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

Abstract

By

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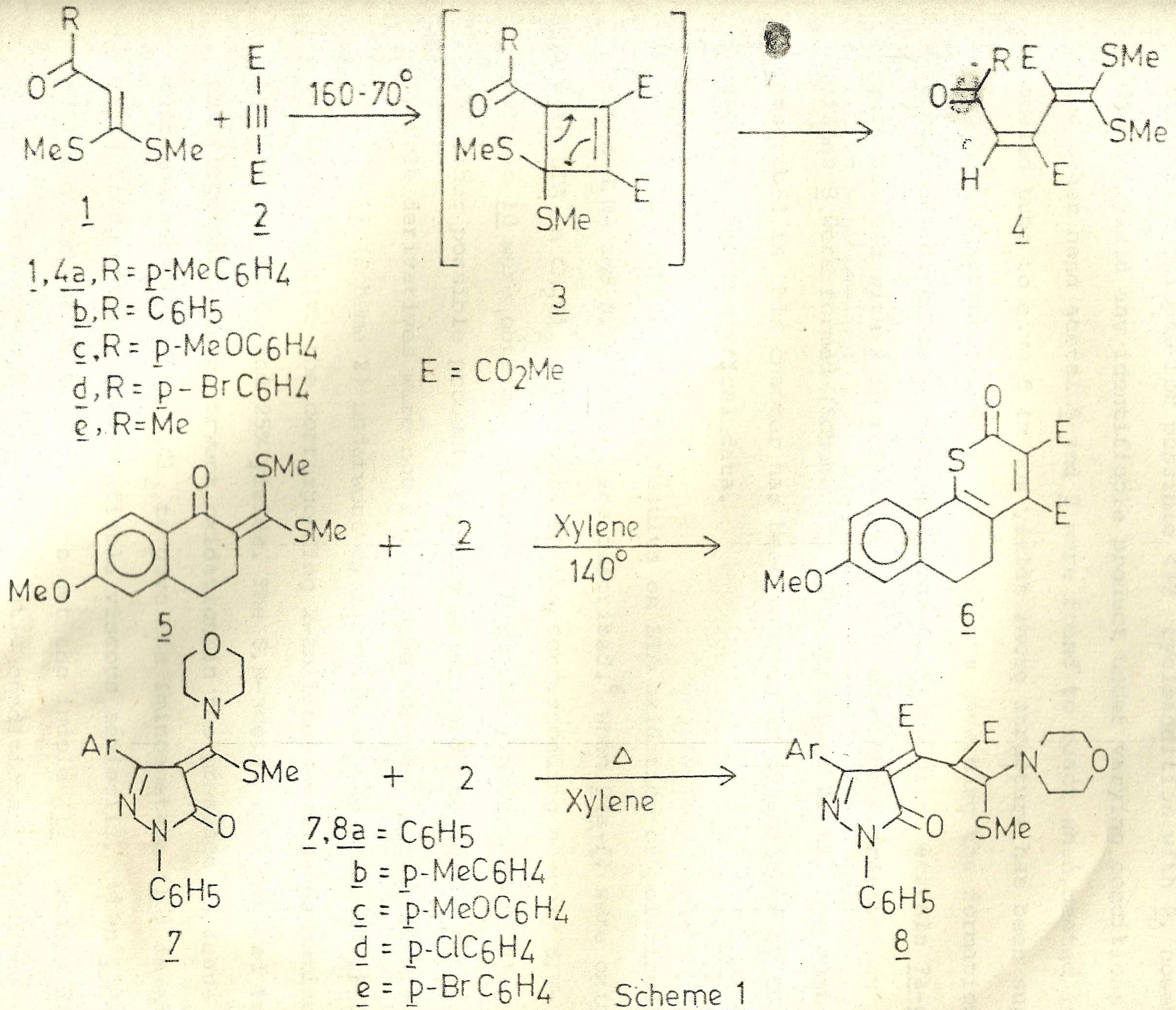
SUMMARY

The chemistry and synthetic application of polarized ketendithioacetals 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.

