CHAPTER III

SECTION A

Total Synthesis of Bouchardatine
Bouchardatine (17) is a naturally occurring alkaloid from the rutaecarpine family. It has been isolated from aerial parts of *Bouchardia neurococa* (Rutaceae).\(^1\) Its structure (Figure 1) closely resembles that of rutaecarpine (18).

![Figure 1: Structure of bouchardatine 17 and rutaecarpine 18.](image)

Bouchardatine (17) contains an indole and a quinazolinone moiety in its core structure. Most of the quinazolinone alkaloids have been isolated from number of families of the plant kingdom, from animals and from microorganisms.\(^2\) Quinazolinone derivatives are of interest because of their pharmacological properties, e.g., protein tyrosine kinase inhibitory, cholecystokinin inhibitory, anti-microbial, anticonvulsant, sedative, hypotensive, anti-depressant, anti-inflammatory, and anti-allergic properties.\(^3,4\) Some of these compounds also have interesting biological properties such as anti-malarial activity, bio-fungicide, and diuretic properties.\(^4\) Different substituted quinazolinones have been isolated and reported for their biological activities. Some of these quinazolinone alkaloids are shown in Chart I.

![Chart I: Quinazolinone alkaloids](image)

Rutaecarpine (18) is also a quinazolinone type alkaloid isolated from *Evodia rutaecarpa* and shows numerous biological activities.\(^5\) Rutaecarpine and its analogs are simplest quinazolinone alkaloids having a quinazolinone ring fused with a piperidine ring system. The first known representatives of the quinazolinocarboline
alkaloids were rutaecarpine and evodiamine. Rutaecarpine and its derivatives have been reported to possess strong analgesic, anti-emetic, astringent, anti-hypertensive, uterotonic, TCDD-receptor, anti-nociceptive, anti-inflammatory, and cyclooxygenase-2 (COX-2) inhibitory activities. Rutaecarpine was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca\(^{2+}\) in endothelial cells. 1-Methoxyrutaecarpine, 7,8-dehydrorutaecarpine, 2-methoxyrutaecarpine, 7-hydroxyrutaecarpine, 3-hydroxyrutaecarpine, 1,2-dihydroxyrutaecarpine, 2-methoxyrutaecarpine, 2-methoxy-13-methyl-rutaecarpine etc. have been reported as naturally occurring rutaecarpines. Many methods have been reported so far for the synthesis of rutaecarpine and its analogues. Some of the synthetic methods for rutaecarpine have been listed below.


2. Lee et al\(^10\) (2001)


4. Kametani et al\(^12\) (1977)
Bouchardatine can be utilised as a precursor in the synthesis of rutaecarpine. So far, there is only one report available for the synthesis of bouchardatine by Bubenyak et al in 2008. They have also reported cytotoxic activity for bouchardatine against HeLa cells. The reported synthetic route for bouchardatine is shown below.


Taking into account the importance of bouchardatine, and the limited literature available, it was planned to explore new routes for synthesis of bouchardatine. One of the routes involved formation of Schiff’s base and subsequent cyclization of the imine formed to obtain the targeted compound.

Schiff bases have been known since 1864 when Hugo Schiff reported the condensation of primary amines with carbonyl compounds. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R', where R and R' are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. These compounds are also known as anils, imines or azomethines. Several studies showed that the presence of a lone pair of electrons in sp^3 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance. Because of the relative easiness of preparation, synthetic flexibility, and the special property of C=N group, Schiff bases are generally excellent chelating agents, especially when a functional group like –OH or –SH is present close to the azomethine group so as to form a five or six membered ring with the metal ion.

Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent.
to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis.

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base.

Schiff’s bases have been used in many organic reactions as useful intermediates. Some reactions involving synthesis of biologically important molecules through the intermediate Schiff’s base are shown below.

1. **Zhang et al**\(^{18}\) (2012)

   ![Diagram 1](image1.png)

2. **Zarei et al**\(^{19}\) (2011)

   ![Diagram 2](image2.png)

3. **Ding et al**\(^{20}\) (2010)

   ![Diagram 3](image3.png)

![Chemical reaction diagram]

5. Yang et al\textsuperscript{22} (2005)

![Chemical reaction diagram]


![Chemical reaction diagram]

**Heck reaction**

Another route envisaged for the synthesis of bouchardatine was through a Heck type reaction. The palladium-catalysed arylation of an alkene with an organic halide (Figure 2) was first reported by Mizoroki and Heck in the early 1970s.

\[ R^1X + \text{alkene} + \text{Base} \xrightarrow{\text{Pd}} R^1\text{alkene} + \text{Base}^+X^- \]

\( R^1 = \text{aryl, vinyl} \)

\( X = I, Br, Cl, OTf \)

**Figure 2:** The Mizoroki-Heck Reaction
Chapter III (Section A)

Figure 3: Mechanism of Heck reaction

The classical reaction involves bond formation between two sp\(^2\) carbon centres by an overall substitution of a C-H bond of an alkene by R\(^1\) from the R\(^1\)X substrate (where R\(^1\) = aryl or vinyl; X = I or Br; R\(^2\) = electron withdrawing or releasing group) under basic conditions. The transformation has since become known as the Heck reaction. The general mechanism for this coupling is shown in Figure 3.

Since its discovery, the methodology has been found to be highly versatile and applicable to a wide range of aryl species Ar-X, where X= Cl, Br, I, OTf, OTs and N\(_2^+\). A diverse range of olefins has also been found to undergo the Heck reaction readily. The reaction was scarcely used in the first two decades following its discovery. Its popularity only started to flourish in the mid-1980s when synthetic chemists found that they were able to control the selectivity by using certain reaction protocols to give fairly predictable results. This led to the publication of a handful of review articles from the mid-1990s onwards, on the development of ligands for the
reaction, as well as the application of the Heck reaction to natural product synthesis. More recently, coverage has been provided on the reactivity and selectivity of the Heck reaction, as well as the development of the subject in the light of mechanistic studies. The utilisation of Heck reaction in construction of complex molecules can be seen from the examples listed below.


\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{N}_2\text{BF}_4
\end{align*}
\]

\[
\text{+}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{OAc}
\end{align*}
\]

\[
\text{Pd(OAc)}_2, \text{CO, NaOAc, PhCN}
\]

\[
25 \degree C, 12 \text{ h}
\]

\[
\text{MeO} & \quad \text{OMe} \\
\text{OAc}
\]

\[
\text{i) BCl}_3, \text{n-Bu}_4\text{NiI, CH}_2\text{Cl}_2, 0 \degree \text{C}, 1 \text{ h}
\]

\[
\text{MeO} & \quad \text{OMe} \\
\text{OH}
\]

\[
\text{ii) NaOH 50\% aq., THF, reflux, 2 h}
\]

Resveratrol


\[
\begin{align*}
\text{(HO)B} & \quad \text{Ph}
\end{align*}
\]

\[
\text{Pd(OAc)}_2 (10 \text{ mol\%})
\]

\[
\text{AcOH(4 equiv.), BQ (2 equiv.), dioxane (0.33 M), rt, 4 h}
\]


\[
\begin{align*}
\text{I} & \quad \text{CHO}
\end{align*}
\]

\[
\text{Pd(OAc)}_2
\]

\[
\text{PPh}_3, \text{DMF, K}_2\text{CO}_3, 140 \degree \text{C}, 24 \text{ h}
\]


\[
\begin{align*}
\text{MeO} & \quad \text{O}
\end{align*}
\]

\[
\text{Pd(OAc)}_2 (6 \text{ mol\%})
\]

\[
\text{Ligand (12 \text{ mol\%})}
\]

\[
\text{Cy}_2\text{NMe (4 equiv.)}
\]

\[
\text{CHCl}_3, 2 \text{ days reflux}
\]
5. Danishefsky et al\textsuperscript{32} (1993)

Heck coupling reactions using aryl bromides and chlorides are more reluctant to undergo catalytic reactions due to their stronger C-X bonds, a problem made worse if the aryl group carries electron-rich substituents.\textsuperscript{33} Aryl bromides and chlorides are however much more useful substrates to synthetic chemists, as they are cheaper and more readily available. Also, we came across very few examples of Heck type reaction where imine carbon was utilised for the coupling.\textsuperscript{34}

**Present Plan**

Thus, considering the importance of bouchardatine (17), and after the literature survey about Schiff’s bases and Heck reaction, it was decided to use these two strategies for the synthesis of bouchardatine as shown in Scheme 1.

![Scheme 1: Retrosynthetic analysis](image)

**Results and Discussions**

**Route I: Synthesis of bouchardatine (17) by cyclization of Schiff’s base**

This is a linear approach in which bouchardatine (17) was synthesized starting from simple starting material, indole (Scheme 2). Indole was initially protected using benzene sulfonyl chloride, since the further reactions demanded the absence of free -
NH group. To protect indole, it was stirred in dry DMSO and potassium hydroxide and treated with benzene sulfonyl chloride at room temperature. The solid product obtained was purified and characterized by spectral analysis. The formation of product 20 was confirmed by comparing the melting point (78-79°C) with the reported value. The mass spectrum showed a molecular ion peak at m/z 257 and a base peak at m/z 116 corresponding to indole, whereas ¹H NMR confirmed the absence of exchangeable proton.

Further, to obtain 1-(phenylsulfonyl)-¹H-indole-2-carbaldehyde 21, phenylsulfonyl indole 20 was formylated at C-2 in presence of LDA and DMF. LDA was freshly prepared from 1.6 M solution of n-butyl lithium in hexane and diisopropyl amine in THF. Melting point of product (156-158°C) was comparable with the reported value. Its formation was also confirmed by the presence of a peak at 1672 cm⁻¹ and 2755 cm⁻¹ in IR, one singlet at δ 10.53 in ¹H NMR and at δ 183.1 in ¹³C NMR corresponding to the aldehyde group.

The imine of 1-(phenylsulfonyl)-¹H-indole-2-carbaldehyde, 23, was subsequently formed by treatment of 21 with anthranilamide (22) in presence of acetic acid which played the role of a catalyst as well as a solvent. The reaction proceeded in a good yield. The IR spectrum of the product showed a broad band at 3371 cm⁻¹ corresponding to NH₂ group and a broad band at 1653 cm⁻¹ for the conjugated amide carbonyl and imine functionality. Formation of product was also established by the absence of aldehydic proton and carbon and the presence of a singlet for the imine proton at δ 6.53 in ¹H NMR. A singlet for amide carbonyl was seen at δ 163.2 in ¹³C NMR. Since this compound has not been reported in the literature, HRMS was obtained which showed good agreement between the calculated and observed values.

