Syntheses of fused pyrroloheterocycles, isatins, approach towards the indole fragment of nosiheptide and a base-mediated formation of 3-hydroxycarbazoles

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Syntheses of Fused Pyrroloheterocycles, Isatins, Approach Towards the Indole Fragment of Nosiheptide and a Base-Mediated Formation of 3-Hydroxycarbazoles

Sobha Priyadarshini Gorugantula

Dissertation submitted to the
Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy
in
Chemistry

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Abstract

Syntheses of Fused Pyrroloheterocycles, Isatins, Approach Towards the Indole Fragment of Nosiheptide and a Base-Mediated Formation of 3-Hydroxycarbazoles

Sobha Priyadarshini Gorugantula

The nitro group has been and still is one of the few functional groups widely studied in synthetic organic chemistry. The reactivity of the nitro group has had important applications in the syntheses of many complex organic molecules, either through its assistance in the formation of new carbon-carbon bonds or in the formation of carbon-heteroatom bonds. Of late, the nitro group has become an important source of nitrogen in organic molecules, thus spawning the syntheses of a range of nitrogen heterocycles.

This dissertation is one such work, wherein the reactivity of the nitro group has been exploited with respect to the syntheses of nitrogen heterocycles. The palladium-catalyzed reductive N-heteroannulation reaction discovered in our laboratories a decade ago, has been utilized to synthesize a group of fused pyrroloheterocycles from the corresponding nitro-alkenylarenes. Also, these annulation conditions, when applied to 1-(2-haloethynyl)-2-nitrobenzenes, led to the formation of isatins. The isolation of a few stable 2-haloisatogens en route to the isatins is an important aspect in this conversion.

In addition, the possibility of executing an intramolecular nucleophillic attack on 3-(2-nitrophenyl)-2-cyclohexenone derivatives to afford hydroxy-carbazoles was investigated. A short synthetic approach to a model indole fragment of the natural product nosiheptide was also designed and attempted.
To
My Mother
And To
The Memory Of My Father

Great works are performed, not by strength, but by perseverance.

Samuel Johnson
Acknowledgements

As I sit down to pen a few words on this page, I cannot help reflecting upon the story of a little boy who drew an empty hand, when asked to draw a picture of something he was thankful for. The abstract drawing of his teacher’s hand speaks more than any word can ever say about being thankful. With great pleasure and profound respect, I take this opportunity today to express my sincere gratitude to my teacher, advisor and mentor, Dr. Björn Söderberg, the hand that accompanied me in my graduate education. I consider myself very fortunate for being a student to such a patient, broad-minded exceptional chemist, an excellent teacher and above all, a wonderful person.

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Also in my thoughts are my colleagues and fellow group members, past and present. I thank each one of them for their co-operation and help in my academics and research. To all my friends who stood by me through this journey, I say “Thank You!”

Most importantly, I am very grateful to my family, especially to Babai, Uma Aunty, Prem Uncle and Marie Aunty for their love, support and guidance throughout my life. Ultimately, to my parents: Had it not been for you, Mommy and Daddy, I would have never been the person I am today. For all that you gave me and for all that you are to me, words are never enough to say how thankful and fortunate I am to have you both as my parents.
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Chapter 1
Syntheses of Fused Pyrroloheterocycles

1.1 Introduction:

Aromatic ring systems with at least one heteroatom fused to a pyrrole nucleus are defined as “fused bicyclic pyrroloheterocycles”. These compounds belong to a class of nitrogen heterocycles that have been of interest to many researchers for over half a century. The interest in these ring systems stems from their isosteric relationship to indole and their presence as the structural components in many biologically active compounds. Among the several possible fused bicyclic pyrroloheterocycles, those that belong to the fused (5,5) category are the subjects under study in this chapter. Thienopyrroles, furopyrrroles and pyrrolopyrroles belong to the A,B-diheteropentalene system under this classification of compounds. Pyrroloimidazoles, pyrrolothiazoles, pyrroloisoxazoles and pyrroloisothiazoles, are some of the examples of ring systems with three heteroatoms from the (5,5) fused class of compounds (Figure 1).
Figure 1: Some examples of the (5,5) fused pyrroloheterocyclic system

Thienopyrrole subunits are found in several biologically active compounds used in the treatment of inflammation, viral infections and CCK antagonists, as well as in inhibitors of glycogen phosphorylase, cyclooxygenase, lipoxygenase, MCP-1 and biosteric analogs of serotonin agonist N,N-dimethyltryptamine. Bioisosteres of Tenidap, Tenoxicam and Lornoxicam, obtained by replacing the benzene ring with thiophene gave the analogous compounds 2, 3, 4 which were found to exhibit anti-inflammatory activity against rat-paw edema.²
Figure 2: Bioisosteric analogs of Tenidap

With furan and its derivatives categorized as the most studied five membered heterocyclic system for the Diels-Alder reaction, furo[3,2-b]pyrroles and the isomeric furo[2,3-b]pyrroles have become potential synthetic targets. A glance at the extensive work on these compounds by Krutosikova and his group depict the popularity of these compounds. Many of the compounds prepared by the Krutosikova group were tested for their carcinogenic activity. Additional studies on these compounds by the same researchers show that they react with dimethylbutylenedioate (6) to form substituted indoles 8. The formation of these substituted indoles was attributed to a [4+2] cycloaddition on the furan ring followed by a facile ring opening of an undetected adduct 7. A similar reaction was observed with ethyl propynoate (9), an unsymmetrical dienophile, and this reaction gave a mixture of the two possible isomers 10 and 11 (Scheme 1).
Several pyrrolo[2,3-d]imidazole-5-carboxylate derivatives were synthesized and tested for their anti-inflammatory activity against carrageenan-induced rat hindpaw. The 4-chlorobenzoyl derivative 12 displayed almost thrice the potency of aspirin (Figure 3) and sodium 4-(4-bromo-benzenesulphonyl)-pyrrolo[2,3-d]imidazole-5-carboxylate (13), a little less anti-inflammatory activity than indomethacin.\textsuperscript{5}

\textbf{Figure 3: Sodium 1-methyl-2-(4-Chlorobenzoyl)pyrrolo[2,3-d]imidazole-5-carboxylate (12) and sodium 4-(4-bromo-benzenesulphonyl)-pyrrolo[2,3-d]imidazole-5-carboxylate (13)}

The pyrrolopyrrole scaffold has been found in the blue M1 and M2 pigments (Figure 4). These compounds have been identified during the “Mailard reaction” between D-
xylose and glycine and were suggested to be Maillard reaction intermediates through the formation of melanoidins.\(^6\)

\[\text{Figure 4: Blue M1 (14) and Blue M2 (15)}\]

1,3,4-Trimethyl and 1,2,4-trimethylpyrrolo[3,2-b]pyrroles (Figure 5) have received considerable attention as candidates for electropolymerization. Their polymeric films have been prepared and found to have electrochromic property.\(^7\)

\[\text{Figure 5: 1,3,4-Trimethylpyrrolo[3,2-b]pyrrole (16) and 1,2,4-trimethylpyrrolo[3,2-b] pyrrole (17)}\]

Pyrrolo[3,2-d]thiazoles have been reported as anti-phlogistic pharmaceuticals and immunomodulators,\(^8\) inhibitors and anticoagulants for the prevention and treatment of
thrombosis and embolism,\textsuperscript{9} and as components of photomaterials.\textsuperscript{10} Lexitropsins form a group of synthetically designed compounds that have been examined for their DNA binding activity.\textsuperscript{11}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{lexitropsin1.png}
\caption{Lexitropsin 1}
\end{figure}

\textbf{1.2 Notable synthetic routes to (5,5) fused pyrroloheterocyclic compounds:}

With the ubiquitous acceptance of pyrroloheterocycles as indole isosteres, it is not unusual to speculate the applicability of “indole syntheses” to these compounds. Despite the plethora of the synthetic pathways, most of the routes available to synthesize indole and indole-derivatives were unfavorable to the (5,5) fused pyrroloheterocycles. The reason could be attributed to either the lack of availability of suitable starting materials or to low yields of the respective products.

\textbf{1.2 (a) Hemmetsberger-Knittel synthesis:}

Among the favored syntheses was the “Hemetsberger synthesis”\textsuperscript{12}, which features the thermolysis of an intermediate aryl azido acrylate as the key step to construct the “pyrrole ring”. Two examples reported by Garcia and Galvez forming a thieno[3,2-b]pyrrole and a thieno[2,3-b]pyrrole are shown in Scheme 2.\textsuperscript{13} The aryl azido acrylates
(20 & 23) are prepared from the Knoevenagel condensation between the aromatic aldehydes (18 & 22) and an azido ester (19)

Scheme 2: Hemmetsberger-Knittel synthesis of the thieno[3,2-b]pyrrole and thieno[2,3-b]pyrrole

This reaction can be formally seen as going through a nitrene intermediate 27, which subsequently inserts into the C-H bond of the arene. However, the isolation of azirine intermediates (26) at lower temperatures (80 °C) suggests that this reaction also proceeds through the formation of azirine (Scheme 3).

Scheme 3: The azirine intermediates isolated by Knittel en route to indole-2-carboxylates.
With this result, it is assumed that there is an equilibrium between the azirine (26) and the nitrene (27) (Scheme 4).

![Scheme 4: Equilibrium between the nitrene and the azirine](image)

By far the Hemmetsberger-Knittel synthesis has been the major reaction utilized to synthesize several furo[2,3-b]pyrrole and the furo[3,2-b]pyrrole derivatives. Analogous to the furopyroles, the construction of both the isomeric pyrroloimidazole rings was carried out by this reaction (Entry 9 and 10, Table 1). The 1,3,4-trimethyl and 1,2,4-trimethylpyrrolo[3,2-b]pyrroles, thieno[3,2-b:4,5-b']dipyrrrole, pyrrolo[2,3-b]pyrrole dicarboxylate (Entry 8, Table 1), seleno[3,2-b]pyrrole-2-carboxylate (Entry 7, Table 1), seleno[2,3-b]pyrrole-2-carboxylate (Entry 6, Table 1) and furo[2,3-b]pyrrole-2-carboxylate (Entry 4, Table 1) were also synthesized by the same method.

### Table 1: Hemmetsberger-Knittel synthesis of (5,5) fused pyrroloheterocycles

<table>
<thead>
<tr>
<th>Entry</th>
<th>The Aldehyde</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>OHC-(\text{Fur}[\text{3}][\text{2}][\text{1}])C-(\text{COOMe}) &amp; MeOOC-(\text{Fur}[\text{3}][\text{2}][\text{1}])N-(\text{COOMe}) &amp; 76%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(\text{CHO}) &amp; (\text{Fur}[\text{3}][\text{2}][\text{1}])COOMe &amp; 61% (\text{^15})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(\text{CHO}) &amp; (\text{SeFur}[\text{3}][\text{2}][\text{1}])COOEt &amp; 58% (\text{^15})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(\text{CHO}) &amp; (\text{SeFur}[\text{3}][\text{2}][\text{1}])COOEt &amp; 86% (\text{^15})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(\text{SeCHO}) &amp; (\text{SeFur}[\text{3}][\text{2}][\text{1}])COOEt &amp; 82% (\text{^15})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>EtOOCC(\text{Fur}[\text{3}][\text{2}][\text{1}])C-(\text{CHO}) &amp; EtOOCC(\text{Fur}[\text{3}][\text{2}][\text{1}])N-(\text{COOEt}) &amp; 80% (\text{^15})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(\text{CHO}) &amp; (\text{PrFur}[\text{3}][\text{2}][\text{1}])N-(\text{COOEt}) &amp; 21% (\text{^14})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(\text{CHO}) &amp; (\text{PrFur}[\text{3}][\text{2}][\text{1}])N-(\text{COOEt}) &amp; 27% (\text{^14})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.2 (b) The Fischer indole synthesis:

The “Fischer indole synthesis”,\textsuperscript{19} developed in 1883 remains a popular reaction to construct the indole nucleus even today. Despite its fame, the use of Fischer indole synthesis in the construction of pyrroloheterocycles has been sparse.\textsuperscript{20,21} The essence of this reaction is an acid assisted sigmatropic rearrangement of an aryl hydrazone, formed from the condensation of a ketone with the arylhydrazine. An example\textsuperscript{21} of a “Fischer indole synthesis” in the preparation of a thieno[2,3-b]pyrrole derivative (31) from 2-butanone (22) and N-t-butoxycarbonyl-N-2-thienylhydrazine (29) is represented in Scheme 5.

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {28};
\node (B) at (2,0) {29};
\node (C) at (4,0) {30};
\node (D) at (4,-2) {31 (85%)};
\draw (A) -- (B) node[midway, above] {HCl, Ether};
\draw (B) -- (C) node[midway, above] {AcOH} edge[double, double distance=1.5pt, -] node[midway, below] {(22)};
\end{tikzpicture}
\end{center}

\textbf{Scheme 5: The synthesis of a thieno[2,3-b]pyrrole via Fischer’s indole synthesis}

1.2 (c) Batcho-Leimgruber synthesis:

The two-step Batcho-Leimgruber indole synthesis\textsuperscript{22} provides a major alternative to Fisher’s indole synthesis. In spite of the popularity in indole synthesis, there has been
only one report on the applicability of the Batcho-Leimgruber synthesis in the synthesis of a thieno[3,2-b]pyrrole. A base catalyzed formation of an enamine (33) from 5-methyl-4-nitrothiophene-2-carboxylic acid (32) and N,N-dimethylformamide dimethyl acetal (DMF-DMA) forms the first step of this reaction. This step is followed by the reductive cyclization of the enamine to afford the desired thieno[3,2-b]pyrrole (34) as the product (Scheme 6).23

Scheme 6: Batcho-Liemgruber synthesis

1.2 (d) Sundberg synthesis:

Another synthetic route to furo-, thieno- and seleno[3,2-b]pyrroles from substituted thiophenes, furans and selenophenes that displays the versatility of azides was reported by Salo Gronowitz et al.24 The reaction, referred to as “Sundberg synthesis” was performed earlier on substituted benzaldehydes to synthesize indoles.25 The Sundberg synthesis utilizes the thermal decomposition of azidoalkenylarenes 36 to form the corresponding products 38. The azido compounds required for this synthesis were prepared by ‘aldol’ condensation of an azidoaldehyde (35) (Scheme 7).
Scheme 7: The preparation of furo-, thieno- and seleno[3,2-b]pyrroles by the Sundberg reaction.

This reaction is mechanistically regarded as an insertion of the intermediate nitrene (37) into a C-H bond to give the intermediate (37a) followed by a $6\pi$ electrocyclization to generate the fused heterocycle (38) (Scheme 8).

Scheme 8: Plausible mechanism of the Sundberg reaction

1.2 (e) Cadogan-Sundberg synthesis:

Another versatile indole synthesis that also involves a nitrene intermediate is the Cadogan-Sundberg synthesis.$^{26,27}$ The generation of the nitrene in this reaction is carried out through a trialkyl phosphite assisted reductive deoxygenation of the corresponding o-nitroalkenylarene (39). The nitrene intermediate could be imagined to
have formed from a nucleophillic attack of the phosphite on the nitro group of 39, leading to the intermediate (40). Subsequent loss of triethyl phosphate to form the nitroso compound (43), followed by another similar addition and elimination would produce the nitrene intermediate (47). Insertion of the nitrene into the C-H bond, as suggested in the Sundberg synthesis would generate the required product 48 (Scheme 10). Successful applications of this reaction with respect to pyrroloheterocycles include 5-arylthieno[3,2-b]pyrrole and 5-arylthieno[2,3-b]pyrrole as well as their respective parent thienopyrroles (Table 2).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
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<td><img src="image2" alt="Product 1" /></td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>42%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>NA</td>
</tr>
</tbody>
</table>

1.2 (f) Snyder’s synthetic approaches to thienopyrroles:

Among the numerous syntheses of the thienopyrrole scaffold by various researchers, the synthetic efforts of Snyder and his co-workers deserve to be mentioned. The earliest report by the Snyder group was an application of the Reissert indole synthesis in the synthesis of the parent thieno[3,2-b]pyrrole (55). With a slight modification of the Reissert indole synthesis, the Snyder group synthesized the parent thieno[3,2-b]pyrrole (55) through the intermediate pyruvic acid (53), that was prepared from 2-methyl-3-nitrothiophene (49) via an azlactone (52). The pyruvic acid (53) was then subjected to reductive cyclization in presence of aqueous NH₃ and ferrous sulphate to afford the thienopyrrole carboxylic acid (54). Decarboxylation of 54 gave the thieno[3,2-b]pyrrole (55), which proved to be unstable when exposed to air (Scheme 11).
A similar reaction sequence, when employed to synthesize the isomeric thieno[2,3-b]pyrrole, resulted in its decomposition prior to purification.

Scheme 11: Modified Reissert indole synthesis; preparation of thieno[3,2-b]pyrrole

The “Reissert indole synthesis” sequence of preparing the pyruvic ester (56) from 2-methyl-3-nitrotoluene (49) and diethyloxalate was utilized in the preparation of 5-carboethoxy thieno[2,3-b]pyrrole (21a) (Scheme 12).

Scheme 12: 5-carboethoxy thieno[2,3-b]pyrrole via the Reissert indole synthesis

With the observed instability of the parent thienopyrroles, an alternate approach to synthesize the thieno[3,2-b]pyrrole (55) as well as the N-benzyl derivative (55a) from pyrrole was designed by Snyder. This route features the unusual formation of 3-
thiocyanopyrrole (58) from the pyrrole (57) and thiocyanogen. The 3-thiocyanopyrrole (58) was converted into the 3-pyrrolylthioacetic acid (59) which was cyclized to the thieno[3,2-b]pyrrole-3-one (60) in presence of polyphosphoric acid. Sodium borohydride reduction of 60 afforded the desired thieno[3,2-b]pyrrole (55) (Scheme 13).

\[ \text{Scheme 13: The alternate syntheses of thieno[3,2-b]pyrroles via "thiocyanation" route.} \]

The isomeric N-benzylthieno[2,3-b]pyrrole (67) was synthesized by a slightly different procedure\textsuperscript{34} from N-benzyl-3,4-pyrroledicarboxylate (61). Compound 61 was converted into the intermediate 2-thiocyanopyrrole derivative (62) utilizing thiocyanogen chloride in the first step. This step was followed by the preparation of the pyrrolylthioacetate (63) by sodium borohydride reduction and subsequent alkylation with ethylbromoacetate. The pyrrolylthioacetate (63) cyclized to the thieno[2,3-b]pyrrole diester (64) through a NaH driven Dieckmann condensation. Hydrolysis and decarboxylation in presence of sulphuric acid led to the keto acid (64), which was converted to the desired N-benzylthieno[2,3-b]pyrrole (67) by subsequent reduction and decarboxylation (Scheme 14).
Scheme 14: Synthesis of N-benzylthieno[2,3-b]pyrrole via thiocyanation

1.2 (g) Synthesis from ketene-N,S-acetals:

Active methylene compounds have become a significant resource in the construction of several complex molecules. This strategy has been used to construct a thieno[2,3-b]pyrrole in two steps, using alkyl or arylisothiocyanate as shown in the Scheme 15.\(^{35}\)

The first step in this synthesis involved a base catalyzed condensation of an activated methylene compound (68) with an alkyl or an aryl-isothiocyanate to form an intermediate ketene aminothioacetal (69), which reacts with α-bromoethylacetate to form the corresponding aminothioacetal (70). A Dieckman cyclization or a Thorpe-Ziegler cyclization of 70 affords the thiophene (71). The fusion of the pyrrole ring occurred as the second step, with the reaction between the thiophene 71 and α-bromoethylacetate in the presence of anhydrous potassium carbonate. The thieno[2,3-b]pyrrole (72) was obtained as the product after 5 days when acetone was chosen as the solvent.
In a comparative study, the same compound was synthesized from the pyrrole derivative (74). The first step in this study involved the formation of N-phenyl-S-methylketene-N,S-acetal (73) from compound 68, phenylisothiocyanate and methyliodide under similar basic conditions. Subsequent transformation into the 2-methylsulfanylpyrrole derivative (74) was easily achieved from a base mediated concurrent substitution condensation of 73 with α-bromoethylacetate. The ultimate construction of the thiophene ring on the pyrrole 74 was brought forth by a nucleophillic aromatic substitution with thiogycolate in presence of a strong base. These two routes developed by the Kirsch group36 were used to synthesize a variety of thieno[2,3-b]pyrroles. However, this reaction is limited to the synthesis of penta-substituted thieno[2,3-b]pyrroles only.