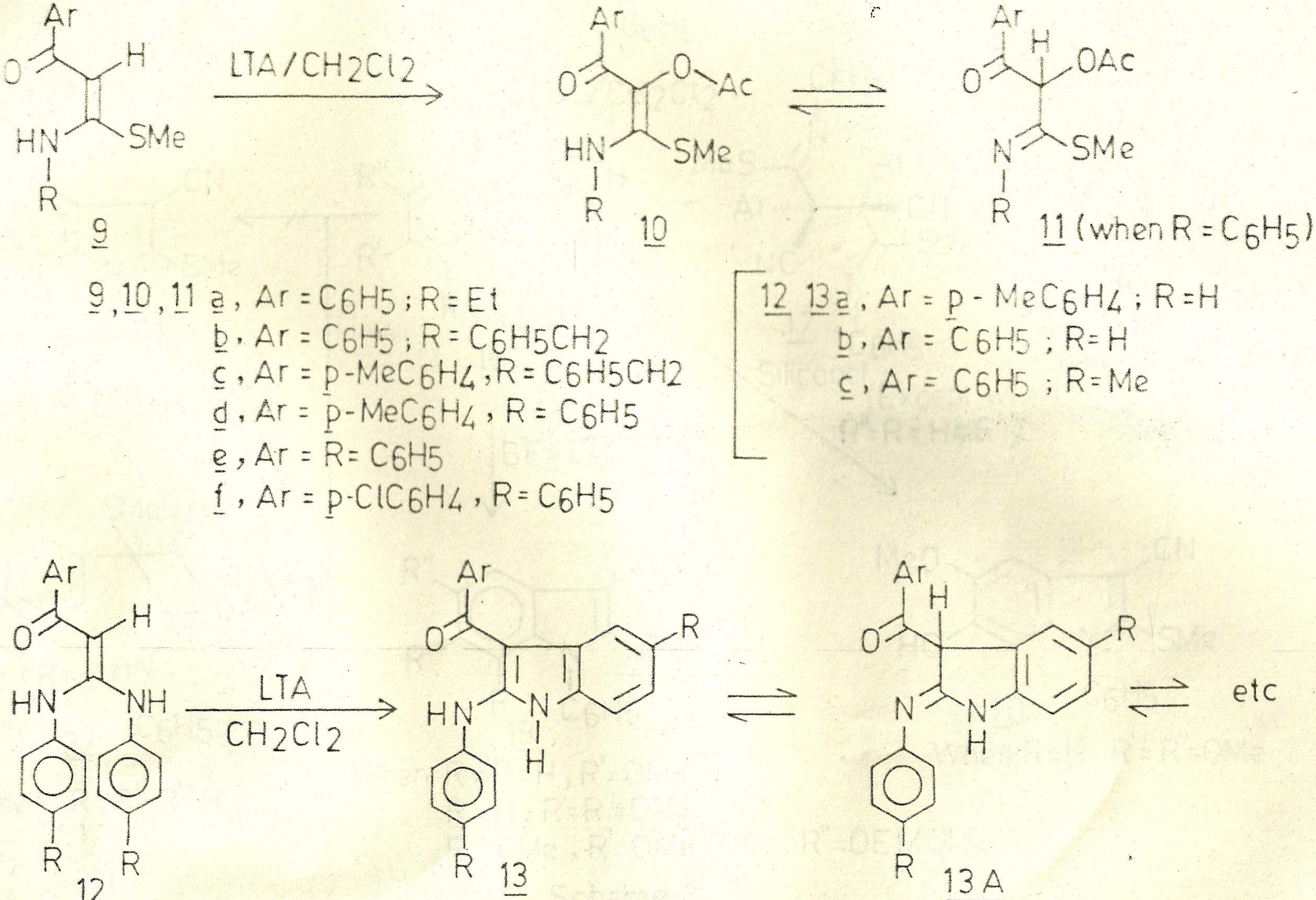
In chapter II the reactions of polarized keten-S,S- and S,N-acetals with dimethylacetylenedicarboxylate (DMAD) have been described.[5] While the reaction of thioacylketendithioacetals with DMAD is reported to yield the corresponding Diels-Alder adducts, the oxoketendithioacetals (1) react with 2 only 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 oxoketendithioacetal derived from cyclohexanone which was considered to be


1
2
160-70°
3
4
1,4a, R = p-MeC6H4
b, R = C6H5
c, R = p-MeOC6H4
d, R = p-BrC6H4
e, R = Me
E = CO2Me
5
Xylene
140°
6
7
Δ
Xylene
8
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.

