NEW SYNTHETIC STRATEGIES FOR HETEROCYCLES OF BIOLOGICAL INTEREST

ABSTRACT

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Thesis

ABSTRACT

New Synthetic Strategies for Heterocycles of Biological Interest

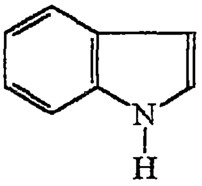
The thesis consists of four chapters.

CHAPTER I :

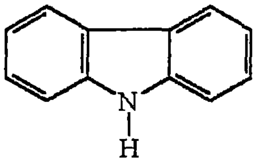
New Synthetic Strategies for Heterocycles of Biological Interest

This chapter is further subdivided into four sections :

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

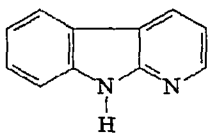


1



2

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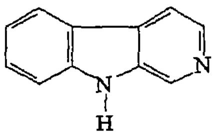
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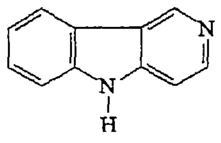
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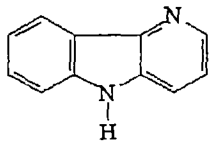

6

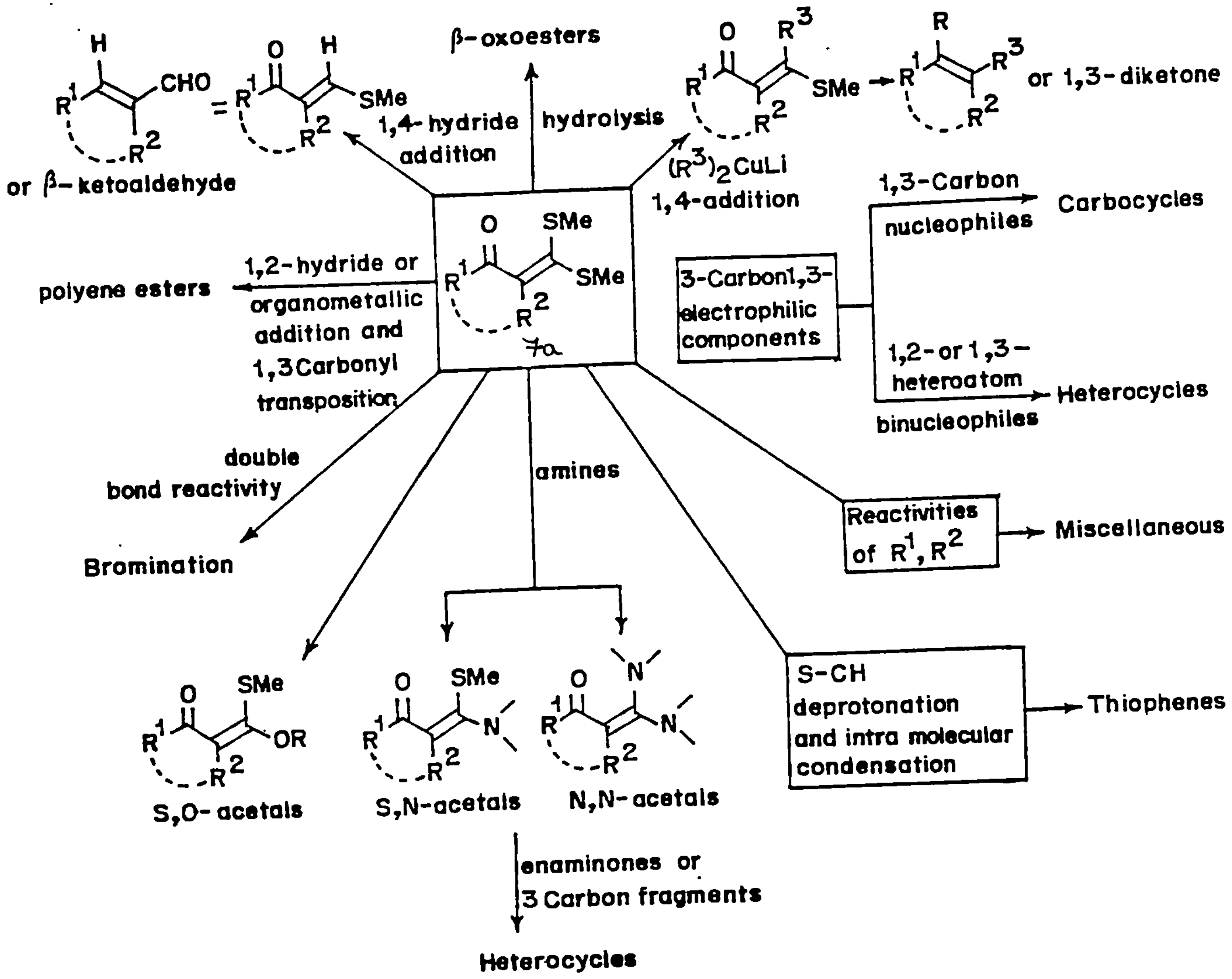
antiviral[4], and cytotoxic[5] properties. Some of the known three or four fused rings, containing indole moiety and their biological properties is described in this section.

Section 2. : The polarized ketenedithioacetals 7a-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.

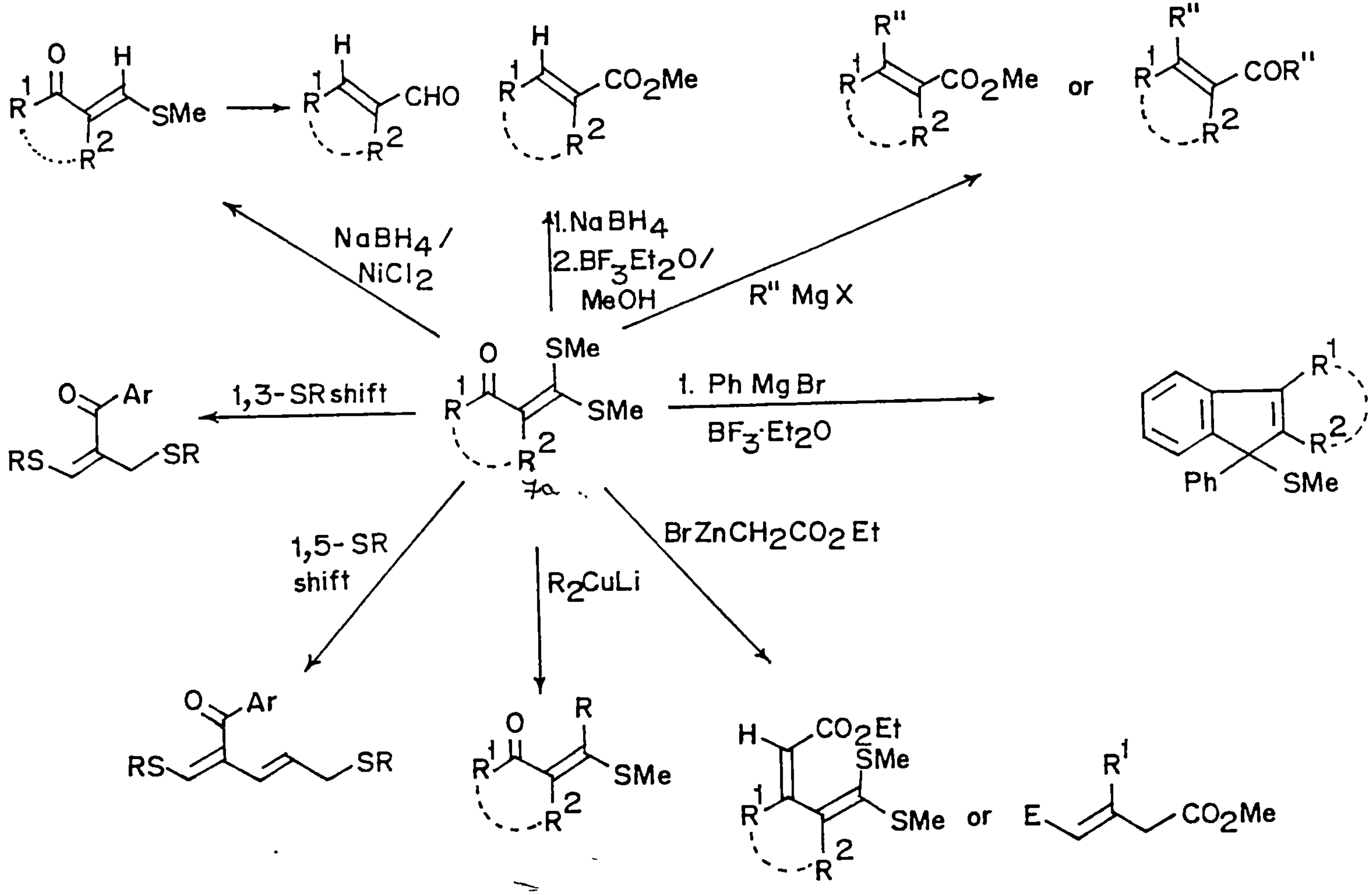
Section 4 : The work presented in the following chapters of thesis is briefly outlined in this section.

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.

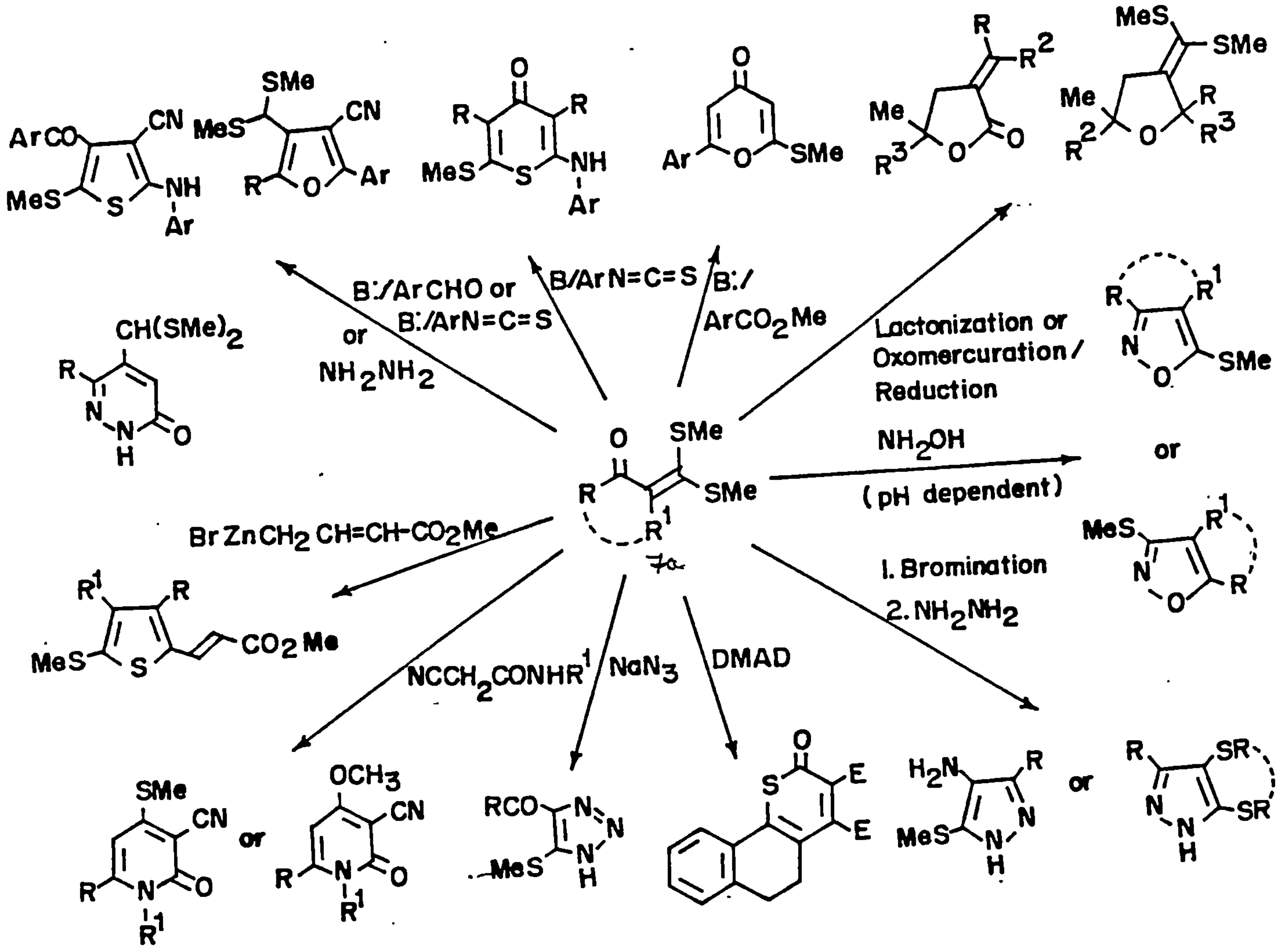


or β- ketoaldehyde
1,4- hydride addition
β- oxoesters
hydrolysis
(R^3)$_2$CuLi
1,4-addition
or 1,3- diketone
1,3-Carbon nucleophiles
Carbocycles
3-Carbon1,3-electrophilic components
1,2- or 1,3- heteroatom binucleophiles
Heterocycles
polyene esters
1,2- hydride or organometallic addition and 1,3Carbonyl transposition
7a
double bond reactivity
Bromination
amines
Reactivities of R^1, R^2
Miscellaneous
S-CH deprotonation and intra molecular condensation
Thiophenes
S,O- acetals
S,N-acetals
N,N- acetals
enaminones or 3 Carbon fragments
Heterocycles

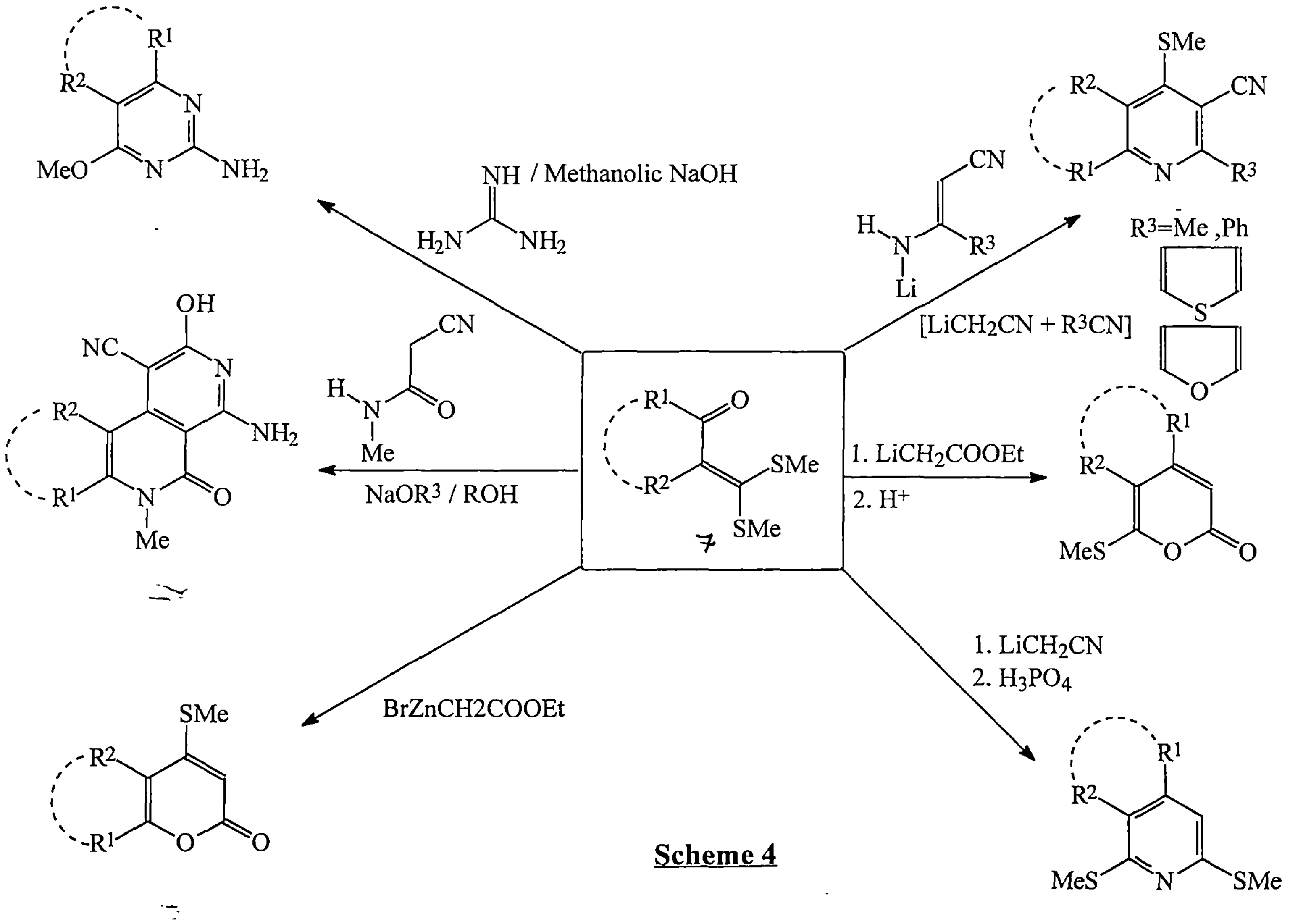
Scheme - 1


NaBH4 /
NiCl2
1.NaBH4
2.BF3Et2O/
MeOH
R'' MgX
or
1,3-SR shift
1. Ph MgBr
BF3·Et2O
7a
1,5-SR
shift
R2CuLi
BrZnCH2CO2Et
or

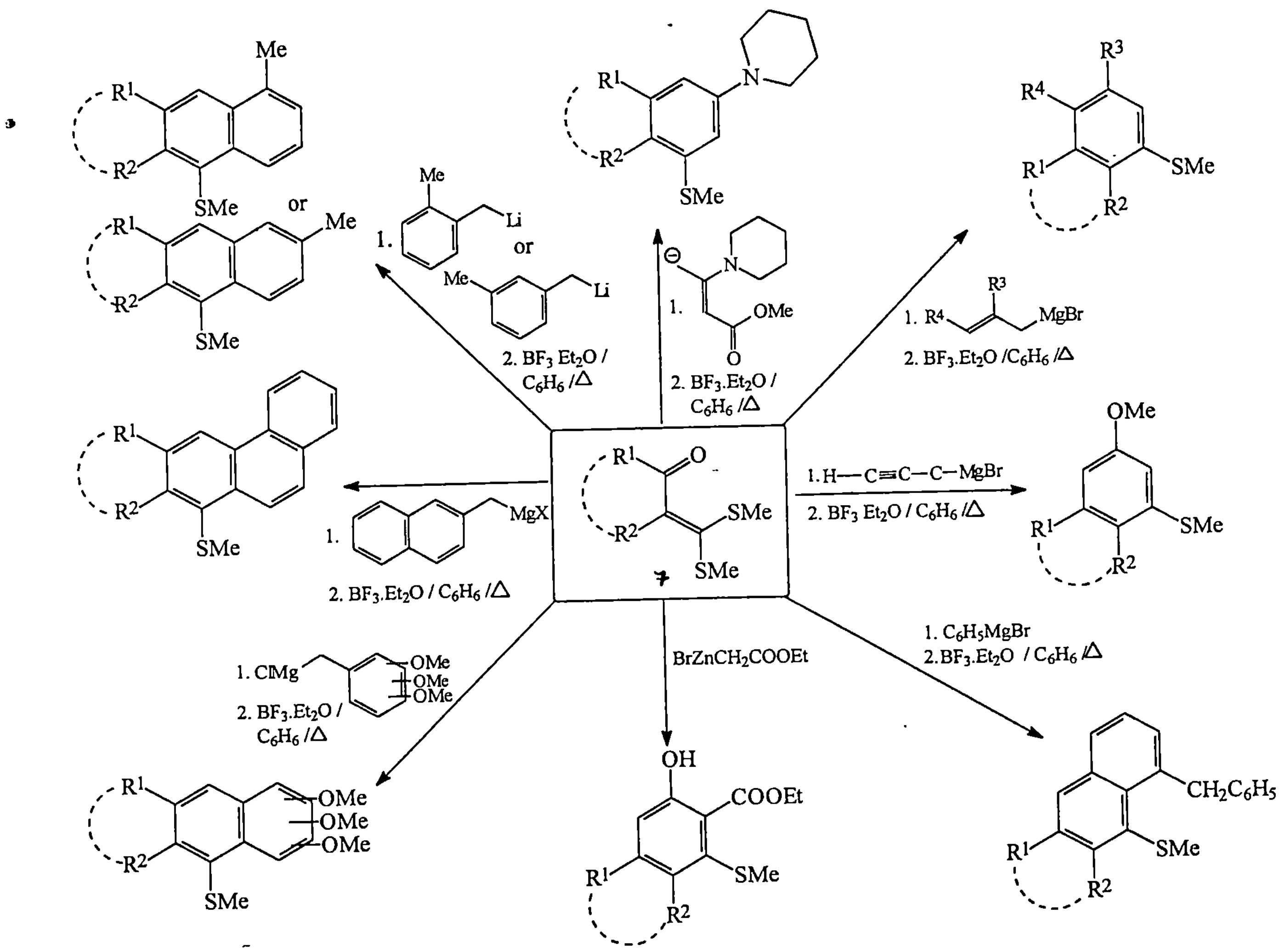
Scheme-2


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

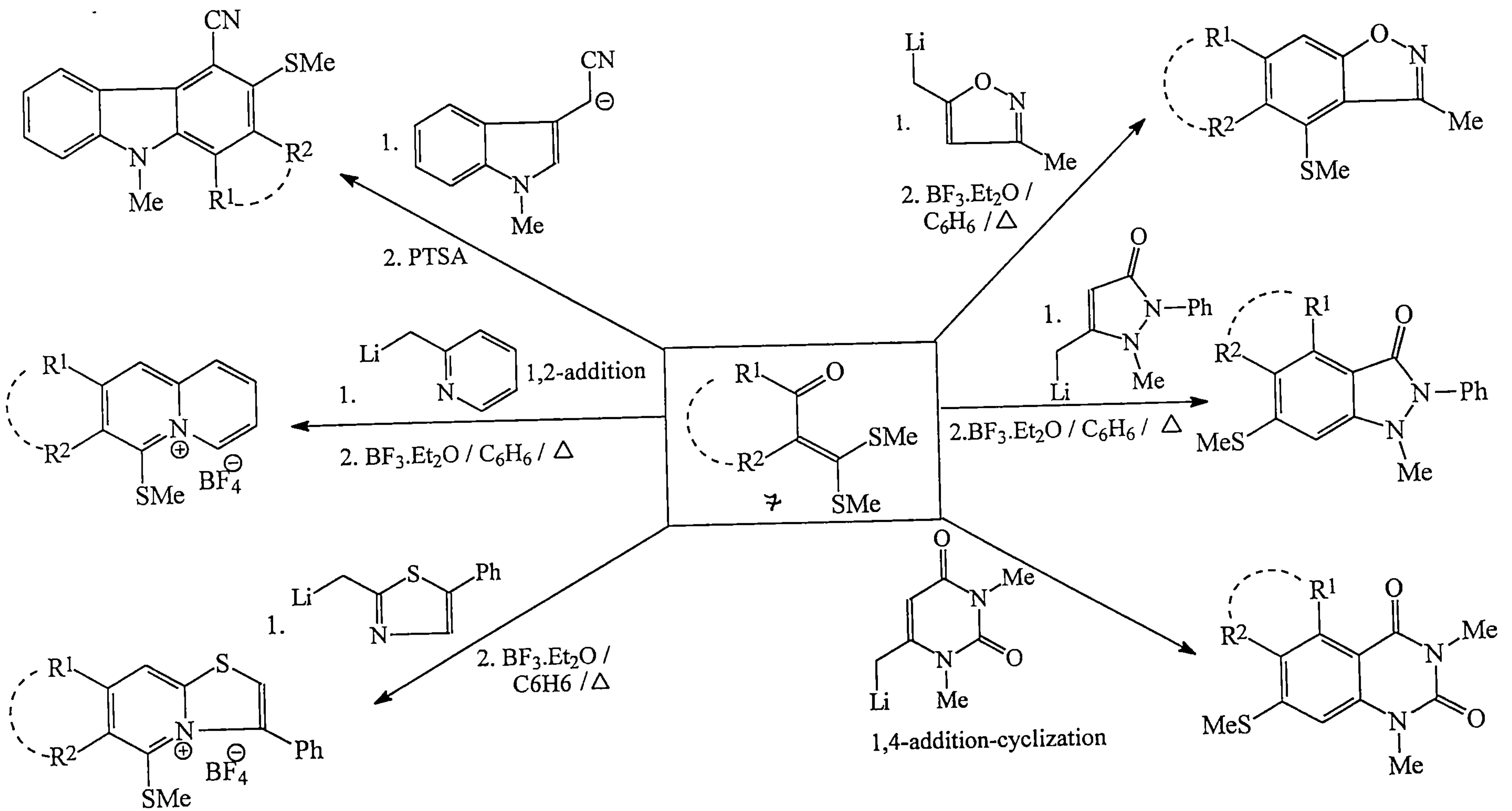
Scheme-3


NH / Methanolic NaOH
H$_2$N NH$_2$
H N Li CN R3
[LiCH$_2$CN + R^{3}CN]
R^3=Me ,Ph
1. LiCH$_2$COOEt
2. H$^+$
H N Me CN O
NaOR^3 / ROH
BrZnCH2COOEt
1. LiCH$_2$CN
2. H$_3$PO$_4$
7

Scheme 4


1. H—C≡C—C—MgBr
2. BF3 Et2O / C6H6 /Δ
1. R4 ... MgBr R3
2. BF3.Et2O /C6H6 /Δ
1. ... 2. BF3.Et2O / C6H6 /Δ
1. ... or ... 2. BF3 Et2O / C6H6 /Δ
1. ... MgX 2. BF3.Et2O / C6H6 /Δ
1. ClMg ... OMe OMe OMe 2. BF3.Et2O / C6H6 /Δ
BrZnCH2COOEt
1. C6H5MgBr
2.BF3.Et2O / C6H6 /Δ
R1 R2 R3 R4 SMe OMe Me Li N O OH COOEt CH2C6H5
or
7

Scheme 5

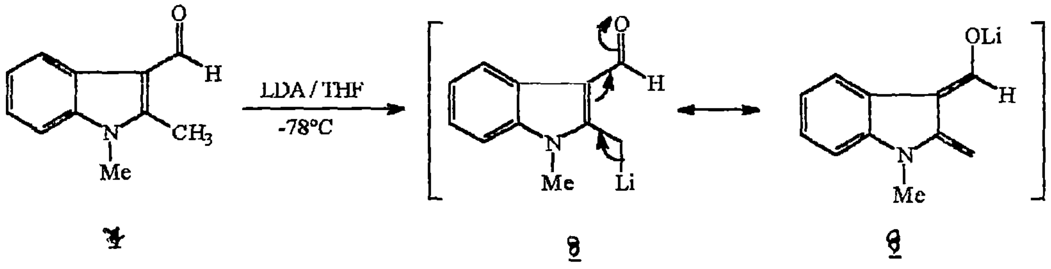

1.
2. PTSA
1.
1,2-addition
2. $BF_3.Et_2O$ / C_6H_6 / Δ
1.
2. $BF_3.Et_2O$ / C6H6 / Δ
1.
2. $BF_3.Et_2O$ / C_6H_6 / Δ
1.
2.$BF_3.Et_2O$ / C_6H_6 / Δ
1,4-addition-cyclization
7

Scheme 6

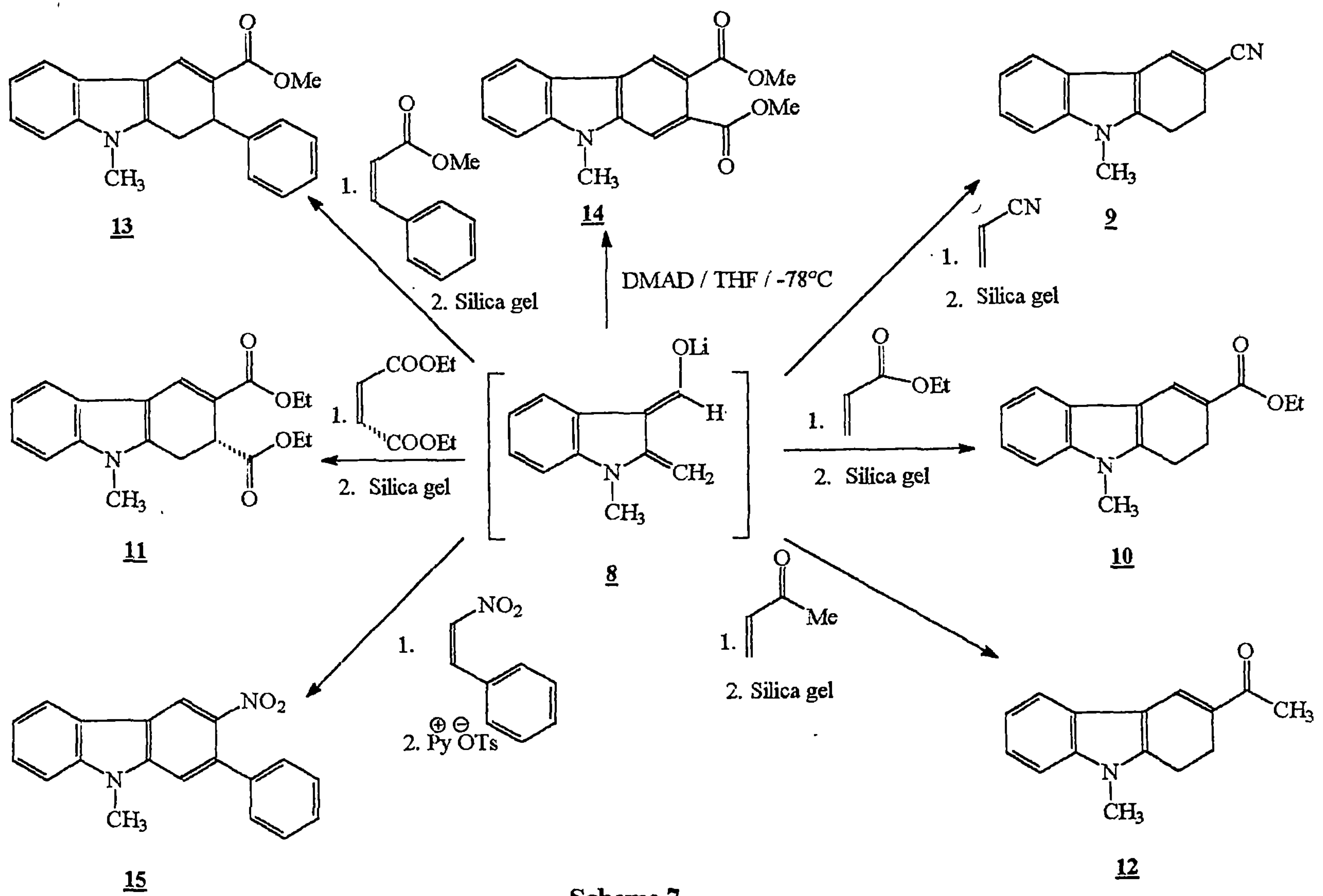
CHAPTER II :

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*.

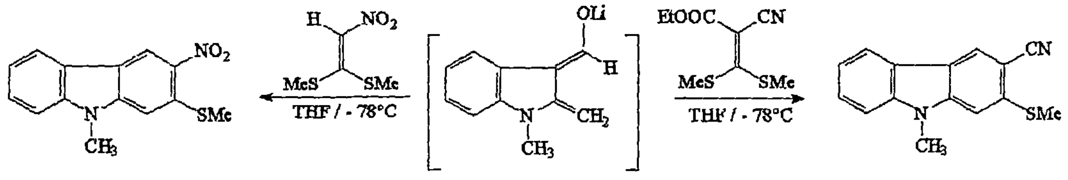


Mandava V.Basaveswara Rao, Janagani Satyanarayana, Hiriyakkanavar Ila* and Hiriyakkanavar Junjappa*. *Tetrahedron lett., 1995, ***36*, 3385-3388.**


13
O
OMe
N
CH3
1.
O
OMe
2. Silica gel
14
O
OMe
OMe
O
N
CH3
DMAD / THF / -78°C
9
CN
N
CH3
1.
CN
2. Silica gel
11
O
OEt
OEt
O
N
CH3
1.
COOEt
COOEt
2. Silica gel
8
OLi
H
CH2
N
CH3
10
O
OEt
N
CH3
1.
O
OEt
2. Silica gel
15
NO2
N
CH3
1.
NO2
2. ⊕ ⊖ Py OTs
12
O
CH3
N
CH3
1.
O
Me
2. Silica gel

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)

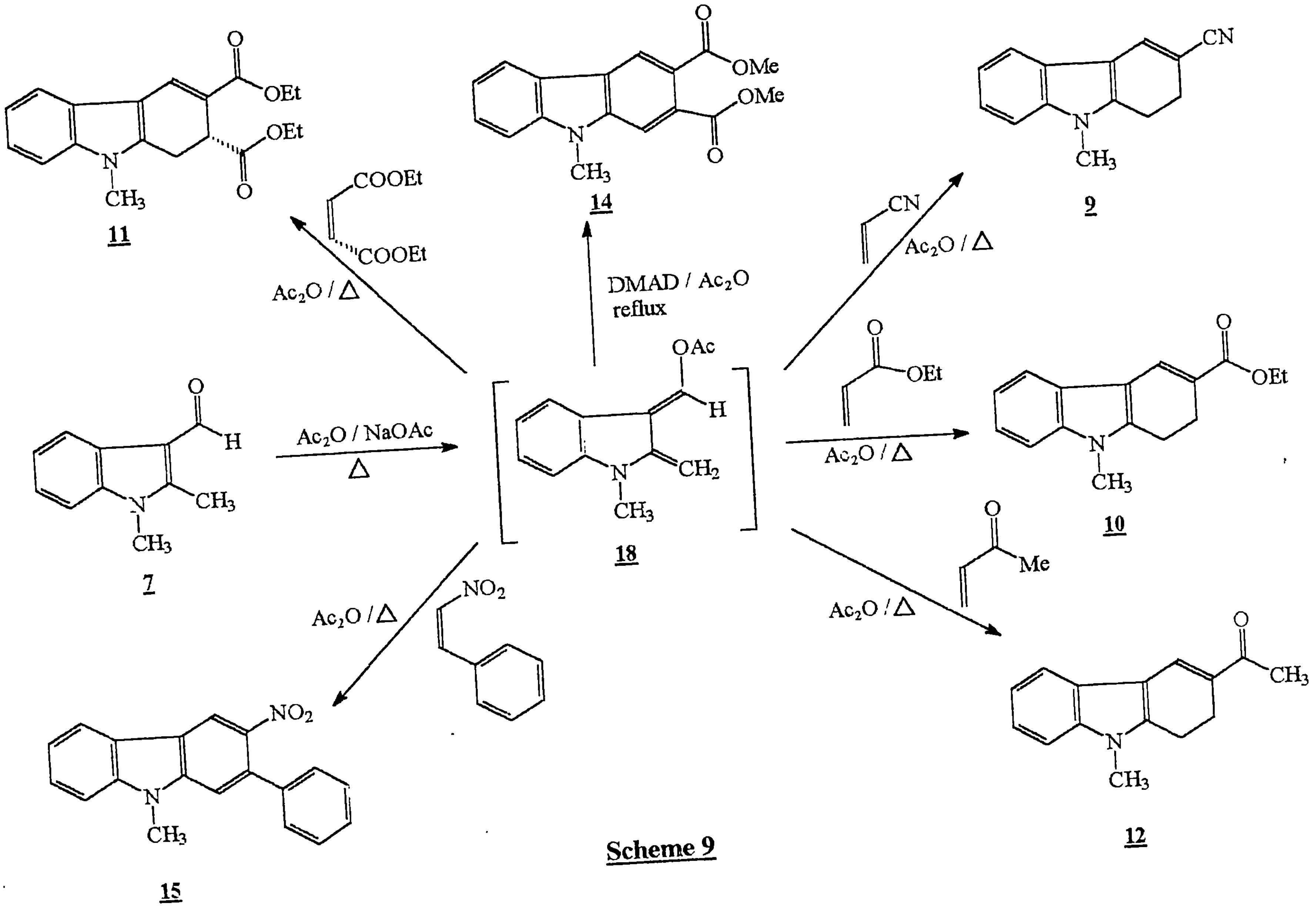


16 8 17

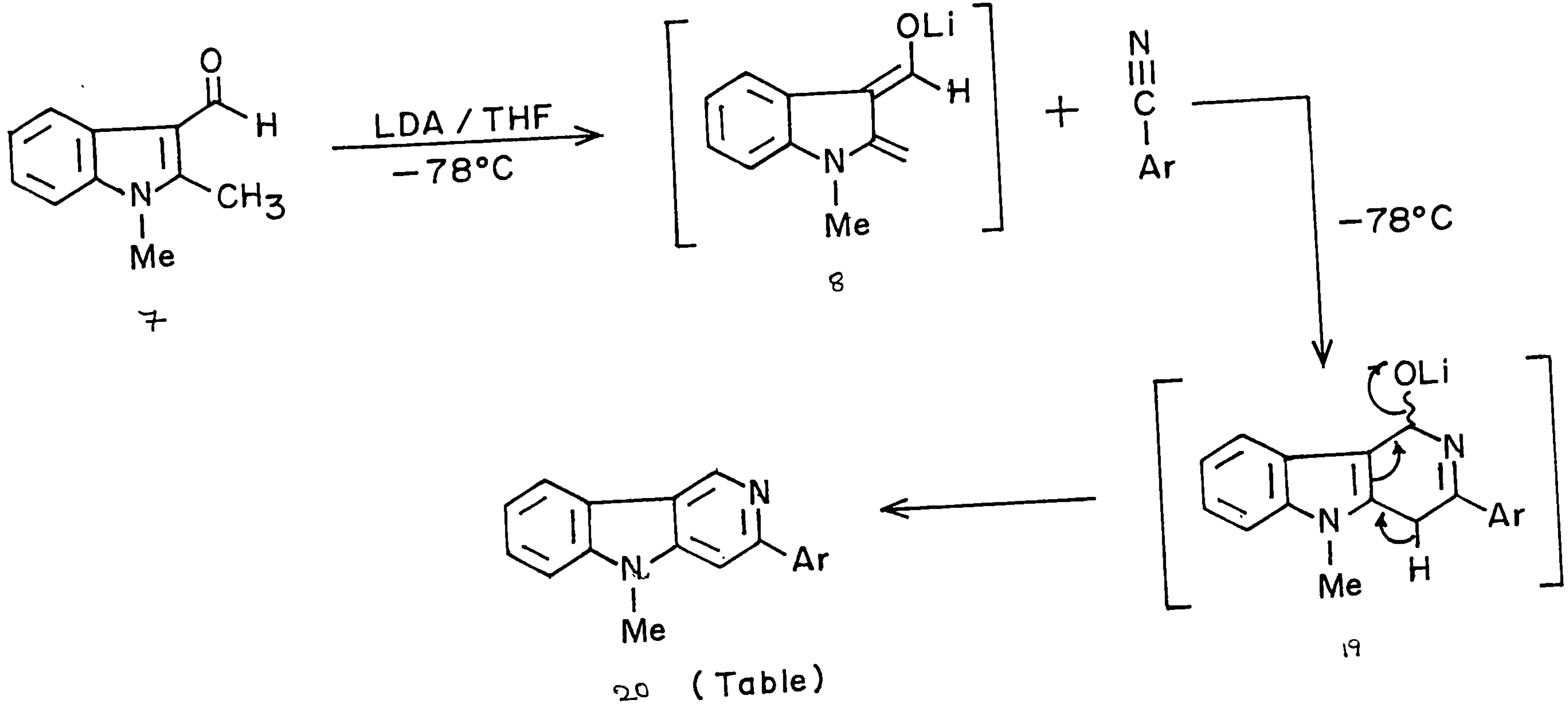
Scheme 8

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
COOEt
COOEt
Ac$_2$O / Δ
14
DMAD / Ac$_2$O reflux
9
CN
Ac$_2$O / Δ
7
Ac$_2$O / NaOAc Δ
18
OAc
H
CH$_2$
10
OEt
Ac$_2$O / Δ
NO$_2$
Ac$_2$O / Δ
15
Me
Ac$_2$O / Δ
12
N
CH$_3$
OMe
OEt

Scheme 9


O
H
CH3
N
Me
7
LDA / THF
−78°C
OLi
H
N
Me
8
+
N
C
Ar
−78°C
OLi
N
Ar
N
Me
H
19
N
Ar
N
Me
20
(Table)

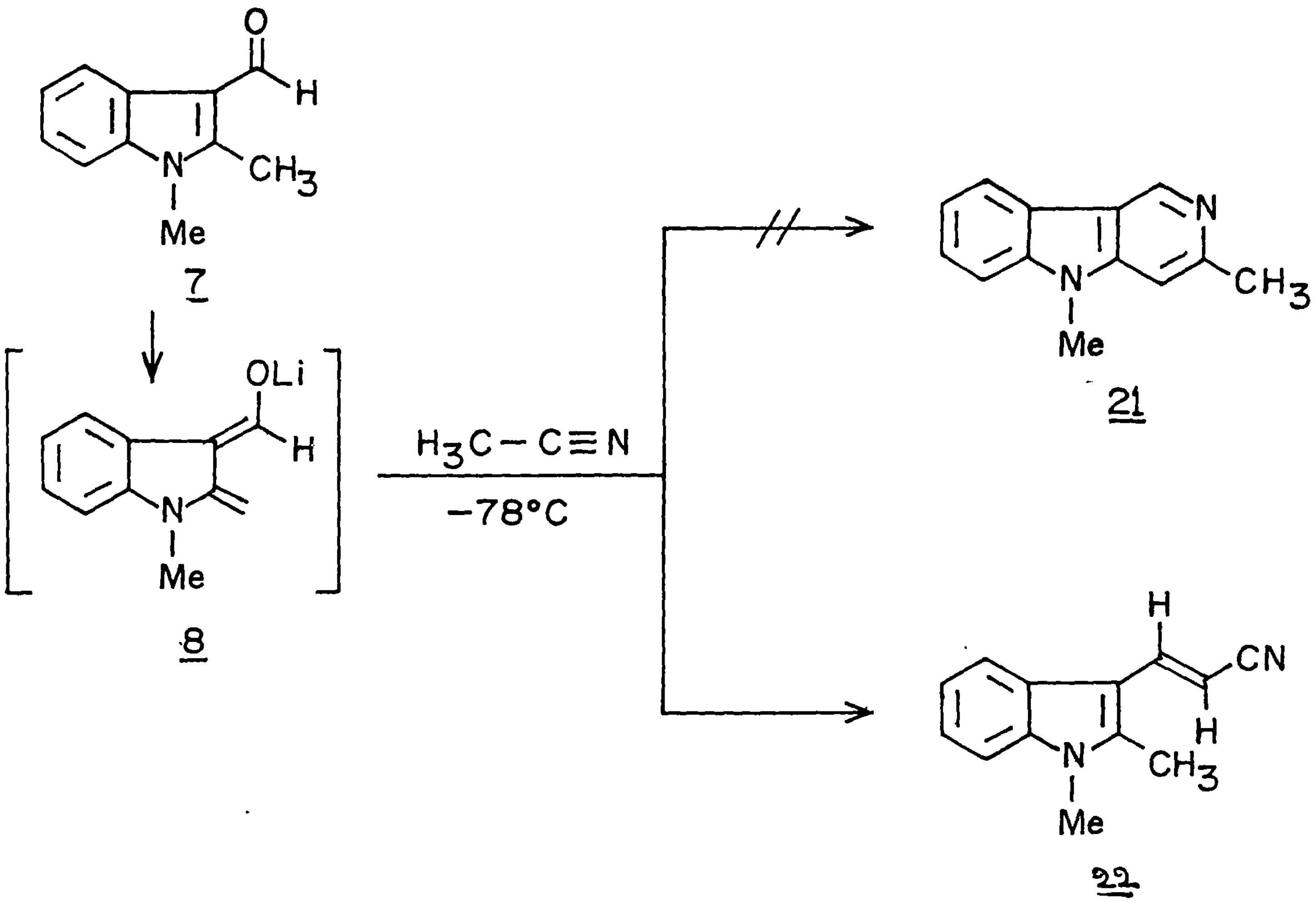
Scheme—10

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 :

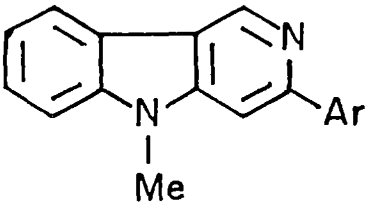
The importance of γ-carbolines increased due to the demand as DNA intercalators, useful for developing anticancer drugs[11]. Synthetic methods for the γ-carbolines were not extensively studied unlike β-carbolines which can be easily prepared from the corresponding tryptomines. Reaction of Indolo-2,3-dienolate **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



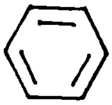
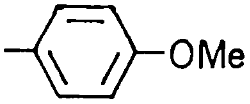
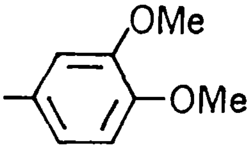
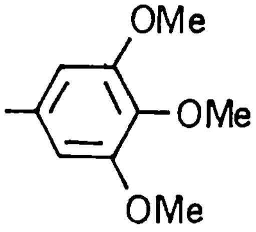
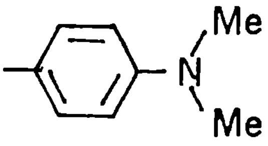
Scheme - 11

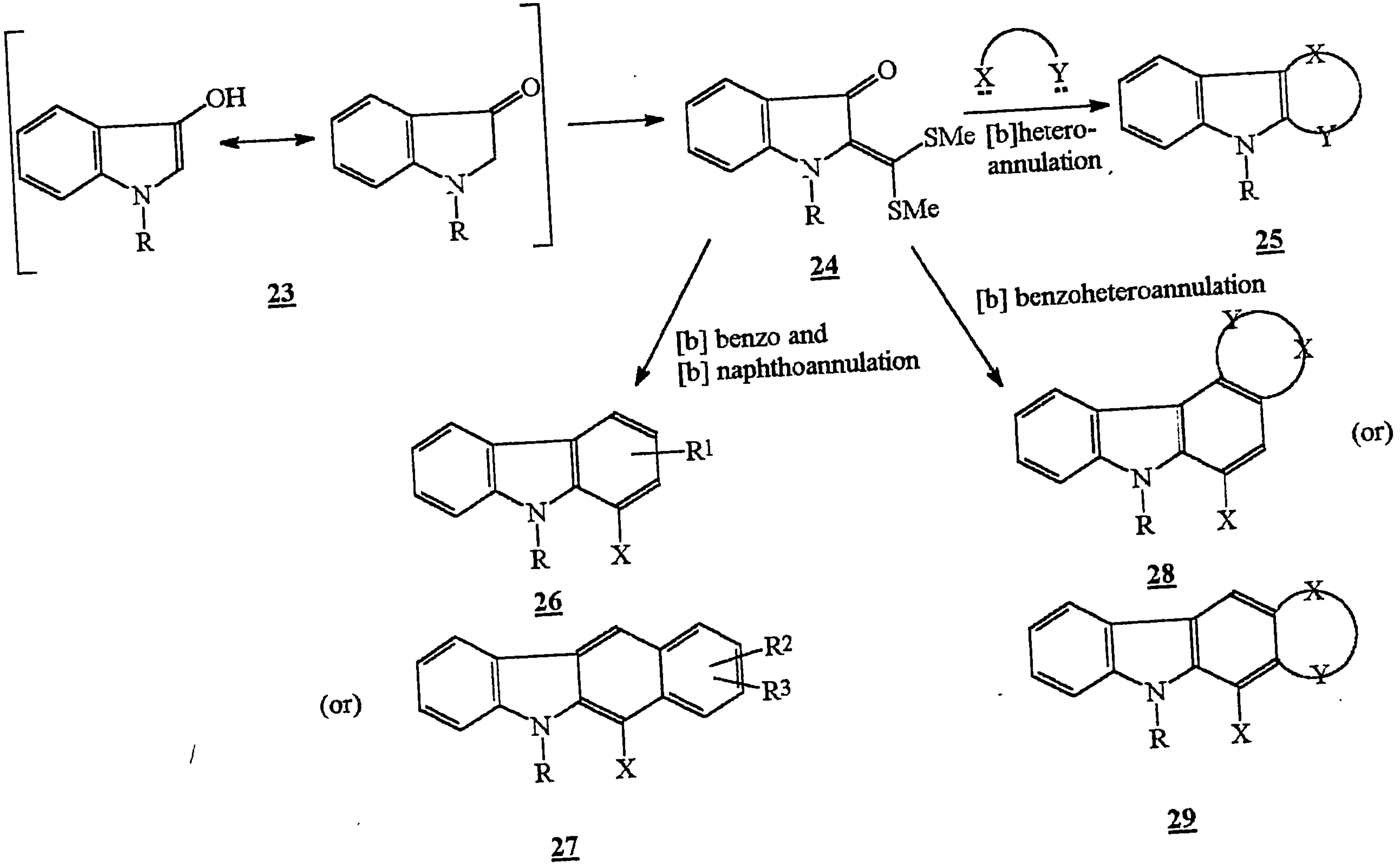
Table .

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

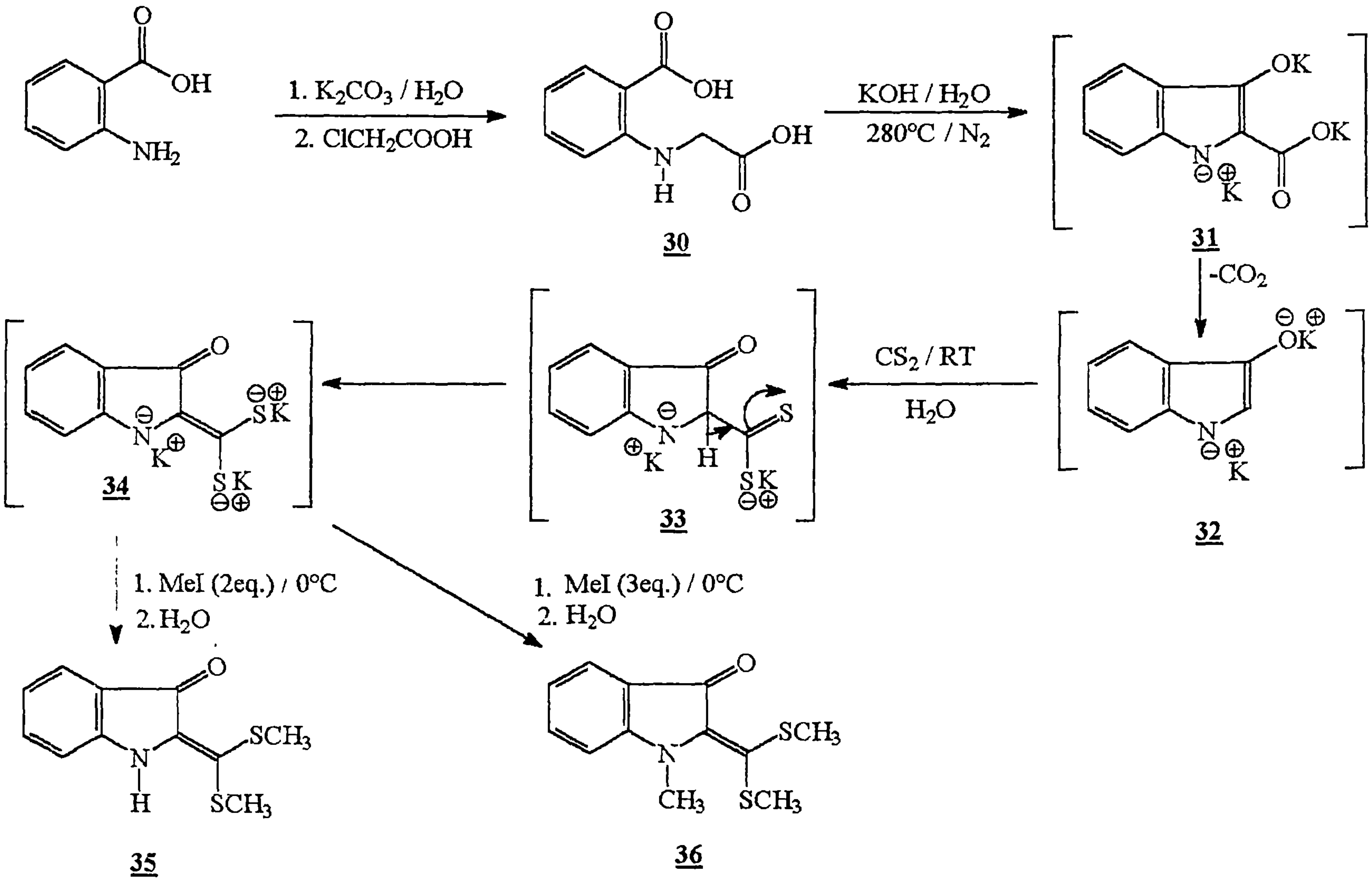


20

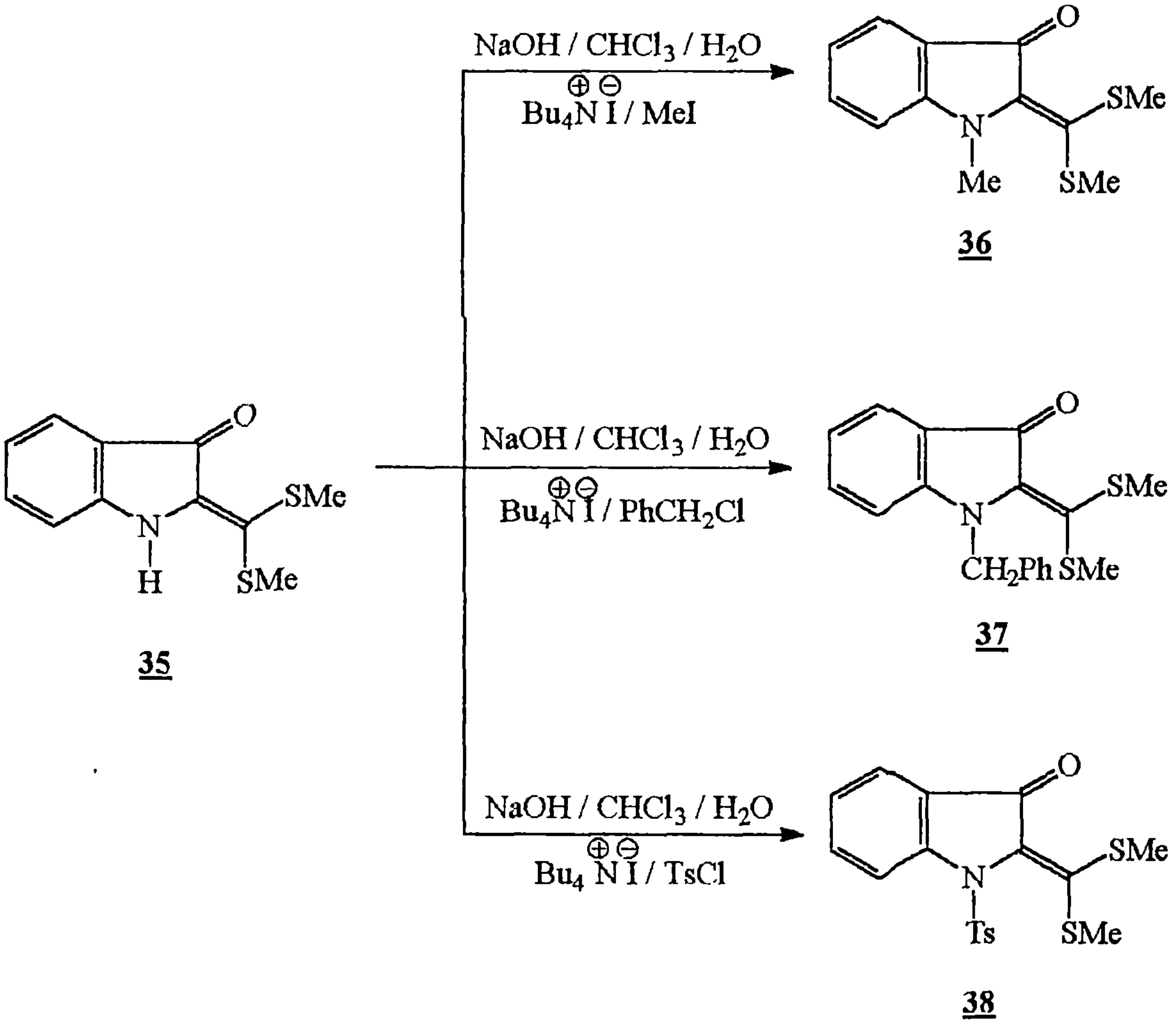
Entry	Product	Ar	% Yield
1.	20a		47
2.	20b		56
3.	20c		59
4.	20d		51
5.	20e		49


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


NaOH / CHCl3 / H2O
Bu4N⊕ I⊖ / MeI
NaOH / CHCl3 / H2O
Bu4N⊕ I⊖ / PhCH2Cl
NaOH / CHCl3 / H2O
Bu4 N⊕ I⊖ / TsCl
O
SMe
SMe
N
H
Me
CH2Ph
Ts
35
36
37
38

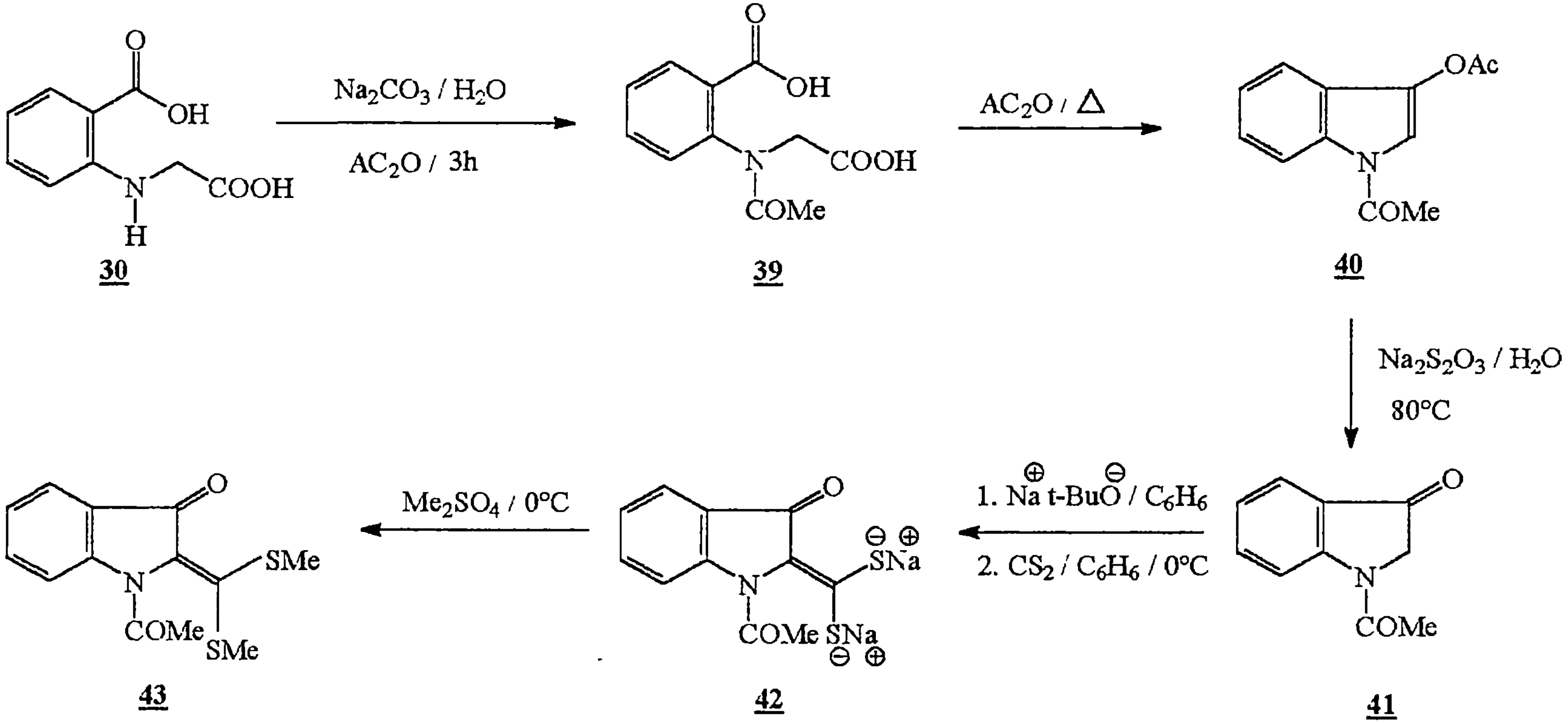
Scheme 14

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)

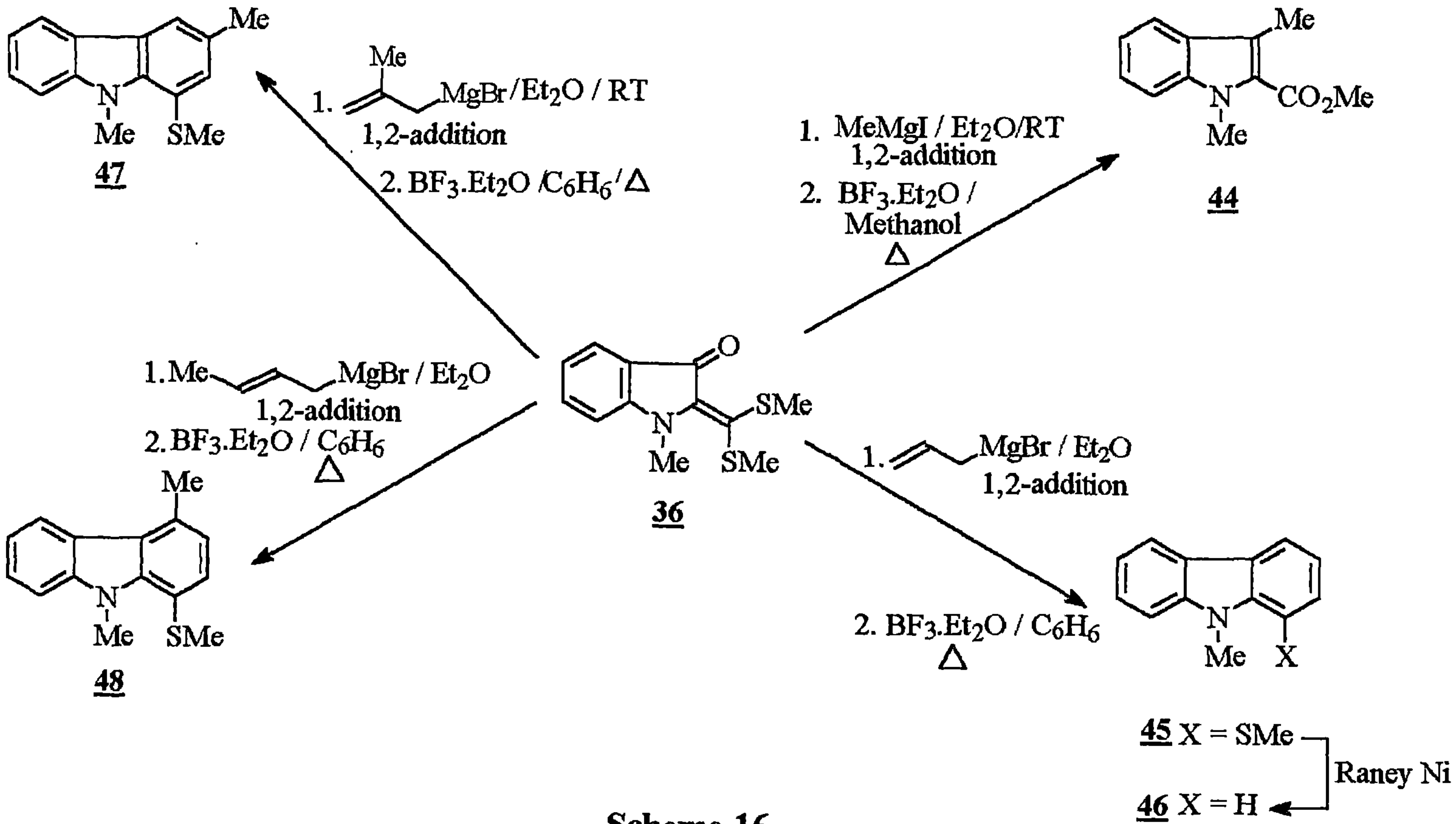
CHAPTER III

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.

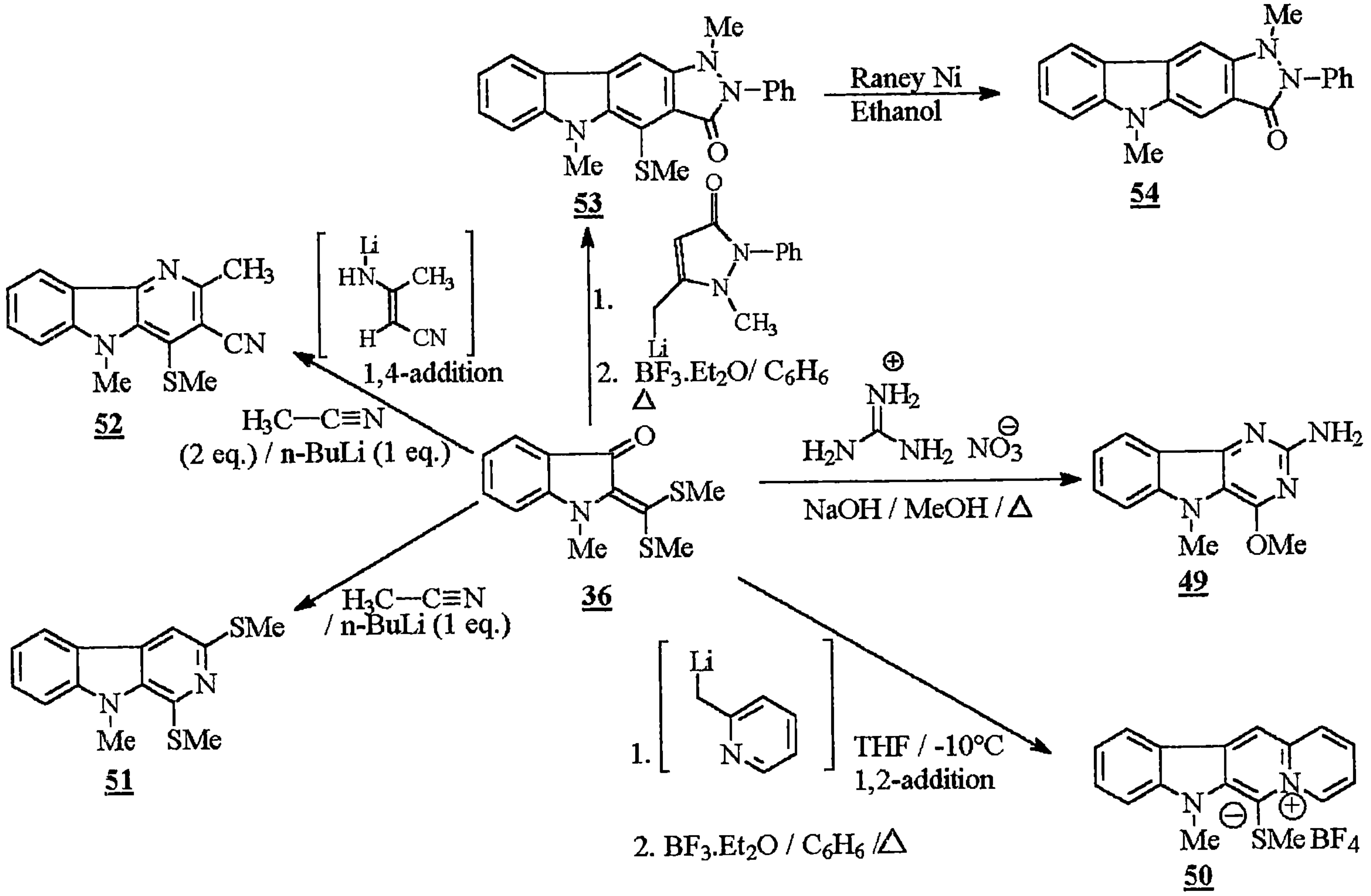
In this particular study we desired to make 1-substituted -2-bis(methylthio)methylene-3-oxoindole **24** from the corresponding indoxyl **23**. The master key intermediate would serve as a potential precursor for hetero[b], benzo[b] and naphtho[b] annulations of indole to yield structurally diversified 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**.


30
Na$_2$CO$_3$ / H$_2$O
AC$_2$O / 3h
39
AC$_2$O / Δ
40
Na$_2$S$_2$O$_3$ / H$_2$O
80°C
41
1. Na$^{\oplus}$ t-BuO$^{\ominus}$ / C$_6$H$_6$
2. CS$_2$ / C$_6$H$_6$ / 0°C
42
Me$_2$SO$_4$ / 0°C
43

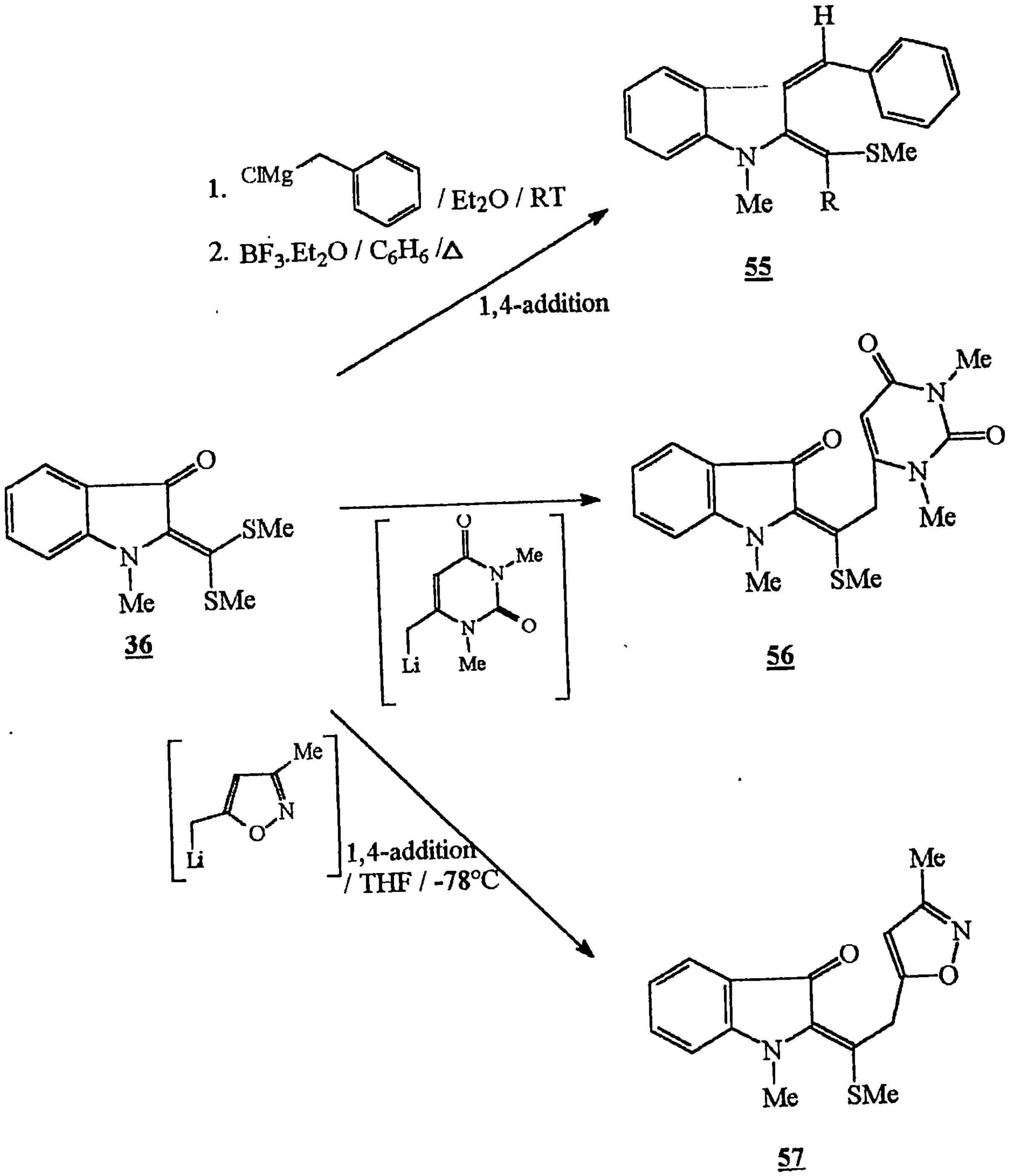
Scheme 15


Me
Me SMe
47
Me
1. MgBr/Et$_2$O / RT
1,2-addition
2. BF$_3$.Et$_2$O /C$_6$H$_6$/Δ
1. MeMgI / Et$_2$O/RT
1,2-addition
2. BF$_3$.Et$_2$O /
Methanol
Δ
Me
CO$_2$Me
Me
44
1.Me MgBr / Et$_2$O
1,2-addition
2. BF$_3$.Et$_2$O / C$_6$H$_6$
Δ
O
SMe
Me SMe
36
1. MgBr / Et$_2$O
1,2-addition
2. BF$_3$.Et$_2$O / C$_6$H$_6$
Δ
Me
Me SMe
48
Me X
45 X = SMe
Raney Ni
46 X = H

Scheme 16


53
Raney Ni
Ethanol
54
52
1,4-addition
H3C—C≡N
(2 eq.) / n-BuLi (1 eq.)
1.
2. BF3.Et2O/ C6H6
Δ
NaOH / MeOH / Δ
49
36
H3C—C≡N
/ n-BuLi (1 eq.)
51
1.
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
H
N
Me
SMe
R
55
O
SMe
N
Me
SMe
36
O
N
Me
O
Li
N
Me
O
O
Me
N
O
N
Me
O
N
Me
SMe
56
Me
N
O
Li
1,4-addition / THF / -78°C
Me
N
O
O
N
Me
SMe
57

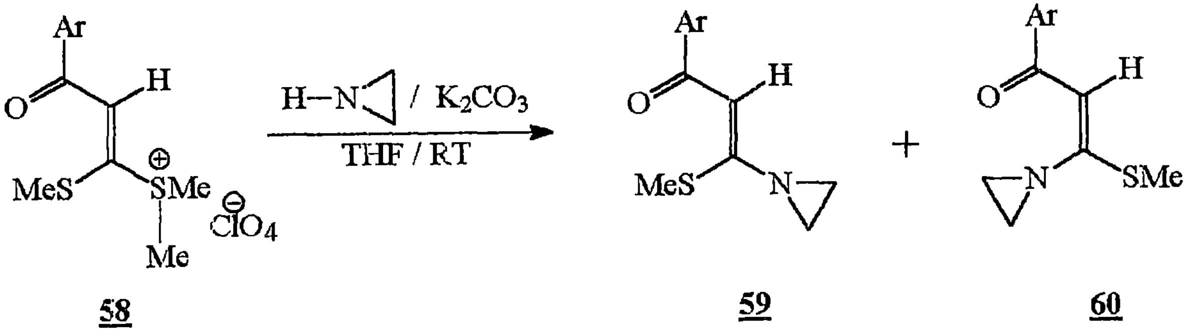
Scheme18

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.

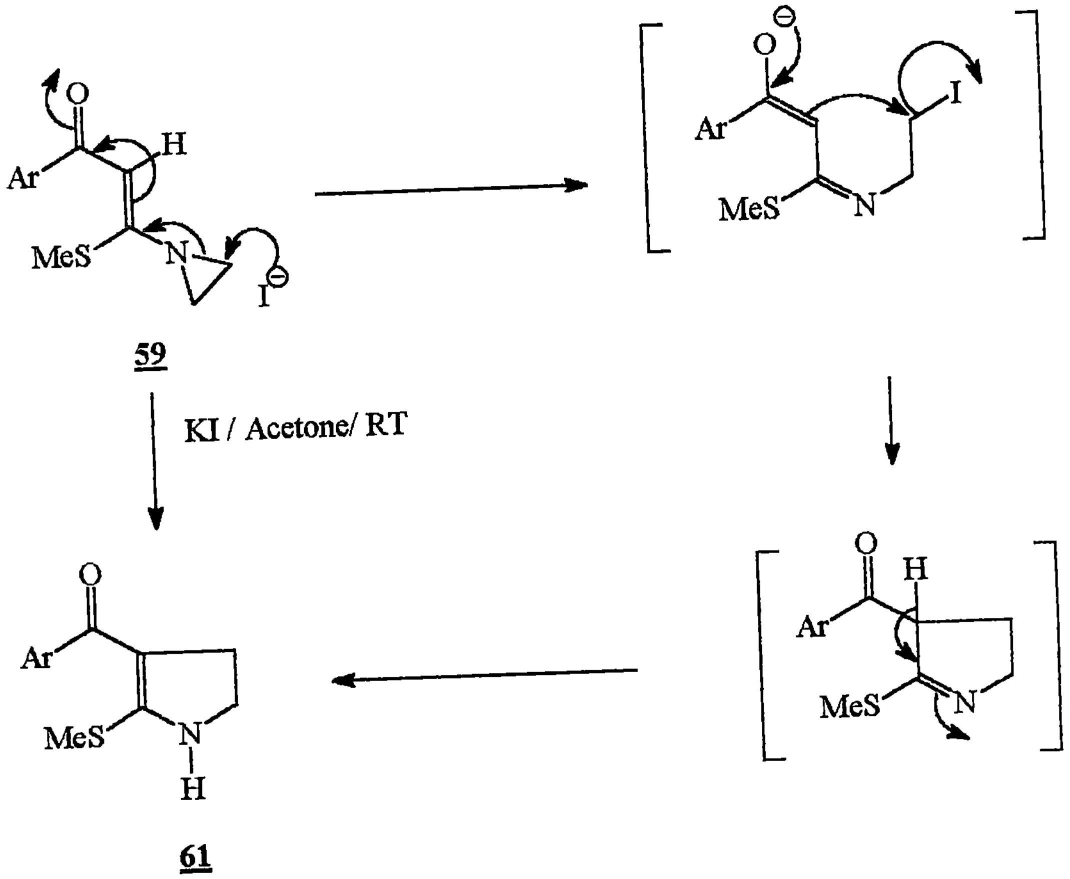
CHAPTER IV

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.



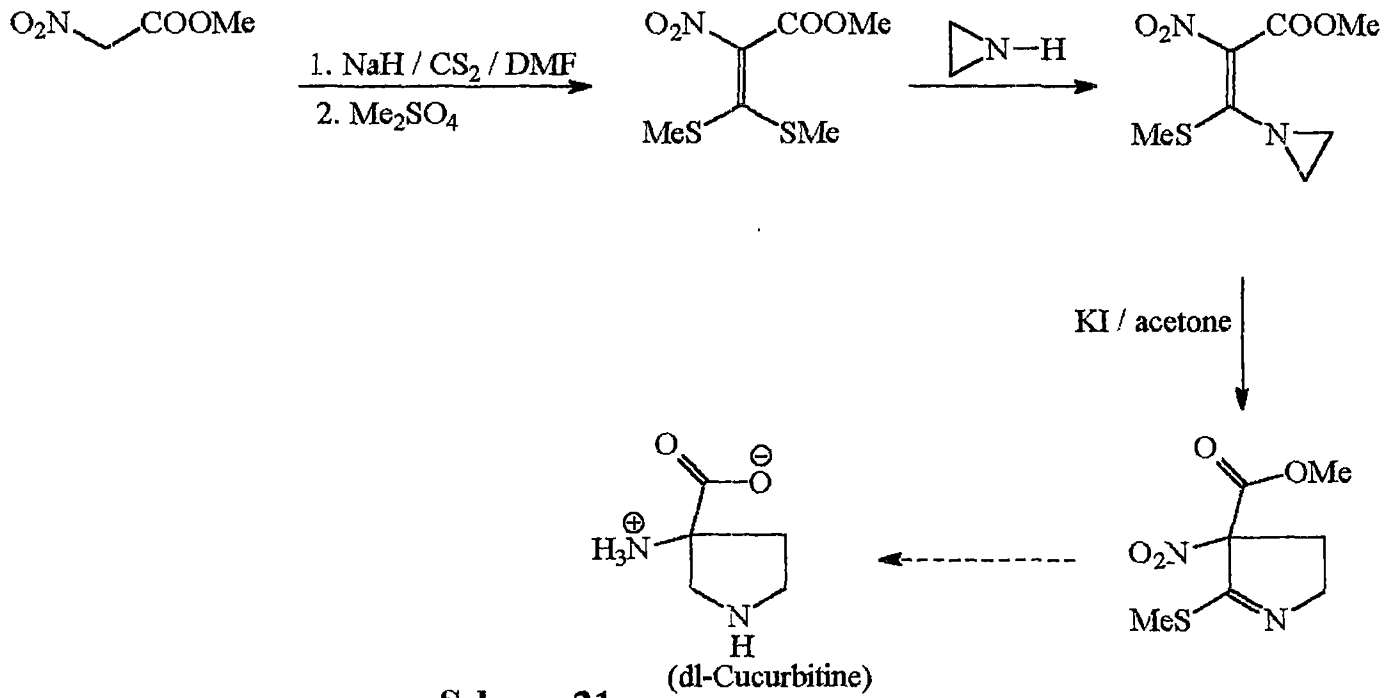
58,59,60 **a**, Ar = C_6H_5
b, Ar = 4-$MeOC_6H_4$
c, Ar = 4-ClC_6H_4

Scheme 19



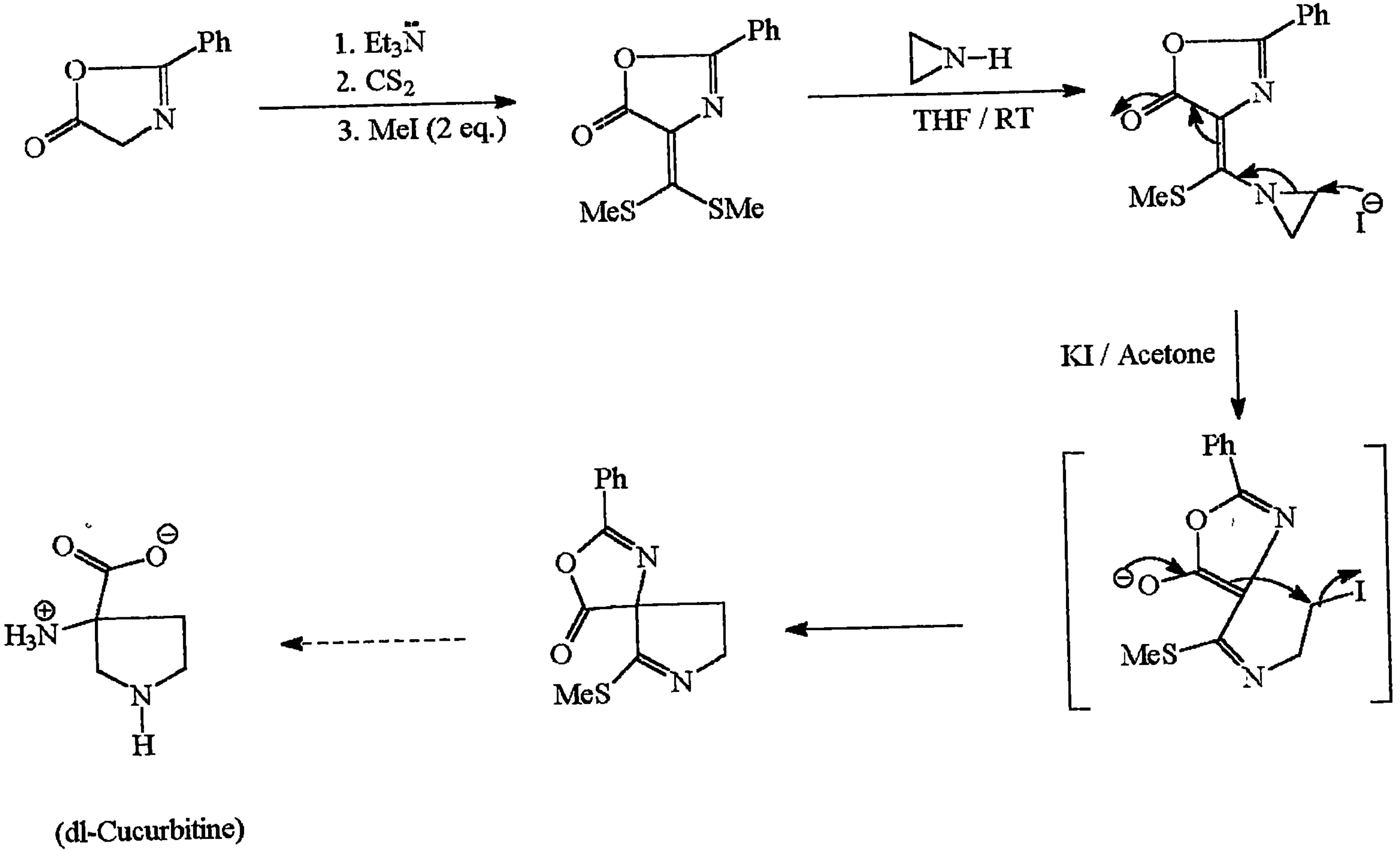
59, **61** **a** Ar = C_6H_5
b Ar = 4-$MeOC_6H_4$
c Ar = 4-ClC_6H_4

Scheme 20



O_2N
COOMe
1. NaH / CS_2 / DMF
2. Me_2SO_4
O_2N
COOMe
MeS
SMe
N—H
O_2N
COOMe
MeS
N
KI / acetone
O
OMe
O_2N
MeS
N
O
O
H_3N
N
H
(dl-Cucurbitine)

Scheme 21


1. Et$_3$N
2. CS$_2$
3. MeI (2 eq.)
N–H
THF / RT
KI / Acetone
Ph
MeS
SMe
(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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NEW SYNTHETIC STRATEGIES FOR HETEROCYCLES OF BIOLOGICAL INTEREST

BY

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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
INDIA
1997

DEDICATED

TO

OUR BELOVED

Late Dr. NANDAMURI TARAKA RAMARAO
(NTR)

(Even though he is no more with us,
he is highly revered and remembered
deeply in our hearts.)

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Certificate

I hereby certify that the entire work embodied in this thesis has been carried out by Mr.M.V. Basaveswara Rao under my guidance in the Department of Chemistry, North-Eastern Hill University, Shillong, and it has not been submitted elsewhere for any degree or diploma.

