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

Scheme 1

1

2

3

4

5

$X = N - R$
$X = O$
$X = S$

$X - X, X = O$,
$b, X = N$
cycloadditions with various dienophiles resulting in the formation of both carbocycles and heterocycles depending on the nature of the dienophiles. 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. Besides open chain o-quinodimethane systems 1, 2, and 4 a number of cyclic systems such as isobenzofurans 3, 3a, 2H-isoindoles 4b, 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. 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 the papers published on 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 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 \textit{o-quinodimethane} intermediates derived from 2,3-disubstituted indoles and their reactions with dienophiles to yield corresponding carbazoles including some alkaloids.

\textbf{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 \textit{o-quinodimethane} intermediates and their reactions.
2. \textit{o-quinodimethane} intermediates involving intramolecular dienophile component.
3. The stable cyclic analogues of \textit{Indolo}-2,3-quinodimethane systems related to type 5.

\textbf{l) Open chain \textit{o-quinodimethane} Intermediates and their reactions.}

N-Protected-2,3-disubstituted indoles have been generally employed as precursors for the \textit{in situ} generation of \textit{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\textsuperscript{7} from the corresponding silylated indolylammonium salts \textit{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 3

Scheme 4

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 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-acetonitrile 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. 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
Scheme 5a
amount of bicyclic product of the benzyne addition to 6,11-carbon atoms.

Interestingly in another study, 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 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).
Scheme-6

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 within the molecule undergo intramolecular Diels-Alder addition sequence is well established in the recent literature\(^\text{12}\). Interesting applications of this approach have been elegantly implemented by Magnus\(^\text{13}\) 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 stereocentres especially those of the Aspidosperma and Kopsane types, was first achieved by this group\(^\text{14,15,16,17,18}\). Highly stereospecific synthesis of these alkaloids with control on their regio- and stereochemistry was achieved by trapping 2,3-quinodimethane structural frame \textit{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 \textit{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.
Scheme 8

31, 31a, 31b, 32a', R1=R2=OMe; R3=R4=H
b', R1=R4=H; R2=R3=OMe
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 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 closure 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 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
Scheme 9

1. Reaction with THF to form compound 35.

2. Compound 35 underwent Diels-Alder reaction to form compound 35b.

3. Compound 35b treated with DDQ to form compound 40.


5. Compound 39 had a yield of 75%.

6. Compound 35 did not undergo Diels-Alder reaction.
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\textsuperscript{20,21} and co-workers reacted 2,4-dihydropyrrolo[3,4-b]indole\textsuperscript{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 11

52, 53 a, R = Me; R, = CH2Ph
b, R = Me; R, = C6H4Me – P
c, R = Me; R, = C6H4OMe – P

Similarly Kreher and Dyker prepared\textsuperscript{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\textsuperscript{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 \textit{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\textsuperscript{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\textsuperscript{26}. Both
Scheme 14

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\textsuperscript{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\textsuperscript{28,29} (Scheme 13). The o-quinodimethane analogue 66 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\textsubscript{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.\textsuperscript{30}

Mohri\textsuperscript{31} and co-workers were able to generate o-quinodimethane intermediate 66 (Scheme 14) utilising the anhydride 65 by reported methods\textsuperscript{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 \textit{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
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\textsuperscript{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 tumors\textsuperscript{35}.