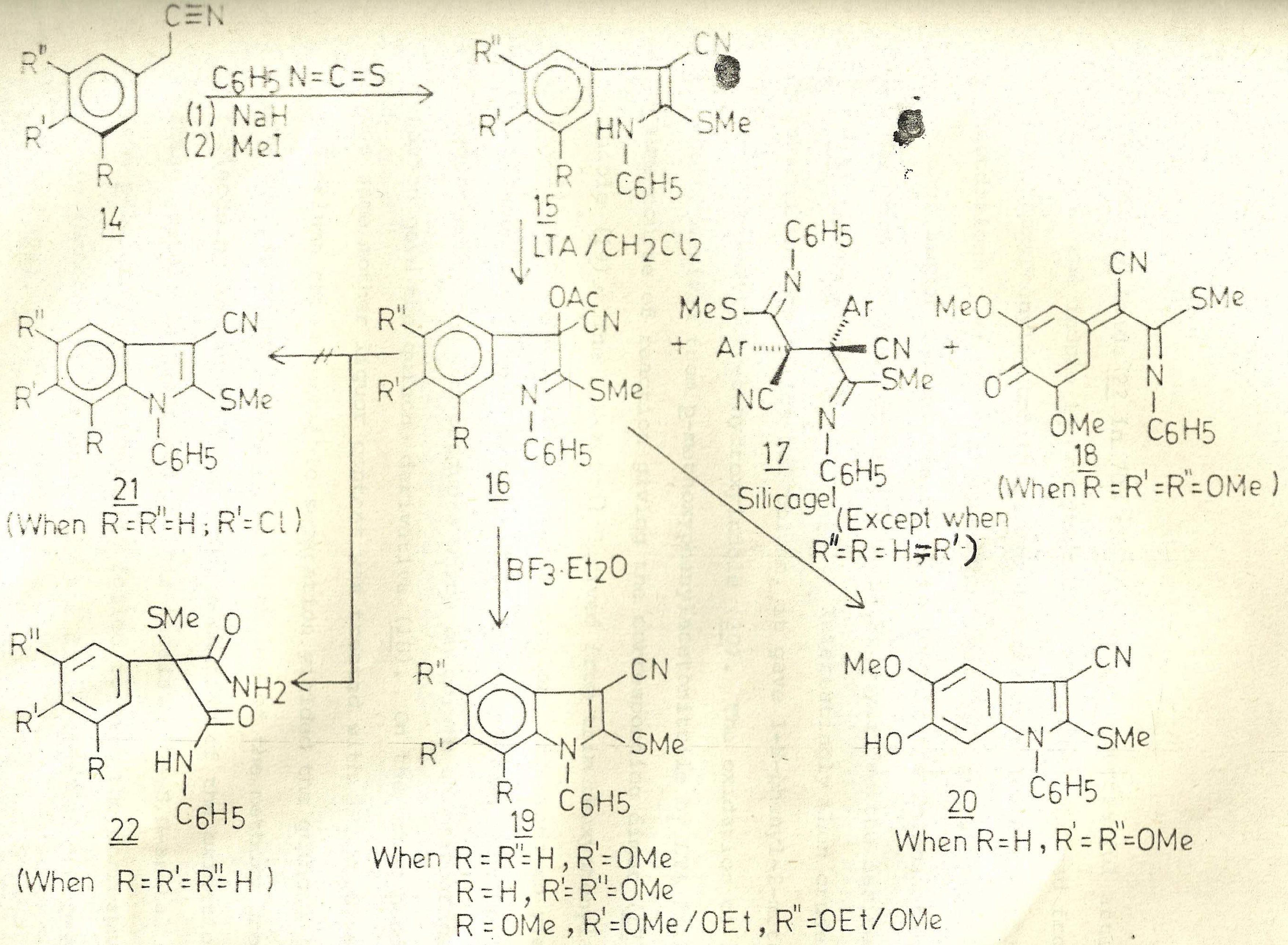
In chapter III the results on LTA oxidation of polarized keten-S,N- and N,N-acetals are described.[6] When 9(a-f) were oxidised with LTA in CH_2Cl_2 after work up the corresponding acetoxy S,N-acetals 10 were obtained in about 50 to 55% yields (Scheme 2). While the other possible products such as dimers 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 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