Route 1:
Route 2:

\[
\begin{align*}
\text{R} \rightarrow & \quad 1. K_2CO_3/DMF \\
& \quad 2. PhNCS \\
& \quad 3. CH_3I
\end{align*}
\]

Scheme 15: Preparation of thieno[2,3-b]pyrroles from ketene-N-S-acetals

1.2 (h) Synthesis of a pyrrolo[3,2-d]thiazole derivative:

A lately reported two step synthesis of a pyrrolo[3,2-d]thiazole ring system involved the preparation of an intermediate thiooxamide (76) from an aminopyrrole derivative (75) using sulphur and chloroacetamide. The oxidative cyclization of the intermediate thioxamide (76) with $K_3[Fe(CN)_6]$ under basic conditions gave the pyrrolo[3,2-d]thiazole derivative (77) as the product (Scheme 16).\textsuperscript{36}

Scheme 16: Synthesis of the pyrrolo[3,2-d]thiazole derivative via oxidative cyclization
1.3. Transition metal mediated syntheses of pyrroloheterocycles

1.3 (a) Introduction:

A glance at the Hemmetsberger-Knittel, Sundberg, and Cadogan-Sundberg syntheses depict the formation of nitrenes as intermediates. Current research has focussed on either generating or trapping these nitrenes with transition metals. Nickel, platinum, rhodium, ruthenium, molybdenium and tin have been used in these strategies. A number of fused nitrogen-heterocycles were synthesized in high yields by Driver and his group utilizing the concept of rhodium (II) mediated insertion of nitrene into a C-H bond (Table 3). The highlight of this reaction was the tolerance of 5% rhodium perfluorobutyrate to both electron donating and withdrawing substituents on the aryl ring and the generation of the rhodium nitrenoid (79) at sufficiently low temperatures.

![Scheme 17: Rhodium (II) catalyzed synthesis of nitrogen heterocycles](image-url)
Table 3: Examples of the N-heterocyclic compounds synthesized with 5% Rh(II) at 60 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
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<td><img src="image1" alt="Substrate" /></td>
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<td>79%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td><img src="image4" alt="Product" /></td>
<td>84%</td>
</tr>
</tbody>
</table>
| 3     | ![Substrate](image5) | ![Product](image6) | R= piv: 88%  
R= Boc: 94% |

The ability to form stable complexes with ligands has rendered palladium as an ideal catalyst in a number of bond formation reactions in organic chemistry. An application of the palladium-catalyzed intramolecular Heck reaction has been described by Wensbo and Gronowitz to synthesize all the three isomeric thienopyrrole derivatives from the respective Boc-protected aminohalo-thiophenes (Table 4).
Table 4: Intramolecular Heck reaction in the synthesis of the three isomeric thienopyrroles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>58%</td>
</tr>
</tbody>
</table>

Catalyst: Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$

1.3 (b) Palladium-catalyzed reductive N-heteroannulation:

Among the multitude of palladium-catalyzed reactions that have been and are still being used by a number of researchers around the world, a class of reactions known as “palladium-catalyzed reductive N-heteroannulation” reactions has created a niche for itself in the realm of palladium chemistry. Cenini et al. reported the first palladium catalyzed de-oxygenation of o-substituted nitrostyrenes in the presence of carbon monoxide under high temperatures and high pressures. An example from their study on (2-pyridyl)-o-nitrostyrene (81) with 5 mol% Pd(TMB) under 40 atm. of CO at 180 °C for 3 hours gave 2-pyridylindole (82) in good yield (Scheme 18).
Scheme 18: The palladium-catalyzed reductive de-oxygenation reaction by the “Cenini group”

With the product, an indole, being the same as the one obtained from the conventional Cadogan-Sundberg reaction, Cenini proposed that this reaction also goes through a nitrene intermediate, likely bound to the metal (Figure 7). Evidence for this proposition was later established by Cenini when a ruthenium carbonyl-bound nitrene (84) was isolated from a reaction between 2-nitrobiphenyl (83) and a stoichiometric amount of Ru3(CO)12. This intermediate metal-bound nitrene reacted with carbon monoxide to yield the carbazole (85) (Scheme 19).

Figure 7: The hypothetical palladium-bound nitrene intermediate

Scheme 19: Reduction of the ruthenium-bound nitrene
Watanabe and his co-workers reported a similar palladium catalyzed reductive N-heteroannulation of nitroarenes to form indoles. The formation of indole-2-carboxylate (87) from the nitroarene (86) under the catalytic conditions of bis-triphenylphosphine palladium(II)chloride and stannous chloride is shown under Scheme 20.\textsuperscript{44} Although the reaction conditions were milder than Cenini’s protocol, yields of indoles were moderate.

\[
\text{\CHEM{Ph-CN}} \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2, \text{SnCl}_2} \text{CO (20 atm), 100 °C} \quad \xrightarrow{\text{Dioxan}} \text{\CHEM{Ph-NHCOOCH_3}}
\]

\textbf{Scheme 20: Watanabe conditions- the palladium-SnCl\textsubscript{2} catalyzed formation of indoles}

Much milder conditions for the reductive heteroannulation were discovered in our laboratory a decade ago.\textsuperscript{45} The reaction behind this discovery was the formation of 4-bromoindole (89) from 1-(2-bromo-6-nitrophenyl)-ethene (88) (Scheme 21). Since then, this methodology has been thoroughly investigated on a wide range of substrates.\textsuperscript{46} This reaction is performed with 6-10 mol % palladium catalyst, a ligand, and carbon monoxide (4-6 atm) pressure in a suitable solvent. It was also observed that the reductive N-heteroannulation of a mixture of (E/Z) isomers of 90 gave the indole 91 indicating that the stereochemistry at the double bond in the o-nitrostyrene does not effect the yield or the rate of the reaction (Scheme 22).\textsuperscript{46}

\[
\text{\CHEM{Br-Ph=CH-CN}} \xrightarrow{\text{Pd(OAc)}_2, \text{PPh}_3} \text{CO (4 atm), MeCN, 70 °C} \quad \xrightarrow{\text{70 °C}} \text{\CHEM{Br-Ph-NH}}
\]

\textbf{Scheme 21: The conditions for reductive N-heteroannulation}
**Scheme 22: The reductive N-heteroannulation of the isomeric mixture**

1.3 (c) Proposed Mechanism:

A plausible mechanism for the N-heteroannulation would involve the coordination of palladium to the nitro group of the o-nitrostyrene 92 to form a palladocycle 93 in the first step. Carbon monoxide insertion would form 94, which would form the intermediate palladium bound o-nitrosostyrene 95 after the loss of carbon dioxide. One of the pathways suggested from this intermediate, proceeds through a reductive elimination of Pd(0) to give a free nitroso styrene 95a. An intramolecular cyclization followed by a [1,5]-H shift would lead to an N-hydroxy indole 95d, which would ultimately be reduced to the indole (96).

The second suggested pathway from 95 parallels the idea of metal bound nitrenes. The insertion of carbon monoxide to form 95e, and subsequent loss of carbon dioxide would form the palladium bound nitrene (95f). Cyclization, reductive elimination and [1,5] H shift would sequentially lead to the indole (96). Another feasible pathway through the loss of Pd(0) to form a free nitrene 95i from the palladium bound nitrene (95f) is also suggested. An electron cyclization of the free nitrene to the intermediate 95j followed by a [1,5]-H shift would form the indole 96 (Scheme 23).
1.4 Results and discussion:

The “reductive N-heteroannulation”, developed in our laboratories, has been successful in the synthesis of substituted and fused indoles, carbazoles, benzimidazoles, azaindoles, diazaioindoles, carbazolones, and several natural products. From this perspective, the synthesis of fused bicyclic pyrroloheterocycles (100) from their respective alkenyl nitroarenes (99) was visualised. These precursor alkenyl nitroarenes could be prepared via Kosugi-Migita-Stille couplings of halo-
nitroarenes (97) or by condensations of methyl-nitroarenes (98) with benzaldehyde as depicted in Scheme 24.

Scheme 24: The general strategy to synthesize the fused pyrroloheterocycles

An account of the synthesis and attempted syntheses of some of the pyrroloheterocycles which belong to the (5,5) fused category is presented henceforth.

1.4 (a) Synthesis of thieno[3,2-b]pyrrole and thieno[2,3-b]pyrrole derivatives:

The compounds chosen to test the applicability of the palladium-catalyzed N-heteroannulation reaction in this category were the previously reported thieno[3,2-b]pyrrole-5-carboxylic acid methyl ester (107) and 5-phenylothieno[2,3-b]pyrrole (109).\textsuperscript{49} The synthesis of the thieno[3,2-b]pyrrole derivative began with the nitration of the 2-methyl-5-thienic acid (101).\textsuperscript{49} Esterification of the nitro derivative 102 afforded 5-
methyl-4-nitrothiophene-2-carboxylic acid methyl ester (103), which underwent a base catalyzed condensation with benzaldehyde to yield the precursor styrylthiophene 104.

2-Nitrothiophene (105) was the compound of choice to synthesize the thieno[2,3-b]pyrrole analogue. Conjugate addition of methyl magnesium chloride to 2-nitrothiophene gave an inseparable mixture of the three possible isomeric methyl-nitrothiophenes (106). Nitration of 3-methylthiophene was also attempted using Rinke’s method, but a low yield of 3-methyl-2-nitrothiophene gave us no alternative other than to proceed with the mixture of the three isomers. Base catalyzed condensation with benzaldehyde yielded 2-nitro-3-styrylthiophene (107) along with some unidentified material illustrating the necessity of an adjacent electron withdrawing group on the arene to activate the methyl group for condensation (Scheme 25).

Scheme 25: Syntheses of the styryl thiophenes, 104 and 107
Heteroannulation of the two styrylthiophenes 104 and 107 with carbon monoxide under the catalytic conditions of palladium diacetate and triphenyl phosphine afforded the respective thienopyrroles 108 and 109 in good yields (Table 5).

**Table 5: Heteroannulation of the styrylthiophenes, 104 and 107**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Time</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="104" /></td>
<td>Pd(OAc)$_2$, PPh$_3$, CH$_3$CN, 70°C</td>
<td>40 h</td>
<td><img src="image2.png" alt="108" /></td>
<td>71%</td>
</tr>
<tr>
<td><img src="image3.png" alt="107" /></td>
<td>Pd(OAc)$_2$, PPh$_3$, CH$_3$CN, 70°C</td>
<td>24 h</td>
<td><img src="image4.png" alt="109" /></td>
<td>83%</td>
</tr>
</tbody>
</table>

The commercial availability of 2,5-thioxene (110) contributed to the task of executing the synthesis of a thieno[3,2-b:4,5-b']dipyrrole derivative (114). 2,5-Dimethyl-3,4-dinitrothiophene (111) was synthesized from 2,5-dimethylthiophene (110) utilizing the procedure reported by Steinkoff et al.$^{52}$ A base catalyzed condensation with benzaldehyde gave the precursor 3,4-dinitro,2-5-distyrylthiophene (112) as bright orange crystals (Scheme 26).$^{53}$

**Scheme 26: Synthesis of 3,4-dinitro-2,5-distyrylthiophene (112)**
When subjected to heteroannulation conditions with 6% Pd(OAc)$_2$, this compound (112) afforded only a trace amount of the dipyrrole 114 and 2-styryl-3-nitro-5-phenyl-4H-thieno[3,2-b]pyrrole (113)$^{53}$. Increasing the catalyst load to 11% gave the dipyrrole exclusively, but in a moderate yield. The cyclization studies on the compounds 112 and 113 under different amounts of catalyst are presented in Table 6.

![Scheme 27: The heteroannulation of 3,4-dinitro,2-5-distyrylthiophene (112)](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst loading</th>
<th>Time</th>
<th>113</th>
<th>114</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>112</td>
<td>11% Pd(OAc)$_2$</td>
<td>4 days</td>
<td>0%</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>112</td>
<td>6% Pd(OAc)$_2$</td>
<td>60 h</td>
<td>89%</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>112</td>
<td>30% Pd(OAc)$_2$</td>
<td>4 days</td>
<td>0%</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>113</td>
<td>6% Pd(OAc)$_2$</td>
<td>2 days</td>
<td>89%</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>113</td>
<td>8% Pd(OAc)$_2$</td>
<td>7 days</td>
<td>31%</td>
<td>15%</td>
</tr>
</tbody>
</table>

The above results, wherein the formation of 114 occurred in trace quantities from 112 and 113 (Entry 2 & 4, Table 6) as well as in a moderate yield (Entry 1 & 3, Table 6) imply that the aforementioned bicyclisation occurs as a discrete step, which requires a greater amount of catalyst loading.
1.4 (b) Synthesis of furo[3,2-b]pyrrole derivatives:

With the requirement of a halo or an alkyl substituent adjacent to the carbon bearing the nitro group, the procurement of an ideal precursor for the synthesis of furan analogues was an arduous task. An article by Saldabol et al. in which the procedure for the nitration of 5-methyl-2-furanaldoxime (115) was reported, assisted us to obtain the required precursor (Scheme 28). 5-Methyl-4-nitro-2-furanaldoxime (117), thus prepared, underwent the base catalyzed condensation with benzaldehyde to afford the precursor 4-nitro-5-styryl-2-furanaldoxime (118). Reductive heteroannulation with bis(dibenzylideneacetone) palladium (Pd(dba)$_2$) and 1,10-phenanthroline gave a mixture of the corresponding furo[2,3-b]pyrrole as the oxime (119) and nitrile (120) (Table 7). Extension of the reaction time led to a decrease in the amount of the oxime, which indicated that the oxime gradually dehydrated to the corresponding nitrile (120). This result was comparable to the observed decomposition of the isolated oxime at room temperature. On the other hand, heteroannulation conditions with Pd(OAc)$_2$ and PPh$_3$ resulted in trace quantities of the nitrile and some unidentified matter.

A test reaction performed on 5-methyl-2-furanaldoxime (115) with Pd(dba)$_2$ did not yield any nitrile. This confirmed the necessity of a fused pyrrole moiety to facilitate the dehydration process (Scheme 29).
Scheme 28: Preparation of 4-nitro-5-styryl-2-furanaldoxime (118)

Table 7: Heteroannulation conditions evaluated on 4-nitro-5-styryl-2-furanaldoxime (118)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
<th>119</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd (dba), DMF, 1,10-phen, 120 °C</td>
<td>12 h</td>
<td>63% (33 % 118 recovered)</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Pd (dba), DMF, 1,10-phen, 120 °C</td>
<td>22 h</td>
<td>45%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>Pd (dba), DMF, 1,10-phen, 120 °C</td>
<td>48 h</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>Pd (dba), DMF, 1,10-phen, 120 °C</td>
<td>72 h</td>
<td>0%</td>
<td>16%</td>
</tr>
<tr>
<td>5</td>
<td>Pd (OAc), CH₃CN, PPh₃, 70 °C</td>
<td>16 h</td>
<td>0%</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Scheme 29: The test reaction on 5-methyl-2-furanaldoxime (116)
1.4 (c) Synthesis of 2-methyl-5-phenyl-4H-pyrrolo[3,2-d]thiazole:

The reaction between an α-haloketone and thioamide to form a thiazole has been known for more than a century. Widely recognized as the “Hantz thiazole synthesis”\(^5^6\), this reaction has become one of the favorite “thiazole” syntheses owing to the ease of transformation of the reactants into the desired product. Low cost of these reactants is an added advantage. The synthesis of the pyrrolo[3,2-d]derivative (127), began with the utilization of Hantz synthesis to prepare 2,4-dimethylthiazole (124) from α-chloroacetone (123) and thioacetamide (122) following literature procedure.\(^5^7\) The sequential nitration\(^5^8\) and condensation,\(^5^9\) followed by annulation, gave the desired pyrrolo[3,2-d]thiazole derivative (127) (Scheme 30). The results of heteroannulation under different catalytic conditions are presented in Table 8.

Scheme 30: Preparation of 2-methyl-4-nitro-5-styrylthiazole (126)
Table 8: Heteroannulation of the styrylthiazole (126) under different catalytic conditions

![Heteroannulation reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
<th>127</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)$_2$, DMF, 1,10-phen, 120 °C</td>
<td>3 days</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$, CH$_3$CN, PPh$_3$, 80 °C</td>
<td>3 days</td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$, CH$_3$CN, PPh$_3$, 80 °C</td>
<td>3 days</td>
<td>6%</td>
</tr>
</tbody>
</table>

**1.4 (d): Syntheses of pyrrolo[3,2-d]imidazole and pyrrolo[2,3-d]imidazole derivatives:**

According to our general methodology outlined under Scheme 21, it was obvious that both the designated pyrroloimidazole derivatives 133 and 134, could be synthesized from 4(5)-nitro-5(4)styrylimidazole (130). The latter compound was easily formed from the condensation of benzaldehyde with 4(5)-methyl-5(4)nitroimidazole (130). Facile benzylation of 130 with benzyl bromide in N,N-dimethylformamide-potassium carbonate afforded an easily separable mixture of the two isomeric precursors 131 and 132 in a ratio of 3:1, with an overall yield of > 85% (Scheme 31).
Scheme 31: Preparation of the two isomeric styrylimidazoles 131 and 132

Subsequent reductive N-heteroannulation of 131 and 132 in DMF with Pd(dba)$_2$ and 1,10-phenanthroline afforded the desired pyrroloimidazoles 133 and 134, respectively.

Table 9: Preparation of the two isomeric pyrroloimidazoles 133 and 134

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Time</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>131</td>
<td>Pd(dba)$_2$, DMF, 1,10-phenanthroline, 120 °C</td>
<td>6 days</td>
<td>133</td>
<td>77%</td>
</tr>
<tr>
<td>132</td>
<td>Pd(dba)$_2$, DMF, 1,10-phenanthroline, 120 °C</td>
<td>3 days</td>
<td>134</td>
<td>32%</td>
</tr>
</tbody>
</table>
1.4 (e) Attempted synthesis of pyrrolo[2,3-d]isoxazole:

With only one reported synthesis of 3-methyl-5-arylpyrrolo[2,3-d]isoxazole (137) to date, the approach via the “palladium-catalyzed heteroannulation” seemed ideal for a second synthetic account. Nitration of 3,5-dimethylisoxazole (135) afforded the 4-nitro-3,5-dimethylisoxazole (136) \(^{63}\), which condensed with benzaldehyde in presence of piperidine to give the precursor 3-methyl-4-nitro-5-styrylisoxazole (137) (Scheme 32).\(^{64}\)

![Scheme 32: Synthesis of 3-methyl-4-nitro-5-styrylisoxazole (137)](image)

However, this precursor failed to yield the expected product (138) under the attempted heteroannulation conditions (Table 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>Pd(dba)(_2), DMF, 1,10-phen, CO (6 atm), 120 °C</td>
<td>4 days</td>
</tr>
<tr>
<td>2(^a)</td>
<td>Pd(OAc)(_2), CH(_3)CN, PPh(_3), CO (6 atm), 80 °C</td>
<td>3 days</td>
</tr>
</tbody>
</table>

\(^a\) Starting material recovered
1.4 (f) Attempted syntheses of pyrrolopyrrole derivatives:

Having met with substantial success so far in effecting cyclization of alkenyl nitroarenes to the expected fused (5,5) pyrroloheterocycles, utilizing the heteroannulation conditions developed in our laboratory, the next target was the fused pyrrolopyrrole system. The first compound chosen in this category was a pyrrolo[3,2-b]pyrrole (1e). The synthesis of compound 1e commenced with the nitration of 1,2,5-trimethylpyrrole (139) following the literature procedure reported by Pavia.65 By the manipulation of the reaction conditions, a trace of the 1,2,5-trimethyl-3,4-dinitropyrrrole (141) along with the mononitroprrole (140) was obtained (Scheme 33). Attempts to procure the requisite heteroannulation precursor 142 were futile, as no expected condensation reaction occurred between the mononitropyrrrole and benzaldehyde (Table 11).

\[
\begin{align*}
\text{Conc H}_2\text{SO}_4 / \text{KNO}_3 & \quad 0 \, ^\circ\text{C} \text{ to RT} \\
\text{139} & \rightarrow \text{140} \quad \text{NO}_2 \quad \text{141} \quad \text{O}_2\text{N} \\
\text{Time} & \\
30 \, \text{min} & \quad 62\% \quad \text{---} \\
40 \, \text{min} & \quad 47\% \quad 2\%
\end{align*}
\]

Scheme 33: Nitration of 1,2,5-trimethylpyrrole (139)
Table 11: Conditions evaluated in the synthesis of the precursor styrylpyrrole 142

![Image of the reaction of 140 with PhCHO to form 142]

