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Suzuki-Type Cross-Coupling Reaction of 1-Benzyl-2-iodo-*1H*-benzimidazoles with Aryl Boronic Acids: A Regioselective Route to N-Alkylated 6-Alkoxy-2-aryl-*1H*-benzimidazoles

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Abstract: The Suzuki-type cross-coupling reaction of 6-substituted 1-benzyl-2-iodo-*1H*-benzimidazoles with aryl boronic acids provided an efficient synthesis of the corresponding 2-ary-*1H*-benzimidazoles. The reaction was catalyzed by palladium(0) under different conditions depending on the aryl group substitution.
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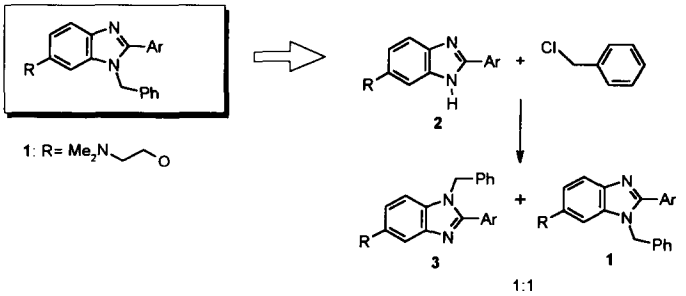
Substituted benzimidazoles have received a considerable amount of attention in various fields of chemistry[1] and medicinal chemistry.[2] Of the methods reported in the literature for the synthesis of 2-aryl-*1H*-benzimidazoles, those involving direct coupling of a carboxylic acid or carboxylic acid derivative with an appropriate 1,2-phenylenediamine, under the influence of a strong acid at high temperature, are the most common.[1c,3] Alternatively, a two-step procedure has been reported where the 1,2-phenylenediamines are initially acylated and the mono-acylated derivatives transformed into the 2-aryl-*1H*-benzimidazole.[4] A much less common route involves diacylation of 1,2-phenylenediamines[5] which are then dehydrated by the Phillips method[6] or by pyrolysis.[7]

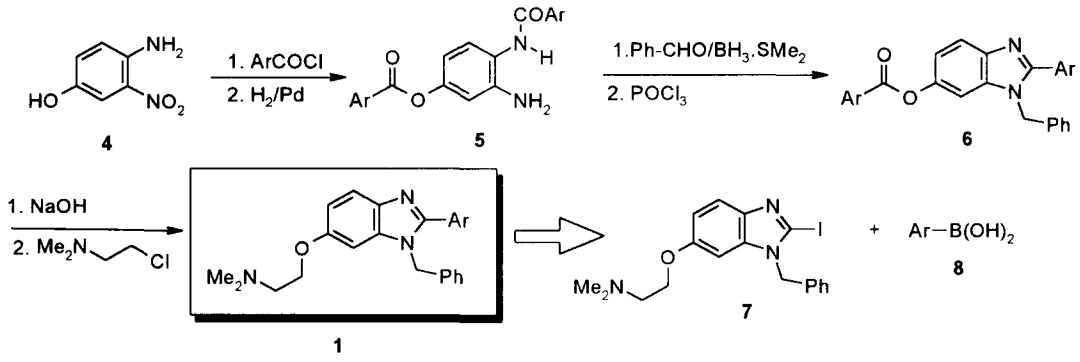
Since 1-benzyl-2-aryl-*1H*-benzimidazoles bearing a dimethylaminoethyloxy substituent on the benzenoid ring were required as starting materials for the synthesis of a new drug candidate, we tried to prepare **1** by alkylation of 6-substituted 2-aryl-*1H*-benzimidazoles, themselves obtained following the classical synthetic route mentioned above. However, when **2** was alkylated with benzyl chloride, either in homogenous or two-phase conditions (PTC), the two isomeric benzimidazoles **1** and **3** were formed in an aproximate 1:1 ratio.[8]



Scheme 1

Because of the separation of both benzimidazoles was difficult, we applied the linear synthetic method shown in Scheme 2. Our initial route to **1** started from 4-amino-3-nitrophenol (**4**) and involved N-acylation and protection of the hydroxyl group with the desired acyl chloride, reduction of the nitro group with H_2/Pd, condensation with benzaldehyde under reductive conditions ($BH_3.SMe_2$), formation of the heterocycle in the presence of $POCl_3$, hydrolysis of the hydroxyl protection with NaOH and final alkylation with dimethylaminoethyl chloride. Overall yields between 25% and 10% were obtained for benzimidazoles **1a** (Ar = 4-methylphenyl) and **1b** (Ar = 2,4,6-trimethylphenyl) respectively, prepared following this procedure (Method E in experimental). Although it was satisfactory for the preparation of several benzimidazole derivatives **1**, it suffers from the drawback that the preparation of each derivative requires several steps as the 2-aryl substituent is incorporated in the first step of this linear strategy.

