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# Studies on the Preparation of 2-Styrylbenzimidazole

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**Studies on the preparation of 2-styrylbenzimidazole by three different methods, namely, (i) condensation of *o*-phenylenediamine with cinnamic acid (dehydrative cyclisation), (ii) condensation of *o*-phenylenediamine with cinnamaldehyde (dehydrogenative cyclisation) and (iii) condensation of 2-methylbenzimidazole with benzaldehyde (styrylation) are reported. Optimum conditions are described for the styrylation of 2-methylbenzimidazole with benzaldehyde.**

Benzimidazoles are an important group of biologically active compounds[1]. Of these, the 2-substituted derivatives have been found to be most potent. This has stimulated further research into the syntheses of substituted benzimidazoles.

During our studies on the syntheses of benzimidazoles, we had the occasion to prepare 2-styrylbenzimidazole. A methyl group attached to the 2-position of benzimidazole ring system constitutes an activated methylene group as it is $\alpha$ to an $sp^2$ nitrogen similar to the one in $\alpha$-picoline[2]. Hence, it condenses with aromatic aldehydes yielding styryl derivatives. In this paper, we report our studies on the preparation of 2-styrylbenzimidazole by different methods and on the optimisation of conditions for the styrylation of 2-methylbenzimidazole with benzaldehyde.

## Results and Discussion

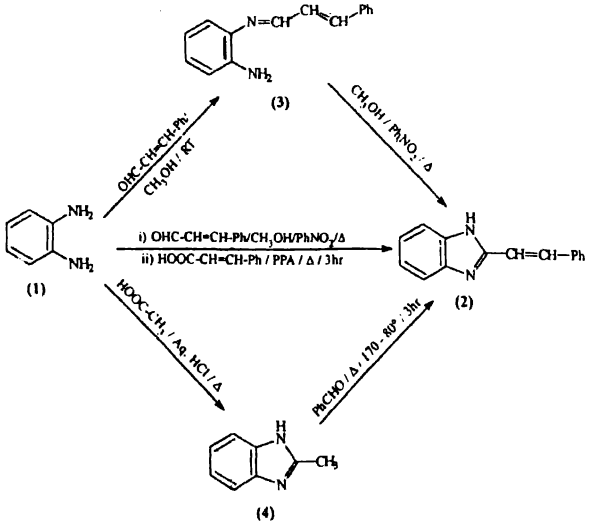
2-Styrylbenzimidazole was prepared by the following three methods.

*(i) Condensation of* o-*phenylenediamine with cinnamic acid* : Treatment of *o*-phenylenediamine (**1**) with cinnamic acid in the presence of 4 *N* HCl under Phillips' conditions[3] did not yield the expected 2-styrylbenzimidazole (**2**). Attempted preparations of the latter compound by condensation of *o*-phenylenediamine with cinnamic acid in refluxing methanol containing a trace of $H_2SO_4$ or in refluxing benzene containing a trace of *p*-toluenesulphonic acid with Dean-Stark removal of water were also unsuccessful. However, reaction of **1** with cinnamic acid in polyphosphoric acid[4] at 180–200° for 4 h gave **2** (30%).

*(ii) Condensation of* o-*phenylenediamine with cinnamaldehyde* : Reaction of **1** with cinnamaldehyde in the presence of nitrobenzene in refluxing methanol gave 2-styrylbenzimidazole (57%). That the latter reaction goes through the intermediacy of the mono-anil was shown by performing the reaction of *o*-phenylenediamine with cinnamaldehyde in 1 : 1 molar ratio in methanol at room temperature. A yellow product separated out having m.p. 138–39°, different (m.p. and tlc) from that of **1** (m.p. 104°) and also from that of **2** (m.p. 203–05°). It analysed for a 1 : 1 composition, showed the presence of $NH_2$ group in the ir spectrum and on heating in methanolic nitrobenzene yielded **2**. However, due to the labile nature of the compound, the mono-anil (**3**) could not be preserved for longer times and had to be used immediately as it showed signs of decomposition on storage.