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhCHO (eq)</th>
<th>Base(eq)</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temp</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.6</td>
<td>KOH (3.3)</td>
<td>DMSO</td>
<td>---</td>
<td>RT</td>
<td>4 h</td>
</tr>
<tr>
<td>2</td>
<td>2.4</td>
<td>KOH (3.3)</td>
<td>DMSO</td>
<td>---</td>
<td>RT</td>
<td>36 h</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>KOH (2.2)</td>
<td>DMSO</td>
<td>---</td>
<td>RT</td>
<td>2 h</td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
<td>piperidine</td>
<td>EtOH</td>
<td>---</td>
<td>60 °C</td>
<td>36 h</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
<td>piperidine</td>
<td>Benzene</td>
<td>---</td>
<td>80 °C</td>
<td>9 h</td>
</tr>
<tr>
<td>6</td>
<td>2.3</td>
<td>piperidine</td>
<td>Benzene</td>
<td>AcOH</td>
<td>80 °C</td>
<td>9 h</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>KOH (2.2)</td>
<td>CH₃CN</td>
<td>---</td>
<td>80 °C</td>
<td>8 h</td>
</tr>
</tbody>
</table>

After several unsuccessful attempts to condense 140 with benzaldehyde, it was decided to try the reaction on a pyrrole with an electron withdrawing substituent. The substrate by choice was 5-methyl-1-(4-chlorophenyl)pyrrole-2-carboxylic acid methyl ester (146), which was synthesized with ease from p-chloronitrosobenzene (144) and methylsorbate (143) in excellent yield. Nitration of 146 afforded the corresponding nitro derivative 147. But, even the presence of the electron withdrawing group on the pyrrole failed to give the desired condensation product 150. Even the 1-(4-chlorophenyl)-2-methyl-3-nitropyrrrole (149), obtained from the decarboxymethylation of 147 (Scheme 34) failed, to respond to the attempted condensations (Table 12 and 13).
Scheme 34: Synthesis of 1-(4-chlorophenyl)-2-methyl-3-nitopyrrole (149)
### Table 12: Attempted condensation of (147) with benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhCHO (eq)</th>
<th>Base(eq)</th>
<th>Solvent</th>
<th>Additive</th>
<th>Temp</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>KOH (7)</td>
<td>THF</td>
<td>---</td>
<td>60 °C</td>
<td>20 h</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>KOH (2.5)</td>
<td>DMSO</td>
<td>---</td>
<td>80 °C</td>
<td>22 h</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>piperidine</td>
<td>MeOH</td>
<td>AcOH, HCOOH</td>
<td>100 °C</td>
<td>72 h</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>piperidine</td>
<td>MeOH</td>
<td>AcOH</td>
<td>60 °C</td>
<td>36 h</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
<td>piperidine</td>
<td>Benzene</td>
<td>---</td>
<td>80 °C</td>
<td>9 h</td>
</tr>
</tbody>
</table>

### Table 13: Attempted condensation of (149) with benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhCHO (eq)</th>
<th>Base(eq)</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>KOH (7)</td>
<td>DMSO</td>
<td>60 °C</td>
<td>3.5 days</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.2</td>
<td>KOH (2.5)</td>
<td>DMSO</td>
<td>RT</td>
<td>3 h</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
<td>KOH (4)</td>
<td>DMSO</td>
<td>60 °C</td>
<td>72h</td>
</tr>
</tbody>
</table>

<sup>a</sup> Products unidentified  
<sup>b</sup> Recovered the starting material 149
The synthesis of 3-nitro-4-(2-phenylethynyl)pyrrole (155) by Albert van Leusen et al. from the nitro-diene 154 and TosMIC (tosyl methylisocyanide) has provided another pyrrole substrate to test the feasibility of heteroannulation conditions. The nitro-diene 154 required for this synthesis was prepared by the Henry reaction between cinnamaldehyde (152) and nitromethane (153).

Scheme 35: Synthesis of 3-nitro-4-(2-phenylethynyl)pyrrole

The pyrrole 155 was then converted into the N-methylpyrrole derivative (156) via a phase transfer catalyzed methylation, and also the tosyl derivative (Scheme 36).

Scheme 36: Preparation of N-methyl and N-tosyl derivatives of 3-nitro-4-(2-phenylethynyl)pyrrole
Despite having an ideal pyrrole precursor, the heteroannulation conditions did not yield the desired pyrrolopyrrole 158; the precursor 156 was recovered unchanged in the two attempts (Table 14). Even the choice of having an N-tosyl derivative 157 proved unsuccessful with the formation of some unidentified substances (Entry 2 & 3 Table 14).

Table 14: Attempted heteroannulation on N-methyl- and N-tosyl-3-nitro-4-(2-phenylethynyl)pyrrole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>156</td>
<td>Pd(dba)&lt;sub&gt;2&lt;/sub&gt;, DMF, 1,10-phen, CO (6 atm), 120 °C</td>
<td>5 days</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>157</td>
<td>Pd(dba)&lt;sub&gt;2&lt;/sub&gt;, DMF, 1,10-phen, CO (6 atm), 120 °C</td>
<td>3.5 days</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>157</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;, CH&lt;sub&gt;3&lt;/sub&gt;CN, PPh&lt;sub&gt;3&lt;/sub&gt;, CO (6 atm), 80 °C</td>
<td>3.5 days</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>156</td>
<td>Se, CO (70 psi), CH&lt;sub&gt;3&lt;/sub&gt;CN, 70 °C</td>
<td>3 days</td>
</tr>
</tbody>
</table>

<sup>a</sup> Starting material recovered  
<sup>b</sup> Unidentified products

1.5 Conclusion:

The syntheses of several fused (5,5) pyrroloheterocyclic systems such as the thieno[2,3-b]pyrrole, thieno[3,2-b]pyrrole, furo[3,2-b]pyrrole, pyrrolo[3,2-d]thiazole, and the two isomeric pyrroloimidazoles has been accomplished through the palladium-catalyzed reductive N-heteroannulation reaction. In addition to these compounds, a
thienodipyrrole derivative was also synthesized. Despite the success in the aforesaid systems, the heteroannulation methodology was unsuccessful in the synthesis of the pyrrolopyrrole and the pyrroloisoxazole analogues. The reason behind the recovery of the precursor 3-methyl-4-nitro-5-styrylisoxazole in all the heteroannulation attempts remains unclear. Quite so, the difficulty in the preparation of 2-styryl-3-nitropyrrrole derivatives has further impaired any conclusive evidence to account for the failure in the synthesis of the pyrrolo[3,2-b]pyrrole system.
Chapter 2

Palladium-Catalyzed Synthesis of Isatins

2.1. Introduction to isatin chemistry:

The history of isatin dates back to 1841 when Erdmann $^{69}$ and Laurent $^{70}$ prepared isatin (indole-2,3-dione) (161) independently by the oxidation of indigo (160) with chromic and nitric acids. Although regarded as a synthetic compound for more than a century, isatin’s existence in nature was found in the fruits of the cannon ball tree Couroupita guianensis Aubl and in Calanthe discolor LINDL.$^{71}$ It is also reported as a metabolite derivative of adrenaline in humans and as a component in the parotid gland secretions of Bufo frogs.$^{71}$

![160](image)

Figure 8: Indigo

The chemistry of isatins emerged as an offspring to the intense research in the branch of indigo chemistry during the late nineteenth century. Baeyer reported the formation of dioxindole (161), along with isatide (162), a white substance when isatin was reduced. Further reduction of dioxindole in presence of hot zinc oxide gave oxindole (163) and finally, indole (96) (Scheme 37).$^{71}$
Scheme 37: The stepwise reduction of isatin to indole as recorded by Baeyer

The ability of isatin to dissolve in an alkali to form the salt of isatinic acid (165) inspired Kekule to suggest that isatinic acid was o-aminobenzoylformic acid and that isatin (164) was its internal anhydride. Baeyer realized Kekule’s proposition, and saw the relationship of dioxindole and oxindole to isatin. This led Baeyer to formulate his synthesis of isatin in 1878 by the oxidation of oxindole and also to propose two structures for isatin: the “stable” lactam isatin (164) and the “labile” lactim isatin (166) (Figure 9).

Scheme 38: The reaction behind Kekule’s proposition

Figure 9: The two proposed structures of isatin by Baeyer
Eventually, Baeyer synthesized isatin by boiling o-nitrophenylpropionic acid with alkali in 1878.\textsuperscript{72}

2.2 Significant isatin syntheses:

The discovery of isatin, an orange crystalline solid has spawned a multitude of reactions pertaining to its synthesis. This section summarizes some of the well-known syntheses of isatin.

2.2 (a) Claisen and Shadwel isatin synthesis\textsuperscript{73}:

One of the earliest preparatory routes to isatin was a three step synthesis from o-nitrobenzoylchloride (167) developed in 1879. Known as the Claisen and Shadwel’s synthesis, the first step was the conversion of o-nitrobenzoylchloride (167) into the nitrile by the action of KCN, which was successively treated with HCl and KOH to afford the potassium salt of o-nitrophenylglyoxalic acid (isatinic acid) (168). Reduction of 168 in an alkaline medium to the potassium salt of o-aminophenylglyoxalic acid (169) as the second step, was ultimately followed by an acid treatment to complete the formation of isatin. In this manner, Claisen and Shadwel's synthesis substantiated the structure of isatin as suggested by Kekule (Scheme 40).
2.2 (b) Sandmeyer's syntheses:

Sandmeyer’s method\textsuperscript{74} of synthesizing isatin and many of isatin derivatives tends to be the favorite of many synthetic organic chemists even today. This reaction begins from an aniline \textbf{170}, being treated with chloral hydrate and hydroxylamine in presence of aqueous sodium sulfate to form an intermediate isonitrosoacetanilide \textbf{171}. The subsequent conversion of \textbf{171} to isatin \textbf{164}, when treated with sulfuric acid or less frequently polyphosphoric acid completes the sequence of Sandmeyer’s synthesis (Scheme 40). Several substituted anilines have been successfully converted into the corresponding isatins, usually in high yields. The advantage of this method lies in the fact that the reagents are cheap and easily available. For example, isatin (\textbf{164}) was prepared in $>75\%$ yields;\textsuperscript{72} however, methyl-3-aminobenzoate (\textbf{170x}) afforded the corresponding methyl-4-isatincarboxylate (\textbf{164x}) in a low yield of 34\%.\textsuperscript{75} The drawback of this method lies in the inefficiency to prepare nitroisatins from nitroisonitrosoacetanilides and also in the formation of two isomers from meta-substituted anilines.
Scheme 41: The Sandmeyer synthesis

A second method developed by Sandmeyer to synthesize isatins, generally referred to as “Sandmeyer’s diphenylurea isatin synthesis”, begins with a reaction between a symmetrical diphenylthiourea (172) and potassium cyanide in the presence of lead carbonate to form a cyanoformamidine (173). The next step is the reduction of 173 with ammonium sulfide and subsequent ring closure to isatin-2-anil (175) in presence of sulphuric acid; The ring closure to isatin-2-anil (175) could also be accomplished with aluminium chloride in the presence of benzene or carbon disulfide. An acid catalyzed hydrolysis of isatin-2-anil (175) afforded the desired isatin (164) (Scheme 42).

Scheme 42: Sandmeyer’s diphenylurea isatin synthesis
2.2 (c) Stolle’s synthesis:

An alternative to Sandmeyer’s synthesis is the Stolle’s method (Scheme 43). This synthesis involves the reaction between the aniline (170) and oxalyl chloride to form the intermediate chlorooxalylanilide (176), which cyclized to the corresponding isatin in the presence of a Lewis acid, usually aluminium chloride or BF₃·Et₂O or TiCl₃. This reaction was particularly useful in the synthesis of 1-aryl and polycyclic isatins. An application of this reaction is seen in the synthesis of Melostatin A, although in low yields.

![Scheme 43: Stolle’s isatin synthesis](image)

2.2 (d) The Martinet isatin synthesis⁷², ⁷³, ⁷⁸:

The Martinet synthesis features a condensation between an aromatic amine and an oxomalonate ester (meso-oxalic acid esters) (178) in the presence of an acid to yield a 3-(3-hydroxy-2-oxindole)carboxylic acid derivative (179), which upon oxidative decarboxylation affords the desired isatin (Scheme 44). This method was successfully applied to synthesize 5,6-dimethoxyisatin (180) from 4-aminoveratrole (177), but was less successful when applied to 2,4-dimethoxyaniline.⁷²
2.2 (e) Gassman synthesis:

Another general procedure was developed by Gassman and his group in the late nineteen seventies. Although rarely used, this procedure deserves to be mentioned because of a different pathway, wherein a sulphur compound was used en route to isatins. The applicability to anilines with a broad spectrum of electron-withdrawing and electron-donating substituents offers an additional advantage of this reaction. The synthetic sequence begins with the preparation of a 3-methylthio-2-oxindole (176) from a substituted aniline (170). Subsequent chlorination of the 3-methylthio-2-oxindole 176 with NCS followed by hydrolysis yields the corresponding isatin. Two methods were designed to synthesize the 3-methylthio-2-oxindole (176), and the method of choice depends upon the substituents on the aromatic ring. With electron-withdrawing groups substituted on the aromatic ring, the synthesis of the oxindole derivative was achieved via an N-chloroaniline intermediate 171, which further reacts with a methylthioacetate ester (172) to give the azasulfonium salt (174) (Method 1). In the case of electron donating substituents, the azasulphonium salt 174 was synthesized by reacting the aniline with the chlorosulphonium salt (173) (Method 2).

The reaction is believed to proceed through a proton abstraction from the azasulfonium salt 174 to form an intermediate sulphur ylide 175, which undergoes a
Sommelet-Hauser rearrangement, followed by ring closure, to afford the 3-methylthio-2-oxindole 176.

\[
\begin{align*}
170 & \xrightarrow{(\text{CH}_3)_3\text{COCl}} \ 171 \\
& \xrightarrow{\text{S}^\ominus\text{OEt}} \ 174 \\
170 & \xrightarrow{\text{Et}_3\text{N}} \ 175 \\
& \xrightarrow{\text{H}^+} \ 176 \\
& \xrightarrow{\text{NCS}} \ 177 \\
& \xrightarrow{\text{HgO/ BF}_3, \ OR \ H_2O, \ THF, \ Heat} \ 164 (R=\text{H})
\end{align*}
\]

**Scheme 45: Gassman’s isatin synthesis**

### 2.3 Miscellaneous Syntheses:

A considerable number of less frequently employed procedures have been developed by several researchers for the preparation of isatin and isatin-derivatives. One of those less frequently referred syntheses is the Reissert’s synthesis
of isatin, documented in 1904. This reaction involves the formation of isatin from thiooxanilide in the presence of sulphuric acid (Scheme 46).\textsuperscript{80}

![Scheme 46: Reissert isatin synthesis](attachment:image)

A relatively recent method, published in 1994, is based upon the directed ortho-metalation of N-pivaloyl- and N-Boc anilines.\textsuperscript{81} The dianions formed are trapped with diethyloxalate and the isatins are obtained after deprotection and cyclization of the intermediate ketoesters \textsuperscript{186} under acidic conditions (Scheme 47). This method has the advantage of being regioselective when meta-substituted anilines with metalation directing groups such as OMe are used.

![Scheme 47: Isatins via metalation of anilide derivatives](attachment:image)

Another report describes the synthesis of isatins via a lithium-halogen exchange reaction of ortho-bromophenylureas. Carbonylation and subsequent cyclization afforded the respective isatins in good yields.\textsuperscript{82}
There have been several articles pertinent to the oxidation of indoles by chromic acid as a preparatory route to isatins. A recent article by Yadav and his group described an indium chloride catalyzed, IBX (2-iodoxybenzoic acid) mediated oxidation of indoles to isatins in excellent yields. Another noteworthy preparation of isatin involving a mild oxidation of 3-bromoindole (183) with N-bromosuccinimide through the formation of the intermediate 3,3-dibromo-2-oxindole (186) has been reported by Parrick and coworkers. Facile hydrolysis of the intermediate 186 in aqueous methanol afforded the isatin in high yield. This strategy was applied to obtain 4- and 6-substituted isatins from the hydrolysis of the corresponding 3,3-dihalo-2-oxindoles (Scheme 49).
The use of a palladium in the synthesis of isatins has been demonstrated by Yamamoto and his coworkers. The synthetic sequence describes the “palladium-catalyzed double carbonylation” of ortho-haloacetanilides (187) in the presence of diethylamine to yield the corresponding α-ketoamide 188. The α-ketoamide afforded the isatin (164) in nearly quantitative yield upon acid hydrolysis (Scheme 50).\textsuperscript{86}

![Scheme 50: Isatins via palladium-catalyzed double carbonylation](image)

2.4 The significance of isatin:

The ability to display a wide variety of biological activities has established isatin as a ‘versatile starting material’ in the design and synthesis of several new compounds. Isatin has been found as an endogenous material in mammalian tissues. The presence of both the keto and the lactam groups in isatins has led to numerous reactions of which reduction and nucleophillic addition at the C-3 keto group are of potential interest. The property of isatins to yield indoles on reduction has been applied in the synthesis of substituted ellipticine derivatives.\textsuperscript{87} Partial reduction of isatins yields dioxindole and oxindole. An acid catalyzed reaction between isatin (164) and oxindole (163) gives isoindigo (189), which is diastereoselectively converted into diazacrisenodiones (191) via reduction and subsequent rearrangement of the intermediate 190 (Scheme 51).\textsuperscript{71}
Scheme 51: Reaction between isatin and oxindole

Isatin was used as the starting material in the synthesis of the analgesic drug, pemedolac (195). The precursor to this drug, an indole derivative, was synthesized from isatin and methyl-3-phenylpropionate (192). This reaction was initiated by a C3 alkylation to yield a dioxoindole derivative (193), which was reduced to the corresponding indole (194) (Scheme 52).
Scheme 52: The intermediate to Pemedolac

A similar reaction sequence was used in the synthesis of the alkaloid, Hobertine (198).\(^7^1\)

Scheme 53: Synthesis of Hobertine

Isatin reacts with hydroxylamine and hydrazine derivatives to give the expected condensation products, but the reaction with ammonia led to the formation of isamic acid (201) and isamide (202). Although these products were known since 1876, it was not until 1976 that their actual structures were elucidated by Sir John Cornforth.\(^8^8\) Isamic acid is structurally regarded as a dimer formed from the reaction between two
molecules of isatin and one molecule of ammonia. The formation of isatin imine, from a condensation in the first step, followed by the imine attack on the second molecule of isatin, would lead to an intermediate 200 that is ultimately transformed into isamic acid 201. This transformation is assumed to proceed via lactamization and subsequent ring opening and re-closure by an internal nucleophillic attack. A second equivalent of ammonia converts the acid into the amide 202 (Scheme 54).

![Chemical structures](image)

**Scheme 54: The reaction between isatin and ammonia**

Contrary to the expected nucleophillic attack at C3, the reaction between ammonia and N-acetylisatin (203) occurred with a nucleophillic attack at C2 resulting in a ring opening reaction. The benzoylformamide (204) obtained as the product further reacts with a second equivalent of ammonia to yield the quinazoline derivative (205) (Scheme 55).
Oxidizing agents like hydrogen peroxide or chromic anhydride oxidize isatin to isatoic anhydride (206), which condenses with proline to afford a pyrrolo[1,4]benzodiazepine ring (207), a structural pattern found in antineoplastics (Scheme 56)\(^1\).

Known as the ‘Pfitzinger reaction’ in organic chemistry, the reaction between isatin (164) and acetone in presence of an aqueous alkali to give quinoline-4-carboxylic acid (cinchoninic acid) (211) was first published by Pfitzinger in 1886.\(^89\) Since its discovery, there have been numerous articles wherein isatin and its derivatives were reacted with several ketones to generate a series a cinchoninic acid derivatives.\(^90\) The generally accepted mechanism for this reaction involves the hydrolysis of the amide bond of isatin to form the salts of isatoic acid (169) that condense with the ketones to form the salt of the enamine (208). The salt undergoes cyclization and dehydration to
yield the desired 4-quinoline-carboxylic acids as the salts (210), which are hydrolyzed with an acid, usually acetic acid to form the desired products (Scheme 57). The Pfitzinger reaction has also been carried out with α-acetoxyacetophenones, in which case 3-hydroxy-quinoline-4-carboxylic acids were obtained. Articles with hydrazides and enamiones leading to 4-carboxamido-quinoline-3-carboxylates as well as imidines, which lead to 2-aminoquinoline-4-carboxamides were also reported.