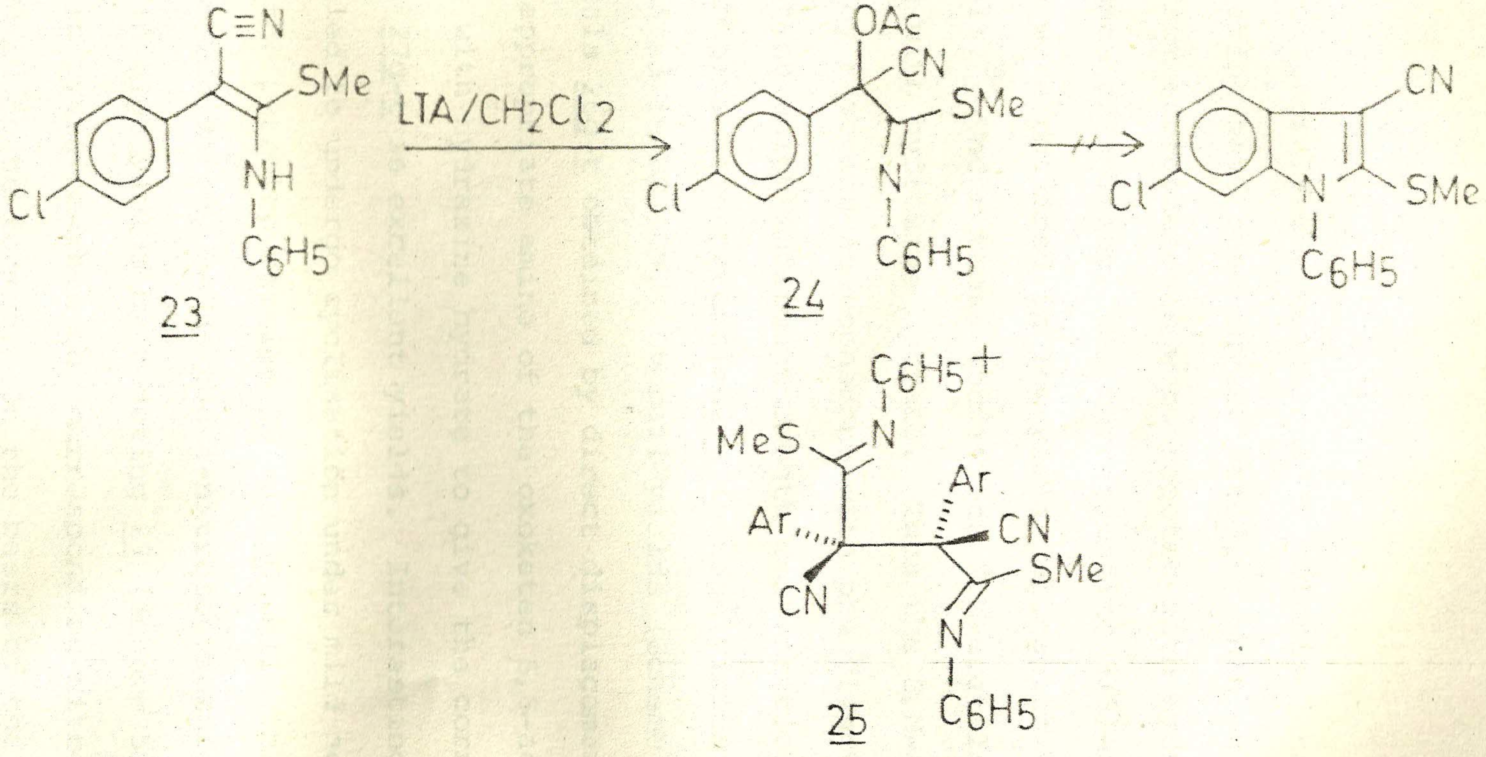
12 13 a, Ar = p-MeC6H4 ; R = H
b, Ar = C6H5 ; R = H
c, Ar = C6H5 ; R = Me

Scheme 2


14
C≡N
R''
R'
R
C6H5 N=C=S
(1) NaH
(2) MeI
15
CN
SMe
HN
C6H5
LTA / CH2Cl2
16
OAc
CN
SMe
N
C6H5
17
MeS
Ar
NC
CN
SMe
+
18
MeO
O
OMe
(When R = R' = R'' = OMe)
Silicagel
(Except when R'' = R = H ≠ R')
BF3·Et2O
21
(When R = R'' = H ; R' = Cl)
22
(When R = R' = R'' = H)
NH2
HN
19
When R = R'' = H , R' = OMe
R = H , R' = R'' = OMe
R = OMe , R' = OMe / OEt , R'' = OEt / OMe
20
HO
When R = H , R' = R'' = OMe