Indolopyridones\textsuperscript{36} \textsuperscript{69} also represent indolo-2,3-quinodimethane analogues which are isoelectronic with their oxygen analogues. Cycloaddition reactivity of these pyridones \textsuperscript{69} with N-phenylmaleimide yielded the corresponding bicyclic system \textsuperscript{70} in 88\% yield. However\textsuperscript{37}, further attempts to eliminate bridged component was not possible to yield the expected carbazole \textsuperscript{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\textsuperscript{36} \textsuperscript{72} also represent more versatile indolo-2,3-quinodimethane analogues\textsuperscript{37,38,39,40}. These intermediates react with dienophiles, with the \textit{in situ} elimination of carbon dioxide to yield functionalized [b] annulated indoles as a mixture of regio isomers \textsuperscript{73} and \textsuperscript{74}. Better regioselectivity\textsuperscript{37} was observed when \textit{R}^1 and \textit{R}^2 in \textsuperscript{72} were methyl groups. The corresponding 1,4-dimethylcarbazole \textsuperscript{75} was obtained in excellent yields, while the other isomer \textsuperscript{76} was formed only in small quantities (Scheme 16).
With indolopyranones the "cycloaddition/ cycloreversion" strategy\textsuperscript{29,41,38} was more facile than in case of the corresponding nitrogen analogues. For example\textsuperscript{41} 77 reacts with 2-chloropropenonitrile 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\textsuperscript{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] annulated 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 greater 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 o-quinodimethane analogue derived from 1,2-dimethylindole 3-carboxaldehyde. To our surprise the expected o-quinomdimethane 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\textsuperscript{42} method. In a typical experiment \textsuperscript{6}
(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=\(\text{N}\) group. Other prominent absorption bands are described in the experimental section. The structure of 84 was unambiguously established by its \(^1\)H NMR spectrum (CDCl\(_3\)). The ring dihydro four proton signal appeared as multiplet at \(\delta\)2.66-3.06. The N-methyl three protons appeared as a singlet at \(\delta\)3.69. The aromatic protons appeared as a multiplet at \(\delta\)7.16-7.36 accounting three protons, were assigned for H-6, H-7 & H-8 protons. The aromatic protons appeared at \(\delta\)7.39-7.69 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
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 2121 cm⁻¹, and in its ¹H NMR spectrum (CDCl₃) the N-methyl three protons appeared at δ 3.60. 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 7.5 Hz 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 C₁₄H₁₀N₂ 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
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 refluxing 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienophile</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MeO$_2$CC=CCO$_2$Me</td>
<td>90</td>
<td>76</td>
</tr>
<tr>
<td>2.</td>
<td>CH$_2$=CH-CN</td>
<td>84</td>
<td>78</td>
</tr>
<tr>
<td>3.</td>
<td>CH$_2$=CHCN</td>
<td>85*</td>
<td>76</td>
</tr>
<tr>
<td>4.</td>
<td>CH$_2$=CHCO$_2$Et</td>
<td>87a</td>
<td>84</td>
</tr>
<tr>
<td>5.</td>
<td>CH$_2$=CHCO$_2$Et</td>
<td>88a*</td>
<td>72</td>
</tr>
<tr>
<td>6.</td>
<td>CH$_2$=CHCOMe</td>
<td>87b</td>
<td>80</td>
</tr>
<tr>
<td>7.</td>
<td>CH$_2$=CHCOMe</td>
<td>88b*</td>
<td>76</td>
</tr>
<tr>
<td>8.</td>
<td>EtO$_2$CCH=CHCO$_2$Et</td>
<td>92a</td>
<td>73</td>
</tr>
<tr>
<td>9.</td>
<td>C$_6$H$_5$CH=CHCO$_2$Me</td>
<td>92b</td>
<td>79</td>
</tr>
<tr>
<td>10.</td>
<td>C$_6$H$_5$CH=CHNO$_2$</td>
<td>93c*</td>
<td>72</td>
</tr>
<tr>
<td>11.</td>
<td>O$_2$NCCH=CH(SMe)$_2$</td>
<td>95</td>
<td>68</td>
</tr>
<tr>
<td>12.</td>
<td>MeO$_2$C(CN)CH=CH(SMe)$_2$</td>
<td>98</td>
<td>69</td>
</tr>
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</table>