Intramolecular cyclization and deprotection of the benzene sulfonyl group to furnish compound 24 was then carried out in one pot in presence of sodium methoxide. However, in case of sodium methoxide very low yield (40%) was obtained and also it took 12 hours to complete the reaction. Hence, sodium methoxide was replaced by potassium tertiary butoxide and it was found that the reaction time reduced along with considerable rise in the yield. The isolated cyclised product did not melt up to 300°C. The reported value of melting point for this compound was found to be 319-320°C. A broad peak at 3357 cm⁻¹ and a peak at 1670 cm⁻¹ in IR spectrum confirmed the presence of NH group and amide carbonyl respectively. A
molecular ion peak was obtained at m/z 261 in the mass spectrum as a base peak along with the peaks for corresponding daughter ions. $^1$H NMR showed two exchangeable protons at δ 11.8 and 12.6 confirming deprotection of the –SO$_2$Ph group. The absence of imine proton was also an additional indication of cyclization reaction. From all this spectral data the structure of the product was confirmed as 24. This cyclised compound has been reported in literature as an important intermediate in the synthesis of quinazolinone type of alkaloids. Lee and co-workers have reported a synthesis of compound 10 in four steps in 31% overall yield. $^{38}$ Recently, Bubenjak and co-workers reported another synthesis of this intermediate by a Fischer indole synthesis. $^{13}$ It required four steps and afforded a 48% overall yield. Many groups have highlighted the need to increase the yield of this compound. $^{39,40}$ Using our strategy, intermediate 24 has been obtained in 64% yield starting from indole.

To complete the synthesis of the targeted bouchardatine molecule, Vilsmeier-Haack formylation reaction of compound 24 was used. Thus compound 24 was treated with POCl$_3$ in DMF to furnish the expected product 17 in 87% yield. The obtained product was found to melt at 255-257°C. FTIR spectrum showed peaks at 3051 cm$^{-1}$ for NH, 1693 cm$^{-1}$ for conjugated aldehyde carbonyl and 1653 cm$^{-1}$ for conjugated amide carbonyl. The presence of a signal at δ 10.13 in $^1$H NMR and δ 184.1 in $^{13}$C NMR corresponding to the aldehyde functionality confirmed the formation of the formylated product. A peak at m/z 289 in GCMS also helped in assigning the structure. Rest of the values were also in good agreement with the reported values. $^{13}$

![Scheme 2](image)

**Scheme 2: Reagents and conditions:** a) KOH, DMSO, PhSO$_2$Cl, rt, 5h, 97%; b) LDA, DMF, THF, -78°C to rt, 4h, 85%; c) Anthranilamide (22), CH$_3$COOH, 80°C, 30 min, 95%; d) t-BuOK, t-BuOH, 85°C, 6h, 82%; e) DMF, POCl$_3$, 0°C, 24h, 87%.
Chapter III (Section A)

Route II: Synthesis of bouchardatine by palladium catalysed Heck type coupling

In search of another route for the synthesis of bouchardatine (17), a convergent route using Heck type reaction as a key step was envisioned and a retrosynthetic scheme was designed accordingly as shown in Scheme 1, Route 2.

In this route, target molecule bouchardatine was visualised from two starting materials 32 and 33. 2-Chloro-1H-indole-3-carbaldehyde 32 was synthesized\(^4\) from 2-indolinone 31 as shown in Scheme 3. To start with, treatment of 1-fluoro-2-nitrobenzene with diethyl malonate in presence of potassium carbonate gave the ipso substitution product diethyl 2-(2-nitrophenyl)malonate 27. A molecular ion peak at m/z 281 corresponding to product 27 could be seen in the mass spectrum. A band for ester carbonyl at 1728 cm\(^{-1}\) was obtained in the FTIR spectrum. A singlet at δ 5.29 in \(^1\)H NMR and a signal at δ 54.4 in \(^13\)C NMR corresponding to the –CH group further confirmed the formation of the product. This diethyl malonate analogue 27 on hydrolysis and mono decarboxylation in 6N HCl furnished acid 28 which was chemically separated. This acid was found to melt\(^2\) at 138-140°C. A broad peak for –OH was seen in FTIR spectrum at 3070 cm\(^{-1}\). An exchangeable broad singlet at δ 12.58 in \(^1\)H NMR and a singlet at δ 171.3 in \(^13\)C NMR confirmed the presence of carboxylic group in the compound. Further, one pot reductive cyclization in acetic acid using H\(_2\), Pd/C provided 2-indolinone 31, in 88% yield.\(^3\) 2-Indolinone showed melting point at 125°C which matched with the reported\(^4\) value. A band for amide carbonyl was observed at 1688 cm\(^{-1}\) in IR spectrum. Additionally, a singlet for methylene protons at δ 3.52 in \(^1\)H NMR and presence of a signal at δ 36.2 for the methylene carbon and at δ 178.4 corresponding to the amide carbonyl in \(^13\)C NMR established the formation of 2-indolinone moiety. 2-Indolinone, 31, was also prepared from commercially available isatin by Wolff-Kishner reduction.\(^5\) Thus, isatin was treated with hydrazine hydrate in ethanol at 80°C, to obtain the hydrazone 30, which on further reaction with 10% NaOH, furnished 2-indolinone. The intermediate hydrazone 30 melted\(^6\) at 225°C and the presence of a NH\(_2\) moiety was indicated by a broad peak at 3352 cm\(^{-1}\) in IR spectrum.

2-Indolinone obtained by these two methods, was then converted into 2-chloro-1H-indole-3-carbaldehyde 32, by using Vilsmeier conditions\(^7\) by treatment with DMF and POCl\(_3\) in DCM. IR spectrum of this compound showed peaks at 2838 and 1636 cm\(^{-1}\) for the conjugated aldehyde functionality. Presence of C–Cl bond was
indicated by a strong band at 733 cm\(^{-1}\) in IR spectrum. A singlet at \(\delta \ 9.99\) in \(^1\)H NMR and a signal at \(\delta \ 183.2\) in \(^{13}\)C NMR confirmed the formation of formylated product.

The quinazolinone system \(33\), required for synthesis of target molecule was obtained by a reaction between anthranilamide and formamide in acetic acid.\(^{48}\) Formation of compound \(33\) was confirmed by GCMS by observing a molecular ion peak at m/z 146 corresponding to quinazolinone. The melting point of the product (213-215°C) matched with the reported\(^{49}\) value. In \(^1\)H NMR only one exchangeable proton was observed at \(\delta \ 12.21\) for the -NH group and signals corresponding to five protons were seen in the aromatic region. Palladium catalysed intermolecular Heck type reaction between quinazolin-4(3\(H\))-one (\(33\)) and 2-chloro-1\(H\)-indole-3-carbaldehyde (\(32\)) was then carried out in the presence of potassium carbonate and triphenyl phosphine. Thus, refluxing the contents together for 12 hours under inert atmosphere furnished a solid product in 68% yield, which was shown to be bouchardatine (\(17\)).

Scheme 3: Reagents and conditions: a) \(K_2CO_3\), DMF, 100°C, 3h, 98%; b) 6N HCl, rt, 12h, 90%; c) \(H_2\), Pd/C, AcOH, rt, 4h, 88%; d) \(NH_2NH_2\cdotH_2O\), ethanol, 80°C, 1h, 97%; e) 10% NaOH, ethanol, 80°C, 3h, 85%; f) DMF, POCl\(_3\), DCM, 0°C to rt, 38h, 70%; g) \(K_2CO_3\), Pd(OAc)\(_2\), PPh\(_3\), DMF, 120°C, 12h, 68%. 

113
Conclusion:

In summary, two convenient routes have been developed for the synthesis of bouchardatine. Route I was linear synthesis and gave 56% overall yield and route II was convergent synthesis which gave 39% overall yield. The intermediate 23, which was reported as an important precursor to quinazolinone alkaloids, has been synthesised in good yield by our approach. All new compounds obtained were characterized by $^1$H NMR, $^{13}$C NMR and HRMS.
Experimental Section

Reaction Index

Expt. No. 3.1.1 Synthesis of 1-(phenylsulfonyl)-1H-indole (20)

\[
\begin{align*}
\text{19} & \xrightarrow{\text{KOH, PhSO}_2\text{Cl, DMSO, rt, 5h}} \text{SO}_2\text{Ph} \\
\end{align*}
\]

97%

Expt. No. 3.1.2 Synthesis of 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (21)

\[
\begin{align*}
\text{20} & \xrightarrow{\text{LDA, DMF, THF, -78°C to rt, 4h}} \text{SO}_2\text{Ph} \\
\end{align*}
\]

85%

Expt. No. 3.1.3 Synthesis of 2-(((1-(phenylsulfonyl)-1H-indol-2-yl)methylene)amino)benzamide (23)

\[
\begin{align*}
\text{21} + \text{22} & \xrightarrow{\text{CH}_2\text{COOH, 80°C, 30 min}} \text{SO}_2\text{Ph} \\
\end{align*}
\]

95%

Expt. No. 3.1.4 Synthesis of 2-(1H-indol-2-yl)quinazolin-4(3H)-one (24)

\[
\begin{align*}
\text{23} & \xrightarrow{\text{t-BuOK, t-BuOH, 85°C, 6h}} \\
\end{align*}
\]

82%

Expt. No. 3.1.5 Synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-indole-3-carbaldehyde (bouchardatine) (17)

\[
\begin{align*}
\text{24} & \xrightarrow{\text{DMF, POCl}_3, 0°C, 24h}} \\
\end{align*}
\]

87%
Expt. No. 3.1.6 Synthesis of diethyl 2-(2-nitrophenyl)malonate (27)

\[
\begin{align*}
25 & \quad + \quad 26 \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{DMF}} \quad 27 \\
\text{NO}_2 & \quad \text{CH}_2 \quad \text{COOCH}_2\text{CH}_3 & \quad \text{COOCH}_2\text{CH}_3 & \quad \text{K}_2\text{CO}_3, \text{DMF} \\
100^\circ\text{C}, 3\text{h} & \quad 98\% & \quad \text{NO}_2 & \quad \text{COOCH}_2\text{CH}_3 & \quad \text{COOCH}_2\text{CH}_3
\end{align*}
\]

Expt. No. 3.1.7 Synthesis of 2-(2-nitrophenyl)acetic acid (28)

\[
\begin{align*}
27 & \quad \xrightarrow{6\text{N} \text{HCl}} \quad 28 \\
\text{NO}_2 & \quad \text{CH}_2\text{COOH} & \quad \text{rt}, 12\text{h} & \quad 90\%
\end{align*}
\]

Expt. No. 3.1.8 Synthesis of indolin-2-one (29)

\[
\begin{align*}
28 & \quad \xrightarrow{\text{H}_2, \text{Pd/C}} \quad 29 \\
\text{CH}_2\text{COOH} & \quad \text{AcOH, rt}, 4\text{h} & \quad 88\%
\end{align*}
\]

Expt. No. 3.1.9 Synthesis of 3-hydrazonoindolin-2-one (31)

\[
\begin{align*}
30 & \quad \xrightarrow{\text{NH}_2\text{NH}_2\text{H}_2\text{O}} \quad 31 \\
\text{H} & \quad \text{NH}_2\text{NH}_2\text{H}_2\text{O} & \quad \text{Ethanol} & \quad 80^\circ\text{C}, 1\text{h} & \quad 97\%
\end{align*}
\]