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	Title	Course No.	Grade
1.	French Language	SPS 601	A
2.	Numerical Methods with applications to Computers	SPS 629	A
3.	Organometallic Chemistry	CHEM 620	A
4.	Spectroscopic Methods in Chemistry	CHEM 622	A

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(Mandava V. Basaveswara Rao)

PREFACE

Drug resistance developed by various cancer cells has prompted the opening of new avenues for successful therapies for cancer. One way of inhibiting proliferation of cancer cells is to arrest the gene replication at transcription as well as transitional levels. Having studied various models of anti cancer activity of many compounds with the emphasis on DNA intercalation / binding, rupture as the basic activity, molecules with three or more fused rings incorporating the indole moiety became synthetic targets here as part of our on going research programme to develop the new heterocycles of biological interest.

This thesis consists of four chapters.

Chapter I comprises of four sections. First section reviews briefly some of the annulated indoles as potential heterocycles. A brief review on some of the recent transformations of α-oxoketene dithioacetals is presented in the second section. Third section describes vinylaziridine as versatile building block for organic synthesis. Fourth section is slated for a brief outline of the present investigation, which is reported in the following chapters.

The second chapter contains two parts. Part A deals with the synthesis of carbazole derivatives involving *in situ* generated indole-2,3-dienolate as diene to react with various dienophiles. Reaction of another indolo-2,3-quinodimethane intermediate generated *in situ* with various dienophiles to afford substituted carbazoles is also reported in this part. Part B highlights the successful exploitation of indole-2,3-dienolate to react with various aromatic nitriles, for the synthesis of γ-carboline derivatives.

Benzo- and hetero [b] annulations of indole has been accomplished *via* hitherto unreported 1-N-methyl-2-bis(methylthio)methylene-3-oxoindole, exploiting aromatic and hetero aromatic annulation approachs. Results of these studies are presented in the chapter III.

The fourth chapter of this thesis deals with the synthesis of vinylaziridines and its rearrangements . An attempt has been made to extend this method for the synthesis of dl-cucurbitine.

Each chapter is framed with an introduction, followed by results and discussion, conclusion and experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The references of the published work of the present investigation are cited in the respective chapters.

CONTENTS

CHAPTER I

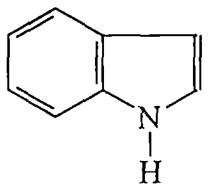
New Synthetic Strategies for Heterocycles of Biological Interest

I.1. General Introduction :

The paramount importance of heterocycles in natural product chemistry and pharmacology constantly drives the search for new methods for their construction. Heterocyclic units such as indole, carbazole, carboline and their condensed analogues are of special significance in pharmacology, due to their important biological properties. The present investigation deals mainly with synthetic strategies, involving indole [b] annulation for the substituted carbazoles, carbolines and their condensed analogues. Chapter IV, deals with the synthesis of vinylaziridines and its synthetic transformations.

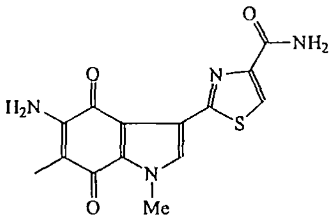
For convenience, this chapter is divided into four sections. In the first section a brief survey on annulated indoles as potential heterocycles is described. The second section describes a brief survey of polarized ketene dithioacetals. In the third section aziridino N,S-acetals (vinylaziridines) and their synthetic transformations are described. Brief outline of the present investigation, reported in the following chapters, is described in the fourth section.

I.2. Section 1. Annulated indoles : Potential heterocycles



1

Indole 1, an important heterocyclic unit has special attention in the organic synthesis[1], due to the fact that many of its derivatives possess a variety of pharmacological properties. The potent topoisomerase II inhibitor BE 109882 2 and the phytoalexins, camalexin 3a and 6-methoxycamalexin 3b, isolated from *Camelina sativa* display appreciable antifungal activity[3] , plays an important role in the indole chemistry.



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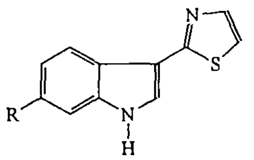
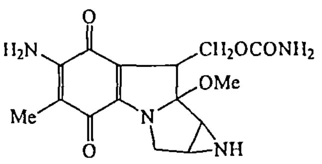


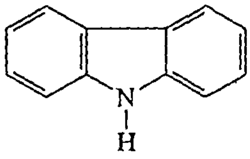
3a, R = H
3b, R = OMe



4

Mitomycin C 4 is an antitumor agent and it inhibits DNA synthesis[4-7]. It has indoloquinone ring system. Its binding to DNA leads to reductive activation of it and alkylation of DNA. It is believed to undergo *in vivo* reduction to hydraquinone from studies on compounds structurally related to Mitomycin C, but lacking the aziridine ring indicated that the presence of aziridine is not essential for its activity.

CC-1065, isolated from streptamyces zelesis, is highly cytotoxic[8]. It binds in a non-intercalative fashion to the minor groove of double-stranded DNA A-T rich region and the cyclopropane ring gets opened up by N-3 of Adenine, in a 1,6-fashion[9,10].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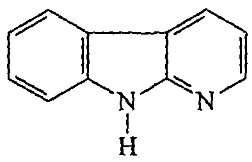
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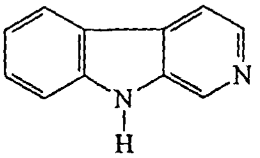
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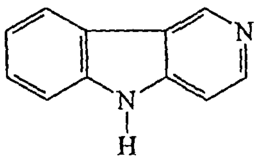
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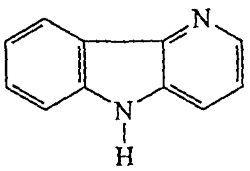
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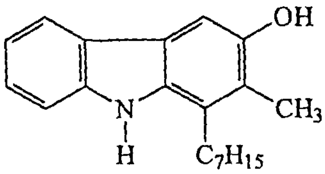
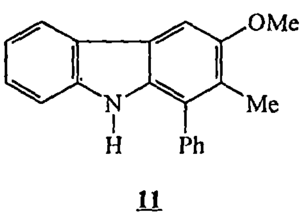

10

Annulated indoles such as carbazole **5**, α-carboline **6**, β-carboline **7**, γ-carboline **8**, δ-carboline **9** and their condensed analogues, have become very important, since most of their derivatives obtained from nature as well as synthetic ones show variety of useful pharmacological properties.

Synthetic approaches to substituted carbazoles and their condensed analogues are of special interest and contemporary importance[11] since the growing variety of carbazole alkaloids isolated show antimicrobial[12], antiviral[13], and cytotoxic[14] properties.

Carazostatin **10** exhibits a strong inhibitory activity against free radical induced lipid peroxidation and, in liposomal membranes it shows a stronger antioxidant activity[15,16]. Carbazoles with an oxygen substituent at the 3-position constitute the frame work of large number of a carbazole alkaloids, like hyellazole **11**, isolated from blue-green algae *Hyella caespitosa*[17], carbazomycins **12**, produced by *Streptoverticillum ehimense*[18] possesses antibiotic activity.



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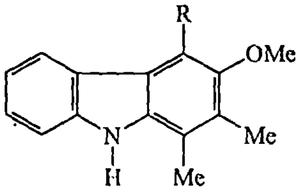

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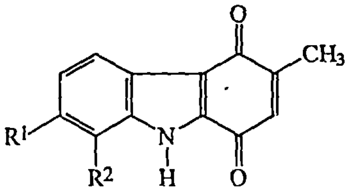
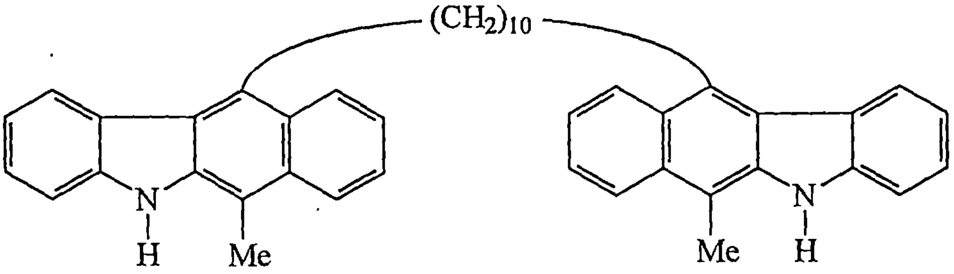


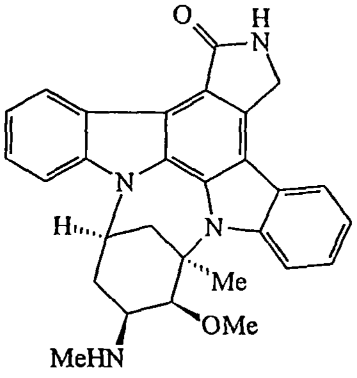
13

Carbazolequinones **13** obtained from the root stem barks of *Murraya euchrestifolia hayata*[19], are having important biological properties[20].



14

It has been discovered that bifunctional intercalators of a specific design can exhibit extraordinary binding affinities and functional sequence specificities for DNA. 1,10-bis (6-methyl-5H-benzo [b] carbazol-11-yl)decane **14** , which is a potential bifunctional nucleic acid intercalating agent and was synthesised by Gribble and co-workers[21].



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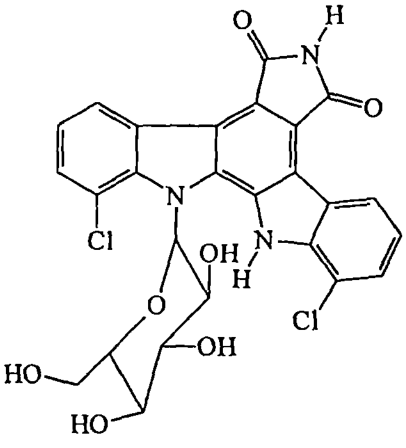
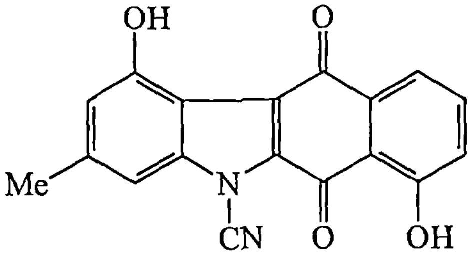


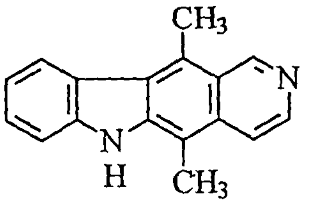
16

The indolocarbazole alkaloids, staurosporine **15** and rebeccamycin[23] **16** are antitumor antibiotics. Rebeccamycin was isolated from fermentations of *Nocardia aerocoligenes* stain C 38383-RK-2. Prekinamycin[24] **17** belonging to the kinamycin group of antibiotic has a benzcarbazoloquinone skeletons with oxygenated A and D rings.



17

Pyrido carbazoles play very important role in carbazole chemistry and has been reviewed[25,26]. The plant alkaloids ellipticine **18**, olivacine **19**, and 2-methyl-9-hydroxy ellipticinium acetate (elliptinium) **20** are antitumor agents and elliptinium is used clinically



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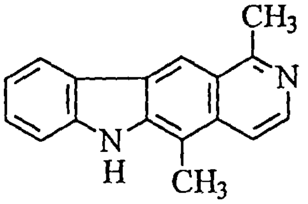
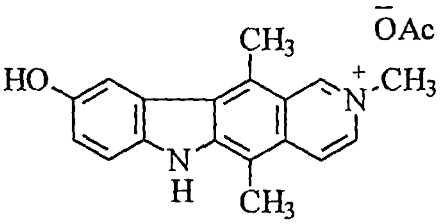


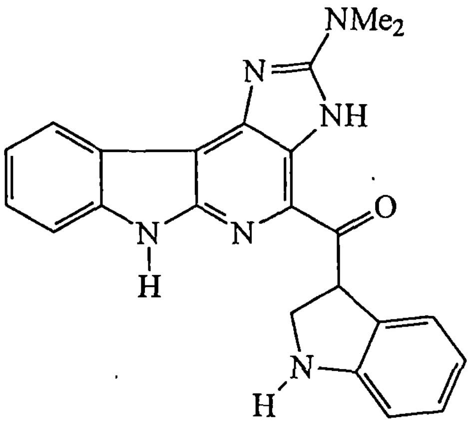
19

as a drug to treat advanced breast cancer, myeloblastic leukemia and some solid tumors[27,28].



20

α-Carboline derivatives such as grossularine-1 **21** and grossularine-2 **22**, isolated from tunicate (*Dendrodoa grossularia*), are cytotoxic[29] indole alkaloids active against L 1210 leukemia cells. They have a cyclic guanidine moiety in the form of 2-dimethylamino imidazole sub unit[30]. **22** acts on adenine dinucleotide as a mono-intercalating agent and it is also active against human tumor cell lines[31].



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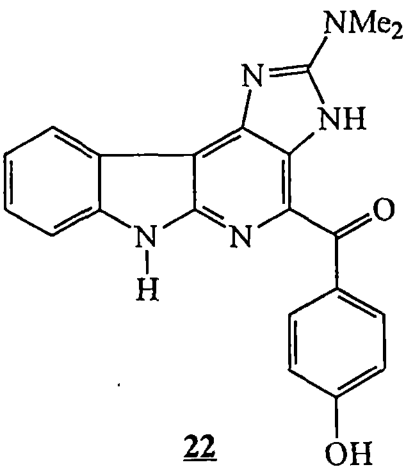
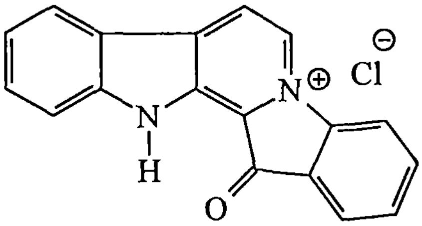


22

Fascaplysin **23**, an antimicrobial and cytotoxic red pigment, is isolated from the marine sponge *Fascaplysinopsis sp.* It inhibits the growth of several microbes and is active against L 12120 mouse leukemia system *in vitro*[32,33].



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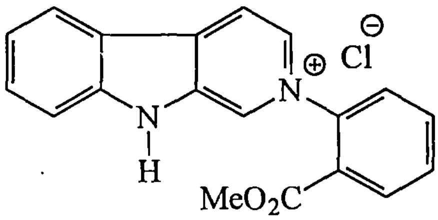
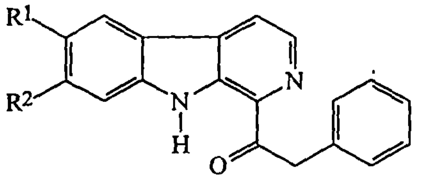


24

Reticulatine **24**, isolated from *Fascaplysinopsis reticulata*, has a similar β-carboline structure except, the carbonyl carbon is not attached to the C-1 position of the β-carboline ring. It is also an antimicrobial agent[34]. Eudistomines **25** are isolated from *Bermudian tunicate, eudistoma olivaceum*[35], and some of their derivatives show antimicrobial and antiviral activity[36]. Canthine-6-one alkaloids **26**, isolated from *Ailanthus altissima, Brucea antidysenteria and Soulamea pancheri,* possess significant cytotoxic and antileukemic activity. Oxidation of canthine-6-one skeleton at positions C-1 and C-11 greatly enhances the cytotoxic and antileukemic activity of these alkaloids[37].



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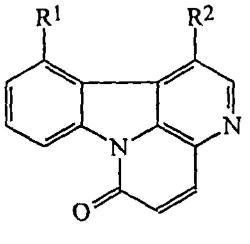

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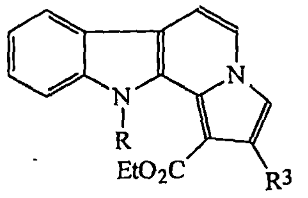
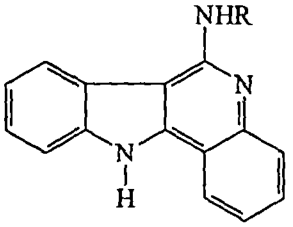


27

Several β-carboline congeners, in which a six membered aromatic ring is fused to the 1,2-position (eg. semiperverin) are known to display anticancer activity. The tetracyclic β-carboline **27** in which a five membered ring is fused to the 1,2-position of β-carboline have been synthesised by potier[38] and co-workers.



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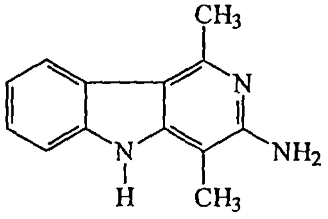

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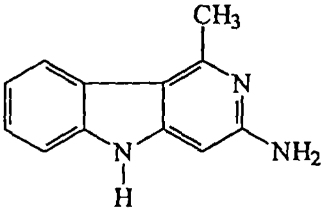
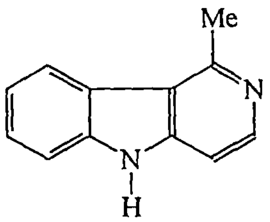


30

γ-carboline derivatives such as 5-alkylamino-[11H]-Indolo [3,2-c] quinoline **28** inhibit DNA polymerase[39]. Also 3-amino-1,4-dimethyl-[5H]-pyrido [4-3-b] indole **29**, 3-amino-1-methyl-5H-pyrido [4,3-b] indole[40] **30** and 1-methyl-[5H]-pyrido [4,3-b] indole[41] **31** mebhydroline **32** are proven to be important, pharmacologically.



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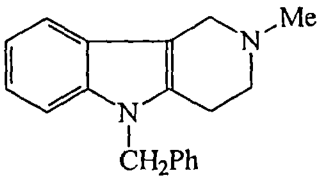

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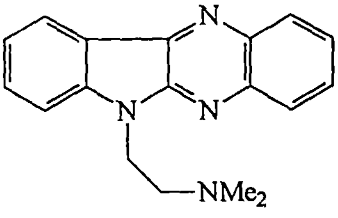
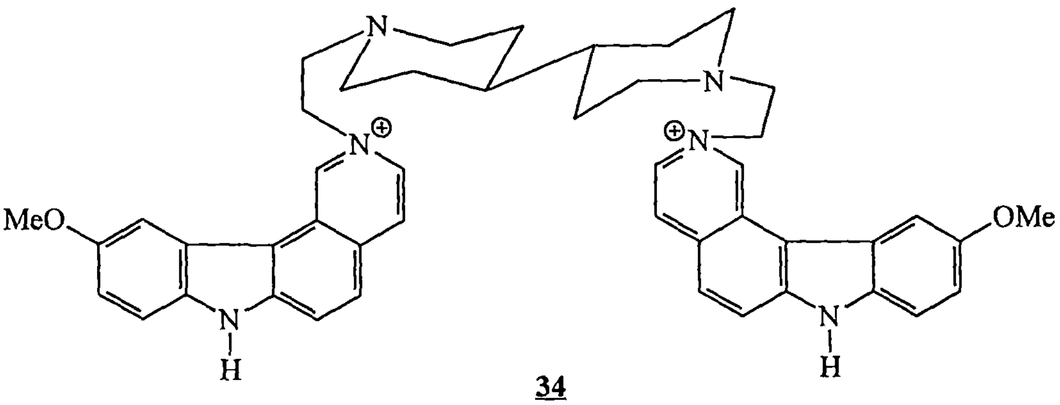


33

6-(2-Dimethylaminoethyl)-6H-indo [2,3-b] quinoxaline 33 binds selectively to DNA and some derivatives like B 220, show interesting antiviral activity including high activity against CMV virus[42].



34

Ditercalinium 34 is an antitumor agent. Nuclear magnetic resonance studies show that, it bisintercalates with its liking group lying in the groove, the flat aromatic part sandwiching two base pairs. It shows delayed toxicity towards cells *in vitro* and may interfere with mitochondrial activity. The activity is dependent on the rigidity of the bis (ethylpiperidinyl) linking chains[43].

Drug resistance developed by various cancer cells has prompted the opening of new avenues for successful therapies for cancer. One way of inhibiting proliferation of cancer cells is to arrest the gene replication at transcriptional as well as translational levels. Having portrayed various models of anti cancer activity of many compounds with the emphasis on DNA intercalation / binding, rupture as the basic activity, a brief account of planar molecules with three or more fused rings incorporating the indole moiety is pertinent here as the present investigation deals with the synthesis of compounds of such types.

Major methods for the preparation of carbazoles include the following
I) dehydrogenation of 1,2,3,4-tetrahydrocarbazoles which are usually prepared by fischer indole synthesis[44], ii) reductive cyclizations of 2-nitrobiphenyls[45], iii) thermal[46], photolytic[47], and palladium-promoted[48] cyclizations of diphenyl amines, iv) iron-mediated oxidative coupling of 1,3-cyclohexadiene and aryl amine[49] and v). [b] annulations of indole skeletons [50-57].

Many methods of types i to iv are problematic, for the synthesis of highly substituted carbazoles involving multistep preparations of appropriate precursors, harsh reaction conditions or poor regioselectivity of the cyclization step. Acordingly, approaches *via* the [b] annulation of indole skeletons are of special importance. The most important methods that fall into this category include (a) thermal-induced and photoinduced electrocyclizations of 2,3-divinylindoles[57], (b) 1,4-additions of indolo-2,3-quinodimethanes[50,54] and of vinylindoles[56] with dienophiles and (c) addition of α-carbanions at C-2 of indoles with michael acceptors, followed by intramolecular cyclization with the ester group at the indole 3-position [51,55].

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.

Brief review on o-quinodimethane intermediates as building blocks for the synthesis of carbazole derivatives is described in the introduction of, PART A, in Chapter II, and for the synthesis of carbolines is described in the introduction of PART B, in Chapter II. 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.

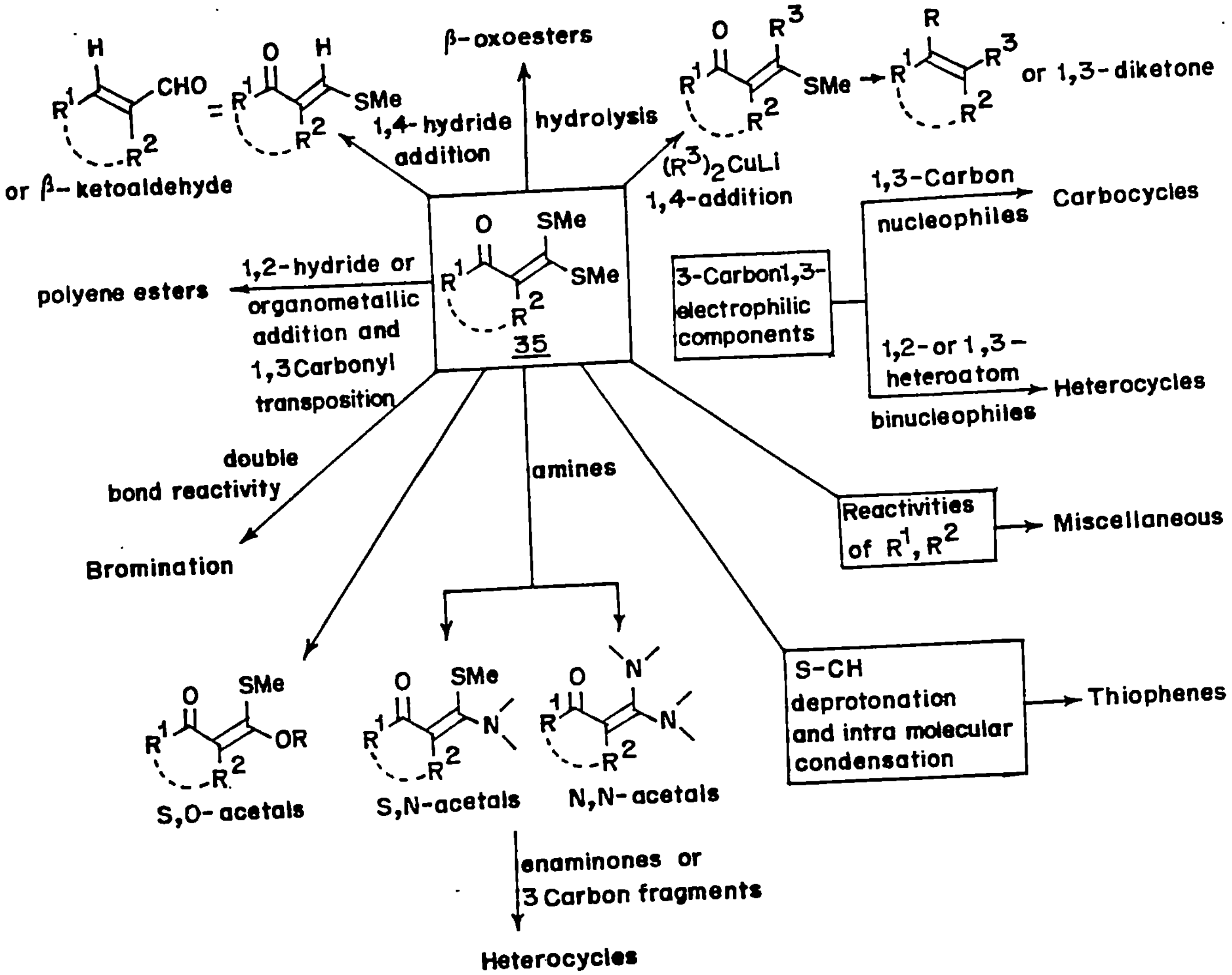
I.3. Section 2. Polarized Ketene Dithioacetals : A Brief Review

The polarized ketene dithioacetals have been recognized as potential building blocks in organic synthesis. The chemistry of these compounds has increased enormously in the recent years and two reviews[58] have already appeared covering the major developments in the area. These class of compounds can be conveniently prepared[59-67] by reacting any active methylene compound with carbon disulphide in the presence of a suitable base followed by alkylation.

The first synthesis of α-oxoketene dithioacetals was reported by Kelber and co-workers in 1910[68-70]. However, the chemistry of these intermediates remained unexplored, until Thuillier and co-workers prepared these compounds in high yields in one pot reaction by reacting the active methylene ketones with carbon disulphide in the presence of sodium amylate followed by alkylation[59-62]. Subsequently, several modifications in the reaction conditions have been made for obtaining higher yields of α-oxoketene dithioacetals[63-67]. These compounds possess well defined physical properties and can be purified by any of the conventional purification methods. They are stable at room temperature and can withstand mild acidic and alkaline conditions. On the other hand, the corresponding O,O-acetals are moisture sensitive and are susceptible for hydrolysis.

The oxoketene dithioacetals can be visualized as masked β-ketoesters in which the ester functionality is manifested as a ketene dithioacetal moiety. Alternatively, they may be considered as α,β-unsaturated ketones containing a highly functionalized β-carbon. The α-oxoketene dithioacetals have been shown to be excellent three carbon fragments possessiing 1,3-electrophilic centres with differing electrophilic properties. Taking advantage of this difference, they have been exploited to construct stereo- and regioselective bonds in various transformations. Also, oxoketene dithioacetals are primary precursors for the corresponding O,S-, N,S- and N,N-acetals. The preparatioan of O,S-acetals is accomplished through the displacement by oxygen nucleophiles of the sulfonium salts[71]. The N,S-acetals can be prepared by the displacement of one of the thiomethyl groups by a suitable amine in refluxing ethanol[72-73]. Alternatively, they can be prepared directly from active methylene ketones by reacting their enolate anions with alkyl and arylisothiocyanates followed by alkylation[74]. The oxoketene N,N-acetals can be prepared in high yields by displacing both the thiomethyl groups by amines in refluxing acetic acid[73-75]. The oxoketene S,S-, N,S- and N,N-acetals have been extensively utilized in this laboratory for the synthesis of both heterocyclic and carbocyclic compounds, while the chemistry of O,S-acetals remains unexplored.

Various reactivity profiles of α-oxoketene dithioacetals of general formula **35** are outlined in scheme 1. Hydrides and organometallic reagents give 1,2-addition products characteristic of carbonyl function reactivity[69]. These additions can be directed in a 1,4-manner by suitably manipulating the reagent and reaction conditions[76-78]. Further transformations, after the initial 1,2- or 1,4-additions are

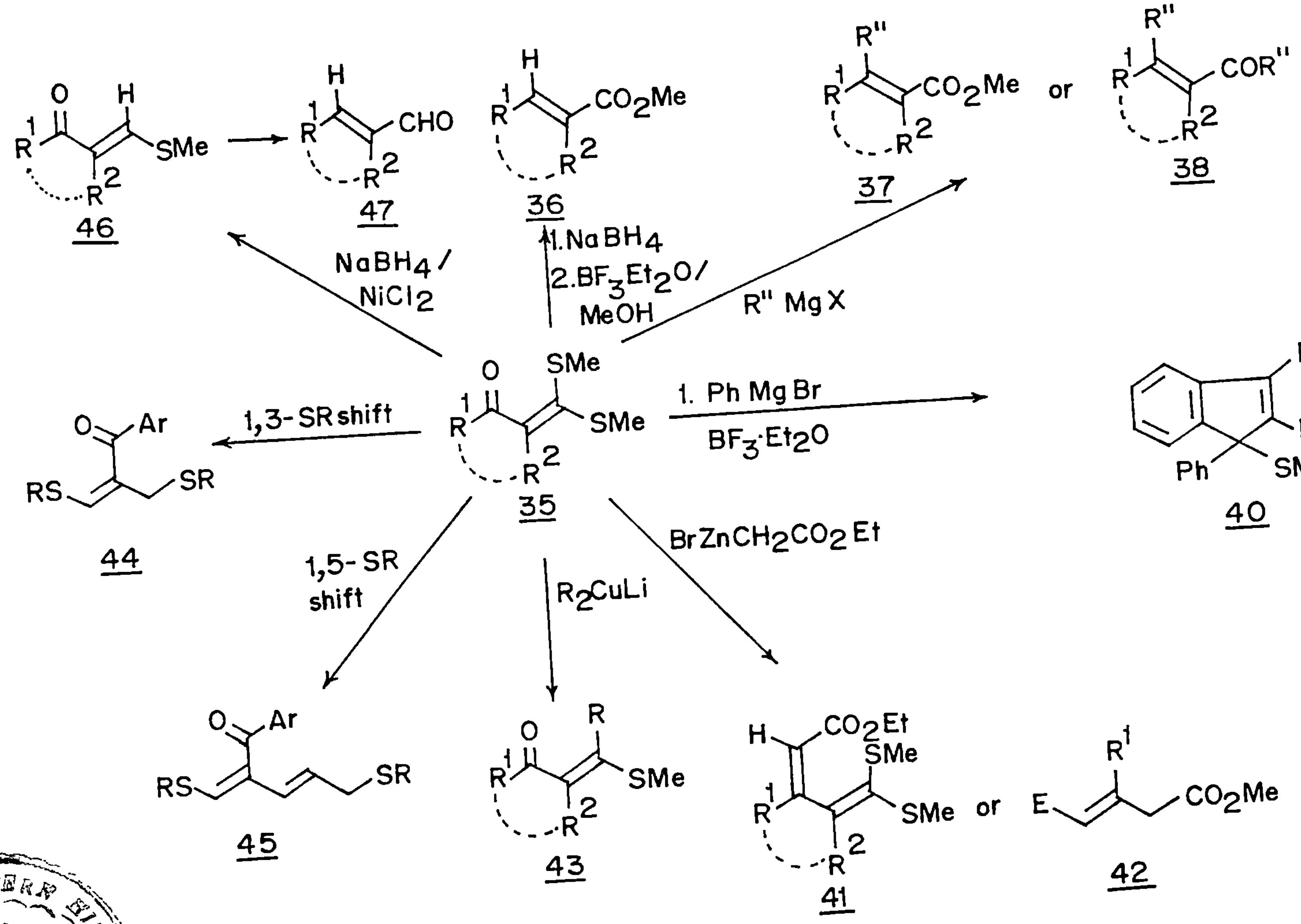

β-oxoesters
hydrolysis
1,4-hydride addition
or β-ketoaldehyde
CHO
SMe
(R^3)$_2$CuLi 1,4-addition
or 1,3-diketone
1,3-Carbon nucleophiles
Carbocycles
3-Carbon1,3-electrophilic components
1,2-or 1,3-heteroatom binucleophiles
Heterocycles
polyene esters
1,2-hydride or organometallic addition and 1,3Carbonyl transposition
35
double bond reactivity
Bromination
amines
Reactivities of R^1, R^2
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

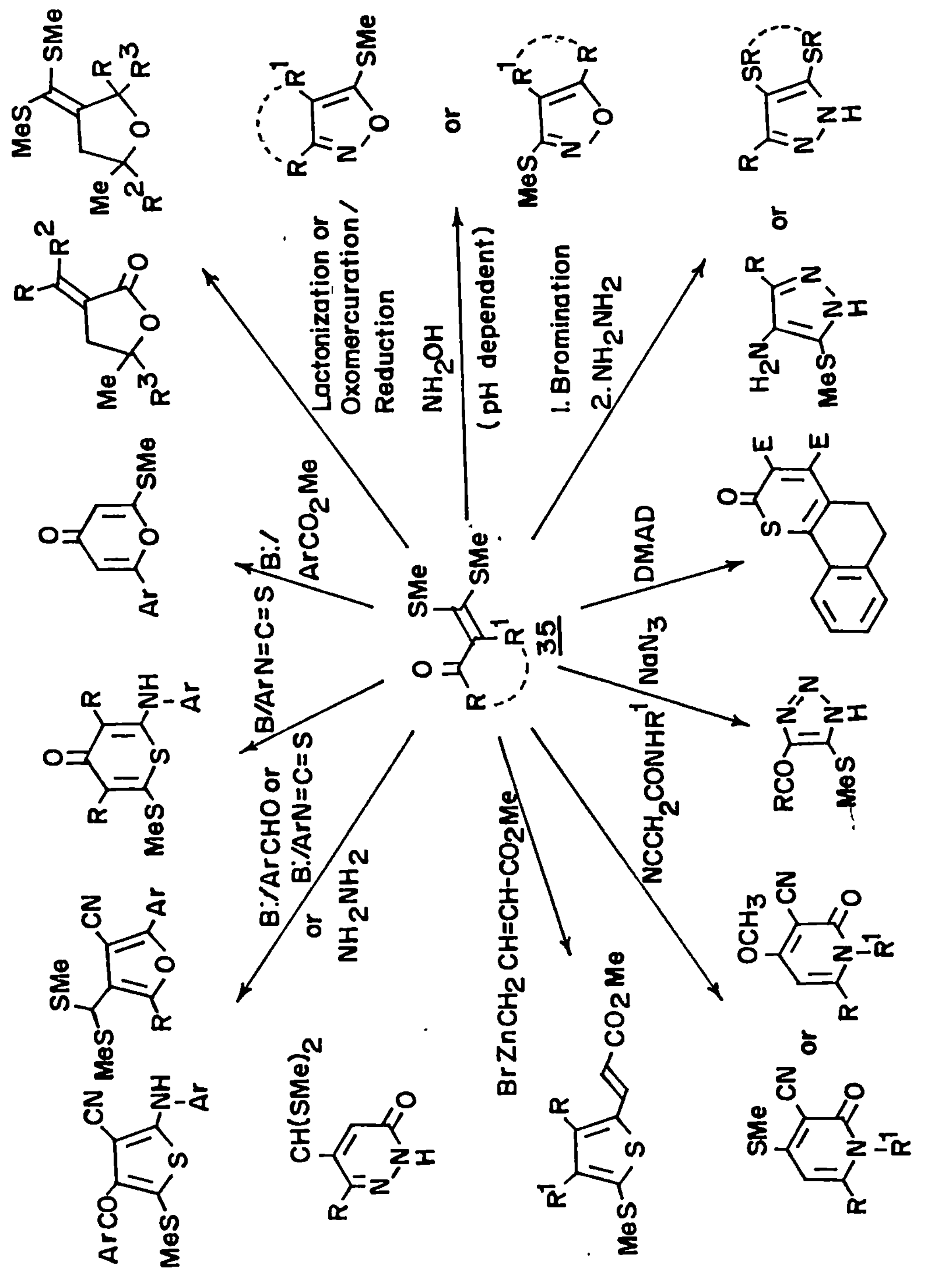
also reported[76]. The α-oxoketene dithioacetals possess typical 1,3-electrophilic centres. These intermediates react with 1,2-and 1,3-heteroatom binucleophiles to give 5- and 6-membered heterocyclic compounds, while 1,3-carbon nucleophiles give carbocyclic compounds. The enolate ion formed by the deprotonation (when R^1=alkyl) can undergo condensation with aldehydes to give α-enoyl ketene dithioacetals[59,79]. An allylic anion formation has been reported when R^2 is a methyl group, leading to rearranged products[80]. Also, deprotonation of the thiomethyl group followed by intramolecular aldol type condensation to thiophene is also reported[81,82]. The reactivity of the mercapto double bond is also exploited in reactions with electrophiles. Thus oxoketene dithioacetals **35** (R^2=H) undergo bromination at α-position with N-bromosuccinimide[83]. It is apparent that the oxoketene dithioacetals of general formula **35** constitute an important class of synthons with reactive electrophilic and nucleophilic centres distributed in various centres of its skeleton permitting reactions, which are of great synthetic importance. Some of the selected transformations reported from this laboratory are briefly described in the following section.

The carbonyl group of α-oxoketene dithioacetals has been reported to undergo reduction with sodium borohydride to give the corresponding carbinol acetals[84-85]. These carbinol acetals were shown to undergo smooth methanolysis in the presence of borontrifluoride etherate to afford α,β-unsaturated methyl esters[85] **36** in high yields. The overall transformation is considered as homologation of active methylene ketones involving 1,3-carbonyl transposition.

The grignard and organolithium reagents undergo either regioselective 1,2-addition to afford the α-hydroxy ketene dithioacetals or a sequential 1,4- and 1,2-additions to afford the β-hydroxyvinylsulfides[76-78]. The borontrifluoride etheraate catalysed solvolysis or the hydrolysis of these carbinols yield either β-substituted


NaBH4/ NiCl2
1.NaBH4 2.BF3Et2O/ MeOH
R'' MgX
1. Ph MgBr BF3·Et2O
1,3-SR shift
BrZnCH2CO2Et
1,5-SR shift
R2CuLi
35
36
37
38
40
41
42
43
44
45
46
47
or

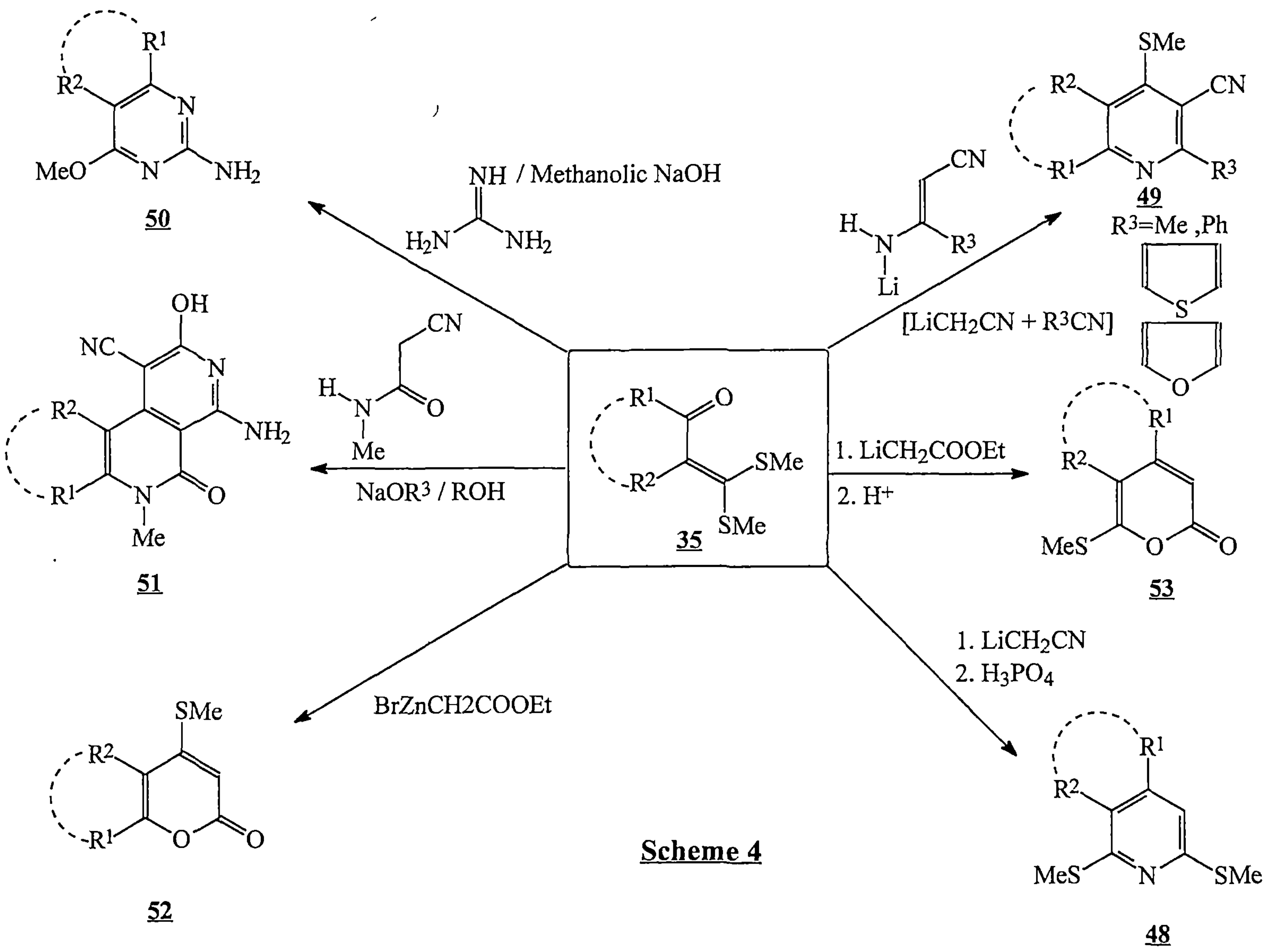
Scheme-2


35
Lactonization or
Oxomercuration /
Reduction
NH$_2$OH
(pH dependent)
or
1. Bromination
2. NH$_2$NH$_2$
or
DMAD
NaN$_3$
NCCH$_2$CONHR^1
or
BrZnCH$_2$CH=CH-CO$_2$Me
B:/ArCHO or
B:/ArN=C=S
or
NH$_2$NH$_2$
B/ArN=C=S
B:/
ArCO$_2$Me

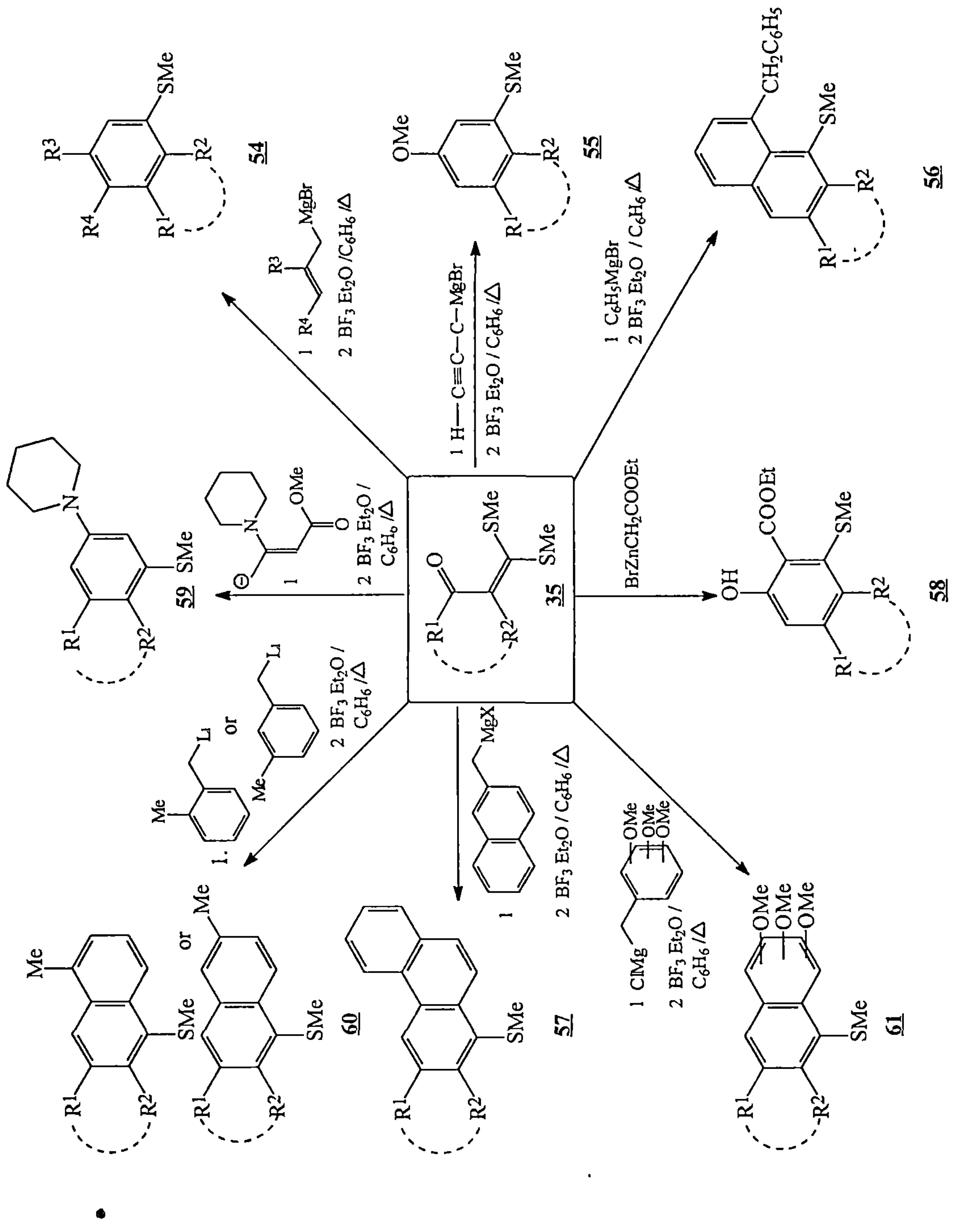
Scheme-3

α,β-unsaturated esters **37** or the corresponding ketone **38** (Scheme 2) in good yields[76]. However, when R^1 is alkyl or aryl group the open chain cinnamates were not formed, instead, the corresponding 2,3-disubstituted indenones **39** were formed[76]. The reaction of phenylmagnesium bromide followed by borontrifluoride etherate treatment is reported to give the 1-methylthio-1-phenyl indane[57] **40**. The Reformatsky reaction on dithioacetal **35** is reported to give the diene ester **41** and the β,γ-unsaturated ester[87] **42**. Dieter and co-workers have reported the chemo- and stereoselective addition of organocuprates to dithioacetals[77,78] **35**. Thus, organocuprates are shown to undergo conjugate addition to give β-alkylthio-β-substituted α,β-unsaturated ketones. In another study from this laboratory, base catalysed rearrangement of α-oxoketene dithioacetals derived from propiophenones are reported[80]. The 2-alkylthiomethyl acrylophenones **44** are formed by a 1,3-RS shift. A base assisted 1,5-RS shift to the diene **45** is also reported[88]. The α-oxoketene dithioacetals were also shown to undergo nickel boride ($NaBH_4$ / $NiCl_2$) reduction to the corresponding β-methylthioalkenyl ketones[89] **46**. These intermediates are hydrolysed to the α,β-unsaturated aldehydes[89] **47** (Scheme 2).

The α-oxoketene dithioacetals have been extensively explored in this laboratory for the construction of various substituted and fused five and six membered heterocyclics[90-91]. Some of the selected transformations, developed recently are shown in Scheme 3. From these transformations, it is apparent that α-oxoketne dithioacetals with wide functional group variation and many easily accessible reagents and reaction intermediates manifest various possibilities leading to diverse product range. Heteroaromatic annulation for the six membered heterocycles are outlined in scheme 4. lithioacetonitrile[102] and lithioaminocrotononitrile[103] were shown to react with α-oxoketene dithioacetals and subsequently cyclized to yield substituted pyridines **48** and **49** respectively in


NH / Methanolic NaOH
H2N NH2
50
H N Li CN R3
[LiCH2CN + R3CN]
49
R3=Me ,Ph
H N Me CN O
NaOR3 / ROH
51
35
1. LiCH2COOEt
2. H+
53
BrZnCH2COOEt
52
1. LiCH2CN
2. H3PO4
48

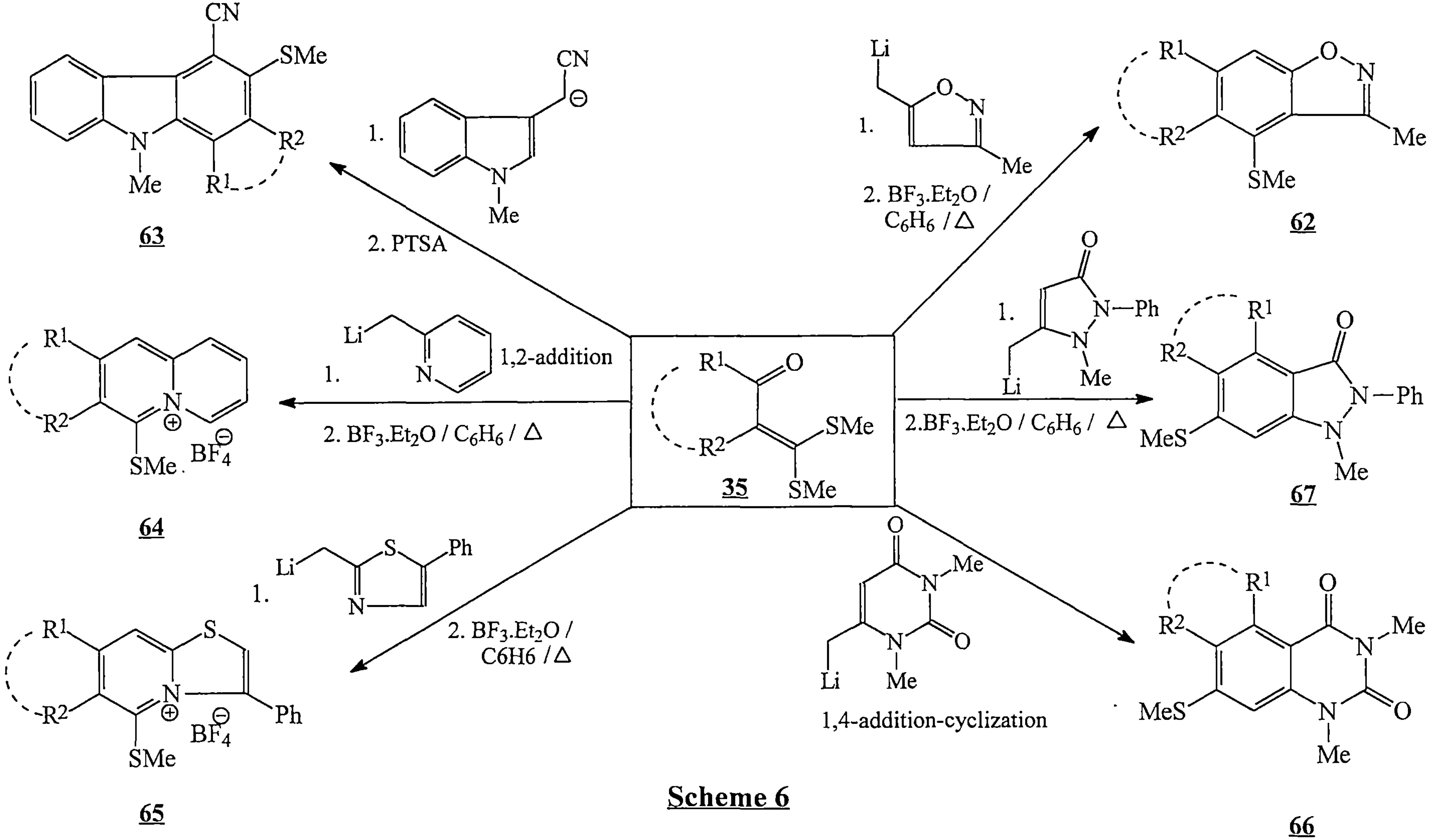
Scheme 4


35
54
55
56
57
58
59
60
61
SMe
OMe
CH2C6H5
COOEt
OH
R1
R2
R3
R4
Me
or
1 H—C≡C—C—MgBr
2 BF3 Et2O / C6H6 /Δ
1 C6H5MgBr
2 BF3 Et2O / C6H6 /Δ
BrZnCH2COOEt
1 ClMg
2 BF3 Et2O / C6H6 /Δ
MgX
Li
1.
2 BF3 Et2O /C6H6 /Δ

Scheme 5

good yields. Similarly, guanidine nitrate, cyanoacetamide lithioethylacetate and bromozincacetate were shown to react with α-oxoketene dithioacetal to yield substituted pyrimidines[104] **50**, pyridones[105] **51**, pyrones[106] **52**, and **53**[107] respectively in good yields..

Aromatic annulation *via* α-oxoketene dithioacetals, developed from this laboratory has emerged as an area of great synthetic potential. Some of the important synthetic outcome of this aromatic annulation methodology is outlined in Scheme 5. The reaction of allylmagnesium bromide with α-oxoketne dithioacetals have been shown to undergo exclusive 1,2-addition to yield the corresponding carbinol acetal in high yields, which on borontrifluoride etherate assisted cationic cyclization yield the substituted and fused benzene derivatives[108] **54**. This method is further shown to be extremely versatile and found general, when extended to methylallylmagnesium bromide, crotylmagnesium bromide and propargyl magnesium bromide[109] to afford substituted benzoannulated products. Subsequently, this method is of aromatic annulation was extended to naphtho annulation. When benzylmagnesium chloride was reacted with α-oxoketene dithioacetals, followed by borontrifluoride etherate assisted cyclization gave the corresponding naphthalene derivatives[110,111] **56** through benzene ring participation in the cyclization. This naphtho annulation methodology, was extended to α-napthylmethylmagnesium chloride and β-naphthylmethylmagnesium chloride to yield the corresponding phenanthrenes[111] **57** (or its linear isomer. With ethylzincbromoacetate, α-oxoketene dithioacetals yielded the corresponding regiospecific substituted and annulated 6-methylthiobenzolates **58** in good yields[112]. The Diels-Alder cycloadditions of vinyl ketene dithioacetals derived from the corresponding α-oxoketene dithioacetals with maleic anhydride afforded the phthalic anhydrides in good yields[113]. In the same sequence aromatic annulation methodology was well established for the synthesis of regiospecifically substituted amino aromatics **59**,


63
1.
CN
N
Me
2. PTSA
Li
O
N
Me
2. BF3.Et2O / C6H6 / Δ
62
SMe
R1
R2
1. N—Ph N Me Li
2.BF3.Et2O / C6H6 / Δ
67
MeS
64
1.
1,2-addition
2. BF3.Et2O / C6H6 / Δ
BF4
35
SMe
65
Li S Ph N
2. BF3.Et2O / C6H6 / Δ
1,4-addition-cyclization
66

Scheme 6

when α-oxoketene dithioacetals were reacted with lithiomethylamino crotonate[114]. This method was further shown to be extremely versatile and general, when extended for the synthesis of fused aromatics. Thus, the reaction of o-and m-lithioxylenes were reacted with α-oxoketene dithioacetals to yield the corresponding methyl substituted fused aromatics[115] **60**. Similarly mono, di-and-tri methoxy substituted benzyl magnesium bromides were shown to react with α-oxoketene dithioacetls to yield corresponding methoxy substituted fused aromatic compounds[116] **61**. With a view to enhance the scope of heteroaromatic annulation methodology, this method was extended in this laboratory for the synthesis of benzoheterocycles, by reacting appropriately substituted heteroallyl systems with α-oxoketene dithioacetals. Thus, the reaction of lithiomethyl isoxazole with α-oxoketene dithioacetal yielded the corresponding benzoisoxazoles **62** in excellent yield[117,118]. This method was further shown to be extremely significant and general when extended for the synthesis of carbazoles **63**, quinozilinium salts **64**, thioazaxolopyridinium salts[121] **65**, pyrimidones[114] **66** and indazolones **67** This methodology developed is of considerable synthetic importance, due to the fact that, a large number of azallyl anions could be used to construct various heteroaromatic compounds.

The α-oxoketene dithioacetals, therefore with a wide ranging functional group variation and many easily accessible reagents and reactive intermediates manifestly hold many new synthetic possibilities leading to diverse product range, including carbocyclic, heterocyclic and their fused analogues.

I.4. Section 3. N-Vinylaziridines as polarised ketene S,N-acetals:

Like α-oxoketene-S,S-acetals, the S,N-acetals also posses 1,3-electrophilic centres and undergo a number of reactions with various binucleophiles to yield various heterocycles and carbocycles. As stated in the preceding section, they can be prepared by displacement of one of the thiomethyl group on α-oxoketene dithioacetal by the amine[123]. The α-oxoketene N,S-acetals like α-oxoketene dithioacetals are well defined compounds which can be preserved without apparent decomposition. They can be considered as vinylogous amides. On the other hand, the ketene S,N-acetals are more stable and exhibit properties identical to enamines. They can undergo nucleophilic displacement with various binucleophiles[124-136] followed by intramolecular cyclization with α-oxo functionality. Like enamines the α-carbon in the ketene S,N-acetals is nucleophilic enough to react with various electrophilic species so that these reactions can be utilized to construct heterocycles of different structural features. The chemistry and synthetic application of α-oxoketene S,N-acetals have been reviewed and a number of synthetic methods have been developed in this laboratory[124-137].

Aziridine ring is a versatile building block for organic synthesis[138]. Ring-opening can be effected by various carbon[139] and heteroatom nucleophiles[140], often with regiocontrol to produce a variety of functionalised amino compounds. The recent development of metal catalysed, enantioselective aziridination of alkenes[141] has created renewed interest in the chemistry of these compounds. Vinylaziridines are also useful synthetic building blocks and can be converted to allyl amines by stereoselective conjugate addition of organocuprates[142], to pyrroline derivatives by rearrangement[143] and to β-lactams by Pd-catalysed carbonylation[144]. The synthesis of vinlyaziridines is usually accomplished by carbon-carbon bond formation after the aziridine ring has been formed[145]. There are only a few reports for the direct addition of nitrene to 1,3-dienes, yields range from low to good, with inherent problems of photolysis and thermolysis of azides resulting in a variety of byproducts[146]. Recently copper catalysed alkene aziridination under very mild conditions was developed[141]. Hudlicky reported the use of vinylaziridines which were obtained by aziridination of 1,3-dienes derived from the microbial oxidation of benzene[147]. The reaction of aziridine with α-oxoketene dithioacetal to yield the N-vinylaziridines, have been reported from this laboratory[148]. Iodide ion assisted rearrangement of these N-vinylaziridines to yield substituted pyrrolines also been reported[148] from this laboratory.

2-substituted 5-oxo-4,5-dihydro-1,3-oxazolones are important synthetic intermediates and interest in their chemistry continues, as is evidenced by the number of reviews on this subject[151-154]. Recently, some unsaturated 5-oxazolones[155] and the corresponding acyclic derivatives[156] were reported to exhibit anti-cancer activity. 5-oxo-1,3-oxazole was prepared by the cyclisation of N-acyl glycines with ethylchloroformate in the presence of triethylamine[157]. Various 2-substituted-4-alkylidene-5-oxo-4,5-dihydro-1,3-oxazoles prepared[158] in the literature to exploit their biological profiles.

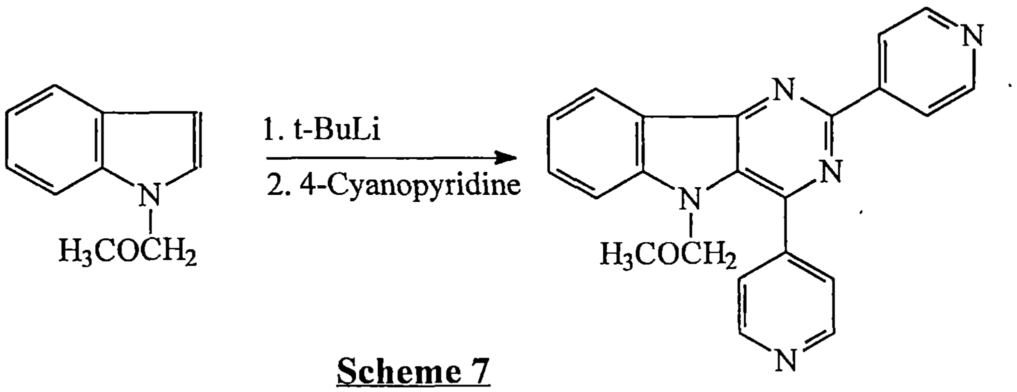
The dl-cucurbitine is a naturally occurring aminoacid found in the seeds of several cucurbita (pumpkin) species which are known to inhibit the growth of immature *Schistosoma Japonicium*[159].

I.5. Section 4. The work presented in this Thesis:

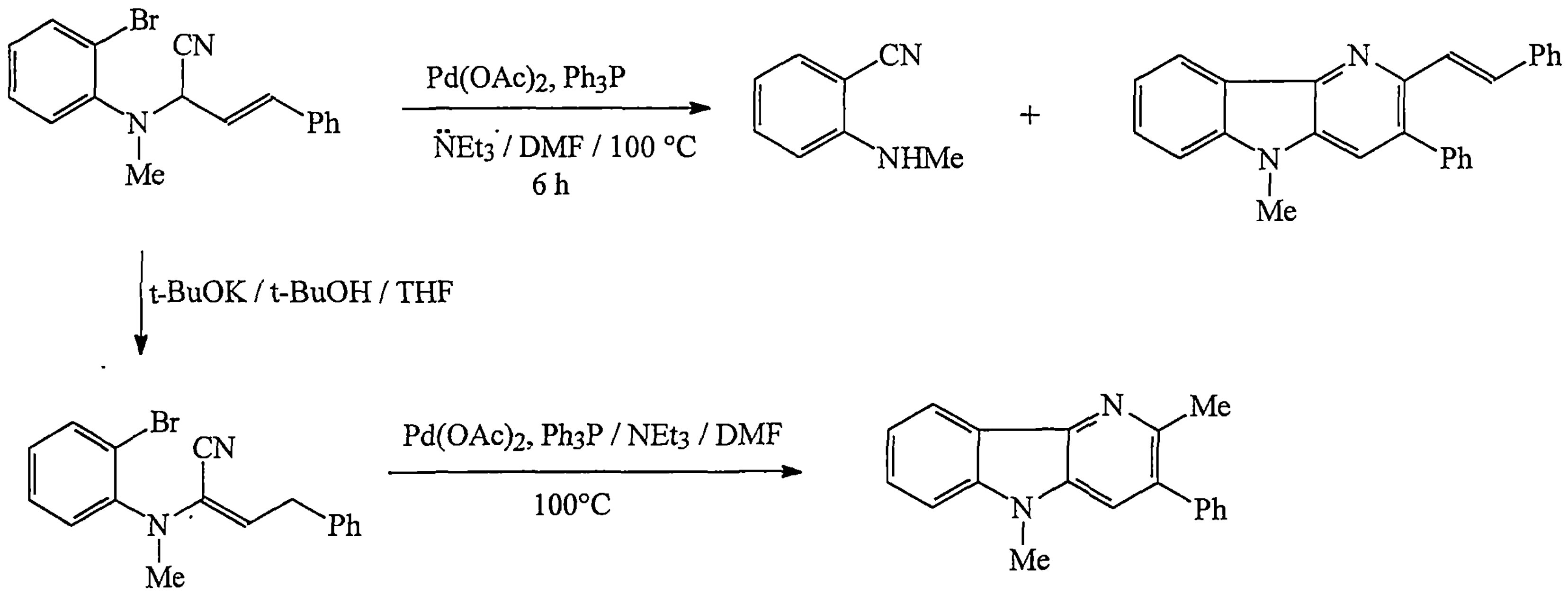
As part of our strategy to develop new heterocyclics, to find the efficacy against topoisomerase enzymes, we have developed various methods for [b] annulation of indoles to yield new carbazoles, carbolines and their condensed analogues.

In the part A of the second chapter, [b] annulation of indoles was well explained for the synthesis of carbazole derivatives. Indole 2,3-dienolate generated by the deprotonation of 1,2-dimethylindole-3-carboxaldehyde have been shown to react *in situ* with various unsymmetrical dienophiles, regiospecifically to yield substituted carbazoles in excellent yields. Interestingly, the Indolo-2,3-quinodimethane generated from 1,2-dimethyl indole-3-carboxaldehyde, with acetic anhydride / sodium acetate was also shown to react *in situ* with variety of dienophiles to yield the carbazole derivatives also presented in the part A of Chapter II. Reaction of Indolo-2,3-dienolate with aromatic nitriles to yield substituted γ-carbolines are discussed in the part B of Chapter II.

In Chapter III, 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. Indoxyl S,S-acetal was prepared by trapping air sensitive indoxyl, under nitrogen atmosphere with carbon disulphide followed by alkylation. Indoxyl-S,S-acetal was reacted with allylgrignards to yield carbinol acetals in near quantitative yields and were cycloaromatised under acedic conditions to yield substituted carbazoles. Indoxyl-S,S-acetal was reacted with guanidine nitrate in presence of alcoholic sodium hydroxide to yield 2-amino-5-methyl-4-methoxy pyrimido [5,4-b] indole in good yield. very few methods are known of the preparation of pyrimido [5,4-b] indoles (Scheme 7).



Scheme 7



Scheme 8

Indoxyl-S,S-acetal was reacted with picolyllithium and the cycloaromatised under acidic conditions to yield hitherto unreported frame work indolo [3,2-b] quinozilinium tetrafluoroborate salts. Similarly lithioacetonitrile and lithioaminocrotononitrile was reacted with the S,S-acetal to yield β- and γ-carbolines 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.

Synthetic methods for δ-carbolines are less encountered. Recently Yang and co-workers reported[161] their synthesis involving palladium-catalysed cyclisations of α-(o-bromoanilino) alkenenitriles, which is shown in the scheme 81. Lithiomethylantipyrine, also shown to react with S,S-acetal 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. It is to be stated that this is the first report for this pyrazolo [4,3-b] carbazole synthesis. All these results are presented in the Chapter III.

In Chapter IV, aziridino N,S-acetals prepared from monoactivated α-oxoketene dithioacetals for the first time are reported and their rearrangement to substituted pyrrolines has been well explained. Attempts were made for the synthesis of dl-cucurbitine, 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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CHAPTER-II

Part A:

Anionic [4+2] Cycloaddition Reactions of Indole-2,3-dienolate with Dienophiles: A Facile Regiospecific Route to Substituted Carbazoles:*

II.A.1 Introduction :

The o-quinodimethane intermediates of general formula 1 (Scheme 1) and their corresponding derivatives have been recognised as potential dienes for the regio- and stereocontrolled

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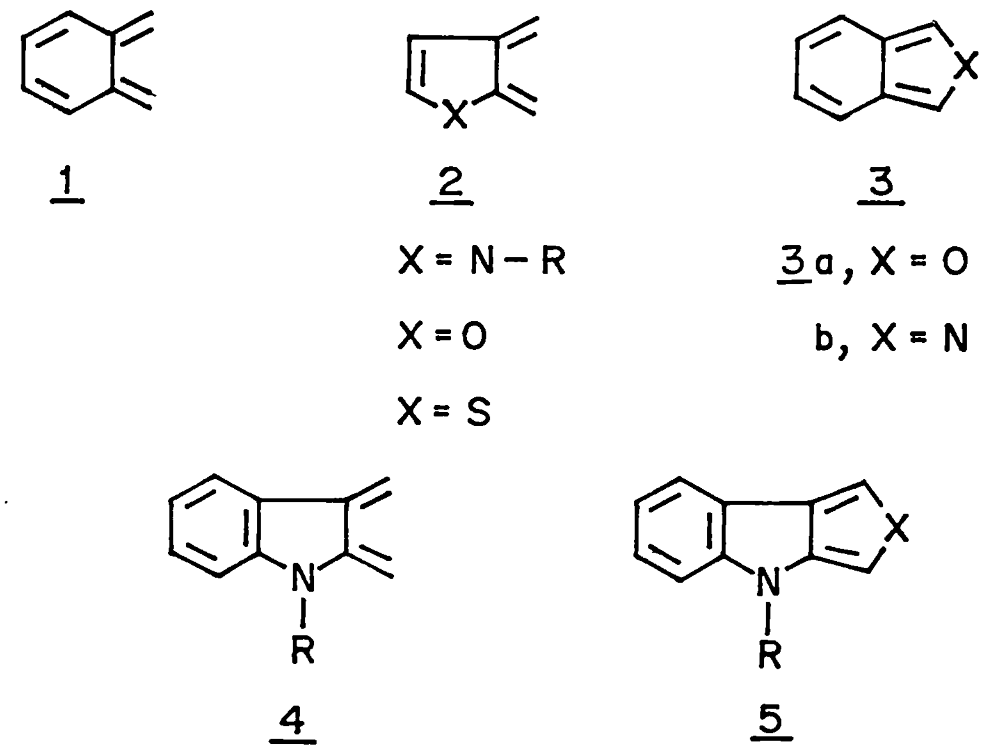
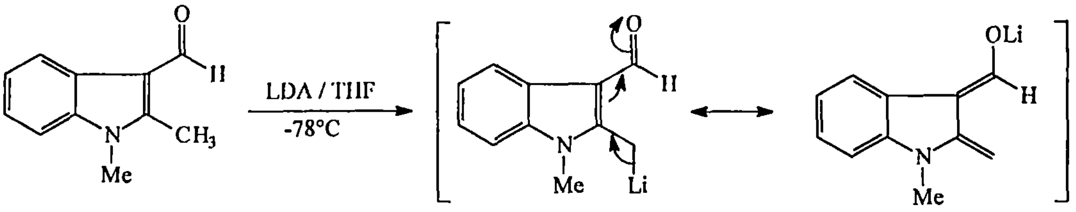
Mandava V.Basaveswara Rao, Janagani Satyanarayana, Hiriyakkanavar Ila and Hiriyakkanavar Junjappa*. *Tetrahedron lett.*, **1995**, *36*, 3385-3388.



Scheme −1

cycloadditions with various dienophiles resulting in the formation of both carbocycles and heterocycles depending on the nature of the dienophiles[1]. o-quinodimethane intermediates can also be derived from five membered heterocycles to yield the dienes of general formula **2** which are also known to undergo cycloaddition reactions in the same fashion[2]. Besides open chain o-quinodimethane systems **1**, **2**, and **4** a number of cyclic systems such as isobenzofurans[3] **3a**, 2H-isoindoles[4] **3b**, and **5** have been proved to be synthetically attractive dienes in the Diels-Alder reactions. The o-quinodimethane intermediate 2,3-bis(methylene)-2,3-dihydroindole **4** and its cyclic analogues **5** have been shown to be extremely important for the synthesis of many of indoles and carbazole derivatives of pharmacological applications[5] . The o-quinodimethane approach has become one of the most attractive methods for the synthesis of carbazoles and other indole alkaloids. There are several related reviews[6] the papers published on various methods of preparation of Indolo-2,3-quinodimethanes and their utility in subsequent important synthetic transformations. In the present



6 **7** **7**

investigation we have generated for the first time o-quinodimethane system from 1,2-dimethylindole-3-carboxaldehyde **6** and reacted it *in situ* with various dienophiles to yield the corresponding carbazole derivatives. We therefore would like to briefly present the related literature on various o-quinodimethane intermediates derived from 2,3-disubstituted indoles and their reactions with dienophiles to yield corresponding carbazoles including some alkaloids.

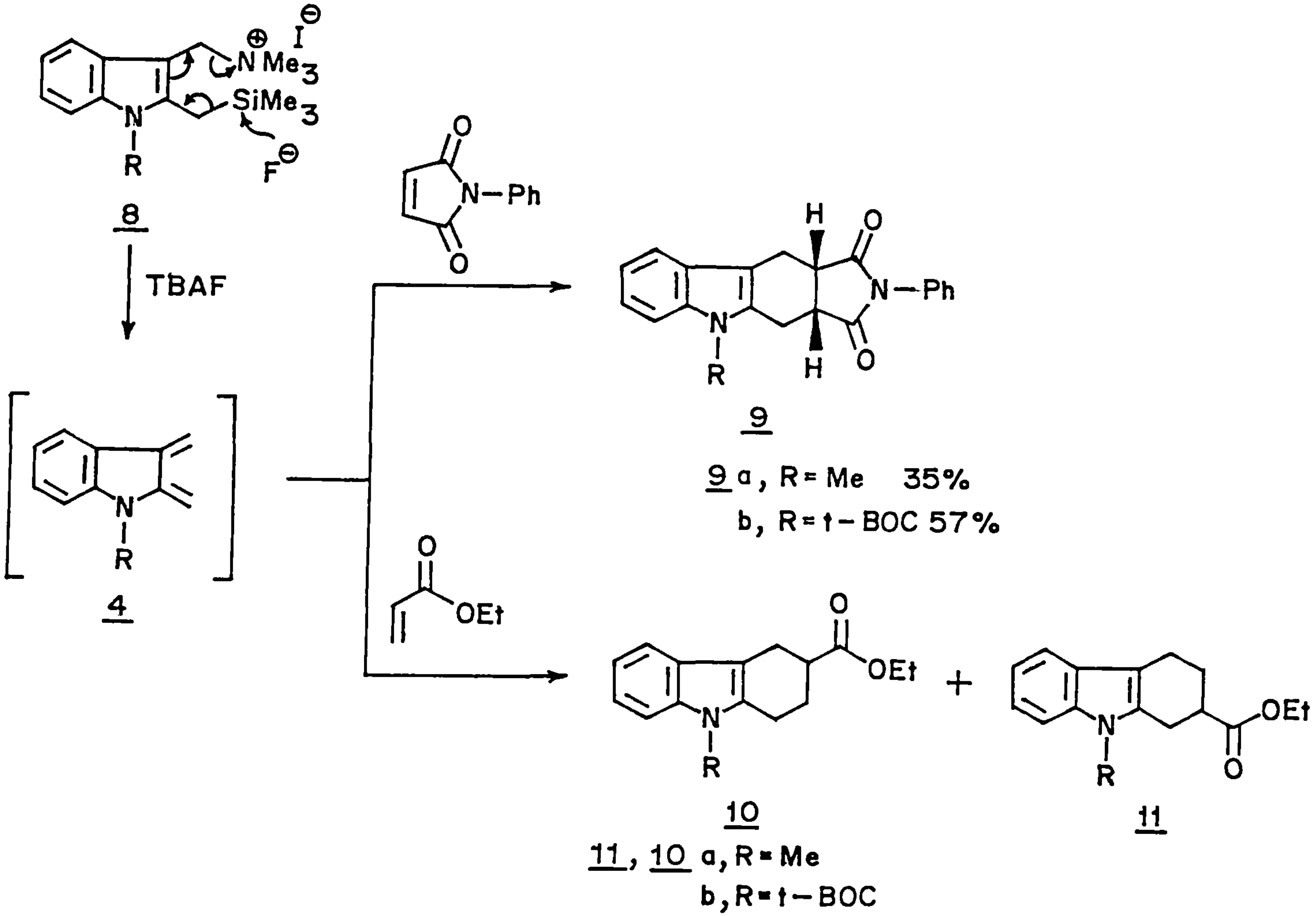
II.A.2 Indolo-2,3-quinodimethanes : A brief review.

The presentations of the reported literature is classified in the following headings.

1. Open chain o-quinodimethane intermediates and their reactions.
2. 0-quinodimethane intermediates involving intramolecular dienophile component.
3. The stable cyclic analogues of Indolo-2,3-quinodimethane systems related to type 5 .

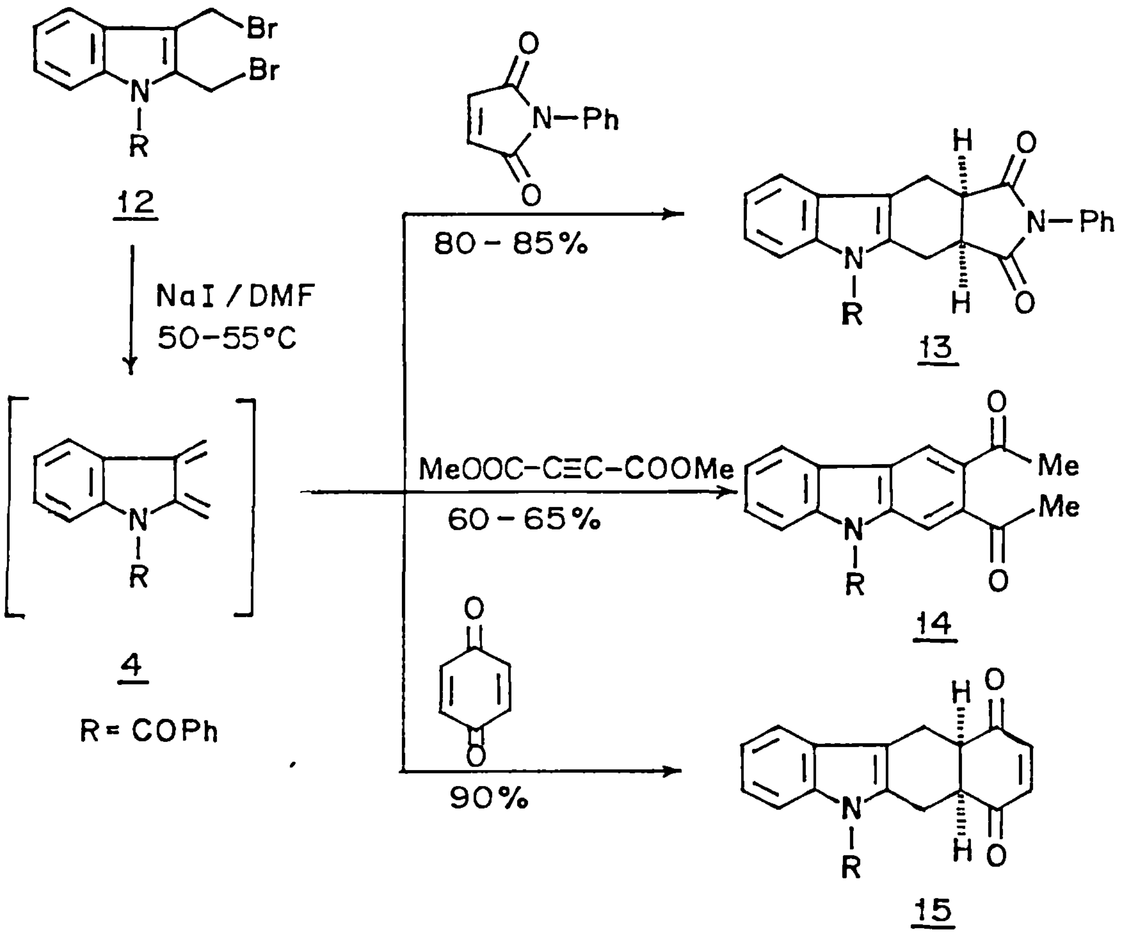
I) Open chain o-quinodimethane Intermediates and their reactions.

N-Protected-2,3-disubstituted indoles have been generally employed as precursors for the *in situ* generation of Indolo-2,3-quinodimethanes of type 4 described in the scheme 1. Thus N-methyl and N-(tert-butyloxycarbonyl)indolo-2,3-quinodimethanes 4, were generated[7] from the corresponding silylated indolylammonium salts *in situ* in the presence of tetrabutylammonium fluoride involving fluoride ion induced 1,4- elimination. The dienes 4 thus generated were trapped with N-phenylmaleimide to yield the corresponding cycloadducts, 9. Similarly isomeric mixture of tetrahydro carbazoles



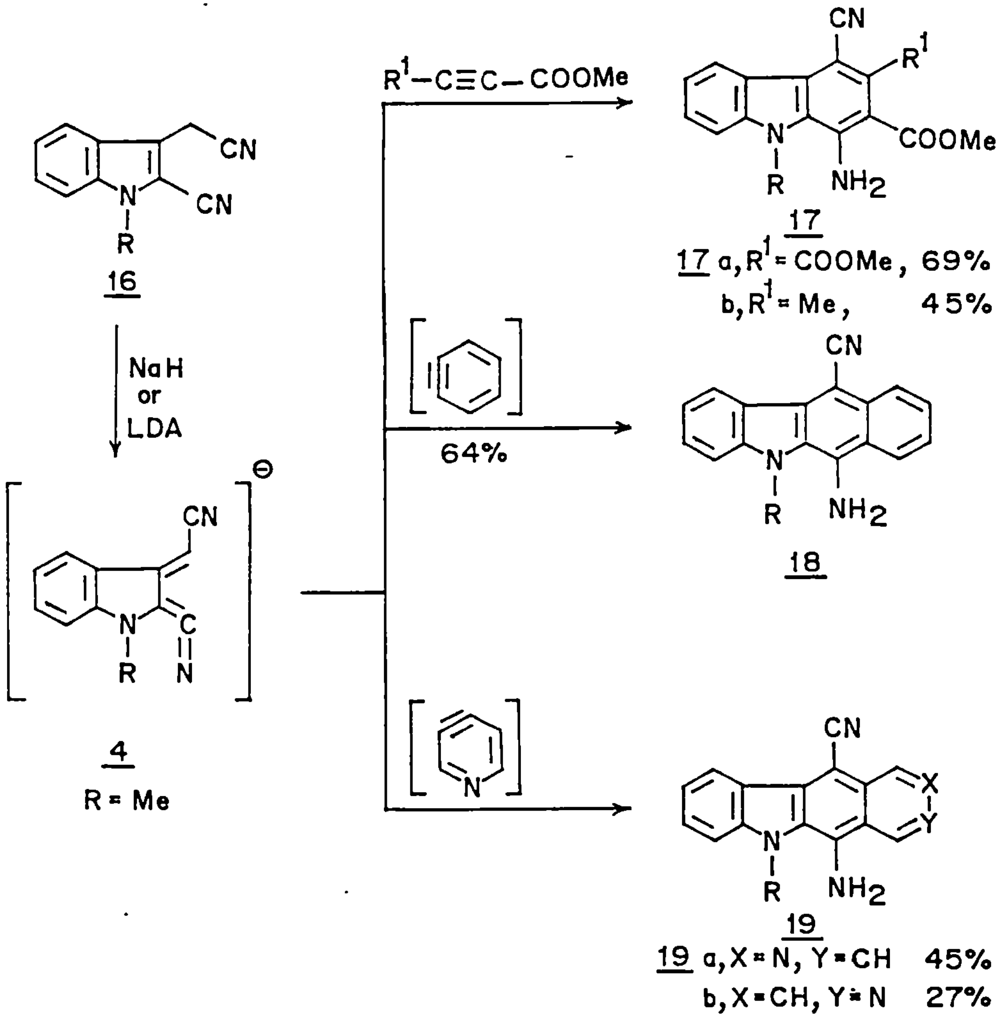
Scheme-2

Merinelli, E. R. Tetrahedron Lett. 1982, 23, 2745.



Scheme - 3

Saroja, B.; Srinivasan, P.C. Tetrahedran Lett. 1984, 25, 5429-5430.



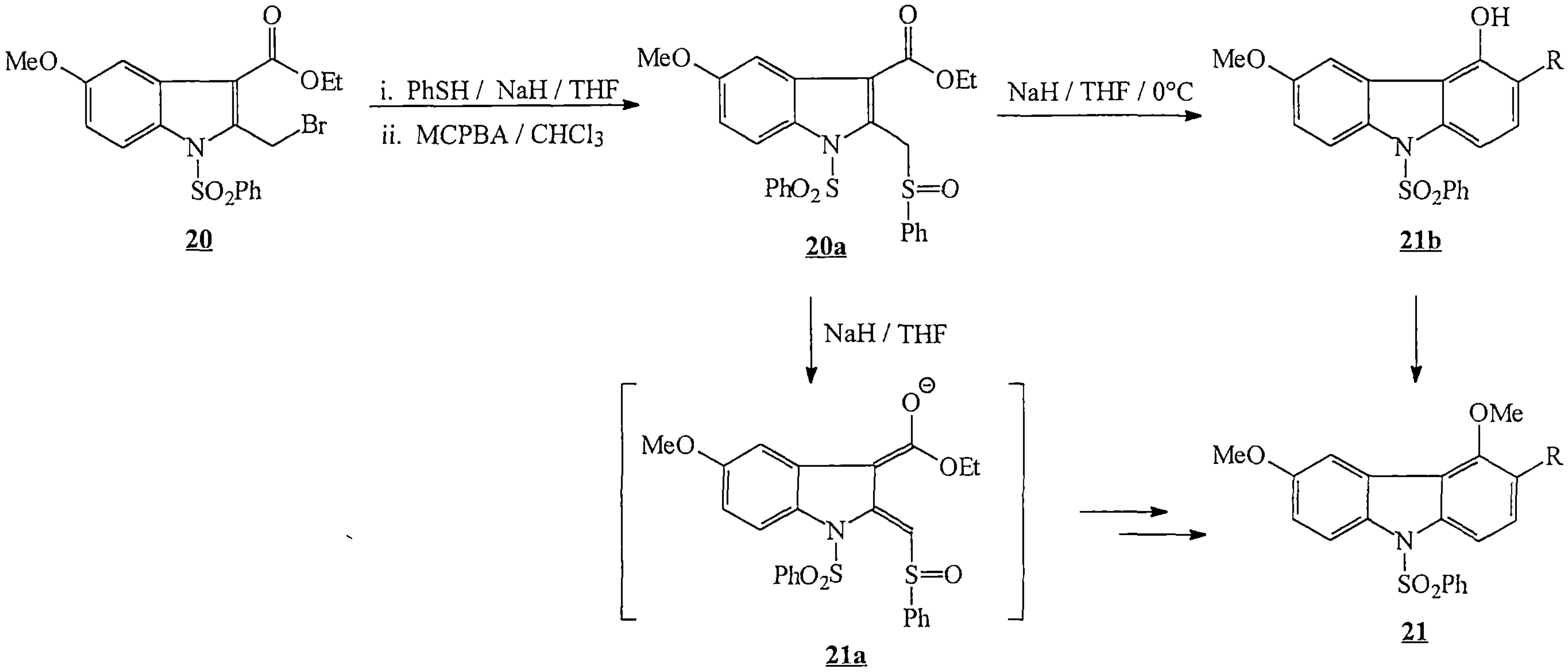
Scheme – 4

Kurihara, T, ; Hanakawa, M. ; Wakita, T.; Harusawa, S. Heterocycles. 1985, 23, 2221-2224.
Kurihara, T.; Hanakawa, M.; Harusawa, S.; Yoneda, R. Chem. Pharma. Bull. 1986, 34, 4545-4553.

10 & 11 was formed when 4 were reacted with ethylacrylate. It is to be noted that the diene 4 generated in this experiment yields a mixture of isomers, when reacted with unsymmetrical dienophiles, lacking regioselectivity (Scheme 2).