* Obtained after refluxing with pyridinium tosylate in dry benzene

Table 1
Scheme 20

MeOOC-CCC-COOME

THF/-78°C
Scheme 21

91, 92, 93

91, a, R = CO₂Et; X = CO₂Et
92, b, R = C₆H₅; X = CO₂Me
93, c, R = C₆H₅; X = NO₂
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\textsuperscript{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 \textbf{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 corresponding 3-carbomethoxy-1,2-dihydro-9-methyl-2-phenylcarbazole \textbf{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 \textbf{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 \textbf{93C} underwent in 72% yield. Interestingly the dihydrocompound \textbf{92C} underwent dehydrogenation as described earlier, though heating the dihydrocompound alone did not give satisfactory yields of \textbf{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-
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 nitroketene-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_{2}O_{2}S (272.32). In its IR spectrum (KBr) displayed an absorption band at 1302 cm\(^{-1}\) due to nitro group. Also the \(^1\)H NMR spectrum (90 MHz, CDCl\(_3\)) was clearly in support of the structure assigned. Thus the singlet at \(\delta\) 2.60 integrating for three protons was assigned for S-methyl protons and another singlet at \(\delta\) 3.87 was assigned for N-methyl protons. The singlet integrating for one proton at \(\delta\) 7.13 clearly indicates the H-1 proton, having methylthio group on its adjacent carbon atom. The three aromatic protons appeared as multiplet \(\delta\) 7.30-7.73 was assigned for H-6, H-7 and H-8 protons. Doublet at \(\delta\) 8.13 having 9Hz coupling constant was assigned for H-5 proton. The H-4 proton on the otherhand appeared at \(\delta\) 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 ethylcyanoacetate 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_{2}S with a molecular weight 252.33. It may be noted
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 \(\text{98}\) was unambiguously established by its \(^1\text{H}\) NMR spectrum (CDCl\(_3\)). The three protons singlet at \(\delta 2.66\) and \(\delta 3.36\) were assigned for S-Methyl and N-Methyl protons respectively. The singlet appeared at \(\delta 7.33\) integrating for one proton indicated that the proton H-1 adjacent to the carbon atom bearing methylthio group. The other singlet appeared at \(\delta 8.32\) was assigned for the proton H-4 having cyanogroup on the adjacent carbon. The structure \(\text{98}\) was further supported by its mass spectrum exhibited a molecular ion peak at m/z 252 (M+, 100%) corresponding to the molecular weight of \(\text{98}\). Thus confirms the structure assigned for \(\text{98}\).

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 \(\text{7}\) by treating 1,2-dimethylindole-3-carboxaldehyde \(\text{6}\), with sodium hydride in tetrahydrofuran.

* This work appeared in \textit{J.Org.Chem.}, three months after the publication of our paper in Tetrahedron Letters.
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
\[ \text{Ac}_2\text{O}/\text{NaOAc} \xrightarrow{\Delta/4\text{hr}/140^\circ\text{C}} \]

\[ \text{106} \]

\[ \text{R} - \equiv - \text{X} \]

\[ 76\text{hr}/\Delta \]

\[ \text{109} \]

90 \( R = X = \text{COOMe} \)

93c \( R = \text{Ph} ; X = \text{NO}_2 \)

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 regiocontrol 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 \(^\text{66}\) (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 olivaccine 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 olivaccine 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 ¹H NMR spectra were recorded on Varian EM-390, 90 MHz spectrometer in CDCl₃ (or) CCl₄ 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 CDCl₃ and are reported in δ units downfield from Tetramethylsilane. The coupling constants are given in Hertz. ¹³C NMR (75.46 MHz) spectra were recorded on Bruker ACF 300 spectrometer in CDCl₃ and are reported in δ units in CDCl₃ 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\(^4^5\). 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\(^4^2\). 1,1-bis(methylthio)-2-nitroethylene\(^4^6\) and 1,1-bis(methylthio)-2-cyano-2-carboethoxy ethylene\(^4^7\) 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^°. 131-132°C. yield 96%.

