CHAPTER - V
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CONDENSATION OF O-PHENYLENEDIAMINE WITH
UNSATURATED ACIDS

Introduction

Since bromination of 2-styrylbenzimidazoles failed to give the corresponding
dibromo products and, consequently the 2-[[β]-phenylacetylenyl] benzimidazoles, it
was considered worthwhile to attempt an alternate synthesis of the title compound
by condensation of o-phenylenediamine with phenylpropionic acid. Literature survey
revealed that not much work has been done on the condensation of acetylenic and
other unsaturated acids with o-phenylenediamine.

\[
\begin{align*}
\text{NH}_2 & & \text{NH}_2 & & \text{HOOC-C=C-Ph} &\xrightarrow{?} & \text{C=C-Ph} \\
& & & & & & \\
\end{align*}
\]

Thus, this chapter deals with studies on the condensation of unsaturated acids
with o-phenylenediamine and study of the spectral characteristics of the products
obtained.

Results and Discussion

For the preparation of 2-[[β]-phenylacetylenyl] benzimidazole, phenylpropionic
acid forms a crucial synthon and is not readily available. Therefore, it was considered
worthwhile to prepare phenylpropiolic acid from cinnamic acid by literature method1.

**Preparation of Phenylpropiolic acid**

Bromination of cinnamic acid with liquor bromine in refluxing CCl₄ gave the known (±)-dibromocinnamic acid (24). Its IR spectrum in KBr (Fig-30) showed peaks at ~3000 (m, vb, bonded –OH and –CH stretchings), 1715 (unsplit doublet, vs, –CO–), 1460 (m), 1433 (m), 1323 (w), 1300 (m), 1284 (s) cm⁻¹ etc. Its ¹H-NMR in CDCl₃/TMS (Fig-31) showed signals at δ 5.29 (1H, d, J = 12 Hz, ph–CH(Br)–), 5.525 (1H, d, J = 12 Hz, –CH(Br)–CO–), 7.25–7.62 (complex m, 5H, phenyl protons), 14.0 (broad s, 1H, –COOH). Its ¹³C-NMR spectrum (Fig-32) showed signals at δ 47.37 (ph–C(=O)), 51.99 (–CH(Br)–CO–), 128.41, 128.69, 129.07 (five phenyl carbons carrying hydrogens), 138.25 (quaternary phenyl carbon), 169.11 (–CO–). Its electron impact mass spectrum (Fig-33) recorded at 70 eV showed peaks at m/z (% I) 310 (2.34, M+4), 308 (7.08, M+2), 306 (3, M+), 229 (26.5), 227 (27.6), 184 (28.9), 182 (31.4), 148 (31.8), 147 (49.7), 131 (13.2), 107 (20.6), 104 (24.7), 103 (100), 102 (25.4), 91 (10.5), 82 (15.9) etc.

24 on treatment with two equivalents of methanolic KOH followed by simple processing gave a compound with m.p 98–100° (yield = 56%, based on monodehydrobromination). Its IR spectrum in KBr phase (Fig-34) showed peaks at ~2900 (m, vb, bonded –OH and –CH stretchings), 1680 (vs, unsplit doublet, –CO–), 1600 (m), 1573 (w), 1511 (vw), 1425 (s) cm⁻¹ etc. Its ¹H-NMR spectrum (Fig-35)
showed signals at δ 7.2-7.45 (complex m, 5H, phenyl protons), 7.55 (1H, s, ph-CH=), 11.8 (broad s, 1H, -COOH). Its $^{13}$C-NMR spectrum (Fig-36) showed signals at δ 110.6 (=C(Br)-COOH), 128.49, 128.51, 128.57, 129.37, 129.40, 134.44 (six phenyl carbons), 143.73 (ph-CH=), 169.37(-CO-). Its electron impact mass spectrum (Fig-37) recorded at 70 eV showed peaks at m/z (%) 227 and 229 (4.24 and 1.92, M+1 ion peaks corresponding to $^{79}$Br and $^{81}$Br respectively), 226 and 228 (twin peaks, 18.6 and 20.12, M**), 147 (100), 129 (17.38), 103 (9.31), 102 (20.6), 77 (13.5), 50 (13.8), 49 (10.5) etc. Based on this data, the compound was formulated as bromocinnamic acid.

In the dehydrobromination of 24 to bromocinnamic acid, four stereoisomers are possible. The structures and appropriate chemical shift values for these stereoisomers were calculated as shown in Tables 30 and 31, based on the method of calculations cited in literature 2.

By comparing the calculated $^{13}$C - chemical shift values of the isomeric bromocinnamic acids (Table -30) with the actual values of the bromocinnamic acid obtained in our work, it may be concluded that the compound obtained in question is α-bromocinnamic acid. Furthermore, by comparing the calculated $^1$H - chemical shift values of the isomeric (E)-α and (Z)-α bromocinnamic acids (Table - 31) with the actual value of the bromocinnamic acid obtained in our work, it may be concluded that the compound in question is decisively (E)-α bromocinnamic acid (25).
FIG. 37

![Chemical Structure]

(M+ = 226)
Table - 30: Calculation of $^{13}$C-NMR Chemical Shift values for vinylic carbons of isomeric bromocinnamic acids:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the isomer</th>
<th>Structure of the isomer</th>
<th>Chemical Shift Value</th>
<th>$\alpha$-Carbon</th>
<th>$\beta$-Carbon</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\alpha$-Bromo-cinnamic acid</td>
<td><img src="image" alt="Structure of $\alpha$-Bromo-cinnamic acid" /></td>
<td>Base Value = 123.3</td>
<td>One pair of cis substituent = -1.1</td>
<td>One pair of cis substituent = -1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One pair of geminal substituent on 'C'$_1$ = -4.8</td>
<td>'Br' on 'C'$_1$ = -7.9</td>
<td>Ph on 'C'$_1$ = +12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH on 'C'$_1$ = +6.3</td>
<td>'Br' on 'C'$_2$ = -1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph on 'C'$_2$ = -11.0</td>
<td>-COOH on 'C'$_2$ = +7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>δ = 104.8</td>
<td>δ = 142.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$\beta$-Bromo-cinnamic acid</td>
<td><img src="image" alt="Structure of $\beta$-Bromo-cinnamic acid" /></td>
<td>Base Value = 123.3</td>
<td>One pair of cis substituent = -1.1</td>
<td>One pair of cis substituent = -1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One pair of geminal substituent on 'C'$_2$ = +2.5</td>
<td>'Br' on 'C'$_1$ = -1.4</td>
<td>Ph on 'C'$_1$ = +12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH on 'C'$_1$ = +6.3</td>
<td>'Br' on 'C'$_2$ = -7.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph on 'C'$_2$ = -11.0</td>
<td>-COOH on 'C'$_2$ = +7.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>δ = 118.6</td>
<td>δ = 129.0</td>
<td></td>
</tr>
</tbody>
</table>
Table - 31: Calculation of 'H-NMR Chemical Shift Values for vinylic proton of isomeric bromocinnamic acids:

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the isomer</th>
<th>Structure of the isomer</th>
<th>Chemical Shift Value (ppm units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(E)-α-Bromo-cinnamic acid</td>
<td><img src="image1" alt="" /></td>
<td>Base Value= + 5.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>geminal 'Ph'=  + 1.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cis 'Br' =  + 0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans, conguated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH =  + 0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>δ=  7.40</td>
</tr>
<tr>
<td>2</td>
<td>(Z)-α-Bromo-cinnamic acid</td>
<td><img src="image2" alt="" /></td>
<td>Base Value= + 5.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>geminal 'Ph'=  + 1.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans 'Br' =  + 0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cis, conguated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH =  + 0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>δ=  8.16</td>
</tr>
<tr>
<td>3</td>
<td>(E)-β-Bromo-cinnamic acid</td>
<td><img src="image3" alt="" /></td>
<td>Base Value= + 5.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans 'Ph' =  - 0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cis 'Br' =  + 0.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>geminal, conguated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH =  + 0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>δ=  6.43</td>
</tr>
<tr>
<td>4</td>
<td>(Z)-β-Bromo-cinnamic acid</td>
<td><img src="image4" alt="" /></td>
<td>Base Value= + 5.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cis 'Ph' =  + 0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>trans 'Br' =  + 0.55</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>geminal, conguated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-COOH =  + 0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>δ=  6.96</td>
</tr>
</tbody>
</table>
It may be mentioned here that Dalcanale et al., reported the preparation of the so called "(E)-α-bromocinnamic acid", m.p 129-30°, by the NaClO₂-H₂O₂ oxidation of α-bromocinnamaldehyde. These authors assumed the configuration of α-bromocinnamaldehyde to be (E)-α and assigned the configuration (E)-α to the bromocinnamic acid obtained from its oxidation. Moreover, the chemical shift value for the vinyl proton of the bromocinnamic acid was reported as δ 8.1. It is obvious from Table -31 that the configuration assigned by Dalcanale et al., to the bromocinnamic acid they obtained (mp 129-30°) is erroneous and that it actually has (Z)-α configuration.