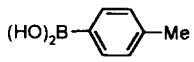
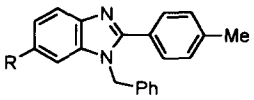
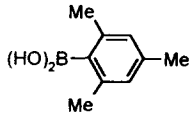
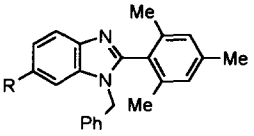
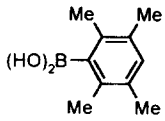
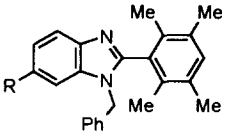
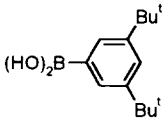
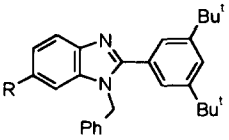
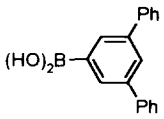
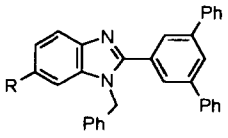
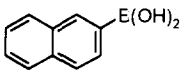
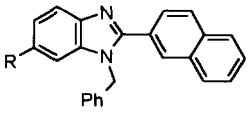
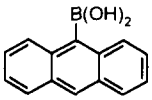
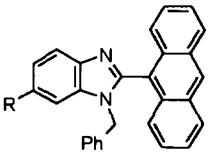
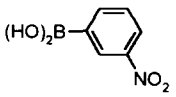
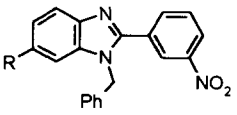
Since the heterocyclic chemistry is undergoing a dramatic change with the coming of palladium-catalyzed coupling reactions,[9] we decided to explore whether this methodology could be applied to a convergent synthesis of these 6-substituted 2-aryl-1-benzyl-*1H*-benzimidazoles **1**. Here, we report the successful arylation of 6-substituted 2-iodo-1-benzyl-*1H*-benzimidazole (**7**) with aryl boronic acids **8** under Suzuki-type conditions (Scheme 2).[10]



Scheme 2

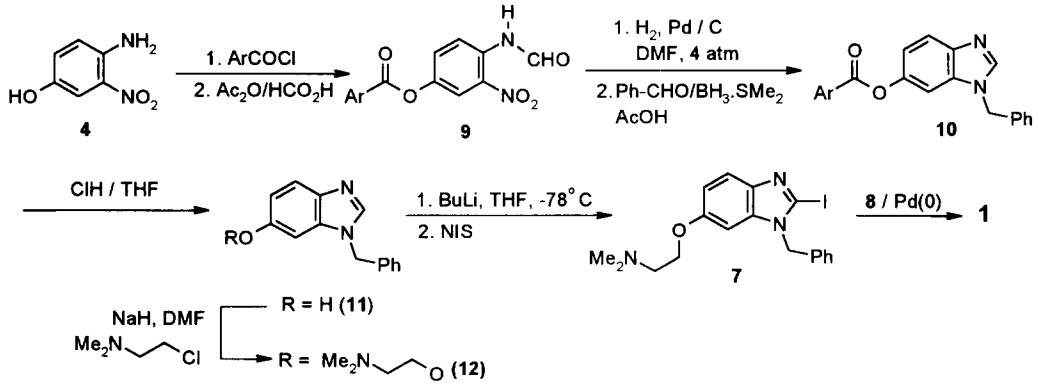
The preparation of **7**, the chosen candidate to test the coupling, required a similar protocol to that shown in Scheme 2, although in this case formic-acetic anhydride was used in the formylation step leading to **9** and the hydrolysis of the ester group in **10** was achieved with HCl by heating in THF (Scheme 3). Metallation of the *1H*-benzimidazole **12** at C-2 with *n*-BuLi at -78 °C and subsequent treatment with N-iodosuccinimide (NIS) efficiently provided the hitherto 2-iodo-*1H*-benzimidazole derivative **7** in a 81% yield. The crucial coupling of **7** and different aryl boronic acids **8** was carried out in the presence of tetrakis(triphenyl)phosphine palladium (0) as catalyst, giving the desired coupled compounds in moderate to good yields (45-78%, Table 1). The optimum reaction conditions depended on the nature and position of the substituents on the aryl boronic acid. Thus, sterically hindered substrates

Table 1. Cross-Coupling Reactions of Benzimidazole **7** with Arylboronic Acids **8**