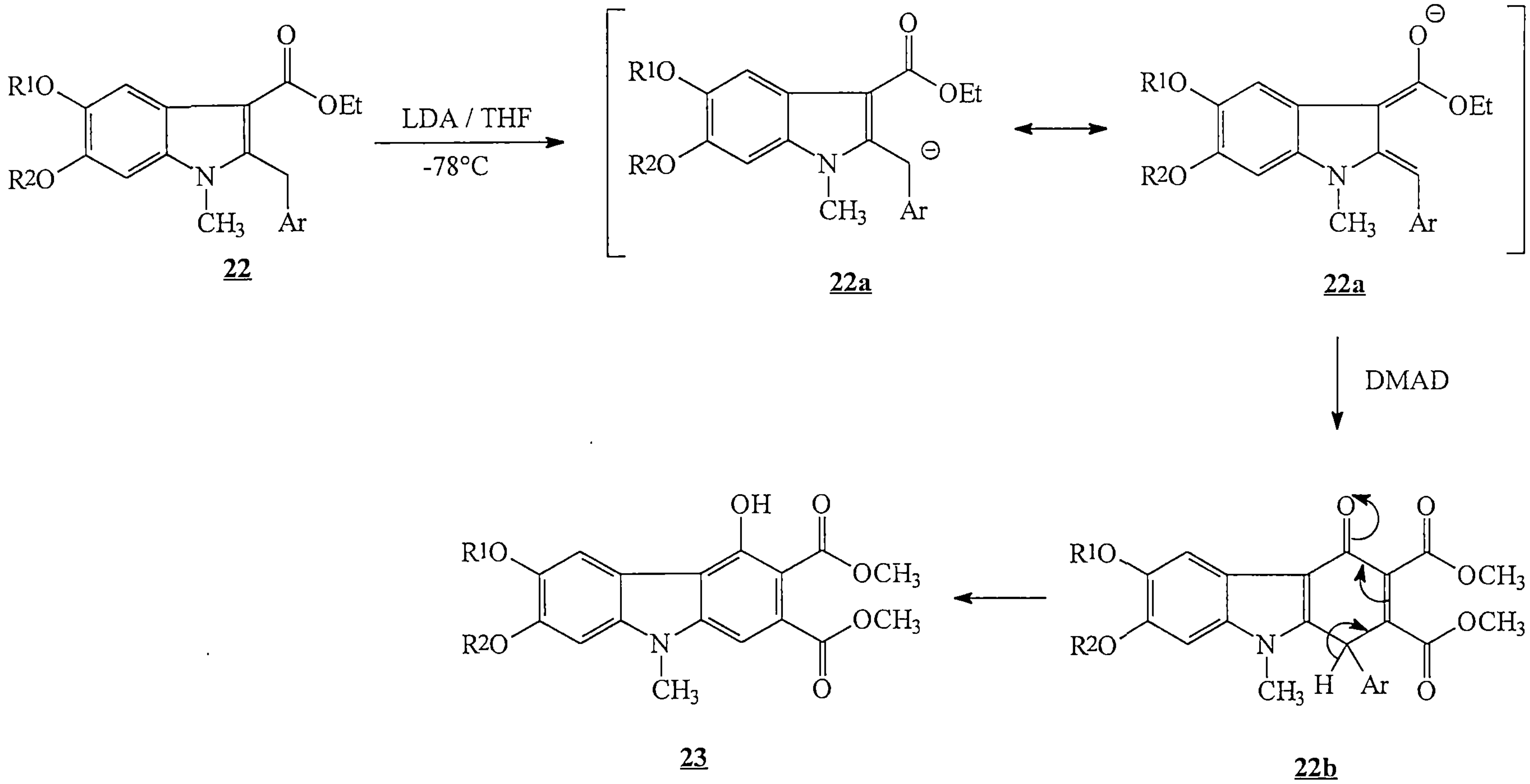
Srinivasan[8] and Saroja, in connection with their studies on N-protected-2,3-dibromomethylindoles have used it for the generation of the corresponding o-quinodimethane 4. The o-quinodimethane thus generated, was trapped with N-phenylmaleimide to yield the corresponding cycloadduct 13. When dimethyl acetylenedicarboxylate was reacted with 4 the corresponding 2,3-bis(methoxycarbonyl) carbazole 14 was obtained in 60-65% yield. Similar reaction with 1,4-benzoquinone yielded the corresponding cycloadduct 15 in 90% yield. All the dienophiles used in this investigation are symmetrical and therefore regioselectivity in the adduct with unsymmetrical dienophiles is to be ascertained (Scheme 3).

Kurihara and co-workers have reported an interesting method for the preparation of 2-cyanoindole-3-acetonitrite[9] 16, from N-protected indole-3-carboxaldehyde. Thus indole-3-carboxaldehyde was treated with DEPC (Diethyl phosphoro cyanidate) in the presence of lithium cyanide to get 2-cyanoindole 3-acetonitrile 16, which was used to generate the corresponding o-quinodimethane 4 *in situ* (Scheme 4) in excellent yields[9]. The intermediate 4 was then reacted with dimethyl acetylenedicarboxylate and methyl propiolate to yield the corresponding 1-amino-4-cyano-9-methylcarbazoles 17a and 17b in 69 and 45% yields respectively. The intermediate 4 was also reacted with one equivalent of benzyne to give the corresponding 6-amino-11-cyano-9-methylcarbazole 18 in 64% yield along with a small



21b, 21 **a'**, R = COCH$_3$
b', R = CN
c', R = CO$_2$Et

Scheme 5a

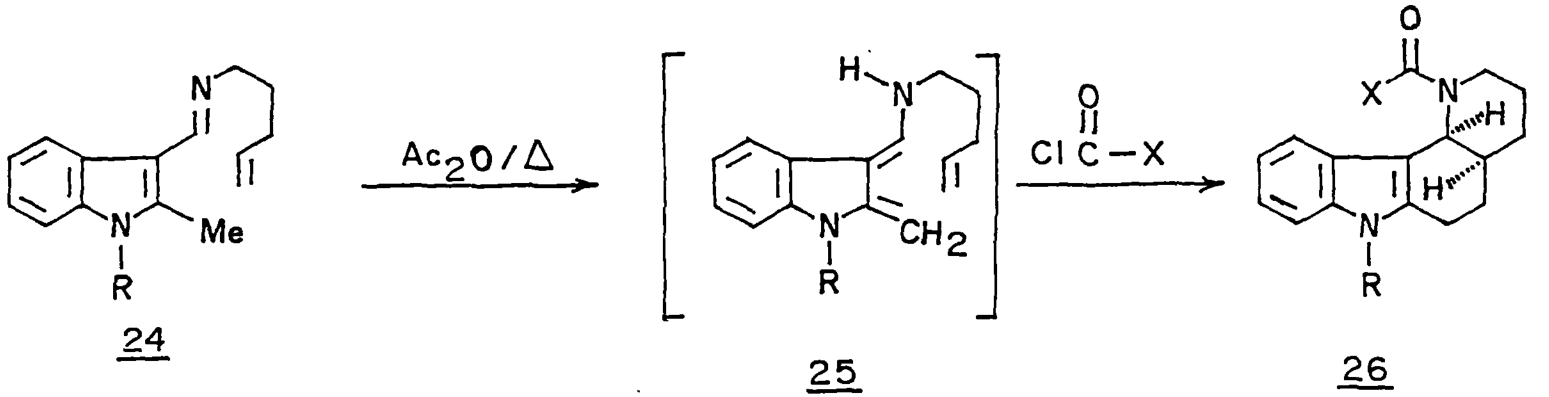


Scheme 5b

amount of bicyclic product of the benzyne addition to 6,11- carbon atoms.

Interestingly in an another study[10] reaction of **4** with 3,4-pyridyne generated from 3-chloropyridine and lithium diisopropylamide furnished the corresponding cycloadduct as a mixture of **19a** and **19b** in 45 and 27% yields respectively. Here again o-quinodimethane intermediate **4** in its reaction with 3,4-pyridyne did not display regioselectivity yielding a mixture of both the regioisomers.

Recently Srinivasan[11] and co-workers reported an elegant one pot synthesis of 4-hydroxy-3-substituted carbazoles (Scheme 5a). They prepared a strategic precursor **20a** from the corresponding 2-bromomethylindole derivative **20** as described in scheme 5a. The indole derivative **20a** was reacted with unsymmetrical dienophiles in the presence of sodium hydride when the corresponding highly regioselectively substituted carbazoles **21** were obtained in overall 50-72% yields. However, the authors have proposed michael addition followed by cyclization. And it is quite likely the corresponding o-quinodimethane intermediate **21a** is likely reacting species to yield the corresponding carbazoles. The observed regioselectivity in product carbazoles can also be explained on the o-quinodimethane which exists in its enolate form. Similarly Mali and co-workers have treated[11a] 2-aryl-1-methylindole-3-carboxylates **22** with dimethyl acetylenedicarboxylate in the presence of lithium diisopropylamide in dry tetrahydrofuran at -78°C when the corresponding 1-aryl-2,3-bis(carbomethoxy)-4-hydroxy-9-methylcarbazole **23** was formed in moderate yields (scheme 5b) The



26 a, $X = CH_3$

b, $X = OEt$

c, $X = OPh$

d, $X = Cl_3C-CH_2O$

e, $X = ClCH_2CH_2O$

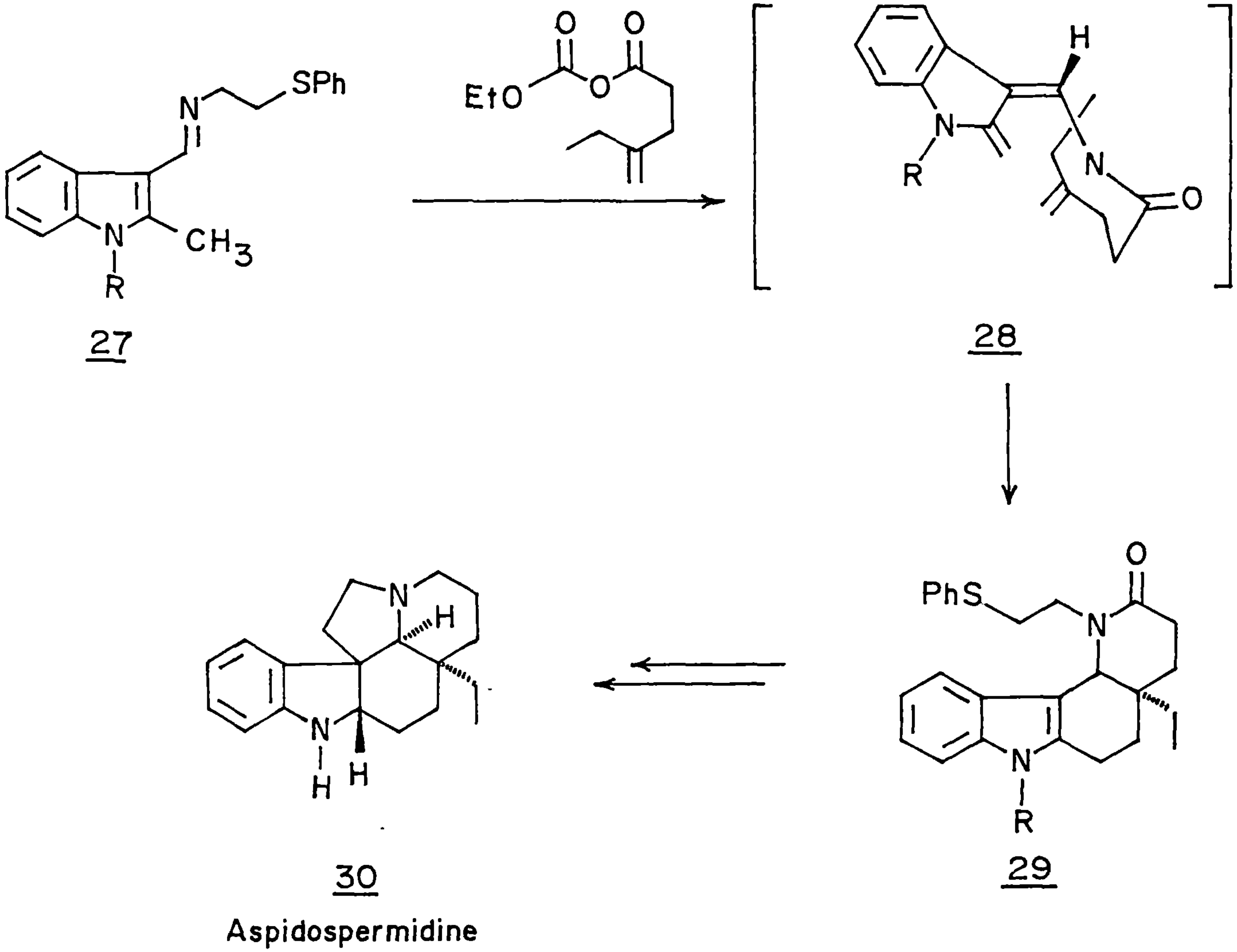
Scheme-6

Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. Acc. Chem. Res. 1984, 17, 35 and References there in.

formation of carbazole is likely to have followed either michael addition condensation or [4+2] addition to a hypothetical o-quinodimethane intermediate **22a**.

2. o-quinodimethane intermediates involving intramolecular dienophile component :

Both the diene and dienophile components with in the molecule undergo intramolecular Diels-Alder addition sequence is well established in the recent literature[12]. Interesting applications of this approach have been elegantly implemented by Magnus[13] and co-workers for the synthesis of penta and hepta cyclic indole alkaloids. Highly convergent and elegant reaction for the synthesis of indole alkaloids possessing more than one sterocentres especially those of the Aspidosperma and Kopsane types, was first achieved by this group[14,15,16,17,18]. Highly stereospecific synthesis of these alkaloids with control on their regio- and stereochemistry was achieved by trapping 2,3-quinodimethane structural frame *in situ*. As a model for their strategy, cyclization of Indole-2,3-quinodimethane **25** was generated from the corresponding **24** and highly stereoselective cycloaddition was achieved by treating **24** in acetic anhydride to yield tetracyclic amide **26** in 64% yield (Scheme 6). In all these cyclizations the newly formed ring junction was *cis* and no trace of *trans* fused tetracyclic amide adducts was detected. Extending this strategy, the highly stereo controlled synthesis of pentacyclic alkaloid aspidospermidine **30** was achieved through intramolecular cycloaddition involving o-quinodimethane intermediate **28**, which underwent cycloaddition to yield strategic tetracyclic intermediate **29**



27

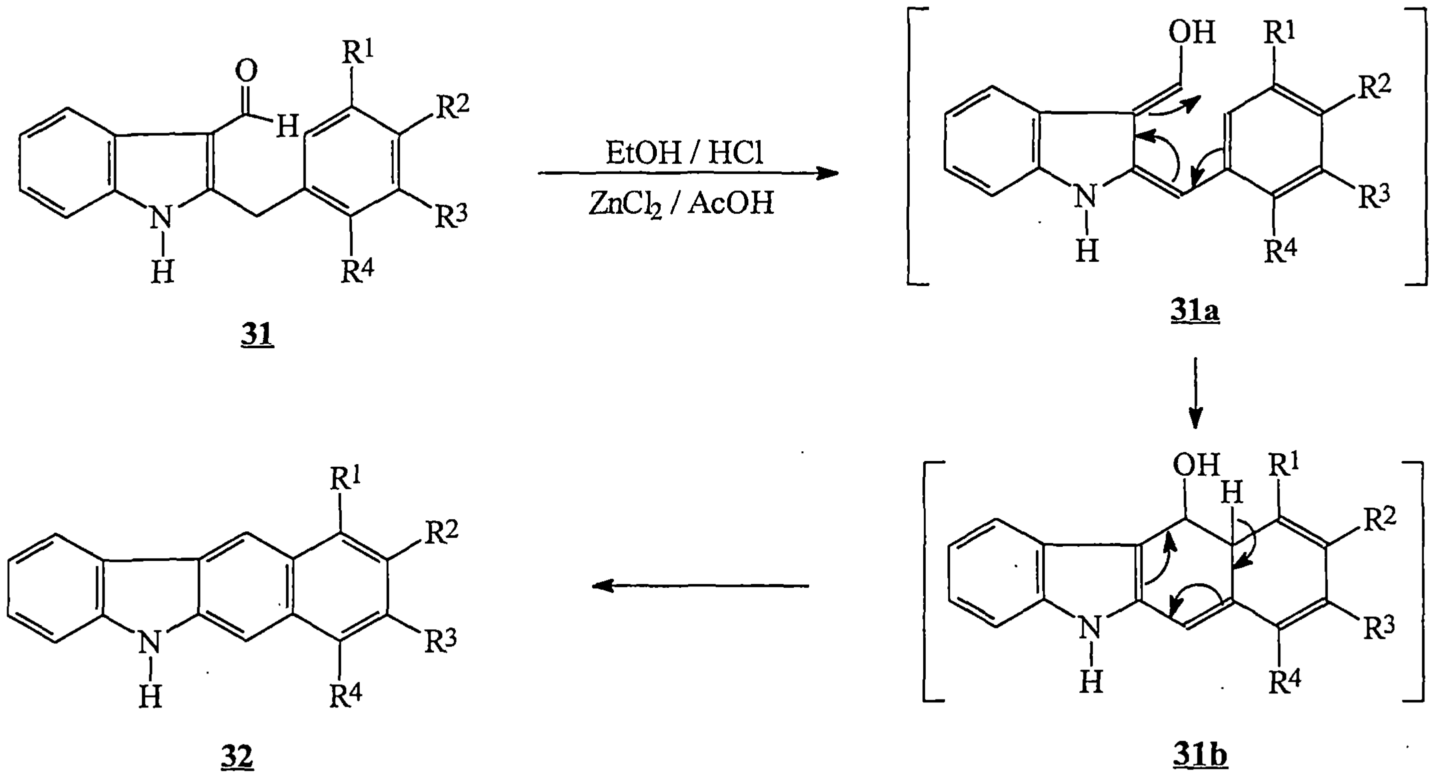
28

29

30

Aspidospermidine

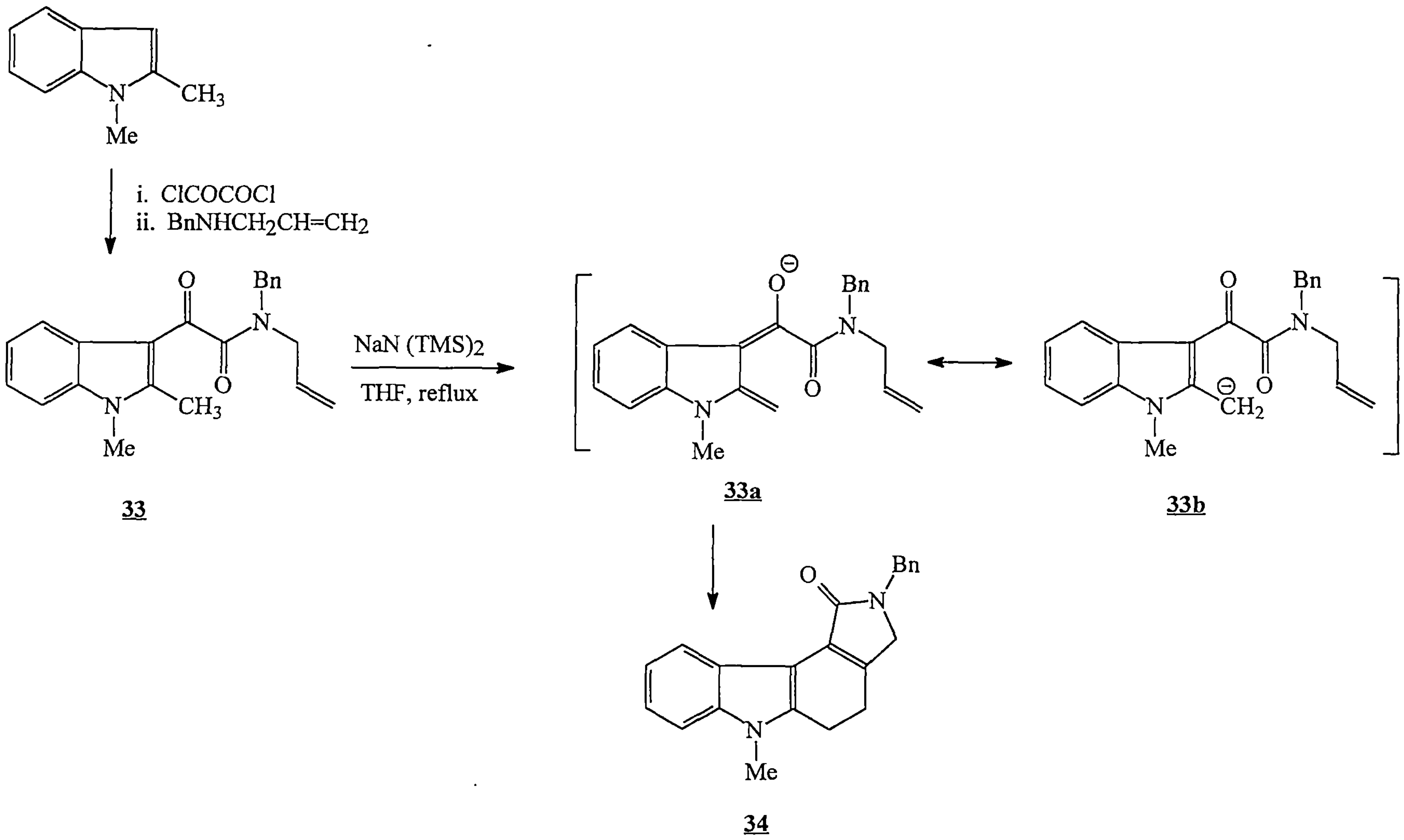
Scheme-7



31, 31a, 31b, 32 a', $R^1=R^2=OMe$; $R^3=R^4=H$

b', $R^1=R^4=H$; $R^2=R^3=OMe$

Scheme 8


i. ClCOCOCl
ii. $BnNHCH_2CH=CH_2$
NaN (TMS)2
THF, reflux
33
33a
33b
34
Me
CH_3
CH_2
O
Bn
N

Scheme 8a

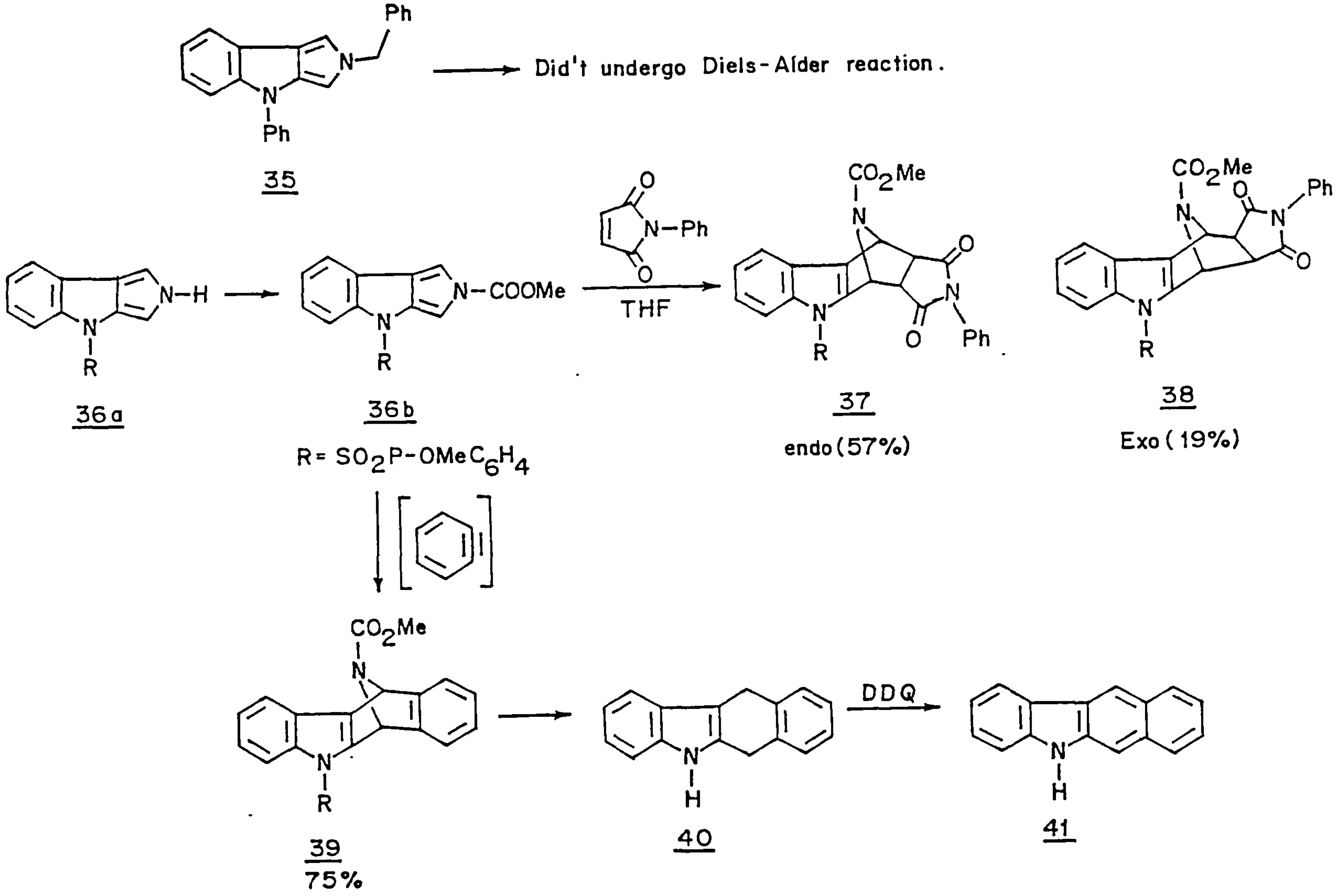
with the required *cis* ring junction. The intermediate **29** was subsequently transformed into **30** (Scheme 7).

Under this intramolecular [4+2] Diels-Alder strategy the synthesis of benzo [b] carbazoles **32** is accomplished by sequence of reactions formulated in scheme 8. Though the authors presumed[19] to have achieved this transformation through the acid or lewis acid assisted electrophillic attack by the aromatic ring followed by elimination of water to yield the same product **32**. It is also quite likely that the reaction may involve o-quinodimethane intermediate **31a**. This approach involving acid assisted ring closer without having to protect the ring nitrogen holds considerable scope to apply this strategy to many other important carbazole derivatives.

Recently Ciganek and Schubert have reported[44] an elegant intramolecular Diels-Alder approach for pyrrolo [3,4-c] carbazole as formulated in scheme 8a. Thus, enolate **33a** was generated from 1,2-dimethyl-α-oxo-N-(phenylmethyl)-N-2-propenyl-1H-indole-3-acetamide **33**, by treating **33** with sodium bis(tri-methylsilyl)amide in refluxing tetrahydrofuran. The enolate underwent intramolecular Diels-Alder reaction to yield 6-methyl-2-(phenylmethyl)-3,4,5,6-tetrahydropyrrolo [3,4-c]carbazole-1(2H)-one **34** in low yield (scheme 8a).

3. The stable cyclic analogues of Indolo-2,3-quinodimethane systems related to type 5 :

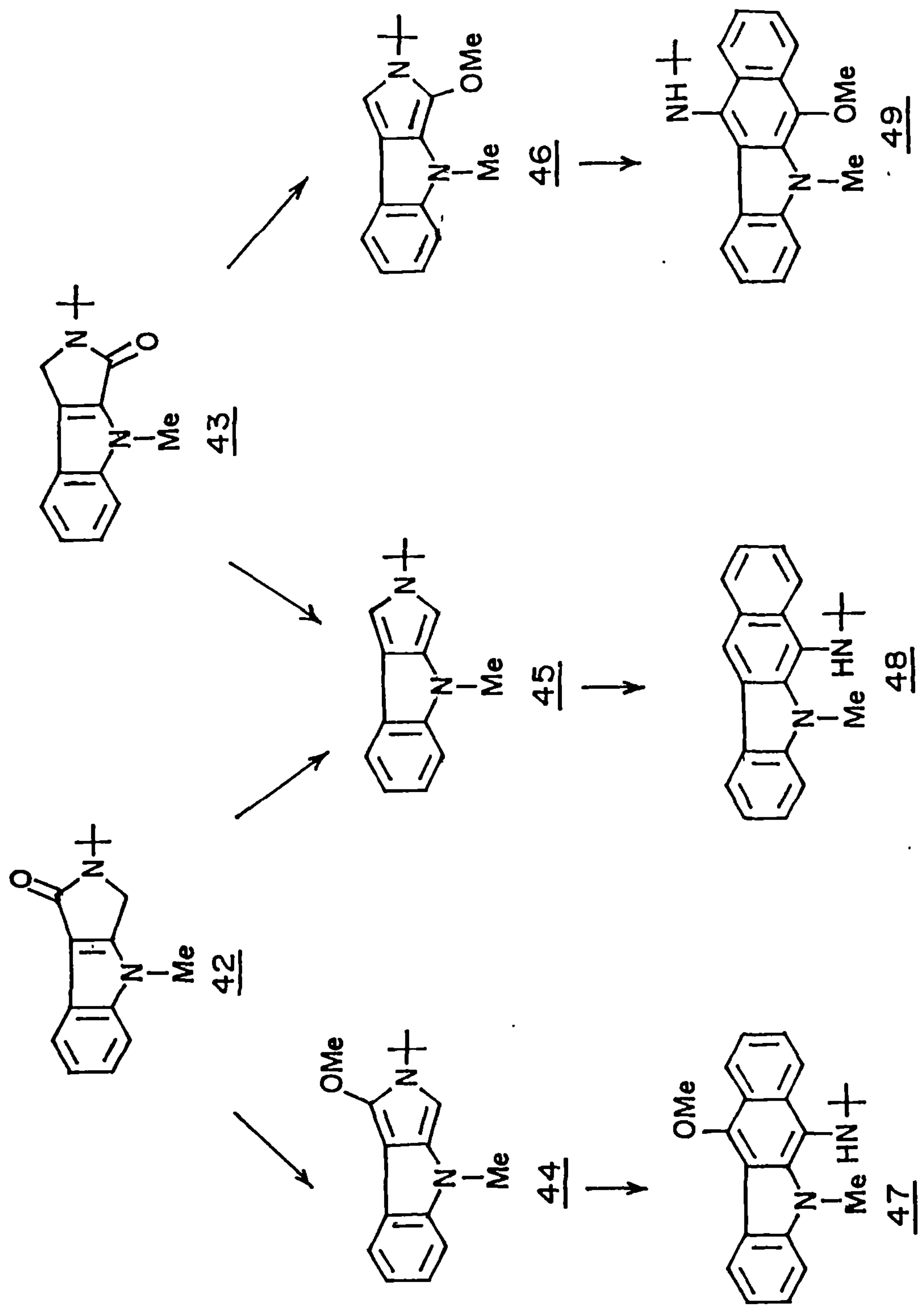
The stable cyclic analogues of the type **5** also formed versatile diene systems for [4+2] cycloaddition reactions. In these systems

Ph
N
Ph
35
Did't undergo Diels-Alder reaction.
N-H
N
R
36a
N-COOMe
36b
R= SO2P-OMeC6H4
O
N-Ph
O
THF
CO2Me
N
O
N
Ph
37
endo(57%)
CO2Me
Ph
38
Exo (19%)
CO2Me
39
75%
H
40
DDQ
41

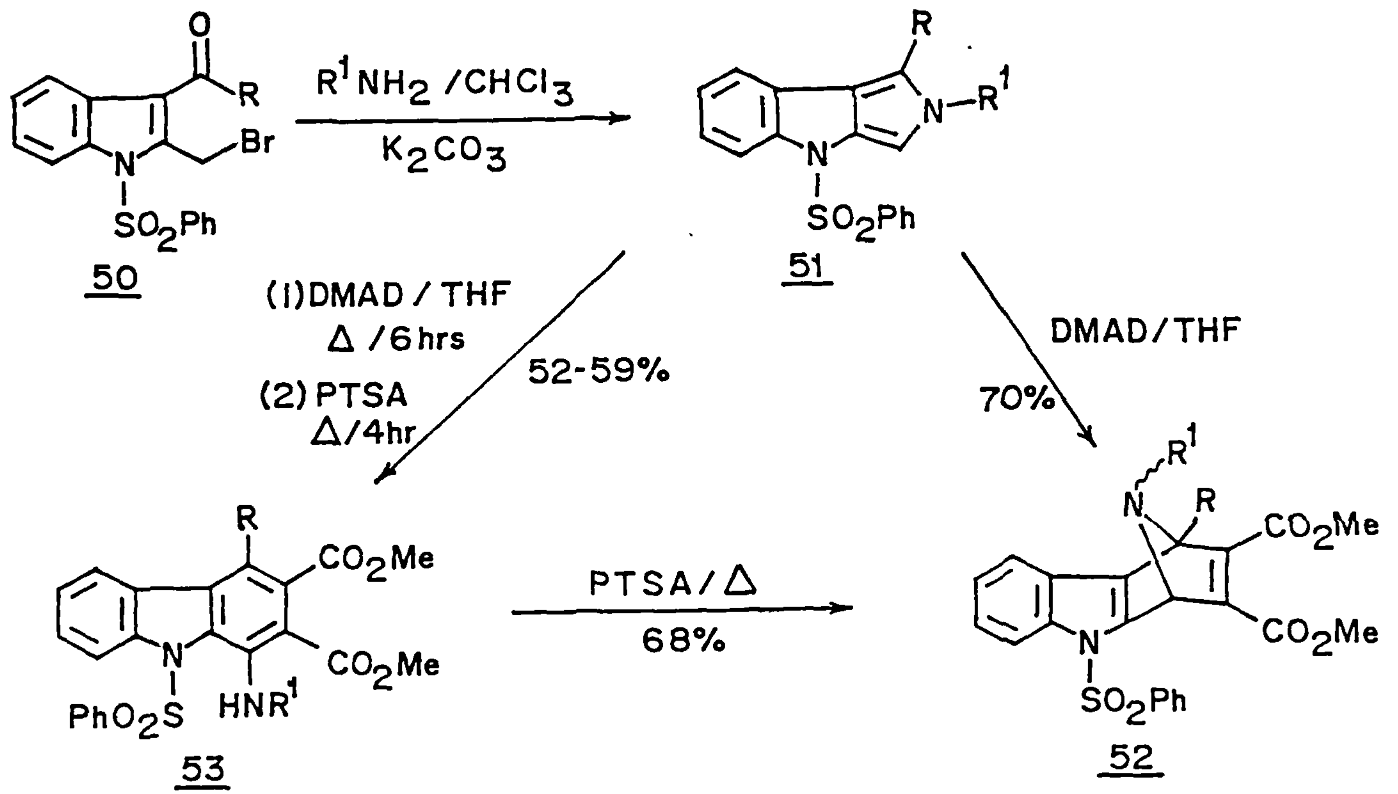
Scheme - 9

2,3- bis(methylene)-2,3-dihydroindole moiety is stabilised by the presence of heteroatom with a pair of nonbonding electrons capable of conjugation over the ring. Despite this possible resonance these structural frames display excellent diene properties and undergo cycloaddition reactions. In accordance with the Diels-Alder reaction initially the corresponding bridged bicyclic adducts are formed which eventually collapse to yield the corresponding carbozoles (or) [b] annulated indoles.

Thus Sha[20,21] and co-workers reacted 2,4-dihydropyrrolo[3,4-b]indole[22] ring system **35** as a stable analogue of Indolo-2,3-quinodimethane and found that it failed to undergo Diels-Alder reaction. However, they prepared new compounds **36a** and **36b** of which **36a** again failed to undergo the expected Diels-Alder reaction with N-phenylmaleimide. The unreacted indole **36a** was recovered, due the lone pair of electrons on nitrogen could delocalize over the ring, destroying the diene character. They reasoned analogy with pyrrole which undergoes Diels-Alder reaction only when electron withdrawing substituent on nitrogen is located. This reason was extended to this system **36a** and nitrogen was protected with carbomethoxy group to yield **36b** which was then treated with N-Phenylmaleimide to yield a mixture of endo and exo products in 57 and 19% yields respectively. Similarly **36b** reacted with benzyne to yield the adduct **39** in 75% yield . They subsequently subjected the adduct **39** , for the reductive removal of the bridged nitrogen to yield the corresponding benzo [b] dihydrocarbazole **40** which on treatment with DDQ yielded the corresponding 5H-benzo [b] carbazole **41**. (Scheme 9).



Scheme-10



52, 53 a, R = Me ; R^1 = CH$_2$Ph
b, R = Me ; R^1 = C$_6$H$_4$Me — P
c, R = Me ; R^1 = C$_6$H$_4$OMe — P

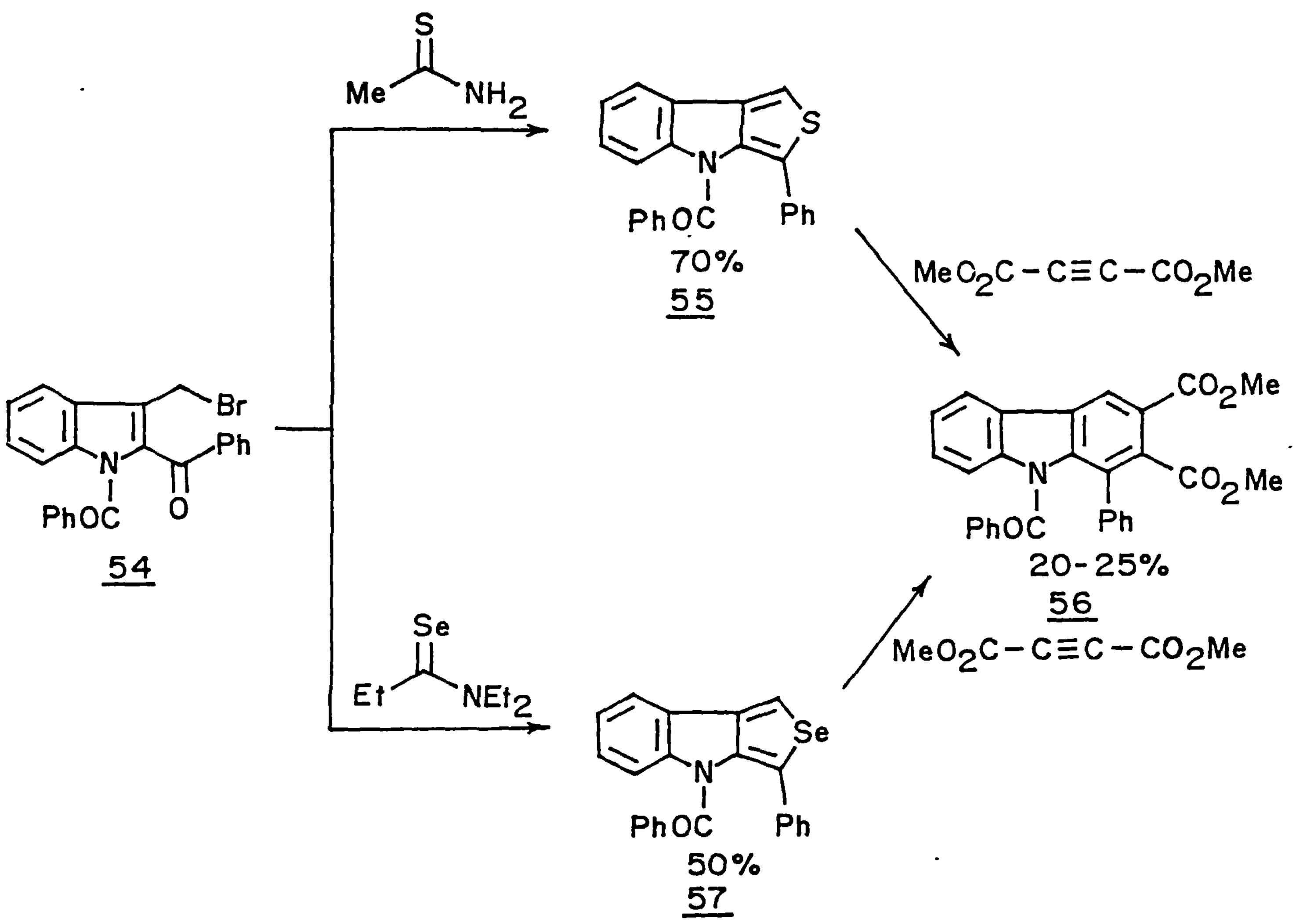
Scheme-11

Srinivasan, P.C.; Jeevanandam, A. J. Chem. Soc. Perkin Trans I, 1995, 2663

Similarly Kreher and Dyker prepared[23] 2-(tert-butyl)-4-methyl-2,4-dihydropyrrolo [3,4-b] indole **45** *via* selective reduction of 2-(tert-butyl)-4-methyl-2,4-dihydropyrrolo [3,4-b] indol-1(2H)-one **42** (or) 2-(tert-butyl)-4-methyl-2,4-dihydropyrrolo[3,4-b]indol-3(2H)-one **43** with diisobutyl aluminiumhydride (DIBAH). The same precursors **42** and **43** were transformed into the 2-(tert-butyl)-4-methyl-2,4-dihydro [3,4-b] indoles **44** and **46** bearing a methoxy group in the 1- or 3-position, respectively, *via* a two-step procedure comprising o-alkylation and CH deprotonation. These three novel o-quinodimethane analogues **44**,**45**, and **46** reacted as heterocyclic dienes with benzyne to yield initially bridged adducts which underwent selective ring opening at aminobridge to give the corresponding 5H-benzo [b] carbazoles **47**,**48** and **49** readily (Scheme 10).

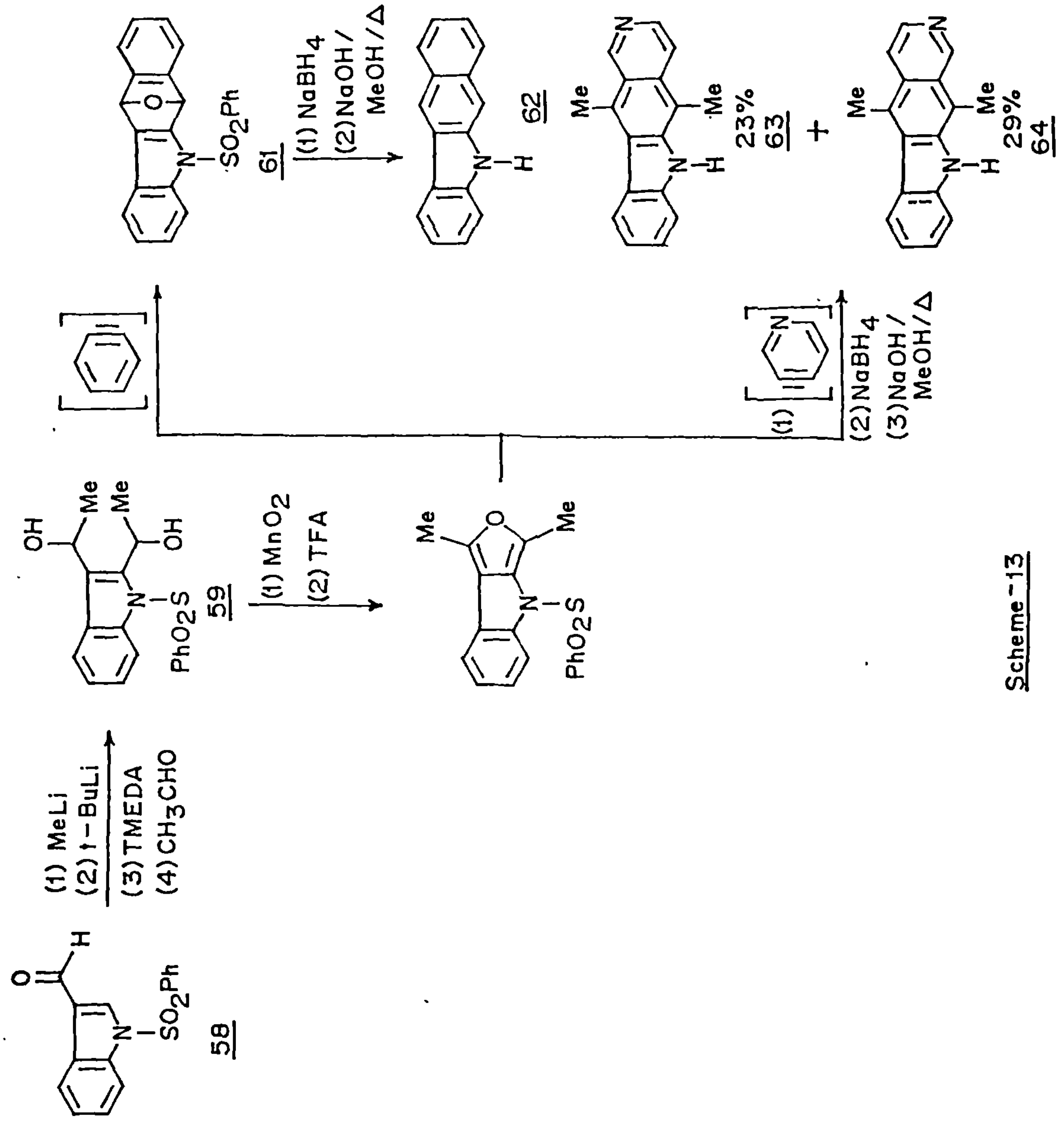
Again Srinivasan[24] and co-workers have prepared a number of pyrrolo[3,4-b] indoles **51** and reacted with highly reactive dienophile dimethyl acetylenedicarboxylate to get the corresponding cycloadducts **52** and transformed these bridged adducts to the corresponding carbazoles **53** *in situ* treating the reaction mixture with p-toluenesulphonic acid in 52-59% over all yields (Scheme II). Although there are many methods for functionalized carbazoles, there are few reports for the synthesis of amino substituted carbazoles[25]. This methodology constitutes an attractive route for the synthesis of such compounds.

Starting from selectively functionalised indolylketones, a series of substituted thieno [3,4-b] indoles **55** and seleno [3,4-b] indoles **57**, both representing new classes of hetrocycles, were prepared[26]. Both

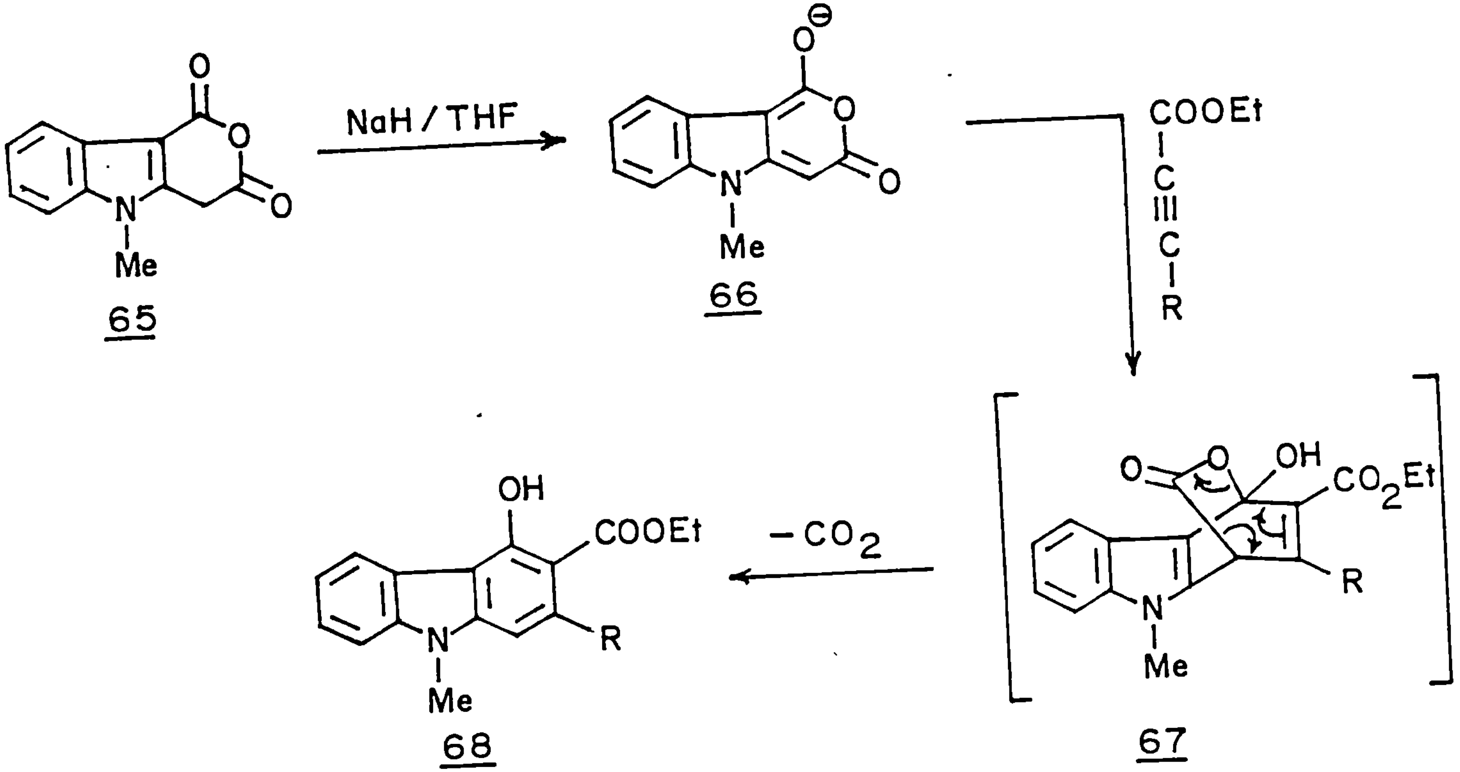


Scheme-12

Shafiee, A.; Sattari, S. J. Heterocycl. Chem. 1982, 19, 227


58
(1) MeLi
(2) t-BuLi
(3) TMEDA
(4) CH3CHO
59
(1) MnO2
(2) TFA
61
(1) NaBH4
(2) NaOH / MeOH / Δ
62
(1)
(2) NaBH4
(3) NaOH / MeOH / Δ
23%
63
29%
64

Scheme-13



R = CO_2Et 45%

R = H 21%

Scheme-14

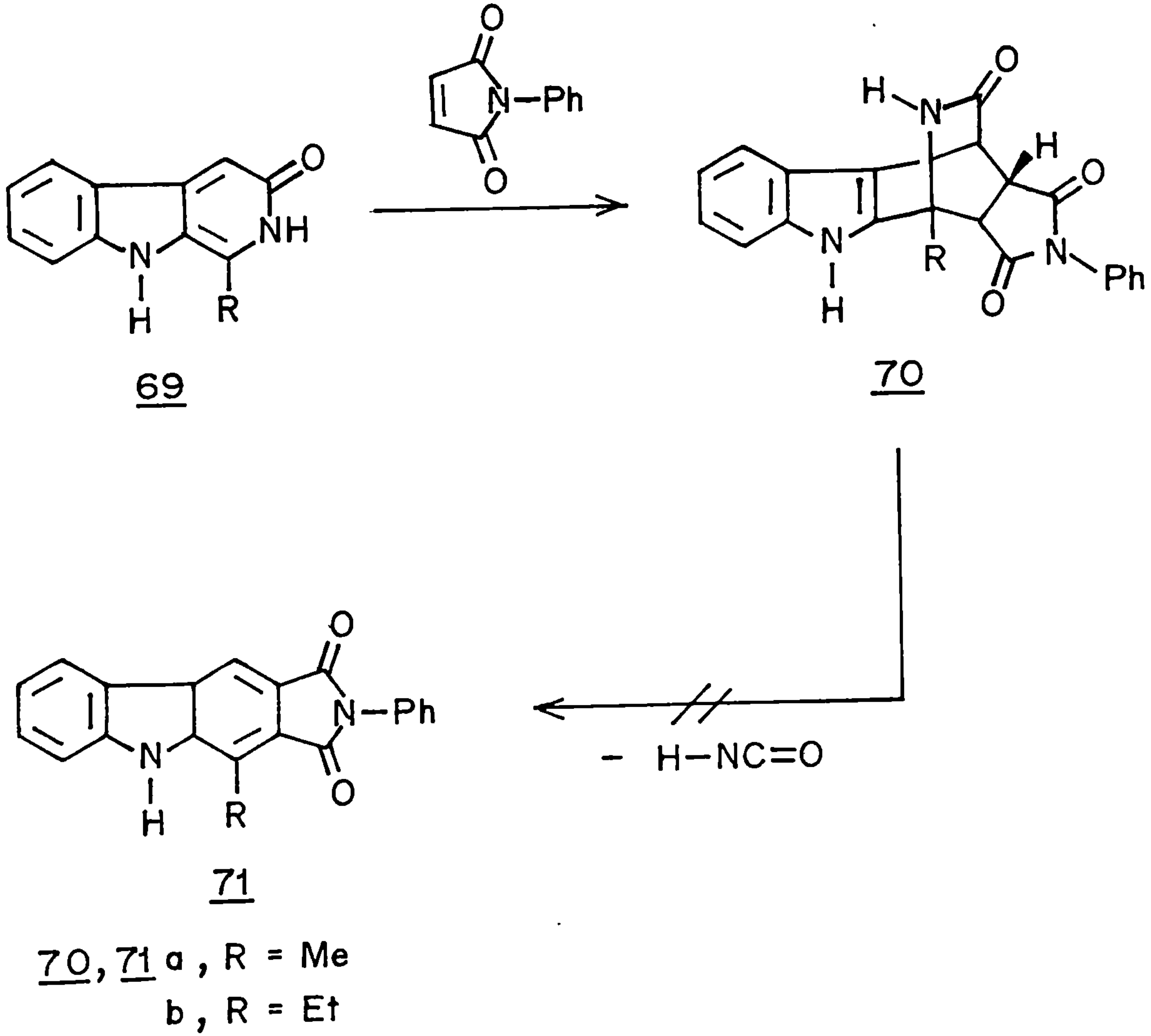
Tamura, Y.; Mohri, S.; Maeda, H.; Tsugoshi, T.; Sasho, M.; Kita, Y. Tetrahedran left. 1984, 25, 309-312

Fleming, I. "Frontier Orbitals and Chemical Reactions"; Wiley : New York, 1976.

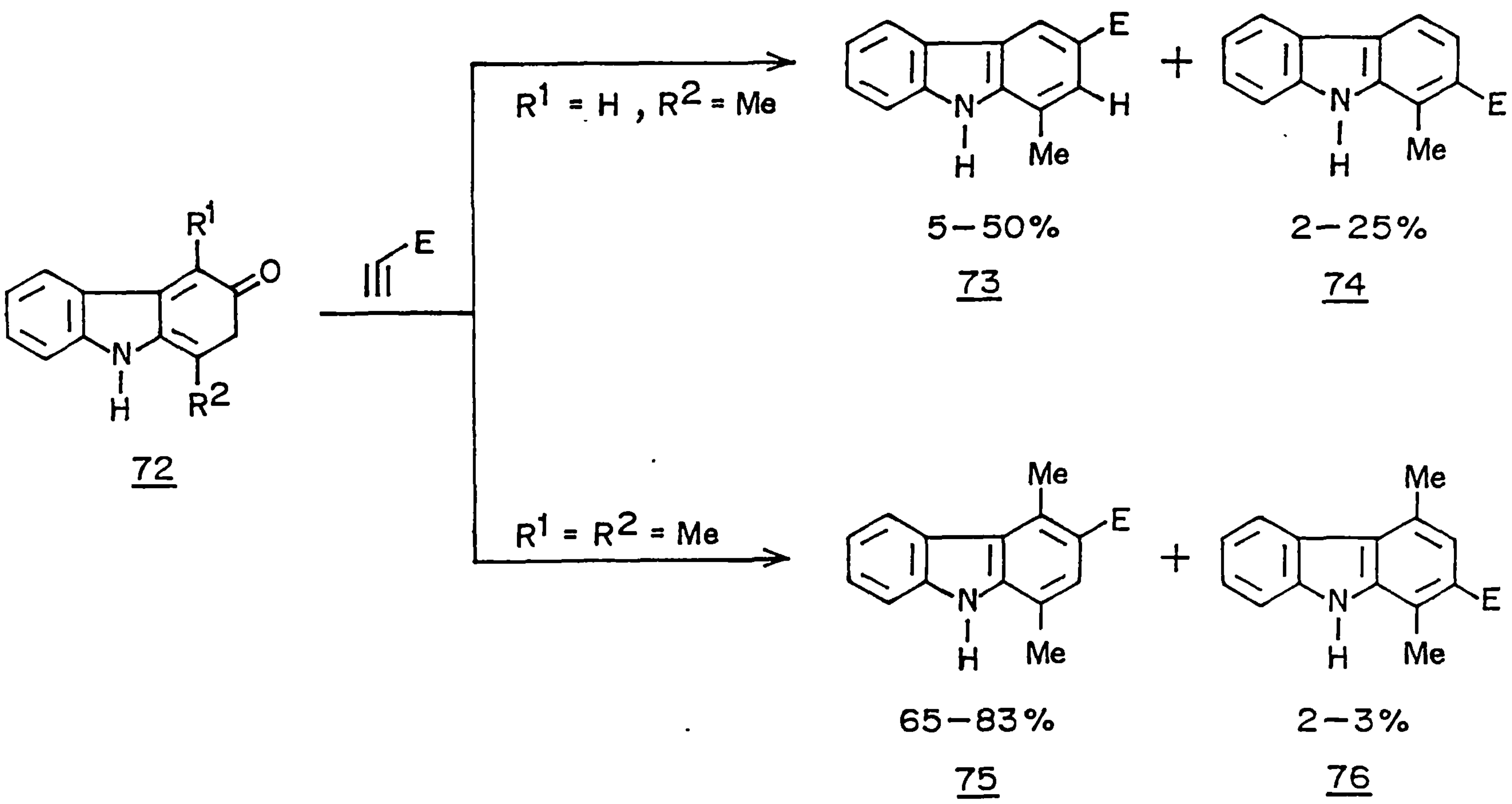
of them **55** and **57** were reacted with dimethyl acetylenedicarboxylate to give the corresponding carbazoles **56** in moderate yields. (Scheme 12).

4H-Furo[3,4-b] indoles **60** were also employed successfully for the regiocontrolled [b] annulation of the indole skeleton[27,28,29,30] . The reaction of **60** with Benzyne yielded the corresponding benzo [b] adducts **61** with a bridged oxygen, which on subsequent reductive cleavage with sodium borohydride and sodium hydroxide resulted in the removal of oxygen bridge and N-protecting group, yielded the corresponding benzo[b] carbazole **62**. More importantly this annulation strategy was also used to produce cytostatically active alkaloids such as ellipticine and isoellipticine[28,29] (Scheme 13). The o-quinodimethane analogue **60** when reacted with 3,4-pyridyne yielded the isomeric mixture of the Diels-Alder adducts. The oxygen bridge and the N-protecting group were removed by treatment with $NaBH_4$ and NaOH, to yield the 23% of ellipticine **63** and 29% of the isoellipticine **64**. Following an analogous strategy, a new, potential bifunctional nucleic acid intercalating agent, namely 1,10-bis(6-methyl-5H-benzo [b] carbazol-11-yl) decane was synthesized.[30]

Mohri[31] and co-workers were able to generate o-quinodimethane intermediate **66** (Scheme 14) utilising the anhydride **65** by reported methods[32,33]. This important o-quinodimethane **66** was then reacted with various dienophiles to yield the corresponding 4-hydroxycarbazoles **68**. Extrusion of carbon dioxide from the bicyclic adduct **67** was achieved *in situ* under the same reaction conditions to yield the product carbazole **68** in one pot reaction. Method is of interest because it yielded only one regioisomer with ethyl



Scheme -15



E = CN , COOMe etc

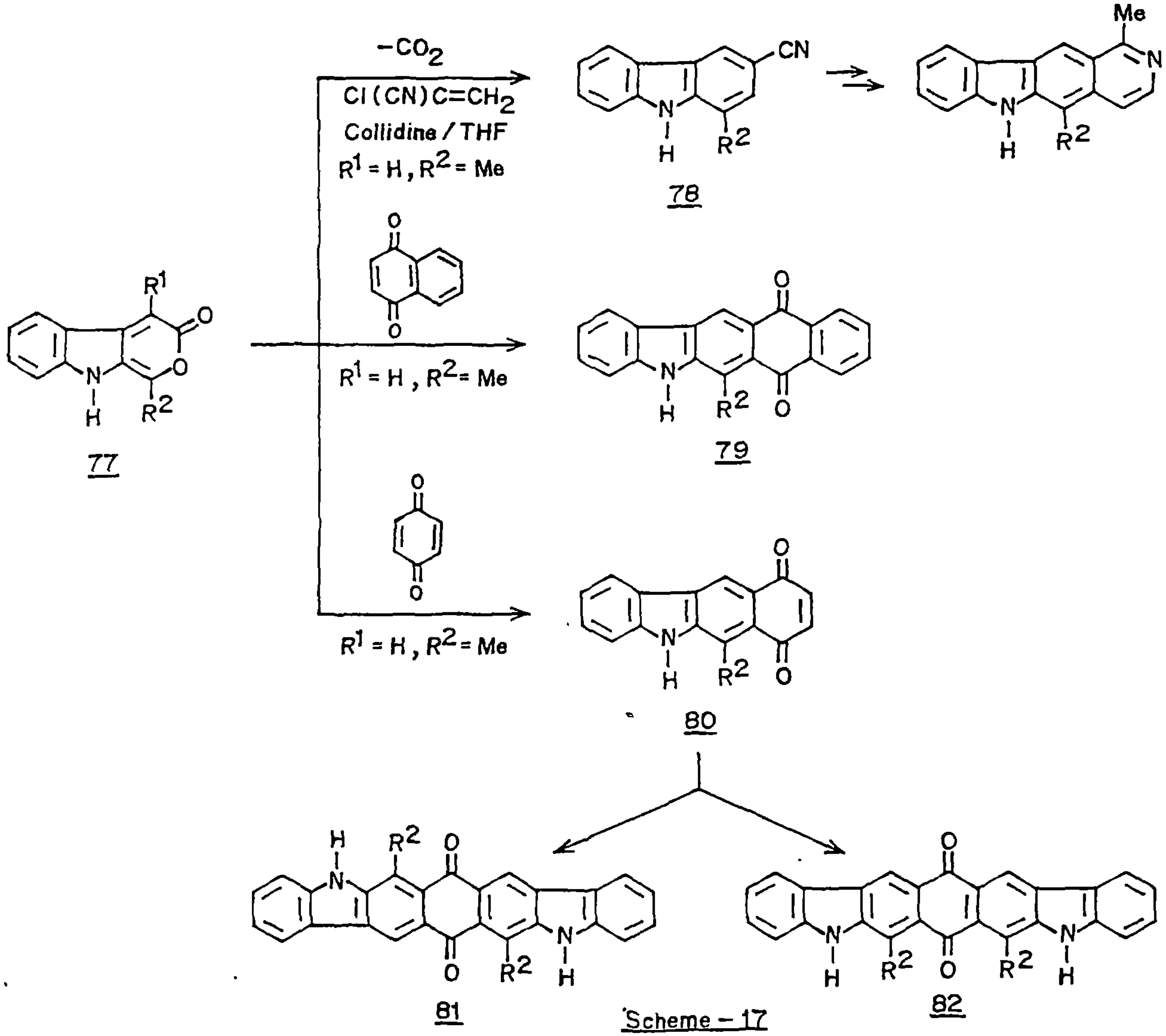
Scheme—16

propynoate unlike symmetrical o-quinodimethane intermediates described in the preceding section. The regiochemistry obtained in the reaction is without doubt the result of charge-controlled orientation[34] of the two reaction partners in the transition state.

This strategy was exploited for the regiospecific total synthesis of very important D-ring indole analogue of daunomycin, which is a powerful antitumor agent widely used in the clinic to treat leukaemia and solid turmors[35].

Indolopyridones[36] **69** also represent indolo-2,3-quinodimethane analogues which are isoelectronic with their oxygen analogues. Cycloaddition reactivity of these pyridones **69** with N-phenylmaleimide yielded the corresponding bicyclic system **70** in 88% yield. However[37], further attempts to eliminate bridged component was not possible to yield the expected carbazole **71**, since the isocyanic acid that would be formed on extrusion of the bridge represents an extremely poor retro dienophile.

Pyrano [3,4-b] indol-3-ones[36] **72** also represent more versatile indolo-2,3-quinodimethane analogues[37,38,39,40]. These intermediates react with dienophiles, with the *in situ* elimination of carbon dioxide to yield functionalized [b] annulated indoles as a mixture of regio isomers **73** and **74**. Better regioselectivity[37] was observed when R^1 and R^2 in **72** were methyl groups. The corresponding 1,4-dimethylcarbazole **75** was obtained in excellent yields. while the other isomer **76** was formed only in small quantities (Scheme 16).


-CO2
Cl(CN)C=CH2
Collidine / THF
R1 = H, R2 = Me
R1 = H, R2 = Me
R1 = H, R2 = Me
77
78
79
80
81
82

Scheme – 17

With indolopyranones the "cycloaddition/ cyclorevertion" strategy[29,41,38] was more facile than in case of the corresponding nitrogen analogues. For example[41] **77** reacts with 2-chloropropenenitrile in the presence of collidine to yield the corresponding 3-cyanocarbazole **78** which is an important precursor in the synthesis of alkaloid olivacine (Scheme 17). Reaction[39] of **77** with napthaquinone yielded the expected [b] annulated carbazolequinone **79**. However when 1,4-benzoquinone was reacted with **77** the intermediate quinone **80** reacted with second molecule of **77** to yield the corresponding dimeric adducts **81** and **82** as a mixture.

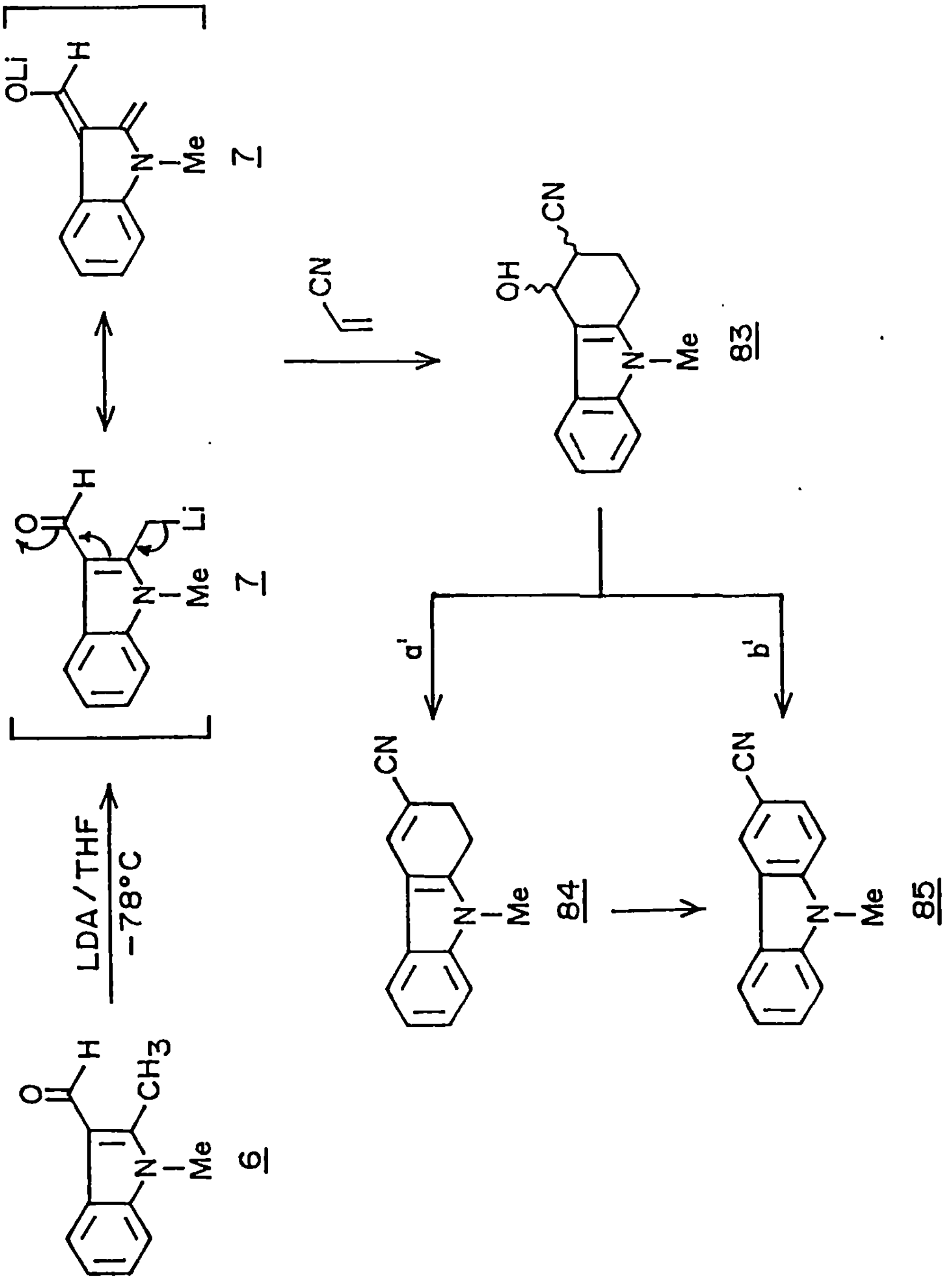
In conclusion it may be inferred that o-quinodimethane approach to the synthesis of carbazoles and many related alkaloids has been very. productive. From the result it is possible to select appropriate structural frame of o-quinodimethane analogues so as to exercise control on the product regioselectivity. There, synthetic methodology should provide an useful path way for the synthesis of important substituted carbazoles of biological interest.

II.A.3 Results and Discussion :

Present Investigation:

In the preceding section the brief survey on Indolo-2,3-quinodimethanes and their use as dienes with various dienophiles to yield functionalized [b] annualed indoles, indole alkaloids and carbazoles have been amply demonstrated. The merits and demerits of these o-quinodimethane intermediates in terms of yields and regiochemistry has also been highlighted. Apparently many of these intermediates did not display expected high regioselectivity, particularly when there are unsymmetrical structural frames. On the other hand *in situ* generated electron rich anionic o-quinodimethane analogues displayed not only pronounced reactivity towards various dienophiles, but also grater regio control in the cycloadduct. On the basis of these reported literature it was considered of interest to examine the ability of the diene properties and regio selectivity of the 0-quinodimethane analogue derived from 1,2-dimethylindole 3-carboxaldehyde. To our surprise the expected o-quniodimethane intermediate was indeed formed and underwent cycloaddition with wide range of dienophiles particularly the unsymmetrical ones to yield the corresponding [b] annulated carbazoles with marked regioselectivity. Results of these studies are presented in this section.

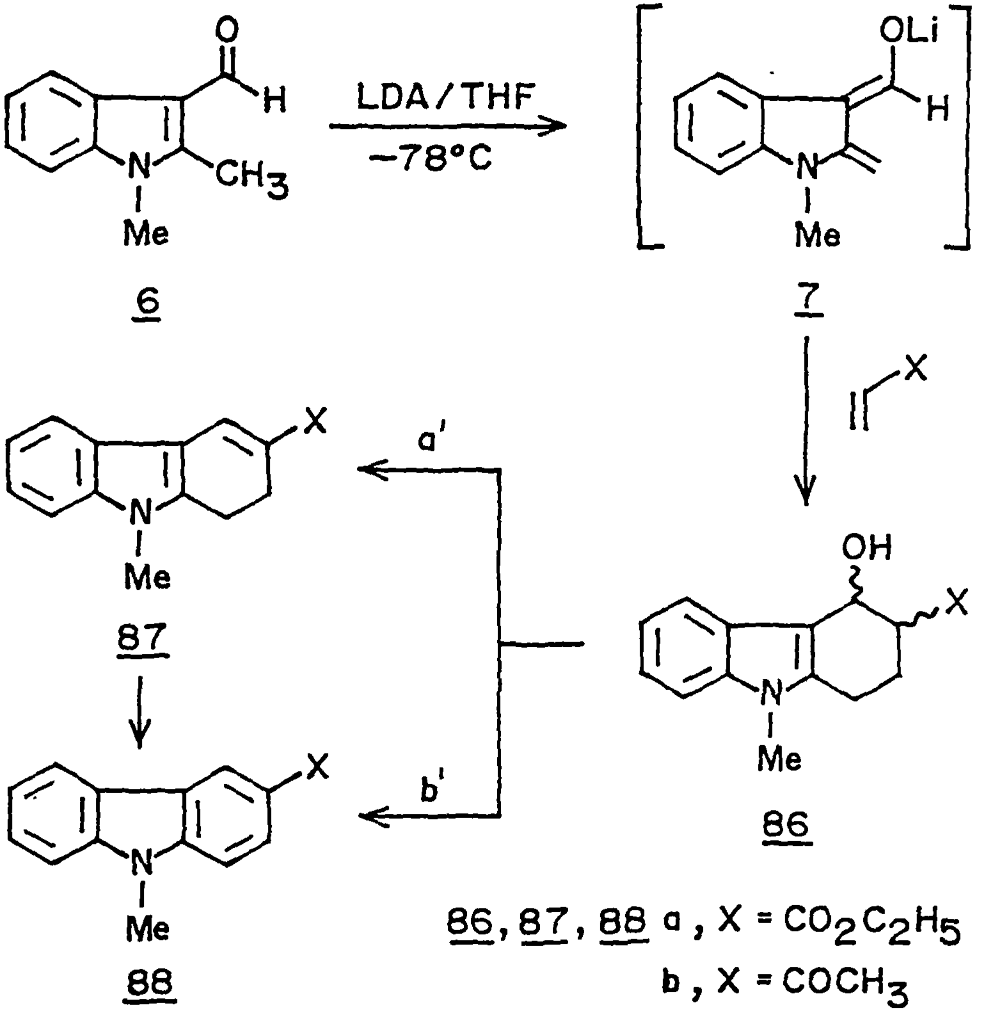
1,2-dimethylindole-3-carboxaldehyde was prepared by the alkylation of 2-methylindole-3-carboxaldehyde which was synthesised according to the reported[42] method. In a typical experiment <u>6</u>



a', Silica gel ; b', $Py^{\oplus}\,{}^{\ominus}OTS$ / C_6H_6 / Δ

Scheme–18

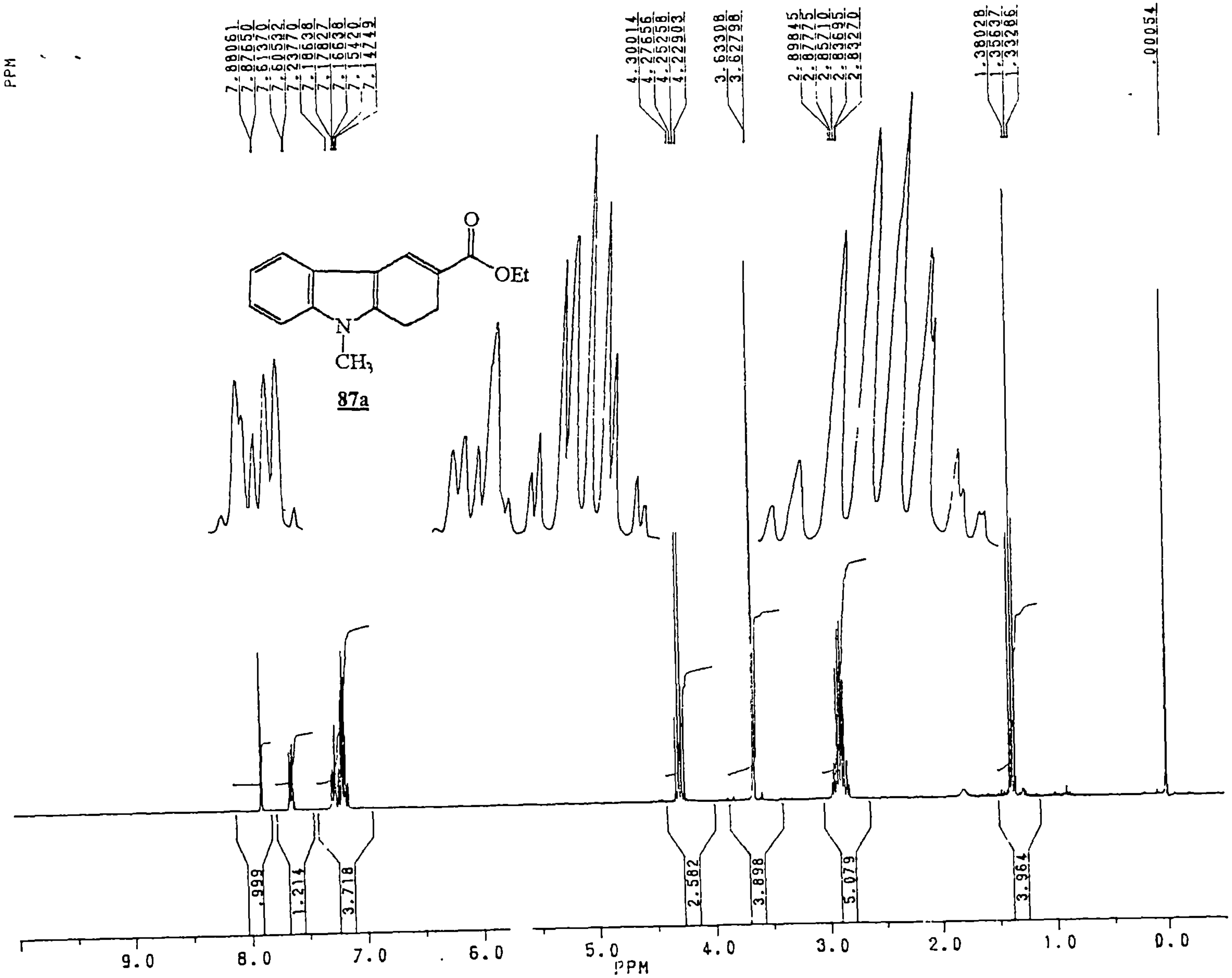
(scheme 18) was treated with lithium disopropylamide in dry tetrahydrofuran under masked nitrogen atmosphere at –78°C to yield a bright red solution presumably due to formation of indole-2,3-dienolate intermediate 7. To establish authenticity and reactivity of this indole 2,3-dienolate, the reaction mixture was then reacted with acrylonitrite at the same temperature, which after workup and silica gel chromatographic separation yielded the corresponding 3-cyano-1,2-dihydro-9-methyl carbazole **84** as light yellow crystals (chloroform/ hexane) in 78% yield, m.p. 120-121°C. The expected regioselectivity was observed in the reaction and no traces of other regio isomers was detected . The structure of **84** was established on the basis of its analytical and spectral data . It was analysed for the molecular formula $C_{12}H_{12}N_2$ with a molecular weight 208.26, which was supported by its mass spectrum exhibiting a molecular ion peak at m/z 208 (M^+, 100%) corresponding to the molecular weight of **84**. In its IR spectrum (KBr), it displayed characteristic absorption band at 2183 cm^{-1}, which was assigned to C≡N group. Other prominent absorption bands are described in the experimental section. The structure of **84** was unambiguously established by its ^1H NMR spectrum ($CDCl_3$). The ring dihydro four proton signal appeared as multiplet at δ2.66-3.06. The N-methyl three protons appeared as a singlet at δ3.69. The aromatic protons appeared as a multiplet at δ7.16-7.36 accounting three protons, were assigned for H-6, H-7 & H-8 protons. The aromatic protons appeared at δ7.39-7.69 integrating for two protons which were assigned for H-4 and H-5 protons. Thus, the structure of **84** was confirmed, which on further heating with pyridinium tosylate in benzene to yield the corresponding 3-cyano-9-methylcarbazole (dichloromethane/hexane), (m.p. 94-95°C) **85** in 76% yield. The



86, 87, 88 a, X = $CO_2C_2H_5$
b, X = $COCH_3$

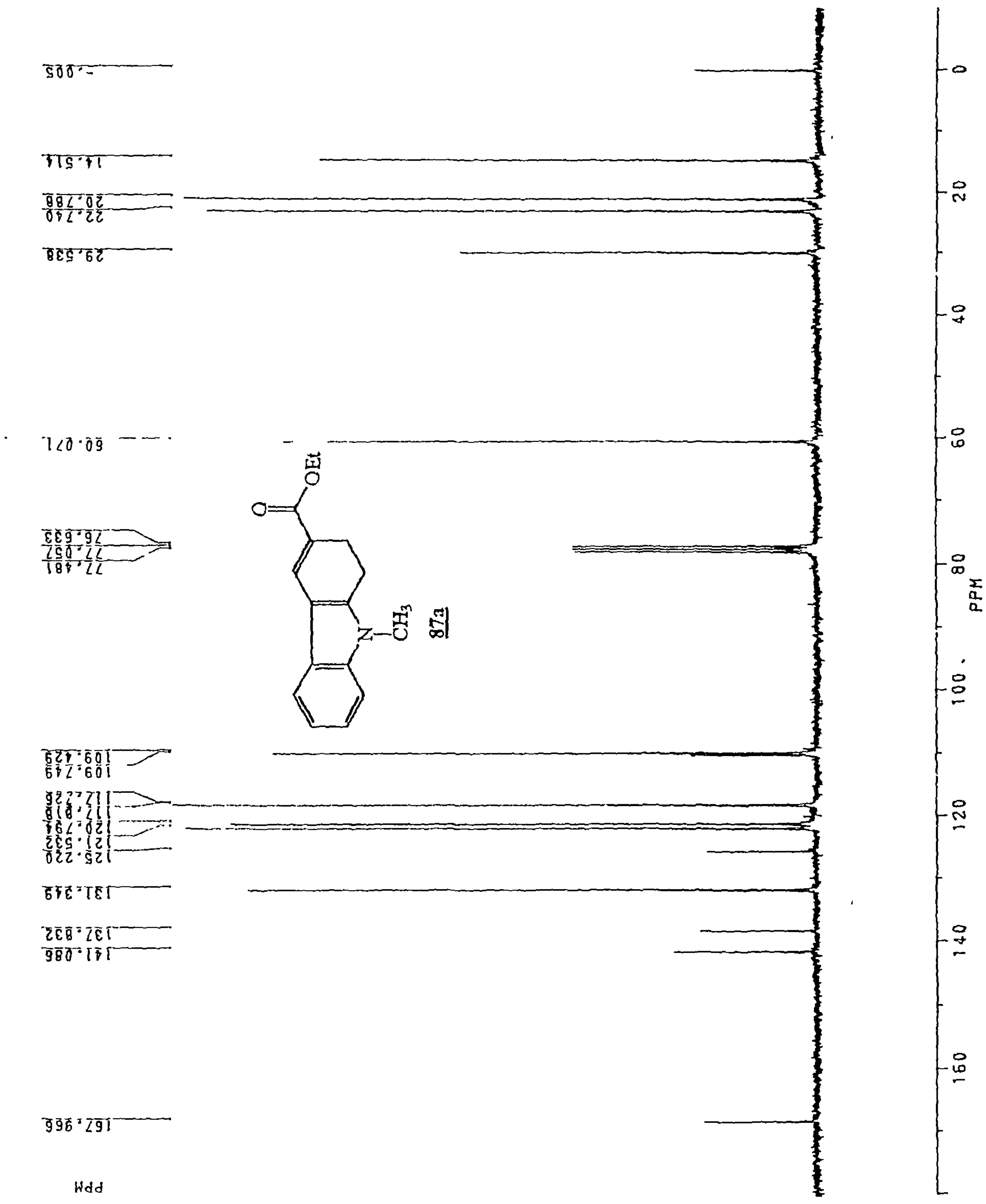
a', Silica gel ; b', $Py^{\oplus}\overset{\ominus}{O}TS$ / C_6H_6 / Δ

Scheme-19



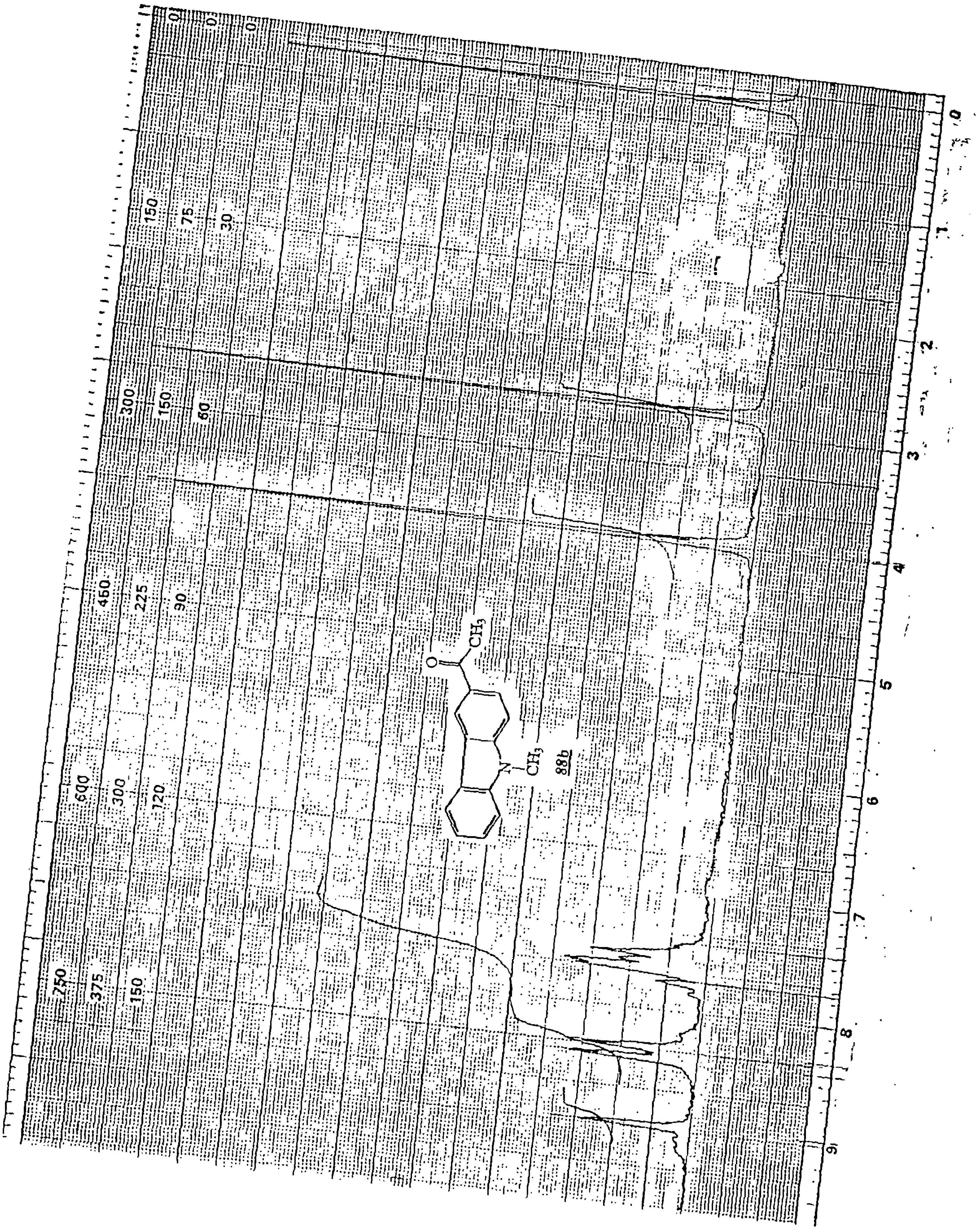
PPM
7.88061
7.87650
7.61370
7.60532
7.23770
7.18638
7.17827
7.16638
7.15420
7.14749
4.30014
4.27656
4.25258
4.22903
3.63308
3.62798
2.89845
2.87775
2.85710
2.83695
2.83270
1.38028
1.35637
1.33286
.00054
O
OEt
N
CH₃
.999
1.214
3.718
2.582
3.898
5.079
3.964
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0

87a


-.005
14.514
20.786
22.740
29.538
60.071
76.633
77.057
77.481
109.429
109.749
117.228
117.818
120.794
121.532
125.220
131.349
137.832
141.086
167.966
PPM
O
OEt
N
CH3
87a
0
20
40
60
80
100
120
140
160
PPM

carbazole **85** was also directly obtained when **83** was treated with pyridinium tosylate in refluxing benzene. The structure of 3-cyano-9-methylcarbazole **85** was confirmed from its spectral and analytical data. The characteristic (C≡N) absorption in its IR spectrum (KBr) appeared at 2121cm^{-1}, and in its ^{1}H NMR spectrum ($CDCl_3$) the N-methyl three protons appeared at δ3.60. the multiplet for five protons at δ 7.13-7.66 were assigned for the aromatic protons H-1, H-2, H-6, H-7 and H-8. The peak integrated for one proton at δ 7.80-7.96 as doublet with a coupling constant 7.5Hz was assigned for H-5. The peri proton H-4 appeared as a singlet at δ 8.06. In its mass spectrum, **85** displayed molecular ion peak m/z at 206 (M^+, 100%) corresponding to its molecular weight and it was analysed for $C_{14}H_{10}N_2$ with a molecular weight (206.24). All the structures assigned were in conformity with their spectral and analytical data which are described in the experimental section.