**General procedure for the generation of indole-2,3-dienolate Z, 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 0°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 (CCl4) \( \nu_{\text{max}} = 3461 \text{ (OH)}, 3136, 2915, 2237 \text{ (C=N) cm}^{-1} \); \(^1\text{H NMR (90 MHz, CDCl}_3\)): \( \delta = 2.26-2.40 \text{ (m, 1H, CHCN), 2.83-3.06 (m, 4H, CH}_2\), 3.13-3.23 (m, 1H, CHOCH), 5.33 (s, with fine splitting, 1H, OH) exangable with D\(_2\)O), 7.91-7.50 (m, 3H, ArH), 7.66 (m, 1H, ArH).

3-Cyano-1,2-dihydro-9-methylcarbazole (84) obtained as light yellow Crystals (chloroform/hexane), m.p. 120-121°C; yield :78%; IR (KBr); \( \nu_{\text{max}} = 1462, 1518 \text{ and 2183 (C=N) cm}^{-1} \); \(^1\text{H NMR (90 MHz, CDCl}_3\): \( \delta = 2.66-3.06 \text{ (m, 4H, CH}_2\), 3.69 (s, 3H, NCH}_3\), 7.16-7.36 (m, 3H, ArH), 7.39-7.69 (m, 2H, ArH); 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; N13.40; 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); \( \nu_{\text{max}} = 1215, 1465,1681 \text{ (C=O) cm}^{-1} \); \(^1\text{H NMR...} \)
(300.13 MHz, CDCl₃): δ = 1.35 (t, 3H, J=7Hz, CH₃), 2.86-2.89 (m, 4H, CH₂), 3.63 (s, 3H, NCH₃), 4.26 (q, 2H, J=7Hz, OCH₂), 7.17-7.21 (m, 2H, ArH), 7.25-7.28 (m, 1H, ArH), 7.62-7.65 (m, 1H, ArH), 7.88 (s, 1H, ArH); ¹³C NMR (75.46 MHz, CDCl₃): δ = 14.51 (CH₃), 20.79 (CH₂), 22.74 (CH₂), 29.54 (NCH₃), 60.07 (OCH₂), 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⁺-COOC₂H₅, 90%);
Anal. calculated for C₁₆H₁₇NO₂ (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 (CCl₄) ;νmax = 1624 (C=O), 1509, 1262 cm⁻¹; ¹H NMR (90 MHz, CDCl₃): δ =2.43 (s, 3H, CH₃), 2.86 (brrs, 4H, CH₂), 3.66 (s, 3H, NCH₃), 7.16-7.50 (m, 3H,ArH), 7.63-7.76 (m, 1H, ArH), 7.79 (s, 1H, ArH); m/z : 225 (M⁺, 66.7%), 224 (M⁺ -1, 34%), 210 (34.8%), 182 (100%); Anal. calculated for C₁₅H₁₅NO (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); νmax = 1711 (C=O), 1678 (C=O), 1212 cm⁻¹; ¹H NMR (300.13MHz,CDCl₃): δ = 1.16 (t, 3H,J=7.3Hz, CH₃), 1.36 (t, 3H, J=7.3 Hz, CH₃), 3.05 (dd, 1H, J=8.83, 8.20Hz, CH₂) 3.61 (dd, 1H, J=14.5,2.58 Hz, CH₂), 3.68 (s, 3H, NCH₃), 4.00-4.09 (m, 3H, OCH₂, CHCOOC₂H₅), 4.29 (q, 2H,J=7Hz, OCH₂), 7.17 (m, 2H, ArH), 7.26 (m, 1H, ArH), 7.63 (m, 1H, ArH), 7.98 (s, 1H, ArH); ¹³C NMR (75.46 MHz, CDCl₃): δ = 13.99 (CH₃), 14.49 (CH₃), 23.79 (CH₂), 29.73 (NCH₃), 38.95 (CHCOOC₂H₅), 60.29 (OCH₂), 61.16(OCH₂), 100