*(iii) Condensation of 2-methylbenzimidazole* (**4**) *with benzaldehyde* : Compound **1** was condensed with acetic acid under Phillips' conditions[3] to yield **4**. The latter on heating with benzaldehyde at 170–80° for 3 h followed by processing gave **2**. Processing was done by either of the following four methods : (a) trituration with n-hexane, (b) HCl method, (c) sulphate method and (d) oxalate method.

It may be mentioned here that out of the four methods described above, styrylation of **4** with benzaldehyde appeared to be the best for preparing **2** (Scheme 1) and that




Scheme 1

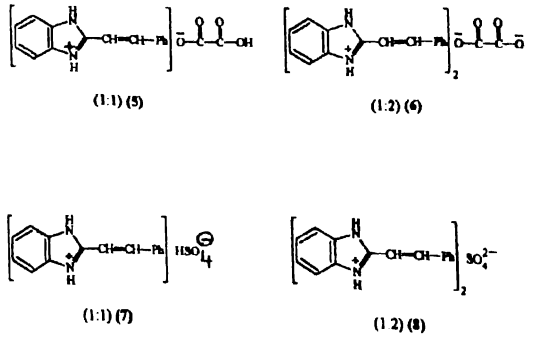
TABLE 1–PREPARATION OF **2** BY DIFFERENT METHODS

| Reagents (i) | Reagents (ii) | Reaction condition | Yield of product | Remarks |
|---|---|---|---|---|
| **1** (1.1 g, 10 mmol) | Cinnamic acid (1.5 g, 10 mmol) | PPA/Δ/180–200°/ 4 h | 0.66 g (30%) | Product isolated by pouring in $H_2O$ and neutralised with aq. $NH_3$ |
| **1** (1.1 g, 10 mmol) | Cinnamaldehyde (1.26 ml, 10 mmol) | MeOH/$PhNO_2$/Δ/3 h | 1.254 g (57%) | Product isolated by oxalate method |
| **4** (1.32 g, 10 mmol) | Benzaldehyde 40 mmol) | Δ/170–80°/3 h | 1.76 g (80%) | Product isolated by trituration method |
| **4** (1.32 g, 10 mmol) | Benzaldehyde (4.0 ml, 40 mmol) | Δ/170–80°/3 h | 1.32 g (60%) | Product isolated by HCl/$C_6H_6$ method |
| **4** (1.32 g, 10 mmol) | Benzaldehyde (4.0 ml, 40 mmol) | Δ/170–80°/3 h | 1.056 g (48%) | Product isolated by sulphate method |
| **4** (1.32 g, 10 mmol) | Benzaldehyde (4.0 ml, 40 mmol) | Δ/170–80°/3 h | 1.87 g (85%) | Product isolated by oxalate method |

the oxlate method is the best method for isolating the product clean and in excellent yields (Table 1).

Since oxalic acid is a dibasic acid and **2** is a monoacidic base, it is conceivable that the oxalate of **2** could be a 1 : 1 or a 2 : 1 product. However, it has been found from simple volumetric estimation that it is a 1 : 1 product having structure **5** and not 2 : 1 product as in structure **6** (Scheme 2). Similarly, it was established in a simple way that the sulphate of **2** is a 1 : 1 salt having structure **7** rather than a 2:1 salt having structure **8** (Scheme 2).

It has been reported in literature that the styrylation of a compound containing an active methylene group such as



Scheme 2

$\alpha$-picoline[2] or $\gamma$-picoline[5] with benzaldehyde is acid-catalysed[6,7], base-catalysed and an uncatalysed (neutral or thermal) reaction[7]. With a view to obtain the optimum conditions for the styrylation of **4** with benzaldehyde, this reaction was studied under a variety of conditions and the results are shown in Table 2. It is obvious that acidic conditions (with the exception of $ZnCl_2$), basic conditions (with the exception of $K^{\oplus}$t-$BuO^{\ominus}$/DMSO), neutral/thermal conditions (upto 150°) or even phase-transfer catalysed reactions did not specifically favour the formation of styryl compound from **4**.

