Condensation of \(\alpha\)-phenylenediamine with phenylpropionic acid

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We have reported earlier\(^1\) that bromination of 2-styrylbenzimidazoles, in order to saturate the double bond, and then dehydrobrominate it with a view to preparing 2-\(\beta\)-phenylacetylenylbenzimidazole under a variety of conditions such as in refluxing methanol, in hot PPA, in refluxing benzene with Dean-stark removal of water etc., leads to the recovery of starting materials. However, condensation of \(\alpha\)-phenylenediamine dihydrochloride and dihydrobromides with phenylpropionic acid in refluxing ethylene glycol yield the respective 2-haloarylvinylbenzimidazoles. The latter are dehydrohalogenated under basic conditions to obtain the desired 2-\(\beta\)-phenylacetylenylbenzimidazole. The mechanism of formation of 2-haloarylvinylbenzimidazoles has been discussed.

Condensation of \(\alpha\)-phenylenediamine with phenylpropionic acid was carried out to prepare 2-\(\beta\)-phenylacetylenylbenzimidazole under a variety of conditions such as in refluxing methanol, in hot PPA, in refluxing benzene with Dean-stark removal of water etc., leading to the recovery of starting materials. However, condensation of \(\alpha\)-phenylenediamine dihydrochloride and dihydrobromides with phenylpropionic acid in refluxing ethylene glycol yielded the respective 2-haloarylvinylbenzimidazoles. The latter were dehydrohalogenated under basic conditions to obtain the desired 2-\(\beta\)-phenylacetylenylbenzimidazole. The mechanism of formation of 2-haloarylvinylbenzimidazoles has been discussed.

Results and Discussion

Attempted condensation of \(\alpha\)-phenylenediamine 1 or its sulphate salt (1\(\text{H}_2\text{SO}_4\)) respectively, with phenylpropionic acid 2 in refluxing ethylene glycol did not yield the expected 2-\(\beta\)-phenylacetylenylbenzimidazole and gave back the starting materials. Similar treatment of 1 with 2 in ethylene glycol under reflux in the presence of \(p\)-toluenesulphonic acid led to the recovery of starting materials.

However, treatment of \(\alpha\)-phenylenediamine dihydrochloride (1\(\text{H}_2\text{Cl}\)) with 2 in refluxing ethylene glycol followed by simple processing gave a compound (homogenous on TLC) having m.p. 159-60\(^\circ\). Its IR in KBr showed peaks at 2800 (vb, m, -NH), 1620 (vw), 1532 (w), 1412 (s), 1362 (m), 1321 (w), 1235 (w), 1017 (w) cm\(^{-1}\). Its \(^1\)H NMR in CDCl\(_3\) recorded at 400 MHz exhibited signals at \(\delta\) 7.28-7.83 (complex m, five phenyl, four aryl and one vinylic proton). Its \(^13\)C NMR showed resonances at \(\delta\) 115.515, 116.480, 123.574, 126.680, 128.727, 129.923, 135.596, 137.109, 147.971 and 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 showed peaks at m/z (%I): 256 and 254 (6 and 28; \(M^+\) corresponding to \(^1\)Cl and \(^3\)Cl)), 255 and 253 (30 and 100, \(M^+\) corresponding to \(^1\)Cl and \(^3\)Cl)), 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; Calc. for \(C_{13}H_{10}ClN_2\) (M-1) : 253.0532 amu. Based on this data, the compound was assigned the structure 2-chlorostyrylbenzimidazole 3. Similarly, condensation of \(\alpha\)-phenylenediaminedihydrobromide (1, 2 HBr) with 2 in refluxing ethylene glycol yielded a compound (homogenous on TLC) having m.p. 159-60\(^\circ\). Its IR in KBr showed peaks at -2800 (vb, m, -NH), 1620 (vw), 1595 (vw), 1520 (vw), 1500 (vw), 1450 (m), 1440 (s), 1390 (vw), 1305 (vw), 1290 (w), 1230 (w) cm\(^{-1}\). Its \(^1\)H NMR in CDCl\(_3\) recorded at 400 MHz exhibited signals at \(\delta\) 7.31-7.73 (complex m, five phenyl, four aryl and one vinylic proton). Its \(^13\)C NMR showed resonances at \(\delta\) 115.532, 120.330, 123.666, 127.326, 127.746, 128.670, 129.840, 138.039, 139.145 and 148.152 (six phenyl carbons, six aryl carbons, two vinylic carbons and one imidazole quaternary carbon). Its electron impact
mass spectrum showed peaks at m/z (%I) 300 and 298 (25 and 30, M+ corresponding to 81Br and 79Br), 299 and 297 (100 and 93.3, M-1 corresponding to 81Br and 79Br), 219 (35), 218 (66), 217 (101), 190 (6.6), 128 (6.6), 109 (26.3), 102 (20), 77 (30), 76 (19), 65 (31.6), 64 (30), 63 (53.3), 52 (31.6), 51 (31.6), 50 (23.3) etc. Based on this data, the compound was assigned the structure 2-bromostyrylbenzimidazole 4. On the basis of the available spectral data, the stereochemical orientations of H and Cl and also their relative positions (α or β) could not be ascertained in 3 or 4.

