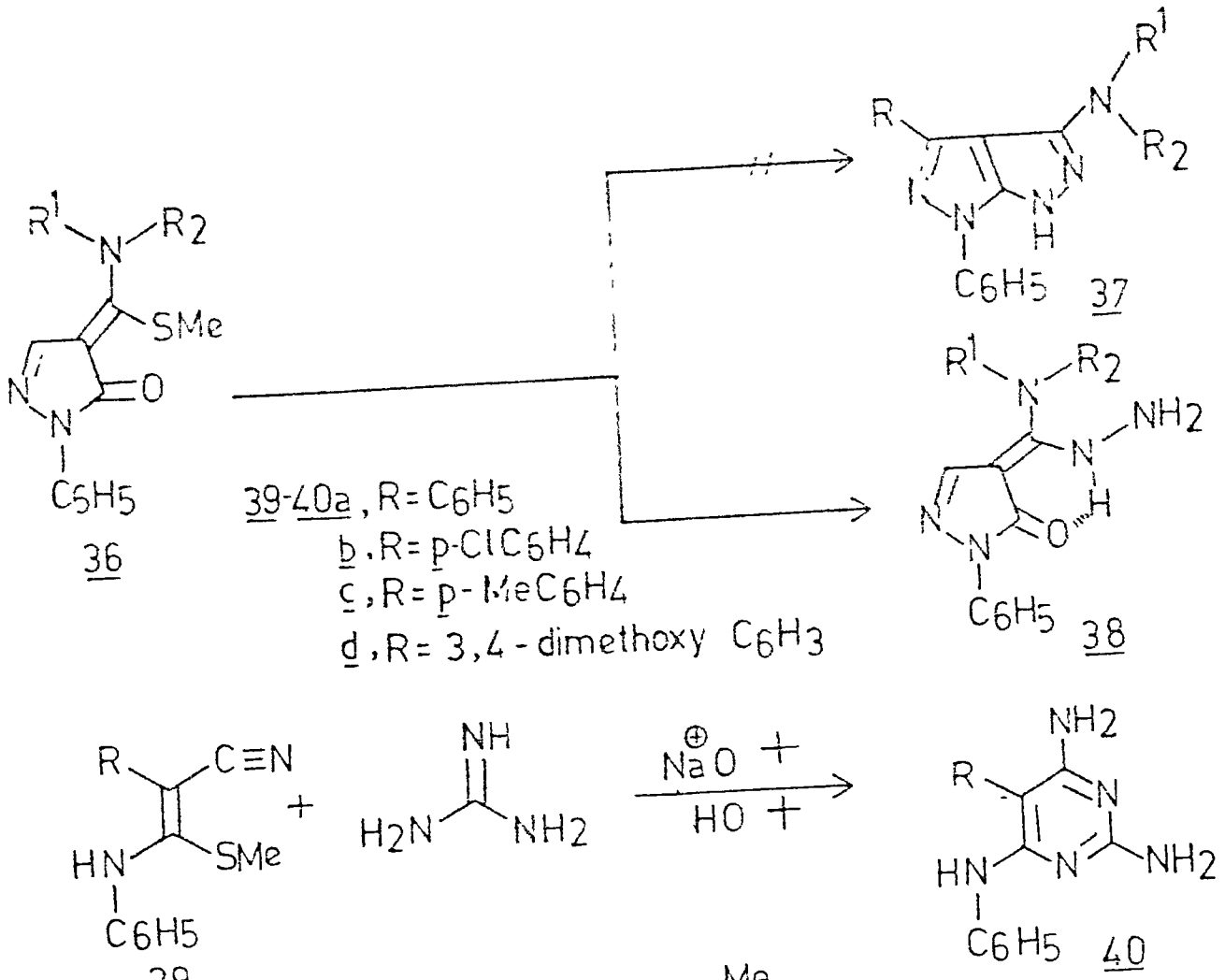
Similarly while S,N-acetal 31 gave 32, 33 gave only 35 and the formation of 34 was not observed (Scheme 6). The reaction of hydrazine hydrate with 36 (Scheme 7) gave only open chain compound 38.

The reaction of guanidine with S,N-acetals 39 derived from phenyl acetonitriles yielded the corresponding 2,4-diamino-5-aryl-6-anilinopyrimidines in 65-90% overall yields (Scheme 7). Similarly the S,N-acetals 41, 43, 45 (Scheme 8), when reacted with guanidine in the presence of a base gave the corresponding pyrimidines 42, 44 and 46 respectively.[9]

In another experiment the pyrimidine 48 obtained by reacting the corresponding S,N-acetal (47) with guanidine, underwent smooth nitrosation ($X=NH_2$) to give the corresponding 4-nitrosopyrimidine 49 in excellent yields.[9](Scheme 9). Attempted cyclisation of 49 were unsuccessful.


N2H4
EtOH
31, 32a, R=CN, Ar=p-MeC6H4
b, R=(OMe)2C6H3, Ar=C6H4
N2H4
31
32
33
34
35
35a

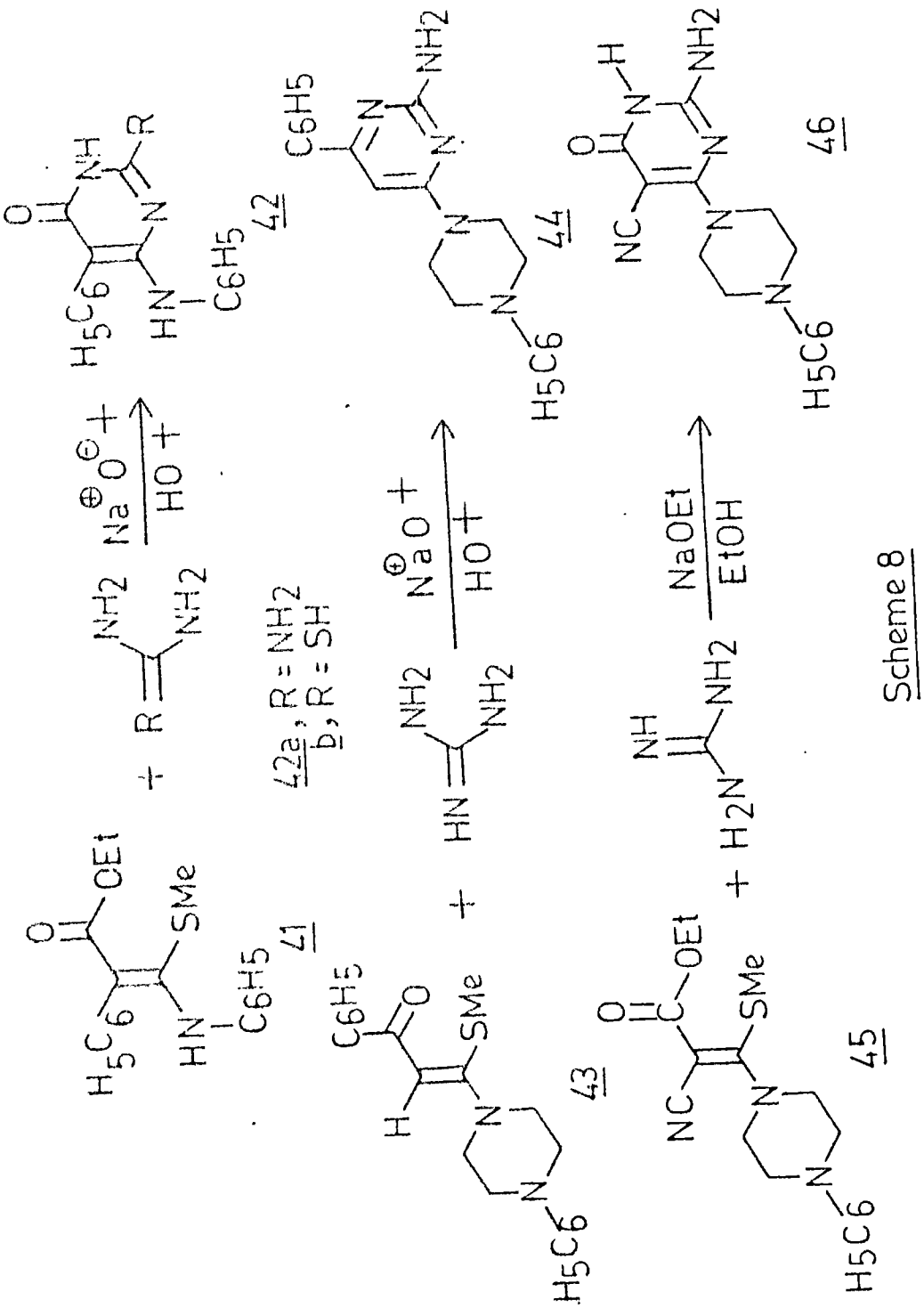
Scheme 6



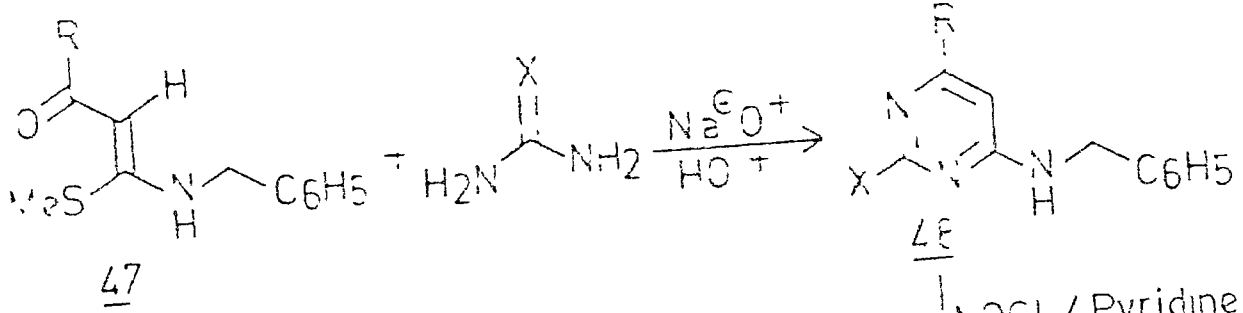
36-38a, R = C_6H_5 ; R' = H ; R_2 = Me

b, R = p BrC6H4 ; R' = R_2 = $-(CH_2)_2-\underset{\underset{Me}{|}}{N}-(CH_2)_2-$

Scheme 7



Scheme 8



47

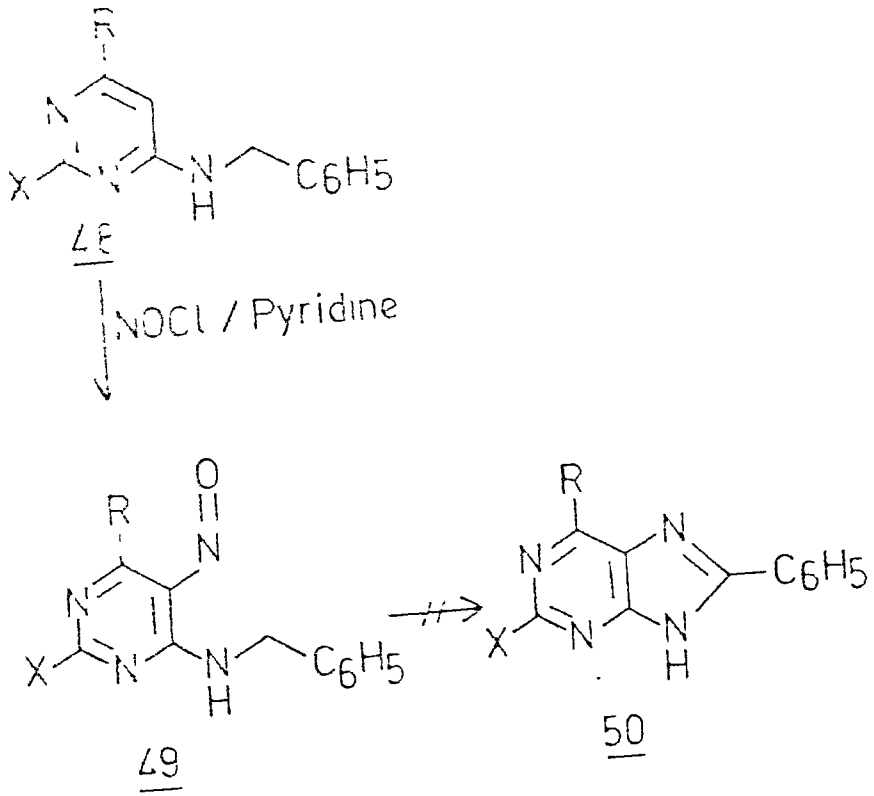
48a, X = NH_2, R = Me

b, X = NH_2, R = p-ClC_6H_4

c, X = SH, R = p-ClC_6H_4

49a, X = NH_2, R = Me

49b, X = NH_2, R = p-ClC_6H_4



Scheme 9

REFERENCES

1. S.M.S. Chauhan and H. Junjappa, Synthesis, 880 (1974).

2. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).

3. S.M.S. Chauhan and H. Junjappa, Tetrahedron, 1779 (1976).

4. S.M.S. Chauhan and H. Junjappa, Tetrahedron, 1911 (1976).

5. J.N. Vishwakarma, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans. I, 1099 (1983).

6. J.N. Vishwakarma, H. Ila and H. Junjappa, unpublished result.

7. J.N. Vishwakarma, B. K. Roychowdhury, H. Ila and H. Junjappa, Indian J. Chem., 000 (1984)

8. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).

9. J.N. Vishwakarma, S. Apparao, H. Ila and H. Junjappa, Indian J. Chem., 000 (1984).

****

INVESTIGATIONS
ON
HETEROCYCLIC SYNTHESIS
VIA
OXOKETEN-S,S; S,N AND N,N-ACETALS

By

JAI NARAIN VISHWAKARMA

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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

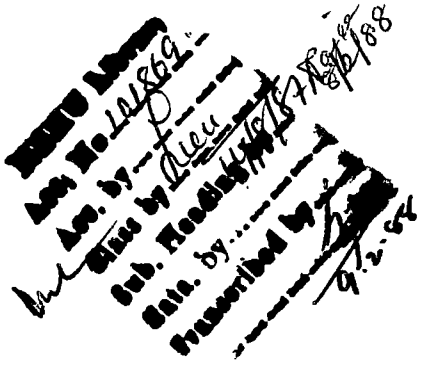
DOCTOR OF PHILOSOPHY

To

NORTH EASTERN HILL UNIVERSITY
SHILLONG-793 001
MEGHALAYA (INDIA)

DECEMBER, 1984

Chem



Dr. (Mrs) H. Ila
READER

NORTH-EASTERN HILL UNIVERSITY
DEPARTMENT OF CHEMISTRY
SHILLONG - 793 003 (INDIA)

CERTIFICATE

This is to certify that the work described in this thesis has been carried out by Mr. Jai Narain Vishwakarma 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 dimploma in this or any other university.

for H. Ila
(H. ILA)
20.12.84

Date : 20th December 1984

Department of Chemistry
School of Physical Sciences
North-Eastern Hill University
Laitumkhrah, Shillong-793003.

phone : 6593
Grams : NEHU

Pre- Ph.D Course Work evaluation Report

Name : J.N. Vishwakarma

No.	Course	Description	Grade	GPA
1.	Chem 401	Inorganic Chemistry I	A	4.80
2.	Chem 421	Organic Chemistry I	A	4.87
3.	Chem 403	Inorganic Chemistry II	B	4.00
4.	Chem 541	Chemical Binding	A	4.93
Final Grade point average :			'A'	4.65

The following additional Course (s)have been cleared satisfactorily by the candidate :

1. Chem 423 Organic Chemistry II
2. Chem 542 Physical Methods
3.
4.

21/1/82

Head
Department of Chemistry
North Eastern Hill University
Shillong-793003

ACKNOWLEDGEMENT

The research work described in this thesis was carried out in the Department of Chemistry, North-Eastern Hill University, Shillong under the supervision of Dr.(Mrs) H. Ila Reader in the department. I take this opportunity with great pleasure to thank her for suggesting the problems and guiding me throughout the course of this investigation. I also wish to express my sincere thanks to Prof. H. Junjappa, Head, Department of Chemistry, NEHU, Shillong for his guidance,help and encouragement.

I am also grateful to Prof. R.D. Singh, Retired Head, Department of Chemistry, St. Andrew's Post-graduate college, Gorakhpur,UP who gave me the first insight in modern chemistry.

Thanks are also due to my colleagues Dr. A. Kumar, Dr. V. Aggarwal, Dr. S. Apparao, Dr. B. Myrboh, Dr. Shakti S, Bhattacharjee, Mr. A. Rahman, G. Singh, Mr. C.V. Asokan, Mr. L. Warjeet Singh, Mr. R. Chakrasali, Mr. A. Thomas, Miss. Dipah Pooranchand, Mr. R.S. Verma, Mr. Akhilesh Gupta, Mr. Arun Kumar Gupta, Mr. M.P. Balu, Md. Mofizuddin, Mr. M.L. Purkayastha, Mr. A. Dutta, Mr. B. Deb, Mr. R. Borkatoki and Prof. B.K. Roy Chowdhury for their cooperation during the course of this investigation.

I also wish to express my gratefulness to the technicians of RSIC, NEHU, Shillong for recording the spectra used in this thesis.

I also thank Mr. Vijayan T.R. who has very carefully typed my thesis.

I also express my sincere gratitute to Dr. R.N. Prasad, Senior Scientist, and Mr. S.N. Goswami, Technical Officer of ICAR for their help in processing this thesis.

Lastly I express my gratitute to my family members for their encouragement and patience.

J. N. Vishwakarma

Jai Narain Vishwakarma

Date : 20th December 1984

C O N T E N T S

.....

P R E F A C E

The chemistry and synthetic application of polarized ketendithioacetals which are derived from a wide variety of active methylene compounds is well documented. They have been shown to be versatile three carbon fragments towards binucleophiles yielding a wide variety of heterocycles. It was considered to undertake further investigation on hitherto unreported transformations of the polarized keten-S,S; S,N- and N,N-acetals. The results of these investiations are described in this thesis.

In chapter I of this thesis, a brief introduction is described.

In chapter II, the reactions of polarized keten-S,S and S,N-acetals with dimethylacetylenedicarboxylate (DMAD) have been described.

In chapter III of this thesis, the results on Lead tetraacetate (LTA) oxidation of S,N and N,N-acetals have been described.

In chapter IV, the reactions of polarized keten-S,N-acetals with hydrazine yielding pyrazoles have been described. Some of the pyrazoles were treated with nitrosylchloride in pyridine to give 4-nitrosopyrazoles. Reactions of some of the

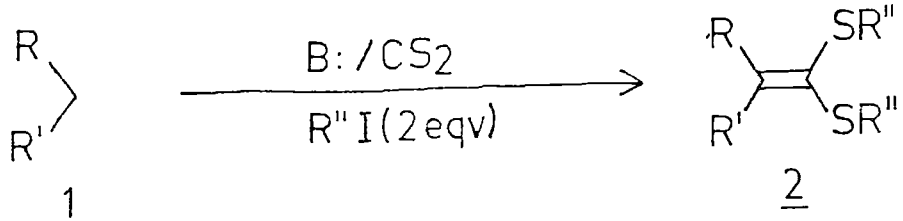
S,N-acetal with guanidine and thiourea have also been described in this chapter. Some of the pyrimidines underwent smooth nitrosation to yield 4-nitrosopyrimidines.

CHAPTER I

I N T R O D U C T I O N

The development of newer and efficient synthetic methods based on easily accessible reagents and reactive intermediates which are capable of a wide functional group variations and general applicability, is one of the central problems in synthetic organic chemistry. The organic chemists have always enjoyed evolving newer and efficient methods than using comprehensively worked-out existing methods. The development of enamines, phosphorous, sulfur ylids, organotransition metal and organosilicon compounds represent a few of intermediates and synthons developed in last 30-40 years.

In this connection, it was realized about ten years back that a variety of active methylene compounds with different functionalities react with carbon disulfide in the presence of base to give the corresponding dithioacids which on subsequent alkylation with two eqv. of alkyl halides afford a class of compounds called polarized keten dithioacetals (Scheme 1). These dithioacetals 2 are either liquids with well defined boiling points or solids with sharp melting points which can be purified by conventional purification methods. They are stable at room temperature, under mild acidic and alkaline conditions and can be stored indefinetely without apparent decomposition.[1] Literature survey at this stage showed that despite a large number of reports on their preparations and physical properties, a systematic investigation on their synthetic utility was not much explored.[1-7] The easy availability of these intermediates from a wide variety of active methylene compounds, their stability towards mild acidic and basic conditions prompted us to exploit these intermediates for various synthetic transformations by reacting 1,3-electrophilic centres with numerous nucleophilic species. The polarized keten dithioacetals emerged out as useful three carbon fragments for the synthesis of a wide variety of novel heterocycles like alkylthio, alkoxypyrimidines, pyridones, napthyridines, pyrazoles and other fused



1 2

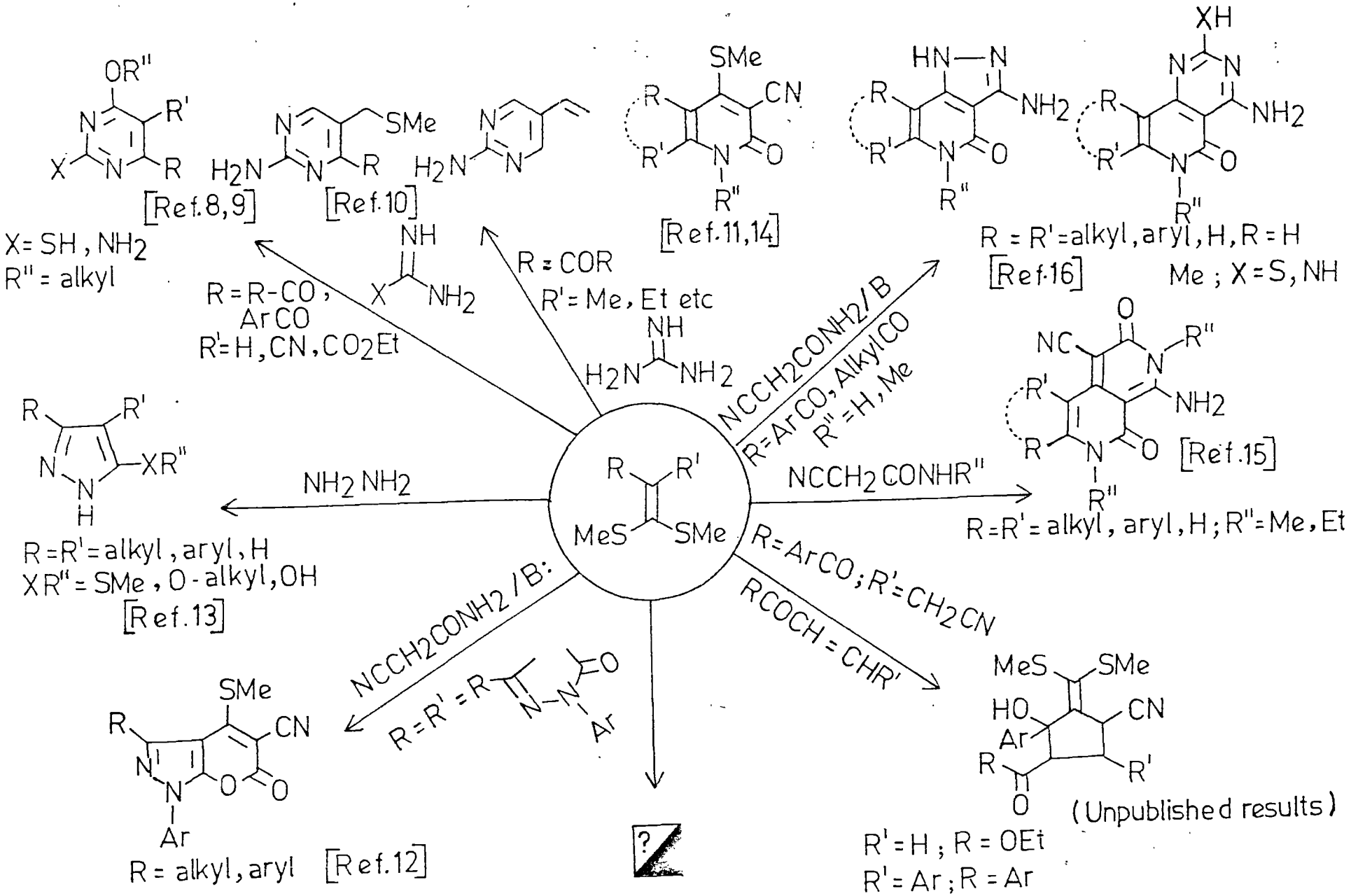
1,2, R = H, Alkyl, Aryl, ArCO, AlkylCO, CO_2R, CN, $CONH_2$, NO_2, Sulphonyl etc.

R' = ArCO, AlkylCO, H, CO_2R, CN, $CONH_2$, NO_2 etc.

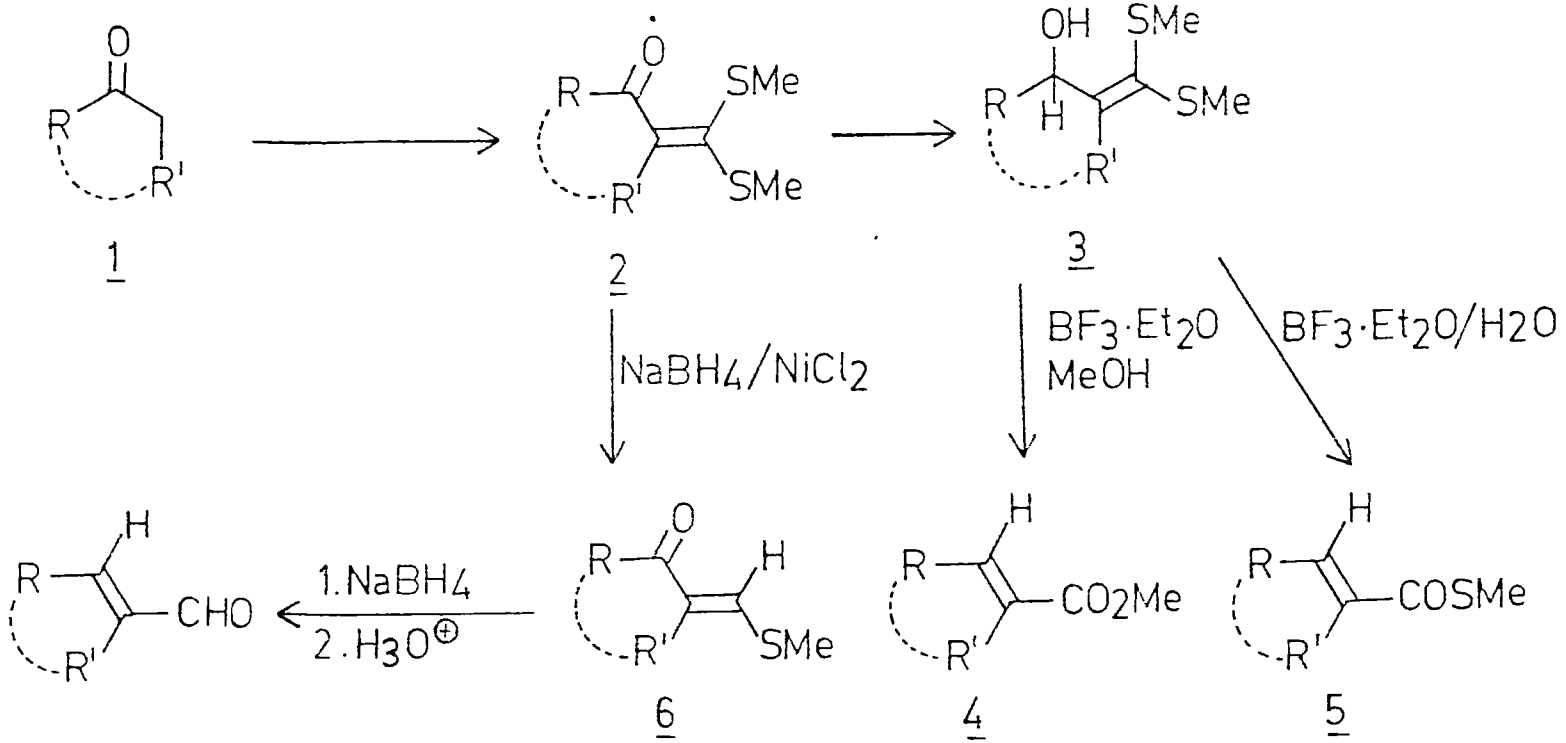
R" = alkyl

Scheme 1

heterocycles[8-17] by reaction with bifunctional nucleophiles. Some of these transformations developed in this laboratory are shown in the Scheme 2. The methods thus developed have been shown to be of general synthetic applications since the choice of the structural variants of active methylene compounds is quite large. The studies of the reactions of the corresponding α-oxoketendithioacetals with metal hydride had demonstrated that unlike their corresponding oxygen or nitrogen counterparts, these intermediates undergo exclusive 1,2-reduction at carbonyl carbon in presence of either sodium boronhydride or lithium aluminium hydride. The α-oxoketen dithioacetals were therefore developed as useful intermediates for reductive 1,3-carbonyl transposition.[18] Thus a highly stereoselective and regiospecific method for homologation of easily available ketones to α,β-unsaturated esters 4 via α-oxoketendithioacetals (Scheme 3).[19] was developed. The carbinolacetals which are obtained in nearly quantitative yields by 1,2-reduction of 2 with sodium borohydride, undergo boron trifluoride etherate assisted methanolysis to afford the corresponding α,β-unsaturated esters 4 in good to excellent yields (Scheme 3). On the otherhand borontrifluoride catalysed hydrolysis of 3 in presence of water yielded the corresponding


[Ref.8,9]
X = SH, NH2
R'' = alkyl
[Ref.10]
[Ref.11,14]
[Ref.16]
R = R' = alkyl, aryl, H, R = H
Me ; X = S, NH
R = R-CO, ArCO
R' = H, CN, CO2Et
R = COR
R' = Me, Et etc
NCCH2CONH2 / B
R = ArCO; Alkyl CO
R'' = H, Me
[Ref.15]
NH2 NH2
NCCH2CONHR''
R = R' = alkyl, aryl, H; R'' = Me, Et
R = R' = alkyl, aryl, H
XR'' = SMe, O-alkyl, OH
[Ref.13]
NCCH2CONH2 / B:
R = ArCO; R' = CH2CN
RCOCH = CHR'
R = alkyl, aryl [Ref.12]
R' = H ; R = OEt
R' = Ar ; R = Ar
(Unpublished results)
?

Scheme 2

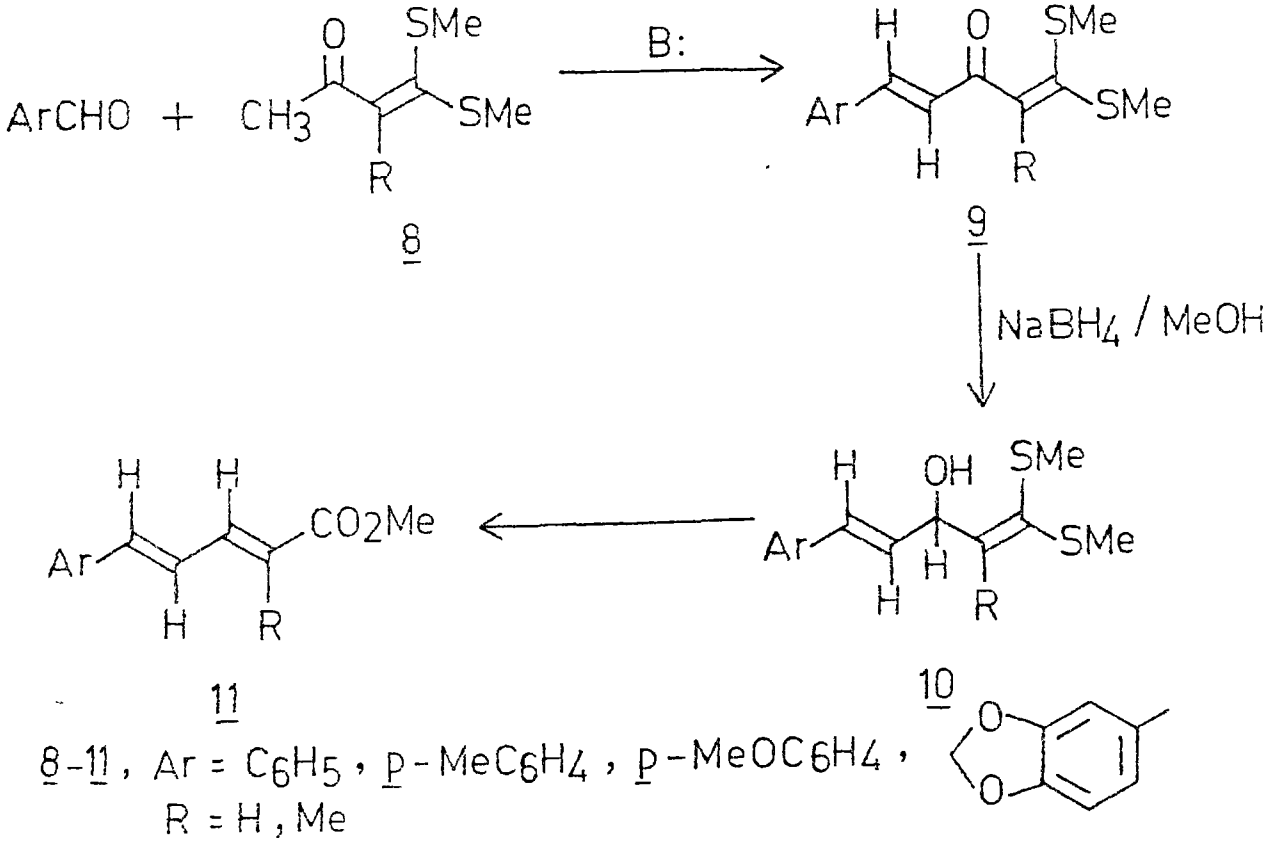


1,2,6–10, R and/or R' = Ar, alkyl, H ; R = R' = $-(CH_2)_n-$

Scheme 3

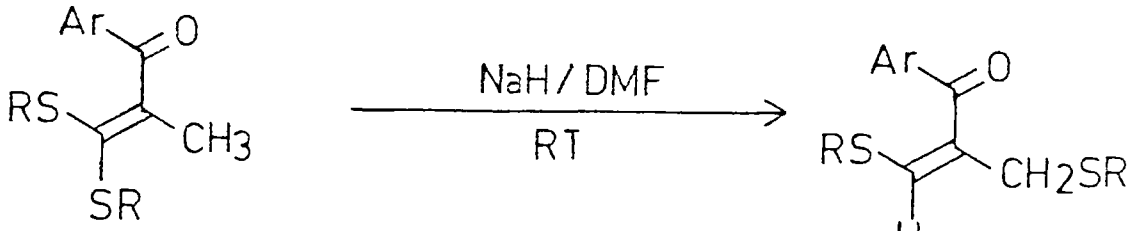
α,β-unsaturated S-methylesters 5. Further a facile route for β-alkylthiomethyleneketones 6 was developed[20] by partial reductive dethioalkylation of the corresponding α-oxoketendithioacetals 2 with sodium borohydride and nickel chloride (Scheme 3). These alkylthiomethyleneketones 6 could be converted to α,β-unsaturated aldehyde 7 by 1,2-reduction with sodium borohydride and subsequent hydrolytic rearrangement (Scheme 3).[19] Similarly a facile general route for methyl 5-aryl-2,4-pentadienoates 11 has been developed by borohydride reduction and subsequent methanolysis of the arylidene dithioacetals 9 obtained by condensation of the corresponding acylketendithioacetals 8 with aromatic aldehydes (Scheme 4).[21] Thus α-oxo-ketendithioacetals 2 have been shown to be common precursors for α,β-unsaturated O-methyl-S-methyl esters, α,β-unsaturated aldehydes and methyl 5-aryl pentadienoates (Scheme 3 and 4).

The ketoketendithioacetals 12 derived from propiophenones and other higher analogs are shown to undergo interesting 1,3-alkylthio shift to give the rearranged acrylophenones 13 in the presence of base like sodium hydride (Scheme 5).[22] A detailed mechanistic studies on this interesting 1,3-RS shift



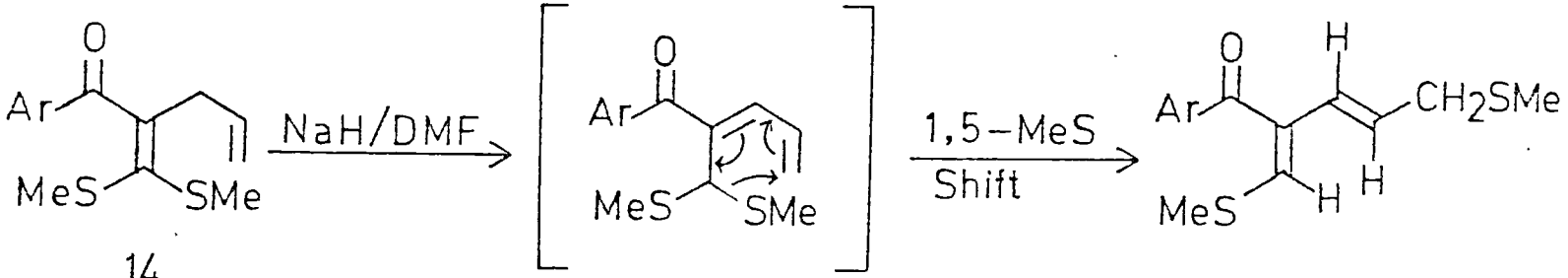
8-11, Ar = C_6H_5, p-MeC_6H_4, p-$MeOC_6H_4$,
R = H, Me

Scheme 4



12 13

12, 13, Ar = C_6H_5, p-MeC_6H_4, p-ClC_6H_4, p-$MeOC_6H_4$

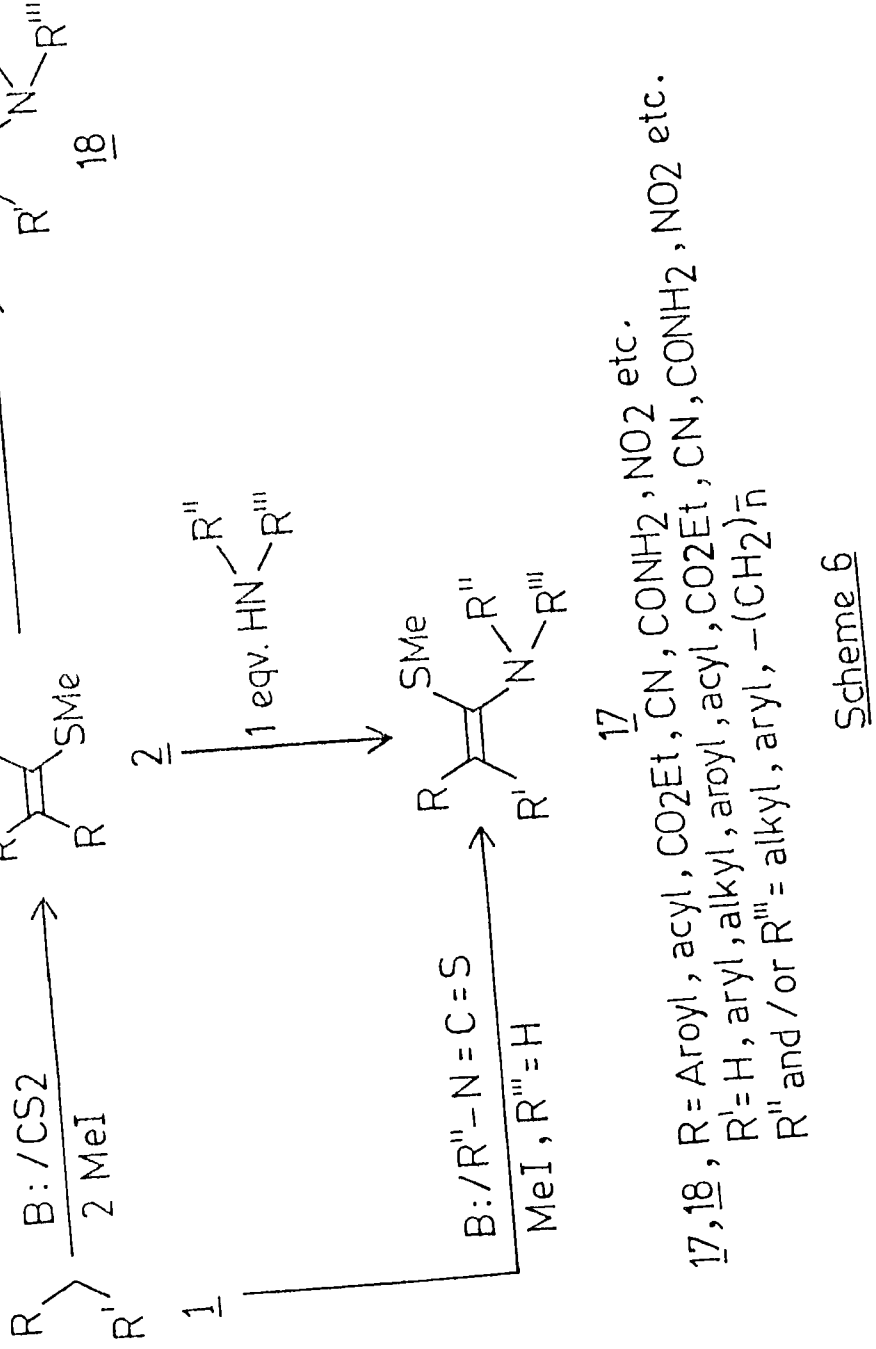


14 15 16

Scheme 5

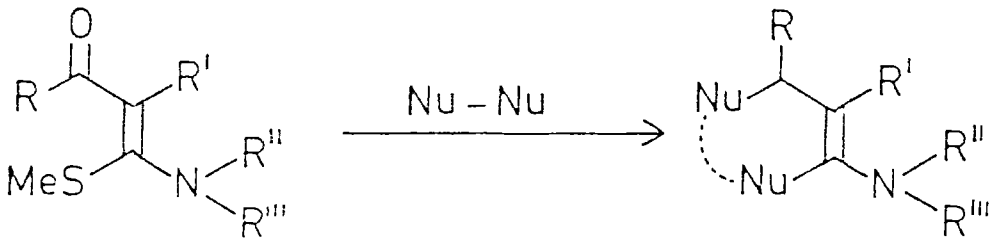
observed in these dithioacetals[23] and some of the cyclic α-oxoketendithioacetals.[24] was carried out. Similarly the α-allyl-α-oxoketendithioacetals 14 are shown to undergo an unprecedented highly stereoselective 1,5-alkylthio shift in presence of sodium hydride and dimethylformamide to give novel dienes 16 (Scheme 5).[25] Mechanistic studies on this rearrangement has shown an intermolecular non-concerted pathway instead of concerted 1,5-RS shift.

The dithioacetals are shown to undergo facile displacement reactions with primary and secondary amines to give the corresponding S,N-(17) and N,N-acetals 18 depending upon the stoichiometry of the amines used (Scheme 6). The polarized keten S,N-acetals are best prepared by treating active methylene compounds with appropriate isothiocyanates in the presence of base followed by alkylation (Scheme 6).[26] These polarized keten S,N- and N,N-acetals, which are either stable solids or viscous semisolids, were also found to be useful intermediates for construction of a variety of heterocyclic ring systems. They serve as useful three carbon fragments for the synthesis of substituted aminoheterocycles (Scheme 7) with alkylamino, arylaminosubstituted 1-N-azacycloalkyl groups by reaction with binucleophiles.[13,27-29] Some of these



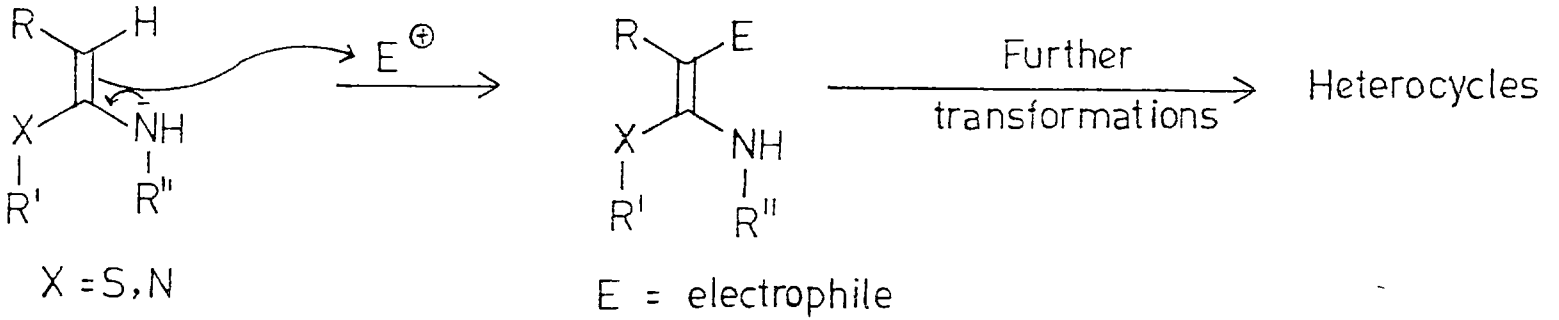
17, 18, R = Aroyl, acyl, CO_2Et, CN, $CONH_2$, NO_2 etc.
R' = H, aryl, alkyl, aroyl, acyl, CO_2Et, CN, $CONH_2$, NO_2 etc.
R'' and / or R''' = alkyl, aryl, $-(CH_2)_{\overline{n}}$

Scheme 6



17 19

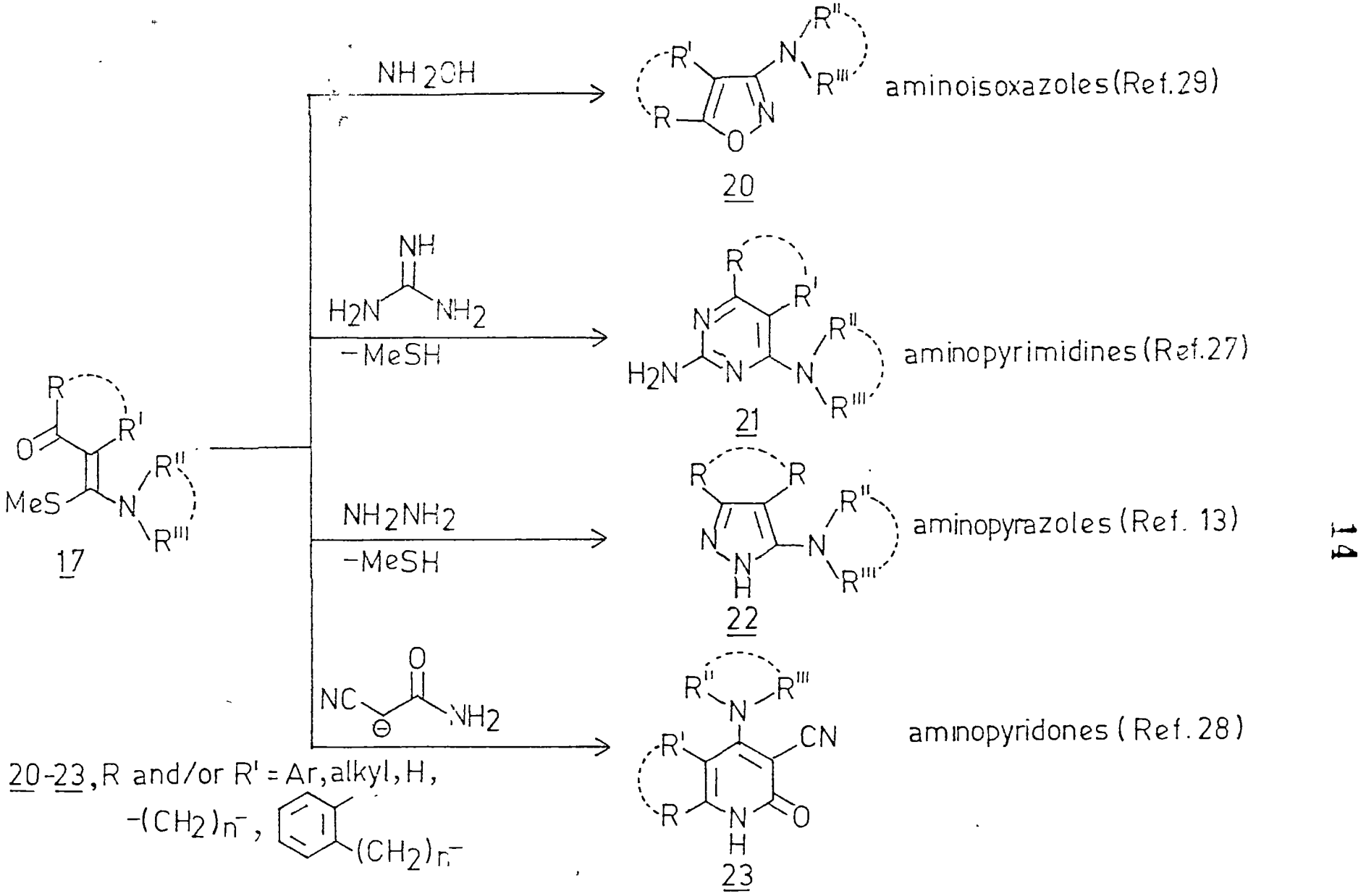
S,N-acetals are three carbon fragments for synthesis of aminoheterocycles



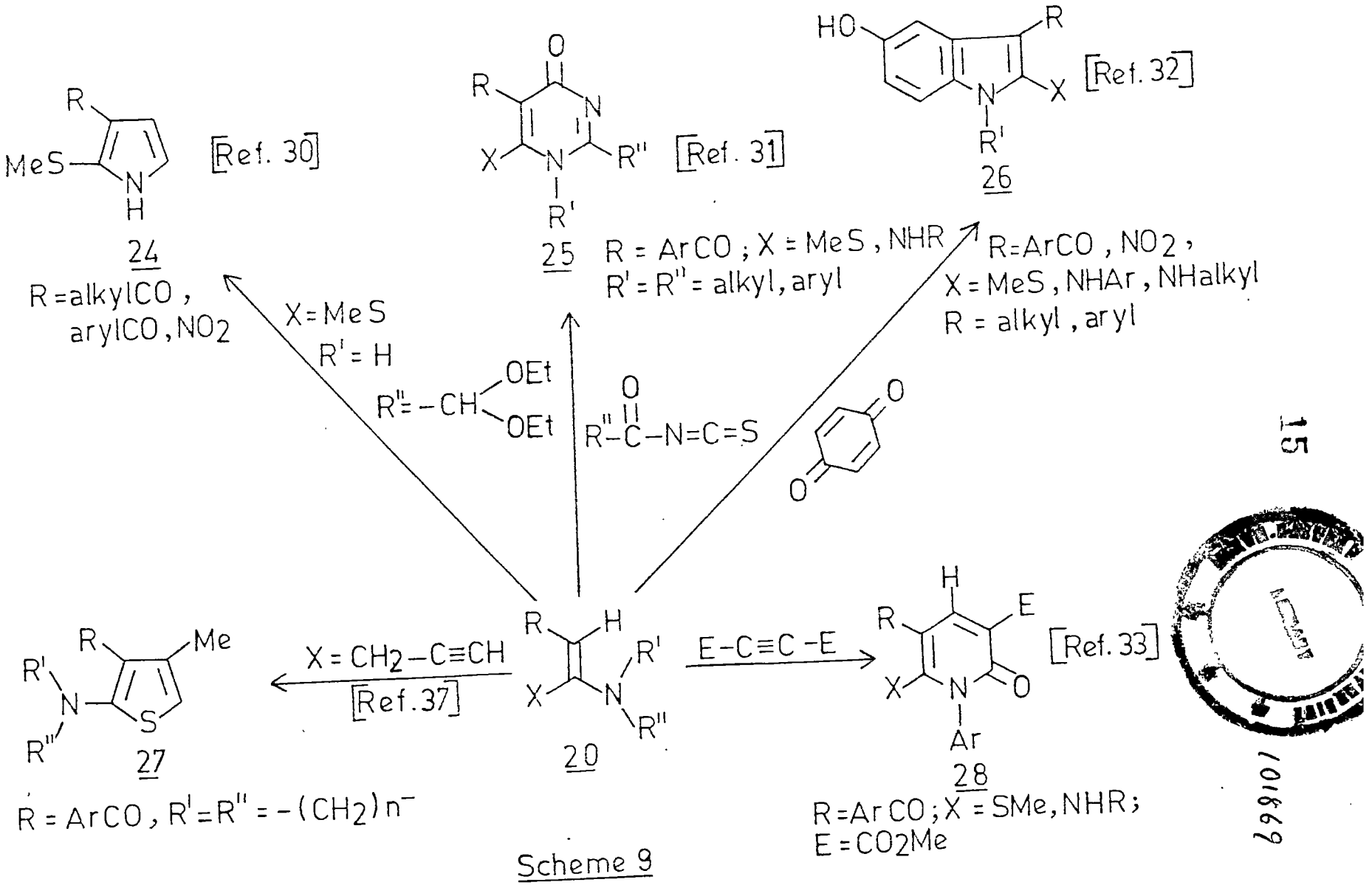
S,N and N,N-acetals as functionalized enamines and enaminones

Scheme 7

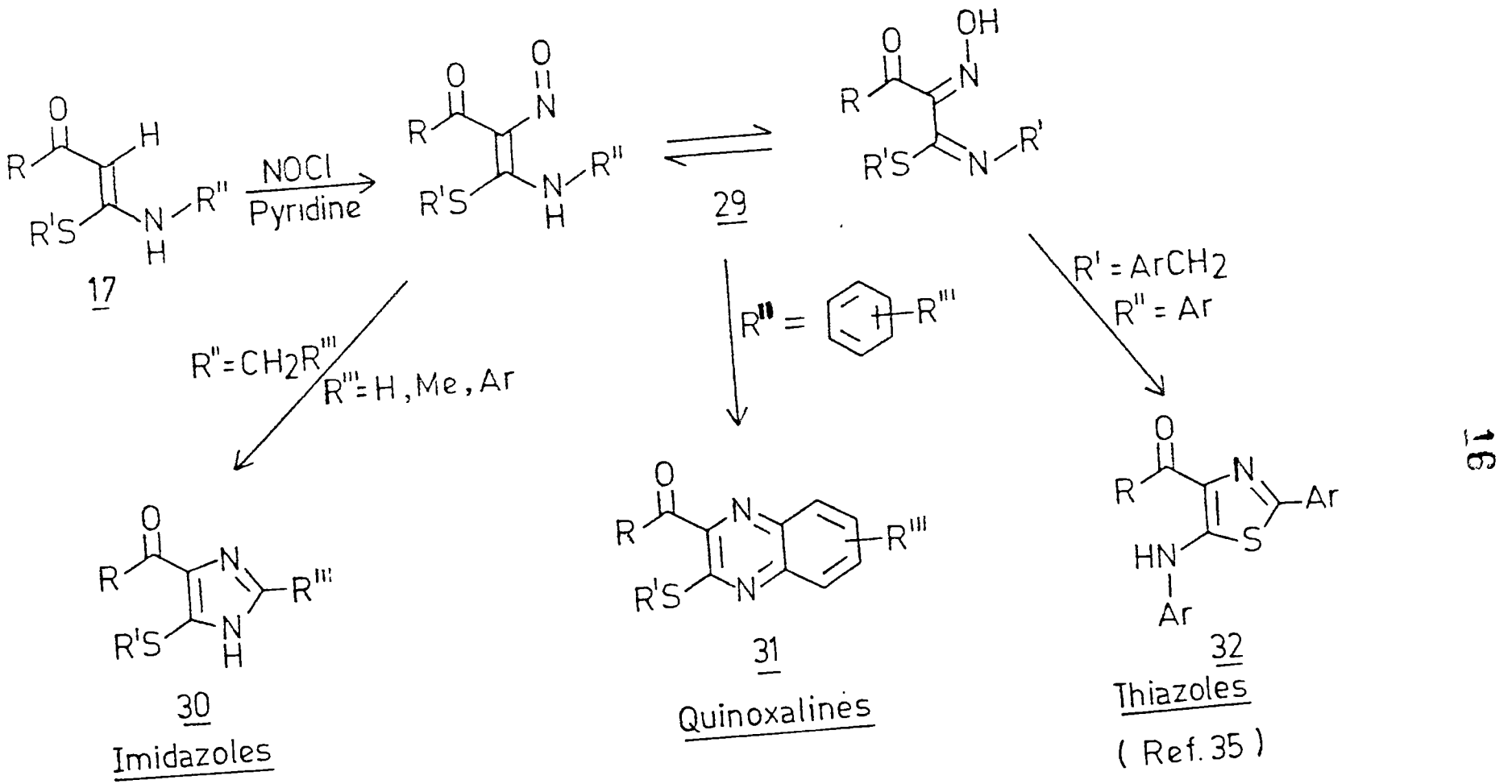
transformations which are achieved in this laboratory are shown in the scheme 8. Similarly these polarized keten S,N- and N,N-acetals represent novel class of stable functionalized enaminones, enaminoesters, enaminonitriles or polarized enamines. This behaviour of S,N- and N,N-acetals is manifested in their reactions with compounds having activated multiple bonds (acetylenic ester, quinone, aroylisothiocyanate, nitrosylchloride and nitrosobenzene and thionylchloride at electron reach β-carbon (with respect to amine) leading to the synthesis of a wide variety of amino and alkylthioheterocycles.[30-39] (Scheme 7) Some of these transformations achieved in this laboratory are shown in the scheme 9. From the foregoing discussions it is evident that the polarized keten S,S-, S,N- and N,N-acetals which can be prepared from a large variety of active methylene ketones can serve as building blocks for the construction of novel heterocyclic ring systems. In the present investigation, the behaviour of a few α-oxoketen S,S-acetals derived from acyclic and cyclic ketones and some S,N-acetals derived from pyrazolone towards dimethylacetylenic ester,[40] has been studied. The results of these studies with appropriate mechanism of the formation of the products have been discussed in Chapter II. The oxidation of imines, enamines and enamino-


NH2OH
aminoisoxazoles (Ref.29)
20
NH
H2N NH2
−MeSH
aminopyrimidines (Ref.27)
21
NH2NH2
−MeSH
aminopyrazoles (Ref. 13)
22
NC NH2
aminopyridones (Ref. 28)
23
17
MeS
20-23, R and/or R' = Ar, alkyl, H,
-(CH2)n-, (CH2)n
R and/or R''' = Ar, alkyl, H -(CH2)n-, -(CH2)n-X-(CH2)n-

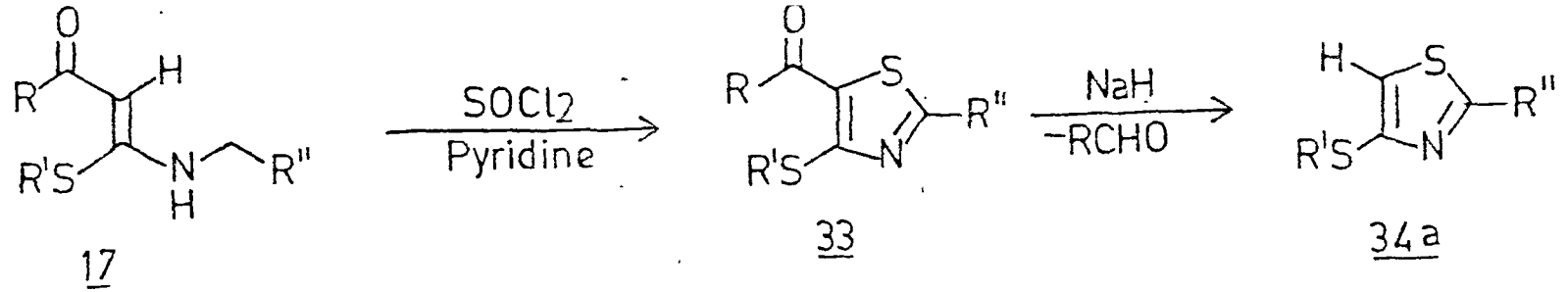
Scheme 8



Scheme 9

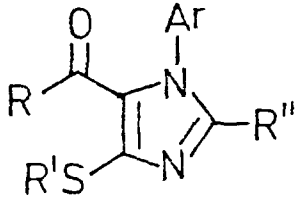

NOCl
Pyridine
17
29
R" = CH2R'''
R''' = H, Me, Ar
R" = Ar
R' = ArCH2
30
Imidazoles
31
Quinoxalines
32
Thiazoles
(Ref. 35)

Scheme 10



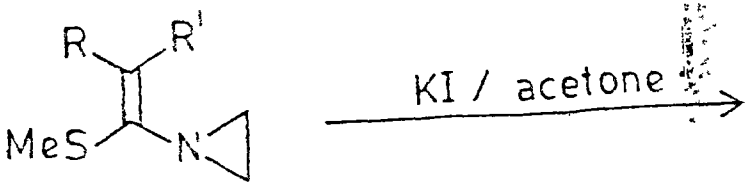
17 33 34a

33, 34a, R = aryl, alkyl
R' = alkyl
R'' = aryl, CO_2Et
[Ref. 34]



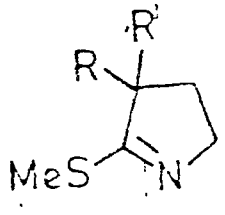
34 — 34, R = aryl, alkyl; R' = alkyl; R'' = H, Me, aryl Ref. [35, 36]

Scheme 11



35

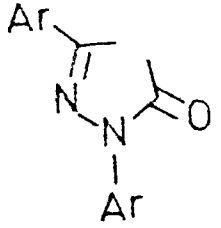
KI / acetone

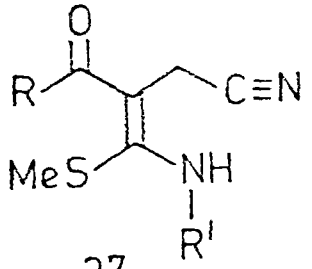


36

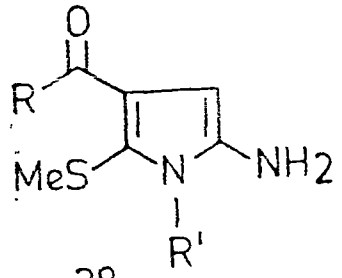
[Ref. 12] A. Kumar, H. Ila and H. Junjappa, J.C.S. Chem. Comm., 592 (1976).

