NEW SYNTHETIC STRATEGIES FOR HETEROCYCLES OF BIOLOGICAL INTEREST

ABSTRACT

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ABSTRACT

New Synthetic Strategies for Heterocycles of Biological Interest

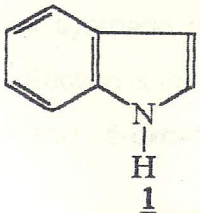
The thesis consists of four chapters.

CHAPTER I :

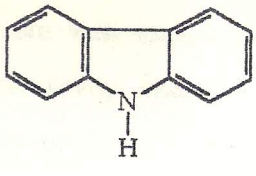
New Synthetic Strategies for Heterocycles of Biological Interest

This chapter is further subdivided into four sections :

Section 1. : Indole **1**, an important heterocyclic unit has special attention in the



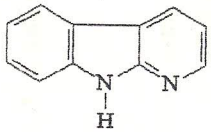
1



2

organic synthesis[1] due to the fact that many of its derivatives possess a variety of useful pharmacological properties. Annulated indoles *viz.*, carbazole **2**, α-carboline **3**, β-carboline **4**, γ-carboline **5**, δ-carboline **6** and their condensed analogues play very important role in pharmacology due to their out standing biological properties. Synthetic approaches to substituted carbazoles and their condensed analogues are of special interest and contemporary importance[2]

since the growing variety of carbazole alkaloids isolated show antimicrobial[3],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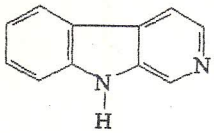
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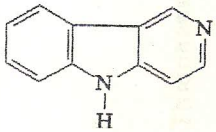
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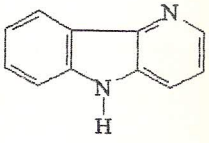

6

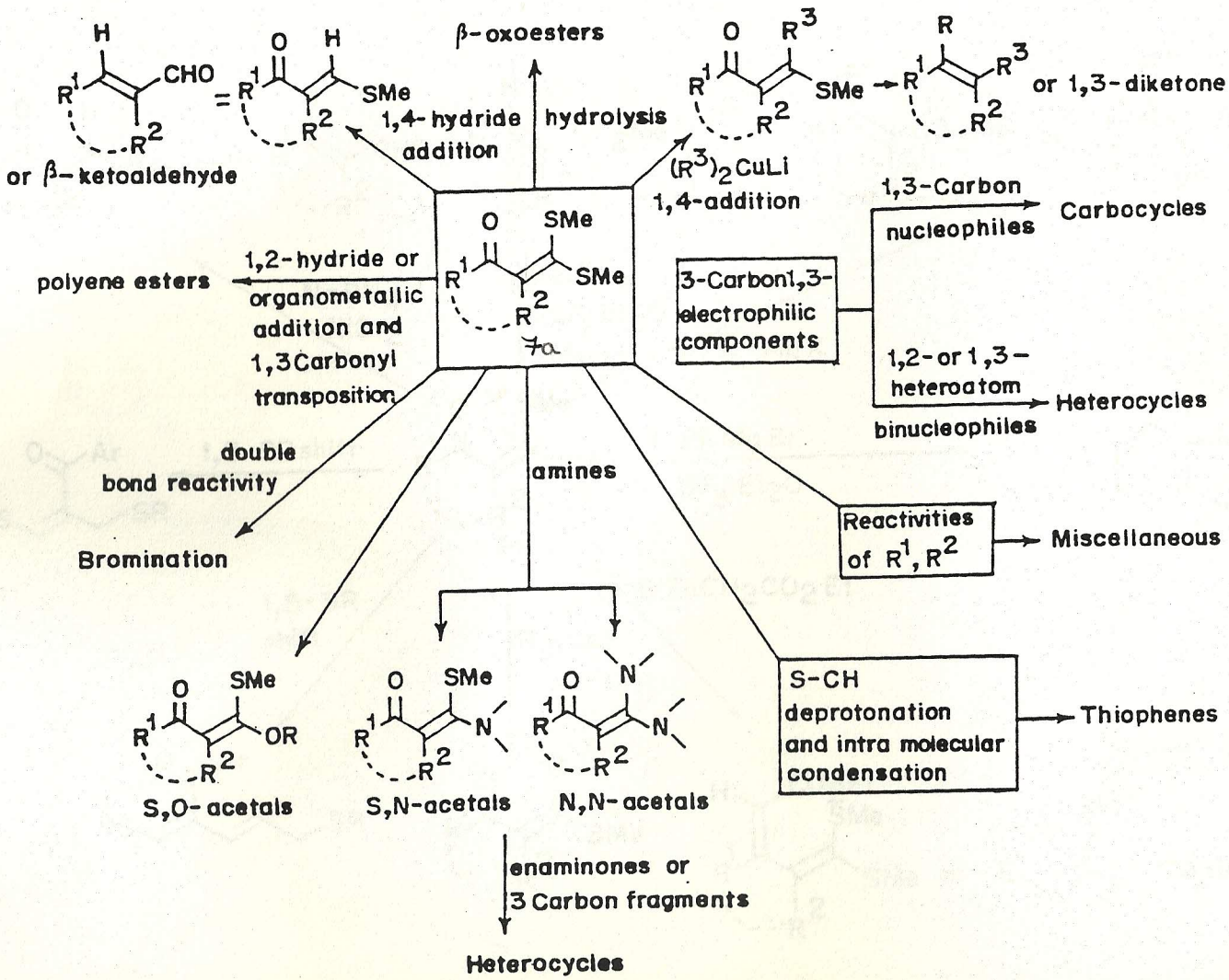
antiviral[4], and cytotoxic[5] properties. Some of the known three or four fused rings, containing indole moiety and their biological properties is described in this section.

Section 2. : The polarized ketenedithioacetals 7 have been recognised as potential building blocks in organic synthesis . The chemistry of these compounds has increased enormously in the recent years and two reviews[6] have already appeared covering the major developments in the area. These synthetic precursors, which are been exploited for the variety of heterocyclic and carbocyclic compounds are briefly reviewed in this section. (Schemes 1 to 6).

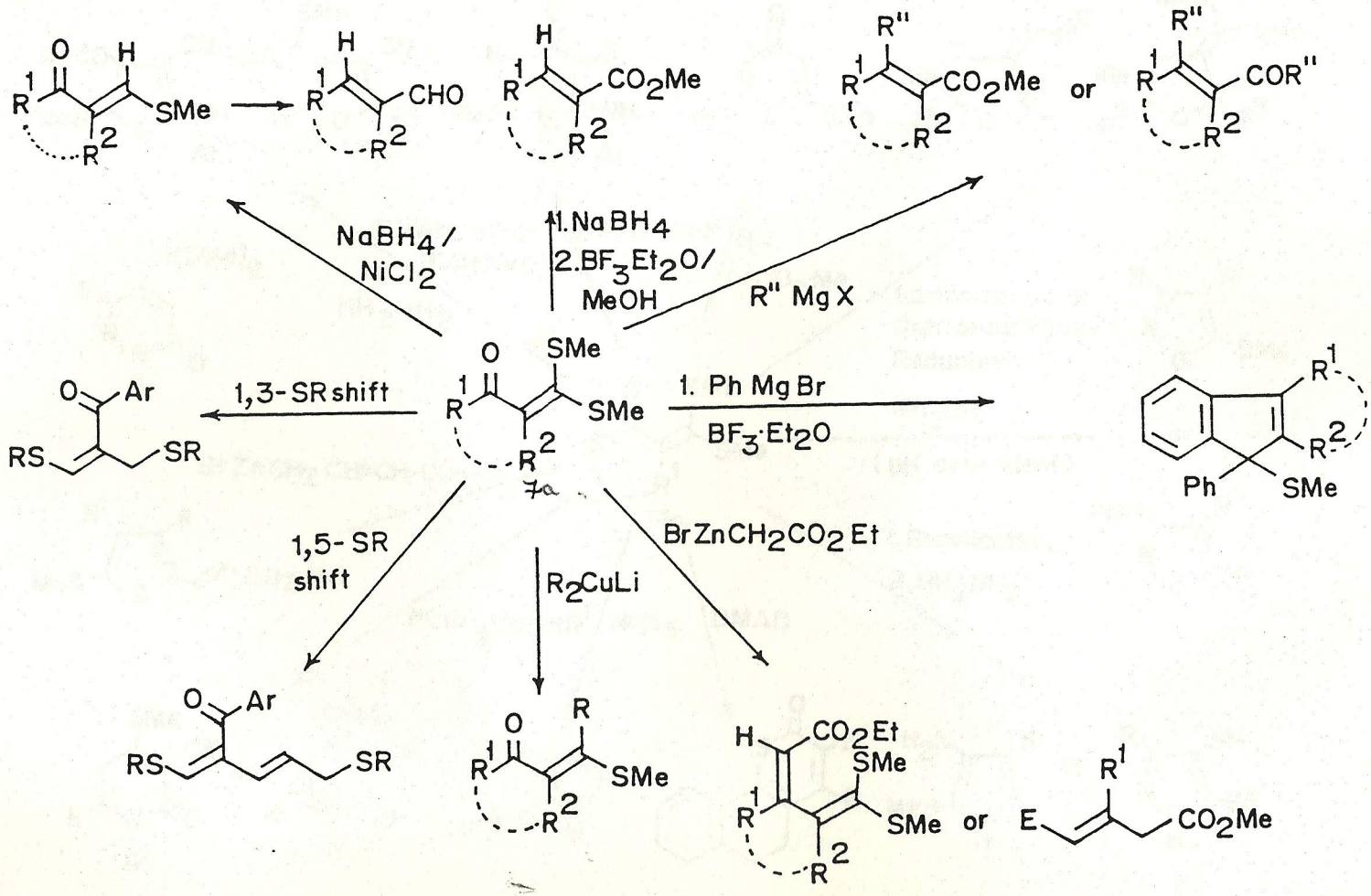
Section 3 : Like α-oxoketenedithioacetals, the S,N-acetals also possess 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield variety of heterocycles and carbocycles. Vinylaziridines are also useful synthetic building blocks and are well exploited in synthetic chemistry[7-9]. Section 3 includes a brief literature survey related to N-S,acetals, vinylaziridines and 5-oxo-4,5-dihydro-1,3-oxazolones.

Section 4 : The work presented in the following chapters of thesis is briefly outlined in this section.