The o-quinodimethane intermediate **7**, when reacted with ethylacrylate and methyl vinylketone the corresponding 1,2-dihydro-3-ethoxycarbonyl-9-methylcarbazole **87a** and 3-acetyl-1,2-dihydro-9-methyl carbazole **87b** in 84% and 80% yield respectively. Both the compounds **87a** and **87b** were stable during silica gel chromatographic separation and thus were fully characterised. The corresponding spectral and analytical data of both **87a** and **87b** which were in accord with the assigned structures are recorded in experimental section. Both **87a** and **87b** underwent aromatization after prolonged heating with pyridinium tosylate in dry benzene to yield corresponding 3-ethoxycarbonyl-9-methylcarbazole **88a** and 3-acetyl-9-methylcarbazole **88b** in quantitative yields. Alternatively


0
1
2
3
4
5
6
7
8
9
0
0
0
150
75
30
300
150
60
450
225
90
600
300
120
750
375
150
O
CH3
N
CH3

88b

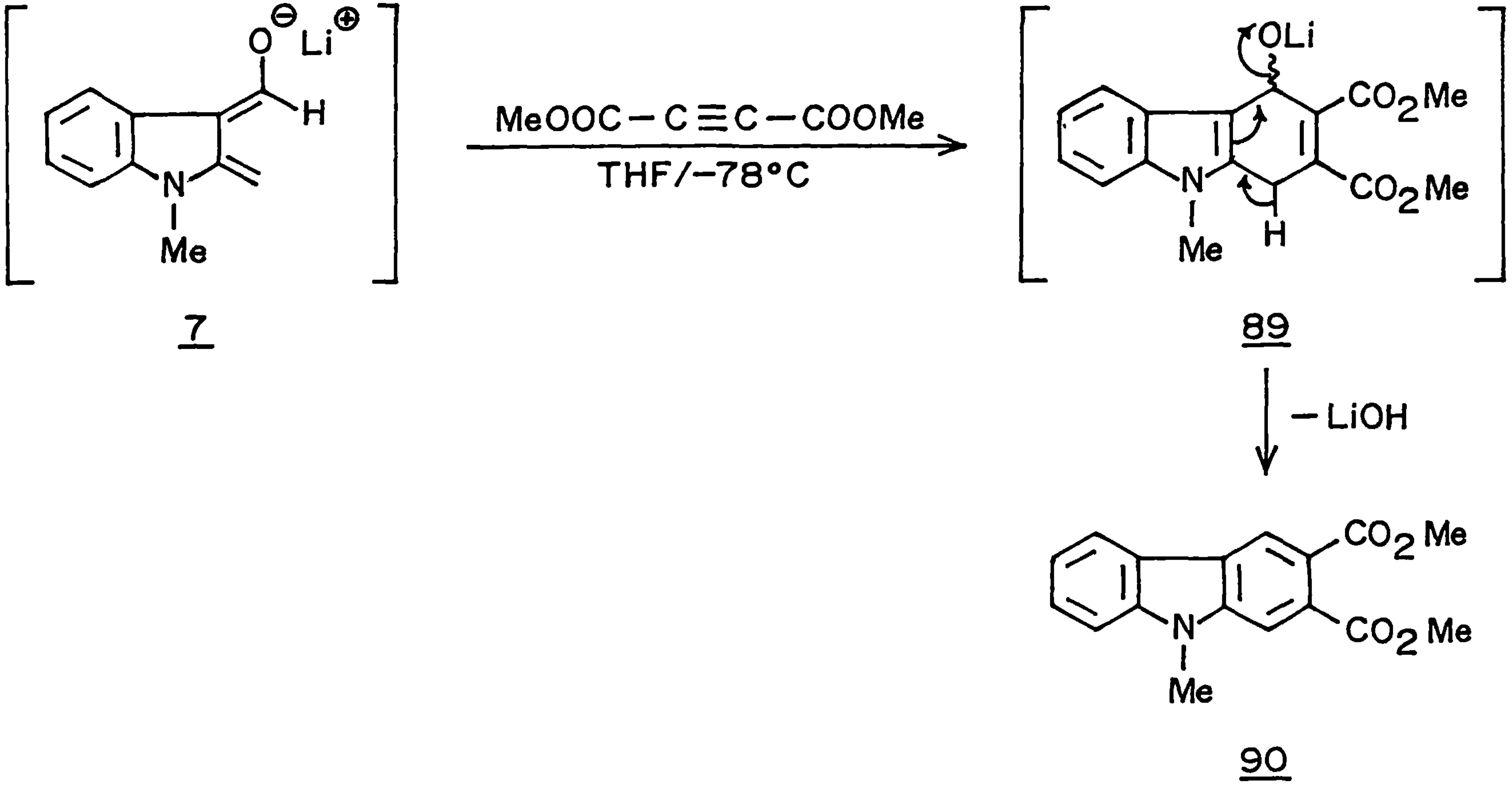
the adducts **86a** and **86b** both underwent elimination aromatization directly to yield the corresponding carbazoles **88a** and **88b** respectively when **86a** and **86b** were treated with pyridinium tosylate in reflxing benzene. In this case also the expected regioselectivity was observed and no trace of other regio isomers were detected.

Cycloaddition of Indole-2,3-dienolate **7** with Dienophiles: Formation of Carbazole Derivatives.

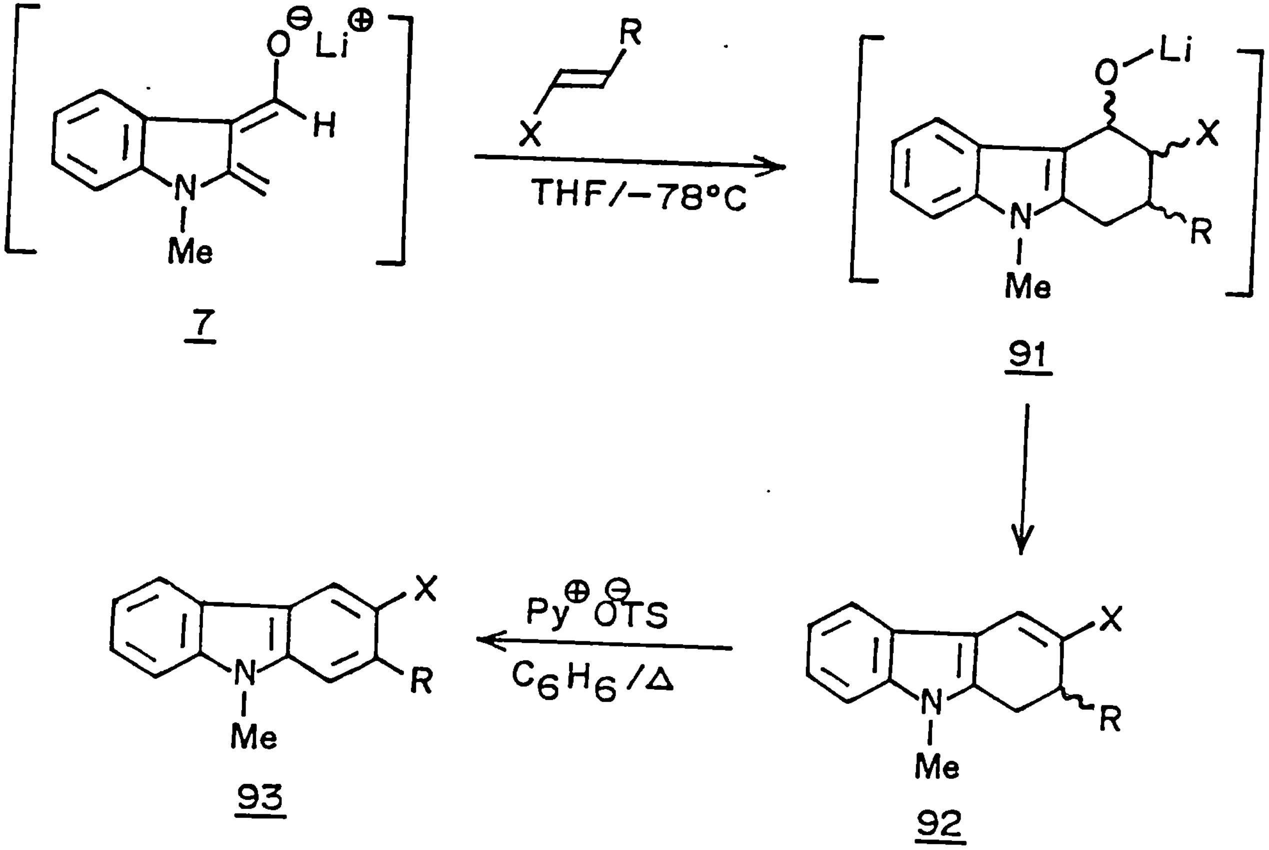
Entry	Dienophile	Product	% Yield
1.	$MeO_2CC{\equiv}CCO_2Me$	90	76
2.	$CH_2{=}CH\text{-}CN$	84	78
3.	$CH_2{=}CHCN$	85*	76
4.	$CH_2{=}CHCO_2Et$	87a	84
5.	$CH_2{=}CHCO_2Et$	88a*	72
6.	$CH_2{=}CHCOMe$	87b	80
7.	$CH_2{=}CHCOMe$	88b*	76
8.	$EtO_2CCH{=}CHCO_2Et$	92a	73
9.	$C_6H_5CH{=}CHCO_2Me$	92b	79
10.	$C_6H_5CH{=}CHNO_2$	93c*	72
11.	$O_2NCH{=}CH(SMe)_2$	95	68
12.	$MeO_2C(CN)CH{=}CH(SMe)_2$	98	69

* Obtained after refluxing with pyridinium tosylate in dry benzene

Table 1


O⊖ Li⊕
H
N
Me
7
MeOOC − C ≡ C − COOMe
THF/−78°C
OLi
CO2Me
CO2Me
N
Me
H
89
− LiOH
CO2 Me
CO2 Me
N
Me
90

Scheme – 20



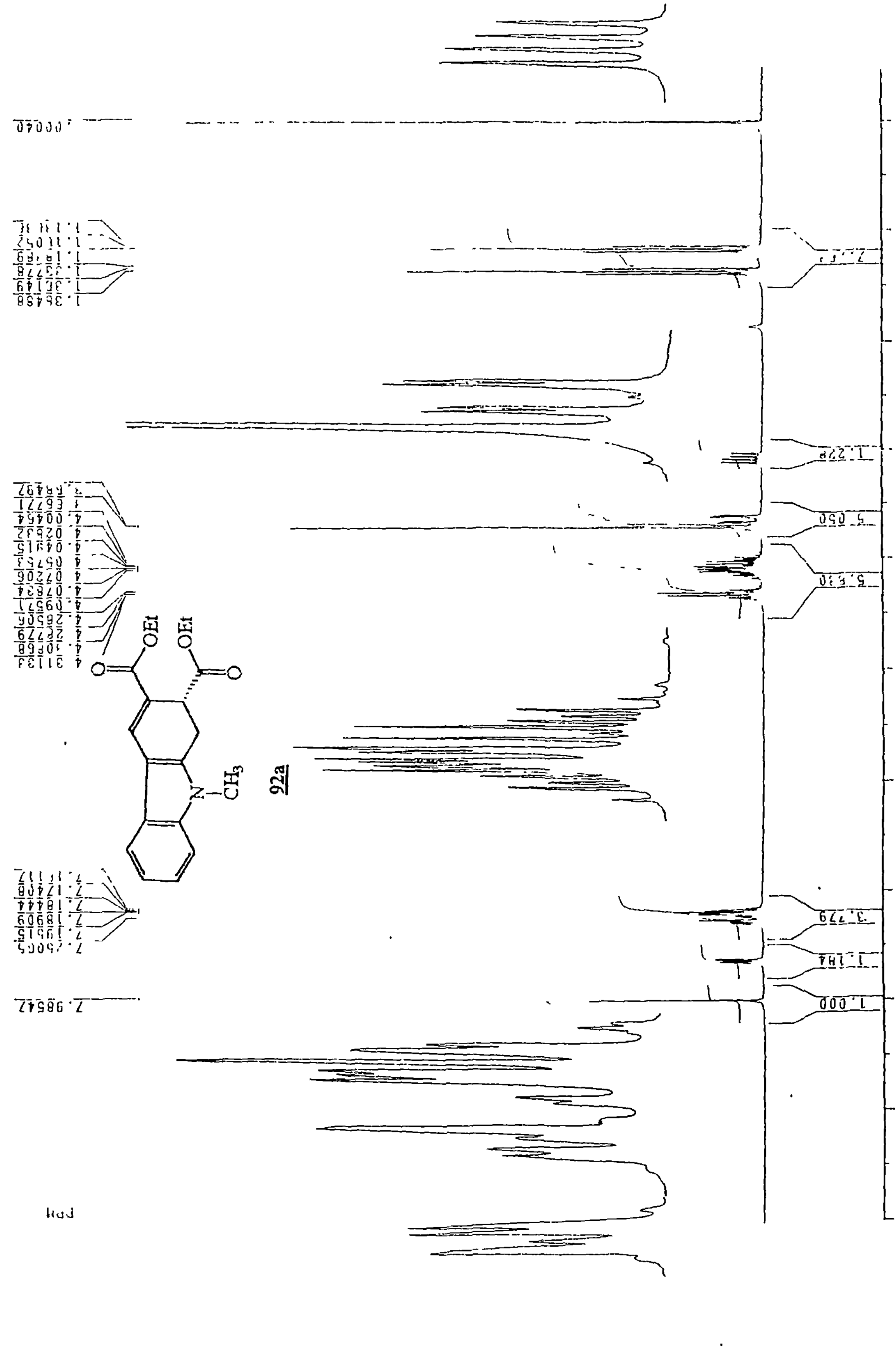
$\underline{91}, \underline{92}, \underline{93}$ a, R = CO_2Et ; X = CO_2Et
b, R = C_6H_5 ; X = CO_2Me
c, R = C_6H_5 ; X = NO_2

Scheme—21

The Indole-2,3- dienolate **7** was reacted with dimethyl acetylene dicarboxylate to yield directly 2,3-bis(carbomethoxy)-9-methylcarbazole **90** in 76% yield as light yellow crystals from dichloromethane / hexane. m.p. 128-129°C lit[43] m.p. 132-133°C and the compound was identical with that reported earlier. It shows superimposable IR and other spectral data in accordance with the assigned structure which are described in the experimental section.

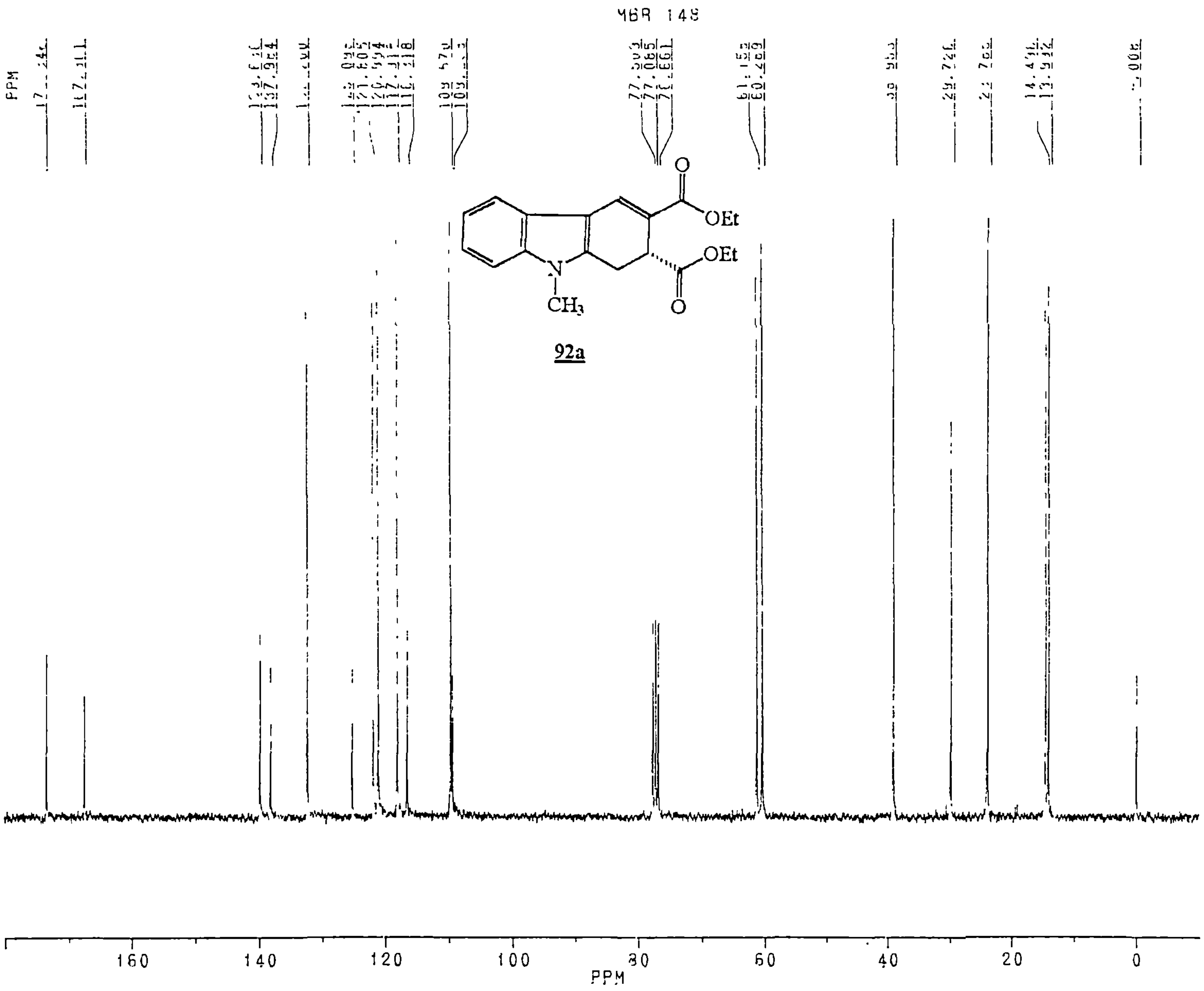
In additional series of dienophiles when Indole 2,3-dienolate **7** was reacted with symmetrical dienophile diethyl fumarate the corresponding 1,2-dihydro-2,3-bis(ethoxycarbonyl)-9-methylcarbazole **92a** (Scheme 21) (see also table 1) in 73% yield. Interestingly when Indole-2,3-dienolate **7** was reacted with unsymmetrical activated ethylene derivatives highly regioselective cycloaddition was observed. Thus **7** reacted with *trans* methyl cinnamate to yield the corre-sponding 3-carbomethoxy-1,2-dihydro-9-methyl-2-phenylcarbazole **92b** was obtained in 79% yield. This amply demonstrates the high regioselectively of the diene as expected. However, when **7** was reacted with *trans* nitrostyrene the corresponding dihydrocompound **92C** was not found to be stable and the reaction mixture was treated with pyridinium tosylate in refluxing benzene to yield the corresponding fully aromatic 9-methyl-3-nitro-2-phenylcarbazole **93C** underwent in 72% yield. Interestingly the dihydrocompound **92C** underwent dehydrogenation as described earlier, though heating the dihydrocompound alone did not give satisfactory yields of **93C**. The role of pyridinium tosylate in this and other reactions of dehydrogenation is not clear.

The nitroketene-S,S-acetal when reacted with Indole-2,3-dienolate **7**, highly regioselective cycloaddition yielded the 2- methylthio-9-



7.98542
7.25065
7.19515
7.18909
7.18444
7.17408
4.31133
4.30868
4.28729
4.26506
4.09571
4.07834
4.07206
4.05753
4.04815
4.02632
4.00454
1.36498
1.36149
1.35778
1.18969
.00040
1.000
1.184
3.779
5.050
1.228
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM
N
CH3
OEt
OEt
O
O

92a

MBR 148
PPM
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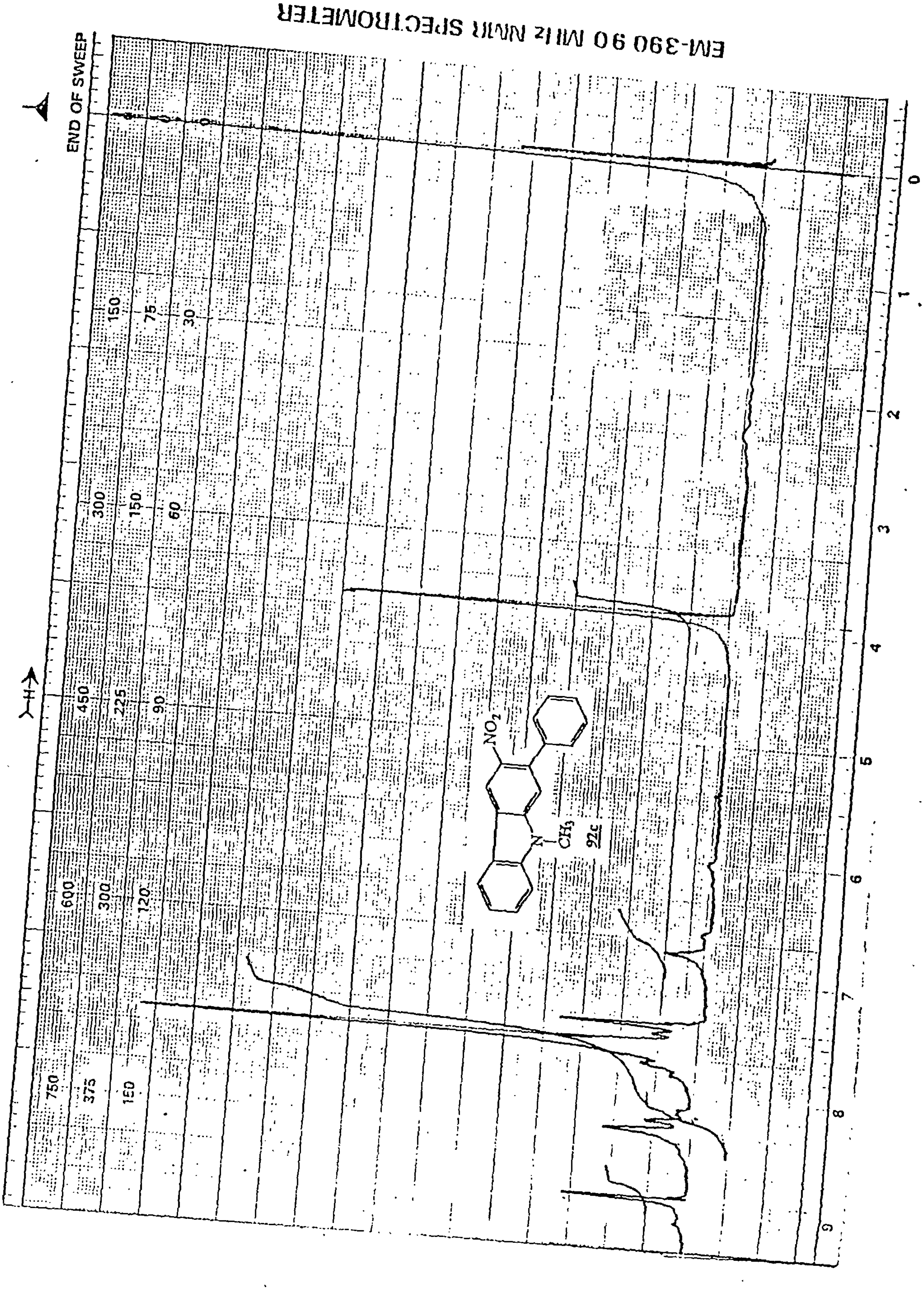
117.318
116.218
77.503
77.085
76.661
61.152
60.469
29.726
14.496
13.912
OEt
OEt
O
O
N
CH₃
160
140
120
100
80
60
40
20
0
PPM

92a


EM-390 90 MHz NMR SPECTROMETER
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5
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7
8
9
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75
30
300
150
60
450
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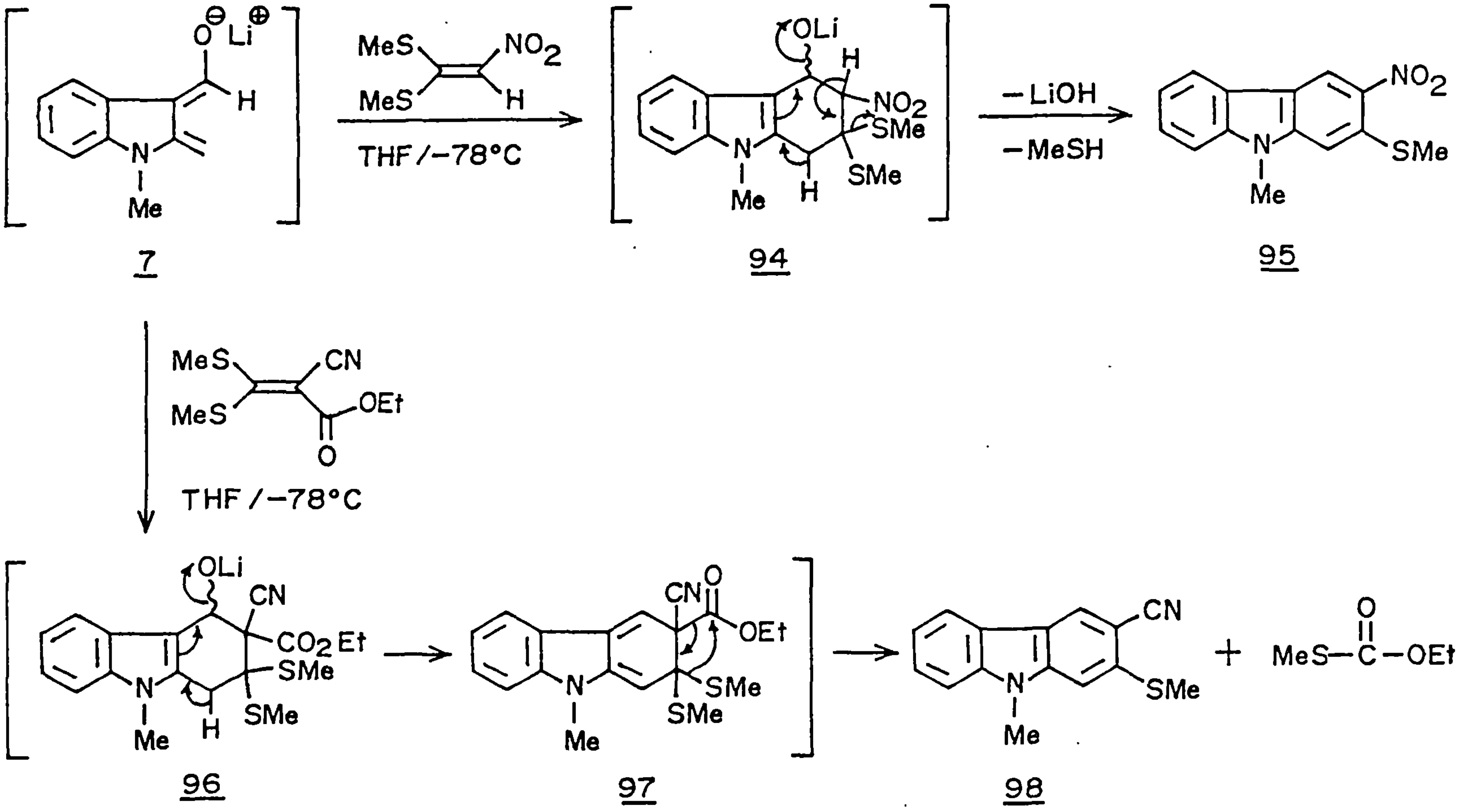
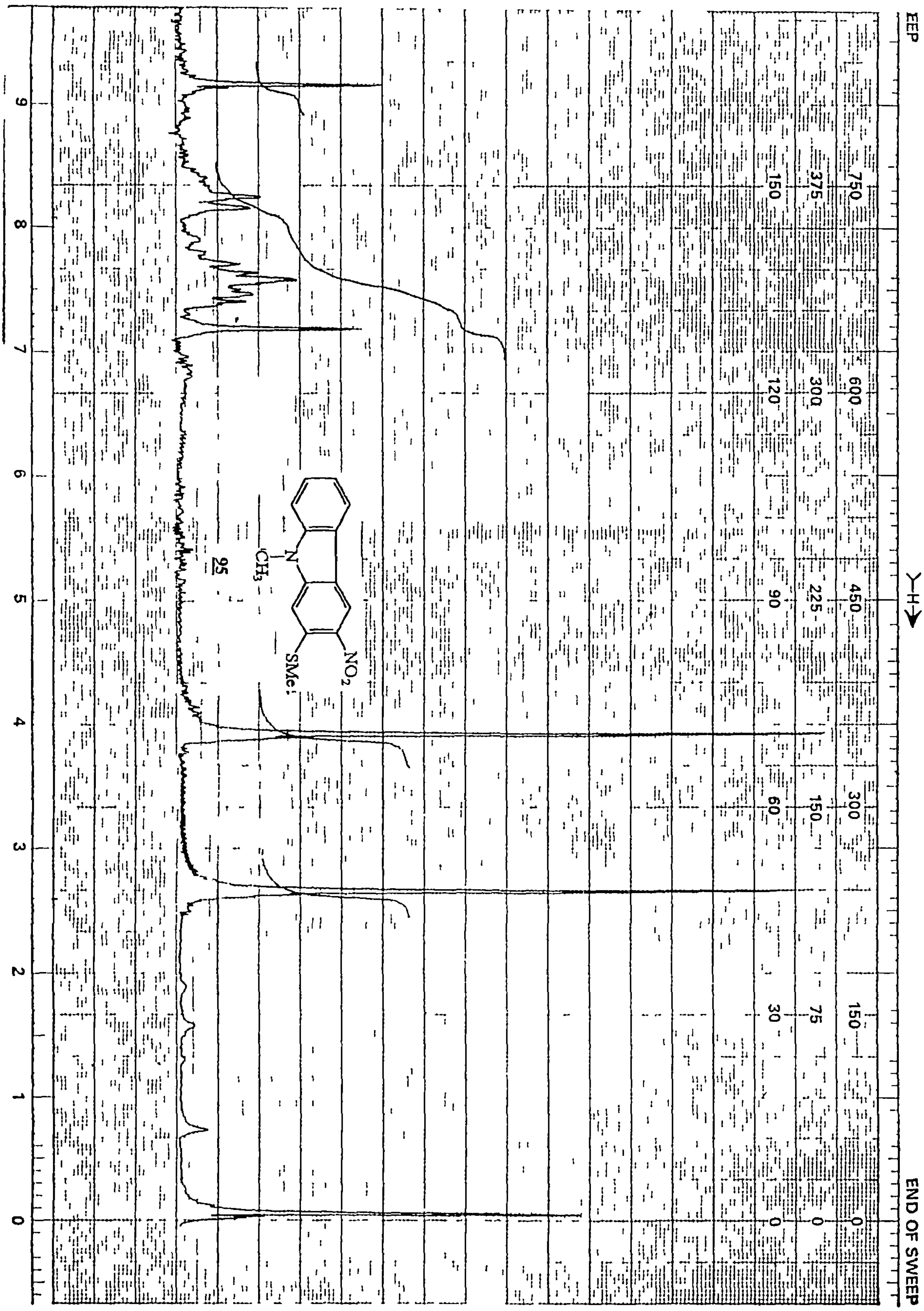
750
375
150
NO2
N
CH3
92c


MeS
MeS
NO2
H
THF/−78°C
−LiOH
−MeSH
OLi
CN
OEt
CO2Et
SMe
MeS—C—OEt
7
94
95
96
97
98

Scheme−22


EEP
END OF SWEEP
750
375
150
600
300
120
450
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90
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150
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30
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0
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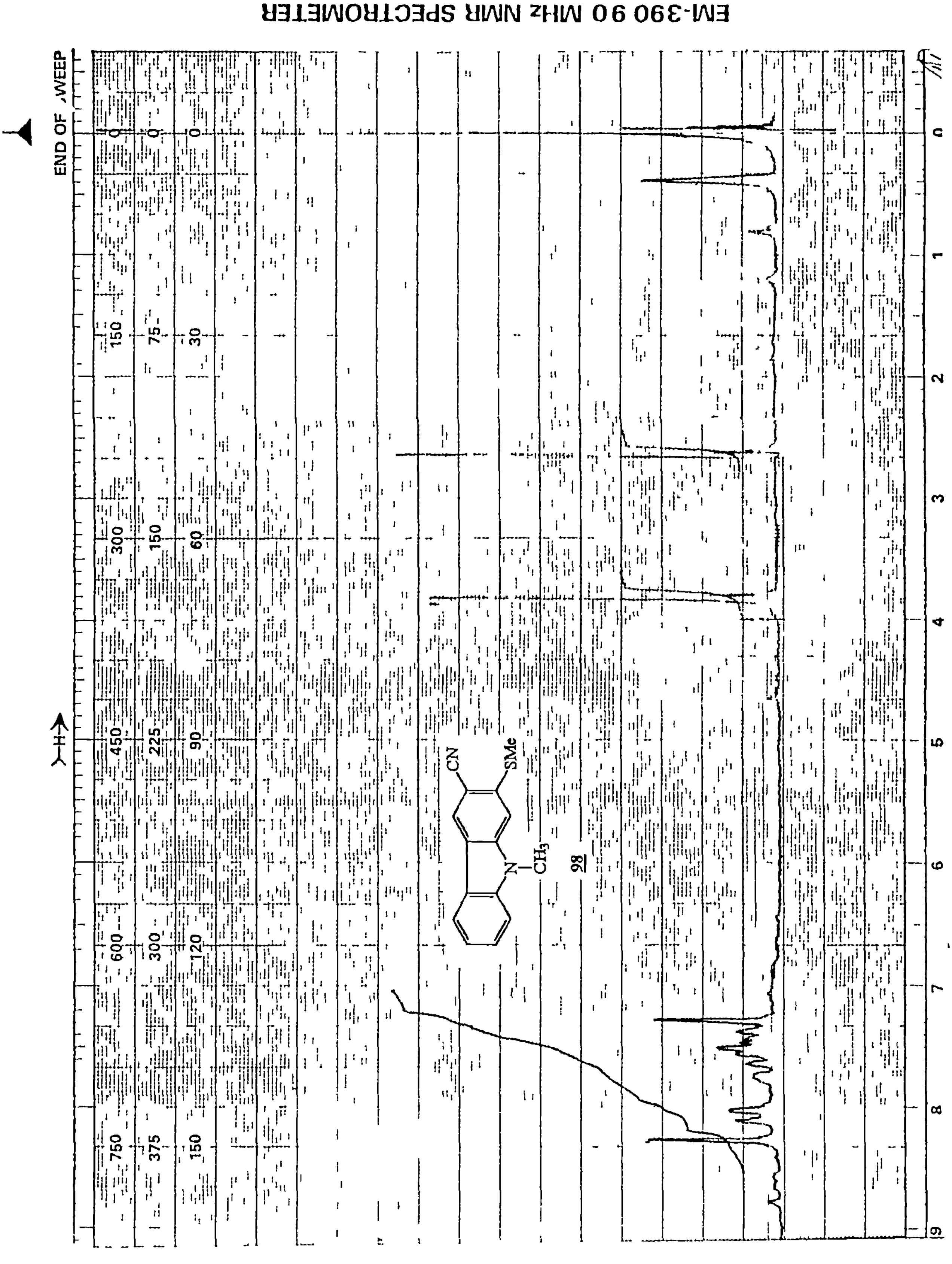
SMe
N
CH3
95
EM-390 90 MHz NMR SPECTROMETER


EM-390 90 MHz NMR SPECTROMETER
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300
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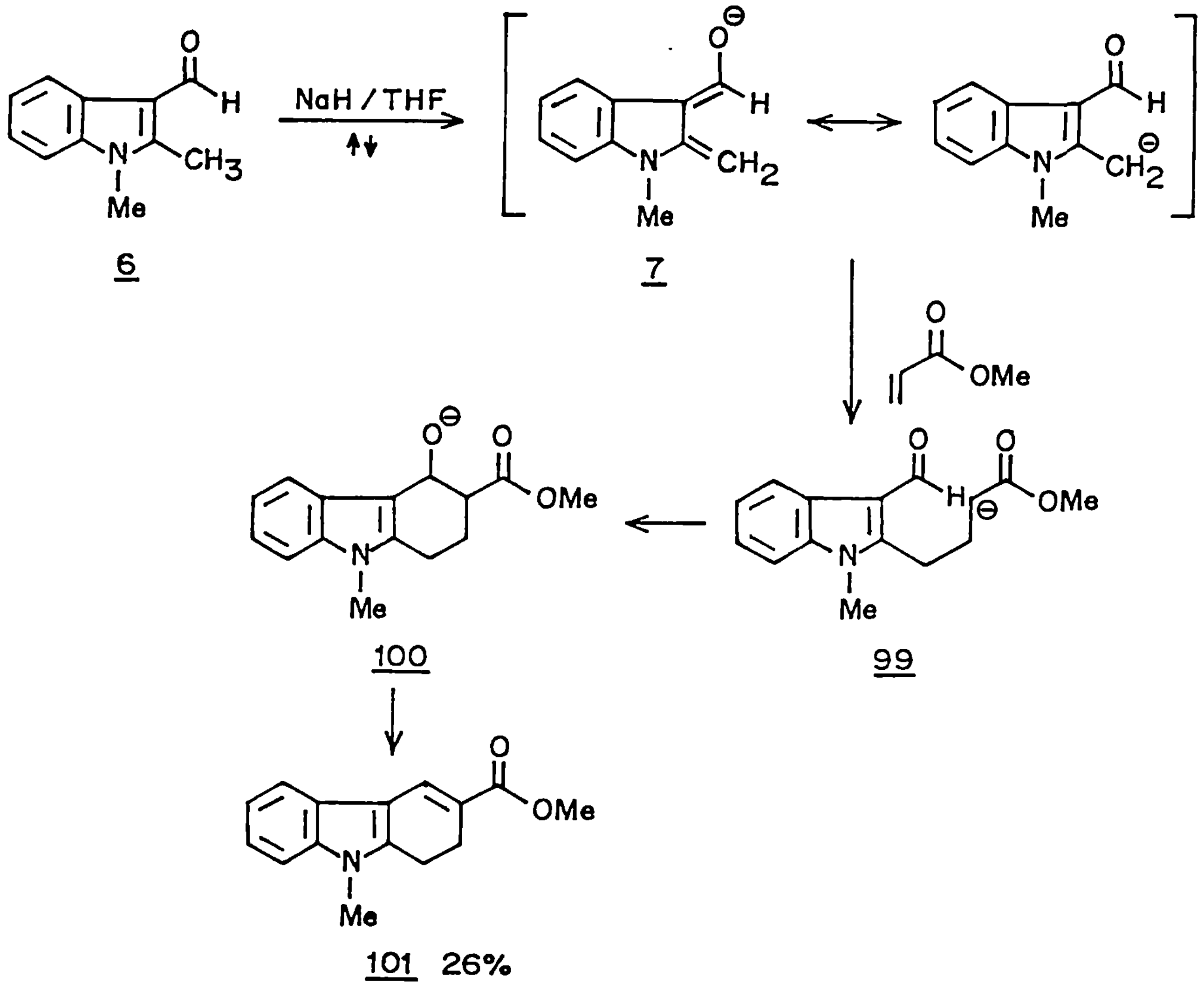
600
750
75
150
225
300
375
30
60
90
120
150
0
CN
SMe
N
CH3

98

methyl-3-nitrocarbazole **95** in 68% yield. m.p. 228-229°C. The formation and the assignment of the substituent positions of methylthio and nitro groups at 2 and 3 positions was in accordance with the reactivity of the polarised nitroketne-S,S-acetal where the bis(methylthio) carbon atom is known to be highly electron deficient displaying marked electrophilic character. The structure of 2- methylthio-9-methyl-3-nitrocarbazole **95** was established on the basis of its spectral and analytical data. It was analysed for $C_{14}H_{12}N_2O_2S$ (272.32). In its IR spectrum (KBr) displayed an absorption band at 1302 cm^{-1} due to nitro group. Also the ^1H NMR spectrum (90 MHz, $CDCl_3$) was clearly in support of the structure assigned. Thus the singlet at δ 2.60 integrating for three protons was assigned for S-methyl protons and another singlet at δ 3.87 was assigned for N-methyl protons. The singlet integrating for one proton at δ 7.13 clearly indicates the H-1 proton, having methylthio group on its adjacent carbon atom. The three aromatic protons appeared as multiplet δ 7.30-7.73 was assigned for H-6, H-7 and H-8 protons. Doublet at δ 8.13 having 9Hz coupling constant was assigned for H-5 proton. The H-4 proton on the otherhand appeared at δ 9.13 as a singlet due to strong deshielding because of nitrogroup on the adjacent carbon atom. No trace of other regioisomer was detected from the reaction mixture.

Similarly when Indole-2,3-dienolate **7** was reacted with ethylcyanoacelate ketenedithioacetal the corresponding 3-cyano-2-methylthio-9-methylcarbazole **98** was obtained in 68% yield. The structure of **98** was established on the basis of its analytical and spectral data. (m.p.158-160°C). It was analysed for molecular formula $C_{15}H_{12}N_2S$ with a molecular weight 252.33. It may be noted



Scheme – 23

that the cyano group which displayed in its IR spectrum (KBr) characteristic absorption band at 2203 cm^{-1} and the absence of IR frequency band for ester carbonyl confirms the loss of carboethoxy group from the cycloadduct, possibly involving a transition state of methylthio assisted decarboethoxylation. The structure of **98** was unambiguously established by its ^1H NMR spectrum ($CDCl_3$). The three protons singlet at δ 2.66 and δ 3.86 were assigned for S-Methyl and N-Methyl protons respectively. The singlet appeared at δ 7.33 integrating for one proton indicated that the proton H-1 adjacent to the carbon atom bearing methylthio group. The other singlet appeared at δ 8.32 was assigned for the proton H-4 having cyanogroup on the adjacent carbon. The structure **98** was further supported by its mass spectrum exhibited a molecular ion peak at m/z 252 (M+, 100%) corresponding to the molecular weight of **98**. Thus confirms the structure assigned for **98**.

The analytical and spectral data for all the compounds were fully in agreement with the assigned structures which are described in the experimental section.

When this work was published in Tetrahedron Letters, Engelbert* and co-workers reported[44] the formation of Indole-2,3-dienolate **7** by treating 1,2-dimethylindole-3-carboxaldehyde **6**, with sodium hydride in tetrahydrofuran.

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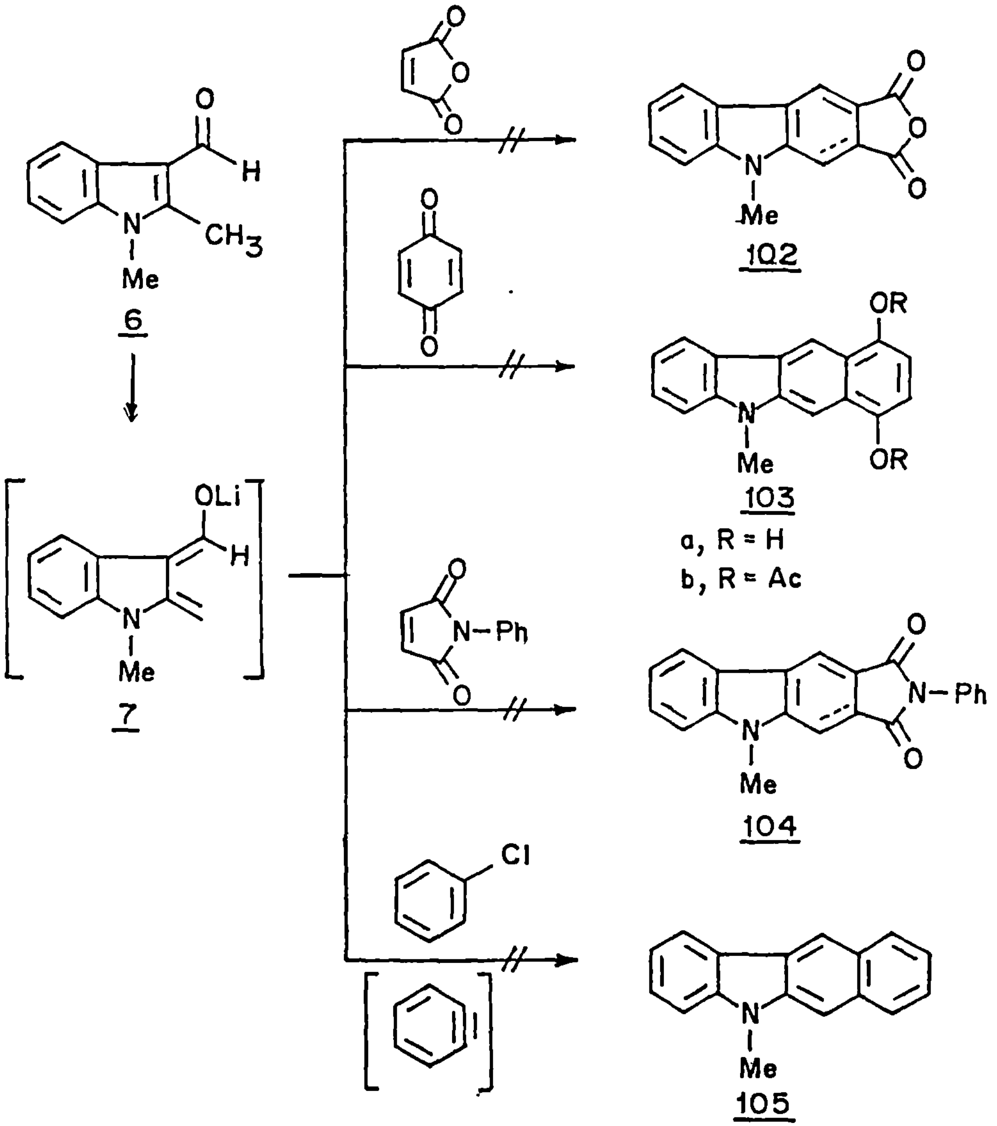
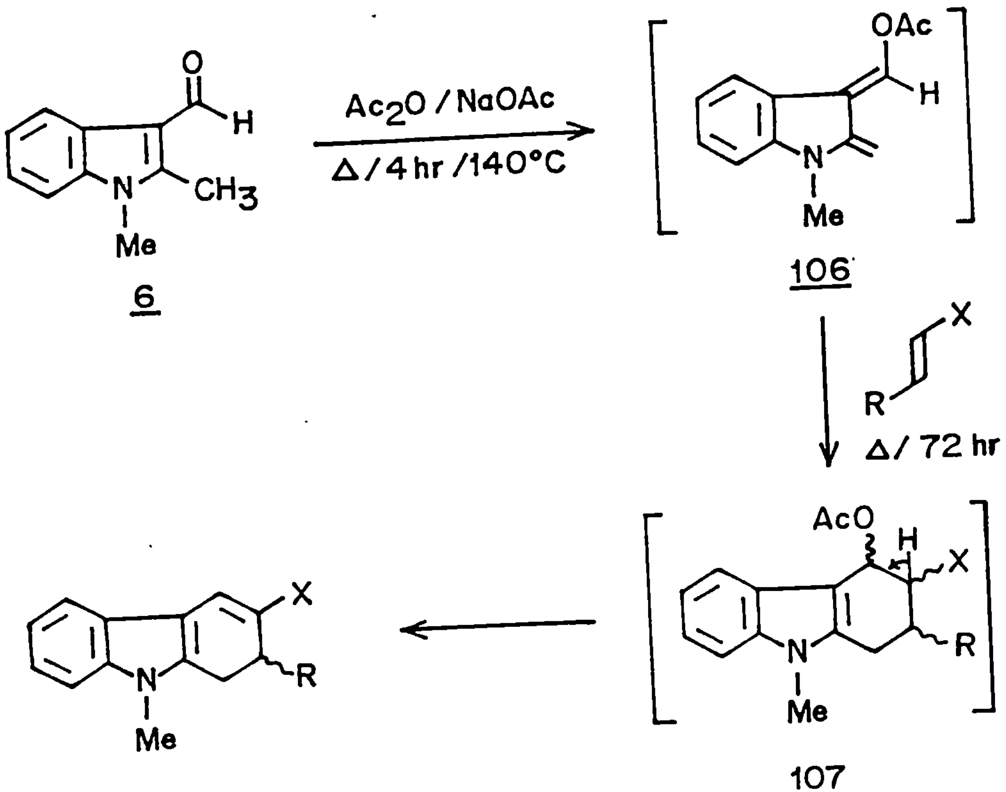
* This work appeared in *J.Org.Chem.*, three months after the publication of our paper in Tetrahedron Letters.


O
H
CH$_3$
N
Me
6
OLi
H
N
Me
7
O
O
O
O
O
N-Ph
O
O
Cl
O
O
O
N
Me
102
OR
OR
N
Me
103
a, R = H
b, R = Ac
O
N-Ph
O
N
Me
104
N
Me
105

Scheme-24



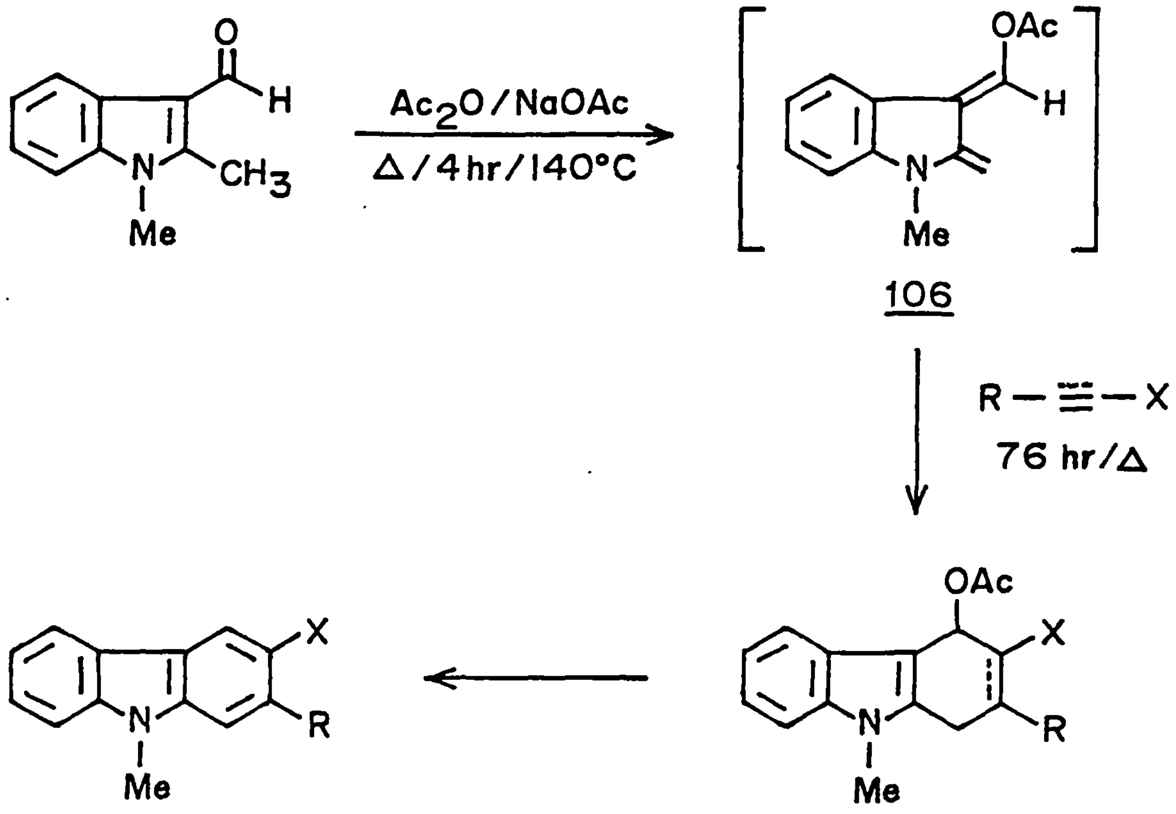
84, R = H ; X = CN
87a, R = H ; X = CO_2Et
87b, R = H ; X = COMe
92a, R = X = CO_2Et

Scheme—25

The o-quinodimethane intermediate was reacted with methylacrylate to yield the corresponding 1,2-dihydro-3-methoxycarbonyl -9-methylcarbazole **101** in a poor 26% yield. Possibly the observed poor yield in their reaction reflects the use of sodium hydride as a base.

Most interesting factor experienced in the course of this investigation was the surprised failure of Indole-2,3-dienolate **7** to undergo cycloaddition with maleic anhydride, 1,4-benzoquinone, N-phenylmaleimide and benzyne to yield the corresponding benzo [b] carbazoles (or) their dihydro derivatives **102**, **103**, **104** and **105**
respectively. In all the three cases (maleic anhydride, 1,4-benzoquinone, N-phenylmaleimide). The unreacted starting material were recovered. In case of benzyne reaction with **7** , the product could not be characterised which was not the expected benzo[b]carbazole **105**. At present we are unable to explain the failure of these dienophiles to undergo cycloaddition reaction with **7**. More careful studies under different reaction conditions is required to be examined and such studies are still been continued.

In another set of experiments a successful attempt was made to generate more stable neutral o-quinodimethane in its protected form **106**, using readily available and inexpensive chemicals. (Scheme 25). Though the o-quinodimethane intermediate was not isolated it was presumed to be in its acetate form as it was generated by reacting **6** with acetic anhydride in the presence of sodium acetate. The o- quinodimethane intermediate thus generated was reacted



90 R = X = COOMe

93c R = Ph ; X = NO$_2$

Scheme – 26

with various dienophiles to yield the corresponding carbazole derivatives.

When **106** was reacted with ethylacrylate in Acetic anhydride under refluxing conditions for 72 hr and the product obtained was chromatographed on silica gel to yield the 1,2-dihydro-3-ethoxycarbonyl -9-methylcarbazole **87a** in 76% yield. The spectral and analytical data and the melting points were identical with **87a** described earlier. **106** was also reacted with methyl vinylketone, diethyl fumarate, acrylonitrile to give the corresponding dihydro carbazole derivatives **92a**, **87b** and **84** in 63,67, and 59 % yields respectively. When **106** was reacted with dimethyl acetylenedicarboxylate and nitrostyrene the corresponding fully aromatized carbazoles were obtained in 74% and 58% yields respectively. The 1,2-dihydro-3-nitrocarbazole would not be detected in the reaction mixture possibly due to more regorous reaction conditions employed in this transformation. All the compounds obtained in this transformation were in conformity with their spectral and analytical data which are also superimpossible on the data described earlier.

II.A.4. CONCLUSIONS

In summary we have demonstrated that the Indole-2,3-dienolate derived from 1,2-dimethylindole-3-carboxaldehyde is a useful 1,4-dipole synthon (or) anionic indolo-2,3-quinodimethane which undergoes facile cycloaddition with a variety of dienophiles affording wide range of substituted carbazoles under remarkably mild conditions with most predictable and observed regiocontrol. It has been observed from the preceding review that regiocontroll is always at stake. It is pertinent to note that, in most of the cases they have observed a mixture of regioisomers barring few exceptions, where anionic indolo-2,3-quinodimethane intermediates are involved as observed in case of Indolopyrane **66** (Scheme 14). Also it may be noted that yields are consistently higher than those reported in the literature. The addition of polarised ketene dithioacetals to Indole-2,3-dienolate **7** yielding the functionalized carbazole derivatives further adds to the versatility of this procedure. The 2-methylthio-3-nitro / cyano carbazoles thus obtained provide interesting starting point particularly 3-cyano-2-methylthio-9-methylcarbazole which may well become the potential starting intermediate for the synthesis of olivacine and ellipticine derivatives. Also 3-acetyl-9-methyl carbazole **88b** is a potential intermediate in the synthesis of ellipticine derivatives (in place of 9-methyl group, deprotectable group and 2-ethyl-1-protected indole-3-carboxaldehyde as starting material would make this process directly useful in olivacine synthesis). We are currently extending this strategy to 2-ethyl-3-Indoylketones/esters to generate their dienolates as potential o-quinodimethane intermediates for the synthesis of biologically important carbazoles.

The generation of o-quinodimethane intermediate using acetic anhydride, sodium acetate combination and the exploitation of this diene generated with various dienophiles to yield substituted carbazoles further adds the importance to this investigation.

II.A.5 EXPERIMENTAL SECTION :

General:

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected . The IR spectra were recorded on a Perkin Elmer 297 spectrophotometer and frequencies are expressed in cm^{-1}. The ^{1}H NMR spectra were recorded on Varian EM-390, 90 MHz spectrometer in $CDCl_3$ (or) CCl_4 and are reported in δ units down field from Tetramethylsilane. High resolution ^{1}H NMR (300.13MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ are reported in δ units downfield from Tetramethylsilane. The coupling constants are given in Hertz. ^{13}C NMR (75.46 MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ and are reported in δ units in $CDCl_3$ downfield from TMS. Mass spectra were obtained on a Joel D-300 spectrometer and relative intensities are expressed in percentage. Carbon, Hydrogen and Nitrogen elemental analysis were carried out on a Heraus CHN-O-RAPID instrument. T. L.C. (ACME's) was used for monitoring the reactions.

All the reactions involving organolithium were performed in oven-dried glassware under masked dry nitrogen atmosphere using syringe-septum technique. Low temperature reactions were carried out in a bath made of ethylacetate and liquid nitrogen .

Chemicals and Solvents :

The commercial samples of phenyl hydrazine, N,N-diisopropylamine, n- butyl bromide, dimethyl formamide, phosphorous oxychloride, acetone, acrylonitrile, ethylacrylate, dimethyl acetylenedicarboxylate, diethyl fumarate, methyl vinylketone, were purified by distillation under reduced pressure before use. Methylcinnamate, nitrostyrene, N-phenylmaleimide, maleicanhydride, P-benzoquinone, were purified by crystallisation before use. Benzyne was generated *in situ* in the reaction mixture by taking one more equivalent of lithium diisopropylamide and one equivalent of bromobenzene. n-Butyllithium was prepared according to the reported procedure[45]. Diethylether and benzene were distilled and dried by keeping over sodium wire. Tetrahydrofuran was initially deperoxidized and then dried by keeping over sodium wire followed by distillation. 2-methylindole 3-carboxaldehyde was prepared according to the reported procedure[42]. 1,1-bis(methylthio)-2-nitroethylene[46] and 1,1-bis(methylthio)-2-cyano-2-carboethoxy ethylene[47] were prepared according to the reported procedures.

Preparation of 1,2-dimethylindole-3-carboxaldehyde (6):

2-methylindole-3-carboxaldehyde (0.05mol, 7.95gm) and anhydrous potassium carbonate (0.5mol) were refluxed in dry acetone 200ml for 3hrs with stirring. The reaction mixture was cooled to 0°C and methyliodide (0.075mol, 10.65 gm) in 50ml dry acetone was added drop wise fashion over a period of 0.5hr and the reaction mixture was stirred at room temperature for a period of 6hrs (monitored by T.L.C). It was refluxed for 0.5hr to ensure complete conversion. Upon completion acetone was distilled off from the reaction mixture and the ice cold water (100 ml) was added to it. It was extracted with chloroform (3x100 ml) and the organic layer was washed with water (3x100 ml). The chloroform layer was dried over anhydrous sodium sulphate and was concentrated to give the crude product, which on silica gel chromatographic purification, followed by crystallisation (chloroform / hexane) yielded 1,2-dimethylindole-3-carboxaldehyde as light yellow crystalline solid. (m.p.128-129°C)lit[48]. 131-132°C. yield 96%.

General procedure for the generation of indole-2,3-dienolate 7, and its reaction with various dienophiles to yield dihydrocarbazole derivatives (84, 87a, 87b, 92a & 92b) and substituted carbazoles (90, 95, 98) :

A solution of n-BuLi (1.4m in diethylether solution, 1.5ml, 2.1 mmol) was added dropwise to a stirred solution of diisopropylamine (210mg, 2.1 mmol) in dry tetrahydrofuran (50 mL), at O°C under masked nitrogen atmosphere. The reaction mixture was stirred for 15 min . A solution of 1,2-dimethylindole-3-carboxaldehyde (330 mg, 1.9 mmol) in tetrahydrofuran (25 ml) was added to the solution of lithium diisopropylamide (under nitrogen atmosphere) over a period of 10 min at –78°C. Stirring was continued for 0.5h at the same temperature. Then dienophile (1.9 mmol) in tetrahydrofuran (5 ml) was added dropwise fashion at –78°C with stirring. The reaction mixture was stirred at the same temperature for 0.5hr and was left stirring over night at ambient temperature (monitored by T.L.C). Upon the completion of the reaction, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (30 ml). The organic layer was separated and the aqueous layer was extracted with diethylether (3x50 ml). The combined organic extracts were washed with water (3x20 ml) dried over anhydrous sodium sulphate, and concentrated in vacuum to give the crude carbinol. (crude carbinol was identified with its spectral and analytical data). Attempted purification of the carbinol obtained, by silica gel chromatography using ethylacetate / hexane (10:90) as eluent yielded corresponding dihydrocarbazole or carbazole derivatives. The structures of products were fully established from their spectral and analytical data which are given below.

3-Cyano-4-hydroxy-9-methyl-1,2,3,4-tetrahydrocarbazole (83) was obtained as brown coloured viscous liquid and was identified by IR and NMR with out purification; IR (CCl_4) ν_{max} =3461 (OH) ,3136, 2915 , 2237 (C≡N) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$):δ= 2.26-2.40 (m,1H, C<u>H</u>CN), 2.83-3.06 (m, 4H, C$\underline{H}_2$), 3.13-3.23 (m, 1H, C<u>H</u>OH) ,5.33 (s, with fine splitting, 1H, O<u>H</u> exangable with D_2O), 7.91-7.50 (m, 3H, Ar<u>H</u>), 7.66 (m, 1H, Ar<u>H</u>).

3-Cyano-1,2-dihydro-9-methylcarbazole (84) obtained as light yellow Crystals (chloroform/hexane), m.p.120-121°C; yield :78%; IR (Kbr) ; ν_{max} = 1462, 1518 and 2183 (C≡N) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$); δ = 2.66-3.06 (m, 4H, C$\underline{H}_2$), 3.69 (s, 3H, NC$\underline{H}_3$), 7.16-7.36 (m, 3H, Ar<u>H</u>), 7.39-7.69 (m, 2H, Ar<u>H</u>); m/z : 208 (M^+, 100%), 207 (M^+-1,53.7%), 192 (34%); 168 (10%); Anal. calculated for $C_{14}H_{12}N_2$ (208.26) : C, 80.73; H, 5.81; N, 13.45. Found :C, 80.71; N,13.40; H, 5.68%.

3-Carboethoxy-1,2-Dihydro-9-methylcarbazole (87a) was obtained as light yellow crystals (dichloromethane/hexane), m.p. 125-126°C; Yield : 84%; IR (KBr); ν_{max} =1215, 1465,1681 (C=O) cm^{-1}; ^1H NMR

(300.13 MHz, $CDCl_3$): δ= 1.35 (t, 3H, J=7Hz, $C\underline{H}_3$), 2.86-2.89 (m, 4H, $C\underline{H}_2$), 3.63 (s, 3H, $NC\underline{H}_3$), 4.26 (q, 2H, J=7Hz, $OC\underline{H}_2$), 7.17-7.21 (m, 2H, Ar$\underline{H}$), 7.25-7.28 (m, 1H, Ar$\underline{H}$), 7.62-7.65 (m, 1H, Ar$\underline{H}$), 7.88 (s, 1H, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 14.51 ($\underline{C}H_3$), 20.79 ($\underline{C}H_2$), 22.74 ($\underline{C}H_2$), 29.54 ($N\underline{C}H_3$), 60.07 ($O\underline{C}H_2$), 109.43, 109.74, 117.73, 117.82, 120.79, 121.53, 125.22, 131.35, 137.83, 141.09, 167.96 (C=O); m/z : 255 (M^+, 100%) 182 (M^+–$COOC_2H_5$, 90%); Anal. calculated for $C_{16}H_{17}NO_2$ (255.31) : C, 75.27; H, 6.71; N, 5.49. Found: C, 75.26; H, 6.72 ; N,5.46%.

3-Acetyl-1,2-dihydro-9-methylcarbazole (87b) was obtained as yellow crystals (chloroform / hexane), m.p.147-149°C; yield 80%; IR (CCl_4) ;ν_{max} = 1624 (C=O), 1509, 1262 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ =2.43 (s, 3H, $C\underline{H}_3$), 2.86 (brs, 4H, $C\underline{H}_2$) ,3.66 (s, 3H, $NC\underline{H}_3$), 7.16-7.50 (m, 3H,Ar$\underline{H}$), 7.63-7.76 (m, 1H, Ar$\underline{H}$), 7.79 (s, 1H, Ar$\underline{H}$); m/z : 225 (M^+, 66.7%), 224 (M^+ –1, 34%), 210 (34.8%), 182 (100%); Anal. calculated for $C_{15}H_{15}NO$ (225.28) : C, 79.97; H, 6.71; N, 6.22. Found : C, 79.86; H, 6.67; N, 6.30%.

2,3-Bis(carboethoxy)-1,2-Dihydro-9-methylcarbazole (92a) was obtained as light yellow crystals (dichloromethane/hexane); m.p 127-128°C; IR (KBr); ν_{max} = 1711 (C=O), 1678 (C=O), 1212 cm^{-1}; ^1H NMR (300.13MHz,$CDCl_3$): δ = 1.16 (t, 3H,J=7.3Hz, $C\underline{H}_3$), 1.36 (t, 3H, J=7.3 Hz, $C\underline{H}_3$), 3.05 (dd, 1H, J=8.83, 8.20Hz, $C\underline{H}_2$) 3.61 (dd, 1H, J=14.5,2.58 Hz, $C\underline{H}_2$), 3.68 (s, 3H, $NC\underline{H}_3$), 4.00-4.09 (m, 3H, $OC\underline{H}_2$, $C\underline{H}COOC_2H_5$), 4.29 (q, 2H,J=7Hz, $OC\underline{H}_2$), 7.17 (m, 2H, Ar$\underline{H}$), 7.26 (m, 1H, Ar$\underline{H}$), 7.63 (m, 1H, Ar$\underline{H}$), 7.98 (s, 1H, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 13.99 ($\underline{C}H_3$), 14.49 ($\underline{C}H_3$), 23.79 ($\underline{C}H_2$), 29.73 ($N\underline{C}H_3$), 38.95 ($\underline{C}HCOOC_2H_5$), 60.29 ($O\underline{C}H_2$), 61.16($O\underline{C}H_2$), 109.26, 109.57, 116.32, 117.92, 120.99, 121.81, 125.10, 132.20, 137.98, 139.64, 167.36 (C=O), 173.35 (C=O); m/z: 327 (M$^+$, 41%), 254 (60.5%), 227 (28%), 208 (53%), 182 (45%), 181 (100%), 180 (45.5%); Anal. calculated for $C_{19}H_{21}NO_4$ (327.37) : C,69.70; H,6.47; N,4.28. Found: C, 69.63; H, 6.41, N, 4.29%.

3-Carbomethoxy-1,2-Dihydro-9-methyl-2-phenylcarbazole (92b) was obtained as light yellow crystals (acetone/hexane), m.p.180-182°C; Yield: 79%; IR (KBr):ν_{max} = 1669 (C=O), 1461, 1261, 1222, 1187, 1079 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ= 3.00-3.33 (m, 2H, CH_2), 3.46 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 4.10-4.46 (m, 1H, CHPh), 7.11-7.36 (m, 7H, ArH), 7.60-7.93 (m, 2H, ArH), 8.23 (s, 1H, ArH); m/z : 318 (M$^+$+1, 20.4%), 317 (M$^+$, 86.4%), 259 (20.8%), 258 (100%), 243 (37.5%), 208 (23.9%), 181(37.7%); Anal. calculated for $C_{21}H_{19}NO_2$ (317.37) : C, 79.47; H, 603; N,4.41. Found : C ,79.39; H, 6.12; N, 4.39%.

2,3-Bis(carbomethoxy)-9-methylcarbazole (90) was obtained as light yellow crystals (dichloromethane/hexane), m.p.128-129°C ; Lit^{43}.m.p.132-133°C ; yield:76%; IR (Kbr): ν_{max} =1706 (C=O), 1722 (C=O) cm^{-1} ; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 3.66 (s, 3H, NCH_3), 3.97 (brs, 6H, OCH_3), 7.16-7.63 (m, 4H, ArH), 8.00 (d, 1H, J=9Hz, ArH); m/z: 297(M$^+$,88%), 266 (M$^+$-OCH3,100%); Anal. Calculated for $C_{17}H_{15}NO_4$ (297.29) : C, 68.68; H, 5.08; N, 4.71. Found: C, 68.78; H, 5.12; N, 4.68%.

9-Methyl-2-methylthio-3-nitrocarbazole (95) was obtained as bright orange crystals (chloroform / hexane), m.p.228-229°C; yield: 68%; IR (Kbr) : ν_{max} = 1596, 1302 (NO_2) cm^{-1}; ^{1}H NMR (90 MHz,

$CDCl_3$): δ= 2.60 (s, 3H, $SC\underline{H}_3$), 3.87 (s, 3H, $NC\underline{H}_3$), 7.13 (s, 1H, Ar$\underline{H}$), 7.30-7.73 (m, 3H, Ar$\underline{H}$), 8.13 (d, 1H, *J*=9Hz, Ar$\underline{H}$), 9.13 (s, 1H, Ar$\underline{H}$); m/z:272 (M^+, 99.8%), 242 (23.8%), 208 (41%), 193 (63%), 181 (46.7%), 167 (23.7%); Anal. Calculated for $C_{14}H_{12}N_2O_2S$ (272.32): C, 61.74; H, 4.45; N, 10.29. Found:C, 61.70; H, 4.42; N, 10.20%.

3-Cyano-9-methyl-2-methylthiocarbazole (98) was obtained as a bright yellow solid (chloroform/hexane), m.p.158-160°C; yield 69%; IR(KBr) : ν_{max} = 3128, 2203 (C≡N), 1587 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ = 2.66 (s, 3H, $SC\underline{H}_3$), 3.86 (s, 3H, $NC\underline{H}_3$), 7.33 (s, 1H, Ar$\underline{H}$), 7.36-7.73 (m, 3H, Ar$\underline{H}$), 8.12 (d,1H, *J*=9Hz, Ar$\underline{H}$), 8.32 (s, 1H, Ar$\underline{H}$); m/z : 252 (M^+, 100%), 237 (94.6%), 219 (48.7%), 193 (47.5%); Anal. Calculated for $C_{15}H_{12}N_2S$ (252.33); C, 71.39; H, 4.79; N, 11.10. Found : C, 71.39; H, 4.83; N, 11.06%.

General procedure for the substituted carbazoles (85,88a,88b and 93c):

The carbinol intermediate (1.9 mmol), obtained from the reaction of 7 with dienophile was refluxed with pyridinium tosylate (0.5 gm) in dry benzene (15 ml). Refluxing was continued with stirring for 24hr (monitored by T.L.C). Upon the complete conversion, benzene was distilled off from the reaction mixture on a water bath . The reaction mixture was cooled and ice cold water (15 ml) was added to it . It was extracted with diethyl ether (3x50 ml) . The ethereal extracts were washed with water (3x50 ml) and the organic layer was dried over anhydrous sodium sulphate and was concentrated to yield crude product, which was chromatographed on silica gel using hexane / ethyl acetate (9:1) as eluent. The structures of the products were fully established from their spectral and analytical data which are given below.

3-Cyano-9-methylcarbazole (85) was obtained as light yellow crystals (dichloromethane/hexane), m.p.94-95°C; yield : 76%; IR (CCl_4) : ν_{max} =2921, 2213 (C≡N), 1588, 1471, 1245 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ: 3.60 (s, 3H, NC$\underline{H}_3$), 7.13-766 (m, 5H, Ar$\underline{H}$), 7.88 (d, 1H, J=7.5Hz, Ar$\underline{H}$), 8.06 (s, 1H, Ar$\underline{H}$); m/z: 206 (M^+, 100%), 205 (85%), 191 (17.2%); Anal. Calculated for $C_{14}H_{14}N_2$ (206.24) : C, 81.53; H, 4.89; N, 13.59. Found: C, 81.45; H, 4.77; N, 13.57%.

3-Ethoxycarbonyl-9-methylcarbazole (88a) was obtained as yellow crystals (dichloromethane/hexane), m.p.99-100°C; yield :72%: IR (KBr) CCl_4: ν_{max} = 2925, 1707 (C=O), 1367, 1255, 1237, 1095 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ = 1.20-1.39 (t, 3H, C$\underline{H}_3$), 3.60 (s, 3H, NC$\underline{H}_3$), 4.30-4.54 (q, 2H, OC$\underline{H}_2$), 7.20-7.73 (m, 4H, Ar$\underline{H}$), 8.13-8.46 (m, 2H, Ar$\underline{H}$), 8.93 (s, 1H, Ar$\underline{H}$); m/z: 253 (M+, 100%); Anal. Calculated for $C_{16}H_{15}NO_2$ (253.30); C, 75.87; H, 5.97; N, 5.53. Found: C, 75.89, H, 5.93; N, 5.54%.

3-Acetyl-9-methylcarbazole (88b) was obtained as light yellow crystals (dichloromethane / hexane), m.p.105-106°C; yield 76%; IR (KBr): ν_{max} = 2958, 2929, 1596 (C=O), 1323 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$): δ =2.73 (s, 3H, C$\underline{H}_3$), 3.93 (s, 3H, NC$\underline{H}_3$), 7.33-7.66 (m, 4H, Ar$\underline{H}$), 8.23 (brs, 1H, Ar$\underline{H}$), 8.87 (s, 1H, Ar$\underline{H}$); m/z: 223 (M^+, 85.7%), 209 (41.6%), 208 (100%), 180 (78.4%), 152 (53.8%); [Found: C, 80.61; H, 5.83; N,6.32 calculated for $C_{15}H_{13}NO$ (223.26); C, 80.69; H, 5.87; N, 6.27%].

9-Methyl-3-nitro-2-phenylcarbazole (93c) was obtained as bright yellow crystals (acetone / hexane), m.p.222-223°C; yield : 72%; IR (Kbr) : ν_{max} = 1513, 1319 (NO_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ = 3.86 (s, 3H, NCH_3), 7.33 (s, 1H, ArH), 7.36-7.76 (m, 7H, ArH), 8.06-8.36 (m, 2H, ArH), 8.80 (s, 1H, ArH); m/z: 303 (M^++1, 47.3%), 302 (M^+, 100%), 285 (42.7%), 273 (26.6%), 257 (69.8%), 256 (38.4%), 255 (54.3%), 241 (79.3%); Anal. calculated for $C_{19}H_{14}N_2O_4$ (302.32); C, 75.48; H, 4.67; N, 9.27. Found: C, 75.52; H, 4.66; N, 9.31%.

Procedure for the generation of quinodimethane intermediate (106) to react *in situ* with dienophiles to yield corresponding dihydrocabazoles (84, 87a, 87b and 92a) and substituted carbazoles (90 and 93c) :

To the freshly pulverised sodium acetate (10 mmol, 700 mg), 1,2-dimethylindole-3-carboxaldehyde (173 mg, 1 mmol) in 10ml Acetic anhydride was added. The reaction mixture was stirred at 140°C for 4hr. Then dienophile (1.5 mmol) was added in 5ml acetic anhydride and the reaction mixture was stirred at the same temperature for 72hr (monitored by T.L.C) . Acetic anhydride was distilled off from the reaction mixture and the residue obtained was cooled and 30 ml of cold water was added to it. It was extracted with chloroform (3x30 ml) and the chloroform extracts were washed with saturated aqueous sodium bicarbonate solution (10 ml) followed by water (3x50 ml) . The organic layer was dried over sodium sulphate and was concentrated to give the crude product, which was chromatographed on silica gel using ethylacetate /hexane (10:90) as eluent. The structures of the products were fully established from their spectral and analytical data which are superimposable on the products data described in the preceding section and are also confirmed by mmp's.

II.A. 6 References

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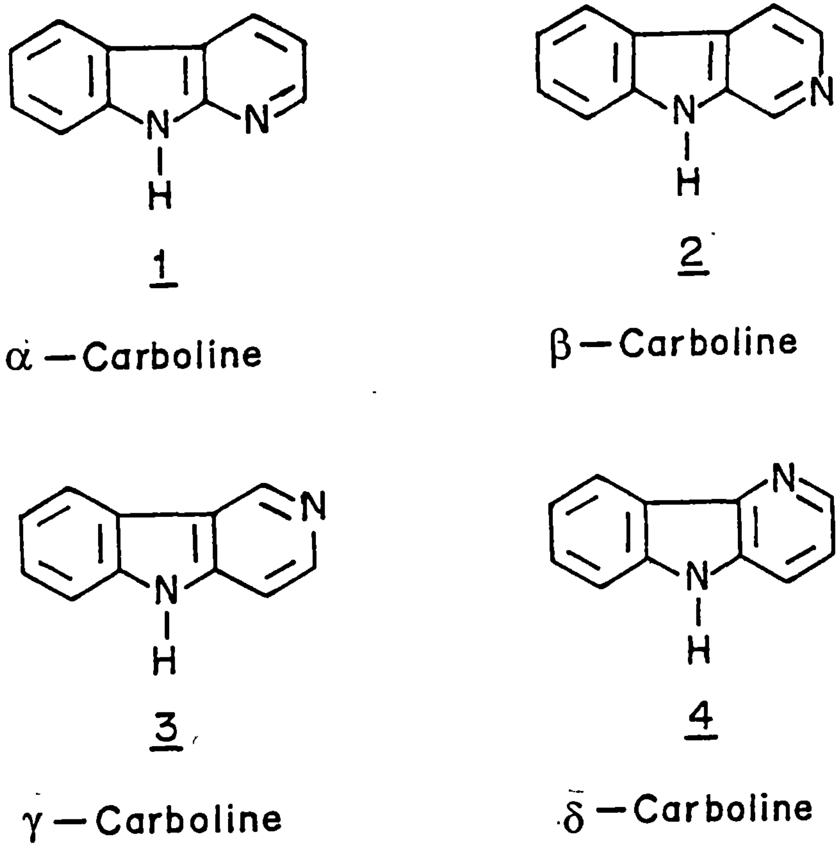
PART B:

A New Synthesis Of Substituted γ-Carbolines *Via* Indole-2,3-dienolate

II.B.1 Introduction :

There are four carbolines namely α-carboline[1] 1, β-carboline[2] 2, γ-carboline[3] 3, and δ-carboline[4] 4, depicted in scheme 1, all of which are known in the literature. The most widely found among these is the β-carboline which occurs in nature as a part of many indole alkaloids[5]. This is understandable, since it can be formed by genetically from the corresponding tryptomine or tryptophan. However the other three carbolines are less frequently encountered though naturally occurring alkaloids having these structural features have been isolated[6] and found to be possessing significant biological activity[7]. The synthetic approaches employed for 2 generally involves tryptomine as a starting material, which is easily available in large quantities. Similarly γ-carboline 3 can be prepared starting from starting from isotryptomine following the methods employed for β-carboline 2, though the possibility of hetero cyclization through indole ring nitrogen to yield corresponding pyrimidine derivatives exists as observed in some reports[9]. On the other hand synthetic methods for α-, γ- and δ-carbolines were not extensively studied. Since the strategies for the synthesis of these



Scheme -1

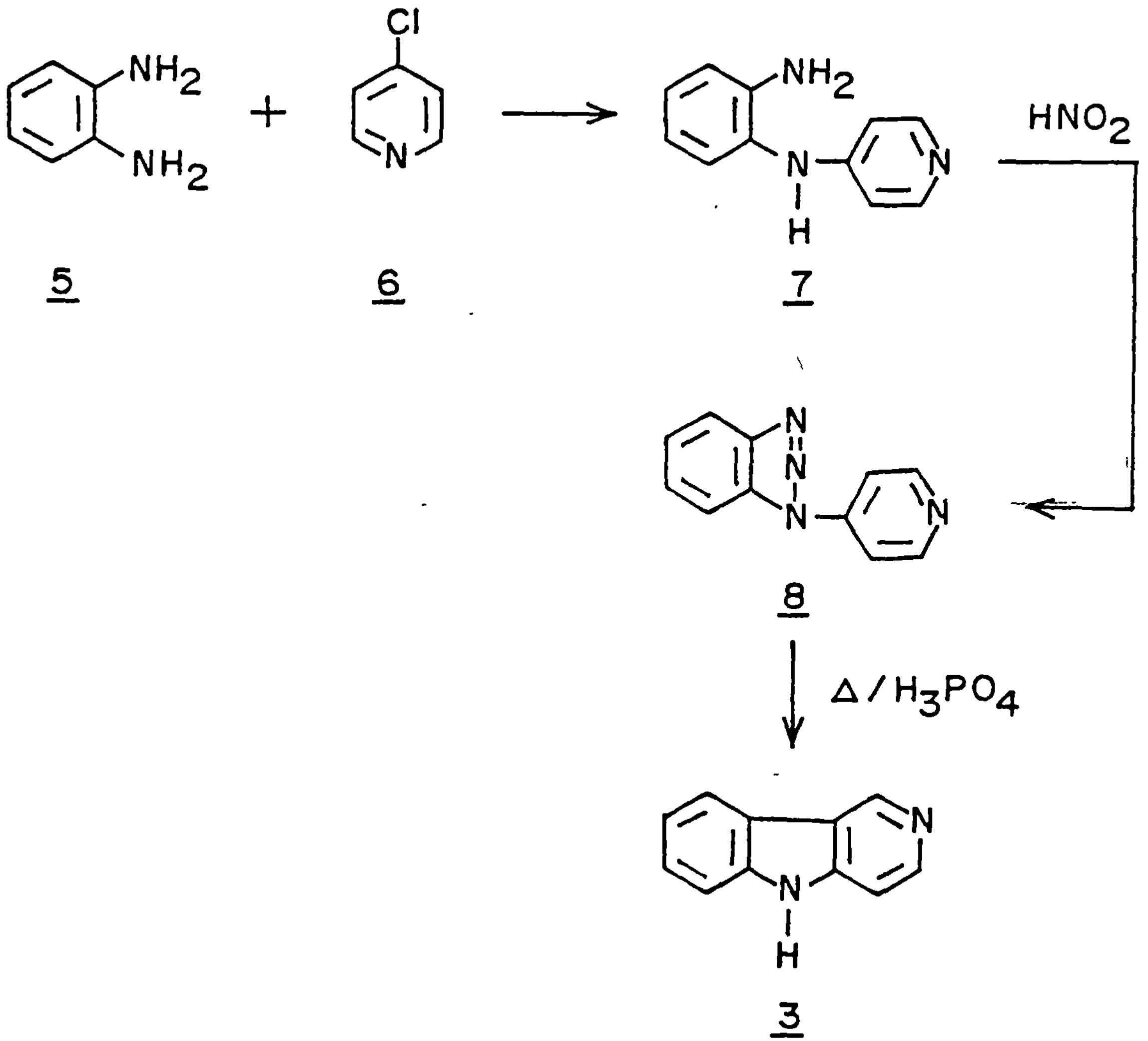
compounds have to be designed on a totally different lines. The importance of all these carbolines has increased due to the demand as DNA intercalators , useful for developing anticancer drugs[10]. The first isolated and highly potent mutagens among these compounds are the γ-carboline derivatives 3-amino-1,4-dimethyl-5H-pyrido[4,3-b] indole and 3-amino-1-methyl-5H-pyrido[4,3-b]indole isolated from tryptophan pyrolysates[7]. Thus efforts are made to build synthetic strategies for less encountered γ-carbolines.

In the course of present investigation it was considered of interest to make an attempt to trap the indole-2,3-dienolate described in the preceding part with various nitriles as dienophiles so that the cycloadduct will have basic skeleton of the γ-carboline. The expected γ-carbolines <u>3</u> were indeed formed though with some nitriles the reaction did not go in the expected [4+2] cycloaddition route. Before we present results of these investigations a brief survey on the methods of synthesis of γ-carbolines is reviewed.

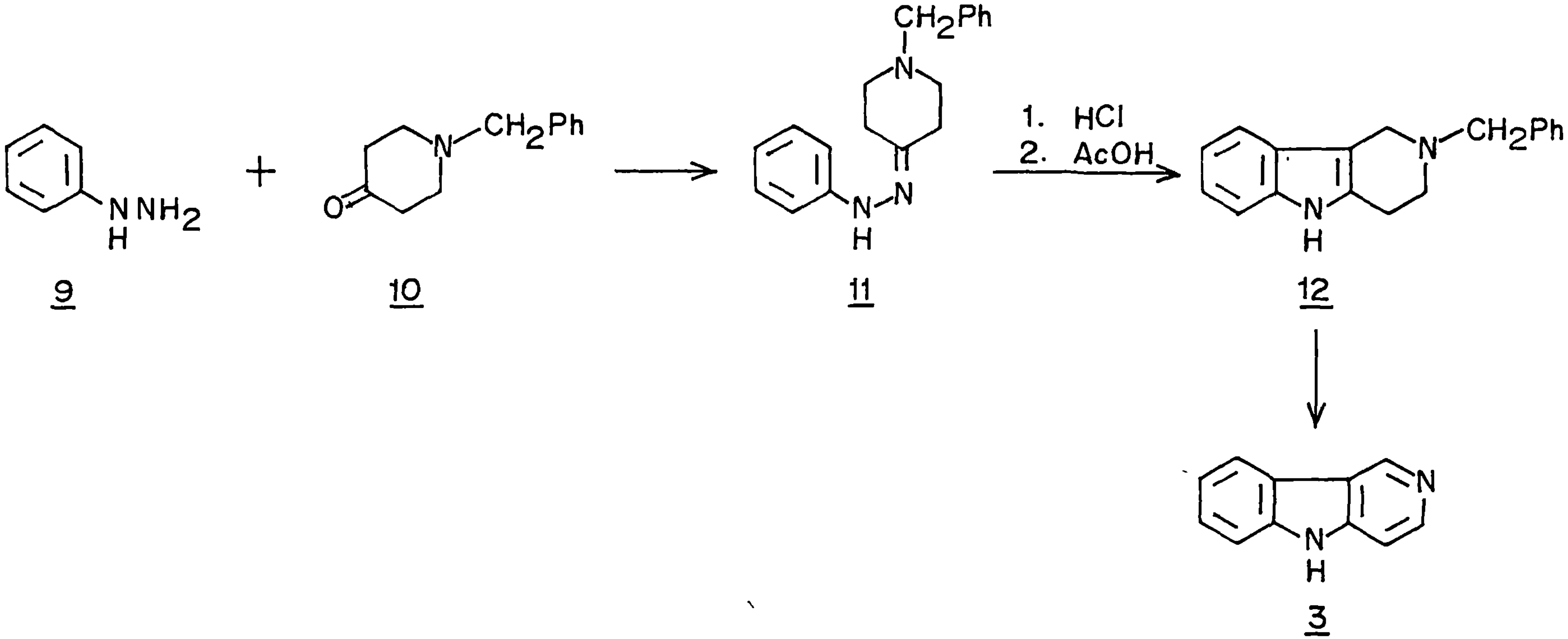
II.B. 2. [5H] Pyrido [4,3-b] indoles : A Brief Review

There are very few reports in the literature on the methods of synthesis of γ-carbolines and its derivatives.