35, 36, R and/or R' = CO_2Me, CN, $CONH_2$,





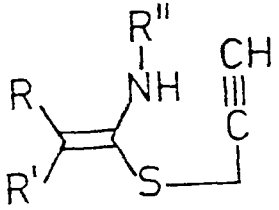
37



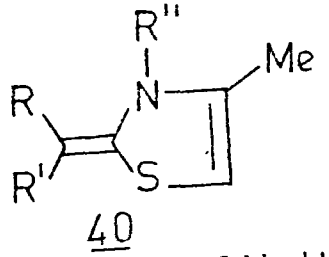
38

[Ref. 38]

37, 38, R = substituted aryl; R' = Me, Et, cyclohexyl etc.



39



40

[Ref. 39]

R and/or R' = ArCO, MeCO; Ar, CN, H; R'' = alkyl, aryl

Scheme 12

esters with lead tetraacetate have been extensively studied in recent years to give a variety of products. In the Chapter III of the thesis a detailed investigation on the LTA oxidations of a few representative α-oxoketen S,N-acetals derived from ketones and α-cyano S,N-acetals derived from arylacetonitriles has been carried out. These reactions yielded products of either α-acetoxylation or oxidative dimerization. The iminoacetates obtained by LTA oxidations of the corresponding α-cyano-α-arylketen S,N-acetals were subsequently cyclized to novel indole derivatives in the presence of borontrifluoride etherate. Thus a novel approach for a few indole derivatives has been developed which is capable of wide applications. The structures of all the products formed were determined with the help of analytical data. The probable mechanism for the formation of these products have also been suggested.

The preliminary studies of the reactions of α-oxoketen S,N-acetals with guanidine and hydrazine to give the corresponding 4-substituted aminopyrimidines and 3(5)-amino-pyrazoles respectively have been reported earlier.[41,42] In the chapter IV of the thesis a detailed investigation of these reactions to develop a general synthetic method[43,44] by taking S,N-acetals derived from a variety of amines and nitriles has been carried out.

R E F E R E N C E

1. D. Borrmann, in Houben-Weyl, Methoden Der Organischen Chemie, B. VII/4, pp. 404, Georg Thieme Verlag, Stuttgart (1968).
2. (a) R. Gompper and W. Topftl, Chem. Berl, 95, 2861 (1962); (b) A. Thuillier and J. Vialle, Bull. Soc. Chim Fr., 2182 (1962); ibid, 1938 (1959); (c) J. Sandstrom and I. Wennerbeck, Acta. Chem. Scand. 1191 (1970); (d) I. Shakak and Y. Sasson, Tet. Lett. 4207 (1973).
3. G. Isaksson, J. Sandstrom and I. Wennerbeck, Acta. Chem. Scand, 24, 3102 (1970).
4. I. Wennerbeck, Acta. Chem. Scand., 27, 258 (1973).
5. G. Isaksson and J. Sandstrom, Acta. Chem. Scand., 27, 1183 (1973).
6. P. Yates and T.R. Lynch, Canad. J. Chem., 49, 1477 (1971) and references therein.
7. L. Dalgaard, L. Jensen and S.-O. Lawesson, Tetrahedron, 30, 93 (1974).
8. S.M.S. Chauhan and H. Junjappa, Synthesis, 880 (1974).
9. S.M.S. Chauhan and H. Junjappa, Tetrahedron, 32, 1911 (1976).
10. S.M.S. Chauhan and H. Junjappa, Tetrahedron, 32, 1779 (1976).
11. R.R. Rastogi, A. Kumar, H. Ila and H. Junjappa, J.C.S. Chem. Comm., 645 (1975).

12. A. Kumar, H. Ila and H. Junjappa, Synthesis, 324 (1976).

13. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).

14. R.R. Rastogi, A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans., 549 (1978).

15. R.R. Rastogi, A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans. I, 554 (1978).

16. A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans. 857 (1978).

17. S. Apparao, A. Rahman, H. Ila and H. Junjappa, Synthesis, 792 (1982).

18. For recent synthetic applications of these reactions by other group of workers see. R.K. Dieter and J.W. Dieter, J.C.S. Chem. Comm. 1378 (1983); R.K. Dieter and L.A. Silks, J. Org. Chem., 48, 2786 (1983) and references therein.

19. B. Myrboh, H. Ila and H. Junjappa, J. Org. Chem., 48, 5327 (1983).

20. B. Myrboh, L.W. Singh, H. Ila and H. Junjappa, Synthesis, 307 (1982).

21. B. Myrboh, C.V. Asokan, H. Ila and H. Junjappa, Synthesis, 50 (1984).

22. S. Apparao, H. Ila and H. Junjappa, Tet. Lett., 23, 971 (1982).

23. S. Apparao, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans. I, 2837 (1983).

24. S. Apparao, A. Datta, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans. I, 921 (1984).

25. S. Apparao, S.S. Bhattacharjee, H. Ila and H. Junjappa, J. Chem. Soc., Perkin Trans. I (in press).

26. For complete review on preparation and synthetic applications of polarized keten S,N- and N,N-acetals: V. Aggarwal, Ph.D. Dissertation submitted to North-Eastern Hill University, Shillong-3, Chapter I (1982).

27. A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 748 (1980).

28. V. Aggarwal, G. Singh, H. Ila and H. Junjappa, Synthesis, 214 (1982).

29. A. Rahman, J.N. Vishwakarma, R.D. Yadav, H. Ila and H. Junjappa, Synthesis, 247 (1984).

30. A. Kumar, H. Ila and H. Junjappa, J.C.S. Chem. Comm., 593 (1976).

31. V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 65 (1982).

32. V. Aggarwal, A. Kumar, H. Ila and H. Junjappa, Synthesis, 157 (1981).

33. V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 147 (1983).

34. A Rahman, H. Ila and H. Junjappa, Synthesis, 000 (1984).

35. A. Rahman, H. Ila and H. Junjappa, J.C.S. Chem. Comm., 430 (1984).

36. A. Rahman, R.T. Chakrasali, H. Ila and H. Junjappa, Ind. J. Chem., 000 (1984).

37. V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 147 (1983).

38. S. Apparao, H. Ila and H. Junjappa, Synthesis, 65 (1981).

39. S.S. Bhattacharjee, C.V. Asokan, H. Ila and H. Junjappa, Synthesis, 1062 (1982).

40. J.N. Vishwakarma, H. Ila and H. Junjappa, J.Chem. Soc., Perkin Trans. I, 1099 (1983).

41. A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 748 (1980).

42. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).

43. J.N. Vishwakarma, S. Apparao, H. Ila and H. Junjappa, Ind. J. Chem., 000 (1984).

44. J.N. Vishwakarma, B.K. Roy Chowdhury, H. Ila and H. Junjappa, Ind. J. Chem., 000 (1984).

CHAPTER II

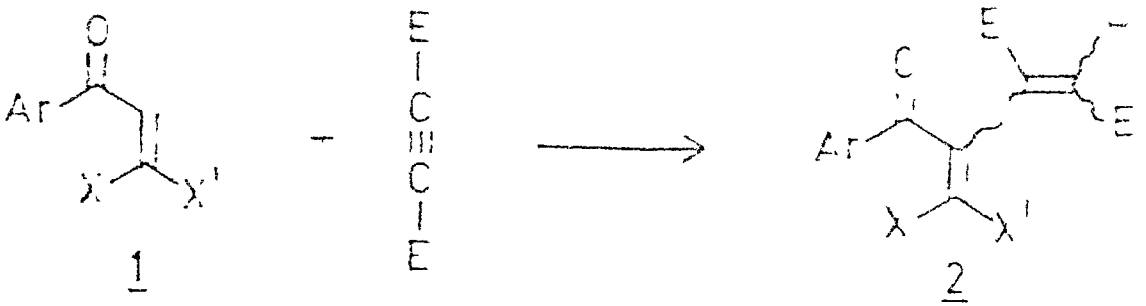
REACTIONS OF POLARIZED KETOKETEN-S,S- AND S,N-ACETALS WITH DIMETHYLACETYLENE DICARBOXYLATE*

II. 1 INTRODUCTION

We have shown in our earlier work[1] that the polarized ketoketen S,N- (1a) and N,N-acetals (1b) derived from primary aromatic and aliphatic amines react with dimethylacetylene dicarboxylate (DMAD) at α-carbon to give 1:1 Michael adducts 2 (Scheme 1). Further, the adducts 2 derived from N,N-anilino-acetals (X=X'=ArNH) undergo intramolecular cyclization in the presence of triethylamine (in refluxing methanol) to give the

---

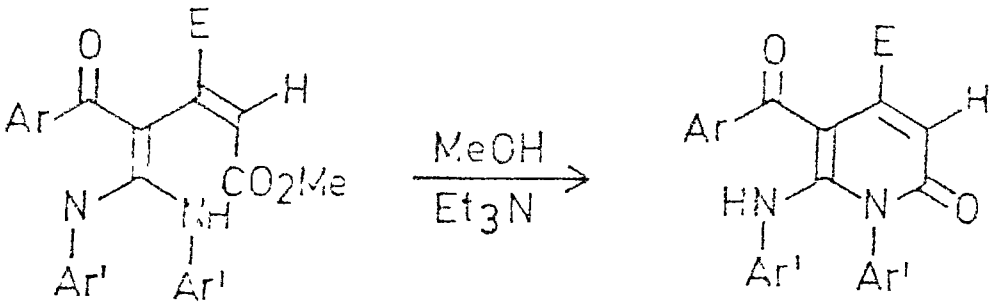
* J.N. Vishwakarma, H. Ila and H. Junjappa, J.Chem. Soc., Perkin, Trans. I, 1099 (1983).



1 2

1,2a X = MeS, X' = Ar'NH or EtNH

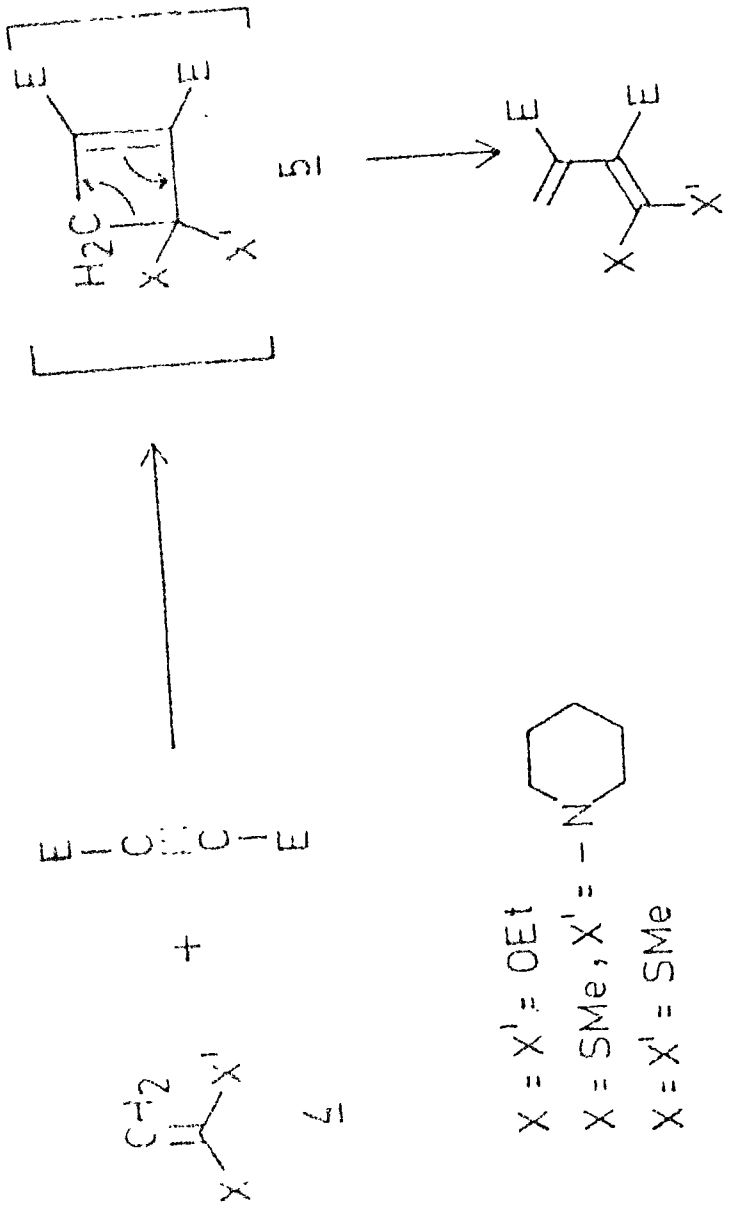
1,2b X = X' = Ar'NH or EtNH



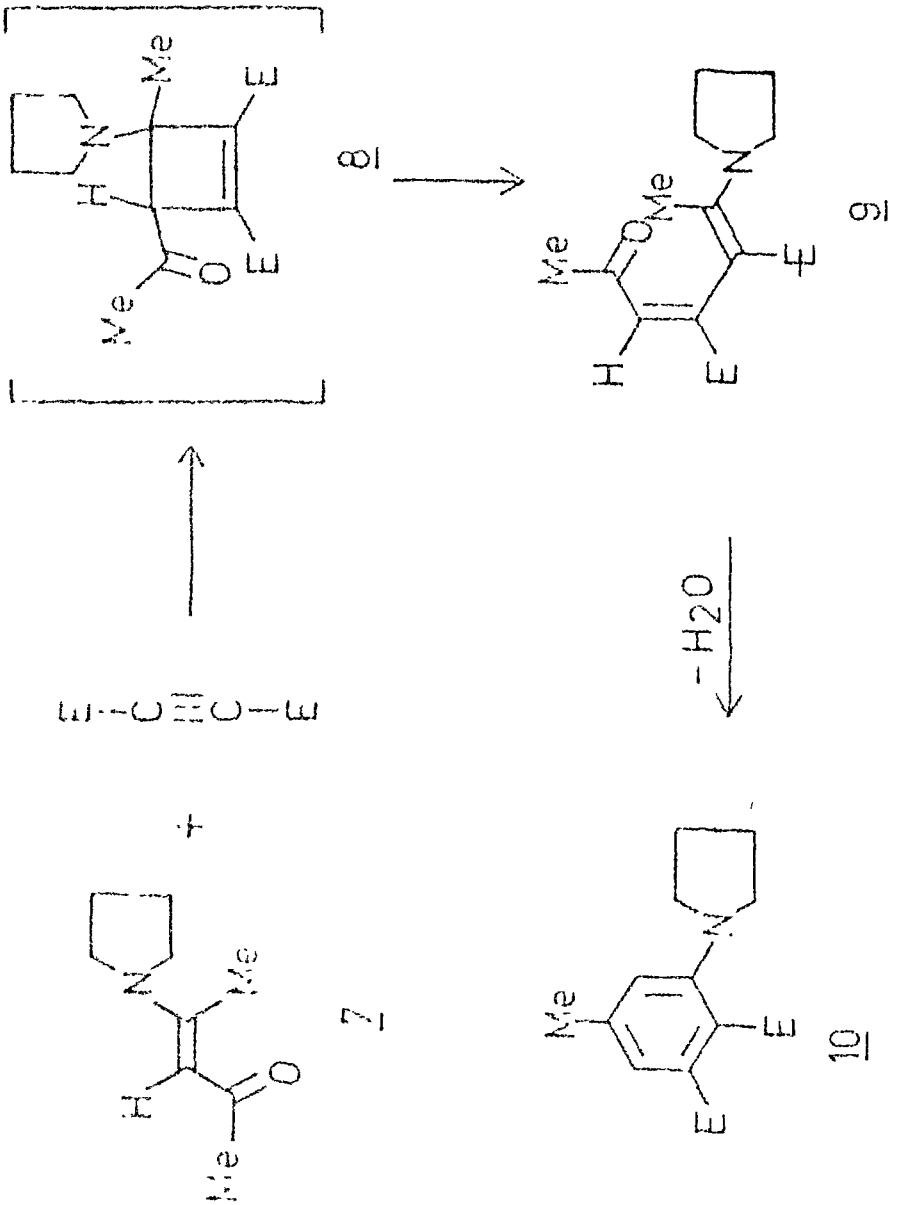
2 3

Scheme 1

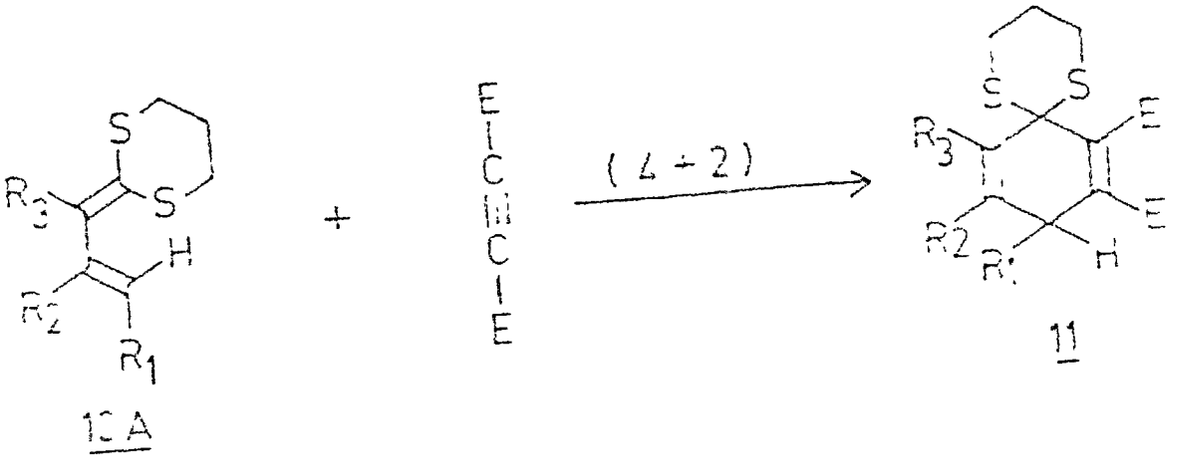
corresponding 1-N-aryl-2-arylamino-3-aroyl-4-methoxycarbonyl-2(1H)-pyridones 3 (Scheme 1). Our literature survey at this stage revealed that the reactions of simple keten O,O- S,S-, O,N, S,N- and N,N-acetals 4 (derived from secondary cyclic amines) with dimethylacetylenecarboxylate yield dienes 6 (Scheme 2) formed by initial [2+2] cycloaddition of these acetals with DMAD and subsequent ring opening of cyclobutene intermediates.[2-5] The reaction of enaminone 7 with DMAD on the otherhand gives aromatic diester 10 which is formed by intramolecular cyclodehydration of initially formed dienaminone 9 (Scheme 3).[6] The conjugated vinylketen O,O-acetals and dithioacetals 10A are reported to undergo either [4+2] cyclo-addition with DMAD to give 11 (Scheme 4) or the corresponding open chain Michael adducts 13 (Scheme 5).[7,8] Similarly thioacylketendithioacetals 14 react with dimethylacetylene dicarboxylate and other dienophiles to give the corresponding Diel's-Alder adducts 15 and 17 in good yields (Scheme 6).[9-11] However the behaviour of polarized ketoketendithioacetals with dimethylacetylene dicarboxylate has received no attention and their easy accessibility from a wide variety of active methylene compounds warrants a systematic investigation. The present study was therefore undertaken as a part of our interest in the chemistry of ketoketendithioacetals (Chapter I) and the results of the



Scheme 2

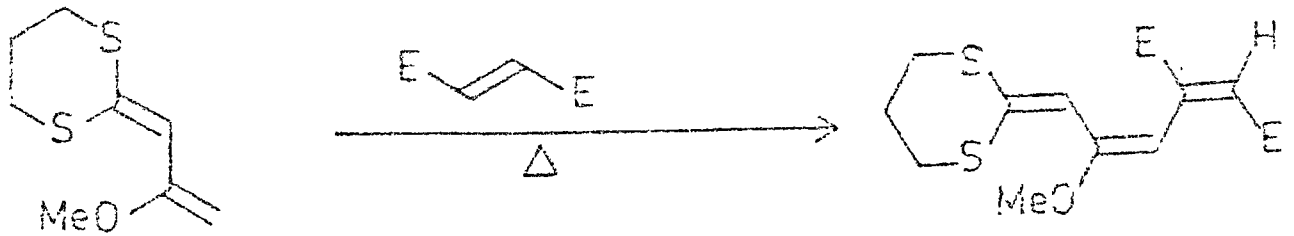


Scheme 3



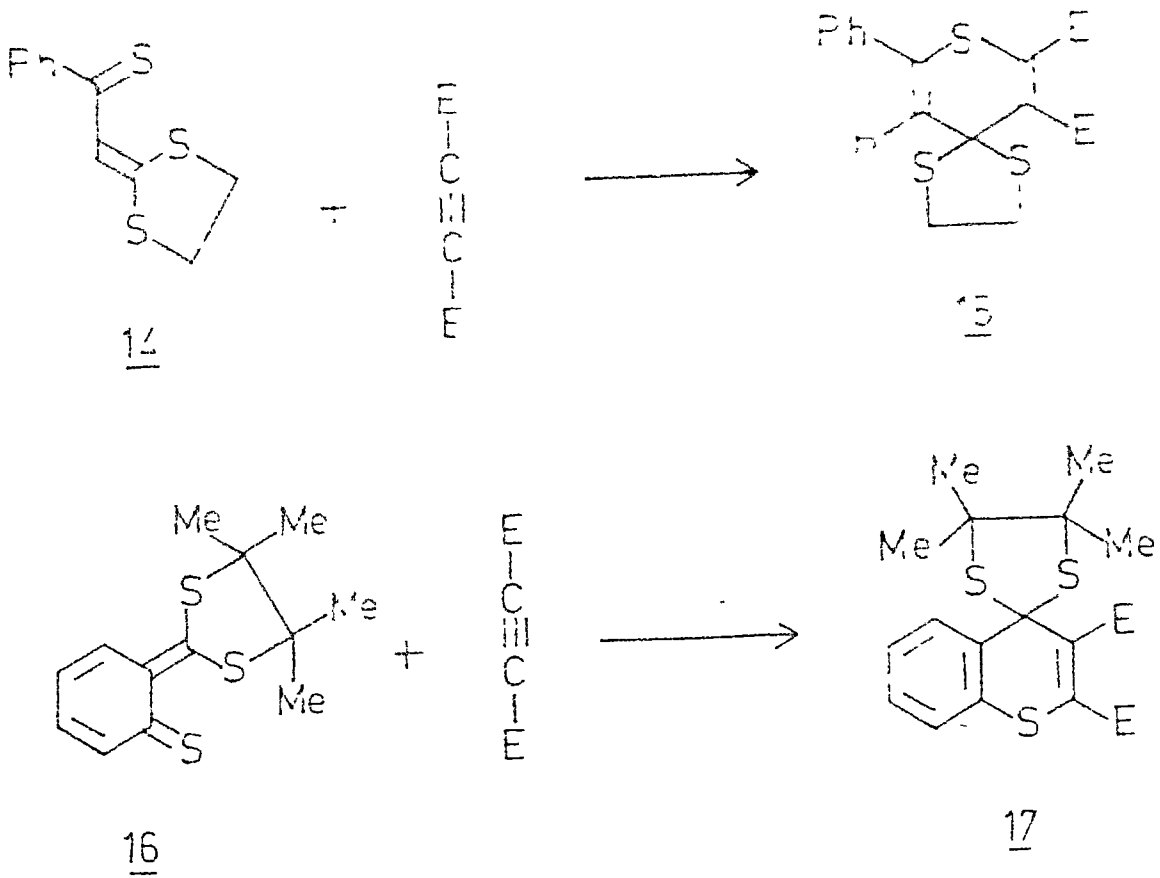
$R_1, R_2, R_3, = CH_3, H, Ph, -(CH_2)_4-$ etc

Scheme 4



12 13

Scheme 5



14 15

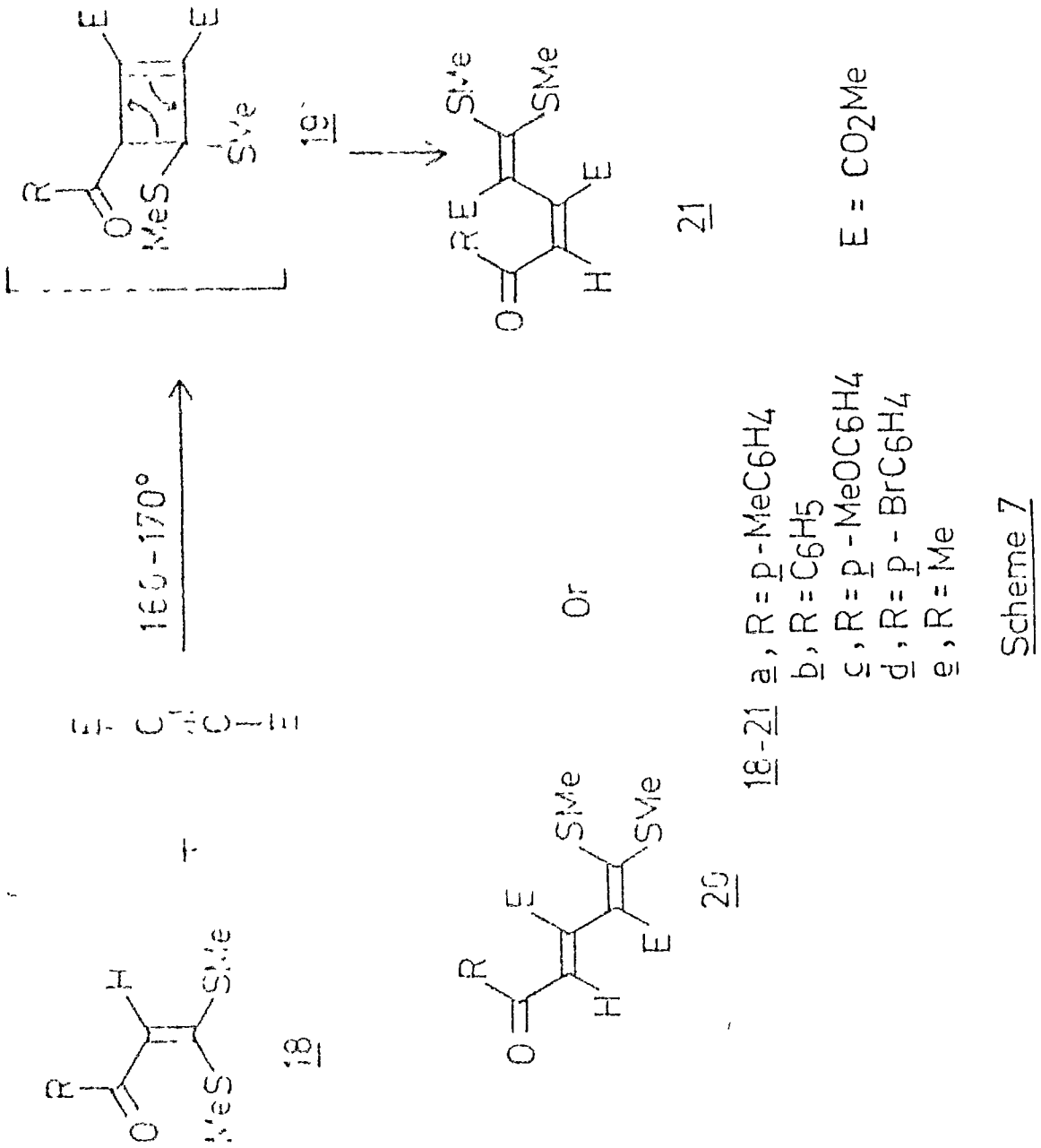
16 17

Scheme 6

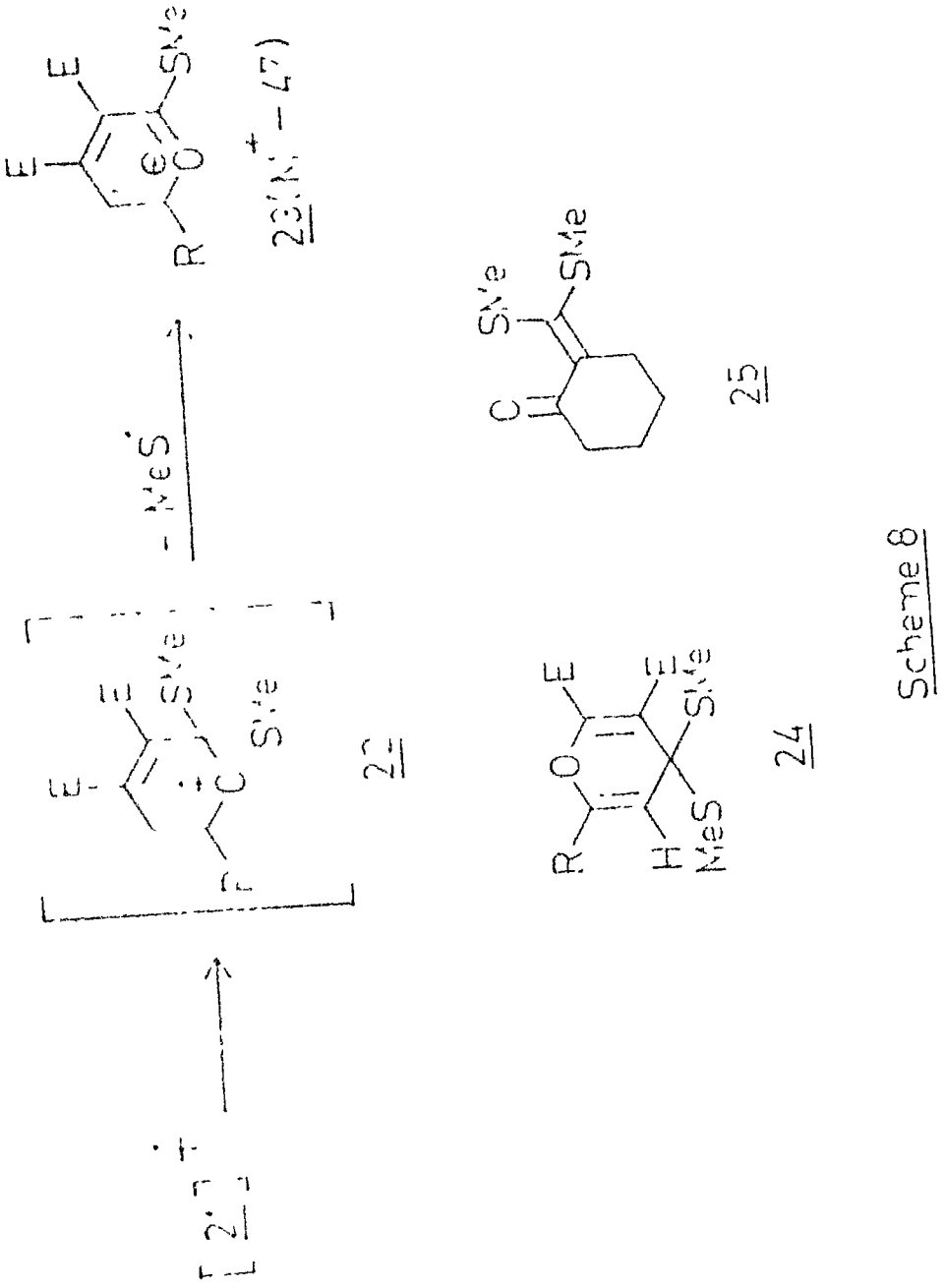
of dimethylacetylene dicarboxylate with ketoketendithioacetals and ketoketen-S,N-acetals are described in this chapter.

II.2 RESULTS AND DISCUSSIONS

When the ketoketendithioacetals 18a derived from p-methylacetophenone was reacted with excess of DMAD in refluxing benzene, it was recovered unchanged. However 18a was found to react with DMAD in refluxing xylene and after 20 hr, a pale coloured solid was obtained in 20% yield, which was found to be 1:1 adduct. The yield of the product was further improved to 60% when 18a and DMAD were heated neat at 170-180°C. The 1:1 adduct was characterized as diene 21a on the basis of spectral and analytical data (Scheme 7). Thus 21a analysed for $C_{18}H_{20}O_5S_2$ and its mass spectrum exhibited extremely weak (3%) molecular ion peak at m/z 380 (M^+), while the base peak (100%) was present at m/z 333 (M^+-47), which was assigned to the ion 23 (R=p-MeC_6H_4) (Scheme 8). Apparently the major ionic fragment arose from M^+ via electrocyclic ring closure followed by loss of a methylmercapto group (Scheme 8). The infra-red spectrum (KBr) of 21a showed strong absorption peaks at 1728, 1708 and 1630 cm^{-1}, which were assigned to two methoxy carbonyl groups (non-conjugated and conjugated) and aromatic carbonyl group respectively. The presence of strong band at 1630 cm^{-1} due to


E
E
SMe
R
O
MeS
19
SMe
SMe
E
RE
O
H
21
E = CO2Me
160-170°
Or
18-21 a, R = p-MeC6H4
b, R = C6H5
c, R = p-MeOC6H4
d, R = p-BrC6H4
e, R = Me
H
SMe
R
O
MeS
18
SMe
SMe
E
R
O
H
20

Scheme 7



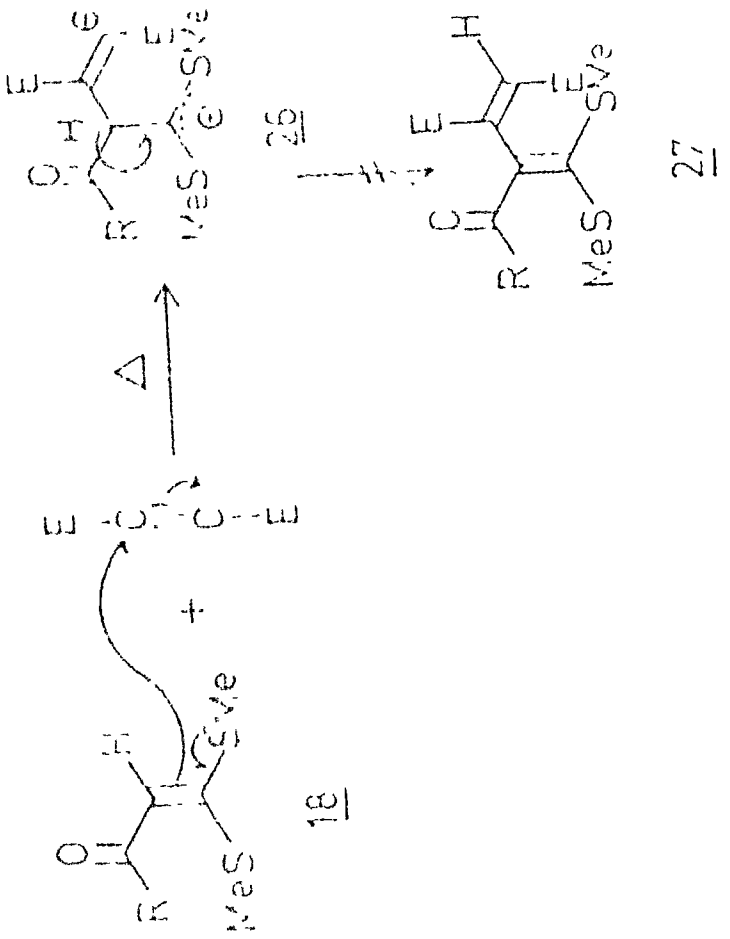
Scheme 8

aromatic carbonyl group supports the open chain structure ruling out the formation of the [4+2] adduct 24 (Scheme 8). Further structural proof for 21a was obtained from its ^{1}H-n.m.r. spectrum ($CDCl_3$), which showed two singlets at δ 2.20 (3H) and δ 2.35 (3H), which were assigned to two methylmercapto groups located in different environments while the other singlet at δ 2.40 (S, 3H) was assigned to aromatic methyl group. Presence of two singlets at δ 3.65 (3H) and 3.85 (3H) due to two methoxycarbonyl groups further supported the 1:1 adduct structure, while the aromatic protons appeared as A_2B_2 multiplet (4H) at δ 7.05-7.60, of the two possible geometrical isomers 20a and 21a, the isomeric structure 21a was assigned on the basis of the chemical shift value of the vinylic proton. Thus ^{1}H-n.m.r. signal for the vinylic proton which appeared at δ 6.60 in the n.m.r. spectrum of 18a, was shifted to lower field (7.40, S, 1H) indicating strong deshielding due to cis methoxycarbonyl group on the adjascent carbon atom which is possible in the isomer 21a and not in 20a.

The adduct 21a is apparently formed by initial [2+2] cyclo-addition of 18a and DMAD and subsequent cleavage of cyclobutene intermediate 19a (Scheme 7). The ketendithio-acetals (18b-e) similarly reacted with DMAD under identical

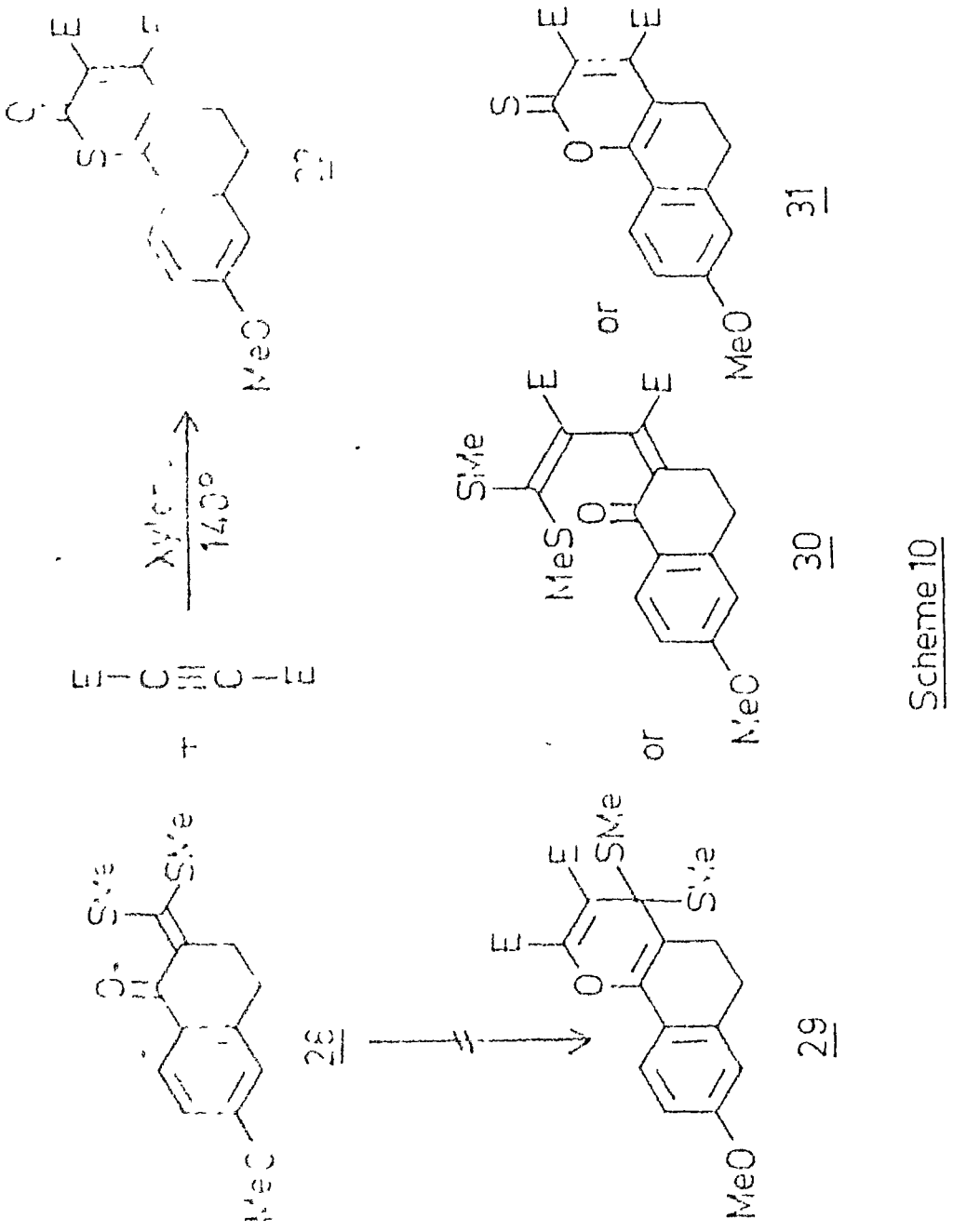
conditions to yield the novel push-pull dienes 21b-e (Scheme 7) respectively in 52-58% overall yields and no trace of [4+2] adducts were obtained in any case. Thus these results are similar to the earlier reports of formation of linear dienes by [2+2] cycloadditions of simple keten θ,O; S,S; S,N- and N,N-acetals with DMAD. The diene structure 27 formed by nucleophilic addition of α-carbon of 18 on DMAD in Michael-wise manner was also ruled out on the basis of earlier studies (Scheme 9). The spectral and analytical data of 21b-e are described in Table 1 and 2 respectively which are in conformity with the assigned structures. The mass spectral fragmentations of all the dienes 21b-e showed extremely weak molecular ion peaks while the base peaks were present at (M^+-47) due to ions 23 (Scheme 8).

The cyclic ketendithioacetal 25 derived from cyclohexanone (Scheme 8) appeared to be good candidate for [4+2] cycloaddition with DMAD. However the reaction of 25 and DMAD did not yield any identifiable product under varying conditions. Either the unchanged 25 was recovered, under mild conditions or an intractable tar was obtained at higher temperatures. Similarly 28 derived from 6 -methoxytetralone and DMAD did not react under mild conditions, while they gave a bright yellow crystalline solid in low yield (16%), when the reactants were heated in a



Scheme 9

steel bomb in xylene. The product thus obtained was not the expected 1:1 adducts 29 or 30 formed either by [4+2] or [2+2] cycloadditions, respectively (Scheme 10). On the otherhand it was characterized as the thiapyran-2-one 32 on the basis of its analytical and spectral data (Scheme 10). It showed in its mass spectrum, the molecular ion peak at m/z 360 (72%), while its analytical data was in agreement with the molecular formula $C_{18}H_{16}O_6S$. The i.r. spectrum of 32 showed two strong absorption bands at 1740 and 1720 cm^{-1}, which were assigned due to ester carbonyl groups. The other strong band at 1625 cm^{-1} was assigned to the thiapyran-2-one carbonyl group, which is in agreement with the reported values (thiapyran-2-ones exhibit carbonyl peaks between 1620-1634 cm^{-1}).[12,13] The ^{1}H-n.m.r. spectrum ($CDCl_3$) of 32 exhibited an A_2B_2 quartet at δ 3.08 (4H) due to four methylene protons. The three closely spaced singlets which appeared at δ 3.80 (3H); 3.85 (3H) and 3.86 (3H) were assigned to methoxy and two methoxycarbonyl protons. The aromatic protons exhibited signals at δ 6.79 (1H, d, J=2.5 Hz, H-4); 6.86 (1H, dd, J=7 and 2.5 Hz, H-2) and δ 8.02 (1H, d, J=7Hz, H-1). The u.v. spectrum (MeOH) of 32 showed absorption bands at λ max: 233 (log ϵ, 4.08); 310 (4.15); 336 (4.20) and 348 (Sh) nm (3.99) thus ruling out the alternative pyran-2-thione structure 31 (Scheme 10), which has a characteristic

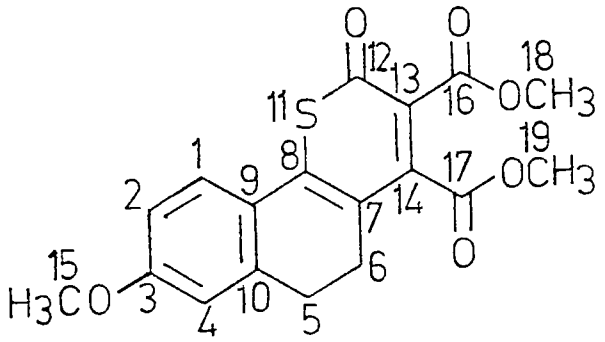


Scheme 10

absorption in the visible region (above 400 nm).[14,15] Final confirmation of the thiapyran-2-one (32) was derived from its ^{13}C n.m.r. spectrum (Figure 1). The characteristic signal at δ 184 was assigned to the thiopyran carbonyl carbon, while the thiocarbonyl carbon of pyran-2-thione is reported to appear at δ 196.[16]

The probable mechanistic pathway for the conversion of 28 into 32 is shown in scheme 11, which appears to involve an interesting series of rearrangements. The formation of cyclobutene 33 via [2+2] cycloaddition followed by ring opening and electrocyclic ring closure in succession to give the intermediate 35 is logical. The intermediate 35 appears to undergo either an interesting concerted 1,5-suprafacial shift of the methylthio group or a stepwise elimination addition process leading to the dihydropyran intermediate 36. In the subsequent steps, the intermediate 36, which is succeptible to electrocyclic ring opening undergoes cleavage to give an activated S-methyl ester intermediate 37, which on intramolecular ring closure and elimination of dimethylsulfide yields the thiopyranone 32.

The mass spectrum of 32 exhibited an interesting fragmentation pattern. The molecular ion peak at m/z 360 (72%)

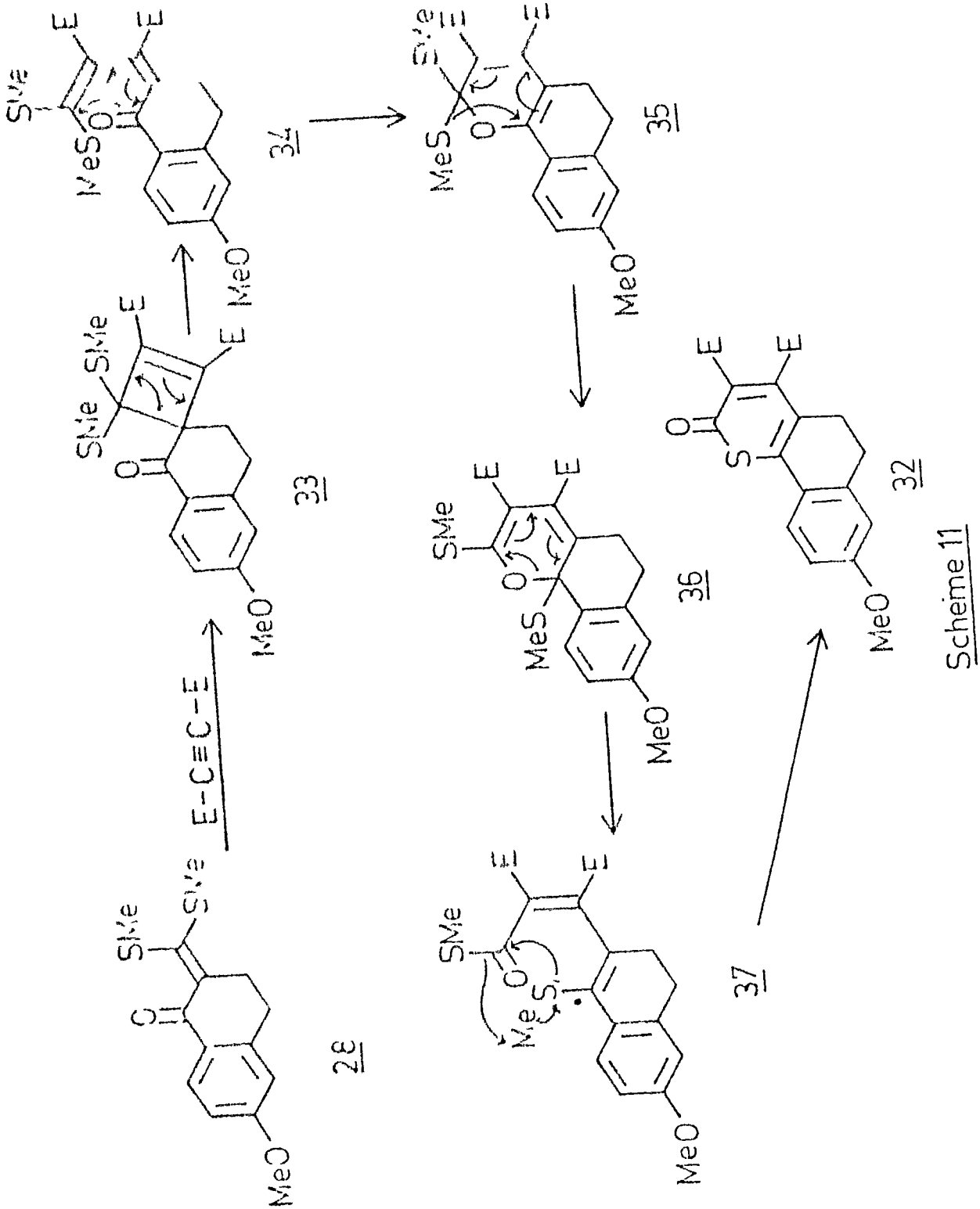


^{13}C NMR Spectrum of 32 in $CDCl_3$

(measured at 40 MHz recorded as δ)

C-1	133·5d	C-7	129·3	C-14	146·2
C-2	112·5d	C-8	144·5	C-15	55·3
C-3	161·0	C-9	136·0	C-16	163·4
C-4	114·9d	C-10	143·1	C-17	164·8
C-5	34·5t	C-12	184·0	C-18	52·6q
C-6	26·9t	C-13	138·9	C-19	52·6q

Figure 1

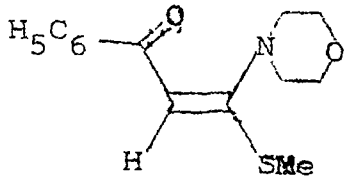


Scheme 11

was followed by most intense peak at m/z 328 (M^+-32, 100%, $C_{17}H_{12}OS$) which is possibly due to the ion 39 (Scheme 12). It is pertinent to note that the thiapyran-2-ones undergo facile loss of carbon monoxide during electron impact.[17] Thus although, the loss of methanol in preference to the carbon monoxide in 32 appears to be unusual, the presence of adjacent methoxycarbonyl groups probably favours elimination of methanol[18] to give the ion 39 as shown in the scheme 12.

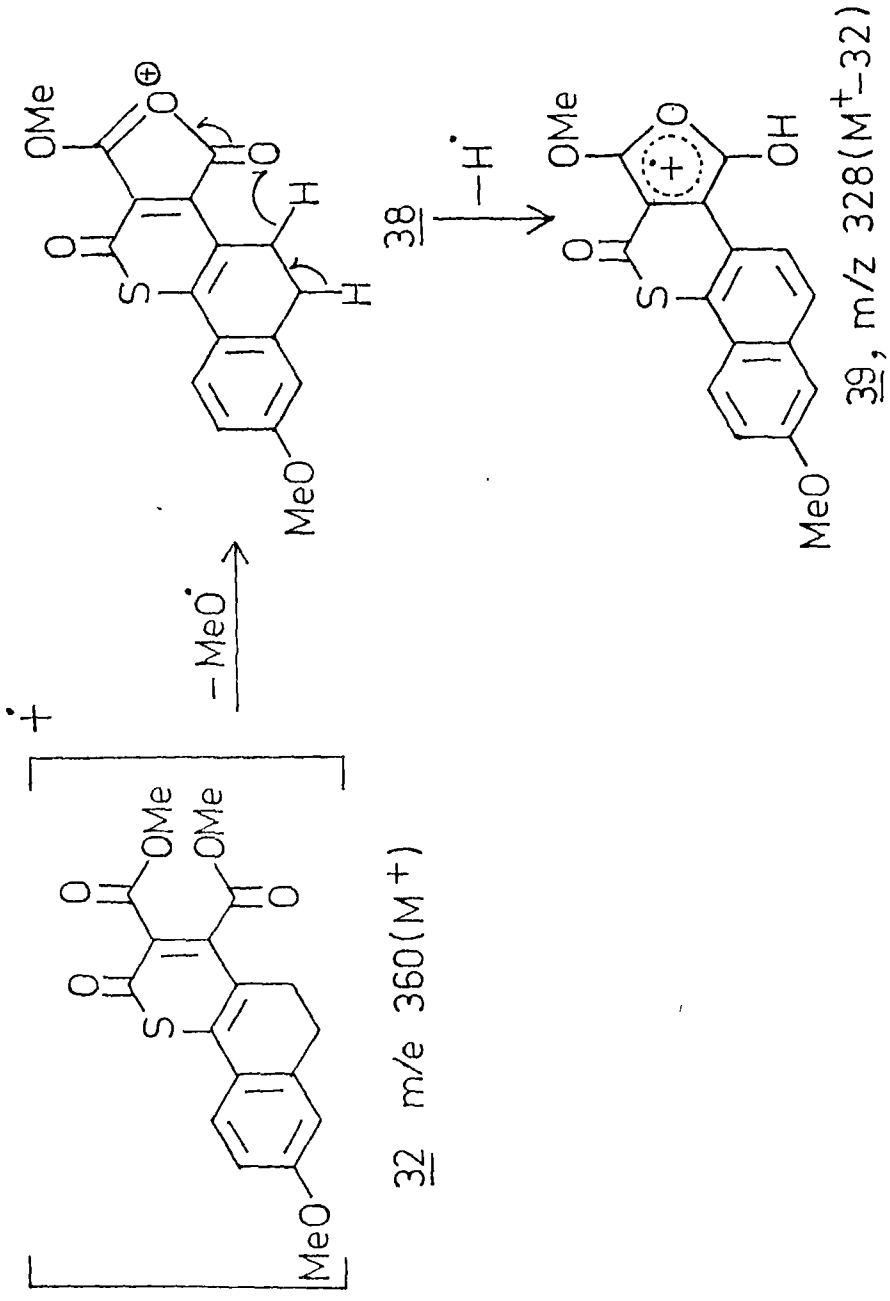
The attempted reaction of DMAD with ketoketendithioacetal 40 derived from pyrazolone did not yield any identifiable product.