The (E)-α-bromocinnamic acid (25) obtained in our work, m.p 98-100°, on treatment with methanolic KOH gave phenylpropionic acid (26). 26 was also obtained by treating 24 with excess of methanolic KOH for prolonged period. Attempted preparation of 26 directly from trans-cinnamic acid by dehydrogenation over palladium-carbon or nitrobenzene in refluxing methanol led to the recovery of starting material. All these reactions are briefly summarised in scheme -2.

**SCHEME-2**

![Scheme 2](attachment:Scheme2.png)
The structure of 26 is supported by its m.p, tlc and spectral data. Its IR spectrum as KBr pellet (Fig-38) showed peaks at ~2900 (m, vb, bonded –OH and –CH stretchings), 2236 and 2203 (unequal, sharp, strong doublet, –C=–C–), 1680 (vs, –CO–), 1495 (w), 1417 (s), 1307 (s), 1208 (s) cm\(^{-1}\) etc. Its \(^1\)H-NMR spectrum in CDCl\(_3\)/TMS (Fig-39) showed resonances at δ 7.25-7.63 (complex m, 5H, phenyl protons), 11.76 (sharp s, 1H, –COOH). Its \(^{13}\)C-NMR spectrum (Fig-40) showed peaks at δ 80.10 (acetylenic carbon α to –COOH), 89.26 (acetylenic carbon β to –COOH), 119.04 (quaternary carbon of phenyl group), 128.68, 131.22, 133.32 (two ortho, two meta and one para carbons of phenyl ring), 159.1 (–CO–). Its electron impact mass spectrum (Fig-41) at 70 eV showed peaks at m/z (%I), 147 (9.33, M+1), 146 (97.4, M*), 130 (9.9), 129 (100), 118 (56.2), 102 (74.3), 101 (11.2), 98 (6.7), 89 (18.9), 77 (5.4), 76 (28.6), 75 (79.6), 74 (41.1), 73 (9.3), 62 (20.5), 51 (14.9), 50 (30.4) etc.

Based on these results, formation of 26 from trans-cinnamic acid can be shown to take place mechanistically in three steps as shown below:

1) trans-cinnamic acid undergoes trans bromination to yield 24 via a cyclic bromonium ion intermediate (eqn.1 of scheme -3).

2) 24 undergoes selective monodehydrobromination when treated carefully with two equivalents of methanolic KOH to yield 25. This is a regiospecific process, in which the proton α to –COOH is preferentially abstracted by the OH because of its more acidic nature compared with the β-proton (please see the \(^1\)H-NMR
% Relative intensity

m/z

Ph-CCCCO
(M+ = 146)
of 24 given above). The abstraction of α-proton by $\ddot{\text{O}}\text{H}$ is followed by simultaneous loss of bromine as Br similar to an $E_2$-elimination process and goes through a transition state in which the proton α to −COOH and 'Br' β to −COOH group are anti to each other (eqn-2 of scheme -3).

If the monodehydrobromination of 24 to give 25 was not an $E_2$-elimination, assuming it to be $E_1$CB, $E_1$ or anchimerically assisted mechanism, a different isomer of 25 would have been formed in which the phenyl and −COOH groups are present on the opposite sides of the double bond [i.e. (Z)-α-bromocinnamic acid, ] thus decreasing the steric crowding in the product [please see eqns. 3, 4 and 5 respectively of scheme -3].

3) 25 thus formed has the 'H' and 'Br' groups in cis-orientation to each other. Further loss of HBr from such a molecule would normally be very difficult since cis-eliminations do not occur easily. Nevertheless, the fact is 25 undergoes facile dehydrobromination on treatment with methanolic KOH under relatively mild conditions to yield 26. This is probably due to rotation across the double bond, on heating in methanolic KOH, of 25 facilitated by carbonyl moiety of carboxyl group resulting in an intermediate with 'H' and 'Br' groups trans oriented to each other, followed by loss of HBr similar to an $E_2$-elimination. This is shown in eqn-6 of scheme-3. Thus, what appears apparently as cis-elimination is in reality a trans-elimination process.
Scheme - 3

Addition of Bromine to cinnamic acid:

Addition of Bromine to cinnamic acid:

Elimination of HBr (E2 mechanism)

Elimination of HBr (E2 mechanism)

Elimination of HBr (E1 CB mechanism)

Elimination of HBr (E1 CB mechanism)
Elimination of HBr (E1 mechanism)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(24)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(Planar carbocation)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(fast)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(24)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(Planar carbocation)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(Eq. 4)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(Z)-α-Bromocinnamic acid

Elimination of HBr (Anchimeric assistance)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(24)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(24)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(24)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(Z)-α-Bromocinnamic acid

Conversion of 25 to 26

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(25)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(26)

\[
\begin{align*}
\text{Ph} & \quad \text{HBr} \\
& \quad \text{HO}^- \\
\text{Ph} & \quad \text{HBr} \\
\end{align*}
\]

(eq. 6)
Attempted condensation of 26 with 1

Treatment of 26 with 1 (i) in 4N HCl at 100° for 3 hrs (ii) at 200° for 3 hrs or by
(iii) heating the reactants in polyphosphoric acid at 180° did not yield the expected
2-[β-phenylacetylenyl] benzimidazole and starting material was recovered back in
each case.

Since condensation of 26 with 1 failed to give 2-[β-phenylacetylenyl]
benzimidazole, it was considered worthwhile to standardise first conditions for
condensation of simple unsaturated acids like cinnamic acids and then extend the
same conditions for the condensation of 26. Use of cinnamic acids for condensation
in the present work is two fold. Firstly, the 2-styrylbenzimidazoles obtained by the
condensation of cinnamic acids with 1 can be authenticated with the products
prepared by the condensation of 4a and 4b with aromatic aldehydes quoted in Chapter
II. Secondly, substituted cinnamic acids can be easily prepared by reported methods.

Condensation of 1 with cinnamic acids

Dandegaonker reported⁵ that reaction of 1 with cinnamic acid yields
benzodiazepinone derivative and not 2-styrylbenzimidazole.

\[
\text{NH}_2
\begin{array}{c}
\text{CH} = \text{CH} - \text{Ph} (2a)
\end{array}
\]

\[
\text{NH}_2 \quad + \quad \text{HOOC-CH=CH-Ph} \quad \rightarrow \quad \text{NH} \quad \text{O} \quad \text{Ph} \quad \text{NH}_2
\]
This was subsequently proved to be erroneous by Govindachari and co-workers who showed that condensation of o-phenylenediaminedihydrochloride (1.2 HCl) with cinnamic acid at 200° gives the styryl derivative i.e. 2a in 57% yield rather than diazepinone.

Obviously, under thermal conditions, the greater stability of fused aromatic rings than that of an unconjugated heteroring decides the course of reaction.

Singh and co-workers reported the condensation of arylalkanoic acids with 1.2 HCl in refluxing ethylene glycol to give the 2-substituted benzimidazoles in high yields.