Compound 3 on treatment with pot. tert. butoxide in DMSO at 100° yielded a compound having m.p. 207-9°. Its IR in KBr 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. Its ¹H NMR in DMSO-d₆ showed signals at 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, -NH). Its ¹³C NMR exhibited 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 showed peaks at m/z (%I) 219 (26, M+1), 218 (100, M⁺), 217 (4), 216 (2), 190 (1), 128 (0.9), 127 (1.5), 116 (1), 114 (2.8), 109 (6), 91 (0.7), 64 (1.4), 51 (1.7) HRMS: Found : 218.0829 ± 0.0008 amu; Calc. for C₁₃H₁₀N₂⁺ : 218.0844 amu. Based on this data, the compound was assigned the structure 2-β-phenylacetylenylbezimidazole 5. The structure of 5 was further confirmed by hydrogenation to the known 2-β-phenylethylbenzimidazole 6 with 10% Pd-C in methanol at RT, which was identical [m.p. (188-89°), mmp, TLC and superimposable IR spectrum] with an authentic sample prepared by condensation of 1, 2 HCl with dihydrocinnamic acid in refluxing ethylene glycol. Similar treatment of 4 with pot. tert. butoxide in DMSO at 100° yielded 5 (Scheme I).

**Mechanism of formation of 3 and 4**

To account for the formation of 3 from 1, 2 HCl and 2 and 4 from 1, 2 HBr and 2, the following two mechanisms have been proposed.

(i) 1, 2 HCl or 1, 2 HBr decomposes reversibly at refluxing temperature of ethylene glycol to form 1 and HX. 1 condenses with 2 which is catalysed by HX to form 5. Then the free HX adds on to the triple bond of 5 to form 3 or 4 (Scheme II).

(ii) The HX which is formed by the reversible decomposition of HCl or 1, 2 HBr adds on to triple bond of 2 to form halocinnamic acid which then condenses with 1 under acid catalysis to form 3 or 4 (Scheme III).

To decide between the two mechanisms, condensation of 1 with 2 under acidic conditions, in which no halogen is involved, was attempted. Since condensation of 1, H₂SO₄ with 2 led to the recovery of starting materials, it is clear that the condensation of 1, 2 HX with 2 in refluxing ethylene glycol follows second mechanism proposed above.
Structures of 3 and 4

The addition of hydrohalic acids to 2 may be conceived to take place on mechanistic consideration as shown in Scheme IV. The halocinnamic acids thus obtained condense with 1 to give β-halostyrylbenzimidazoles (Scheme V).

Thus, the products obtained by the condensation of 1, 2HX with 2 in ethylene glycol under reflux may be assigned structures 3 and 4 (Scheme V). Condensation of E-(α)-bromocinnamic acid7 with 1,2 HCl in refluxing ethylene glycol gave a product which has been assigned 2-α-bromostyrylbenzimidazole structure 8. The compound 8 has been characterised by its spectral and analytical data. Its IR spectrum 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. Its ¹H NMR in CDCl₃ showed signals at δ 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 recorded at 70 eV exhibited resonances at m/z (%) 298 and 300 (44 and 26.5, M⁺ corresponding to ⁷⁷Br and ⁷⁹Br), 297 and 299 (100 and 64.7, M-1), 220 (14.7), 219 (47), 218 (29.4), 190 (6), 189 (9), 167 (11.8), 149 (32.4), 77 (17.64), 63 (32.4) etc. Furthermore, the two products 4 and 8 were found to be different from each other in mps and IR spectra but showed identical Rf values on TLC. Compound 8 also on treatment with pot.tert.-butoxide in DMSO at 100° yielded 5 (Scheme VI). Based on this data the compounds 3 and 4 were assigned stereochemical structures as shown in Scheme V.

Experimental Section

All melting points are uncorrected and were determined using open capillary tubes in sulphuric acid bath. TLC was monitored on glass plates coated with Silica Gel-G and spotting was done using iodine

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\begin{align*}
\text{Scheme II} \\
2HX + \text{HOOC-C=C-Ph} & \rightarrow \text{HOOC-C=C-Ph} + HX \\
(2) \\
\text{Scheme III} \\
\text{NH}_2 + 2HX \rightarrow \text{NH}_2 \\
\end{align*}
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or UV lamp. IR spectra in KBr were recorded using Perkin-Elmer Model-446 instrument, $^1$H NMR and $^13$C NMR on a Bruker instrument operating at 400 MHz, 250 MHz and 62.9 MHz respectively and mass spectra on a CEC-21-110 Mass spectrometer under electron impact conditions. Compounds 2 and 7 were prepared using the method reported by us earlier.

