Synthesis of *N*-Boc-Protected Bis(2-benzimidazolylmethyl)amines

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Abstract: Preparation of bis(1-*tert*-butoxycarbonyl-2-benzimidazolylmethyl)amines from *N*-*tert*-butoxycarbonyl-protected 2-chloromethylbenzimidazole is described. The reaction with primary amines containing several functional groups afforded bis(1-*tert*-butoxycarbonyl-2-benzimidazolylmethyl)amines in good yields. Hydrogenolysis of bis(2-benzimidazolylmethyl)benzylamine, catalyzed by $Pd(OH)_2/C$, cleaved the benzyl group, leaving the *tert*-butoxycarbonyl and 2-benzimidazolylmethyl groups intact. The product of the latter reaction, bis(1-*tert*-butoxycarbonyl-2-benzimidazolylmethyl)amine, was thus obtained in 56% yield; the presence of the *tert*-butoxycarbonyl groups at the *N*-benzimidazole positions makes it amenable to further functionalization at the central nitrogen atom.

Key words: chemoselectivity, benzimidazoles, protecting groups, ligands

Benzimidazoles constitute a class of compounds that have attracted increasing interest in recent years due to their biological activity as antitumor,[1] antiparasitic,[1c,2] and antihelminthic agents.[3] In addition, the biological activity of benzimidazoles can be modified upon formation of metal complexes;[4] this finding has encouraged the design of benzimidazole derivatives with the potential to act as ligands in transition-metal chemistry. This development of benzimidazole-based ligands has also led to the synthesis of metal complexes with applications in the field of catalysis[5] and in bioinorganic chemistry where they can act as mimics of metalloenzyme active sites.[6] In this context, the assembly of two or more benzimidazole units is necessary for the preparation of chelating compounds with at least two nitrogen donors. In catalysis, benzimidazole derivatives have applications in metal-catalyzed transformations: the cycloaddition of alkynes and organic azides (click chemistry),[5a] and the selective oxidation of hydrocarbons are representative examples.[5b] The assembly of two or more benzimidazoles is also crucial in the field of bioinorganic chemistry because this class of compounds can also be employed as ligands in biomimetic systems in which they can emulate the active sites of histidine-rich metalloenzymes.[7]

In the specific case of benzimidazoles assembled around a central nitrogen atom, the reported synthetic method for the preparation of both tris- and bis(2-benzimidazolylmethyl)amines requires elevated reaction temperatures.[5a] Whereas the tris(benzimidazole) compound **1** (Figure 1) can only be further functionalized at the benzimidazole nitrogen atoms, the bis(benzimidazole) compound **2** offers an additional reactive site at the secondary amine. This can be exploited for the incorporation of different functional groups to obtain novel bis(benzimidazoles) with modified biological activity, as well as for generating a series of new chelating ligands for transition-metal chemistry. Discrimination of the nucleophilic sites of **2** to attain a regioselective substitution at the central nitrogen atom exclusively, poses a synthetic challenge that requires careful analysis.

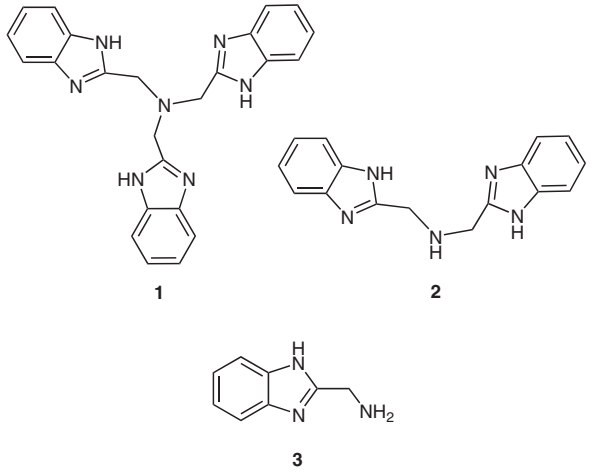

Figure 1 Chemical structures of benzimidazoles **1–3**

The dihydrochloride of 2-aminomethylbenzimidazole (**3**) was employed as a model system. It is reasonable to assume that addition of one equivalent of triethylamine to **3**·2HCl would result in the selective deprotonation of the more acidic N-H proton of the benzimidazole ring; the free base sp^2-hybridized nitrogen atom would thus be available to act as a nucleophile upon treatment with di-*tert*-butyldicarbonate [$(Boc)_2O$], resulting in a Boc-protected benzimidazolic nitrogen atom (Scheme 1, path a). Instead, the reaction resulted in the protection of both the benzimidazolic and aliphatic nitrogen atoms (Scheme 1, path b). The double substitution occurred even in the presence of only 1.1 equivalents of triethylamine and $(Boc)_2O$, albeit in low yield.[8] A similar behavior has