Thus, condensation of 1.2 HCl with cinnamic acid in refluxing ethylene glycol for 5 hrs gave 2a in 85% yield. The identity of 2a was confirmed by comparison of its mp, mmp, tlc and IR spectrum with that of an authentic sample of 2a prepared by the condensation of 4a with benzaldehyde as described in Chapter-II. The processing of reaction mass was simple and the isolation of the product was easy.

\[
\text{Ethylene glycol/5 hrs} \quad \text{(2a)}
\]

The above reaction of 1.2 HCl with cinnamic acid has been extended to 14 more cinnamic acids. Results of this study are shown in Table-32. 1.2 HCl and
Table - 32 : Condensation of 1.2 HCl with Cinnamic acids in refluxing ethylene glycol to get 2, 10, 27, 28 and 29

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name</th>
<th>Acid Used</th>
<th>Structure</th>
<th>Product obtained</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cinnamic acid</td>
<td>~Methylcinnarnic acid</td>
<td>2a</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>p-Methylcinnamic acid</td>
<td>%L</td>
<td>2b</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>o-Chlorocinnamic acid</td>
<td>coon</td>
<td>2c</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>p-Chlorocinnamic acid</td>
<td>ON</td>
<td>2d</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>m-Nitrocinnamic acid</td>
<td>NO</td>
<td>2a</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>p-Nitrocinnamic acid</td>
<td>w</td>
<td>2f</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>α-Methylcinnamic acid</td>
<td>CH₃</td>
<td>10a</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4-Methyl-α-methylcinnamic acid</td>
<td>CH₃</td>
<td>10b</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2-Chloro-α-methylcinnamic acid</td>
<td>CH₃</td>
<td>10c</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4-Chloro-α-methylcinnamic acid</td>
<td>CH₃</td>
<td>10d</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3-Nitro-α-methylcinnamic acid</td>
<td>CH₃</td>
<td>10e</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4-Nitro-α-methylcinnamic acid</td>
<td>CH₃</td>
<td>10f</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>α-Phenylcinnamic acid</td>
<td>(27)</td>
<td>(27)</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>β-Methylcinnamic acid</td>
<td>(28)</td>
<td>(28)</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>β-Phenylcinnamic acid</td>
<td>(29)</td>
<td>(29)</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>
cinnamic acids used for condensation were prepared by the methods reported in literature. The advantage of this method is that the compounds which cannot be obtained by the condensation of 4a with acetophenone and benzophenone can be obtained by this method.

The structures of compounds 27, 28 and 29 are assigned based on their spectral and analytical data.

The IR spectrum of 27 in KBr (Fig-42) showed peaks at ~2900 (v, m, -NH), 1703 (m), 1624 (vw), 1497 (vw), 1443 (m), 1395 (m), 1323 (vw), 1279 (vw), 1233 (vw) cm⁻¹ etc. Its ¹H-NMR (Fig-43) showed signals at δ 7.11 - 7.50 (complex m, 14H, 2x five phenyl protons and four aryl protons), 8.12 (sharp s, 1H, vinylic proton). Its electron impact mass spectrum showed (Fig-44) peaks at m/z (%I) 296 (100, M⁺), 219 (41.2), 218 (18), 181 (10), 178 (11.1), 176 (8.9), 169 (10), 148 (14.7), 147 (14.9), 146 (15), 131 (25), 119 (25), 92 (5.9), 91 (5.9), 77 (19.1), 69 (90), 65 (14.9), 64 (10), 63 (14), 51 (34), 44 (54.4) etc.

The IR spectrum of 28 in KBr showed (Fig-45) peaks at ~2950 (v, m, -NH), 1634 (m), 1524 (w), 1493 (vw), 1447 (s), 1414 (vs), 1370 (s), 1333 (m), 1277 (s), 1233 (m) cm⁻¹ etc. Its ¹H-NMR (Fig-46) showed signals at δ 2.8 (s, 3H, CH₃), 6.82 (s, 1H, vinylic proton), 7.16-7.72 (complex m, 9H, five phenyl and four aryl protons), 12.4 (broad s, 1H, -NH). Its ¹³C-NMR (Fig-47) showed resonances at δ 17.93 (CH₃), 115.124, 121.996, 125.86, 128.146, 128.633, 142.532, 144.088, 150.998 (six phenyl carbons, six aryl carbons, two vinylic carbons and one imidazole quaternary carbon).
FIG. 43
Its electron impact mass spectrum (Fig-48) showed peaks at m/z (%I) 236 (4.2, M+2), 235 (22.8, M+1), 234 (46, M"'), 233 (100, M-1), 231 (4.6), 219 (8.85), 218 (7), 156 (4), 131 (3.5), 128 (3.5), 117 (3.5), 116 (8.85), 115 (10.6), 109 (4), 105 (4.4), 104 (5.3), 103 (8), 102 (4.4), 92 (4.4), 91 (6.2), 90 (3.5) etc.

The IR spectrum of 29 in KBr showed (Fig-49) peaks at ~2800 (vb, m, -NH), 1622 (m), 1493 (m), 1435 (s), 1345 (s), 1277 (s), 1208 (vw) cm⁻¹ etc. Its ¹H-NMR (Fig-50) showed signals at δ 7.1-7.7 (complex m, for 2 x five phenyl protons, four aryl protons and one vinylic proton). Its ¹³C-NMR (Fig-51) showed resonances at δ 117.327, 122.896, 127.316, 128.57, 128.71, 129.043, 129.662, 129.76, 139, 140.5, 146.4, 150 (for twelve phenyl carbons, six aryl carbons, two vinylic carbons and one imidazole quaternary carbon). Its electron impact mass spectrum (Fig-52) showed at m/z (%I) 298 (3.7, M+2), 297 (17.7, M+1), 296 (29.7, M"'), 295 (100, M-1), 293 (7.1), 219 (9.7), 218 (4.9), 147 (10.6), 105 (2.6), 91 (3.1) etc.

**Mechanism of condensation**

The mechanism involves an initial decomposition of 1.2 HCl, reversibly, at the refluxing temperature of ethylene glycol to form 1 and HCl. The HCl thus formed activates the carboxyl group of acid by addition of proton to oxygen forming a carbonium ion with electron deficiency at the carbon atom. The unshared electron pair of one of the nitrogen atoms of 1 enters into the carbonium ion of the protonated acid to form an intermediate which looses two molecules of water to form the product.
FIG. 45
It may be mentioned here that Holljes and Wagner proposed a similar mechanism for the formation of 2-substituted benzimidazoles from 1.2 HCl and nitrile

Condensation of 1.2 HCl with 26 in ethylene glycol

Treatment of 1.2 HCl with 26 in refluxing ethylene glycol followed by a simple processing gave a compound m.p 179–80°. Its IR in KBr (Fig-53) showed peaks 2900 (vb, m, –NH), 1622 (vw), 1532 (w), 1412 (s), 1362 (m), 1235 (w), 1017 (w) cm⁻¹ etc. Its ¹H-NMR in CDCl₃ recorded at 400 MHz (Fig-54) showed signals at δ 7.28-7.83 (complex m, five phenyl, four aryl and one vinylic proton). Its ¹³C-NMR (Fig-55) showed resonances at δ 115.515, 116.480, 123.574, 126.680, 128.72, 129.923, 135.596, 137.109, 147.971, 169.223 (six phenyl carbons, six aryl carbons, two vinylic carbons and one imidazole quaternary carbon). Its electron impact mass spectrum recorded at 70 eV (Fig-56) showed peaks at m/z (%) 256 and 254 (6 ar
28; M$^{+}$ corresponding to 37Cl and 36Cl), 255 and 253 (30 and 100, M-1 corresponding to 37Cl and 36Cl), 220 (2), 219 (14), 218 (6), 194 (3), 109 (2.6), 91 (1.13), 77 (0.75), 65 (1.2) HRMS: found = 253.0535 ± 0.0008 amu; calculated for C$_{12}$H$_{10}$ClN$_2$(M-1) was 253.0532 amu. Based on this data, the compound was assigned the structure 2-chlorostyrylbenzimidazole (30).