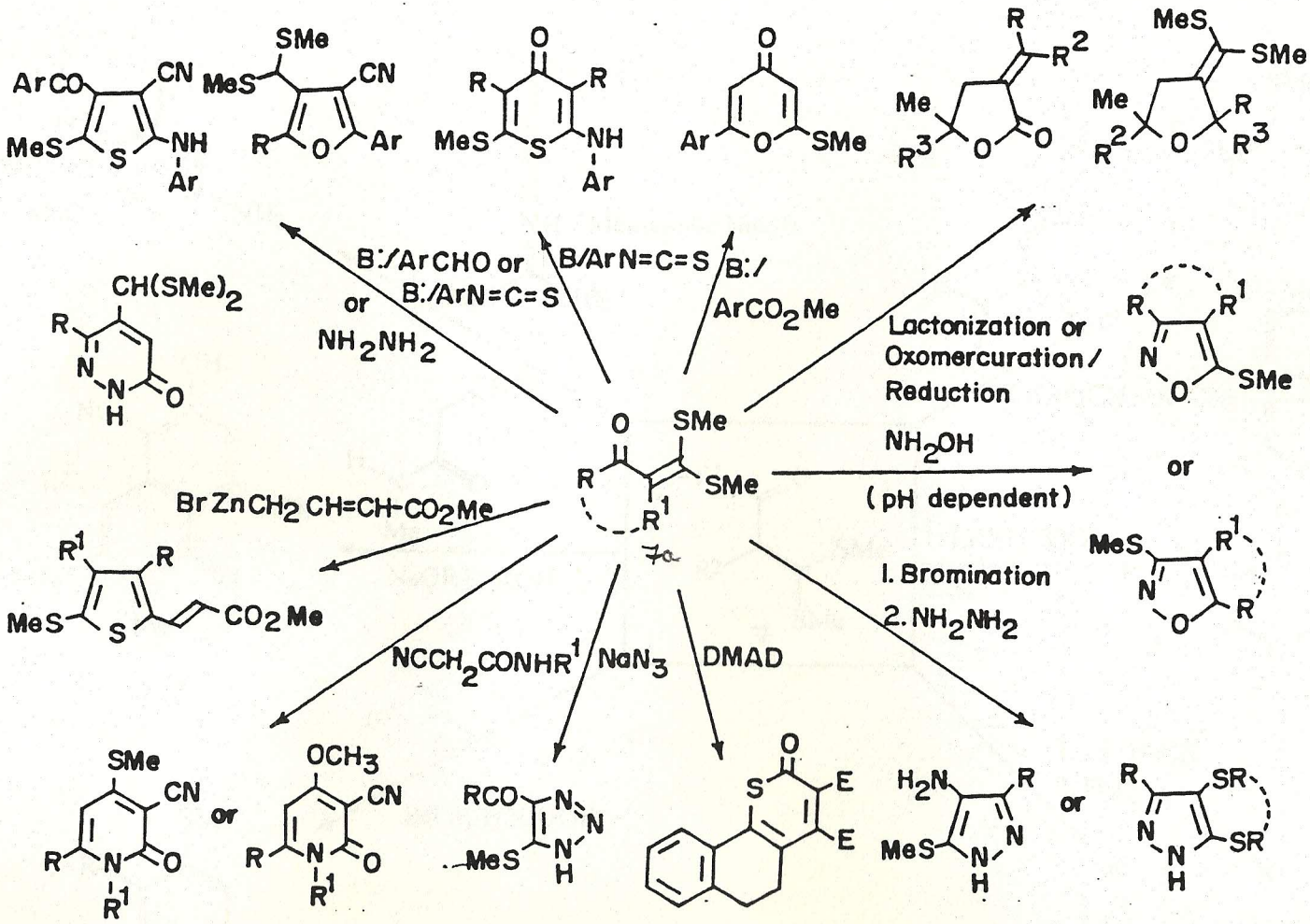
As part of our strategy to develop new heterocyclic derivatives to find the efficacy against topoisomerase enzymes, we have developed various methods for the [b] annulation of indoles to yield carbazole, carboline, pyrimidoindole and other heterocyclic analogues.


β-oxoesters
hydrolysis
1,4-hydride addition
or β-ketoaldehyde
(R3)2CuLi 1,4-addition
or 1,3-diketone
1,3-Carbon nucleophiles
Carbocycles
3-Carbon1,3-electrophilic components
1,2-or 1,3-heteroatom binucleophiles
Heterocycles
polyene esters
1,2-hydride or organometallic addition and 1,3Carbonyl transposition
7a
double bond reactivity
Bromination
amines
Reactivities of R1, R2
Miscellaneous
S-CH deprotonation and intra molecular condensation
Thiophenes
S,O-acetals
S,N-acetals
N,N-acetals
enaminones or 3 Carbon fragments
Heterocycles

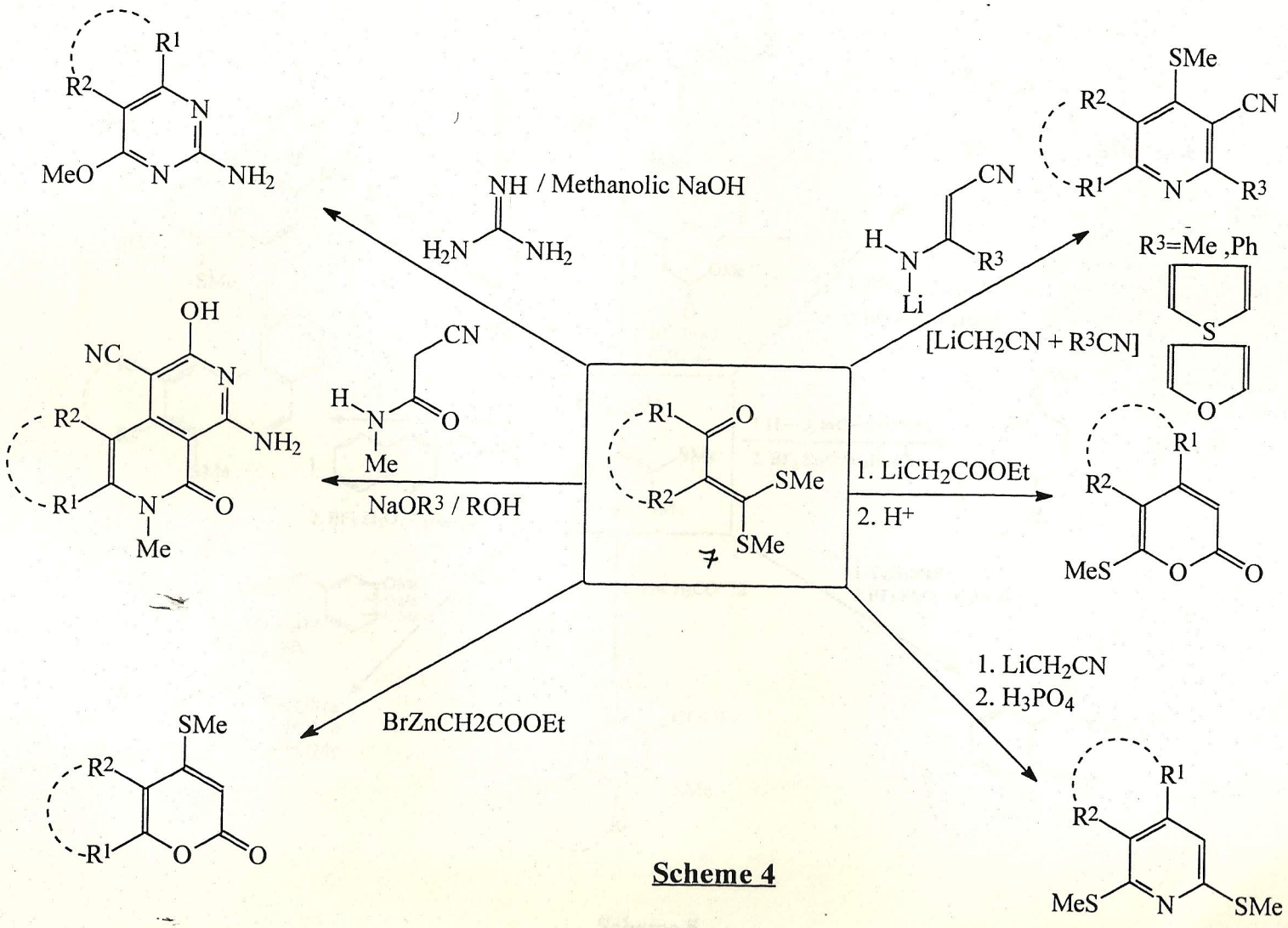
Scheme-1


NaBH4 / NiCl2
1. NaBH4
2. BF3Et2O / MeOH
R'' Mg X
1,3-SR shift
1. Ph Mg Br
BF3·Et2O
1,5-SR shift
R2CuLi
BrZnCH2CO2Et
or
or

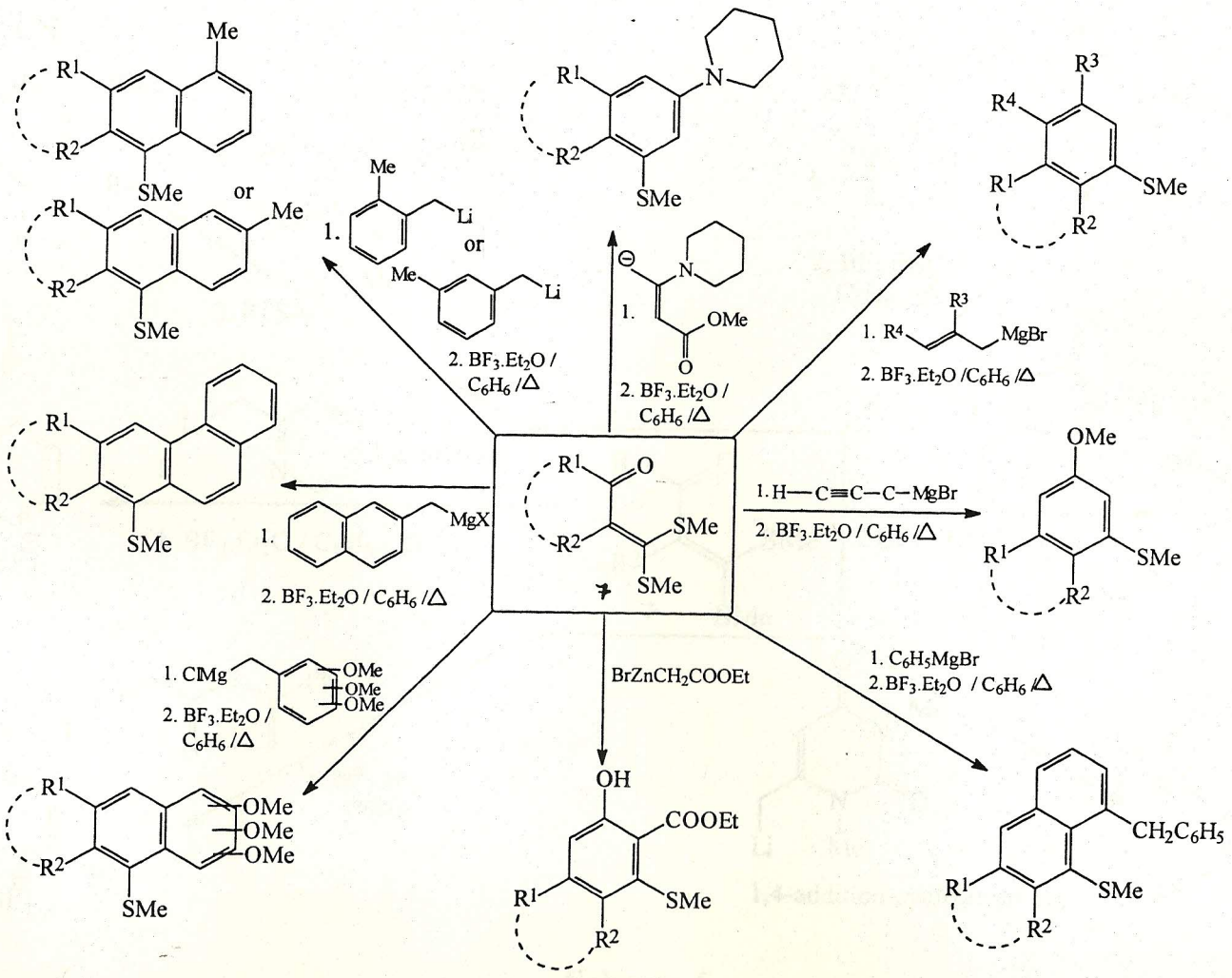
Scheme-2


B:/ArCHO or
B:/ArN=C=S
or
NH2NH2
B/ArN=C=S
B:/
ArCO2Me
Lactonization or
Oxomercuration/
Reduction
NH2OH
(pH dependent)
or
BrZnCH2 CH=CH-CO2Me
1. Bromination
2. NH2NH2
NCCH2CONHR1
NaN3
DMAD
7a