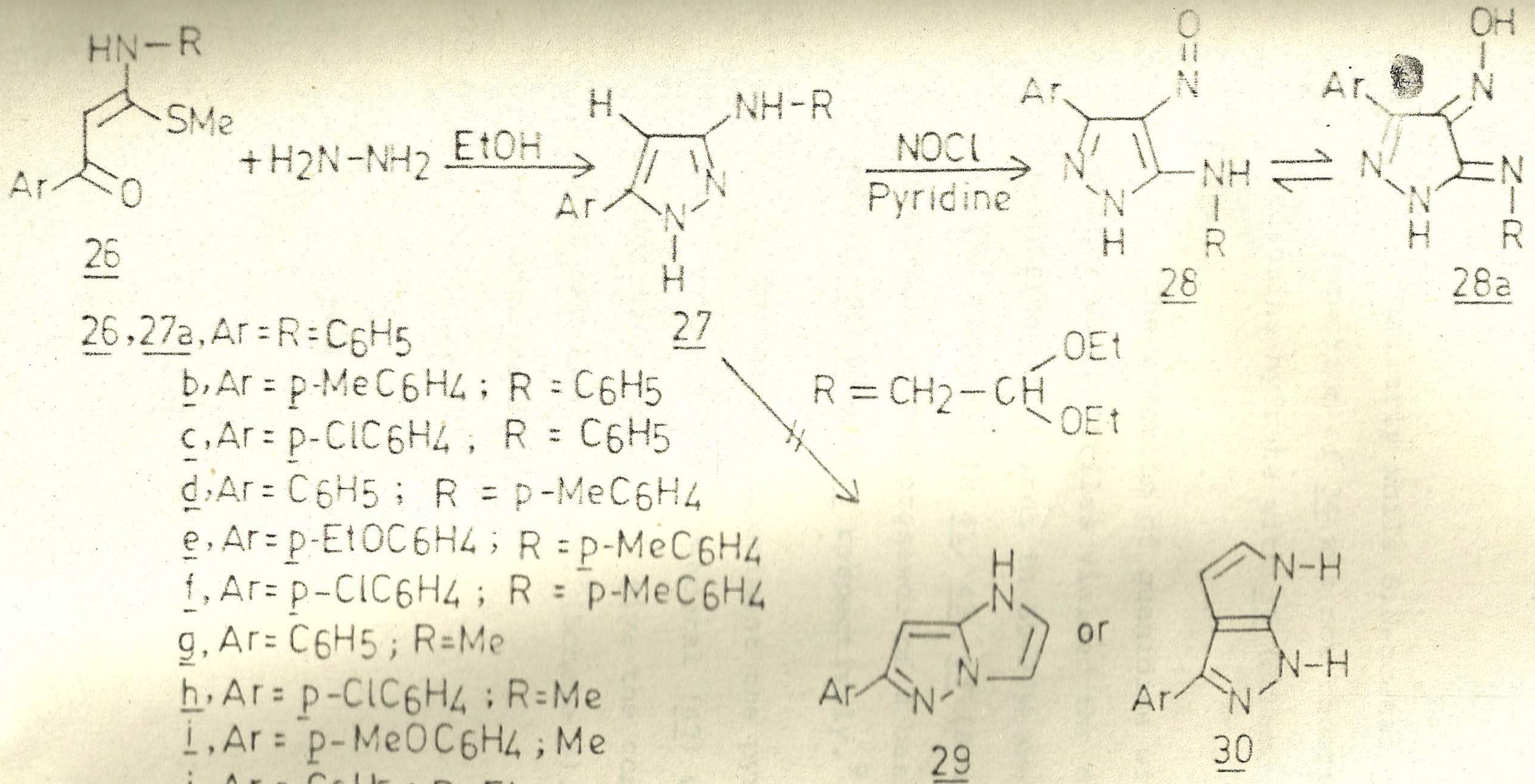
Scheme 3

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 trimethoxyphenylacetonitrile 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 iminoacetate (24).



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-acetal 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.



$R = CH_2-CH(OEt)_2$

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

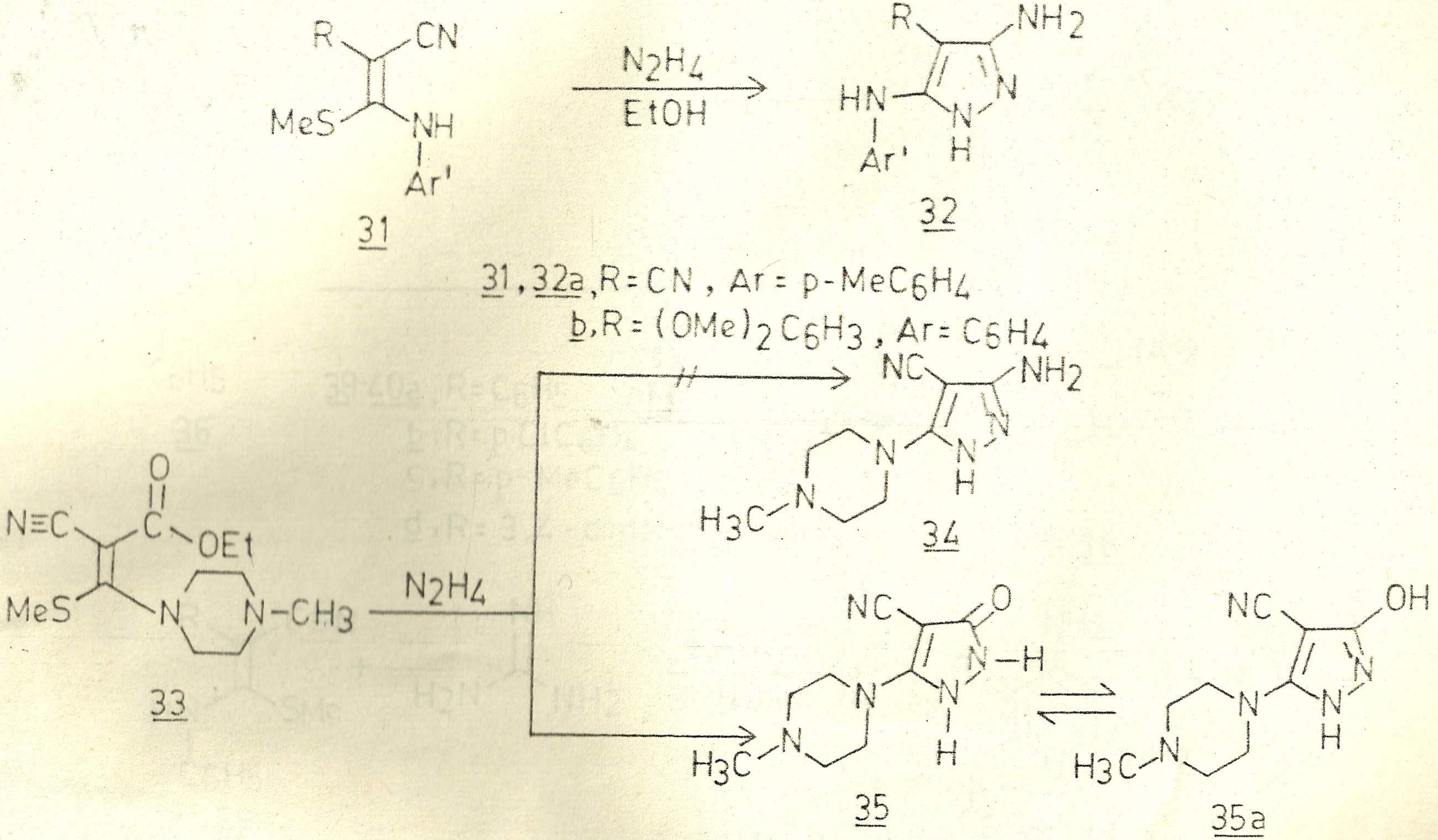
p, Ar = p-MeC_6H_4
q, Ar = p-$MeOC_6H_4$
r, Ar = p-$EtOC_6H_4$
s, Ar = p-ClC_6H_4
t, Ar = p-BrC_6H_4