![Chemical structure of 2-chlorostyrylbenzimidazole](image)

Similarly condensation of o-phenylenediaminedihydrobromide (1.2 HBr) with 26 in refluxing ethylene glycol yielded a compound having m.p 159–60°. Its IR in KBr (Fig-57) showed peaks at ~2800 (vb, m, –NH), 1620 (m), 1595 (vw), 1520 (vw), 1500 (vw), 1450 (m), 1440 (s), 1390 (vw), 1305 (vw), 1290 (w), 1230 (w) cm$^{-1}$ etc. Its ¹H-NMR in CDCl$_3$/TMS recorded at 400 MHz (Fig-58) showed signals at δ 7.31–7.73 (complex m, five phenyl, four aryl and one vinylic proton). Its ¹³C-NMR (Fig-59) showed signals at δ 115.532, 120.330, 123.666, 127.326, 127.746, 128.670, 129.840, 138.039, 139.145, 148.152 (six phenyl carbons, six aryl carbons, two vinylic carbons and one imidazole quaternary carbon). Its mass spectrum (Fig-60) showed peaks at m/z (%) 300 and 298 (25 and 30, M$^{+}$ corresponding to ³¹Br and ³⁵Br), 299 and 297 (100 and 93.3, M-1 corresponding to ³¹Br and ³⁵Br), 219 (35), 218 (66), 217 (10.1), 190 (6.6), 128 (6.6), 109 (26.6), 102 (53.3), 91 (20), 90 (20), 77 (30), 76 (19), 65 (31.6), 64 (30), 63 (53.3), 52 (31.6), 51 (36.6), 50 (23.3) etc. Based on this data
140 MHz SPECTRUM
(400 MHz SPECTRUM, AROMATIC REGION EXPANDED)
the compound was assigned the structure 2-bromostyrylbenzimidazole (31). 1.2 HBr was prepared by the reaction of hydrobromic acid with 1 in dioxan at RT.

\[
\text{2HBr} + \text{HOOC-CH=CH-Ph} \xrightarrow{\text{Ethylene glycol/\ reflux}} \text{(31)}
\]

To account for the formation of 30 from 1.2 HCl and 26, 31 from 1.2 HBr and 26, two mechanisms have been proposed which are as follows.

First Mechanism: 1.2 HCl or 1.2 HBr decomposes reversibly at the refluxing temperature of ethylene glycol to form 1 and HX. 1 condenses with 26 which is catalysed by HX to form 2-{[β-phenylacetylenyl]benzimidazole. Then the free HX adds on to the triple bond to form 30 or 31. Mechanistically it can be shown as follows:

(i). \[
\begin{align*}
\text{2HX} &\xrightarrow{} \left[ \begin{array}{c}
\text{2HX} + \\
\text{2HN} \\
\text{2HN}
\end{array} \right]
\end{align*}
\]

(ii). \[
\begin{align*}
\left[ \begin{array}{c}
\text{2HN} \\
\text{2HN}
\end{array} \right] + 
\text{HOOC-C-C-Ph} &\xrightarrow{} \left[ \begin{array}{c}
\text{2HX} + \\
\text{2HN} \\
\text{2HN}
\end{array} \right]
\end{align*}
\]

(iii). \[
\begin{align*}
\text{2HX} &\xrightarrow{} \left[ \begin{array}{c}
\text{2HX} + \\
\text{2HN} \\
\text{2HN}
\end{array} \right]
\end{align*}
\]

(30 or 31) \( X=\text{Cl or Br} \)

Second Mechanism: The HX which is formed by the reversible decomposition of
1.2 HCl or 1.2 HBr adds on to triple bond of 26 to form halocinnamic acid which then condenses with 1 under acid catalysis to form 30 or 31.

(i) \[
\begin{align*}
&\text{2H}X \\
\text{condensation} &\text{ of 1 with 26 under acidic conditions} \\
\end{align*}
\]

(ii) \[
\begin{align*}
&\text{HX + HOOC-C=Ph} \\
&\text{condensation of 1 with 26 with p-toluenesulphonic acid} \\
\end{align*}
\]

(iii) \[
\begin{align*}
&\text{condensation of 1 with 26 in refluxing ethylene glycol} \\
\end{align*}
\]

(30 or 31) \(X=Cl\) or \(Br\)

To decide the mechanism of formation of 30 and 31 it is necessary to carry out the condensation of 1 with 26 under acidic conditions in which no halogen acid was used.

Attempted condensation of o-phenylenediamine sulphate (1.\(H_2SO_4\)) with 26 in refluxing ethylene glycol did not yield the expected 2-\([\beta\text{-phenylacetylenyl}]\) benzimidazole and gave back the starting materials. Similar treatment of 1 with 26 in ethylene glycol under reflux in the presence of p-toluenesulphonic acid led to the recovery of the starting materials. It may be mentioned here that condensation of 1.\(H_2SO_4\) with cinnamic acid in refluxing ethylene glycol gave 2a in 95% yield.

From the experiments done above, four important observations can be made. They are
(i) 1.2 HCl condenses with cinnamic acids in refluxing ethylene glycol to yield 2-styrylbenzimidazoles.

(ii) 1.2 HCl and 1.2 HBr respectively condense with 26 in refluxing ethylene glycol to form 30 and 31 respectively.

(iii) \( \text{H}_2\text{SO}_4 \) condenses with cinnamic acid in refluxing ethylene glycol to yield 2a.

(iv) \( \text{H}_2\text{SO}_4 \) does not condense with 26 to give 2-\([\beta\text{-phenylacetylenyl}]\) benzimidazole.

From the above data, it is clear that the condensation of 1.2 HX with 26 in refluxing ethylene glycol follows second mechanism proposed above, according to which the hydrogen halide first adds to the triple bond of 26 to form halocinnamic acid which then condenses with 1 to give 30 and 31 respectively. Since there is no possibility for the formation of halocinnamic acid in the condensation of \( \text{H}_2\text{SO}_4 \) with 26, no product is formed.

Based on these experiments, it may be inferred that 26 does not condense with 1 under the above described conditions and the reactivity of different acids to condense with 1 is as follows:

alkanoic acids > alkenoic acids > alkynic acids
Structures of 30 and 31

The addition of hydrohalic acids to 26 may be conceived to take place, on mechanistic considerations in the following manner.

$$\text{Ph}-\text{C} = \text{C} = \text{C} - \text{OH} \xrightarrow{\text{X}^-} \text{Ph}-\text{C} = \text{C} = \text{C} - \text{OH} + \text{H}^+ \xrightarrow{\text{X}^-} \text{Ph}-\text{C} = \text{C} = \text{C} - \text{OH}$$

The halocinnamic acids obtained above may then be imagined to condense with 1 resulting in a halostyrylbenzimidazoles shown below.

Thus, the products obtained in the condensation of 26 with 1.2 HX in ethylene glycol under reflux may be assigned the structures (30, X=Cl; 31, X=Br) given above. It may be mentioned here that the product obtained in the condensation of 25 (which has been prepared earlier and whose structure was unambiguously assigned above) with 1.2 HCl in refluxing ethylene glycol has 2-α-bromostyrylbenzimidazole structure (32). The compound 32 has been characterised by its spectral and analytical data. Thus, its IR spectrum (Fig-61) showed peaks at 2850 (vb, m, -NH), 1620 (w), 1590 (vw), 1500 (w), 1490 (w), 1450(m) 1410 (s), 1300(m), 1270 and 1260 (d,m) cm⁻¹ etc.
Its $^1$H-NMR in CDCl$_3$ (Fig-62) showed resonances at $\delta$ 7.29 - 7.80 (complex m, 9H, five phenyl protons and four aryl protons), 8.49 (s, 1H, vinylic proton). Its electron impact mass spectrum (Fig -63) showed peaks at m/z (%I) 298 and 300 (44 and 26.5, M$^+$ corresponding to $^{79}$Br and $^{81}$Br), 297 and 299 (100 and 64.7, M–1), 220 (14.7), 219 (47), 218 (29.4), 189 (9), 190 (6), 167(11.8), 149 (32.4), 77 (17.64), 63 (32.4) etc. Further more, the two products 31 and 32 were found to be different from each other in m.ps and IR spectra but showed identical $R_f$ values on tlc. Based on these considerations, the structures of these compounds 31 and 32 are as follows:

![Chemical Structure 31](image1)

(31) (assigned)

![Chemical Structure 32](image2)

(32) (authentic)

Analogously, the structure of 30 may be considered to be as shown below.