Expt. No. 3.1.10 Synthesis of indolin-2-one (29)

\[
\begin{align*}
31 & \quad \xrightarrow{10\% \text{NaOH}} \quad 29 \\
\text{NH}_2\text{NH}_2\text{H}_2\text{O} & \quad \text{Ethanol} & \quad 80^\circ\text{C}, 3\text{h} & \quad 85\%
\end{align*}
\]

Expt. No. 3.1.11 Synthesis of 2-chloro-1H-indole-3-carbaldehyde (32)

\[
\begin{align*}
29 & \quad \xrightarrow{\text{DMF, POCl}_3} \quad 32 \\
\text{N} & \quad \text{CHO} & \quad \text{DMF}, 0^\circ\text{C to rt} & \quad 38\text{h}, 70\%
\end{align*}
\]
Expt. No. 3.1.12 Synthesis of quinazolin-4(3H)-one (33)

![Chemical structure of quinazolin-4(3H)-one](image)

**Expt. No. 3.1.13 Synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-indole-3-carbaldehyde (bouchardatine) (17)**

![Chemical structure of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-indole-3-carbaldehyde](image)

**Expt. No. 3.1.1 Synthesis of 1-(phenylsulfonyl)-1H-indole (20)**

In dry dimethylsulphoxide DMSO (100 ml), potassium hydroxide pellets (8 g, 140 mmol) were added and mixture was vigorously stirred with cooling. After 15 minutes, indole (5.8 g, 50 mmol) was added to it. Stirring was continued till the solution turned faint pink. After stirring for one and half hour, benzenesulfonyl chloride (14 ml, 57 mmol) was added dropwise and the solution was stirred. After completion of reaction, the mixture was poured on crushed ice and stirred overnight. The obtained precipitate was filtered off, and washed with water. Compound was dried and passed through a neutral alumina column bed (5:95, ethyl acetate: hexane) to remove traces of indole.

Yield : 97%

Mp : 78-79°C

Mass, m/z (% abundance) : m/z (rel. intensity): 257 (M⁺, 50), 165 (75), 141 (30), 116 (100), 89 (46), 77 (65)

FTIR (KBr) cm⁻¹ : 1446, 1359, 1134, 753

¹H NMR (300 MHz, CDCl₃) δ:

<table>
<thead>
<tr>
<th>6.65, d, J = 3.3 Hz,</th>
<th>1H</th>
<th>ArH</th>
</tr>
</thead>
</table>
### Chapter III (Section A)

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity</th>
<th>Proton Count</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.21, t, J = 7.1 Hz</td>
<td>1H ArH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.27-7.33, m</td>
<td>1H ArH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.38, t, J = 7.2 Hz</td>
<td>2H ArH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.45-7.53, m</td>
<td>2H ArH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.56, d, J = 3.4 Hz</td>
<td>1H ArH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.86, d, J = 7.1 Hz</td>
<td>2H ArH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.01, d, J = 8.6 Hz</td>
<td>1H ArH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**13C NMR (75 MHz, CDCl₃) δ:**

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>109.1 ArC</td>
<td></td>
</tr>
<tr>
<td>113.4 ArC</td>
<td></td>
</tr>
<tr>
<td>121.3 ArC</td>
<td></td>
</tr>
<tr>
<td>123.3 ArC</td>
<td></td>
</tr>
<tr>
<td>124.5 ArC</td>
<td></td>
</tr>
<tr>
<td>126.2 ArC</td>
<td></td>
</tr>
<tr>
<td>126.6 ArC</td>
<td></td>
</tr>
<tr>
<td>129.1 ArC</td>
<td></td>
</tr>
<tr>
<td>130.6 ArC</td>
<td></td>
</tr>
<tr>
<td>133.7 ArC</td>
<td></td>
</tr>
<tr>
<td>134.7 ArC</td>
<td></td>
</tr>
<tr>
<td>138.1 ArC</td>
<td></td>
</tr>
</tbody>
</table>

**Expt. No. 3.1.2 Synthesis of 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (21)**

To a stirred solution of LDA [prepared from 1.6 M solution of n-butyl lithium in hexane (26 ml) and diisopropyl amine (4 ml) in THF (25 ml)] was added a solution of N-(benzenesulphonyl)indole (20) (5 g, 19.4 mmol) in THF (25 ml) at -78°C. After stirring the solution for 30 min, dimethylformamide (4.5 ml) in THF (10 ml) was added at -78°C. The reaction mixture was gradually warmed to room temperature and kept under stirring for 4 hours. The mixture was poured into saturated NH₄Cl solution and extracted with ethyl acetate. The extract was washed with water, dried over Na₂SO₄, and evaporated under reduced pressure. The resulting solid was purified with column chromatography (10: 90, ethyl acetate: hexane) to give 1-(phenylsulfonyl)-1H-indole-2-carbaldehyde (21).
Yield: 85%

Mp: 156-158°C

FTIR (KBr) cm⁻¹: 2755, 1672, 1530, 1367, 1171, 1039, 754

Mass, m/z (% abundance): m/z (rel. intensity): 281 (M+, 10), 271 (12), 130 (100), 116 (10), 77 (62)

¹H NMR (300 MHz, CDCl₃) δ:

- 7.32, t, J = 7.2 Hz 1H ArH
- 7.41, t, J = 7.2 Hz 2H ArH
- 7.48, s 1H ArH
- 7.51-7.56, m 2H ArH
- 6.61, d, J = 7.6 Hz 1H ArH
- 7.78, d, J = 8.6 Hz 2H ArH
- 8.24, d, J = 8.6 Hz 1H ArH
- 10.53, s 1H CHO

¹³C NMR (75 MHz, CDCl₃) δ:

- 115.3 ArC
- 123.6 ArC
- 126.6 ArC
- 128.9 ArC
- 134.3 ArC
- 137.7 ArC
- 183.1 CHO

125
**Expt. No. 3.1.3 Synthesis of 2-(((1-(phenylsulfonyl)-1H-indol-2-yl)methylene)amino)benzamide (23)**

To a solution of N-protected indole-2-carbaldehyde (21) (0.5 g, 1.7 mmol) in acetic acid (5 ml) was added anthranilamide (0.2 g, 1.7 mmol) at room temperature. The mixture was then heated at 80°C for 30 min. Product was filtered and washed with excess of water to get white solid of imine 23.

Yield : 95%

Mp : 258-260°C

FTIR (ATR) cm\(^{-1}\) : 3371, 3226, 1653, 1607, 1498, 1366, 737

HRMS (ESI) (M+H) : 404.1075  
Calculated for C\(_{22}\)H\(_{18}\)N\(_3\)O\(_3\)S : 404.1068

\(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\):

<table>
<thead>
<tr>
<th>6.53, s</th>
<th>1H</th>
<th>(\text{CH})</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.67-6.71, m</td>
<td>2H</td>
<td>(\text{NH, ArH})</td>
</tr>
<tr>
<td>6.89, d, J = 8.1 Hz</td>
<td>1H</td>
<td>(\text{ArH})</td>
</tr>
<tr>
<td>7.10, s</td>
<td>1H</td>
<td>(\text{ArH})</td>
</tr>
<tr>
<td>7.15-7.32, m</td>
<td>3H</td>
<td>(\text{ArH})</td>
</tr>
<tr>
<td>7.51-7.57, m</td>
<td>3H</td>
<td>(\text{ArH})</td>
</tr>
<tr>
<td>7.64-7.69, m</td>
<td>2H</td>
<td>(\text{ArH})</td>
</tr>
<tr>
<td>7.88-7.96, m</td>
<td>3H</td>
<td>(\text{ArH})</td>
</tr>
<tr>
<td>8.42, s</td>
<td>1H</td>
<td>(\text{NH})</td>
</tr>
</tbody>
</table>

\(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\):

| 109.5 | \(\text{CH}\) | 111.6 | \(\text{ArC}\) |
| 114.3 | \(\text{ArC}\) | 114.5 | \(\text{ArC}\) |
| 115.3 | \(\text{ArC}\) | 117.5 | \(\text{ArC}\) |
Expt. No. 3.1.4 Synthesis of 2-((1H-indol-2-yl)quinazolin-4(3H)-one (24)

Potassium tertiary butoxide (0.4 g, 3.7 mmol) was added to a solution of imine 23 (0.5 g, 1.2 mmol) in dry tertiary butanol (2 ml) and reaction was refluxed for 6 hours. The progress of reaction was monitored by TLC. After completion of reaction, solvent was evaporated and the contents were poured on crushed ice and extracted with ethyl acetate (3 × 20 ml). Organic layer was dried over sodium sulphate and concentrated under vacuum. Subsequently, the product was purified by column chromatography (3:7, Ethyl acetate: Hexane) to get white solid of compound 24.

Yield : 82%
Mp : Above 300°C
FTIR (ATR) cm⁻¹ : 3417, 3357, 1670, 1592, 1466, 786
MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 261 (M⁺, 100), 142 (10), 119 (70), 92 (20)

¹H NMR (300 MHz, DMSO-d₆) δ:

| 7.06, t, J = 7.6 Hz | 1H | ArH |
| 7.23, t, J = 8.1 Hz | 1H | ArH |
| 7.48-7.54, m | 2H | ArH |
| 7.62-7.66, m | 2H | ArH |
Chapter III (Section A)

7.73, d, J = 8.1 Hz  
1H  
ArH

7.85, t, J = 8.1 Hz  
1H  
ArH

8.14, d, J = 7.6 Hz  
1H  
ArH

11.80, s  
1H  
NH

12.62, s  
1H  
NH

$^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$:

<table>
<thead>
<tr>
<th></th>
<th>ArC</th>
<th></th>
<th>ArC</th>
</tr>
</thead>
<tbody>
<tr>
<td>104.9</td>
<td></td>
<td>112.3</td>
<td></td>
</tr>
<tr>
<td>119.9</td>
<td>ArC</td>
<td>121.1</td>
<td>ArC</td>
</tr>
<tr>
<td>121.4</td>
<td>ArC</td>
<td>124.0</td>
<td>ArC</td>
</tr>
<tr>
<td>126.0</td>
<td>ArC</td>
<td>126.2</td>
<td>ArC</td>
</tr>
<tr>
<td>126.8</td>
<td>ArC</td>
<td>127.4</td>
<td>ArC</td>
</tr>
<tr>
<td>129.9</td>
<td>ArC</td>
<td>134.6</td>
<td>ArC</td>
</tr>
<tr>
<td>137.6</td>
<td>ArC</td>
<td>146.5</td>
<td>ArC</td>
</tr>
<tr>
<td>148.6</td>
<td>ArC</td>
<td>161.7</td>
<td>CONH</td>
</tr>
</tbody>
</table>

Expt. No. 3.1.5 Synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-indole-3-carbaldehyde (bouchardatine) (17)

The solution of 2-(1H-indol-2-yl)quinazolin-4(3H)-one (24) (0.52 g, 2 mmol) in dimethyl formamide (13 ml), was added drop wise in the solution of phosphoryl chloride (1.71 ml, 18 mmol) in anhydrous dimethyl formamide (9 ml) at 0°C. The mixture was stirred at 0°C for 24 hours, after which the solution was added dropwise to 15 ml of saturated sodium bicarbonate solution. 10% sodium hydroxide solution (10 ml) was poured onto the mixture after which, the precipitated solid was filtered off and washed with water. Recrystallization from ethanol provided an off white solid of bouchardatine 17.

