Synthesis of 1-alkyl/aralkyl-2-(1-arylsulfonylalkyl)benzimidazoles under PTC conditions

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2-(α-chloroalkyl)benzimidazoles 1 on reaction with arylsulphinate sodium salt 2, in CH₃CN under PTC conditions, gives 3 which on alkylation yields 1-alkyl/aralkyl-2-(α-aryl sulfonylalkyl)benzimidazoles 4. Alternatively, 4 can also be prepared by the reaction of 2 with 1-alkyl/aralkyl-2-(α-chloroalkyl)benzimidazole 5 in CH₃CN using triethylbenzylammonium chloride (TEBAC) as PTC. 5 are obtained from 1 in turn, by alkylation in CH₃CN under PTC conditions.

Keywords: 1-substituted-2-(α–chloroalkyl)benzimidazole, Ar-SO₂⁻ Na⁺, TEBAC, sulphones

IPC: Int.Cl.⁸ C07D

Benzimidazoles are an important class of heterocyclic compounds, several derivatives of which have been found to possess diverse types of biological activities¹. The sulfonyl moiety has received much attention as a potential pharmacophore in medicinal chemistry. Sulphones exhibit noteworthy antibacterial, antimalarial, antifungal and antitubercular properties²-⁸. In continuation of the earlier work⁹-¹¹ on synthesis of new benzimidazole derivatives with potential biological activity, the present work involves the synthesis of 1-alkyl/aralkyl-2-(1-arylsulfonylalkyl) benzimidazoles. The results of these studies in this direction are presented in this communication.

Results and Discussion

Condensation of o-phenylenediamine with lactic acid gave¹² 1H-2-(α-hydroxy ethyl)benzimidazole, which on chlorination with SOCl₂ gave the previously reported¹³ 2-(α-chloroethyl)benzimidazole 1a (i.e., R=CH₃). The latter on reaction with p-tolyl sulphinate sodium salt 2a [i.e., Ar=-C₆H₄-CH₃-(p)] in CH₃CN using triethyl benzylammonium chloride (TEBAC) as PTC yielded a neat product, which has been characterised as 1H-2-(p-tolysulfonylthethyl)benzimidazole 3a₁ [i.e., R=CH₃, Ar=-C₆H₄-CH₃-(p)] on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed a strong broad band around 3000 cm⁻¹ assignable to imidazole –NH stretching as diagnostic absorption. Its ¹H NMR (CDCl₃+DMSO-d₆/TMS) spectrum showed signals at δ 1.84 (d, J=7.16 Hz, 3H, -CH-CH₃), 2.36 (s, 3H, -C₆H₄-CH₃-(p)), 4.68 (q, J=7.14 Hz, 1H, -CH₂-CH₃), 7.2-7.7 (m, 8H, four aryl protons of the benzimidazole ring and four aryl protons of the phenyl ring), 10.3 (bs, 1H, -NH-, D₂O exchangeable). Its mass spectrum (CIMS) showed its molecular ion peak at m/z 301 corresponding to a molecular mass of 300 when recorded in the Q+1 mode.

The above reaction has been found to be a general one and has been extended to other 1a and 2a and the products thus obtained were assigned structure 3 on the basis of their spectral and analytical data (Table I).

Reaction of 3a₁ [i.e. 3, R=CH₃, Ar=-C₆H₄-CH₃-(p)] with dimethyl sulphate under PTC conditions gave the corresponding N-methylated product, 1-methyl-2-(α-p-tolysulfonylthethyl)benzimidazole 4a₁, which was characterised on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed the absence of a strong broad band at ~3000 cm⁻¹ assigned earlier to benzimidazole –NH stretching in 3a₁. Its ¹H NMR (CDCl₃/TMS) spectrum showed signals at δ 1.85 (d, J=7.18 Hz, 3H, -CH-CH₃), 2.40 (s, 3H, -C₆H₄-CH₃-(p)), 3.95 (s, 3H, -NCH₃), 4.70 (q, J=7.0 Hz, 1H, -CH₂-CH₃), 7.2-7.7 (m, 8H, four aryl protons of the benzimidazole ring and four aryl protons of the
Table I — Spectral and physical characterisation data of compounds 3, 4 and 5