## Experimental

*Preparation of* **2** *from* **1** *and cinnamic acid in PPA* :

A mixture of **1** (1.1 g, 10 mmol), cinnamic acid (1.5 g, 10 mol) and polyphosphoric acid (15 ml) was heated at 180–200° for 4 h. It was then poured in water and neutralised with aq. $NH_3$. The separated solid was washed with water and dried (0.66 g, 30%).

*Preparation of* **2** *from* **1** *and cinnamaldehyde* :

A mixture of **1** (1.1 g, 10 mmol), cinnamaldehyde (1.26 ml, 10 mmol), methanol (10 ml) and nitrobenzene (5 ml) was refluxed for 3 h. It was then cooled to room temperature and treated with a solution of oxalic acid (2 g) in methanol (10 ml). The separated solid (which is the oxalate salt

TABLE 2–STYRYLATION OF 4 WITH BENZALDEHYDE UNDER DIFFERENT CONDITIONS

| 4 used | Benzaldehyde used | Reaction conditions | Yield* of product | Remarks |
|---|---|---|---|---|
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | Reflux in AcOH for 3 h | Nil | Reaction followed by tlc and processed to obtain starting material |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | Reflux in AcOH for 20 h | 0.528 g (12%) | Reaction mixture processed by pouring in warer, extraction with ether and trituration with hexane |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | Reflux in $Ac_2O$ for 3 h | Nil | Reaction followed by tlc and processed to obtain starting material |
| 2 64 g (20 mmol) | 2.1 ml (20 mmol) | Reflux in $Ac_2O$ for 20 h | 1.012 g (23%) | Reaction mixture processed by pouring in water, extraction with ether, evaporation of ether and trituration of residue with hexane |
| 2.64 g (20 mmol) | 4.2 ml (40 mmol) | Heating at 170–80° in presence of anh. $ZnCl_2$ | 3.168 g (72%) | Reaction mixture processed by pouring in aq HCl, filtration of the HCl salt and neutralisation of the salt with aq $NH_3$ |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | Toluene/*p*-toluenesulphonic acid/–$H_2O$ (Dean-Stark)/$\Delta$/3 h | Nil | Reaction followed by tlc and processed to recover the starting material |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | PPA/$\Delta$/100°/3 h | Nil | Reaction mixture on processing gave back the starting material |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | Reflux in pyridine for 3 h | 0.44 g (10%) | Reaction mixture processed by adding i-propanol followed by oxalic acid, isolating the oxalate and then decomposing it with aq. $NH_3$ |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | MeOH/KOH/RT/48 h | Nil | Reaction followed by tlc and processed to recover starting material |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | MeOH/KOH/Reflux 6 h | Nil | Reaction followed by tlc and processed to recover starting material |
| 1.32 g (10 mmol) | 1.0 ml (10 mmol) | DMSO[a] (10 ml)/aq. NaOH (50%; 4 ml)/ RT/24 h | Nil | Reaction followed by tlc and processed to recover starting material |
| 1 32 g (10 mmol) | 1.0 ml (10 mmol) | DMF[a] (15 ml)/aq. NaOH (50%; 4 ml)/ RT/24 h | Nil | Reaction followed by tlc and processed to recover the starting material |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | $K^{\oplus}$t-Bu$O^{\ominus}$/DMSO/RT 45 min | 0.321 g (7.3%) | Reaction followed by tlc and processed by pouring in water, neutralisation with AcOH and extraction with ether to isolate the product |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | $K^{\oplus}$t-Bu$O^{\ominus}$/t-BuOH/ RT/24 h | Nil | Reaction followed by tlc and processed to recover starting material |

*Table–2 (contd.)*

| | | | | |
|---|---|---|---|---|
| 2.64 g (20 mmol) | 6.0 ml (60 mmol) | Heating an intimate mixture of reactants at 100° for 3 h | Nil | Reaction followed by tlc and processed to recover the starting material |
| 2.64 g (20 mmol) | 6.0 ml (60 mmol) | Heating an intimate mixture of reactants at 150° for 3 h | 1.32 g (30%) | Reaction incomplete as observed by tlc and processed to obtain the product in lower yield |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | Benzene/PTC[b]/ 50% aq. NaOH/RT/ 24 h | Nil | Reaction followed by tlc and processed to recover the starting material |
| 2.64 g (20 mmol) | 2.1 ml (20 mmol) | $CH_2Cl_2$/PTC[b]/ 50% aq. NaOH/RT/ 24 h | Nil | Reaction followed by tlc and processed to recover the starting material |

*Yields are reported to the extent product has been isolated from the reaction mixtures.[a]Ref. 9. [b]Phase transfer catalyst (PTC) used was triethylbenzylammonium chloride (TEBAC).

of **2**) was neutralised with aq. $NH_3$ to obtain **2** (1.254 g, 57%).