Yield : 87%
Mp : 255-257°C$^{13}$
FTIR (ATR) cm\(^{-1}\): 3051, 2922, 2852, 1693, 1665, 1607, 1572, 1437, 1188

MS (GCMS, EI, 70 eV): m/z (rel. intensity): 289 (M\(^+\), 1), 261 (1), 144 (100), 130 (20), 102 (30), 76 (20).

\(^1\)H NMR (300 MHz, DMSO-d\(_6\)) \(\delta\):

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Integer</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.17 - 7.2, m</td>
<td>2H</td>
<td></td>
<td>ArH</td>
</tr>
<tr>
<td>7.35, t, J = 7.1 Hz</td>
<td>1H</td>
<td></td>
<td>ArH</td>
</tr>
<tr>
<td>7.60 - 7.65, m</td>
<td>2H</td>
<td></td>
<td>ArH</td>
</tr>
<tr>
<td>7.83, d, J = 7.1 Hz</td>
<td>1H</td>
<td></td>
<td>ArH</td>
</tr>
<tr>
<td>8.01, m</td>
<td>2H</td>
<td></td>
<td>ArH</td>
</tr>
<tr>
<td>10.13, s</td>
<td>1H</td>
<td></td>
<td>CHO</td>
</tr>
<tr>
<td>11.69, s</td>
<td>1H</td>
<td></td>
<td>NH</td>
</tr>
<tr>
<td>12.35, s</td>
<td>1H</td>
<td></td>
<td>NH</td>
</tr>
</tbody>
</table>

\(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)) \(\delta\):

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>112.5</td>
<td>ArC</td>
</tr>
<tr>
<td>120.1</td>
<td>ArC</td>
</tr>
<tr>
<td>123.4</td>
<td>ArC</td>
</tr>
<tr>
<td>124.3</td>
<td>ArC</td>
</tr>
<tr>
<td>128.9</td>
<td>ArC</td>
</tr>
<tr>
<td>133.1</td>
<td>ArC</td>
</tr>
<tr>
<td>138.4</td>
<td>ArC</td>
</tr>
<tr>
<td>160.3</td>
<td>ArC</td>
</tr>
<tr>
<td>184.1</td>
<td>CHO</td>
</tr>
</tbody>
</table>
Expt. No. 3.1.6 Synthesis of diethyl 2-(2-nitrophenyl)malonate (27)

In a round bottom flask, potassium carbonate (2 g, 14.5 mmol) was taken in dry DMF (10 ml) under nitrogen atmosphere. 1-Fluoro-2-nitro-benzene (1 g, 7 mmol) was added and reaction was stirred for 30 minutes. Dimethyl malonate (1.3 g, 8.5 mmol) was added drop wise to above reaction mixture and stirring was continued for three hours. Reaction was monitored by TLC. After completion of reaction, it was poured on crushed ice. The precipitate was filtered, washed with water and dried under IR lamp to give diethyl 2-(2-nitrophenyl)malonate, 27 in almost quantitative yield.

Yield : 98%
Mp : 45-46°C

FTIR (ATR) cm\(^{-1}\): 2987, 1729, 1728, 1525, 1349, 1033, 856, 715

MS (GCMS, EI, 70 eV): m/z (rel. intensity): 281 (M+), 235 (35), 207 (20), 179 (15), 164 (20), 146 (25), 135 (22), 120 (35), 92 (100), 77 (45), 65 (50)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\):

<table>
<thead>
<tr>
<th>1.28, t, (J = 7.2) Hz</th>
<th>6H</th>
<th>2 (?)CH(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.28, q, (J = 7.2) Hz</td>
<td>4H</td>
<td>2 (?)CH(_2)</td>
</tr>
<tr>
<td>5.29, s</td>
<td>1H</td>
<td>CH</td>
</tr>
<tr>
<td>7.50-7.55, m</td>
<td>2H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.64-7.68, m</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>8.06, d, (J = 8.1) Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
</tbody>
</table>

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\):

| 13.7 | CH\(_3\) | 54.4 | CH\(_2\) |
| 62.0 | CH | 125.0 | ArC |
| 128.0 | ArC | 129.1 | ArC |
### Expt. No. 3.1.7 Synthesis of 2-(2-nitrophenyl)acetic acid (28)

To a solution of diethyl 2-(2-nitrophenyl)malonate (27) (2 g, 7.1 mmol) in ethyl alcohol (15 ml), 6N aqueous hydrochloric acid was added. The reaction was refluxed for 1 hour to give 2-(2-nitro-phenyl)-acetic acid, 28 as a hydrolytic decarboxylation product.

<table>
<thead>
<tr>
<th>Yield</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mp</td>
<td>138-140°C</td>
</tr>
<tr>
<td>FTIR (ATR) cm⁻¹</td>
<td>3070, 2983, 1704, 1614, 1522, 1351, 1237, 862, 710</td>
</tr>
<tr>
<td>MS (GCMS, EI, 70 eV)</td>
<td>m/z (rel. intensity): 181(M⁺), 164 (3), 149 (10), 136 (100), 120 (80), 91 (90), 70 (95), 65 (60), 51 (35), 39 (30)</td>
</tr>
</tbody>
</table>

**¹H NMR (300 MHz, DMSO-d₆)** δ:

<table>
<thead>
<tr>
<th>4.0, s</th>
<th>2H</th>
<th>CH₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.55, t, J = 7.7 Hz</td>
<td>2H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.6-7.7, m</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>8.06, d, J = 8.1 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>12.58, s, D₂O exchangeable</td>
<td>1H</td>
<td>COOH</td>
</tr>
</tbody>
</table>

**¹³C NMR (75 MHz, DMSO-d₆)** δ:

<table>
<thead>
<tr>
<th>38.8</th>
<th>CH₂</th>
<th>124.7</th>
<th>ArC</th>
</tr>
</thead>
<tbody>
<tr>
<td>128.5</td>
<td>ArC</td>
<td>130.4</td>
<td>ArC</td>
</tr>
<tr>
<td>133.6</td>
<td>ArC</td>
<td>133.7</td>
<td>ArC</td>
</tr>
<tr>
<td>148.5</td>
<td>ArC</td>
<td>171.2</td>
<td>COOH</td>
</tr>
</tbody>
</table>
Expt. No. 3.1.8 Synthesis of indolin-2-one (29)

To a solution of 2-(2-nitro-phenyl)-acetic acid (28) (1 g, 5.2 mmol) in methanol (10 ml), activated Pd-C (60 mg, 10 mol%) was added. Reaction was stirred for 24 hours at room temperature. After completion of reaction, the mixture was filtered through celite bed and washed with methanol. Methanol was evaporated under reduced pressure and the residue was diluted with ice cold water followed by extraction with ethyl acetate. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure on rota vapour to give indolin-2-one, 29.

Yield : 88%
Mp : 125-127°C

FTIR (ATR) cm$^{-1}$ : 3066, 2949, 1688, 1617, 1469, 1331, 746

MS (GCMS, EI, 70 eV) : m/z (rel. intensity), 133 (M+, 92), 104 (100), 78 (65), 51 (40)

$^1$H NMR (300 MHz, CDCl$_3$) δ:

| 3.52, s | 2H | CH |
| 6.90, d, J = 8.1 Hz | 1H | ArH |
| 6.99, t, J = 7.6 Hz | 1H | ArH |
| 7.19, t, J = 6.7 Hz | 2H | ArH |
| 9.61, s | 1H | NH |

$^{13}$C NMR (75 MHz, CDCl$_3$) δ:

| 36.2 | CH$_2$ | 109.8 | ArC |
| 122.2 | ArC | 124.4 | ArC |
| 125.2 | ArC | 127.8 | ArC |
| 142.6 | ArC | 178.4 | CONH |
Expt. No. 3.1.9 Synthesis of 3-hydrazonoindolin-2-one (31)

To a stirred solution of isatin (5 g, 34.9 mmol) in ethanol (20 ml), hydrazine hydrate (3.4 ml, 69.9 mmol) was added dropwise. The reaction mixture was refluxed for one hour. The reaction colour changed from red to dark yellow indicating completion of reaction. Ethanol was evaporated under reduced pressure on rotavapour. Thick residue was poured on crushed ice and obtained compound was filtered and washed with water. Yellow fluffy solid of 3-hydrazonoindolin-2-one, 31 was dried under IR lamp.

Yield : 97%

Mp : 225°C

FTIR (ATR) cm\(^{-1}\) : 3352, 3145, 1681, 1585, 1547, 1464, 1189, 975, 744

\(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\):

<table>
<thead>
<tr>
<th>3.00, brs, D(_2)O exchangeable</th>
<th>2H</th>
<th>NH(_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.88, d, J = 7.7 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>6.98, t, J = 7.7 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.15, t, J = 7.6 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.43, d, J = 7.7 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>10.05, s</td>
<td>1H</td>
<td>NH</td>
</tr>
</tbody>
</table>

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\):

<table>
<thead>
<tr>
<th>109.6</th>
<th>ArC</th>
<th>117.5</th>
<th>ArC</th>
</tr>
</thead>
<tbody>
<tr>
<td>121.0</td>
<td>ArC</td>
<td>121.7</td>
<td>ArC</td>
</tr>
<tr>
<td>126.7</td>
<td>ArC</td>
<td>127.6</td>
<td>ArC</td>
</tr>
<tr>
<td>138.4</td>
<td>C=N</td>
<td>162.9</td>
<td>CONH</td>
</tr>
</tbody>
</table>
**Expt. No. 3.1.10 Synthesis of indolin-2-one (29)**

To a stirred solution of 3-hydrazonoindolin-2-one (31) (5.4 g, 34.9 mmol) in ethanol (20 ml), was added 10% solution of NaOH (2.7 g, 69.9 mmol). The reaction mixture was refluxed for 3 hours. After completion of reaction ethanol was evaporated under reduced pressure. The residue was neutralized with dilute hydrochloric acid and the mixture was poured in ice water and extracted with ethyl acetate. The ethyl acetate layer was dried over sodium sulphate and solvent was evaporated on rota vapour to give indoline-2-one, 29.