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Starting Material</th>
<th>Reagent used (Ar-SO2Na)</th>
<th>Product obtained</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>1H NMR(δ)</th>
<th>MS (Q+1) mode</th>
<th>Data given in text</th>
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<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>3a1, R=CH3, Ar=-C6H4-CH3(α)</td>
<td>85</td>
<td>154-56</td>
<td>Data given in text</td>
<td>Data given in text</td>
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<td>2</td>
<td>1a</td>
<td>2b</td>
<td>3a2, R=CH3, Ar=-C6H5</td>
<td>82</td>
<td>180-82</td>
<td>4.7 (q, J=7.12Hz, 1H, -CH-CH3), 7.2-7.7 (m, 9H, Ar-H), 10.3 (bs, 1H, -NH-, D2O exchangeable)</td>
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<tr>
<td>3</td>
<td>1b</td>
<td>2a</td>
<td>3b1, R=H, Ar=-C6H4-CH3(α)</td>
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<td>202</td>
<td>2.4 (s, 3H, -CH3), 4.95 (s, 2H, -CH2-)</td>
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<td>2b</td>
<td>3b2, R=H, Ar=-C6H5</td>
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<td>198-200</td>
<td>4.85 (s, 2H, -CH2-), 7.15-7.80 (m, 9H, Ar-H), 12.6 (bs, 1H, -NH-, D2O exchangeable).</td>
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<td>5</td>
<td>3a1</td>
<td>DMS</td>
<td>4a1, R=R1=CH3</td>
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<td>172</td>
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<td>DES</td>
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<td>160-62</td>
<td>1.5 (t, J=18Hz, 3H, -N-CH2-CH3), 1.75 (d, J=12Hz, 3H, -CH-CH3), 2.45 (s, 3H, -CH3), 4.45 (q, J=14.6Hz, 1H, -CH-CH3), 6.55-6.90 (dd, 2H, -N-CH2-CH3), 7.15-7.65 (m, 8H, Ar-H).</td>
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<td>Ph-CH2Cl</td>
<td>4a3, R1=CH2-Ch3, R=CH3</td>
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<td>170</td>
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<td>4b1, R1=CH3</td>
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<td>182-84</td>
<td>1.70(d, J=7.18Hz, 3H, -CH-CH3), 3.85 (s, 3H, -N-CH3), 5.10 (q, J=7.0Hz, 1H, -CH-CH3), 7.2-7.78 (m, 9H, Ar-H).</td>
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<td>4b2, R1=CH2-Ch3, R=CH3</td>
<td>69</td>
<td>130-32</td>
<td>1.65 (d, J=7.12Hz, 3H, -CH-CH3), 4.6 (q, J=7.16Hz, 1H, -CH-CH3), 5.5-5.7 (dd, 2H, -N-CH2-Ph), 6.95-7.65 (m, 14H, Ar-H).</td>
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<td>DMS</td>
<td>4c1, R1=CH3, R=H</td>
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<td>206</td>
<td>2.45 (s, 3H, -CH3), 3.95 (s, 3H, -N-CH3), 4.75 (s, 2H, -CH2-), 7.2-7.7 (m, 8H, Ar-H).</td>
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<td>168-70</td>
<td>1.24 (t, J=18Hz, 3H, -N-CH2-CH3), 2.45 (s, 3H, -CH3), 4.45 (q, J=16Hz, 2H, -N-CH2-CH3), 7.15-7.7 (m, 8H, Ar-H).</td>
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<td>3b1</td>
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<td>4c3, R1=CH2-Ch3, R=H</td>
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<td>182-84</td>
<td>2.45 (s, 3H, -CH3), 4.72 (s, 2H, -CH2-), 5.65 (s, 2H, -N-CH2-Ph), 7.1-7.8 (m, 13H, Ar-H).</td>
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<td>5a1, R=R1=CH3, R=H</td>
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<td>60</td>
<td>2.15 (d, J=7.16Hz, 3H, -CH-CH3), 3.84 (s, 3H, -N-CH2-CH3), 5.30 (q, J=7.12Hz, 1H, -CH-CH3), 7.1-7.8 (m, 4H, Ar-H).</td>
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<td>6a2</td>
<td>5a2, R=CH3, R1=CH2-Ch3</td>
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<td>Liquid</td>
<td>1.5 (t, J=18.2Hz, 3H, -N-CH2-CH3), 2.12 (d, J=7.12Hz, 3H, -CH-CH3), 4.35 (q, J=16Hz, 2H, -N-CH2-CH3), 5.25 (q, J=7.0Hz, 1H, -CH-CH3), 7.2-7.8 (m, 4H, Ar-H).</td>
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<td>6a1</td>
<td>5a3, R=CH3, R1=CH2-Ch3</td>
<td>69</td>
<td>72-76</td>
<td>2.10 (d, J=7.12Hz, 3H, -CH-CH3), 5.10 (q, J=7.0Hz, 1H, -CH-CH3), 5.55 (s, 2H, -N-CH2-Ph), 7.05-7.8 (m, 9H, Ar-H).</td>
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<td>5b1, R=H, R1=CH3</td>
<td>62</td>
<td>94-96</td>
<td>3.95 (s, 3H, -N-CH3), 4.95 (s, 2H, -CH2-), 7.1-7.8 (m, 4H, Ar-H).</td>
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<tr>
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<td>6a1</td>
<td>5b2, R=H, R1=CH3</td>
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<td>100-02</td>
<td>4.96 (s, 2H, -CH2-), 5.60 (s, 2H, -N-CH2-Ph), 7.15-7.80 (m, 9H, Ar-H).</td>
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</table>

*All the products showed satisfactory IR Spectra complying with their structures.
phenyl ring). Its mass spectrum (CIMS) showed its molecular ion peaks at m/z 315 corresponding to a molecular mass of 314 when recorded in the Q+1 mode.

This reaction of 3a1 with DMS was extended to diethyl sulphate (DES) and benzyl chloride to obtain N-alkyl substituted derivatives of 4. The structures of 4 were assigned on the basis of analytical and spectral data (Table I).

Condensation of N-methyl-o-phenylenediamine14 6a1 (i.e. 6, R=CH3), with α-chloropropionic acid 7a (i.e. 7, R=CH3), under Phillips conditions11 gave the known 1-methyl-2-(α-chloroethyl)benzimidazole 5a1 (i.e. 5, R=R1=CH3). The latter compound could also be prepared by the alkylation of 1a (i.e. 1, R=CH3) with DMS in CH3CN using TEBAC as PTC. The products obtained from the two routes were found to be identical in m.p., m.m.p., TLC, and IR spectra (Table I).

This reaction of 1a was extended to diethyl sulphate and benzyl chloride under PTC conditions resulting in the formation of N-ethyl/benzyl derivatives of 5. The structure of 5 was assigned on the basis of analytical and spectral data (Table I).

The title compound could also be prepared by the reaction of 5 with 2 to obtain the corresponding product 4.

The above reactions of 1a have also been carried out with 1b (i.e. R=H) (Scheme I) and similar results were obtained (Table I).

All the above reactions are summarised in the Scheme I.

Experimental Section
Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC were run on silica gel-G and visualization was done using iodine or UV light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr pellets. 1H NMR spectra were recorded in CDCl3/DMSO-d6, using TMS as internal standard, with 200 MHz or with 400 MHz spectrometers. Mass spectra were recorded on Agilent-LC-MS instrument under CI conditions and are given by Q+1 values only.

General procedure for the preparation of 3/4
To a solution of TEBAC (0.2 g) in CH3CN (20 mL) was added 2 (11 mmole) and the mixture was stirred at RT for 5-10 min. To this mixture, under stirring was added a solution of 1/5 (10 mmole) in CH3CN (10 mL). The whole mixture was stirred at RT for 4 h and then poured into ice-cold water. The separated product was filtered, washed with ice-cold water, dried and purified by recrystallisation from hot benzene to obtain pure 3/4.

General procedure for the preparation of 5 from 1
To a solution of TEBAC (0.2 g) in CH3CN (20 mL) was added K2CO3 (1.4 g, 10 mmole) and the mixture stirred at RT. To this mixture, under stirring, was added a solution of 1 in CH3CN (10 mL) followed by alkylating agent (11 mmol). The progress of the reaction was monitored by TLC for the disappearance of 1. On completion of the reaction (~3 h) the mixture was filtered and insoluble material washed with CH3CN (2 × 5 mL). The CH3CN filtrate was evaporated to dryness and the residue treated with CHCl3 (30 mL). The chloroform layer was washed with water (3 × 30 mL) and the CHCl3 layer was evaporated to dryness to obtain crude 5. The crude products were purified by recrystallization from mixture of CHCl3-hexane to obtain pure 5.

General procedure for the preparation of 4 from 3
To a solution of TEBAC (0.2 g) in CHCl3 (20 mL) was added K2CO3 (1.4 g, 10 mmole) and the mixture
stirred at RT for 5-10 min. To this mixture, under stirring, a solution of 3 (10 mmole) in CHCl₃ (10 mL) was added followed by the alkylating agent (11 mmole). The whole mixture was then stirred at RT for 3 h. The mixture was filtered and the CHCl₃ filtrate washed with water (2 × 30 mL), dried over anhyd. MgSO₄, filtered and evaporated to give crude 4. The latter was purified by recrystallisation from benzene to obtain pure 4 (Table I).

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References

(b) Preston P N, Chem Rev, 74, 1974, 279;