Scheme 57: The Pfitzinger reaction

A large number of isatin applications are listed in several scientific journals, including those in medicine and pharmacy. The use in colorimetry, owing to the property of isatin to form coloured substances with certain amino acids and steroids and also the use in catalysis, when complexed with transition metals, are some of the miscellaneous applications worth mentioning.
2.5 Results and discussion:

As a result of the success encountered in the synthesis of indoles and pyrroloheterocycles via the ‘palladium-catalyzed reductive N-heteroannulation methodology’, the similar annulation conditions of palladium diacetate (6 mol%), triphenylphosphine and carbon monoxide (6 atm) were tried by a former student Chet Howerton on a new substrate, 2-(2-bromoethynyl)-1-nitrobenzene (212a). He observed that 212a was completely consumed within an hour at 70 °C yielding a new product, identified as isatin (Scheme 58).

\[
\begin{align*}
\text{Br} & \quad \text{Pd(OAc)}_2, \text{PPh}_3 \\
\text{CO (6 atm),CH}_3\text{CN} & \quad \text{O} \\
\text{212a} & \quad \text{164 (35\%)}
\end{align*}
\]

Scheme 58: The discovery of the palladium-catalyzed synthesis of isatin

Reflecting upon the unique position isatin occupies in the annals of medicinal and organic chemistry, this reaction was subjected to further investigation. Executing the reaction in the absence of carbon monoxide, nevertheless resulted in the formation of isatin, indicating that carbon monoxide was not a requirement in this reaction (Table 15). The addition of benzoquinone as an oxidant did not produce any remarkable change except when THF was used as the solvent (Table 15, Entry 6). When this reaction was performed in the presence of triphenylphosphine in water, without any palladium catalyst at room temperature, isatin was obtained after 24 h in a low yield along with the acetylene 213. This result indicated that palladium does indeed catalyze the formation of isatin from its precursor 212a (Scheme 59).
This reaction was then tested with a variety of solvents and two other palladium catalysts, bis(acetonitrile)palladiumchloride [PdCl$_2$(MeCN)$_2$] and bis(triphenylphosphine)palladiumchloride [PdCl$_2$(PPh$_3$)$_2$] under different conditions. The results of this study are presented in Table 15. Isatin was obtained in all the cases, but was either in low yield, or was contaminated with some inseparable material in most attempts. The reaction was also examined with the chloro and iodo analogues (212b and 212c) (Table 15, entry 14,16,17,18). The best result was observed when the temperature was 60 °C with the solvent as acetone and PdCl$_2$(PPh$_3$)$_2$ as the catalyst, wherein isatin was obtained in a yield of 83% (Entry 16). With this observed result, iodo-alkynes were chosen as the “substrate of choice” with PdCl$_2$(PPh$_3$)$_2$ as the catalyst and acetone as the solvent.
Table 15: Optimization of the reaction conditions, as recorded by Chet Howerton

![Diagram of molecular structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Solvent(^a)</th>
<th>Catalyst (mol%)</th>
<th>Additive</th>
<th>Temp</th>
<th>Time</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>MeCN</td>
<td>Pd(OAc)(_2) (10)</td>
<td>PPh(_3) (40 mol%), CO (4 atm)</td>
<td>70 °C</td>
<td>1 h</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>MeCN</td>
<td>Pd(OAc)(_2) (10)</td>
<td>CO (4 atm)</td>
<td>70 °C</td>
<td>1 h</td>
<td>11%</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>MeCN</td>
<td>Pd(OAc)(_2) (10)</td>
<td>----</td>
<td>70 °C</td>
<td>4.5 h</td>
<td>~ 22%</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>MeCN</td>
<td>Pd(OAc)(_2) (10)</td>
<td>Benzoquinone (100 mol %)</td>
<td>70 °C</td>
<td>4 h</td>
<td>~ 42%(^c)</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>MeCN</td>
<td>Pd(OAc)(_2) (10)</td>
<td>Benzoquinone (100 mol %)</td>
<td>70 °C</td>
<td>22 h</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>THF</td>
<td>Pd(OAc)(_2) (10)</td>
<td>Benzoquinone (100 mol %)</td>
<td>70 °C</td>
<td>3.5 h</td>
<td>52%</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>THF</td>
<td>Pd(OAc)(_2) (5)</td>
<td>----</td>
<td>65 °C</td>
<td>3.5 h</td>
<td>10%</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>MeCN</td>
<td>PdCl(_2)(MeCN)(_2) (10)</td>
<td>----</td>
<td>70 °C</td>
<td>3 h</td>
<td>~ 24%(^c)</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>THF</td>
<td>PdCl(_2)(MeCN)(_2) (5)</td>
<td>----</td>
<td>70 °C</td>
<td>3 h</td>
<td>~ 24%(^c)</td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>THF</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>65 °C</td>
<td>3.5 h</td>
<td>~ 44%(^c)</td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td>DMSO</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>65 °C</td>
<td>3.5 h</td>
<td>~ 25%(^c)</td>
</tr>
<tr>
<td>12</td>
<td>Br</td>
<td>CH(_2)Cl(_2)</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>65 °C</td>
<td>24 h</td>
<td>~ 48%(^d)</td>
</tr>
<tr>
<td>13</td>
<td>Br</td>
<td>Acetone</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>rt</td>
<td>20 h</td>
<td>48%</td>
</tr>
<tr>
<td>14</td>
<td>Cl</td>
<td>Acetone</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>rt</td>
<td>22 h</td>
<td>47%</td>
</tr>
<tr>
<td>15</td>
<td>Br</td>
<td>Toluene</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>60 °C</td>
<td>20 h</td>
<td>~ 47%</td>
</tr>
<tr>
<td>16</td>
<td>I</td>
<td>Acetone</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>60 °C</td>
<td>4 h</td>
<td>83%</td>
</tr>
<tr>
<td>17</td>
<td>I</td>
<td>Acetone</td>
<td>PdCl(_2)(PPh(_3))(_2) (5)</td>
<td>----</td>
<td>rt</td>
<td>20 h</td>
<td>73%</td>
</tr>
<tr>
<td>18</td>
<td>I</td>
<td>Acetone</td>
<td>AgNO(_3) (5)</td>
<td>----</td>
<td>rt</td>
<td>237 h</td>
<td>11%</td>
</tr>
</tbody>
</table>

(a) 0.02-0.06 M solution of the substance (b) total consumption of the starting material (c) impure product obtained (d) in a closed vessel
The synthesis of 2-(2-bromoethynyl)-1-nitrobenzene (212a) was carried out in two steps from the commercially available ortho-iodonitrobenzene (214). The first step involved the preparation of 2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216) utilizing the palladium(0) catalyzed “Sonagashira reaction”\(^{92}\) between 214 and trimethylsilylyethyne (215). The typical Sonagashira conditions: a palladium(0) complex and a halide salt of copper(I) were used with triethylamine as the solvent. The palladium(0) complex used in our case was the tetrakis(triphenylphosphine)palladium generated in situ from PdCl\(_2\)(PPh\(_3\))\(_2\) and triphenylphosphine, and the product 2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216)\(^{93}\) was obtained in almost quantitative yield. This compound was then transformed into desired 2-(2-bromoethynyl)-1-nitrobenzene (212a) in the presence of NBS and a catalytic amount of silver nitrate in DMF as the solvent (Scheme 60).\(^{94}\)

![Scheme 60: The two step synthesis of 2-(2-bromoethynyl)-1-nitrobenzene (212a)](image)

A series of iodo-alkynes were then synthesized from a selection of ortho-iodonitrobenzenes having both electron withdrawing and electron donating substituents, following the aforementioned sequence. The Sonagashira coupling products were obtained in good yields (80-99\%) for all substrates. However, it was found that the iodo-alkynes (217a...217g) were unstable and transformed into a red
substance on standing at room temperature. Although most of them were beyond identity, the one obtained from the iodo-alkyne 217d was identified as the corresponding 2-iodoisatogen (249). This bright red solid was stable at room temperature, and its structure was confirmed by a single crystal X-ray analysis. The formation of this isatogen 249 was also observed when the TMS-alkyne 216d was treated with NIS-AgNO₃ under different catalyst loading and reaction times, at room temperature (Scheme 61). These results as recorded by us are presented in Table 16.

Scheme 61: Formation of the 2-iodo-5-methoxyisatogen (249), alongside the iodoalkyne 217d

Table 16: The reaction conditions evaluated on 5-methoxy-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216d)

<table>
<thead>
<tr>
<th>Entry</th>
<th>AgNO₃</th>
<th>Time</th>
<th>% Yield</th>
<th>217d</th>
<th>249</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 mol %</td>
<td>1 hr</td>
<td>77%</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50 mol %</td>
<td>5 hr</td>
<td>-----</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>100 mol %</td>
<td>5 min</td>
<td>95%</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5 mol %</td>
<td>24 hr</td>
<td>-----</td>
<td>83%</td>
<td></td>
</tr>
</tbody>
</table>

64
The obtained iodoalkynes were ultimately treated with PdCl$_2$(PPh$_3$)$_2$ (5%) in acetone, under an inert atmosphere and at ambient temperature, and the corresponding isatins were obtained in moderate yields (Table 17). It was, however, the pyridine derivative (220), which failed to yield the corresponding 4-azaisatin. An unidentified orange substance was formed in all attempts.

Table 17: The sequential conversion of 2-halonitrobenzenes to the corresponding isatins

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sonagashira Coupling</th>
<th>Iodination</th>
<th>Isatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>214a R = 4-NO$_2$</td>
<td>216a</td>
<td>217a$^1$ (89%)</td>
</tr>
<tr>
<td>2</td>
<td>214b R = 4-Cl</td>
<td>216b</td>
<td>217b$^1$ (89%)</td>
</tr>
<tr>
<td>3</td>
<td>214c R = 4-OMe</td>
<td>216c</td>
<td>217c$^1$ (77%)</td>
</tr>
<tr>
<td>4</td>
<td>214d R = 5-OMe</td>
<td>216d</td>
<td>217d$^1$ (77%)</td>
</tr>
<tr>
<td>5</td>
<td>214e R = 3-Me</td>
<td>216e</td>
<td>217e$^{1,2}$ (93%)</td>
</tr>
<tr>
<td>6</td>
<td>214f R = 4-Me</td>
<td>216f</td>
<td>217f$^1$ (73%)</td>
</tr>
<tr>
<td>7</td>
<td>214g R = 6-Me</td>
<td>216g</td>
<td>217g$^1$ (93%)</td>
</tr>
<tr>
<td>8</td>
<td>218</td>
<td>219</td>
<td>220 (69%)</td>
</tr>
</tbody>
</table>

$^1$ The compounds decompose on standing at room temperature
$^2$ The compound decomposes on attempted purification on silica.

Taking into account the availability of the inexpensive 6-nitropiperonal (221) and foreseeing the method to convert it into the corresponding isatin, the precursor
bromoalkyne 223 was synthesized in two steps: a Corey-Fuchs reaction\textsuperscript{95} as the first step to give the dibromide 222, and a cesium carbonate mediated dehyrobromination as the second step. The precursor bromoalkyne 223 thus obtained gave the expected 5,6-methylenedioxyisatin (224) in 35\% yield in the presence of PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} and acetone (Scheme 62).

Scheme 62: Preparation of 5,6-methylenedioxyisatin (224)

A notable observation during the conversion of the iodoalkynes to isatins was a gradual colour change of the reaction mixture from yellow to orange, and then to red. Having identified the isatogen 249 as the transformed product from the iodoalkyne 217d, an analysis of the reaction at the intermediate “orange-colour” stage was attempted.

The bromoalkyne 212a was refluxed in dichloromethane with PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} (10\%) at 45 °C for 80 minutes under an inert atmosphere. The orange solution was cooled to room temperature, the solvent evaporated, and the crude was quickly purified by flash chromatography. The product obtained was an orange solid, which gradually changed
to isatin at room temperature. The spectroscopic analysis of this orange solid indicated it to be 2-bromoisatogen (225) (Scheme 63).

![Scheme 63: Formation of 2-bromoisatogen (225)]

2.6 Isatogens:

Isatogens, also known as 2-substituted-3H-indole-3-one-1-oxides were first described by Baeyer during his years of research on indigo in 1881. The parent isatogen 227 reported by Baeyer was the 2-carboxylic acid ethylester (227), prepared by the action of cold sulphuric acid on the o-nitrophenylpropionic acid ethylester (226) (Scheme 64).

![Scheme 64: Baeyer's synthesis of the “parent isatogen”]

Synthetic routes to 2-aryl-substituted isatogens have been reported from “alkynic derivatives”. One of the reported reactions involved a coupling between the 2-ethynylbenzene 228 and ortho-iodonitrobenzene (214) under the Stephen-Castro conditions to yield the (o-nitrophenyl)phenylacetylene (229), which cyclized to 2-
phenylisatogen (230). A recent publication utilized the Sonagashira conditions on the same substrate and the isatogen 230, was isolated as the product after 3-4 days in good yield. The same procedure was successful in preparing the 2-pyridyl isatogen 233 in good yield (Scheme 65).

A reaction that involves an ultraviolet irradiation of pyridinium ethanol derivatives 236, prepared from 2-nitrobenzaldehydes 234 and benzyl pyridinium salts 235 to form 2-arylistogens 236, has been developed by Krohnke and his coworkers. These isatogens 238 were also obtained by the action of a base on vinylpyridinium salts 237, the dehydrated products of the pyridinium ethanol derivatives 236 (Scheme 66).
Scheme 66: Krohnke’s isatogen synthesis

Alternately, photochemical transformations of 2-nitrophenylalkyne derivatives have also been published.\(^9^9\) Oxidation of 2-substituted indolines provides another route to isatogens. Indolines, usually obtained by the reduction of 2-substituted indoles with sodium cyanoborohydride, were oxidized to the corresponding isatogens in the presence of m-CPBA.

Bond and Hooper have reported the formation of 2-phenylisatogen (230) in high yield from the peracid oxidation of the corresponding N-hydroxy-2-phenylindole (239) (Scheme 67).\(^1^0^0\) A direct oxidation of 2-phenylindole to 2-phenylisatogen (230) via oxidation with Mimoun’s reagent (MoO\(_5\)-HMPA) deserves to be mentioned as MoO\(_5\) was found to exhibit this property only when complexed with HMPA (Scheme 68).\(^1^0^1\)
Interest in isatogens has been due to their biological activities against a range of bacteria and fungi. Some isatogens have been known to inhibit the synthesis of ATP from mitochondrial preparations. Isatogens were also suggested as spin trap adducts for trapping hydroxyl and superoxide radicals. The redox potentials of isatogens are comparable to naphthaquinones and benzoquinones; a property that renders them as good oxidizing agents.

The ability of isatogen to exhibit reactivities at both the nitrone and carbonyl groups is apparent from its structure. This has instigated a study on the reactivity of these compounds, an outcome of which has been the formation of ring expansion products. The reaction carried out by Noland and Jones on the 2-phenylisatogen with ammonia in presence of ethanol gave 3-phenyl-4-cinnolinol-1-oxide, which was reduced to 3-phenyl-4-cinnolinol. This transformation has been visualized as a nucleophilic attack of NH\textsubscript{3} on C-2, followed by a ring-cleavage to form the
intermediate nitroso-derivative 242. A second intramolecular nucleophillic attack would lead to a ring closure to give the intermediate 243 which would undergo air-oxidation to the 1-oxide 244 (Scheme 69).\textsuperscript{104}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_69}
\caption{Scheme 69: Ring expansion reaction of 2-phenylisatogen with NH$_3$}
\end{figure}
\end{center}

A different type of ring expansion was encountered with trichloacetonitrile in xylene and phenylacetylene as two separate reactions. The products observed were a quinazolinone derivative (246) and 3-phenyl-4-quinolinol (247) respectively (Scheme 70).\textsuperscript{105}
On the other hand, nucleophilic additions at the carbonyl carbon were very rare, with only Grignard's reagents and organolithiums reacting predominantly at the carbonyl site to yield the corresponding alcohols. This result substantiates the nature of the nitrone group as a potential site of a nucleophilic attack, as is evident from the structure.

An overview of the reactivity of isatogens encountered so far in literature portrays them as interesting intermediates. To our knowledge, 2-haloisatogens have not been reported in literature to date. Taking into consideration the isolation of the two isatogens 249 and 225, an attempt was made by Chet Howerton to isolate the corresponding isatogens from all the prepared iodo-alkynes, 212a and 217(a-g). These attempts were unsuccessful, as the isolated orange intermediates either displayed signs of decomposition immediately after purification or were contaminated with the respective isatin. The only stable isatogen, apart from 249 and 225 was 248, obtained in 85% yield along with a trace of the isatin when the solution of compound 223 in acetone was reacted with PdCl$_2$(PPh$_3$)$_2$ for 50 minutes at room temperature.
(Scheme 71). Unlike the 2-bromoisatogen 225, this compound was stable enough at room temperature to carry out the respective chemical analysis.

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
PdCl_2(PPh_3)_2 \\
\text{Acetone, 50 min, RT}
\end{array}
\quad
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O}
\end{array}
\]

\textbf{Scheme 71: The preparation of 2-bromo-5,6-methylenedioxyisatogen (248)}

An auric bromide catalyzed cyclization of \( \text{o-(arylalkynyl)nitrobenzenes} \) to the 2-aryl-isatogens has been developed by Yamamoto \textit{et al.} Intrigued by the success of this \( \text{AuBr}_3 \)-catalyzed reaction, the similar reaction was done on compound 212a. The reaction was followed by TLC. With no progress after 20 hours, the reaction was allowed to stir for 4 days, wherein a red substance was isolated from the crude in a low yield. The spectral data showed traces of isatin contaminated with some substance, most probably the isatogen. The low yield of a contaminated product, after 4 days has led us to believe that the conditions developed by Yamamoto \textit{et al.} are not ideal for the conversion of 212a to isatin or the isatogen (Scheme 72).

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O}
\end{array}
\quad
\begin{array}{c}
\text{AuBr}_3 (3.5 \text{ mol\%}) \\
\text{CH}_2\text{Cl}_2, 4 \text{ d, rt}
\end{array}
\quad
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{O}
\end{array}
\]

\textbf{Scheme 72: The attempted auric bromide catalyzed reaction}

As the carbon atom of the nitrone group is prone to be attacked by nucleophiles, the likeliness of substituting the halogen by a suitable nucleophile cannot be overlooked.
A test reaction was performed on the 2-bromoisatogen (225) by allowing it to stir in ethanol for 24 hours, under an inert atmosphere. Purification of the crude afforded the 2-ethoxyisatogen as a yellow solid in an excellent yield of 90% (Entry 1, Table 17). However, the reaction with allyl alcohol proved to be unsatisfactory with the corresponding allyloxyisatogen obtained in low yield along with the isatin (Table 17).

A one pot reaction carried out on 1-(2-bromoethynyl)-2-nitrobenzene 212a in dichloromethane as a solvent with Pd(PPh₃)₂Cl₂ (10%) and ethanol also afforded the 2-ethoxyisatogen (250a) in 70% yield within 3 hours. As an ultimate example, 4-chloro-2-nitro-1-(2-iodoethynyl)benzene (212c) was dissolved in dichloromethane and reacted with Pd(PPh₃)₂Cl₂ (10%) and ethanol. However, this reaction afforded the corresponding 2-ethoxy-6-chloroisatogen (250c) in a low yield of 23% after 6 hours (Scheme 73).

Scheme 73: The one pot synthesis of 2-ethoxyisatogens, 250a and 250c
Table 18: Conditions evaluated in the preparation of 2-alkoxyisatogens

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp.</th>
<th>2-alkoxyisatogen</th>
<th>isatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>-----</td>
<td>24 h</td>
<td>RT</td>
<td>90%</td>
<td>----</td>
</tr>
<tr>
<td>2</td>
<td>HO----- 33 eq</td>
<td>Methylene chloride</td>
<td>24 h</td>
<td>RT</td>
<td>30%</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>HO----- 2.5 eq</td>
<td>THF, NaH</td>
<td>3 h</td>
<td>RT</td>
<td>-----</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>HO----- 1 eq</td>
<td>Chloroform</td>
<td>40 min</td>
<td>RT</td>
<td>-----</td>
<td>38%</td>
</tr>
<tr>
<td>5</td>
<td>HO----- 4 eq</td>
<td>Chloroform</td>
<td>21 h</td>
<td>RT</td>
<td>44%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13%</td>
</tr>
<tr>
<td>6</td>
<td>HO----- 5 eq</td>
<td>Methylene chloride</td>
<td>16 h</td>
<td>RT</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>7</td>
<td>HO----- 2 eq</td>
<td>Methylene chloride</td>
<td>26 h</td>
<td>RT</td>
<td>-----</td>
<td>30%</td>
</tr>
<tr>
<td>8</td>
<td>HO----- 4 eq</td>
<td>Toluene</td>
<td>18 h</td>
<td>RT</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>HO----- 4 eq</td>
<td>Toluene</td>
<td>2.5 h</td>
<td>RT</td>
<td>8%</td>
<td>45%</td>
</tr>
<tr>
<td>10</td>
<td>HO----- 2 eq</td>
<td>Toluene</td>
<td>4 h</td>
<td>RT</td>
<td>-----</td>
<td>44%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Contaminated
2.7 Conclusion:

Although at this stage, the mechanism of these transformations remains unclear, it is certain that palladium has catalyzed the novel transformation of 1-(2-haloethynyl)-2-nitrobenzenes into the corresponding isatins. This transformation is perceived to have taken place through the intermediate thermally labile 2-haloisatogens. It was also observed that silver had the unusual ability to catalyze only the formation of 5-methoxyisatogen (249) from the TMS-alkyne. The reactions executed on the isolated 2-bromoisatogen (225) have demonstrated that the halogen could be substituted with a good nucleophile besides the fact that the prepared 2-ethoxyisatogen and the 2-allyloxyisatogen are very stable.
Chapter 3

Carbazolones and 3-Hydroxycarbazoles

3.1. Introduction:

Carbazoles are identified with a structure consisting of a benzene ring fused onto the five-membered ring at 2,3 position of an indole nucleus. The presence of the carbazole moiety in many biologically active compounds has garnered widespread attention in the branch of heterocyclic chemistry. Most of the alkaloids isolated from plants of Glycosmis, Clausena and Murraya genera were found to contain the carbazole scaffold; the genus Murraya, being the richest source of carbazole alkaloids based on C₁₃, C₁₈, C₂₃ skeletons. Different species of Streptomyces, slime moulds and marine sponges have also been the source to several carbazole alkaloids. In addition to the biological sources, abiologic sources such as coal tar, petroleum oil, soil humus and mud were also reported to yield carbazoles. Treatment of psoriasis with coal tar has been known, although not favored by patients due to aesthetic reasons. Investigations on psoriasis treatment with fractionated components of coal tar have confirmed carbazole to be the active ingredient in coal tar.