Yield : 85%

![Image of indolin-2-one (29)](image)

**Expt. No. 3.1.11 Synthesis of 2-chloro-1H-indole-3-carbaldehyde (32)**

A three-neck round-bottomed flask was equipped with a mechanical stirrer, pressure equalizing dropping funnel, and N₂ atmosphere. To a stirred solution of DMF (5.5 ml, 74.4 mmol) and DCM (10.5 ml), was added drop wise a solution of POCl₃ (17.8 g, 62.0 mmol) in DCM (12.5 ml) at such a rate to maintain a gentle reflux via the exothermic reaction for 1 hour. After complete addition, reaction was brought down at room temperature. The resulting thick tan mixture was stirred vigorously for 2 hours, and then indoline-2-one (29) (3.65 g, 24.8 mmol) was added portion wise over 20 min. The mixture was stirred at 25 °C for 38 hours. The solution was poured slowly on crushed ice. The resulting suspension was stirred for 30 min, and the phases were then separated. The golden aqueous phase was extracted with 20 ml of DCM and then was allowed to stir at 25°C for 18 hours. The flocculent tan precipitate that had formed was collected by filtration and washed well with water. The aqueous filtrate was stirred for 24 hours during which additional precipitate formed. The combined crops were dried under IR lamp to leave light tan solid of 32.

Yield : 70%

Mp : 212-114°C

FTIR (ATR) cm⁻¹ : 3073, 2838, 1636, 1579, 1450, 1371, 1343, 1091, 733

![Image of 2-chloro-1H-indole-3-carbaldehyde (32)](image)
MS (GCMS, EI, 70 eV) : m/z (rel. intensity) 171 (M+, 35), 179 (80), 178 (100), 150 (30), 123 (28), 114 (20), 89 (22), 75 (30)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 

| 7.25, brs | 2H | ArH |
| 7.42, d, J = 7.1 Hz | 1H | ArH |
| 8.07, d, J = 6.7 Hz | 1H | ArH |
| 9.99, s | 1H | CHO |
| 13.06, s | 1H | NH |

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 

| 111.6 | ArC | 111.9 | ArC |
| 119.8 | ArC | 122.7 | ArC |
| 123.7 | ArC | 124.2 | ArC |
| 134.5 | ArC | 134.6 | ArC |
| 183.1 | CHO | |

Expt. No. 3.1.12 Synthesis of quinazolin-4(3H)-one (33)

To a stirred solution of 2-aminobenzamide (15 g, 110 mmol) in acetic acid (20 ml), was added formamide (24.8 g, 22 ml, 550 mmol). The reaction mixture was heated at 100°C for 15 min. A white fluffy mass was observed in reaction mixture. After completion of reaction, the mixture was poured on crushed ice and stirred for 1 hour. The solid precipitate of quinazolin-4(3H)-one was filtered, washed with excess of water and dried under IR lamp.

Yield : 98%

Mp : 213-215°C$^{49}$

FTIR (ATR) cm$^{-1}$ : 3166, 2981, 1701, 1605, 1463, 1231, 909, 761
**Expt. No. 3.1.13 Synthesis of 2-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-indole-3-carbaldehyde (bouchardatine) (17)**

2-Chloro-1H-indole-3-carbaldehyde 32, (0.5 g, 2.7 mmol) and quinazolin-4(3H)-one 33 (0.4 g, 2.7 mmol) in dry DMF were taken in two necked round bottom flask fitted with a reflux condenser. Palladium acetate (0.06 g, 10 mol%), triphenylphosphine (0.21 g, 30 mol%) and potassium carbonate (0.46 g, 3.3 mmol) were then added to the above reaction mixture. The contents were heated at 120 °C for 12 hours under nitrogen atmosphere. After completion of reaction, the mixture was filtered over celite through sintered funnel. Water was then added to the filtrate and was extracted with ethyl acetate (3 × 20 ml). Concentration of solvent under vacuum and purification by column chromatography (1:9, Ethyl acetate: Hexane) provided bouchardatine 17 as an off white solid.

**Yield** : 68%
References

1. Wattanapiromsakul, C.; Forster, P.I.; Waterman, P.G. *Phytochemistry* 2003, 64, 609.


CHAPTER III

SECTION B

$\text{AlCl}_3$, Ionic Liquid and MW as an Efficient Combination for Dehydration and 1,3-Dipolar Cycloaddition
An ionic liquid (IL) is a salt in the liquid state. Ionic liquids are made of ions, whereas, liquids such as water are made of electrically neutral molecules. Ionic liquids are also known as liquid electrolytes, ionic melts, ionic fluids, fused salts, liquid salts, or ionic glasses. Ionic liquids are used as solvents in many chemical reactions and they are also useful as electrolytes. The properties of ionic liquids make them important for electric battery applications, and they also find utility as sealants due to their very low vapor pressure.

Ethanolammonium nitrate (m.p. 52–55°C) was reported in 1888 by S. Gabriel and J. Weiner. Ethylammonium nitrate \((\text{C}_2\text{H}_5\text{NH}_3^+\cdot\text{NO}_3^-)\) (m.p. 12°C) was synthesized in 1914 by Paul Walden. In the initial stages of discovery, ionic liquids based on alkyl-substituted imidazolium and pyridinium cations, with halide or tetrahalogenoaluminate anions, were developed for use as electrolytes in battery applications. Some ionic liquids which are generally used in organic reactions are shown in Figure 1.

An important property of the imidazolium halogenoaluminate salts is that their physical properties, such as viscosity, melting point, and acidity, could be adjusted by changing the alkyl substituents and the imidazolium/pyridinium and halide/halogenoaluminate ratios. Moisture sensitivity and acidity/basicity were the two major drawbacks for the use of IL's. The range of applications was broadened after the discovery of ionic liquids with 'neutral' weakly coordinating anions such as hexafluorophosphate \((\text{PF}_6^-)\) and tetrafluoroborate \((\text{BF}_4^-)\) by Wilkes and Zawarotko.
Later, a new class of air and moisture stable, neutral ionic liquids became available. Research has also been developed from hexafluorophosphate and tetrafluoroborate towards less toxic alternatives such as bistriflimide \[(\text{CF}_3\text{SO}_2)_2\text{N}\]^-. Efforts are also being concentrated towards developing less toxic cations with compounds like ammonium salts proving to be as flexible a scaffold as imidazolium.

Ionic liquids are often moderate to poor conductors of electricity, non-ionizing (e.g. non-polar), highly viscous and frequently exhibit low vapor pressure. Their other properties are diverse: many have low combustibility, excellent thermal stability, wide liquid regions, and favorable solvating properties for a range of polar and non-polar compounds. Walker has shown that ionic liquids can serve as solvents for biocatalysis. The miscibility of ionic liquids with water or organic solvents varies with side chain lengths on the cation and with choice of anion. They can be functionalized to act as acids, bases or ligands, and have been used as precursor salts in the preparation of stable carbenes. Because of their distinctive properties, ionic liquids are attracting increasing attention in many fields, including organic chemistry, electrochemistry, catalysis, physical chemistry, and engineering.

The solubility of different species in imidazolium ionic liquids depends mainly on polarity and hydrogen bonding ability. Saturated aliphatic compounds are generally only sparingly soluble in ionic liquids, whereas olefins show somewhat greater solubility, and aldehydes can be completely miscible. This can be exploited in biphasic catalysis, such as hydrogenation and hydrocarbonylation processes, allowing for relatively easy separation of products and/or unreacted substrate(s).

Room temperature ionic liquids (RTILs) are made up of bulky and asymmetric organic cations such as 1-alkyl-3-methylimidazolium, 1-alkylpyridinium, \(N\)-methyl-\(N\)-alkylpyrrolidinium and ammonium ions. Phosphonium cations are less common, but have some advantageous properties. A wide range of anions are employed, ranging from simple halides, which generally suffer high melting points, to inorganic anions such as tetrafluoroborate and hexafluorophosphate, and to large organic anions like bistriflimide, triflate or tosylate. There are also many interesting uses of ionic liquids with simple non-halogenated organic anions such as formate, alkylsulfate, alkylphosphate or glycolate.
Room-temperature ionic liquids\(^9\) such as [bmim]PF\(_6\) are finding growing applications as alternative reaction media for separations\(^10\) and organic transformations. Some examples of such organic transformations include hydrogenations,\(^11\) Friedel–Crafts reactions,\(^12\) Diels–Alder reactions,\(^13\) Heck reactions,\(^14\) olefin hydrodimerizations/ telomerizations,\(^15\) olefin dimerizations,\(^16\) cross-couplings,\(^17\) hydroformylations\(^18\) and oxidations.\(^19\) The desirable advantages of ionic liquids such as the lack of vapor pressure, wide liquid range and thermal stability have made them good reaction media and environmentally benign solvents. Accordingly, they are emerging as novel replacements for volatile organic compounds (VOCs) which are used as solvents in organic synthesis and transformations. They are promising solvents in catalysis reactions where the activity, selectivity, and stability of catalysts are enhanced. Different types of reactions where ionic liquids play an important role are listed below.

1. Li et al\(^20\) (2013)

\[
\text{Cl-}[\text{phenyl}]-\text{CHO} + \text{CN} + \text{COOH} \xrightarrow{\text{Et}_3\text{N}, \text{rt}} \text{Cl-}[\text{phenyl}]-\text{NH}_2
\]

2. Rajesh et al\(^21\) (2012)

\[
\text{OH} + \text{CHO} + \text{Br} \xrightarrow{\text{Pyridine}, 80^\circ\text{C}, 2h} \text{Z}
\]
3. Chen et al\textsuperscript{22} (2011)

\[
\begin{align*}
\text{OH} & + \text{CHO} + \text{R}_1 \text{R}_2 \\
& \xrightarrow{[\text{DMDBS}]_2\text{HSO}_4, \text{H}_2\text{O, reflux}} \text{R}_1 \text{R}_2 \\
[\text{DMDBS}]_2\text{HSO}_4 = & \text{HO}_3\text{S} + \text{N} + \text{N} + \text{SO}_3\text{H}
\end{align*}
\]

4. Sterrenburg et al \textsuperscript{23} (2001)

\[
\text{Grubbs' Catalyst} \xrightarrow{[\text{BMIM}[\text{PF}_6]} \text{80 °C, 1 h}
\]

5. Khadilkar et al\textsuperscript{24} (2001)

\[
\text{NH}_2\text{NH}_2 + \text{CO} \xrightarrow{1-(\text{n-butyl})\text{pyridinium chloride} - \text{AlCl}_3} \text{40 min} \xrightarrow{180-185 \degree\text{C}} \text{H}
\]

6. Shirakami et al\textsuperscript{25} (2001)

\[
\text{lipase, vinyl acetate} \xrightarrow{[\text{BMIM}[\text{PF}_6]} \text{OAc}
\]

7. Song et al\textsuperscript{26} (2000)

\[
\text{[Mr^{III}(salen)] catalyst, NaOCl} \xrightarrow{[\text{BMIM}[\text{PF}_6] / \text{CH}_2\text{Cl}_2 (1/4, \text{v/v})} 0 \degree\text{C, 2 h}}
\]

8. Carmichael et al\textsuperscript{27} (1999)

\[
\text{PdCl}_2 \xrightarrow{[\text{CyPy}]\text{Cl or [BMIM][BF}_4]} \text{Bu}_7
\]
Microwave assisted organic synthesis

Reactions using microwave ovens have been used extensively in recent organic synthesis. Microwave ovens provide a clean and cheap alternative to conventional heating devices like oil baths, heating mantles and hot plates. There are several comparative reports of various types of reactions carried out in microwave and by conventional methods. It was observed that the reactions in microwave oven are very clean and rapid. It was also demonstrated that the reactions show regioselectivity and stereoselectivity and are high yielding.