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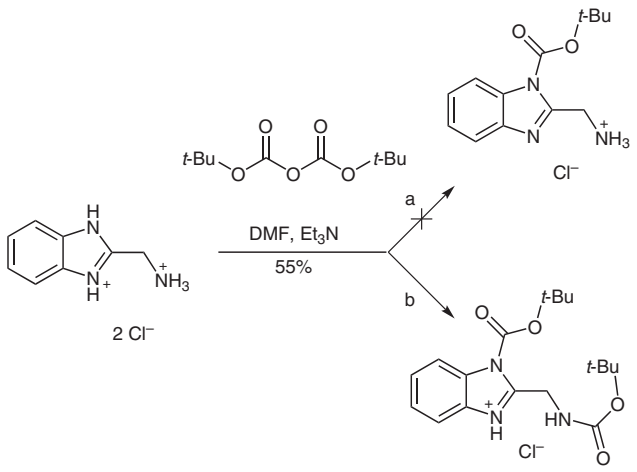
been observed in the reaction of diethyl pyrocarbonate with histidine-containing peptides, which results in the protection of both amino and imidazole nitrogen atoms.[9] This regioselectivity issue has been addressed by reductive amination of the aliphatic N-atom of a benzimidazole derivative similar to **3**.[10]

As an alternative, we devised a method to circumvent this regioselectivity problem of discrimination between the benzimidazolic and aliphatic N-atoms by assembling 2-benzimidazolylmethyl moieties previously protected with Boc. This methodology offers the possibility of easily removing the Boc group, through known procedures, after the introduction of the desired substituents at the aliphatic amine. The synthetic route required the initial preparation of *N*-Boc-2-(chloromethyl)benzimidazole (**4**) by a slight modification of the literature procedure.[10] Reaction of two equivalents of **4** with benzylamine resulted in formation of the crystalline compound bis(1-*tert*-butoxycarbonyl-2-benzimidazolylmethyl)benzylamine (**5**) in good yield (Scheme 2).

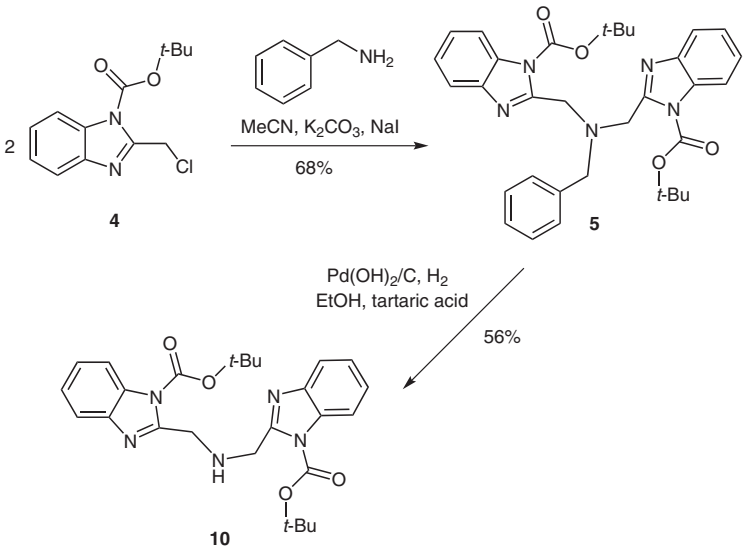


Scheme 1 Reaction of **3**·2HCl with 1.1 equivalents of Et_3N and $(Boc)_2O$

This method allows the assembly of two benzimidazole units around a central nitrogen atom, avoiding the drastic reaction conditions necessary in the condensation of *o*-phenylenediamine with iminodiacetonitrile or iminodiacetic acid, to obtain compound **2**. In addition, compound **5** has already incorporated two Boc groups as substituents on the benzimidazolic nitrogen positions, which would otherwise be difficult to introduce onto compound **2** selectively. As mentioned earlier, protection of **2** would likely result in the introduction of Boc groups at both the benzimidazole nitrogen atoms and the secondary amine, based on the observations described for the model compound **3** and on literature reports.[9]

The procedure shown in Scheme 2 was adapted for use with primary amines with different functional groups to give a range of bis(2-benzimidazolylmethyl)amines; the reactions were performed with 2-(aminomethyl)thiophene, 2-(2,4-dimethylphenylthio)ethylamine [**6**; prepared from (*N*-benzyloxycarbonyl)-2-aminoethyl *p*-toluenesulfonate[11] and 2,4-dimethylbenzenethiol], and 2-(*S*)-aminobutanol. The corresponding compounds **7**–**9**, which incorporate additional heteroatoms for potential ligation, were obtained in good yields. In the case of **9**, which was obtained from 2-(*S*)-aminobutanol, the chiral center lends itself to potential applications in asymmetric catalysis.