![Chemical Structure 30](image3)

32 on treatment with potassium tert. butoxide in DMSO at 100° yielded a compound having m.p. 207-9°. Its IR in KBr (Fig - 64) showed peaks at ~2800 (vb, m, –NH), 1600 (vww), 1570 (vww), 1500 (w), 1470 (w), 1420 (m), 1400 (s), 1350 (s), 1300 (m), 1250 (w), 1220 (w) cm$^{-1}$ etc. Its $^1$H-NMR in DMSO (Fig - 65) showed signals at $\delta$ 7.22 - 7.30 (m, 2H, two protons of the aryl ring), 7.4 - 7.5 (complex m, 5H, phenyl protons), 7.56 - 7.64 (m, 2H, two protons of the aryl ring), 12.87 (broad s, 1H,
(EXPANDED SPECTRUM)
Its $^{13}$C-NMR (Fig -66) showed resonances at δ 80.749 (acetylenic carbon), 90.604 (acetylenic carbon), 120.690, 122.813, 128.691, 129.599, 131.580, 134.775 (six phenyl carbons, six aryl carbons and one imidazole quaternary carbon). Its electron impact mass spectrum recorded at 70 eV (Fig -67) showed peaks at m/z (%I) 219 (26, M+1), 218 (100, M$^+$), 217 (4, M−1), 216 (2, M−2), 190 (1), 128 (0.9), 127 (1.5), 116 (1), 114 (2.8), 109 (6), 91 (0.7), 84 (1.4), 63 (1.7) HRMS found = 218.0829 ± 0.0008 amu; calcd for C$_{15}$H$_{10}$N$_2$ was 218.0844 amu. Based on this data, the compound was assigned the structure 2-[[β-phenylacetylenyl] benzimidazole (33).

![Chemical structure of 33](image)

The structure of 33 was further confirmed by its hydrogenation to 2-β-phenylethylbenzimidazole (34) with 10% Pd-C in methanol, which has same m.p., mmp, tlc and superimposable IR spectrum with an authentic sample prepared by condensation of 1.2 HCl with dihydrocinnamic acid in refluxing ethylene glycol.

![Chemical structure of 34](image)
Relative intensity

% Relative intensity

FIG. 67
Similarly 30 and 31 on treatment with potassium tert. butoxide in DMSO at 100° yielded 33.

\[ \text{Chart- 5} \]

**Mass Spectral Study**

The mass spectra of 2-β-methylstyrylbenzimidazole (28), 2-β-phenylstyrylbenzimidazole (29) and 2-β-phenylacetylenylbenzimidazole (33) have been studied critically as representative cases.

The mass spectrum of 28 (Chart- 5) shows the molecular ion as fairly intense peak at m/z 234 (46%) which looses hydrogen to form an ion (28a) at m/z 233 as the base peak, similar to 2a and 10a. The molecular ion (M⁺) looses a phenyl radical and a molecule of acetylene (77+26=103 amu) to form an ion (28b) at m/z 131 (3.5%). Loss of phenyl and hydrogen radicals (77+1=78 amu) from M⁺ yields the ion 28c at m/z 156 (4%). A loss of methyl radical (15 amu) from M⁺ yields a reasonably
intense ion $28d$ at m/z 219 (8.85%) which looses phenylacetylene molecule (102 amu) to form benzimidazole ion ($28e$) at m/z 117 (3.5%) and benzimidazole radical (117 amu) to form phenylacetylene radical ion ($28f$) at m/z 102 (4.4%). The ion $28g$ at m/z 115 (10.6%) is assumed to be formed by the loss of one hydrogen radical, one phenyl radical and a molecule of acetylene (1+77+26=104 amu) from $28d$. The ion $28a$ looses a methyl radical (15 amu) to form the reasonably intense ion $28h$ at m/z 218 (7%). The ion $28i$ at m/z 128 (3.5%) is probably formed by the loss of four molecules of acetylene and one hydrogen radical (104 +1= 105 amu) from $28a$. The ion $28a$ looses two hydrogen atoms to form the ion $28j$ at m/z 231 (4.6%). Loss of 4-Methylquinoline radical (142 amu) from $28a$ gives the benzoaziridine radical ion $28k$ at m/z 91 (6.2%) which further looses a hydrogen atom to form the ion $28l$ at m/z 90 (3.5%). Apart from these peaks, the mass spectrum of $28$ shows a doubly charged ion at m/z 109 (4%).

The mass spectrum of $29$ (Chart-6) shows the molecular ion as reasonably good intense peak at m/z 296 (29.7%) which looses hydrogen to form an ion $29a$ at m/z 295 as the base peak as in the case of other 2-styrylbenzimidazoles. The ion $29b$ at m/z 219 (9.7%) is formed either by the loss of phenyl radical (77 amu) from the molecular ion or by the loss of benzyne unit (76 amu) from $29a$. Formation of radical ion $29c$ at m/z 218 (4.9 %) may be explained either by the loss of benzyne unit and a hydrogen radical (76+1=77 amu) from $29a$ or by the loss of hydrogen atom from $29b$. The benzoaziridine radical ion $29d$ at m/z 91 (3.1%) is formed by the loss of 4-phenylquinoline radical (204 amu) from $29a$. The ion $29e$ at m/z 293 (7.1%) is probably formed by the loss of two atoms of hydrogen from $29a$ as shown in Chart-6.
The mass spectrum of 33 shows molecular ion as the base peak at m/z 218 which looses hydrogen atom to form a feeble ion 33a at m/z 217 (4%). This is in contrast to the 2-styrylbenzimidazoles which showed the (M−1) ion as the base peak due to formation of highly resonance stabilised benzimidazoquinoline ion. Formation of benzimidazoquinoline ion is not possible in case of 33 due to 'sp' character of \(-\text{C}^*\text{C}-\). The radical ion 33b at m/z 114 (2.8%) is formed either by loss of four molecules of acetylene (104 amu) or by loss of phenyl radical, acetylene molecule and a hydrogen atom (77+26+1 = 104 amu) from the molecular ion (M+) as in the case of 33c. The ion 33d at m/z 128 (0.9%) is formed by the loss of benzoaziridine free radical (90 amu) from 33 and the ion 33e at m/z 127 (1.5%) is formed by the loss of benzoaziridine molecule (91 amu) from 33. The M+ looses a phenylacetylene molecule (102 amu) to form the benzimidazole radical ion 33f at m/z 116 (1%) which further looses two molecules of acetylene to form the ion 33g at m/z 64 (1.4%). The very feeble benzoaziridine radical ion 33h at m/z 91 (0.7%) is probably formed by the loss of 127 amu from M+. The ion 33i looses a hydrogen atom to form the ion 33i at m/z 216 (2%) which further looses a molecule of acetylene (26 amu) to form the ions 33j or 33k at m/z 190 (1%). Apart from these peaks the mass spectrum of 33 shows a modestly intense doubly charged ion at m/z 109 (6%).