Mechanism of microwave dielectric heating

On the electromagnetic spectrum, microwave region lies between infrared radiation and radio waves. Microwaves have wavelengths of 1 mm to 1m corresponding to frequency between 0.3 to 300 GHz.

The microwave radiations can be divided into an electric field component and a magnetic field component. The electric field component is responsible for dielectric heating, which is effected via two major mechanisms, one is dipolar polarization and other is conduction.

Dipolar polarization mechanism

The dipolar polarization mechanism is one of the interactions of the electrical field component with the matrix. For a substance to generate heat when irradiated in microwaves, it must possess a dipole moment. For example when water and dioxane are heated at a fixed radiation power for a fixed time, temperature is found to be
higher in water sample. Water has dipole moment and dioxane lacks the dipole characteristics necessary for microwave dielectric heating. The dipolar and interfacial polarization are important to heating effects associated with microwave irradiation. When a molecule is irradiated with microwave it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation and consequently the molecule continuously attempts to realign itself with the changing field and energy is absorbed.

The material converts electromagnetic energy into heat energy. The larger the dielectric constant, greater is the coupling with microwaves. Thus solvents like water, methanol, DMF, ethyl acetate, acetone, chloroform, acetic acid and dichloromethane are all heated when irradiated with microwaves and are microwave active solvents. Solvents such as hexane, toluene, diethyl ether, carbon tetrachloride are not heated with microwave irradiation and are microwave inactive solvents. It is necessary that the reactant or the solvent must be microwave active. It may be possible to use a microwave active additive or supported metal catalyst to generate heat.

**Conduction mechanism**

In a solution containing free ions or ions with hydrogen bonds cluster, the ions move through the solution under the influence of a dielectric field, resulting in expenditure of energy due to increased collision rate converting the kinetic energy to heat. The conductivity mechanism is stronger than the dipolar mechanism with regards to the heat generating capacity. This can be shown by an example. If two samples containing tap water and distilled water are heated at a fixed microwave radiation power and for a fixed time, the temperature is higher in tap water.

**Techniques for Microwave assisted reaction**

It was found that dipolar solvents are essential in microwave heating, and it is often necessary to adopt solvent systems in synthetic reactions to accommodate this. Most of the time the domestic ovens have been used for this purpose and use of organic solvents introduces a risk of explosion. The problem can be avoided by omitting the solvent. Thus the reactions can be performed on solid supports such as Montmorillonite clays, alumina, silica, alkali metal fluoride doped alumina, and commercial Bentonitic earths. This solvent free technique has been claimed to be particularly environmental friendly. In many cases higher boiling solvents are used to
enhance the efficiency of the synthesis. A number of reflux systems as microwave synthesizers have been developed in an effort to use low boiling solvents in microwave assisted organic synthesis and also for reactions under pressure without risk of explosion. Some modified microwave systems are well equipped with good temperature control and pressure measurements.

Various microwave-assisted reactions are reviewed by Stephen Caddick\textsuperscript{30a} in 2009 and recently by Davide et al\textsuperscript{30b} in 2013. Since our present work is in this area, some examples of microwave assisted reactions are listed below.

1. Kandre et al\textsuperscript{31} (2013)

2. Majumdar et al\textsuperscript{32} (2012)

3. Kamila et al\textsuperscript{33} (2011)

4. Brummond et al\textsuperscript{34} (2005)
5. Saaby et al\textsuperscript{35} (2005)

\[
\begin{align*}
\text{DMF} & \\
\text{MW} & \\
\end{align*}
\]

6. Appukkuttan et al\textsuperscript{36} (2004)

\[
\begin{align*}
\text{NaN}_3, \text{Cu(O)} & \\
\text{CuSO}_4, \text{MW} & \\
\end{align*}
\]


\[
\begin{align*}
\text{CuSO}_4, \text{DMF} & \\
\text{MW} & \\
\end{align*}
\]

8. Katritzky et al\textsuperscript{38} (2002)

\[
\begin{align*}
\text{MW} & \\
\end{align*}
\]

9. Wilson et al\textsuperscript{39} (2001)

\[
\begin{align*}
\text{DCE} & \\
\text{MW} & \\
\end{align*}
\]

**Present Plan**

Ionic liquids, being polar and ionic in character, couple to microwave irradiation efficiently and consequently may be ideal microwave-absorbing entities.
for organic reactions. There are reports of preparation of ionic liquids using microwave irradiation. Advantages such as rapid reactions, high yields, and selectivity in microwave-assisted reactions have become well known in recent years. We have been using this methodology for some other reactions.

There are many methods reported for the conversion of oximes to nitriles. Some recent examples of this type are shown below.

1. Pedras et al

\[
\text{MeO-} \xrightarrow{\text{C}_{6}\text{H}_{5}\text{N}, \text{Ac}_{2}\text{O}, \text{THF}} \xrightarrow{9\text{h, reflux}} \text{MeO-}
\]

2. Chandrappa et al

\[
\text{Cl-} \xrightarrow{\text{PCC, CHCl}_{3}} \xrightarrow{3\text{h, reflux}} \text{Cl-}
\]

3. Deprez et al

\[
\text{N} \xrightarrow{\text{Et}_{3}\text{N, F}_{3}\text{OCOOH}} \xrightarrow{\text{Dioxane, rt - 0°C, 24h}} \text{N}
\]

4. Castro et al

\[
\text{Cl} \xrightarrow{\text{SOCl}_{2}, \text{CHCl}_{3}, 24\text{h, rt}} \xrightarrow{\text{NaHCO}_{3}, \text{H}_{2}\text{O, pH=4}} \text{Cl}
\]

5. Huck et al

\[
\text{Br} \xrightarrow{(\text{PrP}(-\text{O})_{2}, \text{DMF}} \xrightarrow{45\text{min, 100°C}} \text{Br}
\]

In our earlier work, we have also observed conversion of oxime to nitrile in presence of Vilsmeier–Haack reagent followed by work up with water. In view of our interest in microwave-assisted reactions and the importance of ionic liquids as
solvents, and in continuation with our earlier work, we decided to use them in combination for a dehydration reaction of aldoximes.

**Results and Discussions**

Initially, it was decided to investigate the dehydration of oximes with AlCl$_3$ at different conditions. Butyl methyl imidazolium bromide ([Bmim]$^+$Br$^-$) was selected as ionic liquid to be used for this study (Scheme 1).

![Scheme 1: Dehydration of furfuraldoxime to furan-2-nitrile](image)

Thus, furan-2-aldoxime (35a) was chosen as one of the substrates to start with the study. Table 1 describes the results of this investigation. The reaction carried out using furan-2-aldoxime with AlCl$_3$ in xylene at room temperature did not produce any product. Using a combination of AlCl$_3$ and ionic liquid in xylene also did not yield any product. When the reaction using a combination of AlCl$_3$ and ionic liquid in microwave oven was tried, nitrile 36a could be obtained in 15 minutes. However, the yield obtained was only 40%. The reaction of furan-2-aldoxime in the presence of ionic liquid, AlCl$_3$ and xylene in the microwave oven was extremely rapid, and in 15 minutes the corresponding nitrile was obtained in very good yield of 80%. The formation of nitrile was confirmed by comparing the melting point (146-148°C) with the reported value. Also the GCMS spectrum was matched with the NIST (National Institute of Standard Technology) library.

**Table 1: Reaction conditions and yields of nitrile formation reaction of furfuraldoxime 36a**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Method</th>
<th>Time</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>35a</td>
<td>AlCl$_3$</td>
<td>Xylene</td>
<td>RT</td>
<td>35 h</td>
<td>No</td>
<td>- Reaction</td>
</tr>
<tr>
<td>2.</td>
<td>35a</td>
<td>AlCl$_3$/[Bmim]$^+$Br$^-$</td>
<td>Xylene</td>
<td>RT</td>
<td>35 h</td>
<td>No</td>
<td>- Reaction</td>
</tr>
</tbody>
</table>
Thus, after identifying the proper combination of reagents as ionic liquid, AlCl$_3$ and xylene in the microwave oven, for dehydration of oxime to furnish nitrile, it was generalized using five different aldoximes (Scheme 2, Table 2).

In the reaction with 4-methoxybenzaldoxime (35b), without using ionic liquid, it was observed that corresponding nitrile was formed in 52% yield along with demethylated product 35c. With ionic liquid, the demethylated product 35c was in very minor amount (1-2%) and the methylated nitrile 36b was obtained in 70% yield. Both the products were characterised by matching melting points with the reported compounds. The nitrile 36b melted$^{49}$ at 59-61°C, whereas demethylated nitrile 36c melted$^{50}$ at 110-112°C. When thienyl aldoxime 35c was used, nitrile 36d was formed in 150 minutes in the absence of ionic liquid. In the presence of ionic liquid, however, the the same product was obtained in 12 minutes and the yield was increased from 40% to 80%. (Scheme 2, Table 2) Formation of product 36d was confirmed by matching the reported$^{48}$ and observed (99-101°C) melting points of the product.

Analogous to 4-methoxybenzaldoxime (35b), the demethylation reaction was also expected in the case of 3,4-dimethoxybenzaldoxime 35d in absence of ionic liquid. Surprisingly, demethylated product was not obtained in this reaction though the nitrile 36e was obtained in less yield. Nevertheless, in presence of ionic liquid, nitrile 36e was obtained in 80% yield and its structure was confirmed by comparing the observed and reported$^{49}$ melting points.

Scheme 2: Dehydration of oximes to nitriles
When the reaction was carried out using 4-chloro benzaldoxime 35e, in presence of AlCl$_3$, ionic liquid and microwave, the corresponding nitrile 36f was obtained in 90% yield which melted$^{31}$ at 91-93$^\circ$C. All the above results indicated that combination of ionic liquids and microwave irradiation in xylene constitutes a good method for dehydration of oximes.