Entry	Boronic Acid (**8**)	Method[a]	2-Arylbenzimidazole (**1**)	Yield (%)[b]
1		A		78
2		B		76
3		B		75
4		A		57
5		A		45
6		A		58
7		B		57
8		C, D		15

[a]*A*: $Pd(PPh_3)_4$/Toluene-EtOH/ (20:1)/ Na_2CO_3; *B*: $Pd(PPh_3)_4$/DME-H_2O (6:1) /$Ba(OH)_2$;
C: $Pd(PPh_3)_4$/Toluene-EtOH/Na_2CO_3/Bu_4NF(1.2 equiv); *D*: $Pd(OAc)_2$/P(*o*-Me-C_6H_4)$_3$/Et_3N/DMF, 100°C, 3 days.
[b]Isolated yield. R=$Me_2NCH_2CH_2O$

(entries 2, 3 and 7, Table 1) required a stronger base [$Ba(OH)_2$] in DME-H_2O[11] whereas the coupling of the 4-substituted and 3,5-disubstituted aryl boronic acids could be achieved using Na_2CO_3 in toluene-EtOH (entries 1,4,5 and 6).[10c] The much lower reactivity found in the attempted coupling of boronic acids bearing electron-withdrawing substituents (entry 8) must be noted. Attempts to prepare the corresponding 2-(3-nitrophenyl)-*1H*-benzimidazole were unsuccessful under conditions similar to those used for the coupling of sterically unhindered boronic acids. The use of other bases, solvents and addition of catalytic amounts of phase-tranfer catalyst were also unsuccessful. Finally, we found that the addition of 1.2 equiv of tetrabutylammnonium fluoride[12] allowed the formation of the coupled product in 15% yield. The same yield was obtained by using palladium acetate, tris-(*ortho*-tolyl)phosphine and triethylamine in DMF at 100°C for 3 days in a sealed tube.



Scheme 3

In conclusion, the Suzuki type cross-coupling procedure reported here represents a new regioselective and convergent synthetic approach to 6-substituted 1-benzyl-2-aryl-*1H*-benzimidazoles, which was particularly successful with electron rich aryl boronic acids, even when sterically hindered (2- and 2,6-substituted).

Experimental

General Procedures. Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Unity 300 spectrometer and were referenced to TMS. IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. Microanalyses were performed on a Heraeus CHN Rapid analyzer and MS were obtained on a Hewlett-Packard 5988 A spectrometer. Positive FAB-MS mass spectra were recorded using 3-nitrobenzyl alcohol matrix on a VG AutoSpec mass spectrometer. Chromatography was performed on silica gel 60 (230-400 mesh). All reagents were obtained from commercial sources and were used as acquired. Solvents were dried before use. The aryl boronic acids corresponding to entries 4 and 5 in the table are not commercially available and were prepared following the literature procedure.[13]

4-Formylamino-3-nitrophenyl 3,5-dimethylbenzoate **(9)**. To a stirred suspension of 4-amino-3-nitrophenol **6** (6.17 g, 40 mmol) and 3,5-dimethylbenzoic acid (6.0 g, 40 mmol) in CH_2Cl_2 (50 mL), DCC (8.25 g, 40 mmol) and DMAP (4.88 g, 40 mmol) in the same solvent (20 mL) were added and then heated under reflux for 15 h.The mixture was cooled in an ice bath and the precipitate was removed by filtration. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2) giving the 4-amino-3-nitrophenyl 3,5-dimethylbenzoate as a yellow powder. Yield: 89%. Mp 159-160 °C. IR (KBr) ν_{max} 3348, 1730, 1633, 1572, 1513, 1338, 1307, 1269, 1245, 1198. ^{1}H-NMR (DMSO-d_6) δ 7.38 (d, J= 2.5 Hz, 1H), 7.70 (s, 2H), 7.49 (s, 2H, NH_2), 7.40-7.32 (m, 2H), 7.07 (d, J= 9.1 Hz, 1H), 2.35 (s, 6H).

A solution of acetic anhydride (10 mL, 100 mmol) and formic acid (6 mL, 150 mmol) was heated at 60 °C for 3 h.[14] Then the previously obtained aniline (1.54 g, 10 mmol) was added and the mixture stirred for another hour at 60 °C. When the mixture was cooled to room temperature, water (200 mL) was added. The precipitated solid was filtered and washed with water and finally with Et_2O to yield the expected formanilide as a bright yellow powder. Yield: 97%. Mp 172-173 °C. IR (KBr) ν_{max} 3294, 1706, 1670, 1514, 1411, 1341, 1310, 1275, 1240, 1146. ^{1}H-NMR (DMSO-d_6) δ 10.61 (bs, 1H, CHO); 8.40 (bs, 1H, NH), 8.07 (d, J= 2.5 Hz, 2H), 7.76 (s, 2H), 7.71 (dd, J= 8.8 and 2.5 Hz, 1H), 7.40 (s, 1H), 2.37 (s, 6H, $2CH_3$). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found C, 61.26; H, 4.40; N, 8.74.

