Pergamon

Tetrahedron Letters 39 (1998) 2643–2644

TETRAHEDRON LETTERS

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

Galia Bar-Haim and Moshe Kol*

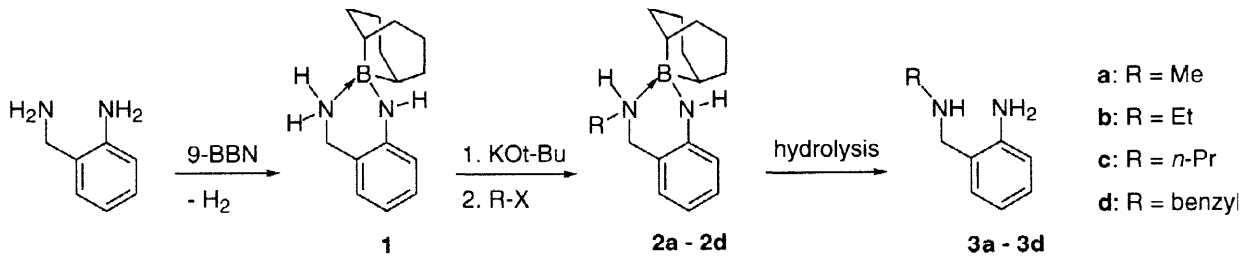
School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Ramat Aviv, Tel Aviv 69978, Israel

Received 1 January 1998; accepted 23 January 1998

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.

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 NH_2 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 H_2N group to the boron atom is supported by the boron chemical shift in the ^{11}B 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

0040-4039/98/$19.00
PII: S0040-4039(98)00227-5

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] ^{1}H 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.

Acknowledgment: *This research was supported by the Israel Science Foundation administered by the Israel Academy of Sciences and Humanities.*

References and Notes

1. Bar-Haim, G.; Kol, M. *J. Org. Chem.* **1997**, *62*, 6682.
2. Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, *11*, 1208.
3. Ishikawa, F.; Watanabe, Y.; Saegusa, J. *Chem. Pharm. Bull.* **1980**, *28*, 1357.
4. Kornet, M. J. *J. Heterocyclic Chem.* **1992**, *29*, 103.
5. Orth, R. E.; Jones, J. W. *J. Pharm. Sci.* **1961**, *50*, 866.
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: ^{1}H NMR (C_6D_6, 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, N*H*), 3.06 (t, 2 H, CH_2), 2.06-1.05 (m, 12 H), 0.52 (bs, 2 H, C*H*-B). ^{11}B-NMR (C_6D_6, 115.5 MHz) δ -3.7.
7. Bar-Haim, G.; Shach, R.; Kol, M. *Chem Commun.* **1997**, 229.
8. Selected spectral data: **2a**: ^{1}H NMR (C_6D_6) 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, N*H*), 2.68 (m, 2 H, CH_2), 2.13-1.78 (m, 12 H), 1.62 (d, 3 H, CH_3), 1.29 (m, 1 H) 0.61 (bs, 2 H, C*H*-B). EI-MS 255.2 (M^+, 100%); **2b**: ^{1}H NMR (C_6D_6) 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, C*H*-B), 0.31 (t, 3 H). EI-MS 269.3 (M^+, 100%); **2c**: ^{1}H NMR (C_6D_6) 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, C*H*-B), 0.37 (t, 3 H). EI-MS 283 (M^+, 100%); **2d**: ^{1}H NMR (C_6D_6) 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, C*H*-B). EI-MS 331.3 (M^+, 80%), 106 (100%).
9. Brown, H. C.; Vara Prasad, J. V. N. *J. Org. Chem.* **1986**, *51*, 4526.