**Table 2: Reaction conditions and yields of nitrile formation reaction of oximes 35b-35e**

| Sr. No. | Substrate | Catalyst | Solvent | Method | Time | Product | Yield (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>35b</td>
<td>AlCl$_3$</td>
<td>Xylene</td>
<td>MW</td>
<td>20 min</td>
<td>36b</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36c</td>
<td>37</td>
</tr>
<tr>
<td>2.</td>
<td>35b</td>
<td>AlCl$_3$/[Bmim]$^+\text{Br}^-$</td>
<td>Xylene</td>
<td>MW</td>
<td>2 min</td>
<td>36b</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36c</td>
<td>1-2</td>
</tr>
<tr>
<td>3.</td>
<td>35c</td>
<td>AlCl$_3$</td>
<td>Xylene</td>
<td>MW</td>
<td>150 min</td>
<td>36d</td>
<td>40</td>
</tr>
<tr>
<td>4.</td>
<td>35c</td>
<td>AlCl$_3$/[Bmim]$^+\text{Br}^-$</td>
<td>Xylene</td>
<td>MW</td>
<td>12 min</td>
<td>36d</td>
<td>80</td>
</tr>
<tr>
<td>5.</td>
<td>35d</td>
<td>AlCl$_3$</td>
<td>Xylene</td>
<td>MW</td>
<td>5 min</td>
<td>36e</td>
<td>40</td>
</tr>
<tr>
<td>6.</td>
<td>35d</td>
<td>AlCl$_3$/[Bmim]$^+\text{Br}^-$</td>
<td>Xylene</td>
<td>MW</td>
<td>5 min</td>
<td>36e</td>
<td>80</td>
</tr>
<tr>
<td>7.</td>
<td>35e</td>
<td>AlCl$_3$</td>
<td>Xylene</td>
<td>MW</td>
<td>20 min</td>
<td>36f</td>
<td>70</td>
</tr>
<tr>
<td>8.</td>
<td>35e</td>
<td>AlCl$_3$/[Bmim]$^+\text{Br}^-$</td>
<td>Xylene</td>
<td>MW</td>
<td>2 min</td>
<td>36f</td>
<td>90</td>
</tr>
</tbody>
</table>

It was further envisaged to use the same combination of ionic liquids and microwave irradiation for the 1,3-dipolar reaction of oximes with conventional dipolarophiles. Thus, the reaction of furan-2-aldoxime as a 1,3-dipole with methyl acrylate as a dipolarophile in presence of AlCl$_3$ in [Bmim]$^+\text{Br}^-$ using microwave irradiation was carried out to furnish 1,3-dipolar cycloadduct 37 (Scheme 3).
Scheme 3: 1,3-dipolar cycloaddition reaction

Table 3: Reaction conditions and yield of formation of cycloadduct 37 using microwave assisted cycloaddition reaction of oxime 35a with methyl acrylate

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Catalyst</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No catalyst</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>2.</td>
<td>AlCl₃</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>3.</td>
<td>[Bmim]⁺Br⁻</td>
<td>30</td>
<td>89</td>
</tr>
<tr>
<td>4.</td>
<td>AlCl₃/ [Bmim]⁺Br⁻</td>
<td>5</td>
<td>85</td>
</tr>
</tbody>
</table>

This reaction was carried out using different combinations of the catalysts. In the reaction without any catalyst, the desired cycloadduct was obtained in 90% yield, however, the time required for completion of reaction was 74 minutes. Use of only AlCl₃ reduced the reaction time, but the yield also decreased to 71%. With only ionic liquid, although the yield was not hampered, the time required could not be reduced to a greater extent. The use of the combination of AlCl₃, ionic liquid and microwave irradiation furnished 1,3-dipolar cycloadduct 37 in a very short time. The structure of the cycloadduct could not be confirmed from the proton NMR as it was obtained as mixture of regioisomers. However, the GCMS spectrum was in good agreement with the NIST library match which helped us to assign structure 37 to the product.

When the same reaction was carried out using oximes 35d and 35e, instead of the expected 1,3 dipolar cycloadducts, the products obtained were nitriles 36e and 36f respectively (Table 4). This indicated that, rapid dehydration of these aldoximes dominated the cycloaddition reaction.
Table 4: Reaction conditions and yield of microwave assisted reaction of oximes 35d-e with methyl acrylate

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Method</th>
<th>Time</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35d</td>
<td>AlCl₃/[Bmim]⁺Br⁻</td>
<td>Methyl acrylate</td>
<td>MW</td>
<td>7 min</td>
<td>36e</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>35e</td>
<td>AlCl₃/[Bmim]⁺Br⁻</td>
<td>Methyl acrylate</td>
<td>MW</td>
<td>5 min</td>
<td>36f</td>
<td>75</td>
</tr>
</tbody>
</table>

To our surprise, when acrylonitrile was used as a dipolarophile in this reaction instead of methyl acrylate, with furfuraldoxime 35a, substituted amide 38a resulted from the reaction (Scheme 4). The reaction was carried out using different conditions as shown in Table 5.

![Scheme 4: Rearrangement of oxime to amide](image)

Table 5: Reaction conditions and yield of microwave assisted reaction of oxime 35a and 35d with acrylonitrile

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>R</th>
<th>Catalyst</th>
<th>Method</th>
<th>Time</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Furyl (35a)</td>
<td>AlCl₃/[Bmim]⁺Br⁻</td>
<td>RT</td>
<td>30 h</td>
<td>38a</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>Furyl (35a)</td>
<td>AlCl₃/[Bmim]⁺Br⁻</td>
<td>120 °C</td>
<td>5.5 h</td>
<td>38a</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Furyl (35a)</td>
<td>AlCl₃</td>
<td>MW</td>
<td>15 min</td>
<td>38a</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>Furyl (35a)</td>
<td>AlCl₃/[Bmim]⁺Br⁻</td>
<td>MW</td>
<td>2.5 min</td>
<td>38a</td>
<td>90</td>
</tr>
</tbody>
</table>
Thus, with furfuraldoxime, when the reaction was tried at room temperature, the corresponding amide was obtained in 48% yield after 30 hours. Use of AlCl₃ in combination with ionic liquid at 120°C, afforded the amide in 80% yield but the reaction took more than 5 hours for completion. The reaction using AlCl₃ as a catalyst in microwave oven, furnished the corresponding amide in just 15 minutes. But, the yield obtained was very poor. Employing the combination of AlCl₃, ionic liquid and microwave irradiation, not only helped to raise the yield to 90%, but also reduced the reaction time substantially to just about 2.5 minutes. Formation of the product was confirmed by using spectral data. A peak at 1664 cm⁻¹ in FTIR spectrum confirmed the presence of amide carbonyl in the molecule, whereas, ¹H NMR of compound 38a showed two triplets for the methylene groups at δ 2.72 and 3.69, along with an D₂O exchangeable broad singlet corresponding to NH at δ 6.82.

The other substrate, 3,4-dimethoxybenzaldoxime, 35d also showed similar results and the reaction to amide 38b was completed within 5 minutes, the yield being 80%. In the case of 3,4-dimethoxybenzaldoxime, a small amount of nitrile 36e was also produced along with the substituted amide during this reaction. Conversion of this nitrile to the amide 38b was not observed under the same reaction conditions, indicating that nitrile might not be the intermediate for the formation of substituted amide. Structure of the amide 38b was confirmed from ¹H NMR which showed a triplet for one methylene group at δ 2.75. However, the signal for other methylene group was obtained as a quartet at δ 3.71. This might be due to the coupling with neighbouring NH proton which was seen as a broad singlet at δ 6.51. The formation of substituted amide can be explained using initial Beckmann rearrangement, followed by addition to acrylonitrile (Scheme 5). The difference in the reaction of methyl acrylate and that of acrylonitrile could be attributed to the better dipolarophilic ability of methyl acrylate than acrylonitrile.
Scheme 5: Mechanism for formation of amide

Conclusion

Dehydration of aldoximes was achieved efficiently using combination of microwave assisted reactions in xylene and ionic liquid in the presence of aluminium chloride. The same combination was also proved to be effective for 1,3-dipolar reaction of furfuraldoxime. However, as an unusual observation, acrylonitrile furnished substituted amide instead of 1,3-dipolar cycloadduct indicating its less reactivity as a dipolarophile.
Experimental

Reaction Index

Expt. No. 3.2.1 Synthesis of furfuraldoxime (35a)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{NH}_2\text{N}=\text{O} \\
\text{NaOH, MeOH,} & \text{rt, 1h, 96\%} \\
35a
\end{align*}
\]

Expt. No. 3.2.2 Synthesis of 4-methoxy benzaldoxime (35b)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{N}=\text{O} \\
\text{NaOH, MeOH,} & \text{rt, 1h, 92\%} \\
35b
\end{align*}
\]

Expt. No. 3.2.3 Synthesis of thienyl-2-aldoxime (35c)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{NH}_2\text{N}=\text{O} \\
\text{NaOH, MeOH,} & \text{rt, 1h, 94\%} \\
35c
\end{align*}
\]

Expt. No. 3.2.4 Synthesis of 3,4-dimethoxybenzaldoxime (35d)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{N}=\text{O} \\
\text{NaOH, MeOH,} & \text{rt, 1h, 95\%} \\
35d
\end{align*}
\]

Expt. No. 3.2.5 Synthesis of 4-chlorobenzaldoxime (35e)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{NH}_2\text{OH.HCl}} \text{N}=\text{O} \\
\text{NaOH, MeOH,} & \text{rt, 1h, 96\%} \\
35e
\end{align*}
\]
Expt. No. 3.2.6 Synthesis of furan-2-carbonitrile (36a)

\[
\begin{array}{c}
\text{O} \\
\text{N-OH} \\
\text{35a} \\
\end{array} \xrightarrow{\text{AlCl}_3, \text{Xylene}} 
\begin{array}{c}
\text{O} \\
\text{CN} \\
\text{36a} \\
\end{array}
\]

Expt. No. 3.2.7 Synthesis of 4-methoxybenzonitrile (36b)

\[
\begin{array}{c}
\text{N-OH} \\
\text{35b} \\
\end{array} \xrightarrow{\text{AlCl}_3, \text{Xylene}} 
\begin{array}{c}
\text{CN} \\
\text{36b} \\
\end{array}
\]

Expt. No. 3.2.8 Synthesis of 4-hydroxybenzonitrile (36c)

\[
\begin{array}{c}
\text{N-OH} \\
\text{35b} \\
\end{array} \xrightarrow{\text{MW, 20 min, 37%}} 
\begin{array}{c}
\text{CN} \\
\text{36c} \\
\end{array}
\]

Expt. No. 3.2.9 Synthesis of thiophene-2-carbonitrile (36d)

\[
\begin{array}{c}
\text{N-OH} \\
\text{35c} \\
\end{array} \xrightarrow{\text{AlCl}_3, \text{Xylene}} 
\begin{array}{c}
\text{CN} \\
\text{36d} \\
\end{array}
\]

Expt. No. 3.2.10 Synthesis of 3,4-dimethoxybenzonitrile (36e)

\[
\begin{array}{c}
\text{N-OH} \\
\text{35d} \\
\end{array} \xrightarrow{\text{AlCl}_3, \text{Xylene}} 
\begin{array}{c}
\text{CN} \\
\text{36e} \\
\end{array}
\]
Expt. No. 3.2.11 Synthesis of 4-chlorobenzonitrile (36f)