Contrary to the notion that the numbering of a heterocyclic compound begins with the heteroatom, carbazole and its derivatives are numbered beginning with the carbon atom closest to the nitrogen atom on the benzene ring, thus assigning the number 9 to the nitrogen atom in the molecule (Figure 10).
Carbazolones, the oxo analogues of carbazole and substituted carbazoles are also documented in journals as biologically active compounds. They are frequently encountered as intermediates in the synthetic efforts of several carbazole alkaloids, such as murrayquinone A, murrayanine, koenigine-quinones A and B, clausenalene, glycoborine, (+)-aspidospermidine, clausenamine, clausenol and clausenine, clausenal, dimeric murrayafoline A, pyrrayaquinones A and B, murrayafoline B and murrayquinone B, hepazolidine, glycozolinol, (-)-gilbertine, and glycozoline. An example of a carbazolone drug used to prevent nausea in patients undergoing chemotherapy and radiation treatments for cancer is ondansetron.\textsuperscript{111}

3.2. The construction of the carbazole ring

3.2 (a) The Fischer indole synthesis:

A common method to construct the carbazolone ring is the Fischer indole synthesis. Beginning with cyclohexane-1,3-dione (252), the requisite phenyl hydrazone 253 was
prepared and converted into the carbazolone in presence of a Lewis acid (Scheme 74). This reaction usually works quite well with 2- and 4-substituted phenylhydrazines, but a mixture of regioisomers is obtained with the 3-substituted analogues.

![Scheme 74: Fischer indole synthesis for carbazolones](image)

Another widely accepted preparation of the intermediate phenylhydrazone 257 is the Japp-Klingmann reaction between benzene diazonium salt and 2-(hydroxymethylene)-1-cyclohexanones (255). An acid mediated “Fischer indole synthesis” on the phenylhydrazone 257 would form the carbazolone (254) in the ultimate step (Scheme 75).

![Scheme 75: Japp-Klingemann synthesis of the hydrazone 257, the substrate for the Fischer indole synthesis](image)

3.2 (b) “The heteroannulation” method:

A group of carbazolone derivatives have been prepared by Tricia Scott, a former member of our group by utilizing the palladium-catalyzed reductive N-heteroannulation reaction developed in our laboratory. The synthetic strategy comprised of treating 2-(2-
nitrophenyl)-2-cycloalkenones 257 and 3-(2-nitrophenyl)-2-cycloalkenones 261 to the annulation conditions of the palladium catalyst, ligands and carbon monoxide to afford the respective carbazoles in good yields. The synthesis of the cyclization precursors 257 and 261 was achieved by adopting the “Stille reaction” conditions reported by Johnson et.al. to couple 2-iodocycloalkenones 260 or 3-iodocycloalkenones 256 with aryl stannanes 255.<sup>115</sup>

![Scheme 76: The strategy to synthesize carbazolones](image)

3.3. Results and Discussion:

Among the numerous carbazolones prepared by Tricia Scott, were the carbazolones 258(a-d), synthesized in excellent yields by the palladium catalyzed reductive heteroannulation reaction (Table 19). These four carbazolones could also be prepared by the Fischer’s indole synthesis. Also, the carbazoles, 258c and 258d, are bound to be formed as an isomeric mixture, had they been synthesized by Fisher’s method from their common precursor hydrazone 262.
Table 19: Carbazolones synthesized via palladium-catalyzed reductive N-heteroannulation reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Stille Coupled Product</th>
<th>Carbazolone</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="257a" /></td>
<td><img src="image" alt="258a" /></td>
<td>78%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="257b" /></td>
<td><img src="image" alt="258b" /></td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="257c" /></td>
<td><img src="image" alt="258c" /></td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="257d" /></td>
<td><img src="image" alt="258d" /></td>
<td>100%</td>
</tr>
</tbody>
</table>

A report published in the year 1998 by Chowdhury and his group referred to the formation of 2-methoxy-6-methyl-8-oxo-5,6,7,8-tetrahydrocarbazole (258c) from a sequential Japp-Klingemann reaction and Fischer indole synthesis as a colourless solid in 65% yield.116 Another article by the same research group, published a few years...
earlier in 1992, has quoted that 4-methoxy-6-methyl-8-oxo-5,6,7,8-tetrahydrocarbazole (258d) has formed in a yield of 50% from the same reaction, with no reported yield of isomer 258c. Puzzled by these ambiguous results, the reaction was repeated by us under the same reported conditions. The partner for the Japp-Klingemann reaction, 2-(hydroxymethylene)-5-methylcyclohexanone (264), was prepared from 3-methylcyclohexanone (263) and reacted with m-methoxybenzene diazonium chloride (265) under basic conditions. The hydrazone 262 thus obtained, was treated with acetic acid and HCl to afford a mixture of the carbazolones 258c and 258d in an approximate ratio of 7:1 (Scheme 77).

Scheme 77: The two isomeric carbazolones, 258c and 258d, obtained via the Fischer indole synthesis

In the year 2001, another group of researchers led by A. Chakravorty, a former member of the Chowdhury group, reported a Fischer indole synthesis on the 4-methylcyclohexanehydrazone derivative 268, which was prepared in situ from a condensation between m-methoxyphenylhydrazine (267) and 4-methylcyclohexanone (266). The outcome of this reaction was the formation of two isomeric
tetrahydrocarbazoles 269c and 269d in a ratio of 9:1 (Scheme 78). These results are comparable to the results of the reaction executed by us as shown in Scheme 77.

Scheme 78: The two isomeric tetrahydocarbazoles as reported by the Chakravorty group

To further substantiate our results, a Wolff-Kishner-Huang-Minlon reduction of 258c gave 269c having \(^1\)H-NMR chemical shifts, identical to those reported by the Chakravorty group.\(^{119}\)

While the main focus of our group has been to construct the carbazolone ring from 3-(2-nitrophenyl)-2-cyclohexeneone derivatives via the heteroannulation reaction, the concept of initiating an internal nucleophillic addition on the nitro group to form a hydroxycarbazole was a possible consideration. Moskalev and Makosza have reported a reaction between the nitroarene 270 and cyclohexanone (271) in the presence of a base that has resulted in the formation of o-hydroxydiarylamines 272. The formation of 272 was apparent from a direct nucleophillic addition of the cyclohexanone enolate on the nitro group. As a result of the problem encountered in the isolation and purification, 272 was ultimately converted into the stable o-methoxy derivative 273 by the authors (Scheme 79).\(^{120}\)
Another reaction that demonstrates an intermolecular carbanion attack on the nitro group has also been reported by the same research group, which observed that acenaphthenone (274) gave an inseparable mixture of 275 and 276 when reacted with NaOH. A reduction of this mixture led to compound 275 exclusively. As a final part in their study, the mixture was treated with methyl iodide to isolate these products as their N-methoxy and N-methyl analogues 277 and 278 (Scheme 80).121
Scheme 80: The “Makosza” group’s experiments on acenathenone

With these reactions in mind, it was speculated that a similar reaction of the compound 257b with a base would lead to a carbazole derivative. Thus, a test reaction was performed on 257b at 70 °C with DBU as the base and DMF as the solvent. The reaction afforded the 1-methyl-3-hydroxycarbazole (279), with no trace of the N-hydroxy carbazole derivative.
Scheme 81: The formation of 1-methyl-3-hydroxycarbazole (279)

The reaction was also examined on 3-(2-nitrophenyl)-2-cyclohexeneone (257e), which afforded 3-hydroxycarbazole (283) in 20% yield under identical conditions. A number of conditions were tried in an effort to maximize the yield (Table 20), but the yield could not be increased beyond 23%. The reaction could be accounted with an initial nucleophillic addition of the carbanion 281a on the nitrogen atom of the nitro group. However, such a mechanism, as seen through the intermediate stages 281b through 281g seems to lead to a 3,9-dihydroxycarbazole (282) as opposed to the 3-hydroxycarbazole (283) (Scheme 82). A similar type of transformation was seen on acenaphthenone,\textsuperscript{121} depicted in Scheme 80. The inseparable mixture of 275 and 276 gave the indole 275, when reduced with zinc and acetic acid. Comparing our results with those reported by the Makosza group, it is likely to assume that the N-hydroxycarbazole (282) is very unstable and is quickly transformed (reduced) into the carbazole 283. Also, the failure to obtain any N-hydroxymethylcarbazole upon the addition of methyl iodide (Entries 8 and 10, Table 20) substantiates the assumption that the N-hydroxycarbazole is too short-lived to be trapped as its methoxyderivative.
Table 20: Conditions evaluated in the synthesis of 3-hydroxycarbazole (283)

![Diagram of the reaction]

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Base</th>
<th>Eq.</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp.</th>
<th>283</th>
<th>SM (257e) recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU</td>
<td>2</td>
<td>THF</td>
<td>15 hrs</td>
<td>70 °C</td>
<td>20%</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>2</td>
<td>THF</td>
<td>6 hrs</td>
<td>70 °C</td>
<td>17%</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>2</td>
<td>THF</td>
<td>19 hrs</td>
<td>70 °C to 90 °C</td>
<td>17%</td>
<td>22%</td>
</tr>
<tr>
<td>4</td>
<td>KOH</td>
<td>1.3</td>
<td>DMSO</td>
<td>30 min</td>
<td>reflux</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>DBU</td>
<td>1</td>
<td>THF</td>
<td>21 hrs</td>
<td>70 °C</td>
<td>24%</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>DBU</td>
<td>1</td>
<td>CH₃CN</td>
<td>15 hrs</td>
<td>70 °C</td>
<td>--</td>
<td>35%</td>
</tr>
<tr>
<td>7</td>
<td>DBU</td>
<td>2</td>
<td>DMF</td>
<td>2 hrs</td>
<td>100 °C</td>
<td>24%</td>
<td>--</td>
</tr>
<tr>
<td>8*</td>
<td>DBU</td>
<td>1.7</td>
<td>DMF</td>
<td>2 hrs</td>
<td>100 °C</td>
<td>21%</td>
<td>--</td>
</tr>
<tr>
<td>9**</td>
<td>DBU</td>
<td>1</td>
<td>DMF</td>
<td>4 days</td>
<td>RT</td>
<td>14%</td>
<td>--</td>
</tr>
<tr>
<td>10***</td>
<td>DBU</td>
<td>1</td>
<td>DMF</td>
<td>3.5 days</td>
<td>RT</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

* Mel added after 2 h, let it go for another 15 min
** another product, tentatively assigned as 4,5-dihydroxycarbazole through NMR isolated in 10%, not detected through HRMS
*** MeI was added after 36 h, unable to characterize the products
Scheme 82: The plausible mechanistic pathway to the 3-hydroxycarbazole (283)

3.4. Conclusion:

In summary, a comparative study on the syntheses of carbazolones via the palladium-catalyzed reductive N-heteroannulation methodology and Fischer’s synthesis was executed. It was evident from the results that the Fischer indole synthesis affords the desired products in a lower yield with an additional disadvantage of forming two regioisomers from the precursor \textit{m}-methoxyphenylhydrazone derivative 262. Further, it
was also demonstrated that a base mediated reaction on 3-(2-nitrophenyl)-2-cyclohexenone (257e) forms the 3-hydroxycarbazole (283). Although the yield of the 3-hydroxycarbazole was low, it undoubtedly provides an insight into the mechanism and the stability of the predicted 3,9-dihydroxycarbazole (282).
Chapter 4:

Attempted Synthesis of the Model Indole Fragment of Nosiheptide

4.1. Introduction:

Nosiheptide, a sulphur-containing polypeptide antibiotic was isolated from Streptomyces actuosus 40037 (NRRL 2954) in the early 1960’s by a group of French researchers.\textsuperscript{122,123} It inhibits protein synthesis in gram positive bacteria by binding to the ribosomal unit in vitro. Found to be non-toxic, it is frequently employed as a food additive to promote growth and weight gain in pigs and chicken. The structure of nosiheptide, determined by a series of chemical degradation processes, X-ray crystallographic and NMR studies indicated the presence of two macrocyclic regions, incorporating five thiazoles, one pyridine and one indole rings.\textsuperscript{124}

To date, there have been no routes to the total synthesis of this antibiotic. However, approaches to the fragments have been reported.\textsuperscript{125} From a retro-synthetic perspective, nosiheptide is divided into two hemispheres, each comprising of three fragments: dehydroalanine and fragments A (2,3,5,6-tetrasubstituted pyridine), B (threonine), C (threonine–cysteine derived propenylthiazole), D (modified glutamate) and E (2,3,4-trisubstituted indole).
4.2 The “Moody” group’s syntheses of the indole fragment:

Synthetic routes to the various fragments of nosiheptide, including that of a potential precursor to the B-C-D fragment have been described. Many of these were synthesized with protecting groups, which appear to prevent their use in the total synthetic sequences. Two syntheses of the trisubstituted indole fragment have been reported by Christopher Moody’s group. Their first synthesis of the indole fragment involved the application of the Hemmetsberger indole synthesis, which is noted as an efficient synthesis to prepare indole-2-carboxylate derivatives. The required substrate for this reaction, the α-azidocinnamate derivative 286a was synthesized through a base catalysed condensation between o-methylbenzaldehyde 285a and methyl azidoacetate. Thermal decomposition of 286a gave the indole 284, which was subsequently formylated at the 3-position after a series of reactions to yield the intermediate 289 in
good yield. The synthesis of the indole 284 was also carried out from a 2-tetrahydropyranoyloxymethyl benzaldehyde (285b), but the yields were lower compared to the synthesis from o-tolualdehyde (285a). Additionally, the indole 284 was also synthesized through Sundberg's phosphite mediated deoxygenative cyclisation of the 2-nitrocinnamate derivative 288, which was prepared from 2-bromo-3-nitrotoluene (287) and methylacrylate via the palladium catalyzed Heck reaction (Scheme 83). The formyl group at the 3-position in the intermediate indole 289 served as an ideal functional group that was easily transformed into the desired methyl group seen in the indole fragment of nosiheptide molecule.

Scheme 83: Synthesis of the indole fragment by the Moody group
A shorter approach to the indole fragment was also developed by the Moody group using the Fischer indole synthesis as the key step (Scheme 84). The requisite hydrazine 293 was synthesized from the commercially available 3-amino-4-chloro-benzoic acid 291 in three steps comprising of a diazotization, followed by reduction and an immediate condensation of the intermediate arylhydrazine 292, with methyl-2-oxobutanoate. The polyphosphoric acid assisted Fischer cyclization of 293 gave the indole 294, which was subjected to hydrogenolysis to remove the masking chloro substituent. Reduction of the carboxylic acid 295 was then carefully executed with borane dimethylsulfide complex, and the resulting alcohol 296 was ultimately protected as the TBS ether to yield the model indole moiety 290.

Scheme 84: Synthesis of the indole fragment by the Fischer indole synthesis

4.3 Results and discussion:

In the course of extending the viability of the conditions for the "reductive N-heteroannulation", a group of 2,3-substituted indoles with an electron withdrawing group,
present at the 3-position were synthesized. Also, a survey of “indole literature” reveals the preparation of a plethora of indole-3-carboxylates synthesized by the Hemmetsberger-Knittel synthesis. With the requirement of an ester and an alkyl group at the 2- and 3-positions, respectively, on the indole fragment of nosiheptide, and the results of 2,3-substituted indoles in hand, the synthesis of the indole fragment appeared feasible via the palladium-catalyzed annulation reaction.

Retrosynthetically, the construction of the indole fragment could be seen as a palladium-catalyzed reductive N-heteroannulation of the styrene 298. The styrene, 298 could be envisioned as the coupling product from the stannane 300, a previously reported compound synthesized from methyl-2-butynoate 301 and the aryl halide 299.

![Scheme 85: Retrosynthesis of the indole fragment of nosiheptide](image)

The synthesis of the aryl halide 299 required the commercially available 2-bromo-3-nitrobenzoic acid (302a) to begin with, but owing to its high price, it was synthesized
from a relatively less expensive 3-nitrophthalic acid (303) in two steps following a published procedure.\textsuperscript{127} The first step involved the conversion of 3-nitrophthalic acid into anhydro-2-hydroxymercuri-3-nitrobenzoic acid (304) using mercuric acetate, sodium hydroxide, and acetic acid. Subsequent bromination\textsuperscript{127} of 304 in the second step afforded the 2-bromo-3-nitrobenzoic acid (302a) as a colorless solid.

Reduction of 2-bromo-3-nitrobenzoic acid (305) with BH\textsubscript{3}.DMS complex gave the 2-bromo-3-nitrobenzyalcohol (305)\textsuperscript{126} that was brominated using carbon tetrabromide and triphenylphosphine to afford 2-bromo-3-nitrobenzyl bromide (306)\textsuperscript{125} in a moderate yield. The allyloxy ether 307 was then prepared from 306 by Williamson’s ether synthesis (Scheme 86).\textsuperscript{126}

The corresponding iodo-analogue (309) of compound 306 was also prepared using the same reaction sequence. It was then easily converted into the methoxy ether 299b in a good yield.
Scheme 86: Syntheses of the 2-halo-3-nitrobenzyl ethers, 307 and 299b

The coupling partner for 299b, the stannane 300 was prepared as a mixture of the E and Z-isomers from methyl-2-butynoate (301) by a lithium diisopropylamide mediated reaction with tributyltin hydride in the presence of solid copper bromide-dimethyl sulfide complex (Scheme 87).

Scheme 87: Preparation of the stannane 300

A Stille coupling between the prepared stannane 300 and the methoxy ether 299b failed to yield the required styrene derivative 298a. The two reactants, 299b and 300 were recovered unchanged. (Scheme 88). A test reaction between 2-iodo-3-nitro-methylbenzoate (310) and the stannane 300 also failed to yield the corresponding coupled product 311; a total recovery of the two reactants was observed in this case.
With the recovery of the two reactants, the idea of executing the Stille-coupling on the aryl stannane 312 and methyl-3-iodo-2(Z)-butenoate (313) was considered. Following the procedure of Lu and his coworkers, the regiospecific hydroiodination was executed on methyl-2-butynoate (301) to afford methyl-3-iodo-2(Z)-butenoate (313) (Scheme 89). 129

A palladium-catalyzed reaction between the methoxy ether 299b and hexamethyldistannane gave the desired stannane 312, but in a low yield. The starting material was recovered along with α-methoxy-2-methyl-3-nitrotoluene (314). A better yield was obtained when the reaction was carried out at 90 °C (Table 21, Entry 3), but 314 was also obtained as a second product. These results are shown below (Table 21).
The Stille coupling conditions, when attempted on the stannane 312 and methyl-3-iodo-2(Z)-butenoate (313), showed no formation of the desired styrene derivative 298a; however, α-methoxy-3-nitrotoluene (315)\textsuperscript{130} was obtained in a yield of 68% (Scheme 91).