1-Benzyl-6-(3,5-dimethylbenzoyloxy)-1H-benzimidazole **(10)**. A suspension of the above nitroformanilide **9** (10 mmol) and 10% Pd/C (1.6 g) in DMF (10 mL) was placed in a teflon vessel, purged with hydrogen and the mixture was then hydrogenated for 16 h (60 °C, 60 psi). The reaction vessel was cooled to room temperature and the suspension was filtered through a small pad of celite which was finally washed with DMF (5 mL). The filtrate was diluted with 200 mL of ice-cooled water. The white powder so obtained was filtered, washed with water and rinsed with Et_2O and used in the next step without further purification.

A suspension of the so obtained *o*-amino-formanilide (5 mmol) in CH_2Cl_2 (20 mL), glacial acetic acid (20 mL) and benzaldehyde (530 mg, 5.5 mmol) was stirred under argon for 5 min. $BH_3{\cdot}SMe_2$ (2.7 mL, 5 mmol, 2 M solution in CH_2Cl_2) was then added dropwise to the imine solution and the mixture stirred at room temperature for 30 min.[14] A 30% solution of NH_4OH was used to adjust the pH to 7 and the mixture extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure yielding an oily residue which was purified by column chromatography (CH_2Cl_2/MeOH, 9.5:0.5) affording **10** as a white powder.Yield: 40%. Mp 140-141 °C. IR (KBr) ν_{max} 1729, 1492, 1453, 1357, 1308, 1245, 1200, 1158, 1098, 753. ^{1}H-NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.86-7.80 (m, 3H), 7.36-7.32 (m, 3H), 7.26 (s, 1H), 7.20-7.16 (m, 3H), 7.12 (dd, J= 8.4 and 2.2 Hz, 1H), 5.30 (s, 2H, CH_2), 2.40 (s, 6H, $2CH_3$). Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found C, 77.68; H, 5.74; N, 7.67).

1-Benzyl-6-hydroxy-1H-benzimidazole hydrochloride **(11)**. The ester **10** (713 mg, 2 mmol) and a 1:1 mixture of THF and 30 % HCl (20 mL) was refluxed for 3 days. The solvent was evaporated under reduced pressure and the phenol was obtained as a brown powder when Et_2O (200 mL) was added to the aqueous residue. Yield: 94 %.

Mp 120-121 °C. IR (KBr) ν_{max} 3342, 3021, 2917, 2851, 1628, 1498, 1338, 1244, 831, 771. ^{1}H-NMR (CD_3OD) δ 9.35 (s, 1H), 7.64 (d, J= 8.8 Hz, 1H), 7.41 (s, 5H), 7.10 (dd, J= 8.8 and 2.2 Hz, 1H), 7.02 (d, J= 2.2 Hz, 1H), 5.64 (s, 2H). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 74.77; H, 5.47; N, 12.54.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-1H-benzimidazole **(12)**. To an ice-cooled solution of NaH (0.24 g, 10 mmol, 95 % in oil) in dry DMF (3 mL), a solution of **11** (224 mg, 1 mmol) in the same solvent (5 mL) was added. The reaction mixture was stirred under an argon atmosphere for 1 h and then dimethylaminoethyl chloride hydrochloride (432 mg, 3 mmol) was added. The resulting mixture was stirred at room temperature for 6 h. A saturated solution of NH_4Cl (10 mL) was added and the mixture extracted with CH_2Cl_2 (4 x 25 mL).The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure yielding an oily residue which was purified by column chromatography (CH_2Cl_2/MeOH, 9:1). Yield: 78%. Mp 113-114 °C (white powder). IR (KBr) ν_{max} 1627, 1496, 1455, 1366, 1271, 1213, 1187,1024, 835, 721. ^{1}H-NMR ($CDCl_3$) δ 7.81 (s, 1H), 7.66 (d, J= 8.8 Hz, 1H), 7.35-7.24 (m, 3H), 7.16-7.10 (m, 2H), 6.91 (dd, J= 8.8 and 2.2 Hz, 1H), 6.73 (d, J= 2.2 Hz, 1H), 5.26 (s, 2H, CH_2), 4.02 (t, J= 5.8 Hz, 2H, CH_2), 2.70 (t, J= 5.8 Hz, 2H, CH_2), 2.31 (s, 6H, $2CH_3$). Anal. Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found C, 73.42; H, 7.03; N, 14.36.