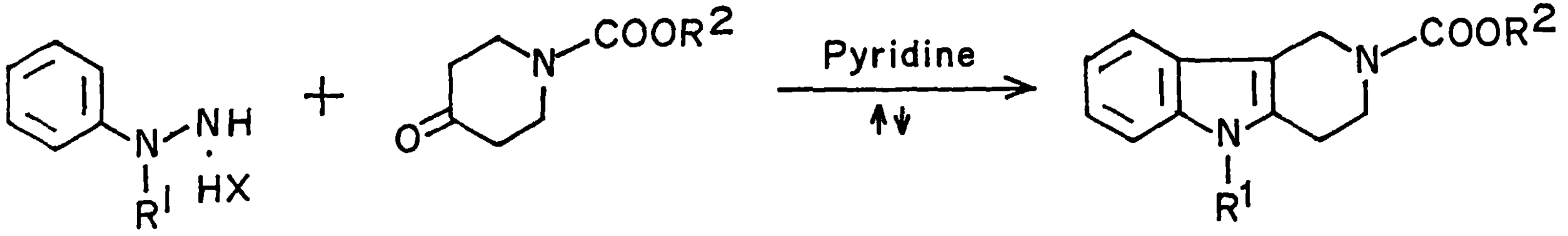
γ-carboline was first prepared by Robinson[11] and co-workers in 1924, by reacting N-γ-pyridyl-0-phenylenediamine <u>7</u>, with 4-chloropyridine <u>6</u> with nitrous acid to yield the corresponding 1- γ-pyridylbenzotriazole <u>8</u>, which on subsequent heating in the presence of syrupy phosphoric acid yielded the γ-carboline <u>3</u>.



Scheme –2



Scheme – 3

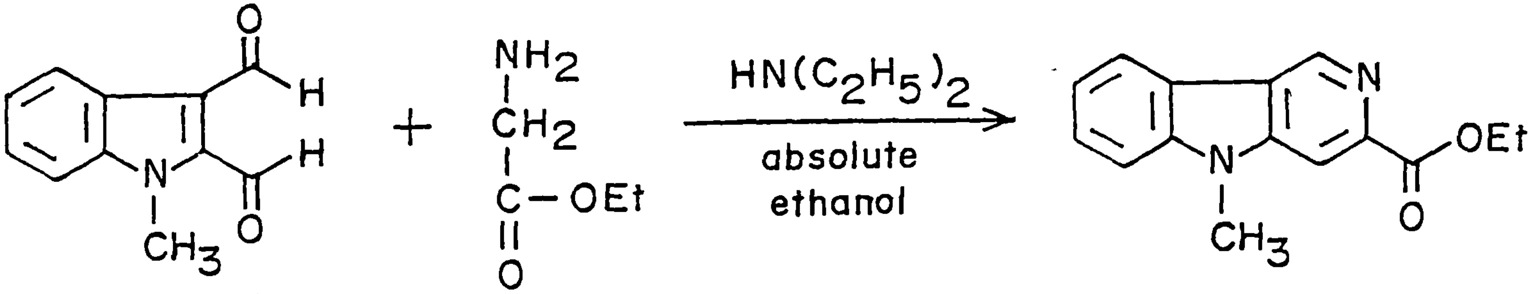


13 14 15

$R^1 = H, C_6H_5$
$R^2 = C_2H_5, C_6H_5$

$R^1 = H, C_6H_5$
$R^2 = C_2H_5, C_6H_5$

Scheme – 4



16 17 18

Scheme-5

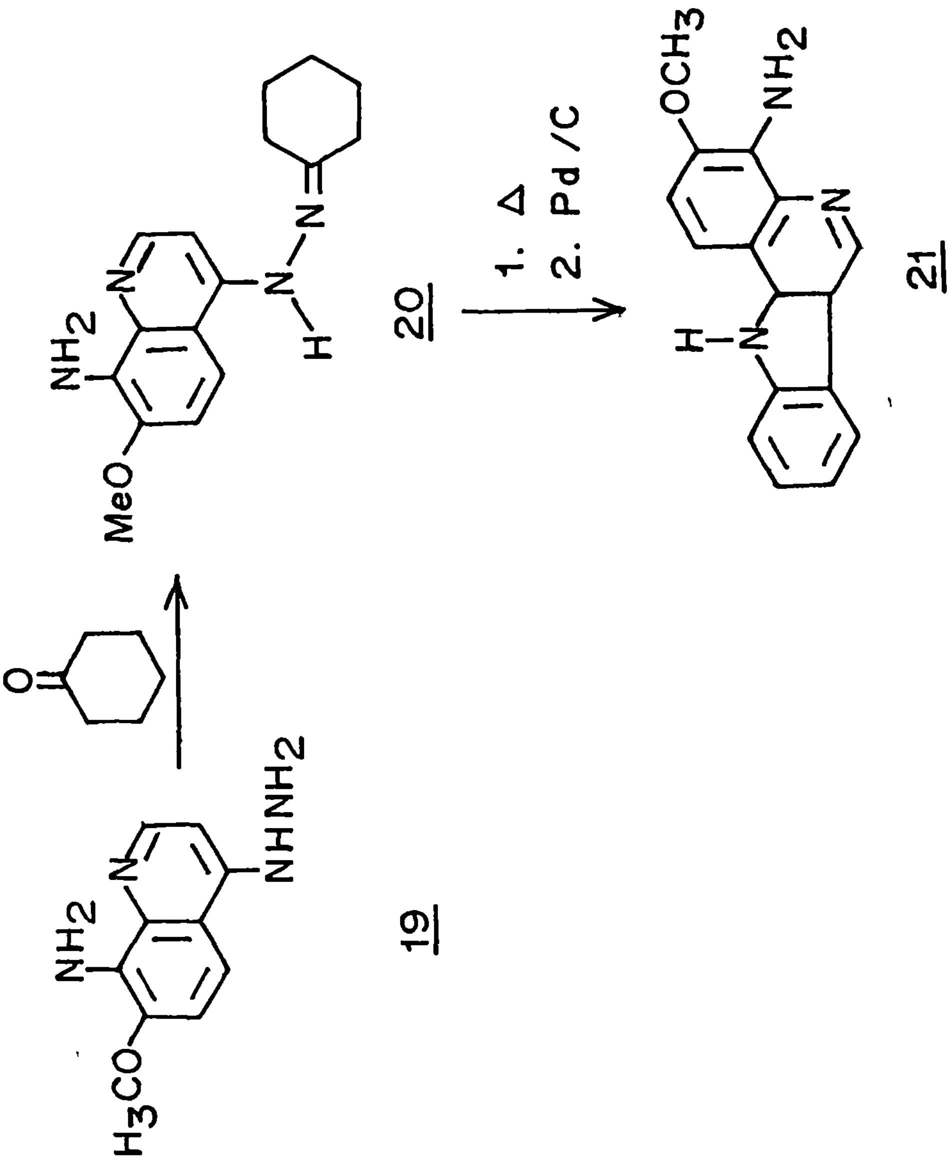
(scheme 2). Bremer[12] attempted in vain to exploit this strategy to prepare γ-carboline derivatives.

There are reports on the synthesis of γ-carboline analogues in recent years which are briefly reviewed in this section.

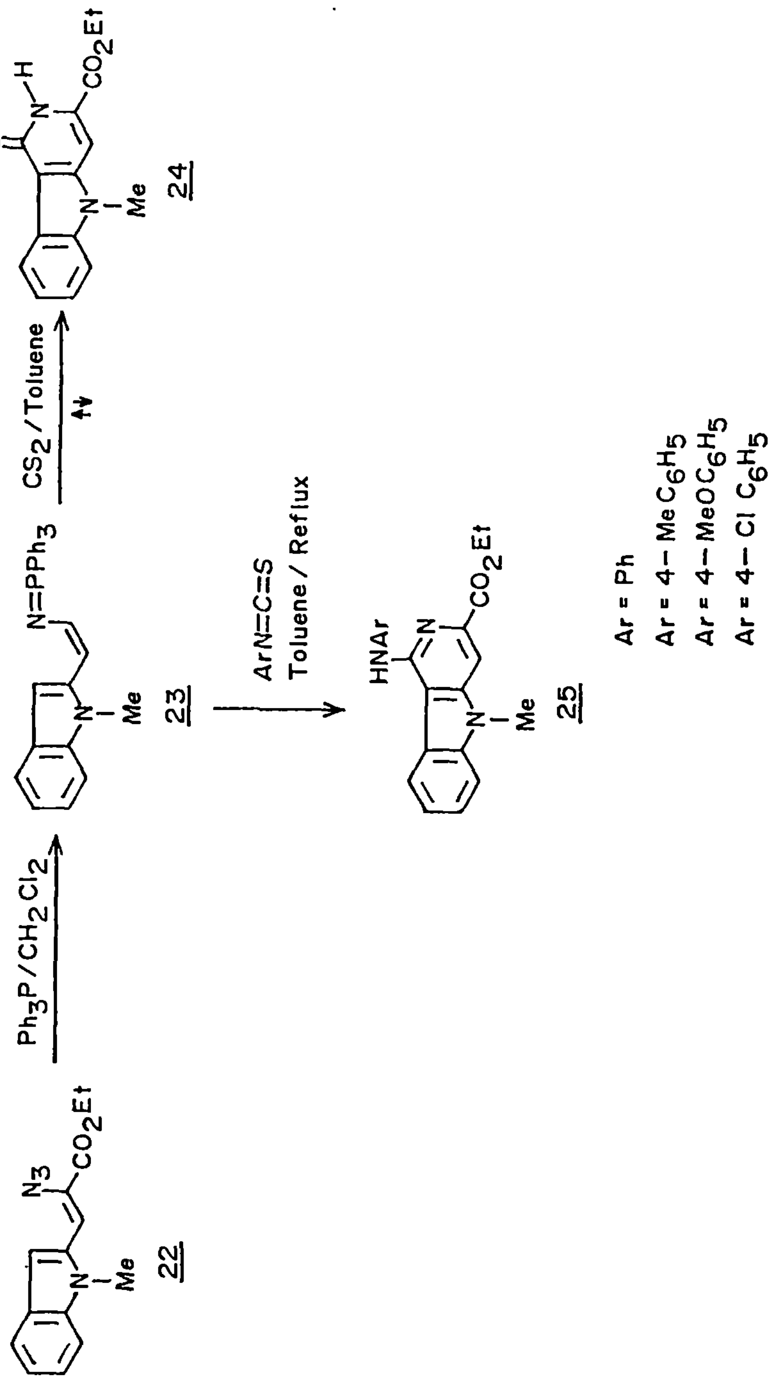
Jacquignon[13] and co-workers reported the γ-carboline synthesis by means of fisher indolisation of aryl hydrazone and subsequent dehydrogenation and debenzylation of the intermediate 1,2,3,4-tetrahydro compounds. Thus 1-benzyl-4-piperidone, which was readily available was reacted with phenyl hydrazine to yield 1-benzyl-4-piperidone phenylhydrazone **11**, which was cyclised to 2-benzyl-1,2,3,4-tetrahydro -γ-carboline **12**, by means of hydrogen chloride in acetic acid. The compound **12** thus obtained underwent debenzylation and dehydrogenation to yield γ-carboline **3**. (scheme 3)

Welch has extended the same strategy and reported[14] some 1,2,3,4-tetrahydro-γ-carbolines using pyridiniumhydrochloride catalysed fisher indole reactions. Thus the N-carboethoxypiperidone hydrazone **14** obtained by the reaction of phenyl hydrazine hydrochloride, was treated with pyridine under inert atmosphere to yield corresponding N-carboethoxy-1,2,3,4-tetrahydro-γ-carbolines **15** in 47-86% overall yields (scheme 4).

Queguiner[15] and co-workers reported 5-methyl-3-carboethoxy-[5H]-pyrido[4,3-b] indole **18** as formulated in scheme 5. Thus 1-methylindole-2,3-carboxaldehyde **16** and ethylaminoacetate **17** were



Scheme – 6



N3
CO2Et
Me
22
Ph3P/CH2Cl2
N=PPh3
Me
23
CS2/Toluene
S
N–H
CO2Et
Me
24
ArN=C=S
Toluene / Reflux
HNAr
N
CO2Et
Me
25
Ar = Ph
Ar = 4– Me C6H5
Ar = 4– MeOC6H5
Ar = 4– Cl C6H5

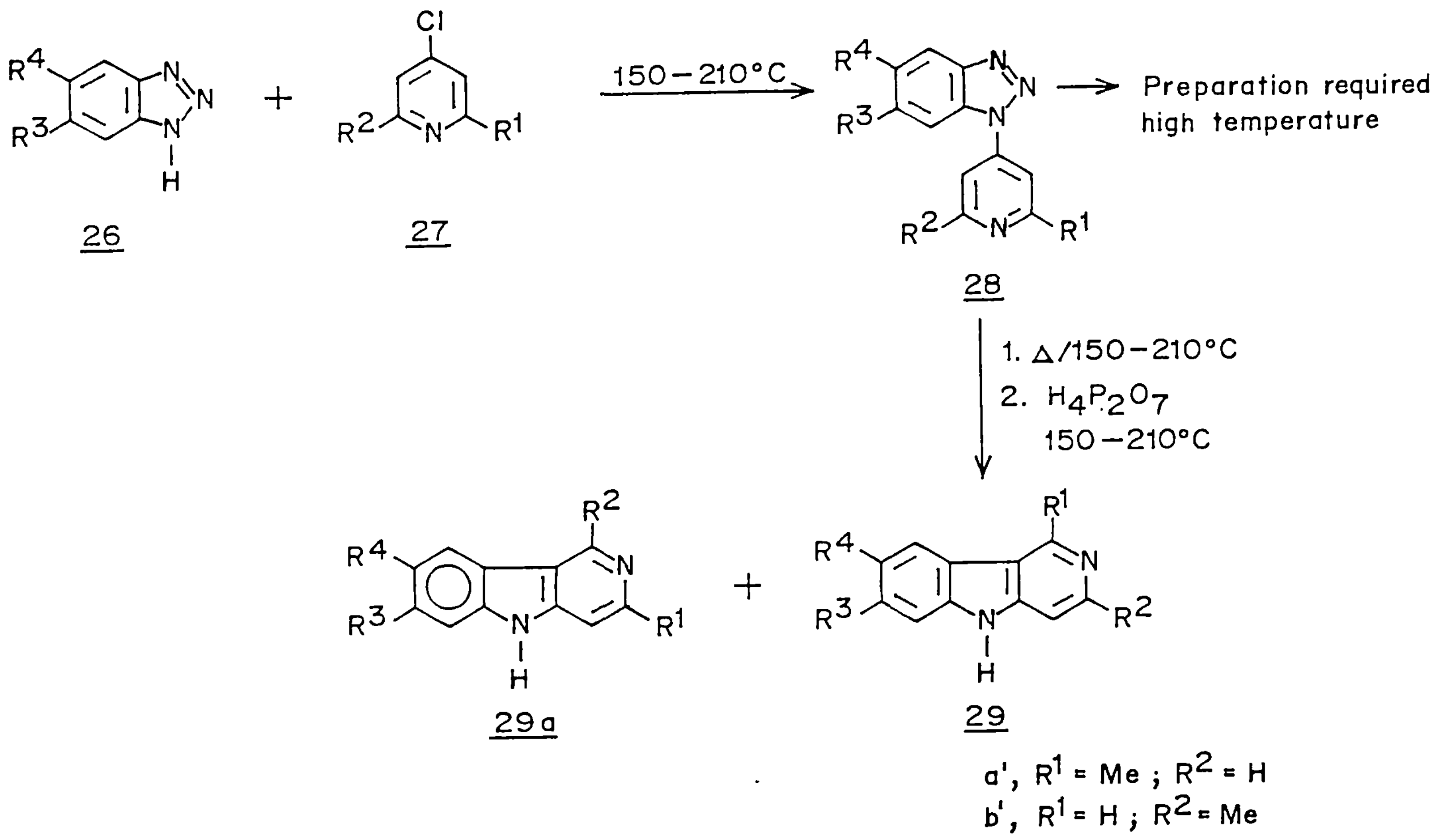
Scheme – 7

treated with diethyl amine in absolute alcohol to yield corresponding γ-carboline **18** in 90% yield.

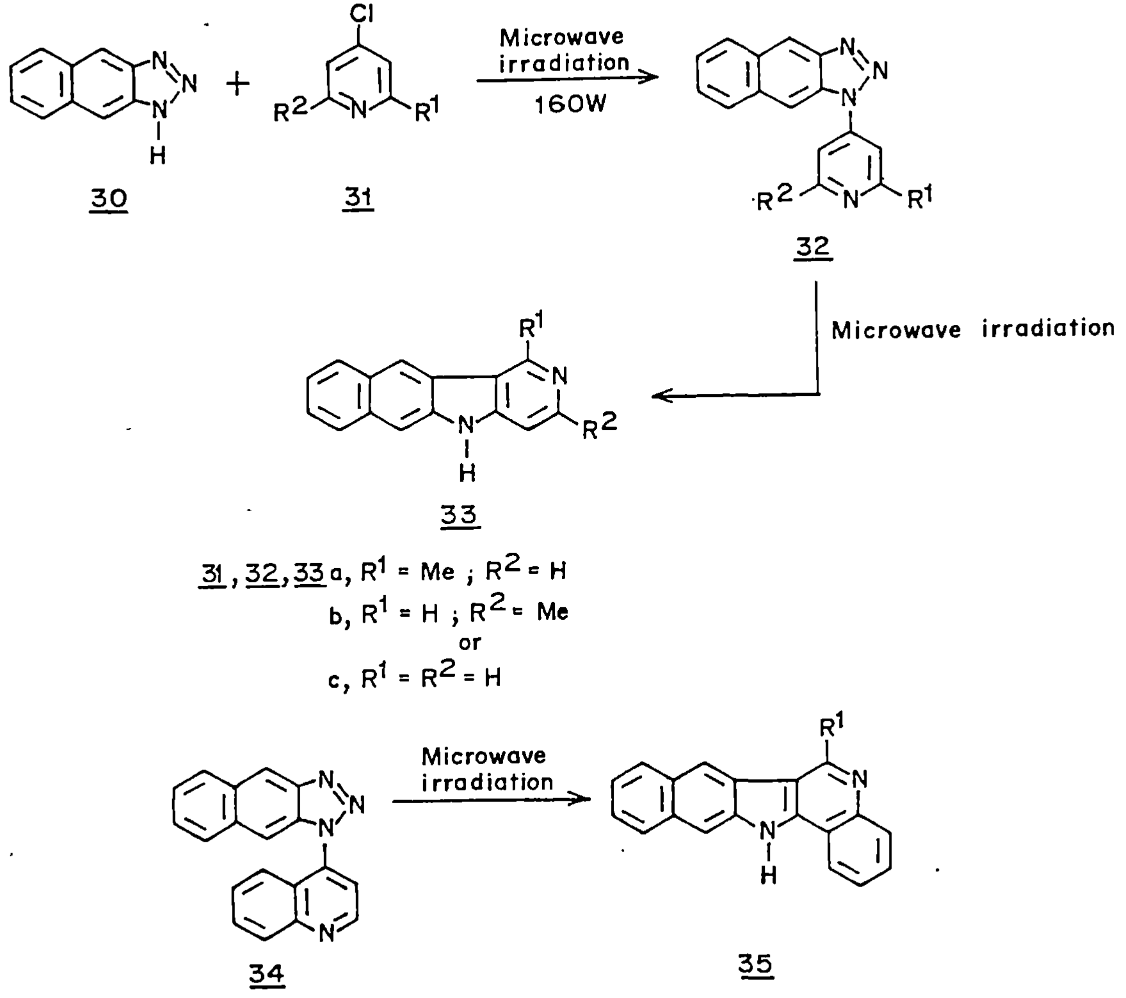
Renault and co-workers reported a series of papers[16,17,18,19,20] on several γ-carboline derivatives and their condensed variants. Their approach was to start from hydrazino quinoline and build the carbazole ring involving fisher indole cyclization. Thus 4-hydrazino-7-methoxy-8-amino quinoline **19** was reacted with cyclohexanone **20** (scheme 6) which was then cyclized to yield the corresponding tetrahydro-γ-carboline followed by dehydrogenation to yield the corresponding γ-carboline derivative **21**.

Molina and Fresneda reported[21] a simple general procedure for the preparation of γ-carbolines under complete neutral conditions, based on the aza-wittig reaction of iminophosphoranes derived from azido-acrylates bearing indolyl substituents. Thus, iminophosphorane 23, was reacted with aryl isothiocyanates under dry toluene refluxing conditions to yield 1-arylamino-3-ethoxycarbonyl-5-methylpyrido[4,3-b]indoles 25 in 81-94% overall yields. However, they reported the reaction between iminophosphorane 23 and carbon disulphide in toluene at reflux temperature leads to 3-ethoxycarbonyl-1,2-dihydro-5-methyl-1-thiopyrido[4,3-b]indole 24 in 96% yield (scheme 7).

The Robinsons γ-carboline approach was extended with some modification by Molina[22] and co-workers. Thus benzotriazole **26** were reacted with functionlized 4-chloropyridines under Grabe-Ullmann reaction conditions at 150°C to yield the corresponding N-pyridylbenzotriazole **28**, which was then thermally rearranged in the


26
27
150−210°C
28
Preparation required high temperature
1. Δ/150−210°C
2. H4P2O7 150−210°C
29a
29
a', R1 = Me ; R2 = H
b', R1 = H ; R2 = Me

Scheme − 8

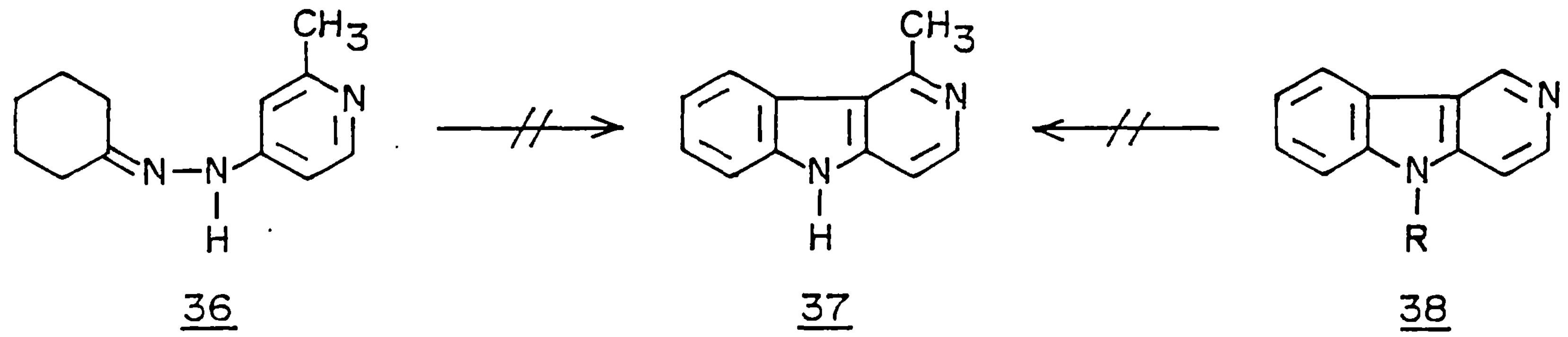


30 31 32 33

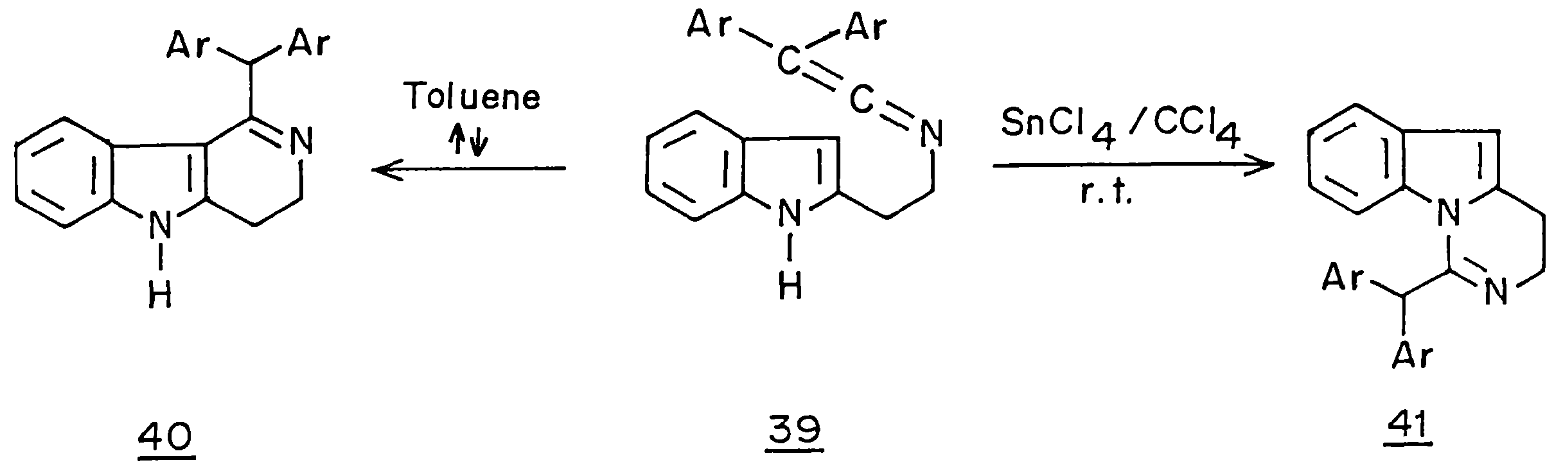
31, 32, 33 a, R^1 = Me ; R^2 = H
b, R^1 = H ; R^2 = Me
or
c, R^1 = R^2 = H

34 35

Scheme -9

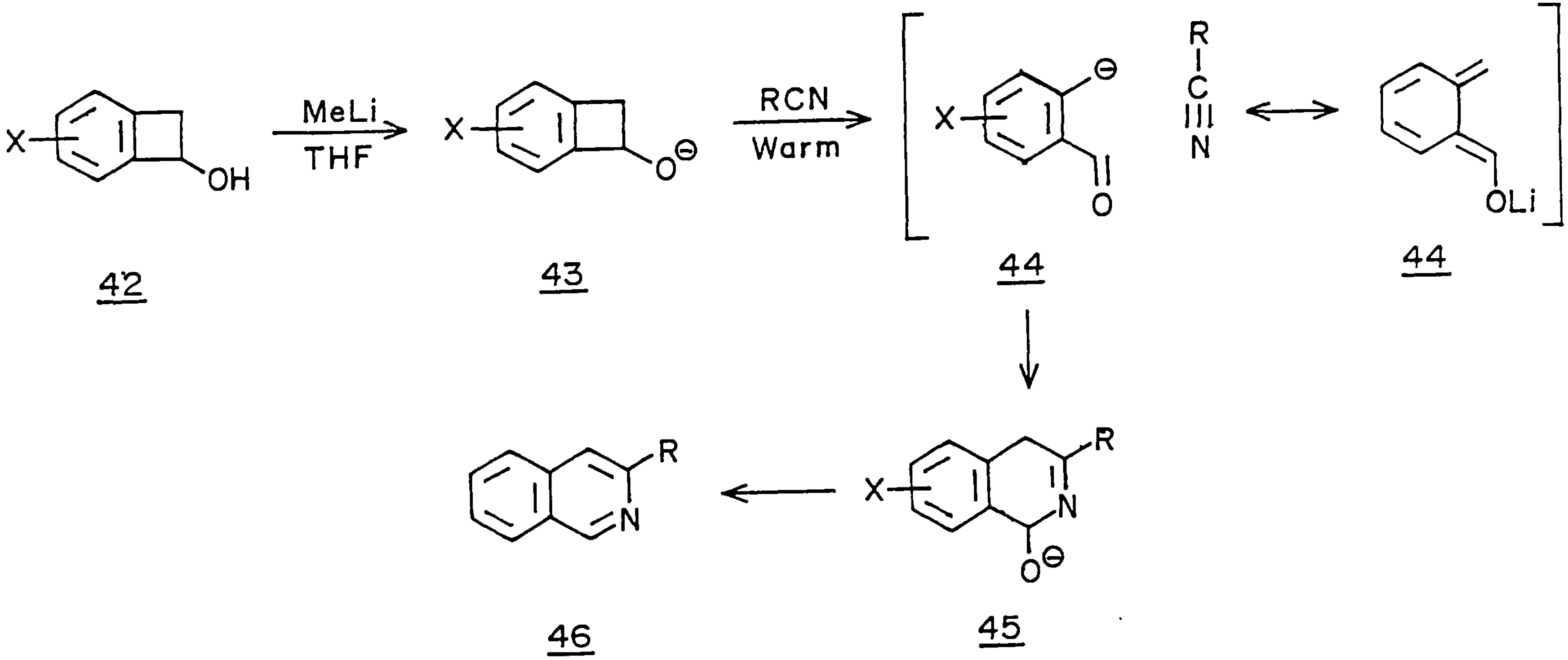


Scheme - 10



Molina , P. ; Alcantara , J. ; Lopez-Leonardo , C. Tetrahedron Lett., 1995 , 36, 953.

Scheme – 11



Fitzgerald , J.J.; Michael , F.F.; Olofson , R.A. Tetrahedron Letters vol 35 , 9191–9194, 1994

Scheme–12

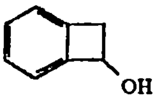
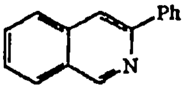
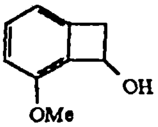
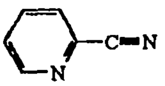
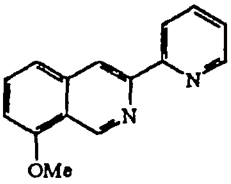
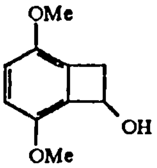
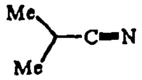
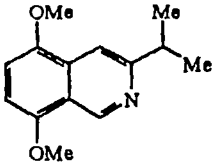
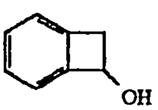
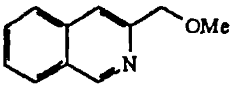
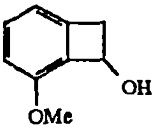
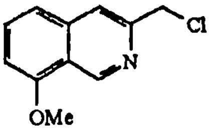
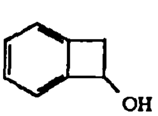
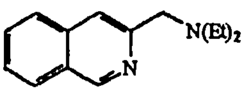
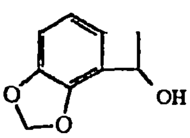
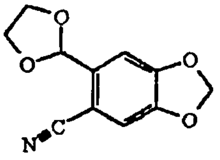
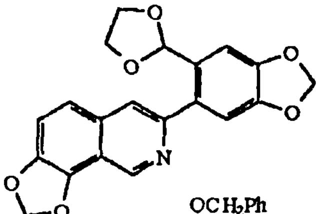
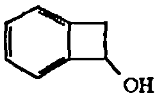
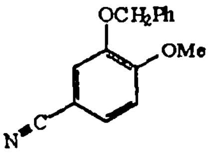
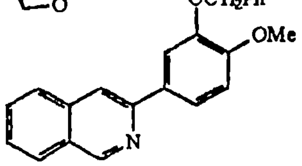
presence of $H_4P_2O_7$ to yield a mixture of γ-carbolines **29** and **29a** (scheme 8). The same authors used naphthotriazole **30** under the reaction conditions described above to get the corresponding pyridyl naphthotriazole **32**, which on microwave irradiation rearranged to the corresponding γ-carbolines **33** . Under the similar conditions quinolinyl naphthotriazole **34** was also formed, which on microwave irradiation yielded **35** in good yield (scheme 9).

Molina and co-workers failed to achieve fisher indole cyclization of the hydrazone derived from 2-methylpyridine hydrazine to get the corresponding 1-methyl-[5H]-pyrido[4,3-b]indole **37**, which is a potent DNA intercalator[23,24]. However, they also attempted in vain to achieve same compound **37** by direct methylation of its protected precursor **38** (scheme 10).

Molina and co-workers reported[25] a new regiospecific intramolecular cyclization of heterocumulene substituted indoles, which were expected to under go two types of cyclizations , either involving indole-3-position to yield the corresponding γ-carboline derivative **40** or the corresponding pyrimido[3,4-a]indoles **41**. They observed that in the case of isothiocyanate they under went cyclization across the 3-position of indole ring in the presence of lewis acid catalysed conditions. On the other hand the reaction in the presence of strong basic conditions the cyclization under went through the indole ring nitrogen atom (scheme 11).

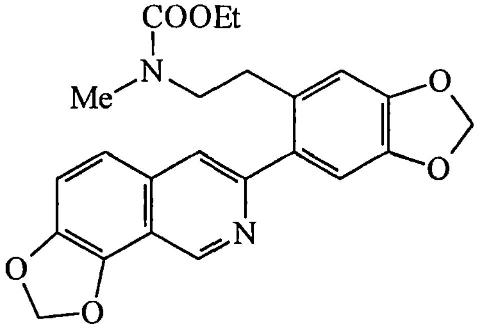
Olofson and co-workers have recently reported[26] a novel approach for the synthesis of isoquinolines **46** (scheme 12). They treated benzocyclobuten-2-ols **42** with methyllithium to yield the

Table 1

Benzocyclobutenol	Nitrile	Product	Yield	mp
	Ph—C≡N		47%[a]	104-105 °C[b]
			55%[c]	139-140 °C
			49%[c]	72-73 °C
	$MeOCH_2$—C≡N		60%[c,d]	bp 71-73 °C at 0.2 mm[e]
	$ClCH_2$—C≡N		68%[c]	77-79 °C
	Et_2NCH_2—C≡N		80%[a]	oil; NMR, tlc pure
			48%[a]	163-166 °C
			90%[f,g]	oil; NMR, tlc pure

[a]With 1.1 equiv. nitrile. [b]lit. mp 104-105°C. [c]With 1.5 equiv. of nitrile. [d]Quantitative yield of crude (pure, ^1H NMR); given yield distilled on a 0.5 g scale. [e]lit. bp 82°C at 0.6 mm; [f]Yield is with 5.0 equiv. [g]42% yield with 1.5 equiv.

corresponding o-tolualdehyde anion **44**, which can be considered as o-quinodimethane species in the presence of various nitriles as dienophiles. The cycloadducts **45**, thus formed under went dehydration to yield the corresponding isoquinolines **46**.



Hypecumine

Various isoquinolines including the natural product Hypecumine were prepared by this route which are described in Table 1.

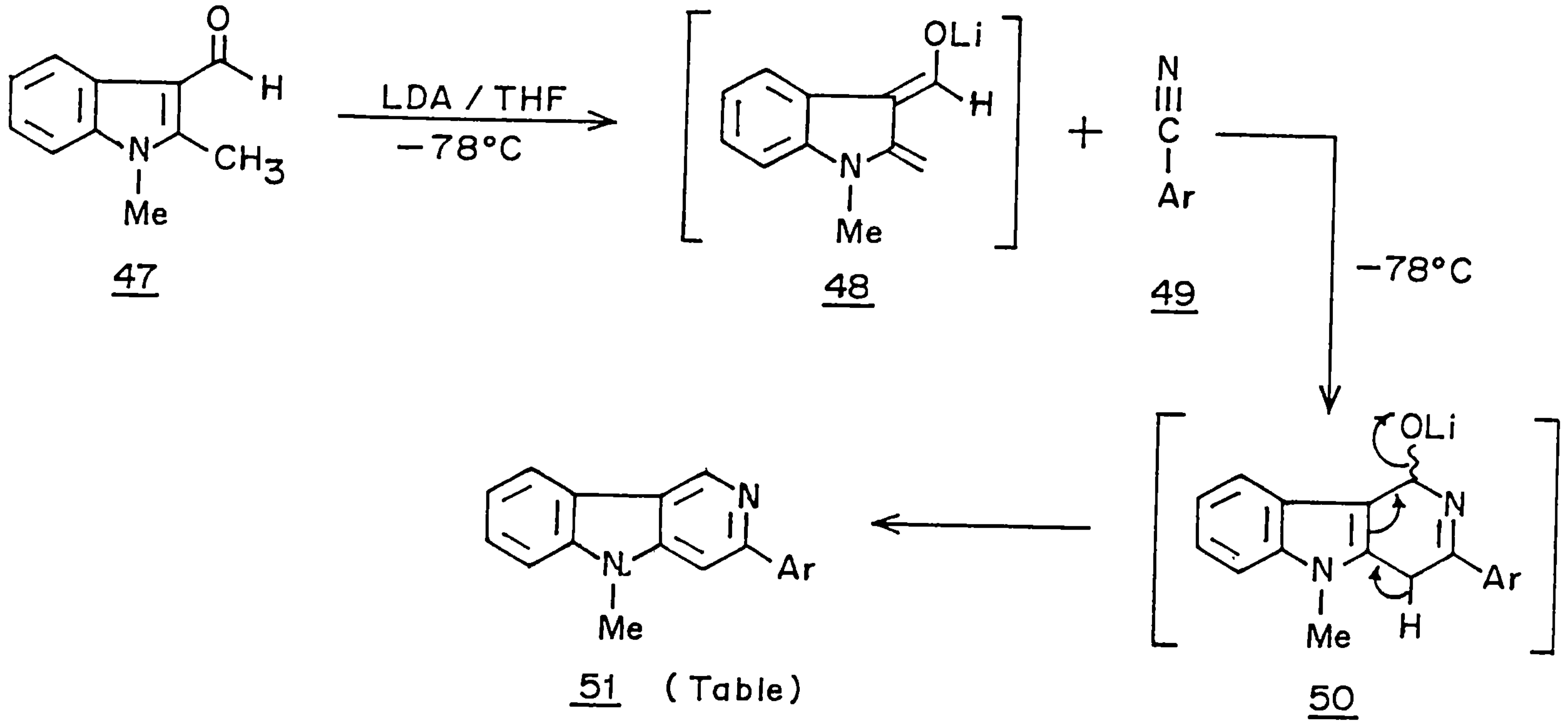
Thus it was considered of interest to extend the Diels-Alder strategy using indole-2,3-dienolate (indolo-2,3-quinodimethane species) as diene and various nitriles as dienophiles to synthesise substituted γ-carbolines.

II. B.3. Results and Discussion :

Present Investigation :

From the preceding section it is to be noted that there are not many methods for the synthesis of γ-carbolines and most of these approaches involve either Robinsons method or direct cyclization of hydrazone derived from piperidone and aryl hydrazine's under fisher indole conditions. Interestingly Olofsons o-tolualddehyde anions reaction using various nitriles as dienophiles for the efficient synthesis of isoquinolines has not been extended to Indole-2,3-dienolate[27] to yield γ-carbolines. It was there fore considered of interest to explore studies on the reactivity of indole-2,3-dienolate **48** as a potential diene with various nitriles as dienophiles to yield the corresponding γ-carbolines. Results of these studies are presented in this section.

Indole-2,3-dienolate **48** was generated *in situ* from 1,2-dimethylindole-3-carboxaldehyde **47** according to our earlier report[27]. To establish authenticity and reactivity of this indole-2,3-dienolate, it was reacted with benzonitrile **49** at −78°C under masked nitrogen atmosphere and after work up of the reaction mixture the product obtained purified using silica gel chromatography and was characterised as 5-methyl-3-phenyl[5H]pyrido[4,3-b]indole **51a**, which was obtained as light yellow needles, m.p.126-127°C (dichloromethane/hexane) in 47% yield. The structure of the product was established on the basis of

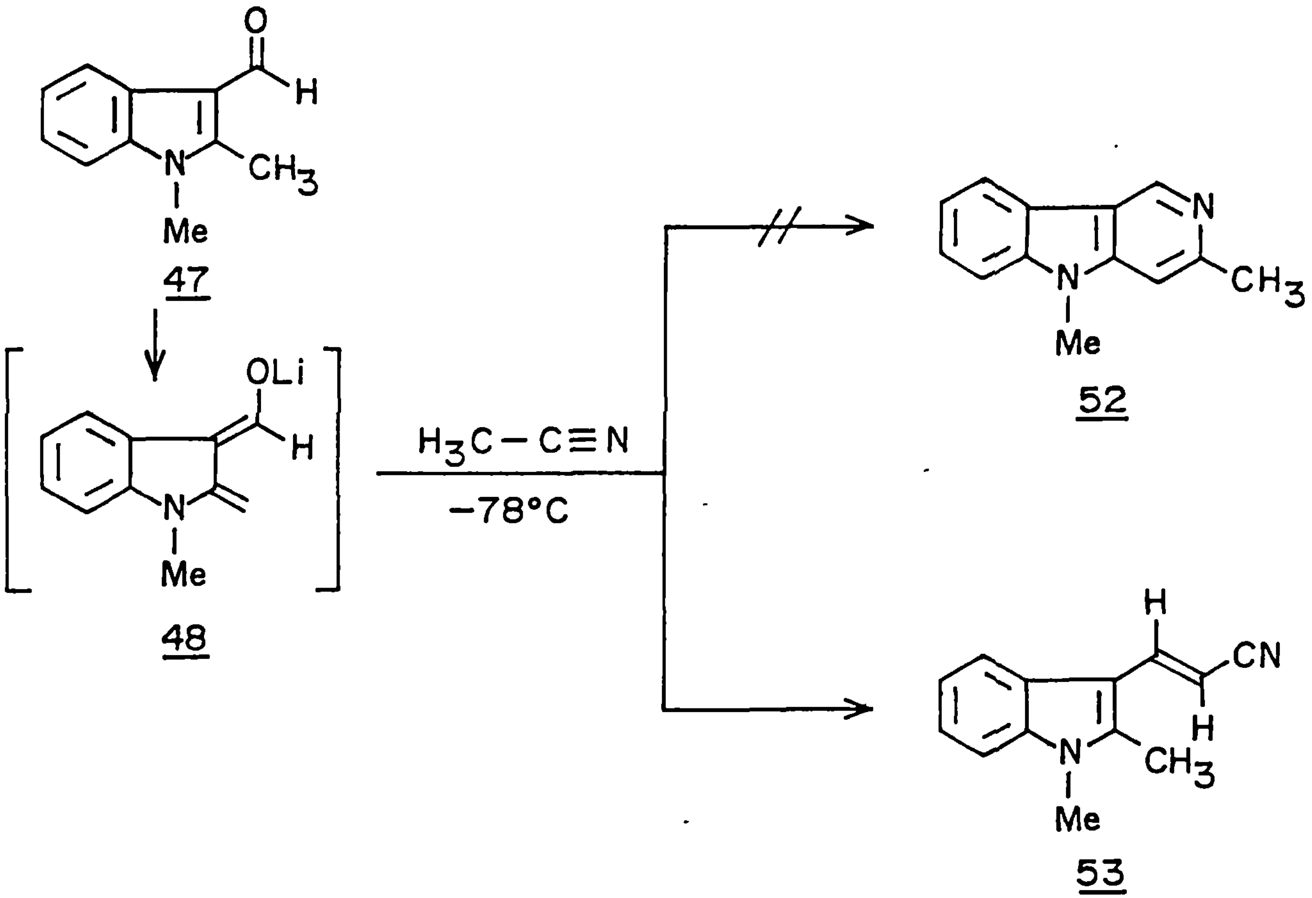


Scheme—13

analytical and spectral data. Thus it was analysed for $C_{18}H_{14}N_2$ for a molecular weight 258.31 which was conformed by its mass spectrum with a peak at m/z: 258 (M^+, 73.4%). Its IR spectrum (CCl_4), displayed a characteristic absorption band at 1593cm^{-1} (C=N) . The structure was further conformed by from its ^1H NMR spectrum (300.13MHz, $CDCl_3$). The singlet at δ3.81 integrating for three protons was assigned for N-methyl protons and two singlets at δ9.32 and δ7.62 each integrating for one proton were assigned for the protons H-1 and H-4 respectively ,of the newly formed pyridine ring in the product γ-carboline. The other aromatic protons appeared as six proton multiplet at δ7.51 and three proton multiplet at δ8.08 were accounted for all the remaining aromatic protons which are described in the experimental section. The structure was unambiguously confirmed by its ^{13}C NMR spectrum (75.46MHz) . Thus the peak at δ29.06 was assigned for the N-methyl carbon and all other peaks are described in the experimental section which are in conformity with the assigned structure.

Similarly indole-2,3-dienolate <u>48</u> was reacted with p-methoxy benzonitrile, veratronitrile, 3,4,5-trimethoxy benzonitrile and p-N,N-dimethylamino benzonitrile to yield the corresponding 3-aryl-γ-carbolines **51b-e** in 49-59% overall yields. The structures of all these 3-aryl-5-methyl[5H]pyrido[4,3-b]indoles **51a-e** were established on the basis of their analytical and spectral data which are described in the experimental section.

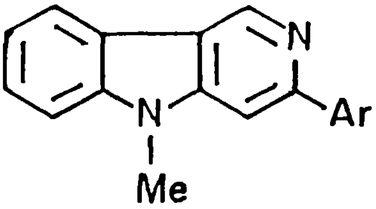
However, indole-2,3-dienolate **48** when reacted with acetonitrile did not yield expected 3,5-dimethyl-γ-carboline **52** and the compound isolated was characterised as 1,2-dimethyl-3-(2'-cyanoethenyl)indole

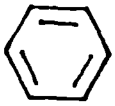
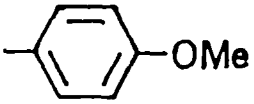
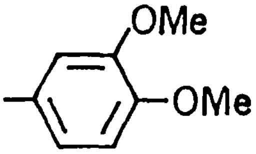
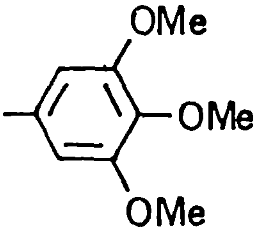
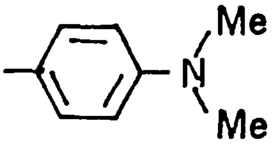


Scheme −14

Table

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



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

53, which was obtained as pale yellow needles from chloroform/ hexane crystallised product m.p.123-124°C in 69% yield. The structure was established on the basis of its spectral and analytical data. It was analysed for the molecular formula $C_{13}H_{12}N_2$ for the molecular weight 196.25 which was conformed by its mass spectrum with a peak at m/z: 196 (M^+, 100%). The characteristic C≡N absorption band in its IR spectrum at ν_{max} 2199 cm^{-1} conformed the free nitride group. It was further supported by its ^1H NMR (90MHz, $CDCl_3$) spectrum. The two singlets at δ2.50 and at δ3.73 each integrating for three protons were assigned for the S-methyl and N-methyl protons respectively. Doublet integrating for one proton at δ5.70-5.86 with a coupling constant 15Hz was assigned for the trans vinylic proton peri to the indole ring. The remaining aromatic protons which were in conformity with the assigned structure were described in the experimental section.

The structures of all these products synthesised were in agreement with their analytical and spectral data which are described in the experimental section.

II.B.4 Conclusions :

Indole-2,3-dienolate **48** (indolo-2,3-quinodimethane species) has been shown to react with various aromatic nitriles in Diels-Alder manner to give the corresponding 3-aryl-5-methyl-[5H]-pyrido[4,3-b]indole **51a-e** (substituted γ-carbolines) in moderate yields. The reaction failed to give the expected 3,5-dimethyl-γ-carboline **52** when reacted with acetonitrile . Only the aldol adduct **53** was isolated in 69% yield. The method therefore is useful only when aromatic nitriles were used as dienophiles. Only a few selected examples have been investigated and the potential of this methodology for the synthesis of structural variants of γ-carbolines remain unexplored area. In the absence of many efficient methods for the synthesis of γ-carboline derivatives this simple approach should serve as an alternative choice.

II.B. 5. EXPERIMENTAL SECTION:

General:

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected . The IR spectra were recorded on a Perkin Elmer 297 spectrophotometer and frequencies are expressed in cm^{-1}. The ^{1}HNMR spectra were recorded on Varian EM-390, 90 MHz, spectrometer in $CDCl_3$ (or) CCl_4 and are reported in δ units down field from Tetramethylsilane. High resolution ^{1}HNMR (300.13MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ are reported in δ units downfield from Tetramethylsilane. The coupling constants are given in Hertz. ^{13}CNMR (75.46 MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ and are reported in δ units, downfield from TMS. Mass spectra were obtained on a Joel D-300 spectrometer and relative intensities are expressed in percentage. Carbon, Hydrogen and Nitrogen elemental analysis were carried out on a Heraus CHN-O-RAPID instrument. T. L.C. (ACME's) was used for monitoring the reactions.

All the reactions involving organolithium were performed in oven-dried glassware under masked dry nitrogen atmosphere using syringe-septum technique.Low temperature reactions were carried out in a bath made of ethylacetate and liquid nitrogen .

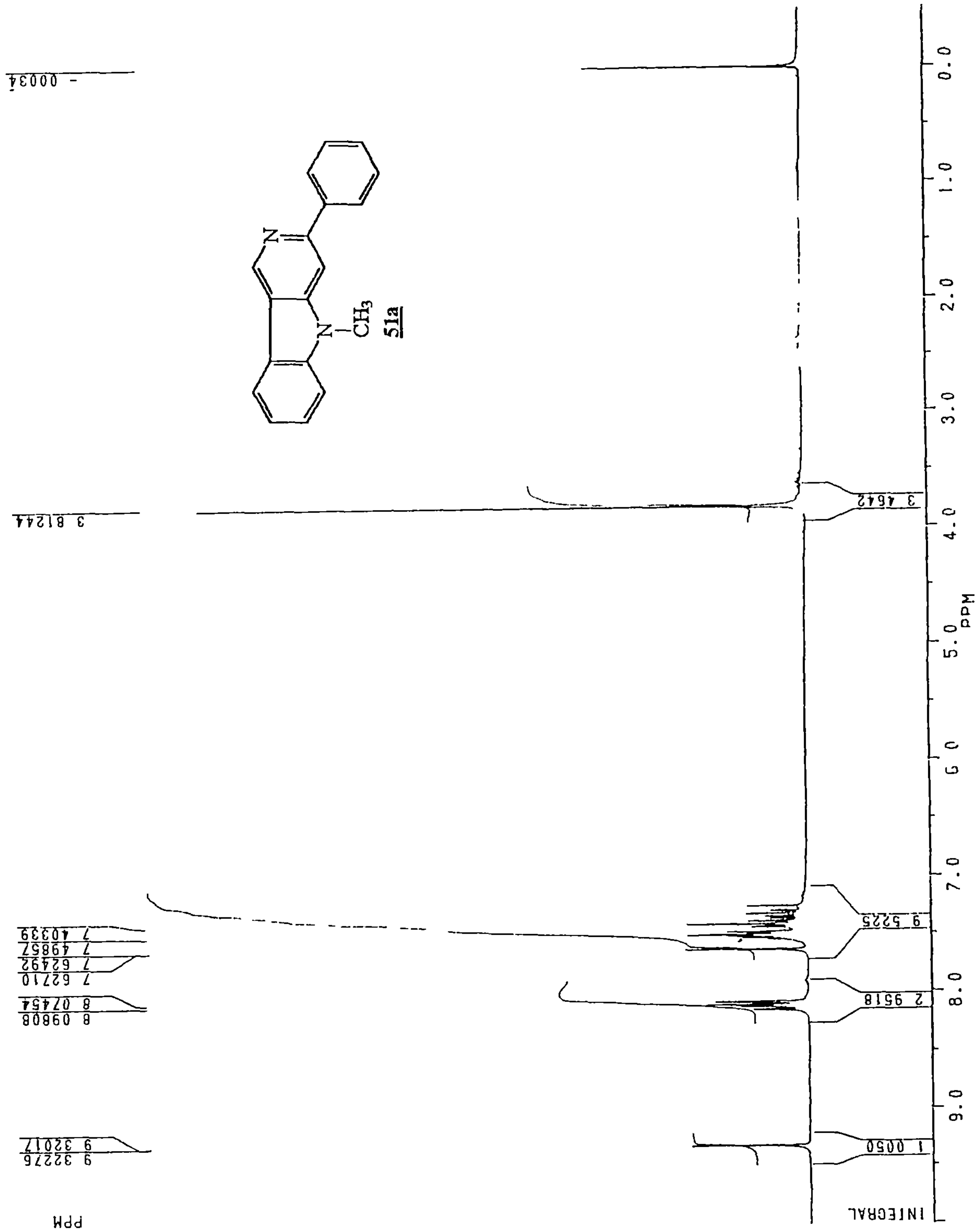
Chemicals and Solvents :

The commercial samples of phenyl hydrazine, N,N-diisopropylamine, n-butyl bromide, dimethyl formamide, Phosphorous oxychloride, acetone, benzonitrile, p-methoxy benzonitrile, 3,4-dimethoxy benzonitrile, 3,4,5-trimethoxy benzonitrile, p-N,N-dimethyl benzonitrile were purified before use. Butyl Lithium was prepared according to the reported procedure. Diethylether and benzene were distilled and dried by keeping over sodium wire. Tetrahydrofuran was initially deperoxidized and then dried by keeping over sodium wire followed by distillation. 2-methylindole 3-carboxaldehyde was prepared according to the reported procedure.

General procedure for the synthesis of 3-Aryl-5-methyl-[5H]-pyrido[4,3-b] indoles (51a-e):

To a solution of diisopropylamine (2ml, 14mmol) in sodium dried tetrahydrofuran (10ml) under masked nitrogen atmosphere was added n-BuLi (10mmol) in diethylether with stirring at temperature (0°C) controlled by an ice water bath and the solution was stirred for 20min at the same temperature. The resulting solution of lithium diisopropylamide (LDA) was cooled down to –78°C and was added a solution of 1,2-dimethylindole-3-carboxaldehyde (865mg, 5mmol) in 25ml dry THF, the reaction mixture was stirred at the same temperature for 45min. To the resulting enolate solution at −78°C was added arylnitile (4mmol) in 15ml dry THF dropwise fashion over a period of 15min. The reaction mixture was stirred for 0.5hr at the same temperature and then was left stirred at the ambient temperature (monitored by T.L.C) over night. The reaction mixture was quenched with aqueous saturated ammonium chloride solution (50ml) and the aqueous layer was extracted with chloroform (3x50 ml) . The combined organic extracts were washed with water (3x25 ml), and the organic layer was dried over sodium sulphate which was concentrated to give the crude product, which was purified by chromatography over silica gel using ethyl acetate / hexane (2:8) as eluent. The structures of all the products obtained were in agreement with their analytical and spectral data which are described data which are described below.

5-Methyl-3-phenyl [5H]pyrido[4,3-b]indole (51a) was obtained as a light yellow needles (dichloromethane/hexane), m.p.126-127°C; yield : 47%; IR(CCl_4):ν_{max} =1593 (C=N), 1494, 1469,1244 cm $^{-1}$; ^{1}H NMR (300.13MHz, $CDCl_3$): δ=3.81 (s,3H, N$C\underline{H}_3$), 7.51 (m,6H, Ar$\underline{H}$), 7.62 (s,1H, Ar$\underline{H}$,H-4), 8.08 (m,3H, Ar$\underline{H}$), 9.32 (s,1H, Ar$\underline{H}$, H-1); ^{13}C NMR (75.46MHz, $CDCl_3$): δ =29.06 (N$\underline{C}H_3$), 100.58, 108.87, 118.59, 120.55, 120.65, 121.22, 126.66, 127.20, 128.39, 128.72, 140.52, 141.42, 142.23, 146.04, 153.50(C=N). m/z: 258 (M+, 73.4%), 243 (48%) ; Anal. Calculated for $C_{18}H_{14}N_2$ (258.31) : C,83.69; H,5.46; N,10.85. Found: C,83.61; H,5.43; N,10.81%.


51a
N
N—CH3
- 00034
3 81244
7 40339
7 49857
7 62492
7 62710
8 07454
8 09808
9 32017
9 32276
PPM
3 4642
9 5225
2 9518
1 0050
INTEGRAL
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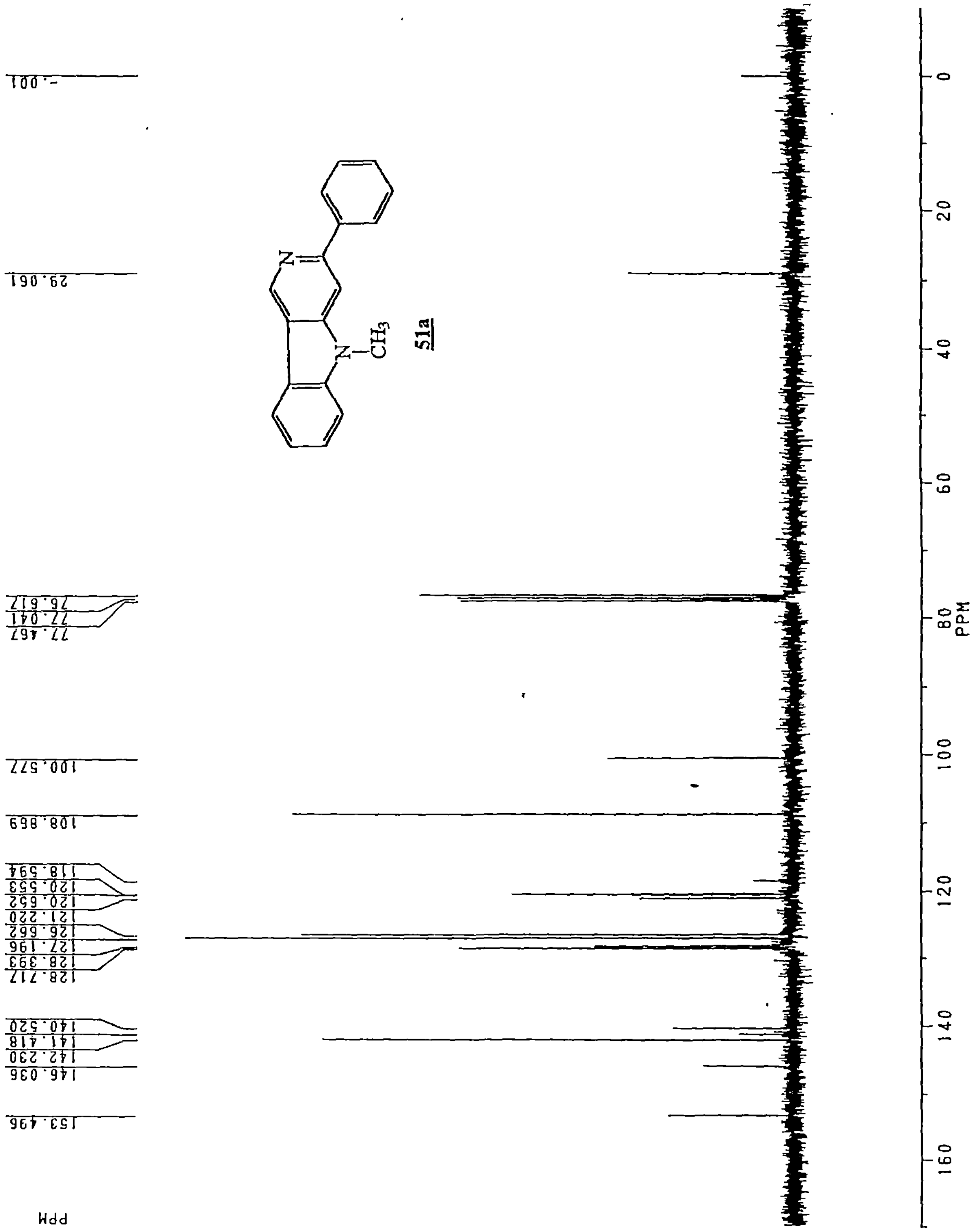
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
PPM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77.041
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100.577
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120.553
120.652
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127.196
128.393
128.717
140.520
141.418
142.230
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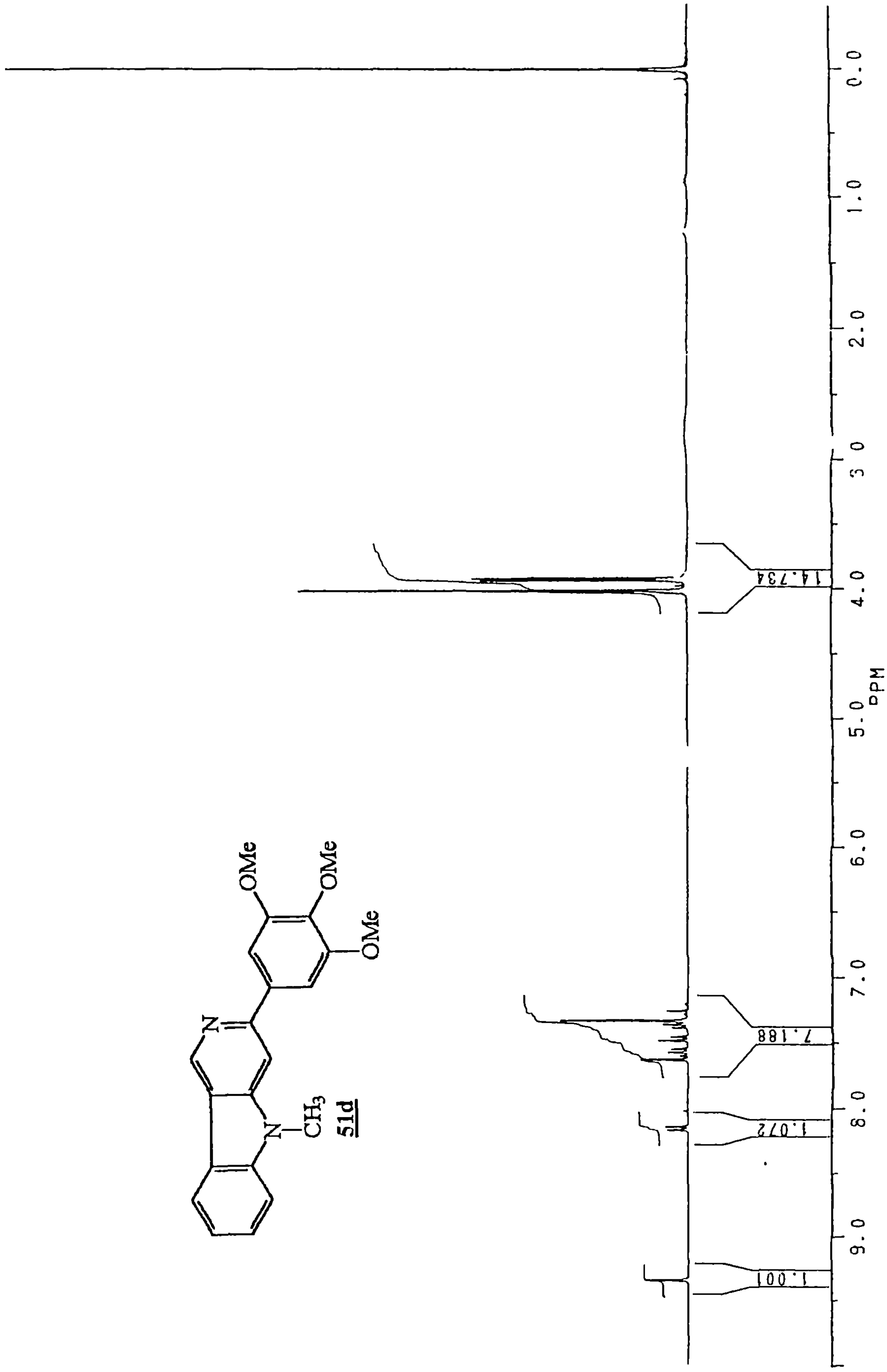
PPM
N
N
CH3
0
20
40
60
80
PPM
100
120
140
160

51a



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OMe
OMe
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N
CH3
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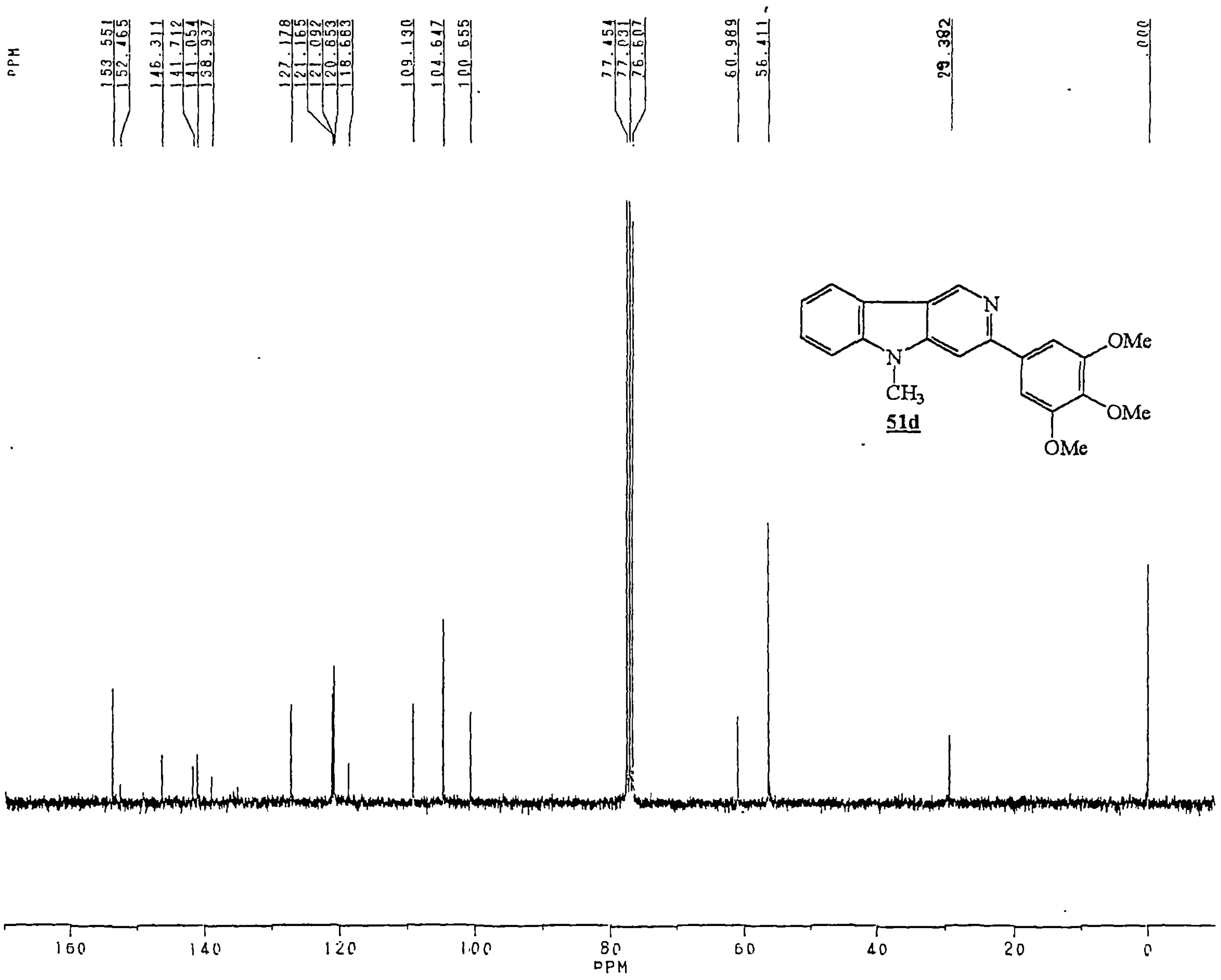
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
PPM

51d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121.165
121.092
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104.647
100.655
77.454
77.031
76.607
60.989
56.411
29.382
.000
N
N
CH3
OMe
OMe
OMe
160
140
120
100
80
60
40
20
0
PPM

51d

3-(4'-Methoxyphenyl)-5-methyl[5H]pyrido[4,3-b]indole (51b) was obtained as a pale yellow needles (chloroform/hexane), m.p.168-169°C; yield : 56%; IR(KBr):ν_{max}= 1635 C=N), 1468, 1411, 1392, 1370 cm^{-1}; ^{1}H NMR (90MHz, $CDCl_3$): δ =3.69 (s,3H, NCH_3), 3.86 (s,3H, OCH_3), 6.99 (d, 2H,J=8.5Hz, ArH), 7.10-7.59 (m,4H, ArH), 7.86-8.26 (m,3H, ArH), 9.26 (s,1H, ArH,H-1); Anal. Calculated for $C_{19}H_{16}N_2O$ (288.34) ; C,79.14; H, 5.59; N,9.72. Found: C,79.12; N,5.56; N,9.70%.

3-(3',4'-Dimethoxyphenyl)-5-methyl[5H]pyrido[4,3-b]indole (51c) was obtained as a light yellow needles (chloroform/hexane), yield : 59%; m.p.166-168°C; IR(KBr):ν_{max}= 2993, 2963, 2931, 1602 (C=N), 1512, 1456, 1436, 1258, 1146 cm^{-1}; ^{1}H NMR (90MHz, $CDCl_3$):δ= 3.85(s, 3H, NCH_3), 3.93 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 6.99 (d,1H, J=8.5Hz, ArH), 7.23-7.73 (m, 5H, ArH), 7.79 (s, 1H, ArH, H-4), 8.21 (d, 1H, J=8.5Hz, ArH), 9.39 (s, 1H, ArH, H-1); Anal. Calculated for $C_{20}H_{18}N_2O_2$ (318.36) ; C,75.45; H,5.70; N,8.81. Found: C,75.40; H,5.63; N,8.76%.

5-Methyl-3-(3',4',5'-trimethoxyphenyl)[5H]pyrido[4,3-b]indole (51d) was obtained as a light yellow needles (acetone/hexane), m.p.166-167°C; yield : 51%; IR(KBr) :ν_{max}= 1587 (C=N), 1454, 1123 cm^{-1} ; ^{1}H NMR (300.13MHz, $CDCl_3$): δ=3.92 (s, 3H, NCH_3), 3.94 (s, 3H, OCH_3), 4.02 (s, 6H, OCH_3, OCH_3), 7.33 (s, 2H, ArH), 7.38 (m, 1H, ArH), 7.47 (m, 1H, ArH), 7.56 (m, 1H, ArH), 7.63 (s, 1H, ArH, H-4), 8.15 (d, 1H, J=7.72Hz, ArH), 9.35 (s, 1H, ArH); ^{13}C NMR (75.46MHz, $CDCl_3$) : δ =29.38 (NCH_3), 56.41 (OCH_3), 60.99 (OCH_3), 100.66, 104.65, 109.13, 118.68, 120.85, 121.10, 121.17, 127.19, 138.94, 141.10, 141.71, 146.31, 152.47, 153.55 (C=N); Anal.

Calculated for $C_{21}H_{20}N_2O_3$ (348.39); C,72.39; H,5.79; N,8.04. Found: C,72.35; H, 5.78; N,7.98%.

3-(4'-N,N-Dimethylaminophenyl)-5-methyl[5H]pyrido[4,3-b]indole (51e) was obtained as a light yellow needles (dichloromethane/hexane), m.p.141-142°C; yield : 49%; IR(KBr) :ν_{max}= 2990, 2964, 1601, 1457, 1259 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$): δ= 3.03 (s, 6H, $2NCH_3$), 3.83 (s, 3H, NCH_3), 6.76-7.03 (m, 2H, ArH), 7.13-7.56 (m, 4H, ArH), 7.59 (s, 1H, ArH, H-4), 7.93-8.33 (m, 2H, ArH), 9.36 (s, 1H, ArH, H-1); Anal. Calculated for $C_{20}H_{19}N_3$ (3000.37); C,79.71; H,6.35; N, 13.94. Found: C,79.69; H, 6.35; N,13.89 %.

1,2-Dimethyl-3-(2'-cyanoethenyl)indole (53) was obtained as a pale yellow needles (chloroform/hexane); m.p.123-124°C; yield : 69%; IR(KBr) : ν_{max} =2199 (C≡N), 1597, 1408 cm^{-1}; ^1H NMR (90MHz, $CDCl_3$): δ= 2.50 (s, 3H ,CH_3), 3.73 (s, 3H, NCH_3), 5.79 (d, 1H, J=15Hz (trans) vinylic H) , 7.23-7.49 (m, 3H, ArH), 7.56-7.93 (m, 2H, ArH) ; Anal. calculated for $C_{13}H_{12}N_2$ (196.25); C,79.56; H,6.16;N,14.28. Found : C,79.51; H,6.10; N,14.22%.

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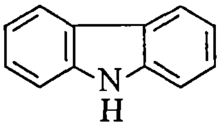
CHAPTER III

Benzo [b] and Hetero [b] Annulation Of 1-N-Methyl-2-bis(methylthio)methylene-3-oxoindole

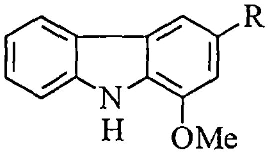
III. 1. Introduction :



1

The carbazole 1, which itself is a natural product, was isolated[1] in 1872 by Graebe and Glazer as one of the Coal tar products. However, the first group of carbazole alkaloids from biological origin were discovered only in 1965 by D.P. Chakraborty[2] and co-workers. The plants of the genus murraya (Rutaceae) are the major source of carbazole alkaloids, of which there are now more than 50 known[3] .

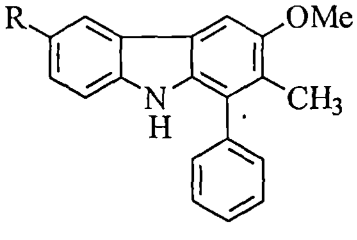
Murrayanine **2a** was the first carbazole alkaloid isolated from Murraya Koenigii spring[2].



2

2a, R=CHO	(Murrayanine)
2b, R=COOH	(Mukoeic acid)
2c, R=CO_2Me	(Mukonine)
2d, R=Me	(Murrayafoline-A)

Since then a broad range of carbazole alkaloids has been isolated from terrestrial plants over the past 30 years[4], and found to be possessing important biological activities[5]: In more recent times a large number of carbazole alkaloids has been found in different sources viz. algae and streptomyces[4]. Hyellazole **3a** and 6-chlorohyellazole **3b** were the first carbazole alkaloids of marine origin isolated from the blue-green alga Hyella Caesposita[6].

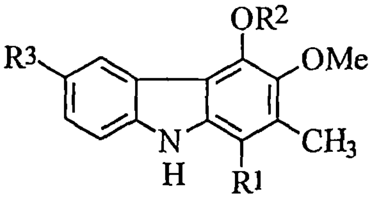


3

3a, R=H, Hyellazole

3b, R=Cl, 6-chlorohyellazole

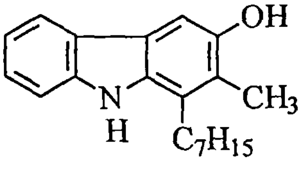
Most important among these carbazole alkaloids are carbazomycins **4**, isolated[7] from actinomycete streptoverticillium ehimence, which are having broad spectrum of antibacterial properties.



4

4a, R^1=Me, R^2=R^3=H	Carbazomycin A
4b,R^1=R^2=Me,R^3=H	Carbazomycin B
4c,R^1=Me,R^2=H,R^3=OMe	Carbazomycin C
4d, R^1=R^2=Me, R^3=OMe	Carbazomycin D
4e, R^1=CHO, R^2=R^3=H	Carbazomycin E
4f, R^1=CHO,R^2=H,R^3=OMe	Carbazomycin F 6-methoxy carbazomycinal

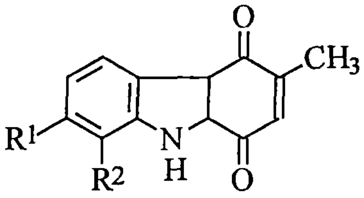
Carazostatin **5**, found in streptomyces chromofuscus[8] possesses interesting antioxidative property,



5

(free radical scavenger)

All the eight kinds of carbazolequinone alkaloids **6** were obtained from the root stem barks of Murraya euchrestifolia Hayata[9], which are proved to be having interesting biological[10] properties.



6

6a, $R^1=R^2=H$, Murrayaquinone A

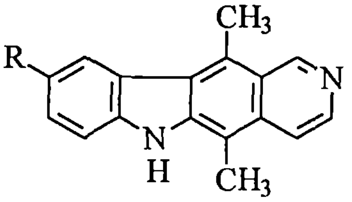
6b, $R^1=OMe,R^2=$ Prenyl, Murrayaquinone-B

6c, $R^1=OMe,R^2=$ Geranyl, Murrayaquinone-C

6d, $R^1=OH,R^2=$ Geranyl, Murrayaquinone-D

6e, $R^1=OH$, $R^2=$ Prenyl, Murrayaquinone-F

Most important properties associated with carbazoles and their condensed analogues is their molecular flat area which permits intercalation with DNA double helix and known to interfere in the functioning of topoisomerase I and Topoisomerase II enzyme activities.

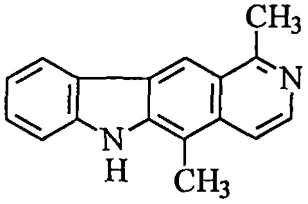


7

7a, R=H

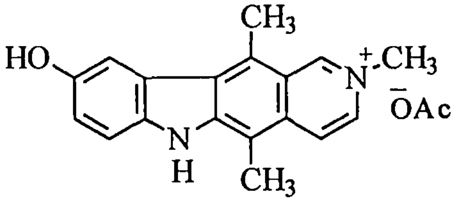
7b, R=OCH3

7c, R= OH



8

Besides these,there is another class of carbazole alkaloids, pyrido [b] carbazoles, which possesses important biological properties. The ochrosia, Aspidosperma, Tabernaemontana, and strychnos plant alkaloids[11], Ellipticine **7a** (5,11-dimethyl-6H-pyrido[4,3-b]carbazole), 9-methoxyellipticine **7b** and olivacine **8** respectively, exhibit pronounced anticancer activity in several animal and human tumor systems[12].

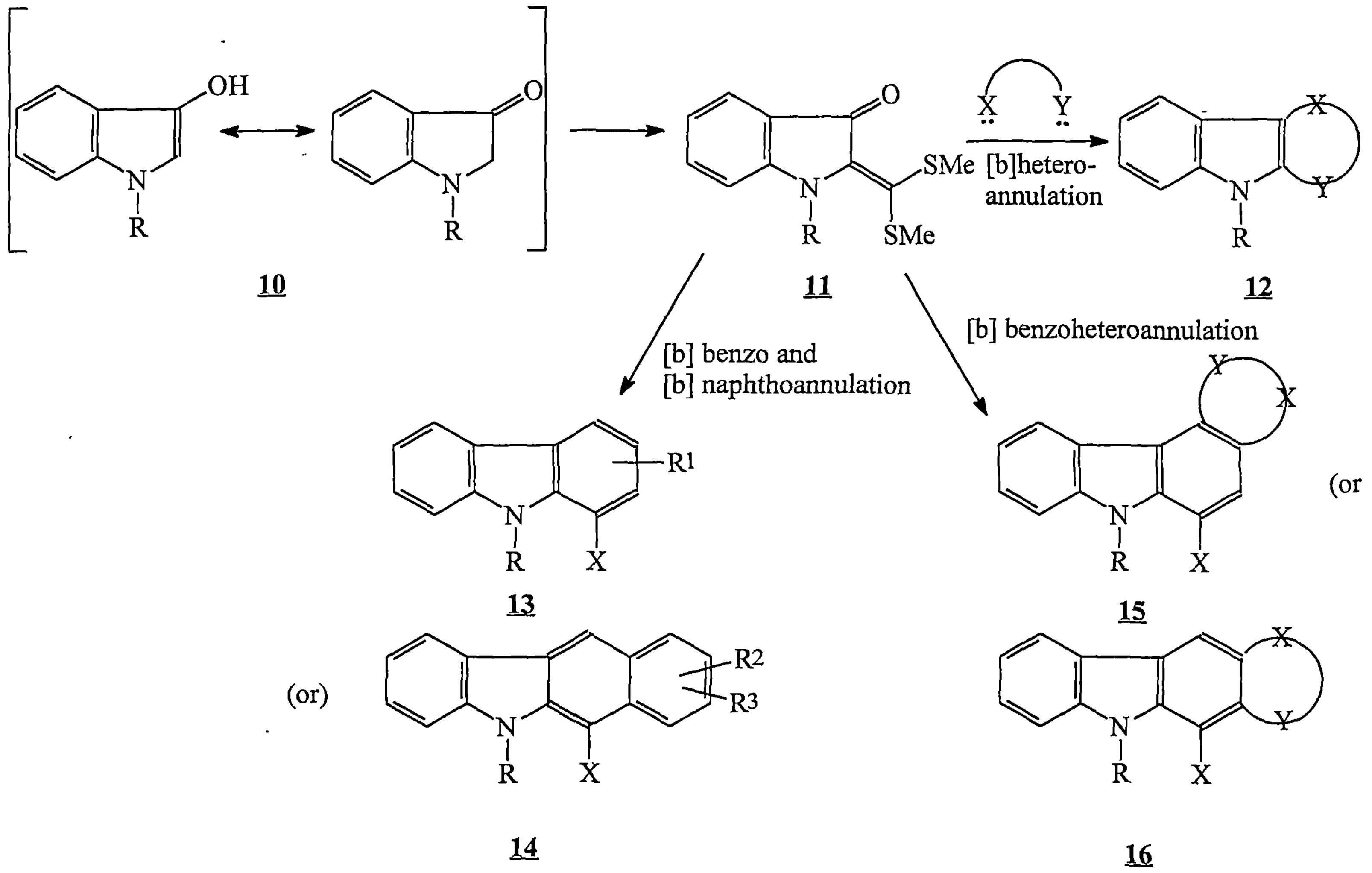


9

Recently, a derivative of 9-hydroxyellipticine **7c**, 2-methyl-9-hydroxyellipticinium acetate **9** ("elliptinium") was commercialized[13] for clinical use and is effective in the treatment of myleoblastic leukemia, advanced breast cancer and other solid tumors[14].

Due to these outstanding biological properties many synthetic approaches were developed to prepare pyrido[4,3-b]carbazole skeletons with a view to developing with improved biological properties with less toxicity. There have been many reviews published on the work of pyrido[4,3-b] carbazole chemistry[15].

The antibiotic activity of carbazomycins, oxidative action of carazostatin and antitumor property of ellipticine group of alkaloids have made these classes of carbazole derivatives interesting synthetic targets by several active groups in the world. The interest


OH
N
R
O
N
R
10
O
N
R
SMe
SMe
11
X
Y
[b]hetero-
annulation
X
N
Y
R
12
[b] benzo and
[b] naphthoannulation
[b] benzoheteroannulation
N
R
X
R1
13
(or)
N
R
X
R2
R3
14
Y
X
N
R
X
15
(or
X
Y
N
R
X
16

Scheme 1

in carbazole chemistry and a number of new carbazole molecules became our target since we could efficiently apply the aromatic annulation and heteroaromatic annulation approach to make many derivatives belonging to this class. In this particular study we desired to make 1-substituted-2-bis(methylthio) methylene-3-oxoindole **11** from the corresponding sensitive indoxyl **10**. The master key intermediate **11** would serve as a potential precursor for the hetero [b], benzo [b] annulation, Naphtho [b] annulation and [b] benzoheteroannulation of indole to yield structurally diversified derivatives, which are depicted in scheme 1.

From this structural diversity all the carbazoles derivable from **11** makes it most attractive key intermediate as a single starting material for the synthesis of many structurally diverse carbazoles and their heterocyclic analogues. In this present studies the target molecules **11** has indeed been prepared despite in low yields and employed as an intermediate for the synthesis of carbazoles and their heterocyclic analogues. We describe these results in this chapter.

Before we present the actual work a brief review on the reported synthesis of [b]annulation of indoles is discussed so that the results of our investigation will be better appreciated.