Finally, it may be said that the above work completes the projected aim of the synthesis of 2-[β-phenylacetylenyl] benzimidazole. By using substituted phenylpropiolic acids, extensive work may be done in future to prepare various 2-[β-arylacetylenyl] benzimidazoles which may be subjected to biological activity screening.
CHART 6

(m/z 218, 4.9%)  
(29c)

(m/z 296, M⁺; 29.7%)  
(29a)

(m/z 219, 9.7%)  
(29b)

(m/z 91, 3.1%)  
(29d)

(m/z 293, 7.1%)  
(29e)

(29f)

(29g)
EXPERIMENTAL SECTION

(i) Preparation of 26

(a) Preparation of 24 from trans-cinnamic acid

To a refluxing solution of trans-cinnamic acid (7.4 gms, 50 mM) in CCl₄ (200 ml) was added, slowly, dropwise, a solution of bromine (3 ml, 55 mM) in CCl₄ (10 ml) during a period of 30 mts. After the complete addition, the reaction mixture was cooled to RT. The solid that separated was filtered, washed with CCl₄ and dried. A sample of this material was recrystallised from boiling benzene to obtain pure 24. Yield = 14.8 gms (96.7%), m.p=200–01°(Lit'. mp=203–04°).

(b) Preparation of 25 from 24

A solution of KOH (1.684 gms, 30 mM) in CH₃OH (25ml) was added at RT to solid 24 (4.62 gms, 15 mM) in an evaporating china dish. The contents were heated on waterbath till all the methanol was evaporated. The residue was dissolved in water (40 ml) and pH of the solution was adjusted to 3.0–4.0 with conc. HCl. The mixture was cooled, and the separated solid was filtered, washed with cold water (2x20 ml) and dried. Yield = 1.906 gms (56%). A portion of this product was recrystallised from hot benzene. m.p=98–100°.
(c) Preparation of 26 from 25

A solution of KOH (1.0 gm, 18 mM) in CH₃OH (15 ml) was added at RT to solid 25 (1.13 gms, 5 mM) in an evaporating china dish. The contents were heated on water bath till all the methanol was evaporated. The residue was dissolved in H₂O (25 ml) and pH was adjusted to 3–4 with conc. HCl. The solid, which separated after cooling, was filtered, washed with cold water (2x5 ml) and dried. Yield = 0.42 gm (57.5%). A sample of this product was recrystallised from hot CCl₄ to obtain pure 26. m.p = 132–34° (Lit'. mp = 134–35°).

(d) Preparation of 26 from 24

A solution of KOH (5 gms, 90 mM) in CH₃OH (20 ml) was added at RT to solid 24 (5 gms, 16.3 mM) in an evaporating china dish. The contents were heated on water bath till all the methanol was evaporated. Once again, methanol (20 ml) was added to the contents in the china dish and heated on water bath until all the methanol evaporated off. The residue was then dissolved in water (30 ml) and pH of the solution was adjusted to 3–4 with conc. HCl. The mixture was cooled, the separated solid filtered, washed with water (2x5 ml) and dried. Yield = 1.4 gms (58.7%). A sample of this product was recrystallised from hot CCl₄ to obtain pure 26. m.p = 132–34° (Lit'. mp=134–35°).
(ii) Preparation of 1.2 HCl

1 (28 gms, 0.26 mole) was dissolved in aq.HCI (60%, 100 ml) and heated to boiling. The solution was treated with charcoal (2 gms) and the mixture heated for further 5 mts. Then, the solution was filtered while hot. To the filtrate was added conc. HCl (100 ml) and the mixture cooled in ice-chest. The colourless, separated solid was filtered, washed with conc. HCl and dried in a vacuum desiccator over NaOH. Yield = 33.9 gms (72%).

(iii) Preparation of cinnamic acids

a) Cinnamic acids: A mixture of aromatic aldehyde (20 mM), malonic acid (40 mM), piperidine (0.4 ml) and pyridine (10 ml) was heated on waterbath for a period of 6 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into ice-cold aq.HCI (20%, 50 ml). The separated solid was filtered, washed with water, dried and recrystallised to obtain pure substituted cinnamic acids (please see Table - 33).

b) α-Methylcinnamic acids: A mixture of aromatic aldehyde (20 mM) methylmalonic acid (40 mM), piperidine (40 mM) and pyridine (2.5 ml) was heated on steam bath for the length of time given in Table - 33. At the end of this period, the reaction mixture was cooled to RT and poured into ice-cold aq.HCI (50%, 12 ml). The separated solid was filtered, washed with water, dried and recrystallised to obtain pure substituted α-methyl cinnamic acids. For details, please see Table - 34.
Table - 33 : Preparation of substituted cinnamic acids

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Aromatic aldehyde used</th>
<th>Maconic acid</th>
<th>Pyridine</th>
<th>Piperidine</th>
<th>Yield (%)</th>
<th>Rem solvent</th>
<th>M.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-Toluicdehyde (2.4 gms, 20 mM)</td>
<td>4.16 gms (40 mM)</td>
<td>10 ml</td>
<td>0.4 ml</td>
<td>93</td>
<td>gl. AcOH</td>
<td>197 - 98° (Lit m.p=196-97°)</td>
</tr>
<tr>
<td>2</td>
<td>o-Chloro benzaldehyde (2.5 gms, 20 mM)</td>
<td>4.16 gms (40 mM)</td>
<td>10 ml</td>
<td>0.4 ml</td>
<td>95</td>
<td>Aq. MeOH</td>
<td>205 - 8° (Lit m.p=212°)</td>
</tr>
<tr>
<td>3</td>
<td>p-Chloro benzaldehyde (2.8 gms, 20 mM)</td>
<td>4.16 gms (40 mM)</td>
<td>10 ml</td>
<td>0.4 ml</td>
<td>93</td>
<td>gl. AcOH</td>
<td>250° (Lit m.p=245°)</td>
</tr>
<tr>
<td>4</td>
<td>m-Nitro benzaldehyde (3.02 gms, 20 mM)</td>
<td>4.16 gms (40 mM)</td>
<td>10 ml</td>
<td>0.4 ml</td>
<td>90</td>
<td>Aq. MeOH</td>
<td>198 - 200° (Lit m.p=200-01°)</td>
</tr>
<tr>
<td>5</td>
<td>p-Nitro benzaldehyde (3.02 gms, 20 mM)</td>
<td>4.16 gms (40 mM)</td>
<td>10 ml</td>
<td>0.4 ml</td>
<td>90</td>
<td>gl. AcOH</td>
<td>250° (Lit m.p=295°)</td>
</tr>
<tr>
<td>Aromatic aldehyde used</td>
<td>Methyl malonic acid</td>
<td>Pyridine</td>
<td>Piperidine</td>
<td>Reaction time (hrs)</td>
<td>Structure of cinnamic acid obtained</td>
<td>Yield (%)</td>
<td>Rem. solvent</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>-----------</td>
<td>---------------------</td>
<td>--------------------------------------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Benzaldehyde (2.1 gms, 20 mM)</td>
<td>4.72 gms (40 mM)</td>
<td>2.5 ml</td>
<td>3.5 ml</td>
<td>27</td>
<td><img src="image" alt="structure" /></td>
<td>90</td>
<td>aq alcohol</td>
</tr>
<tr>
<td>p-Toluic acid (2.4 gms, 20 mM)</td>
<td>4.72 gms (40 mM)</td>
<td>2.5 ml</td>
<td>3.5 ml</td>
<td>42</td>
<td><img src="image" alt="structure" /></td>
<td>60</td>
<td>aq alcohol</td>
</tr>
<tr>
<td>o-Chloro benzaldehyde (2.8 gms, 20 mM)</td>
<td>4.72 gms (40 mM)</td>
<td>2.5 ml</td>
<td>3.5 ml</td>
<td>15</td>
<td><img src="image" alt="structure" /></td>
<td>84</td>
<td>aq alcohol</td>
</tr>
<tr>
<td>p-Chloro benzaldehyde (2.8 gms, 20 mM)</td>
<td>4.72 gms (40 mM)</td>
<td>2.5 ml</td>
<td>3.5 ml</td>
<td>24</td>
<td><img src="image" alt="structure" /></td>
<td>95</td>
<td>aq alcohol</td>
</tr>
<tr>
<td>m-Nitro benzaldehyde (3.02 gms, 20 mM)</td>
<td>4.72 gms (40 mM)</td>
<td>2.5 ml</td>
<td>3.5 ml</td>
<td>10</td>
<td><img src="image" alt="structure" /></td>
<td>99</td>
<td>aq alcohol</td>
</tr>
<tr>
<td>p-Nitro benzaldehyde (3.02 gms, 20 mM)</td>
<td>4.72 gms (40 mM)</td>
<td>2.5 ml</td>
<td>3.5 ml</td>
<td>24</td>
<td><img src="image" alt="structure" /></td>
<td>85</td>
<td>aq alcohol</td>
</tr>
</tbody>
</table>
c) α-phenylcinnamic acid: A mixture of benzaldehyde (8.1 ml, 80 mM), phenylacetic acid (10.9 gms, 80 mM), acetic anhydride (16 ml, 160 mM) and anhydrous triethylamine (8.6 ml, 85 mM) was refluxed for 5 hrs. At the end of this period, the reaction mixture was steam distilled till the distillate was clear. The residue was dissolved in aq. ethanol (50%, 200 ml), charcoal (2 gms) was added and the mixture was heated to boiling. The hot solution was filtered and the filtrate acidified immediately with HCl (1:1) to a pH of 3-4. The separated solid was cooled, filtered, washed with water (2x25 ml) and dried. Yield = 9.86 gms (55%). This was recrystallised from aq. ethanol to obtain pure α-phenylcinnamic acid, m.p = 171-73°C (Lit12, mp=172-73°C).