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.

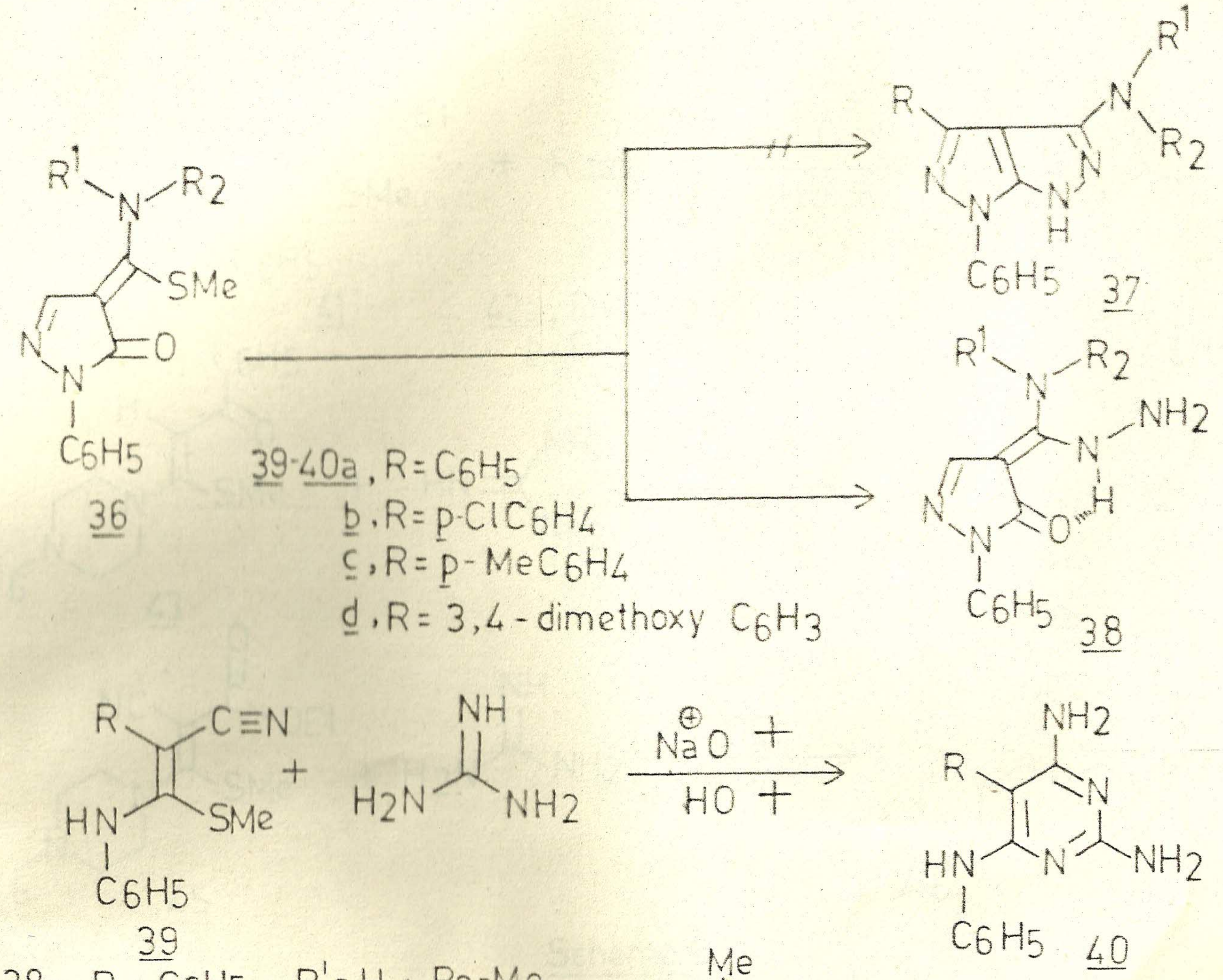
The reaction of guanidine with S,N-acetals 39 derived from phenyl acetonitriles yielded the corresponding 2,4-diamino-5-aryl-6-anilinopyrimidines in 65-90% overall yields (Scheme 7). Similarly the S,N-acetals 41, 43, 45 (Scheme 8), when reacted with guanidine in the presence of a base gave the corresponding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