*Preparation of* **2** *from* **4** *and benzaldehyde* :

An intimate mixture of **4** (1.32 g, 10 mmol) and benzaldehyde (4 ml, 40 mmol) was heated at 170–80° for 3 h. It was then cooled to room temperature and processed by different methods given below.

*(a) Trituration method* : The reaction mixture was triturated with n-hexane to obtain **2** as residue (1.76 g, 80%).

*(b) HCl method* : The reaction mixture was dissolved in benzene (75 ml) and treated with aq. HCl (20%; 50 ml). The separated HCl-salt was neutralised with aq. $NH_3$ to get **2** as free base (1.232 g, 56%). The aq. HCl layer was neutralised with aq. $NH_3$ to obtain a second lot of **2** (0.09 g, 4%). Total yield of **2** was 1.322 g (60%).

*(c) Sulphate method* : The reaction mixutre was dissolved in acetone (75 ml) and treated with dil. $H_2SO_4$ (20%; 10 ml). The separated sulphate salt was neutralised with aq. $NH_3$ to obtain **2** (1.056 g, 48%).

*(d) Oxalate method* : The reaction mixture was dissolved in isopropanol (10 ml) and treated with a solution of oxalic acid (1.5 g) in isopropanol (10 ml). The separated oxalate salt was neutralised with aq. $NH_3$ to obtain **2** (1.87 g, 85%).

A portion of this solid was crystallised from boiling toluene to get a pure product, m.p. 203–05° (lit.[8] 201–02°); $\nu_{max}$ (KBr) 3100–2500 (NH), 1640, 1595, 1530, 1420, 1310 and 1280 $cm^{-1}$; $^1H$ nmr $\delta$(DMSO-$d_6$/TMS) 7.2–7.8 (11H, complex m, $^3J_{H-H}$ for vinylic 16.5 Hz, five phenyl and four aryl and two vinylic protons), 12.04 (1H, NH); $^{13}C$ nmr $\delta$114.93, 117.10, 122.61, 126.93, 128.76, 128.81, 135.36, 135.79, 139.23, 151.65 (for all the carbons of **2**); m/z 221 (6%, M+1), 220 (40%, $M^+$), 219 (100%, M–1), 218 (12%, M–$H_2$), 110 (8%), 109 (12%), 108 (4%), 92 (4%), 91 (6%), 77 (3%), 51 (2%).

*Determination of structure of the oxalate salt of* **2** *by titration method* :

The oxalic acid content in the oxalate salt of **2** was determined volumetrically by using standard $KMnO_4$ solution. $KMnO_4$ itself was standardised by titration against Mohr's salt[10]. In this method[10], a known quantity of the oxalate salt of **2** was suspended in water (5 ml) and neutralised with bicarbonate solution (5%; 15 ml). The separated solid (which is **2** as free base) was washed with water (5 ml). The filtrate (consisting of aq. sodium oxalate) was acidified with dil. $H_2SO_4$ (25%; 10 ml) and titrated against standardised $KMnO_4$ at 90–95°.

*Determination of structure of the sulphate salt of* **2** :

The sulphate salt of **2** (1.15 g) was suspended in water (15 ml) and neutralised with aq. $NH_3$ (pH ~10.0). The separated solid was washed with water and dried to obtain the free base (0.80 g). That is, 1.15 g of sulphate salt of **2** contains 0.80 g of **2** and 0.35 g of $H_2SO_4$. Therefore, molar ratio of **2** and $H_2SO_4$ is 1 : 1.

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