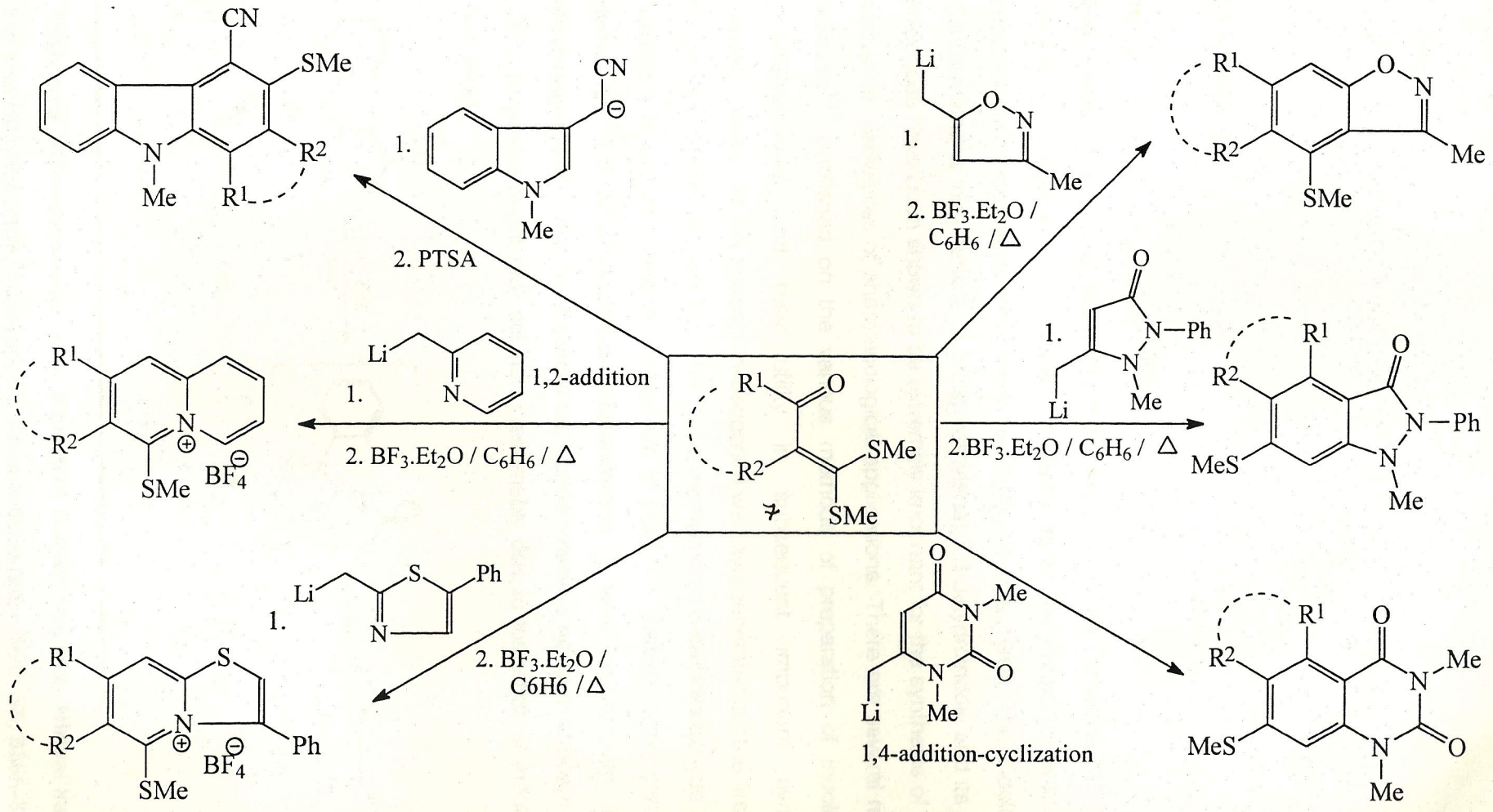
Scheme-3


NH / Methanolic NaOH
H2N
NH2
MeO
N
NH2
R1
R2
CN
H
N
R3
Li
[LiCH2CN + R3CN]
SMe
R2
CN
R1
N
R3
R3=Me ,Ph
S
O
OH
NC
N
NH2
R2
R1
N
O
Me
CN
H
N
O
Me
NaOR3 / ROH
R1
O
R2
SMe
SMe
1. LiCH2COOEt
2. H+
R1
R2
MeS
O
O
1. LiCH2CN
2. H3PO4
BrZnCH2COOEt
SMe
R2
R1
O
O
R1
R2
MeS
N
SMe

Scheme 4


Me
R1
R2
SMe
or
Me
SMe
1.
Me
Li
or
Me
Li
2. BF3.Et2O / C6H6 /Δ
R1
N
R2
SMe
1.
N
OMe
O
2. BF3.Et2O / C6H6 /Δ
R3
R4
R1
SMe
R2
1. R4
R3
MgBr
2. BF3.Et2O /C6H6 /Δ
R1
R2
SMe
1.
MgX
2. BF3.Et2O / C6H6 /Δ
R1
O
R2
SMe
SMe
1. H—C≡C—C—MgBr
2. BF3.Et2O / C6H6 /Δ
OMe
R1
SMe
R2
1. ClMg
OMe
OMe
OMe
2. BF3.Et2O / C6H6 /Δ
BrZnCH2COOEt
1. C6H5MgBr
2.BF3.Et2O / C6H6 /Δ
R1
R2
OMe
OMe
OMe
SMe
OH
COOEt
R1
SMe
R2
CH2C6H5
R1
SMe
R2

Scheme 5

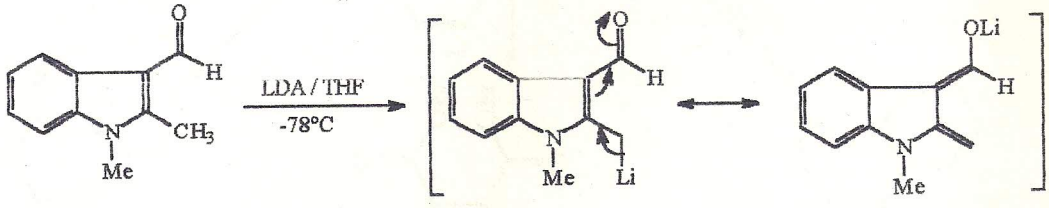

CN
SMe
N
Me
R2
R1
1.
CN
N
Me
2. PTSA
Li
1.
O
N
Me
2. BF3.Et2O /
C6H6 /Δ
R1
O
N
R2
Me
SMe
Li
1.
N
1,2-addition
2. BF3.Et2O / C6H6 / Δ
R1
O
R2
SMe
7
SMe
1.
O
N—Ph
N
Li
Me
2.BF3.Et2O / C6H6 / Δ
R1
O
R2
N—Ph
MeS
N
Me
R1
S
Ph
N
R2
BF4
SMe
Li
S
Ph
1.
N
2. BF3.Et2O /
C6H6 /Δ
O
Me
N
O
Li
N
Me
1,4-addition-cyclization
R1
O
R2
N
Me
MeS
N
O
Me

Scheme 6

CHAPTER II :

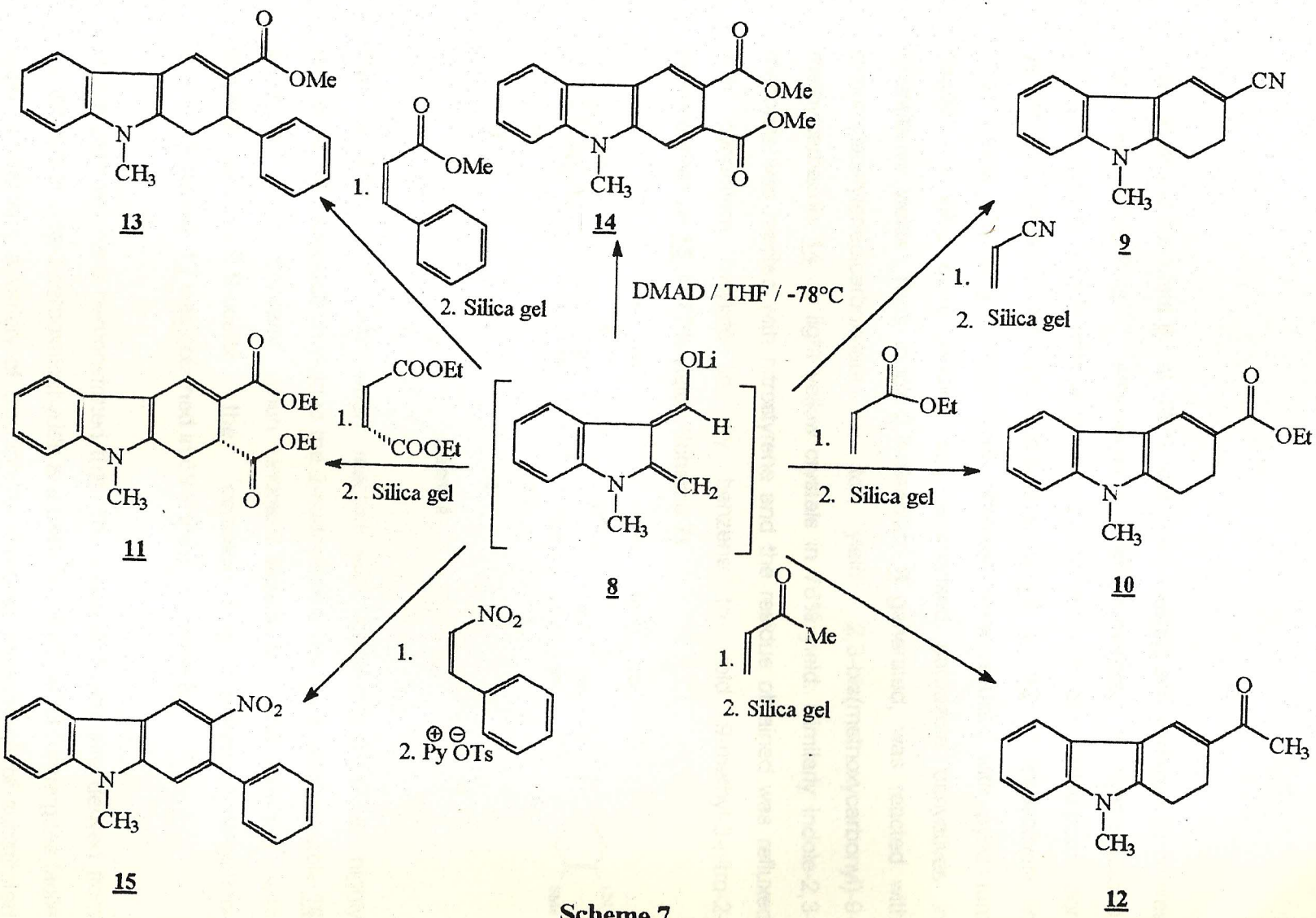
Part A :

The interest in carbazole chemistry and a number of new carbazole molecules became our target since we could efficiently apply the indole [b] annulation approach to make many derivatives belonging to this class. The indolo-2,3-quinodimethane intermediate, 2,3-bis(methylene)-2,3-dihydroindole and its cyclic analogues have been shown to be extremely important for the synthesis of many carbazole derivatives of pharmacological applications. There are several related reviewes[10] published on the various methods of preparation of indolo-2,3-quinodimethanes and their utility in subsequent important synthetic transformations. In the present investigation we have generated for the first time o-quinodimethane system from the 1,2-dimethylindole-3-carboxaldehyde **8** and reacted it *in situ* with various dienophiles to yield the corresponding carbazole derivatives. 1,2-dimethylindole-3-carboxaldehyde **7** was treated with lithium diisopropylamide in dry tetrahydrofuran, under masked nitrogen atmosphere at -78°C to yield a bright red solution presumably due to formation of indole-2,3-dienolate*.