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{Cl} & \quad \text{AlCl}_3, \text{ Xylene} \\
\text{CN} & \quad \text{Cl} \\
\text{35e} & \quad \text{36f}
\end{align*}
\]

Expt. No. 3.2.12 Cycloaddition reaction of oxime using methyl acrylate (37)

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{COOMe} & \quad \text{AlCl}_3, \text{ Methyl Acrylate} \\
\text{O} & \quad \text{COOMe} \\
\text{35a} & \quad \text{37}
\end{align*}
\]

Expt. No. 3.2.13 Synthesis of N-(2-cyanoethyl)furan-2-carboxamide (38a)

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{AlCl}_3, \text{ Acrylonitrile} \\
\text{HN} & \quad \text{O} \\
\text{35a} & \quad \text{38a}
\end{align*}
\]

Expt. No. 3.2.14 Synthesis of N-(2-cyanoethyl)-3,4-dimethoxybenzamide (38b)

\[
\begin{align*}
\text{N} & \quad \text{OH} \\
\text{MeO} & \quad \text{MeO} \\
\text{AlCl}_3, \text{ Acrylonitrile} \\
\text{O} & \quad \text{MeO} \\
\text{35d} & \quad \text{38b}
\end{align*}
\]

General procedure for synthesis of oximes

In a round bottom flask, hydroxyl amine hydrochloride (2 mmol) and sodium hydroxide (2 mmol) were added to a solution of suitable aldehyde (34a-e) (1 mmol) in methanol. The reaction mixture was stirred at room temperature for 1 hour. After the completion of reaction, methanol was evaporated under reduced pressure followed by addition of crushed ice. The obtained precipitate was then filtered off and washed with water to give corresponding oxime (35a-e).
Expt. No. 3.2.1 Synthesis of furfuraldoxime (35a)

Yield : 96%
Mp : 113-115°C
FTIR (KBr cm⁻¹) : 3412, 1637, 1384, 849
MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 111 (M+, 75), 95 (20), 95 (20), 94 (25), 68 (72), 39 (100)

Expt. No. 3.2.2 Synthesis of 4-methoxy benzaldoxime (35b)

Yield : 92%
Mp : 130-132°C
FTIR (KBr cm⁻¹) : 3282, 2925, 1606, 1514, 1251, 954
MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 151(M+, 60), 133 (100), 108 (52), 103 (60), 90 (70)

¹H NMR (300 MHz, CDCl₃) δ:

| 3.74, s | 3H | OCH₃ |
| 6.80, d, J = 8.5 Hz | 2H | ArH |
| 7.40, d, J = 8.8 Hz | 2H | ArH |
| 7.99, s | 1H | CH |

Expt. No. 3.2.3 Synthesis of thienyl-2-aldoxime (35c)

Yield : 94%
Mp : 99-101°C
FTIR (ATR cm⁻¹) : 3132, 2862, 1662, 1400, 1215, 1105, 759
MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 127 (M+, 60), 109 (100), 84 (90), 58 (50), 45 (55), 39 (75)
Expt. No. 3.2.4 Synthesis of 3,4-dimethoxybenzaldoxime (35d)

Yield : 95%

Mp : 92-95°C

FTIR (KBr cm\(^{-1}\)) : 3448, 2962, 1598, 1515, 1265, 1145, 1024, 954

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 181 (M+, 50), 163 (100), 148 (55), 120 (40), 92 (50), 77 (65), 65 (55)

Expt. No. 3.2.5 Synthesis of 4-chlorobenzaldoxime (35e)

Yield : 96%

Mp : 108-110°C

FTIR (KBr cm\(^{-1}\)) : 3297, 2996, 1594, 1493, 1316, 1106, 971

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 155 (M+, 50), 137 (100), 112 (70), 102 (60), 75 (50)

General Procedure for Conversion of Aldoximes to Nitriles

A mixture of anhydrous AlCl\(_3\) (1.2 mmol), ionic liquid (1 mmol) and aldoxime (1 mmol) in xylene (20 ml) was irradiated in a microwave oven (750 W) for suitable time. Completion of reaction was monitored by TLC. Solvent was distilled out, and the reaction mixture was extracted with ethyl acetate. The product was purified by column chromatography using hexane and ethyl acetate as an eluent.

Expt. No. 3.2.6 Synthesis of furan-2-carbonitrile (36a)

Yield : 80%

Mp : 146-148°C

FTIR (KBr cm\(^{-1}\)) : 2962, 2224, 1597, 1515, 1467, 1270, 1018, 880

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 93 (M+, 100), 64 (55), 38 (26), 29 (15),
Expt. No. 3.2.7 Synthesis of 4-methoxybenzonitrile (36b)

Yield : 70%

Mp : 59-61°C

FTIR (KBr cm\(^{-1}\)) : 2962, 2925, 2448, 1637, 1405, 1185, 1046, 977

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 133 (M+, 100), 103 (50), 90 (60)

Expt. No. 3.2.8 Synthesis of 4-hydroxybenzonitrile (36c)

Yield : 37%

Mp : 110-112°C

FTIR (KBr cm\(^{-1}\)) : 3132, 2862, 2246, 1656, 1531, 1400, 1105, 948

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 119 (M+, 100), 91 (25), 64 (30)

Expt. No. 3.2.9 Synthesis of thiophene-2-carbonitrile (36d)

Yield : 80%

Mp : 125°C

FTIR (KBr cm\(^{-1}\)) : 2925, 2224, 1682, 1514, 1269, 1022, 782

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 109 (M+, 100), 83 (45), 26 (35)

Expt. No. 3.2.10 Synthesis of 3,4-dimethoxybenzonitrile (36e)

Yield : 80%

Mp : 65-67°C

FTIR (KBr cm\(^{-1}\)) : 2962, 2224, 1597, 1467, 1270, 1018, 880

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 163 (M+, 100), 148 (40), 120 (35), 102 (20), 92 (30)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\):

<table>
<thead>
<tr>
<th>3.90, s</th>
<th>3H</th>
<th>OCH(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.93, s</td>
<td>3H</td>
<td>OCH(_3)</td>
</tr>
<tr>
<td>6.89, d, J = 8.3 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>---------------------</td>
<td>----</td>
<td>-----</td>
</tr>
<tr>
<td>7.07, d, J = 1.9 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.27, dd, J = 8.3 Hz, 1.9 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
</tbody>
</table>

Expt. No. 3.2.11 Synthesis of 4-chlorobenzonitrile (36f)

Yield : 90%
Mp : 91-93°C

FTIR (KBr cm\(^{-1}\)) : 2917, 2849, 2360, 1595, 1465, 1321, 1126, 717

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 137 (M+, 100), 102 (35), 75 (20), 50 (20)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\):

<table>
<thead>
<tr>
<th>7.45, d, J = 8.0 Hz</th>
<th>2H</th>
<th>ArH</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.58, d, J = 8.0 Hz</td>
<td>2H</td>
<td>ArH</td>
</tr>
</tbody>
</table>

Expt. No. 3.2.12 Cycloaddition reaction of oxime using methyl acrylate (37)

A mixture of anhydrous AlCl\(_3\) (1.2 mmol), ionic liquid (1 mmol) and aldoxime (1 mmol) in methyl acrylate (20 ml) was irradiated in a microwave oven (750 W) for suitable time. Completion of reaction was monitored by TLC. Solvent was distilled out, and the reaction mixture was extracted with ethyl acetate. The product was purified by column chromatography using hexane and ethyl acetate as an eluent.

Yield : 85%

FTIR (KBr cm\(^{-1}\)) : 2955, 1735, 1438, 1207, 1012, 747

MS (GCMS, EI, 70 eV) : m/z (rel. intensity): 283 (M+, 10), 253 (15), 224 (15), 210 (25), 194 (30), 165 (100), 136 (15), 121 (55), 105 (25)
General Procedure for Conversion of Aldoximes to amides

A mixture of anhydrous AlCl$_3$ (1.2 mmol), ionic liquid (1 mmol) and aldoxime (1 mmol) in acrylonitrile (20 ml) was irradiated in a microwave oven (750 W) for suitable time. Completion of reaction was monitored by TLC. Solvent was distilled out, and the reaction mixture was extracted with ethyl acetate. The product was purified by column chromatography using hexane and ethyl acetate as an eluent.

Expt. No. 3.2.13 Synthesis of \( N \)-(2-cyanoethyl)furan-2-carboxamide (38a)

Yield \( : 90\% \)

Mp \( : 101-103 ^\circ C \)

FTIR (KBr cm$^{-1}$) \( : 3384, 2245, 1664, 1595, 1525, 1298, 1014, 754 \)

MS (GCMS, EI, 70 eV) \( : m/z \) (rel. intensity): 164 (M+, 100), 138 (35), 97 (20), 67 (20)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$:

<table>
<thead>
<tr>
<th>2.72, t, J = 6.3 Hz</th>
<th>2H</th>
<th>CH$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.69, t, J = 6.4 Hz</td>
<td>2H</td>
<td>CH$_2$</td>
</tr>
<tr>
<td>6.49-6.51, m</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>6.82, brs (D$_2$O exchangeable)</td>
<td>1H</td>
<td>NH</td>
</tr>
<tr>
<td>7.14, dd, J = 0.9 Hz, 2.7 Hz</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.45, m</td>
<td>1H</td>
<td>ArH</td>
</tr>
</tbody>
</table>

Expt. No. 3.2.14 Synthesis of \( N \)-(2-cyanoethyl)-3,4-dimethoxybenzamide (38b)

Yield \( : 80\% \)

Mp \( : 148-151 ^\circ C \)

FTIR (KBr cm$^{-1}$) \( : 3292, 2963, 2251, 1631, 1512, 1261, 1045, 873 \)

MS (GCMS, EI, 70 eV) \( : m/z \) (rel. intensity): 234 (M+, 100), 208 (55), 180 (35), 137 (20), 97 (65)
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$:  

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>Multiplicity</th>
<th>Integration</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.75, t, $J = 6.0$ Hz</td>
<td>2H</td>
<td>CH$_2$</td>
<td></td>
</tr>
<tr>
<td>3.71, q, $J = 6.0$ Hz</td>
<td>2H</td>
<td>CH$_2$</td>
<td></td>
</tr>
<tr>
<td>3.93, s</td>
<td>6H</td>
<td>OCH$_3$ x 2</td>
<td></td>
</tr>
<tr>
<td>6.51, brs (D$_2$O exchangeable)</td>
<td>1H</td>
<td>NH</td>
<td></td>
</tr>
<tr>
<td>6.86, d, $J = 8.2$ Hz</td>
<td>1H</td>
<td>ArH</td>
<td></td>
</tr>
<tr>
<td>7.27, m</td>
<td>1H</td>
<td>ArH</td>
<td></td>
</tr>
<tr>
<td>7.38, s</td>
<td>1H</td>
<td>ArH</td>
<td></td>
</tr>
</tbody>
</table>
References