The reaction of S,N-acetal 40A derived from cyclic secondary amines was next investigated. When 40A and DMAD were



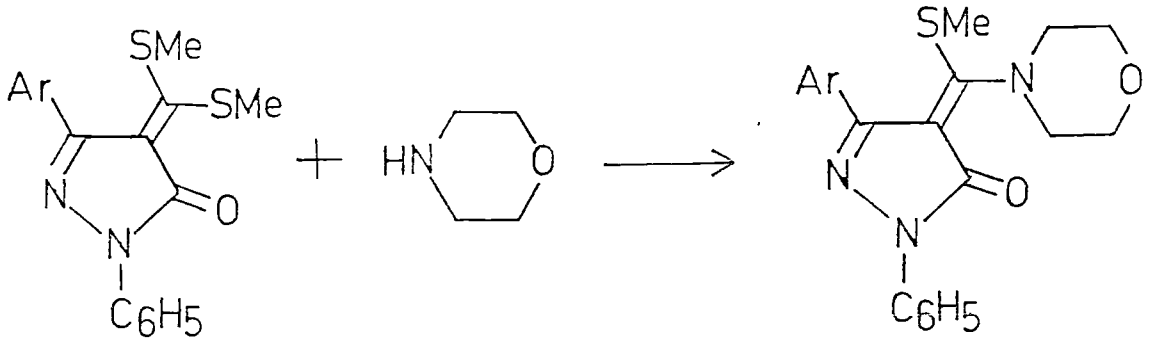
40A

reacted in refluxing xylene the starting material was found unchanged (tlc). However when 40A and DMAD were reacted neat at 150-160°C, although the starting material disappeared completely, no well defined product could be isolated from the complex reaction mixture.



Scheme 12

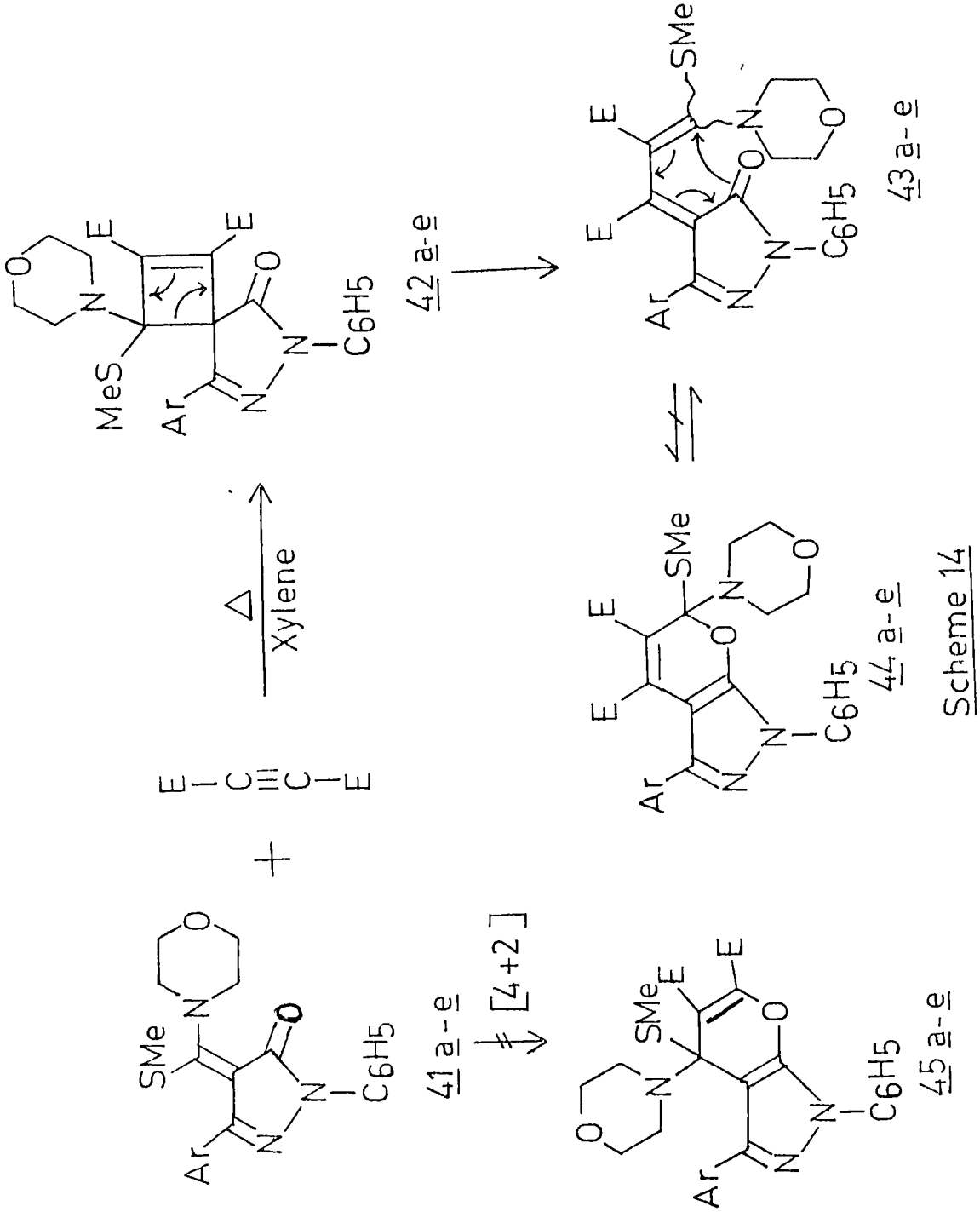
The reactions of S,N-morpholinoacetals 41a-e with dimethylacetylenedicarboxylate were next investigated. The S,N-acetals 41a-e were obtained by replacement of methylthio group of the corresponding pyrazolone ketendithioacetals 40a-e by one equivalent of morpholine (Scheme 13). When 41a was refluxed with one equivalent of DMAD in xylene for 6-8 hrs, after work-up the reaction mixture yielded light yellow crystalline solid (34%) which was characterized as the diene 43a formed by [2+2] cycloaddition followed by subsequent ring opening of the resulting cyclobutene intermediate 42a (Scheme 14). The adduct (43a) was analyzed for $C_{27}H_{27}N_3O_6S$ and its i.r. spectrum exhibited three strong peaks at 1728, 1705 and 1648 cm^{-1} due to two esters and pyrazolone carbonyl groups respectively. The presence of strong peak at 1648 cm^{-1} due to pyrazolone carbonyl group (1640 cm^{-1} in 41a) rules out the alternate pyrazolopyrone S,N-acetal structures 44a or 45a (Scheme 14). The n.m.r. spectrum ($CDCl_3$) of 43a exhibited a singlet (3H) at δ 2.13 due to methylthio group, while the two singlets (3H each) at δ 3.58 and δ 3.71 were assigned to two methoxycarbonyl groups. The morpholinomethylene protons appeared as broad multiplet (8H) spread over between δ 3.30-4.50, while the two multiplets at δ 7.06-7.55 (8H) and δ 7.76-8.18 (2H) were assigned to aromatic protons. The other substituted pyrazolone S,N-acetals



40 41

40,41 a, Ar = C_6H_5
b, Ar = p-MeC_6H_4
c, Ar = p-$MeOC_6H_4$
d, Ar = p-ClC_6H_4
e, Ar = p-BrC_6H_4

Scheme 13



Scheme 14

41b-e similarly afforded the corresponding diene S,N-acetals 43b-e in 26-31% overall yields. The structures of 43a-e were confirmed with the help of spectral and analytical data.

II.3 CONCLUSION

From the foregoing description it is apparent that the oxoketen S,S-acetals are less reactive towards acetylenicesters in comparison to the simple keten S,S-acetals which require drastic reaction conditions. The unexpected course of the reaction observed in the case of cyclic S,S-acetal 28 to give the thiapyrone derivative 32 (Scheme 10) is also probably due to drastic conditions employed in the reactions. Both oxoketen S,S-acetals 18 and 28 afford products formed by initial [2+2] cycloaddition instead of [4+2] cycloaddition. Similarly the S,N-acetals 41a-e, inspite of having favourable geometry for [4+2] cycloadditions, yield dienes 43a-e formed by initial [2+2] cycloadditions with DMAD.

II.4 EXPERIMENTAL

M.ps. were determined on a "Boetius" (German) apparatus and are uncorrected. The i.r. and u.v. spectra were recorded on Perkin-Elmer 297 and Beckmann 26 spectrophotometers respectively. The NMR spectra were recorded on a Varian EM-390 spectrometer using TMS as an internal standard and the chemical shifts are expressed in δ (ppm).

The Starting Materials

The commercial samples of acetophenone, p-methylacetophenone, p-methoxyacetophenone, p-bromoacetophenone, p-chloroacetophenone, acetone, morpholine, cyclohexanone and 6-methoxytetratone were purified before use. 1,3-Diphenyl-2-pyrazolin-5-one, m.p. 128°; 1-phenyl-3-(p-methylphenyl)-2-pyrazolin-5-one, m.p. 146°; 1-phenyl-3-(p-methoxyphenyl)-2-pyrazolin-5-one, m.p. 120-22°; 1-phenyl-3-(p-chlorophenyl)-2-pyrazoline-5-one, m.p. 158-59° and 1-phenyl-3-(p-bromophenyl)-2-pyrazolin-5-one, m.p. 125-27° were prepared by the reported method.[19]

3,3-Bis(methylthio)-1-(p-methylphenyl)-2-propen-1-one (18a), m.p. 104-5;[20] 3,3-Bis(methylthio)-1-phenyl-2-propen-1-one (18b), m.p. 93°;[20] 3,3-Bis(methylthio)-1-(p-methoxyphenyl)-2-propen-1-one (18c), m.p. 100-1°;[20] 3,3-Bis(methylthio-1-(p-bromophenyl)-2-propen-1-one (18d), m.p. 106-7°;[20] 3,3-Bis(methylthio)-1-methyl-2-propene-1-one (18e), m.p. 66-7°;[21] 2-Bis(methylthio)-methylenecyclohexanone (25), b.p. 123-24;[22] 2-Bis(methylthio)-methylene-6-methoxy tetralone (28), m.p. 78°[23] were prepared by the reported procedure.

Similarly 4-bis(methylthio)methylene-5-oxo-1,3-diphenyl-4,5-dihydropyrazole (40), (40a) m.p. 150°; 4-bis(methylthio)-

methylene-5-oxo-1-phenyl-3-(p-methylphenyl)-4,5-dihydropyrazole (40b) m.p. 116°; 4-bis(methylthio)methylene-5-oxo-1-phenyl-3-(p-methoxyphenyl)-4,5-dihydropyrazole (40c), m.p. 147°, 4-bis (methylthio)methylene-5-oxo-1-phenyl-3-(p-chlorophenyl)-4-5-dihydropyrazole (40e) m.p. 121°C were prepared by the reported procedure.[24]

General procedure for the preparation of keten-S,S-acetals (18a-e), (25), (28) and (40a-e)

A mixture of ketones or the corresponding pyrazolone (0.5 mol) and carbon disulphide (0.5 mol) was added to a well stirred and cooled suspension of sodium t-butoxide (1.0 mol) in dry benzene (350 ml) and dimethylformamide (100 ml) and the reaction mixture was allowed to stand at room temperature for 4 hr. Methyl iodide (1.1 mol) was gradually added with stirring and external cooling and the reaction mixture was allowed to stand for 4 hr and then refluxed on a water bath for 3 hr. The mixture was poured on crushed ice and benzene layer was separated The aqueous portion was extracted with benzene and the combined extracts was washed with water dried (Na_2SO_4) and concentrated to give the dithioacetals which were purified by crystallisation or by column chromatography.

1-Aryl-3-methylthio-3-morpholino-1-oxo-2-propene (40A) was prepared in two steps by methylation of the corresponding

thiomide. The thiomide, m.p. 127-9°[25] was prepared by the reaction of morpholine with the corresponding dithioester.[26]

Preparation of 5-oxo-1,3-disubstituted-4-[(methylthio-N-morpholino)-methylene]-Δ^2-pyrazolines (41a-e); General procedure:

A solution of ketoketen-S,S-acetals (40a-e) (0.01 mol) and morpholine (0.01 mol) in dry benzene (50 ml) was stirred at room temperature for 1.5 to 2 hr (monitored by TLC) and the solvent was removed under reduced pressure. The residue thus obtained was triturated with hexane. The S,N-acetals (45a-e) were purified by recrystallysation and their physical and spectral data are given below.

5-Oxo-1,3-diphenyl-4-[(methylthio-N-morpholino)methylene]-Δ^2-pyrazoline (41a).- was prepared as yellow needles (ether-hexane), 3.2g (84%), m.p. 178-79°; IR (KBr): ν_{max} 1635 (C=O) cm^{-1}; Hnmr ($CDCl_3$): δ 2.35 (s, 3H, SCH_3), 3.81 (brS, 8H, morpholino), 7.10-7.70 (m, 8H, arom), 8.18 (dd, 2H, arom); Found: C, 66.65; H, 5.38; N, 11.25%; Calc. for $C_{21}H_{21}N_3O_2S$ (379.4); C, 66.42; H, 5.53; N, 11.07%.

5-Oxo-1-phenyl-3-(p-methylphenyl)-4-[(methylthio-N-morpholino) methylene]-Δ^2-pyrazoline (41b) was prepared as yellow needles (EtOAc-hexane); 3.3g (84%) m.p. 240-41°; IR (KBr): ν_{max} 1640 (C=O)

cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.30 (s, 3H, p-CH_3-C_6H_4); 2.36 (s, 3H, SCH_3); 3.76 (brS, 8H, morpholino), 7.01-7.76 (m, 7H, arom), 8.13 (dd, 2H, arom); Found: C, 66.88; H, 6.04; N, 10.24; Calc. for $C_{22}H_{23}N_3O_2S$ (393.4); C, 67.10; H, 5.84; N, 10.67%.

5-Oxo-1-phenyl-3-(p-methoxyphenyl)-4-[(methylthio-N-morpholino) methylene]-Δ^2-pyrazoline (41c) was prepared as yellow needles (EtoAc-hexane); 3.3% (80%), m.p. 219-20°; IR(KBr): ν_{max} 1640 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.33 (s, 3H, SCH_3), 3.83 (s, 3H, p-CH_3O-C_6H_4), 3.85 (s, 8H, morpholine), 6.83-7.61 (m, 7H, arom), 8.15 (dd, 2H, arom); Found: C, 64.13; H, 5.83; N, 10.01; Calc. for $C_{22}H_{23}O_3S$ (409.4); C, 64.48; H, 5.61; N, 10.25%.

5-Oxo-1-phenyl-3-(p-chlorophenyl)-4-[(methylthio-N-morpholino) methylene]-Δ^2-pyrazoline (41d) was prepared as yellow needles (CH_2Cl_2-hexane), 3.3g (80%), m.p. 184°; IR (KBr) ν_{max} 1648 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.28 (s, 3H, SCH_3); 3.36 (br S, 8H, morpholino), 7.33-7.66 (m, 7H, arom), 7.95 (dd, 2H, arom); Found: C, 61.19; H, 4.83; N, 10.15%.

5-Oxo-1-phenyl-3-(p-bromophenyl)-4-[(methylthio-N-morpholino) methylene]-Δ^2-pyrazoline (41e) - was prepared as yellow needles (EtOAc-hexane); 3.8g (83%); m.p. 226°; IR (KBr): ν_{max} 1646 (C=O) cm^{-1};

^{1}Hnmr ($CDCl_3$): δ 2.28 (s, 3H, SCH_3); 3.90 (br S, 8H, morpholino); 7.13-7.60 (m, 7H, arom); 8.13 (dd, 2H, arom); Found: C, 54.81; H, 4.58; N, 9.33; Calc. for $C_{21}H_{20}N_3O_2SBr$ (458.2): C, 54.99, H, 4.36; N, 9.16%.

Reaction of 2,2-Bis(methylthiovinyl)-p-methylphenyl ketone (18a) with Dimethylacetylenedicarboxylate (DMAD) in xylene: A solution of ketone (18a) (2.38g, 0.01 mol) and DMAD (3.7g, 0.22 mol) in dry xylene was refluxed for 20 hr. Xylene was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with benzene-hexane mixture (1:1) yielded dimethyl-1,1-bismethylthio-4-(p-toluoyl)-buta-1,3-diene-2,3-dicarboxylate (21a) (0.76g, 20%) as pale yellow solid which was crystallised from ether-hexane, m.p. 110-112°, spectral data given in text, (Found: C, 56-4; H, 5.55. $C_{18}H_{20}O_5S_2$ requires C, 56.84; H, 5.26%).

Reaction of Aryl (or Alkyl)3,3-Bis(methylthio)vinylketone (18a)-(18e) with dimethyl acetylenedicarboxylate:

General Procedure: A mixture of the keten dithioacetal (18) (0.01 ml) and DMAD was heated at 170-80°C for 6-7 hr until the starting material had disappeared completely (Tlc). The reaction mixture was passed through a silica gel column. Elution with benzene-hexane (1:1) yielded pure compounds (21a-e) which were

further purified by crystallisation from ether-hexane. The spectral and analytical data given in Table 1 and 2, respectively. Under similar conditions the dithioacetal 40 and S,N-acetal 40A gave a complex reaction mixture.

Reaction of 2-bis(methylthio)methylene-6-methoxy tetralone (28) with dimethylacetylene dicarboxylate (DMAD): A solution of compound (28) (2.1g, 0.008 mol) and DMAD (1.42g, 0.01mol) in dry xylene (20 ml) was heated in a sealed tube at 160-70°C for 33 hr. Xylene was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with 6% ethyl-acetate in hexane gave the compound (32) as a bright yellow crystalline solid (0.43g, 16%), m.p. 141-43°C (spectral data given in text) Found: C, 60.25; H, 4.75; S, 8.55, $C_{18}H_{16}O_6S$ requires C, 60.0; H, 4.75; S, 8.88%; m/z 360 (M^+, 72), 329 (53), 328 (100), 313 (19.7); 300 (14), 272 (14), 269 (27.7), 243 (19) and 242 (44).

Reaction of 5-oxo-3-aryl-1-phenyl-4-[(methylthio-N-morpholino) methylene]-Δ^2-pyrazoline (41a-e) with dimethyl acetylenedicarboxylate: A General Procedure: To a solution of (41a-e) (0.005 mol) in boiling xylene (30 ml) dimethylacetylene dicarboxylate (0.71g, 0.005 mol) was added and the reaction mixture was refluxed for 6-8 hr at 150-55°C. The solvent was removed under

vacuum, residue was triturated with hexane, crude product filtered off and purified by column chromatography. The compounds (43a-e) were prepared by this method and their spectral as well as analytical data are given below.

The adduct 43a was purified by chromatography on silicagel using benzene-ethylacetate (85:15) as yellow needles (EtOAc-hexane); yield 0.9g (34%), m.p. 178-80°; IR (KBr): ν_{max}: 1728, (two $\overset{O}{\overset{\|}{C}}$-$OCH_3$), 1648 (C=O) 1578 cm^{-1}; ^1H nmr($CDCl_3$): δ 2.13 (s, 3H, $-SCH_3$), 3.30-3.83 (m, 4H, morpholino) 3.58 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.0-4.50 (m, 4H, morpholino), 7.06-7.55 (m, 8H, arom), 7.76-8.18 (m, 2H, arom); Found: C, 62.48; H, 4.81; N, 7.86; Calc. for $C_{27}H_{27}N_3O_6S$ (521.5): C, 62.12; H, 5.17; N,8.05%.

The adduct 43b was purified by column chromatography on silicagel using benzene-EtOAc (60:40) as red needles (EtOAc); yield 0.7g (26%), m.p. 167-9°; IR (KBr): ν_{max}: 1730, 1708 (two $\overset{O}{\overset{\|}{C}}$-OMe), 1648 cm^{-1}; ^1H nmr($CDCl_3$): δ 2.15 (s, 3H, $-SCH_3$), 2.35 (s, 3H, p-CH_3-C_6H_4), 3.21-3.70 (m, 4H, morpholino), 3.61 (s, 3H, OCH_3) 3.75 (s, 3H, OCH_3), 3.83-4.63 (m, 4H, morpholino), 7.10-7.40 (m, 7H, arom), 7.96-8.10 (m, 2H, arom); Found: C, 62.36; H, 5.61; N, 7.63; Calc. for $C_{28}H_{29}N_3O_6S$ (535.5): C, 62.74, H, 5.41, N, 7.84%.

The adduct 43c was purified by column chromatography on silicagel using benzene-EtOAc (3:2) as dark yellow needles (EtOAc), yield 0.85g (31%), m.p. 163-65°; IR (KBr): ν_{max}: 1720, 1685 (two-C(=O)-OCH_3), 1638 (C=O), 1570 cm^{-1}; ^1H nmr($CDCl_3$): δ2.11 (s, 3H, SCH_3), 3.33-3.70 (m, 4H, morpholino), 3.58 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, p-$CH_3OC_6H_4$) 4.00-4.61 (m, 4H, morpholino), 6.68-7.43 (m, 7H, arom), 7.88-8.18 (m, 2H, arom): Found: C, 60.63: H, 5.41; N, 7.82; Calc. for $C_{28}H_{29}N_3O_7S$ (551.5); C, 60.92, H, 5.25, N, 7.61%.

The adduct 43d was purified by chromatography on silicagel using hexane-EtOAc (7:3) as yellow needles (EtOAc-hexane), 0.86g (31%) m.p. 88-92°; IR(KBr): ν_{max}: 1728, 1700 (two-C(=O)-OCH_3), 1640 (C=O), 1575 cm^{-1}; ^1H nmr($CDCl_3$): δ2.11 (s, 3H, SCH_3); 3.36-3.71 (m, 4H, morpholino), 3.56 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.00-4.41 (m, 4H, morpholino), 7.03-7.46 (m, 7H, arom), 7.88-8.15 (m, 2H, arom); Found: C, 58.56; H, 5.23; N, 7.84; Calc. for $C_{27}H_{26}ClN_3O_6S$ (555.7): C, 58.30; H, 4.67; N, 7.55%.

The adduct 43e was purified by column chromatography on silicagel using benzene-EtOAc (7:3) as yellow needles (EtOAc), 0.9g (30%); m.p. 86-90°; IR (KBr): ν_{max}: 1730, 1705 (two-C(=O)-OMe), 1645 (C=O), 1585 cm^{-1}; ^1H nmr($CDCl_3$): δ2.30 (s, 3H, -SCH_3); 3.40-3.91 (m, 4H, morpholino), 3.58 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3)4.06-4.61 (m, 4H, morpholino), 7.00-7.56 (m, 7H, arom), 7.88-8.16 (m, 2H, arom); Found: C, 53.45; H, 4.01; N, 7.17; Calc. for $C_{27}H_{26}BrN_3O_6S$ (600.2): C, 53.98; H, 4.33; N,6.99%.

Table 1

Spectral data for dimethyl 4,4-bismethyl-thio-1-aroyl(or acyl) butadiene-2,3-dicarboxylates (21a-e)

Compound	νmax. (KBr) (cm^{-1}) Ester CO	Arom/alpha CO	^{1}H-NMR($CDCl_3$); δ (ppm)
21a	given in text		given in text
21b	1722, 1703	1628	2.20 (s, 3H, SCH_3), 2.35 (s, 3H, SCH_3), 3.6 (s, 3H, OCH_3) 3.85 (s, 3H, OCH_3), 7.17 (s, 1H, olefinic), 7.25-7.65 (m, 5H, arom).
21c	1725, 1704	1625	2.30 (s, 3H, SCH_3), 2.45 (s, 3H, SCH_3), 3.65 (s, 3H, OCH_3) 3.8 (s, 3H, OCH_3) 3.9 (s, 3H, OCH_3), 7.55 (s, 1H, olefinic), 6.80-7.75 (m, A_2B_2, 4H, arom).
21d	1710, 1730	1640	2.22 (s, 3H, SCH_3), 2.43 (s, 3H, SCH_3), 3.65 (s, 3H, OCH_3) 3.85 (s, 3H, OCH_3), 7.48 (s, 1H, olefinic), 7.30-7.40 (m, m, A_2B_2, 4H arom)
21e	1712, 1685	1645	2.22 (s, 3H, SCH_3), 2.30 (s, 3H, SCH_3), 2.48 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 7.67 (s, 1H, olefinic

Table 2

Analytical data for compounds (21a-e)

Compound	m.p.(°C)	yield(%)	m/z	Mol formula	Analysis C	Calc (%) found(%) H
21a	given in text					
21b	122-124	52	366 (8%) 319 (100%)	$C_{17}H_{18}O_5S_2$	55.73 55.4	4.91 4.45
21c	130-132	58	396 (2%) 349 (100%)	$C_{18}H_{20}O_6S_2$	54.32 54.5	5.07 5.3
21d	112-113	56	444, 446 (1%) 397, 399 (100%)	$C_{17}H_{17}BrO_5S_2$	45.34 45.15	3.82 3.55
21e	135-136	52	304 (2%) 257 (100%)	$C_{12}H_{16}O_5S_2$	47.36 46.9	5.26 5.35

REFERENCES

1. V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 147 (1983).

2. R. Gompper, Angew. Chem., Int. Ed., 8, 312 (1969).

3. K.C. Brannock, R.D. Burpitt, and J.G. Thweatt, J. Org. Chem., 28, 1697 (1963).

4. S. Karlsson and J. Sandstrom, Acta. Chem. Scand, Ser. B, B.32, 141 (1978); Chem. Abstr., 89, 23352 (1978).

5. S.M. McElvain and H. Cohen, J. Amer. Chem. Soc., 64, 260 (1942).

6. C.F. Heubner, L. Dorfman, M.M. Robinson E. Donoghue, W.G. Pierson and P. Strachan, J. Org. Chem., 28, 3134 (1963).

7. M. Petrzilka and J. Ian Grayson, Synthesis, 760, 766 (1981) and references therein.

8. F.A. Carey and A.S. Court, J. Org. Chem., 37, 4474 (1972).

9. R. Okazaki, A. Kitamura and N. Inamoto, J. Chem. Soc., Chem. Comm., 257 (1975).

10. M. Ooka, A. Kitamura, R. Okazaki and N. Inamoto, Bull. Chem. Soc. Japan, 51, 301 (1978).

11. D.B.J. Easton, D. Leaver and T.J. Rawlings, J. Chem. Soc., Perkin Trans. I, 41 (1972).

12. El-Sayed El-Kholy, F.K. Rafla and M.M. Mishrikey, J. Chem. Soc., C, 1578 (1970).

13. D. Leaver, D.M. McKinnon and W.A.H. Robertson, J. Chem. Soc., 31(1965).

14. P. Beak, D.S. Mueller and J. Lee, J. Am. Chem. Soc., 96, 3867 (1974).

15. W.H. Pirkle and W.V. Turner, J. Org. Chem., 40, 1617 (1975).

16. W.V. Turner and W.H. Pirkle, J. Org. Chem., 39, 1935 (1974).

17. W.H. Pirkle and W.V. Turner, J. Org. Chem., 40, 1644 (1975).

18. H. Budzikiewicy, C. Djerassi and W.H. Williams, 'Mass Spectrometry of Organic Compounds', Holden-Day, Inc.,1967, p. 180-182.

19. (a) L. Knorr, Ber., 16, 2597 (1887); (b) P.C. Freer, J. Prakt. Chem., 47, 247 (1893).

20. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 1398 (1959).

21. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 2182 (1962).

22. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 2194 (1962).

23. I. Shahak and Y. Sasson, Tet. Lett. 4207 (1973).

24. A. Kumar, H. Ila and H. Junjappa, Synthesis, 324 (1976).

25. R. Gompper and H. Schaefer, Chem. Ber. 100, 591 (1967).

26. G. Singh, S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis, 693 (1982).

CHAPTER III

STUDIES ON LEAD TETRACETATE OXIDATIONS OF POLARIZED KETEN S,N- AND N,N-ACETALS

III.1 INTRODUCTION

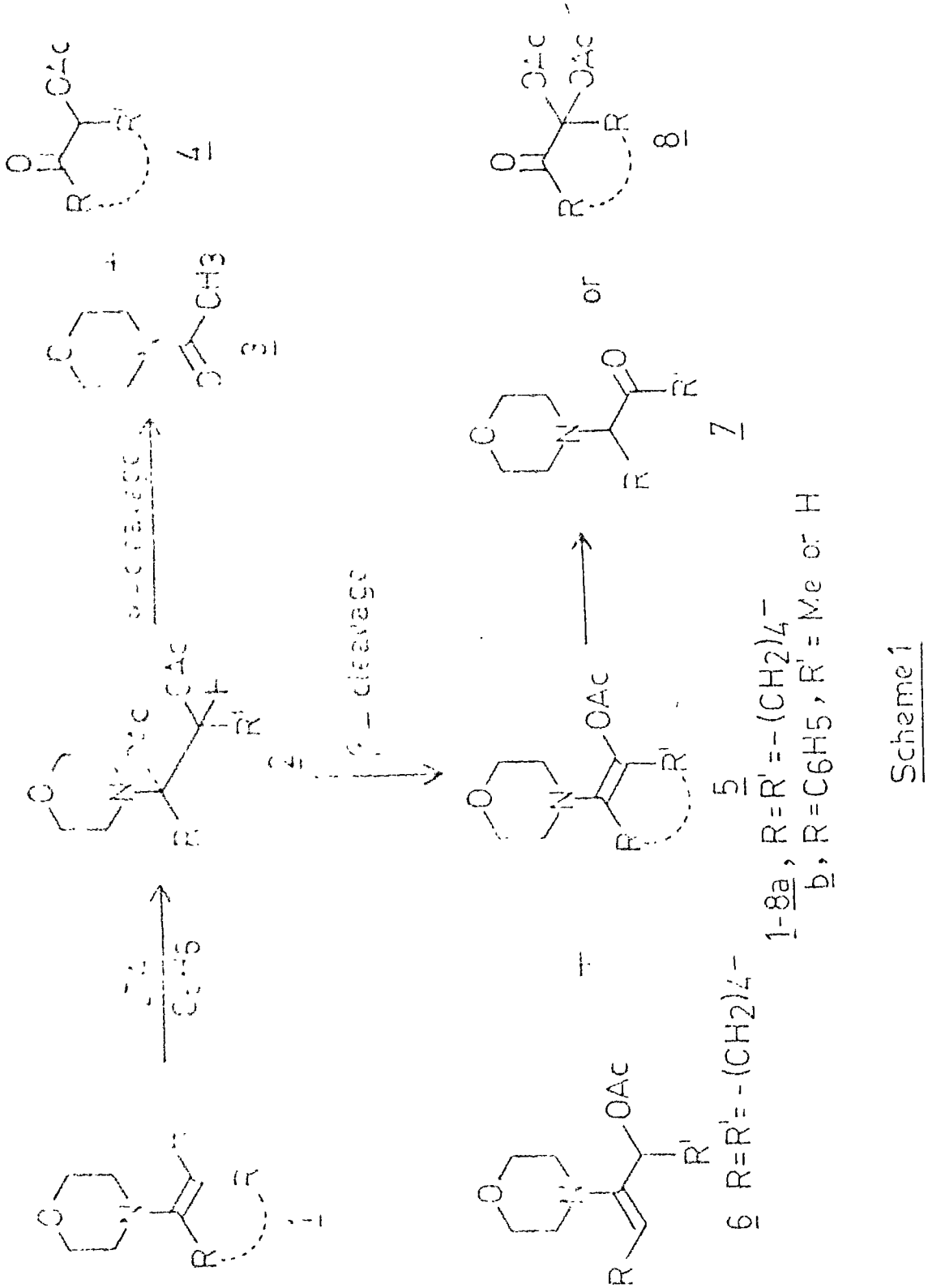
Lead tetraacetate (LTA) has been extensively used for the oxidations of a variety of organic compounds with diverse functionalities. A number of interesting reviews on these oxidations have been published.[1] These oxidations generally involve the reduction of lead(IV) to lead(II) and the variety of pathways by which this can occur include, both ionic and free radical mechanisms, which may involve acetate ion and other inter and intramolecular nucleophiles, leading to a broad and interesting chemistry. Alyward[2] has reviewed the general behaviour of LTA towards organic nitrogen compounds. Also the reviews of the reactions of LTA with hydrazones[3] and with

oximes[4] have also been published. On the other hand, the oxidations of imines, enamines, enaminoesters and the compounds capable of imine-enamine tautomerism have only recently been studied. In the preceding chapter it is shown that polarized keten S,N- and N,N-acetals represent a novel class of functionalized polarized enamines or vinylogous amides which serve as useful intermediates for a variety of heterocyclic compounds. In the present investigation the results of our studies on oxidations of a few polarized S,N- and N,N-acetals derived from acetophenone and arylacetonitriles have been described. A brief literature on oxidations of imine, enamine and enaminoesters with LTA has been described below.

III.2 Lead Tetraacetate oxidations of imine, enamines and enaminoesters:

A Brief Survey

Rindone[5] and coworkers have studied LTA oxidations of a few morpholinoenamines derived from cyclohexanone (1a) and other acyclic ketones (1b) which afforded a mixture of products 3-8 (Scheme 1). The diacetoxy derivative 2 was considered to be initial product, which undergoes two types of transformations: an α-elimination path to give N-acetylmorpholine (3) and a 2-acetoxyketone such as (4) or alternatively a β-elimination

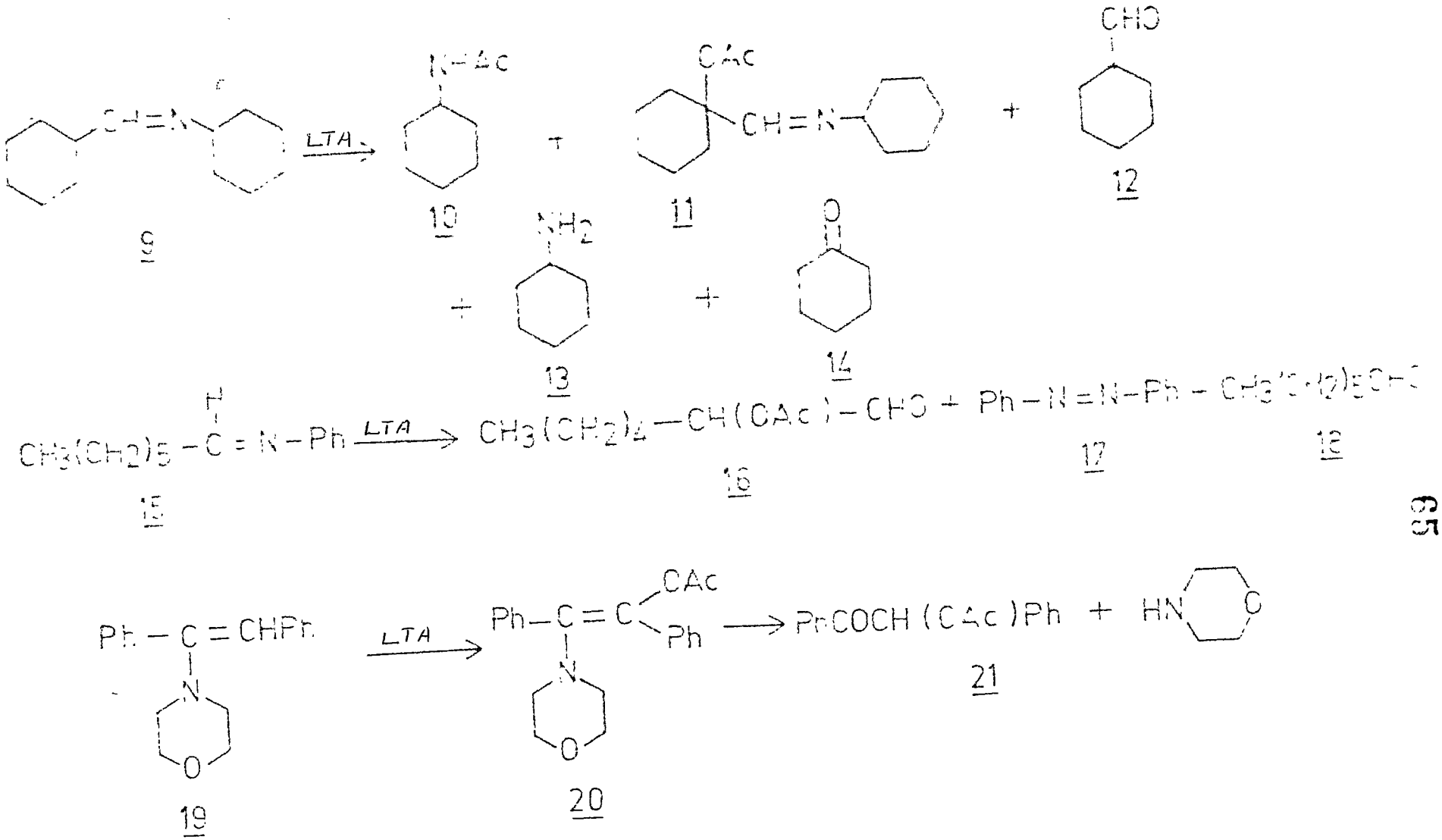


6 R=R'= -(CH2)4-

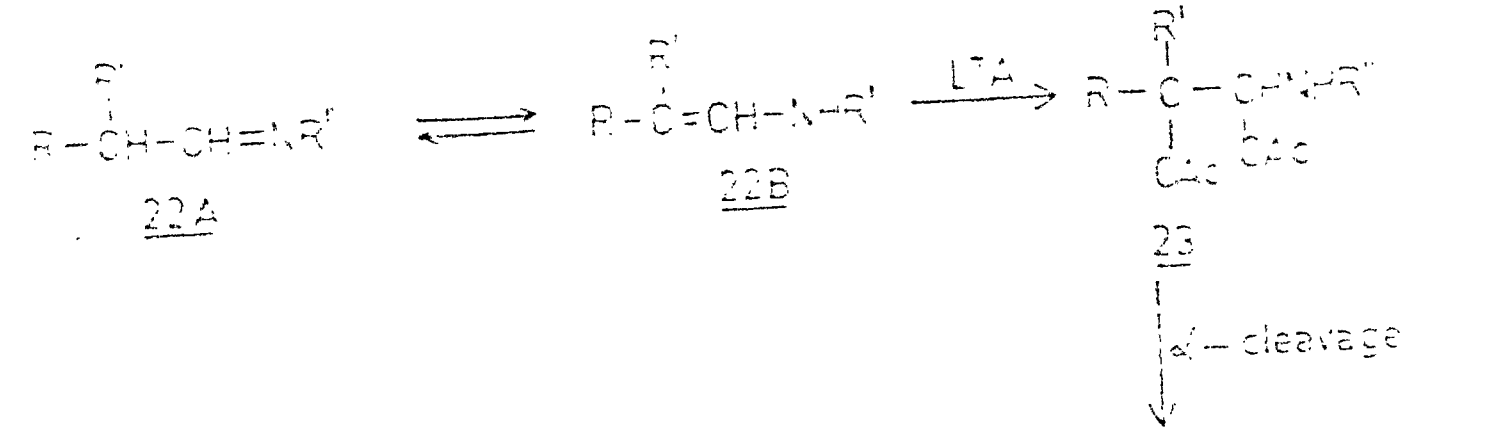
1-8a, R=R'= -(CH2)4-
b, R=C6H5, R'= Me or H

Scheme 1

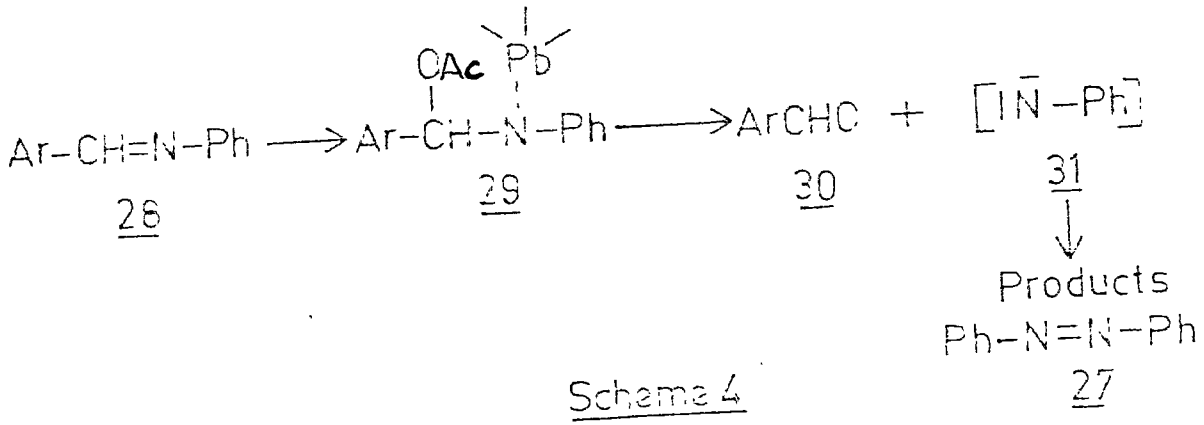
path to give compounds with an enamine-enol acetate structures 5 or 6. The compounds of the type 5 could then undergo an acid catalysed transformation to give the 2-morpholinoketone 7 or in a few cases 8 (Scheme 1).[5] The same authors have subsequently studied[6] the LTA oxidation of various substrates (9 and 15) capable of imine-enamine tautomerism under Lewis acid conditions (Scheme 15). The product distribution in these oxidations reveals that the course of the reaction derives from their enamine reactivity. This can be explained by LTA catalysis of the imino-enamino/tautomerism (22A ⇌ 22B) acting as Lewis acid. The enamino form (22B) is oxidized faster by LTA than the imino form and its fate is shown in the scheme 3. The 2-acetoxy aldehyde 24 formed via α-cleavage of initial diacetoxy derivative 23, equilibriates with the starting material 22 to give the acetoxyimine 26 and the unsubstituted aldehyde 27 (Scheme 3). The formation of the aldehyde 18 and azobenzene 17 in the oxidation of 15 is explained via the intermediate 29 and phenyl-nitrenoid 31 as noted previously in the oxidation of aromatic anils 28 (Scheme 4).[7,8] However, only a minor part of the reaction occurs via >C=N-bond fission. In all these cases, the faster oxidation of the enamine tautomer over the imine isomer could be attributed to extra nucleophilicity of its β-carbon making the attack easier by electron deficient molecule.[6]


CH=N
LTA
NHAc
CAc
CH=N
CHO
9
10
11
12
NH2
O
13
14
CH3(CH2)5-C(H)=N-Ph
LTA
CH3(CH2)4-CH(CAc)-CHO + Ph-N=N-Ph
15
16
17
18
Ph-C=CHPh
LTA
Ph-C=C(CAc)Ph
PhCOCH(CAc)Ph + HN
O
19
20
21

Scheme 2

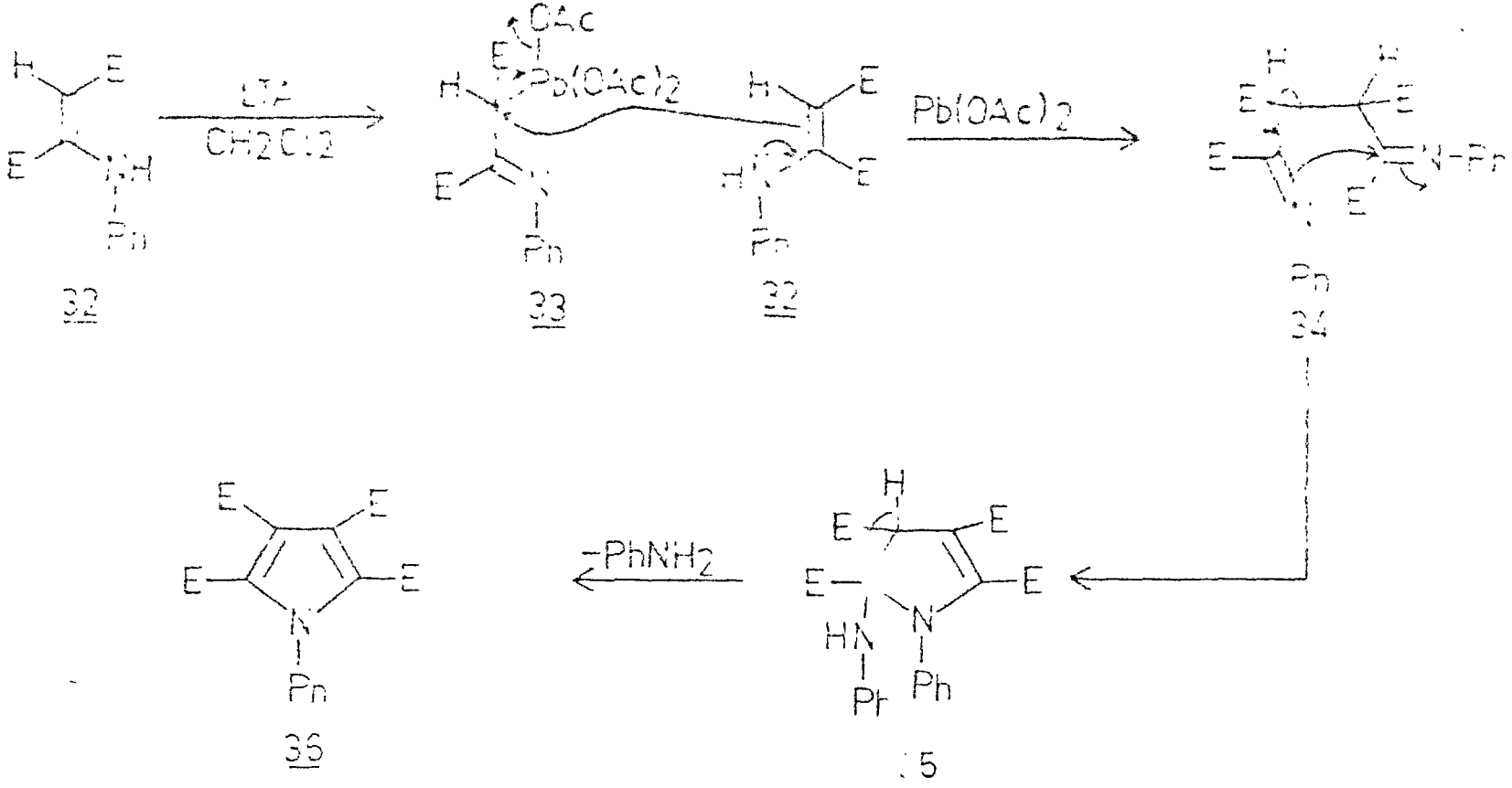


Scheme 3

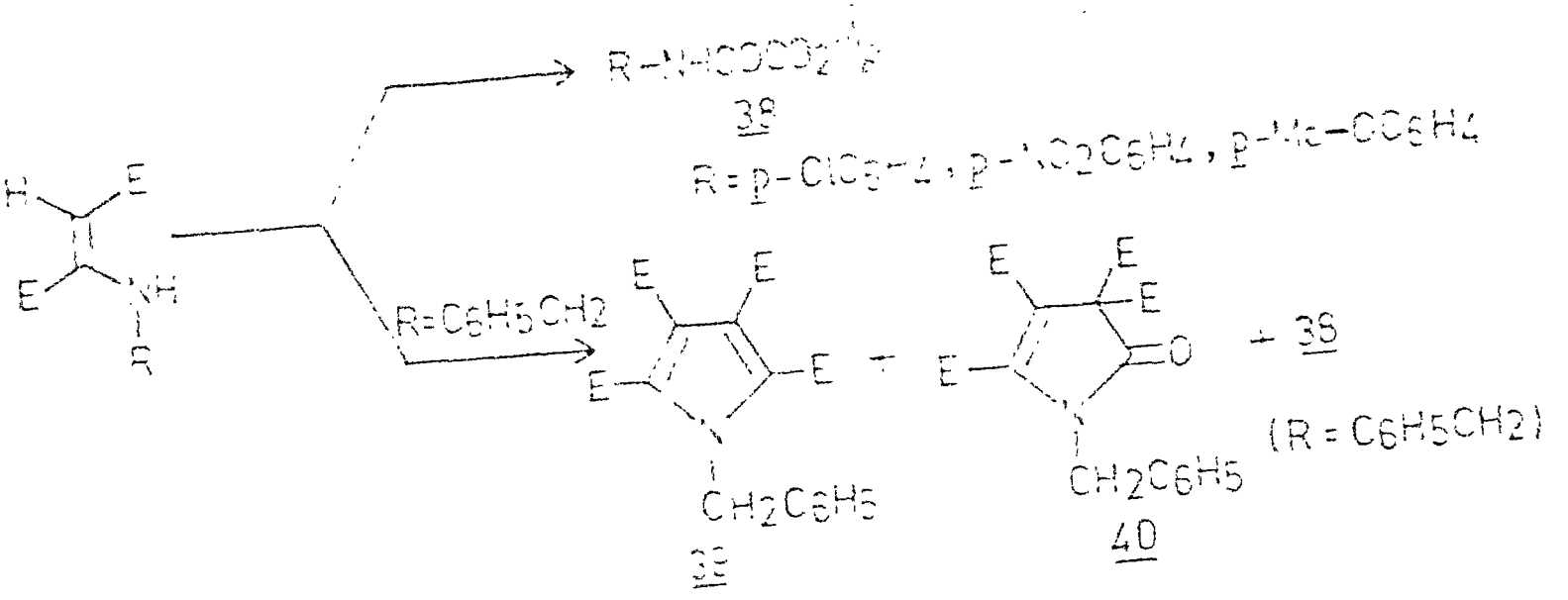


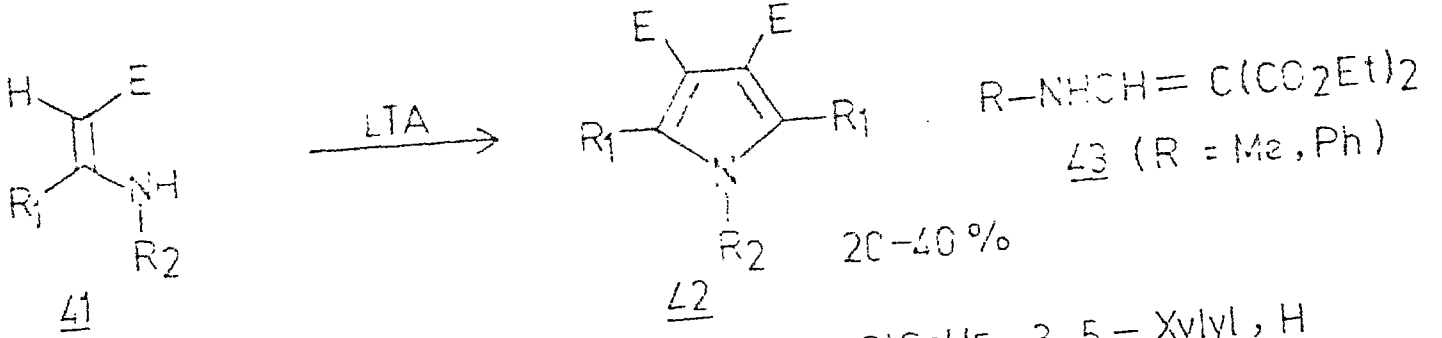
Scheme 4

The enamine dimethylanilinofumarate 32 has been reported to yield the pyrrole derivative 36 on oxidation with LTA and no α-acetoxylated product was isolated (Scheme 5).[9] A mechanism for the dimerization involving attack by unchanged substrate 32 on an organo-lead intermediate 33 has been proposed (Scheme 5). Later on Vernon and coworkers have isolated the pyrroline intermediate 35 under similar oxidation conditions which afforded the pyrrole 36 on treatment with acid.[10] The oxidation of a few other anilinofumarates 37 containing electron withdrawing substituents at p-position gave low yields of the corresponding oxanilates (38) as the only identifiable products.[10] The dimethyl-N-benzylaminofumarate 37 ($R=C_6H_5CH_2$). On the other hand afforded a novel pyrrolone 40 besides the pyrrole 39 and 38 under the similar conditions.[10] The symmetrical 2,5-dimethyl pyrroles (R_1=Me) (42) are also reported to be formed in LTA oxidation of the corresponding β-alkyl/aryl aminocrotonates (41, R_1=Me) while the corresponding β-aminocinnamates (41, $R_1=C_6H_5$) yielded only very low yields of the corresponding 2,5-diarylpyrroles (42, $R_1=C_6H_5$) (Scheme 6).[11] The corresponding aminomethylenemalonates (43) were found to be resistant towards LTA oxidation.[11]



Scheme 5



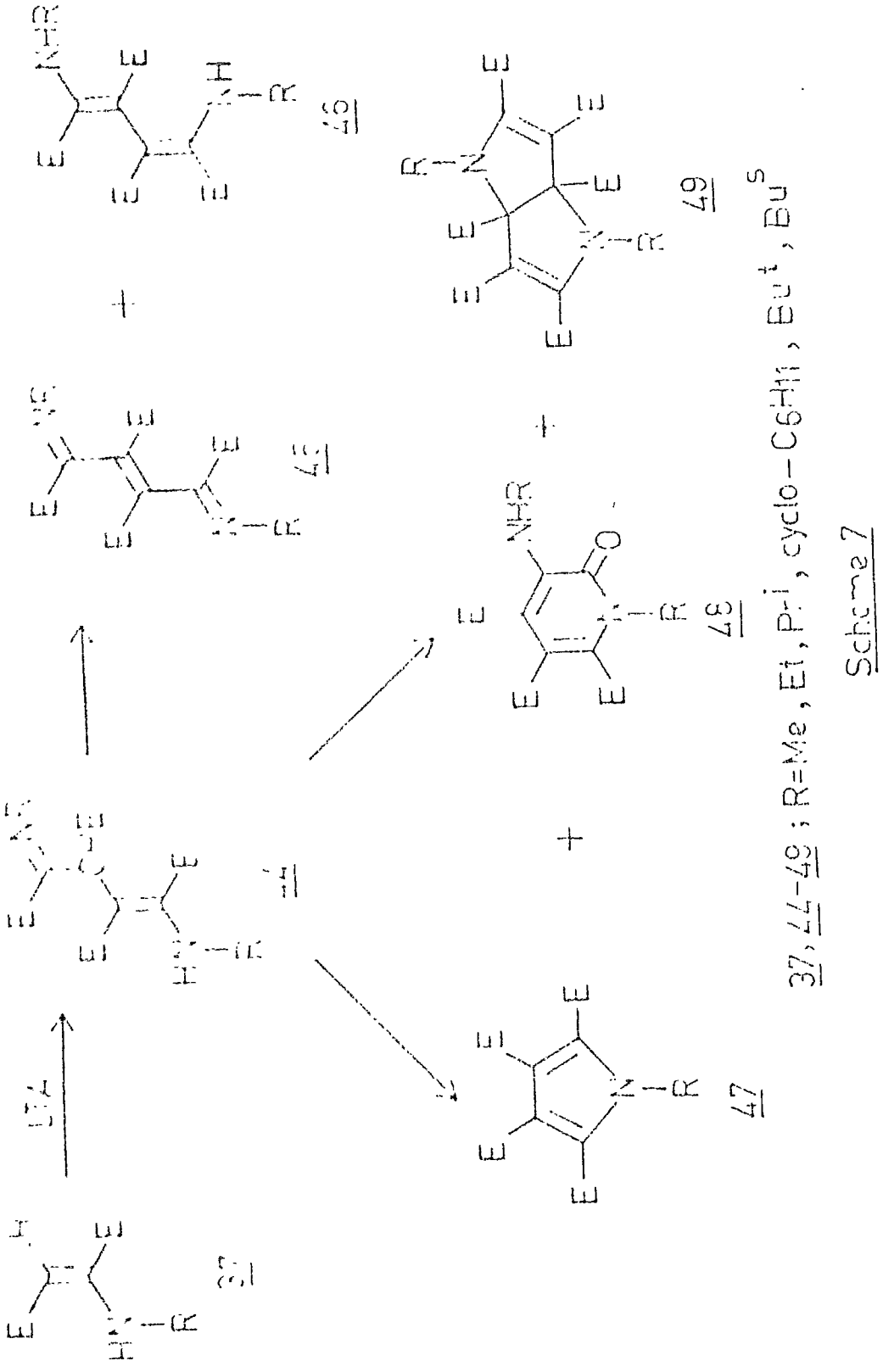


R_1 = Me, C_6H_5 ; R_2 = Me, Bu, $PhCH_2$, p-ClC_6H_5, 3,5 – Xylyl, H

Scheme 6

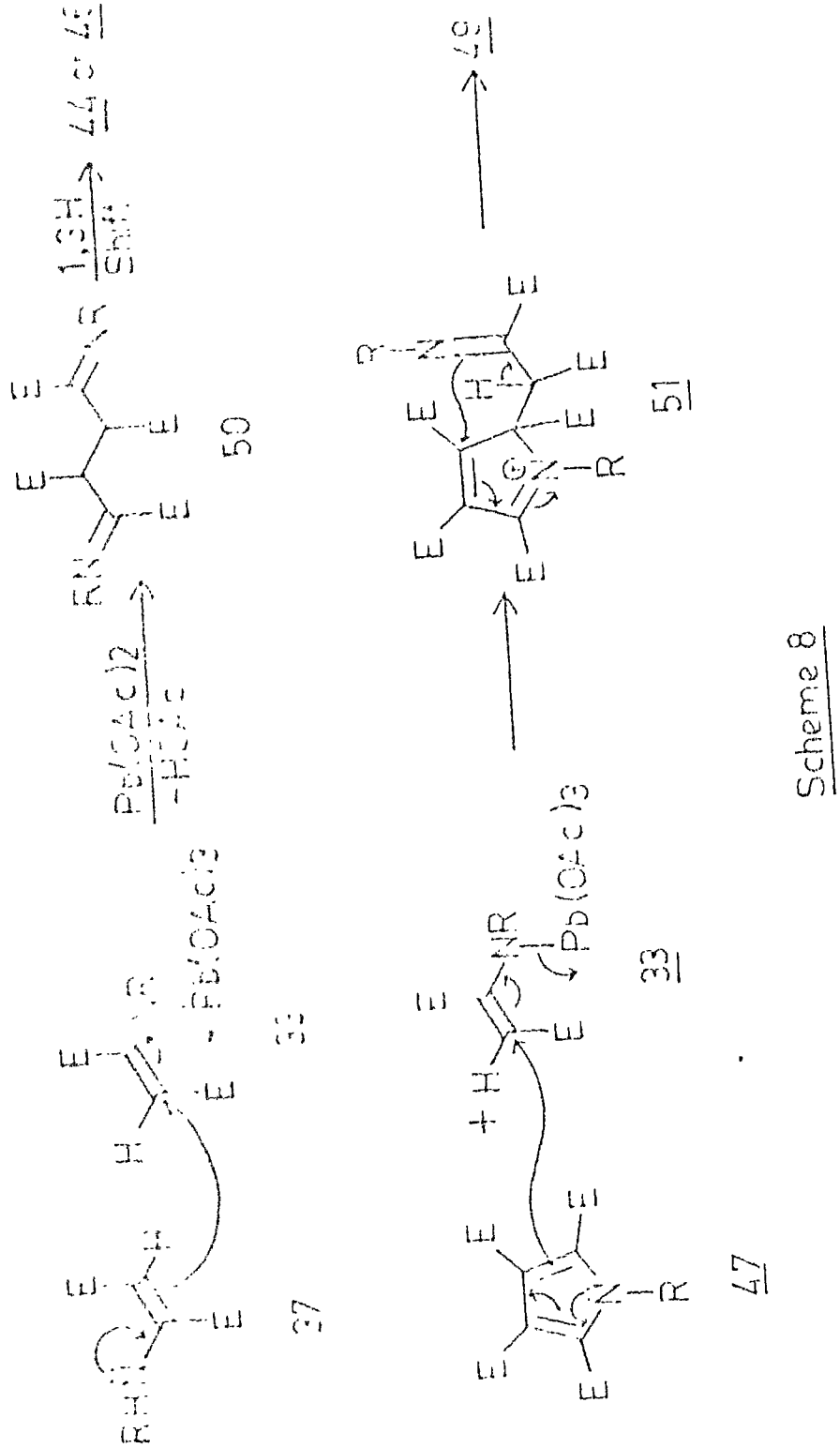
In a detailed investigation on the oxidation of a series of N-alkylaminofumarates (37, R=Me, Et, Pr , C_6H_{11}, Bu^t etc.), with LTA, Vernon and coworkers isolated six types of products (44, 45, 46, 47, 48 and 49) depending on the experimental conditions.[12,13] Thus the oxidative dimers 45 and 46 (R=Pr^i, cyclo C_6H_{11}, Bu^t) were obtained when the enamine (37) was oxidized with equimolar quantities of LTA in dichloromethane and acetonitrile respectively, while with less than one equivalent, the dimeric intermediate 44 could be isolated. All these products 44-46 are oxidative dimers of 37 coupled through β-carbon atom (Scheme 8). The oxidation of the corresponding N-methyl or N-ethyl aminofumarates 37 (R=Me, Et) by LTA in dichloromethane containing trifluoroacetic acid afforded heterocyclic polyester pyrroles (47), pyridines (48) and pyrrolo-[3,2-b]-pyrroles (49) R=Me, Et, Pr^i (Scheme 7). The products 47 and 48 are probably derived from the same intermediate 44 since 44 was independantly cyclized to the corresponding pyrrole (47) or pyridone (48) in acidic or basic conditions respectively. The corresponding pyrrolo-[3,2-b]-pyrrole (49) is probably formed by coupling of pyrrole (47) with plumbylated enamine (33) (Scheme 8).[12]

From the foregoing discussion it is apparent that β-alkyl/aryl aminofumarates having enaminoester moieties and the imines



37, 44-49 ; R=Me , Et , Pr-i , cyclo-C6H11 , Bu-t , Bu-s

Scheme 7



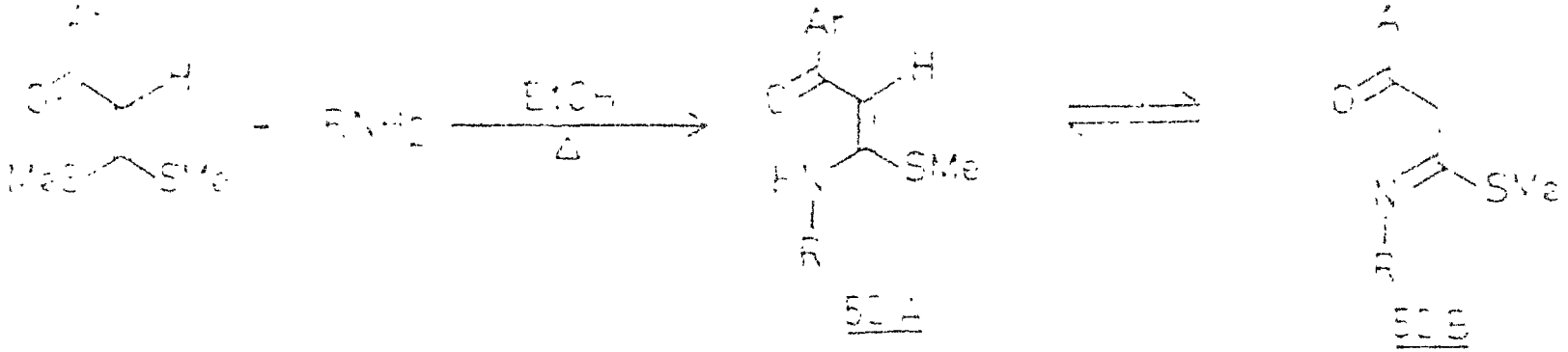
Scheme 8

9, 15 are capable of imine-enamine tautomerism which afford a series of interesting products on LTA oxidations under varying conditions. The oxidations of enaminones by LTA have not been reported in the literature which prompted the present studies on α-oxoketen S,N-acetals (52) and α-oxoketen N,N-acetals (56) having enaminone moieties, which are described in the present chapter.