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): νmax = 1669 (C=O), 1461, 1261, 1222, 1187, 1079 cm⁻¹; ¹H NMR (90 MHz, CDC1₃): δ = 3.00-3.33 (m, 2H, CH₂), 3.46 (s, 3H, NCH₃), 3.76 (s, 3H, OCH₃), 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⁺, 20.4%), 317 (M⁺ 86.4%), 259 (20.8%), 258 (100%), 243 (37.5%), 208 (23.9%), 181(37.7%); Anal. calculated for C₂₁H₁₉NO₂ (317.37): C, 79.47; H, 6.03; 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; Lit⁴³. m.p. 132-133°C; yield:76%; IR (Kbr): νmax =1706 (C=O), 1722 (C=O) cm⁻¹; ¹H NMR (90 MHz, CDC1₃): δ = 3.66 (s, 3H, NCH₃), 3.97 (brs, 6H, OCH₃), 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 C₁₇H₁₅NO₄ (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): νmax = 1596, 1302 (NO₂) cm⁻¹; ¹H NMR (90 MHz,
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): v_{max} = 3128, 2203 (C=N), 1587 cm^{-1}; ^1H NMR (90 MHz, CDCl₃): δ = 2.66 (s, 3H, SCH₃), 3.86 (s, 3H, NCH₃), 7.33 (s, 1H, ArH), 7.36-7.73 (m, 3H, ArH), 8.12 (d, 1H, J=9Hz, ArH), 8.32 (s, 1H, ArH); m/z: 252 (M⁺, 100%), 237 (94.6%), 219 (48.7%), 193 (47.5%); Anal. Calculated for C₁₅H₁₂N₂S (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 (CCl₄): νmax = 2921, 2213 (C=N), 1588, 1471, 1245 cm⁻¹; ¹H NMR (90 MHz, CDCl₃): δ = 3.60 (s, 3H, NCH₃), 7.13-7.66 (m, 5H, ArH), 7.88 (d, 1H, J=7.5Hz, ArH), 8.06 (s, 1H, ArH); m/z: 206 (M⁺, 100%), 205 (85%), 191 (17.2%); Anal. Calculated for C₁₄H₁₄N₂ (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) CCl₄: νmax = 2925, 1707 (C=O), 1367, 1255, 1237, 1095 cm⁻¹; ¹H NMR (90 MHz, CDCl₃): δ = 1.20-1.39 (t, 3H, CH₃), 3.60 (s, 3H, NCH₃), 4.30-4.54 (q, 2H, OCH₂), 7.20-7.73 (m, 4H, ArH), 8.13-8.46 (m, 2H, ArH), 8.93 (s, 1H, ArH); m/z: 253 (M⁺, 100%); Anal. Calculated for C₁₆H₁₅NO₂ (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): νmax = 2958, 2929, 1596 (C=O), 1323 cm⁻¹; ¹H NMR (90MHz, CDCl₃): δ = 2.73 (s, 3H, CH₃), 3.93 (s, 3H, NCH₃), 7.33-7.66 (m, 4H, ArH), 8.23 (brs, 1H, ArH), 8.87 (s, 1H, ArH); m/z: 223 (M⁺, 85.7%), 209 (41.6%), 208 (100%), 180 (78.4%), 152 (53.8%); [Found: C,
9-Methyl-3-nitro-2-phenylcarbazole (93c) was obtained as bright yellow crystals (acetone / hexane), m.p. 222-223°C; yield: 72%; IR (Kbr): $\nu_{\text{max}} = 1513, 1319$ (NO$_2$) cm$^{-1}$; $^1$H NMR (90 MHz, CDCl$_3$): $\delta = 3.86$ (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$_2$O$_4$ (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 dihydrocarbazoles (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