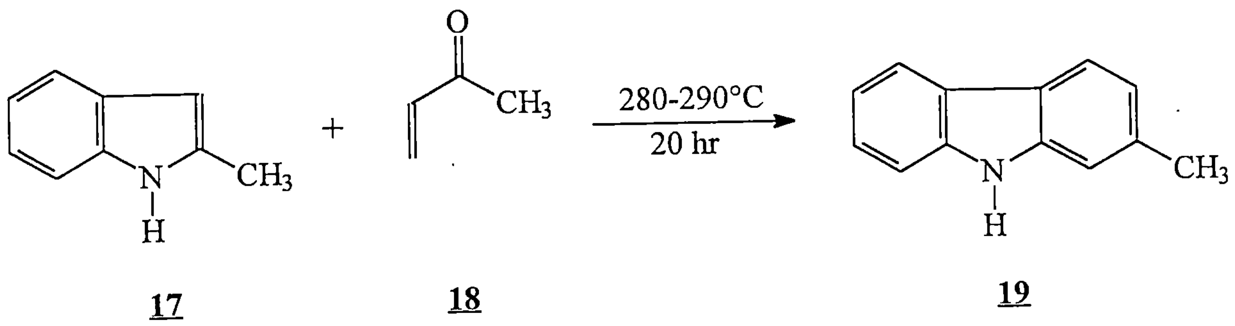
III. 2. Indole [b] Annulation : A Brief Review on the Literature

Major methods for the preparation of carbazoles include the following

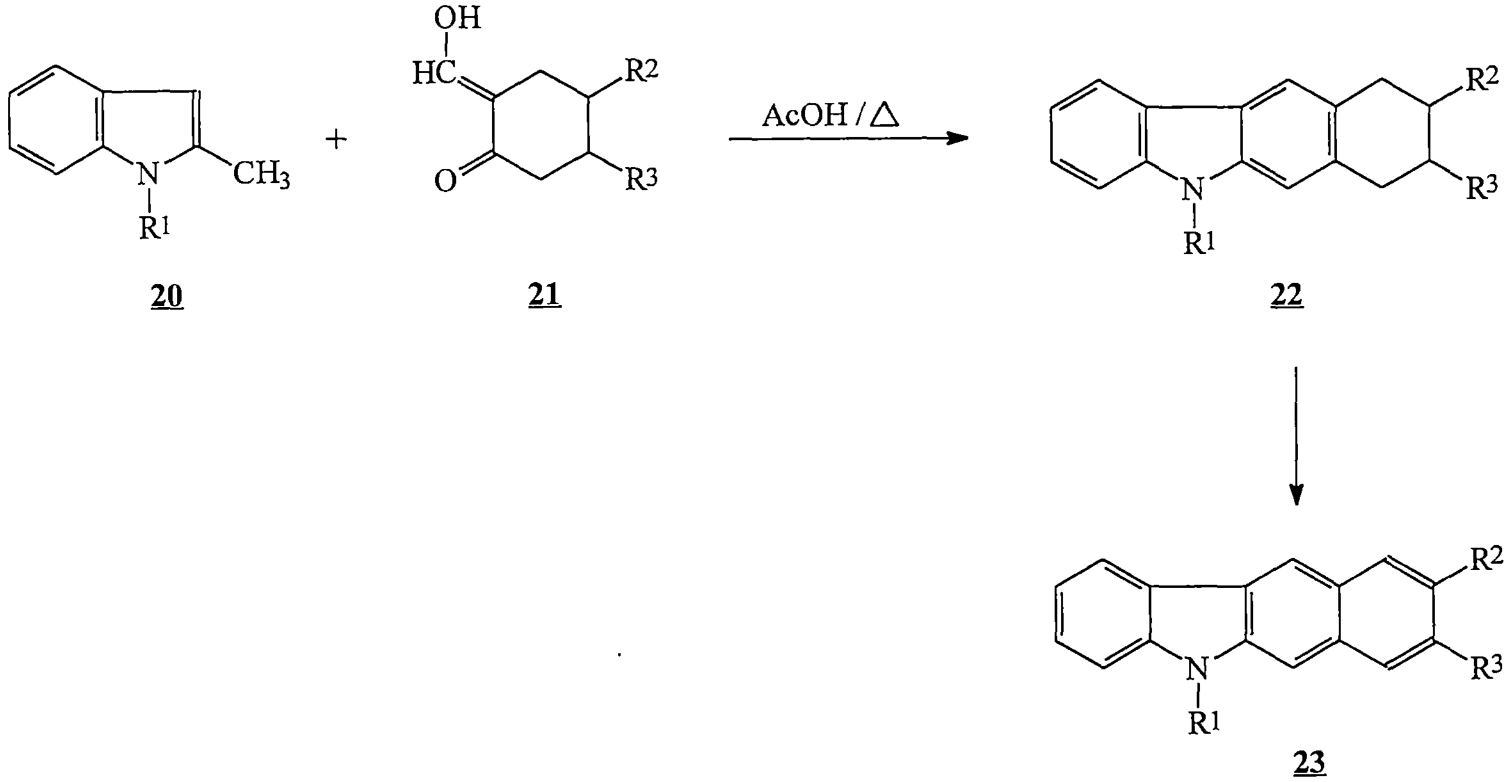
i) dehydrogenation of 1,2,3,4-tetrahydrocarbazoles which are usually prepared by fischer indole synthesis[16], ii) reductive cyclizations of 2-nitrobiphenyls[17], iii) thermal[18],photolytic[19], and palladium-promoted[20] cyclizations of diphenyl amines, iv) iron-mediated oxidative coupling of 1,3-cyclohexadiene and aryl amine[21] and v) [b] annulations of indole skeletons [22,23,24,25,26,27,28,29].

Many methods of types i to iv are problematic for the synthesis of highly substituted carbazoles involving multistep preparations of appropriate precursors, harsh reaction conditions or poor regioselectivity of the cyclization step. Acordingly, approaches *via* the [b] annulation of indole skeletons are of special importance. The most important methods that fall into this category include (a) thermal-induced and photoinduced electrocyclizations of 2,3-divinyl indoles[29], (b) 1,4-additions of indolo-2,3-quinodimethanes[22,26] and of vinylindoles[28] with dienophiles and (c) addition of α-carbanions at C-2 of indoles with michael acceptors, followed by intramolecular cyclization with the ester group at the indole 3-position [23,27].

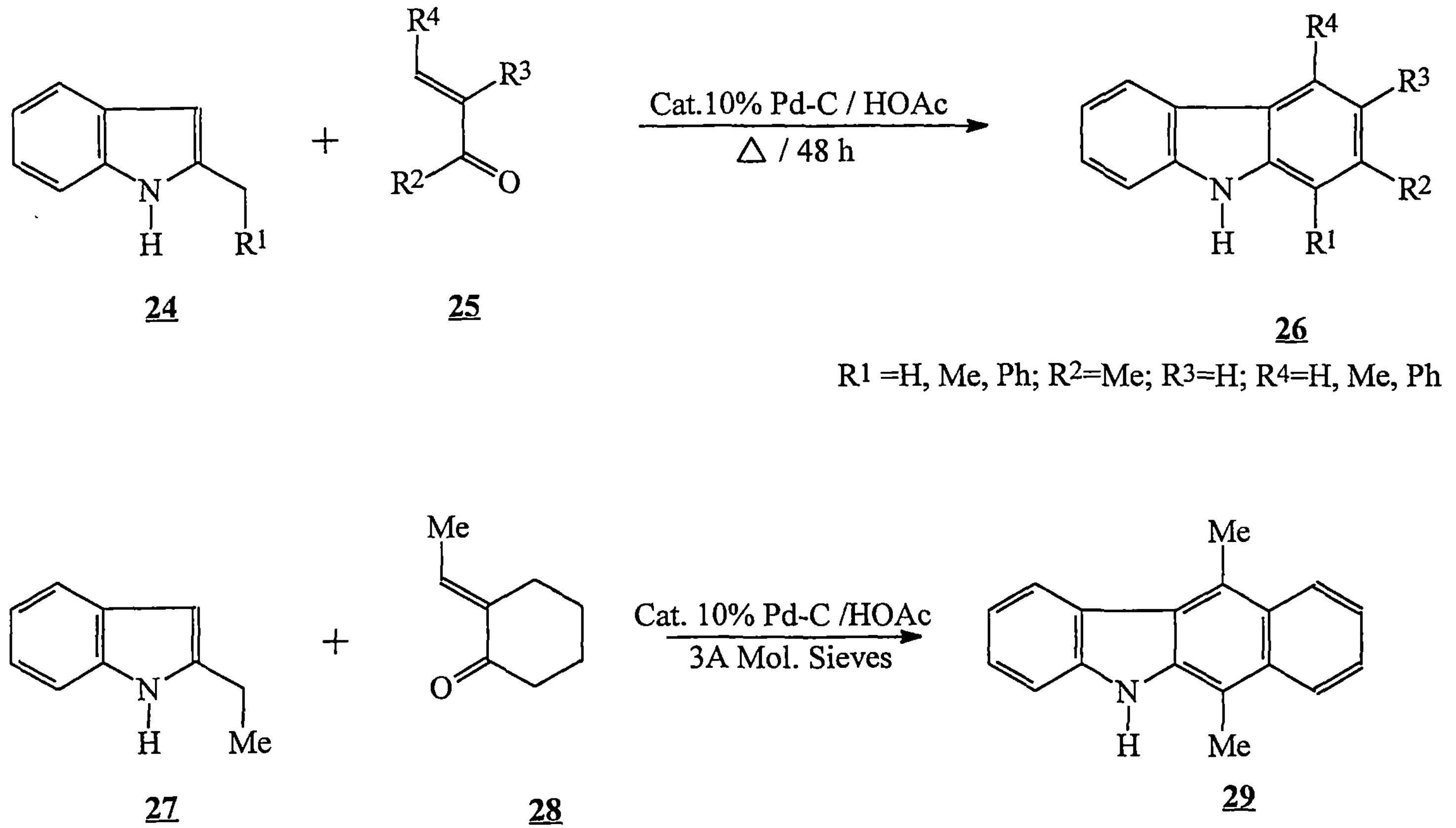
Among these approaches there are very few [3+3] annulation approaches. The known [3+3] annulation approaches are described in this section.



Scheme 2



Scheme 3



R1 =H, Me, Ph; R2=Me; R3=H; R4=H, Me, Ph

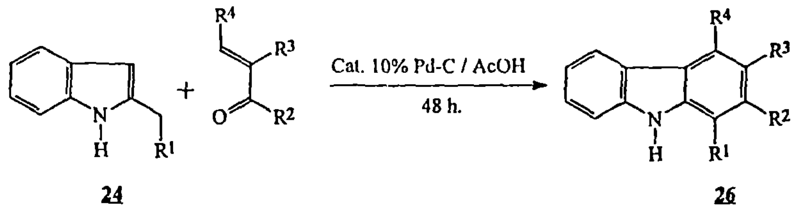
Scheme 4

Szmuszkovicz[30] reported the reaction of 2-methylindole **17** (Scheme 2) with vinylketone **18** at 280-300°C temperature for 20 hrs to yield the corresponding 2-methylcarbazole in 11% yield.

Johnson and co-workers have reported[31] the reaction of 2-methylindole **20** with α-hydroxymethylene cycloalkanones **21** to yield the corresponding 7,8,9,10-tetrahydro[5H]benzo[b]carbazole **22** in 38% yield. The tetrahydro derivative was subsequently dehydrogenated to yield fully aromatic [5H]benzo[b]carbazoles **23**, when **22** was refluxed in the presence of chloranil (Scheme 3).

Recently Bergman and co-workers developed[32] carbazole synthesis to structurally related carbazomycins and other benzo[b]carbazoles. 2-alkylindoles of general formula **24** of scheme 4 have been known to undergo alkylation with 2,3-unsaturated carbonyl compounds **25** in 3-position. The addition generally proceed in 1,4-fashion and the ketones or aldehydes thus formed were subsequently cyclized to yield the corresponding carbazoles **26** in varying yields. Some times the intermediate ketones were heated neat or refluxed in acetic acid to yield the product carbazoles **26**. A number of carbazole derivatives were prepared by this method, yields varying a minimum of 23% to 81% (Scheme 4). Same authors attempted another approach for the synthesis of 4-methoxy substituted carbazoles using the same protocol (see entry 12 in the Table). Unfortunately, the methoxy group could not be retained in the final product.

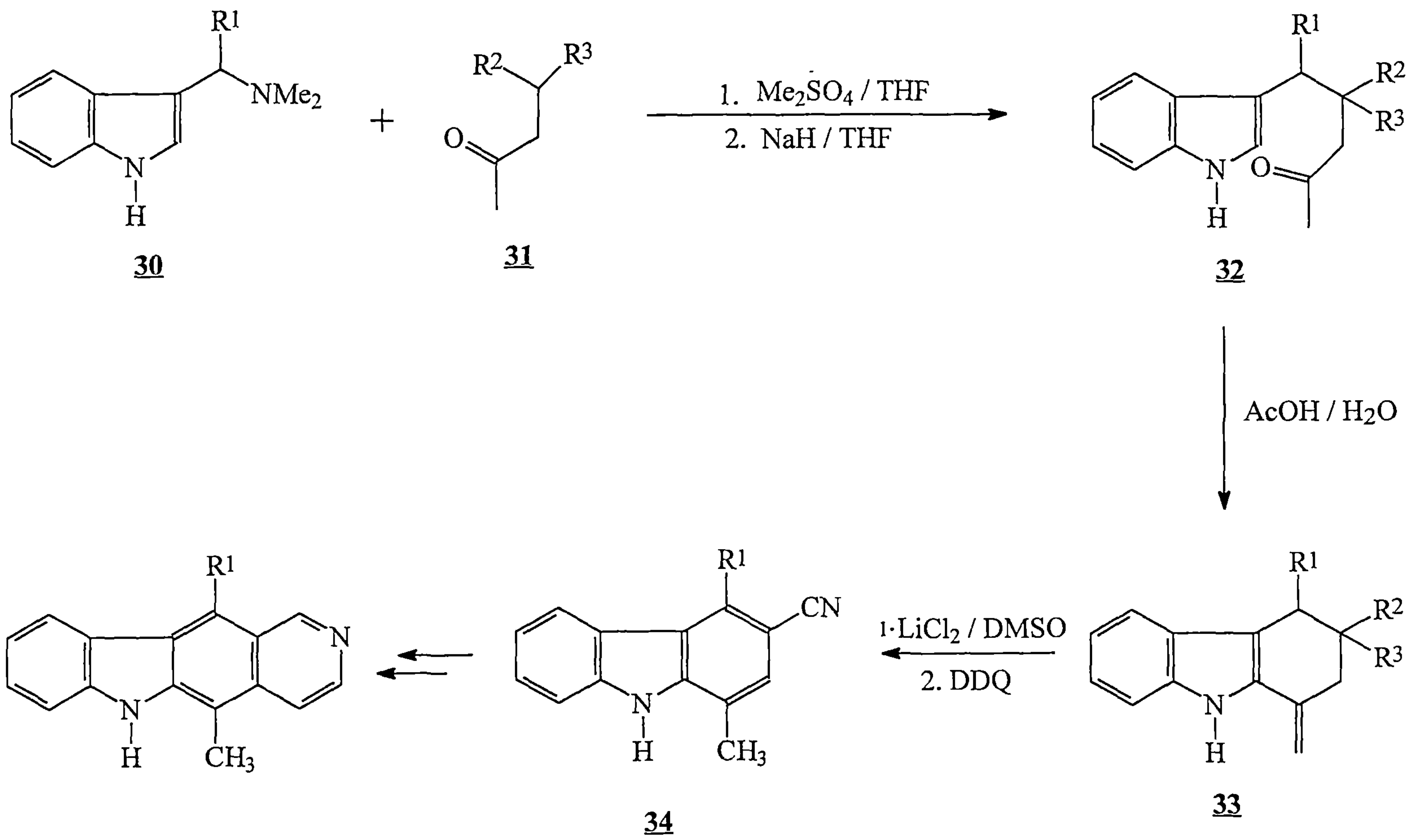
Sainsbury and co-workers developed[33,34] synthesis of the carbazoles with unsymmetrical 1,4-disubstituents. They started from various substituted gramines **30** and treated with sodium salts of 2-cyano-4-oxopentanonitriles 31 to yield the corresponding alkylated ketones 32, which on cyclization in the presence of acetic acid yielded the corresponding tetrahydrocarbazoles 33a which were subsequently dehydrogenated in the presence of DDQ to yield the corresponding substituted carbazoles 34. They subsequently utilized this 3-cyano group to reduce to the corresponding amino functionality and utilized



Entry	R1	R2	R3	R4	Product	Yield
1.	H	Me	H	H	26a	28 (30*)
2.	Me	Me	H	H	26b	81
3.	Ph	Me	H	H	26c	80
4.	Me	Et	H	H	26d	63
5.	H	Me	H	Me	26e	35
6.	Me	Me	H	Me	26f	36
7.	H	Me	H	Ph	26g	23 (26*)
8.	Me	Me	H	Ph	26h	32*
9.	H	$-(CH_2)_4-$		Me	26i	38 (44*)
10.	Me	$-(CH_2)_4-$		Me	26j	29 (38*)
11.	Ph	$-(CH_2)_4-$		Me	26k	64 (76**)
12.	H	Me	H	OMe	26a	24
13.	Me	Me	H	OMe	26b	28 (31*)

* The reaction performed in the presence of 3A molecular seives.
** Based on recovered 2-benzylindole

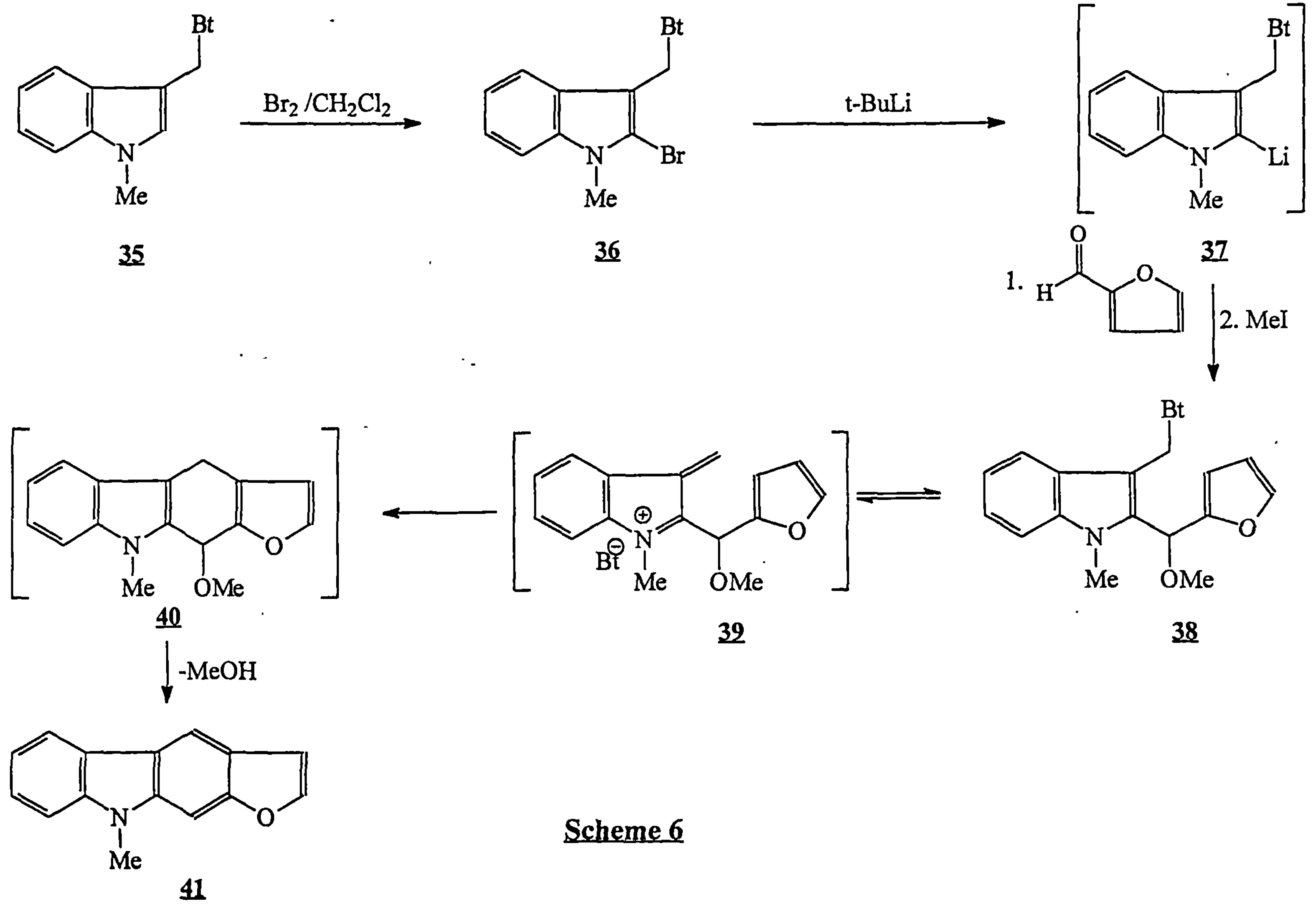
Table



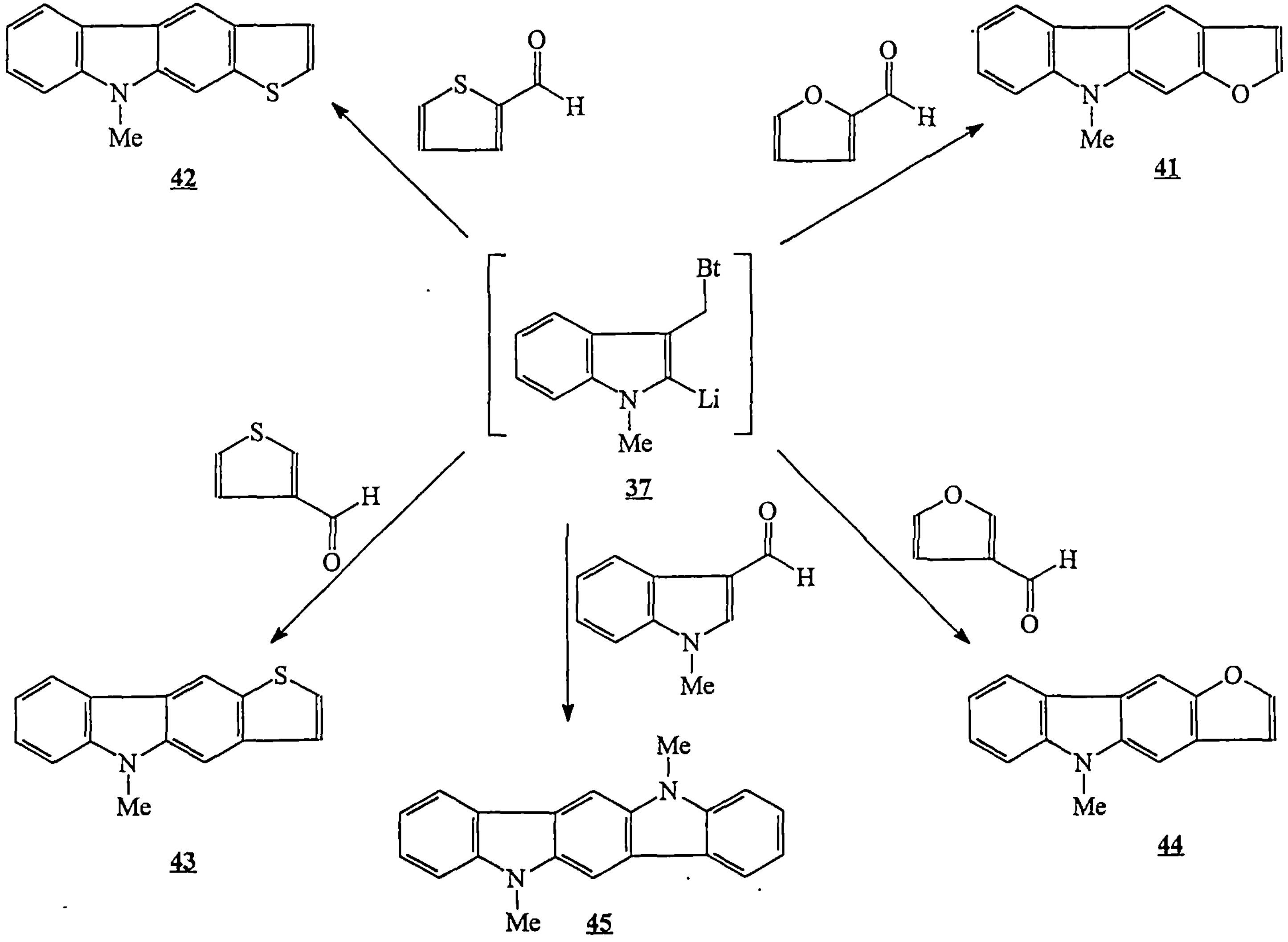
R^1= H, Me; R^2=R^3=CN
R^1= H, Me; R^2=CN; R^3= COOEt
R^1= H, Me; R^2=CN; R^3= COMe

R^2=CN; R^3=COOEt

Scheme 5


Bt
N
Me
35
Br2 /CH2Cl2
Bt
N
Br
Me
36
t-BuLi
Bt
N
Li
Me
37
1. H O O
2. MeI
Bt
N
Me
OMe
O
38
N
Me
OMe
O
Bt
39
N
Me
OMe
O
40
-MeOH
N
Me
O
41

Scheme 6

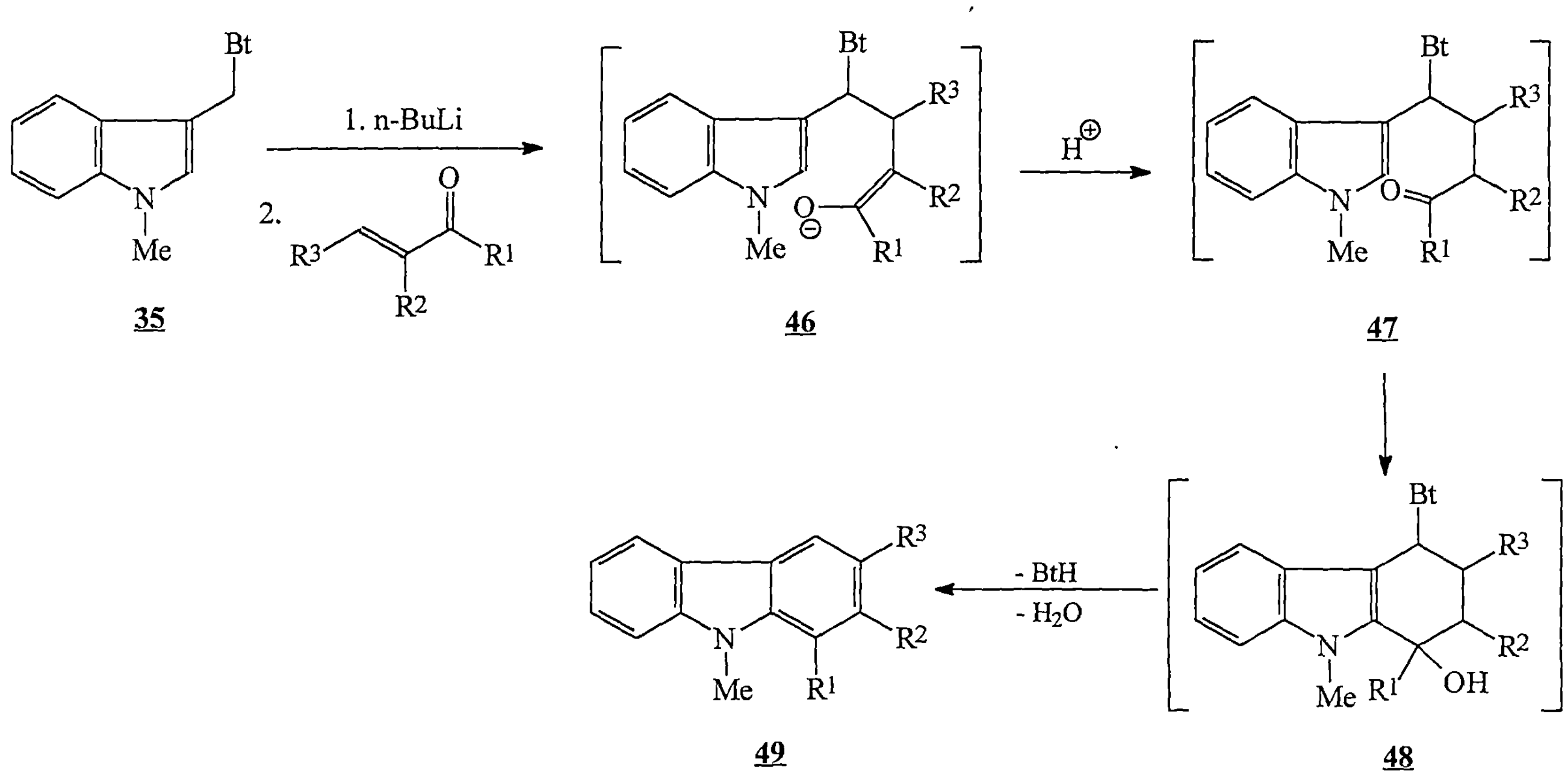


Scheme 7

it to build olivacine 8, which is an important alkaloid possessing anticancer properties (Scheme 5).

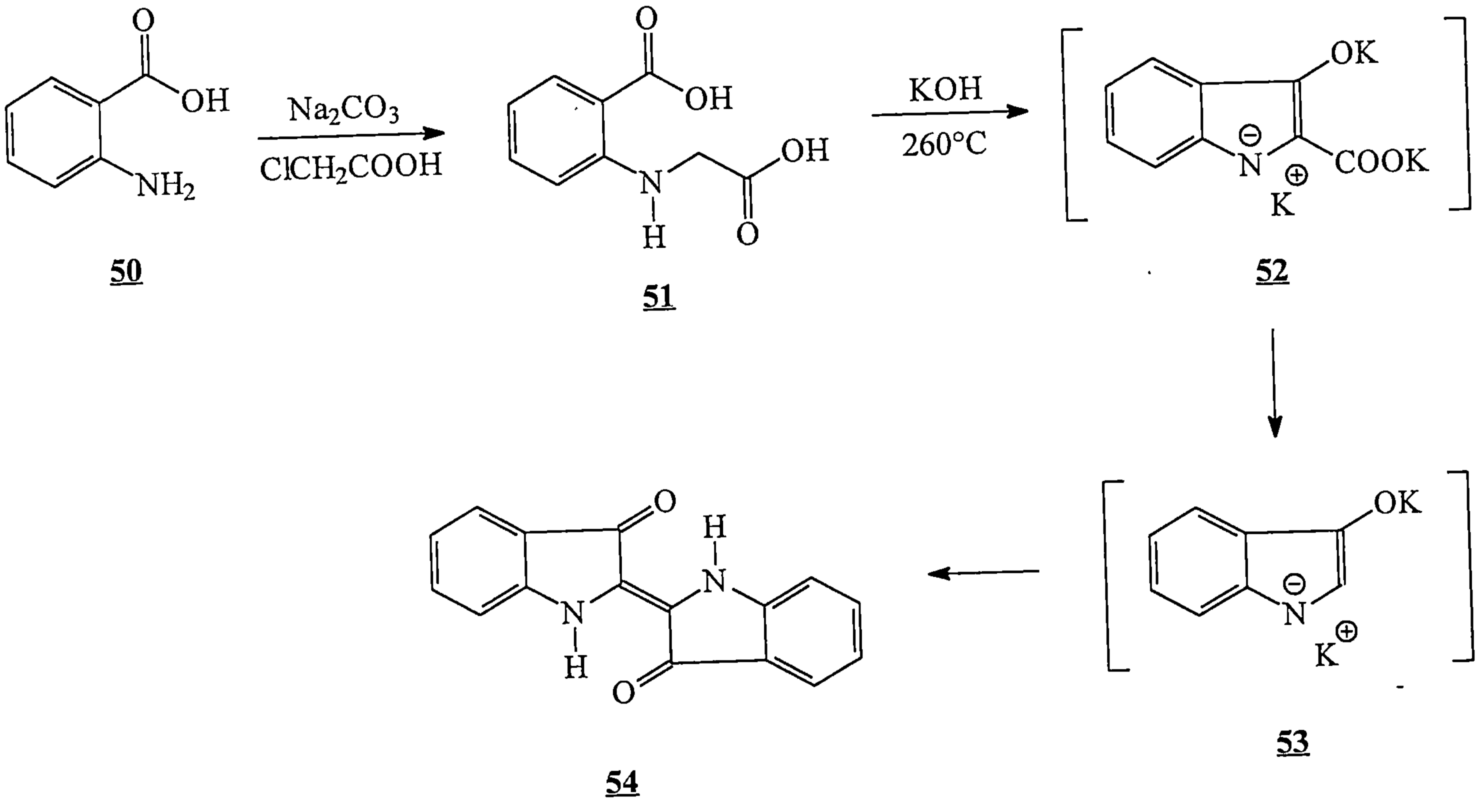
Katritzky and Xie have recently developed very efficient general method for the synthesis of hetero[b]carbazoles[35]. They started with 1-methyl-3-[(benzotriazol-1-yL) methyl]-indole 35 which was prepared in 50% yield from 1-methylindole[36]. The intermediate 35, however could not be used directly to prepare the 2-lithioderivative 37 since the methylene protons of the side chain (CH_2 group) attached to benzotriazole were acidic enough under reaction conditions to compete with the acidity of the hydrogen atom at 2nd position of indole ring due to the electron with drawing nature of the benzotriazolyl group[36]. They therefore brominated the indole 35 and treated the bromoindole 36 with tert-butyllithium to yield the corresponding 2-lithioindole 37 *in situ* in excellent yield. These lithio derivatives were condensed with furfuraldehyde which underwent intramolecular cyclization to yield hetero[b] annulated carbazoles 41 in excellent yields (Scheme 6). Similarly they have reacted 37 with variety of hetero arylaldehydes and was successful in exploiting corresponding hetero [b] carbazoles. Thus they have developed a general route for the synthesis of carbazoles starting from 1-methyl indoles. Depending on the choice of hetero arylaldehydes, the method was efficiently used to make a large number of hetero [b] fused carbazoles (Scheme 7).

In an another report[37] Katritzky and co-workers have utilized 1-methyl-3-(benzotriazol-1-yl-methyl) indole 35 for the efficient synthesis of carbazoles. Thus they deprotonated 35 with n-butyllithium and achieved 1,4-addition with a variety of α,β-



R1= Ph, Me, H
R2= H, CN, COOEt, Ph , Me
R3= Ph, n-Pr, Me, Et, t-Bu

Scheme 8


OH
NH$_2$
O
50
Na$_2$CO$_3$
ClCH$_2$COOH
O
OH
N
H
OH
O
51
KOH
260°C
OK
N
⊖
K
⊕
COOK
52
OK
⊖
N
K
⊕
53
O
H
N
N
H
O
54

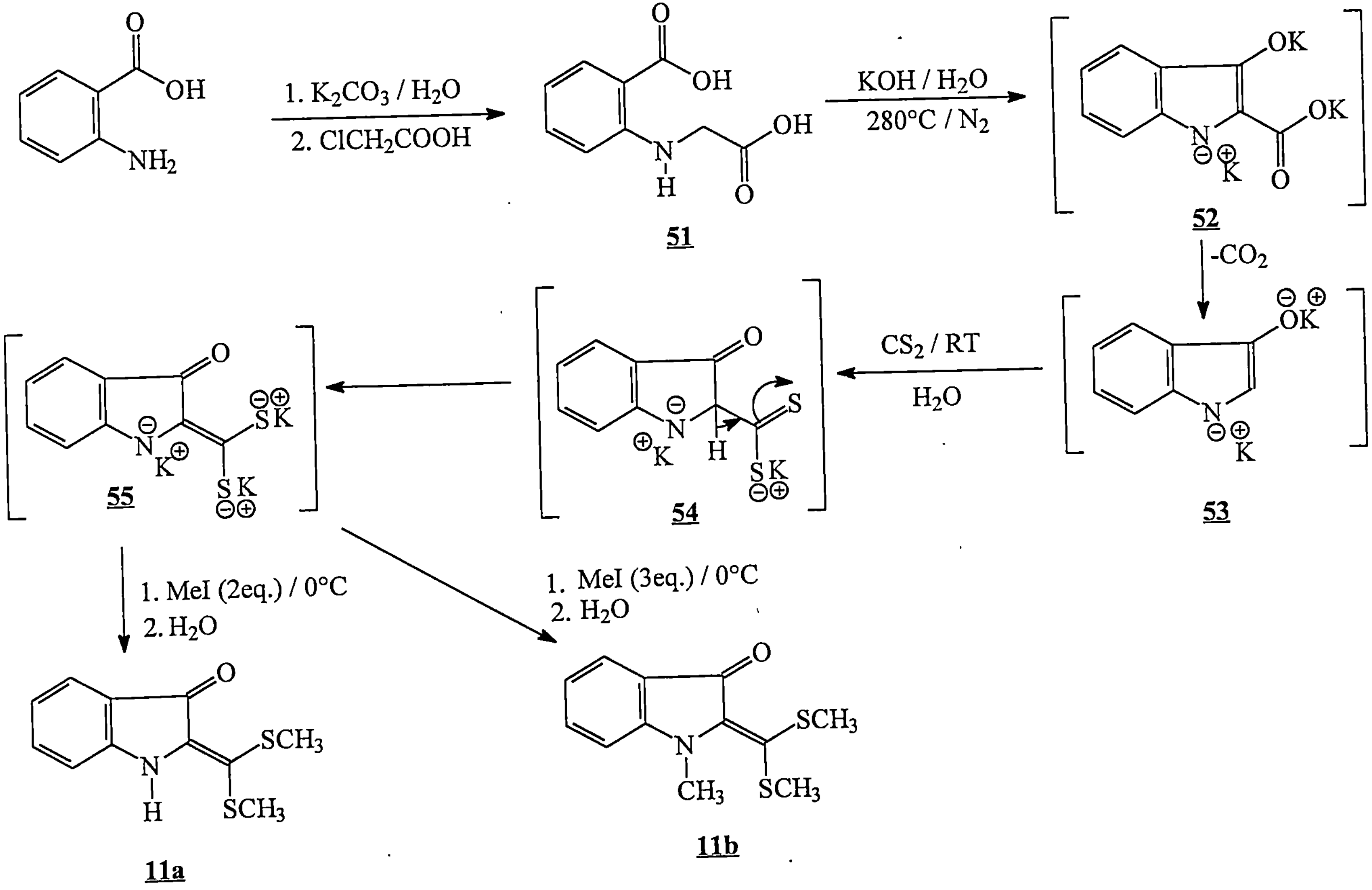
Scheme 9

unsaturated aldehydes and ketones. Subsequently the treatment of these ketones in acidic medium resulted in intramolecular cyclization to yield the corresponding 1,3-di-, 2,3-di-, and 1,2,3-trisubstituted carbazoles 49 in excellent yields (Scheme 8). They also exploited 35 for the efficient synthesis of 1-functionalised cyclopenta[b] indoles with high degree of stereoselectivity.

This method is latest innovative approach on [b] annulation of indoles.

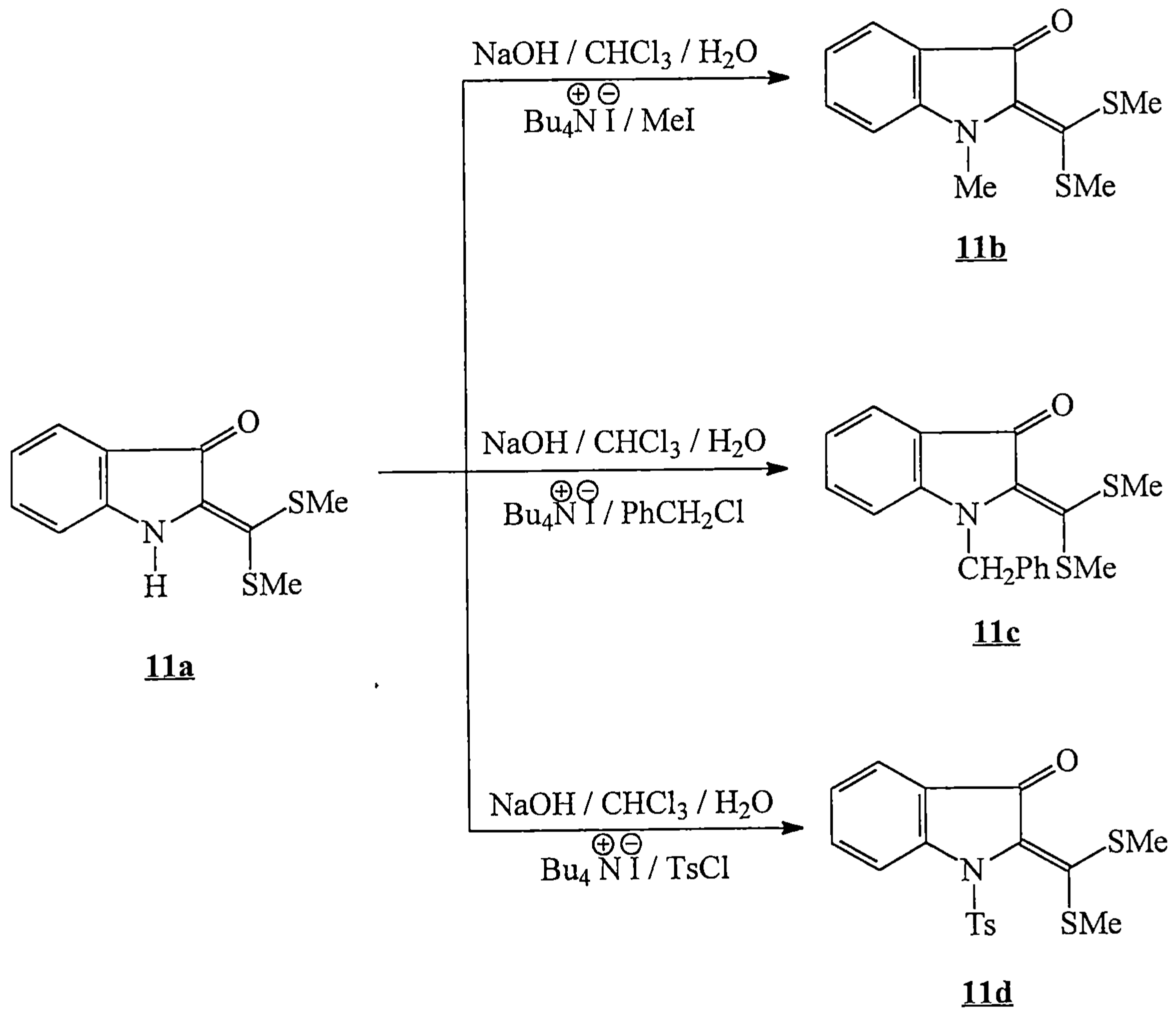
III. 3. Results and Discussion :

The entire work described in this section is centred around intermediate 11 which is hitherto unreported in the literature. It is well known that indoxyl 53 (Scheme 9) is quite unstable under ordinary conditions, it rapidly undergoes oxidative coupling to yield the corresponding indigo 54 which is an end product described in the literature[38] involving the thermal fusion of N-phenylglycine O-carboxylic acid 51 with potassium hydroxide. This is well known procedure described every where[39] to make indigo 54 starting from anthranillic acid 50. We became interested to trap sensitive indoxyl potassium derivative 53 with carbon disulphide under masked nitrogen atmosphere so that the enolate would react with carbon disulfide *in situ* to yield the corresponding dithioate 55 which can be alkylated either to isolate more stable 11a or 11b as the case may be depending on the amount of methyl iodide used for alkylation. When one equivalent of methyl iodide was used the reaction mixture after work up yielded a compound characterised as

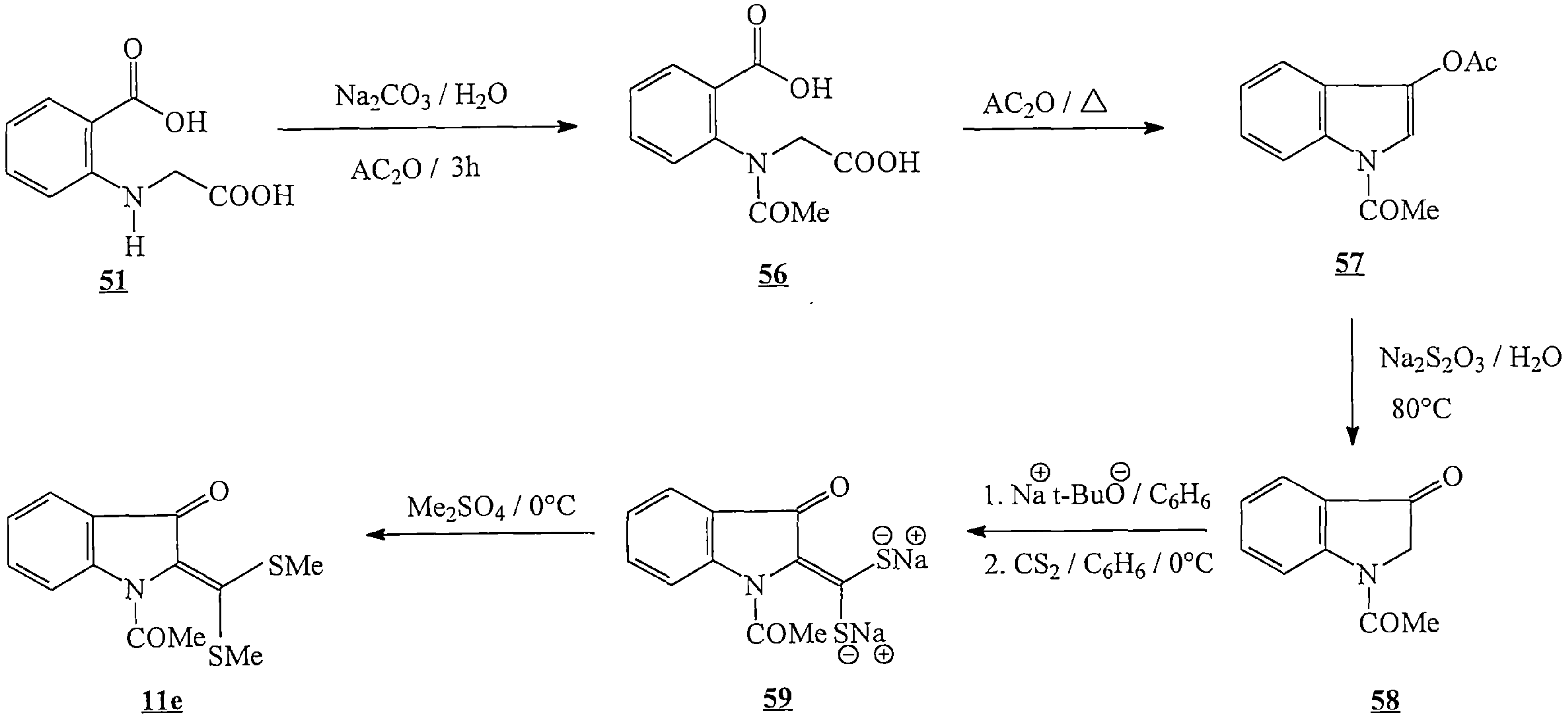

1. K_2CO_3 / H_2O
2. $ClCH_2COOH$
51
KOH / H_2O
280°C / N_2
52
-CO_2
53
CS_2 / RT
H_2O
54
55
1. MeI (2eq.) / 0°C
2. H_2O
1. MeI (3eq.) / 0°C
2. H_2O
11a
11b

Scheme 10

2-bis(methylthio) methylene-2,3-dihydro-3-oxoindole 11a which was obtained as orange coloured crystals from chloroform/hexane. m.p.158-159°C in 43% yield. The structure of 11a was characterised on the basis of its spectral and analytical data. Thus it was analysed for the molecular formula $C_{11}H_{11}NOS_2$. In its IR spectrum the absorption band at ν_{max} 3487cm^{-1} was assigned to NH stretching. The strong band at ν_{max} 1644 cm^{-1} was characteristic of 3-oxo group. Its structure was further confirmed from its ^{1}H NMR spectrum (90MHz, $CDCl_3$). The singlet at δ 2.47 integrating for three protons was assigned to the one of the thiomethyl protons. The other singlet at δ 2.50 integrating for three protons was assigned to the other thiomethyl protons. The multiplet at δ 6.89-7.10 integrating for two protons was assigned for H-5 and H-6 aromatic protons. The broad peak integrating for one proton at δ 7.13-7.29, which was exchangeable with deuterium oxide was assigned for ring N-H proton. The multiplet integrating for one proton at δ 7.39-7.60 was assigned for H-7 proton. The doublet at δ 7.80 with a coupling constant 9Hz was accounted for H-4 proton. Thus the structure of 11a was unambiguously established and was used as a model for all other reactions investigated in this chapter. It was also further alkylated using three equivalents of methyl iodide to yield the corresponding 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole 11b in excellent yields (Scheme 10). The structure of 11b was confirmed from its analytical and spectral data which are described in the experimental section and the ^{1}H NMR spectrum is also displayed. The 2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole 11a was alkylated under phase transfer conditions using methyl iodide, benzyl bromide and p-toluenesulphonyl chloride, to yield the corresponding 2-


NaOH / CHCl$_3$ / H$_2$O
$Bu_4\overset{\oplus}{N}\,\overset{\ominus}{I}$ / MeI
NaOH / CHCl$_3$ / H$_2$O
$Bu_4\overset{\oplus}{N}\,\overset{\ominus}{I}$ / PhCH$_2$Cl
NaOH / CHCl$_3$ / H$_2$O
$Bu_4\overset{\oplus}{N}\,\overset{\ominus}{I}$ / TsCl
O
SMe
SMe
N
H
11a
Me
11b
CH$_2$Ph
11c
Ts
11d

Scheme 11


51
Na2CO3 / H2O
AC2O / 3h
56
AC2O / Δ
57
Na2S2O3 / H2O
80°C
58
1. Na t-BuO / C6H6
2. CS2 / C6H6 / 0°C
59
Me2SO4 / 0°C
11e
OH
COOH
COMe
OAc
SNa
SMe

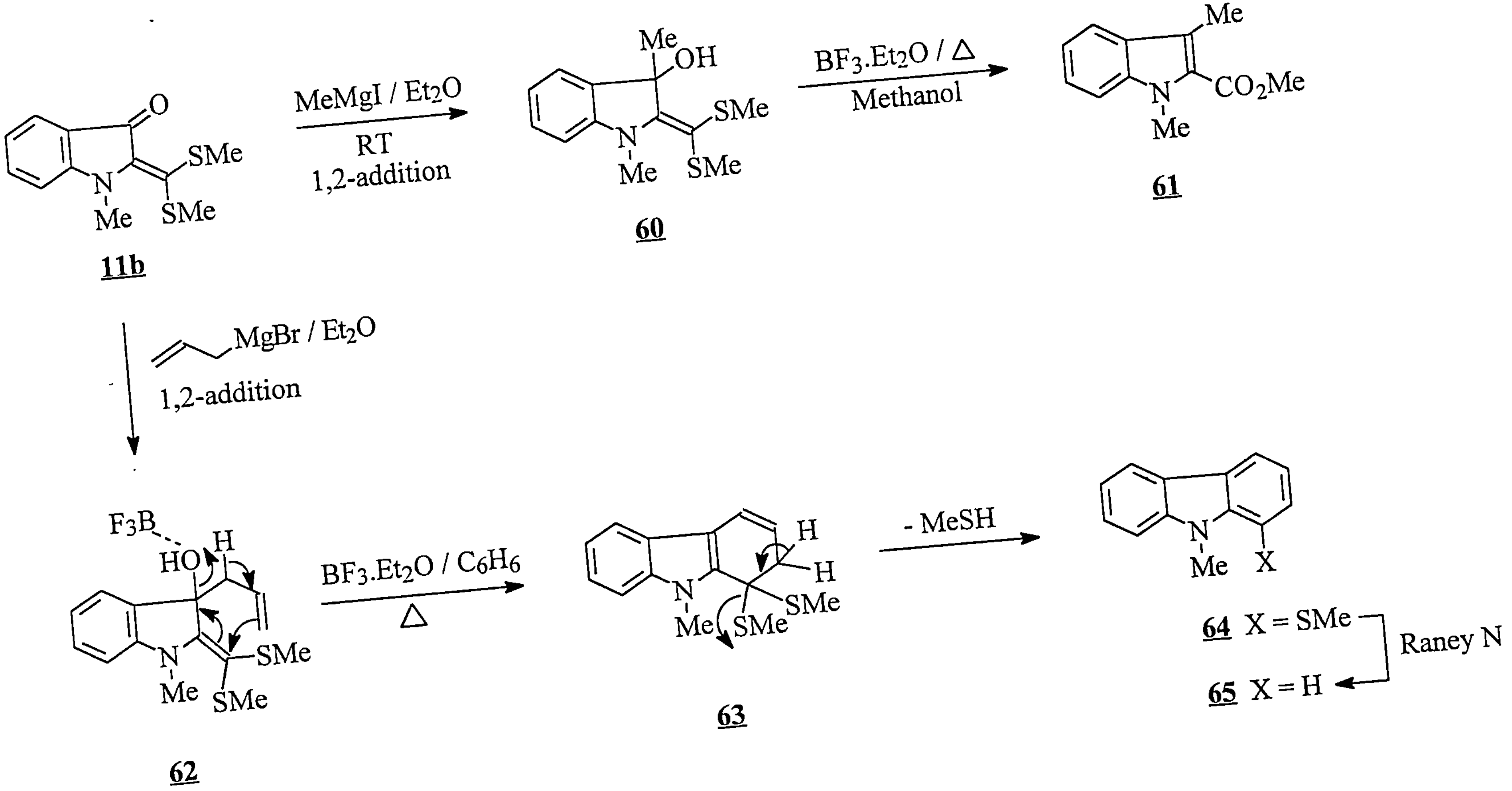
Scheme 12

bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole **11b**, 1-benzyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole **11c** and 2-bis(methylthio)methylene-2,3-dihydro-3-oxo-1-(4'-toluenesulphonyl) indole **11d** respectively in excellent yields (Scheme 11).

The structures of all these compounds were established from their analytical and spectral data which are described in the experimental section. The spectrums for selected group of these substituted indoxyl S,S-acetals are also displayed so that these structures assigned are fully established.

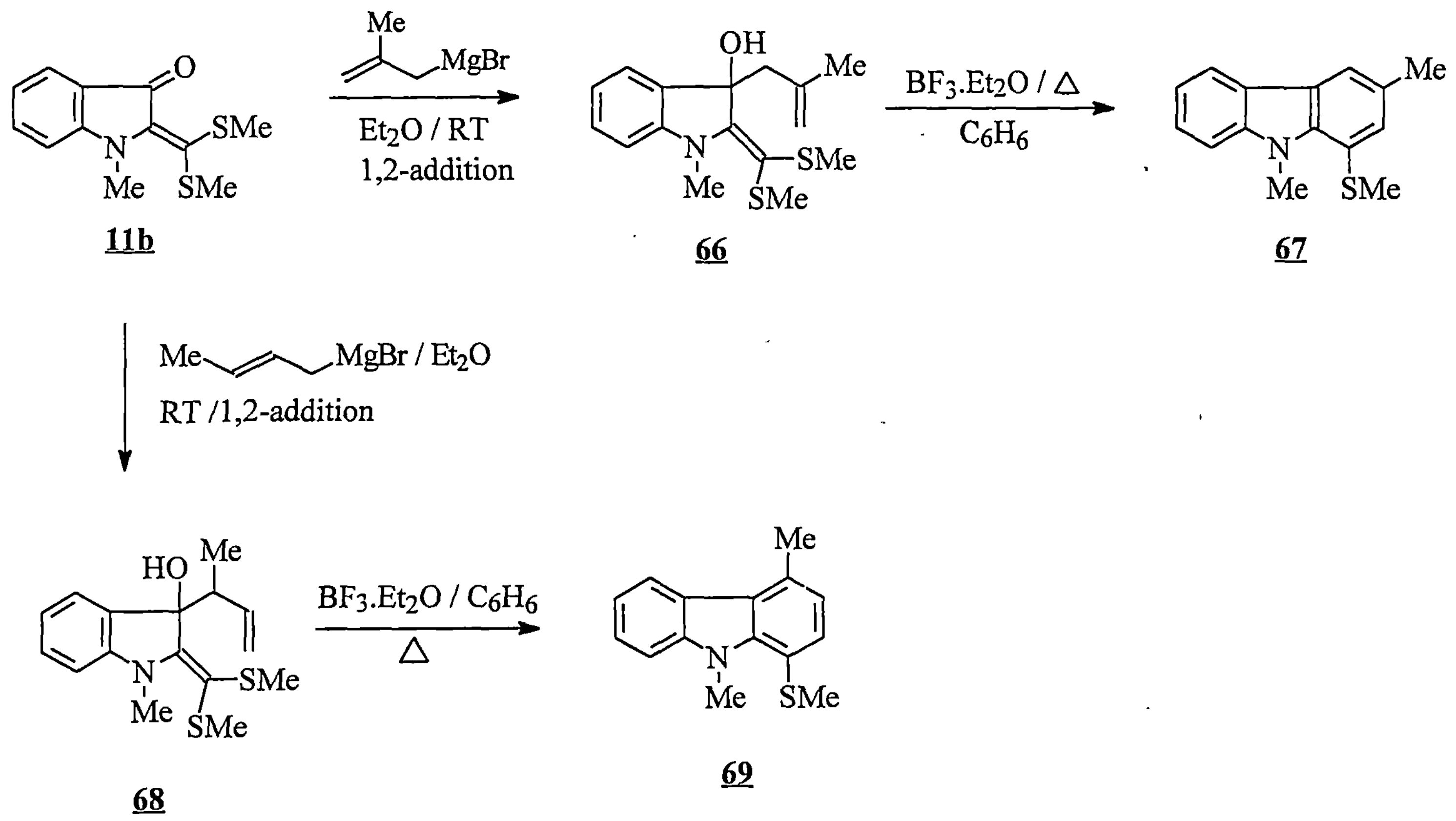
Before we actually started the reactivity with these compounds the reaction conditions for **11a** and **11b** was standardised in repeat experiments.

1-Acetyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole **11e** was alternatively prepared in improved yield as formulated in Scheme 12. The N-acetyl-N-phenylglycine-O-carboxylic acid **56** was directly treated with acetic anhydride as reported in literature[40] to yield the corresponding 1,3-diacetyl indole **57**. Thus **57** was hydrolysed to 1-acetyl indoxyl **58** by treating **57** with sodium thiosulfate. The more stable 1-acetyl indoxyl **58** was formed in 60% yield. The indoxyl **58** was then converted into the corresponding 1-Acetyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole **11e**. Hitherto unreported **11e** was characterised by its analytical and spectral data which are described in the experimental section.


11b
MeMgI / Et$_2$O
RT
1,2-addition
60
BF$_3$.Et$_2$O / Δ
Methanol
61
MgBr / Et$_2$O
1,2-addition
F$_3$B
62
BF$_3$.Et$_2$O / C$_6$H$_6$
Δ
63
- MeSH
64 X = SMe
Raney N
65 X = H

Scheme 13

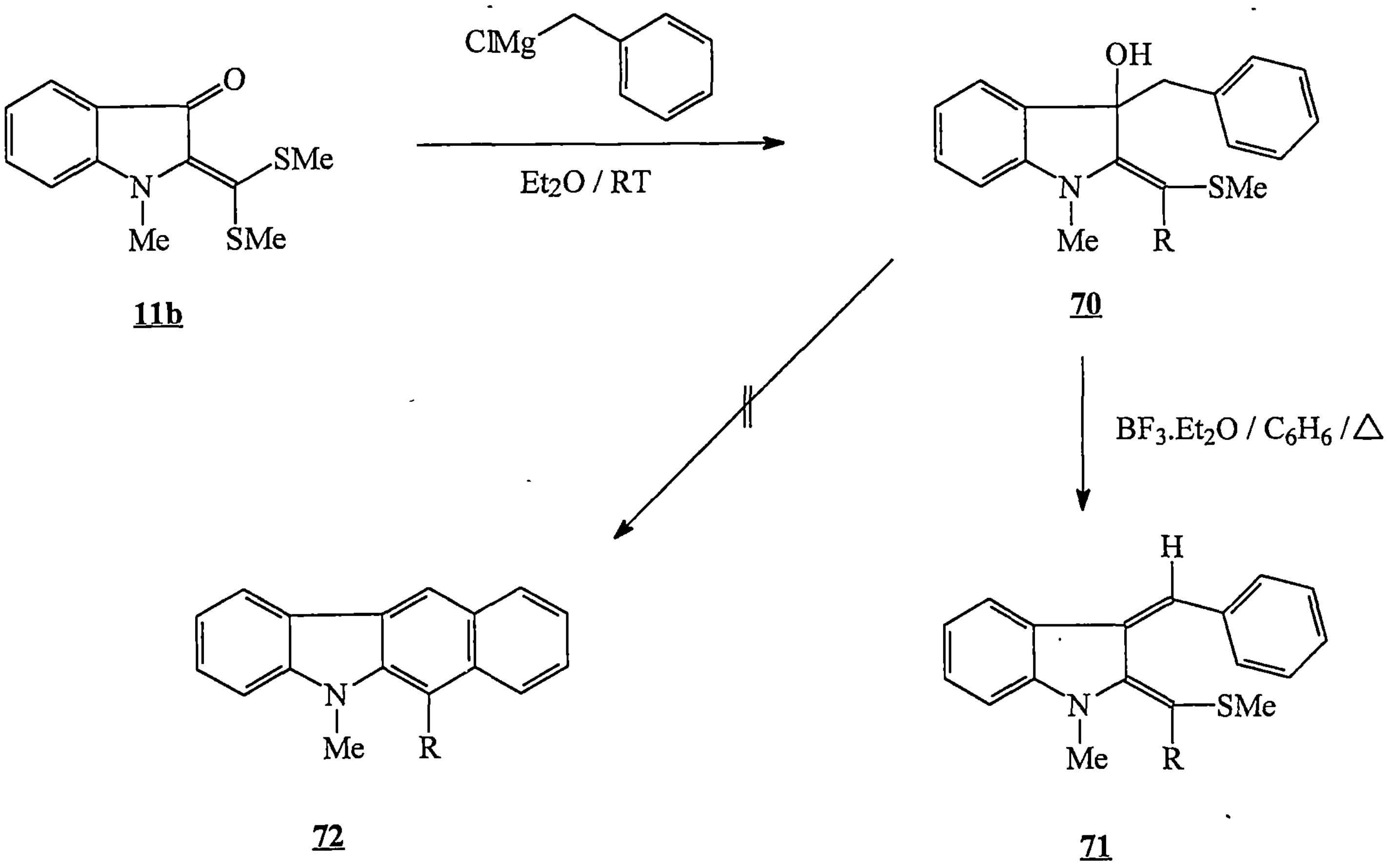
It is well known that the α-oxoketene dithioacetal[41,42,43,44,45,46,47] and their β-oxodithio acetal[48] react with allyl anions[49,50,51,52] to give the corresponding carbinol acetals, which on cyclo amortisation transforms into fully amortised benzene ring or its condensed variants. The aromatic annulation and hetero aromatic annulation have been extensively studied[53] in this laboratory. It was decided to utilise all this knowledge on this key intermediate **11b** to [b] annulate a number of aromatic, condensed aromatic and heteroaromatic ring systems, with indole using **11b** as 1,3-dielectrophilic 3-carbon component and cyclizing it with 3-carbon nucleophiles. The **11b** is different from other α-oxoketene dithioacetals reported in the literature in that nitrogen lone pair is in conjugation with the mercapto double bond while the carbonyl group at third position is purely electron deficient electrophilic carbon which may facilitate charge controlled 1,2-addition of various allyl anions. The resulting carbinol acetal would possibly undergo cycloaromatization in the presence of acid without regard to deactivating effect of nitrogen lone pair, on the mercapto double bond. We did a model experiment in the beginning to examine the nature of reactivity of **11b** . Thus when **11b** was reacted with methylmagnesium iodide the corresponding carbinol acetal **60** indeed formed in quantitative yield which was subjected to methanolysis under earlier reported procedure[54] using borontrifluoride etherate to yield the corresponding 2-carbomethoxy-1,3-dimethylindole **61** (Scheme 13) in 67% yield. The structure of **61** was established by its analytical and spectral data which are described in the experimental section .


O
SMe
N
Me
SMe
11b
Me
MgBr
Et$_2$O / RT
1,2-addition
OH
Me
N
Me
SMe
SMe
66
BF$_3$.Et$_2$O / Δ
C$_6$H$_6$
Me
N
Me
SMe
67
Me
MgBr / Et$_2$O
RT /1,2-addition
HO
Me
N
Me
SMe
SMe
68
BF$_3$.Et$_2$O / C$_6$H$_6$
Δ
Me
N
Me
SMe
69

Scheme 14

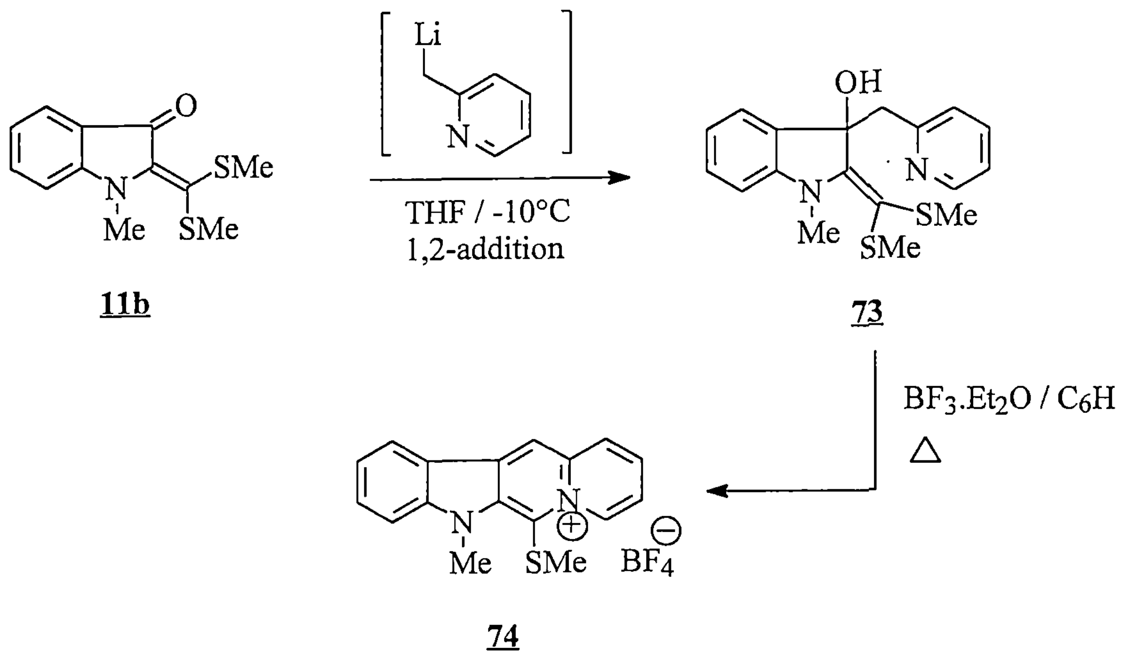
The intermediate **11b** was then reacted with allyl magnesium bromide[49] to yield the corresponding carbinol acetal **62** in near quantitative yield. The acetal **62** on subsequent treatment with borontrifluoride etherate in refluxing dry benzene yielded the corresponding 9-methyl-1-methylthiocarbazole **64** as light yellow crystals from dichloromethane/hexane (m.p. 68-70°C) in 63% yield (Scheme 13). The structure of this compound **64** was fully in accord with its analytical and spectral data as described in experimental section. It was further confirmed by subjecting it to raney nickel desulfurization to yield the known 9-methylcarbazole **65** (m.p 86°C) in 94% yield. The compound was found to be having superimposable IR and NMR data and identical melting point with the reported[55] compound. Thus, the transformation of the Indoxyl to carbazoles *via* 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole **11b** using our aromatic annulation methodology is attractive to be used as a general method for the synthesis of a number of carbazole derivatives and to use this intermediate **11b** to construct heterocyclic ring systems annulated to indole moiety.

In principle, a large number of allyl anions can be used to construct carbazoles using **11b** as a key intermediate. We have, however, examined a few select group of allyl anions to demonstrate the generality of the method . Thus, methylallyl magnesium bromide[50] (Scheme 14) reacted with **11b** to yield the corresponding carbinol **66** which on subsequent acid assisted cyclization yielded the corresponding 3,9-dimethyl-1-methylthiocarbazole **67** as pale yellow crystals (dichloromethane/hexane) m.p. 92-94°C in 68% yield. The structure **67** was established by its analytical and spectral data which are described in the experimental section.



70, **71**, **72** **a,** R = SMe
b, R = $CH_2C_6H_5$

Scheme 15

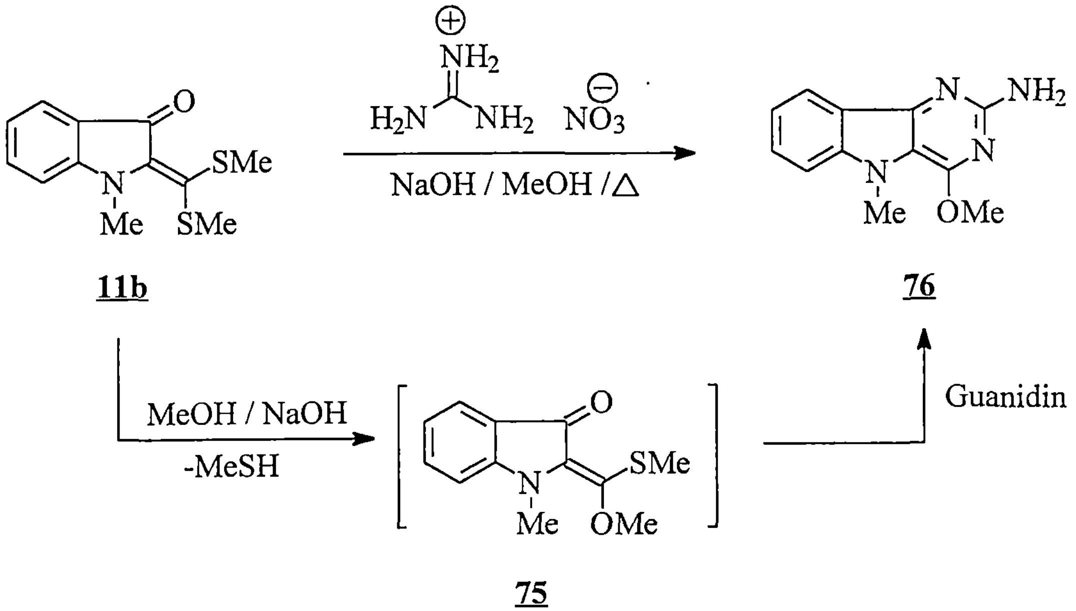


Scheme 16

The crotylmagnesium bromide also reacted with **11b** to yield the corresponding carbinol **68** in quantitative yield, which upon borontrifluoride etherate assisted cyclization yielded 4-9-dimethyl1-methylthiocarbazole **69** (Scheme 14) as light yellow crystals from dichloromethane/hexane (m.p. 92-94°C) in 68% yield. The structure of **69** was also established on the basis of analytical and spectral data which are described in the experimental section. These two reactions demonstrate that the intermediate **11b** could be used to make regioselectively substituted carbazoles with a control on the regiochemistry on 1,2,3 & 4-positions.

Benzyl magnesium chloride[57] was then reacted with **11b** and it was found that the order of reactivity was sequential 1,4- and 1,2-addition mode. The intermediate **70b** on treatment with borontrifluoride etherate in refluxing benzene yielded only open chain dehydrated product **71b** in 69% yield as light orange crystals from chloroform/hexane, m.p. 103-104°C. The analytical and spectral data described in the experimental section were in agreement with the assigned structure. The expected carbazoles neither **72a** nor **72b** were detected in the reaction mixture. We are unable to explain the failure of ring closer of the triene **71b** to yield expected benzo[b]carbazole. Only few reaction conditions have been tested to achieve cyclization and it requires more experiments to find suitable reaction conditions to achieve the cyclization (Scheme 15). The studies are still being continued.

2-Picolyllithium[58] (2-lithiomethylpyridine) was then reacted with **11b** (Scheme 16). The carbinol acetal **73** obtained in excellent yield was

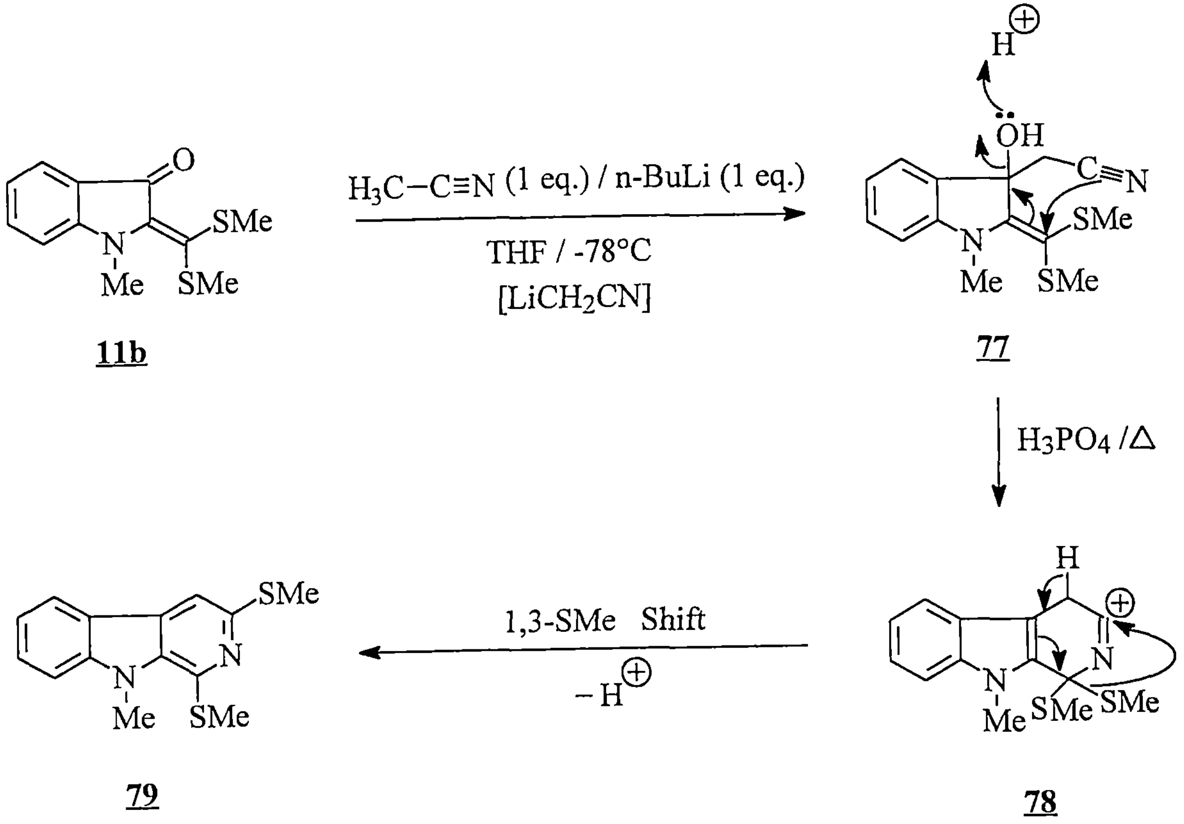

O
SMe
N
Me
SMe
11b
NH2
H2N
NH2
NO3
NaOH / MeOH /Δ
N
NH2
N
N
Me
OMe
76
MeOH / NaOH
-MeSH
O
SMe
N
Me
OMe
75
Guanidin

Scheme 17

cyclized in the presence of borontrifluoride etherate in refluxing benzene to yield corresponding 6-methyl-5-methylthio [6H]indolo [3,2-b] quinozilinium tetrafluoroborate **74** in 96% yield as bright yellow needles m.p 275-277°C(dec.) and the structure **74** was fully established from its spectral and analytical data. Thus, it was analysed for $C_{17}H_{15}N_2SBF_4$ (366.18). Its mass spectrum showed *molecular ion peaks at m/z = 365* (M^+-1, 2.1%), 304 (15.4%), 276 (97%), 244 (100%). Its IR spectrum (KBr) showed characteristic tetrafluoroborate cation absorption band ν_{max} at 1061 (br) cm^{-1}. Its structure was further confirmed from ^1H NMR (300.13 MHz, DMSO/D_6/$CDCl_3$) spectrum. The singlet at δ 2.62 integrating for three protons was assigned to the methylthio group. The singlet integrating for three protons at δ 4.49 was assigned to the N-methyl protons. The two singlets integrating for one proton each at δ 9.42 further supports the assigned structure. The other aromatic protons which are in accord with the assigned structure are described in the experimental section. The structure of **74** was unambiguously confirmed from its ^{13}C NMR spectral data which are described in the experimental section. ^1H NMR spectrum is displayed in support of the assigned structure.

Guanidine nitrate[59] and **11b** were refluxed in methanolic potassium hydroxide and the corresponding 2-amino-5-methyl-4-methoxypirimido[5,4-b]indole[60] **76** was obtained in 58% yield as pale yellow crystals from chloroform/hexane m.p 213-215°C.

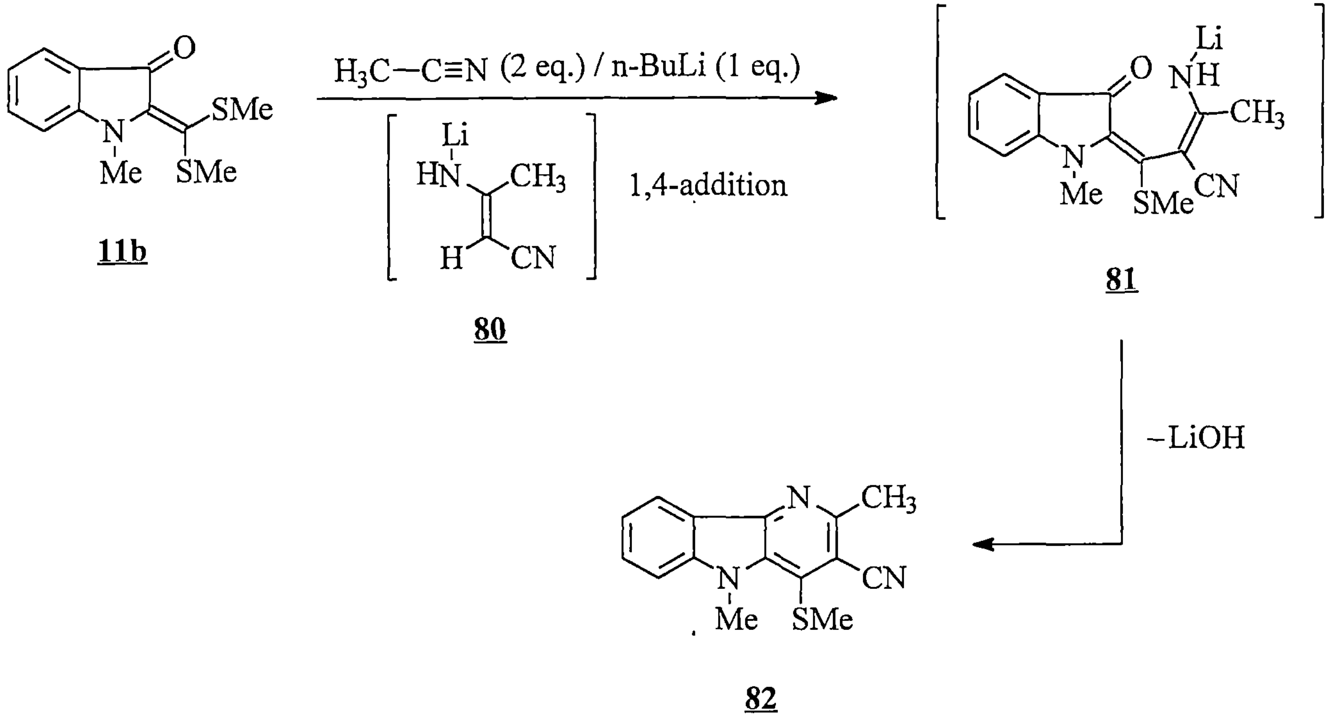
The analytical and spectral data were in agreement with the assigned structure **76** which are described in the experimental


11b
H$_3$C−C≡N (1 eq.) / n-BuLi (1 eq.)
THF / -78°C
[LiCH$_2$CN]
77
H$_3$PO$_4$ /Δ
78
1,3-SMe Shift
− H⊕
79
SMe
Me
N
O
ÖH
C≡N
H⊕
H

Scheme 18

section. This reaction demonstrate that the intermediate **11b** could be used to react with binucleophiles to yield hetero annulated indoles. Only a selected example is examined. There are many other potential binucleophiles to be examined for their reactivity with this intermediate **11b** for the hetero annulated indoles.

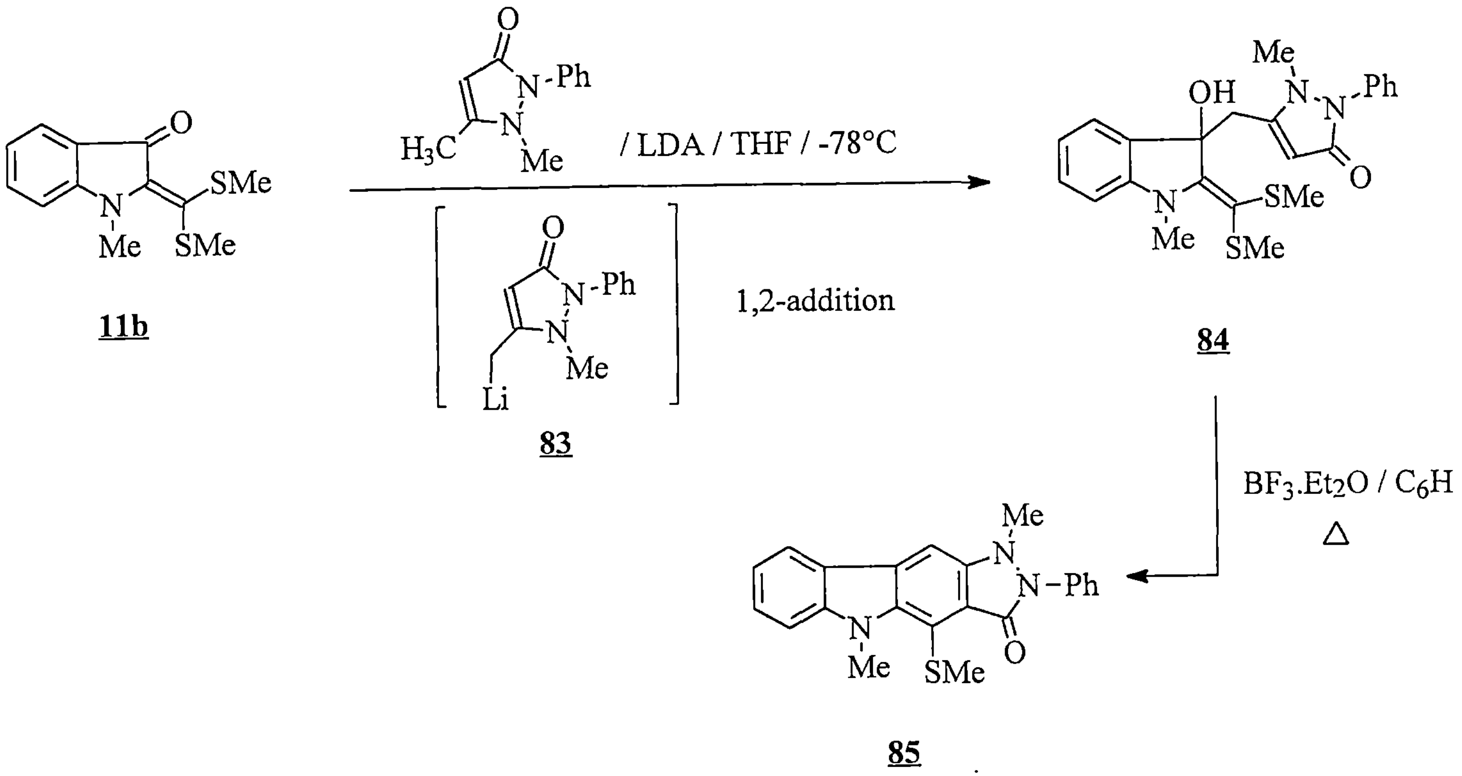
Lithioacetonitrile also reacted with **11b** to yield the corresponding 1,2-adduct **77** in quantitative yield (Scheme 18), which on treatment with orthophosphoric acid underwent reter type of cyclization as reported earlier from this laboratory[61] to yield the corresponding 1,3-bis(methylthio)-9-methyl[9H]pyrido[3,4-b]indole **79** in 51% yield from diethyl ether/hexane m.p 108-109C. The 1,3-methylthio shift is in accordance with the earlier observation in these systems. Both the methylthio groups can be replaced by alkyl groups and amino nucleophiles to develop more derivatives if needed. The structure **79** was established on the basis of its analytical and spectral data. Thus, it was analysed for $C_{14}H_{14}N_2S_2$ with a molecular weight 274.4. The molecular weight was confirmed by its mass spectrum which exhibited molecular ion peak at m/z 274 (M^+, 36%). Its IR spectrum (KBr) displayed the major absorption bands at ν_{max} 2955, 2923, 2853, 1616 and 1529 cm^{-1}. The structure was further confirmed from its ^1H NMR (90 MHz, $CDCl_3$) spectrum. The two singlets each integrating for three protons at δ 2.60 & 2.69 were assigned for the two thiomethyl groups and the three proton singlet at δ 4.16 was assigned for the N-methyl group. The other aromatic protons appeared as three proton multiplet and one proton doublet were in accord with the assigned structure which are described in experimental section.



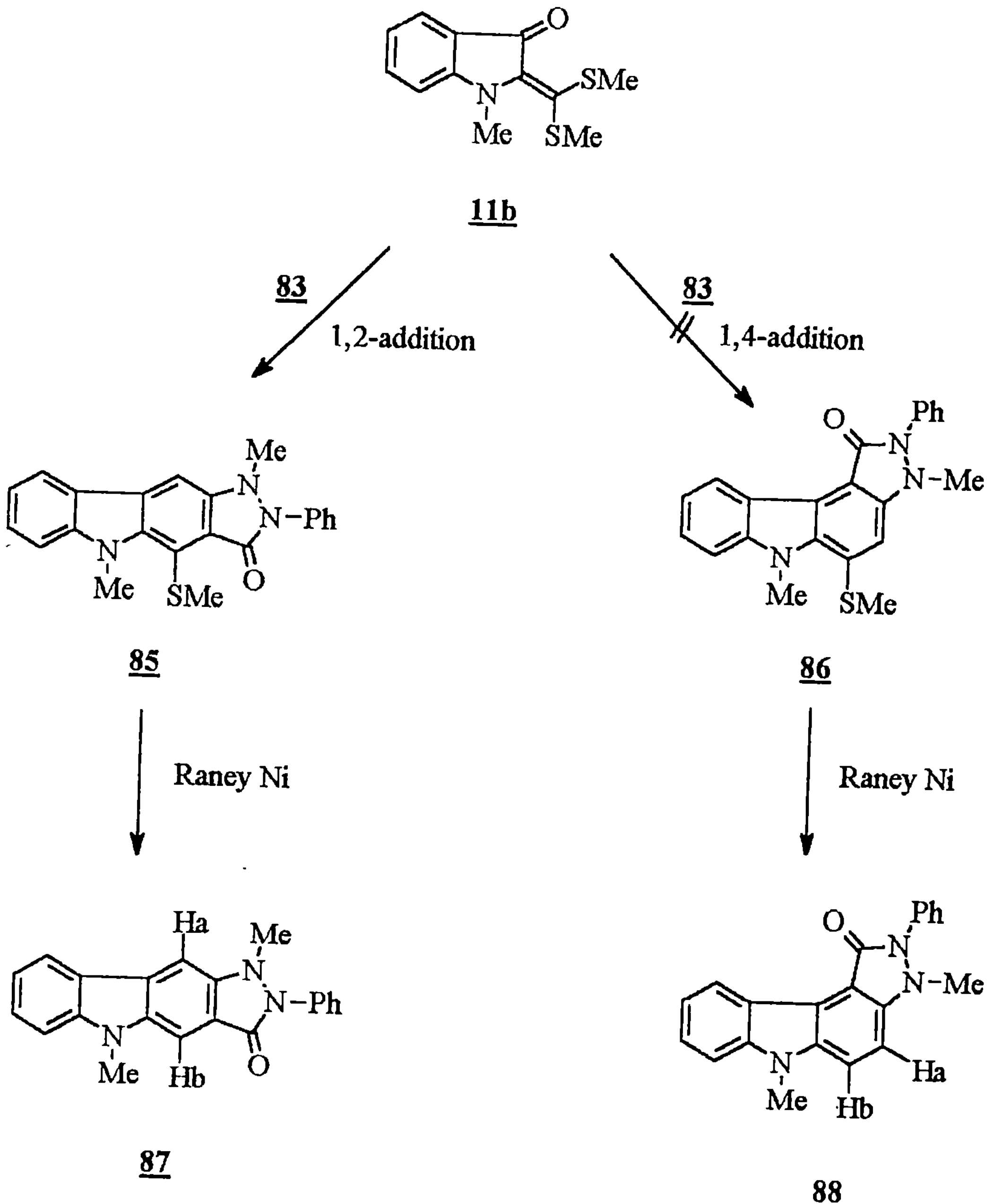
Scheme 19

The regiochemistry was altered when two equivalents of acetonitrile was treated with one equivalent of butyllithium and the corresponding anion β-lithioamino crotononitrile[62] **80** preferably follows 1,4-addition-elimination mode to give intermediate **81** which was *in situ* cyclized to yield δ-carboline[63] analogue **82** in 79% yield as light yellow crystals from chloroform/hexane. The structure of the compound **82** was established on the basis of its analytical and spectral data. The compound **82** was analysed for $C_{15}H_{13}N_3S$ with a molecular weight 267.35. The molecular weight was confirmed by its mass spectrum, which exhibited molecular ion peak at m/z 267 (M^+, 100%). In its IR spectrum (KBr) the nitrile band was observed at ν_{max} 2213 cm^{-1}. The other major bands at 1616 & 1383, 1218 cm^{-1} were also observed, which are described in the experimental section. The structure was further supported by its ^1H NMR (300.13 MHz, $CDCl_3$) spectrum. The three singlet at δ 2.63, 2.89 and 4.26 each integrating for three protons were assigned for the S-methyl, methyl and N-methyl group protons, respectively. The aromatic protons which are in accord with the assigned structure are described in the experimental section. The established structure **82** was further supported by its ^{13}C NMR values which are described in the experimental section. The ^1H NMR and ^{13}C NMR spectrums are also displayed to further support the unambiguously established structure **82**.