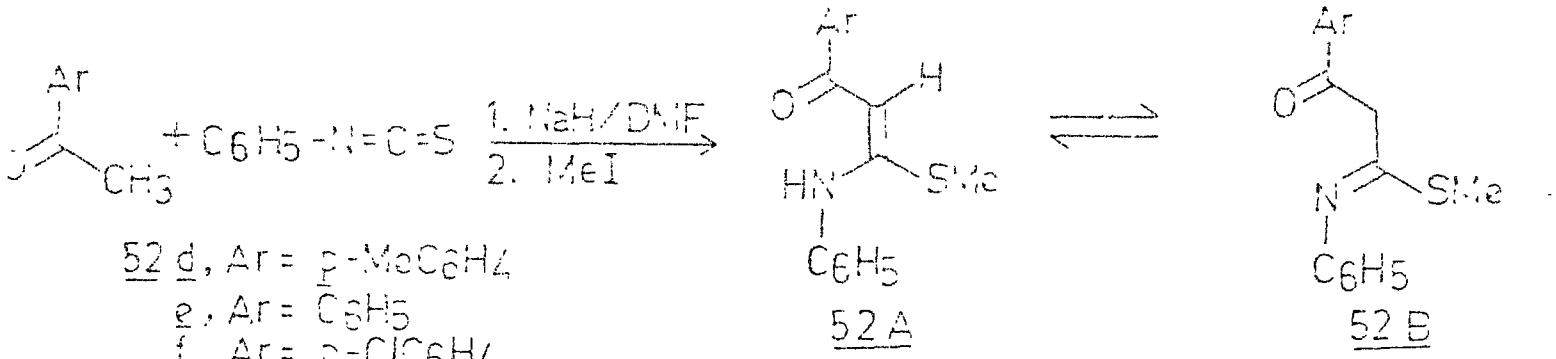
III.3 Lead Tetraacetate Oxidations of 3-Methylthio-3-aryl/alkyl/benzylamino-1-aryl-2-propen-1-ones (52a-f):

III.3.1 RESULTS AND DISCUSSIONS

The representative α-oxoketen S,N-acetals derived from ethylamine (52a) benzylamine (52b-c) and aniline (52d-f) required for the oxidation studies were prepared according to the reported procedures from this laboratory, either by direct displacement method (52a-c) or by reaction of the respective acetophenones with phenylisothiocyanate in the presence of sodium hydride and DMF followed by subsequent alkylation with one eqv. of methyl iodide (52d-f) (Scheme 9) (Chapter I). The i.r. and n.m.r. spectral studies of these S,N- acetals 52a-f have shown that they exist exclusively in enamino tautomeric form (A) and no trace of iminoform (B) could be detected.



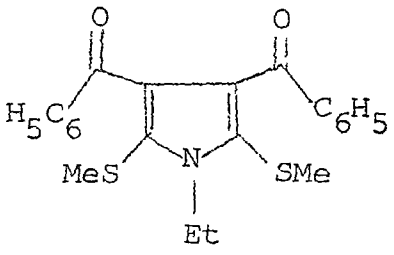
52 a, Ar = C6H5, R = Et
b, Ar = C6H5, R = C6H5CH2
c, Ar = p-MeC6H4, R = C6H5CH2



52 d, Ar = p-MeC6H4
e, Ar = C6H5
f, Ar = p-ClC6H4

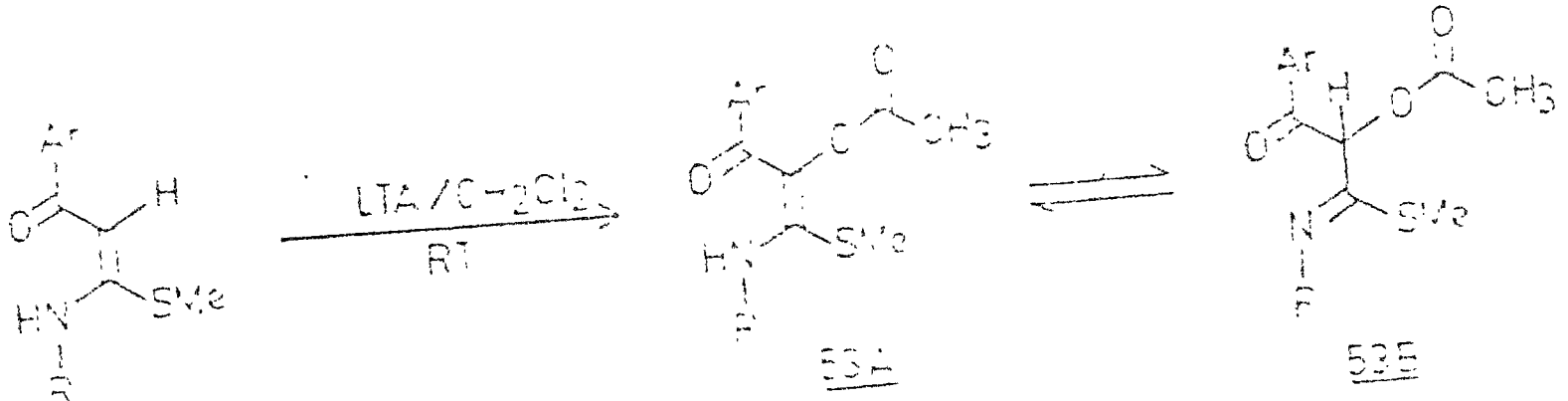
Scheme 9

When the S,N-ethylacetal (52a) was stirred with 1 eqv. of LTA in dichloromethane at room temperature, work-up and column chromatography of the reaction mixture afforded a white solid (55%) which was characterized as acetoxy S,N-acetal 53a (Scheme 10) and no trace of dimeric pyrrole (54) was isolated from the reaction mixture. The mass spectrum (m/z 279, 70%, M^+) and the analytical data ($C_{14}H_{17}NO_3S$) for 53a were in



54

agreement with the assigned structure. The infrared spectrum of 53a in KBr showed broad band at 3350 cm^{-1} and strong peaks at 1750, 1695 and 1673 cm^{-1}, while in chloroform it showed only two peaks at 1761 and 1686 cm^{-1} which were assigned to the acetoxy and aromatic carbonyl groups respectively. The n.m.r. spectrum ($CDCl_3$) of 53a showed that it exists in enaminoform (53a A) in chloroform. Thus the N-ethyl protons appeared as a triplet (3H) and a quartet (2H) at δ 1.02 and δ 3.60, respectively. Similarly the siglets at δ 2.02 (3H) and δ 2.20 (3H) were assigned to SMe and acetyl protons. The signal due to



52

53A

53B

a, Ar = C6H5, R = Et
b, Ar = C6H5, R = C6H5CH2
c, Ar = p-MeC6H4, R = C6H5CH2

d, Ar = p-MeC6H4
e, Ar = C6H5
f, Ar = p-ClC6H4

Scheme 10

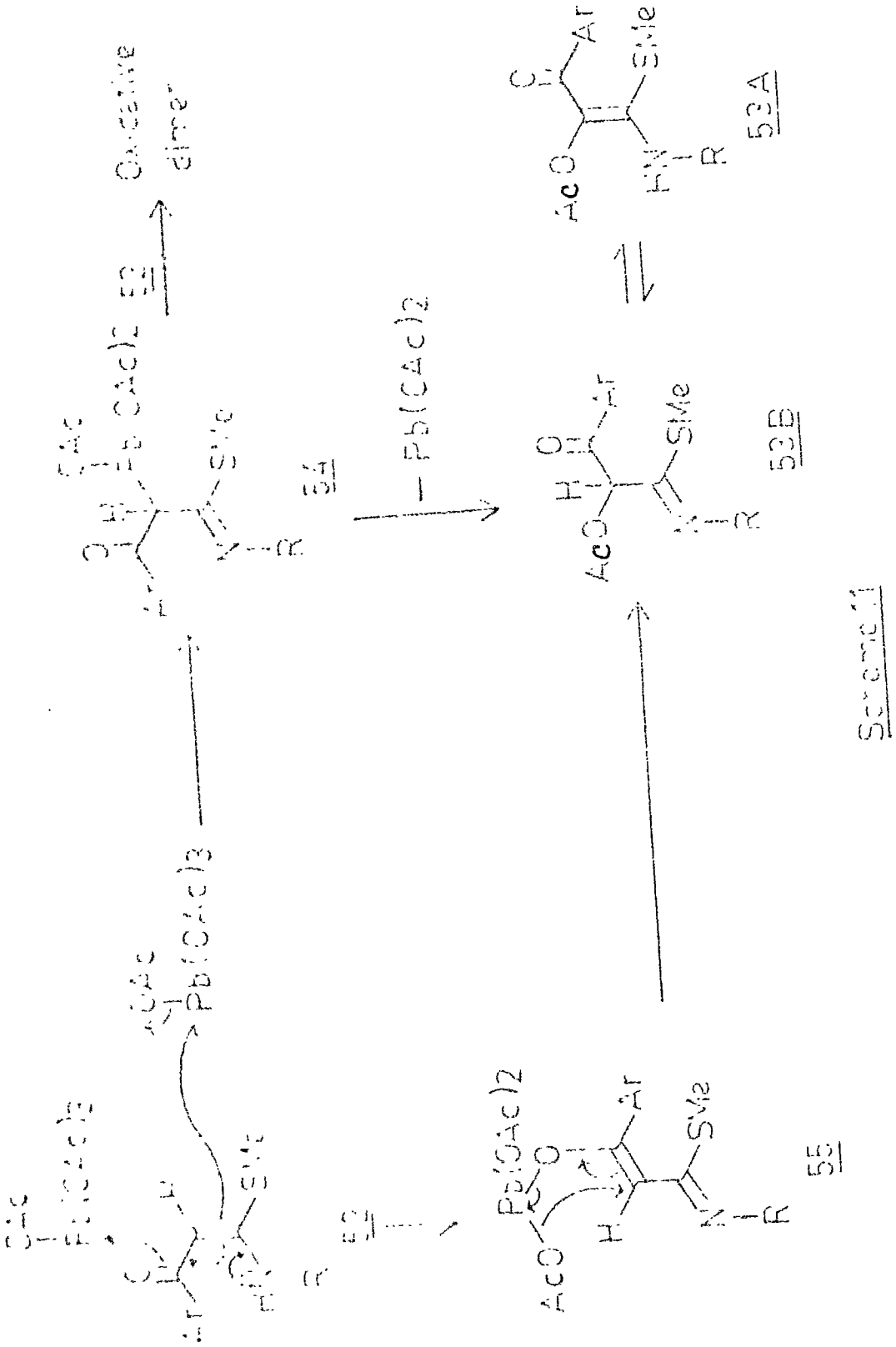
olefinic proton at δ 5.66 in the n.m.r. spectrum of 52a was absent in 53a, thus showing that it is replaced by acetoxy group. The two multiplets present at δ 7.25-7.62 (3H) and 7.80-8.21 (2H) were assigned to the aromatic protons. The i.r. spectrum of 53a in solution also supports the enamino tautomeric form. However the presence of 1697 cm^{-1} band in KBr spectrum of 53a appears to be due to H-bonded acetoxy group or due to aromatic carbonyl group of iminotautomeric form (53a B).

The oxidations of the corresponding S,N-benzylacetals 52b and 52c with LTA, under identical conditions also afforded the corresponding acetoxy S,N-acetals 53b and 53c in 45% and 52% yields, respectively. The spectral and analytical data for 53b-c were in conformity with the assigned structures which showed that they exist in enamino tautomeric forms (53b A and 53c A) in chloroform. The LTA oxidation of the corresponding S,N-anilinoacetals 52d-f similarly afforded the corresponding acetoxy S,N-acetals 53d-f in good yields. However their spectral studies demonstrated that they exist in both enamino and imino form (Scheme 10). Thus n.m.r. spectrum ($CDCl_3$) of 53d exhibited a singlet (1H) at δ 4.52, which was assigned to α-methine proton, while its i.r. spectrum

($CHCl_3$) showed two strong bands at 1757 and 1697 cm^{-1} due to acetoxy and unconjugated carbonyl groups respectively. On the other hand the KBr spectrum of 53d exhibited sharp bands at 3283, 1786, 1761, 1705, 1666 and 1606 cm^{-1} probably due to the presence of both tautomeric and other H-bonded isomeric species in solid form. However in $CHCl_3$, 53d exists exclusively in iminoform (53d B). The probable mechanism for the formation of acetoxy S,N-acetals 53 by LTA oxidation of 52 is shown in the scheme 11. The nucleophilic attack of α-carbon of 52 on LTA will give the C-plumbylated adduct 54 which decomposes with the transfer of acetoxy group at α-carbon to give 53. Unlike β-aminofumarates, 54 does not afford dimeric product by coupling with S,N-acetals 52. Alternatively the nucleophilic oxygen atom of 52 can attack electrophilic LTA to give O-plumbylated adduct 55 which decomposes by transfer of acetoxy group at α-carbon to give 53. Since the formation of dimeric products are not observed in the oxidation it appears that the latter pathway via O-plumbylation is more probable (Scheme 11).

III.3.2 CONCLUSION

The LTA oxidations of α-oxoketen-S,N-acetals derived from primary alkylamine and aniline affords α-acetoxylated S,N-acetals. The formation of any oxidative dimer was

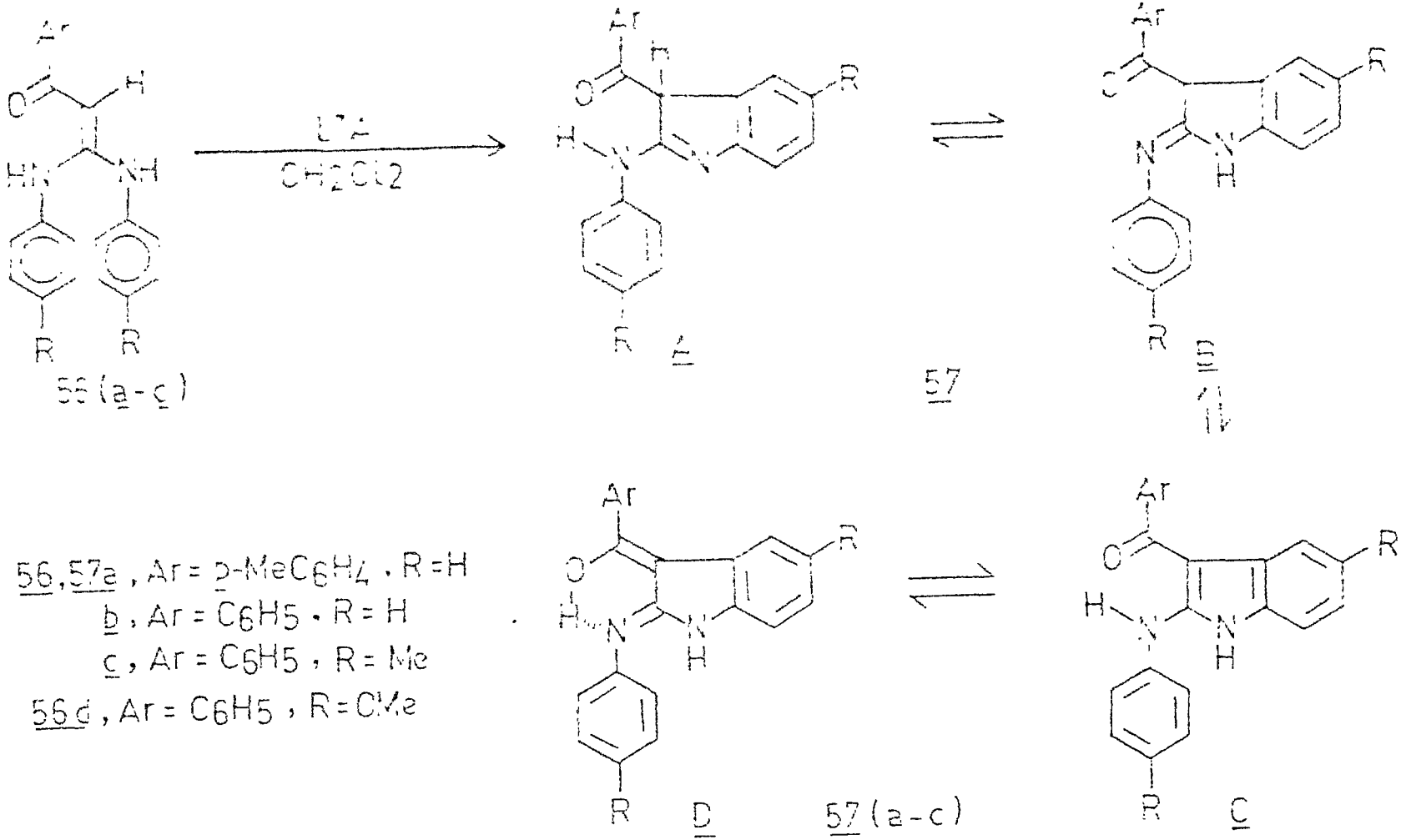


not observed in these reactions. Thus the α-oxo-S,N-acetals which possess enaminone moiety behave differently from the corresponding β-substituted aminofumarates (enaminoesters) which afford either dimeric products or the heterocycles derived from their dimers. Our attempts to isolate the dimeric products under varying conditions were not successful.

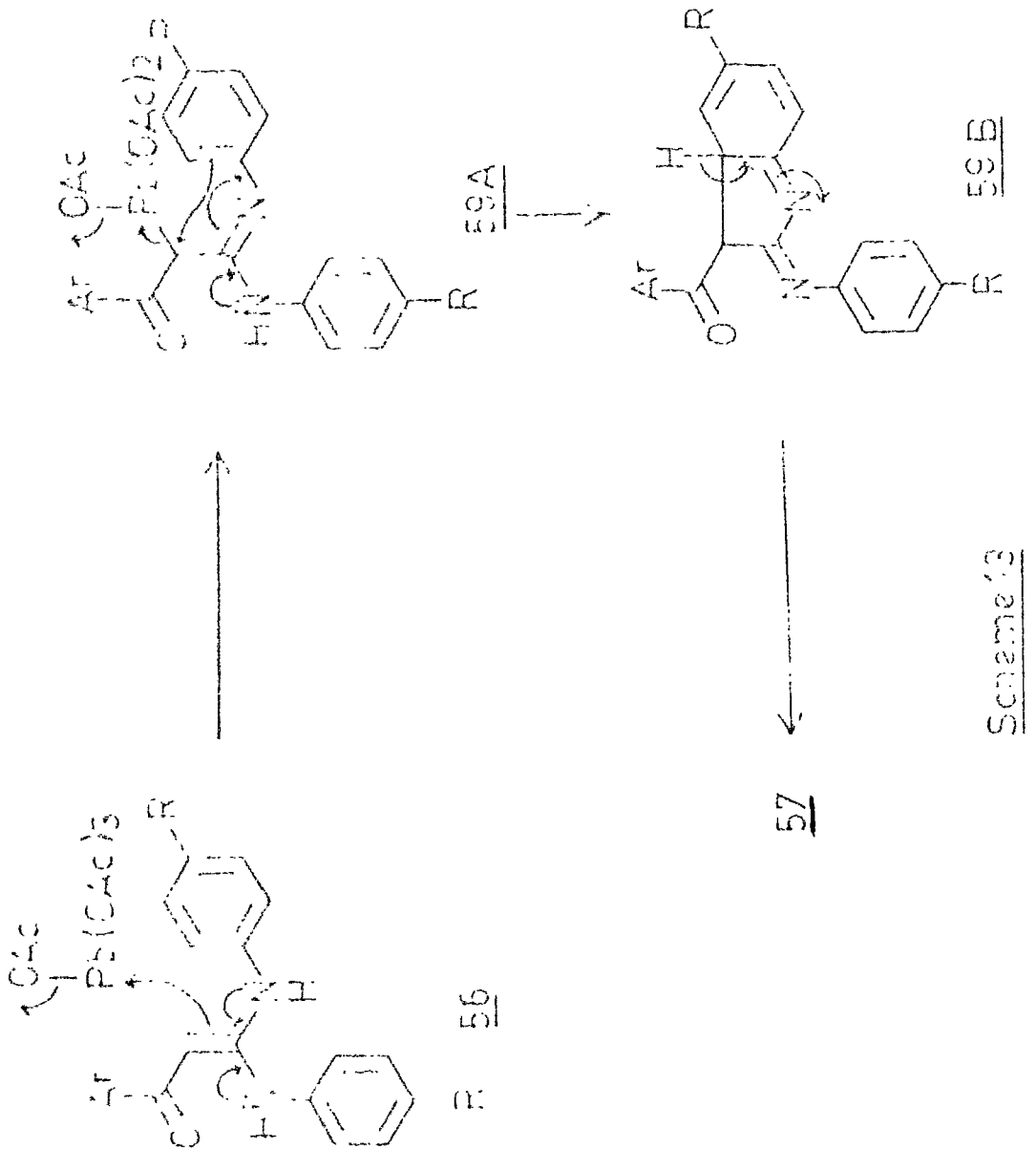
III.4 Lead Tetraacetate Oxidation of 3,3-Bis(arylamino)-1-aryl-2-propen-ones (56a-d)

III.4.1 RESULTS AND DISCUSSIONS

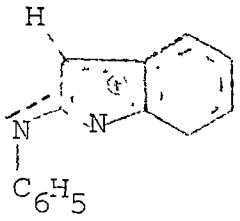
The LTA oxidations of α-oxo-N,N-arylaminoacetals (56a-d) were next investigated. The required N,N-acetals (56a-d) were obtained via direct displacement by the respective aryl amines on the corresponding α-oxoketen-S,S-acetals. When the N,N-anilinoacetals 56a was oxidized with one eqv. of LTA at room temperature, work-up and column chromatography of the reaction mixture afforded light yellow colored solid which was assigned the structure as 2-anilino-3-p-methylbenzoyl-indole (57a) on the basis of its i.r., n.m.r. and mass spectral data and elemental analysis. Thus elemental analysis of 57a was in agreement with the molecular formula ($C_{22}H_{18}N_2O$), while its mass spectrum exhibited molecular ion peak at m/z 326 (M^+, 100%). Another peak at m/z 207 (20%) was assigned due to


Ar
O
H
HN
NH
R
R
56 (a-c)
CH2Cl2
A
57
B
C
56,57a , Ar = p-MeC6H4 , R = H
b , Ar = C6H5 , R = H
c , Ar = C6H5 , R = Me
56d , Ar = C6H5 , R = OMe

Scheme 12


56
57
Esquema 13

ion 58 (M^+-PMe C_6H_4CO). The indole 57a was found to be fast equilibriating mixture of tautomeric species A-D on the basis of its i.r. and n.m.r. spectrum. Its i.r. (KBr) exhibited broad band at 3450 cm^{-1} and weak bands at 3150 and 3100 cm^{-1} due to H-bonded OH and NH stretching vibrations. It further showed strong bands at 1685, 1658, 1596, 1590 cm^{-1} due to unconugated H-bonded aromatic carbonyl group and C=N stretching vibrations. Its spectrum in chloroform exhibited broad band at 3450, weak bands at 3150, 3090, 1687, 1653, 1590 cm^{-1} confirming the presence of various tautomeric forms. The n.m.r.



58 m/z, 207

spectrum ($CDCl_3$) of 57a exhibited sharp singlet at δ 2.30 (3H) due to methyl protons while the aromatic protons appeared as multiplets at δ 6.30-7.50 (11H) and 7.50-7.81 (2H). However the corresponding 3-methine and NH protons could not be detected in the n.m.r. spectrum, which is probably due to fast exchange between different tautomeric forms of 57a (A, B, C and D) on n.m.r. time scale. The u.v. spectrum of 57a showed absorption maxima at λ_{max} 230 (log ϵ 4.88), 295 (log ϵ 4.87); 307 (log ϵ 4.83) nm. The 2-aminoindoles are known to exist in various

tautomeric forms,[14-16] and further confirmation of the structure of 57a from its ^{13}C n.m.r. spectrum is under investigation. The N,N-acetal 56b similarly afforded the corresponding indole 57b in 60% yield, while 56c on LTA oxidation gave 25% of the corresponding indole (57c), along with other unidentifiable products. The LTA oxidation of the 56d, yielded only intractable complex reaction mixture, from which no well defined compound could be isolated.

The probable mechanism for the formation of 57 from 56 is shown in the scheme 13. The C-plumbylated adduct 59A formed by nucleophilic attack through α-carbon of 57, undergoes intramolecular ring closure followed by a proton transfer to yield hither to unreported 57.

III.5 Lead Tetraacetate Oxidation of 3-Anilino-3-methylthio-2-arylacrylonitriles (66a-e)

Norman and coworkers have extensively studied the Lead tetraacetate oxidations of arylhydrazones (60) derived from aldehydes and ketones which afford the corresponding azoacetate 61 in excellent yields (Scheme 14). These azoacetates undergo a facile cyclization in the presence of Lewis acids like boron trifluoride etherate or aluminium chloride to afford substituted indazoles (63) in excellent yields

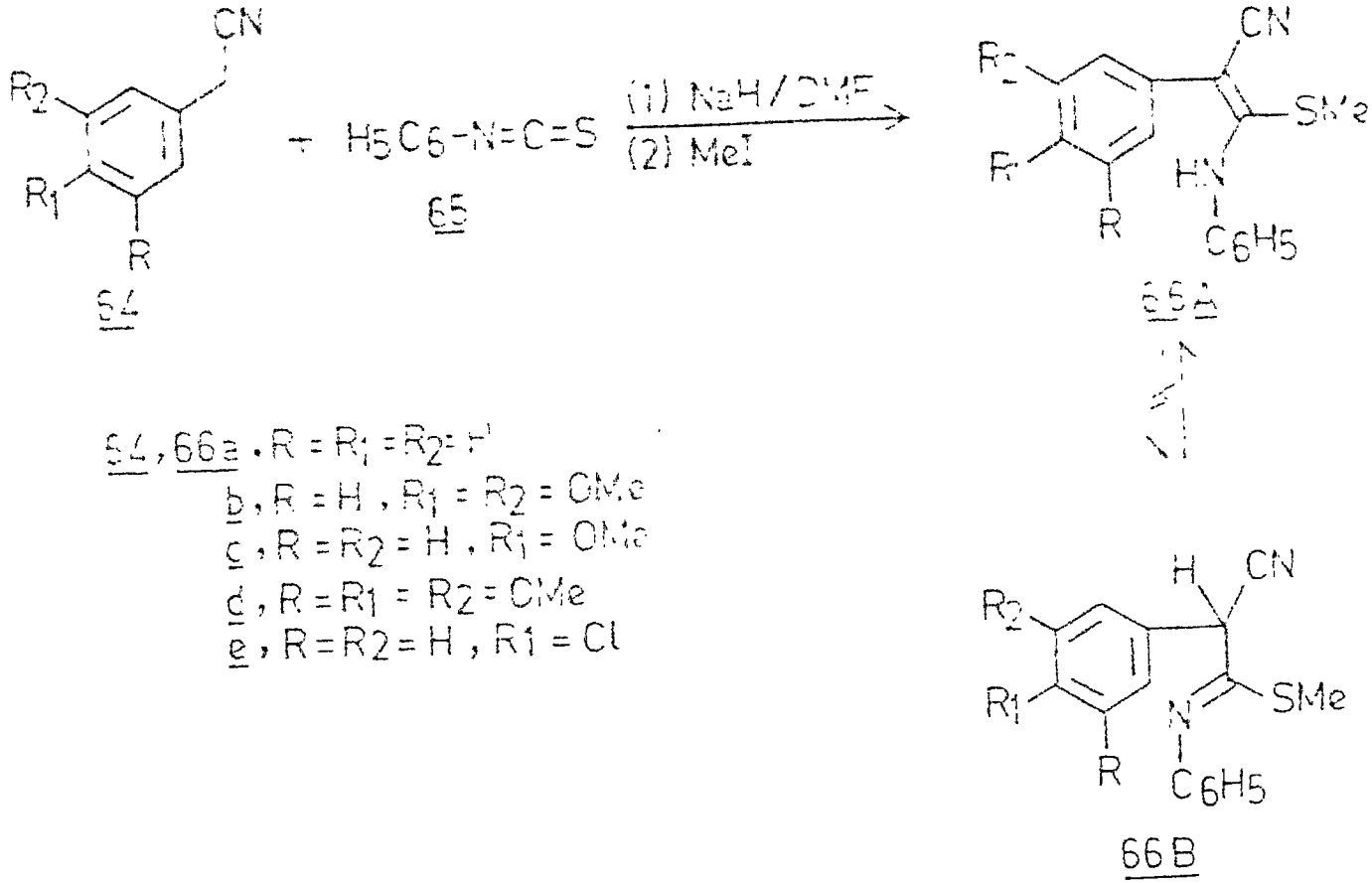
61 → 62 → 63, R1, R2 = H, Me, OMe, CO2Me etc
R3 = substituted aryl, alkyl, CO2Me etc

Scheme 14

(Scheme 14).[17-20] These studies prompted us to undertake oxidation of S,N-anilinoacetals (66a-e) derived from arylacetonitriles since the borontrifluoride etherate cyclization of the resulting N-aryl iminoacetates like 78 (Scheme 21) should in principle afford the corresponding indole derivatives, 79 (Scheme 21). On oxidations, the S,N-acetals yielded only the iminoacetates along with dimeric products. However attempts to cyclize the iminoacetates to indole derivatives, could be achieved only with the iminoacetates having electron donating groups (methoxy) in the aromatic rings. The results of these investigations are presented in the following section.

III.5.1 RESULTS AND DISCUSSIONS

The unknown S,N-acetals 66a-e required for the present investigation were prepared by reactions of the corresponding arylacetonitriles 64a-e with phenyl isothiocyanate in presence of sodium hydride in DMF followed by methylation with one eqv. of methyl iodide (Scheme 15). The i.r. spectra (KBr) of S,N-acetals 66a-e showed a medium intensity band between 3250-3300 cm^{-1} due to NH stretching vibrations while their n.m.r. spectra ($CDCl_3$) exhibited a broad singlet between δ 6.20-6.45 (exchangeable with D_2O) due to NH proton. These data show

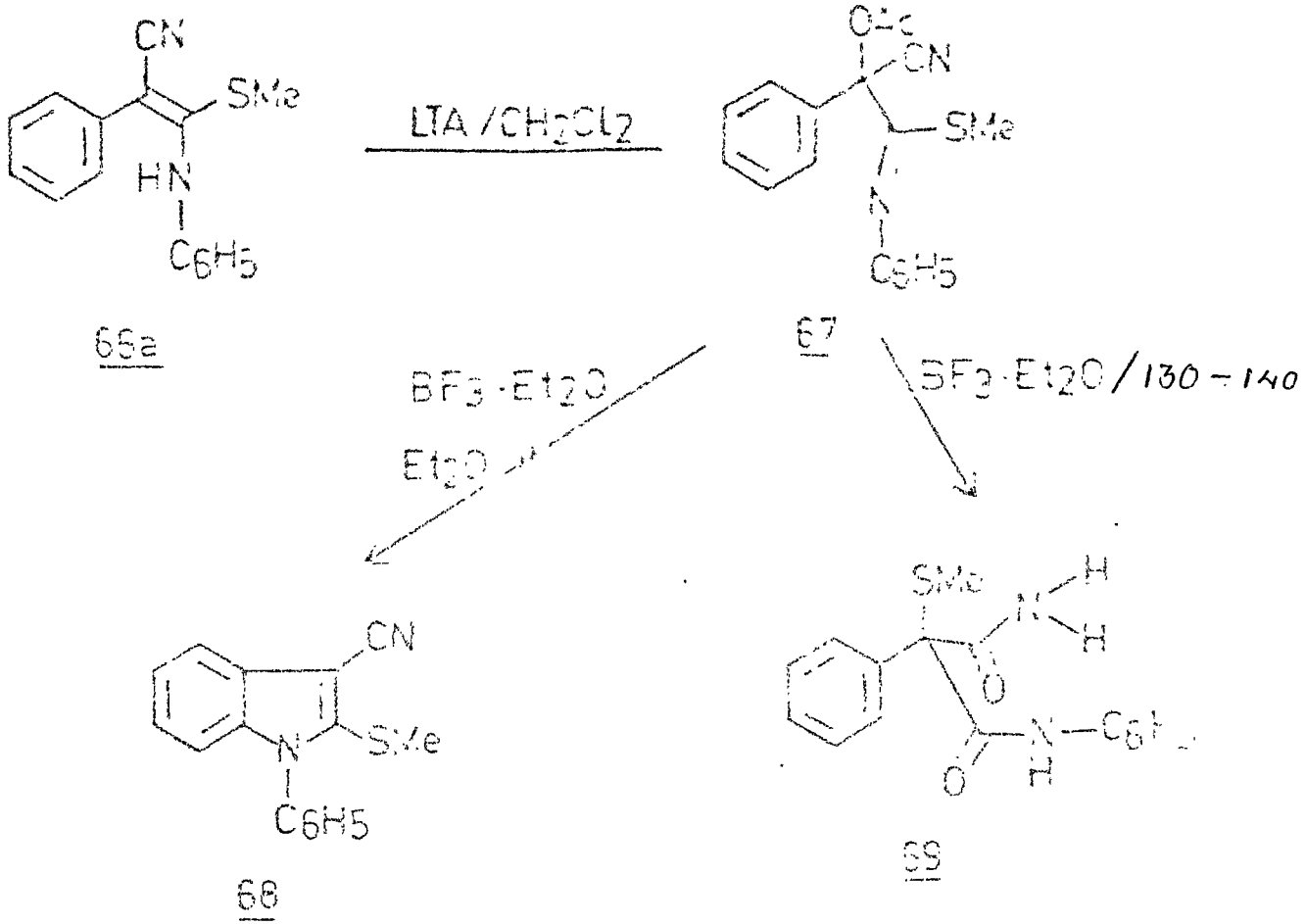


54, 66a . R = R1 = R2 = H
b , R = H , R1 = R2 = OMe
c , R = R2 = H , R1 = OMe
d , R = R1 = R2 = OMe
e , R = R2 = H , R1 = Cl

Scheme 15

that all S,N-acetals exist in enamino tautomeric form (66A) and rule out the imino tautomeric structure 66B (Scheme 15).

When the S,N-anilinoacetal (66a) derived from phenylacetonitrile was oxidized with one eqv. of LTA in methylene chloride, work-up and column chromatography of the reaction mixture afforded a solid (52%) along with an unidentifiable viscous semisolid. The solid was characterized as the iminoacetate 67 on the basis of its spectral and analytical data. Thus it exhibited molecular ion peak at m/z (324, 30%) and analysed for $C_{18}H_{16}N_2O_2S$. The other peaks in the mass spectrum of 67 were assigned to the respective fragments shown in the scheme 17. The infrared spectrum (KBr) of 67 exhibited strong absorption at 1760, 1615 and 1595 cm^{-1} due to acetoxy carbonyl and C=N stretching vibrations and the ν C≡N appeared at 2242 cm^{-1} as a weak band. The intensity of nitrile vibration band is known to be weakened when electron withdrawing group like acetoxy is present in the α-position.[21,22] Further confirmation of the structure of 67 was obtained from its n.m.r. spectrum ($CDCl_3$). It showed the disappearance of NH proton present in the n.m.r. spectrum of 66a at δ 6.2-6.45. The two singlets at δ 1.60 (3H) and 2.25 (3H) were assigned to the protons of methylthio and acetoxy methyl protons



66a

67

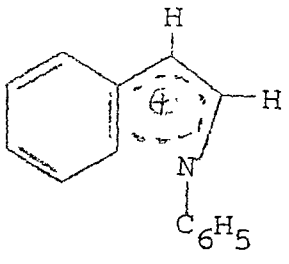
68

69

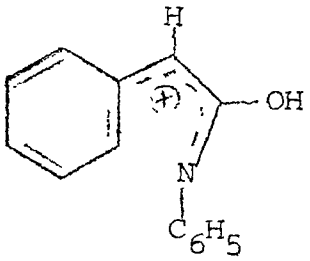
Scheme 16

respectively, while the aromatic protons appeared as multiplet between δ 6.85-6.79 (10H).

When the acetate (67) was refluxed with boron trifluoride etherate in ether for prolonged time in order to get the indole 68 (Scheme 16), it remained unchanged. However, when the cyclization of 67 was attempted by refluxing it directly with boron trifluoride etherate (130-140°) for 20 hrs, on work-up and column chromatography of the reaction mixture a light yellow colored semisolid (70%) was obtained which was characterized as the hydrolysed amide 69. It was analysed for $C_{16}H_{16}N_2O_2S$ and its mass spectrum exhibited molecular ion peak at m/z 300 (M^+, 15%), and the base peaks at m/z 194 (100%) and 210 (90%) were assigned to the ion 73 and 74 respectively. The i.r. spectrum (neat) of 69 exhibited broad band at 3400 cm^{-1}

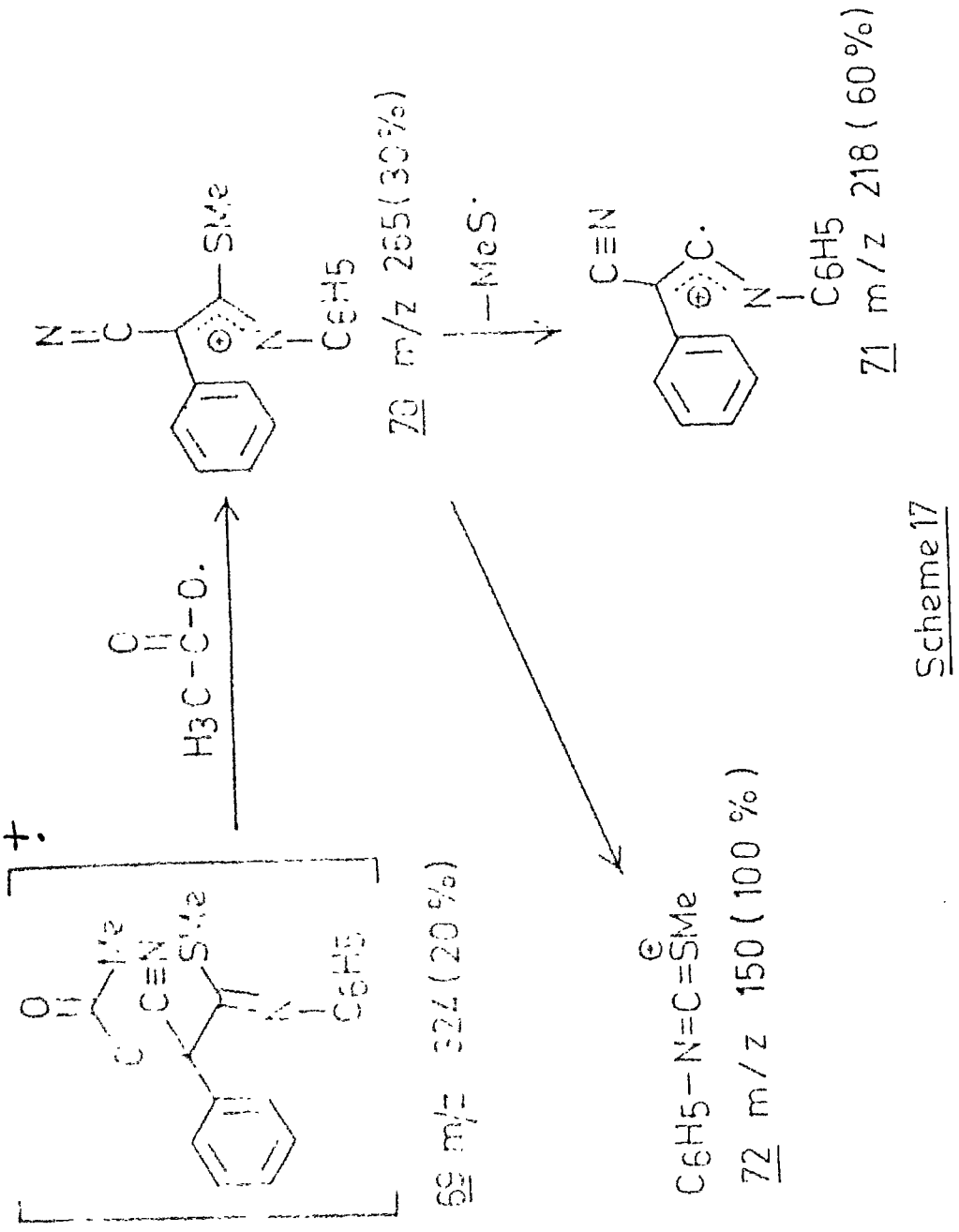


73 m/z, 194



74 m/z, 210

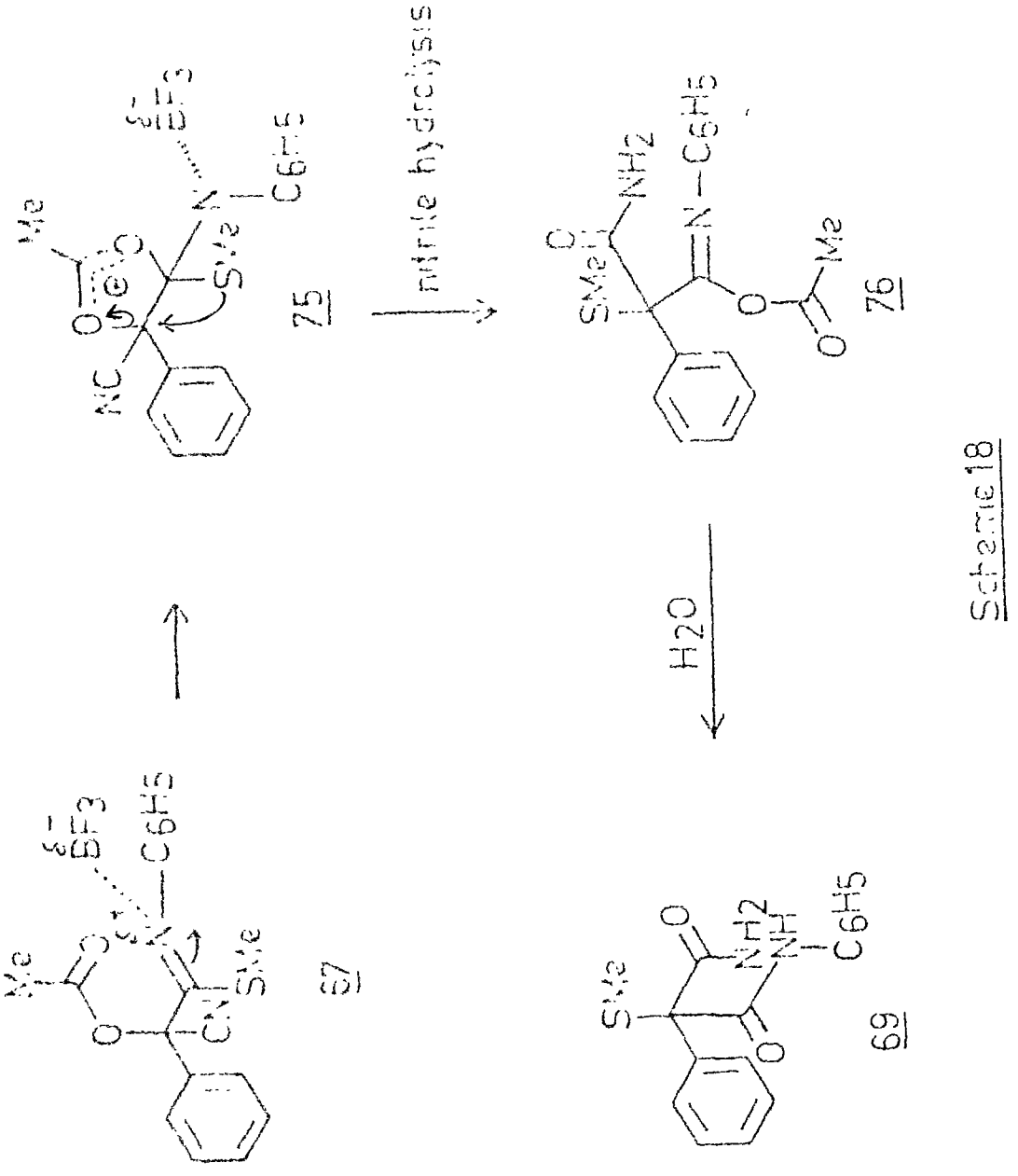
and bands at 1680 and 1660 due to NH of anilide and amide carbonyl stretching vibrations respectively. Its n.m.r.