\[ \text{N-H} \quad 2 \quad \beta - \text{Carboline} \]

\[ \text{N-H} \quad 4 \quad \delta - \text{Carboline} \]

\[ \text{N-H} \quad 1 \quad \alpha - \text{Carboline} \]

\[ \text{N-H} \quad 3 \quad \gamma - \text{Carboline} \]
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. 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. 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 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 and co-workers in 1924, by reacting N-γ-pyridyl-0-phenylenediamine with 4-chloropyridine with nitrous acid to yield the corresponding 1- γ-pyridylbenzotriazole, which on subsequent heating in the presence of syrupy phosphoric acid yielded the γ-carboline.
Scheme 3

1. HCl
2. AcOH

\( \text{CH}_2\text{Ph} \)
\( \text{N} \)
\( \text{N} \)
\( \text{N} \)
\( \text{N} \)
\( \text{O} \)

10

+ 

\( \text{NH}_2 \)

11

12

13

14

15

16
If $X$ in $^XCO$ in $^oXo$ II $\Rightarrow (r_1 - a_r) < 0$

Scheme 4

Pyridine

$\rightarrow$

$COOR^2$

$\rightarrow$

$\rightarrow$

$+\quad +$

$NH_2RX$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

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$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$

$H_2C_6H_5$
Scheme 5

\[
\text{HN(C}_2\text{H}_5\text{)}_2\xrightarrow{\text{absolute ethanol}} \text{NH}_2\text{CH}_2\text{C}^\prime\text{OEt} + \text{CH}_3\text{N}^\prime\text{CO} \]

17

16

18
Bremer\textsuperscript{12} attempted in vain to exploit this strategy to prepare $\gamma$-carboline derivatives.

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

Jacquignon\textsuperscript{13} and co-workers reported the $\gamma$-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 \textsuperscript{11}, which was cyclised to 2-benzyl-1,2,3,4-tetrahydro -$\gamma$-carboline \textsuperscript{12}, by means of hydrogen chloride in acetic acid. The compound \textsuperscript{12} thus obtained underwent debenzylation and dehydrogenation to yield $\gamma$-carboline \textsuperscript{3}. (scheme 3)

Welch has extended the same strategy and reported\textsuperscript{14} some 1,2,3,4-tetrahydro-$\gamma$-carbolines using pyridiniumhydrochloride catalysed fisher indole reactions. Thus the N-carboethoxypiperidone hydrazone \textsuperscript{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-$\gamma$-carbolines \textsuperscript{15} in 47-86\% overall yields (scheme 4).

Queguiner\textsuperscript{15} and co-workers reported 5-methyl-3-carboethoxy-[5H]-pyrido[4,3-b] indole \textsuperscript{18} as formulated in scheme 5. Thus 1-methylindole-2,3-carboxaldehyde \textsuperscript{16} and ethylaminoacetate \textsuperscript{17} were
Scheme 6
Scheme 7

Ar = Ph

Ar = 4- MeC6H5

Ar = 4- MeO C6H5

Ar = 4- Cl C6H5
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 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 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 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
Scheme 8

![Chemical Structures and Reactions](image)
Scheme 9

\[ 30 + 31 \xrightarrow{\text{Microwave irradiation, } 160 \text{W}} 32 \]

\[ 33 \xrightarrow{\text{Microwave irradiation}} \]

31, 32, 33

- a, \( R^1 = \text{Me} \); \( R^2 = \text{H} \)
- b, \( R^1 = \text{H} \); \( R^2 = \text{Me} \) or
- c, \( R^1 = R^2 = \text{H} \)

\[ 34 \xrightarrow{\text{Microwave irradiation}} 35 \]