1-Benzyl-2-iodo-6-[2-(N,N-dimethylamino)ethyloxy]-1H-benzimidazole **(7)**. To a -78 °C cooled solution of **12** (520 mg, 2.5 mmol) in dry THF (10 mL), *n*-BuLi (1.72 mL, 2.75 mmol, 1.6 M solution in THF) was added dropwise under argon. After stirring the reaction for 1 h at this temperature, a recently prepared solution of NIS (619 mg, 2.75 mmol) in dry THF (10 mL) was added and the mixture was allowed to warm to room temperature. The reaction mixture was quenched with a saturated solution of NH_4Cl (10 mL), extracted with CH_2Cl_2 (3 x 25 mL) and the organic extracts washed with $NaHCO_3$ aqueous solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. Elution with hexane/EtOAc (1:1) gave pure **7**. Yield: 81%. Mp 108-109 °C (white powder). IR (KBr) ν_{max} 1613, 1480, 1447, 1421, 1332, 1264, 1183, 1017, 823, 708. ^{1}H-NMR ($CDCl_3$) δ 7.60 (d, J= 8.8 Hz, 1H), 7.36-7.24 (m, 3H), 7.16-7.10 (m, 2H), 6.85 (dd, J = 8.8 and 2.2 Hz, 1H), 6.72 (d, J= 2.2 Hz, 1H), 5.31 (s, 2H, CH_2), 4.00 (t, J= 5.8 Hz, 2H, CH_2), 2.69 (t, J= 5.8 Hz, 2H, CH_2), 2.31 (s, 6H, $2CH_3$). ^{13}C-NMR ($CDCl_3$) δ 155.7 (C), 140.3 (C), 136.1 (C), 134.9 (C), 128.8 (2CH), 127.9 (CH), 126.5 (2CH), 119.5 (CH), 111.7 (CH), 101.9 (C), 94.6 (CH), 66.1 (CH_2), 57.9 (CH_2), 50.2 (CH_2), 45.6 ($2CH_3$).Anal. Calcd for $C_{18}H_{20}IN_3O_2$: C, 51.32; H, 4.79; N, 9.97. Found C, 50.95; H, 5.04; N, 9.59.

2-Aryl-1-benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-1H-benzimidazoles **1**. *General procedures.*

Method A. To a suspension of the 2-iodo-1*H*-benzimidazole **7** (422 mg, 1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in a mixture of toluene-EtOH (20 mL:1 mL), 2 M Na_2CO_3 solution (2 mL) was added followed by the addition of the corresponding aryl boronic acid **8** (1.1 mmol). The reaction mixture was refluxed for 24 h. The cooled suspension was extracted with CH_2Cl_2 (3 x 40 mL). The organic layer was washed with a saturated solution of NaCl (2 x 20 mL).The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced

presure. The residue was purified by column chromatography (CH_2Cl_2:MeOH, 9:1). In all cases the oily residues were transformed into the corresponding hydrochlorides.

Method B: The reaction was carried out as described in the method A but the mixture of solvents and base were changed to DME:H_2O (6 mL:1 mL) and $Ba(OH)_2 \cdot 8H_2O$ (473 mg, 1.5 mmol). In all cases the oily residues were transformed into the corresponding hydrochlorides.

Method C: Similar to method A but using TBAF (314 mg, 1.2 mmol) as co-catalyst.

Method D: A suspension of **7** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), tris-(*o*-tolyl)phosphine (0.1 mmol) and triethylamine (0.4 mL) in DMF (4 mL) was placed in a pyrex sealed vessel and heated at 100 °C for 3 days. After cooling, the reaction mixture was poured over 10% solution of NH_4OH and then extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2:MeOH, 9:1). The oily residue was treated with a saturated solution of hydrogen chloride in dry ether to yield the hydrochoride.

Method E: The linear synthesis of these 2-aryl-*1H*-benzimidazoles was carried out by diacylation of 4-amino-3-nitrophenol (**4**) (154 mg, 1 mmol) with the corresponding acyl chloride (2.5 mmol) in the presence of dimethylaniline (0.42 mL, 3.3 mmol) in refluxing toluene (3 mL) for 17 h. The diacylated nitro compounds were then hydrogenated as described before to afford the expected anilines **5** which were alkylated in the primary amino group through a reductive alkylation with benzaldehyde (1.1 mmol) using $BH_3.SMe_2$ (0.52 mL, 1 mmol, 2M) and then, cyclodehydrated by heating with $POCl_3$ (0.6 mL, 1 mmol) in $CHCl_3$ (10 mL) for 15 h yielding the expected 6-acyloxy-1-benzyl-2-arylbenzimidazoles **6**. Basic hydrolysis [1N solution of NaOH (10 mL) and THF (10 mL)] and alkylation with dimethylaminoethyl chloride hydrochloride (432 mg, 1 mmol) in the presence of NaH (240 mg, 10 mmol) in DMF (3 mL) produced 6-[(2-dimethylaminoethyl)oxy]-*1H*-benzimidazoles **1.**