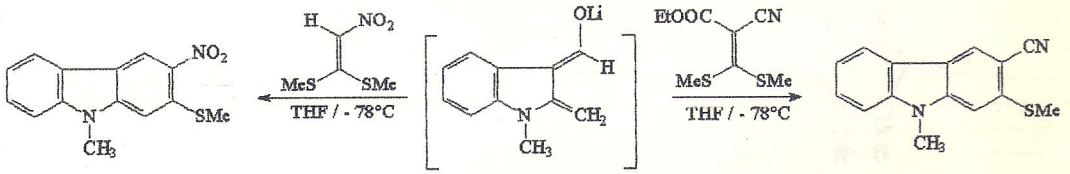
4 **9** **9**

Mandava V.Basaveswara Rao, Janagani Satyanarayana, Hiriyakkanavar lla* and Hiriyakkanavar Junjappa*.** ***Tetrahedron lett., 1995, ***36*, 3385-3388.**



Scheme 7

The indole-2,3-dienolate **8**, at -78°C was then treated with various dienophiles such as acrylonitrile , ethylacrylate, diethylfumarate, methylvinylketone, methylcinnamate , which after work up and silica gel chromatographic separation yielded the corresponding dihydrocarbazoles **9**, **10**, **11**, **12**, **13** respectively in good yields. The dihydro derivatives obtained were refluxed with pyridinium tosylate to yield corresponding fully aromatised carbazole derivatives in quantitative yields. Thus indolo-2,3-dienolate **8** generated, was reacted with dimethylacetylenedicarboxylate to yield 2,3-bis(methoxycarbonyl)-9-methylcarbazole **14** as light yellow crystals in 76% yield. Similarly indole-2,3-dienolate was reacted with nitrostyrene and the residue obtained was refluxed with pyridinium tosylate in dry benzene to yield 9-methyl-3-nitro-2-phenylcarbazole **15** in 72% yield. (Scheme 7)

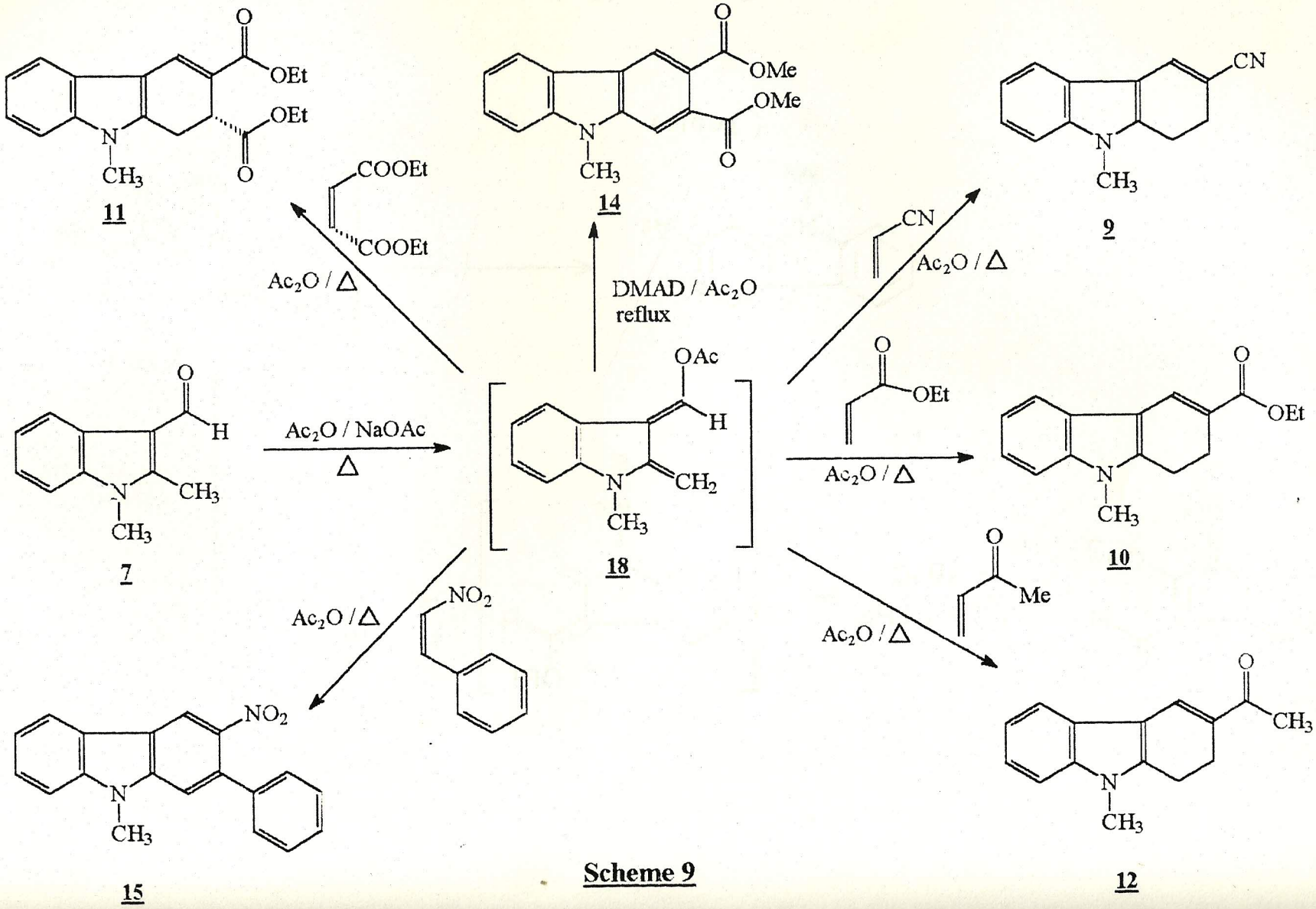


16 **8** **17**

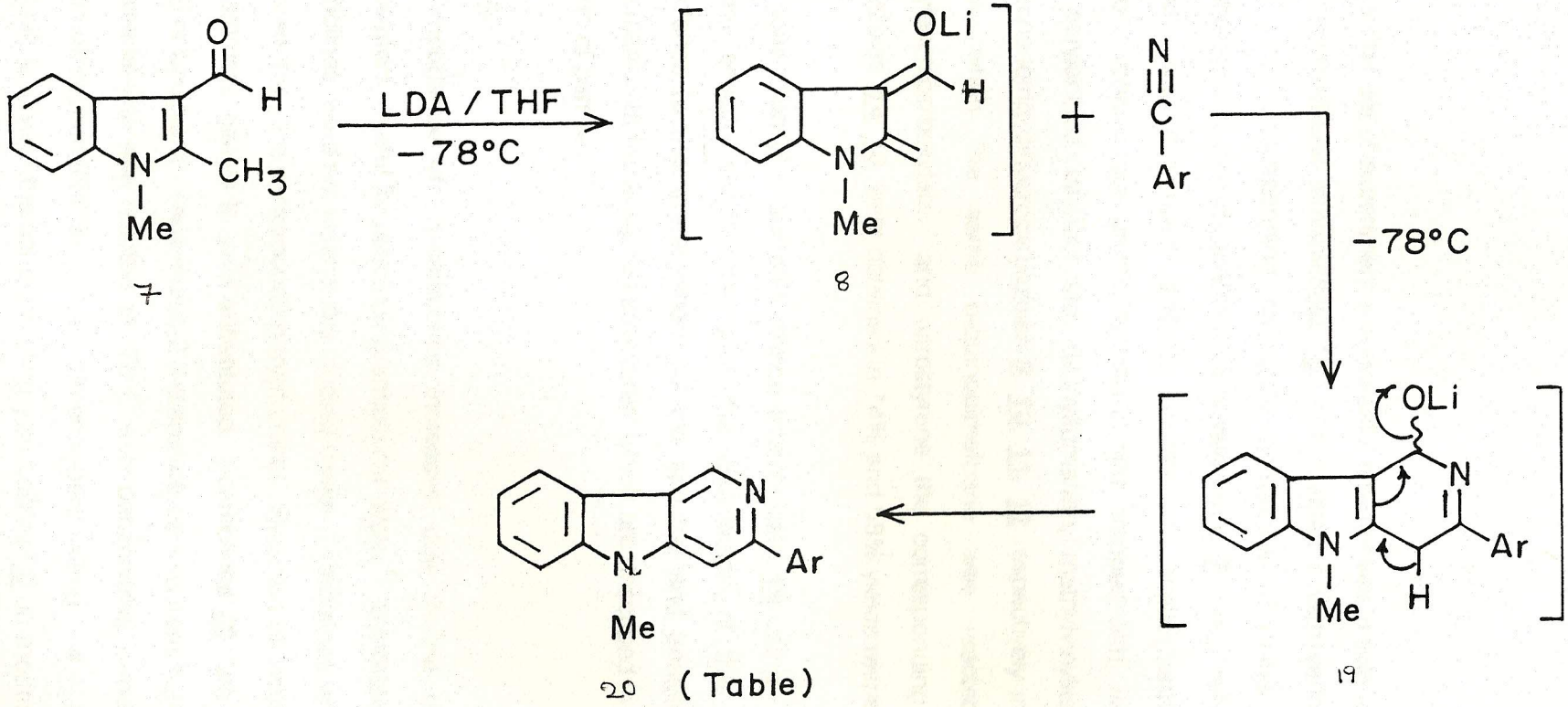
Scheme 8

The nitroketene-S,S-acetal when reacted with indole-2,3-dienolate, highly regioselective cycloaddition yielded the 2-methylthio-9-methyl-3-nitrocarbazole **16** in 68% yield. Similarly when indole-2,3-dienolate was reacted with ethylcyanoacetate-S,S-acetal the corresponding 3-cyano-2-methylthio-9methylcarbazole **17** was obtained in 68% yield (Scheme 8).

In this part we have demonstrated that the indole-2,3-dienolate derived from 1,2-dimethylindole-3-carboxaldehydde is a useful synthon which undergoes facile cycloaddition with a variety of dienophiles affording wide range of substituted carbazoles under remarkably mild conditions with most predictable and observed regio control .


11
14
9
7
18
10
15
12
Ac2O / Δ
DMAD / Ac2O
reflux
Ac2O / NaOAc
Δ
Ac2O / Δ
Ac2O / Δ
Ac2O / Δ
Ac2O / Δ

Scheme 9



7 8 19 20 (Table)

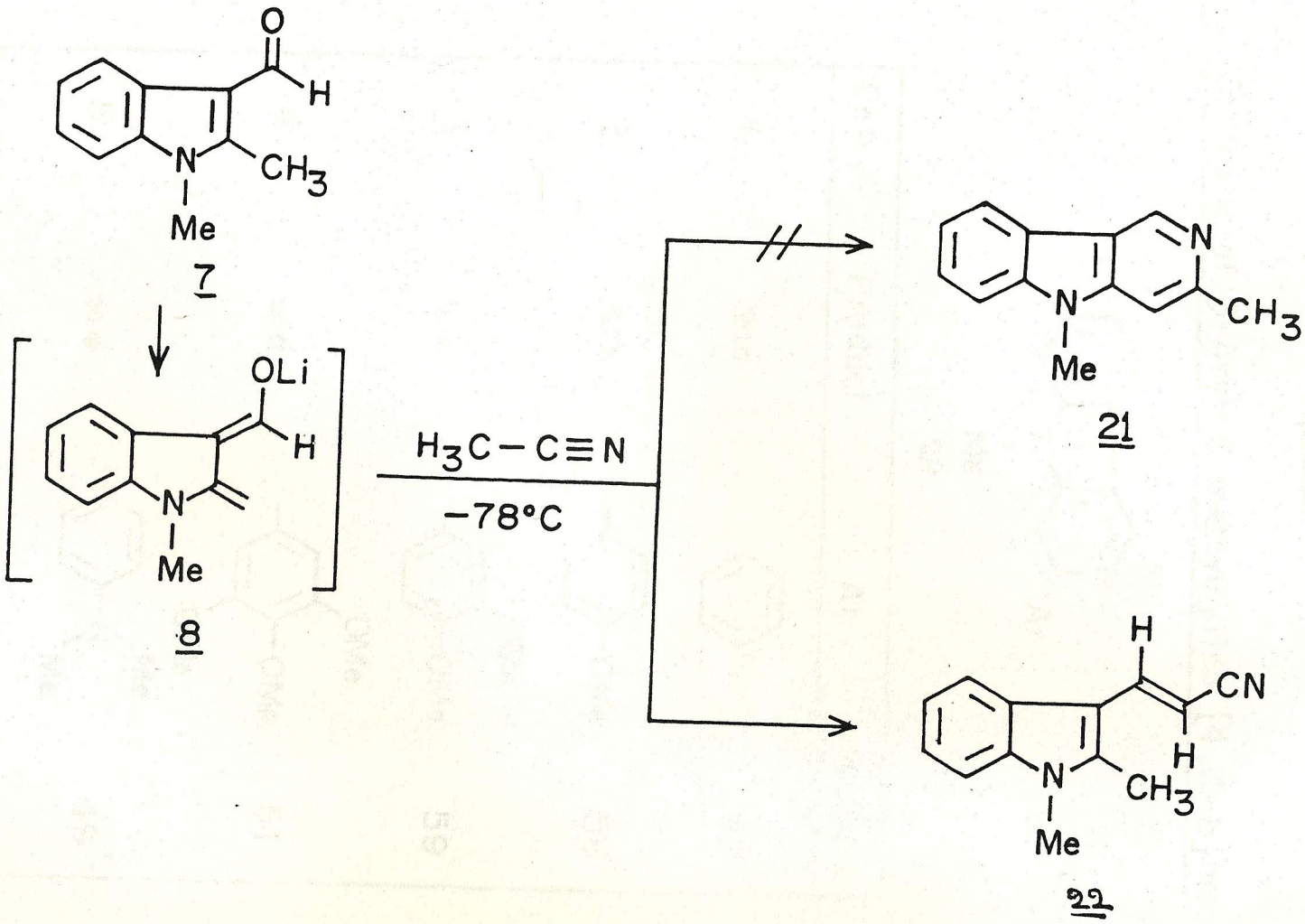
Scheme—10

In Another set of experiment a successful attempt was made to generate neutral o-quinodimethane intermediate **18** and reacted it with various dienophiles to yield the corresponding carbazole derivatives (Scheme 9). In a typical experiment 1,2-dimethylindole-3-carboxaldehyde **7** was refluxed with freshly molten and polvarised sodium acetate in acetic anhydride and the quinodimethane thus generated was *in situ* trapped with various dienophiles *viz.*, acrylonitrile, ethylacrylate, diethylfumarate, methylvinylketone to give the corresponding dihydrocarbazoles **9**, **10**, **11**, **12** respectively in 59-67% over all yields. when the same o-quinodimethane was reacted with dimethyl acetylenedicarboxylate and nitrostyrene the corresponding fully aromatised carbazoles **14**, **15** were obtained in 74% and 58% yields respectively.