Scheme - 9
Scheme - 11

Scheme 12


126
presence of $\text{H}_4\text{P}_2\text{O}_7$ to yield a mixture of $\gamma$-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 $\gamma$-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 undergo two types of cyclizations, either involving indole-3-position to yield the corresponding $\gamma$-carboline derivative 40 or the corresponding pyrimido[3,4-a]indoles 41. They observed that in the case of isothiocyanate they underwent 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 methylolithium to yield the
<table>
<thead>
<tr>
<th>Benzocyclobutenol</th>
<th>Nitrile</th>
<th>Product</th>
<th>Yield</th>
<th>mp</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Ph—C=N</td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>47%</td>
<td>104-105 °C</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 2" /></td>
<td><img src="image4.png" alt="Nitrile 2" /></td>
<td><img src="image5.png" alt="Product 2" /></td>
<td>55%</td>
<td>139-140 °C</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure 3" /></td>
<td><img src="image7.png" alt="Nitrile 3" /></td>
<td><img src="image8.png" alt="Product 3" /></td>
<td>49%</td>
<td>72-73 °C</td>
</tr>
<tr>
<td><img src="image9.png" alt="Structure 4" /></td>
<td>MeOCH2—C=N</td>
<td><img src="image10.png" alt="Product 4" /></td>
<td>60%</td>
<td>bp 71-73 °C at 0.2 mm</td>
</tr>
<tr>
<td><img src="image11.png" alt="Structure 5" /></td>
<td><img src="image12.png" alt="Nitrile 5" /></td>
<td><img src="image13.png" alt="Product 5" /></td>
<td>68%</td>
<td>77-79 °C</td>
</tr>
<tr>
<td><img src="image14.png" alt="Structure 6" /></td>
<td><img src="image15.png" alt="Nitrile 6" /></td>
<td><img src="image16.png" alt="Product 6" /></td>
<td>80%</td>
<td>oil; NMR, tlc pure</td>
</tr>
<tr>
<td><img src="image17.png" alt="Structure 7" /></td>
<td><img src="image18.png" alt="Nitrile 7" /></td>
<td><img src="image19.png" alt="Product 7" /></td>
<td>48%</td>
<td>163-166 °C</td>
</tr>
<tr>
<td><img src="image20.png" alt="Structure 8" /></td>
<td><img src="image21.png" alt="Nitrile 8" /></td>
<td><img src="image22.png" alt="Product 8" /></td>
<td>90%</td>
<td>oil; NMR, tlc pure</td>
</tr>
</tbody>
</table>

*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* 842% 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.

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 Robinson's method or direct cyclization of hydrazone derived from piperidone and aryl hydrazine's under fisher indole conditions. Interestingly Olofson's o-tolualdehyde anions reaction using various nitriles as dienophiles for the efficient synthesis of isoquinolines has not been extended to Indole-2,3-dienolate\textsuperscript{27} to yield γ-carbolines. It was therefore considered of interest to explore studies on the reactivity of indole-2,3-dienolate\textsuperscript{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\textsuperscript{48} was generated \textit{in situ} from 1,2-dimethylindole-3-carboxaldehyde\textsuperscript{47} according to our earlier report\textsuperscript{27}. To establish authenticity and reactivity of this indole-2,3-dienolate, it was reacted with benzonitrile\textsuperscript{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\textsuperscript{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
analytical and spectral data. Thus it was analysed for $\text{C}_{18}\text{H}_{14}\text{N}_{2}$ 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 1593 cm$^{-1}$ (C=N). The structure was further conformed by from its $^1$H NMR spectrum (300.13 MHz, CDCl$_3$). The singlet at $\delta$3.81 integrating for three protons was assigned for N-methyl protons and two singlets at $\delta$9.32 and $\delta$7.62 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 $\gamma$-carboline. The other aromatic protons appeared as six proton multiplet at $\delta$7.51 and three proton multiplet at $\delta$8.08 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 (75.46 MHz). Thus the peak at $\delta$29.06 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 48 was reacted with p-methoxy benzonitrile, veratronitrile, 3,4,5-trimethoxy benzonitrile and p-N,N-dimethylamino benzonitrile to yield the corresponding 3-aryl-$\gamma$-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-$\gamma$-carboline 52 and the compound isolated was characterised as 1,2-dimethyl-3-(2'-cyanoethyl)indole.
Table