Deprotection of **5** to obtain the debenzylated bis(1-*tert*-butoxycarbonyl-2-benzimidazolylmethyl)amine (**10**) was achieved by palladium-catalyzed hydrogenolysis, which did not affect the Boc groups. We carried out the hydrogenolysis of **5** in the presence of a weak acid (tartaric acid) in order to prevent coordination of the nitrogen donors to the palladium catalyst and avoid cleaving the acid-sensitive Boc groups. The reaction proceeded at a relatively slow rate, possibly due to the steric hindrance at the *N*-benzyl moiety, which arises from the proximity of the two Boc substituents. Compound **10** was thus obtained in crystalline form as the free base after neutralization with



Scheme 2 Synthesis of bis(2-benzimidazolylmethyl)amine (**10**)

potassium carbonate. The ^{1}H NMR spectrum of **10** reveals the presence of inequivalent benzimidazole groups, as evidenced by the presence of two *tert*-butyl Boc signals, as well as two N-CH_2-benzimidazole resonances. This behavior needs further investigation, however, we attribute it to intramolecular hydrogen bonding between the amine N-H group and the C=O moiety of a Boc group. Nonetheless, the identity of **10** was firmly established by combustion analysis.

In summary, we have developed a method for the assembly of Boc-protected benzimidazoles around a central nitrogen atom.[12] Based on the examples presented, the choice of the primary amine can result in the development of bis(benzimidazole)amines with a variety of amine N-functional groups. This can also be achieved via **5**, which allows the selective deprotection of the *N*-benzyl group to obtain **10** with an amine N-H group available for further functionalization.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) **3**·2HCl (220 mg, 1.00 mmol), Et_3N (111 mg, 1.10 mmol), and $(Boc)_2O$ (240 mg, 1.10 mmol) in DMF (10 mL) were stirred at 40 °C for 4 h to give crystals upon cooling to 4 °C (212 mg, 55%). *tert*-Butyl 2-[(*tert*-butoxycarbonylamino)-methyl]-1*H*-benzo[*d*]imidazole-1-carboxylate: ^{1}H NMR: δ = 1.48 (s, 9 H), 1.72 (s, 9 H), 4.79 (s, 2 H), 5.85 (br s, 1 H), 7.31 (m, 2 H), 7.68 (m, 1 H), 7.93 (m, 1 H). MS (EI): *m/z* (%) = 347 (3) $[M]^+$.

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(12) Synthesis of bis(1-*tert*-butoxycarbonyl-2-benzimidazolylmethyl)amines **5**–**10**; General procedure: To K_2CO_3 (7.74 g, 40 mmol), **4** (5.00 g, 18.7 mmol) and NaI (280 mg, 1.87 mmol) in MeCN (75 mL), were added the amines (9.35 mmol), and the mixture was heated to reflux for 10 h. After filtering and washing the solid with CH_2Cl_2, the combined organic layers were concentrated. Cooling to –25 °C resulted in the formation of colorless crystals; alternatively, purification could be achieved by column chromatography on silica gel.
Compound **5**: 68% yield; mp 145–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61 (s, 18 H), 4.25 (s, 2 H), 4.63 (s, 4 H), 7.16 (m, 3 H), 7.28 (m, 6 H), 7.71 (m, 2 H), 7.84 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.81, 52.23, 56.80, 84.86, 114.42, 119.67, 123.60, 124.05, 126.46, 127.71, 128.64, 132.87, 139.10, 142.04, 148.51, 153.61. IR (KBr): 3025, 2975, 2923, 2859, 1743, 1542, 1453, 1365, 1344, 1258, 1209, 1155, 1118, 1090, 976, 939, 887, 840, 767, 741, 699, 571, 478 cm^{-1}. Anal. Calcd for $C_{33}H_{40}N_5O_{5.5}$ (**5**·1.5H_2O): C, 66.65; H, 6.78; N, 11.78. Found: C, 66.27; H, 6.31; N, 11.53.
Compound **7**: 87% yield; mp 150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (s, 18 H), 4.45 (s, 2 H), 4.63 (s, 4 H), 6.84 (m, 2 H), 7.14 (dd, *J* = 1.8, 4.6 Hz, 1 H), 7.30 (m, 4 H), 7.70 (m, 2 H), 7.87 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.02, 51.36, 51.90, 85.12, 114.66, 119.90, 123.81, 124.25, 124.69, 125.99, 126.22, 133.05, 142.17, 142.84, 148.68, 153.63. IR (KBr): 3060, 2977, 2925, 2855, 1745, 1608, 1542, 1479, 1452, 1364, 1343, 1258, 1209, 1157, 1118, 1090, 971, 939, 887, 842, 767, 741, 692 cm^{-1}. Anal. Calcd for $C_{31}H_{35}N_5O_4S$ (7·1.5H_2O): C, 61.98; H, 6.38; N, 11.66. Found: C, 61.79; H, 5.89; N, 11.41.
Compound **8** was generated from (*N*-benzyloxycarbonyl)-2-aminoethyl (2,4-dimethyl)benzenethioether hydrobromide (**6**·HBr), which was prepared from 2,4-dimethylbenzenethiol and 2-tosyl-benzylformylaminoethane, and treatment with HBr/AcOH. **6**·HBr: mp 105–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.36 (s, 3 H), 3.22 (m, 4 H), 6.9 (d, *J* = 1.8 Hz, 1 H), 6.98 (s, 1 H), 7.30 (d, *J* = 1.8 Hz, 1 H), 8.04 (br s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.74, 21.07, 30.47, 39.09, 127.64, 128.34, 131.60, 137.65, 139.75. IR (KBr): 3015, 2918, 2817, 2624, 2430, 1866, 1580, 1500, 1478, 1435, 1375, 1260, 1130, 1054, 1006, 930, 878, 812, 781, 745, 617 cm^{-1}.
Compound **8**: 57% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65 (s, 18 H), 2.18 (s, 3 H), 2.21 (s, 3 H), 3.09 (br t, 2 H), 3.30 (br t, 2 H), 4.65 (s, 4 H), 6.69 (d, *J* = 7.8 Hz, 1 H), 6.82 (s, 1 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 7.30 (m, 4 H), 7.68 (m, 2 H), 7.87 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.34, 20.92, 28.20, 31.34, 53.08, 53.31, 85.40, 114.87, 120.05, 124.00, 124.51, 127.09, 128.08, 130.93, 132.00, 133.19, 135.08, 137.24, 142.24, 148.83, 153.62. IR (KBr): 3058, 2978, 2930, 2868, 1746, 1607, 1541, 1478, 1452, 1348, 1296, 1259, 1209, 1154, 1118, 1088, 1059, 973, 939, 881, 842, 766, 744 cm^{-1}. HRMS-FAB$^+$: *m/z* calcd for $C_{36}H_{44}N_5O_4S$ $[M + H]^+$: 642.3114; found: 642.3121.

