

Regioselective *N*-Alkylation of 2-Aminobenzylamine *via* Chelation to 9-BBN

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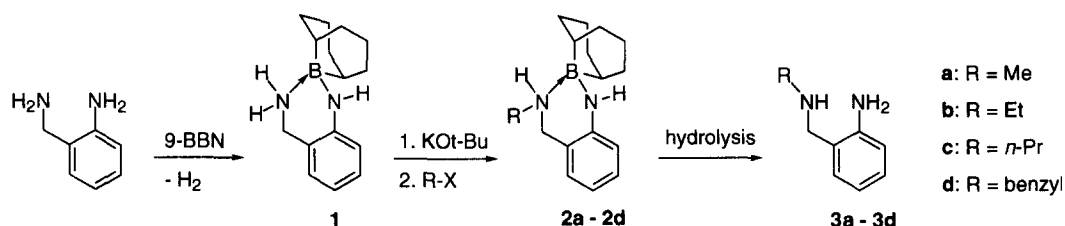
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Abstract: A selective synthesis of 2-amino-*N*-alkylbenzylamines by direct mono alkylation of 2-aminobenzylamine is achieved by a potassium *tert*-butoxide / alkyl halide treatment of a 9-BBN amine-aminoborane chelate. © 1998 Elsevier Science Ltd. All rights reserved.

The synthesis of secondary amines by direct alkylation of primary amines with alkyl halides is not a useful synthetic transformation because the secondary amines react further, giving rise to mixtures of alkylation products. Recently we described the first practical method for *N*-alkylation and *N,N'*-dialkylation of 1,8-diaminonaphthalene relying on an amine-aminoborane chelate formed by reaction with 9-BBN.¹ In that system, *N*-chelation to the boron atom increases the acidity of the NH₂ protons. Treatment with potassium *tert*-butoxide, followed by addition of an alkyl halide and, finally, a mild hydrolysis of the 9-BBN group, leads to the desired *N*-alkyl product in a nearly quantitative yield. It would seem reasonable that the selective *N*-alkylation methodology could work for *any system in which chelation to a 9-BBN group is favored*. In this report we describe a convenient method for regioselective aliphatic mono-*N*-alkylation of 2-aminobenzylamine. Previously, 2-Amino-*N*-substituted benzylamines, which are intermediates in the synthesis of several biologically active compounds, were prepared indirectly, *e.g.* by condensing the appropriate alkyl amine with 2-nitro benzaldehyde followed by borohydride reduction and hydrogenation.²⁻⁵

Addition of 1.0 equiv. of 9-BBN to 2-aminobenzylamine in THF results in evolution of hydrogen gas, and formation of the amine-aminoborane **1**, which is isolated quantitatively as a pure colourless solid upon removal of the solvent under reduced pressure. The formation of a six-membered chelate by coordination of the benzylic H₂N group to the boron atom is supported by the boron chemical shift in the ¹¹B NMR spectrum.^{6,7}



Addition of 1.0 equiv. of potassium *tert*-butoxide to **1** dissolved in THF at RT, followed by a slight excess of the appropriate alkyl halide (methyl iodide, ethyl bromide, *n*-propyl bromide or benzyl chloride) causes an immediate precipitation of a white solid (potassium halide). Filtering off the precipitate and removing

the solvent under reduced pressure yields the alkylated amine-aminoborane chelates (**2a**: R = Me; **2b**: R = Et; **2c**: R = *n*-Pr; **2d**: R = benzyl) in quantitative yields.⁸ ¹H NMR indicates that no polyalkylation products are formed, and that alkylation takes place regioselectively only on the benzylic nitrogen atom.

The synthesis is complete by hydrolyzing the 9-BBN group off either by aqueous HCl, or by aqueous NaOH treatment. An even milder hydrolysis procedure is accomplished by adding 1.0 equiv. of ethanolamine, and precipitating off the ethanolamine-9-BBN adduct.^{1,9} The corresponding 2-amino-*N*-alkyl-benzylamines **3a** - **3d** are obtained in higher than 90% yields.

Relative to previous syntheses, the *N*-alkylation method described herein is direct and efficient. The chelation to the 9-BBN group serves in the dual roles of protecting the aromatic amine and activating the benzylic amine. We are currently investigating the application of the boron-chelate methodology for selective alkylation of other systems.

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References and Notes

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3. Ishikawa, F.; Watanabe, Y.; Saegusa, J. *Chem. Pharm. Bull.* **1980**, *28*, 1357.
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6. **1** is typically prepared on a 3 gram scale in quantitative yield, using commercially available 9-BBN (0.5 M in hexanes) and 2-aminobenzylamine: ¹H NMR (C₆D₆, 200 MHz) δ 7.07 (t, 1 H), 6.61 (d, 1 H), 6.53 (t, 1 H), 6.36 (d, 1 H), 3.63 (bs, 1 H, NH), 3.06 (t, 2 H, CH₂), 2.06-1.05 (m, 12 H), 0.52 (bs, 2 H, CH-B). ¹¹B-NMR (C₆D₆, 115.5 MHz) δ -3.7.
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8. Selected spectral data: **2a**: ¹H NMR (C₆D₆) δ 7.09 (t, 1 H), 6.73 (d, 1 H), 6.58 (t, 1 H), 6.41 (d, 1 H), 3.90 (bs, 1 H, NH), 2.68 (m, 2 H, CH₂), 2.13-1.78 (m, 12 H), 1.62 (d, 3 H, CH₃), 1.29 (m, 1 H) 0.61 (bs, 2 H, CH-B). EI-MS 255.2 (M⁺, 100%); **2b**: ¹H NMR (C₆D₆) δ 7.17 (t, 1 H), 6.75 (d, 1 H), 6.64 (t, 1 H), 6.48 (d, 1 H), 3.91 (m, 1 H), 3.71 (bs, 1 H), 3.17 (m, 1 H), 2.73 (m, 1 H), 2.09-1.40 (m, 14 H), 0.70 (bs, 2 H, CH-B), 0.31 (t, 3 H). EI-MS 269.3 (M⁺, 100%); **2c**: ¹H NMR (C₆D₆) δ 7.17 (t, 1 H), 6.78 (d, 1 H), 6.65 (t, 1 H), 6.50 (d, 1 H), 3.95 (m, 1 H), 3.73 (bs, 1 H), 3.04 (m, 2 H), 2.41-1.47 (m, 16 H), 0.81 (bs, 2 H, CH-B), 0.37 (t, 3 H). EI-MS 283 (M⁺, 100%); **2d**: ¹H NMR (C₆D₆) δ 7.19 (m, 1 H), 7.05 (m, 3H); 6.84 (m, 2 H), 6.68 (m, 2 H), 6.53 (d, 1 H), 3.77 (2, 2 H), 3.4 (m, 3 H), 2.08-1.80 (m, 13 H), 0.83 (bs, 2 H, CH-B). EI-MS 331.3 (M⁺, 80%), 106 (100%).
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