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-(4-methylphenyl)-1H-benzimidazole dihydrochloride (**1a**). *Method A* (white powder, 78 %, mp 145-146 °C). IR (KBr) ν_{max} 3403, 2954, 2708, 1620, 1503, 1475, 1400, 1219, 1150, 822. ^{1}H-NMR (free base, $CDCl_3$) δ 7.71 (d, J= 8.7 Hz, 1H), 7.53 (d, J= 8.1 Hz, 2H), 7.35-7.20 (m, 5H), 7.09 (d, J= 8.1 Hz, 2H), 6.94 (dd, J= 8.7 and 1.8 Hz, 1H), 6.67 (d, J= 1.8 Hz, 1H), 5.37 (s, 2H, CH_2), 4.01 (t, J= 5.7 Hz, 2H, CH_2), 2.70 (t, J= 5.7 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.31 (s, 6H, $2CH_3$). ^{13}C-NMR (free base, $CDCl_3$) δ 155.7 (C), 153.6 (C), 139.7 (C), 137.7 (C), 136.6 (C), 136.3 (C), 129.3 (2 CH), 129.0 (2 CH), 128.9 (2 CH), 127.6 (CH), 127.2 (C), 125.8 (2 CH), 120.2 (CH), 111.9 (CH), 95.3 (CH), 66.5 (CH_2), 58.2 (CH_2), 48.3 (CH_2), 45.8 (2 CH_3), 21.3 (CH_3). HRMS calcd for $C_{25}H_{28}N_3O$ 386.2232, found 386.2233.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-(2,4,6-trimethylphenyl)-1H-benzimidazole dihydrochloride (**1b**). *Method B* (white powder, 76 %, mp 150-151 °C). IR (KBr) ν_{max} 3425, 2925, 2611, 1622, 1503, 1468, 1220, 1176, 1138, 1115. ^{1}H-NMR (free base, CD_3OD) δ 7.58 (d, J= 8.8 Hz, 1H), 7.25-7.16 (m, 3H), 7.12 (d, J= 2.2 Hz, 1H), 7.02-6.90 (m, 5H), 5.10 (s, 2H, CH_2), 4.16 (t, J= 5.5 Hz, 2H, CH_2), 2.87 (t, J= 5.5 Hz, 2H, CH_2), 2.42 (s, 6H, 2 CH_3), 2.33 (s, 3H, CH_3), 1.84 (s, 6H, 2 CH_3). ^{13}C-NMR (free base, CD_3OD) δ 157.2 (C), 153.8 (C), 141.3 (C), 139.4 (2 C), 137.9 (C), 137.4 (C), 136.6 (C), 129.6 (2 CH), 129.4 (2 CH), 128.9 (CH), 128.5 (2 CH), 127.7 (C),

120.3 (CH), 113.5 (CH), 96.5 (CH), 66.9 (CH_2), 58.9 (CH_2), 48.6 (CH_2), 45.6 (2 CH_3), 21.3 (CH_3), 19.7 (2 CH_3). HRMS calcd for $C_{27}H_{32}N_3O$ 414.2545, found 414.2540.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-(2,3,5,6-tetramethylphenyl)-1H-benzimidazole dihydrochloride **(1c)**. *Method B* (white powder, 75 %, mp 190-191 °C). IR (KBr) ν_{max} 3413, 2926, 2697, 1624, 1501, 1472, 1390, 1224, 1106, 708. ^{1}H-NMR (free base, CD_3OD) δ 7.63 (d, J= 9 Hz, 1H), 7.28-7.20 (m, 4H), 7.17 (s, 1H), 7.04 (dd, J= 9.0 and 2.5 Hz, 1H), 6.92 (d, J= 6.5 Hz, 2H), 5.09 (s, 2H, CH_2), 4.22 (t, J = 5.5 Hz, 2H, CH_2), 2.91 (t, J = 5.5 Hz, 2H, CH_2), 2.45 (s, 6H, 2 CH_3), 2.25 (s, 6H, 2 CH_3), 1.71 (s, 6H, 2 CH_3). ^{13}C-NMR (free base, CD_3OD) δ 157.3 (C), 154.8 (C), 137.8 (C), 137.4 (C), 136.6 (C), 135.5 (2 C), 135.2 (CH), 134.1 (2 C), 130.8 (C), 129.5 (2 CH), 128.9 (CH), 128.8 (2 CH), 120.3 (CH), 113.5 (CH), 96.4 (CH), 67.1 (CH_2), 59.1 (CH_2), 48.6 (CH_2), 45.7 (2 CH_3), 19.8 (2 CH_3), 16.7 (2 CH_3). HRMS calcd for $C_{28}H_{34}N_3O$ 428.2702, found 428.2699.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-(3,5-di-tert-butylphenyl)-1H-benzimidazole dihydrochloride **(1d)**. *Method A* (white powder, 57 %, mp 265-266 °C). IR (KBr) ν_{max} 3411, 2959, 1618, 1477, 1390, 1362, 1259, 1215, 1158, 1092. ^{1}H-NMR (free base, $CDCl_3$) δ 7.78 (d, J= 8.8 Hz, 1H), 7.50 (t, J= 1.8 Hz, 1H), 7.46 (d, J= 1.8 Hz, 2H), 7.38-7.30 (m, 3H), 7.13 (d, J= 7.3 Hz, 2H), 6.98 (dd, J= 8.8 and 2.2 Hz, 1H), 6.75 (d, J= 2.2 Hz, 1H), 5.39 (s, 2H, CH_2), 4.08 (t, J= 5.8 Hz, 2H, CH_2), 2.75 (t, J = 5.8 Hz, 2H, CH_2), 2.35 (s, 6H, 2 CH_3), 1.25 (s, 8H, 6 CH_3). ^{13}C-NMR (free base, $CDCl_3$) δ 155.8 (C), 154.8 (C), 151.1 (2C), 137.8 (C), 136.8 (C), 136.6 (C), 129.2 (C), 129.0 (2 CH), 127.5 (CH), 125.7 (2 CH), 123.7 (CH), 123.4 (2 CH), 120.3 (CH), 111.9 (CH), 95.1 (CH), 66.7 (CH_2), 58.3 (CH_2), 48.3 (CH_2), 45.8 (2 CH_3), 34.8 (2 C), 31.2 (6 CH_3). HRMS for $C_{32}H_{42}N_3O$ calcd 483.3328, found 483.3330.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-[(3,5-diphenyl)phenyl]-1H-benzimidazole dihydrochloride **(1e)**. *Method A* (white powder, 45 %, mp 158-159 °C). IR (KBr) ν_{max} 3420, 2926, 2692, 1654, 1483, 1452, 1210, 763, 700. ^{1}H-NMR (free base, $CDCl_3$) δ 7.90 (t, J= 1.6 Hz, 1H), 7.84 (d, J= 1.6 Hz, 2H), 7.78 (d, J= 8.8 Hz, 1H), 7.55-7.50 (m, 4H), 7.50-7.30 (m, 9H), 7.20-7.10 (m, 2H), 6.99 (dd, J= 8.8 and 2.2 Hz, 1H), 6.79 (d, J= 2.2 Hz, 1H), 5.48 (s, 2H, CH_2), 4.08 (t, J= 5.6 Hz, 2H, CH_2), 2.77 (t, J= 5.6 Hz, 2H, CH_2), 2.36 (s, 6H, 2 CH_3). ^{13}C-NMR (free base, $CDCl_3$) δ 155.9 (C), 153.3 (C), 141.9 (2 C), 139.9 (2 C), 137.6 (C), 136.9 (C), 136.4 (C), 130.9 (C), 129.1 (2 CH), 128.7 (4 CH), 127.6 (2 CH), 126.9 (4 CH), 126.8 (2 CH), 126.5 (2 CH), 125.7 (2 CH), 120.4 (CH), 112.2 (CH), 94.8 (CH), 66.2 (CH_2), 58.0 (CH_2), 48.4 (CH_2), 45.6 (2CH_3). HRMS calcd for $C_{36}H_{34}N_3O$ 524.2702, found 524.2693.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-(2-naphthyl)-1H-benzimidazole dihydrochloride **(1f)**. *Method A* (white powder, 58 %, mp 173-174 °C). IR (KBr) ν_{max} 3413, 2958, 2607, 1623, 1503, 1476, 1218, 1146, 822, 720. ^{1}H-NMR (free base, $CDCl_3$) δ 8.09 (s, 1H), 7.87 (d, J= 8.8 Hz, 1H), 7.83 (d, J= 8 Hz, 1H), 7.78-7.72 (m, 3H), 7.52-7.45 (m, 2H), 7.36-7.28 (m, 3H), 7.13 (d, J= 8 Hz, 2H), 6.97 (dd, J= 8.8 and 2.4 Hz, 1H), 6.73 (d, J= 2.4 Hz, 1H), 5.43 (s, 2H, CH_2), 4.03 (t, J= 5.8 Hz, 2H, CH_2), 2.70 (t, J= 5.8 Hz, 2H, CH_2), 2.31 (s, 6H, 2 CH_3). ^{13}C-NMR (free base, $CDCl_3$) δ 156.0 (C), 153.5 (C), 137.9 (C), 136.9 (C), 136.4 (C), 133.5 (C), 132.9 (C), 129.1 (2 CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.7 (CH), 127.5 (C), 127.0 (CH), 126.6 (CH), 126.1