d) β-Methylcinnamic acid:

Ethyl-β-phenyl-β-methyl-β-hydroxy propionate: A mixture of acetophenone (12 gms), ethylbromoacetate (20 gms) and zinc powder (8 gms) in benzene (75 ml) was warmed gently to start the vigorous reaction. After the initial vigorous reaction subsided, the mixture was refluxed for a further period of 1 hr. At the end of this period, the reaction mixture was cooled to RT, the reaction was quenched with dil H₂SO₄ (20%, 40 ml), organic layer separated, washed with dil H₂SO₄ (10%, 50 ml), dried over CaCl₂ and the solvent distilled under vacuum to yield ethyl β-phenyl-β-methyl-β-hydroxy propionate as colourless oil. Yield = 18.0 gms (86.5%).

Ethyl β-methylcinnamate: A solution of the above hydroxy ester (18.0 gms) and
POCl₃ (6 ml) in anh. C₆H₆ (80 ml) was refluxed for 20–25 mts. At the end of this period, the reaction mixture was cooled to RT, washed with water (2x15 ml). The organic layer was dried (CaCl₂) and distilled under vacuum to yield ethyl β-methylcinnamate as colourless oil. Yield = 14.2 gms (86.4%).

β-Methylcinnamic acid: To a solution of ethyl β-methylcinnamate (14.2 gms) in ethanol (40 ml), aq. KOH (50%, 10 ml) was added and refluxed for 2 hrs. At the end of this period, the reaction mixture was cooled to RT, diluted with water (200 ml) and extracted with ether (1 x 25 ml). The aq. layer was concentrated to remove the dissolved alcohol and acidified with HCl (1:1). The separated product which is β-methylcinnamic acid, was filtered, washed with water and dried. Yield = 9.4 gms (77.7%). This was recrystallised from aq. alcohol to get a pure product, m.p = 95–96°C (Lit. mp=97°C).

e) β-phenylcinnamic acid:

Ethyl β, β-diphenyl-β-hydroxypropionate: A mixture of zinc powder (6 gms), copper powder (0.5 gm), benzophenone (15 gms), and ethylbromoacetate (16.5 gms) in C₆H₆ (70 ml) was refluxed for 1 hr. At the end of this period, the reaction mixture was cooled to RT, the reaction was quenched with dil. H₂SO₄ (20%, 60 ml), organic layer separated, washed with dil. H₂SO₄ (20%, 50 ml), aq. Na₂CO₃ (50 ml), dried over CaCl₂ and the solvent evaporated to yield ethyl β, β-diphenyl-β-hydroxy propionate. Yield = 13 gms (58.5%), m.p=85°C (Lit. mp=87°C)
\(\beta,\beta\)-Diphenyl-\(\beta\)-hydroxypropionic acid: Ethyl \(\beta, \beta\)-diphenyl-\(\beta\)-hydroxy propionate (13 gms) was dissolved in methanolic KOH (5 gms of KOH in 20 ml of CH\(_3\)OH) solution and refluxed for 12 hrs. At the end of this period, methanol was evaporated and water was added. The reaction mixture was filtered and the filtrate acidified with AcOH. The separated solid was filtered, washed with water (2x10 ml) and dried. Yield = 10 gms (86%), m.p = 216–17°C (Lit\(^{13\text{a}}\). m.p = 218°C).

\(\beta\)-Phenylcinnamic acid: A mixture of \(\beta, \beta\)-diphenyl-\(\beta\)-hydroxypropionic acid (8 gms) and anhyd. sodium acetate (2 gms) in AcOH (5 ml) was refluxed for 3 hrs. At the end of this period, the reaction mixture was cooled to RT and dissolved in aq. Na\(_2\)CO\(_3\) (50 ml). The solution was acidified with AcOH. The separated solid was filtered, washed with water (2x10 ml) and dried. Yield = 3.2 gms (43%) m.p = 162°C (Lit\(^{13\text{b}}\). m.p = 162°C).

(iv) Condensation of 1.2 HCl with cinnamic acids to obtain 2, 10, 27, 28 and 29 (General procedure): 1.2 HCl (1.81 gms, 10 mM) and cinnamic acid (10 mM) were refluxed in ethylene glycol (8 ml) for a period of 5 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into water (100 ml). The separated solid was filtered, resuspended in water (50 ml) and neutralised with NaHCO\(_3\). The product which is 2/10/27/28/29 was filtered washed with water, dried and recrystallised from a suitable solvent (For details please see Table -35).
Table 35: Condensation of 1.2 HCl with Cinnamic acids in refluxing ethylene glycol to get 2, 10, 27, 28 and 29

<table>
<thead>
<tr>
<th>S.No</th>
<th>Cinnamic acid</th>
<th>Product used</th>
<th>Yield (%)</th>
<th>Reaction solvent</th>
<th>M.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cinnamic acid</td>
<td>2a</td>
<td>85</td>
<td>Toluene</td>
<td>203-05°</td>
</tr>
<tr>
<td>2</td>
<td>p-Methylcinnamic acid</td>
<td>2b</td>
<td>78</td>
<td>aq.CH₃OH</td>
<td>214-16°</td>
</tr>
<tr>
<td>3</td>
<td>o-Chlorocinnamic acid</td>
<td>2c</td>
<td>88</td>
<td>aq.CH₃OH</td>
<td>176-78°</td>
</tr>
<tr>
<td>4</td>
<td>p-Chlorocinnamic acid</td>
<td>2d</td>
<td>82</td>
<td>aq CH₃OH</td>
<td>221-23°</td>
</tr>
<tr>
<td>5</td>
<td>m-Nitrocinnamic acid</td>
<td>2e</td>
<td>84</td>
<td>EtOAc+ Hexane</td>
<td>219-20°</td>
</tr>
<tr>
<td>6</td>
<td>p-Nitrocinnamic acid</td>
<td>2f</td>
<td>86</td>
<td>AcOH</td>
<td>260-02°</td>
</tr>
<tr>
<td>7</td>
<td>α-Methylcinnamic acid</td>
<td>10a</td>
<td>75</td>
<td>CH₃OH</td>
<td>242-44°</td>
</tr>
<tr>
<td>8</td>
<td>4-Methyl-α-methyl cinnamic acid</td>
<td>10b</td>
<td>82</td>
<td>EtOAc+ Hexane</td>
<td>178-80°</td>
</tr>
<tr>
<td>9</td>
<td>2-Chloro-α-methyl cinnamic acid</td>
<td>10c</td>
<td>76</td>
<td>aq.CH₃OH</td>
<td>264-65°</td>
</tr>
<tr>
<td>10</td>
<td>4-Chloro-α-methyl cinnamic acid</td>
<td>10d</td>
<td>83</td>
<td>EtOAc+ Hexane</td>
<td>223-25°</td>
</tr>
<tr>
<td>11</td>
<td>3-Nitro-α-methyl cinnamic acid</td>
<td>10e</td>
<td>80</td>
<td>aq.i-propanol</td>
<td>231-33°</td>
</tr>
<tr>
<td>12</td>
<td>4-Nitro-α-methyl cinnamic acid</td>
<td>10f</td>
<td>88</td>
<td>aq.CH₃OH</td>
<td>294-95°</td>
</tr>
<tr>
<td>13</td>
<td>α-Phenylcinnamic acid</td>
<td>27</td>
<td>78</td>
<td>aq.CH₃OH</td>
<td>281-83°</td>
</tr>
<tr>
<td></td>
<td>(% Nitrogen found = 9.44, calculated for C₁₀H₈N₂=9.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>β-Methylcinnamic acid</td>
<td>28</td>
<td>80</td>
<td>aq.CH₃OH</td>
<td>195 96°</td>
</tr>
<tr>
<td></td>
<td>(% Nitrogen found = 11.94, calculated for C₁₅H₁₈N₂=11.95)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>β-Phenylcinnamic acid</td>
<td>29</td>
<td>86</td>
<td>C₆H₆+Hexane</td>
<td>102-04°</td>
</tr>
<tr>
<td></td>
<td>(% Nitrogen found = 9.44, calculated for C₁₅H₁₈N₂=9.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(v) Condensation of 1.2 HCl with 26 to obtain 30