<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ar</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>51a</td>
<td><img src="Image" alt="Ar1" /></td>
<td>47</td>
</tr>
<tr>
<td>2.</td>
<td>51b</td>
<td><img src="Image" alt="Ar2" /></td>
<td>56</td>
</tr>
<tr>
<td>3.</td>
<td>51c</td>
<td><img src="Image" alt="Ar3" /></td>
<td>59</td>
</tr>
<tr>
<td>4.</td>
<td>51d</td>
<td><img src="Image" alt="Ar4" /></td>
<td>51</td>
</tr>
<tr>
<td>5.</td>
<td>51e</td>
<td><img src="Image" alt="Ar5" /></td>
<td>49</td>
</tr>
</tbody>
</table>
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 C₁₃H₁₂N₂ 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 νmax 2199 cm⁻¹ conformed the free nitride group. It was further supported by its ¹H NMR (90MHz, CDCl₃) 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 \(\delta\) 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 \(\delta\) 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 \(\delta\) 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(CCl₄): ν max =1593 (C=N), 1494, 1469,1244 cm⁻¹; ¹H NMR (300.13MHz, CDCl₃): δ=3.81 (s,3H, NCH₃), 7.51 (m,6H, ArH), 7.62 (s,1H, ArH,H-4), 8.08 (m,3H, ArH), 9.32 (s,1H, ArH, H-1); ¹³C NMR (75.46MHz, CDCl₃): δ =29.06 (NCH₃), 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 C₁₈H₁₄N₂ (258.31) : C,83.69; H,5.46; N,10.85. Found: C,83.61; H,5.43; N,10.81%.
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): \( \nu_{\text{max}} = 1635 \text{ cm}^{-1} \) (C=N), 1468, 1411, 1392, 1370 cm\(^{-1}\); \(^1\)H NMR (90MHz, CDCl\(_3\)): \( \delta = 3.69 \text{ (s, 3H, NCH}_3\)), 3.86 \text{ (s, 3H, OCH}_3\)), 6.99 \text{ (d, 2H, J=8.5Hz, ArH)}, 7.10-7.59 \text{ (m, 4H, ArH)}, 7.86-8.26 \text{ (m, 3H, ArH)}; Anal. Calculated for C\(_{19}\)H\(_{16}\)N\(_2\)O (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): \( \nu_{\text{max}} = 2993, 2963, 2931, 1602 \text{ (C=N), 1512, 1456, 1436, 1258, 1146 cm}^{-1} \); \(^1\)H NMR (90MHz, CDCl\(_3\)): \( \delta = 3.85 \text{ (s, 3H, NCH}_3\)), 3.93 \text{ (s, 3H, OCH}_3\)), 4.03 \text{ (s, 3H, OCH}_3\)), 6.99 \text{ (d, 1H, J=8.5Hz, ArH)}, 7.23-7.73 \text{ (m, 5H, ArH)}, 7.79 \text{ (s, 1H, ArH, H-4)}, 8.21 \text{ (d, 1H, J=8.5Hz, ArH)}; Anal. Calculated for C\(_{20}\)H\(_{18}\)N\(_2\)O\(_2\) (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): \( \nu_{\text{max}} = 1587 \text{ (C=N), 1454, 1123 cm}^{-1} \); \(^1\)H NMR (300.13MHz, CDCl\(_3\)): \( \delta = 3.92 \text{ (s, 3H, NCH}_3\)), 3.94 \text{ (s, 3H, OCH}_3\)), 4.02 \text{ (s, 6H, OCH}_3\)), 7.33 \text{ (s, 2H, ArH)}, 7.38 \text{ (m, 1H, ArH)}, 7.47 \text{ (m, 1H, ArH)}, 7.56 \text{ (m, 1H, ArH)}, 7.63 \text{ (s, 1H, ArH, H-4)}, 8.15 \text{ (d, 1H, J=7.72Hz, ArH)}; \(^1^3\)C NMR (75.46MHz, CDCl\(_3\)): \( \delta = 29.38 \text{ (NCH}_3\)), 56.41 \text{ (OCH}_3\)), 60.99 \text{ (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$_{2}$O$_{3}$ (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) : $\nu_{\text{max}}=2990, 2964, 1601, 1457, 1259$ cm$^{-1}$; $^1$H NMR (90MHz, CDCl$_3$): $\delta =$ 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) : $\nu_{\text{max}}=2199$ (C=O), 1597, 1408 cm$^{-1}$; $^1$H NMR (90MHz, CDCl$_3$): $\delta =$ 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%.
II.B.6 References:


