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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 CH_3CN under PTC conditions, gives **3** which on alkylation yields 1-alky/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 CH_3CN using triethylbenzylammonium chloride (TEBAC) as PTC. **5** are obtained from **1** in turn, by alkylation in CH_3CN under PTC conditions.

Keywords: 1-substituted-2-(α–chloroalkyl)benzimidazole, Ar-SO_2^- Na^+, TEBAC, sulphones

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Benzimidazoles are an important class of heterocyclic compounds, several derivatives of which have been found to posses diverse types of biological activities[1]. The sulfonyl moiety has received much attention as a potential pharmacophore in medicinal chemistry. Sulphones exhibit noteworthy antibacterial, anti-malarial, antifungal and antitubercular properties[2-8]. In continuation of the earlier work[9-11] 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 gave[12] 1*H*-2-(α-hydroxy ethyl)benzimidazole, which on chlorination with $SOCl_2$, gave the previously reported[13] 2-(α-chloroethyl)benzimidazole **1a** (*i.e*. **1**, R=CH_3). The latter on reaction with *p*-tolyl sulphinate sodium salt **2a** [*i.e.* **2**, Ar=-C_6H_4-CH_3-(*p*)]) in CH_3CN using triethyl benzylammoniumchloride (TEBAC) as PTC yielded a neat product, which has been characterised as 1*H*-2-(*p*-tolylsulfonylethyl)-benzimidazole **3a$_1$** [*i.e.* **3**, R=CH_3, Ar=-C_6H_4-CH_3-(*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 ^{1}H NMR ($CDCl_3$+DMSO-d_6/TMS) spectrum showed signals at δ 1.84 (d, *J*=7.16 Hz, 3H, -CH-$^*CH_3$), 2.36 (s, 3H, -C_6H_4-CH_3-(*p*)), 4.68 (q, *J*=7.14 Hz, 1H, -*CH-CH_3), 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-, D_2O 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.

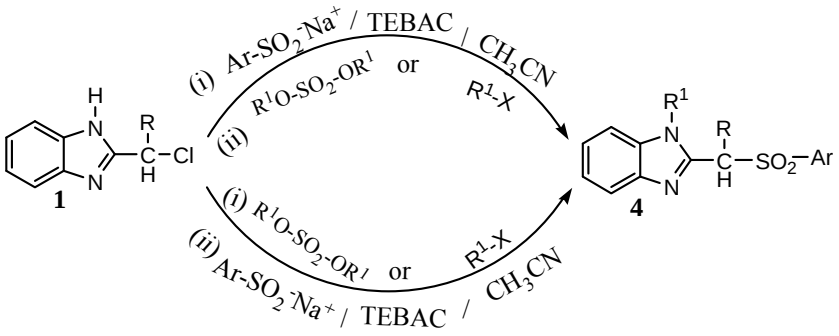
The above reaction has been found to be a general one and has been extended to other **1a** and **2a** and the products thus obtained were assigned structure **3** on the basis of their spectral and analytical data (**Table I**).

Reaction of **3a$_1$ [***i.e*. **3**, R=CH_3, Ar=-C_6H_4-CH_3-(*p*] with dimethyl sulphate under PTC conditions gave the corresponding N-methylated product, 1-methyl-2-(α-*p*-tolylsulfonylethyl)benzimidazole **4a$_1$**, 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 **3a$_1$**. Its ^{1}H NMR ($CDCl_3$/TMS) spectrum showed signals at δ 1.85 (d, *J*=7.18 Hz, 3H, -CH-$^*CH_3$), 2.40 (s, 3H, -C_6H_4-CH_3-(*p*)), 3.95 (s, 3H, -NCH_3), 4.70 (q, *J*=7.0 Hz, 1H, -*CH-CH_3), 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**

SI.No	Starting Material	Reagent used(Ar-SO_2Na)	Product obtained	Yield (%)	m.p. (°C)	^{1}H NMR(δ)	MS (Q+1) mode
1	**1a**	**2a** Ar=-C_6H_4-CH_3-(*p*)	**3a$_1$** R=CH_3, Ar=-C_6H_4-CH_3-(*p*)	85	154-56	Data given in text	Data given in text
2	**1a**	**2b** Ar=-C_6H_5	**3a$_2$** R=CH_3, Ar=-C_6H_5	82	180-82	1.9 (d, *J*=7.16 Hz, 3H, -CH-$^*CH_3$), 4.7 (q, *J*=7.12Hz, 1H, -*CH-CH_3), 7.2-7.7 (m, 9H, Ar-H), 10.3 (bs, 1H, -NH-, D_2O exchangeable)	287
3	**1b**	**2a**	**3b$_1$** R=H, Ar=-C_6H_4-CH_3-(*p*)	79	202	2.4 (s, 3H, -CH_3), 4.95 (s, 2H, -CH_2-)7.2-7.7 (m, 8H, Ar-H), 12.6 (bs, 1H, -NH-, D_2O exchangeable)	287
4	**1b**	**2b**	**3b$_2$** R=H, Ar=-C_6H_5	78	198-200	4.85 (s, 2H, -CH_2-), 7.15-7.80 (m, 9H, Ar-H), 12.65 (bs, 1H, -NH-, D_2O exchangeable).	273
5	**3a$_1$**	DMS	**4a$_1$** R=R^1=CH_3	73	172	Data given in text	Data given in text
6	**3a$_1$**	DES	**4a$_2$** R^1=-CH_2-CH_3, R=CH_3	69	160-62	1.5 (t, *J*=18Hz, 3H, -N-CH_2-$^*CH_3$), 1.75 (d, *J*=12Hz, 3H, -CH-$^*CH_3$), 2.45 (s, 3H, -CH_3) 4.35 (q, *J*=14.6Hz, 1H, -*CH-CH_3), 4.65 (q, *J*=16Hz, 2H, -N-$^*CH_2$-CH_3), 7.15-7.65 (m, 8H, Ar-H).	329
7	**3a$_1$**	Ph-CH_2-Cl	**4a$_3$** R^1=-CH_2-Ph, R=CH_3	71	170	1.68 (d, *J*=14.2Hz, 3H, -CH-$^*CH_3$), 2.45 (s, 3H, -CH_3), 4.45 (q, *J*=14.4Hz, 1H, -*CH-CH_3), 5.55-5.90 (dd, 2H, -N-$^*CH_2$-Ph), 7.0-7.65 (m, 13H, Ar-H).	391
8	**3a$_2$**	DMS	**4b$_1$** R=R^1=CH_3	72	182-84	1.70(d, *J*=7.18Hz, 3H, -CH-$^*CH_3$), 3.85 (s, 3H, -N-CH_3), 5.10 (q, *J*=7.0Hz, 1H, -*CH-CH_3), 7.2-7.87 (m, 9H, Ar-H).	301
9	**3a$_2$**	Ph-CH_2-Cl	**4b$_2$** R^1=-CH_2-Ph, R=CH_3	69	130-32	1.65 (d, *J*=7.12Hz, 3H, -CH-$^*CH_3$), 4.6 (q, *J*=7.16Hz, 1H, -*CH-CH_3), 5.5-5.7 (dd, 2H, -N-$^*CH_2$-Ph), 6.95-7.65 (m, 14H, Ar-H).	377
10	**3b$_1$**	DMS	**4c$_1$** R^1=CH_3, R=H	74	206	2.45 (s, 3H, -CH_3), 3.95 (s, 3H, -N-CH_3), 4.75 (s, 2H, -CH_2-), 7.2-7.7 (m, 8H, Ar-H).	301
11	**3b$_1$**	DES	**4c$_2$** R^1=-CH_2-CH_3,R=H	69	168-70	1.45 (t, *J*=18Hz, 3H, -N-CH_2-$^*CH_3$), 2.45 (s, 3H, -CH_3), 4.45 (q, *J*=16Hz, 2H, -N-$^*CH_2$-CH_3), 4.85 (s, 2H,-CH_2-), 7.15-7.7 (m, 8H, Ar-H).	315
12	**3b$_1$**	Ph-CH_2-Cl	**4c$_3$** R^1=CH_2-Ph, R=H	70	182-84	2.45 (s, 3H, -CH_3), 4.72 (s, 2H, -CH_2-), 5.65 (s, 2H, -N-CH_2-Ph), 7.1-7.8 (m, 13H, Ar-H).	377
13	**1a** **6a$_1$**	DMS **7a**	**5a$_1$** R=R^1=CH_3	68 60	60	2.15 (d, *J*=7.16Hz, 3H, -CH-$^*CH_3$), 3.90 (s, 3H, -N-CH_3), 5.30 (q, *J*=7.12Hz, 1H, -*CH-CH_3), 7.1-7.8 (m, 4H, Ar-H).	195
14	**1a** **6a$_2$**	DES **7a**	**5a$_2$** R=CH_3, R^1=CH_2-CH_3	64 58	Liquid	1.5 (t, *J*=18.2Hz, 3H, -N-CH_2-$^*CH_3$), 2.12 (d, *J*=7.12Hz, 3H, -CH-$^*CH_3$), 4.35 (q, *J*=16Hz, 2H, -N-$^*CH_2$-CH_3), 5.25 (q, *J*=7.0Hz, 1H, -*CH-CH_3), 7.2-7.8 (m, 4H, Ar-H)	209
15	**1a** **6a$_3$**	Ph-CH_2-Cl **7a**	**5a$_3$** R=CH_3, R^1=-CH_2-Ph	69 62	72-76	2.10 (d, *J*=7.12Hz, 3H, -CH-$^*CH_3$), 5.10 (q, *J*=7.0Hz, 1H, -*CH-CH_3), 5.55 (s, 2H, -N-CH_2-Ph), 7.05-7.8 (m, 9H, Ar-H).	271
16	**1b** **6a$_1$**	DMS **7b**	**5b$_1$** R=H, R^1=CH_3	62 55	94-96	3.95 (s,3H, -N-CH_3), 4.95 (s, 2H, -CH_2-), 7.1-7.8 (m, 4H, Ar-H)	181
17	**1b** **6a$_3$**	Ph-CH_2-Cl **7b**	**5b$_2$** R=H, R^1=-CH_2-Ph	64 52	100-02	4.96 (s, 2H, -CH_2-), 5.60 (s, 2H, -N-CH_2-Ph), 7.15-7.80 (m, 9H, Ar-H).	257

*All the products showed satisfactory IR Spectra complying with their structures.



Scheme I

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 **3a$_1$** 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*-phenylenediamine[14] **6a$_1$** (*i.e*. **6**, R^1=CH_3), with α-chloropropionic acid **7a** (*i.e*. **7**, R=CH_3), under Phillips conditions[11] gave the known 1-methyl-2-(α-chloroethyl)benzimidazole **5a$_1$** (*i.e*. **5**, R=R^1=CH_3). The latter compound could also be prepared by the alkylation of **1a** (*i.e.* **1**, R=CH_3) with DMS in CH_3CN 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. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6, 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 CH_3CN (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 at RT a solution of **1/5** (10 mmole) in CH_3CN (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 CH_3CN (20 mL) was added K_2CO_3 (1.4 g, 10 mmole) and the mixture stirred at RT. To this mixture, under stirring, was added a solution of **1** in CH_3CN (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 CH_3CN (2 × 5 mL). The CH_3CN filtrate was evaporated to dryness and the residue treated with $CHCl_3$ (30 mL). The chloroform layer was washed with water (3 × 30 mL) and the $CHCl_3$ layer was evaporated to dryness to obtain crude **5**. The crude products were purified by recrystallization from mixture of $CHCl_3$-hexane to obtain pure **5**.

General procedure for the preparation of 4 from 3

To a solution of TEBAC (0.2 g) in $CHCl_3$ (20 mL) was added K_2CO_3 (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 $CHCl_3$ (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 $CHCl_3$ filterate washed with water (2 × 30 mL), dried over anhyd. $MgSO_4$, 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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