The generation of o-quinodimethane intermediate **18** using acetic anhydride, sodium acetate combination and the exploitation of this diene adds the importance to this investigation. All the spectral and analytical data were in agreement with the assigned structures which are described in the experimental section of part A.

Part B :

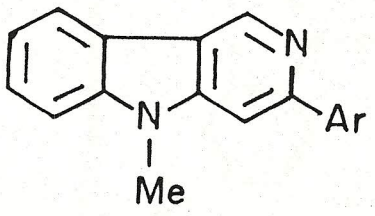
The importance of γ-carbolines increased due to the demand as DNA intercalators, useful for developing anticancer drugs[11]. Synthetic methods for the γ-carbolines were not extensively studied unlike β-carbolines which can be easily prepared from the corresponding tryptomines. Reaction of Indolo-2,3-dienolate **8** with aromatic nitriles to yield substituted γ-carbolines **20** are discussed in the part B of Chapter II. Thus indolo-2,3-dienolate derived from 1,2-dimethylindole-3-carboxaldehyde was reacted at -78°C with benzonitrile, p-methoxybenzonitrile, 3,4-dimethoxybenzonitrile, 3,4,5-trimetoxybenzonitrile, 4'-N,N-dimethylamino-benzonitrile to yield the corresponding γ-carbolines **20** in moderate yields. When the indolo-2,3-dienolate **8** was reacted with acetonitrile at -78°C the



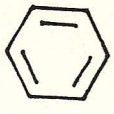
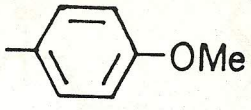
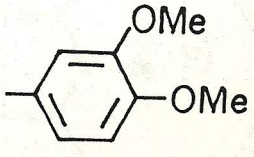
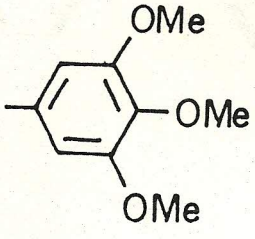
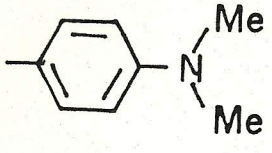
Scheme - 11

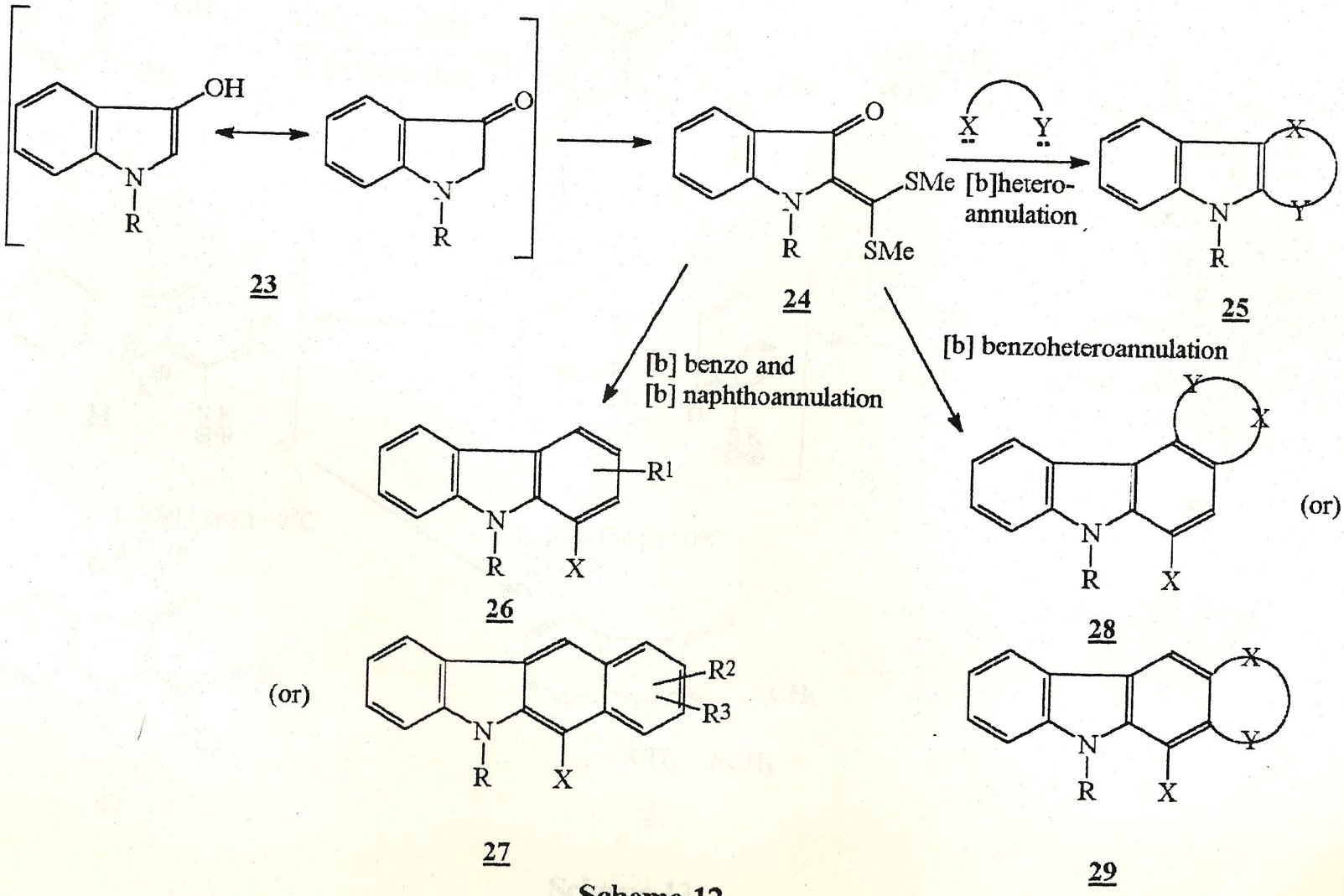
Table

Synthesis of 3-Aryl-5-methylpyrido [4,3-b] indole.