Scheme 91: The attempted Stille coupling between the aryl stannane (312) and 3-iodo-methyl-2-butenoate (313)
The Heck reaction\textsuperscript{131} offers an alternative to prepare aryl substituted alkenes from an aryl halide and an alkene. Commercially available methyl-2-butenoate (316) was reacted with 299b under the ‘Heck reaction conditions’ of palladium acetate (10 mol %), triphenylphosphine (40 mol %) and triethylamine at 70 °C for 4 days. The reaction was unsuccessful, marked by the recovery of 299b along with α-methoxy-3-nitrotoluene (315), as an inseparable mixture (Scheme 92).

Replacing the triphenylphosphine with triphenyl arsine offered no improvement; a mixture of compounds 299b and 315 was formed as in the earlier reaction.

Following the failures to generate the key o-nitrostyrene precursor 298a, a second retrosynthesis of the indole fragment was designed, wherein the idea was to construct the 3,4-fused indole 317, followed by the cleavage of the ether with a lewis acid. A group of 3,4-fused indoles has been synthesized earlier in our laboratory.\textsuperscript{132} Based upon this result, it was proposed to transform the allyl ether 307 into the α,β-unsaturated ester 318a/318b through ozonolysis and a subsequent Wittig reaction with 320. The possibility of preparing the α,β-unsaturated ester 318a/318b from 2-halo-3-nitrobenzylalcohol (305/308) and the commercially available γ-bromo-methylcrotonoate (319) was another option (Scheme 93).
Scheme 93: The second retrosynthetic analysis of the indole fragment

The preparation of the α,β-unsaturated ester 318a from 2-bromo-3-nitrobenzylalcohol (305) and γ-bromo-methylcrotonoate (319) met with no success. Hence, it was decided to try the reaction with γ-hydroxy-methylcrotonoate (321) and the benzyl bromide 306. These attempts were also unsuccessful, with the total recovery of the benzylbromide 306 in both attempts (Scheme 94).
4.4 Conclusion:

In summary, the synthesis of the indole fragment of nosiheptide via the notable Fischer indole synthesis and the Hemmetsberger synthesis by the Moody group offer the desired compound in excellent yields. Had our attempts to synthesize the heteroannulation precursor been successful, there would have been another significant synthesis of nosiheptide’s indole fragment documented in chemical literature.
Experimental Section

All NMR spectra were determined at 600 MHz (\(^1\)H NMR) and 150 MHz (\(^{13}\)C NMR) or 270 MHz (\(^1\)H NMR) and 67.5 MHz (\(^{13}\)C NMR) in a suitable solvent as stated. The chemical shifts are expressed in \(\delta\) values relative to Me\(_4\)Si (0.00, \(^1\)H and \(^{13}\)C) or CDCl\(_3\) (7.26, \(^1\)H and 77.00, \(^{13}\)C) internal standards. \(^1\)H-\(^1\)H coupling constants are reported as calculated from spectra; thus, a slight difference between \(J_{a,b}\) and \(J_{b,a}\) is usually obtained. Results of APT (attached proton test) \(^{13}\)C NMR experiments are shown in parenthesis, where relative to CDCl\(_3\), (-) denotes CH\(_3\) or CH, and (+) denotes CH\(_2\) or C.

Tetrahydrofuran (THF), toluene, and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Pyridine, triethylamine, hexanes, acetonitrile, diisopropylamine, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time they are used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure or by bulb-to-bulb distillation under reduced pressure. Chromatography was performed on silica gel 60 (35-75 mm, VWR). Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.
5-Phenyl-4H-thieno[3,2-b]pyrrole-2-carboxylic acid methyl ester (108)\(^49\)

To an oven dried, threaded ACE glass pressuretube was added stryryl thiophene 104 (80 mg, 0.264 mmol), Pd(OAc)\(_2\) (4 mg, 0.0178 mmol) and PPh\(_3\) (16.3 mg, 0.062 mmol) in 5 ml of CH\(_3\)CN. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 90 °C (oil bath temperature) under CO (6 atm) for 40 h, cooled to room temperature, depressurized and the solvent, removed under reduced pressure. The crude was chromatographed on SiO\(_2\) (hexane/ethyl acetate, 8:2) to yield 108 (32 mg, 0.118 mmol, 71%) as an off-white solid. Mp 244 °C (lit\(^49\) 239 -240 °C); \(^1\)H NMR (600 MHz, DMSO-d\(_6\)), \(\delta\) 12.03 (s, 1H), 7.78 (dd, \(J=8.4, 1.2\) Hz, 2H), 7.67 (s, 1H), 7.45 (t, \(J=7.8\) Hz, 2H), 7.308 (t, \(J=7.2, 7.8\) Hz, 1 H), 6.97 (t, \(J=1.2\) Hz, 1 H), 3.82 (s, 3H); \(^13\)C NMR (dms-o-d\(_6\), 600 MHz): \(\delta\) 162.9, 141.2, 138.6, 131.8, 130.02, 128.9, 128.1, 127.5, 124.6, 117.4, 98.6, 51.8.

5-Phenyl-6H-thieno[2,3-b]pyrrole (109)\(^49\)

Reaction of 2-nitro-3-styrylthiophene (107) (80 mg, 0.346 mmol) with carbon monoxide in presence of Pd(OAc)\(_2\) (8 mg, 0.035 mmol) and triphenylphosphine (37 mg, 0.141
mmol) in 5 ml of CH$_3$CN as described above for 104 (24 h), gave 109 (57 mg, 0.286 mmol, 83%) as a pale yellow solid after chromatography (hexanes/EtOAc, 9:1).

Mp 179 °C (lit$^{49}$ 186 °C-187 °C); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.49 (br s, 1H), 7.53 (d, J= 8.4 Hz), 7.40 (dt, J=8.4, 7.2 Hz), 7.25 (t, J=7.8 Hz, 1H), 7.015 (d, J=5.4 Hz, 1H), 6.85 (d, J=5.4 Hz, 1H), 6.73 (d, J=1.8 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.7, 134.9, 133.2, 132.6, 129.2, 126.9, 124.3, 118.5, 117.9, 99.2.

2,5-distyryl-3,4-dinitrothiophene (112)$^{53}$

To a solution of 3,4-dinitrothioxene (111)$^{52}$ (250 mg, 1.404 mmol) in absolute methanol (15 ml), freshly distilled benzaldehyde (602 mg, 5.679 mmol) and 10 drops of pyrrolidine were added. The solution was refluxed for 8 h during which time, an orange precipitate was seen on the walls of the flask. The flask was cooled to room temperature and then in ice. The orange precipitate was filtered and washed with ice cold methanol (5 ml) and recrystallized from methanol to afford the product 112 (357 mg, 0.994 mmol, 67%) as an orange crystalline solid. Mp 230 °C- 233 °C (lit$^{53}$ 227 °C); IR (neat) 1536, 1322, 1403 cm$^{-1}$; $^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ 7.71 (d, J=6.6 Hz, 4H), 7.58 (d, J=16.2 Hz, 2H), 7.49 (d, J=16.2 Hz, 2H), 7.48-7.42 (m, 3H); $^{13}$C NMR (dms-o-d$_6$,125 MHz): $\delta$ 139.2, 138.1, 135.9, 134.6, 130.2, 129.1, 127.8, 115.5.
2-styryl-3-nitro-5-phenyl-4H-thieno[3,2-b]pyrrole (113)\textsuperscript{53} and 3,6-diphenyl-thieno[3,2-b: 4,5-b']dipyrrole (114): 

Reaction of 2,5-distyryl-3,4-dinitrothiophene (112)\textsuperscript{53} (80 mg, 0.211 mmol) with carbon monoxide in presence of Pd(OAc)\textsubscript{2} (3 mg, 0.0134 mmol) and triphenylphosphine (14 mg, 0.0534 mmol) in 4 ml of CH\textsubscript{3}CN as described above for 104 (50 h) gave 113 (65 mg, 0.188 mmol, 89\%) as a dark violet solid after chromatography (hexanes/EtOAc, 8:2). Mp 252 °C (lit\textsuperscript{53} 248-249 °C) along with a trace of compound 114.

4H, 5H-3,6-diphenyl-thieno[3,2-b: 4,5-b']dipyrrole (114)

Reaction of 2,5-distyryl-3,4-dinitrothiophene (112)\textsuperscript{53} (104 mg, 0.275 mmol) with carbon monoxide in presence of Pd(OAc)\textsubscript{2} (7 mg, 0.0311 mmol) and triphenylphosphine (31 mg, 0.118 mmol) in 6 ml of CH\textsubscript{3}CN as described above for 104 (4 days) gave 114 (32 mg, 0.102 mmol, 37\%) as an off-white solid after chromatography (hexanes/EtOAc, 8:2). Mp 110 °C; IR (neat) 3435, 1599, 1358 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (Acetone-d\textsubscript{6}, 600 MHz): δ 10.415 (s, 2H), 7.66 (d, J= 7.8 Hz, 4H), 7.36 (dt, J=7.2, 8.4 Hz, 4H), 7.18 (dt, J=7.2, 7.8 Hz, 2H), 6.84 (d, J=1.8 Hz, 2H); \textsuperscript{13}C NMR (125 MHz, Acetone-d\textsubscript{6}): δ 135.5, 134.4, 129.8, 127.03, 126.8, 126.6, 124.5, 101.6; HRMS Calcd for C\textsubscript{20}H\textsubscript{14}N\textsubscript{2}S (M+H\textsuperscript{+}) 314.0873; found, 314.0872.

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4-nitro-5-styryl-2-furanaldoxime (118):

A solution of 5-methyl-4-nitro-2-furanaldoxime (117) (80 mg, 0.471 mmol) in 5 ml of absolute methanol was refluxed gently for 2 minutes with 0.1 ml of freshly distilled piperidine and followed by the addition of freshly distilled benzaldehyde (0.247 mg, 2.33 mmol). The resulting solution was then refluxed for three hours. An orange solid was seen appearing on the walls of the round-bottomed flask in about 20 minutes. The solution was cooled to room temperature and finally cooled in an ice bath. The orange solid was filtered and washed with 1 ml of ice-cold methanol. The filtrate was evaporated and the obtained orange solid was combined with the filtered orange precipitate and ultimately chromatographed on silica (hexanes/EtOAc, 8:2) to yield 118 (107 mg, 0.4147 mmol, 88%) as an orange solid. Mp 182-185 °C; $^1$H NMR (600 MHz, Acetone-$d_6$): $\delta$ 11.65 (br s, 1H), 7.79 (d, $J$=16.2 Hz, 1H), 7.69 (d, $J$=16.8 Hz, 1H), 7.76 (d, $J$=7.2 Hz, 2H), 7.62 (s, 1H), 7.47-7.50 (m, 2H), 7.45 (tt, $J$=7.2, 1.2 Hz, 1H), 7.73 (s, 1H)

$^{13}$C NMR (150 MHz, Acetone-$d_6$): $\delta$ 152.3, 144.2, 139.1, 136.4, 135.8, 135.7, 131.1, 130.1, 128.8, 113.75, 113.70; IR (neat) 1619, 1537, 1400, 1346 cm$^{-1}$; HRMS Calcd for C$_{13}$H$_{10}$N$_2$O$_4$ (M$+H^+$) 259.0721; found, 259.0713.
2-cyano-4H-5-phenylfuro[3,2-b]pyrrole (120) and 5-phenyl-4H-furo[3,2-b]pyrrole-2aldoxime (119):

A solution of 4-nitro-5-styryl-2-furanaldoxime (118) (75 mg, 0.2907 mmol) in 3 ml of dry DMF, Pd(dba)$_2$ (10 mg, 0.0174 mmol) and 1,10-phenanthroline (7 mg, 0.0353 mmol) was heated in presence of carbon monoxide as described for 104 (120 °C, 22 hrs). The reaction mixture was cooled to room temperature, diluted with water (10 ml) and extracted with ethyl acetate (3X20ml). The combined organic layers were washed with water (2X50ml) and dried over anhydrous MgSO$_4$ to give an oily crude which was chromatographed on silica with (hexanes/EtOAc, 8:2) to yield the 2-cyano-4H-5-phenylfuro[3,2-b]pyrrole (120) (12 mg, 0.058 mmol, 20 %). Mp 162-163 °C; IR (neat) 3310, 2209, 1707 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.16 (br s, 1H), 7.53 (d, $J$=7.2 Hz, 2H), 7.48 (t, $J$=8.4 Hz, 2H), 7.33 (t, $J$=7.2 Hz, 1H), 7.10 (s, 1H), 6.47 (s, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 152.7, 141.6, 132.0, 129.2, 128.1, 126.3, 124.6, 123.5, 113.4, 109.6, 90.1; HRMS Calcd for C$_{13}$H$_8$N$_2$O (M+H$^+$) 209.0716, found 209.07094.

Further elution afforded the oxime 119 (30 mg, 0.132 mmol, 45 %), which decomposed on standing at room temperature within a few minutes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.05 (br s, 1H), 7.98 (s, 1H), 7.51 (d, $J$=7.8 Hz, 2H), 7.39 (t, $J$=8.4 Hz, 2H), 6.64 (s, 1H), 6.46 (s, 1H).
2-methyl-5-phenyl-4H-pyrrolo[3,2-d]thiazole (127):

Reaction of 2-methyl-4-nitro-5-styrylthiazole (126) \(^{69}\) (60 mg, 0.244 mmol) with carbon monoxide in presence of Pd(OAc)\(_2\) (4 mg, 0.017 mmol) and triphenylphosphine (19 mg, 0.0725 mmol) in 5 ml of CH\(_3\)CN as described above for 104 for 72 h gave 127 (32 mg, 0.149 mmol, 61\%) after chromatography (hexanes/EtOAc, 8:2) as a pale brown solid.

Mp 257-258 °C (decomposed); \(^1\)H NMR (600 MHz, DMSO-d\(_6\)): \(\delta\) 11.82 (s, 1H), 7.67 (d, \(J=7.8\) Hz, 2H), 7.39 (t, \(J=7.8\) Hz, 2H), 7.21 (dt, \(J=7.2, 7.8\) Hz, 1H), 6.78 (d, \(J=1.8\) Hz, 1H), 2.68 (s, 3H); \(^{13}\)C NMR (125 MHz, DMSO-d\(_6\)): \(\delta\) 158.5, 147.3, 136.6, 132.8, 128.8, 127.1, 126.2, 123.5, 96.3; IR (neat) 1602, 1458, 1184 cm\(^{-1}\); HRMS Calcd for C\(_{12}\)H\(_{10}\)N\(_2\)S (M+H\(^+\)) 215.0643; found, 215.06375.

1-Benzyl-1,4-dihydro-5-phenylpyrrolo[3,2-d]imidazole (133):

A solution of 1-benzyl-5-styryl-4-nitroimidazole (131) \(^{60}\) (58 mg, 0.190 mmol) in 2 ml of dry DMF, Pd(dba)\(_2\) (7 mg, 0.012 mmol) and 1,10-phenanthroline (5 mg, 0.134 mmol) was heated in presence of carbon monoxide as described for 104 at 120 °C for 6 days.

Work up and purification of the resulting oily crude by chromatography (hexanes/EtOAc, 8:2, followed by elution with EtOAc) afforded 133 (40 mgs, 0.146 mmol, 77\%) as a
brown solid. Mp 244-247 °C; \(^{1}\)H NMR (600 MHz, Acetone-\(d_6\)) \(\delta\) 5.32 (s, 2H), 6.29 (s, 1H), 7.53 (s, 1H), 7.13 (t, \(J=7.2\) Hz, 1H), 7.29 -7.39 (m, 7H), 7.65 (d, \(J=7.2\) Hz, 2H), 10.33 (s, 1H); \(^{13}\)C NMR (150 MHz, Acetone-\(d_6\)) \(\delta\) 138.7, 138.5, 135.3, 135.25, 133.7, 129.58, 129.63, 128.7, 128.67, 126.5, 124.5, 88.85, 88.8, 50.9 ; IR (neat) 1599, 3111, 1470, 1452 cm\(^{-1}\); HRMS calcd for C\(_{18}\)H\(_{15}\)N\(_3\) (M+H\(^{+}\)) 274.1344; found, 274.1338.

\[
\begin{align*}
\text{Ph} & \quad \text{Pd(db)\textsubscript{2}, DMF, 1,10-phenanthroline} \\
\text{Ph} & \quad \text{CO (6 atm), 120 °C} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

3-Benzyl-3,4-dihydro-5-phenylpyrrolo[2,3-d]imidazole (134)

A solution of 1-Benzyl-4-styryl-5-nitroimidazole (132) (125 mg, 0.409 mmol) in 3 ml of dry DMF, Pd(db)\textsubscript{2} (15 mg, 0.012 mmol) and 1,10-phenanthroline (27 mg, 0.1361 mmol) was heated in presence of carbon monoxide as described for 104 at 120 °C for 3 days. Work up and purifcation of the resulting oily crude by chromatography (hexanes/EtOAc, 8:2, followed by elution with EtOAc) afforded 134 as a brown solid (36 mg, 0.1317 mmol, 32%). Mp 216 °C (decomposed); IR (neat) 1599, 1383, 1219 cm\(^{-1}\);

\(^{1}\)H NMR (600 MHz, Acetone-\(d_6\)): \(\delta\) 5.37 (s, 2H), 6.55 (s, 1H), 7.44 (s, 1H), 7.12 (t, \(J=7.2\) Hz, 1H), 7.28-7.36 (m, 7H), 7.558 (d, \(J=8.4\) Hz, 2H), 10.28 (s, 1H); \(^{13}\)C NMR (150 MHz, Acetone-\(d_6\)) \(\delta\) 138.5, 138.0, 136.2, 135.4, 129.7, 129.6, 128.6, 128.0, 126.3, 124.3, 95.9, 95.8, 49.4; HRMS Calcd for C\(_{18}\)H\(_{15}\)N\(_3\) (M+H\(^{+}\)) 274.1344; found, 274.1338.
1,2,5-trimethyl-3-nitropyrrrole (140) and 1,2,5-trimethyl-3,4-dinitropyrrrole (141):
To concentrated sulphuric acid (10 ml) at 0 °C, was added 1,2,5-trimethylpyrrole (139) (1.042 gm, 9.648 mmol) slowly, during which time the temperature rises to 15 °C. Cool it again to 0 °C, and potassium nitrate (2.078 gm, 20.574 mmol) is added in portions. The resulting solution is stirred at 0 °C for 10 minutes. The temperature is then slowly allowed to rise up to room temperature and the stirring is continued for a further 30 minutes. The mixture is poured into crushed ice with vigorous stirring, when an yellow solid separates. The yellow precipitate is filtered, washed with cold water, dried and chromatographed (hexanes/EtOAc, 6:4) to afford 140 (705 mg, 4.578 mmol, 47%) as an yellow solid. Mp 115-116 °C (lit mp 113 °C); Further elution gave 141 (40 mg, 0.201 mmol, 2%) as a pale yellow solid. Mp 207-210 °C. $^1$H NMR (270 MHz, CDCl$_3$): $\delta$ 3.48 (s, 1H), 2.48 (s, 2H); $^{13}$C NMR (67.5 MHz, CDCl$_3$): $\delta$ 131.3, 128.9, 31.4, 10.9; HRMS calcd. for C$_7$H$_9$N$_3$O$_4$ (M+H$^+$) 200.0671, found 200.0666.
3-nitro-4-styryl-1-tosylpyrrole (157):

To a solution of 3-nitro-4-styrylpyrrole (155)\(^6\) \((190 \text{ mg, 0.888 mmol})\) in anhydrous DMF \((10 \text{ ml})\), was added \(\text{BuOK} \) \((132 \text{ mg, 1.179 mmol})\) at 0 \(\text{°C}\), and the resulting orange solution was allowed to stir at 0 \(\text{°C}\) under an inert atmosphere for 45 min. A solution of tosyl chloride \((224 \text{ mg, 1.179 mmol})\) in DMF \((1 \text{ ml})\) was then added to the above solution with a syringe; the solution turns yellow upon the addition. The reaction mixture was continued to stir under an atmosphere of nitrogen at 0 \(\text{°C}\) for 2.5 h. Aqueous work up at this stage followed by extraction with ethylacetate \((2 \times 25 \text{ ml})\), washing of the organic phase with water \((2 \times 25 \text{ ml})\), drying \((\text{MgSO}_4)\), and concentration gave an yellow crude that was purified on a short column of \(\text{Al}_2\text{O}_3\) \((\text{hexanes/EtOAc, 8:2})\) to afford the product 157 \((257 \text{ mg, 0.698 mmol, 79 %})\) as an yellow solid. Mp 124-125 \(\text{°C}\).