Compound **9**: 68% yield; mp 130–133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 1.8, 7.3 Hz, 3 H), 1.02 (m, 2 H), 1.68 (s, 18 H), 3.18 (m, 1 H), 3.41 (t, *J* = 9.8 Hz, 1 H), 3.62 (m, 1 H), 4.61 (s, 4 H), 7.18 (m, 4 H), 7.53 (m, 2 H), 7.71 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.77, 21.50, 28.19, 50.57, 63.40, 67.23, 85.49, 114.74, 119.60, 123.86, 124.35, 133.12, 141.63, 148.86, 155.86. IR (KBr): 3357, 2971, 2934, 2872, 1741, 1607, 1534, 1345, 1294, 1260, 1155, 1119, 1090, 845, 769, 746, 561 cm^{-1}. Anal. Calcd for $C_{30}H_{39}N_5O_5$: C, 65.55; H, 7.15; N, 12.74. Found: C, 65.56; H, 7.12; N, 12.40. $[\alpha]_D^{20}$ –33.6 (*c* 10 mg/mL, CH_2Cl_2).

Compound **10**: Compound **5** (2.60 g, 4.60 mmol), 20% $Pd(OH)_2$/C (400 mg, 9.35 mmol), and tartaric acid (361 mg, 2.40 mmol) in EtOH (120 mL), were stirred under 60 lb/in^2 H_2 at 45 °C for 18 h. After neutralization with K_2CO_3 (330 mg, 2.40 mmol), the product was dissolved in CH_2Cl_2, filtered through Celite, dried with Na_2SO_4, and concentrated. Purification by column chromatography afforded **10**: 56% yield (1.22 g); mp 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 1.73 (s, 9 H), 4.82 (s, 2 H), 5.13 (s, 2 H), 7.23 (m, 2 H), 7.40 (m, 2 H), 7.57 (br m, 1 H), 7.72 (br m, 1 H), 7.82 (m, 1 H), 7.95 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.94, 28.05, 49.92, 50.89, 81.32, 110.69, 114.96, 115.16, 118.93, 119.23, 121.40, 122.01, 124.62, 124.89, 125.07, 133.09, 133.87, 140.88, 143.73, 153.97, 154.33. IR (KBr): 3051, 2979, 2868, 2792, 2696, 1748, 1697, 1621, 1547, 1454, 1418, 1393, 1363, 1323, 1259, 1209, 1153, 1118, 1092, 1014, 947, 890, 835, 751, 642 cm^{-1}. Anal. Calcd for $C_{33}H_{40}N_5O_{5.5}$: C, 65.39; H, 6.54; N, 14.66. Found: C, 65.53; H, 6.69; N, 14.73.