3-Lithiomethyl antipyrine (3-lithiomethyl-2-methyl-1-phenylpyrazoline-5-one)[64] **83** when reacted with **11b** followed exclusively 1,2-addition to yield the carbinol acetal **84**, which in the presence of borontrifluoride etherate in refluxing benzene yielded


11b
SMe
SMe
Me
N
O
H$_3$C
N-Ph
N
Me
/ LDA / THF / -78°C
83
Li
1,2-addition
84
OH
Me
N
N-Ph
O
SMe
SMe
BF$_3$.Et$_2$O / C$_6$H
Δ
85

Scheme 20

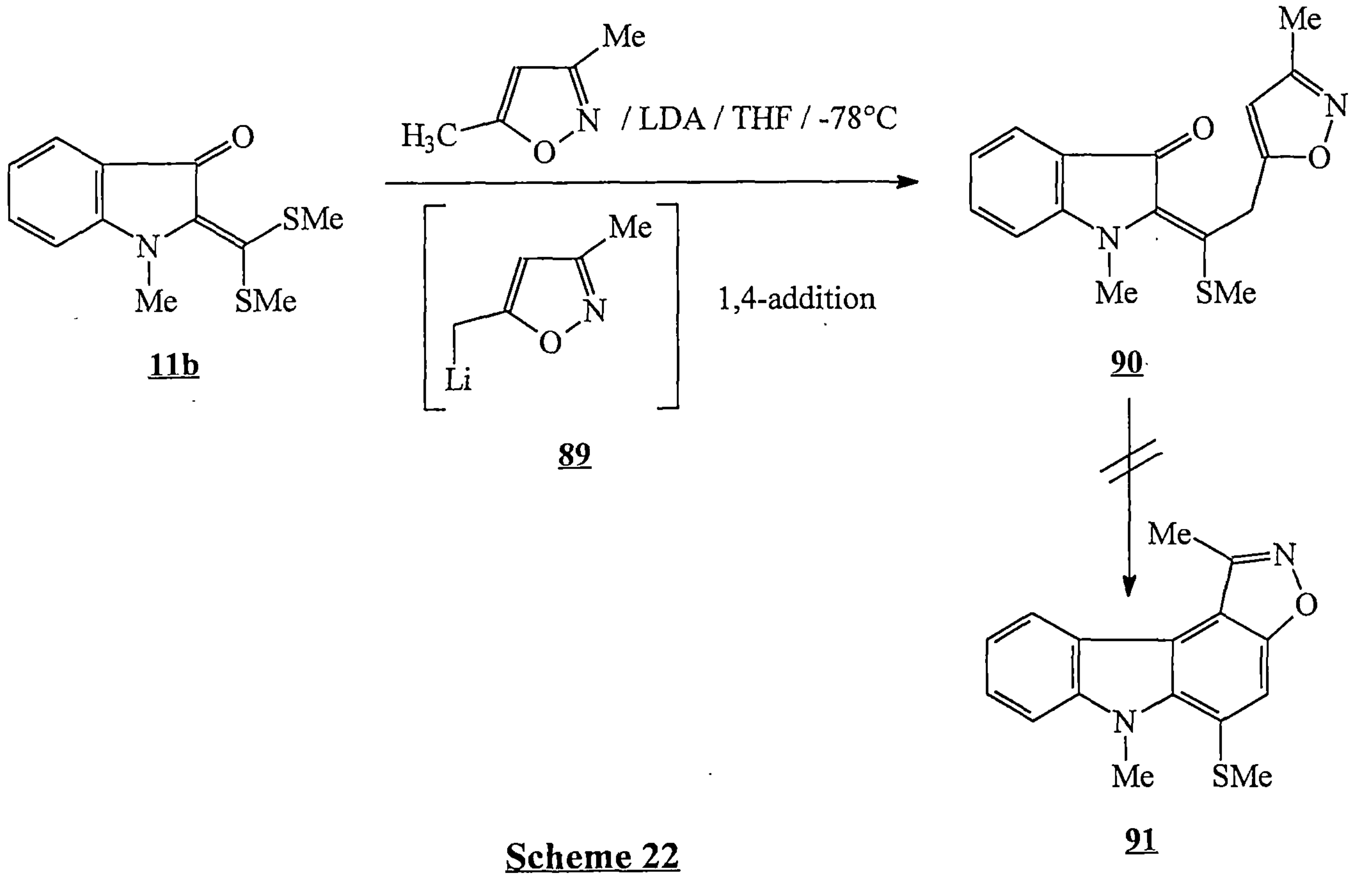

O
SMe
N
Me
SMe
11b
83
1,2-addition
83
1,4-addition
Me
N
N-Ph
N
Me
SMe
O
85
O
Ph
N
N-Me
N
Me
SMe
86
Raney Ni
Raney Ni
Ha
Me
N
N-Ph
N
Me
Hb
O
87
O
Ph
N
N-Me
N
Me
Hb
Ha
88

Scheme 21

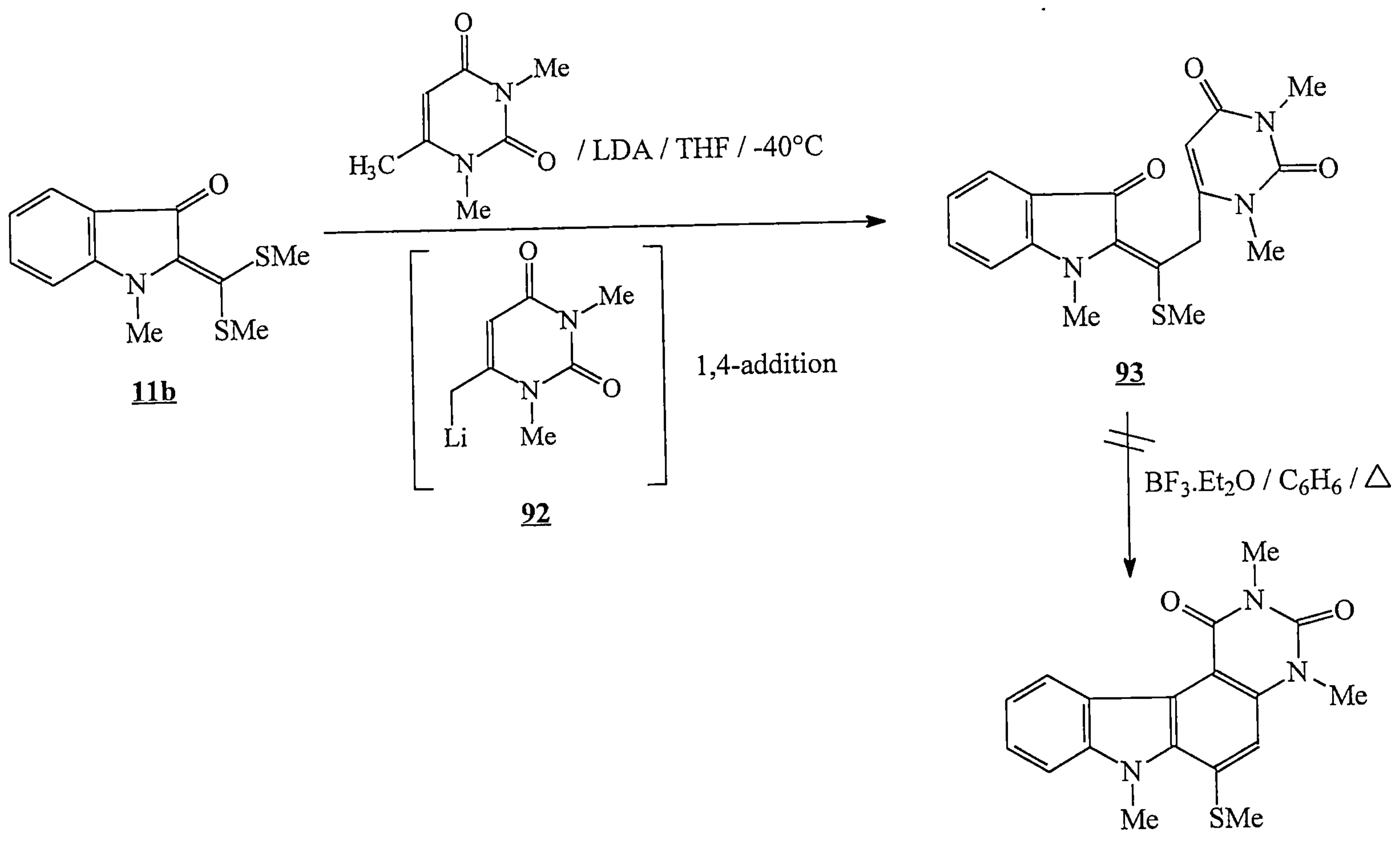
the corresponding 1,2-Dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3H-pyrazolo [4,3-b]carbazole **85** (Scheme 20) as light yellow crystals in 83% yield m.p 276-277°C. No traces of **86** was detected in the reaction mixture and the structural assignment was done on the basis of analytical and spectral data. Thus, it was analysed for $C_{22}H_{19}N_3OS$ with a molecular weight 373.45, which was confirmed by the mass spectrum exhibiting molecular ion peak at m/z: 373 (M^+, 100%). The structure was confirmed and unambiguously established by its ^1H NMR (300.13 MHz, $CDCl_3$) and ^{13}C NMR values, which are described in the experimental section.

The compound **85** was desulfurised in the presence of raney nickel/ethanol when the corresponding sulphur free compound **87** was obtained in 93% yield as light yellow crystals from chloroform/hexane. The structure **87** was assigned on the basis of analytical and spectral data. The two singlets at δ 7.89 and 7.93, which were assigned for H-a and H-b protons, are indicative of the structure **87**. All the analytical, IR, ^1H and ^{13}C NMR values observed were in complete accord with the structure **87** which are described in the experimental section.

The earlier observed reaction pathway on lithiomethylantipyrine **83** with α-oxoketene dithioacetals was 1,4-addition followed by cyclization[64]. However, in this case, the linearity in **87** is established. The corresponding 1,4-addition cyclization pathways to yield angularly fused systems like **86** or **88** were not detected in the reaction mixture (Scheme 21).



Scheme 22



Scheme 23

The other anions derived from 3,5-dimethyl isoxazole and 1,3,6-trimethyl uracil, 3-methyl-5-lithiomethylisoxazole[65,66] **89** (Scheme 22) and 6-lithiomethyluracil **92** (Scheme 23), respectively, reacted with **11b** in the 1,4-addition elimination sequence and the intermediates **90** (Scheme 22) and **93** (Scheme 23), respectively, failed to undergo cyclization to yield the respective heteroannulated carbazoles **91** and **94**. However, **89** was reported to undergo 1,2-addition with other α-oxoketene dithioacetals, where as **92** *underwent usual* 1,4-*addition-elimination mode.* The structures of the 1,4-addition elimination products **90** & **93** were fully established on the basis of their analytical and spectral data which are described in the experimental section. However, attempts to cyclize these two intermediates **90** & **93** in the presence of strong base to yield the corresponding carbazoles **91** and **94** , respectively are still to be completed.

III. 4. Conclusion :

First report on the preparation of 2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole by trapping Indoxyl in the synthesis of indigo has been accomplished. It is characterised. Also, its hitherto unreported substituted analogues prepared and examined for their reactivity with various nucleophiles & binucleophiles and shown that the nucleophiles add in 1,2-fashion followed by solvalitic cleavage to yield the corresponding 3-alkylindole-2-esters. The allyl nucleophiles also reacted in 1,2-fashion and are shown to undergo cationic cycloaromatization to yield the corresponding carbazoles. However, benzylmagnesium chloride underwent 1,4 followed by 1,2-

addition sequence and failed to cycloaromatize as observed in other systems and yielded only dehydrated open chain product. However, acetonitrile anion (1,2-addition) and β-aminocrotononitrile anion (1,4-addition) followed the expected route to yield corresponding carboline derivatives. The guanidine nitrate reaction in methanolic sodium hydroxide yielded the corresponding methoxy pyrimidoindole in excellent yield. The 3-lithiomethyl antipyrine also underwent 1,2-addition followed by acid assisted cyclization to yield a new class of hetero [b] annulated carbazole in excellent yield. Unfortunately, the allyl anions derived from 1,3,6-trimethyl uracil and 3,5-dimethyl isoxazoles yielded 1,4-addition-elimination products 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 1,4-addition-elimination products in the presence of strong base however has not been done and the experiments in this direction are being continued.

III. 5. EXPERIMENTAL SECTION:

General:

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected . The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer and frequencies are expressed in cm^{-1}. The ^{1}H NMR spectra were recorded on varian EM-390, 90 MHz spectrometer in $CDCl_3$ or CCl_4 and are reported in δ units down field from Tetramethylsilane. High resolution ^{1}H NMR (300.13MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ or DMSO/d_6/ $CDCl_3$ and are reported in δ units downfield from Tetramethylsilane. The coupling constants are given in Hertz. The followed abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR (75.46 MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ or DMSO/d_6/ $CDCl_3$ and are reported in δ units in $CDCl_3$ downfield from Tetramethylsilane. Mass spectra were obtained on a Joel D-300 spectrometer and relative intensities are expressed in percentage. The molecular and base peaks are indicated by M^+. Carbon, hydrogen and nitrogen elemental analysis were carried out on a Heraus CHN-O-RAPID instrument. Analytical T. L.C. were performed on glass plates (18x6 and 18x4 cm) coated with ACME's silica gel containing 13% calcium sulphate as binder and various combinations of ethyl acetate-hexane, benzene, methanol were used in glass chambers for running T.L.C in order to monitor the reactions. Visualisation of spots was accomplished by exposure to iodine vapour or potassium permanganate (acidic) solution. ACME's silica gel (60-120 mesh) was used for column chromatography.

All the reactions involving organolithium were performed in oven-dried glassware under masked dry nitrogen atmosphere using syringe-septum technique.Low temperature reactions were carried out in a bath made of appropriate solvent and liquid nitrogen .

Chemicals and Solvents:

The commercial samples of N,N-diisopropylamine, n-butyl bromide, acetone, benzyl chloride, 2-picoline, acetonitrile, allyl bromide,methylallyl bromide, crotyl bromide and 3,5-

dimethylisoxazole were purified by distillation under reduced pressure before use. Commercial samples of guanidine nitrate, antipyrine were purified by crystallisation before use. n-butyllithium was prepared according to the reported procedure[68]. Raney nickel (W4)[69], 2,3,6-trimethyluracil[70] , 3,5-dimethylisoxazole[71] were prepared according to the reported procedure. Tetrabutylammonium iodide was used as phase transfer catalyst. Diethylether, benzene and acetonitrile were distilled and dried by keeping over sodium wire. Tetrahydrofuran was initially deperoxidized and then dried by keeping over sodium wire followed by distillation. Solvents for column chromatography were used after simple distillation of commercial ones. All solvents evaporation's were done on a steam-bath.

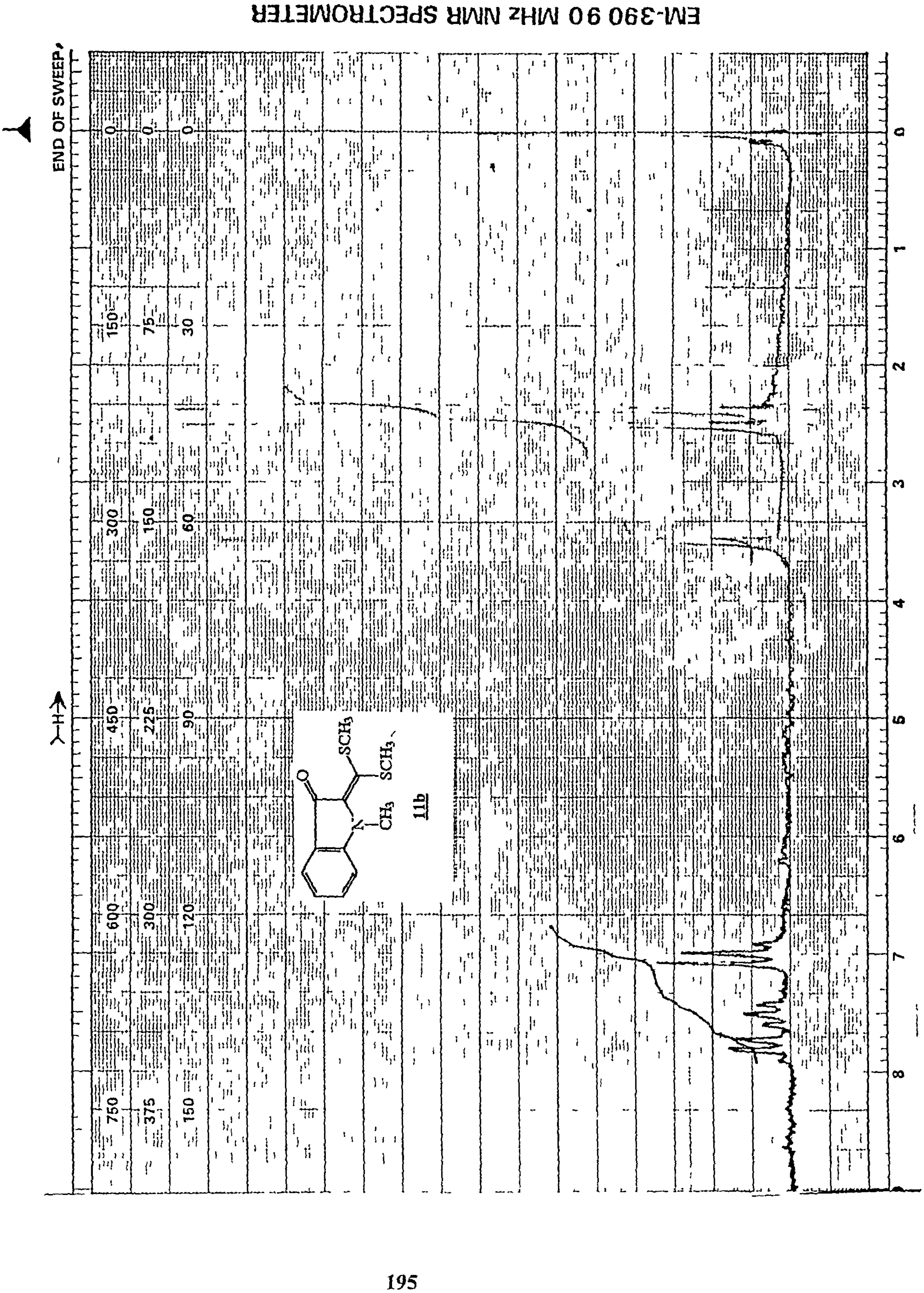
Preparation of 2-Bis(methylthio)methylene-2,3-dihydro-3-oxoindole (11a):

In a three necked flask a mixture of phenylglycine 0-carboxylic acid (3.9g, 0.02 mol), potassium hydroxide (17g, 0.3 mol) and 5ml of water were heated with stirring at 280°C for 45 min in an inert atmosphere until the complete evolution of carbondioxide. The appearance of orange colour indicated the complete formation of indoxyl. The reaction mixture was cooled to room temperature and 75ml of water was added and stirred for 10 min. It was then brought to ice cold temperature, followed by dropwise addition of carbon disulphide and the reaction mixture was stirred for a further period of 2hrs and brought to ice cold temperature. Methyl iodide (2.8 ml, 0.04 mol) was added dropwise and the reaction mixture stirred for further 6 hrs. The reaction mixture was neutralised with saturated ammonium chloride solution and was extracted with dichloromethane (2 x 100 ml). The organic extracts were washed with (3 x 150 ml) water. The organic layer dried over anhydrous sodium sulphate and was concentrated to give the crude product which was purified by column chromatography over silica gel using hexane as eluent, yielding the pure product in 43%.

2-Bis(methylthio)methylene-2,3-dihydro-3-oxoindole (11a) was obtained as orange coloured crystals (chloroform / hexane); m.p.158-159°C ; yield 43%; IR (KBr): ν_{max} = 3487 (NH), 3448, 3289, ,3240, 1644 (C=O), 1610, 1479, 1196 cm^{-1} ; ^1H NMR (90MHz, $CDCl_3$) :δ = 2.47 (s, 3H, $SC\underline{H}_3$), 2.50 (s, 3H, $SC\underline{H}_3$), 6.89-7.10 (m, 2H, Ar$\underline{H}$), 7.13-7.29 (brs, 1H, N$\underline{H}$, exchangeable with D_2O), 7.39-7.60 (m, 1H, Ar$\underline{H}$), 7.80 (d, 1H, *J* = 9Hz, Ar$\underline{H}$); Anal. Calculated for $C_{11}H_{11}NOS_2$ (237.33) : C, 55.67; H, 4.67; N, 5.90. Found : C, 55.63; H, 4.69; N, 5.68%.

Preparation of 2-Bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11b):

In a three necked flask a mixture of phenylglycine 0-carboxylic acid (3.9g, 0.02 mol), potassium hydroxide (17g, 0.3 mol) and 5ml of water were heated with stirring at 280°C for 45 min in an inert a atmosphere until the complete evolution of carbondioxide. The appearance of orange colour indicated complete formation of indoxyl. The reaction mixture was cooled to room temperature, 75ml of water was added and stirred for 10min. It was then brought to ice cold temperature, followed by dropwise addition of carbon disulphide


EM-390 90 MHz NMR SPECTROMETER
END OF SWEEP
H
0
1
2
3
4
5
6
7
8
0
0
0
150
75
30
300
150
60
450
225
90
600
300
120
750
375
150
O
SCH3
SCH3
N
CH3
11b

and the reaction mixture was stirred for further period of 2hr and brought to ice cold temperature. Methyl iodide (4.3 ml, 0.06 mol) was added dropwise and the reaction mixture stirred for further 12hrs. Then the reaction mixture was neutralised with saturated ammonium chloride solution and was extracted with dichloromethane (2 x 100 ml). The organic extracts were washed with water (3 x 150 ml). The organic layer dried over anhydrous sodium sulphate and concentrated to give the crude product which was then purified by column chromatography over silica gel using hexane as eluent yielding the pure product in 42%.

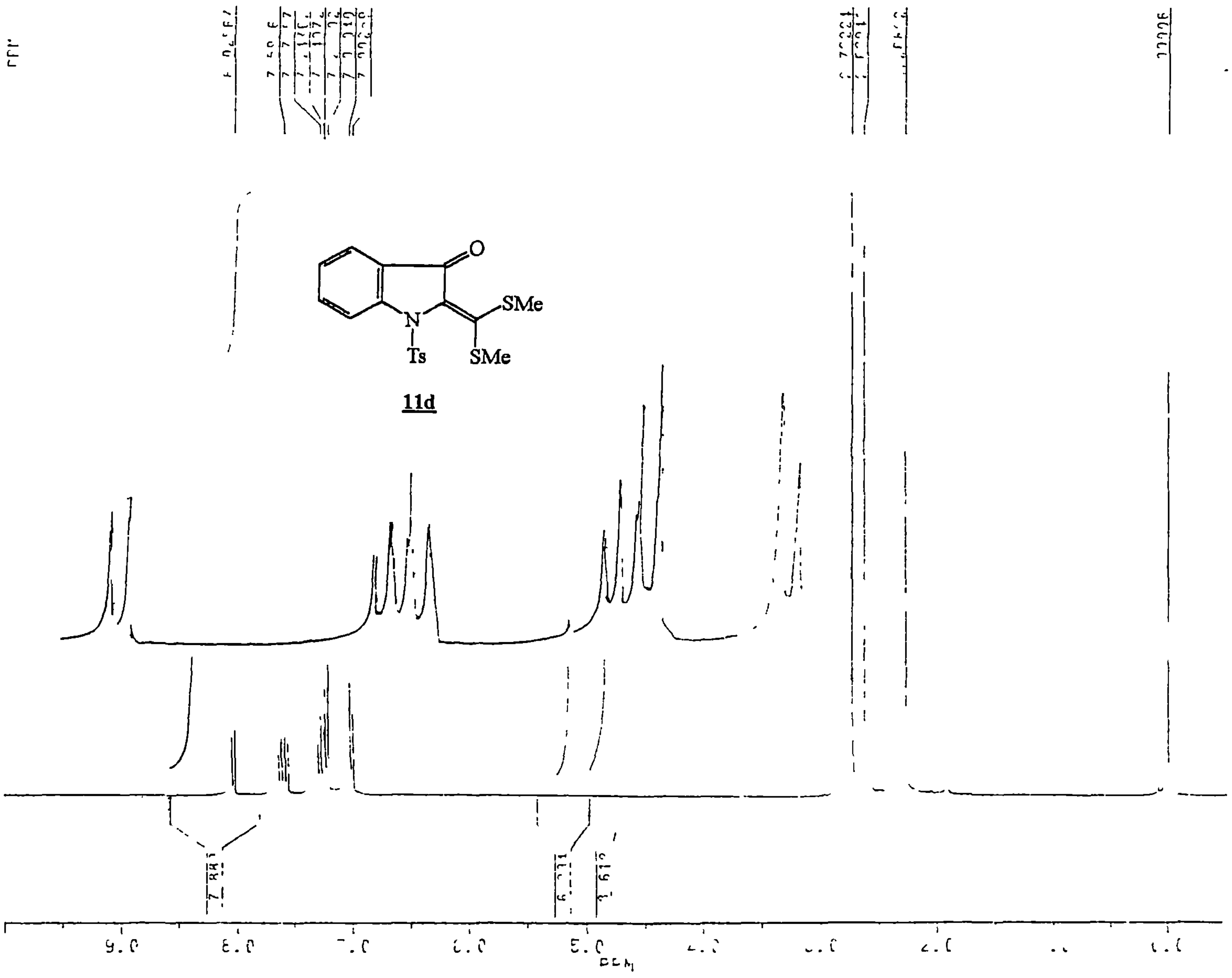
2-Bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11b) was obtained as orange coloured viscous liquid; yield : 42%; IR(KBr): ν_{max} = 1651 (C=O), 1603, 1481,1308 cm^{-1}; ^1H NMR (90 MHz, CCl_4) : δ = 2.36 (s, 3H, SCH_3), 2.50 (s, 3H, SCH_3), 3.46 (s, 3H, NCH_3), 6.90-7.13 (m, 2H, ArH), 7.40-7.63 (m, 1H, ArH), 7.76 (d, 1H, *J* = 9Hz, ArH); m/z: 252 (M^++1, 9.3%), 251 (M^+, 100%), 236 (M^+ $-CH_3$, 18.2%), 189 (65.5%), 188 (96.8%); Anal. calculated for $C_{12}H_{13}NS_2O$ (251.35) : C, 57.33; H, 5.21; N, 5.57. Found: C, 57.21; H, 5.18; N, 5.46%.

General procedure for the 2-Bis(methylthio)methylene-2,3-dihydro-3-oxo-1-substituted indoles (11b-d) :

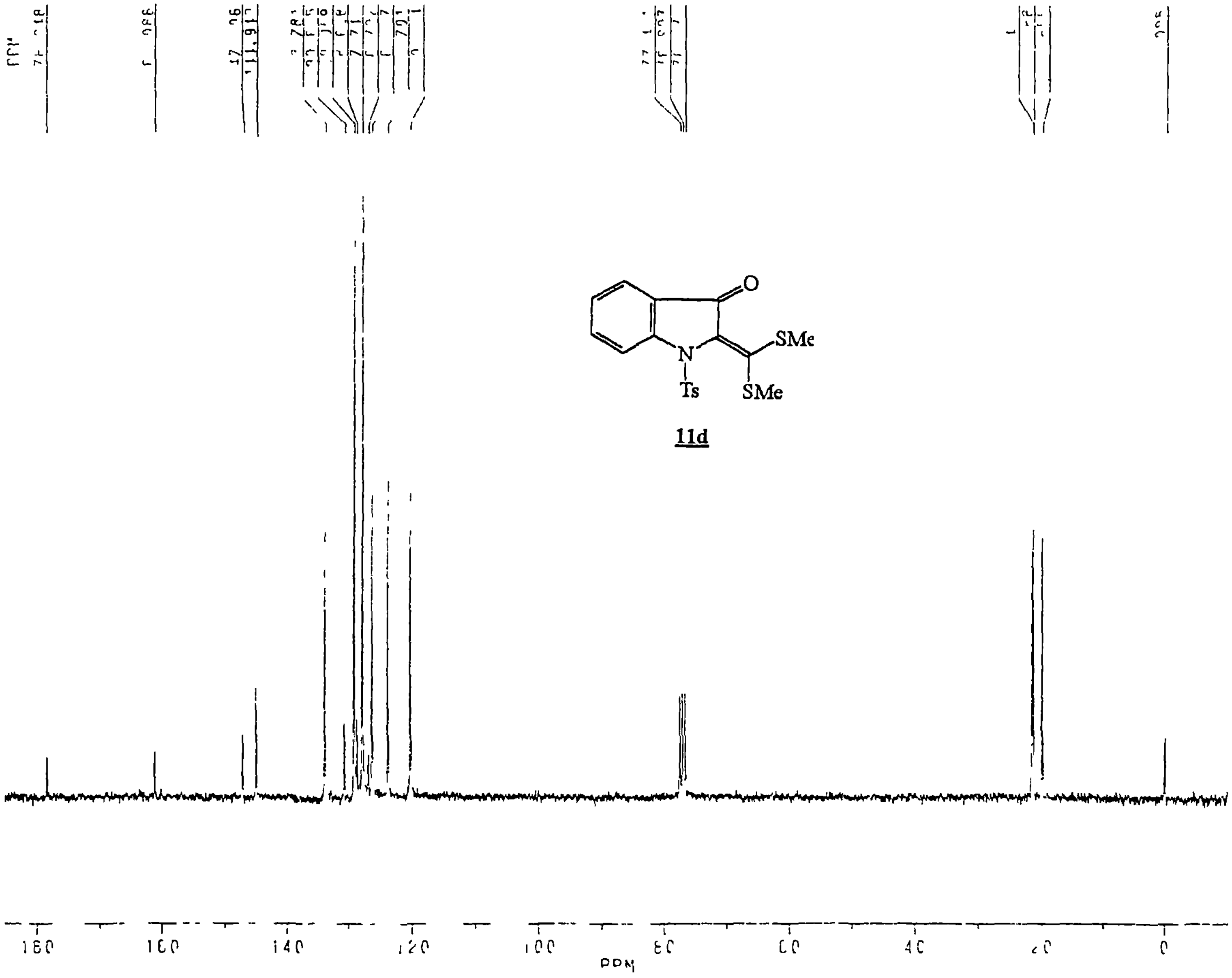
2-Bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11a) (2.37gm, 0.01 mol) was dissolved in 20ml of chloroform and was stirred with 25ml of 50% sodium hydroxide solution and catalytic amount of tetrabutylammonium iodide. Corresponding alkyl halide (0.012 mol), in chloroform (20ml) was added drop wise fashion over a period of 15 min. The reaction mixture was stirred for 5 hrs (monitored bu TLC). It was extracted with chloroform (3x100ml). The chloroform extracts were washed with water (3x100 ml). Organic layer was dried over anhydrous sodium sulphate and was concentrated to give the residue. Ethyl acetate was added to separate out the phase transfer catalyst. Phase transfer catalyst was filtered off and the filtrate was concentrated to give the crude product which was purified by silica gel chromatography using ethyl acetate/ hexane (1:9) to yield the corresponding alkylated products. The products obtained **11b-d** were characterised on the basis of their spectral and analytical data which are described below.

2-Bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11b) : The spectral and analytical data was superimposable with that described above ,which was obtained by the direct alkylation of dithioate **55** using three equivalents of methyl iodide.

1-Benzyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole (11c) was obtained as orange coloured crystals (dichloromethane / hexane) m.p.108-109°C; yield : 96%; IR (CCl_4) :ν_{max} = 1634 (C=O), 1438, 1326, 1173 cm^{-1}; ^1H NMR (300.13MHz, $CDCl_3$): δ = 2.13 (s, 3H, $SC\underline{H}_3$), 2.21 (s, 3H, $SC\underline{H}_3$), 5.15 (s, 2H, $C\underline{H}_2C_6H_5$), 6.86-6.91 (m, 1H, Ar$\underline{H}$), 6.93-6.96 (m, 2H, Ar$\underline{H}$), 7.05-7.09 (m, 4H, Ar$\underline{H}$), 7.39 (ddd, with fine splitting, 1H, *J* =8.34,7.69, 1.20Hz, Ar$\underline{H}$), 7.66 (d, 1H, *J* = 7.69, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 19.02 ($S\underline{C}H_3$), 21.51 ($S\underline{C}H_3$), 48.13 ($N\underline{C}H_2 C_6H_5$), 111.89, 120.85, 123.81, 127.49, 127.60, 128.07, 128.86, 134.23, 135.15, 137.42, 140.03, 173.98 (C=O);



11d



11d

Anal. calculated for $C_{18}H_{17}NOS_2$ (327.48) : C, 66.02; H, 5.23; N, 4.28. Found: C, 65.96; H, 5.21; N, 4.23%.

2-Bis(methylthio)methylene-2,3-dihydro-3-oxo-1-(4'-toluenesulfo- nyl) indole (<u>11d</u>) was obtained as orange coloured needles (dichloromethane / hexane); m.p.154-156°C; yield : 98%; IR (Kbr) : ν_{max} = 1666 (C=O), 1476, 1356, 1165 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 2.27 (s, 3H, $C\underline{H}_3$), 2.63 (s, 3H, $SC\underline{H}_3$), 2.73 (s, 3H, $SC\underline{H}_3$), 7.02 (d, 2H, J =8.35 Hz, Ar$\underline{H}$), 7.21-7.30 (m, 3H, Ar$\underline{H}$), 7.56-7.65 (m, 2H, Ar$\underline{H}$), 8.04 (d, with fine splitting, 1H, J =8.35, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$) : δ = 19.86 ($\underline{C}H_3$), 21.29 ($S\underline{C}H_3$), 21.43 ($S\underline{C}H_3$), 120.13, 123.70, 126.22, 126.79, 127.75, 128.63, 129.10, 130.64, 133.78, 144.95, 147.11, 161.09, 178.35 (C=O); m/z: 392 (M^+, 91%), 236 (100%) ; Anal. calculated for $C_{18}H_{17}NO_3S_3$ (391.52) : C, 55.22; H, 4.38; N, 3.58. Found: C, 55.19; H, 4.32; N, 3.51%.

Preparation of 1-Acetyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole (<u>11e</u>):

A mixture of N-acetylindoxyl and carbon disulphide (0.5 mol) in dry benzene (100 ml) was added dropwise to an ice cold and well stirred suspension of sodium-t-butoxide (1.0 mol) and the reaction mixture was stirred for 4-5 hr. Methyl iodide (1.1mol) was then gradually added with cooling and the reaction mixture was further stirred for 6 hr (monitored by T.L.C). The reaction mixture was poured over ice cold water. The benzene layer was separated and the aqueous phase was extracted with benzene (2x100ml). The combined benzene extracts were washed with water (2x100ml), dried over sodium sulphate and evaporated to yield the crude dithioacetal which were purified by silca gel chromatography using ethyl acetate/hexane (20:80) as eluent.

1-Acetyl-2-bis(methylthio)methylene-2,3-dihydro-3-oxoindole (11e) was obtained as orange coloured needles (dichloromethane / hexane); yield:41%; m.p.132-133°C; IR (Kbr) : ν_{max} = 1671 (C=O), 1619 (C=O), 1276, 1203 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.38 (s, 3H, C$\underline{H}_3$), 2.54 (s, 3H, SC$\underline{H}_3$), 2.71 (s, 3H, SC$\underline{H}_3$), 7.28 (dd, with fine splitting, *J* = 8.4, 7.4 Hz, 1H, Ar$\underline{H}$), 7.60 (dd, with fine splitting, *J* = 8.4, 7.4 Hz, 1H, Ar$\underline{H}$), 7.80 (d, with fine splitting, *J*= 8.4 Hz, 1H, ArH), 8.20 (d,1H,*J* = 8.4Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 17.50 (CO$\underline{C}H_3$), 21.25 (S$\underline{C}H_3$), 24.52 (S$\underline{C}H_3$), 116.13, 122.62, 123.66, 133.75, 134.22, 145.68, 151.57, 168.99 (C=O), 176.93 (C=O); Anal. calculated for $C_{13}H_{13}NO_2S_2$ (279.36) : C, 55.89; H, 4.69; N, 5.01. Found: C, 55.81; H, 4.67; N, 4.98%.

Preparation of 2-Carbomethoxy-1,3-dimethylindole (61):

Under masked nitrogen atmosphere methyl iodide (355mg, 2.5 mmol) was added dropwise to a cooled and stirred suspension of magnesium (96mg, 4 mmol) and iodine (catalytic amount) in dry ether (25 ml). The reaction mixture was further stirred for 30 min and the methylmagnesium iodide, generated *in situ* was used for the reaction. A solution of 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11b) (0.502g, 2 mmol) in dry benzene (20 ml) was added dropwise to the ice-cold reaction mixture. The reaction mixture was further stirred for 2hr (monitored by tlc) and poured into an aqueous saturated solution (100 ml) of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with ether (3x50 ml). The combined organic extracts were washed with water (2x100 ml), dried over sodium sulphate, and evaporated to give the crude carbinol acetal **60** in quantitative yield. The carbinol acetal **60** is directly dissolved in dry methanol (20 ml) followed by the addition of borontrifluoride etherate (1 ml). It was refluxed for 6 hr (monitored by tlc). The reaction mixture was cooled and poured over aqueous saturated solution (100 ml) of sodium bicarbonate. The aqueous layer was extracted with chloroform (3x50 ml), and the chloroform extracts were washed with water (2x50 ml) , dried over sodium sulphate and was concentrated to give the crude product **61** which was further purified by column chromatography over silica gel using hexane as eluent. The structure of **61** was fully characterised on the basis of its spectral and analytical data which are given below.

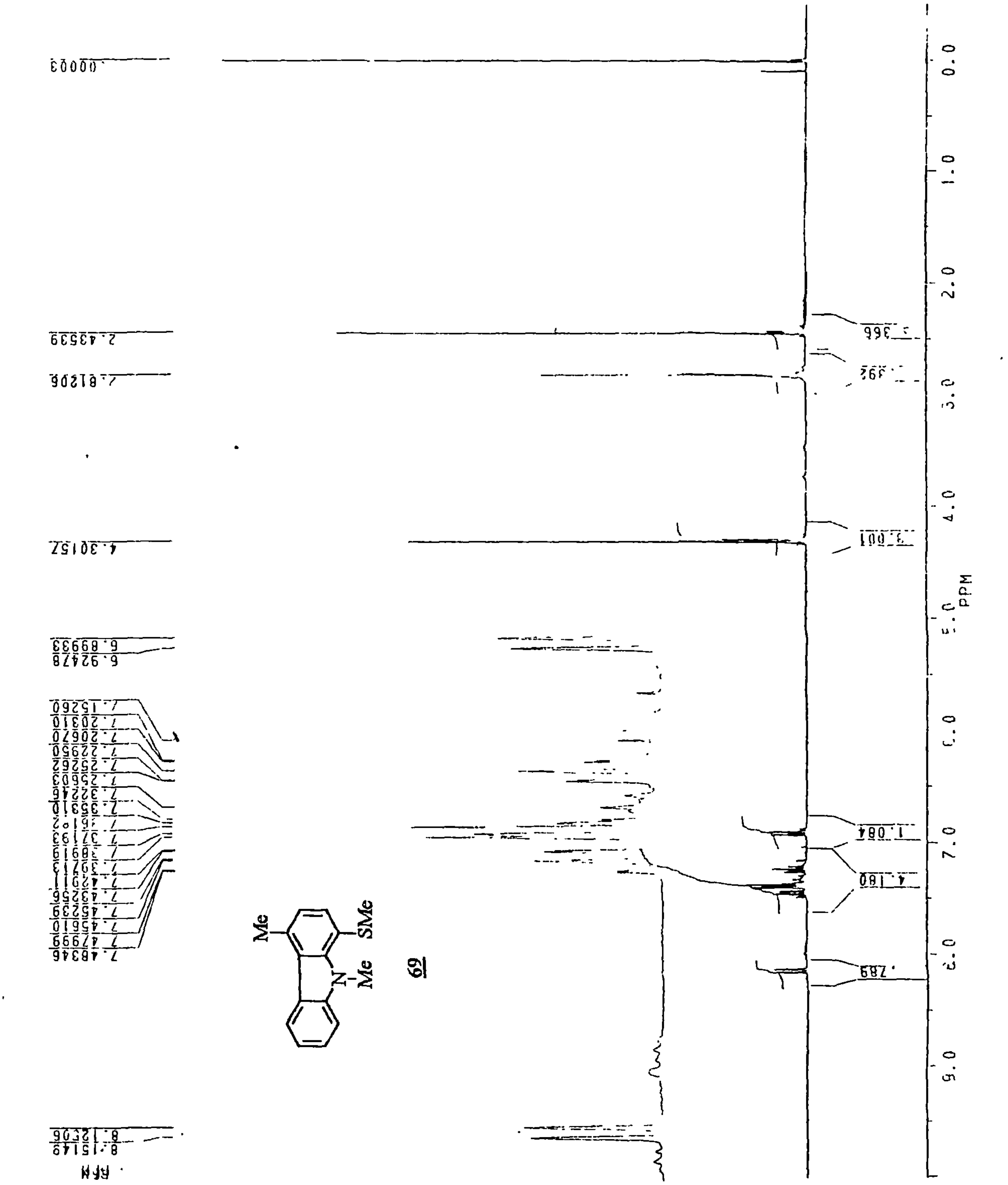
2-Carbomethoxy-1,3-dimethylindole (61) was obtained as colourless crystals (hexane / pentane); m.p.81-82°C; yield : 67%; IR (KBr) : ν_{max} = 1665 (C=O), 1608, 1596, 1394 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ = 2.60 (s, 3H, $C\underline{H}_3$), 3.96 (s, 3H, $NC\underline{H}_3$), 4.03 (s, 3H, $OC\underline{H}_3$), 7.17-7.50 (m, 3H, Ar$\underline{H}$), 7.78 (d, 1H, *J* =9 Hz, Ar$\underline{H}$); Anal. calculated for $C_{12}H_{13}NO_2$ (203.23) :C, 70.92; H, 6.45; N, 6.89. Found: C, 70.92; H, 6.43; N, 6.91%.

Synthesis of 9-Methyl-1-methylthiocarbazole (64):

In a three necked flask under nitrogen atmosphere, to a well stirred grignard reagent [made *in situ* by adding appropriate allyl halide (0.01 mol) to magnesium metal (0.48 g, 0.02 mol) in dry diethyl ether] suspended in dry diethyl ether at 0°C, 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole **(11b)** (0.502 gm, 0.002 mol) in dry ether was added in a dropwise fashion and the reaction mixture was stirred at room temperature for 2 hr (monitored by T.L.C). Then the reaction mixture was quenched with saturated ammonium chloride solution and the product was extracted with ether (2 x 100 ml). The organic extracts were washed with water, dried over anhydrous sodium sulphate and concentrated to give the crude carbinol which was used as such for further reaction.

The crude carbinol was refluxed with borontrifluoride etherate (3 ml) in dry benzene (50ml) for 2 hr . Then it was cooled and neutralised with saturated aqueous sodium bicarbonate solution and was extracted with benzene (2 x 100 ml). The benzene extracts were washed with water (2x100 ml), dried over anhydrous sodium sulphate, and concentrated to give the crude product which was chromatographed over silica gel using hexane as eluent.

9-Methyl-1-methylthiocarbazole (64) was obtained as pale yellow crystals (dichloromethane / hexane); m.p.68-70°C; yield : 63%; IR (CCl_4): ν_{max} = 2917 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ= 2.50 (s, 3H, $SC\underline{H}_3$), 4.33 (s, 3H, $NC\underline{H}_3$), 7.13-7.70 (m, 5H, Ar$\underline{H}$), 8.00-8.23 (m, 2H, Ar$\underline{H}$); m/z : 227 (M^+, 100%), 212 (56.7%), 168 (92.3%), 152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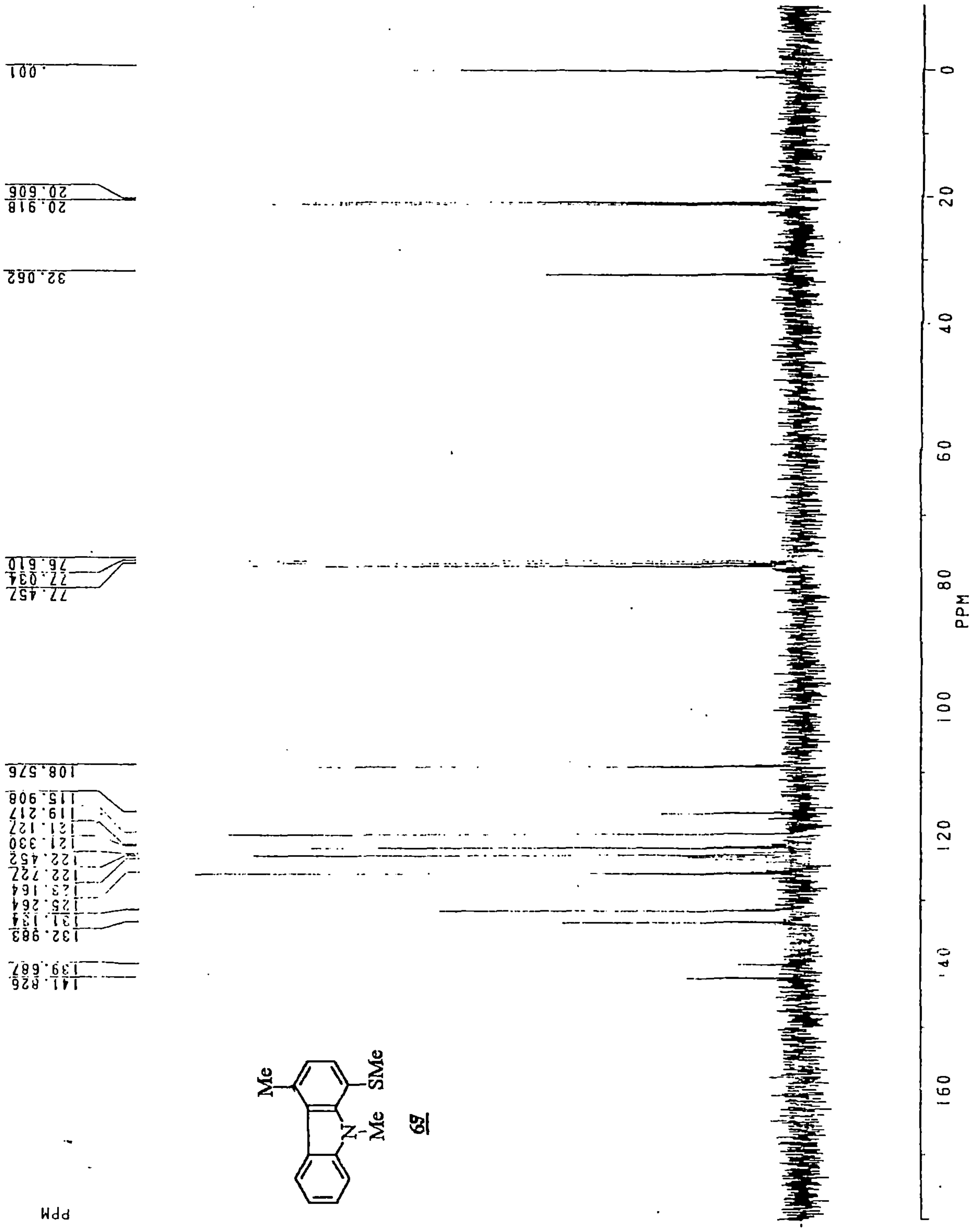
69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PPM
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40
60
80
100
120
140
160
PPM
Me
SMe
N
Me
69

(43.4%); Anal. calculated for $C_{14}H_{13}NS$ (227.31) ; C, 73.97; H, 5.76; N, 6.16. Found: C, 73.91; H, 5.72; N, 6.08%.

3,9-Dimethyl-1-methylthiocarbazole (67) was obtained as pale yellow crystals (dichloromethane / hexane); m.p.97-98°C; Yield 68%; IR (CCl_4): ν_{max} = 2909, 1458 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) : δ = 2.46 (s, 6H, $C\underline{H}_3$, $SC\underline{H}_3$), 4.30 (s, 3H, $NC\underline{H}_3$), 6.99-7.49 (m, 4H, Ar$\underline{H}$), 7.73 (s, 1H, Ar$\underline{H}$), 7.97 (d, 1H, *J* =7.5 Hz, Ar$\underline{H}$); m/z: 241 (M^+, 100%), 226 (69.5%); Anal. calculated for $C_{15}H_{15}NS$ (241.34); C, 74.65; H, 6.26; N, 5.80. Found: C,74.63; H,6.21; N,5.82%.

4,9-Dimethyl-1-methylthiocarbazole (69) was obtained as light yellow crystals (dichloromethane / hexane); m.p.92-94°C; yield: 68%; IR (CCl_4): ν_{max} = 2911, 1543 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 2.43 (s, 3H, $C\underline{H}_3$), 2.81(s, 3H, $SC\underline{H}_3$), 4.30 (s, 3H, $NC\underline{H}_3$), 6.91 (d, 1H, *J* = 7.65 Hz, Ar$\underline{H}$), 7.22 (dd, with fine splitting, 1H, *J* = 7.94, 6.90 Hz, ArH), 7.35-7.39 (m, 2H, Ar$\underline{H}$), 7.45 (dd, with fine splitting, 1H, *J* = 7.94, 6.90, ArH), 8.14 (d, 1H, *J* =7.94 Hz, Ar$\underline{H}$), ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 20.61 ($\underline{C}H_3$), 20.91 ($S\underline{C}H_3$), 32.06 ($N\underline{C}H_3$), 108.57, 115.91, 119.21, 121.13, 122.45, 122.72, 123.16, 125.26, 131.13, 132.98, 139.69, 141.82; Anal. calculated for $C_{15}H_{15}NS$ (241.34); C, 74.65; H, 6.26; N, 5.82. Found: C,74.55; H,6.21; N,5.82 %.

Procedure for dethiomethylation of 9-Methyl-1-methylthiocarbazole (64) :

To a stirred solution of 9-Methyl-1-methylthiocarbazole (0.25 mol) in ethanol (25 ml) was added Raney Nickel (W4, 3 times by weight) and the mixture was stirred at ambient temperature for 6 hrs (monitored by tlc). The reaction mixture was filtered through G-3 cintered funnel and the residue was washed with ethanol (3x10 ml). The bulk of the ethanol was distilled off and residue obtained was extracted with chloroform (2x20 ml). The chloroform extracts were washed with water (2x25 ml), dried over anhydrous sodium sulphate and was concentrated. Analytically pure compound was obtained by passing through a short length silicagel column using hexane as eluent.

9-methylcarbazole (65) was obtained as pale yellow needles from chloroform/hexane ; yield : 94%; m.p. 86°C ; lit[55]. m.p. 88°C. The spectral and analytical data were in accord with the assigned structure and also were superimposable with the reported ones.

Preparation of 2-(2'-Benzyl-2'-methylthiomethylene)-2,3-dihydro-1-methyl-3-(2'-phenyl methylene)indole (71b):

In a three necked flask under nitrogen atmosphere to a well stirred suspension of benzylmagnesium bromide (5 mmol) [*in situ* made at 0°C by adding benzyl bromide (50 mmol) to magnesium metal (240mg, 10 mmol) in dry diethyl ether] in dry diethyl ether at 0°C, 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11b) (0.502 gm, 0.002 mol) in dry ether(25 ml) was added drop wise fashion and the reaction mixture was stirred at room temperature for 2 hr (monitored by T.L.C). Then the reaction mixture was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with chloroform (2 x 100 ml). The combined organic extracts were washed with water (2x50 ml), dried over anhydrous sodium sulphate and concentrated to give the crude carbinol which was used as such for further reaction.

The crude carbinol was refluxed with borontrifluoride etherate (3 ml) in dry benzene (50ml) for 2 hr . Then it was cooled and neutralised with saturated aqueous sodium bicarbonate solution and was extracted with benzene (2 x 100 ml). The benzene extracts were washed with water (2x100 ml) , dried over anhydrous sodium sulphate, and concentrated to give the crude product which was chromatographed over silica gel using hexane/ethyl acetate (4:1) as eluent and was characterised as triene from its spectral and analytical data , which is described below.

2-(2'-Benzyl-2'-methylthiomethylene)-2,3-dihydro-1-methyl-3-(2'-phenyl methylene)indole (**71b**) was obtained as light orange crystals (Chloroform / hexane); m.p.103-104°C; yield 69%; IR (Kbr): ν_{max} = 2965, 1383, 1296, 1124 cm^{-1}; ^1H NMR (90 MHz, CCl_4):δ = 2.39 (s, 3H, $SC\underline{H}_3$), 3.93 (s, 3H, $NC\underline{H}_3$), 4.56 (s, 2H, $C\underline{H}_2C_6H_5$), 6.56-6.63 (m, 1H, Ar$\underline{H}$), 6.93-7.39 (m, 12H, Ar$\underline{H}$), 7.46 (d, 1H, *J* =7.5 Hz, Ar$\underline{H}$), 7.76 (s, 1H, vinylic $\underline{H}$); Anal. calculated for $C_{25}H_{23}NS$ (369.50) : C, 81.26; H, 6.27; N, 3.79. Found: C, 81.21; H, 6.27; N, 3.71%.

Preparation of 1,3-Bis(methylthio)-9-methyl[9H]pyrido[3,4-b] indole (79) :

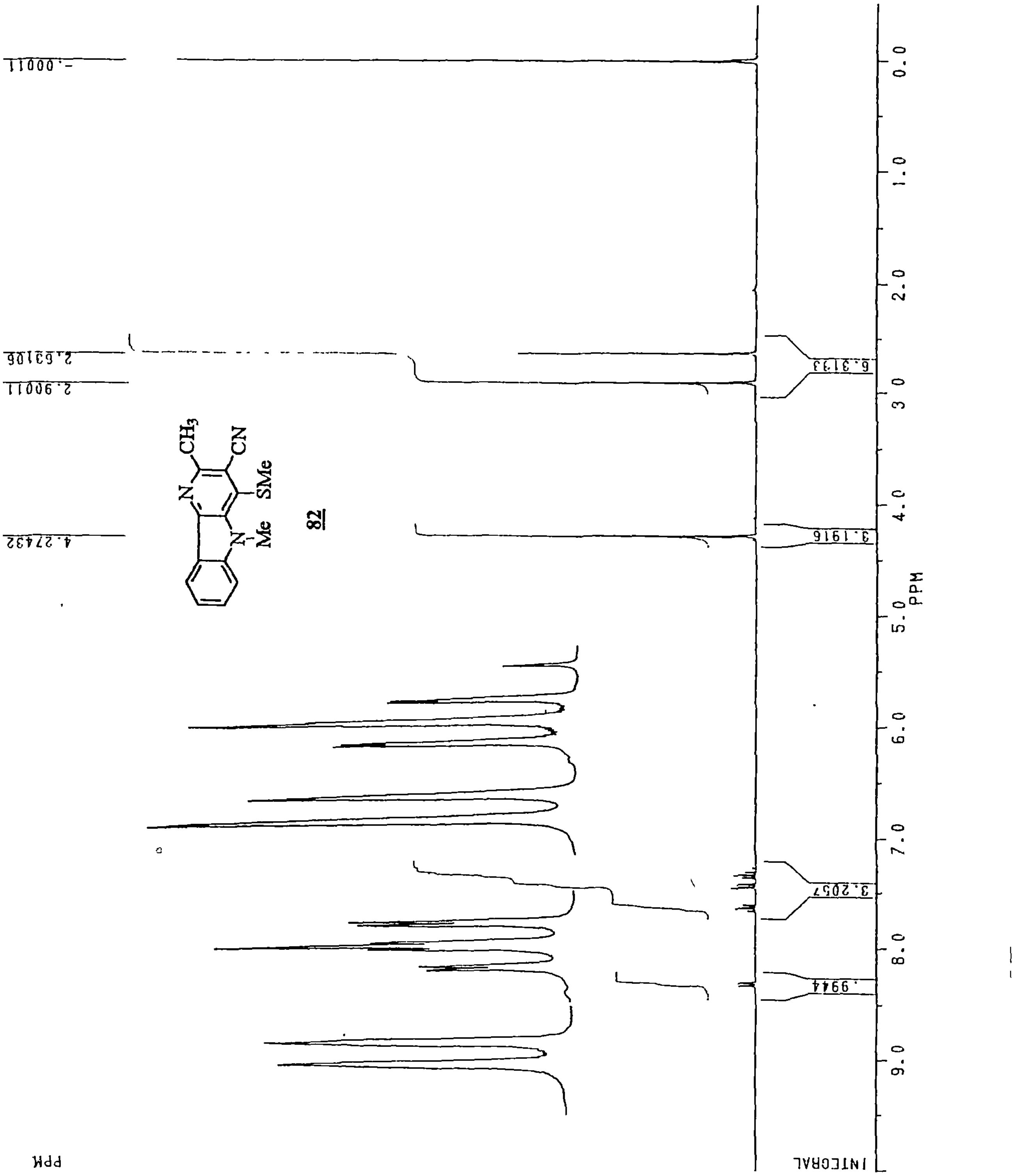
In a three necked round bottom flask under dry nitrogen atmosphere at −78°C, n-butyllithium (10 mmol) was added to a well stirred solution of acetonitrile (0.41g, 10 mmol) in anhydrous tetrahydrofuran (25 ml) and the reaction mixture was stirred at the same temperature for 0.5h to give white suspension of lithioacetonitrile. To the suspension of lithioacetonitrile, 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (**11b**) (1 gm, 0.004 mol) in anhydrous tetrahydofuran (25 ml) was added at −78°C and the reaction mixture was stirred at the same temperature for 0.5h. It was warmed up to room temperature and stirring was continued for 5hr (monitored by T.L.C). The reaction mixture was quenched with saturated ammonium chloride solution (150 ml), and the aqueous layer was extracted with diethyl ether (2x100 ml). The combined organic extracts were washed with water (2x100 ml) and was concentrated to give crude carbinol acetal (77).

The carbinol acetal was heated with ortho phosphoric acid (2 ml) at 130°C for 4h. The reaction mixture was cooled and poured over ice cold water. It was extracted with chloroform (3x50 ml), and the chloroform extracts were washed with water (3x100 ml), followed by aqueous sodium bicarbonate solution (1x50 ml). The resulting organic extracts were once again washed with water (1x50 ml) and was concentrated to give crude product which was purified by column chromatography over silicagel using ethylacetate/ hexane (1:10) as eluent. The spectral and analytical data which are in accord with the assigned structure are described below.

1,3-Bis(methylthio)-9-methyl[9H]pyrido[3,4-b]indole (79) was obtained as bright yellow crystals (diethylether / hexane); m.p. 108-109°C; IR (KBr) : Yield : 51%; ν_{max} = 2955, 2923, 2853, 1616 (C=N), 1529 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 2.60 (s, 3H, $SC\underline{H}_3$), 2.69 (s, 3H, $SC\underline{H}_3$), 4.16 (s, 3H, $NC\underline{H}_3$), 7.16-7.76 (m, 3H, $Ar\underline{H}$), 8.10 (d, 1H, *J* =9Hz, $Ar\underline{H}$); m/z: 274 (M^+, 36%); Anal. calculated for $C_{14}H_{14}N_2S_2$ (274.40) : C, 61.28; H, 5.14; N, 10.19. Found: C, 61.21; H, 5.12; N, 10.19%.

Procedure for 3-Cyano-2,5-dimethyl-4-methylthio[5H]pyrido[3,2-b] indole (82):

To a stirred solution of acetonitrile (0.82 g, 0.02 mol) in anhydrous tetrahydrofuran (25 ml), was added butyllithium (10 mmol) under nitrogen atmosphere at -78C and the mixture was further stirred for 45 minutes at the same temperature to give reddish suspension of β-lithioaminocrotonitrile 80. To the suspension of β-lithioaminocrotononitrile, the 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole (11b) (1.0 gm, 0.004 mol) in anhydrous terahydrofuran (25 ml) was added and the mixture was further stirred at this temperature (-78°C) for 0.5 hr. It was warmed up to room temperature and stirring was continued for 14 hrs (monitored by TLC). It was then poured over saturated ammonium chloride solution (150 ml) and the aqueous layer was extracted with chloroform (2x100 ml). The combined organic extracts were washed with water (2x100 ml), dried over anhydrous sodium sulphate and was concentrated to give dark brown residue which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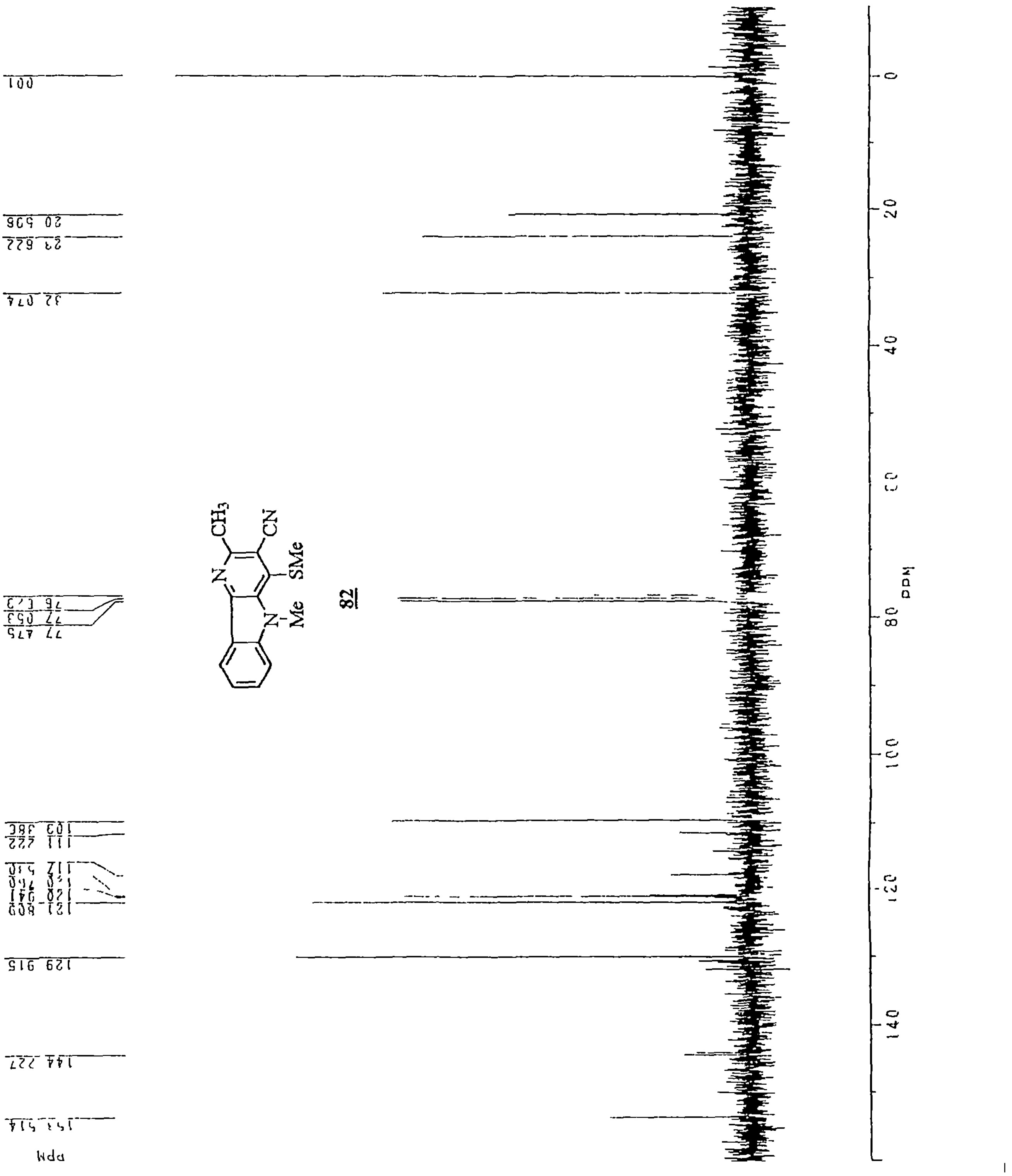
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40
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80
100
120
140
PPM

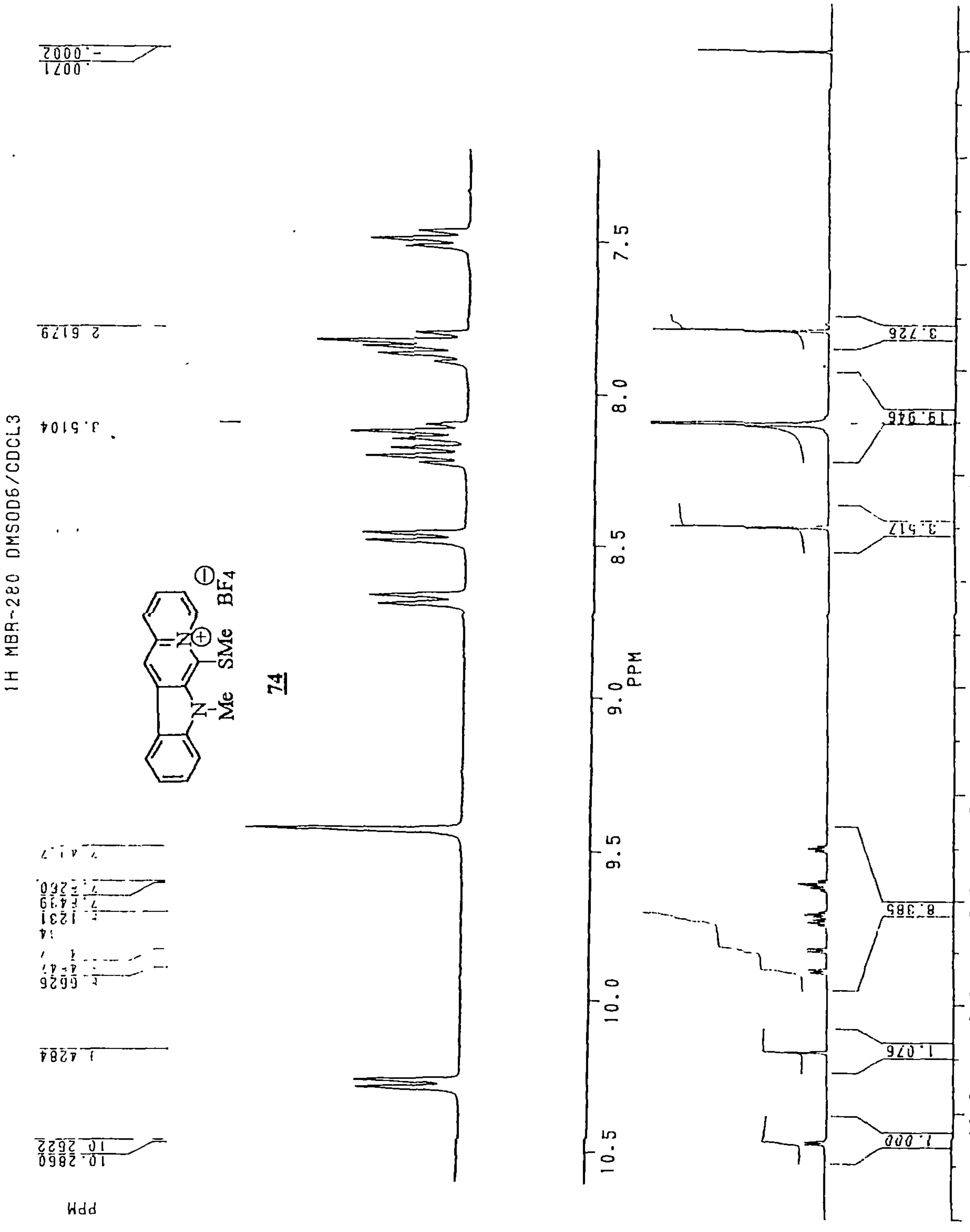
82

was purified by column chromatography over silica gel using ethylacetate / hexane (1:10) as eluent.

3-Cyano-2,5-dimethyl-4-methylthio[5H]pyrido[3,2-b]indole (82) was obtained as light yellow crystals (chloroform / hexane); m.p.227-228°C; yield 79%; IR(KBr): ν_{max}= 2213 (C≡N), 1616 (C=N), 1383, 1218 cm^{-1}; ^{1}H NMR (300.13 MHz, CDCl$_3$) : δ= 2.63 (s, 3H, SC$\underline{H}_3$), 2.89 (s, 3H, C$\underline{H}_3$), 4.26 (s, 3H, NC$\underline{H}_3$), 7.33 (ddd, 1H, *J* = 7.92, 7.12, 1.00 Hz Ar$\underline{H}$), 7.42 (d, 1H, *J* =8.35 Hz, Ar$\underline{H}$), 7.62 (ddd, 1H, *J* = 8.35, 7.12, 1.00 Hz, Ar$\underline{H}$), 8.31 (d, 1H, *J* =7.92 Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, CDCl$_3$): δ = 20.59 (S$\underline{C}$H$_3$), 23.82 ($\underline{C}$H$_3$), 32.07 (N$\underline{C}$H$_3$), 109.38, 111.22, 117.53, 120.94, 121.81, 129.91, 130.49, 131.73, 143.92, 144.23, 153.51; m/z:267 (M$^+$, 100%), 252 (30.6%), 222 (23.3%), 179 (17.9%), 149 (74.5%); Anal. calculated for $C_{15}H_{13}N_3S$ (267.35) ; C, 67.39; H, 4.90; N, 15.72. Found: C, 67.36; H, 4.87; N, 15.67%.

Procedure for 6-methyl-5-methylthio[6H]indolo[3,2-b] quinazilinium tetrafluoroborate (74):

In a three necked flask under dry nitrogen atmosphere n-butyllithium (0.003 mol) was added by drop wise fashion to a well stirred suspension of 2-methylpyridine (1 ml, 0.003 mol) in dry tetrahydrofuran (25 ml), at –10°C , over a period of 5min and was stirred at the same temperature for 1h. The orange coloured suspension of 2-lithiomethylpyridine was added, 2-bis(methylthio)-methylene-2,3-dihydro-1-methyl-3-oxoindole (**11b**) (0.502 gm, 0.002 mol) in dry tetrahydrofuran (50 ml) at –10°C and the reaction mixture was stirred at the same temperature for 2.5h. (monitored by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7.0
8.0
9.0
10.0

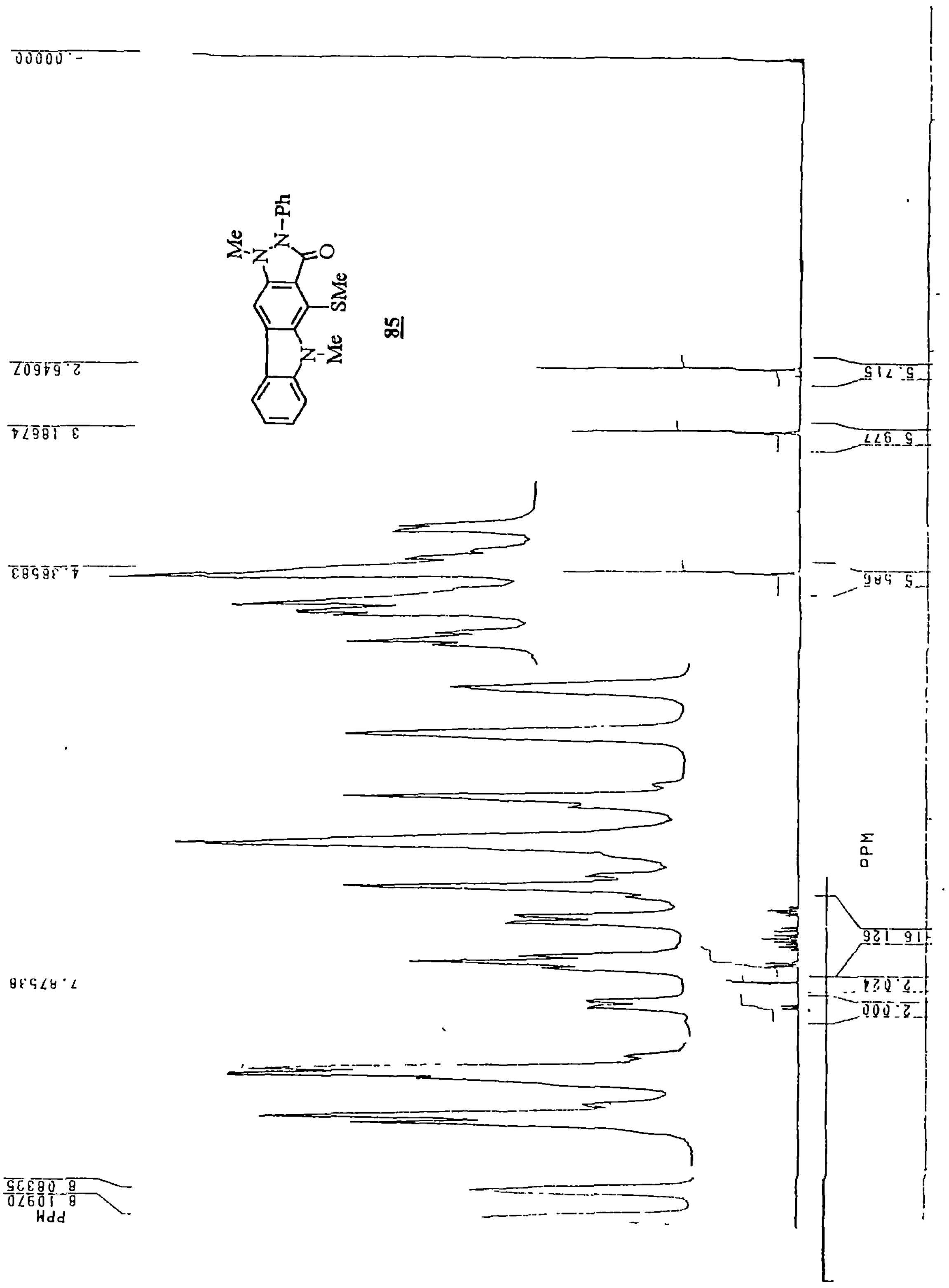
T.L.C). The reaction mixture was stirred at room temperature for 1h and was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with chloroform (3x50 ml) and the combined organic extracts were washed with water (3x50 ml). The organic layer was concentrated to give the crude carbinol (73). The carbinol obtained was dissolved in dry benzene and was refluxed with borontrifluoride etherate (2 ml) , at 90°C for 3h. The reaction mixture was cooled and poured over saturated sodium bicarbonate solution. Bright yellow solid obtained was filtered and was washed with water (100 ml). The solid was dried and crystallised from acetic acid as bright yellow needles, which was characterised as (74). The spectral and analytical data which are in accord with the assigned structure are described below.

6-Methyl-5-methylthio[6H]indolo[3,2-b]quinozilinium tetrafluoroborate (74) was obtained as bright yellow needles (acetic acid); m.p.275-278°C (dec.); yield: 96%; IR (KBr): ν_{max} = 1061cm^{-1} (br, tetrafluoroborate); ^{1}H NMR (300.13 MHz, DMSO/D_6/$CDCl_3$): δ= 2.62 (s, 3H, SC$\underline{H}_3$), 4.49 (s, 3H, NC$\underline{H}_3$), 7.49 (dd, 1H, *J* = 7.10, 7.00 Hz, Ar$\underline{H}$), 7.79-7.86 (m, 2H, Ar$\underline{H}$), 8.13 (ddd, 1H, *J* =7.14, 7.10, 1.7Hz, Ar$\underline{H}$), 8.18 (dd, 1H, *J* =8.37, 7.10Hz, Ar$\underline{H}$), 8.47 (d, 1H, *J* =7.80 Hz, Ar$\underline{H}$), 8.68 (d, 1H, *J* = 8.37 Hz, Ar$\underline{H}$), 9.42 (s, 1H, Ar$\underline{H}$), 10.27 (d, 1H, *J* = 7.14Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, DMSO/D_6/$CDCl_3$): δ = 18.11 (S$\underline{C}H_3$), 33.25 (N$\underline{C}H_3$), 110.85, 117.97, 118.79, 122.22, 123.15, 123.29, 128.90, 131.23, 132.50, 132.72, 138.37, 140.11, 146.78, 180.23, 209.61; m/z : 365 (M^+-1, 2.1%), 304 (15.4%), 276 (97%), 244 (100%), 235 (43%), 228 (13.8%), 187 (13.5%), 122 (43%); Anal. calculated for $C_{17}H_{15}N_2SBF_4$ (366.18) : C,55.76; H,4.13; N,7.61. Found: 55.71;H, 4.10; N,7.61%.

Preparation of 1,2-Dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3H-pyrazolo[4,3-b]carbazole (85) :

Under dry and inert atmosphere, a chilled (0°C) solution of 1.97 ml (14 mmol) of diisopropyl amine in 10 ml of dry tetrahydrofuran was added 10 mmol of n-butyl lithium in ether. The resulting solution of lithium diisopropylamide (10 mmol) at -78°C was added a solution of 0.9g (5 mmol) of antipyrine in 25 ml dry tetrahydrofuran. The reaction mixture was stirred at the same temperature for 45 min. To the resulting enolate solution at -78°C was added 4 mmol of 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole **11b** in 25 ml dry tetrahydrofuran dropwise and was stirred at the same temperature for 45 min. It was stirred at ambient temperature, stirred for 8h (monitored by tlc), and quenched with aqueous saturated ammonium chloride solution (100 ml). The aqueous layer was extracted with chloroform (3x25 ml). The organic extracts were washed with water (2x50 ml), dried over anhydrous sodium sulphate, and was concentrated to give a crude carbinol (γ-1,2-adduct) in quantitative yields.

To a solution of crude carbinol obtained in dry benzene (30 ml), boron trifluride-etherate (3 ml) was added and the reaction mixture was stirred under reflux for 2h (monitored by tlc). The reaction mixture was cooled to room temperature and poured over aqueous saturated sodium bicarbonate solution (100 ml). The aqueous layer was extracted with chloroform (3x25 ml). The combined organic extracts were washed with water (2x50 ml), dried over anhydrous sodium sulphate and concentrated to give the crude cycloaromatized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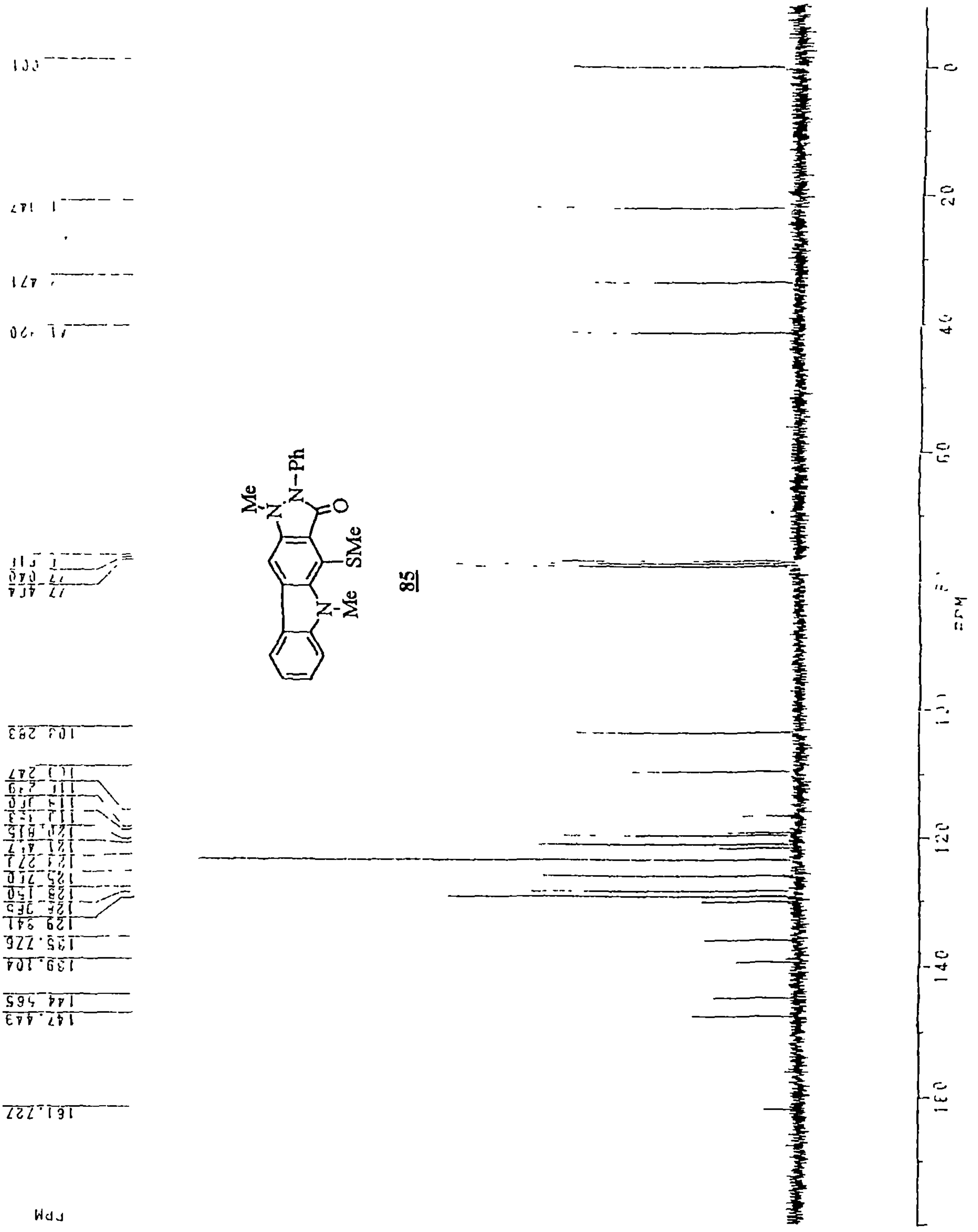
2.021
2.000
PPM
Me
N
N-Ph
O
SMe
N
Me
85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PPM
0
20
40
60
100
120
140
160
Me
N
N–Ph
O
SMe
N
Me

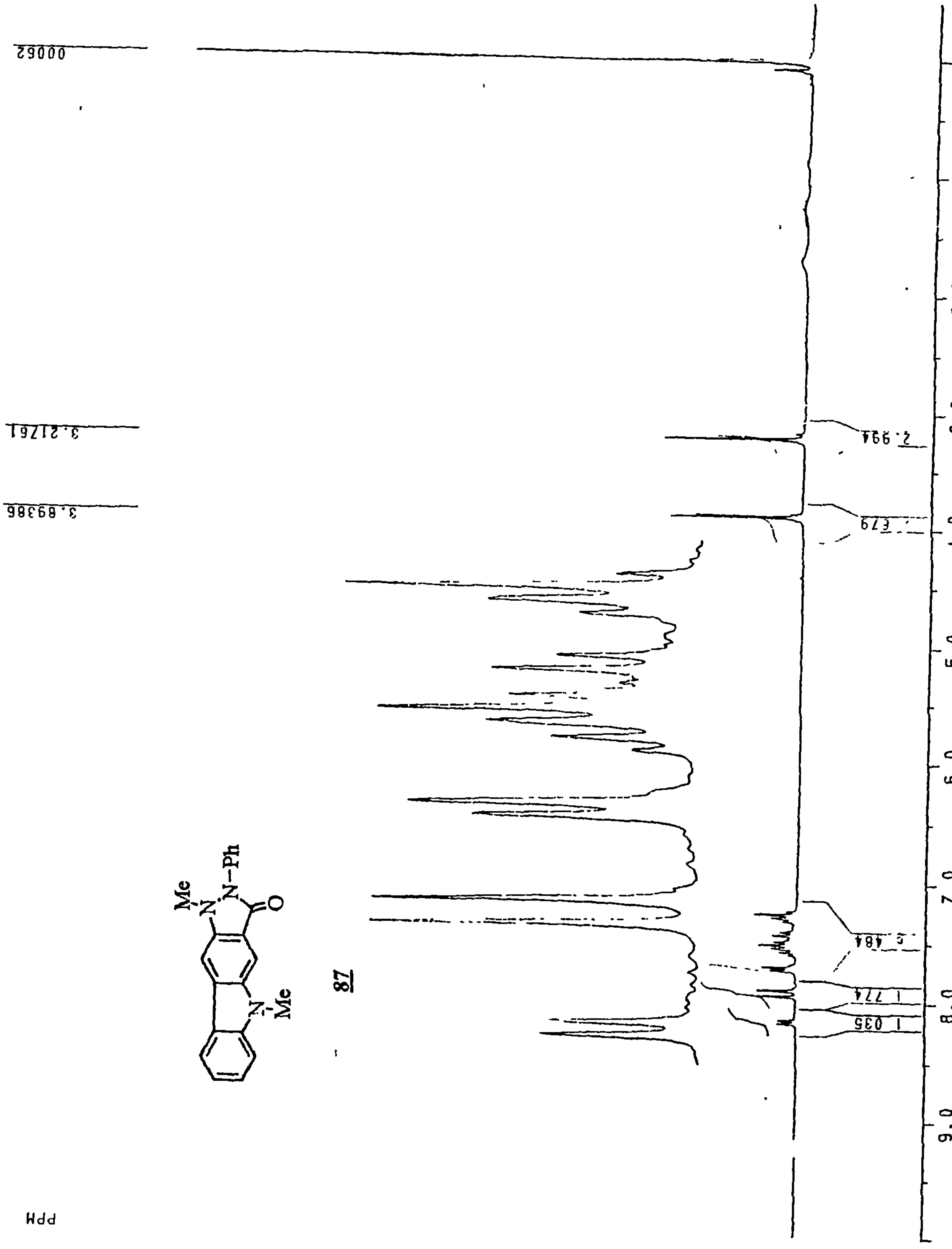
85

product which was chromatographed by passing through silica gel column using ethylacetate-hexane (1:4) as eluent.