\(^1\text{H NMR (600 MHz, CDCl}_3\) \(\delta 8.00 \text{ (d, } J=2.8 \text{ Hz, 1H), 7.87 (d, } J=8.5 \text{ Hz, 2H), 7.48 (d, } J=8.5 \text{ Hz, 2H), 7.34-7.44 \text{ (m, 6 H), 7.40 (dd, } J=16.2, 0.8 \text{ Hz, 1H), 7.30 (tt, } J=7.3, 1.7 \text{ Hz, 1 H), 6.94 (d, } J=16.5 \text{ Hz, 1H), 2.46 (s, 3H); }^{13}\text{C NMR (67.5 MHz, CDCl}_3\) \(\delta 147.1, 137.3, 136.5, 134.2, 132.3, 130.8, 128.9, 128.4, 127.8, 126.8, 122.3, 121.8, 117.0, 116.4, 21.9; IR (neat) 1489, 1370, 1057, 964 \text{ cm}^{-1}; \) HRMS calcd. for \(\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4\text{S} \text{(M+H\textsuperscript{+}) 369.0909, found 369.0903.}}\)
2,4-Dinitro-1-[2-(trimethylsilyl)ethynyl]benzene (216a)

To a solution of 2,4-dinitro-1-bromobenzene (214a) (750 mg, 3.03 mmol) prepared in triethylamine (Et₃N, 20 ml), trimethylsilylethylene (329 mg, 3.35 mol), Cul (58 mg, 0.304 mmol) and PdCl₂(PPh₃)₂ (214 mg, 0.304 mmol) were added and the reaction mixture was stirred under an atmosphere of nitrogen for 24 hours. The solvent was removed under reduced pressure, and the dark crude obtained was purified by chromatography (hexanes/EtOAc, 9:1) to afford 216a (336 mg, 1.42 mmol, 47%) as an yellow solid. Mp 82-83 °C; ¹H NMR (600 MHz, CDCl₃): δ 8.87 (d, J=1.8 Hz, 1H), 7.83 (d, J=9 Hz, 1H), 8.39 (dd, J=8.4, J=2.4 Hz, 1 H), 0.31 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 150.1, 146.5, 136.2, 126.7, 124.3, 120.1, 111.4, 97.7, -0.64; IR (neat) 3092, 2962, 1594 cm⁻¹; Anal calcd for C₁₁H₁₂N₂O₄Si: C, 49.99; H 4.58; N, 10.60. Found: C, 50.26; H 4.58; N, 10.38.

4-Chloro-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216b):

Reaction of 4-chloro-2-nitro-1-iodobenzene (214a) (700 mg, 2.49 mmol) with trimethylsilylethylene (290 mg, 2.95 mol), Cul (38 mg, 0.12 mmol) and PdCl₂(PPh₃)₂ (20 mg, 0.02 mmol) in triethylamine (Et₃N, 30 ml), as described above for 216a (room temperature, 22 hours) afforded 216b (583 mg, 2.29 mol, 92%) as an yellow solid after
4-Methoxy-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216c):

Reaction of 4-methoxy-2-nitro-1-iodobenzene (214c) (500 mg, 1.79 mmol) with trimethylsilylethyne (206 mg, 2.09 mmol), CuI (30 mg, 0.157 mmol) and PdCl$_2$(PPh$_3$)$_2$ (63 mg, 0.09 mmol) in triethylamine (Et$_3$N, 30 ml), as described above for 216a (room temperature, 40 hours) afforded 216c (425 mg, 0.95 mol, 95%) as a pale yellow solid after chromatography (hexanes/EtOAc, 9:1). Mp 68-69 ˚C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J$=9 Hz, 1H), 7.51 (d, $J$=2.4 Hz, 1H), 7.08 (dd, $J$=9, 3 Hz, 1H), 3.88 (s, 3H), 0.27 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 159.8, 151.3, 136.2, 119.7, 110.8, 109.4, 101.6, 99.6, 56.2, -0.11; IR (neat) 2161, 1620, 1530 cm$^{-1}$; Anal calcd for C$_{12}$H$_{15}$NO$_3$Si: C, 57.80; H 6.06; N, 5.62. Found: C, 58.39; H 6.55; N, 5.30.
5-Methoxy-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216d):

Reaction of 5-methoxy-2-nitro-1-iodobenzene (214d) (1.01 gm, 3.62 mmol) with trimethylsilylethyne (399 mg, 4.06 mmol), CuI (60 mg, 0.315 mmol) and PdCl$_2$(PPh$_3$)$_2$ (123 mg, 0.175 mmol) in triethylamine (Et$_3$N, 25 ml), as described above for 216a (room temperature, 18 hours) afforded 216d (790 mg, 3.36 mol, 92%) as an yellow solid after chromatography (hexanes/EtOAc, 8:2). Mp 65-68 °C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.07 (d, $J$=9.6 Hz, 1H), 7.07 (d, $J$=2.4 Hz, 1H), 6.91 (dd, $J$=9, 3 Hz, 1 H), 3.89 (s, 3H), 0.29 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.9, 143.4, 127.2, 120.9, 119.2, 115.1, 103.8, 100.1, 56.2, -0.14; IR (neat) 2966, 2898, 2165,1602 cm$^{-1}$; Anal calcd for C$_{12}$H$_{15}$NO$_3$Si: C, 57.80; H 6.06; N, 5.62. Found: C, 57.97; H 6.31; N, 5.77.

3-Methyl-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216e):

Reaction of 3-methyl-2-nitro-1-iodobenzene (214e) (1.70 gm, 6.45 mmol) with trimethylsilylethyne (690 mg, 7.03 mmol), CuI (123 mg, 0.646 mmol) and PdCl$_2$(PPh$_3$)$_2$ (274 mg, 0.390 mmol) in triethylamine (Et$_3$N, 25 ml), as described above for 216a (room temperature, 26 hours) afforded 216e (1.366 gm, 5.86 mol, 91%) as an oil, that turns into a solid in the freezer after chromatography (hexanes/EtOAc, 95:5). $^1$H NMR (600
MHz, CDCl$_3$): δ 7.39 (d, $J$=7.8 Hz, 1H), 7.29 (t, $J$=7.8 Hz, 1H), 7.23 (d, $J$=7.8 Hz, 1H), 2.32 (s, 3H), 0.23 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 153.2, 131.3, 130.9, 129.9, 129.8, 116.2, 101.8, 97.8, 17.4, -0.50; IR (neat) 2962, 2160, 1600 cm$^{-1}$; Anal calcd for C$_{12}$H$_{15}$NO$_2$Si: C, 61.77; H 6.48; N, 6.00. Found: C, 62.28; H 6.64; N, 6.30.

6-Methyl-2-nitro-1-[2-(trimethylsilyl)ethynyl]benzene (216g):

Reaction of 6-methyl-2-nitro-1-iodobenzene (214g) (1.50 gm, 5.70 mmol) with trimethylsilylethyne (626 mg, 6.37 mmol), CuI (90 mg, 0.473 mmol) and PdCl$_2$(PPh$_3$)$_2$ (210 mg, 0.300 mmol) in triethylamine (Et$_3$N, 25 ml), as described above for 216a (50 °C, 27 hours) afforded 216g (649 mg, 2.78 mmol, 49%) as an oil (turns into an yellow solid in the freezer) after chromatography (hexanes/EtOAc, 95:5). $^1$H NMR (600 MHz, CDCl$_3$): δ 7.76 (d, $J$=8.4 Hz, 1H), 7.45 (d, $J$=7.2 Hz, 1H), 7.30 (t, $J$=8.1 Hz, 1 H), 2.51 (s, 3H), 0.28 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 151.0, 143.7, 133.6, 127.9, 121.6, 117.6, 108.5, 97.6, 21.2, -0.34; IR (neat) 2960, 1528, 1346, 1249 cm$^{-1}$; HRMS calcd for C$_{12}$H$_{15}$NO$_2$Si (M+H$^+$) 234.0950, found 234.0946.
3-Nitro-1-[2-(trimethylsilyl)ethynyl]pyridine (219):

Reaction of 2-bromo-3-nitro-pyridine (218) (502 mg, 2.47 mmol) with trimethylsilylethyne (291 mg, 2.96 mmol), CuI (55 mg, 0.289 mmol) and PdCl₂(PPh₃)₂ (94 mg, 0.134 mmol) in triethylamine (Et₃N, 25 ml), as described above for 216a (room temperature, 54 hours) afforded 219 (388 mg, 1.98 mmol, 80%) as a brown solid after chromatography (hexanes/EtOAc, 8:2). Mp 36-38°C; ¹H NMR (600 MHz, CDCl₃): δ 8.79 (dd, J=1.2, 4.8 Hz, 1H), 8.32 (dd, J=8.4, 1.8 Hz, 1H), 7.43 (dd, J=8.4, 4.2 Hz, 1H), 0.31 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 137.0, 132.4, 123.2, 105.6, 98.9, -0.47; IR (neat) 2962, 2160, 1591, 1527 cm⁻¹;

1-Nitro-2-[2-(trimethylsilyl)ethynyl]benzene (216):

Reaction of 214 (3.00 gm, 12.00 mmol) with trimethylsilylethyne (1.607 gm, 16.4 mmol), CuI (192 mg, 1.01 mmol) and PdCl₂(PPh₃)₂ (423 mg, 0.602 mmol) in triethylamine (50 ml), as described above for 216a (72 h) afforded 216 (2.652 gm, 12.01 mmol) as an yellow oil after chromatography (hexanes/EtOAc, 95:5) in a quantitative yield.
**2-[2-Bromoethynyl]-1-nitrobenzene**\(^{99}\) \((212a)\):

To a solution of \(216\) in anhydrous DMF (10 ml), silver nitrate (134 mg, 0.078 mmol) was added and the flask was covered with an aluminium foil. It was cooled in ice and N-bromosuccinimide (1.38 gm, 7.75 mmol) was added in portions. The reaction mixture was allowed to warm to room temperature and continued to stir for 22 hours. The reaction mixture was cooled in ice and ice water (20 ml) was added and the mixture was extracted with diethyl ether (3 X 20 ml). The combined organic layers were washed with water (3X 20 ml), dried over anhydrous MgSO\(_4\) and filtered. The solvents were removed under reduced pressure and the crude was purified by chromatography (hexanes/EtOAc, 8:2) to yield \(212a\) (1.358 gm, 6.00 mmol, 80%) as a brown solid. Mp 98-102 °C (lit\(^{101}\) 94-98 °C).

**2,4-Dinitro-1-[2-iodoethynyl]benzene** \((217a)\):

Reaction between \(216a\) (182 mg, 0.77 mmol) and NIS (192 mg, 0.85 mmol) in presence of silver nitrate (13 mg, 0.076 mmol) in anhydrous DMF (5 ml) as described above for \(212a\) (4 h) afforded the product \(217a\) (219 mg, 0.689 mmol, 89%) as an yellow solid\(^{135}\) after work up and chromatography (hexanes/EtOAc, 85:15). Mp 112-113 °C; \(^1\)H NMR
(600 MHz, CDCl$_3$): $\delta$ 8.90 (d, $J$=2.4 Hz, 1H), 8.42 (dd, $J$=8.4, 2.4 Hz, 1H), 7.84 (d, $J$=9 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 146.9, 137.3, 127.1, 124.6, 120.5, 92.8, 88.3, 25.9; IR (neat) 3094, 2161, 1592 cm$^{-1}$.

4-chloro-2-nitro-1-[2-iodoethynyl]benzene (217b):

Reaction between 216b (485 mg, 1.91 mmol) and NIS (477 mg, 2.11 mmol) in presence of silver nitrate (40 mg, 0.23 mmol) in anhydrous DMF (10 ml) as described above for 212a (3 h) afforded the product 217b$^{138}$ (523 mg, 1.70 mmol, 89%) as a yellow solid after work up and chromatography (hexanes/EtOAc, 8:2). Mp 94-96 °C; $^1$H NMR (270 MHz, CDCl$_3$): $\delta$ 8.05 (d, $J$=1.6 Hz, 1H); 7.59 (d, $J$=8.9 Hz, 1H), 7.55 (dd, $J$=8.3, 1.8 Hz, 1 H); $^{13}$C NMR (67.5 MHz, CDCl$_3$)$^{136}$: $\delta$ 150.4, 136.6, 135, 133.0, 124.8, 116.9, 88.0, 18.7; IR 2165, 1555 cm$^{-1}$.

4-Methoxy -2-nitro-1-[2-iodoethynyl]benzene (217c):

Reaction between 216c (100 mg, 0.42 mmol) and NIS (107 mg, 0.47 mmol) in presence of silver nitrate (37 mg, 0.22 mmol) in anhydrous DMF (3 ml) as described above for 212a (2 h) afforded the product 217c$^{138}$ (99 mg, 0.33 mmol, 77%) as a yellow solid after work up and chromatography (hexanes/EtOAc, 8:2). Mp 92-94 °C; $^1$H NMR (270
MHz, CDCl$_3$): $\delta$ 7.54 (d, J=8.6 Hz, 1H), 7.53 (d, J=2.7 Hz, 1H), 7.10 (dd, J=8.6, 2.7 Hz, 1H); $^{13}$C NMR (67.5 MHz, CDCl$_3$): $\delta$ 159.9, 151.4, 136.8, 119.8, 110.9, 109.4, 89.0, 56.2, 13.8. IR (neat) 2170, 1560, 1527 cm$^{-1}$.

![ Chemical structure of 216d and 217d ]

5-Methoxy-2-nitro-1-[2-iodoethynyl]benzene (217d):

Reaction between 216d (300 mg, 1.27 mmol) and NIS (318 mg, 1.41 mmol) in presence of silver nitrate (122 mg, 0.658 mmol) in anhydrous DMF (2 ml) as described above for 212a (1 h) afforded the product 217d$^{138}$ (299 mg, 0.987 mmol, 77%) as a pale yellow solid after work up and chromatography (hexanes/EtOAc, 8:2). Mp 87-88°C; $^1$H NMR (270 MHz, CDCl$_3$): $\delta$ 8.09 (d, J=9.1 Hz, 1H), 7.07 (d, J=2.7 Hz, 1H), 6.93 (dd, J=9.3, 2.8 Hz, 1H), 3.89 (s, 3H); $^{13}$C NMR (67.5 MHz, CDCl$_3$)$^{136}$: $\delta$ 162.8, 143.3, 127.1, 120.8, 119.9, 115.1, 89.5, 56.1, 16.8; IR (neat) 2160, 1606, 1573 cm$^{-1}$.

![ Chemical structure of 216e and 217e ]

3-Methyl-2-nitro-1-[2-iodoethynyl]benzene (217e):

Reaction between 216e (175 mg, 0.751 mmol) and NIS (189 mg, 0.838 mmol) in presence of silver nitrate (135 mg, 0.771 mmol) in anhydrous DMF (5 ml) as described above for 212a (20 min) afforded the product 217e (200 mg, 0.697 mmol, 93%) as a
yellow solid after work up. The product decomposes upon standing at room temperature and on attempted purification on silical gel. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.39 (d, $J$=7.8 Hz, 1H), 7.33 (t, $J$=7.8 Hz, 1H), 7.26 (d, $J$=7.5 Hz, 1H); $^{13}$C NMR (67.5 MHz, CDCl$_3$)$^{136}$: $\delta$ 153.6, 131.9, 130.5, 130.1, 116.8, 87.6, 17.8, 14.9;

4-Methyl-2-nitro-1-[2-iodoethynyl]benzene (217f):

Reaction between 216f$^{96}$ (715 mg, 0.751 mmol) and NIS (768 mg, 3.404 mmol) in presence of silver nitrate (58 mg, 0.108 mmol) in anhydrous DMF (5 ml) as described above for 212a (1 h) afforded the product 217f (646 mg, 2.25 mmol, 73%) as a yellow solid$^{138}$ after work up and chromatography (hexanes/EtOAc, 9:1). Mp 94-96 °C; $^1$H NMR (600 MHz) $\delta$ 7.85 (s, 1 H), 7.51 (d, $J$=7.8 Hz, 1H), 7.37 (d, $J$=8.4 Hz, 1 H), 2.44 (s, 3H); $^{13}$C NMR (150 MHz) $\delta$ 150.5, 140.4, 135.8, 125.1, 115.9, 89.2, 21.5, 15.2.

6-Methyl-2-nitro-1-[2-iodoethynyl]benzene (217g):

Reaction between 216g (135 mg, 0.579 mmol) and NIS (144 mg, 0.638 mmol) in presence of silver nitrate (53 mg, 0.303 mmol) in anhydrous DMF (2 ml) as described above for 212a (5.5 h) afforded the product 217g (155 mg, 0.54 mmol, 93%) as a yellow
solid after work up and chromatography (hexanes/EtOAc, 9:1). Mp 87-88 °C. $^1$H NMR (600 MHz) $\delta$ 7.81 (d, $J=8.4$ Hz, 1 H), 7.48 (d, $J=7.8$ Hz, 1H), 7.33 (t, $J=8.1$ Hz, 1 H), 2.53 (s, 3H); $^{13}$C NMR (150 MHz) $\delta$ 151.6, 144.9, 134.0, 128.4, 122.1, 118.1, 87.8, 21.3, 20.5. IR (neat) 2928, 2169 cm$^{-1}$.

$\text{2-(3-Nitropyridyl)-1-iodoethyne (220):}$

To a solution of 219 ( 55 mg, 0.28 mmol) in 5 ml anhydrous DMF, cooled in ice, silver nitrate (6 mg, 0.035 mmol) and NIS (75 mg, 0.332 mmol) are added and the mixture was slowly allowed to warm up to room temperature. The reaction flask was covered with an aluminium foil and the mixture was stirred under nitrogen for 21 h. Work up and chromatography (hexanes/EtOAc, 7:3) as described for 212a gave the product 220 (53 mg, 0.193 mmol, 69%) as a yellow solid. Mp 162-164 °C; $^1$H NMR (600 MHz) $\delta$ 8.81 (dd, $J=4.8$, 1.2 Hz, 1H), 8.36 (dd, $J=8.4$, 1.8 Hz, 1H), 7.46 (dd, $J=8.4$, 4.8 Hz, 1H); $^{13}$C NMR (150 MHz) $\delta$ 153.6, 147.7, 136.9, 132.6, 123.5, 89.9, 21.2. IR (neat) 1593, 1520, 1339, 819, 759 cm$^{-1}$. Anal. calcd. for C$_7$H$_4$IN$_2$O$_2$: C, 30.68; H, 1.10; N, 10.22. Found C, 30.93; H, 1.24; N, 9.73. HRMS calcd for C$_7$H$_4$IN$_2$O$_2$ M+H$^+$ 274.9318, found 274.9312.
5-(2,2-Dibromoethen-1-yl)-6-nitrobenzo[1,3]dioxole (222):

A solution of carbon tetrabromide (679 mg, 2.05 mmol) in dichloromethane (25 ml) was cooled in an ice bath at 0 °C. Triphenylphosphine (1.074 gm, 4.1 mmol) was added in portions in 10 minute intervals followed by the addition of 6-nitropiperonal (221) (200 mg, 1.025 mmol). The resulting wine red mixture was allowed to warm to room temperature, and stirred under an atmosphere of nitrogen for 18 hours. The solvent was removed under reduced pressure, and the orange crude was purified quickly by flash chromatography (hexanes/EtOAc, 8:2) due to the observed gradual decomposition of the product on silica. The product, 222 (273 mg, 0.778 mmol, 76%) was obtained as a yellow crystalline solid. Mp 158-160 °C; 1H NMR (600 MHz) δ 7.71 (s, 1H), 7.63 (s, 1H), 6.95 (s, 1H), 6.16 (s, 2H); 13C NMR (150 MHz) δ 151.9, 148.2, 141.3, 134.5, 128.0, 110.1, 105.5, 103.3, 92.6; IR (neat) 1503, 1483, 1318, 1028, 830 cm⁻¹; HRMS calcd for C₉H₆Br₂NO₄ (M+H⁺) 349.8664, found 349.8658.

5-(2-Bromomoethyny-1-yl)-6-nitrobenzo[1,3]dioxole (223):

To a solution of 222 (105 mg, 0.299 mmol) prepared in DMF (3 ml), crushed and oven dried Cs₂CO₃ (283 mg, 2.99 mmol) was added and the resulting mixture was stirred at room temperature under an inert atmosphere (4 h). Dichloromethane (50 ml) was then
added followed by water (25 ml). The dichloromethane layer was extracted, washed with water (2 X 50 ml), dried (anhydrous MgSO₄), filtered and evaporated under reduced pressure to leave an yellow crude which was purified by flash chromatography (hexanes/ EtOAc, 85:15). The product **223** was obtained as an yellow solid in an almost quantitative yield (80 mg, 0.296 mmol, 99%). Mp 110-112 °C; ¹H NMR (600 MHz) δ 7.55 (s, 1H), 6.98 (s, 1H), 6.14 (s, 2H); ¹³C NMR (150 MHz) δ 151.8, 148.5, 114.2, 113.5, 105.7, 103.6, 75.9, 57.9; IR (neat) 1603 cm⁻¹; Anal. calcd. for C₉H₄BrNO₄: C, 40.03; H 1.49; N, 5.19. Found: C 40.09; H 1.61; N, 4.93.