+·
H3C–C–O·
—MeS·
69 m/z 324 (20 %)
70 m/z 255 (30 %)
71 m/z 218 (60 %)
72 m/z 150 (100 %)
C6H5–N=C=SMe

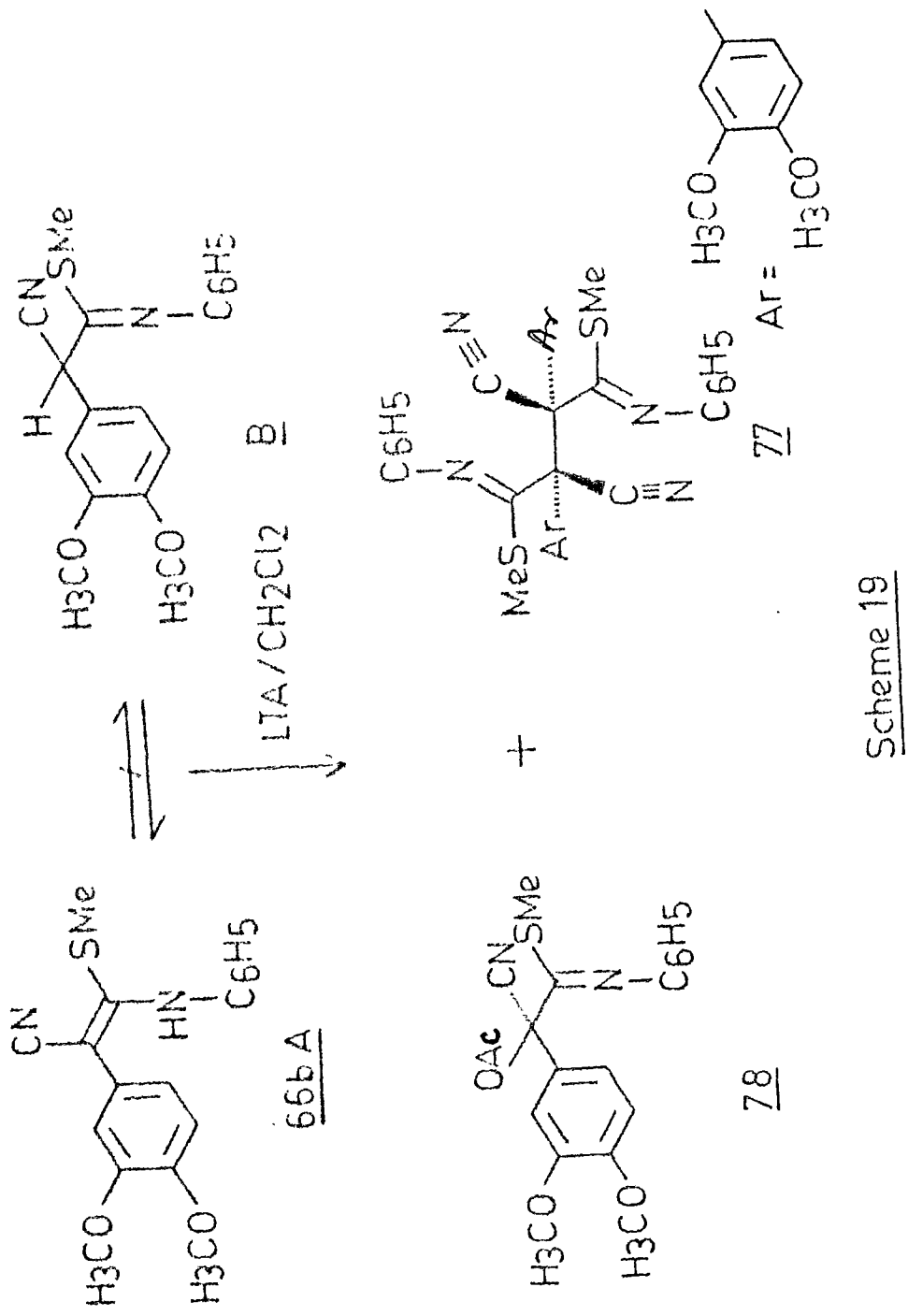
Scheme 17

spectrum ($CDCl_3$) showed a broad singlet (3H) at δ 1.80 due to methylthio group while the multiplet between δ 7.10-7.70 (13H) was assigned to the aromatic amide and anillide NH protons. The formation of 69 is presumed to be formed by BF_3 etherate assisted hydrolysis of 67 involving 1,2-methylthio shift in one of the steps (Scheme 18). Similarly 1,2-MeS shifts have been earlier encountered in acid catalysed hydrolysis of carbinol dithioacetals.[23,24]

After unsuccessful attempts to get indole derivative from the iminoacetate 67, the electron rich S,N-acetal (66b) derived from 3,4-dimethoxyphenylacetonitrile was investigated It was reasoned that the cyclization of iminoacetate 78 to indole derivative would be facilitated by the presence of 3,4-methoxy groups since the 4-methoxy group would assist the elimination of acetate ion during cyclization. Also the positively charged nitrogen would be stabilized by the electron donating effect of 3-methoxy group (Scheme 21).[17] When 66b was stirred with one eqv. of LTA at room temperature for 1.5 hr, the reaction mixture was triturated to give the [redacted] colourless solid which was separated and characterized as the oxidative dimer (77) (Scheme 19) (52%). The mother liquor after evaporation gave a product which was characterized as

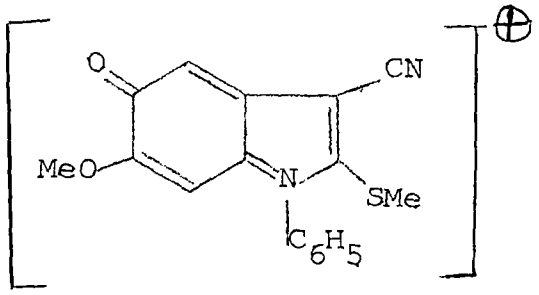


Scheme 18


H3CO
H3CO
CN
SMe
HN
C6H5
66b A
LTA / CH2Cl2
B
H
CN
SMe
N
C6H5
H3CO
H3CO
+
C6H5
N
C≡N
Ar
MeS
SMe
N
C6H5
C≡N
77
Ar =
H3CO
H3CO
OAc
CN
SMe
N
C6H5
H3CO
H3CO
78

Scheme 19

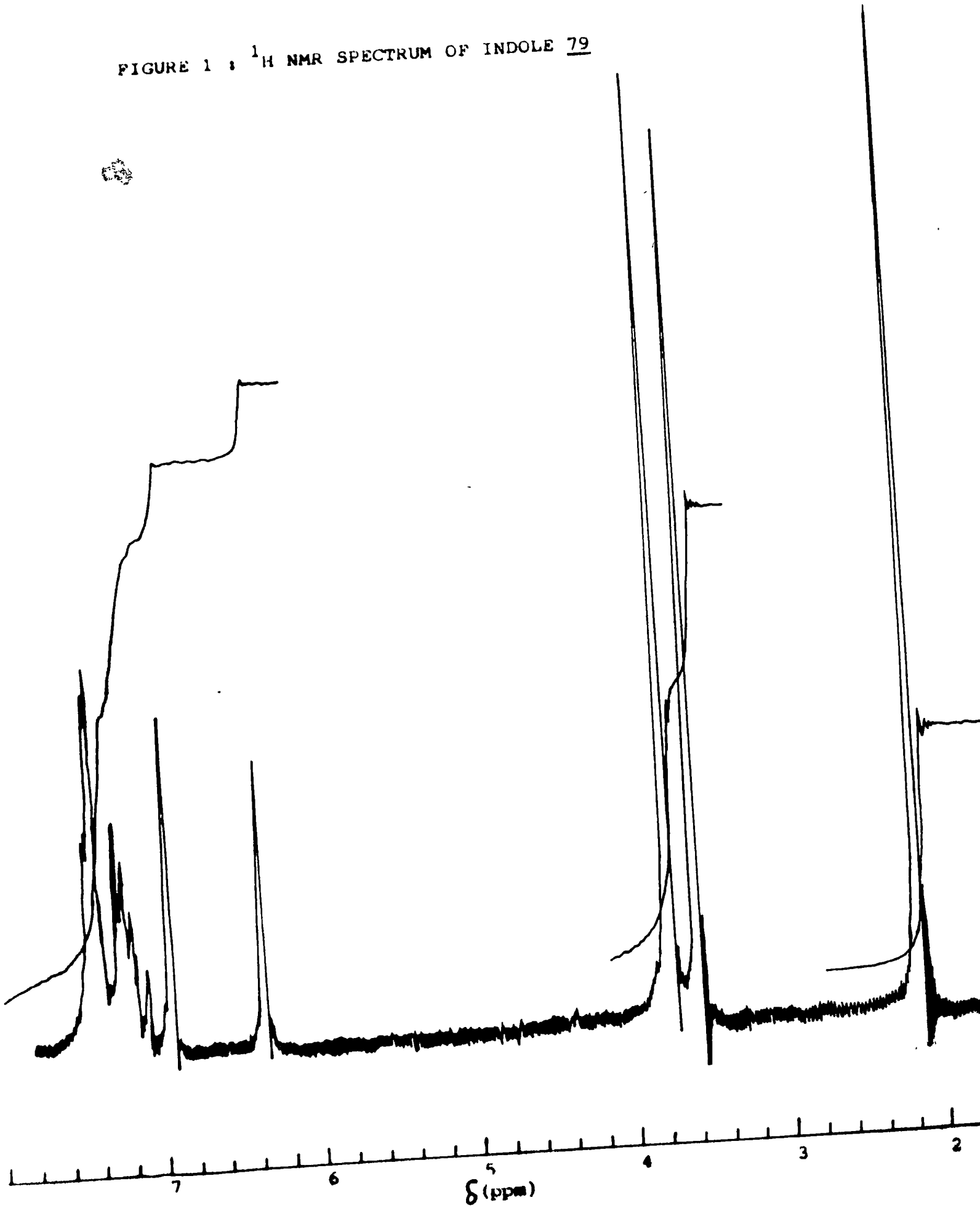
as iminoacetate 78. It was found to be unstable and no attempts were made to purify it further. It was then refluxed with BF_3Et_2O in ether for 0.5 hr, when the t.l.c. of the reaction mixture showed the formation of a new compound which after column chromatographic separation was characterized as 1-N-phenyl-2-methylthio-3-cyano-5,6-dimethoxyindole 79 (40% from S,N-acetal 66b; 95% from iminoacetate 78). It was analysed for $C_{18}H_{16}N_2O_2S$ and exhibited molecular ion peak in its mass spectrum at m/z 324 (M^+, 100%) and an intense peak at m/z 309 (M^+-15) which is probably due to ion 81. Its i.r. (KBr) spectrum showed a medium intensity peak



81 m/z, 309

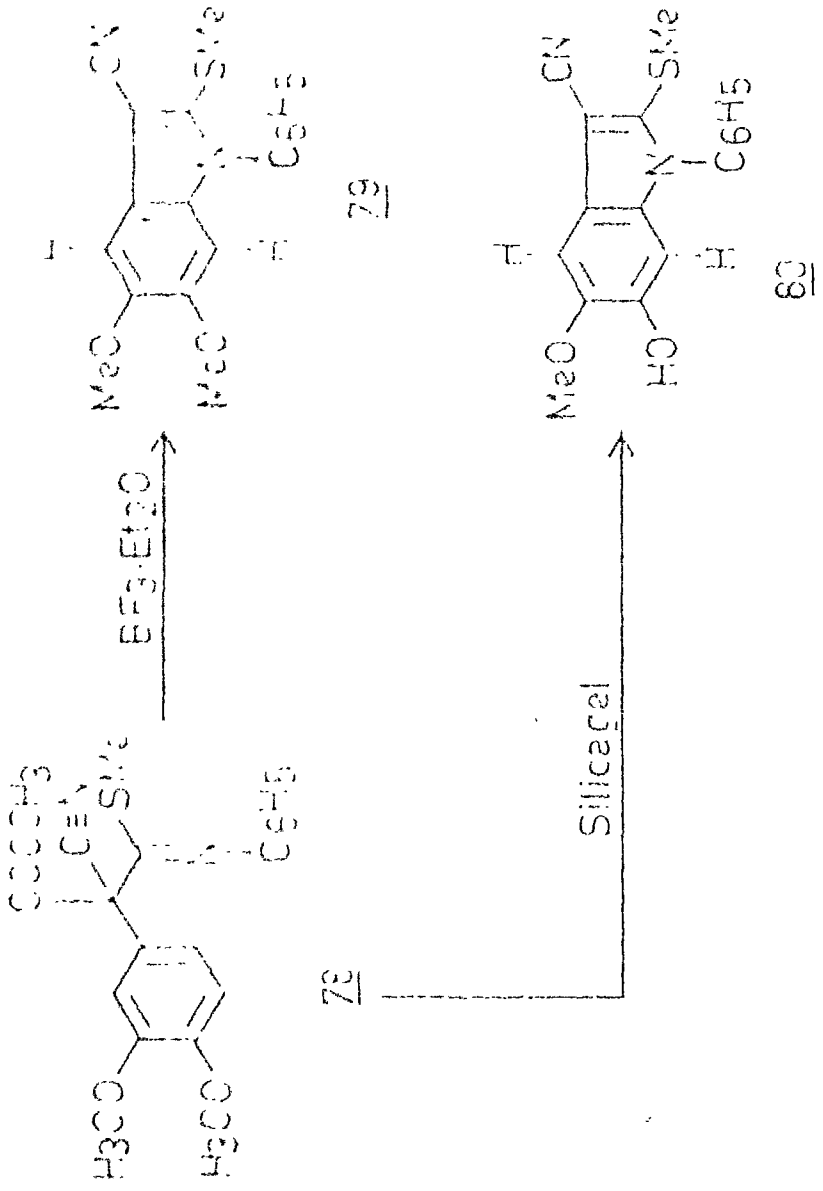
due to nitrile group at 2200 cm^{-1} and other bands at 1620, 1600, 1500, 1485 cm^{-1}. The structure of 79 was further confirmed by its n.m.r. spectrum ($CDCl_3$) (Figure 1). It showed three singlets at δ 2.20, 3.78 and 3.95 (3H each) due to methylthio and two methoxy groups respectively. The H-4 and H-7 protons of indole (79) appeared as singlets at δ 7.13 (1H) and δ 6.52 (1H) respectively which is in conformity with the structure.[25]

FIGURE 1 : ^{1}H NMR SPECTRUM OF INDOLE 79



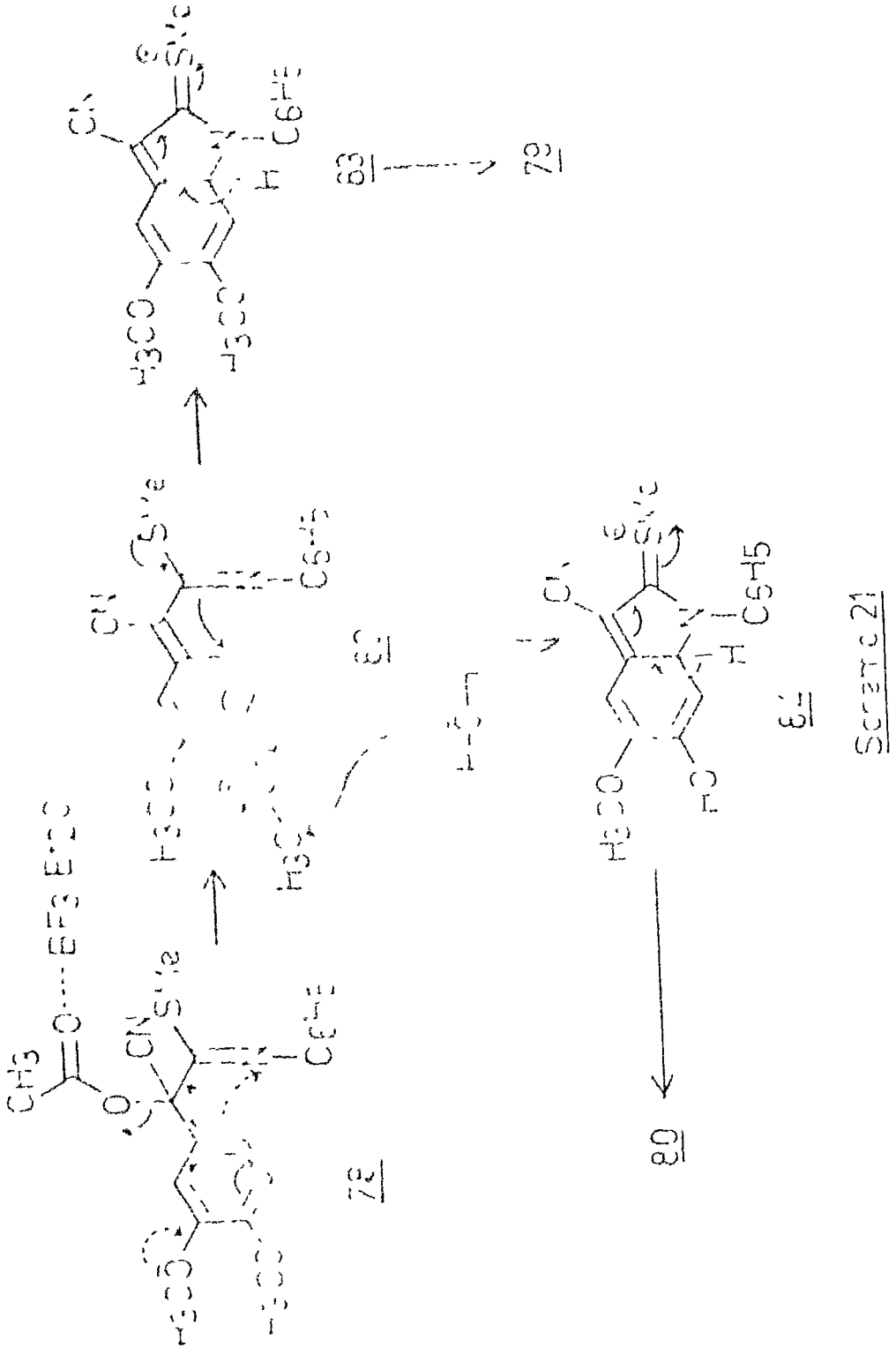
The higher field shift of H-7 proton is due to shielding effect of 1-N-phenyl group. The aromatic protons of 1-N-phenyl group appeared as multiplet (5H) between δ 7.22-7.80.

Interestingly, when the crude iminoacetate (78) was passed through silica gel column in an attempt to purify it, the eluted product was found to be identical with 1-N-phenyl-2-methylthio-3-cyano-5-methoxy-6-hydroxyindole (80) (80% from iminoacetal 78) (Scheme 20). It showed molecular ion peak at m/z 310 (M^+, 100%) and other peak at m/z 295 (M^+-CH_3) due to demethylated indole ion. The elemental analysis of 80 was in conformity with the molecular formula ($C_{17}H_{14}N_2O_2S$) while its i.r. spectrum (KBr) exhibited broad band at 3507 cm^{-1} and a medium intensity band at 2210 cm^{-1} due to phenolic OH and nitrile stretching vibrations. The signal at δ 3.78 due to 6-methoxy protons in n.m.r. spectrum of 78 was absent in 80 and showed instead two singlets at δ 2.32 (3H) and 3.95 (3H) due to SMe and 5-methoxy protons. The corresponding H-4 and H-7 protons appeared as singlets at δ 6.60 (1H) and δ 7.07 (1H) respectively while the signal due to 1-N-phenyl aromatic protons was present as a broad multiplet at 7.20-7.68 (5H). The probable mechanism of the formation of 79 and 80 from the imino-acetate 78 is shown in the scheme 21. Borontrifluoride


BF3.Et2O
Silicagel
Scheme 20

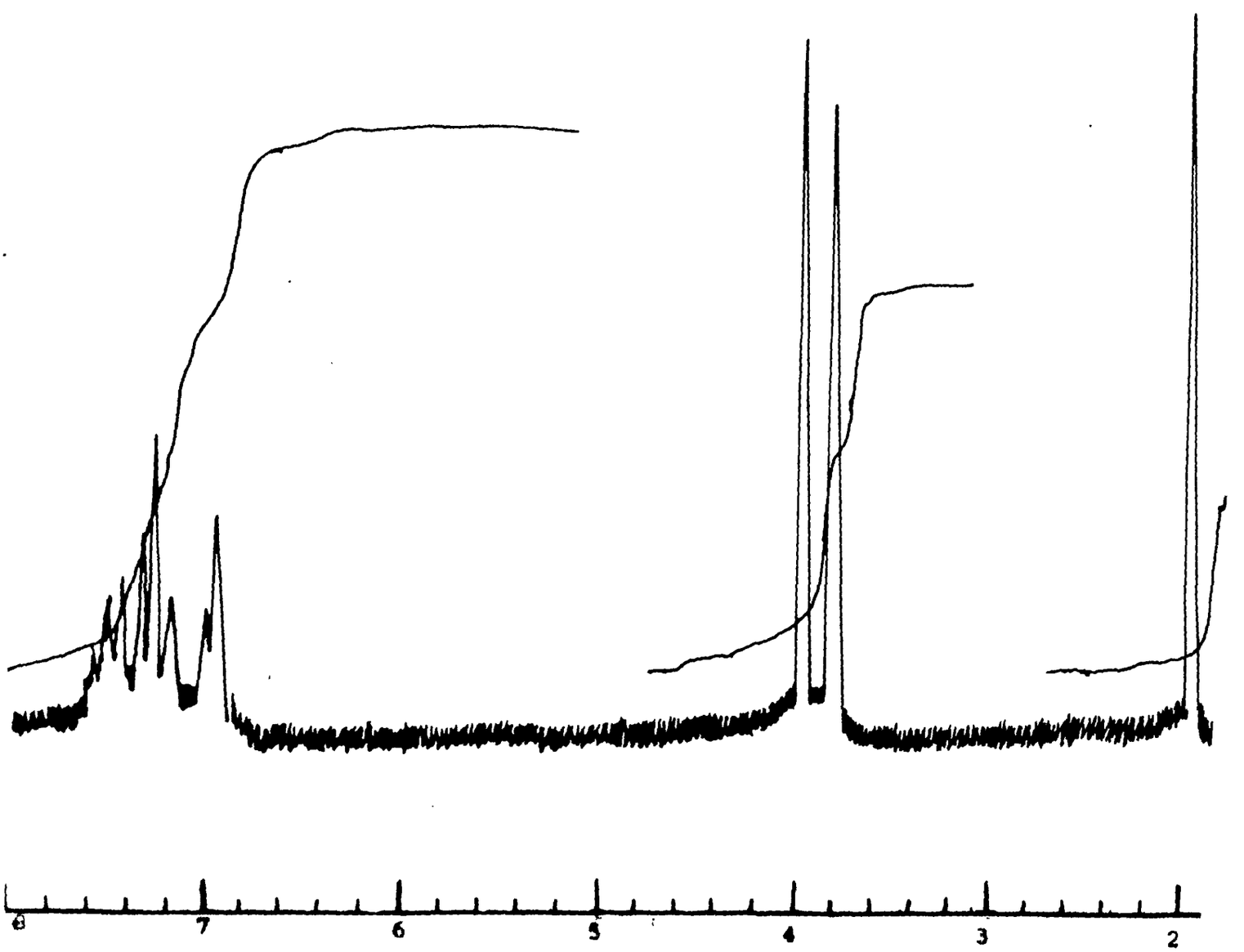
assisted elimination of acetate ion assisted by p-methoxy group (Scheme 21) affords the quinone methide intermediate 82, which on subsequent cyclization yields the indole 79. Alternatively the intermediate 82 undergoes demethylation by water during silicagel column chromatography to give the corresponding 6-hydroxyindole 80 (Scheme 21).

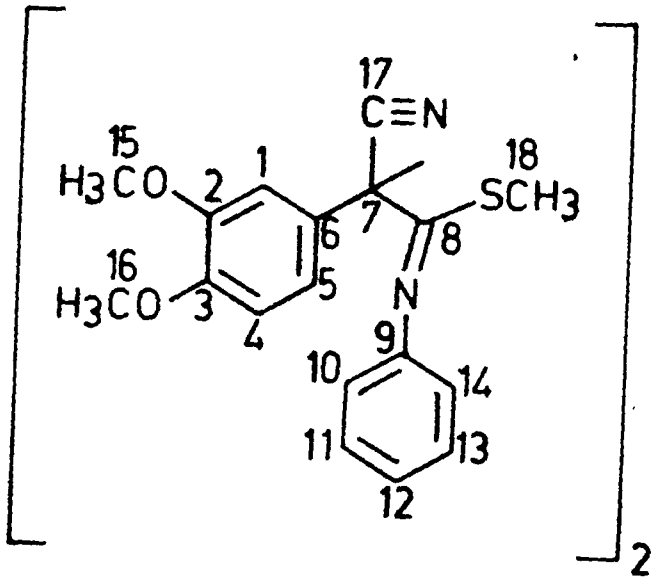
The light yellow solid (A) obtained after oxidation of 66b was assigned the symmetrical dimeric structure 77 formed by coupling of S,N-acetal 66b through its carbon atom (Scheme 19 and 22). The symmetry of the dimer is reflected in its ^{1}H and ^{13}C n.m.r. spectrum (Figures 2 and 3). The characteristic i.r. band at 3310 cm^{-1} of 66b was found absent in 77. The strong band at 1600 cm^{-1} was assigned to C=N stretching vibration, while the weak band at 2200 cm^{-1} was assigned to ν C≡N which was in line with our earlier observations.[21,22] The dimer showed in its n.m.r. ($CDCl_3$) the signals similar to that of 66b: at δ 1.85 (s, 3H, CH_3S-), 3.70 (s, 3H, CH_3O-); 3.85 (s, 3H, CH_3O); 6.75-7.82 (m, 8H, arom) except the signal due to NH proton (δ 6.30, S, 1H) observed in 66b. The absence of signal between δ 5.3-6.70 ([redacted] due to methine proton [redacted]) rules out the tautomeric iminostructure 86. The elemental analysis of 77 was in agreement with the molecular formula



Scheme 21

FIGURE 2 : ^{1}H NMR SPECTRUM OF DIMER 77



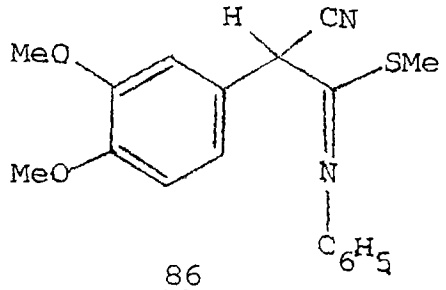


C-1	112.0 d	C-10	119.0 d
C-2	147.8 s	C-11	128.5 d
C-3	149.5 s	C-12	124.5 d
C-4	110.0 d	C-13	128.5 d
C-5	122.0 d	C-14	119.0 d
C-6	123.0 s	C-15	57.5 q
C-7	64.5 s	C-16	57.7 q
C-8	158.0 s	C-17	117.0 s
C-9	146.5 s	C-18	16.0 q

^{13}CNMR CHEMICAL SHIFTS OF 77 as δ (ppm.)

Figure 3

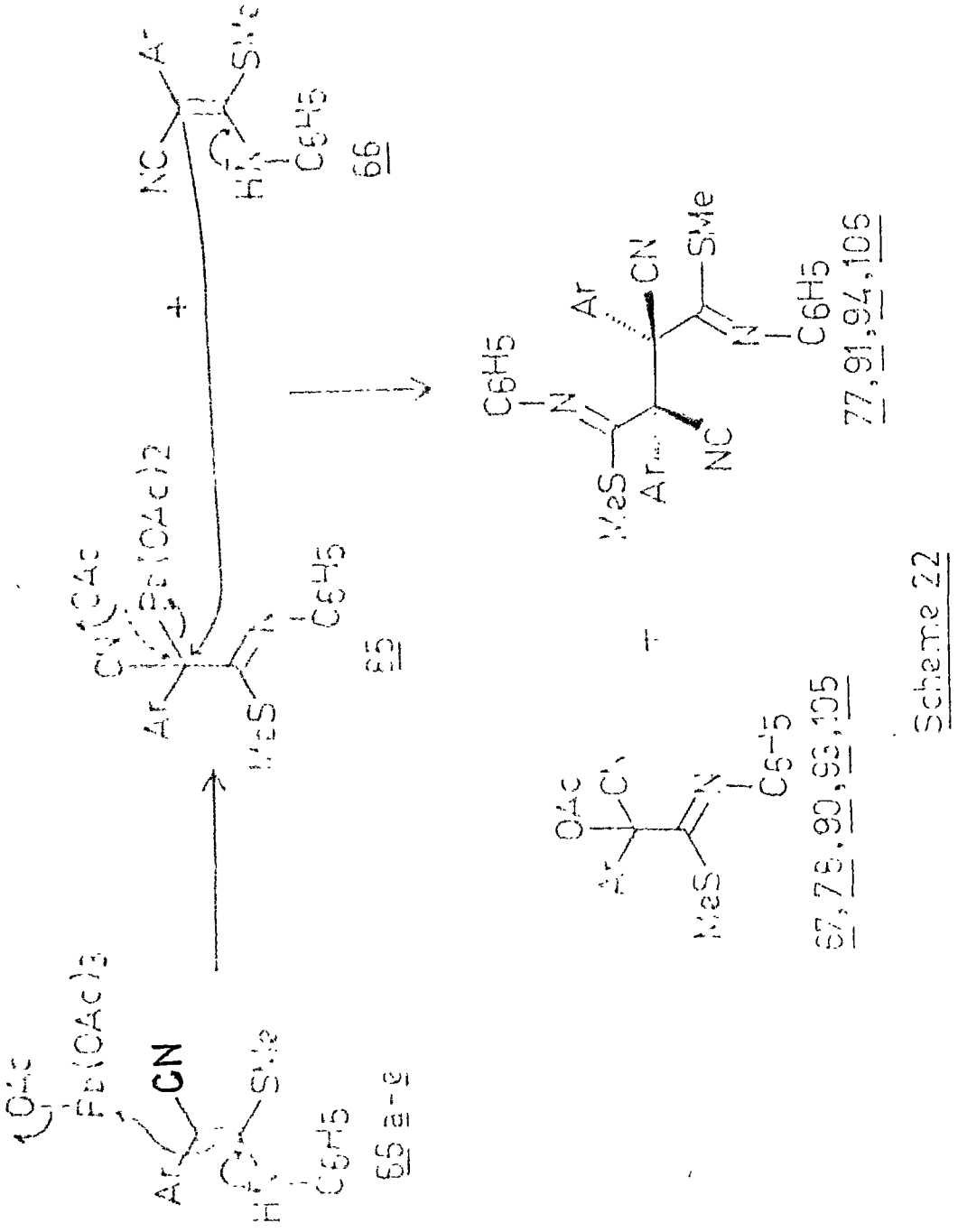
($C_{36}H_{34}N_4O_4S_2$) and its mass spectrum* exhibited peaks at m/z 326 (20%) 278 (75%) and 263 (100%) which are probably due to ions shown in the scheme 23. The definite proof for the symmetrical oxidative dimer 77 was obtained by comparison of



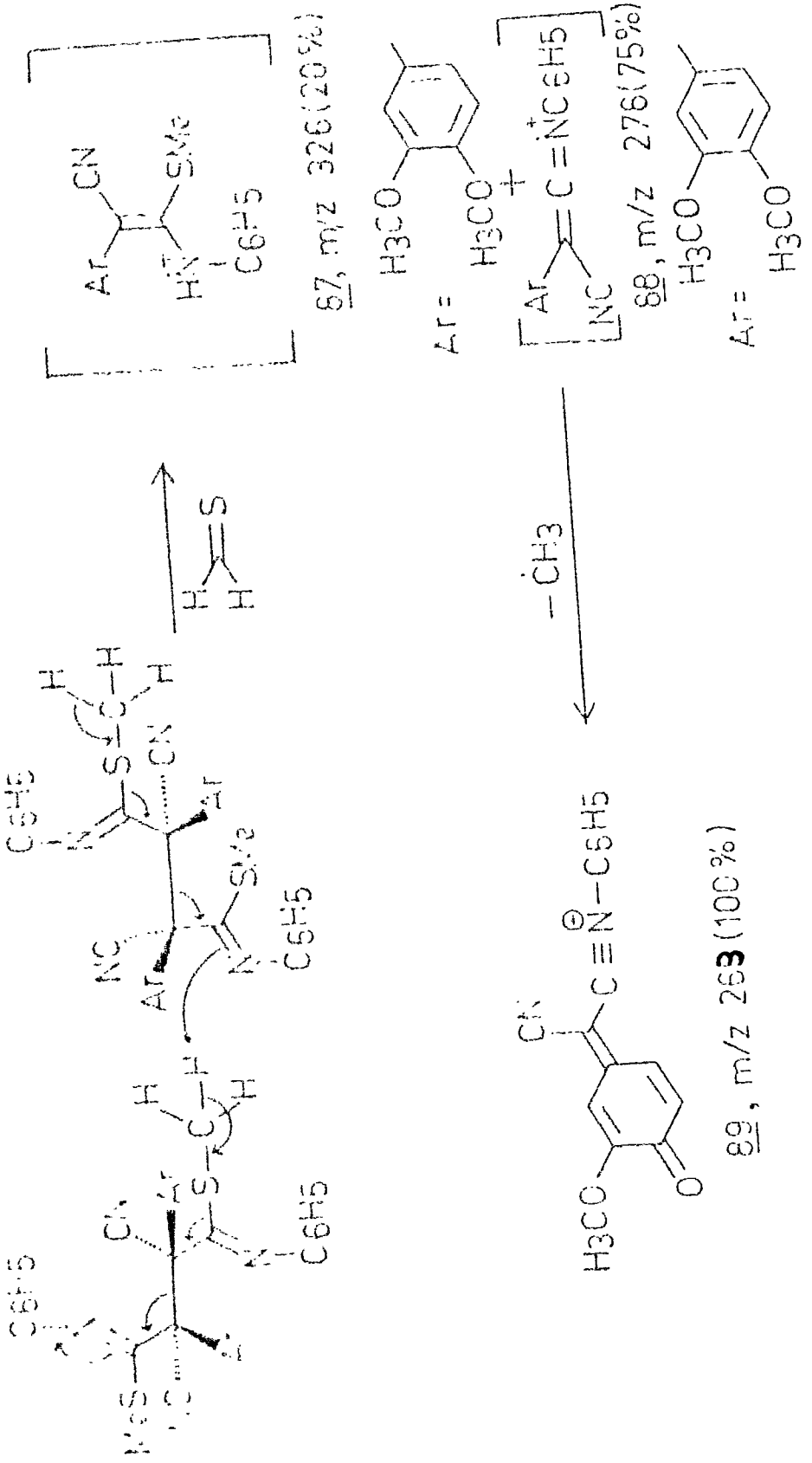
86

^{13}C n.m.r. spectrum of 66b and 77 (Figures 4 &3). The α carbon of 66b (to which nitrile and aryl groups are attached) appeared at δ 93.5 (s.) of 66b which was absent in 77 between δ 70-110. The signal due to α -carbon in 77 appeared at δ 64.5 (s) showing its Sp^3 hydridized nature. The multiplicity of this signal (singlet) in the off resonance spectra rules out the tautomeric structure 86 since the α -carbon in 86 should appear as doublet.

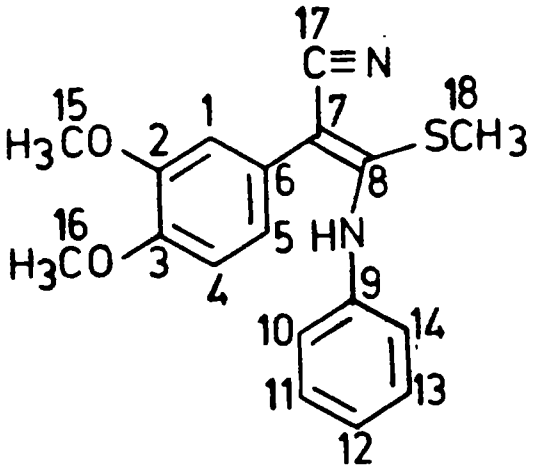
The LTA oxidation of S,N-acetal 66c derived from p-methoxyphenylacetonitrile was next investigated. The reaction followed similar course as in the oxidation of the corresponding dimethoxy derivative 66b. After work-up, the reaction mixture gave the oxidative dimer 91 and the crude iminoacetate 90 in 60% and 34% yields respectively. (Scheme 24). The



Scheme 22



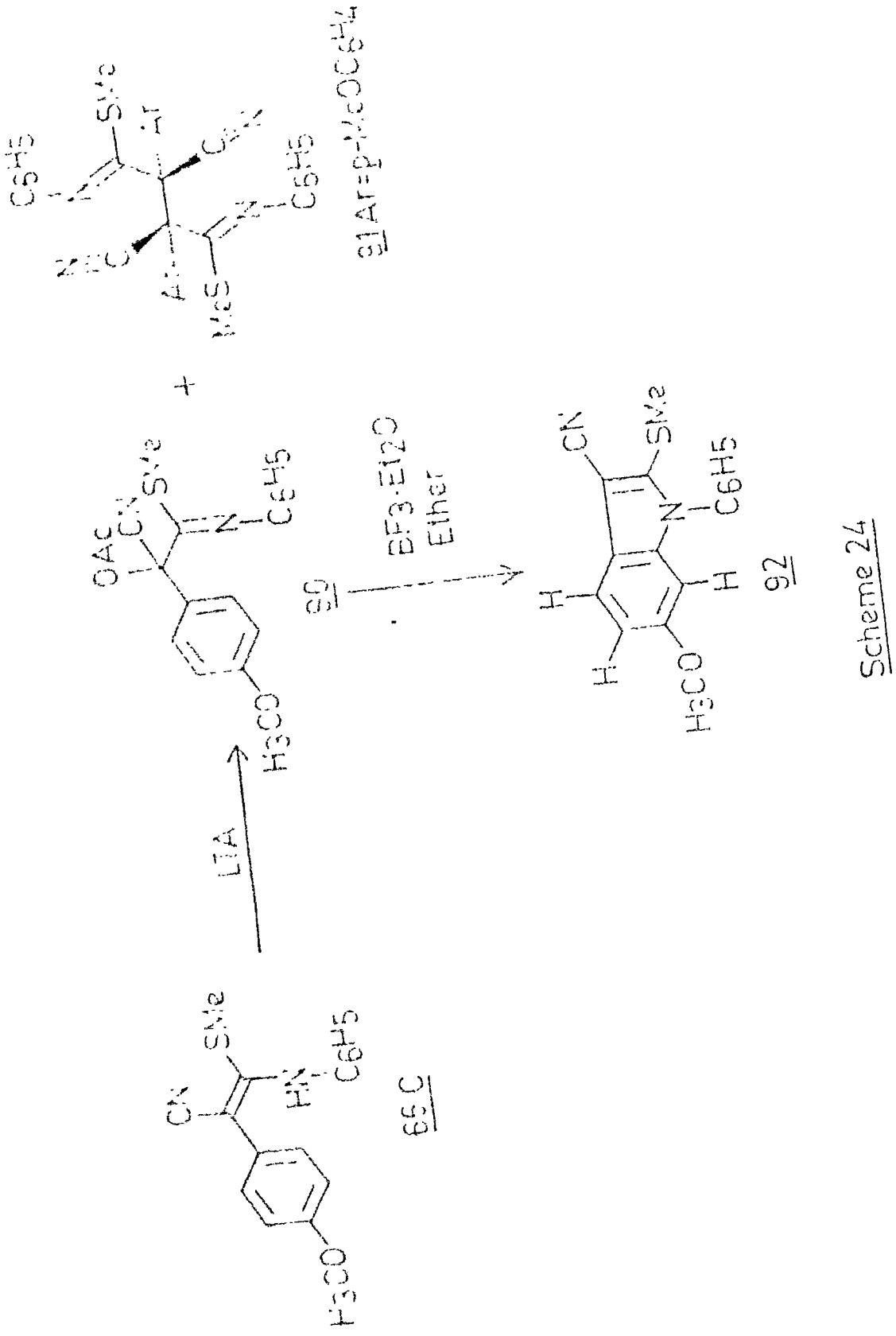
Scheme 23



C-1	110.5d	C-10	119.0d
C-2	148.0s	C-11	128.7d
C-3	148.0s	C-12	120.0d
C-4	110.0d	C-13	128.7d
C-5	123.5d	C-14	119.0d
C-6	125.0s	C-15	55.7q
C-7	93.5s	C-16	55.5q
C-8	151.5s	C-17	120.3s
C-9	139 5s	C-18	15.5q

^{13}C NMR CHEMICAL SHIFTS OF 66b as δ(ppm)

Figure 4



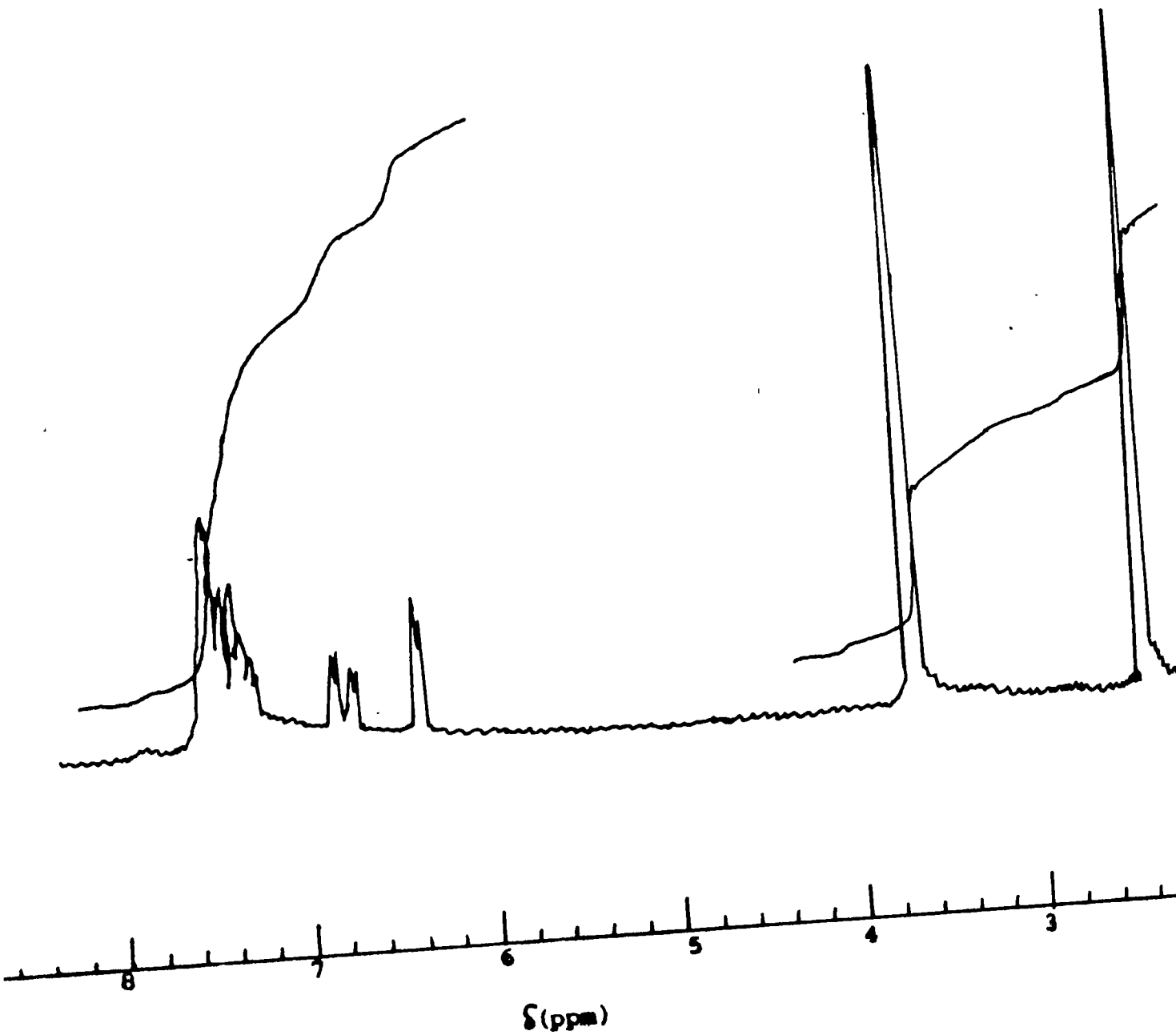
Scheme 24

structure of the dimer (91) was confirmed by analytical and spectral (including ^{13}C n.m.r.) data (experimental). Similarly BF_3 catalyzed cyclization of 90 under identical conditions gave the corresponding 1-N-phenyl-2-methylthio-3-cyano-6-methoxyindole (92) in 92% yield (from iminoacetate 90) (Scheme 24). The i.r., mass spectral and analytical data of 92 were in agreement with the assigned structure (experimental). Its n.m.r. spectrum ($CDCl_3$) exhibited two singlets at δ 2.4 (3H) and δ 3.68 (3H) due to [redacted] methylthio and methoxy protons respectively. The signals due to H-7 and H-5 protons were present at δ 6.35 (d, J=2.5 Hz, 1H) and 6.8 (dd, J=9 Hz and 2.5 Hz; 1H) respectively while the corresponding H-4 proton signal was merged with 1-N-phenyl protons which appeared as multiplet between δ 7.2-7.67 (6H) respectively (Figure 5).

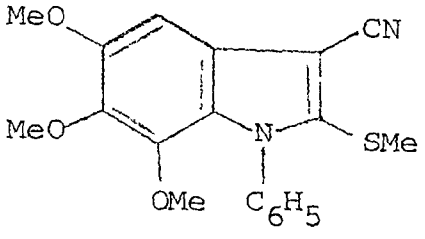
When the crude iminoacetate 90 was passed through silica gel column, no pure identifiable product could be isolated. The mechanism of the formation of indole (92) from iminoacetate 90 is similar to that of 79 (Scheme 21).

When the S,N-acetal 66d derived from 3,4,5-trimethoxyphenyl acetonitrile was oxidized with LTA under the identical conditions and the oxidative dimer (94) was obtained in low

FIGURE 5 : ^{1}H NMR SPECTRUM OF INDOLE 92

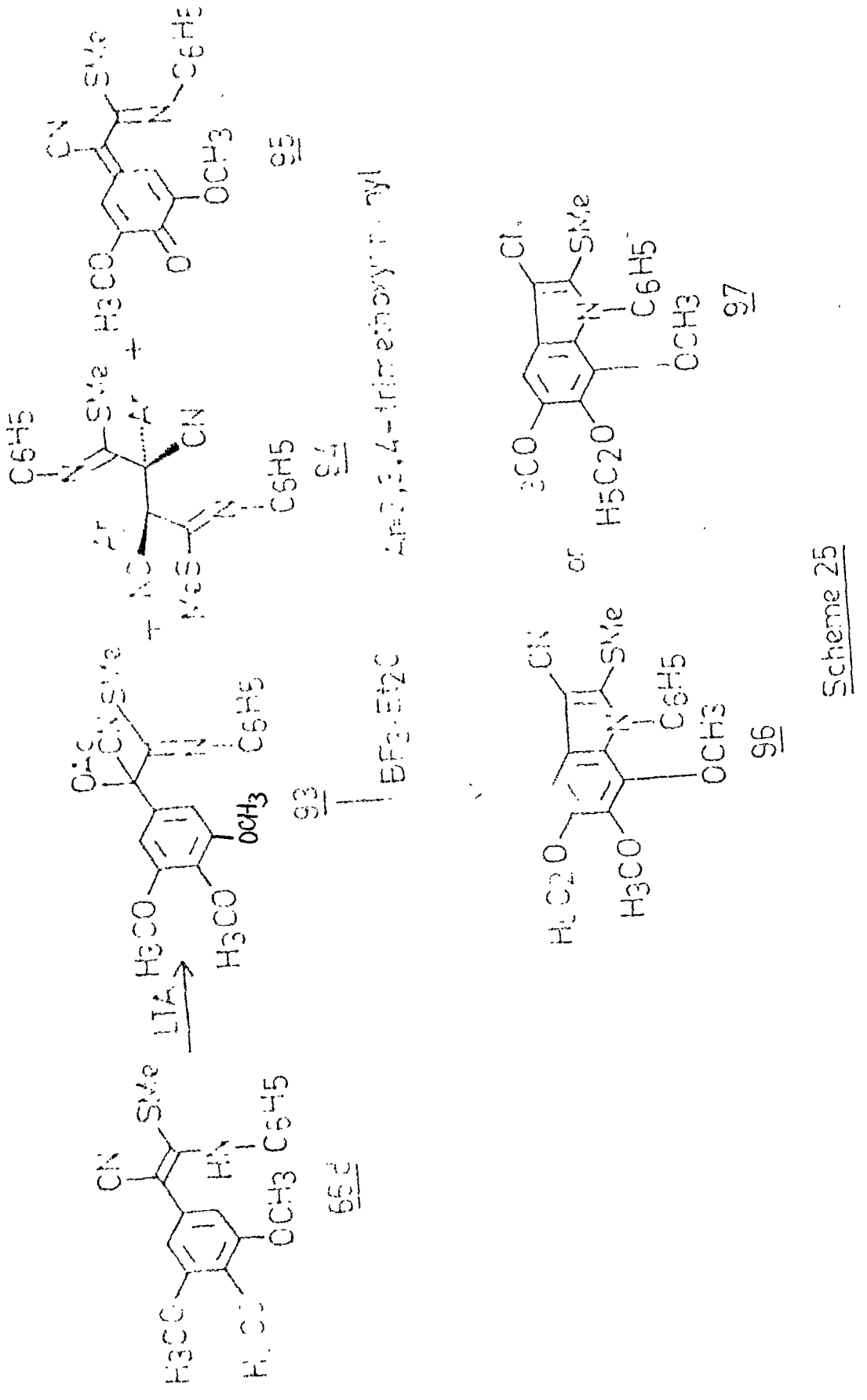


yield (20%). The structure of 94 was confirmed with the help of spectral and analytical data and was in agreement with those of other dimers 77 and 91. Filtration of 94 and evaporation of the mother liquor afforded a viscous residue (A) which was found to be a mixture of two products on tlc. It showed strong absorption at 1760 and 1660 cm^{-1} in its i.r. spectrum. Column chromatography of the mixture on silica gel gave only one product in 35% yield (based on 66d) which was characterized as quinone (95) (Scheme 25). On the other hand when the mother liquor was stirred with boron trifluride etherate at room temperature, it gave an unexpected indole 96 or 97 instead of 98 in which one of the methoxy group was replaced by an ethoxy group.



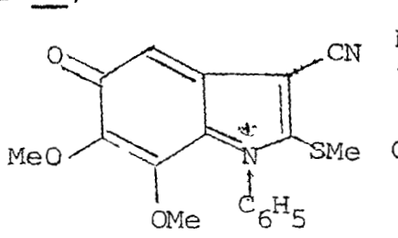
98

In another experiment, quinone 95 was stirred with BF_3Et_2O in ether under similar conditions, which was recovered unchanged and demonstrates that the indole 96 (or 97) is not derived from the 95 but obtained from 93 present in the

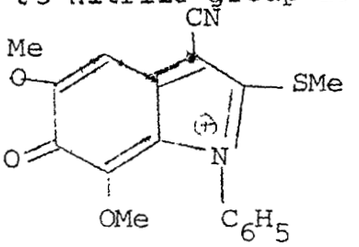


Scheme 25

reaction mixture. The structure of 95 and 96 (or 97) were confirmed with the help of spectral and analytical data. The 95 showed molecular ion peak at m/z 340 and analysed for $C_{18}H_{16}N_2O_3S$. Its infrared spectrum showed strong band at 1660 and 1590 cm^{-1} due to quinone carbonyl and C=N stretching vibration while the band at 2200 cm^{-1} was assigned to the nitrile stretching vibration. The n.m.r. spectrum (Figure 6) of 95 showed a singlet at δ 2.58 (3H) due to methylthio protons, while two methoxy groups appeared as singlets at δ3.75 (3H) and 3.80 (3H), the two quinone ring protons appeared as broad singlets at δ6.1 (1H) and δ 6.31 (1H) respectively while the multiplet between δ 6.72-7.41 (5H) was assigned to the aromatic protons. The ultraviolet spectrum of 95 (λ max (MeOH) 355 (logϵ , 3.194) and 390 (Sh) (logϵ 1.54) was in conformity with the structure 95. The indole (96) (or 97) similarly was analysed for $C_{20}H_{20}N_2O_3S$ and exhibited molecular ion peak at m/z 368 (M^+, 28%) and the base peak was present at m/z 339 (100%) (M^+-29) which probably was due to ions 98A or 99. The i.r. spectrum of 96 (or 97) showed band due to nitrile group at 2215 cm^{-1}.

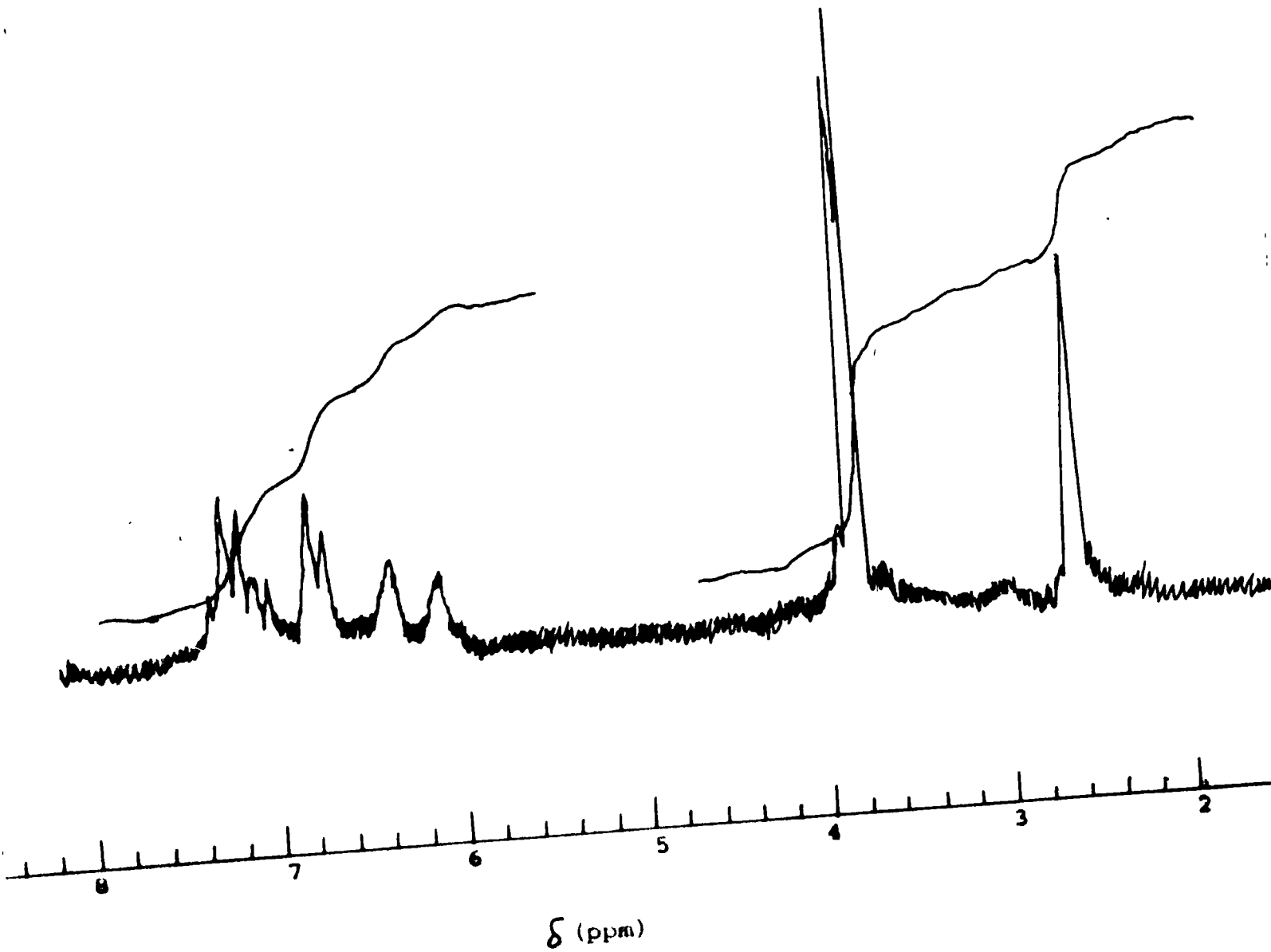


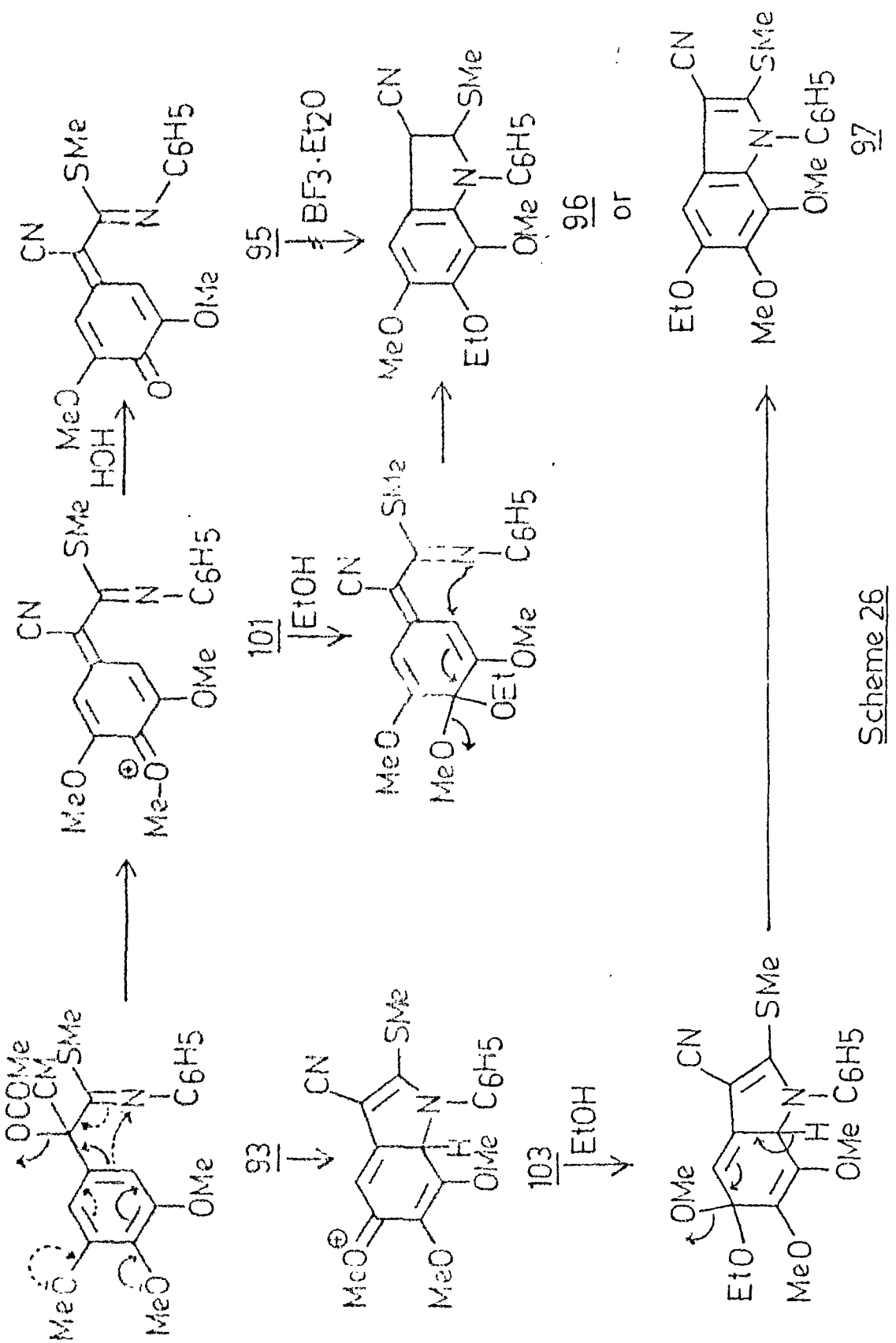
98A



99

FIGURE 6 : ^{1}H NMR SPECTRUM OF QUINONE 95

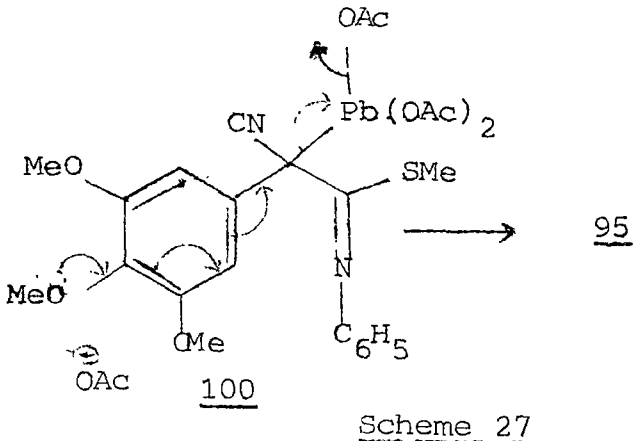




Scheme 26

The three singlets present at δ 2.4 (3H), 3.35 (3H) and 3.90 (3H) were assigned to methylthiogroup and methoxy groups present at 7 and 5 (or 6) positions respectively. The 7-methoxy group appears at higher field due to sheilding by 1-N-aromatic ring. A triplet (3H) and quartet (2H) present at δ 1.35 (3H) and δ 3.9 (2H) respectively were assigned to 5 (or 6) ethoxy group, while the H-4 proton appeared as singlet(1H) at δ 6.85 along with a multiplet between δ 7.20-7.71 (5H) due to 1-N-phenyl aromatic proton. The position of the exchanged alkoxy group however could not be fixed though it is presumed to be exchanged at position 6.