(CH), 125.9 (2CH), 120.4 (CH), 112.2 (CH), 95.2 (CH), 66.7 (CH_2), 58.2 (CH_2), 48.5 (CH_2), 45.8 (2 CH_3). HRMS calcd for $C_{28}H_{28}N_3O$ 422.5538, found 422.5540.

2-(9-Anthranyl)-1-benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-1H-benzimidazole dihydrochloride **(1g)**. *Method B* (white powder, 57 %, mp 168-170 °C). IR (KBr) ν_{max} 3421, 2675, 1625, 1503, 1462, 1312, 1221, 1106, 741, 718. ^{1}H-NMR (free base, CD_3OD) δ 8.76 (s, 1H), 8.14 (d, J= 8.5 Hz, 2H), 7.77 (d, J= 8.8 Hz, 1H), 7.55-7.48 (m, 2H), 7.46-7.38 (m, 4H), 7.19 (d, J= 2.2 Hz, 1H), 7.12 (dd, J= 8.8 and 2.4 Hz, 1H), 7.02-6.92 (m, 3H), 6.67 (d, J= 7.0 Hz, 2H), 5.01 (s, 2H, CH_2), 4.20 (t, J= 5.4 Hz, 2H, CH_2), 2.88 (t, J= 5.4 Hz, 2H, CH_2), 2.43 (s, 6H, 2CH_3). ^{13}C-NMR (free base, CD_3OD) δ 157.6 (C), 151.9 (C), 138.3 (C), 137.0 (C), 136.9 (C), 132.8 (2 C), 132.5 (2 C), 131.1 (CH), 129.9 (2 CH), 129.4 (2 CH), 128.6 (CH), 128.3 (2 CH), 128.2 (2 CH), 126.7 (2 CH), 126.0 (2 CH), 124.2 (C), 120.7 (CH), 114.1 (CH), 96.6 (CH), 67.1 (CH_2), 59.0 (CH_2), 49.1 (CH_2), 45.7 (2 CH_3). HRMS calc for $C_{32}H_{30}N_3O$ 472.2389, found 472.2398.

1-Benzyl-6-[2-(N,N-dimethylamino)ethyloxy]-2-(3-nitrophenyl)-1H-benzimidazole **(1h)**. *Method C*: (white powder, 15 %, mp 140-142 °C). IR (KBr) ν_{max} 3413, 2963, 2706, 1622, 1529, 1484, 1450, 1350, 1221, 1154. ^{1}H-NMR (free base, $CDCl_3$) δ 8.50 (t, J= 2.2 Hz, 1H), 8.25 (dt, J= 8.0 and 2.2 Hz, 1H), 7.98 (dt, J= 8.0 and 2.2 Hz, 1H), 7.73 (d, J= 8.8 Hz, 1H), 7.58 (t, J= 8 Hz, 1H), 7.36-7.30 (m, 3H), 7.07 (d, J= 6.2 Hz, 2H), 6.99 (dd, J= 8.8 and 2.2 Hz, 1H), 6.75 (d, J= 2.2 Hz, 1H), 5.40 (s, 2H, CH_2), 4.04 (t, J= 5.8 Hz, 2H, CH_2), 2.72 (t, J= 5.8 Hz, 2H, CH_2), 2.32 (s, 6H, 2 CH_3). ^{13}C-NMR (free base, $CDCl_3$) δ 156.6 (C), 150.6 (C), 148.4 (C), 137.7 (C), 137.1 (C), 135.7 (C), 134.8 (CH), 131.9 (C), 129.8 (CH), 129.3 (2 CH), 128.2 (CH), 125.8 (2 CH), 124.2 (CH), 123.9 (CH), 120.9 (CH), 112.9 (CH), 95.0 (CH), 66.7 (CH_2), 58.2 (CH_2), 48.5 (CH_2), 45.8 (2CH_3). HRMS calcd. for $C_{24}H_{25}N_4O_3$ 417.1927, found 417.1919.

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