![Chemical structure](image)

**1H-Indole-2,3-dione (164)***

To a solution of **212a** (104 mg, 0.460 mmol) in acetone (10 ml), PdCl₂(PPh₃)₂ (24 mg, 0.0342 mmol) was added and the resulting mixture was stirred under an atmosphere of nitrogen at room temperature. After 22 hours, the solvent was removed under reduced pressure, and the crude residue was purified by chromatography (hexanes/EtOAc, 7:3) to give the product **164** (22 mg, 0.165 mmol, 36%) as a red solid. Mp 195-197 °C (lit.¹³⁷ mp 197-198 °C).
6-Nitroisatin (6-Nitroindole-2,3-dione) (164a):

The reaction between 217a (140 mg, 0.44 mmol) and PdCl$_2$(PPh$_3$)$_2$ (16 mg, 0.023 mmol) in acetone (6 ml), as described for 164 (room temperature, 6 h), afforded the product 164a (25 mg, 0.208 mmol) after chromatography (hexanes/ EtOAc, 6:4) as a yellow solid. Mp 268 °C (decomposed) (lit.$^8$4 288-290 °C); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.35 (br s, 1H), 7.86 (dd, $J$=7.8, 1.8 Hz, 1H), 7.54 (d, $J$=1.8 Hz, 1H); $^{13}$C NMR (150 MHz) $\delta$ 183.1, 158.8, 152.5, 150.7, 125.4, 122.4, 117.7, 106.3.

6-Chloroisatin (6-Chloroindole-2,3-dione) (164b):

The reaction between 217b (50 mg, 0.163 mmol) and PdCl$_2$(PPh$_3$)$_2$ (15 mg, 0.021 mmol) in acetone (10 ml), as described for 164 (room temperature, 96 h), afforded the product 164b (12 mg, 0.076 mmol, 47%) after chromatography (hexanes/ EtOAc, 7:3) as a yellow solid. Mp 268 °C (decomposed) (lit.$^{138}$ 263 °C); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 11.15 (br s, 1H), 7.52 (d, $J$=7.8 Hz, 1H), 7.11 (dd, $J$=8.4, 1.8 Hz, 1H); $^{13}$C NMR (150 MHz) $\delta$ 183.6, 160.1, 152.5, 142.9, 126.9, 123.4, 117.4, 112.8.
6-Methoxyisatin (6-methoxyindole-2,3-dione)\textsuperscript{139} (164c):

The reaction between 217c (90 mg, 0.297 mmol) and PdCl\(_2\)(PPh\(_3\))\(_2\) (12 mg, 0.017 mmol) in acetone (10 ml), as described for 164 (room temperature, 48 h), afforded the product 164c (31 mg, 0.175 mmol, 59\%) after chromatography (hexanes/ EtOAc, 1:1) as a yellow solid. Mp 220 °C (decomposed) (lit\textsuperscript{140} 229-230 °C); \(^1\)H NMR (600 MHz) (DMSO-d\(_6\)): \(\delta\) 10.95 (s, 1H), 7.49 (d, \(J=\) 8.4 Hz, 1H), 6.59 (dd, \(J=8.4, 2.4\) Hz, 1H), 6.40 (d, \(J=2.4\) Hz, 1H), 3.87 (s, 3H); \(^{13}\)C NMR (150 MHz): \(\delta\) 181.5, 167.7, 160.5, 153.5, 127.3, 111.1, 108.8, 97.8, 56.1.

5-Methoxyisatin (5-methoxyindole-2,3-dione)\textsuperscript{141} (164d):

The reaction between 217d (290 mg, 0.957 mmol) and PdCl\(_2\)(PPh\(_3\))\(_2\) (35 mg, 0.049 mmol) in acetone (10 ml), as described for 164 (room temperature, 36 h), afforded the product 164d (103 mg, 0.581 mmol, 61\%) after chromatography (hexanes/ EtOAc, 6:4) as a dark red solid. Mp 190-195 °C (lit\textsuperscript{140} mp 200-201 °C); \(^1\)H NMR (270 MHz) (DMSO-d\(_6\)): \(\delta\) 10.85 (s, 1H), 7.19-7.15 (dd, \(J=\) 8.6 Hz, 8.4 Hz, 1H), 7.05 (dd, \(J=2.4\) Hz, 1H), 6.84 (d, \(J=8.6\) Hz, 1H), 3.73 (s, 3H); \(^{13}\)C NMR (67.5 MHz): \(\delta\) 184.8, 159.7, 155.4, 144.7, 125.0, 118.2, 113.4, 108.9, 55.9.
7-Methylisatin (7-methylindole-2,3-dione) (164e):

The reaction between 217e (170 mg, 0.592 mmol) and PdCl$_2$(PPh$_3$)$_2$ (22 mg, 0.031 mmol) in acetone (10 ml), as described for 164 (room temperature, 30 h), afforded the product 164e (67 mg, 0.416 mmol, 70%) after chromatography (hexanes/EtOAc, 6:4) as an orange solid. Mp 265-268 °C (lit$^{144,145}$ 267-269 °C); $^1$H NMR (600 MHz) (DMSO-d$_6$): $\delta$ 11.06 (br s, 1H), 7.42 (d, $J$=7.8 Hz, 1H), 7.33 (d, $J$=7.2 Hz, 1H), 6.98 (t, $J$=7.8 Hz, 1H), 2.19 (s, 3H); $^{13}$C NMR (125 MHz): $\delta$ 184.7, 150.9, 149.2, 139.4, 122.6, 121.9, 121.5, 117.5, 15.4.

6-Methylisatin (6-methylindole-2,3-dione)$^{143}$ (164f):

The reaction between 217f (165 mg, 0.575 mmol) and PdCl$_2$(PPh$_3$)$_2$ (22 mg, 0.031 mmol) in acetone (10 ml), as described for 164 (room temperature, 36 h), afforded the product 164f (57 mg, 0.342 mmol, 59%) after chromatography (hexanes/EtOAc, 6:4) as an orange-red solid. Mp 182-184 °C (lit$^{146}$ 187-189 °C); $^1$H NMR (600 MHz) (DMSO-d$_6$): $\delta$ 10.97 (br s, 1H), 7.39 (d, $J$=7.8 Hz, 1H), 6.88 (dd, $J$=7.8 Hz & 1.2 Hz, 1H), 6.72 (d,
$J=0.6 \text{ Hz, 1H}$, 2.35 (s, 3H); $^{13}$C NMR (125 MHz): $\delta$ 183.6, 159.8, 151.1, 150.1, 124.7, 123.5, 115.5, 112.6, 22.2.

4-Methylisatin (4-methylindole-2,3-dione) (164g):

The reaction between 217g (115 mg, 0.40 mmol) and PdCl$_2$(PPh$_3$)$_2$ (14 mg, 0.02 mmol) in acetone (10 ml), as described for 164 (room temperature, 20 h), gave 164g (22 mg, 0.137 mmol, 34%) as the product after chromatography (hexanes/EtOAc, 7:3), as an orange solid. Mp 182-184 $^\circ$C (lit $^{144}$ 186-187 $^\circ$C); $^1$H NMR (600 MHz) (CDCl$_3$): $\delta$ 8.13 (br s, 1H), 7.40 (t, $J=7.8$ Hz, 1H), 6.89 (d, $J=7.2$ Hz, 1H), 6.71 (d, $J=7.8$ Hz, 1H), 2.57 (s, 3H); $^{13}$C NMR (125 MHz): $\delta$ 183.5, 159.3, 149.2, 141.9, 138.1, 126.4, 116.7, 109.6, 18.3.

5H-[1,3]Dioxalo[4,5-f]indole-6,7-dione (224)$^{145}$:

The reaction between 223 (80 mg, 0.296 mmol) and PdCl$_2$(PPh$_3$)$_2$ (10 mg, 0.014 mmol) in acetone (6 ml), as described for 164 (room temperature, 5 h), afforded the product 224 (20 mg, 0.105 mmol, 35%) after chromatography (hexanes/EtOAc, 1:1) as a pink solid. Mp 280-281 $^\circ$C (lit$^{146}$ 284 $^\circ$C); $^1$H NMR (600 MHz): $\delta$ 10.76 (s, 1H), 7.05 (s, 1H).
6.55 (s, 1H), 6.13 (s, 2H); $^{13}$C NMR (150 MHz): $\delta$ 181.3, 160.3, 156.1, 150.4, 143.6, 110.0, 103.8, 102.5, 94.6.

2-Bromo-3-oxo-3H-indole-1-oxide (225):

To a solution of 212a (235 mg, 1.03 mmol) in CH$_2$Cl$_2$ (25 ml), PdCl$_2$(PPh$_3$)$_2$ (77 mg, 0.109 mmol) was added and the reaction mixture was heated to reflux for 80 minutes. The solvent was removed under reduced pressure and the resulting crude was purified by chromatography (hexanes/EtOAc, 6:4) to yield the product 225 (230 mg, 1.017 mmol, 99%) as an orange solid. $^1$H NMR (270 MHz): $\delta$ 7.74-7.55 (m, 4H); $^{13}$C NMR (67.5 MHz): $\delta$ 180.5, 147.8, 135.1, 135.0, 131.6, 131.5, 123.0, 122.3, 114.0; IR (ATR) 1735, 1652, 1506 cm$^{-1}$.

6-Bromo-7-oxo-7H-[1,3]dioxalo[4,5-f]indole-5-oxide (248):

To a solution of 223 (28 mg, 0.104 mmol) in acetone (5 ml), PdCl$_2$(PPh$_3$)$_2$ (4 mg, 0.006 mmol) was added and the reaction mixture was allowed to stir at room temperature for
50 minutes. The solvent was removed under reduced pressure and the resulting crude was purified by chromatography (hexanes/EtOAc, 6:4) to yield the product 248 (24 mg, 0.089 mmol, 86%) as a brown solid. Further elution afforded a trace amount of the isatin 224. Mp 125 °C (decomposed); ¹H NMR (600 MHz) δ 7.17 (s, 1H), 7.05 (s, 1H), 6.17 (s, 2H); ¹³C NMR (150 MHz) δ 179.7, 153.1, 150.1, 144.7, 117.4, 117.1, 103.6, 103.3, 97.8; IR (ATR) 1717, 1500, 1292, 1031 cm⁻¹; HRMS (ESI) calcd for C₉H₅BrNO₄ (M+H⁺) 269.9402, found 269.9399.

![Chemical Structure](image)

2-Ethoxyisatogen (250a):

To a solution of 212a (50 mg, 0.221 mmol) in DCM (5 ml), PdCl₂(PPh₃)₂ (12 mg, 0.017 mmol) and EtOH (0.5 ml) was added and the reaction mixture was heated at 45 °C (3 h) under an inert atmosphere. The solvent was removed under reduced pressure and the resulting crude was purified by chromatography (hexanes/EtOAc, 7:3) to yield the product 250a (30 mg, 0.156 mmol, 70%) as an yellow solid. Mp 45-47 °C; ¹H NMR (600 MHz) δ 7.92 (d, J=8.4 Hz, 1H), 7.71 (d, J=9 Hz, 1H), 7.38 (dt, J=9, 2.4 Hz, 1H), 7.23 (dt, J=8.4, 2.4 Hz, 1H), 4.54 (q, 2H), 1.49 (t, 3H); ¹³C NMR (150 MHz) δ 157.7, 157.3, 153.9, 131.3, 127.9, 120.7, 120.5, 116.3, 62.4, 14.5; IR (neat) 1726, 1304, 1224, 1031 cm⁻¹.
6-Chloro-2-ethoxyisatogen (250c):

To a solution of 212c (132 mg, 0.43 mmol) in DCM (20 ml), PdCl₂(PPh₃)₂ (35 mg, 0.05 mmol) and EtOH (0.5 ml) was added and the reaction mixture was stirred at room temperature (6 h) under an inert atmosphere. The solvent was removed under reduced pressure and the resulting crude was purified by chromatography (hexanes/EtOAc, 8:2) to yield the product 250c (25 mg, 0.09 mmol, 23%) as a pale orange solid.

Mp 74-75 °C; ¹H NMR (600 MHz) δ 7.89 (dd, J=9, 0.6 Hz, 1H), 7.72 (dd, J=1.8, 0.6 Hz, 1H), 7.17 (dd, J=9, 1.8 Hz, 1H), 4.55 (q, 2H), 1.49 (t, 3H); ¹³C NMR (150 MHz) δ 157.8, 156.9, 154.6, 137.9, 130.0, 122.1, 118.9, 114.8, 62.7, 14.4; IR (neat) 1737, 1218, 1198 cm⁻¹.

2-Allyloxyisatogen (251):

To a solution of 225 (149 mg, 0.66 mmol) in dichloromethane (10 ml), allyl alcohol (200 mg, 3.46 mmol) was added and the reaction mixture was stirred at room temperature (16 h) under an inert atmosphere. The solvent was removed under reduced pressure.
pressure and the resulting crude was purified by chromatography (hexanes/EtOAc, 9:1) to yield the product 251 (50 mg, 0.25 mmol, 38%) as a pale brown solid. Mp 33-35 °C; ¹H NMR (600 MHz) δ 7.93 (ddd, J=8.8, 0.8, 0.8 Hz, 1H), 7.72 (ddd, J=9.1, 0.9, 0.8 Hz, 1H), 7.39 (ddd, J=9.1, 6.4, 0.6 Hz, 1H), 7.25 (ddd, J=8.8, 6.4, 0.9 Hz, 1H), 6.09 (ddt, J=17.2, 10.5, 5.9 Hz, 1H), 5.51 (dq, J=17.2, 1.3 Hz, 1H), 5.38 (dq, J=10.5, 1.3 Hz, 1H), 4.98 (dt, J=5.9, 1.3 Hz, 1H); ¹³C NMR (150 MHz) δ 157.5, 156.8, 153.5, 131.2, 131.1, 127.9, 120.5, 120.4, 119.8, 116.2, 66.5; IR (neat) 1719, 1306, 1195 cm⁻¹; HRMS Calcd for C₁₁H₉NO₃ (M+H⁺) 204.0660; found 204.0655.

2,3,4,9-Tetrahydro-7-methoxy-3-methyl-1H-carbazol-1-one (257c) and 2,3,4,9-tetrahydro-5-methoxy-3-methyl-1H-carbazol-1-one (257d):
The phenyl hydrazone 262 (197 mg, 0.788 mmol) was dissolved in glacial acetic acid (1.3 ml) and refluxed with Conc. HCl (0.4 ml) for 5 min. The reaction mixture was diluted with ice water and filtered. The precipitate obtained was purified by chromatographed over a silica column (hexane/EtOAc, 9:1) to afford 257c (90 mg, 0.390 mmol, 49%) as a colorless solid. Mp 204-206 °C. (lit.¹¹⁶,¹¹³a mp 211 °C). Further elution with (hexane-ethyl acetate, 7:3) gave 257d (13 mg, 0.057 mmol, 7%) also as a colorless solid. Mp 198 °C (lit.¹¹³a mp 201 °C).
1-methyl-3-hydroxycarbazole (279):

To a solution of compound 257b (105 mg, 0.454 mmol) in anhydrous DMF (3ml), was added DBU (71 mg, 0.466 mmol) and heated under an atmosphere of nitrogen for 16 h. The reaction mixture was cooled to room temperature, diluted with water (20 ml), and extracted with dichloromethane (2X20 ml). The organic phase was dried (anhydrous MgSO₄) and concentrated to give an oily dark crude, that was purified by chromatography (hexanes/EtOAc, 7:3) to yield 279 (25 mg, 0.127 mmol, 27.8%) as an off-white solid. Mp 158-160 °C; ¹H NMR (600 MHz) δ 7.96 (d, J=7.8 Hz, 1H), 7.805 (br s, 1H), 7.42 (d, J=7.8 Hz, 1H), 7.39 (t, J=7.2 Hz, 1H), 7.34 (d, J=1.8 Hz, 1H), 7.19 ( t, J=7.8 Hz, 1H), 6.82 (d, J=1.8 Hz, 1H), 4.63 (br s, 1H), 2.51 (s, 3H); ¹³C NMR (150 MHz) δ 149.5, 140.4, 134.1, 125.9, 123.8, 123.7, 121.0, 120.7, 119.3, 115.8, 111.0, 103.3. IR (neat) 3149, 1492, 1373, 1172, 1061 cm⁻¹; HRMS calcd. for C₁₃H₁₂NO (M+H⁺) 198.0919, found 198.09134.
3-Hydroxycarbazole (283):

To a solution of compound 257e (100 mg, 0.4603 mol) in anhydrous DMF (4 ml) was added DBU (190 mg, 1.248 mmol) and heated under an atmosphere of nitrogen for 2 h. Work up and purification as described for compound 279, gave 3-hydroxycarbazole (283) (20 mg, 0.109 mmol, 24%) after purification by chromatography (hexane/EtOAc, 7:3) as a colorless solid.147 Mp 252-255 °C (lit148 260-261 °C).

2-Iodo-3-nitrobenzylalcohol (308):

To a solution of 2-iodo-3-nitrobenzoic acid (2.95 gm, 0.01 mol) prepared in dry THF (20 ml), was added borane-dimethylsulfide complex (10 ml, 2M) slowly with a syringe and the reaction mixture was heated to reflux under an atmosphere of nitrogen for 2 hours. The solution was cooled to room temperature and methanol (10 ml) was added slowly until the bubbles cease, followed by water (20 ml). Extraction of the resulting solution with ethyl acetate (2X20 ml), drying (anhydrous MgSO₄) and evaporation of the solvent under reduced pressure gave an yellow solid which was purified by
chromatography (hexanes/EtOAc, 6:4) to yield 308 (2.512 gm, 0.009 mol, 90%) as a yellow solid. Mp 78-80 °C; ¹H NMR (600 MHz) δ 7.71 (dt, J=7.8, 1.6, 0.8 Hz, 1H), 7.58 (dt, J=7.8, 1.6, 0.5 Hz, 1H), 7.49 (t, J=7.8 Hz, 1H), 4.78 (s, 2H), 2.27 (br s, 1H); ¹³C NMR (150 MHz) δ 154.9, 146.2, 130.8, 129.3, 123.7, 88.4, 69.9.

2-iodo-3-nitrobenzylbromide (309):

2-Iodo-3-nitrobenzylalcohol (308) (1.04 gm, 3.728 mmol), carbon tetrabromide (1.324 gm, 3.994 mmol) and triphenyl phosphine (1.05 gm, 4.003 mmol) are taken in an oven-dried round-bottomed flask, and dry THF (20 ml) is added with a candula under an inert atmosphere. The resulting reaction mixture is heated to reflux (4 h), cooled to room temperature, and extracted with EtOAc (2X50 ml) after the addition of water (25 ml). The combined organic phases are washed with aq. NaHSO₄ (25 ml), dried (anhydrous MgSO₄) and the solvent is removed under reduced pressure to give an yellow solid, which was purified by chromatography (hexanes/EtOAc, 8:2) to afford 309 (954 mg, 2.79 mmol, 75%) as an yellow solid. Mp 65-67 °C; ¹H NMR (600 MHz) δ 7.66 (dd, J=7.8, 1.8 Hz, 1H), 7.54 (dd, J=7.8, 1.2 Hz, 1H), 7.46 (t, J=7.2 Hz, 1H), 4.70 (s, 2H); ¹³C NMR (150 MHz) δ 156.1, 144.0, 133.2, 129.7, 124.3, 92.1, 38.6; HRMS calcd. for C₇H₅BrINO₂ (M+H⁺) 341.8626, found 341.8621.
2-iodo-3-nitromethoxytoluene (299b):

A solution of sodium methoxide, prepared by dissolving sodium (124 mg, 5.391 mmol) in methanol (10 ml) is added to a methanolic solution of 309 (925 mg, 2.705 mmol) under an inert atmosphere at 0 °C. The resulting reaction mixture is allowed to stir rapidly at 0 °C (4 h). The removal of the solvent under reduced pressure gave an yellow solid, which after purification by chromatography (hexanes/EtOAc, afforded 299b (600 mg, 2.047 mmol, 76%) as an yellow solid. Mp 26-27 °C; ¹H NMR (600 MHz) δ 7.63 (dd, J=7.2, 0.6 Hz, 1H), 7.55 (dt, J=7.8, 0.6 Hz, 1H), 7.46 (t, J=7.8 Hz, 1H), 4.503 (s, 2H); 3.52 (s, 3H); ¹³C NMR (150 MHz) δ 155.0, 144.3, 130.9, 129.1, 123.6, 88.6, 59.1; HRMS calcd. for C₈H₆INO₃ 293.9627, found 293.9621.
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