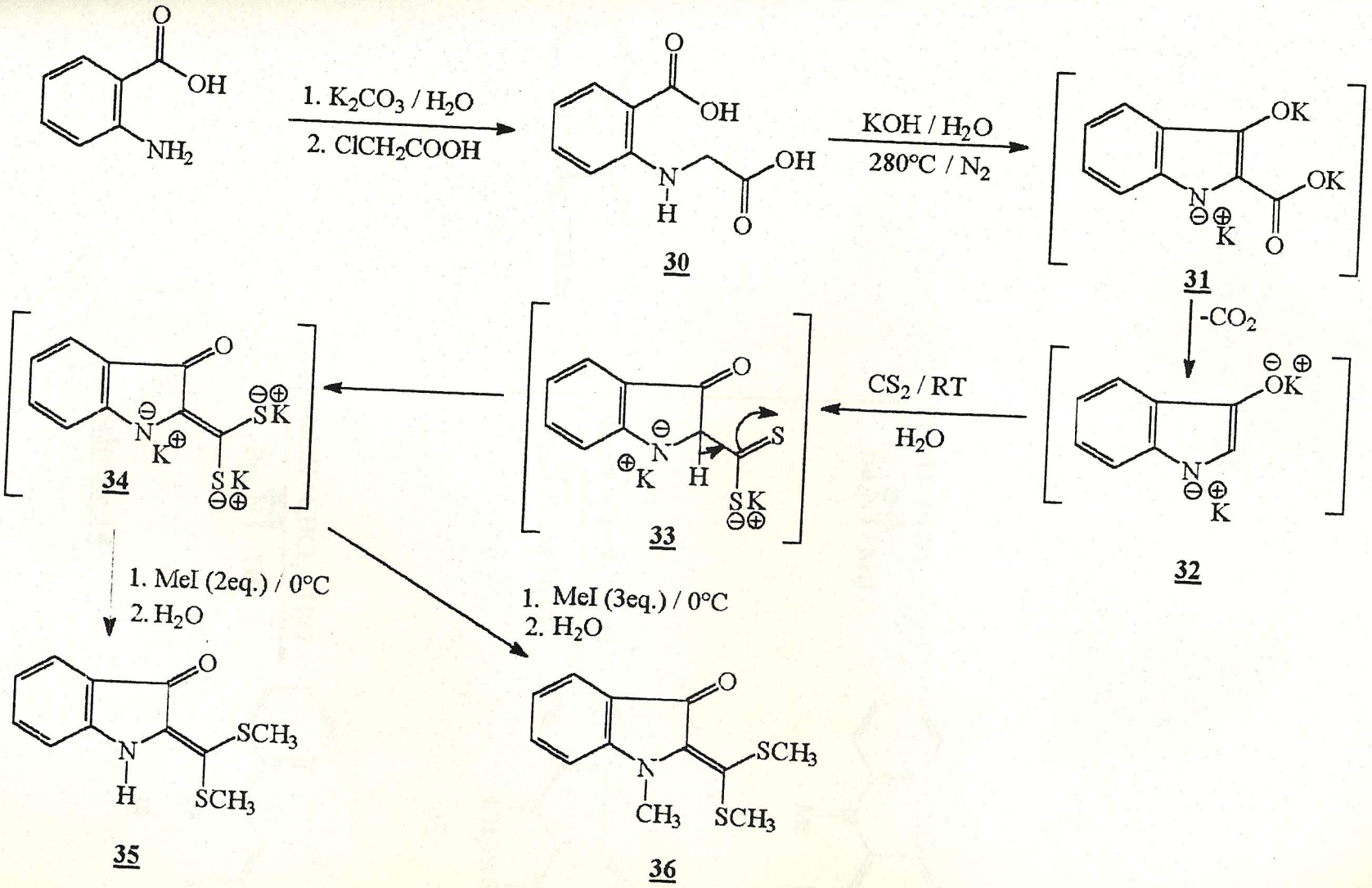


20

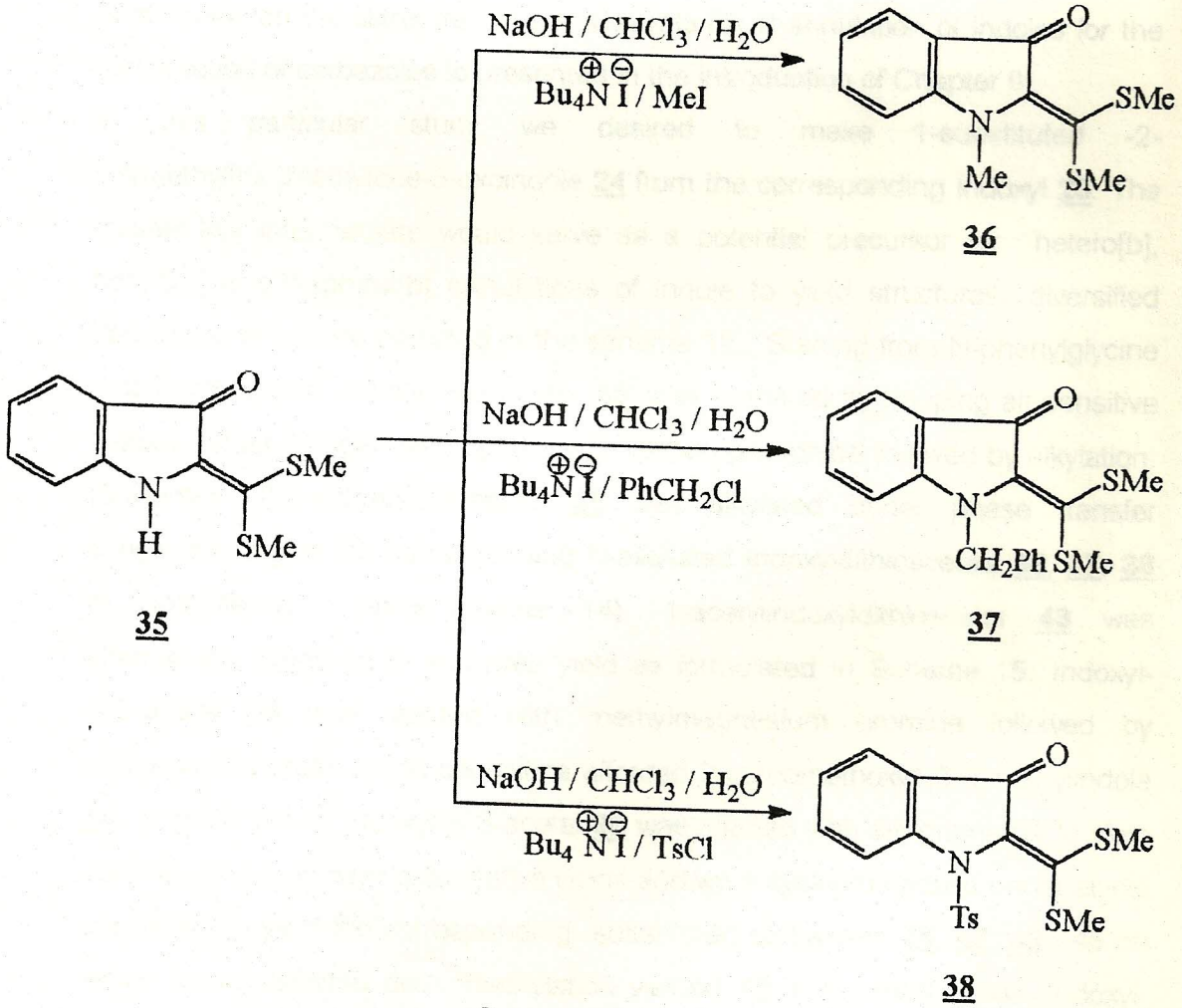
Entry	Product	Ar	% Yield
1.	20a		47
2.	20b		56
3.	20c		59
4.	20d		51
5.	20e		49


OH
O
N
R
23
SMe
SMe
24
X
Y
[b]hetero-
annulation
25
[b] benzo and
[b] naphthoannulation
[b] benzoheteroannulation
R1
26
(or)
R2
R3
27
28
(or)
29

Scheme 12


1. K_2CO_3 / H_2O
2. $ClCH_2COOH$
KOH / H_2O
280°C / N_2
-CO_2
CS_2 / RT
H_2O
1. MeI (2eq.) / 0°C
2. H_2O
1. MeI (3eq.) / 0°C
2. H_2O
30
31
32
33
34
35
36

Scheme 13



35 36 37 38

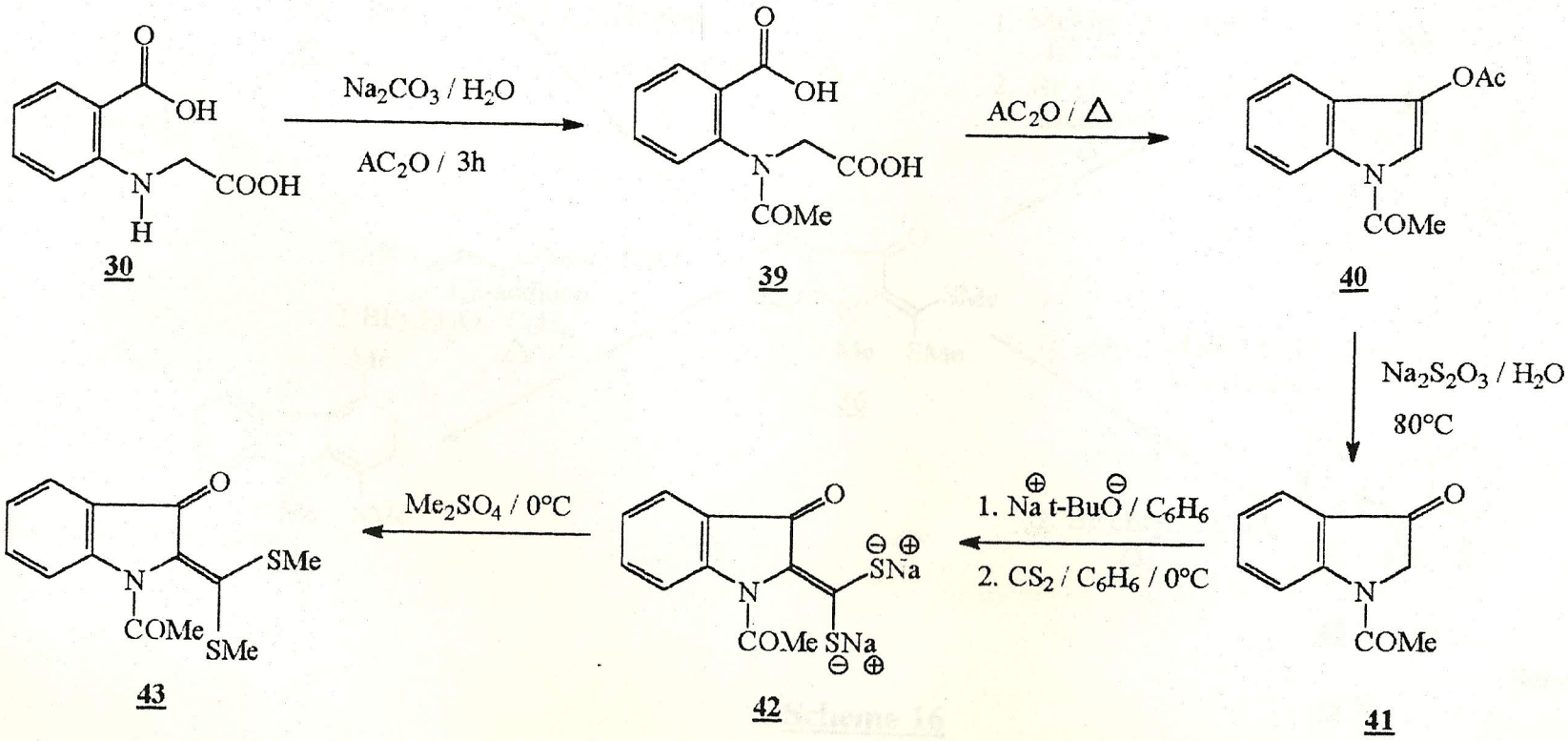
Scheme 14

corresponding methylsubstituted γ-carboline **21** could not be detected in the reaction mixture and the product obtained was characterised as an aldol adduct **22**. (Scheme 11)

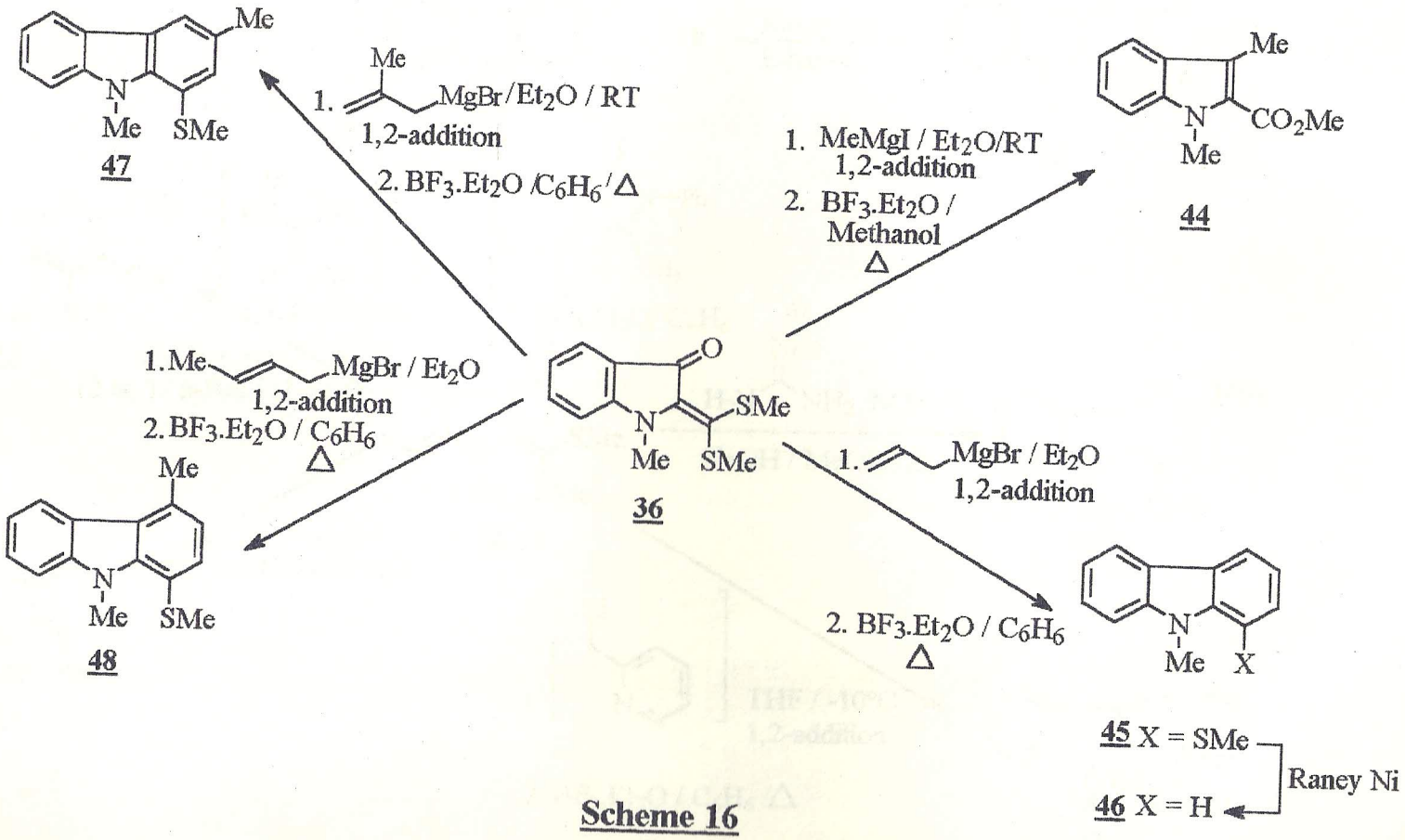
CHAPTER III

Brief review on the literature, for the available [3+3] annulation of indoles for the construction of carbazoles is presented in the introduction of Chapter III.