Preparation of 1. 2 $HCl$. Compound 1 (28 g, 260 mmoles) was dissolved in aq. HCl (60%, 100 mL) and heated to boiling. The solution was treated with charcoal (2 g) and the mixture heated for further 5 min. 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 solid that separated was filtered, washed with conc. HCl and dried in a vacuum desiccator over NaOH, yield 33.9 g (72%).

Preparation of 1. 2 $HBr$. To a solution of 1 (5.4 g, 50 mmoles) 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 was no more separation of solid (20-25 mL). The solution was cooled to 0-5°, filtered, washed with dioxan (2 x 5 mL) followed by C$_6$H$_6$ (2 x 10 mL) and dried, yield 8.5 g (63%), m.p. > 260° (Found: N, 10.35. Calc. for C$_6$H$_{10}$Br$_2$N$_2$: N, 10.37%).

Condensation of 1. 2 $HX$ with 2 to obtain 3 and 4. 1. 2 $HX$ (10 mmoles) and 2 (1.46 g, 10 mmoles) was refluxed in ethylene glycol (8 mL) for 5 hr. The reaction mixture was then 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 was filtered, washed with water (2 x 10 mL) and dried. Recrystallisation from aq. CH$_3$OH followed by C$_6$H$_6$ gave 3, m.p. as 179-80°.
yield 1.78 g (70%) (Found: N, 10.987. Calc. for C₅H₁₁ClIN₂: N, 10.998%). Recrystallisation from aq. CH₃OH followed by C₆H₆ gave 4, m.p. 159-60°, yield 2.1 g (70%) (Found: N, 9.35. Calc. for C₅H₁₁BrN₂: N, 9.36%)

Condensation of 1. 2 HCl with 7 to obtain 8. Compound 1. 2 HCl (1.81 g, 10 mmoles) and 7 (2.26 g, 10 mmoles) was refluxed in ethylene glycol (8 mL) for a period of 5 hr. The reaction mixture was cooled to RT and poured into water (100 mL). The separated solid was filtered, washed with water (50 mL) and neutralised with NaHCO₃. This was extracted with ether and ether layer was evaporated. The residue obtained was dissolved in iso-propanol (15 mL) and treated with a solution of oxalic acid (1.5 g) in iso-propanol (10 mL). The separated solid (which is oxalate salt of 8) was filtered, washed with water (2x10 mL), dried and recrystallised from benzene + n-hexane to give 8. Yield 1.55 g (52%), m.p 163-65° (Found: N, 9.34. Calc. for C₅H₁₁BrN₂: N, 9.36%)

Reaction of 3/4/8 with pot.tert.butoxide in DMSO to obtain 5. A mixture of 3/4/8 (10 mmoles), pot.tert.butoxide (2.24 g, 20 mmoles) in DMSO (30 mL) was heated on a water-bath at 100° for 4-5 hr. The reaction mixture was cooled to RT, and poured into water (150 mL). The pH of the solution was adjusted to 6-7 with AcOH. The separated solid was filtered, washed with water, dried and recrystallised from CH₂OH to give 5, m.p. 207-9°. The yields of 5 from 3, 4 and 8 respectively were 1.92 g (88%), 1.85 g (85%) and 1.875 g (86%) (Found: N, 12.81 Calc. for C₅H₁₀N₂: N, 12.85%)

Reduction of 5 to obtain 6. Compound 5 (1.09 g, 5 mmoles) was dissolved in CH₂OH (50 mL) and Pd-C (10%, 0.3 g) was added. The mixture was transferred to a hydrogenation bottle and shaken with hydrogen gas (40 psi) in a parr-hydrogenator for 2 hr at RT. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated to dryness to give the product 6 as fine solid. Yield 1.08 g (97%). It was recrystallised from aq. CH₃OH to obtain pure 6, m.p 187-89°, mmp 187-89°, co-TLC and IR spectrum of 6 were identical with an authentic sample prepared by the method given below.

Synthesis of 6. A mixture of 1. 2 HCl (1.81 g, 10 mmoles) and dihydrocinamic acid (1.5 g, 10 mmoles) was refluxed in ethylene glycol (8 mL) for 5 hr. 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 and dried. Yield 2.1 g (95%). A portion of this product was recrystallised from aq.CH₂OH to obtain pure 6, m.p. 188-89° (Lit. 3 mp 188-89°). IR (KBr): ν 2800 (vb, m, -NH), 1620, 1600, 1530, 1500, 1460, 1420, 1320, 1270, 1220 cm⁻¹ etc.; ¹H NMR (CDCl₃ / TMS): δ 3.14-3.27 (m, 4H, -CH₂-CH₂-), 7.18-7.58 (complex m, 9H, four aryl protons and five phenyl protons).

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References