The probable mechanism for the formation of 95 and 96 (or 97) is shown in scheme 26. The quinone (95) can also, arise from 66d by the decomposition of plymbylated adduct (100) (Scheme 27). It appears that the ethoxy group is



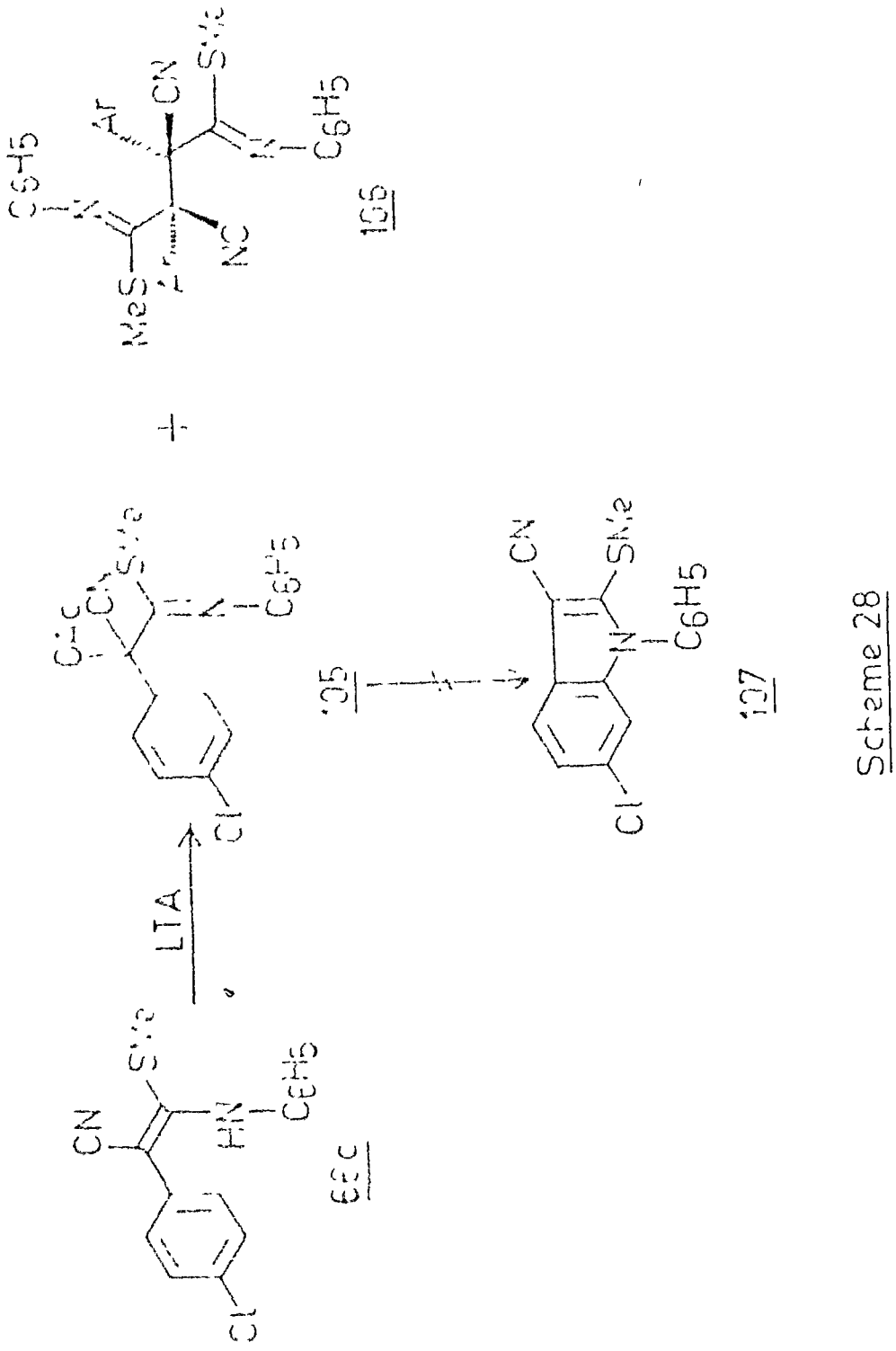
Scheme 27

incorporated in 96 or 97 through displacement of the original methoxy group. The failure of the quinone 95 to undergo cyclization to any of the indoles 96 or 97 is probably due to its rigid structure. The Dreiding model shows considerable steric repulsion between N-phenyl and methoxy group of 95.

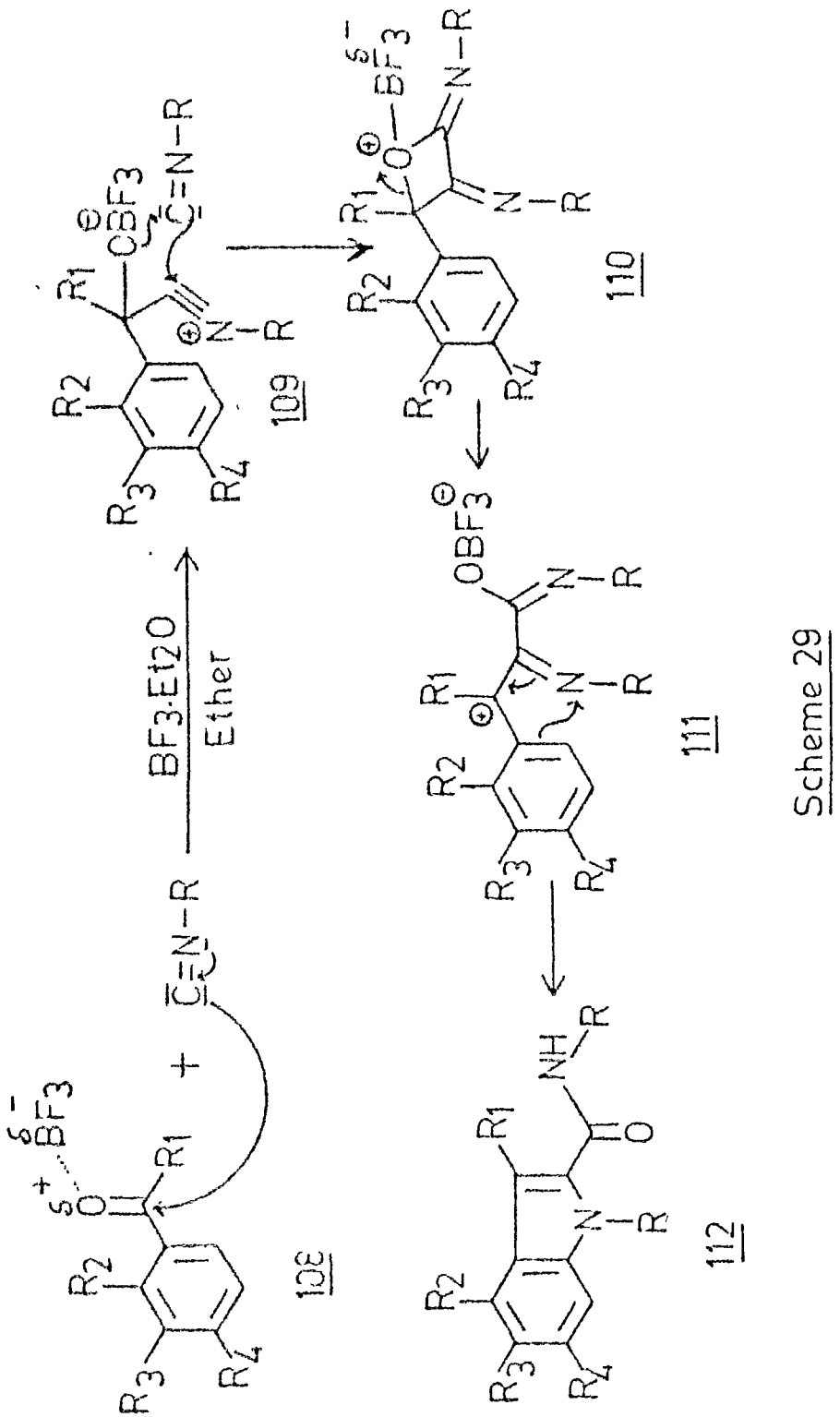
The LTA oxidation of S,N-acetal (66e) derived from p-chlorophenylacetonitrile under similar conditions gave two solid products which were characterized as the imminoacetate (48%) 105 and the oxidative dimer 106 (47%) (Scheme 28). The subsequent attempts to cyclize 105 to the corresponding 6-chloroindole (107) under different acidic conditions were not successful. Only the unreacted starting material was recovered.

III.5.2 CONCLUSION

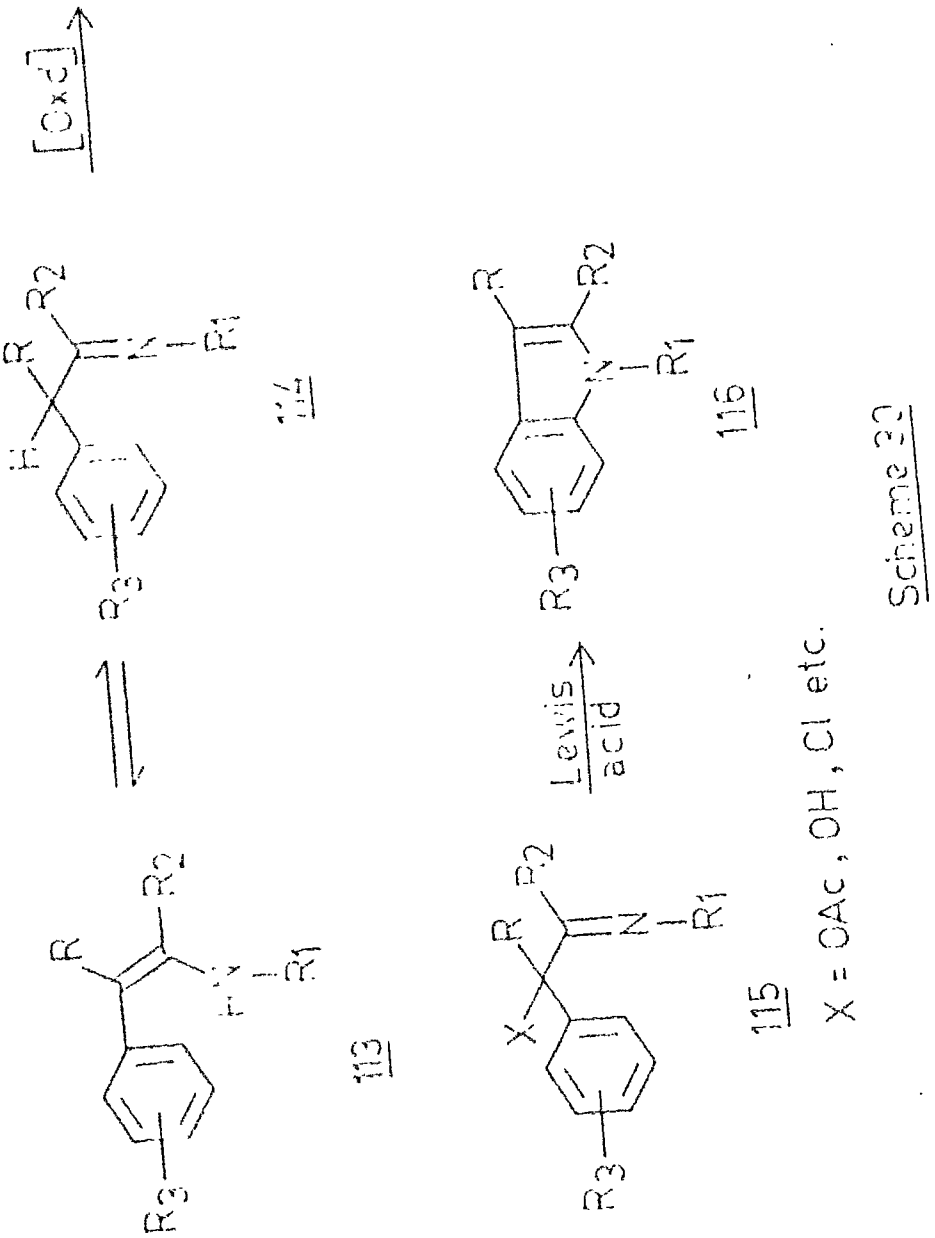
The LTA oxidations of S,N-acetals derived from aryl acetonitriles yield both iminoacetates and dimeric oxidation products. Attempts to isolate iminoacetates exclusively in these oxidations by varying the reaction conditions were not successful. The iminoacetates derived from S,N-acetals (66b-d) having methoxy groups in the aryl ring could be cyclized to the corresponding indole derivatives in good yields. However the corresponding iminoacetates derived from S,N-acetals (66a & 66e) with no activation in the aryl ring failed to cyclize to the



Scheme 28



Scheme 29



Scheme 30

corresponding indole derivatives. The BF_3 catalyzed cyclizations of the iminoacetates 78, 90 and 93 to the respective indoles 79, 80, 92 and 96 provides a novel approach to indole derivatives via cationic cyclization of the corresponding 1,3-diaryl-1-azaallyl carbonium ions which are not reported in the literature.[26,27] (scheme 29 and 30)

III.6 EXPERIMENTAL

Melting points were determined on a 'Boetius' apparatus (made in Germany) and are uncorrected. The i.r. and u.v. spectra were recorded on "Perkin-Elmer 297" and "Beckman 26" spectrophotometers respectively. The ^{1}H n.m.r. spectra were recorded on Varian EM-390 spectrometer using TMS as an internal standard and the chemical shift values are expressed in δ (ppm).

The reagents

The reagent lead tetraacetate (LTA) was prepared before use according to the reported method. A 50% suspension of sodium hydride was used. Dimethyl formamide was dried over lime. Methylene chloride was dried over calcium chloride.

The starting materials

The commercial samples of acetophenone, p-methylacetophenone, p-chloroacetophenone, phenylacetonitrile (64a), 4-methoxyphenylacetonitrile (64c), 3,4-dimethoxyphenylacetonitrile (64b) 3,4,5-trimethoxyphenylacetonitrile (64d), 4-chlorophenylacetonitrile (64e) ethylamine solution (40%), were used without purification.

The commercial samples of aniline, p-toluidine, p-anisidine, benzylamine were purified before use.

The phenylisothiocyanate, b.p. 90° (10 mm)[28] was prepared according to the standard method.

The keten-S,S-acetals: 3,3-bis(methylthio)-1-phenyl-2-propen-1-one, m.p. 93° and 3,3-bis(methylthio)-1-(p-methylphenyl)-2-propen-1-one., m.p. 104-5° were prepared according to the method reported[29] earlier by reacting one eqv. of the respective ketone with one eqv. of carbon disulfide and two eqv. of sodium t-butoxide in dry benzene followed by alkylation with two eqv. of methyl iodide.

The keten-S,N-acetals: 3-ethylamino-3-methylthio-1-phenyl-2-propen-1-one (52a), viscous oil;[30] 3-benzylamino-3-methylthio-1-phenyl-2-propen-1-one (52b), m.p. 58°[31] and 3-benzylamino-3-methylthio-1-(p-methylphenyl)-2-propen-1-one (52c), m.p. 67°[31] were prepared according to reported method by refluxing the respective keten S,S-acetal (1 eqv.) with appropriate amine (.1 eqv.) in ethanol (95%) for 15-20 hr.

The keten-S,N-acetals: 3-anilino-3-methylthio-1-(p-methylphenyl) 2-propen-1-one (52d), viscous liquid;[30] 3-anilino-3-methylthio-1-phenyl-2-propen-1-one (52e), m.p. 56-57°[30] and 3-anilino-3-methylthio-1-(p-chlorophenyl)-2-propen-1-one (52f), m.p. 77°[30] and the unknown ones (66a-e) were prepared by the general method described below.

General method for the preparation of keten S,N-acetals (52d-f) and (66a-e) by the reaction of active methylene compounds with phenyl isothiocyanate: To an ice cooled and well stirred suspension of sodium hydride (2.4g, 0.15 mol) (washed 2 times with dry benzene) in dry dimethylformamide (50 ml), a solution of active methylene compound (0.05 mol) in dry dimethylformamide (25 ml) was added dropwise during 0.5 hr. A solution of phenyl isothiocyanate (0.05 mol) in dry dimethyl formamide (25 ml) was then added and the reaction mixture was further formamide (25 ml) was then added and the reaction mixture was further stirred for 1.5-2 hr, followed by subsequent addition of methyl iodide (0.05 mol) in 25 ml of dry dimethylformamide. After further stirring for 2 hr, the reaction mixture was poured over crushed ice, neutralized with dilute acetic acid and extracted with chloroform (2x100 ml). The chloroform layer was washed with water (3x100 ml), dried (Na_2SO_4). and concentrated to give crude S,N-acetals (52d-f) and (66a-e) which were either purified by crystallization or by passing through silica gel column using benzene/hexane (1:1) as eluent. The physical and spectral properties of the unknown keten S,N-acetals (66a-e) are described below.

3-Anilino-3-methylthio-2-phenylacrylonitrile (66a), was obtained as yellow solid in 84% (9.5g) yield; m.p. 118-120°; i.r. (KBr)

ν_{max}; 3290 (NH), 2200 (CN) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$; δ 2.20 (s, 3H, SCH_3); 6.45 (s, 1H, NH), 6.90-7.40 (m, 10H, arom); Found: C, 72.38, H, 5.05, N, 10.75 Calc. for $C_{16}H_{14}N_2S$ (266): C, 72.18, H, 5.26; N, 10.52%.

3-Anilino-3-methylthio-2-(3,4-dimethoxyphenyl)-acrylonitrile (66b), was obtained as a yellow solid, m.p. 172-74°, in 74% (12g) yield; i.r. (KBr) ν_{max}: 3300 (NH), 2190 (CN) cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 2.20 (s, 3H, SCH_3); 3.65 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.35 (s, 1H, NH), 6.60-7.30 (m, 8H, arom); Found: C, 66.45; H, 5.63; N, 8.29%; Calc. for $C_{18}H_{18}N_2O_2S$ (326); C, 66.25, H, 5.52; N, 8.58%.

3-Anilino-3-methylthio-2-(4-methoxyphenyl)-acrylonitrile (66c), was obtained as a yellow solid, m.p. 105-8°, in 70% (10.36g) yield; i.r. (KBr) ν_{max}; 3240 (NH), 2190 (CN) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$) δ 2.18 (s, 3H, SCH_3); 3.70 (s, 3H, OCH_3); 6.20 (br, 1H, NH, exchangeable with D_2O); 6.60-7.40 (m, 9H, arom). Found: C, 68.72; H, 5.62; N, 9.60; Calc. for $C_{17}H_{16}N_2OS$ (296); C, 68.91; H, 5.40; N, 9.45%.

3-Anilino-3-methylthio-2-(3,4,5-trimethoxyphenyl)-acrylonitril (66d), was obtained as a yellow solid, m.p. 144-6° in 80% (14.24g) yield; i.r.(KBr) ν_{max}: 3040 (NH), 2200 (CN) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$): δ 2.25 (s, 3H, SCH_3); 3.65 (s, 6H, two OCH_3)

3.75 (s, 3H, OCH_3); 6.55 (s, 2H, arom); 6.82-7.32 (m, 6H; 5H aromatic and 1NH); Found: C, 64.21; H, 5.45; N, 7.86%; Calc. for $C_{19}H_{20}N_2OS_3$ (356): C, 64.04; H, 5.61; N, 7.86%.

3-Anilino-3-methylthio-2-(4-chlorophenyl)-acrylonitrile (66e), was obtained as a yellow solid, m.p. 148-50° in 50% (7.51g) yield; i.r.(KBr) ν max: 3280 (NH), 2190 (CN) cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 2.15 (s, 3H, SCH_3); 6.10 (s, 1H, NH, exchangeable with D_2O); 6.70-7.35 (m, 9H, arom); Found: C, 62.70; H,4.42; N, 9.09%; Calc. for $C_{16}H_{13}N_2SCl$ (300.5): C, 62.89; H, 4.26; N, 9.31%.

The known keten N,N-acetal: 3,3-bis(anilino)-1-phenyl-2-propen-1-one (56b), m.p. 132-33°;[30] and the unknown keten N,N-acetals (56a, c-d) were prepared according to the general method described below.

General method for the preparation of keten N,N-acetals (56a-d): A solution of respective keten S,S-acetal (0.01 mol) and the appropriate aniline (0.025 mol) in glacial acetic acid (20 ml) was refluxed for 5-8 hr. The solvent was removed under reduced pressure, the reaction mixture was diluted with water, extracted with ethylacetate. The organic layer was dried (Na_2SO_4) and concentrated to give crude N,N-acetals (56a-d), which were purified by column chromatography over

silica gel using 5-10% EtOAc: hexane as eluent. The physical and spectral data of the unknown keten N,N-acetals (56a, c-d) are described below.

3,3-Bis(anilino)-1-(p-methylphenyl)-2-propen-1-one (56a), was obtained as white solid, m.p. 165°; in 75% (2.46g) yield; i.r.(KBr) ν max: 3250, 3200 (NH); 1600 (CO) cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$); δ 2.30 (s, 3H, CH_3); 5.58 (s, 1H, vinylic); 6.30 (br, s, 2H, two, NH, exchangeable with D_2O); 7.00-7.65 (m, 14H, arom); Found: C, 80.32; H, 6.21; N, 8.39%; Calc. for $C_{22}H_{20}N_2O$ (328): C, 80.48; H, 6.09, N, 8.53%.

3,3-Bis(p-toluidino)-1-phenyl-2-propen-1-one (56c), was obtained as white solid, m.p. 150-51° in 70% (2.4g) yield; i.r.(KBr) ν max: 3450, 3200 (br NH); 1615, 1605 (CO) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$); δ 2.28 (s, 3H, CH_3); 2.30 (s, 3H, CH_3); 5.40 (s, 1H, vinylic); 6.40 (br s, 2H, two NH, exchangeable with D_2O); 7.00-7.30, 7.50-7.75 (2 m, 13H, arom); Found: C, 80.91; H, 6.22; N, 8.32% Calc. for $C_{23}H_{22}N_2O$ (342): C, 80.70; H, 6.43; N, 8.18%.

3,3-Bis(p-anisidino)-1-phenyl-2-propen-1-one (56d), was obtained as white solid, m.p. 128-29° in 68% (2.54g) yield; i.r.(KBr) ν max: 3350, 3300 (NH); 1605 (CO) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$); δ 3.80 (s, 6H, two OCH_3); 5.35 (s, 1H, vinylic); 6.20 (br, s, 2H, two NH); 6.80-7.80 (m, 13H, arom); Found: C, 73.96; H, 5.62; N, 7.65%; Calc. for $C_{23}H_{22}N_2O_3$ (374): C, 73.79, H, 5.88; N,

Oxidation of 3-aryl/alkyl/benzylamino-3-methylthio-1-aryl-2-propen-1-ones (52a-f) with lead tetra acetate: General Procedure: To the ice cooled suspension of lead tetraacetate (LTA) (4.43g, 0.01 mol) in dry methylene chloride (CH_2Cl_2), a solution of keten S,N-acetal 52 (0.01 mol) was added slowly (15 min) with stirring and stirring continued at room temperature for 2 hr (reaction monitored by tlc). When tlc showed the disappearence of starting material, a few drops of ethylene glycol was added to the reaction mixture (to distroy the excess of LTA present) and it was then poured in to cold water, extracted with chloroform (3x100 ml), the combined organic layer was washed with water (2x100 ml), dried (Na_2SO_4), and concentrated to give crude residues, which were purified by column chromatography over silica gel using benzene: hexane (1:1) as eluent, to give the pure acetates (53a-f) whose physical and spectral data are described below.

2-Acetoxy-3-ethylamino-3-methylthio-1-phenyl-2-propen-1-one (53a), was obtained as a white solid, m.p. 198-99°, in 55% yield (1.53g); spectral data is given in text, Found: C, 60.12; H, 6.25; N, 4.85%; Calc. for $C_{14}H_{17}NO_3S$: (279): C,60.21 H, 6.09; N, 5.01%.

2-Acetoxy-3-benzylamino-3-methylthio-1-phenyl-2-propen-1-one (53b), was obtained as a white solid, m.p. 175-6°; in 45% yield (1.53g); i.r.(KBr) ν max: 3371 (NH), 1767, 1697, 1673, 1547 cm^{-1}; i.r.($CHCl_3$) ν max: 3446 (br NH) 1750, 1694, 1602 cm^{-1}; ^{1}H-n.m.r.($CDCl_3$); δ 1.95 (s, 3H, SCH_3); 2.20 (s, 3H, CH_3-C(=O)-O-); 4.50 (d, 2H, CH_2-C_6H_5); 7.00-7.50, 7.70-8.10 (2 m, 10H, arom); m/z: 341 (M^+): Found: C, 66.55; H, 5.81; N, 4.25%; Calc. for $C_{19}H_{19}NO_3S$ (341): C, 66.86; H, 5.57; N, 4.10%.

2-Acetoxy-3-benzylamino-3-methylthio-1-(p-methylphenyl)-2-propen-1-one (53c), was obtained as a dull white solid, m.p. 133-4°; in 52% (1.84g) yield; i.r.(KBr) ν max: 3315 (NH), 1755, 1675, 1640 cm^{-1}; i.r.($CHCl_3$) ν max: 3406, 1750, 1694, 1650 cm^{-1}; ^{1}H-n.m.r.($CDCl_3$): δ 1.95 (br s, 3H, CH_3); 2.15 (br S, 3H, SCH_3); 2.35 (br S, 3H, CH_3-C(=O)); 4.50 (d, 2H, $CH_2C_6H_5$); 7.10-7.40 (m, 9H, arom); m/z; 355 (M^+); Found: C, 67.85; H, 5.63; N, 3.80%; Calc. for $C_{20}H_{21}NO_3S$ (355): C, 67.60; H, 5.91; N, 3.94%.

2-Acetoxy-3-anilino-3-methylthio-1-(p-methylphenyl)-2-propen 1-one (53d), was obtained as a white solid; m.p. 120-1°; in 52% (1.77g) yield; i.r.(KBr) ν max: 3283, 1786, 1761, 1705, 1666 cm^{-1}; i.r.($CHCl_3$) ν max: 3299, 1757, 1697 cm^{-1}; ^{1}H-n.m.r. δ ($CDCl_3$): 2.05 (s, 3H, SCH_3); 2.30 (s, 3H, CH_3-C(=O)), 2.40 (s, 3H, CH_3), 4.52 (s, 1H, methine); 7.10-8.10 (m, 9H, arom);

m/z; 341 (M^+); Found: C, 66.65; H, 5.41; N, 4.35%; Calc. for $C_{19}H_{19}NO_3S$ (341): C, 66.86; H, 5.57; N, 4.10%.

2-Acetoxy-3-anilino-3-methylthio-1-phenyl-2-propen-1-one(53e), was obtained as a white solid, m.p. 143-5°, in 48% (1.56g) yield: i.r.(KBr) ν max: 3412 (NH); 1665, 1601 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.95 (s, 3H, SCH_3); 2.05 (s, 3H, CH_3-C(=O)-O); 7.10-8.00 (m, 10H, arom); m/z; 326 (M^+); Found: C, 66.04; H, 5.98; N, 4.11% Calc. for $C_{18}H_{17}NO_3S$ (326): C, 66.25; H, 5.02; N, 4.29%.

2-Acetoxy-3-anilino-3-methylthio-1-(p-chlorophenyl)-2-propen-1-one (53f), was obtained as a white solid, m.p. 101-3°, in 47% (1.69g) yield; i.r.(KBr): ν max: 3320 (br NH); 1720, 1630, 1640 cm^{-1}; ^{1}H-n.m.r.($CDCl_3$): δ 1.70 (s, 3H, SCH_3); 2.15 (s, 3H, CH_3); 2.15 (s, 3H, CH_3-C(=O)-O); 5.20 (s, 0.5H, methine); 7.20-8.20 (m, 9H, arom); m/z: 361.5 (M^+); Found: C, 59.61; H, 4.60; N, 3.75%; Calc. for $C_{18}H_{16}NO_3SCl$ (361.5): C, 59.75; H, 4.42; N, 3.87%.

Oxidation of 3,3-Bis(arylamino)-1-aryl-2-propen-1-one (56a-c) with lead tetraacetate: Formation of 2-arylamino-3-aroylindoles (57a-c): General Procedure: A solution of keten N,N-acetals (56) (0.01 mol) in 20 ml dry CH_2Cl_2 was slowly added (15 min) to well stirred and cooled suspension of LTA (6.65g, 0.015 mol) in dry CH_2Cl_2 (30 ml) and the reaction mixture was stirred at

room temperature for 8-10 hr, when tlc showed the disappearence of starting material. A few drops of ethylene glycol was added to the reaction mixture and it was then poured into cold water, extracted with CH_2Cl_2 (2x100 ml), the combined extract washed with water (2x100 ml), dried (Na_2SO_4) and concentrated to give the residues, which were purified by column chromatography over silica gel using 5-10% EtOAc-hexane as eluent to give the pure indoles (57a-c) as white solids, whose physical and spectral data are described below.

2-Anilino-3-(p-toloyl)-indole (57a), was obtained as white solid, m.p. 106-7°; in 50% (1.63g) yield: spectral data described in text. Found: C, 80.82; H, 5.69; N, 8.43%, Calc. for $C_{22}H_{18}N_2O$ (326); C, 80.98; H, 5.52; N, 8.58%.

2-Anilino-3-benzoylindole (57b), was obtained as a white solid m.p. 93°, in 60% (1.87g) yield; i.r.(KBr) ν max: 3415 (br), 3160, 3060, 1690, 1650, 1595, 1500 cm^{-1}; ^{1}H-n.m.r.($CDCl_3$); δ 7.00-7.90 (m, arom); m/z; 312 (M^+); Found: C, 80.60; H, 5.31; N, 8.79% Calc. for $C_{21}H_{16}N_2O$ (312): C, 80.76; H, 5.12; N, 8.97%.

2-(p-methylanilino)-3-benzoyl-5-methylindole (57c), was obtained as a white solid, m.p. 136°, in 25% (0.85g) yield: i.r.(KBr) ν max: 3400 (br), 3150, 3060, 1670, 1650, 1605 cm^{-1};

^{1}H-n.m.r.($CDCl_3$):δ 2.32 (br S, 6H, two CH_3); 7.00-7.70 (m, 12H, arom); m/z: 340 (M^+); Found: C, 81.35; H, 5.62; N, 8.40; Calc. for $C_{23}H_{20}N_2O$ (340): C, 81.17; H, 5.88; N, 8.23%.

Oxidation of 3-anilino-3-methylthio-2-arylacrylonitriles(66a-e) with lead tetra acetate; General Procedure:

To a well cooled and stirring suspension of LTA(94.43g, 0.01 mol) in dry CH_2Cl_2 (25 ml), a solution of S,N-acetal (66a-e) (0.01 mol) in 25 ml of CH_2Cl_2 was added dropwise (15 min) and stirring continued for 1-4 hr (till the disappearence of starting material on tlc). A few drops of ethylene glycol was added to the reaction mixture (to distroy the excess of LTA present) and it was then poured into cold water, extracted with CH_2Cl_2(2x100 ml), washed the combined extraction with water (2x100 ml), dried (Na_2SO_4) and concentrated to give crude residues from which, pure products were isolated either by recrystallization or by column chromatography as mentioned below.

The iminoacetate (67), was obtained, after column chromatography over silica gel using hexane: EtOAc (9:1) as eluent as pale yellow solid, m.p. 80-81°, yield: 1.7g (52%); (spectral data described in text): Found: C, 66.47; H, 4.75; N, 8.90%; Calc. for $C_{18}H_{16}N_2O_2S$ (324): C, 66.66; H, 4.93; N, 8.64%.

Treatment of the iminoacetate (67) with Boron-trifluoride etherate: Formation of the amide (69): The iminoacetate (67) (1g, 0.003 mol) in BF_3-Et_2O (10 ml) was heated at 130-140° for 20 hr. The reaction mixture was then poured into cold water, neutralized with sodium bicarbonate, extracted with $CHCl_3$ (2x50 ml), washed the combined extract with water (2x50 ml), dried and concentrated to give a crude residue, which was purified by column chromatography over silica gel using hexane/EtOAc (9:1) as eluent, to give the amide (69) as a pale coloured semisolid, yield 0.63g (70%); spectral data given in text. Found: C,64.21; H, 5.51; N, 9.12; Calc. for $C_{16}H_{16}N_2O_2S$ (300): C, 64.00; H, 5.33; N, 9.33%.

LTA oxidation of 3,4-dimethoxy-S,N-acetal (66b) followed by usual work-up as described above gave viscous residue, which on trituration with hexane gave the dimer (77) as amorphous solid, m.p. 156-7°. yield 1 69g (52%); (spectral data in text); Found: C, 65.85%, H, 5.47; N, 8.94%; Calc. for $C_{36}H_{34}N_4O_4S_2$ (650); C, 66.46; H, 5.23; N, 8.61%.

1-N-phenyl-2-methylthio-3-cyano-5,6-dimethoxy-indole (79), was prepared by refluxing the mother liquor content (i.e. crude iminoacetal 78, 1.71g, 45%) of the above reaction mixture with BF_3-Et_2O (5 ml) in ether (15 ml) for 0.5 hr; followed by work-up

by pouring the resulting reaction mixture over cold water, neutralising with sod. bicarbonate extraction with chloroform. The pure indole (79) was obtained by column chromatographic purification was white solid, m.p. 146-7° yield 1.30g (95%) (40% based on 66b) spectral data described in text; Found: C, 66.53; H, 4.72; N, 8.74%; Calc. for $C_{18}H_{16}N_2O_2S$ (324), C, 66.66; H, 4.90; N, 8.58%.

1-N-phenyl-2-methylthio-3-cyano-5-methoxy-6-hydroxyindole (80) was obtained when the mother liquor content (i.e. crude iminoacetate 78) of the above reaction mixture was subjected to column chromatographic purification on silica gel using 25% benzene/hexane mixture as eluent. The pure hydroxy indole was obtained as a pale coloured solid, m.p. 115-6°C yield 1.11g (80%), spectral data in text. Found: C, 65.66; H, 4.64; N, 8.89 Calc. for $C_{17}H_{14}N_2O_2S$ (310), C, 65.80; H, 4.51; N, 9.03%.

LTA oxidation of 4-methoxy S,N-acetal (66c), followed by usual work-up gave viscous residue, which on trituration with hexane gave the dimer (91) as white solid, m.p. 140°; yield 1.77g (66%); i.r.(KBr) ν max: 2195 (CN), 1615, 1605, 1595 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): δ 1.82 (s, 3H, SCH_3); 3.80 (s, 3H, OCH_3); 6.80-7.70 (m, 9H, arom); ^{13}C-n.m.r. (67.89 MHz, $CDCl_3$): δ 16 (q, SCH_3); 55 (q, OCH_3); 65 (s, C-CN); 113.8, 119.8, 125, 129, 131 (each d, arom), 123, 147, 161 (each, s, arom); 116.5 (s, C≡N), 158.5 (s,-C=N); Found: C, 69.25; H, 5.19; N, 9.35%, Calc. for $C_{34}H_{30}N_4O_2S_2$ (590): C, 69.15; H, 5.08; N, 9.49%.

1-N-phenyl-2-methylthio-3-cyano-6-methoxy-indole (92), was similarly prepared by refluxing the mother liquor content (i.e. crude iminoacetal 90, 1.30g, 37%) of the above reaction mixture with BF_3-Et_2O in ether for 0.5 hr, followed by usual work-up as described above. The pure indole (92) was obtained as white solid, m.p. 114-5° yield: 1.00g (92%) (34% based on 66c) i.r.(KBr) νmax: 2210 (CN) cm^{-1}; ^{1}H-n.m.r.(CCl_4): δ 2.40 (s, 3H, SCH_3); 3.65 (s, 3H, OCH_3); 6.36 (d, 1H, arom); 6.80 (dd, 1H, arom); 7.20-7.67 (m, 6H, arom): m/z: 294 (M^+); Found: C, 69.27; H, 4.90; N, 5.33%; Calc. for $C_{17}H_{14}N_2OS$ (294): C, 69.38; H, 4.76; N, 9.52%.

LTA oxidation of 3,4,5-trimethoxy S,N-acetal (66d), followed by usual work-up similarly gave a viscous residue, which on trituration with hexane gave the dimer (94) as a white solid, m.p. 174-5°C; yield 0.71g (20%): i.r.(KBr) ν max: 2190 (CN), 1600 (m), 1580 (strong) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$): δ 1.80 (s, 3H, SCH_3); 3.75 (s, 6H, two OCH_3); 3.85 (s, 3H, OCH_3); 6.60 (s, 2H, arom); 6.90-7.60 (m, 5H, arom): Found: C, 64.11; H, 5.46; N, 7.75; Calc. for $C_{38}H_{38}N_4O_6S_2$ (710): C, 64.22; H, 5.35; N, 7.80%.

1-N-phenyl-2-methylthio-3-cyano-5-ethoxy-6,7-dimethoxyindole (96) or 1-N-phenyl-2-methylthio-6-ethoxy-5,7-dimethoxyindole (97) and the quinone (95): The mother liquor content (A)

obtained after filtering the dimer 94 was stirred with boron trifluoride etherate (5 ml) in 20 ml ether at room temperature for 2 hr. The reaction mixture after usual work-up gave a viscous residue which was column chromatographed over silica gel. Elution with benzene gave first 1.28g,(52.6%) (35% based on 66d) of the indole 96 or 97 as a white solid, m.p. 124-5° (spectral data in text); Found: C, 65.08; H, 5.54; N, 7.47%; Calc. for $C_{20}H_{20}N_2O_3S$ (368): C, 65.21; H, 5.43; N, 7.60%.

Further elution with benzene/ethylacetate (10:1) gave 1.15g (47.3%) (34% based on 66d) of quinone 95 as an yellowish solid, m.p. 137-8°; (spectral data in text); Found: C, 63.65; H, 4.58; N, 8.05; Calc. for $C_{18}H_{16}N_2O_3S$ (340): C, 63.52; H, 4.70; N, 8.23%.

LTA oxidation of 3-anilino-3-methylthio-2-(p-chlorophenyl)-acrylonitrile (66e); followed by sual work-up as described above gave a solid which was found to be a mixture of two products (tlc). Fractional crystallization of the above mixture gave first 1.40g (47%) of dimer 106, as white solid, m.p. 166-7°C; i.r. (KBr); ν max: 2220 (CN) cm^{-1}; ^1H-n.m.r. ($CDCl_3$): δ 1.8 (s, 3H, SMe); 7.00-7.50 (m, 9H, arom); ^{13}C-n.m.r. (67.39 MHz, $CDCl_3$); δ 16.0 (q, SCH_3), 64.5 (s, C-CN), 116.5 (s, C=N), 119.5, 125, 128.5, 129, 131 (d, aromatic), 129.5; 136, 146 (s, aromatic); 157.5 (s, $C_{vinylic}$); Found: C, 64.24; H, 4.13; N, 9.21; Calc. for $C_{32}H_{24}N_4S_2Cl_2$ (599): C, 64.10; H, 4.00; N, 9.34%.

The iminoacetate 105 was obtained as a second fraction as a white solid, yield 1.72g (48%), m.p. 115-6°C; i.r.(KBr) max: 2240 (CN); 1760 ($\overset{O}{\overset{\|}{C}}-CH_3$); ^{1}H-n.m.r.($CDCl_3$): 1.80 (s, 3H, SCH_3); 2.25 (s, 3H, $CH_3-\overset{O}{\overset{\|}{C}}-$); 6.80-7.80 (m, 9H, arom); Found: C, 60.37; H, 4.31; N, 7.65%; Calc. for $C_{18}H_{15}N_2SClO_2$ (358.5); C, 60.25; H, 4.18; N, 7.81%.

REFERENCES

1. For the most recent review see 'Lead Tetra-acetate', by R.N. Butler in 'Synthetic Reagents' Volume 3, edited by J.S. Pizey, Ellis Horwood Limited, Chapter 4, p. 278 and references therein.
2. J.B. Alyward, Quart. Rev. 25, 407 (1971).
3. R.N. Butler, Chem. and Ind., 437 (1968).
4. R.N. Butler, Chem. and Ind., 523 (1972).
5. F. Corbani, B. Rindone and C. Scolastico, Tetrahedron, 29, 3253 (1973).
6. F. Corbani, B. Rindone and C. Scolastico, Tetrahedron, 31, 455 (1975).
7. B. Rindone, E. Santaniello and C. Scolastico, Tet. Lett., [illegible] 19 (1972)
8. A. Catto, F. Corbani, B. Rindone and C. Scolastico, Tet. Lett., 2723 (1973).
9. S.K. Khetan, J.C.S. Chem. Comm., 917 (1972).
10. J.M. Vernon, R.M. Carr and M.A. Sukari, J. Chem. Res (S), 115 (1982); J. Chem. Res (M), 1310 (1982).
11. M.A. Sukari and J.M. Vernon, Tetrahedron, 39, 793 (1983).
12. R.M. Carr, R.O.C. Norman and J.M. Vernon, J.C.S. Chem. Comm., 855 (1977).

13. R.M. Carr, R.O.C. Norman and J.M. Vernon, J. Chem. Soc., Perkin I, 156 (1980).

14. T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji and Y. Miwa, Tetrahedron, 27, 775 (1971).

15. R.F. Meyer and M. Zwiester, J. Org. Chem. 33, 4274 (1968).

16. A.S. Bailey, M.C. Chum and J.J. Wedgwood, Tet. Lett., 5953 (1968).

17. W.A.F. Gladstone and R.O.C. Norman, J. Chem. Soc., 3048 (1965).

18. W.A.F. Gladstone and R.O.C. Norman, J. Chem. Soc., 5177 (1965).

19. W.A.F. Gladstone and R.O.C. Norman, J. Chem. Soc., 1527 (1966).

20. W.A.F. Gladstone, J.C.S. Chem. Comm., 179 (1969).

21. N.B. Colthup and L.H. Daly and S.E. Wiberley in 'Introduction to Infrared and Raman Spectroscopy' Academic Press, International ed., p. 202, 366.

22. J.P. Jesson and H.W. Thompson, spectrochem. Acta 13, 217 (1958).

23. M. Saquet and A. Thuillier, Bull. Soc. Chim. France, 3969 (1966).

24. G.A. Russell and L.A. Ochrymowycz., J. Org. Chem., 35, 764 (1970).

25. For n.m.r. spectrum of related indole derivatives see (a) T. Kametani, T. Ohsawa, M. Ihara and K. Fukumoto, J. Chem. Soc. Perkin I, 450 (1978); (b) T. Kametani, T. Ohsawa and M. Ihara, J. Chem. Soc. Perkin I, 1981,290; (c) R.T. Borchardt and P. Bhatia, J. Med. Chem. 25, 263 25, (1982)

26. R.K. Brown, in 'Indoles', Part I (edited by W.J. Houlihan), John Willey - Interscience, New York (1972).

27. B. Zeen, Tet. Lett. 3881 (1967).

28. A text book of practical organic chemistry by A.I. Vogel, pp. 643, ELBS and Longman (1968).

29. A. Thuillier and J. Vialle, Bull. Soc. Chim. France,1398 (1959).

30. Veena Aggarwal, Ph.D. Thesis submitted to North-Eastern Hill University, Shillong (1982).

31. Azizur-Rahman, Ph.D. Thesis submitted to North-Eastern Hill University, Shillong (1984).

CHAPTER IV

REACTIONS OF POLARIZED KETEN-S,N-ACETALS WITH HYDRAZINE AND GUANIDINE : FACILE GENERAL ROUTES TO NOVEL 3(5)-ARYL-5(3)-ARYL/ALKYL/ARALKYLAMINO-1(H)-PYRAZOLES* AND 2-AMINO-4-ARYL/ALKYL/N-AZACYCLOALKYLAMINO-5,6-SUBSTITUTED PYRIMIDINES**

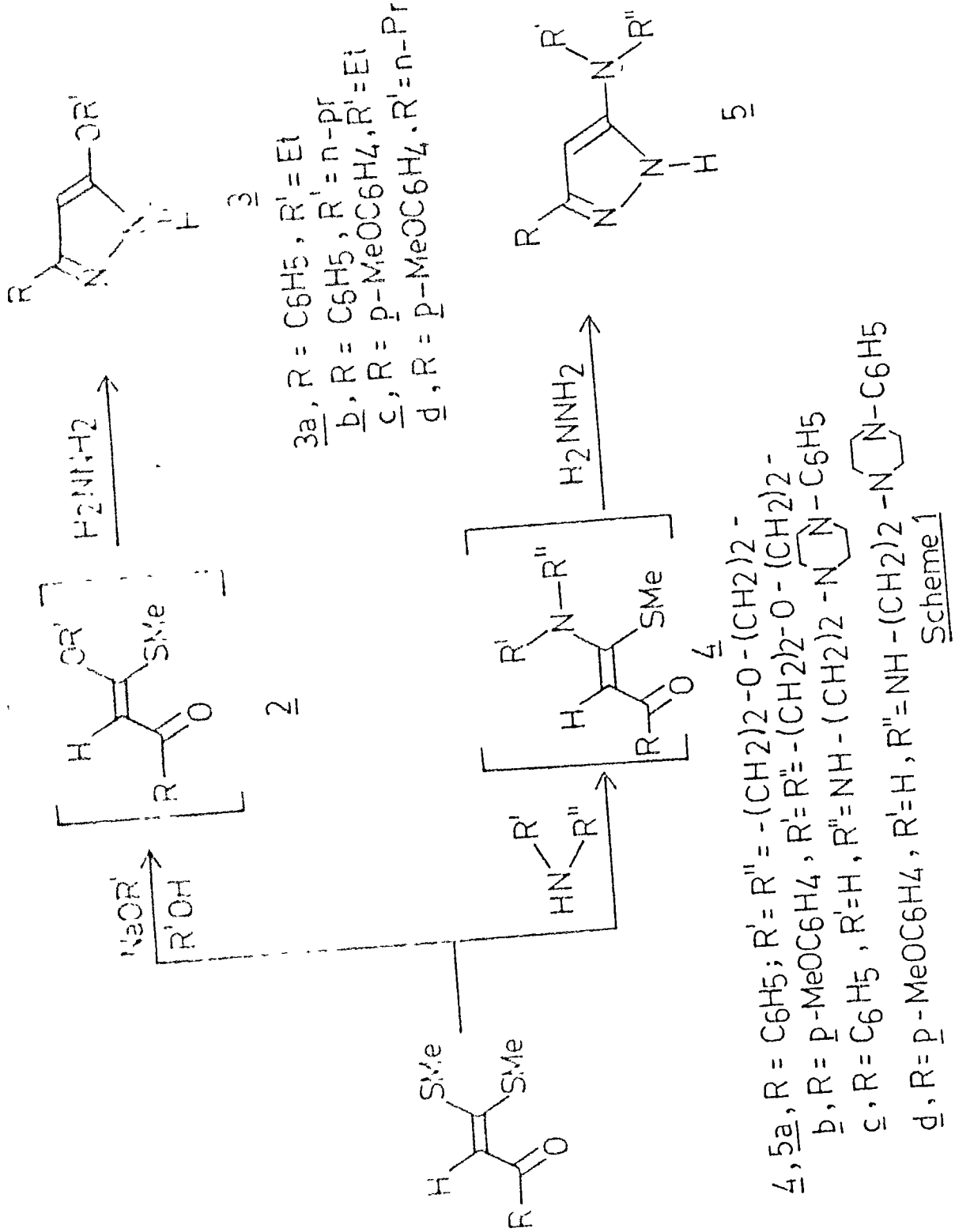
IV.1 INTRODUCTION

Earlier from our laboratory, a facile one pot synthesis[1] of a few 3(5)-aryl-5(3)-alkoxypyrazoles (3a-d) and the corresponding 3(5)-aryl-5(3)-N-azacycloalkyl/N-alkylaminopyrazoles (5a-d) was reported by reaction of the corresponding oxoketen-dithioacetals (1) with the corresponding alkoxide or amine followed by subsequent insitu treatment with hydrazine hydrate (Scheme 1). The corresponding S-methyl-O-alkyl (2) and S-methyl-N-alkyl-(4) acetals formed by displacement of one of the methylthio groups in 1 by either alkoxide or alkylamino group respectively were suggested as intermediates in these transformations (Scheme 1). Similarly a novel one step synthesis of

---

* J.N. Vishwakarma, B.K.Roychowdhutry, H.Ila and H.Junjappa, Ind. J.Chem., ooo(1984).

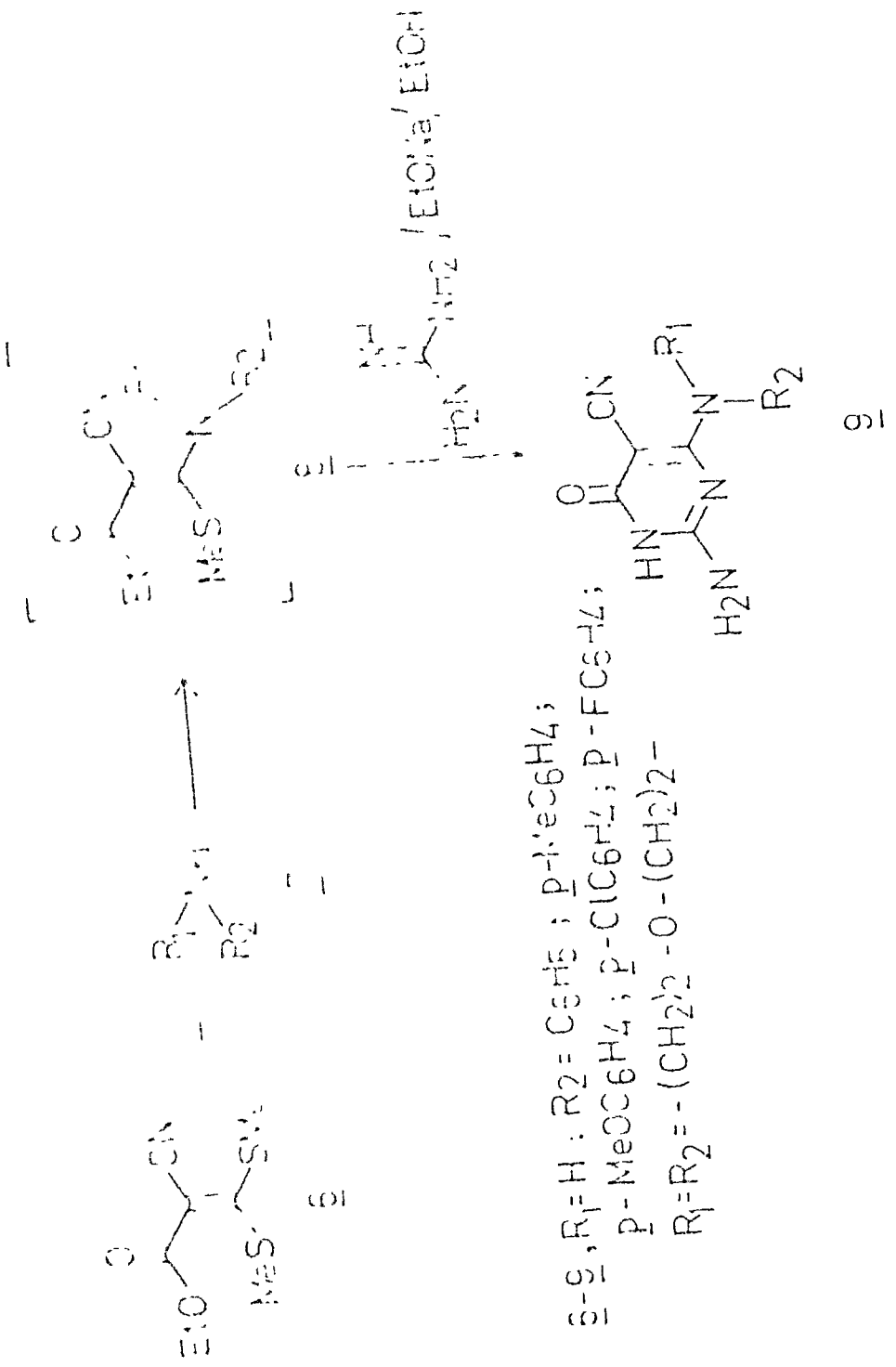
** J.N. Vishwakarma, S.Apparao, H.Ila and H.Junjappa, Ind.J. Chem., 000(1984).



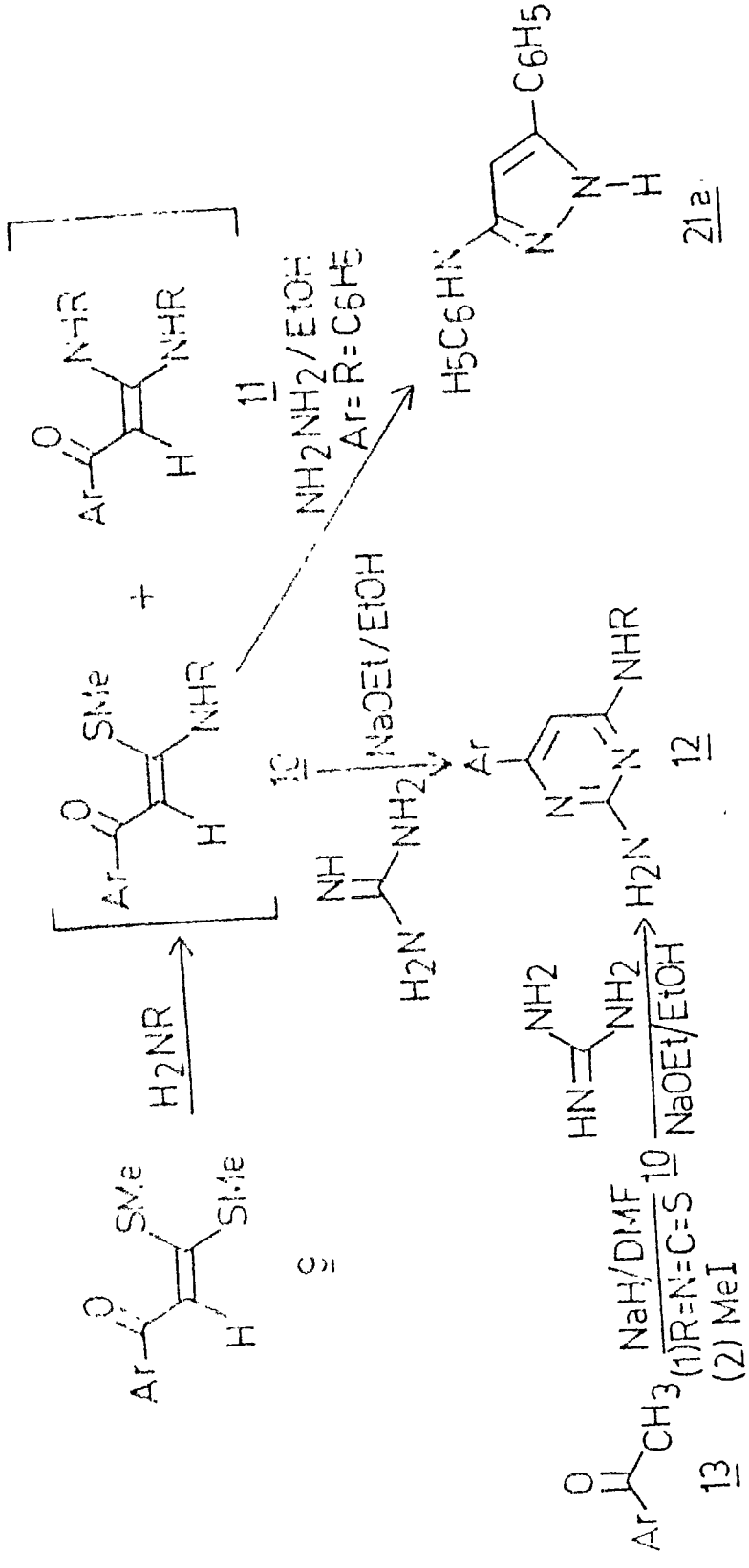
4, 5a, R = C6H5; R' = R'' = -(CH2)2-O-(CH2)2-
b, R = p-MeOC6H4, R' = R'' = -(CH2)2-O-(CH2)2-
c, R = C6H5, R' = H, R'' = NH-(CH2)2-N N-C6H5
d, R = p-MeOC6H4, R' = H, R'' = NH-(CH2)2-N N-C6H5

Scheme 1

2-amino-4-aryl/ethyl aminopyrimidines 9 was developed[2] by insitu generation of the corresponding S,N-acetals 8 followed by subsequent reactions of 8 with guanidine (Scheme 2). However when the similar approach was extended for the synthesis of the corresponding 2-amino-4-aryl/ethylamino-6-aryl pyrimidines, by insitu generation of S,N-acetals 10 the corresponding 4-substituted aminopyrimidines 12 were obtained in low yields (Scheme 3). Later it was shown[2] that ketoketen S,S-acetals 1 react with substituted anilines to give a mixture of both S,N-(10) and N,N-(11) acetals and the N,N-acetals 11 were found to be inactive towards guanidine resulting in the lower yields of pyrimidines 12 (Scheme 3). The pyrimidines 12 were obtained[2] in improved yields by reacting pure S,N-acetals (prepared by isothiocyanate method) with guanidine (Scheme 3). Similarly the corresponding 4-morpholinopyrimidines 16 were obtained in low yields by reaction of the corresponding N,N-morpholino-acetals 15 (generated insitu) with guanidine since the attempted synthesis of the corresponding S,N-morpholino acetals 14 from 1 by direct displacement method afforded only 15 and no trace of 14 were formed in the reaction (Scheme 4). The S,N-acetal 14, being more reactive than the corresponding S,S-acetal 1, reacts faster with morpholine than 1 to give the N,N-acetals



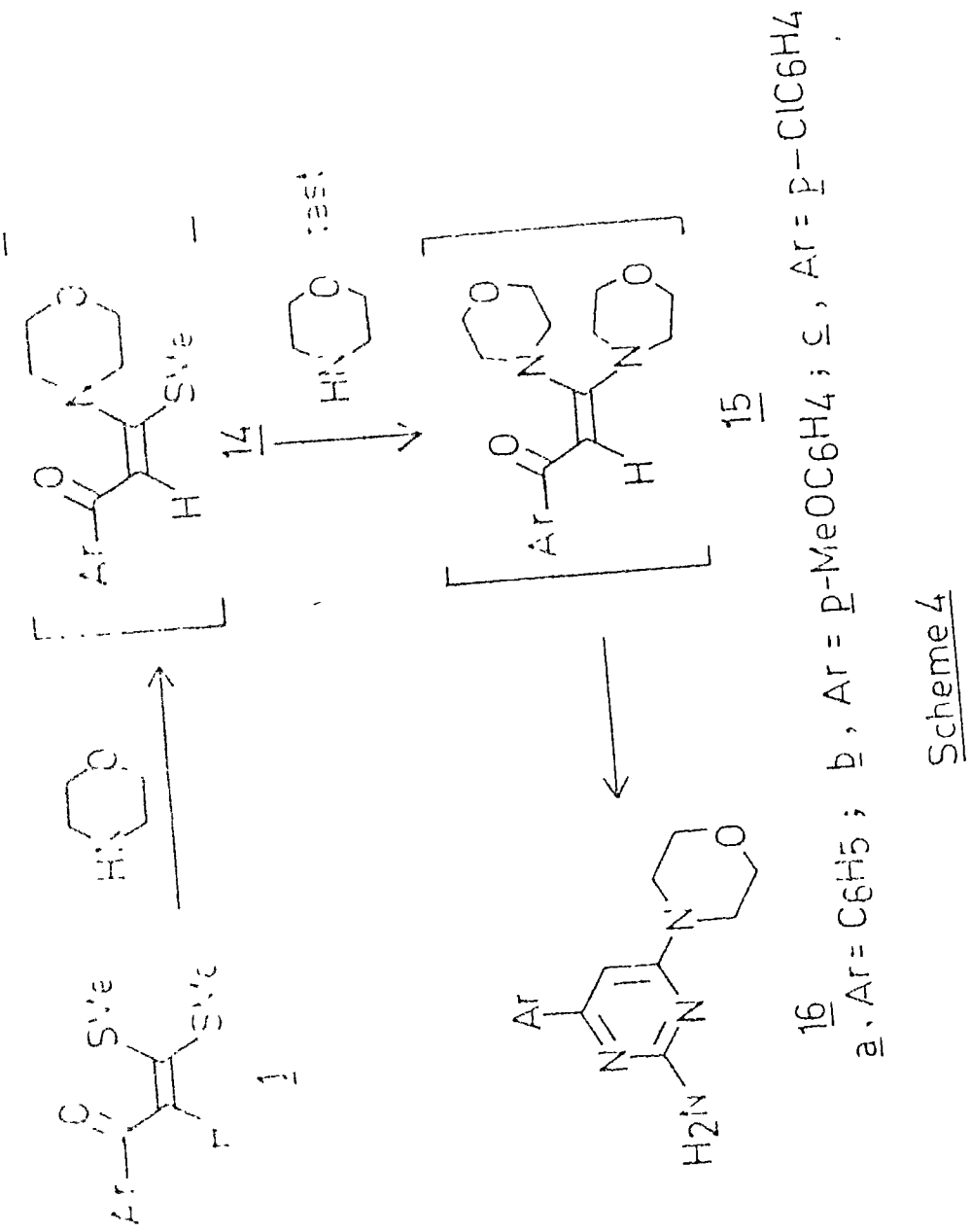
Scheme 2



1, 10, 12, 13 ; Ar = C_6H_5 ; p-$MeOC_6H_4$; p Cl- C_6H_4 ; p-BrC_6H_4

R = C_6H_5 ; p-ClC_6H_4 ; Et, $-CH_2CH(OEt)_2$

Scheme 3



16 a, Ar = C6H5 ; b, Ar = p-MeOC6H4 ; c, Ar = p-ClC6H4

Scheme 4

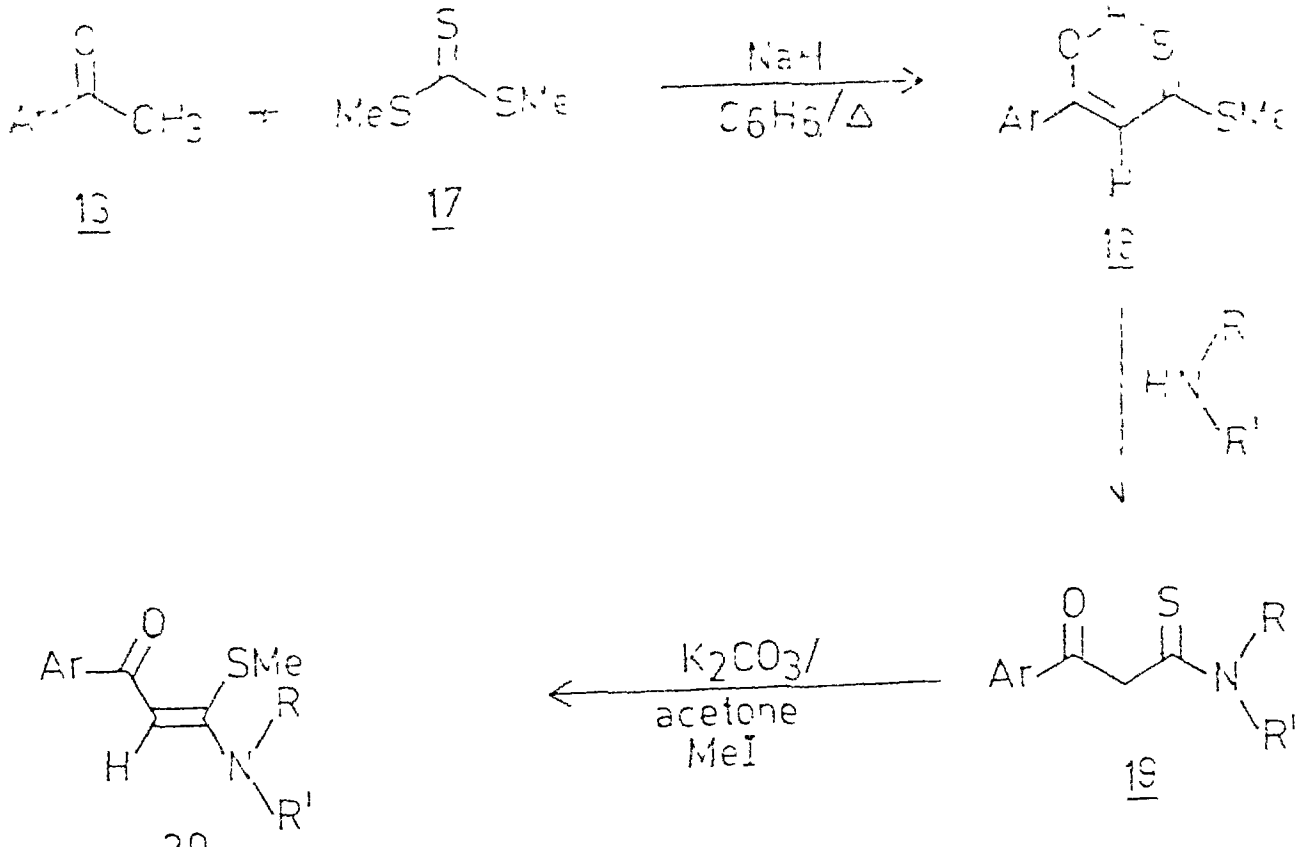
15 exclusively (Scheme 4). However subsequently, the S,N-acetals 20 derived from cyclic secondary amines could be prepared in good yields[3] by alkylation of the corresponding thioamides 19 under mild conditions (Scheme 5). The thioamides 19 were obtained by the reaction of the respective amines with the appropriate ketodithioesters 18. The dithioesters in turn were obtained in good yields by a method developed in our laboratory my methylthiocarbonylation of the respective acetophenones 13 with dimethyltrithiocarbonate 17 in the presence of sodium hydride (Scheme 5).[4]

With a variety of polarized keten S,N-acetals in hand, which were derived from various primary alkyl/aryl and secondary cyclic amines, we have further investigated the reactions of these S,N-acetals with hydrazine and guanidine in order to study the scope and generality of these reactions for synthesis of 3(5)-aryl/alkylaminopyrazoles and the corresponding 4-alkyl/aryl/azacycloalkylpyrimidines. The results of these studies are presented in this chapter.

IV.2 RESULTS AND DISCUSSIONS

IV.2.1 Reactions of Polarized Keten S,N-acetals with Hydrazine: Synthesis of Novel 3(5)-N-Aryl/alkyl/N-azacycloalkyl-aminopyrazoles

In an attempted direct preparation of the pyrazole 21a

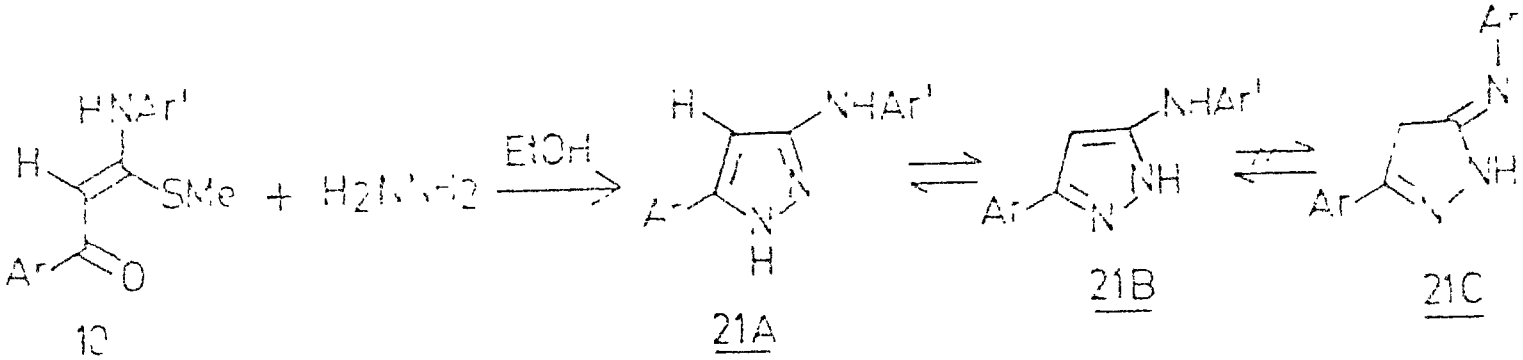


13 + 17 → 18 → 19 → 20

13, 17-20 Ar = substituted phenyl, R=R' = $-(CH_2)n-$, n = 4,5 ;
$-(CH_2)_2-X-CH_2-$, X = O, N—Me, N—C6H5, etc

Scheme 5

from the dithioacetal 1 ($R=C_6H_5$), when a mixture of 10a and aniline was treated at 160°C for 15 hr followed by subsequent treatment with hydrazine hydrate in refluxing ethanol, the corresponding 3(5)-phenyl-5(3)anilino-1(H)pyrazole (21a) was obtained in low yield (35%) (Scheme 3) along with the N,N-acetal 11a (Ar, $R=C_6H_5$) which were separated by column chromatography. However when the pure S,N-anilinoacetal 10a was refluxed with hydrazine hydrate, work-up of the reaction mixture afforded the corresponding 3(5)-phenyl-5(3)-anilino-1(H)-pyrazole (21a) in 85% yield (Scheme 6). The pyrazole 21a has been reported in the literature, which has been prepared either by the reaction of phenylacetylinic thioanilide 22[5,6] or the corresponding N,O-acetal 23[7] with hydrazine Scheme 7). The m.p. (154-55°C) and u.v. spectrum λ max (MeOH): 266 (logϵ 4.20) of 21a were in conformity with the reported values. Its i.r. spectrum (KBr) exhibited absorption bands at 3400 (ν_{NH}) and 1550, 1580 and 1600 ($\nu_{C=N}$) cm^{-1}, while its ^{1}H-n.m.r. spectrum (TFA) showed a singlet (1H) at δ 6.35 and a multiplet (10H) between δ 7.15-7.92 due to H-4 and aromatic proton respectively. The tautomeric 5-arylimino-pyrazolone structure 21c was ruled out due to the absence of 4-methylene proton signal in the n.m.r. spectrum of 21a.



10

10 . 21a , Ar = Ar' = C_6H_5

b , Ar = p-MeC_6H_4 , Ar' = C_6H_5

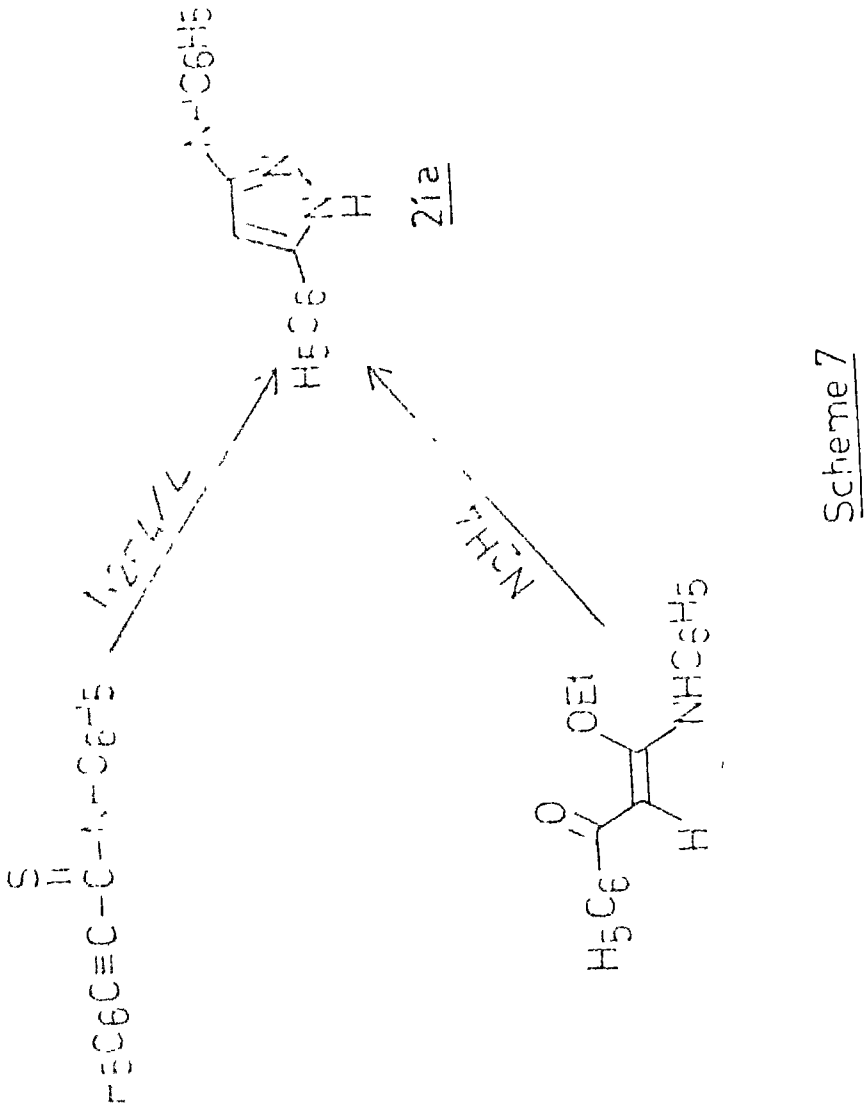
c , Ar = p-ClC_6H_4 , Ar' = C_6H_5

d , Ar = C_6H_5 ; Ar' = p-MeC_6H_4

e , Ar = p-$EtOC_6H_4$, Ar' = p-MeC_6H_4

f , Ar = p-ClC_6H_4 , Ar' = p-MeC_6H_4

Scheme 6

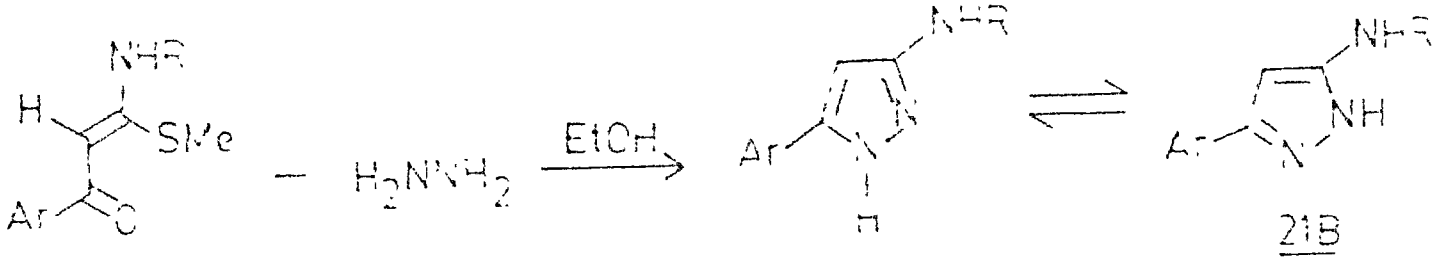


Scheme 7

However, it was not possible to differentiate between the tautomeric structures 21A and 21B on the basis of these data. The reaction of other substituted S,N-acetals 10b-f similarly afforded the corresponding 3(5)-aryl-5(3)anilinopyrazoles 21b-f in 89%-97% overall yields (Scheme 6) on reaction with hydrazine hydrate under similar conditions. The spectral and analytical data of 21b-f were in conformity with the assigned structures (Table 1 and 2).

The reaction was next extended for the synthesis of 3(5)-aryl-5(3)-alkylaminopyrazoles. Thus when the S,N-methyl-acetal 10g was reacted with hydrazine in refluxing ethanol the corresponding 5(3)-methylamino-3(5)-phenylpyrazole (21g) was obtained in 93% yield (Scheme 8). The other substituted 3(5)-aryl-5(3)-N-methylamino (21h-i); 5(3)-N-ethylamino-(21j-l) and 5(3)-N-benzylamino (21m-n) pyrazoles were similarly obtained in excellent yields (Scheme 8). The structures of all the pyrazoles were confirmed with the help of spectral and analytical data which are given in Tables 1 and 2 respectively.

When the keten S,N-acetal 10q-t derived from aminoace-taldehydediethylacetal were reacted with hydrazine hydrate



10 21A 21B

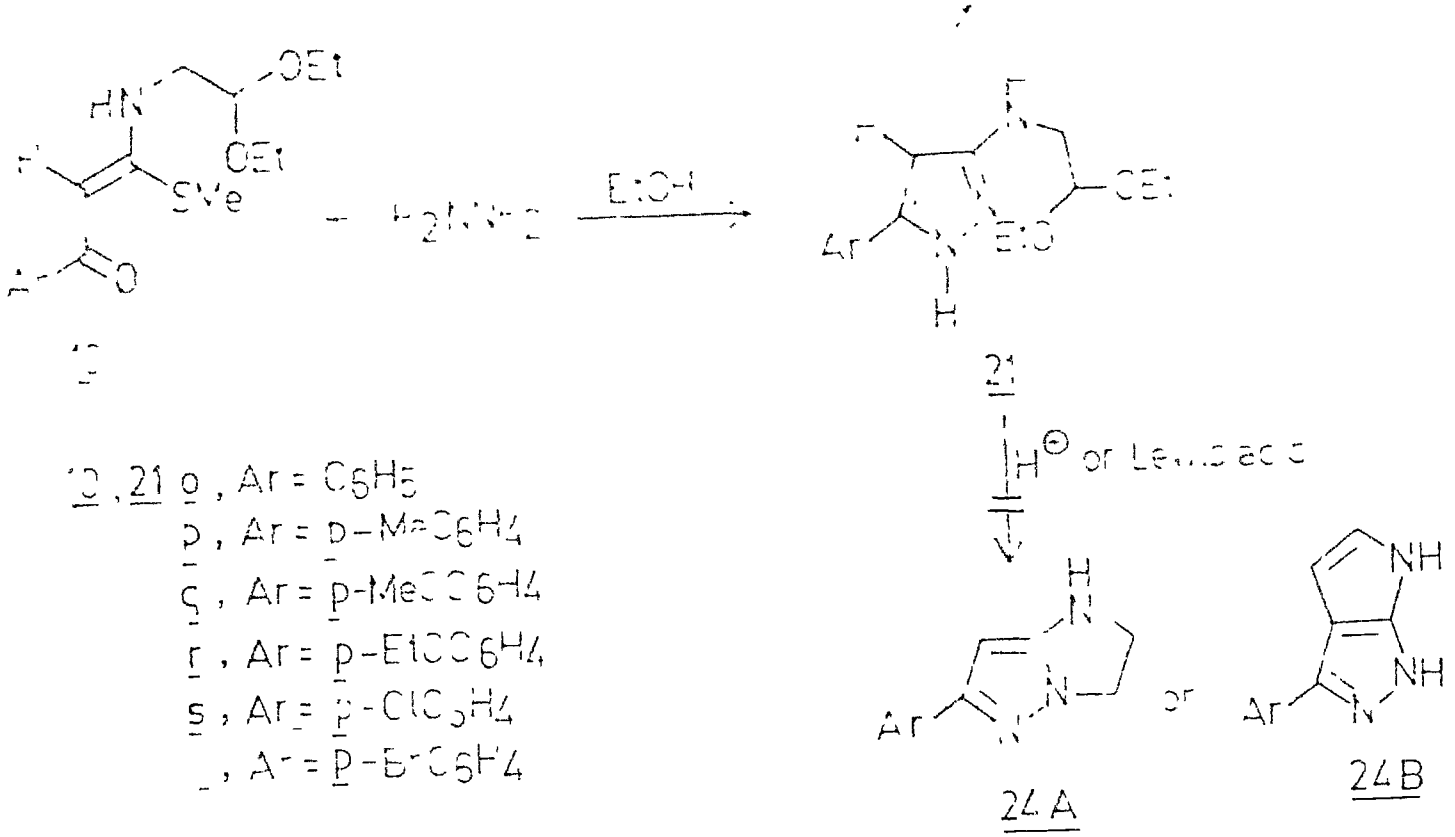
10, 21g, Ar = C_6H_5, R = Me
h, Ar = p-ClC_6H_4, R = Me
i, Ar = p-$MeOC_6H_4$, R = Me
j, Ar = C_6H_5, R = Et
k, Ar = p-ClC_6H_4, R = Et
l, Ar = p-$MeOC_6H_4$, R = Et
m, Ar = C_6H_5, R = $C_6H_5CH_2$
n, Ar = p-MeC_6H_4, R = $C_6H_5CH_2$

Scheme 8

under similar conditions the corresponding 5(3)-N-β-bis(ethoxy)-ethylaminopyrazoles (21q-t) were obtained in 50-72% overall yields (Scheme 9). The spectral and analytical data of 21q-t were in conformity with the assigned structures. However our subsequent attempts to cyclize 21q-t to either the corresponding triazapentalenes (24A) or the pyrolopyrazoles (24B) in the presence of a variety of mineral and Lewis acids (methanolic HCl, H_2SO_4, TFA, PTSA, $BF_3.Et_2O$, $TiCl_4$) were not successful (Scheme 9) although attempts in these directions are still in progress.

When the doubly activated S,N-anilinoacetals 25a and 25b derived from malononitrile were reacted with hydrazine hydrate under similar conditions the corresponding 3(5)-arylamino-4-cyano-5(3)amino-1(H)pyrazoles 26a and 26b were obtained in 95% and 96% yields respectively (Scheme 10). The structures of 26a and 26b were confirmed with the help of spectral and analytical data. Similarly the S,N-acetal 27 derived from dimethoxyphenylacetonitrile reacted with hydrazine hydrate to give the expected pyrazole 28 (Scheme 10).

The reaction of S,N-piperazinoacetal 30 (prepared by the displacement reaction on the dithioacetal 29 by N-methylpiperazine) derived from ethylcyanoacetate with hydrazine hydrate afforded 3(5)-N-methylpiperazino-4-cyano-5(3)-hydroxypyrazole 32

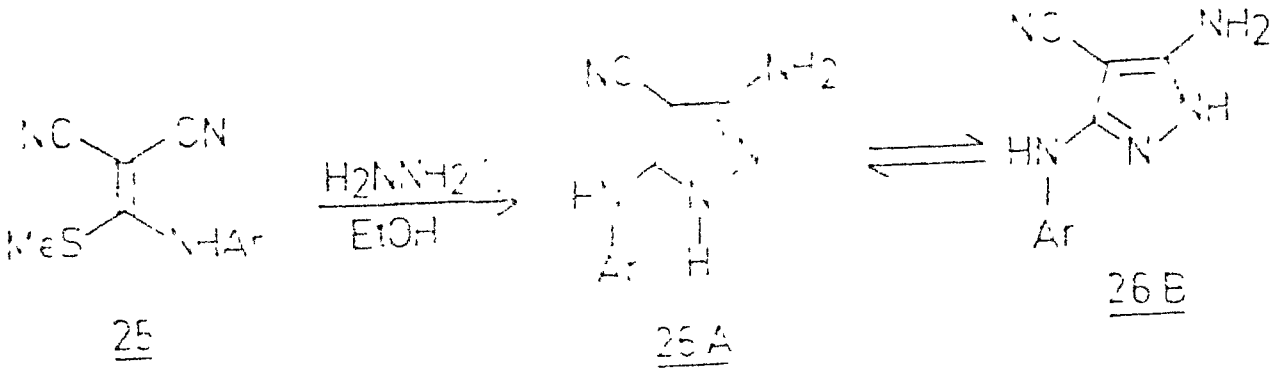


20, 21 o, Ar = C_6H_5
p, Ar = p-MeC_6H_4
q, Ar = p-$MeOC_6H_4$
r, Ar = p-$EtOC_6H_4$
s, Ar = p-ClC_6H_4
, Ar = p-BrC_6H_4

24A

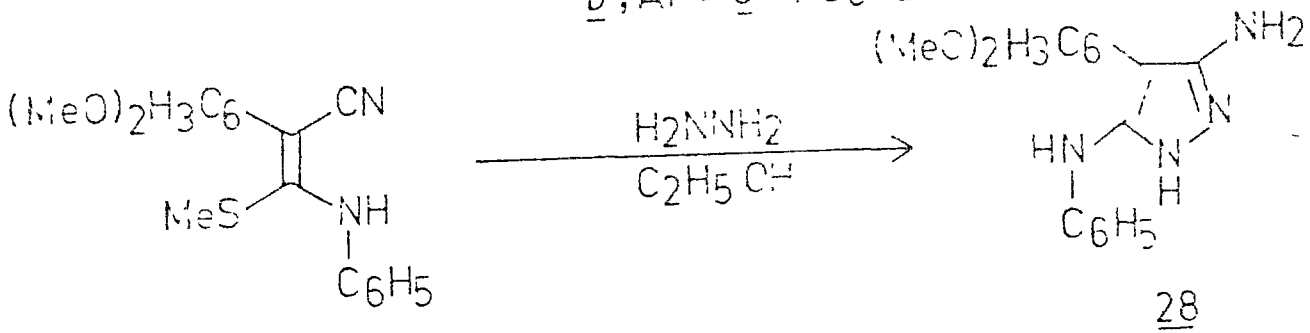
24B

Scheme 9



25 25A 26B

25, 25a, Ar = p-MeC6H4
b, Ar = o-FC6H4



27 28

Scheme 10

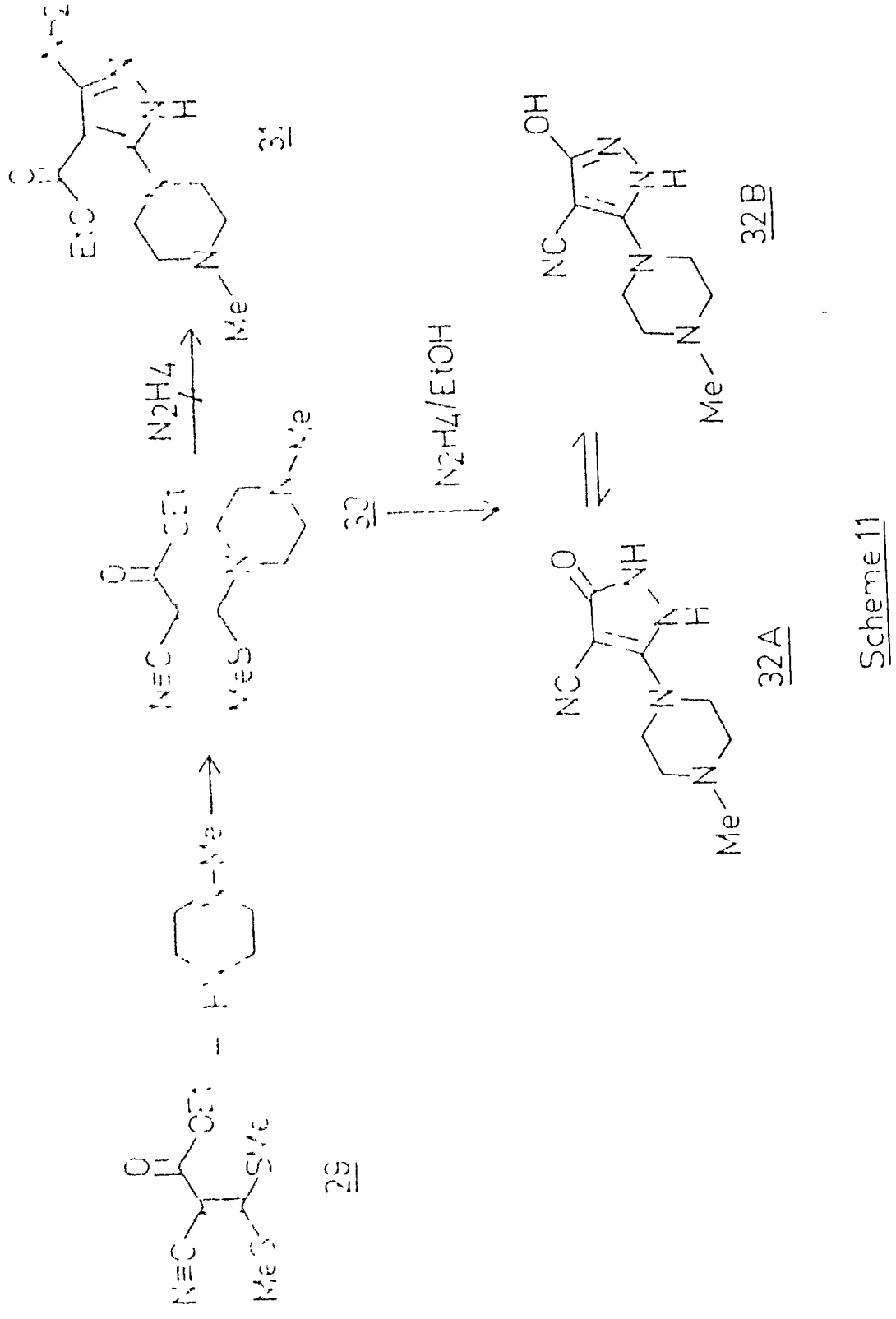
in 68% yield and no trace of the corresponding 5(3)-amino-3(5)-N-methylpiperazino-4-ethoxycarbonylpyrazole (31) formed by the nucleophilic attack of hydrazine on cyano group of 30 was isolated from the reaction mixture. The structure of 32 was confirmed with the help of spectral and analytical data.

The reaction of S,N-acetal 34a-b derived from the corresponding pyrazolone S,S-acetal 33, with hydrazine was next investigated in order to get the corresponding 3-N-aryl/alkyl/cycloalkylaminopyrazolopyrazoles 35. However 35 could not be synthesized from either of the reactions of 34a-b with hydrazine and the products isolated in all these cases were characterized as 36a-b formed by displacement of methylthio group by hydrazine (Scheme 12).

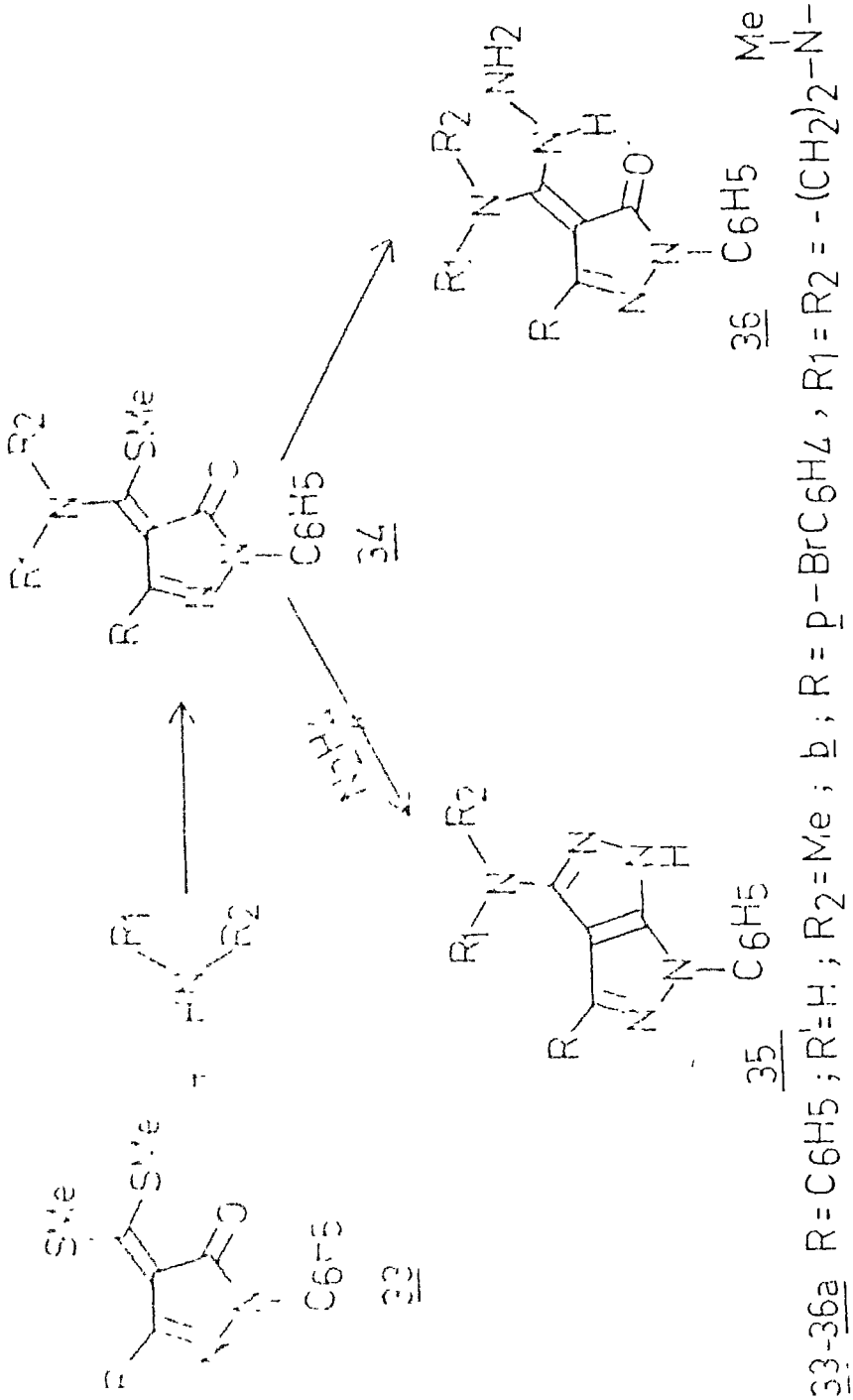
A few of the 4-unsubstituted pyrazoles were reacted with nitrosylchloride in ether using pyridine as a base when corresponding 4-nitrosopyrazoles were obtained (Scheme 13) in 85-95% overall yields.

IV.2.2 CONCLUSION

The reaction of α-oxoketendithioacetal 10a-t with hydrazine provides a facile general route for 3(5)-aryl-5(3)-aryl/alkyl/aralkylaminopyrazole 21a-t. It is pertinent to note that very few 3(5)-substituted aminopyrazoles are reported

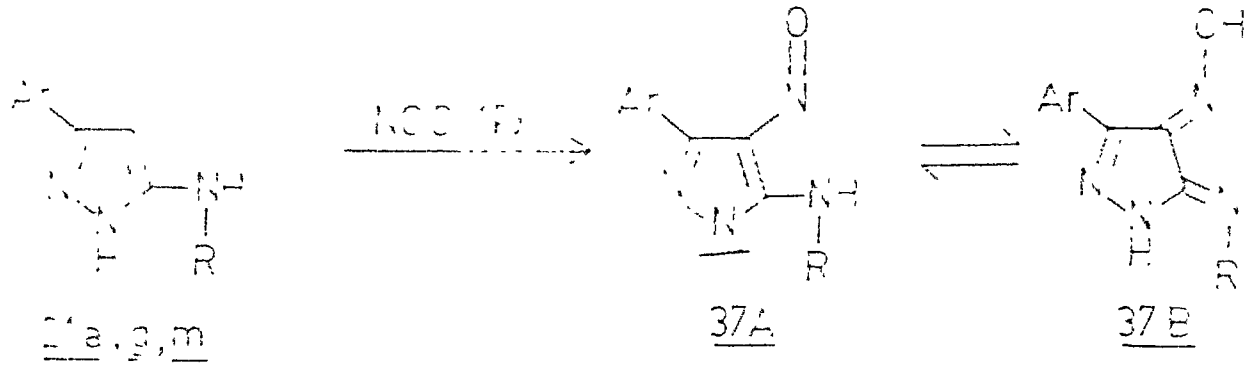


Scheme 11



33-36a R=C6H5 ; R'=H ; R2=Me ; b ; R = p-BrC6H4 , R1=R2 = -(CH2)2-N-(CH2)2-

Scheme12



37a , Ar , R = C_6H_5

b , Ar = C_6H_5 , R = Me

c , Ar = C_6H_5 , R = $C_6H_5CH_2$

Scheme 13

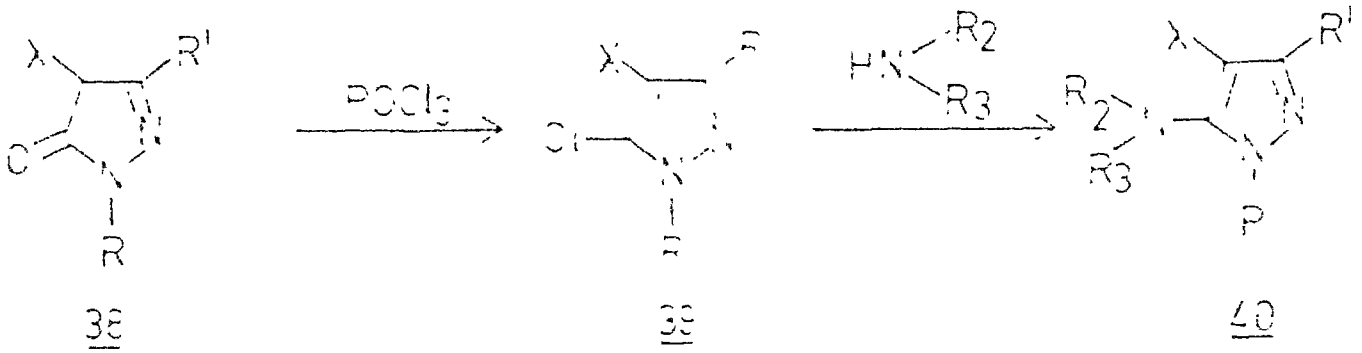
in the literature. The literature methods for the synthesis of 3(5)-substituted amino pyrazoles are as follows:-

IV.2.2.1 By substituted amination of 3(5)-halogenopyrazoles

The replacement of halogen in 3(5)-halogenopyrazoles by substituted amines is one of the oldest methods employed for the synthesis of 3(5)-substituted aminopyrazoles (Scheme 14). The 3(5)-chloro or bromopyrazoles 39 are obtained by treatment of the corresponding 3(5)-pyrazolones 38 with phosphorous oxychloride (or bromide). However, the nucleophilic displacement of halogen by nucleophiles like ammonia, substituted amines or alkoxy group are facile only when an electron withdrawing group is present in the 4 position of the halogenopyrazole (39)[9] or one of the nitrogen atoms of the halogenopyrazoles is quarternized (41, Scheme 14).[8,10]

IV.2.2.2 By Reactions of N-substituted thio-semicarbazides with haloketones.[11,12]

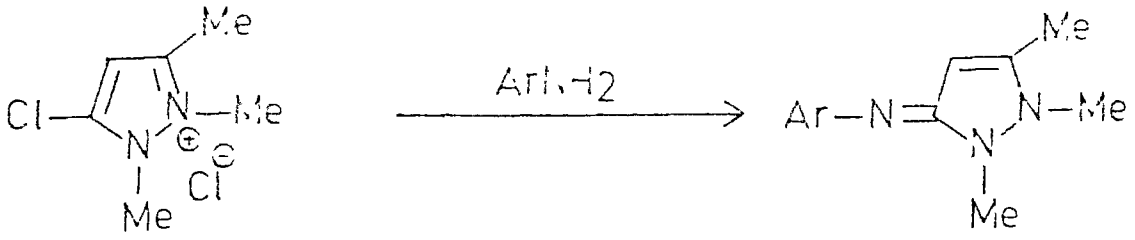
A few of the 3(5)-substituted aminopyrazoles (46) have been synthesized by reactions of N-substituted thiosemicarbazides 44 with α-haloketones to give 1,3,4-thiazidines 45 which undergo facile loss of sulphur to give pyrazoles 46 (Scheme 15).



39 40

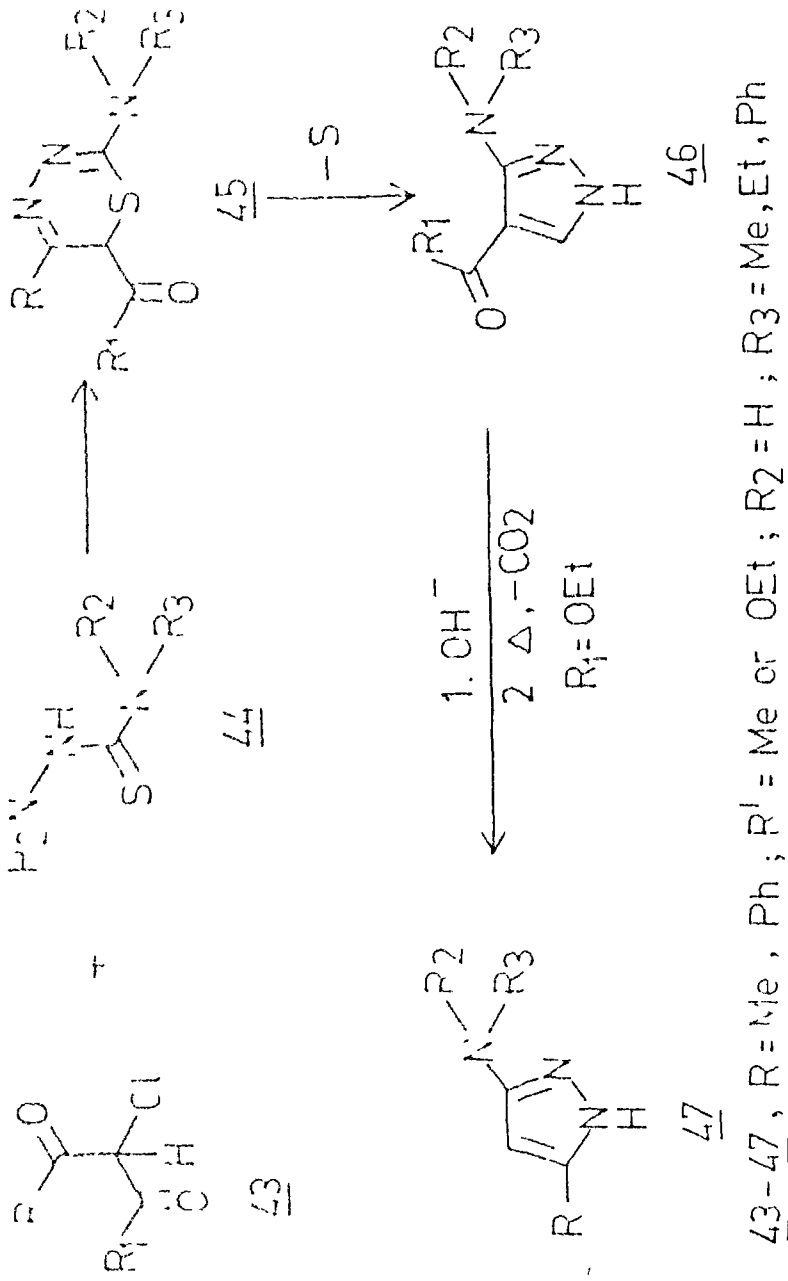
39 40

39-40, λ = ArCO, NO2, e withdrawing group
R3, R2 = H, alkyl, aryl, cyanoalkyl



41 42

Scheme 14


45
-S
46
1. OH⁻
2 Δ, -CO2
R1=OEt
47
43-47, R = Me, Ph ; R1 = Me or OEt ; R2 = H ; R3 = Me, Et, Ph
R2 = R3 = Me

Scheme 15

IV.2.2.3 By Reaction of hydrazine with polarized N,O-acetal[7]

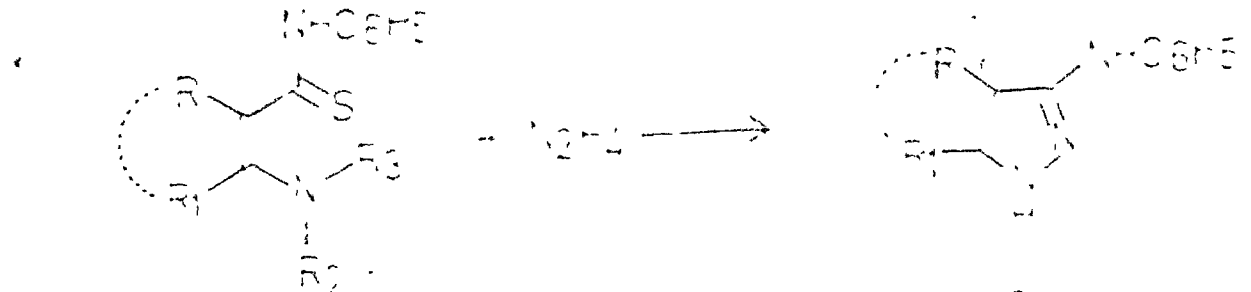
There is only one report of the reaction of polarized oxo-N-anilino-O-ethylacetal (23, Scheme 7) with hydrazine to give the corresponding 3(5)-anilinopyrazole in good yields. However the N,O-acetal are not easily available, besides they undergo fast hydrolysis in the presence of moisture.

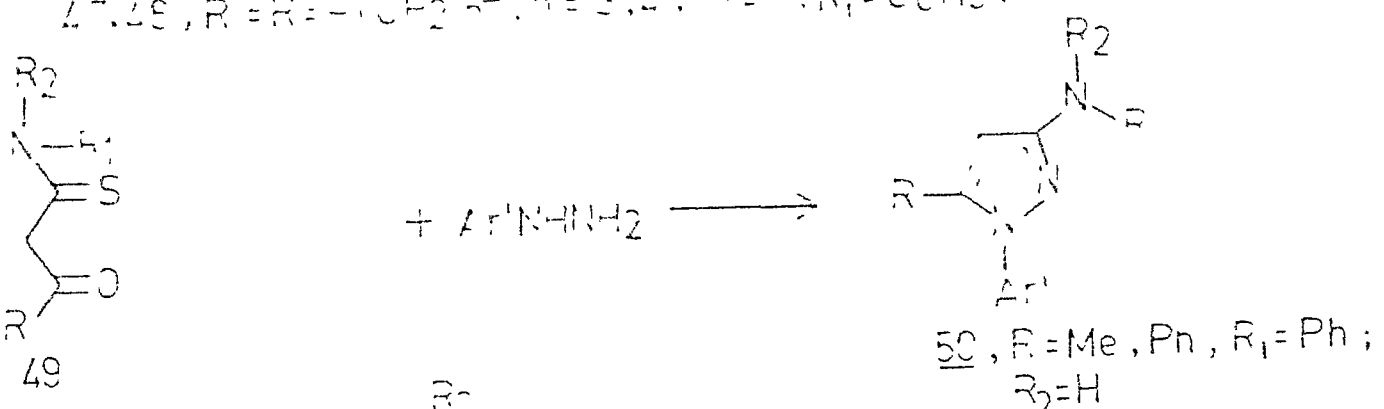
IV.2.2.4 From Thioanilides

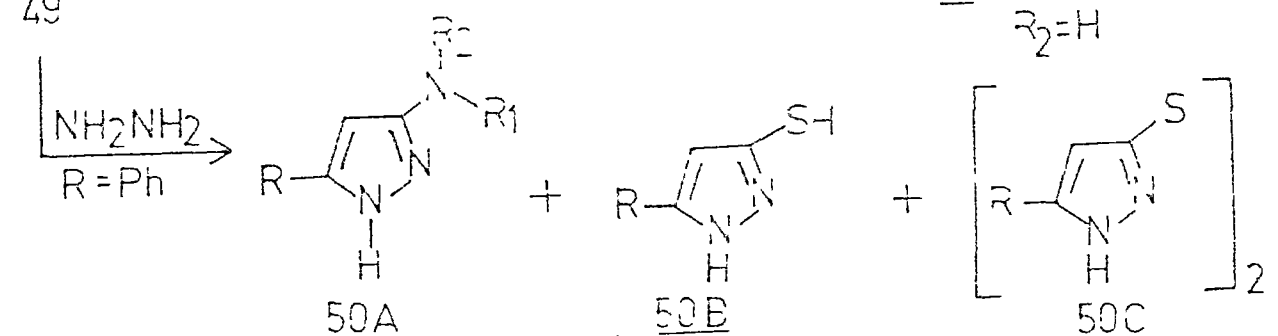
The reaction of phenylacetylenic thioanilides (22, Scheme 7) with hydrazine to give the corresponding 3(5)-anilinopyrazole under this category has been already described[7] (Scheme 7). Only two anilinopyrazoles have been synthesized by this procedure. This method requires prior synthesis of substituted arylacetylenes for wide structural variations.

A few of the α,β-unsaturated thioanilides (17), which are obtained by the reactions of the respective enamines with phenylisothiocyanate, have also been reacted with hydrazine to afford the corresponding 3(5)-anilinopyrazoles 18 in excellent yields[13] (Scheme 16). However this method requires moisture sensitive enamines as the starting materials.

The reactions of a few α-oxothioanilides 19 with aryl hydrazine have also been reported[14-16] to yield the corresponding 1-N-aryl-3(5)anilinopyrazoles 50 in excellent







Scheme 16

yields (Scheme 16). However our attempted synthesis of 3(5)-N-substituted amino-1(H)-pyrazoles (especially-3(5)-alkylaminopyrazoles) has shown that the yields of pyrazoles (50A) were low due to the formation of side products like thiopyrazolones (50B) and their dimers (50C) which were formed by displacement of the corresponding alkylamines in thioanilides 49 by hydrazine (Scheme 16).

From the above discussion it is apparent that the reaction of appropirately substituted oxoketen S,N-acetal (or polarized S,N-acetals) with hydrazine provides a very facile and highly efficient route for 3(5)-alkyl/arylaminopyrazoles. Although the reactions of a few of the doubly polarized S,N-acetals with hydrazine to give the corresponding 3(5)-anilinopyrazole have been reported in the literature,[17,18] the generality of this reaction for the synthesis of various aminopyrazoles with different structural variations was not investigated. The present studies therefore demonstrate that the polarized S,N-acetals are versatile precursors for the synthesis 3(5)-aryl/alkyl/aralkyl/N-azacycloalkyl-5(3)aryl/amino/oxo-4-substituted pyrazoles. The corresponding 4-unsubstituted-3(5)-aminopyrazoles can be further exploited for the synthesis of fused pyrazoloheterocycles by reactions with

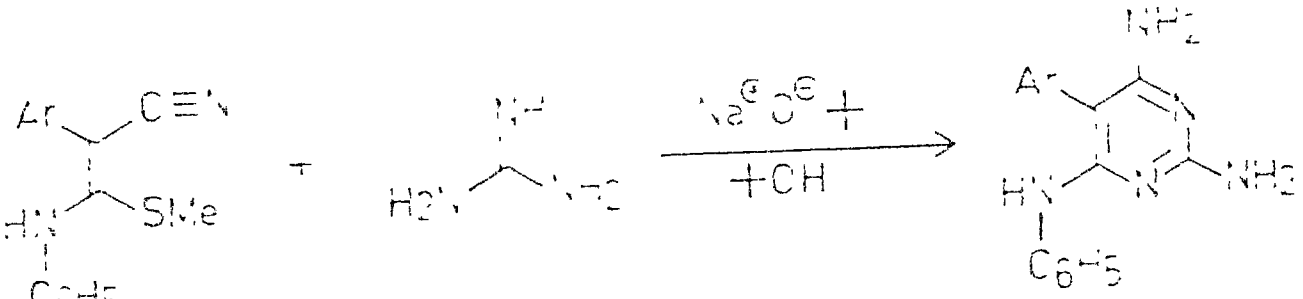
various activated heteromultiple bonds[10] and subsequent transformations. The attempts in these directions are in progress.

IV.2.3 Reactions of Polarized Keten S,N-acetals with guanidine: Synthesis of Novel 2-Amino/mercapto-4-N-aryl/alkyl/N-azacycloalkylamino-5,6-substituted pyrimidines

The earlier reported[2,3] studies on the synthesis of 4-substituted amino pyrimidines by reactions of S,N-acetals with guanidine were mostly carried out on the α-oxo-S,N-acetals derived from active methylene ketones and ethyl cyanoacetate. In the present investigation we have extended these studies to other keten S,N-acetals derived from arylacetonitriles malononitrile, phenylacetate and the oxoketen S,N-acetals derived from benzyl and secondary cyclic amines and the results are described here.

IV.2.3.1 RESULTS AND DISCUSSIONS

When the S,N-anilinoacetal 51a derived from phenylacetonitrile was reacted with guanidine in the presence of sodium t-butoxide in t-butanol, the corresponding 2,6-diamino-4-anilino-5-phenylpyrimidine 52a was obtained in 65% yield (Scheme 17). The structure of 52a was confirmed with the help of mass (M^+, m/z 276); i.r.(KBr) 3150, 3305, 3400, 3460



51

52

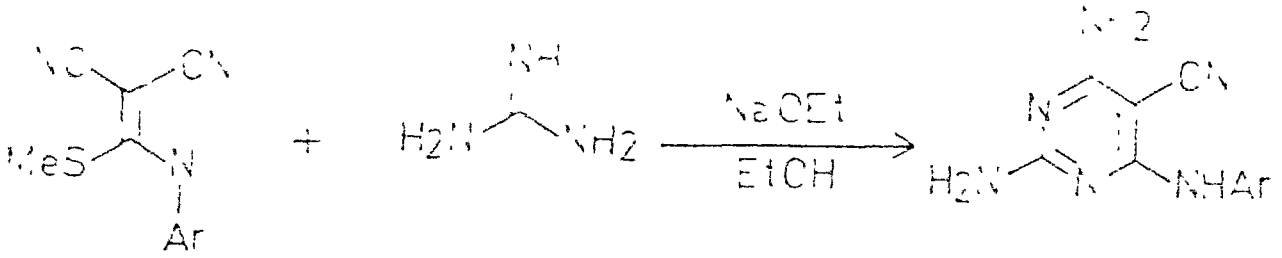
51, 52 a , Ar = C_6H_5
b , Ar = p-ClC_6H_4
c , Ar = p-$MeOC_6H_4$
d , Ar = 3,4-di$MeOC_6H_3$

Scheme 17

(Free and H-bonded) NH); 1640 (δ NH_2) and n.m.r.(TFA) δ 6.90-7.85 (m, arom) spectral and analytical data. The other substituted S,N-acetal 51b-d similarly afforded the corresponding 4-anilino-5-arylpyrimidines 52b-d in 82-90% overall yields. The spectral and analytical data of 52b-d were in conformity with the assigned structures (Tables 3 and 4).

The reaction of S,N-anilinoacetals (53a-b) derived from malononitrile was next investigated. The S,N-anilinoacetals (53a-b) reacted with guanidine to give the corresponding 2,6-diamino-4-arylamino-5-cyanopyrimidines 54a-b in good yields (Scheme 18). The structures of 54a-b were confirmed with the help of spectral and analytical data (Tables 3 and 4).

The reaction was found to be equally facile with the S,N-anilinoacetal (55) derived from ethylphenylacetate and the corresponding 2-amino-4-anilino-5-phenyl-6-oxo-1(H)pyrimidine 56 was obtained in 56% yield under similar conditions (Scheme 19). Also when the S,N-acetal 55 was reacted with thiourea in the presence of sodium t-butoxide in refluxing t-butanol; the corresponding 2-mercapto-4-anilino-6-oxo-1(H)-pyrimidine 57 was obtained in 70% yield (Scheme 19). Thus the S,N-acetals are useful precursors for the synthesis of 2-mercapto-4-substituted aminopyrimidines also.