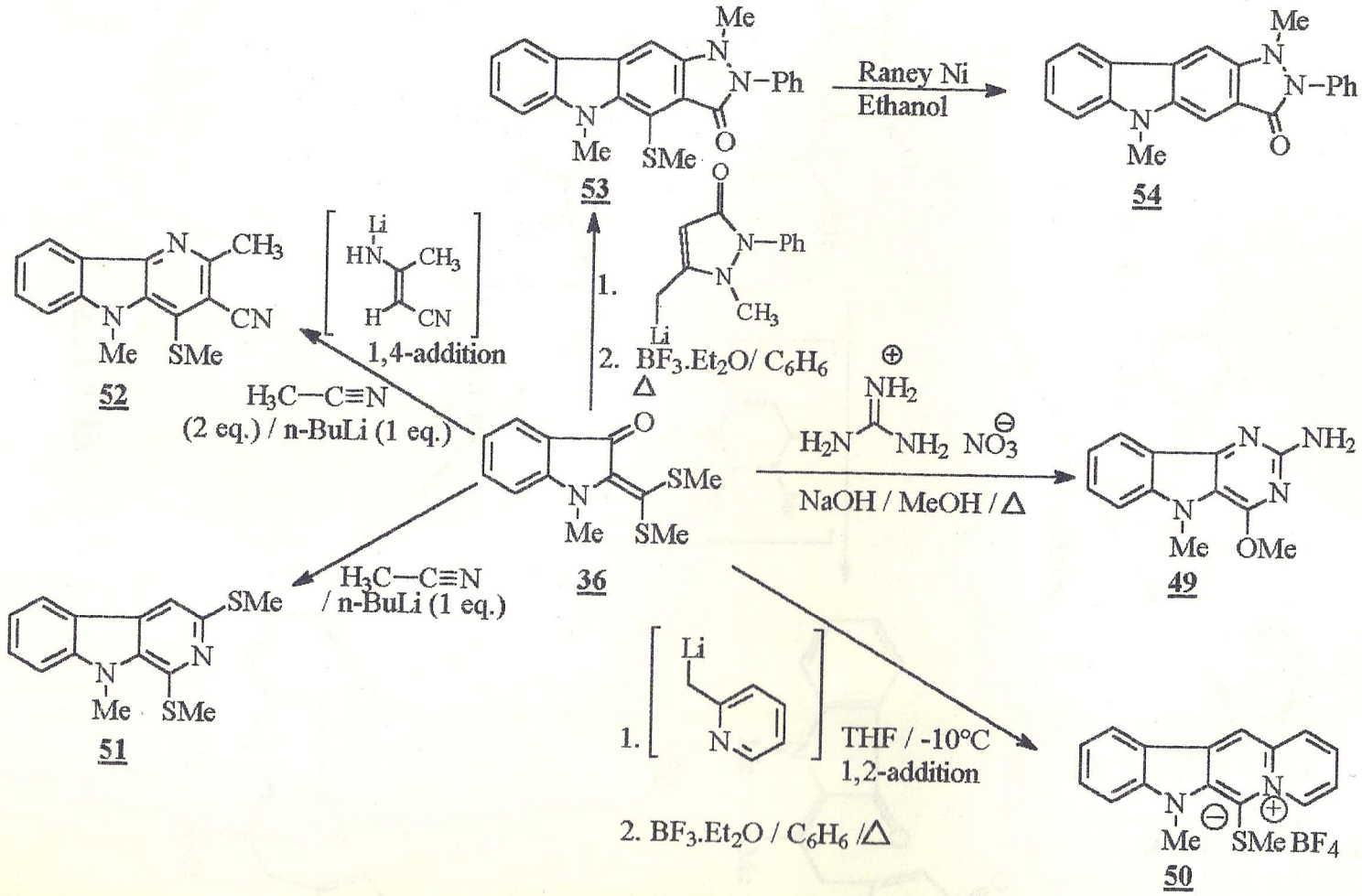
In this particular study we desired to make 1-substituted -2-bis(methylthio)methylene-3-oxoindole **24** from the corresponding indoxyl **23**. The master key intermediate would serve as a potential precursor for hetero[b], benzo[b] and naphtho[b] annulations of indole to yield structurally diversified derivatives which are depicted in the scheme 12. Starting from N-phenylglycine o-carboxaldehyde, indoxyl S,S-acetal **35** was prepared by trapping air sensitive indoxyl, under nitrogen atmosphere with carbon disulphide followed by alkylation. (Scheme 13). Indoxyl-S,S-acetal **35** was alkylated under phase transfer conditions to give the corresponding N-alkylated Indoxyldithioacetals **36**, **37**, **38** in quantitative yields(Scheme 14). 1-acetylindoxyldithioacetal **43** was alternatively prepared in improved yield as formulated in Scheme. 15. Indoxyl-S,S-acetal **36** was reacted with methylmagnesium bromide followed by methanolysis under acidic conditions afforded 2-carbomethoxy1,3-dimethylindole **44** in good yields. Indoxyl-S,S-acetal **36** was reacted with allylgrignards to yield carbinol acetals in near quantitative yields and were cycloaromatised under acidic conditions to yield the corresponding substituted carbazoles **45**, **47**, **48**. 45 on raney Nickel assisted dethiomethylation yielded **45** in excellent yields. Indoxyl-S,S-acetal **36** was reacted with guanidine nitrate in presence of alcoholic sodium hydroxide to yield 2-amino-5-methyl-4-methoxy pyrimido [5,4-b] indole **49** in good yield. Indoxyl-S,S-acetal **36** was reacted with 2-picolyllithium and the carbinol obtained was cycloaromatised under acidic conditions to yield hitherto unreported frame work indolo [3,2-b] quinozilinium tetrafluoroborate salts **50**.


O
OH
N
H
COOH
30
Na_2CO_3 / H_2O
AC_2O / 3h
O
OH
N
COOH
COMe
39
AC_2O / Δ
OAc
N
COMe
40
$Na_2S_2O_3$ / H_2O
80°C
O
N
COMe
41
1. Na t-BuO / C_6H_6
2. CS_2 / C_6H_6 / 0°C
O
SNa
N
COMe SNa
42
Me_2SO_4 / 0°C
O
SMe
N
COMe
SMe
43

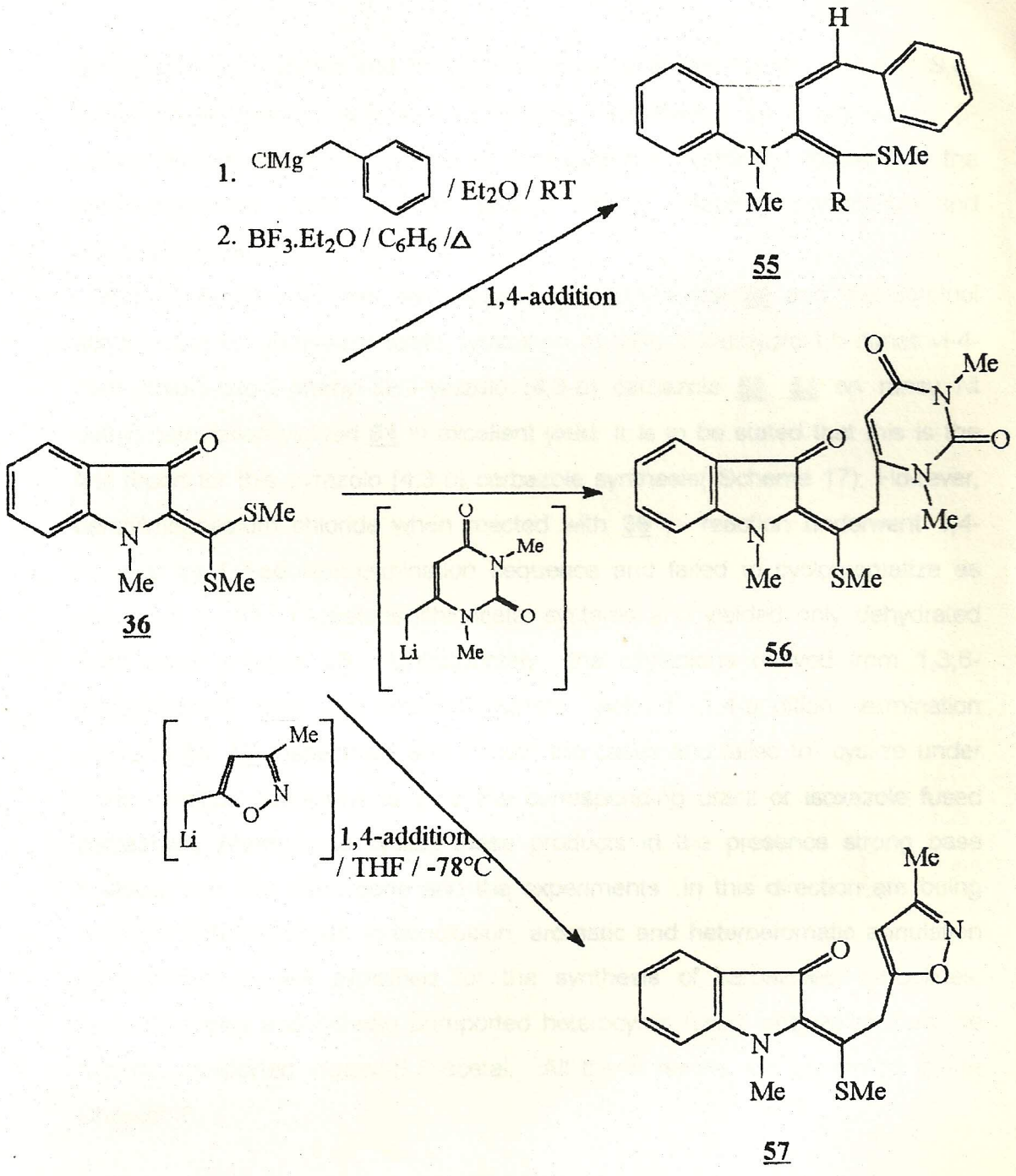
Scheme 15


Me
N
Me SMe
47
1. Me MgBr/Et2O / RT
1,2-addition
2. BF3.Et2O /C6H6/Δ
1. MeMgI / Et2O/RT
1,2-addition
2. BF3.Et2O /
Methanol
Δ
Me
N
CO2Me
Me
44
1. Me MgBr / Et2O
1,2-addition
2. BF3.Et2O / C6H6
Δ
O
SMe
N
Me SMe
36
1. MgBr / Et2O
1,2-addition
2. BF3.Et2O / C6H6
Δ
Me
N
Me SMe
48
N
Me X
45 X = SMe
46 X = H
Raney Ni

Scheme 16


Raney Ni
Ethanol
53
54
52
1,4-addition
1.
2. BF3.Et2O/ C6H6
Δ
H3C—C≡N
(2 eq.) / n-BuLi (1 eq.)
NaOH / MeOH / Δ
36
49
H3C—C≡N
/ n-BuLi (1 eq.)
51
THF / -10°C
1,2-addition
2. BF3.Et2O / C6H6 /Δ
50

Scheme 17


1. ClMg
/ Et2O / RT
2. BF3.Et2O / C6H6 /Δ
1,4-addition
55
36
56
Li
Me
/ THF / -78°C
57

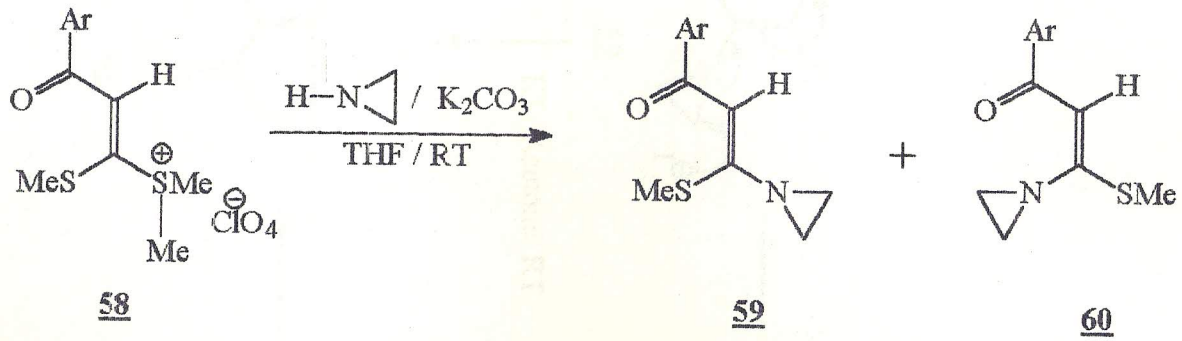
Scheme18

Similarly lithioacetonitrile and lithioaminocrotononitrile was reacted with the S,S-acetal to yield β-and γ-carbolines **51** and **52** respectively. Usual methods for β-carbolines involves the cyclization of corresponding tryptomine followed by the dehydrogenation. This method suffers drastic reaction conditions and considerably low yields.

Lithiomethylantipyrine, was also reacted with S,S-acetal **36** and the carbinol acetal obtained underwent facile cyclization to yield 1,2-dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3H-Pyrazolo [4,3-b] carbazole **53**. **53** on raney Ni dethiomethylation yielded **54** in excellent yield. It is to be stated that this is the first report for this pyrazolo [4,3-b] carbazole synthesis(Scheme 17). However, benzylmegnesium chloride when reacted with **36** , reaction underwent 1,4-followed by 1,2-addition-elimination sequence and failed to cycloaromatize as observed in other oxoketenedithioacetal systems and yielded only dehydrated open chain product **55**. Unfortunately the allylanions derived from 1,3,6-trimethyluracil and 3,5-dimethylisoxazole yielded 1,4-addition elimination products **56**, **57** respectively and in both the cases and failed to cyclize under acidic reaction conditions to yield the corresponding uracil or isoxazole fused carbazoles. Attempts to cyclize these products in the presence strong base however, has not been done and the experiments in this direction are being continued (Scheme 18). In conclusion, aromatic and heteroaromatic annulation methodology is well explained for the synthesis of carbazoles, carbolines, pyrimidoindoles and hitherto unreported heterocyclic fused carbazoles from the hitherto unreported Indoxyl-S,S-acetal. All these results are presented in the Chapter III.

CHAPTER IV

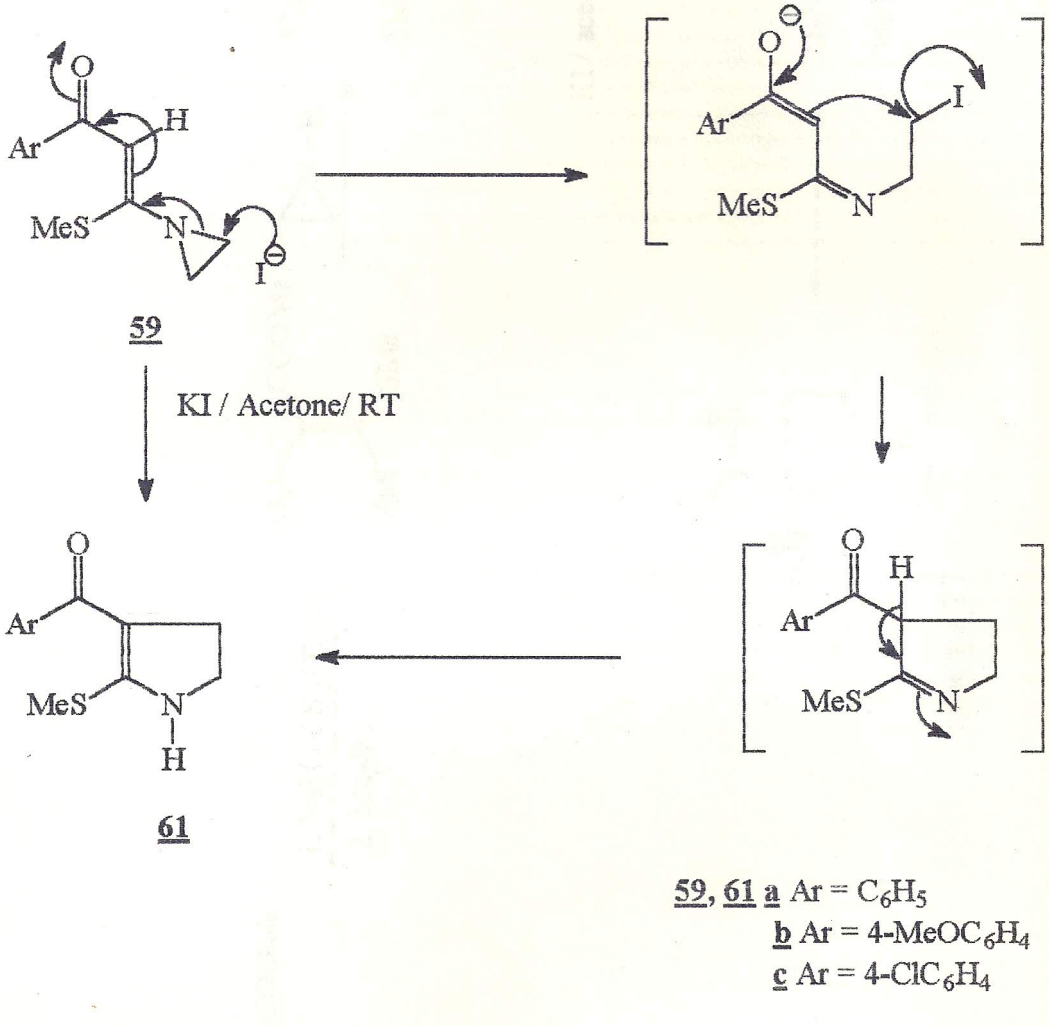
In Chapter IV, aziridino N,S-acetals prepared from monoactivated α-oxoketenedithioacetals for the first time are reported (Scheme 19) and their rearrangement to substituted pyrrolines (Scheme 20) has been well explained.



58 **59** **60**

58,59,60 **a**, Ar = C_6H_5
b, Ar = 4-$MeOC_6H_4$
c, Ar = 4-ClC_6H_4

Scheme 19



59

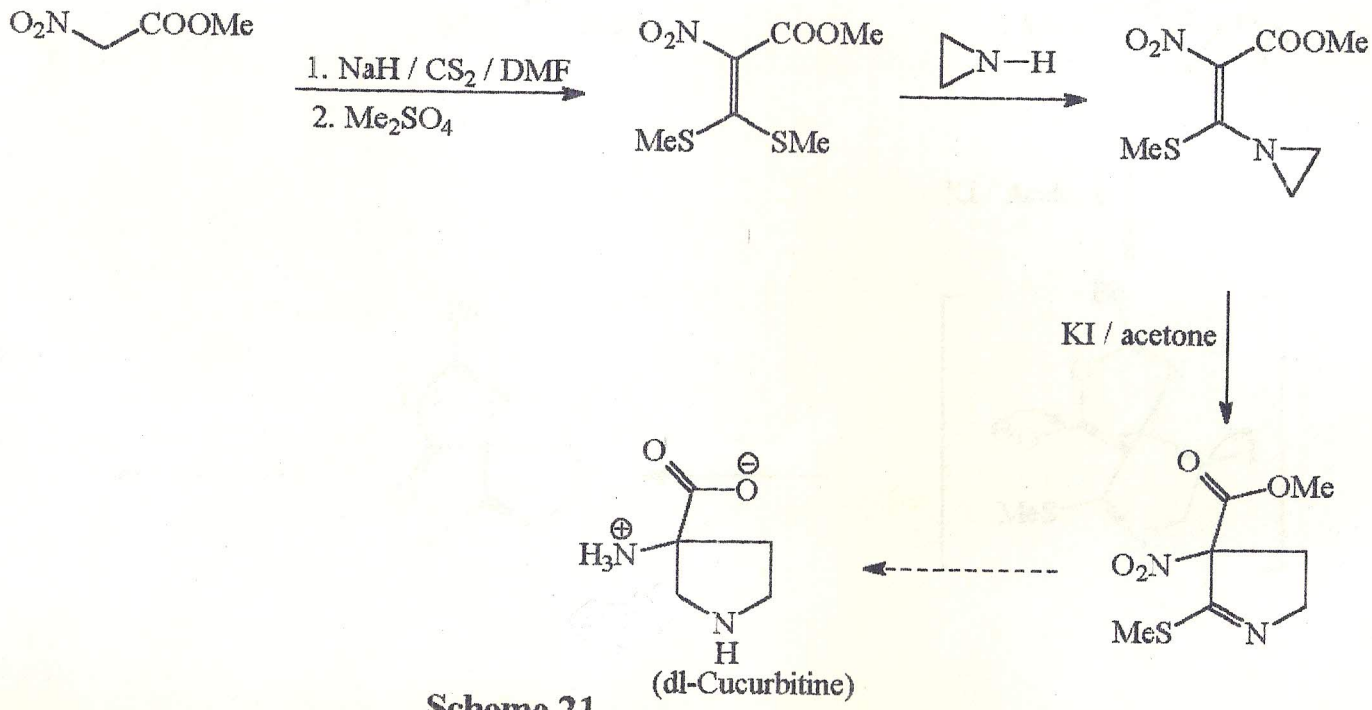
61

59, 61 a Ar = C_6H_5

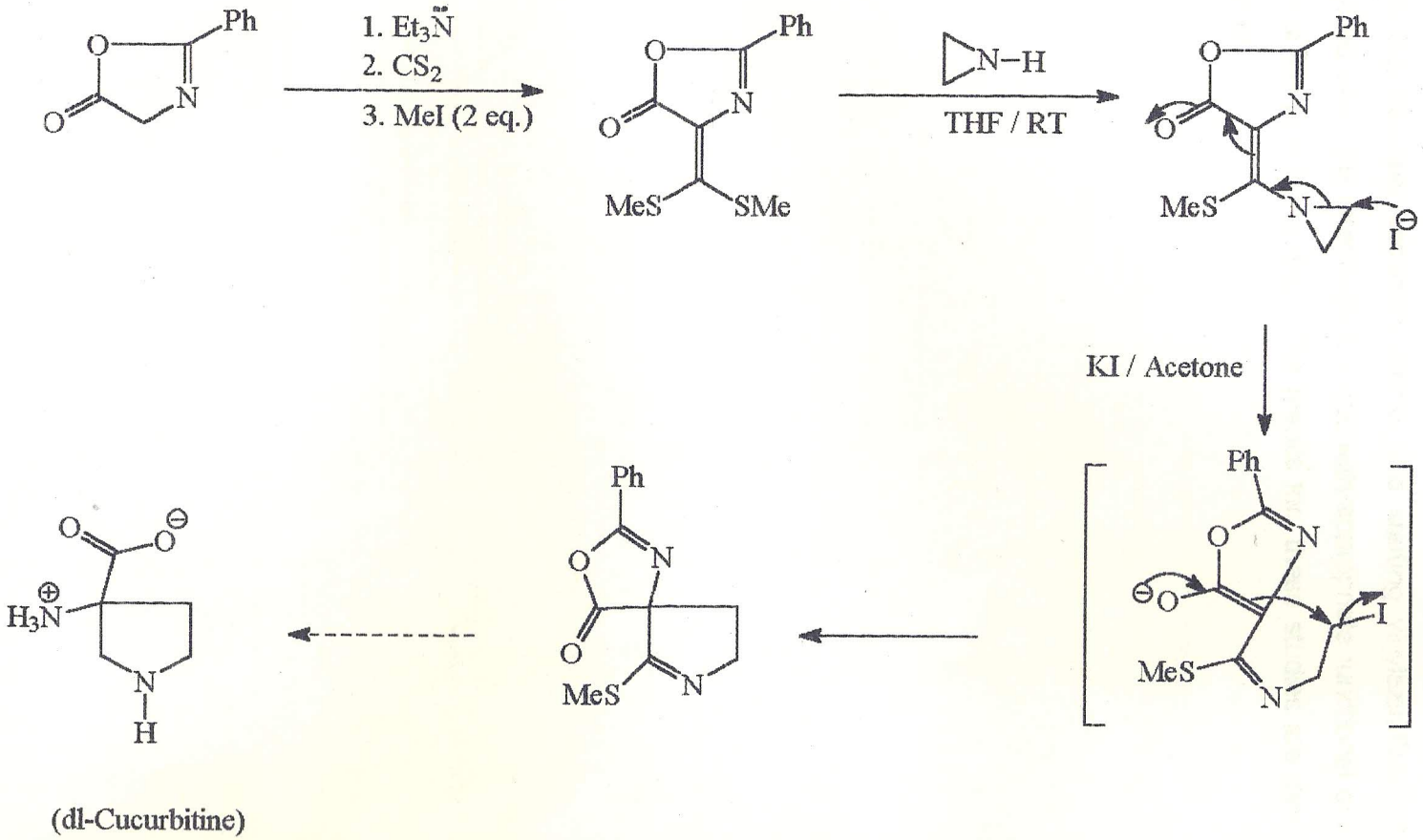
b Ar = 4-$MeOC_6H_4$

c Ar = 4-ClC_6H_4

Scheme 20


O2N
COOMe
1. NaH / CS2 / DMF
2. Me2SO4
MeS
SMe
N–H
KI / acetone
OMe
H3N
N
H
(dl-Cucurbitine)

Scheme 21


Ph
1. $Et_3\ddot{N}$
2. CS_2
3. MeI (2 eq.)
MeS
SMe
N–H
THF / RT
I
KI / Acetone
H_3N
(dl-Cucurbitine)

Scheme 22

Attempts were made for the synthesis of dl-cucurbitine,(Scheme 21 and Scheme 22) naturally occurring amino acid starting vinylaziridino-N,S-acetals have ended up in the intermediate stage with appropriate functional group at 3-position of the pyrrolidine ring. The results for these studies are described in Chapter IV.

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