31, 32a, R = CN , Ar = p-MeC$_6$H$_4$
b, R = (OMe)$_2$C$_6$H$_3$, Ar = C$_6$H$_4$

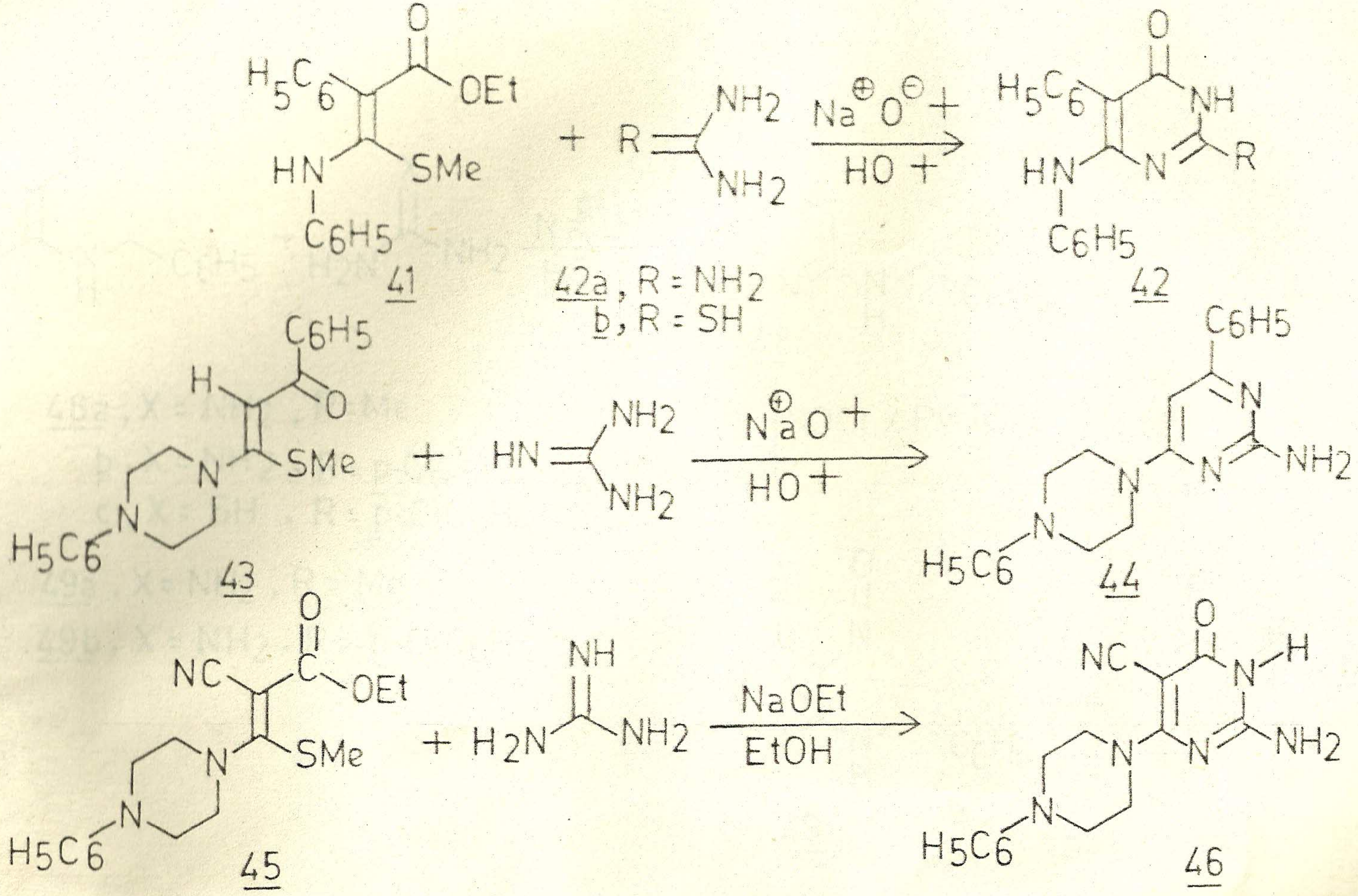
Scheme 6



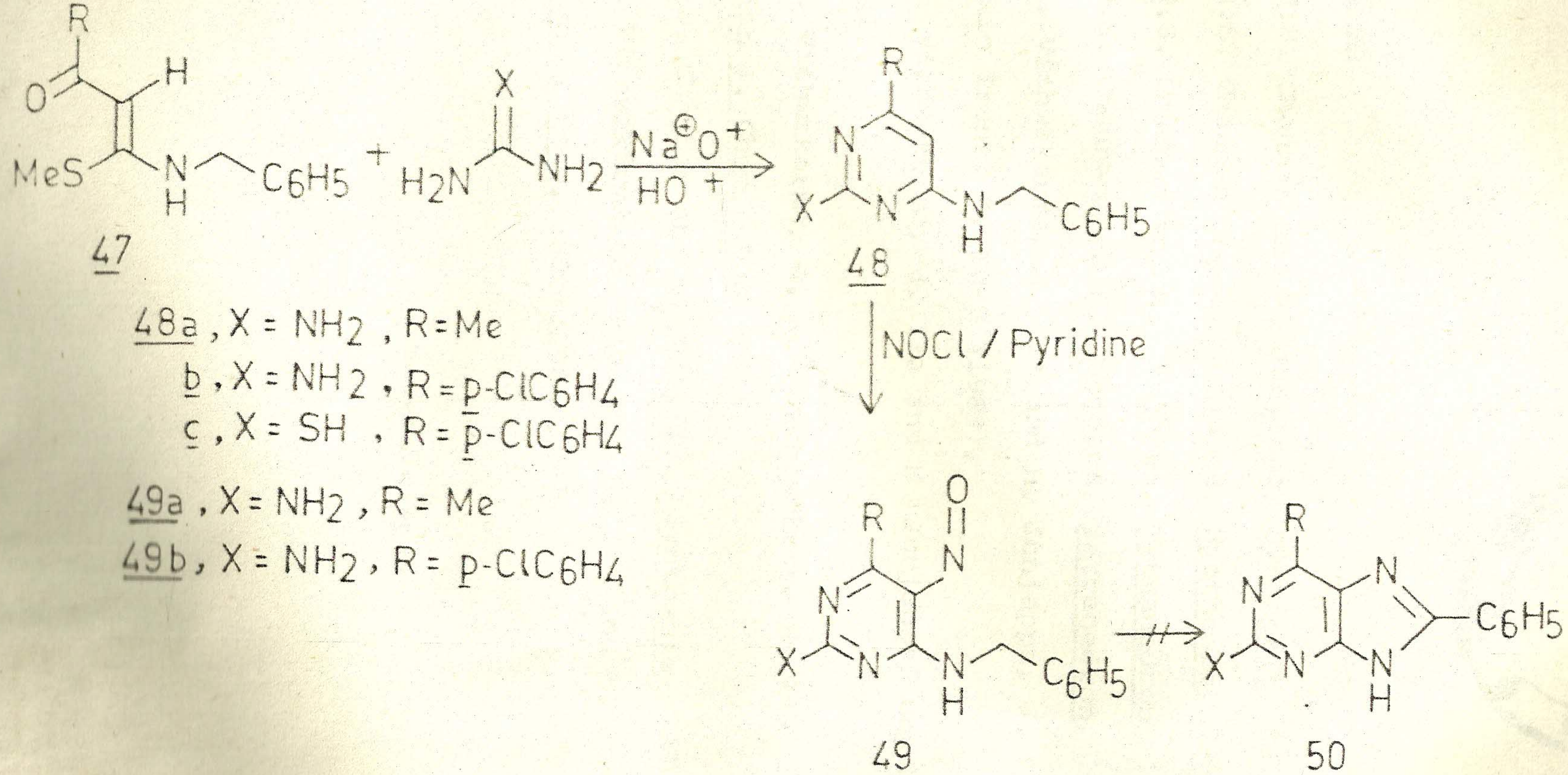
$\underline{39}$-$\underline{40a}$, R = C_6H_5
$\underline{b}$, R = $\underline{p}$-ClC_6H_4
$\underline{c}$, R = $\underline{p}$-MeC_6H_4
$\underline{d}$, R = 3,4-dimethoxy C_6H_3

$\underline{36}$-$\underline{38a}$, R = C_6H_5 ; R' = H ; R_2=Me
$\underline{b}$; R = p BrC_6H_4 ; R' = R_2 = $-(CH_2)_2-\overset{Me}{N}-(CH_2)_2-$

Scheme 7



Scheme 8



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).

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