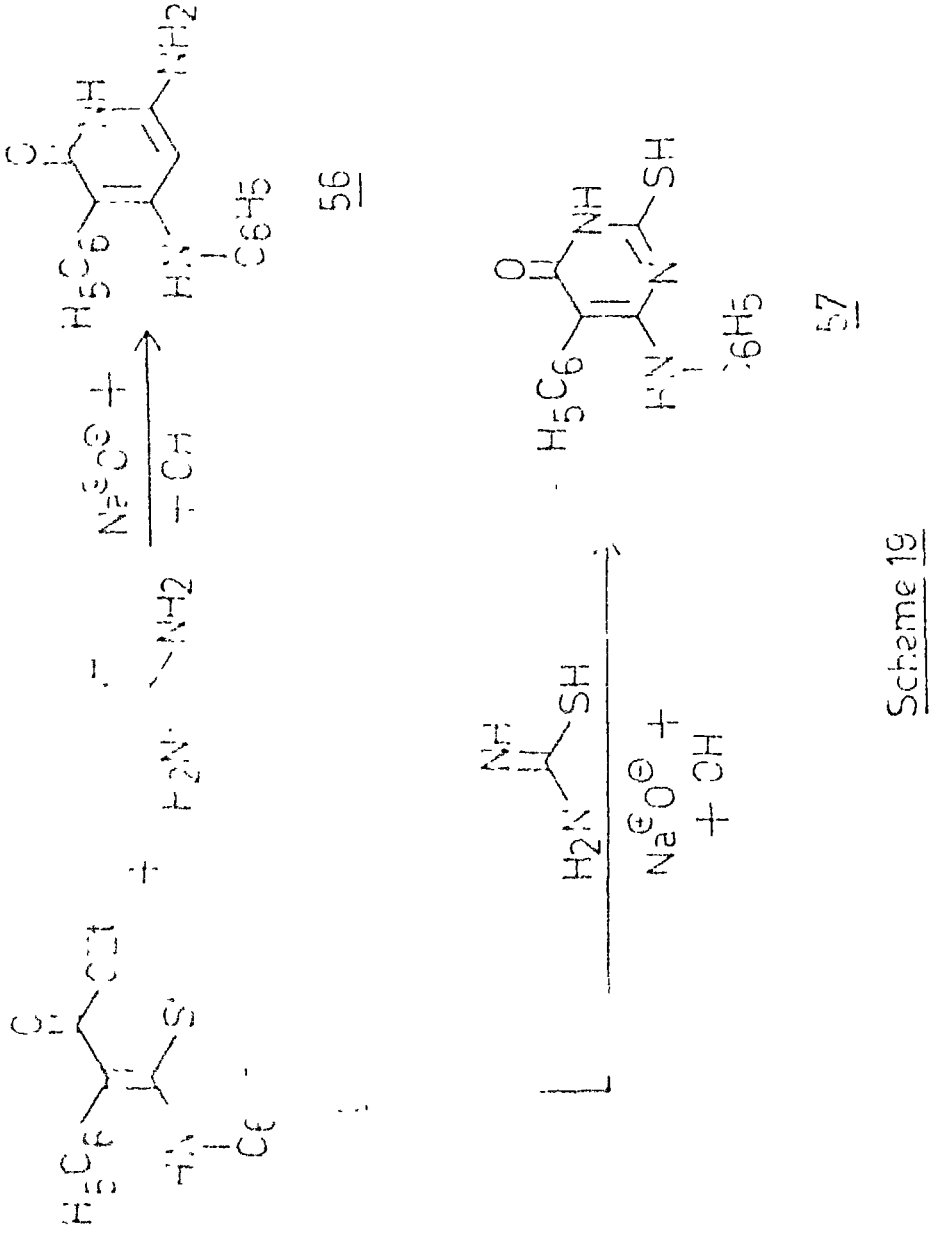


53 + 54

53, 54a, Ar = o-FC_6H_4

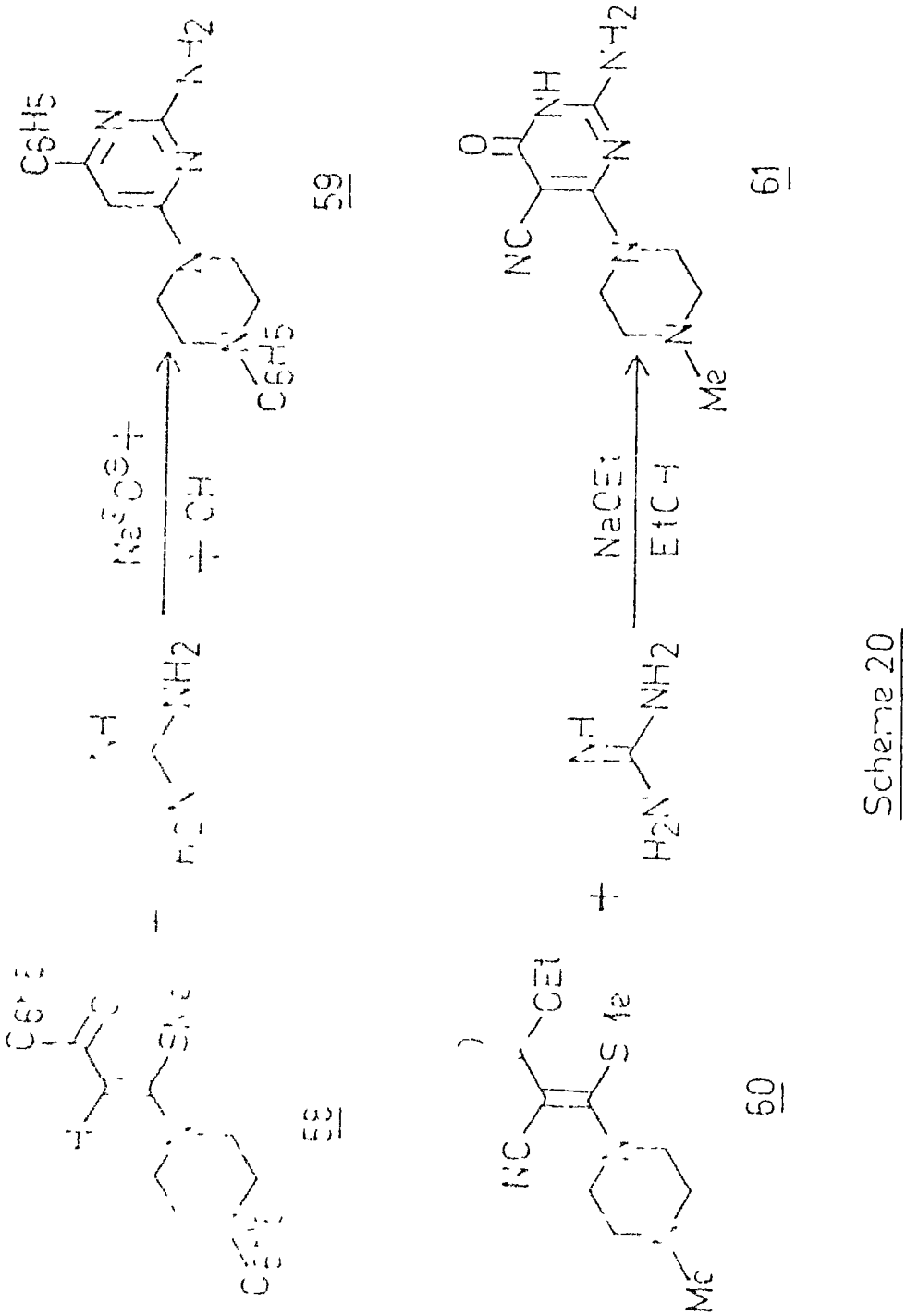
b, Ar = p-ClC_6H_4

Scheme 18



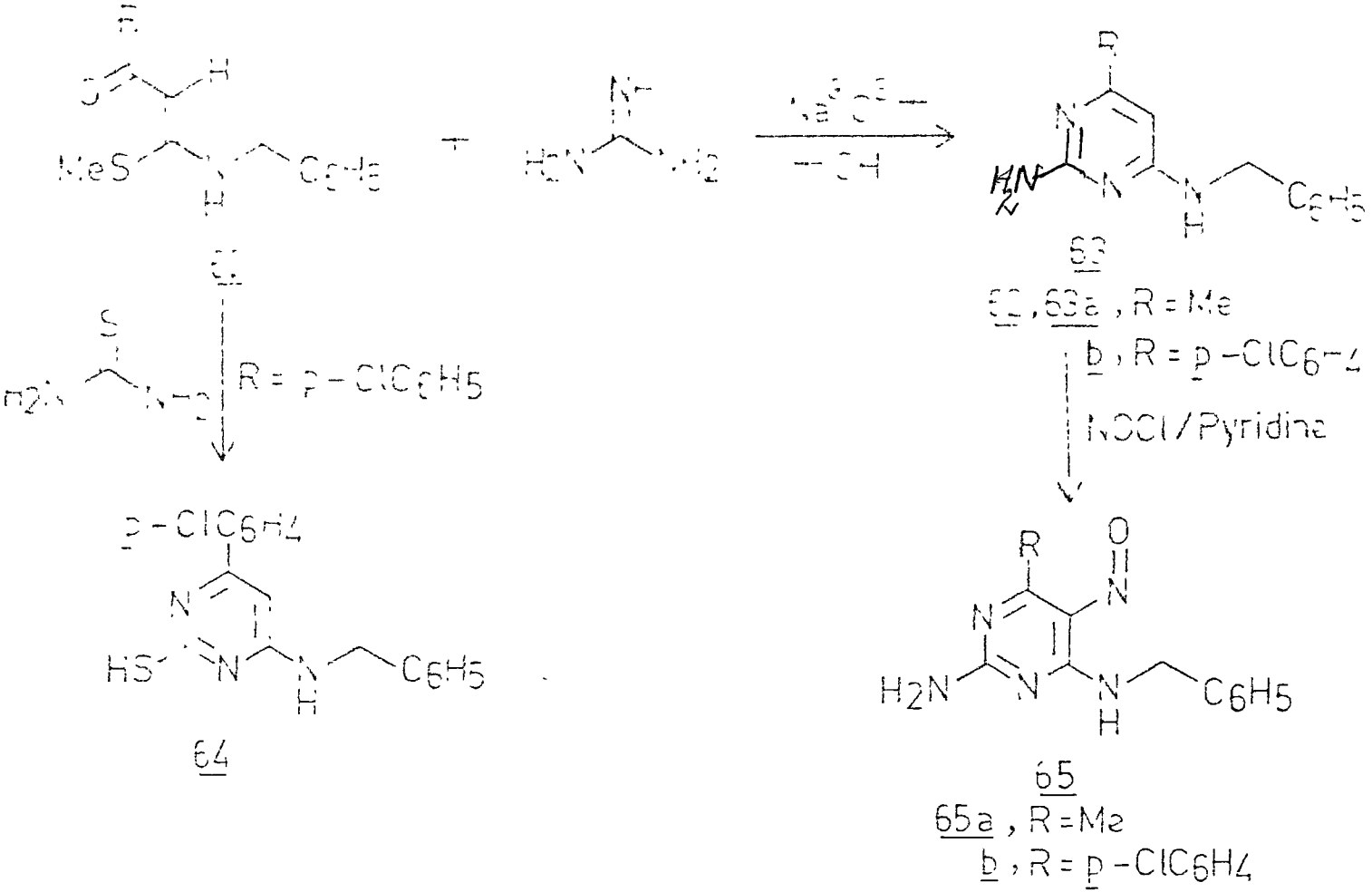
Scheme 19

In our earlier studies[2] a few of the 4-N-morpholino-6-arylpyrimidines (16a-c), (Scheme 4) were obtained in low yields by the reaction of guanidine with the corresponding N,N-morpholino acetals (15a-c) which were generated insitu from the corresponding oxoketen S,S-acetals 1 (Scheme 4). In the present investigation, we have synthesized the corresponding α-oxo-S,N-(N'-phenylpiperazino)acetal 58 according to the route shown in the scheme 5 [Ar=C_6H_5; R=R$_1$ = $-(CH_2)_2-N-C_6H_5-(CH_2)_2$] by methylation of the corresponding thioamide 19. When the S,N-acetal 58 was reacted with guanidine under identical conditions as described earlier, the corresponding 2-amino-4-N-(N-phenylpiperazino) pyrimidine 59 was exclusively obtained in 62% yield (Scheme 20). Similarly the S,N-(N'-methylpiperazino) acetal 60 derived from ethylcyanoacetate afforded the corresponding 2-amino-4-N(N-methylpiperazino)-5-cyano-6-oxo-1(H)-pyrimidine (61) in 48% yield (Scheme 20). Thus these studies demonstrate that the corresponding 4-N-azacycloalkylpyrimidines could be obtained in better yields from the corresponding S,N-acetals rather than via the corresponding N,N-acetals such as 15 (Scheme 4). The structures of all the new pyrimidines 56, 57, 59 and 61 were confirmed with the help of spectral and analytical data (Table 3 and 4).



Scheme 20

When the α-oxo-S,N-benzylacetals 62a and 62b were reacted with guanidine under similar conditions the corresponding 2-amino-4-N-benzylamino-6-substituted pyrimidines 63a and 63b were obtained in good yields (Scheme 21). Similarly the reaction of S,N-benzylacetal (62b) with thiourea under the identical conditions afforded the corresponding 2-mercapto-4-benzylaminopyrimidine (64) in 60% yield. The nitrosation of pyrimidines 63a-b with nitrosyl chloride afforded the corresponding 5-nitrosopyrimidines 65a-b in good yields. However our subsequent attempts to get the purines 67a and 67b by thermal cyclodehydration of the corresponding 5-nitrosopyrimidines 65a-b under varying conditions were not successful (Scheme 22). These results are in line with the earlier reported studies[19] on the thermal cyclodehydration of 5-nitrosopyrimidine 65c which did not afford the purine derivative 67c even under drastic conditions. The authors[19] have attributed this failure of 65c to undergo cyclization to 67c to the presence of stable aromatic system in 65c, which prevents it to exist in hydroxyimino-tautomeric form 66c. According to these authors, the existance of hydroxyimino-tautomeric form 66c is one of the prerequisite for the facile cyclodehydration of 4-aralkylamino-5-nitrosopyrimidine


MeS
C6H5
R = p-ClC6H5
p-ClC6H4
HS
C6H5
64
R
O
N
H2N
C6H5
65
65a , R = Me
b , R = p-ClC6H4

Scheme 21

65-67a, R = Me
b, R = p-C6H4
c, R = NH2

Scheme 22

derivatives (Scheme 22).[19,20] The observed failure of 65a and 65b to give the corresponding 67a and 67b could also be rationalized on the basis of same arguments.

IV.3.2 CONCLUSION

The versatility of polarized keten S,N-acetals as precursors for 4-N-substituted pyrimidines has been demonstrated by extending the reactions of different polarized keten S,N-acetals like 51a-d, 53a-b (α-cyano) 55(α-ethoxycarbonyl) S,N-acetals and novel S,N-acetals 58, 60 and 62 derived from cyclic secondary and benzylamines respectively with guanidine. The reaction provides a facile route to a variety of novel functionalized 4-alkyl/aryl/N-azacycloalkylaminopyrimidines. It is pertinent to note that many of the substituted aminopyrimidines are know to exhibit wide spectrum of biological activity.[21] The usual methods for the synthesis of 4(6)-substituted aminopyrimidines involve substitution of the corresponding chloro-,[22] hydroxy,[23] alkoxy[22] or alkylthiopyrimidines[22] by the appropriate amines. The present procedure from the corresponding S,N-acetals provides synthesis of these pyrimidines from three carbon fragments having built in substituted amino group with wide structural variations.

IV.1 EXPERIMENTAL

Mps were determined on a "Boetius" (German) apparatus and are uncorrected. The i.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer, while u.v. spectra were taken on Beckman 26 spectrophotometer. The ^{1}H-n.m.r. spectra were recorded on a Varian EM-390 (90 MHz) spectrometer using TMS as an internal standard and chemical shifts are expressed in δ (ppm).

The Starting Materials

The commercial samples of acetone, acetophenone, p-chloroacetophenone, p-bromoacetophenone, p-methylacetophenone, p-methoxyacetophenone, p-ethoxyacetophenone, malononitrile, phenylacetonitrile, p-chlorophenylacetonitrile, p-methoxyphenylacetonitrile, dimethoxyphenylacetonitrile, ethylcyanoacetate, ethylacetoacetate, aniline, p-chloroaniline, p-methylaniline, ethylamine, methylamine, benzylamine, 2,2-diethoxyethylamine, p-fluoroaniline, morpholine, N-methylpiperazine, N-phenylpiperazine, phenylhydrazine were purified before use.

Ethylbenzoylacetate, b.p. 132-37 (4 mm)[24] ethyl-p-bromophenylacetate, m.p. 30°;[25] 1,3-diphenyl-2-pyrazolin-5-one, m.p. 128°;[26] 1-phenyl-3-(p-bromophenyl)-2-pyrazolin-5-one, m.p. 125-7;[26] 1-phenyl-3-methyl-2-pyrazolin-5-one, m.p. 126°[26] were prepared by the reported method.

The dimethyltrithiocarbonate, b.p. 225° (760 mm);[27] phenyl isothiocyanate, b.p. 120-1° (35 mm);[28] p-chlorophenylisothiocyanate,[28] p-methylphenylisothiocyanate,[28] ethylisothiocyanate, b.p. 130-1° (760 mm)[29] were also prepared by the reported procedures.

The ketendithioacetals, 3,3-(bismethylthio)-1-phenyl-2-propen-1-one; 3,3-(bismethylthio)-1-(p-methoxyphenyl)-2-propen-1-one; 3,3-(bismethylthio)-1-(p-bromophenyl)-2-propen-1-one and 3,3-(bismethylthio)-1-(p-methylphenyl)-2-propen-1-one were prepared by the reported procedure described in chapter II and 3,3-(bismethylthio)-1-(p-chlorophenyl)-2-propen-1-one, 109-10°[30] was prepared by the reported method (the general procedure given in chapter II). The dithioacetals 4-[bis(methylthio) methylene]-5-oxo-1,3-diphenyl-4,5-dihydropyrazole (33a) m.p. 150°[31] and 4-[bis(methylthio)methylene]-5-oxo-1-phenyl-3-(p-bromophenyl)-4,5-dihydropyrazole (33b), m.p. 121°[31] were prepared by the reported method.

The S,N-acetals 10 (a,b,c,j,m,n), 27 and 51 (a-d) were prepared as described in chapter III.

Preparation of polarized keten S,N-acetals: The S,N-acetals have been prepared by one of the following methods

(A) By displacement method: A solution of respective keten dithioacetal (0.02 mol) in ethanol was refluxed with corresponding amine (0.025 mol) for 3-10 hr. After the completion of the reaction (tlc) the solvent was removed and the crude S,N-acetals thus obtained were purified either by crystallisation or by column chromatography over silica gel using benzene/hexane (1:1) as eluent. The S,N-acetals prepared by this method are described below:-

The known S,N-acetals: 3-methylthio-3-N-methylamino-1-phenyl-2-propen-1-one (10g) m.p. 70-1°;[32] 3-methylthio-3-N-methylamino-1-(p-chlorophenyl)-2-propen-1-one (10h) m.p. 71-2°;[32] 3-methylthio-3-N-ethylamino-1-(p-chlorophenyl-2-propen-1-one (10k)[3] viscous liquid (tlc single spot); 3-methylthio-3-ethylamino-1-(p-methoxyphenyl)-2-propen-1-one (10l)[3] viscous liquid (tlc single spot); 3-methylthio-3-(2,2-dimethoxyethylamino)-1-phenyl-2-propen-1-one (10o)[33] semisolid (tlc single spot); 3-methylthio-3-(2,2-diethoxyethylamino)-1-(p-methylphenyl)-2-propen-1-one (10p)[33] m.p. 62-3°; 3-methylthio-3-(2,2-diethoxyethylamino)-1-(p-methoxyphenyl)-2-propen-1-one (10q)[33] viscous liquid (tlc single spot); 3-methylthio-3-(2,2-diethoxyethylamino)-1-(p-ethoxyphenyl)-2-propen-1-one (10r)[33] m.p. 83-4°; 3-methylthio-3-(2,2-diethoxyethylamino)-1-(p-chlorophenyl)-2-propen-1-one (10s)[33] yellow oil (tlc single spot);

3-methylthio-3-(2,2-diethoxyethylamino)-1-(p-bromophenyl)-2-propen-1-one (10t)[33] yellow oil (tlc single spot); 4-methylthio-4-benzylamino-3-buten-2-one (62a)[32] semisolid (tlc single spot); and 3-methylthio-3-benzylamino-1-(p-chlorophenyl)-2-propen-1-one (62b) m.p. 95-7°[32] were prepared by above method.

3-methylthio-3-(N-methylamino)-1-p-methoxyphenyl-2-propen-1-one (10i), was obtained as a light yellow solid, m.p. 93-95°; in 74% (3.5g) yield; i.r.(KBr) ν max: 3450 (NH); 1600 (CO) cm^{-1}; ^1H n.m.r.($CDCl_3$); δ 2.40 (s, 3H, SCH_3); 2.55 (s, 3H, NCH_3); 3.85 (s, 3H, OCH_3); 6.65 (s, 1H, vinylic); 6.80-6.95 (m, 2H, arom); 7.75-7.90 (m, 2H, arom); Found: C, 60.64; H, 6.43; N, 5.75; Calc. for $C_{12}H_{15}NO_2S$ (237): C, 60.75; H, 6.32; N, 5.90%.

3-Methylthio-3-(p-methylanilino)-2-cyanoacrylonitrile (25a), was obtained as yellow solid, m.p. 164°, in 70% (3.2g) yield, i.r.(KBr) ν max: 3210 (NH), 2170 (CN) cm^{-1}; ^1Hn.m.r.($CDCl_3$); δ 2.25 (s, 3H, SCH_3); 2.33 (s, 3H, $CH_3C_6H_4$); 7.10-7.30 (m, 4H, arom); 8.30 (br, 1H, NH); Found: C, 62.65; H, 4.95; N, 18.56; Calc. for $C_{12}H_{11}N_3S$ (229): C, 62.88; H, 4.80; N, 18.34%.

3-Methylthio-3-(p-fluoroanilino)-2-cyanoacrylonitrile (25b), was obtained as yellow solid, m.p. 68-70°, in 75% (3.5g) yield; i.r.(KBr) ν max: 3225 (NH), 2205 (CN); ^1Hn.m.r.(TFA): δ 2.70 (s, 3H, SCH_3); 7.10-7.65 (m, 4H, arom); Found: C, 56.42; H, 3.71; N, 18.22; Calc. for $C_{11}H_8N_3SF$ (233): C, 56.65; H, 3.43; N, 18.02%.

3-Methylthio-3-(p-chloroanilino)-2-cyanoacrylonitrile (53b) was obtained as yellow solid, m.p. 72-74°, in 80% (3.9g) yield; i.r.(nujol) ν max: 3220 (NH), 2210, 2190 (CN); ^{1}Hn.m.r. (TFA): δ 2.05 (s, 3H, SCH_3); 6.50-7.50 (m, 4H, arom): Found: C, 52.62; H, 3.41; N, 16.51; Calc. for $C_{11}H_{10}N_3SCl$ (219.5): C, 52.90; H, 3.20; N, 16.83%.

3-Methylthio-3-(N-methylpiperazino)-2-cyanoethylacrylate (30) was obtained as pale yellow solid, m.p. 78-80° in 82% (4.4g) yield; i.r.(KBr) ν max: 2200 (CN), 1670 (CO) cm^{-1}; ^{1}Hn.m.r.($CDCl_3$); δ 1.30 (t, 3H, $OCH_2\underline{CH_3}$); 2.33 (s, 3H, SCH_3); 2.51 (t, 4H, piperazino); 2.63 (s, 3H, $N\text{-}CH_3$); 3.93 (t, 4H, piperazino); 4.21 (q, 2H, $O\underline{CH_2}CH_3$); Found: C, 53.25; H, 6.81; N, 15.95; Calc. for $C_{12}H_{19}N_3O_2S$ (269): C, 53.53; H, 7.06; N, 15.61%.

5-Oxo-1,3-diphenyl-4-(methylthio-N-methylamino)methylene-Δ^2-pyrazoline (34a), was obtained as light yellow solid, m.p. 213-5° in 80% (5.16g) yield; i.r.(KBr) ν max: 3340 (NH), 1640 (CO) cm^{-1}; ^{1}Hn.m.r.(TFA): δ 2.22 (s, 3H, SCH_3), 2.80 (s, 3H, $NHC\underline{H_3}$); 6.90-7.50 (m, 10H, arom); Found: C, 67.10; H, 5.02; N, 13.33; Calc. for $C_{18}H_{17}N_3OS$ (323): C, 66.87; H, 5.26; N, 13.00%.

5-Oxo-1-phenyl-3-(p-bromophenyl)-4-methylthio-N,(N'-methyl-piperazino)methylene-Δ^2-pyrazoline (34b), was obtained as yellow needles m.p. 192-93°; i.r.(KBr) ν max: 1620 (CO) cm^{-1}; ^1H-n.m.r. ($CDCl_3$): δ 2.28 (s, 3H, SCH_3); 2.33 (s, 3H, $=N-CH_3$); 2.50 (br, 4H, piperazino); 3.91 (s, 4H, piperazino); 6.96-7.60 (m, 7H, arom); 8.13 (dd, 2H, arom); Found: C, 56.26; H, 5.06; N, 11.72: Calc. for $C_{22}H_{23}N_4OSBr$ (471): C, 56.05; H, 4.88; N, 11.88%.

(B) By arylisothiocyanate method

To an ice cooled well stirred suspension of NaH (2.4g, 0.15 mol) (washed 2-3 times with dry benzene) in dry DMF (50 ml) a solution of active methylene compound (0.05 mol) in dry DMF (25 ml) was added dropwise during 0.5 hr. A solution of aryl isothiocyanate (0.05 mol) in dry DMF (25 ml) was then added and the reaction mixture was further stirred for 1.5-2 hours followed by addition of methyl iodide (0.05 mol) in dry DMF (20 ml). After further stirring for 2 hr, the reaction mixture was poured over crushed ice, neutralized with glacial AcOH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water (3x100 ml) dried (Na_2SO_4) and concentrated to give crude S,N-acetal, which was purified by passing through silica gel column using benzene/hexane (1:1) as eluent. The S,N-acetals prepared by this method are described below:-

The known S,N-acetals: 3-methylthio-3-(p-methylanilino)-1-phenyl-2-propen-1-one (10d), m.p. 84°;[32] 3-methylthio-3-(p-methylanilino)-1-(p-chlorophenyl)-2-propen-1-one (10f), m.p. 105-6°[32] were prepared by the above procedure.

The unknown keten S,N-acetals: 3-methylthio-3-(p-methylanilino)-1-(p-ethoxyphenyl)-2-propen-1-one (10e) was obtained as a brownish solid, m.p. 72-3°, in 70% (11.41g) yield; i.r.(KBr) ν max: 3075 (NH), 1680, 1600 (CO) cm^{-1}; ^1H-n.m.r. ($CDCl_3$): δ 1.50 (t, 3H, $OCH_2\underline{CH_3}$); 2.15 (s, 3H, $\underline{CH_3}C_6H_4$); 2.45 (s, 3H, SCH_3); 4.10 (q, 2H, $O\underline{CH_2}CH_3$); 5.83 (s, 1H, NH); 6.85 (s, 1H, vinylic); 7.20-8.10 (m, 8H, arom); Found: C, 69.61; H, 6.55; N, 4.45; Calc. for $C_{19}H_{21}NO_2S$ (327): C, 69.72; H, 6.42; N, 4.28%.

3-Methylthio-3-anilino-2-phenylethylacrylate (55) was obtained as a semisolid (tlc single spot) in 75% (11.73g) yield; i.r. (KBr) ν max: 3075 (NH), 1620 (CO) cm^{-1}; ^1H-n.m.r.($CDCl_3$): δ 1.40 (t, 3H, $OCH_2\underline{CH_3}$); 2.80 (s, 3H, SCH_3); 4.45 (q, 2H, $O\underline{CH_2}CH_3$); 7.33-8.15 (m, 10H, arom); Found: C, 68.86; H, 6.22; N, 4.36; Calc. for $C_{18}H_{19}NO_2S$ (313): C, 69.00; H, 6.07; N, 4.47%.

(C) Thiomide Method

Procedure for the synthesis of benzoylthioaceticacid-(N-phenyl) piperazide: A solution of methyl β-benzoyldithioacetate (0.05 mol) and N-phenylpiperazine (0.01 mol) was refluxed in ethanol (25 ml) for 7 hr. After completion of the reaction, ethanol was removed on water bath and the residue triturated with hexane to remove excess of amine. The crude thiomide thus obtained was purified by crystallization from ether/hexane mixture as yellow crystalline solid, m.p. 95-7°[34]; yield 78% (2.26g); i.r.(KBr) ν max: 1680 (CO) cm^{-1}; ^{1}H-n.m.r.($CDCl_3$): δ 3.55-4.20 (m, 8H, piperazino); 4.69 (s, 2H, $-CH_2CS$); 7.18-7.62 (m, 10H, arom); m/z: 324 (M^+); Found: C, 69.98; H, 6.35; N, 8.21; Calc. for $C_{19}H_{20}N_2OS$ (324): C, 70.37; H, 6.17, N, 8.64%.

Procedure for the synthesis of 3-methylthio-3-N-(N'-phenyl-piperazino)-1-phenyl-2-propen-1-one (58)

A suspension of thiomide (0.004 mol) and potassium carbonate (0.56g, 0.004 mol) in acetone (30 ml) was refluxed for 3 hr with stirring. The solution was cooled and 0.71g (0.004 mol) of methyliodide was added and the reaction mixture was stirred at room temperature for 3 hr. It was then poured over crushed ice, acidified with 20% AcOH, extracted with $CHCl_3$ (3x50 ml) dried (Na_2SO_4) and solvent evaporated to give the S,N-acetal

(58) which was obtained in pure form by passing through silica gel column using benzene/hexane (2:1) as eluent as yellow viscous semisolid in 90% (1.2g) yield; i.r.(neat) ν max: 1625 (CO) cm^{-1}; ^{1}H-n.m.r.(CCl_4); δ 2.43 (s, 3H, SCH_3); 3.10-3.86 (m, 8H, piperazino); 5.83 (s, 1H, olefinic); 6.68-8.12 (m,10H, arom); Found: C, 71.38; H, 6.21; N, 8.57; Calc. for $C_{20}H_{22}N_2OS$ (338): C, 71.00; H, 6.50; N, 8.28%.

General Procedure for the Synthesis of 3(5)-aryl-5(3)-N-aryl/alkyl/benzyl/β-bisethoxyethylaminopyrazoles (21a-r); 3(5)-amino-5(3)-arylamino-4-cyano/3,4-dimethoxyphenylpyrazoles (26a-b, 28) and 4-cyano-5-N(N'-methylpiperazino)-3-pyrazolone (32):

A solution of the respective S,N-acetal (0.01 mol) and hydrazine hydrate (0.015 mol) in 30 ml of ethanol was refluxed for 7-8 hr (20 hr in 27). The solvent was removed on water bath and the residue was triturated with water, extracted with chloroform (3x50 ml), dried (Na_2SO_4) and evaporated to give pyrazoles which were crystallized from benzene-hexane mixture.

The pyrazoles 26a-b, 28 and 32 separated out while triturating with water and were filtered as such without extraction. Spectral and analytical data are given in tables 1 and 2 respectively.

General procedure for the synthesis of 3(5)-aryl-4-nitroso-5(3)-N-aryl/alkyl/benzyl/aminopyrazoles (37a-c):

To a solution of pyrazole (0.003 mol) and pyridine (0.003 mol) in dry chloroform (20 ml) a solution of nitrosylchloride in dry ether (2 ml) was added with stirring and cooling. The reaction mixture was further stirred for 15 min and then chloroform was removed on water bath. The residue was diluted with ice cold water, extracted with chloroform (3x25 ml), dried and evaporated to give crude nitrosopyrazole which was purified by crystallisation using acetone and hexane.

3-Phenyl-4-nitroso-5-anilinopyrazole (37a) was obtained as reddish brown solid, m.p. 281-2°, in 90% yield; i.r. νmax: (KBr): 3040 (NH); 1620 (N=O); 1580 (C=N) cm^{-1}; ^{1}H-n.m.r. (TFA); δ 7.10-8.05 (m, 10H, arom); λ max(MeOH); 230 nm (log ϵ, 4.12); Found: C, 68.40; H, 4.23; N, 21.50; Calc. for $C_{15}H_{12}N_4O$ (264) C, 68.18; H, 4.54; N, 21.21%.

3-Phenyl-4-nitroso-5-methylaminopyrazole (37b) was obtained as a brown solid, m.p. 184-5°; in 85% yield; i.r. νmax: (KBr): 3250 (NH) 1580 (N=O); 1505 (C=N); ^{1}H-n.m.r. (TFA): δ 3.40 (s, 3H, CH_3NH-); 7.30-8.30 (m, 5H, arom); λ max(MeOH): 240 nm (log ϵ, 3.99); Found: C, 59.62; H, 4.66; N, 27.95; Calc. for $C_{10}H_{10}N_4O$ (202): C, 59.41; H, 4.95; N, 27.72%.

3-Phenyl-4-nitroso-5-benzylaminopyrazole (37c) was obtained as a yellow solid, m.p. 178°, in 94% yield; i.r.(KBr) ν_{max}: 3225 (NH); 1585 (N=O), 1500 (C=N); ^{1}H-n.m.r.(TFA): δ 4.90 (br s, 2H, $C\underline{H}_2C_6H_5$); 7.30-8.10 (m, 10H, arom); λ_{max}: (MeOH); 235 nm (logϵ ,4.09); Found: C, 69.32; H, 5.15; N, 19.32; Calc. for $C_{16}H_{14}N_4O$ (278): C, 69.06; H, 5.03; N,20.14%.

General Procedure for the Synthesis of 4-anilino-2,6-diamino-5-arylpyrimidines (52a-d); 4-arylamino-5-cyano-2,6-diaminopyrimidines (54a-b); 2-amino-4-anilino-5-phenyl-6-oxo-1,6-dihydropyrimidine (56) ; 2-amino-4-N-(N'-phenylpiperazino)-6-phenylpyrimidine (59) 2-amino-5-cyano-4-N-(N'-methylpiperazino)-6-oxo-1,6-dihydropyrimidine (61) and 2-amino-6-alkyl/aryl-4-benzylaminopyrimidines (63a-b):

A solution of respective S,N-acetal (51a-d), 55, 58 and (62a-b) (0.01 mol) in dry t-butanol (10 ml) was added to a suspension of guanidine nitrate (1.22g, 0.01 mol) and sodium t-butoxide (from 0.01g atom of Na) in t-butanol (50 ml) and the reaction mixture was refluxed for 18-20 hr (monitored by tlc). The solvent was removed under reduced pressure and the residue was diluted with ice cold water and extracted with chloroform (2x150 ml). The chloroform layer was dried

(Na_2SO_4) and evaporated to give crude pyrimidines which were purified by crystallisation from dichloromethane/hexane mixture.

The pyrimidines (54a-b) and 61 were synthesized under similar conditions using sodium ethoxide in dry ethanol instead of t-butoxide, t-butanol the spectral and analytical data of the pyrimidines thus synthesised are given in tables 3 and 4 respectively.

General Procedure for the Synthesis of 4-anilino-2-mercapto-6-oxo-5-phenyl-1,6-dihydropyrimidine (57) and 4-benzylamino-2-mercapto-6-(p-chlorophenyl)pyrimidine (64):

A solution of respective S,N-acetal 55 and 62 (0.01 mol) in dry t-butanol (10 ml) was added to a suspension of thiourea (0.76g, 0.01 mol) and sodium t-butoxide (from 0.01g atom of sodium) in t-butanol (50 ml) and the reaction mixture was refluxed for 18-20 hr (monitored by tlc). The solvent was removed under reduced pressure and the residue was diluted with ice cold water and extracted with chloroform (2x150 ml). The chloroform layer was dried (Na_2SO_4) and evaporated to give crude pyrimidines which were purified by crystallization from dichloromethane/hexane mixture.

4-Anilino-2-mercapto-6-oxo-5-phenyl-1,6-dihydropyrimidine (57) was obtained as yellow solid; m.p. 225-6°C, in 70% (2.06g) yield; i.r.(KBr) ν max: 3440 (br OH, NH), 1600, 1620 cm^{-1}; ^{1}H-n.m.r.(TFA): δ 6.80-7.70 (m, 10H, arom); m/z (M^+) 295; Found: C, 65.47; H, 4.77; N, 14.68; Calc. for $C_{16}H_{13}N_3OS$ (295) C, 65.08; H, 4.40; N, 14.23%.

4-Benzylamino-2-mercapto-6-(p-chlorophenyl)pyrimidine (64) was obtained as a light yellow solid; m.p. 85-6°, in 75% (2.45g) yield i.r.(KBr) ν max: 3450 (SH), 3250 (NH); 1640, 1580 cm^{-1}; ^{1}H-n.m.r.($CDCl_3$); δ 4.50 (d, 2H, NH-C$\underline{H}_2$); 7.20-8.20 (m, 10H, arom), Found: C, 62.51; H, 4.06; N, 13.05; Calc. for $C_{17}H_{14}N_3SCl$ (327.5); C, 62.29; H, 4.27; N, 12.82%.

Synthesis of 2-amino-4-N-benzylamino-5-nitroso-6-methylpyrimidine (65a) and 2-amino-4-N-benzylamino-5-nitroso-6-p-chlorophenylpyrimidine (65b)

To a solution of pyrimidines (63a-b) (0.003 mol) in pyridine (0.003 mol) in dry chloroform (20 ml) a solution of nitrosyl chloride (2 ml) in dry ether was added with stirring and ice cooling. The reaction mixture was further stirred for 15 min and chloroform was removed on water bath. The residue was diluted with ice cold water (15 ml), extracted with chloroform

(3x25 ml), dried (Na_2SO_4) and evaporated to give crude pyrimidines 65a and 65b which were crystallized from acetone and hexane mixture.

2-Amino-4-benzylamino-5-nitroso-6-methylpyrimidine (65a), was obtained as a light green solid, m.p. 180-2°, in 70% (0.51g) yield; i.r.(KBr) ν max: 3125, 2950 (br NH), 1670, 1630 (N=O), 1580 (δ NH); ^{1}H-n.m.r.(TFA): δ 2.00 (s, 3H, CH_3); 4.50 (d, 2H, $NHCH_2$); 7.18 (s, 5H, arom); λ max(MeOH): 220 nm (log ϵ, 4.25); 575 nm (log ϵ, 1.91); Found: C, 59.08; H, 5.50; N, 28.62; Calc. for $C_{12}H_{13}N_5O$ (243): C, 59.25; H, 5.34; N, 28.80%.

2-Amino-4-N-benzylamino-5-nitroso-6-(p-chlorophenyl (65b) was obtained as a greenish solid, m.p. 218-19°; in 75% (0.76g) yield; i.r.(KBr) ν max: 3300, 3450 (NH); 1590 (δ NH): 1640 (N=O); ^{1}H-n.m.r.(TFA): δ 4.81 (d, 2H, CH_2NH); 7.10-7.85 (m, 9H, arom); λ max(MeOH): 230 nm (log ϵ, 4.36); 590 nm (log ϵ, 1.83); Found: C, 60.38; H, 4.47; N, 20.92%; $C_{17}H_{14}N_5OCl$ (339.5) requires: C, 60.00; H, 4.15, N, 20.61%.

Table 1

Spectral Data for Pyrazoles (21a-t, 26a-b, 28, 32 and 36a-b)

Product	IR ν_{max} (KBr)	^{1}H-NMR(TFA) δ
21a	3405,3275 (NH) 1600 (C=N)	6.35 (s, 1H, H-4); 7.15-7.90 (m, 10H, arom).
21b	3400, 3270 (NH) 1600 (C=N)	2.50 (s, 3H, CH_3); 6.55 (s, 1H, H-4); 7.30-8.15 (m, 9H, arom).
21c	3400, 3300 (NH) 1600 (C=N)	6.31 (s, 1H, H-4); 7.00-8.23 (m, 9H, arom).
21d	3400, 3300 (NH) 1610, 1600 (C=N)	2.28 (s, 3H, CH_3); 6.18 (s, 1H, H-4); 6.70-7.75 (m, 9H, arom).
21e	3400, 3420 (NH) 1604 (C=N)	1.55 (t, 3H, CH_2-CH_3); 2.40 (s, 3H, CH_3), 4.40 (q, 2H, CH_2-CH_3); 6.42-(s, 1H, H-4); 7.15-8.10 (m, 8H, arom).
21f	3405 (br, NH) 1610, 1600 (C=N)	2.50 (s, 3H, CH_3); 6.4 (s, 1H, H-4); 7.25-8.10 (m, 8H, arom).
21g	3150, 3405 (NH) 1560, 1580 (C=N)	3.15 (br s, 3H, CH_3NH); 6.25 (s, 1H, H-5); 7.72 (br s, 5H, arom).

Table 1 (Contd.)

21h	3400, 3180 (NH) 1560, 1578 (C=N)	3.15 (br s, 3H, CH_3NH); 6.28 (s, 1H, H-5); 7.72 (br s, 1H, arom).
21i	3250, 3150 (NH) 1610, 1600 (C=N)	3.10 (s, 3H, CH_3NH); 3.95 (s, 3H, CH_3O); 6.10 (s, 1H, H-5); 7.15-7.90 (m, 4H, arom).
21j	3380, 3150 (NH) 1600, 1580 (C=N)	1.40 (t, 3H, CH_3CH_2-); 3.12 (q, 2H, CH_3-CH_2-); 6.15 (s, 1H, H-5); 7.68 (br s, 5H, arom).
21k	3390, 3150 (NH) 1605, 1540 (C=N)	1.48 (t, 3H, CH_3-CH_2-); 2.58 (q, 2H, CH_3CH_2-); 6.28 (s, 1H, H-4); 7.30 (m, 4H, arom).
21l	3310, 3210 (NH) 1600, 1540 (C=N)	1.42 (t, 3H, CH_3CH_2-); 3.50 (q, 2H, CH_3CH_2); 4.10 (s, 3H, CH_3-O-); 6.23 (s, 1H, H-4); 7.20-8.15 (m, 4H, arom)[a]
21m	3125, 3300, 3175 (NH) 1595, 1580 (C=N)	4.20 (br s, 2H, $CH_2C_6H_5$); 6.80-7.70 (m, 10H, arom).
21n	3405, 3325 (NH) 1610 (C=N)	2.40 (br s, 3H, CH_3); 4.50 (br s, 2H, $CH_2C_6H_5$); 6.00 (s, 1H, H-4); 7.35 (br s, 9H, arom).
21o	3250 (NH) 1600 (C=N)	1.18 (t, 6H, CH_3CH_2O); 3.31 (d, 2H, $NHCH_2$); 3.40-3.90 (two, q, 4H, CH_3-CH_2O); 4.65 (t, 1H, -CH(OEt)$_2$; 5.83 (s, 1H, H-4); 7.13-7.70 (m, 5H, arom).[a]

Table 1 (Contd.)

21p	3240	(NH)	1.18 (t, 6H, $C\underline{H}_3$-CH_2O); 2.31 (s, 3H, CH_3); 3.31 (d, 2H, $C\underline{H}_2$-NH); 3.30-3.90 (m, 4H, two $C\underline{H}_2CH_3$); 4.65 (t, 1H, -$C\underline{H}(OEt)_2$); 5.80 (s, 1H, H-4); 7.30 (m, 4H, arom)[a]
	1602	(C=N)	
21q	3235	(NH)	1.21 (t, 6H, $C\underline{H}_3CH_2O$); 3.31 (d, 2H, $C\underline{H}_2NH$); 3.30-3.80 (m, 4H, $CH_3C\underline{H}_2O$); 3.80 (s, 3H, CH_3O); 4.68 (t, 1H, -$C\underline{H}(OEt)_2$); 5.76 (s, 1H, $\underline{H}$-4); 6.86-7.46 (m, A_2B_2, 4H, arom).[a]
	1605	(C=N)	
21r	3245	(NH)	1.00-1.50 (m, 9H, $C\underline{H}_3CH_2O$); 3.30 (d, 2H, $C\underline{H}_2NH$); 3.36 - 3.71 (m, 4H, $CH_3C\underline{H}_2O$); 4.00 (q, 2H, -$OC\underline{H}_2CH_3$); 4.61 (t, 1H, $C\underline{H}(OEt)_2$); 5.76 (s, 1H, H-4), 6.83-7.46 (m, A_2B_2, 4H, arom).
	1605	(C=N)	
21s	3255	(NH)	1.18 (t, 6H, $C\underline{H}_3CH_2O$); 3.28 (d, 2H, $C\underline{H}_2NH$); 3.36-3.90 (m, 4H, $C\underline{H}_3C\underline{H}_2O$); 4.63 (t, 1H, $C\underline{H}$(OEt) 5.76 (s, 1H, $\underline{H}$-4); 7.36 (m, 4H, arom).[a]
	1610	(C=N)	
21t	3260	(NH)	1.15 (t, 6H, $C\underline{H}_3CH_2O$), 3.23 (d, 2H, $C\underline{H}_2NH$) 3.38-3.91 (m, 4H, $CH_3C\underline{H}_2O$); 4.65 (t, 1H, $C\underline{H}$(OEt).); 5.80 (s, 1H, H-4); 7.38 (m, 4H, arom).
	1615	(C=N)	

Table 1 (Contd.)

26a	3240, 3340 (NH) 2210 (CN) 1610, 1620 (C=N)	2.45 (s, 3H, CH_3), 7.10 (m, 4H, arom).
26b	3450, 3405, 3350, (NH), 2200 (CN) 1615, 1585 (C=N)	7.20 - 7.60 (m, 4H, arom).
28	3410, 3340, (NH) 1605, 1600 (C=N)	4.00 (s, 6H, two OCH_3); 7.76 (m, 8H, arom).
32	3450, 3150 (NH) 2210, (CN), 1610)	2.36 (s, 3H, CH_3N); 2.50-2.83 (m, 4H, piperazino); 3.18-3.50 (m, 4H, piperazino).
36a	3400 (br NH) 1610 (CO), 1600 (C=N)	insoluble
36b	3450 (br NH) 1620 (C=O) 1610 (C=N)	insoluble

[a] $CDCl_3$

Table 2

Analytical Data for the pyrazoles (21a-t, 26a-b, 28, 32, 36a-b)

Product	Yield (%)	m.p. (°C)	Molecular Formula	Analysis Calc. / found	C	H	N
21a	85	155-6	$C_{15}H_{13}N_3$		76.60	5.53	17.87
			(235)		76.81	5.80	17.63
21b	91	188	$C_{16}H_{15}N_3$		77.10	6.02	16.86
			(249)		77.31	6.25	16.57
21c	92	190	$C_{15}H_{12}N_3Cl$		66.79	4.45	15.58
			(269.5)		66.58	4.67	15.79
21d	96	161	$C_{15}H_{15}N_3$		77.47	5.92	16.60
			(249)		77.73	5.71	16.45
21e	97	190	$C_{18}H_{19}N_3O$		73.70	6.48	14.33
			(293)		73.47	6.23	14.15
21f	89	230	$C_{16}H_{14}N_3Cl$		68.17	4.86	14.60
			(287.5)		68.41	4.52	14.37
21g	93	130	$C_{10}H_{11}N_3$		69.36	6.36	24.28
			(173)		69.58	6.61	24.42
21h	88	134	$C_{10}H_{10}N_3Cl$		57.83	4.82	20.24
			(207.5)		57.56	4.58	20.05
21i	95	121	$C_{11}H_{13}N_3O$		65.02	6.40	20.69
			(203)		64.87	6.68	21.91

Table 2 (Contd.)

21j	88	110	$C_{11}H_{13}N_3$ (187)	70.58 70.79	6.95 7.63	22.46 22.21
21k	94	144	$C_{11}H_{12}N_3Cl$ (221.5)	59.59 59.75	5.41 5.20	18.96 18.81
21l	94	92-4	$C_{12}H_{15}N_3O$ (217)	66.36 66.42	6.91 7.20	19.35 19.12
21m	95	76	$C_{16}H_{15}N_3$ (253)	77.47 77.63	5.92 5.71	16.60 16.37
21n	96	120-22	$C_{17}H_{17}N_3$ (263)	77.57 77.41	6.46 6.28	15.96 16.67
21o	72	70-2	$C_{15}H_{21}N_3O_2$ (275)	65.45 65.67	7.63 7.81	15.27 15.53
21p	51	71	$C_{16}H_{23}N_3O_2$ (289)	66.43 66.27	7.95 7.68	14.53 14.28
21q	65	77	$C_{16}H_{23}N_3O_3$ (305)	62.95 62.71	7.54 7.26	13.77 13.51
21r	50	95-6	$C_{17}H_{25}N_3O_3$ (319)	63.94 63.80	7.83 7.65	13.16 13.35
21s	71	100-1	$C_{15}H_{20}N_3O_2Cl$ (309.5)	58.15 58.43	6.46 6.68	13.57 13.81
21t	51	105-6	$C_{15}H_{20}N_3O_2Br$ (354)	50.84 51.50	5.64 5.42	11.86 11.50

Table 2 (Contd.)

26a	95	180	$C_{11}H_{11}N_5$	61.97	5.16	32.86
			(213)	61.68	5.05	32.67
26b	96	200	$C_{10}H_8N_5F$	55.30	3.69	32.26
			(217)	55.58	3.91	32.48
28	95	200	$C_{17}H_{18}N_4O_2$	65.80	5.80	18.06
			(310)	65.53	5.48	17.80
32	68	292	$C_9H_{13}N_5O$	52.17	6.28	33.81
			(207)	52.38	6.49	33.68
36a	40	350	$C_{17}H_{17}N_5O$	66.44	5.53	22.80
			(307)	66.23	5.71	22.62
36b	45	350	$C_{21}H_{23}N_6OBr$	55.38	5.05	18.46
			(455)	55.56	5.31	18.68

Table 3

Spectral Data for Pyrimidine (52a-d), (54a-b), 56, 59, 61 and (63a-b)

Product	IR (KBr) ν_{max}	^{1}H-NMR($CDCl_3$) δ
52a	3140, 3305, 3400, 3460 (NH) 1620, 1600 (NH)	7.00-7.80 (m, 10H, arom)[a]
52b	3120, 3290, 3300, 3420, 3470 (NH); 1620, 1600 (δ NH)	6.70-7.70 (m, 9H, arom)[a]
52c	3150, 3310, 3390, 3470, (NH); 1620, 1640, (NH, C=N)	3.72 (s, 3H, CH_3O); 6.90-7.79 (m, 9H, arom)[a]
52d	3150, 3300, 3340, 3490, (NH); 1620 (δ NH)	3.80 (br s, 6H, two CH_3O); 6.80-7.79 (m, 9H, arom)[a]
54a	3215, 3380, 3480 (NH) 1620 (δ NH)	7.30-8.01 (m, 4H, arom)[a]
54b	3200, 3340, 3490 (NH) 1620 (δ NH)	7.40-7.89 (m, 4H, arom)[a]
56	3200, 3250, 3400 (NH) 1592, 1605, 1630	6.80-7.70 (m, 10H, arom)[a]

Table 3 (Contd.)

59	3220, 3330, 3370, (NH) 1560, 1590 (δ NH)	3.20 (m, 4H, piperazino); 3.85 (m, 1H, piperazino); 4.92 (br s, 2H, NH_2); 6.30 (s, 1H, H-5); 6.70-7.98 (m, 10H, arom).
61	3230, 3450 (br NH)	2.21 (s, 3H, CH_3); 2-20-2.50 (m, 4H, piperazino); 3.38-3.80 (m, 4H, piperazino)[a]
63a	3120, 3260, 3305, 3490 (NH), 1595, 1610 (δ NH)	2.01 (s, 3H, CH_3); 4.30 (d, 2H, NH-CH_2) 4.95 (br s, 2H, NH_2); 5.50 (s, 1H, H-5); 7.23 (s, 5H, arom).
63b	3210, 3340, 3425 (NH), 1595 (δ NH)	4.40 (d, 2H, $NHCH_2$); 5.02 (br s, 2H, NH_2); 6.00 (s, 1H, H-5); 7.25 (m, 7H, arom); 7.70 (dd, 2H, arom).

[a] TFA

Table 4

Analytical Data of Pyrimidines (52a-d), (54a-b), 56, 59, 61 and (63a-b)

Product	Yield (%)	m.p. (°C)	Molecular formula	Analysis			M.S. m/z (M^+)
				Calc. Found	C	H	N
52a	65	210	$C_{16}H_{15}N_5$ (277)		69.31 69.72	5.41 5.65	25.27 25.48	277
52b	88	250-2	$C_{16}H_{14}N_5Cl$ (311.5)		61.63 61.92	4.49 4.82	22.47 22.80	311.5
52c	82	205	$C_{17}H_{17}N_5O$ (307)		66.44 66.78	5.53 5.90	22.80 22.75	307
52d	90	252-54	$C_{18}H_{19}N_5O_2$ (337)		64.09 64.43	5.63 5.90	20.77 20.92	337
54a	48	300	$C_{11}H_9N_6F$ (244)		54.09	3.68	34.42	-

Table 4 (Contd.)

54b	52	298	$C_{11}H_9N_6Cl$	50.67	3.45	32.24	-
			(260.5)	50.87	3.83	32.47	
56	53	205	$C_{16}H_{14}N_4O$	69.06	5.03	20.14	278
			(278)	69.41	5.47	20.47	
59	62	158-60	$C_{20}H_{21}N_5$	72.50	6.34	21.14	-
			(331)	72.81	6.67	21.38	
61	48	300	$C_{10}H_{14}N_6O$	51.28	5.98	35.89	-
			(234)	51.61	5.79	36.02	
63a	59	132-34	$C_{12}H_{14}N_4$	67.28	6.54	26.16	214
			(214)	67.52	6.31	26.42	
63b	85	130-2	$C_{17}H_{15}N_4Cl$	65.70	4.83	18.03	310.5
			(310.5)	65.54	4.57	18.28	

REFERENCES

1. S.M.S. Chauhan and H. Junjappa, Synthesis, 798 (1975).

2. A. Kumar, V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 748 (1980).

3. V. Aggarwal, Ph.D. Dissertation, submitted to Department of Chemistry, North-Eastern Hill University, Shillong 1982.

4. G. Singh, S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis, 693 (1982).

5. D.E. Worrall, J.Am. Chem. Soc., 59, 933 (1937).

6. D.E. Worrall and E. Lavin, J. Am. Chem. Soc., 61, 104 (1939).

7. H-D. Stachel, Chem. Ber., 96, 1088 (1963).

8. K. Schofield, M.R. Grimmett and B.R.T. Keene, in 'The Azoles'; Chapter IV, 'Amination and substituted Amination', Cambridge University Press, 1976, pp. 133-135.

9. J. Zauhar and B.F. Ladouceur, Canad. J. Chem., 46, 1169 (1968).

10. A. Kocwa, Chem. Abstr., 31, 1804 (1937).

11. E. Bulka, H-G Rohde and H. Beyer, Chem. Ber., 98, 259 (1965).

12. H. Beyer, H. Honeck, L. Reichelt, Justus, Liekiys Ann. Chem. 741, 45 (1970).

13. S. Hünig and K. Hübner, Chem. Ber., 95, 937 (1962).

14. D. Pocar, G. Bianchetti, S. Maiorana, Gazz. Chem. Ital., 93; 100 (1963); Chem. Abstr., 59, 2975 (1963).

15. A.N. Borisevich and P.S. Pel'kis, Chem. Abstr., 71, 22058 (1969).

16. G. Barinkow, Chem. Ber., 100, 1389 (1967).

17. W.D. Rudorf, Tetrahedron, 34 , 725 (1978).

18. A. Dornow and K. Dehmer, Chem. Ber., 100, 2577 (1967).

19. H. Goldner, G. Dietz and E. Carstens, Liebigs Ann. Chem. 691, 142 (1966) and references therein.

20. H. Fuchs, M. Gottlieb andW.Pfleiderer, Chem. Ber., 111, 982 (1978).

21. (a) P.B. Russel and G.H. Hitchings, J. Am. Chem. Soc., 73, 3763 (1951); (b) L.N. Ferguson, Chem. Soc. Reviews, 4, 289 (1975).

22. D.J. Brown, 'The Pyrimidines' edited by A. Weissberger, Chapter IX, p. 306, interscience, New York, 1962, p. 306 supplement I, Chapter 9, p. 230, 1970.

23. E.B. Pederson, D. Carlsen, Synthesis, 844 (1978).

24. Organic Synthesis Vol. II, pp. 267.

25. Bedson, J.C.S., 37, 94 (1880)

26. (a) L. Knorr, Ber, 16, 2597 (1883); (b) P.C. Freer, J. Prakt, Chem., 47, 247 (1893).

27. D.J. Martin, C.C. Greco, J. Org. Chem., 33, 1275 (1968).

28. A text book of practical organic chemistry by A.I. Vogel, pp. 643, ELBS and Longman (1968).

29. M. Deliphe, Compt, Rend., 144, 1125-27; Chem. Abstr.1, 2236 (1907).

30. A. Thuillier and J. Vialle, Bull. Soc. Chim. France, 1398 (1959).

31. A. Kumar, H. Ila and H. Junjappa, Synthesis, 324 (1976).

32. A. Rahman, Ph.D. Thesis submitted to NEHU, Shillong (1984).

33. A. Kumar, H. Ila and H. Junjappa, J.C.S. Chem. Comm. 593 (1976).

34. S.S. Bhattacharjee, H. Ila and H. Junjappa, Synthesis, 410 (1983).