1,2-Dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3H-pyrazol o[4,3-b] carbazole (85) was obtained as yellow crystals (acetone / hexane); m.p= 198-199°C; yield: 83%; IR (KBr) : ν_{max} = 2822, 1667 (C=O), 1490, 1471, 1319 cm^{-1}; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ= 2.65 (s, 3H, $SC\underline{H}_3$), 3.19 (s, 3H, $NC\underline{H}_3$), 4.39 (s, 3H, $NC\underline{H}_3$), 7.22-7.30 (m, 2H, Ar$\underline{H}$), 7.42 (d, 1H, J =8.34 Hz, Ar$\underline{H}$), 7.48 (d, 1H, J =8.4Hz, Ar$\underline{H}$), 7.51 (d, 1H, J =7.2Hz, Ar$\underline{H}$); 7.57 (ddd, 1H, J =8.34, 7.2, 1.2Hz, Ar$\underline{H}$), 7.71 (dd, with fine splitting, 1H, J =8.4, 1.2Hz, Ar$\underline{H}$), 7.87 (s, 1H, Ar$\underline{H}$), 8.09 (d, 1H, J =7.73 Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ = 21.94 ($S\underline{C}H_3$), 33.47 ($N\underline{C}H_3$), 41.32 ($N\underline{C}H_3$), 103.28, 109.247, 116.24, 118.96, 119.38, 120.82, 121.46, 123.28, 125.76, 128.15, 128.98, 129.84, 135.78, 139.10, 144.59, 147.45, 161.73 (C=O); m/z: 373 (M^{+}, 100%); Anal. calculated for $C_{22}H_{19}N_3OS$ (373.45) : C, 70.75; H, 5.13; N, 11.25. Found:C, 70.71; H, 5.10; N, 11.22%.

Procedure for the preparation of 1,2-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-3H-pyrazolo[4,3-b] carbazole (87) :

To a stirred solution of 1,2-Dihydro-1,5-dimethyl-4-methylthio-3-oxo-2-phenyl-3H-pyrazolo[4,3-b] carbazole (85) (0.025 mol) in ethanol (25 ml) was added raney nickel (W4, 3 times by weight) and the mixture was stirred at ambient temperature for 6 hrs (monitored by tlc). The reaction mixture was filtered through G-3 cintered funnel and the residue was washed with ethanol (3x10 ml). The bulk of the ethanol was distilled off and chloroform (20 ml) was added. The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4.0
5.0
6.0
7.0
8.0
9.0
PPM
Me
N
N-Ph
O
N
Me

87

aqueous layer was extracted with chloroform (2x50 ml) and the combined chloroform extracts were washed with (2x25ml), dried over sodium sulphate and was concentrated to give crude product. Analytically pure compound was obtained by passing through a short length silicagel column using ethylacetate/hexane (2:3) as eluent.

1,2-Dihydro-1,5-dimethyl-3-oxo-2-phenyl-3H-pyrazolo[4,3-b] carbazole (87) was obtained as light yellow crystals (chloroform / hexane); yield: 93% ;m.p.276-277°C; IR (KBr): ν_{max} = 1670 (C=O), 1492, 1474 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 3.21 (s, 3H, $NC\underline{H}_3$), 3.89 (s, 3H, $NC\underline{H}_3$), 7.23-7.30 (m, 2H, Ar$\underline{H}$), 7.41 (d, 1H, *J* = 8.36 Hz, Ar$\underline{H}$), 7.48-7.58 (m, 3H, Ar$\underline{H}$), 7.71 (d, 2H, *J* =7.83 Hz, Ar$\underline{H}$); 7.89 (s, 1H, Ar$\underline{H}$), 7.93 (s, 1H, Ar$\underline{H}$), 8.15 (d, 1H, *J* =7.92 Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz,$CDCl_3$) : δ= 29.42 ($N\underline{C}H_3$), 41.55 ($N\underline{C}H_3$), 102.64, 103.30, 108.78, 118.20, 118.95, 121.15, 121.74, 123.35, 125.91, 127.79, 128.58, 129.11, 135.71, 138.61, 143.19, 146.05, 162.89 (C=O); Anal. calculated for $C_{21}H_{17}N_3OS$ (327.37) : C, 77.04; H, 5.24; N, 12.83. Found :C, 77.01; H, 5.21; N, 12.62%.

Preparation of 2-Amino-5-methyl-4-methoxypyrimido[5,4-b]indole (76) : Guanidine nitrate (6 mmol) is added to a stirred suspension of methanolic sodium hydroxide solution (prepared from 20 ml methanol and 1.6 g of sodium hydroxide in 10 ml of water) and the reaction mixture is stirred for 30 minutes. A solution of the 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole 11b (6 mmol) in methanol (10 ml) is added to the reaction mixture. The reaction mixture is stirred at room temperature for 7hours and was refluxed for one hour (monitored by TLC). Methanol was removed under vacuo and ice-cold water (15 ml) is added to the residue. The crude products, thus obtained, are filtered at pump and are further purified by column chromatography over silica gel using hexane/ethyl acetate (19:1) as eluent. The structure of <u>76</u> was fully established from its spectral and analytical data which is given below.

2-Amino-5-methyl-4-methoxypyrimido[5,4-b]indole (<u>76</u>) was obtained as pale yellow crystals (chloroform / hexane); m.p.213-215°C; yield: 58%; IR (KBr) : ν_{max} = 3333 (br, NH), 1754 (C=N), 1706 (C=N), 1612, 1375, 1199, 1121 cm^{-1}; ^1H NMR (300.13 MHz, $CDCl_3$): δ = 3.23 (s, 3H, $NC\underline{H}_3$), 3.73 (s, 3H, $OC\underline{H}_3$), 4.48 (brs, 2H, $N\underline{H}_2$, exchangeable with D_2O), 6.88 (d, 1H, *J* =7.85Hz, Ar<u>H</u>), 7.10 (ddd, 1H, *J* =7.8, 7.4, 1.2 Hz, Ar<u>H</u>), 7.30 (d, with fine splitting, 1H, *J* = 7.4Hz, Ar<u>H</u>); 7.39 (ddd, 1H, *J* =7.85 Hz, 7.80, 1.20 Hz, Ar<u>H</u>); ^{13}C NMR (75.46 MHz, $CDCl_3$) : δ = 26.67 ($N\underline{C}H_3$), 53.87 ($O\underline{C}H_3$), 108.91, 112.84, 123.46, 123.92, 126.76, 130.83, 144.69, 166.81, 170.41, 207.53 ; Anal. calculated for $C_{12}H_{12}N_4O$ (228.26) ; C, 63.14; H, 5.30; N, 24.55. Found:C, 63.07; H, 5.21; N, 24.51%.

Preparation of 1,2-Dihydro-1-methyl-3-oxo-2-{[(1',3'-dimethyluracil-6'yl)methyl] methylthio- methylene}indole (<u>93</u>) :

To a cooled (-40°C) solution of preformed LDA (0.03 mol) [prepared by the addition of n-butyllithium (0.03 mol) to an ice cooled solution of diisopropylamine (0.035 mol) in tetrahydrofuran (25 ml) and stirring for 15 min.] under nitrogen atmosphere was added 1,3,6-

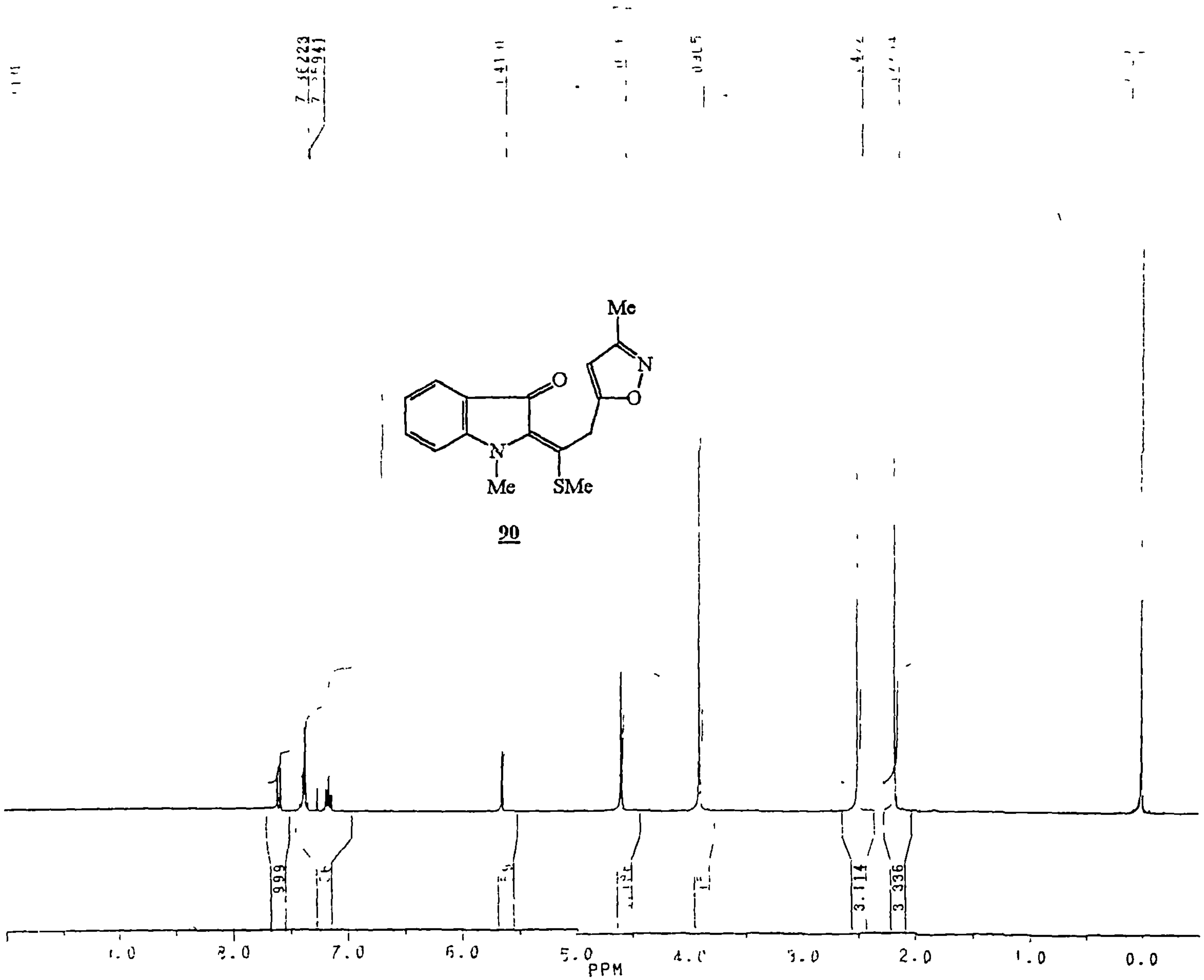
trimethyluracil (0.03 mol) in dry tetrahydrofuran (50 ml) slowly dropwise through syringe and the reaction mixture was stirred for 45 min. The 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole **11b** (0.02 mol) in dry tetrahydrofuran (25 ml) was then added (at −40°C) slowly and the reaction mixture was brought to ambient temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with chloroform (2x100 ml). The organic extracts were washed with water (2x50 ml), dried over anhydrous sodium sulphate, concentrated to give the crude product which was crystallised from chloroform/hexane.

1,2-Dihydro-1-methyl-3-oxo-2-{[(1',3'-dimethyluracil-6'yl)methyl] methylthio- methylene}indole (93) was obtained as bright orange crystals (chloroform / hexane) ; m.p.186-187°C; yield: 63%; IR (KBr) : ν_{max} = 1695 (C=O), 1657 (C=O), 1615 (C=O), 1534, 1463, 1437, 1320 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ = 2.46 (s, 3H, $SC\underline{H}_3$), 3.43 (s, 3H, $NC\underline{H}_3$), 3.66 (s, 3H, $NC\underline{H}_3$), 3.73 (s, 3H, $NC\underline{H}_3$), 4.50 (s, 2H, $C\underline{H}_2$), 5.83 (s, 1H, $=C\underline{H}$), 6.96-7.30 (m, 2H, $Ar\underline{H}$); 7.60-7.93 (m, 2H, $Ar\underline{H}$); Anal. calculated for $C_{18}H_{19}N_3O_3S$ (357.414) ; C, 60.48; H, 5.36; N, 11.76. Found:C, 60.42; H, 5.30; N, 11.72%.

Preparation of 1,2-Dihydro-1-methyl-3-oxo-2-{[(3'-methylisaxazol-5'-yl)methyl] methylthiomethylene}indole (90) :

To a cooled (-78°C) solution of preformed LDA (0.02 mol) [prepared by the addition of n-butyllithium (0.02 mol) to an ice cooled solution of diisopropylamine (0.025 mol) in tetrahydrofuran (25 ml) and stirring for 15 min.] under nitrogen atmosphere was added 3,5-dimethylisoxazole (0.02 mol) in dry tetrahydrofuran (20 ml) slowly dropwise through syringe and the reaction mixture was stirred for 45 min at the same temperature. The 2-bis(methylthio)methylene-2,3-dihydro-1-methyl-3-oxoindole **11b** in dry tetrahydrofuran (25 ml) was then added (at −78°C) slowly and the reaction mixture was brought to ambient temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution. The aqueous layer was extracted with chloroform (2x50 ml). The combined organic extracts were washed with water (2x50 ml), dried over anhydrous sodium sulphate, concentrated to give the crude product which was purified by column chromatography to yield the analytically pure product , for which spectral and analytical data is given below.

1,2-Dihydro-1-methyl-3-oxo-2-{[(3'-methylisaxazol-5'-yl)methyl] methylthio-methylene}indole (90) was obtained as a light orange crystals (acetone / hexane); m.p.106-108°C; IR (KBr) : ν_{max} = 1635, 1601, 1206 cm^{-1}; ^{1}H NMR (300.13 MHz, CDCl$_3$): δ = 2.18 (s, 3H, C$\underline{H}_3$), 2.50 (s, 3H, SC$\underline{H}_3$), 3.91 (s, 3H, NC$\underline{H}_3$), 4.59 (s, 2H, C$\underline{H}_2$), 5.64 (s, 1H, =C$\underline{H}$), 7.12-7.18 (m, 1H, Ar$\underline{H}$), 7.35-7.38 (m, 2H, Ar$\underline{H}$); 7.59 (d, withfine splitting, 1H, *J* =8.10 Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, CDCl$_3$): δ =11.42 ($\underline{C}$H$_3$), 12.27 (C$\underline{H}_2$), 23.62 (S$\underline{C}$H$_3$), 32.04



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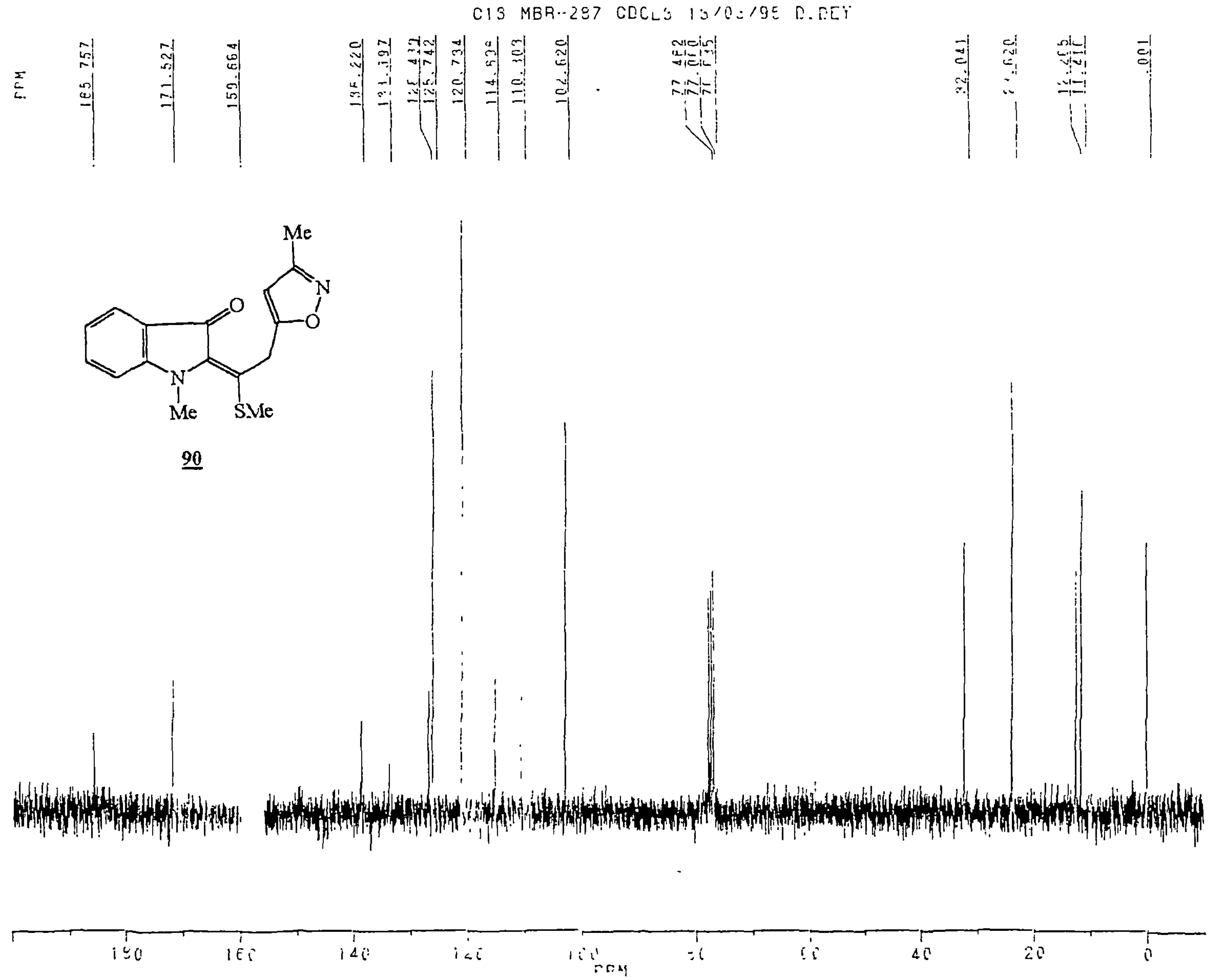
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40
20
0
PPM

90

(NC$\underline{H}_3$), 102.62, 110.30, 114.90, 120.74, 125.74, 126.44, 133.40, 138.22, 159.86, 171.53 (C=N), 185.76 (C=O); Anal. calculated for $C_{16}H_{16}N_2O_2S$ (300.374) : C, 63.97; H, 5.37; N, 9.33. Found:C, 63.92; H, 5.29; N, 9.27%.

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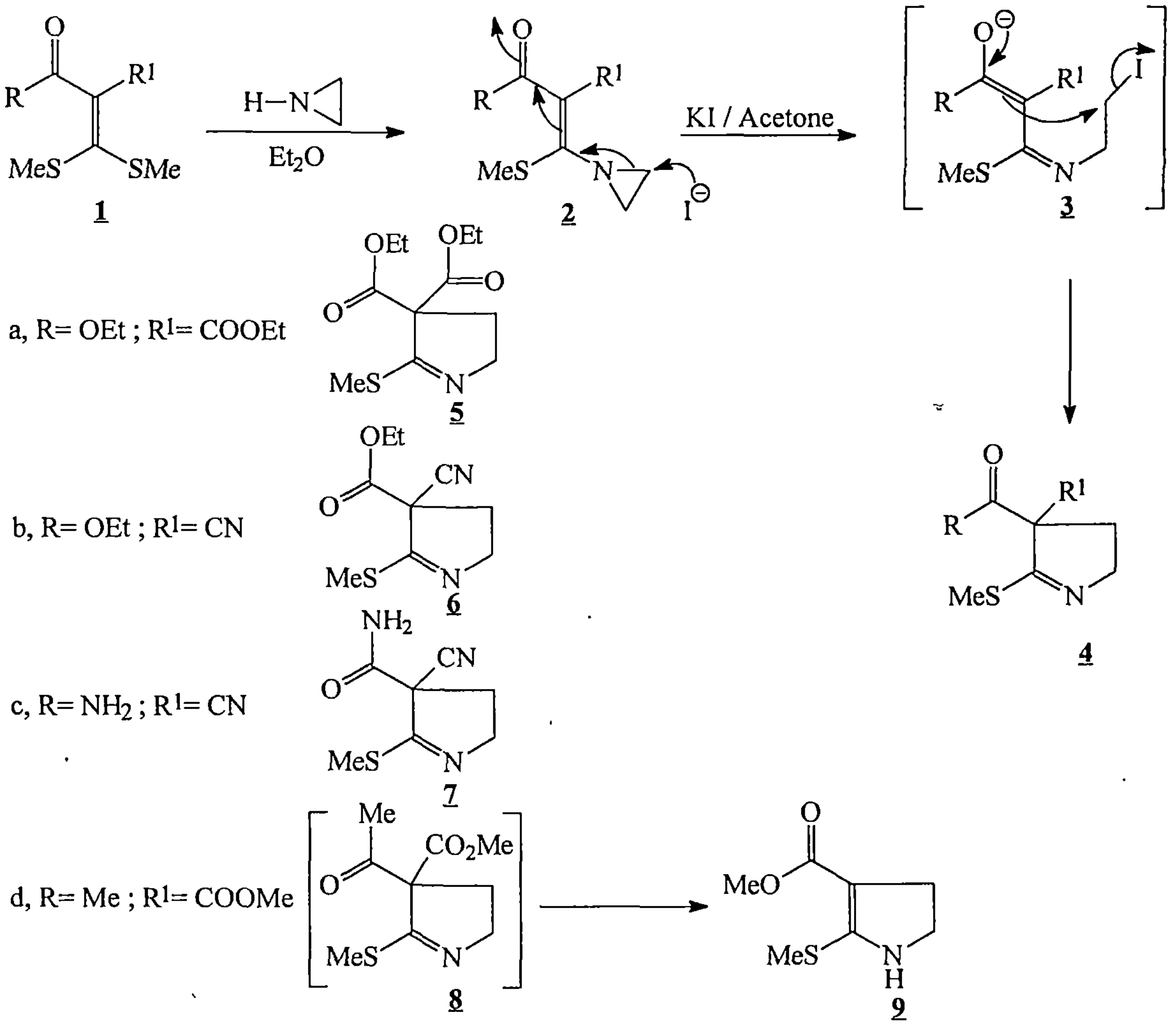
CHAPTER IV

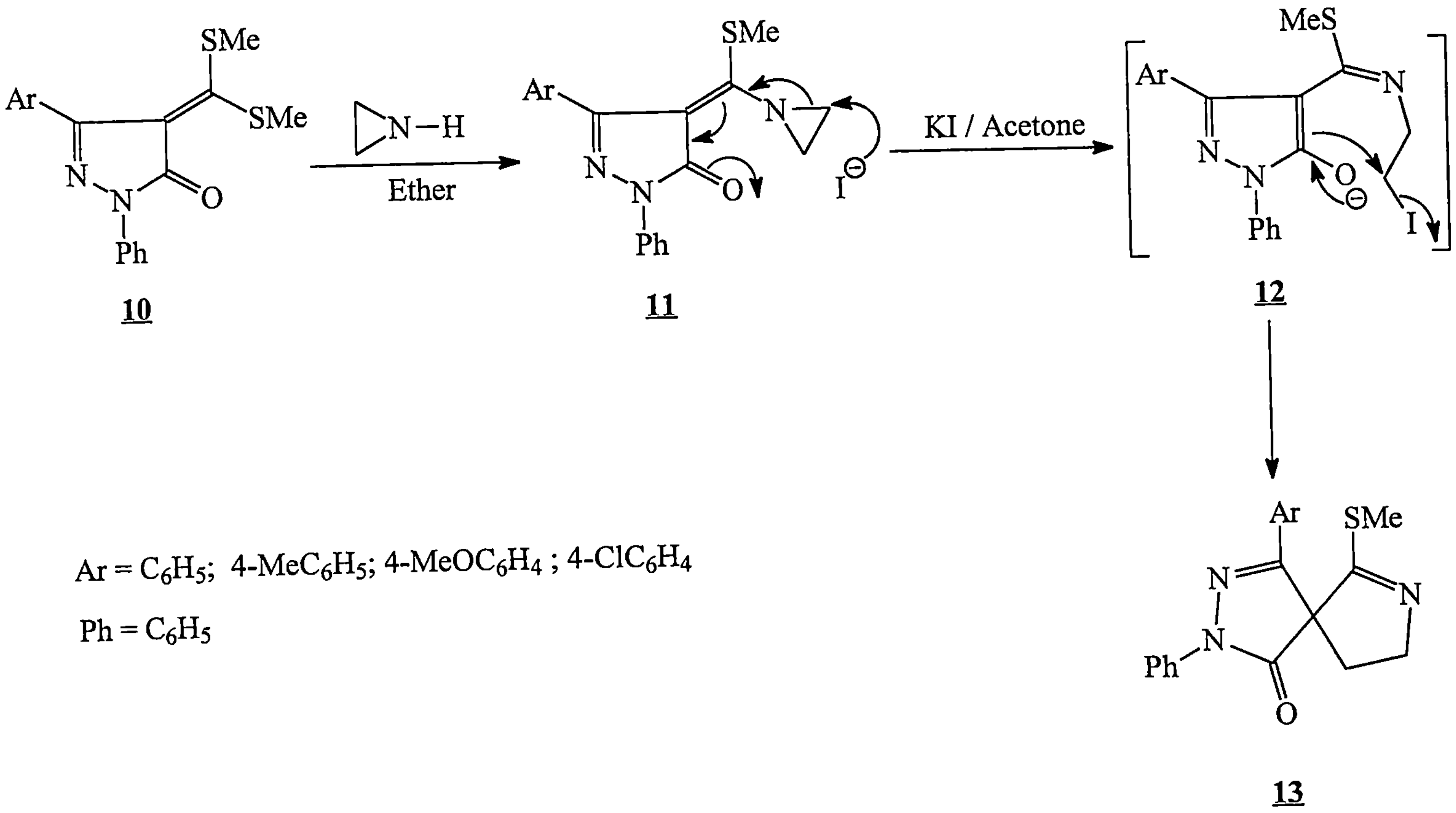
Reaction of Aziridine with α- oxoketene dithioacetals : An Efficient Synthesis of 3-Aroyl-2-methylthiopyrrolines And Related Spiro Compounds

IV. 1. Introduction :

The α-oxoketene dithioacetals[1] are known to undergo displacement reactions of one of the methylthio group by different nucleophiles. The nucleophiles generally belong to amines[2], carbon[3] and oxygen[4] compounds. The displacement of methylthio group by any one of these nucleophiles generally results in the formation of the corresponding α-oxoketene-N,S-acetals, thiolesters and the O,S-acetals. All these three types of displacement reactions have been extensively studied in recent years. Among these N,S-acetals play an important role as 1.3-dielectrophillic synthetic intermediates for the synthesis of a large number of amino heterocycles[5,6,7]. When these N,S-acetals react with binucleophiles the reaction generally proceeds with ring closer followed by elimination of methylthio group to yield the corresponding amino


H–N
Et$_2$O
KI / Acetone
1
2
3
4
a, R= OEt ; R^1= COOEt
5
b, R= OEt ; R^1= CN
6
c, R= NH$_2$; R^1= CN
7
d, R= Me ; R^1= COOMe
8
9
MeS
SMe
OEt
CN
NH$_2$
CO$_2$Me
MeO

Scheme 1



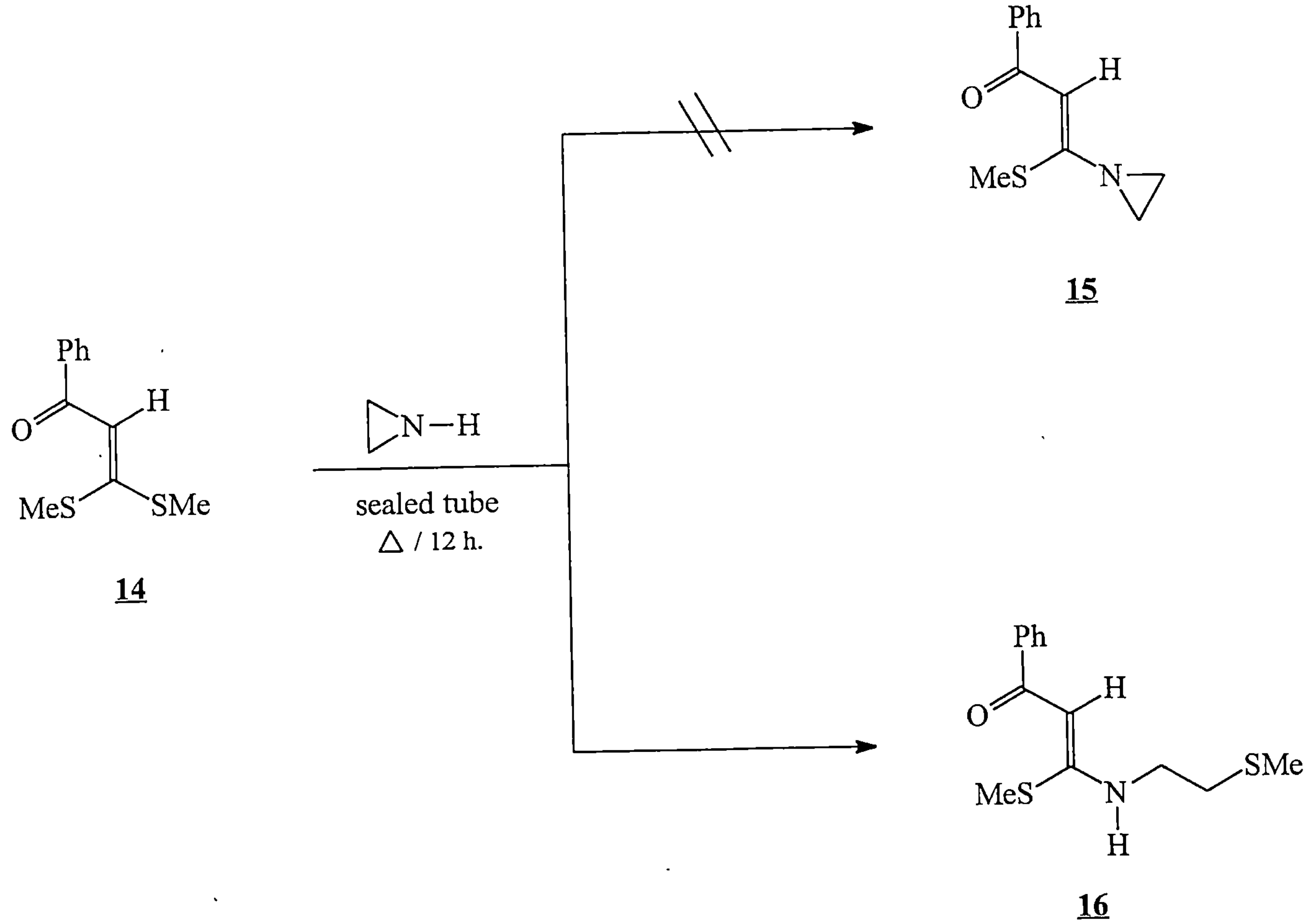
Ar = C_6H_5; 4-MeC_6H_5; 4-MeOC_6H_4 ; 4-ClC_6H_4

Ph = C_6H_5

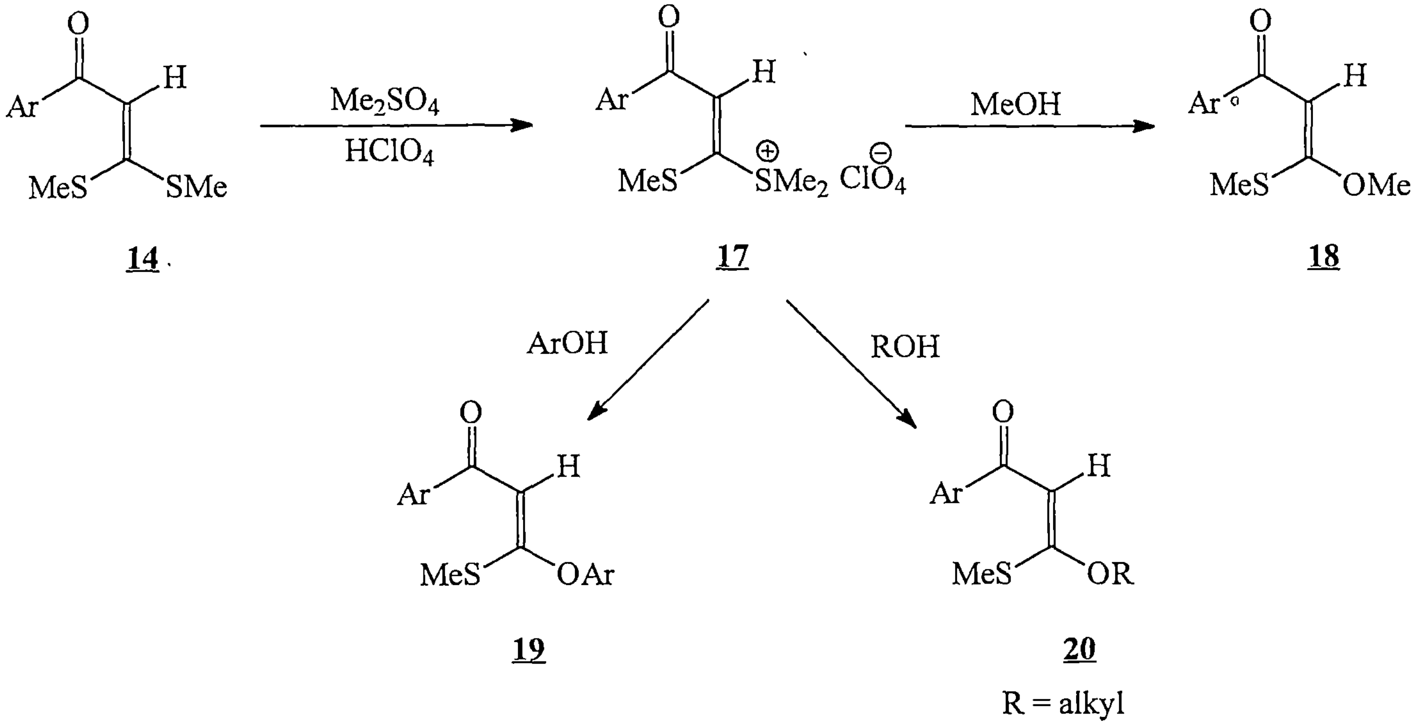
Scheme 2

heterocycles[8,9,10,11]. The N,S-acetals[2] have been generally prepared by reacting amines with α-oxoketene dithioacetals. When the α-oxoketene dithioacetal has additional electron withdrawing group at α-position, the displacement of methylthio group with one equivalent of amine to yield the corresponding N,S-acetal is very facile[12]. However, more drastic reaction conditions are required when α-oxoketene dithioacetal with hydrogen at α-position reacted with amines. Generally in these cases excess amine is employed and the corresponding N,N-acetals[13] are the main products in these reactions. This became one of the serious limitations of amine reactions with α-oxoketene dithioacetals. The reaction of more labile aziridine with ketene dithioacetals having an additional electron withdrawing group **1a-d** (Scheme 1) to yield corresponding N-vinylaziridines of general formula **2** in excellent yields, have been reported from this laboratory[14]. The N-vinylaziridines thus formed were then neatly rearranged in the presence of potassium iodide and acetone to yield the corresponding 2-methylthio-3,3-disubstituted pyrrolines **4** in excellent yields. Different pyrrolines **5**, **6** and **7** were prepared following this method. The one obtained from methylacetoacetate mercaptal **8** underwent acyl group cleavage to yield the corresponding 2-methylthio-3-carbomethoxy pyrroline **9** as the sole product.

α-oxoketene dithioacetal **10** derived from pyrazolone also behaved like activated dithioacetal described in scheme 1. Thus the N-vinylaziridine **11** was obtained in quantitative yield by merely stirring aziridine with **10** in diethylether. The intermediate without further purification was treated with potassium iodide in acetone and the corresponding spiro compound 1-aryl-3-phenyl-6-methylthio-2,3,7-triazaspiro [4,4] non-6-en-4-one **13** formed in excellent yields (Scheme 2). However, singly activated S,S-acetal **14** under the similar reaction conditions with aziridine did not give **15** at room temperature, when **14** heated with aziridine in sealed tube the product obtained was characterised as 3-methylthio-3-(2-methylthioethylamino)-1-aryl-2-propen-1-one **16** but not N-vinylaziridine **15**.


Ph
O
H
MeS
SMe
14
N—H
sealed tube
△ / 12 h.
Ph
O
H
MeS
N
15
Ph
O
H
MeS
N
H
SMe
16

Scheme 3



Scheme 4

Apparently, the formation of **16** was explained by the attack of the nucleophile, methyl mercaptan formed *in situ,* on the N-vinylaziridine. Therefore it was considered difficult to react aziridines with singly activated α-oxoketene dithioacetals retaining the aziridine ring without being ruptured by thiomethyl group (Scheme 3).

Subsequently Schroth[15] and Co-workers have demonstrated that singly activated α-oxoketene dithioacetal **14** can be quarternized by treating them with dimethyl sulphate to yield the corresponding dimethylsulphonium perchlorates **17** in excellent yields, which were reacted with methanol to yield the corresponding Z-O,S-acetals **18**, in 61% yield along with 13% of **14** through demethylation. This reaction was successfully employed in this laboratory to prepare a number of aryloxy and alkoxy thio esters **19** and **20** respectively in excellent yields[16]. The O,S-acetals thus obtained were assigned exclusive Z-configuration which were shown to be excellent precursors[17] for the synthesis of alkoxy and aryloxy thiophenes under the Simmons-Smith reaction conditions.

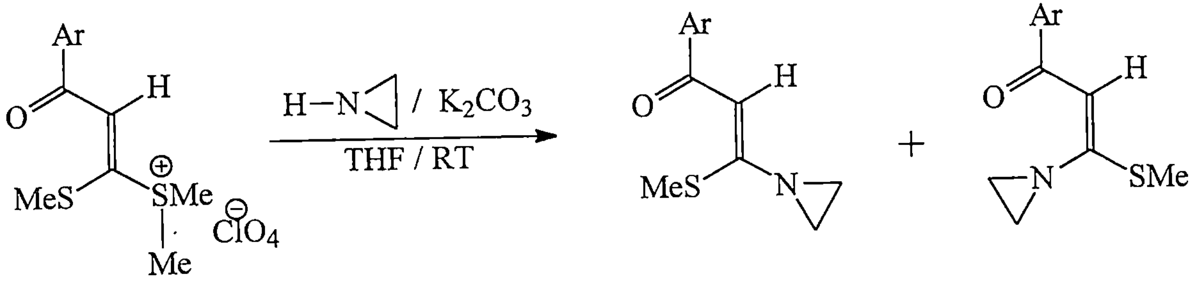
On the experience gained for these facile reactions of alcohols and phenols on **17** it was contemplated that the perchlorate salts **17** could well be excellent precursors for amines to yield the corresponding N,S-acetals under very mild reaction conditions (Scheme 4).

It was therefore decided to study the reactivity of aziridine with various quaternary salts and other ketene dithioacetals. The results are presented in the following section.

IV. 2. Results and Discussion:

Present investigation:

The dimethyl sulphonium perchlorate **17a** when reacted with one equivalent of aziridine at room temperature , corresponding 3-(N-aziridino)-3-methylthio-1-phenyl-2-propene-1-ones (**21a+22a**) were obtained in 61% yield as a mixture of Z- and E-configuration. The structure was established on the basis of its analytical and spectral data. It was analysed for molecular formula $C_{12}H_{13}NO$ with a molecular weight 219.29. The molecular weight was confirmed by its mass spectrum, which exhibited molecular ion peak at m/z: 263 (M^+). In its IR spectrum (KBr) , the carbonyl band was observed at 1606 cm^{-1} and the other major bands at 1495, 1479, 1463, 1432, 1424 , 1150 cm^{-1} . The structure was further confirmed from its ^1H NMR (300.13 MHz , $CDCl_3$) spectrum. The broad singlet at δ2.26 integrated for four protons was assigned for the aziridine ring protons. The singlet integrating for three protons was assigned for the thiomethyl protons. The one proton singlet at δ 6.57 was assigned for the vinylic proton. The aromatic protons appeared as three proton multiplet and two proton doublet were in agreement with the assigned structure , which are described in the experimental section. The structure was further supported by its ^{13}C NMR spectra, which are described in the experimental section. ^{13}C NMR (chart 1) , displays the correct assignment of the configuration to the vinylaziridines **21a** and **22a**. All the spectral data for these compounds were found to be in agreement with their assigned structures described in the experimental section. The reactions of **17b** and **17c** similarly yielded the corresponding **21b** / **22b**, and **21c** / **22c** respectively as a mixture of two configurations of which Z configurations was the larger. The other analytical spectral data of the mixtures were in accord with the assigned structures which are described in the experimental section.



17 **21** **22**

17,21,22 **a**, Ar = C_6H_5
b, Ar = 4-$MeOC_6H_4$
c, Ar = 4-ClC_6H_4

Scheme 5

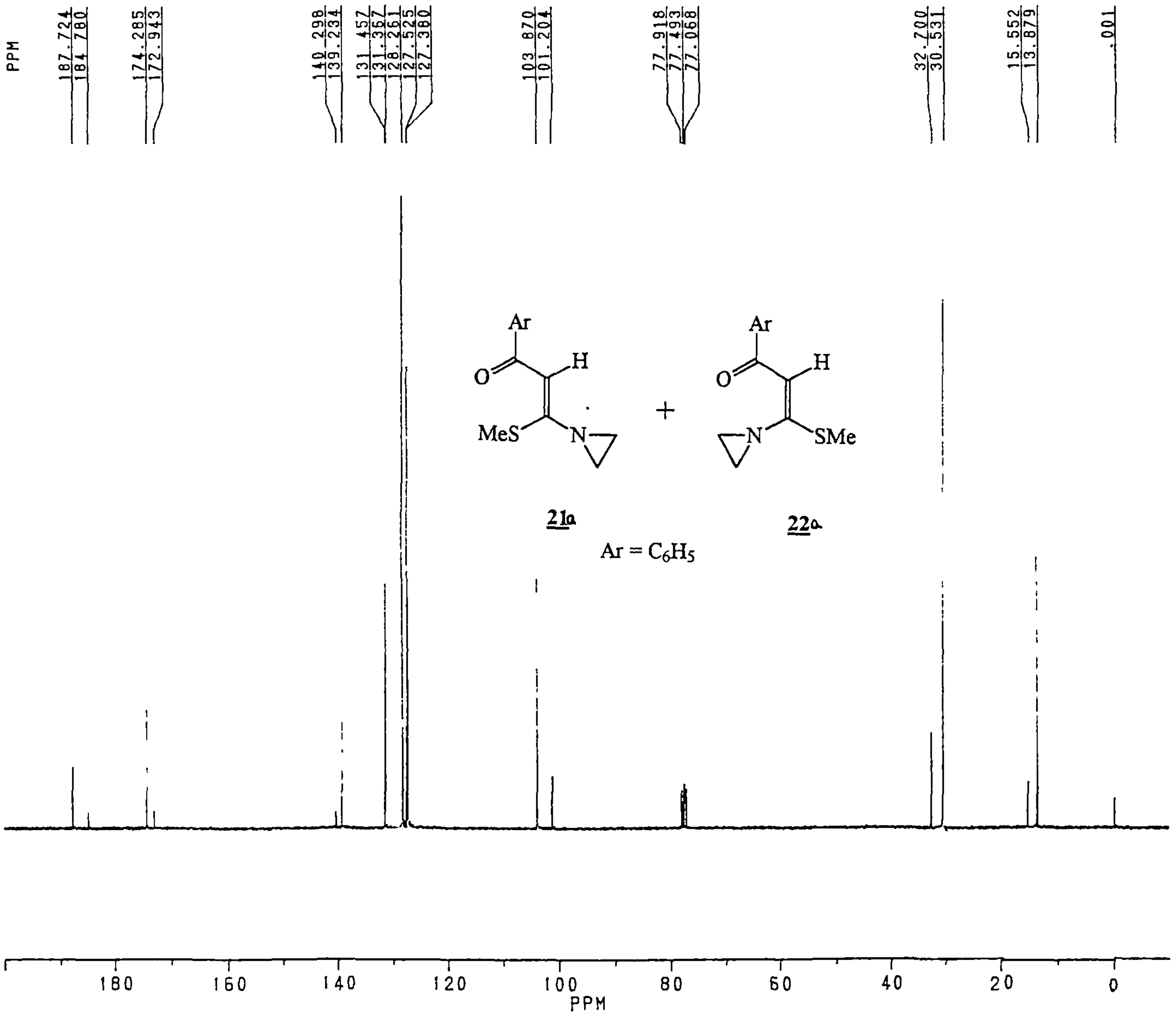
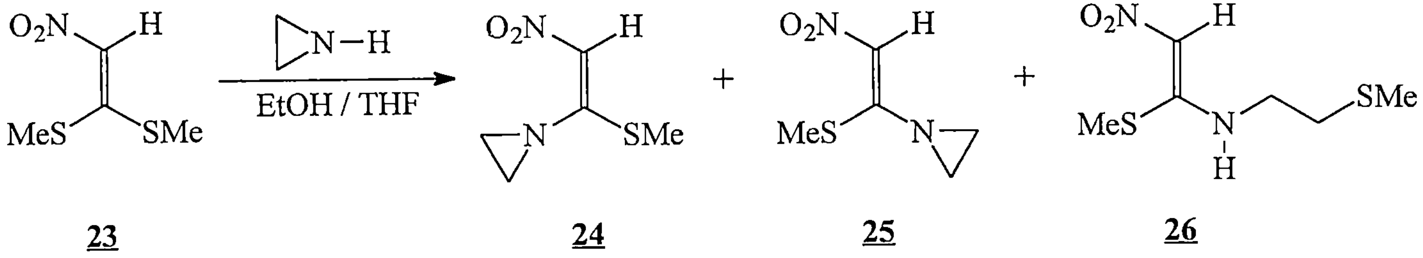
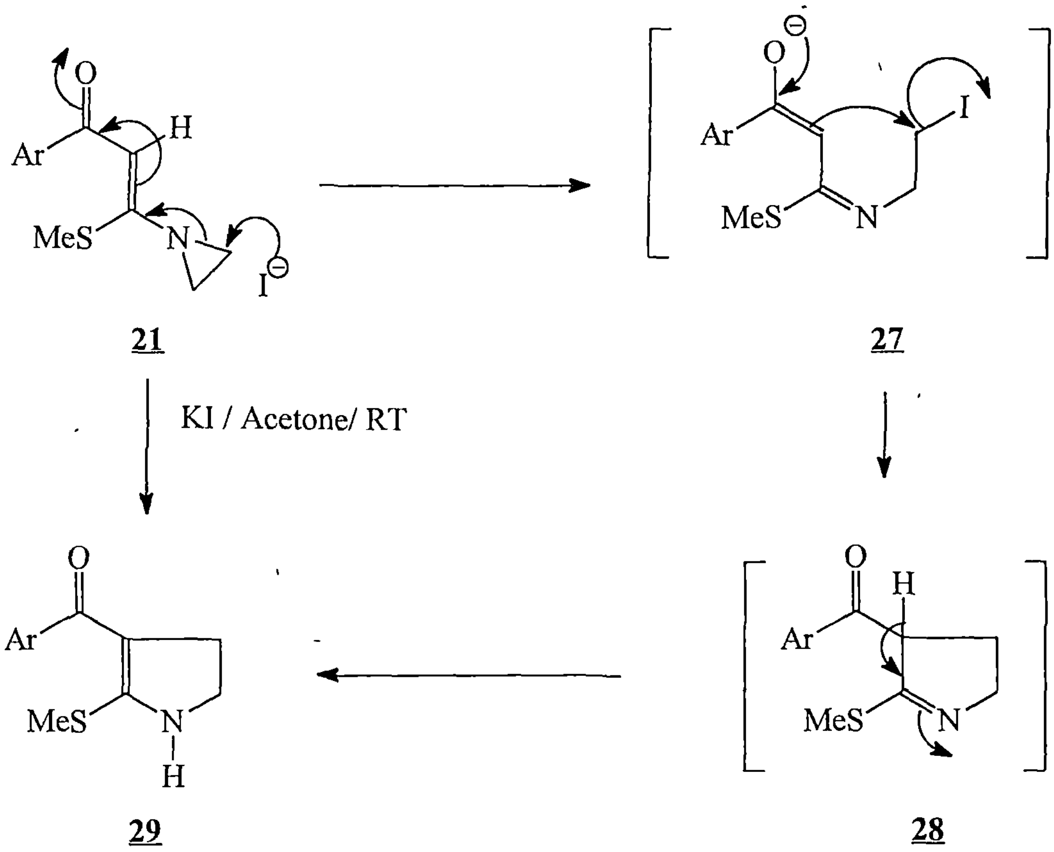

PPM
187.724
184.780
174.285
172.943
140.298
139.234
131.457
131.367
128.261
127.525
127.380
103.870
101.204
77.918
77.493
77.068
32.700
30.531
15.552
13.879
.001
Ar
O
H
MeS
N
+
SMe
21a
22a
Ar = C$_6$H$_5$
180
160
140
120
100
80
60
40
20
0
PPM

CHART -I



Scheme 6



21, 27, 28, 29 a Ar = C_6H_5
b Ar = 4-$MeOC_6H_4$
c Ar = 4-ClC_6H_4

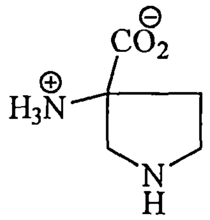
Scheme 7

The nitroketene S,S-acetal **23** was reacted with aziridine and the corresponding vinylaziridines and the S,N-acetal **26** were obtained as a mixture. The formation of **26** in 68% yield and the mixture of **24** and **25** in 21% yield in ~ 4:1 ratio indicates that the vinylaziridines **24** with Z-configuration was the larger between two isomers **24** and **25** while **25** was opened by thiomethyl group to yield the corresponding N,S-acetal **26** in 68% yield. The formation of **26** in exclusive Z - configuration is evident from the clear absence of the other isomeric nitroketene S,N-acetal for **26**. The structure of **26** was confirmed by its analytical and spectral data which are described in the experimental section. The S,N-acetal came as last fraction when the reaction mixture was passed through alumina column using ethylacetate / hexane (1:4) as eluent. Vinylazriridines **24** and **25** came as first fraction together accounting for only 21% containing Z/ E ~ 4:1 ratio, which was assigned on the basis of spectral data. The structures of these compounds were fully established by their spectral and analytical data which are described in the experimental section.

The vinylaziridines **21a-c** obtained as described in scheme 5 were conveniently rearranged in the presence of potassium iodide in acetone at room temperature to yield the corresponding 2-methylthio-3-aroylpyrrolines **29a-c** in 62-69% over all yields. These pyrrolines **29** were confirmed by their analytical and spectral data, which are described in the experimental section.

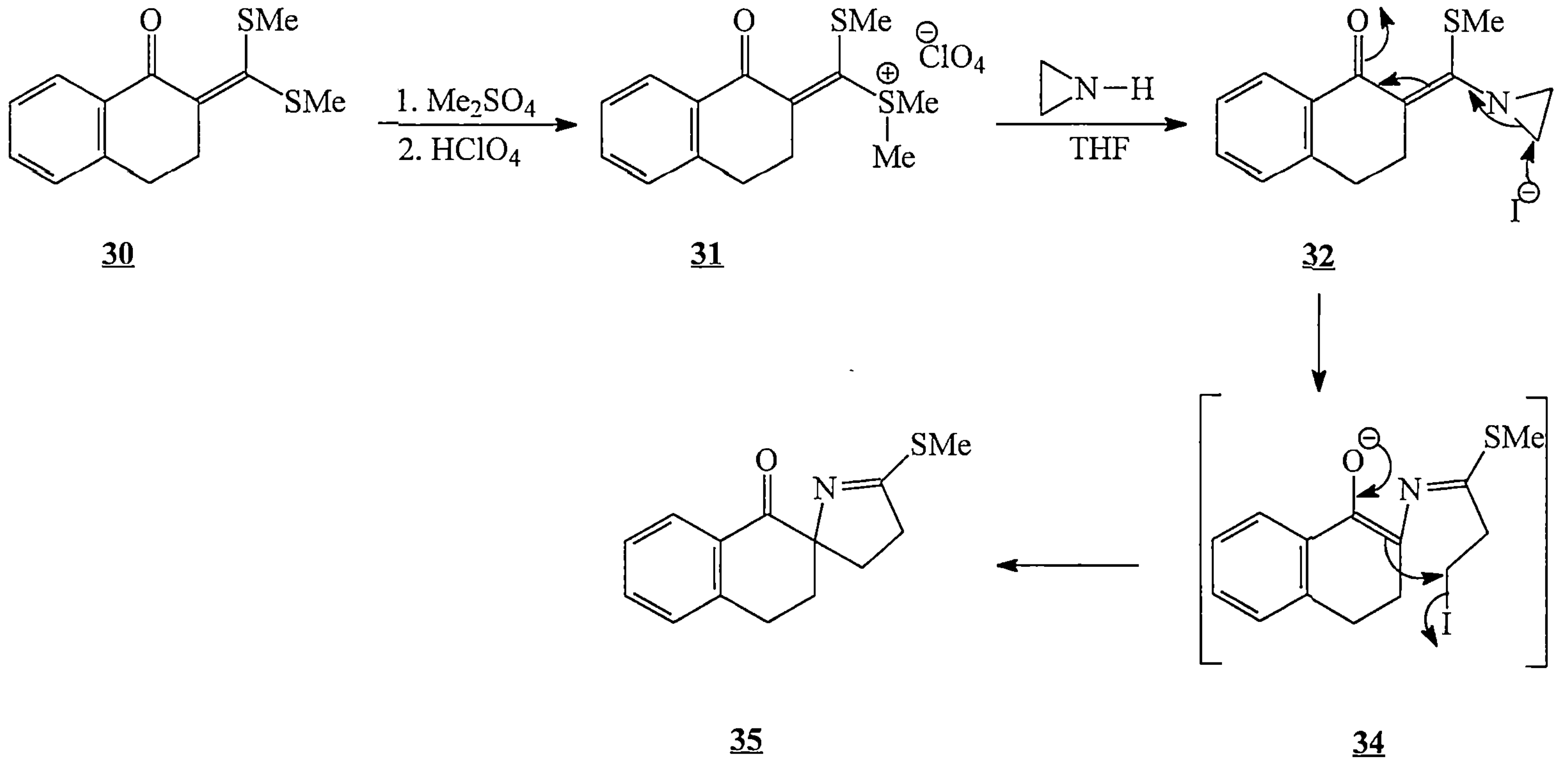
The tetralone S,S-acetal quaternary salt **31** similarly reacted with aziridine to give the corresponding vinylaziridine **32** in excellent yield which was treated with potassium iodide to yield the corresponding spiro compound **35** in 47% yield. The structure of **35** was established on the basis of analytical and spectral data which are described in the experimental section.

IV. 3. An attempted synthesis of dl-cucurbitine:

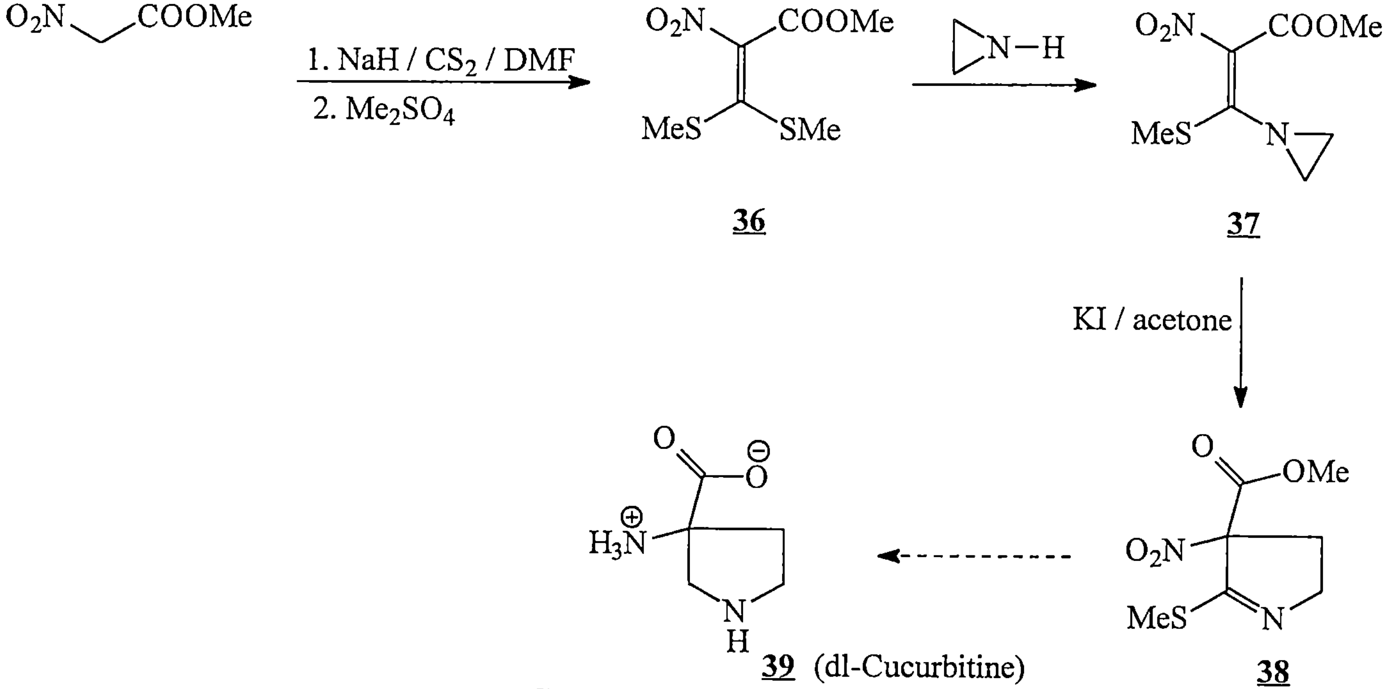


dl-Cucurbitine

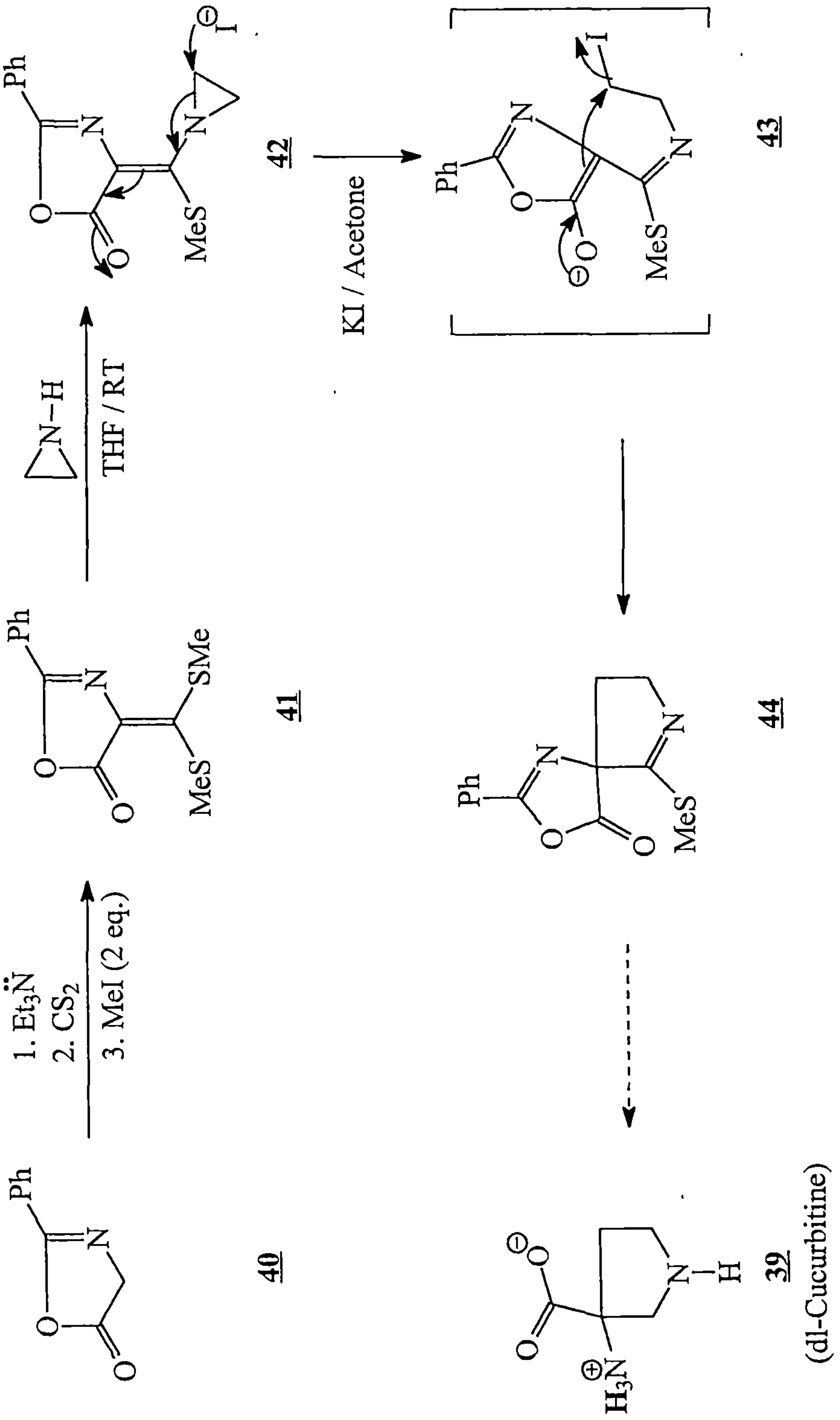
The dl-cucurbitine 39 is a naturally occurring amino acid found in the seeds of several *Cucurbita* (pumpkin) species and known to inhibit the growth of immature *Schistosoma japonicum*. It was first isolated by Fang[18] and co-workers from *Cucurbita moschata*. Its absolute stereochemistry was later determined to be of the -(S)- configuration[19]. Its racemic synthesis was reported by sun[20] in 1961 and Monteiro[21] in 1973 respectively. Enantiospecific synthesis was reported by Morimoto in 1987. The enantiospecific synthesis of (-)-cucurbitine was accomplished by a method involving 1,3-dipolar cycloaddition of azomethine ylide, derived from N-benzyl-N-(methoxymethyl) trimethylsilyl methylamine, to diethyl methylenemalonate. Subsequent pig liver esterase-catalysed hydrolysis of the pro-(R) ester group followed by conversion of the free carboxylate to an amino acid *via* the curtius rearrangement, provided the cucurbitine nucleus. In this case the maximum observed enantiomeric excess for the esterase hydrolyses was only 10%. Recently Williams and Fegley reported[23] asymmetric synthesis of S- (-) cucurbitine, involving the 1,3-dipolar cycloaddition of azomethine ylid to dehydrolactone to give S- (-)-cucurbitine in greater than 98% ee. In the present investigation an attempt has been made to reach the basic skeleton 38 which is apparently an important key intermediate for making dl-cucurbitine. The Nitroketene-S,S-acetal 36 was then reacted with aziridine to yield the corresponding vinylaziridine 37 in good yield. This compound was found to be stable and purified by passing through neutral alumina before it was subjected for


O
SMe
SMe
1. Me_2SO_4
2. $HClO_4$
$ClO_4^{\ominus}$
$\oplus$SMe
Me
N—H
THF
N
$I^{\ominus}$
O$^{\ominus}$
N
I
30
31
32
34
35

Scheme 8


O2N
COOMe
1. NaH / CS2 / DMF
2. Me2SO4
O2N
COOMe
MeS
SMe
36
N−H
O2N
COOMe
MeS
N
37
KI / acetone
O
OMe
O2N
MeS
N
38
O
O
H3N
N
H
39
(dl-Cucurbitine)

Scheme 9


40
1. Et$_3$N̈
2. CS$_2$
3. MeI (2 eq.)
41
THF / RT
42
KI / Acetone
43
44
39
(dl-Cucurbitine)
Ph
MeS
SMe

Scheme 10

rearrangement. The structure was in agreement with the spectral and analytical data which are described in the experimental section . The vinylaziridine 37 on treatment with potassium iodide yielded the 2-methyl thio-3-carbomethoxy-3-nitropyrroline 38 in 67% yield. The structure was confirmed by spectral and analytical data. An alternative strategy for the synthesis of dl-cucurbitine was conceived through the intermediate 44 (scheme 10), which was prepared from 2-phenyl-5-oxazolone involving the synthesis of 4-[Bis(methylthio)]methylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole[24] 41 . Its analytical and spectral data were in accord with assigned structure. The vinylaziridine 42 obtained by reacting aziridine with 41 was purified and characterised by its analytical and spectral data, which are described in the experimental section. The aziridine 42 on treatment with potassium iodide in acetone resulted in the expected spiro compound 44 in good yields. Attempted hydrolysis through the opening of oxazolone ring with various sodium alkoxides were not successful and no identifiable compound isolated from the reaction mixture. The spiro compound 44 however, requires further investigation to carry it to the target dl-cucurbitine molecule. The studies are being still continuing.

IV. 4. Conclusion:

The less activated α-oxoketene dithioacetals react with aziridine as their quaternary perchlorate salts to yield the corresponding vinylaziridines which are shown to undergo potassium iodide assisted rearrangement to yield the corresponding 3-aroyl-2-methylthiopyrrolines in excellent yields. Attempts to extend this method for the synthesis of dl-cucurbitine have ended up in the intermediate stage with appropriate functional group at 3-position of the pyrrolidine ring. No successful experiment could be devised to transform this intermediates 44 (Scheme 9) to the respective dl-cucurbitine. We therefore continue to extend this work to get dl-cucurbitine in the near future.

IV. 5. Experimental Section:

General

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected . The IR spectra were recorded on a Perkin Elmer 983 spectrophotometer and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on Varian EM-390, 90 MHz spectrometer in $CDCl_3$ or CCl_4 and are reported in δ units down field from Tetramethylsilane. High resolution ^1H NMR (300.13MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ or DMSO/d_6/ $CDCl_3$ and are reported in δ units downfield from Tetramethylsilane. The coupling constants are given in Hertz. The followed abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR (75.46 MHz) spectra were recorded on Bruker ACF 300 spectrometer in $CDCl_3$ or DMSO/d_6/ $CDCl_3$ and are reported in δ units in $CDCl_3$ downfield from Tetramethylsilane. Mass spectra were obtained on a Joel D-300 spectrometer and relative intensities are expressed in percentage. The molecular and base peaks are indicated by M^+. Carbon, hydrogen and nitrogen elemental analysis were carried out on a Heraus CHN-O-RAPID instrument. Analytical T. L.C. were performed on glass plates (18x6 and 18x4 cm) coated with ACME's silica gel containing 13% calcium sulphate as binder and various combinations of ethyl acetate-hexane, benzene, methanol were used in glass chambers for running T.L.C in order to monitor the reactions. Visualisation of spots was accomplished by exposure to iodine vapour or potassium permanganate (acidic) solution.

Chemical and Solvents:

The commercial samples of acetophenone, p-methoxyacetophenone, p-chloroacetophenone, acetone, nitromethane were purified before use. The ketene S,S-acetals 3,3-bis (methylthio)-1-phenyl-2-propen-1-one[25] , 3,3-bis(methylthio)-1-(4'-methoxyphenyl)-2-propen-1-one; mp.100°C, 3,3-bis(methylthio)-1-(4'-chloro phenyl)-2-propen-1-one, mp.109-110°C, 1,1-bis(methylthio)-2-nitroethylene[25a], m.p. 125-126°C, 1-tetralone[26], 2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole[27], methyl nitroacetate[28], were prepared according to the reported procedures. Perchlorate salts were made from the respective S,S-acetals according to the reported[15] procedure. The commercial solvents benzene, dethylether, diethylamine were dried before use. Tetrahydrofuran was initially deperoxidized and then dried by keeping over sodium wire followed by distillation. Solvents for column chromatography were used after simple distillation of commercial ones. All the solvent evaporation's were done on a steam bath.

Reaction of 17 with aziridine: Preparation of 1-Aryl-3-(N-aziridino)-3-methylthio-2-propen-1-one : (21+22):

To a well stirred suspension of potassium carbonate (2 gm), in dry tetrahydrofuran (25 ml), at ice cold (0°C) temperature, aziridine (1 ml) in dry tetrahydrofuran (3 ml) was added at once and stirring was continued at the same temperature for 15 min. Perchlorate salt 17 (29, 0.008 mol) was added to the stirred suspension slowly pinchwise over a period of 0.5 hr. The reaction mixture was stirred for 3 hr (monitored by T.L.C.) and potassium carbonate was filtered off from the reaction mixture using *G-3* sintered funnel. Solvent was removed under reduced pressure and the residue obtained was chromatographed over neutral alumina using hexane / ethylacetate (4:1) as eluent. The product obtained was characterised from its analytical and spectral data, which are described below.

3-(N-aziridino)-3-methylthio-1-phenyl-2-propen-1-one **21a** was obtained as yellow needles (acetone/hexane); m.p.85-86°C; yield 61%; IR (Kbr) :ν_{max} : 1606 (C=O), 1495, 1479, 1463, 1432, 1424, 1227, 1150 cm^{-1}: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 2.26 (brs, 4H, NC$\underline{H}_2$), 2.44 (s, 3H, SC$\underline{H}_3$), 6.57 (s, 1H, vinylic $\underline{H}$), 7.40-6.73 (m, 3H, Ar$\underline{H}$), 7.89 (d, with fine splitting, 2H, J=8Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$) (**21a** ,*Z*) : δ = 13.88 (S$\underline{C}H_3$), 30.53 (N$\underline{C}H_2$), 103.87, 127.38, 128.26, 131.46, 139.24, 174.29, 187.72 (C=O); ^{3}C NMR (75.46 MHz, $CDCl_3$) (**22a,** *E*) : δ = 15.55 (S$\underline{C}H_3$), 32.70 (N$\underline{C}H_2$), 101.20, 127.53, 128.26, 131.37, 140.29, 174.94, 184.78 (C=O); m/z : 219 (M$^+$, 3.6%), 218 (M$^+$ −1, 16%), 217 (M$^+$ −2, 59.3%), 202 (38.5%), 170 (13.5%), 104 (100%); Anal. calculated for $C_{12}H_{13}NOS$ (219.29) ; C,65.72; H,5.97; N, 6.38. Found: C,65.69; H, 5.92; N,6.36%.

3-(N-aziridino)-1-(4'-methoxyphenyl)-3-methylthio-2-propen-1-one **21b** was obtained as yellow needles (acetone / hexane); m.p.84-85°C; yield 68%; IR (KBr): ν_{max}:1592 (C=O), 1492, 1458, 1229, 1162 cm^{-1}: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ= 2.28 (brs, 4H, NC$\underline{H}_2$), 2.46 (s, 3H, SC$\underline{H}_3$), 3.79 (s, 3H, OC$\underline{H}_3$), 6.55 (s, 1H, vinylic $\underline{H}$), 6.88 (d, 2H, J=8.84Hz, Ar$\underline{H}$), 7.88 (d, 2H, J=8.84 Hz, Ar$\underline{H}$); ^{13}C NMR (75.46 MHz, $CDCl_3$) (**21b,** ***Z***) : δ= 13.92 (S$\underline{C}H_3$), 30.52 (N$\underline{C}H_2$) , 55.29 (O$\underline{C}H_3$), 103.80, 113.45, 129.52, 132.01, 162.28, 173.29, 186.69 (C=O); ^{13}C NMR (75.46 MHz, $CDCl_3$) (**22b**, *E*): δ= 15.57 (S$\underline{C}H_3$), 32.68 (N$\underline{C}H_2$) , 55.29 (O$\underline{C}H_3$), 101.28, 113.44, 129.67, 132.96, 162.28, 171.80, 183.86 (C=O); m/z: 249 (M$^+$, 12.6%), 134 (100%); Anal. calculated for $C_{13}H_{15}NO_2S$ (249.32) ; C,62.62; H,6.07; N, 5.62. Found: C,62.59; H, 6.02; N,5.63%.

3-(N-aziridino)-1-(4'-chlorophenyl)-3-methylthio-2-propen-1-one **21c** was obtained as light yellow needles (acetone/hexane); m.p.80-82°C; yield 64%; IR

(KBr): ν_{max} : 1612 (C=O), 1510, 1495, 1217cm^{-1}: ^{1}H NMR (90MHz, $CDCl_3$): δ = 2.36 (brs, 4H, NC$\underline{H}_2$), 2.53 (s, 3H, SC$\underline{H}_3$), 6.60 (s, 1H, vinylic $\underline{H}$), 7.48 (d, 2H, J=7.5Hz, Ar$\underline{H}$), 8.01 (d, 2H, J=7.5Hz, Ar$\underline{H}$); m/z: 254 (M^+ +1, 3.2%), 253 (M^+, 21.1%): Anal. calculated for $C_{12}H_{12}NOSCl$ (253.75) ; C,56.80; H,4.77; N,5.52. Found: C, 56.81; H, 4.69; N,5.54%.

3,4-Dihydro-2-{N-aziridino-methylthio)methylene}-naphthalen-1-one <u>32</u> was obtained as light yellow needles (acetone/hexane); m.p.134-135°C; yield 54%; IR (CCl_4): ν_{max} : 1608 (C=O), 1500, 1490, 1213cm^{-1}: ^{1}H NMR (90MHz, $CDCl_3$): δ= 2.43 (brs, 4H, NC$\underline{H}_2$), 2.50 (s, 3H, SC$\underline{H}_3$), 2.96 (brs, 4H, C$\underline{H}_2$), 7.23-7.73 (m, 3H, Ar$\underline{H}$), 8.25 (d, *with fine splitting*, 1H, J=9Hz, Ar$\underline{H}$); Anal. calculated for $C_{14}H_{15}NOS$ (245.33) ; C,68.54; H,6.16;N, 5.71. Found: C,68.51; H, 6.12;N,5.65%.

Iodide Ion catalysed isomerization of aziridino-N,S,-acetals (vinylaziridines): Preparation of 3-Aroyl-2-methylthio pyrrolines : <u>29a-c</u> and <u>35</u> :

A mixture of aziridino-N,S-acetal (00.1 mol) and potassium iodide (3.32g, 0.02 mol) in dry acetone (50 ml) was stirred at room temperature for 2 hr. Acetone was removed under vacuum and the residue was treated with ice cold water (50 ml). It was extracted with chloroform (3x50 ml) and the chloroform extracts were washed with water (3x50 ml). The organic layer was dried over anhydrous sodium sulphate and was concentrated under reduced pressure to yield yellow viscous liquid, which was purified by column chromatography over neutral alumina using hexane / ethylacetate (4:1) as eluent. The products obtained were characterised from its analytical and spectral data which are given below.

3-Benzoyl-2-methylthio-2-pyrroline <u>29a</u> was obtained as yellow viscous liquid; yield 69%; IR (CCl_4): ν_{max} :3480br (NH), 1695 (C=O), 1600, 1220cm $^{-1}$: ^{1}H NMR (90MHz, CCl_4): δ= 2.36 (brs, 5H, C$\underline{H}_2$, SC$\underline{H}_3$), 3.83-4.26 (m, 2H, NC$\underline{H}_2$), 4.67 (t,1H, J=7.5, N<u>H</u>, exchangeable with D_2O), 7.39-7.73 (m, 3H,Ar<u>H</u>), 7.93-8.16 (m, 2H, Ar<u>H</u>); Anal. calculated for $C_{12}H_{13}NOS$ (219.29) ; C,65.72; H,5.97;N, 6.38. Found: C,65.70; H, 5.94; N,6.39%.

3-(4'-Methoxybenzoyl)-2-methylthio-2-pyrroline <u>**29b**</u> was obtained as orange coloured viscous liquid; yield 62%; IR (CCl_4): ν_{max} : 3340 (NH), 1585 (C=O), 1210 cm^{-1}: ^1H NMR (90MHz, CCl_4): δ 2.36 (brs, 5H, C<u>H</u>$_2$, SC<u>H</u>$_3$), 3.89 (brs, 5H, OC<u>H</u>$_3$, NC<u>H</u>$_2$), 4.65 (t, 1H, J=7.5, N<u>H</u>,exangable with D_2O), 6.06 (d, 2H, J=9Hz, Ar<u>H</u>), 7.16 (d, 2H, J=9Hz, Ar<u>H</u>); Anal. calculated for $C_{13}H_{15}NO_2S$ (249.32) ; C,62.62; H,6.07; N, 5.62. Found: C,62.60; H,6.01; N,5.68%.

3-(4'-Chlorobenzoyl)-2-methylthio-2-pyrroline <u>**29c**</u> was obtained as orange coloured viscous liquid; yield 69%; IR(CCl_4): ν_{max} : 3420 (NH), 1683 (C=O), 1213 cm^{-1}: ^1H NMR (90MHz, CCl_4): δ=2.39 (brs, 5H, C<u>H</u>$_2$, SC<u>H</u>$_3$), 3.86-4.19 (m, 2H, NC<u>H</u>$_2$), 4.67 (t, 1H, J=7.5, N<u>H</u>, exchangeable with D_2O), 7.50 (d, 2H, J=8.5Hz, Ar<u>H</u>), 8.03 (d, 2H, J=8.5Hz, Ar<u>H</u>); Anal. calculated for $C_{12}H_{12}NOSCl$ (253.74) ; C,56.80; H,4.77;N, 5.52. Found: C,56.76; H,4.73; N,5.49%.

3,4-Dihydronaphthalene-1-one-2-spiro-2'-aza-1'-(methylthio)cyclopent-1-ene <u>**35**</u> was obtained as yellow needles; m.p.138-139°C; yield 47%; IR (KBr): ν_{max} :1652 (C=O), 1608 (C=N), 1513, 1465, 1283 cm^{-1}: ^1H NMR (90MHz, CCl_4): δ= 1.36-1.66 (m, 2H, C<u>H</u>$_2$), 2.46 (s, 3H, SC<u>H</u>$_3$) , 2.73-3.29 (m, 6H, C<u>H</u>$_2$, NC<u>H</u>$_2$), 7.19-7.70 (m, 3H, Ar<u>H</u>), 8.18 (d, with fine splitting, 1H, J=7.5Hz, Ar<u>H</u>); Anal. calculated for $C_{14}H_{15}NOS$ (245.33) ; C,68.54; H,6.18;N, 5.71. Found: C,68.50; H,6.09; N,5.63%.

Reaction of 1,1-bis(methylthio)-2-nitroethylene with aziridine:

A mixture of nitroketene, S,S-acetal (0.005 mole)(and aziridine (0.05 mol) in dry tetrahydrofuran (10 ml) and dry ethanol (10 ml) was stirred at O°C for 3 hrs (monitored by T.L.C.). Solvent was distilled off from the reaction mixture under reduced pressure and the residue was chormatographed over alumina using hexane/ethylacetate (9:1) as eluent. The products obtained was characterised as 26 and 24 for which spectral and analytical data are described below.

1-methylthio-1-(2'-methylthioethylamino)-2-nitroethylene 26 was obtained as light yellow needles(chloroform/hexane); m.p.61-62°C; yield 68%; IR (KBr): ν_{max} :3420 (NH), 3360, 1605, 1254 (NO_2)cm^{-1}: ^1H NMR (90MHz, CCl_4): δ = 2.16 (s, 3H, SCH_3), 2.43 (s, 3H, SCH_3) , 2.73 (t, 2H, J=7.5Hz, CH_2), 3.49-3.77 (m, 2H, $HNCH_2$), 6.63 (s, 1H, vinylic H), 11.19 (brs, 1H, exchangeable with D_2O, NH); Anal. calculated for $C_6H_{12}N_2O_2S_2$ (208.24) ; C,34.60; H,5.80;N,13.47. Found: C,34.56; H,5.73; N, 13.43

1-Aziridino-1-methylthio-2-nitroethylene 24 was obtained as yellow needles; m.p.52-54°C; yield 21%; IR (KBr): ν_{max} :1463 ,1252 (NO_2)cm^{-1}: ^1H NMR (90MHz, CCl_4): δ =2.33 (brs, 4H, NCH_2), 2.49 (s, 3H, SCH_3) , 7.03 (s, 1H, vinylic H); Anal. calculated for $C_5H_8N_2O_2S$ (160.16) : C, 37.49;H,5.03;N, 17.51. Found: C,37.41; H,5.01; N, 17.48%.

Reaction of 1,1-bis(methylthio)-2-carbomethoxy-2-nitroethylene 36 with aziridine:

Aziridine (0.05 mol) in dry diethyl ether (20 ml) was added dropwise to a well stirred solution of S,S-acetal 36 (0.05 mol) in dry diethylether (25 ml) at 0°C. The reaction mixture was stirred at 0°C for 0.5 hr and at room temp for 1 hr (monitored by T.L.C). Solvent was distilled off from the reaction mixture under reduced pressure and the solid separated out was filtered and was crystallised from chloroform/hexane (4:6). The product was characterised as 37 for which analytical and spectral data are given below.

1-(N-Aziridino)-2-carbomethoxy-1-methylthio-2-nitroethylene 37 was obtained as yellow needles; m.p.91-92°C; yield 55%; IR (KBr): ν_{max} :1683 (C=O), 1251 (NO_2) cm^{-1}: ^1H NMR (90MHz, $CDCl_3$) : δ = 2.59 (brs, 4H, $NC\underline{H}_2$), 2.73 (s, 3H, $SC\underline{H}_3$) , 4.26 (s, 3H, $OC\underline{H}_3$); Anal. calculated for $C_6H_{10}N_2O_4S$ (206.19) : C, 34.95; H,4.89; N, 13.60. Found: C,34.91; H,4.82; N, 13.57%.

Iodide ion catalysed rearrangement of 37 : Preparation of 2-methylthio-3-carbomethoxy-3-nitropyrroline 38:

A mixture of S,N-acetal 37 (0.219 gm, 0.001 mol) and potassium iodide (0.5 gm, 0.003 mol) in dry acetone at room temperature was stirred for 1 hr (monitored by T.L.C) yellow colour disappears, apparently due to the rearrangement and the solvent was removed from the reaction mixture. Water (50 ml) was added to the residue obtained and it was extracted with dichloromethane (3x50 ml) and the organic extracts were washed with water (3x50 ml) concentrated to give the yellow viscous liquid. The product obtained was purified over neutral alumina and was characterised as 2-methylthio-3-carbomethoxy-3-nitropyrroline 38, from its analytical and spectral data which are described below:

2-methylthio-3-carbomethoxy-3-nitropyrroline 38 was obtained as yellow viscous liquid; yield 67%; IR (CCl_4): ν_{max} :1715 (C=O), 1639 (C=N), 1213 (NO_2) cm^{-1}: ^1H NMR (90 MHz, $CDCl_3$): δ =2.56 (t, 2H, $C\underline{H}_2$), 2.76 (s, 3H, $SC\underline{H}_3$) , 4.29 (m, 2H, $NC\underline{H}_2$), 4.33 (s, 3H, $OC\underline{H}_3$); Anal. calculated for $C_6H_{10}N_2O_4S$ (206.19) : C, 34.95; H,4.89; N, 13.60. Found: C,34.93; H,4.85; N, 13.54%.

Reaction of 41 with aziridine: Synthesis of 4-[N-aziridino-methylthio) methylene]-2-phenyloxazol-5-one: 42:

Aziridine (0.04 mol) was added to an ice cold solution of S,S-acetal 41 (0.0075 mol) in tetrahydrofuran (50 ml) and the mixture was stirred with cooling (0°C) for 2 hr and then at room temperature for 1 hr (monitored by T.L.C.). Solvent was removed from the reaction mixture under reduced pressure. The residue obtained was chromatographed over neutral alumina using hexane/ethylacetate (4:1) as eluent. The spectral and analytical data which are in accord with the structure are described below.

4-{N-aziridino-methylthio)methylene}-2-phenyloxazol-5-one 42 was obtained as light yellow needles (acetone/hexane); m.p.193-194°C; yield 68%; IR (KBr): ν_{max} :1624 (C=O), 1574 (C=N), 1546, 1409, 1322 cm^{-1}: ^1H NMR (300.13MHz, $CDCl_3$): δ= 2.46 (brs, 4H, $NC\underline{H}_2$), 2.59 (s, 3H, $SC\underline{H}_3$), 7.40-7.48 (m, 3H, Ar$\underline{H}$), 7.93-8.06 (m, 2H, Ar$\underline{H}$); ^{13}C NMR (75.46MHz, $CDCl_3$): δ=19.54 ($S\underline{C}H_3$), 30.58 ($2N\underline{C}H_2$) , 110.21, 125.54, 128.35, 130.36, 153.58, 165.48 (C=N), 169.32 (C=O); Anal. calculated for $C_{13}H_{12}N_2O_2S$ (260.26) ; C,59.99; H,4.64; N,10.77. Found: C,59.91; H, 4.62; N,10.73

Preparation of 6-Methylthio-2-phenyl-1,7-diaza-3-oxaspiro (4,4) non-1, 6-dien-4-one : 44.

A mixture of S,N-acetal 42 (0.005 mol) and potassium iodide (0.05 mol) in dry acetone was stirred at room temperature for 3 hrs (monitored by T.L.C.) and the acetone was distilled off under reduced pressure. The residue obtained was chromatographed over neutral alumina using hexane/ethylacetate (9:1) as eluent and the product obtained was characterised as 44 for which spectral & analytical data are described below:

6-Methylthio-2-phenyl-1,7-diaza-3-oxaspiro(4,4)non-1,6-dien-4-one 44 was obtained as pale yellow needles (acetone/hexane) m.p.260-261°C; yield 59%; IR (KBr): ν_{max} :1690 (C=O), 1640 (C=N), 1620 (C=N) cm^{-1}: ^{1}HNMR (90MHz, CD_3CN): δ 3.33 (t, 2H, J=7.5Hz, $C\underline{H}_2$), 3.60 (s, 3H, $SC\underline{H}_3$), 4.23 (t, 2H, $NC\underline{H}_2$), 7.30-7.53 (m, 3H, Ar$\underline{H}$), 7.76-7.95 (m, 2H, Ar$\underline{H}$); m/z: 243 (M^+ - 17, 11.8%), 229 (M^+ - 31, 95%); Anal. calculated for $C_{13}H_{12}N_2O_2S$ (260.26) ; C,59.99; H,4.64; N,10.77. Found: C,59.94; H, 4.63; N,10.71%.

IV. 6. References:

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