1.2 HCl (1.81 gms, 10 mM) and 26 (1.46 gms, 10 mM) was refluxed in ethylene glycol (8 ml) for a period of 5 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into water (100 ml). The separated solid was filtered, resuspended in water (50 ml) and neutralised with NaHCO₃. The product, which is 30, was filtered, washed with water (2 x 10 ml) and dried. Yield of 30 was 1.78 gms (70%). This was recrystallised from aq. methanol followed by benzene to obtain pure 30, m.p=179–80° (% Nitrogen found = 10.987; calculated for C₁₅H₁₁ClN₂=10.998). 

(vi) Preparation of 1.2 HBr

To a solution of 1 (5.4 gms, 50 mM) in 1,4-dioxan (60 ml) at RT was slowly added, dropwise a solution of hydrobromic acid (48%). This addition of HBr was continued till there is no more separation of solid (~20-25 ml) The solution was cooled to 0–5°. filtered, washed with dioxan (2x5 ml) followed by C₆H₆ (2x10 ml) and dried. Yield = 8.5 gms (63%), m.p = >260° (% Nitrogen found = 10.35; calculated for C₆H₁₀Br₂N₂ = 10.37).

(vii) Condensation of 1.2 HBr with 26 to obtain 31

1.2 HBr (2.68 gms, 10 mM) and 26 (1.46 gms, 10 mM) was refluxed in ethylene glycol (8 ml) for a period of 5 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into water (100 ml). The separated solid was filtered,
resuspended in water (50 ml) and neutralised with NaHCO₃. The product, which is 31, was filtered, washed with water (2x10 ml) and dried. Yield = 2.1 gms (70%). This was recrystallised from aq. methanol followed by C₆H₅ to obtain pure 31, mp = 159-60° (% Nitrogen found = 9.35; calculated for C₁₅H₁₁BrN₂ = 9.36).

(viii) Condensation of 1.2 HCl with 25 to obtain 32

1.2 HCl (1.81 gms, 10 mM) and 25 (2.26 gms, 10 mM) was refluxed in ethylene glycol (8 ml) for a period of 5 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into cold water (100 ml). The separated solid was filtered, resuspended in water (50 ml) and neutralised with NaHCO₃. This was extracted with ether and ether layer was evaporated to get a residue. This residue was dissolved in i-propanol (15 ml) and treated with a solution of oxalic acid (1.5 gms) in i-propanol (10 ml). The separated solid (which is oxalate salt of 32) was filtered, resuspended in water (20 ml) and neutralised with NaHCO₃. This product was then filtered, washed with water (2x10 ml), dried and recrystallised from benzene + n-hexane to obtain 32. Yield = 1.55 gms (52%), mp = 163-65° (% Nitrogen found = 9.34; calculated for C₁₅H₁₁BrN₂ = 9.36).

(ix) Reaction of 30/31/32 with potassium tert.butoxide in DMSO to obtain 33

A mixture of 30/31/32 (10 mM), pot. tert. butoxide (2.24 gms, 20 mM) in DMSO (30 ml) was heated on waterbath at 100° for a period of 4-5 hrs. At the end of this period, the reaction mixture was cooled to RT, and poured into water (150 ml).
pH of the solution was adjusted to 6-7 with AcOH. The separated solid was filtered, washed with water, dried and recrystallised from CH₃OH.

Yield of 33 from 30 was 1.92 gms (88%), yield of 33 from 31 was 1.85 gms (85%), yield of 33 from 32 was 1.875 gms (86%). The m.p of 33 obtained in each case was 207–09° (% Nitrogen found =12.81; calculated for C₁₅H₁₀N₂=12.835)

(x) Reduction of 33 to obtain 34

33 (1.09 gms, 5 mM) was dissolved in CH₃OH (50 ml) and Pd-C (10%, 0.3 gm) was added. The mixture was transferred to a hydrogenation bottle and shaken with hydrogen gas (40 psi) in a parr-hydrogenator for 2 hrs at RT. At the end of this period, the mixture was filtered to remove the catalyst. The filtrate was evaporated to dryness giving the product i.e 34 as fine solid. Yield = 1.08 gms (97%). A portion of this solid was recrystallised from aq.methanol to obtain pure 34, m.p = 187–89°. mmp (187–89°) co-tlc and IR spectrum were identical with an authentic sample (see xi below).

(xi) Synthesis of 34

A mixture of 1.2 HCl (1.81 gms, 10 mM) and dihydrocinnamic acid (1.50 gms, 10 mM) was refluxed in ethylene glycol (8 ml) for a period of 5 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into water (100 ml). The pH of the solution was neutralised to >7 with NaHCO₃. The separated solid was
filtered, washed with water and dried. Yield = 2.1 gms (95%). A portion of this product was recrystallised from aq.CH₃OH to obtain pure 34. m.p = 188–89° (Lit⁶. mp = 188–89°)

**IR (KBr) ν, cm⁻¹**

- ~2800 (vb, m, –NH), 1620 (vw), 1600 (vwv), 1530 (m), 1500 (w), 1460 (vs), 1420 (vs), 1320 (w), 1270 (m), 1220 (w) etc.

**¹H-NMR (CDCl₃/TMS)**

δ 3.14–3.27 (m, 4H, –CH₂CH₂–) 7.18–7.58 (complex m, 9H, four aryl protons and five phenyl protons).

(xii) Preparation of 1.H₂SO₄

To a solution of 1 (5.4 gms, 50 mM) in CH₃OH (50 ml), conc. H₂SO₄ (4ml) was added, very slowly, dropwise under ice-cold conditions, during a period of 30 mts. After the completion of addition, the separated product, which is 1.H₂SO₄ was filtered, washed with methanol (2x5 ml) followed by benzene (2x10ml) and dried. Yield = 7.21 gms (70%) (% Nitrogen found = 13.565; calculated for C₆H₁₀N₂O₄S = 13.58).

(xiii) Condensation of 1.H₂SO₄ with cinnamic acid to obtain 2a

A mixture of 1.H₂SO₄ (2.06 gms, 10mM) and cinnamic acid (1.46 gms, 10 mM) in ethylene glycol (8 ml) was refluxed for a period of 3 hrs. At the end of this period, the reaction mixture was cooled to RT and poured into water (100 ml). The pH of the solution was adjusted to > 7 with NaHCO₃. The separated solid was filtered, washed with water (2x10 ml), dried and recrystallised from boiling toluene to obtain pure 2a, Yield = 2.1 gms (95%), m.p = 203–05°.
REFERENCES


4. For a detailed discussion on mechanism of elimination reactions, the following may be referred:


