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Selective Mono-*N*-alkylation of 3-Amino Alcohols via Chelation to 9-BBN

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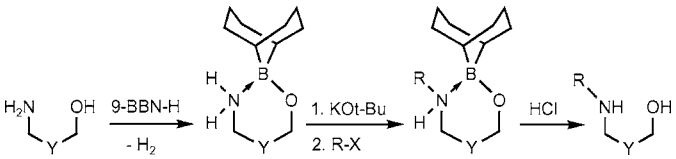
ABSTRACT



A method for selective mono-N-alkylation of amino alcohols is introduced. This method relies on formation of a stable chelate with 9-BBN, which serves in the dual roles of protecting and activating the amine group. Three prototypical amino alcohols featuring various three-carbon bridging units led selectively to the monoalkylated derivatives in very high yields. The straightforward synthesis of the *N*-CD_3 derivatives demonstrates the effectiveness of this approach.

The selective mono-N-alkylation of primary amines by direct nucleophilic substitution on alkyl halides is a familiar challenge in organic synthesis. Since the produced secondary amines are usually at least as reactive as the starting primary amines, they react further, yielding mixtures of alkylation products.[1] The common solutions are either the use of an excess of the primary amine followed by distillation or utilizing an alternative route such as reductive amination. However, if the amine is expensive, or when other functional groups in the molecule are sensitive to reduction, these schemes may become unsatisfactory. Recently, we introduced a method for selective mono-N-alkylations of certain diamines with alkyl halides relying on formation of a chelate with 9-BBN that enabled the efficient N-alkylation and N,N′-dialkylation of 1,8-diaminonaphthalene[2,3] and the regioselective mono-N-alkylation of 2-aminobenzylamine.[4] In this paper we report that the "chelation to 9-BBN" approach is applicable for selective mono-N-alkylation of various amino alcohols.[5−7] Several representative 1,3-amino alcohols were chosen for this preliminary feasibility study, and all proved to undergo exclusive mono-N-alkylation in high yields (Figure 1).

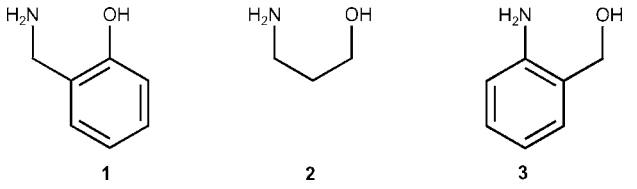


Figure 1. Amino alcohols studied in this work.

The essential requirement for successful mono-N-alkylation by this approach would be the formation of a stable chelate between the amino alcohol and 9-BBN. This chelate

(1) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th ed.; Kluwer Academic: New York, 2001; Part B, Chapter 3.2.5.

(2) Bar Haim, G.; Kol, M. *J. Org. Chem.* **1997**, *62*, 6682. See also: Bar Haim, G.; Shach, R.; Kol, M. *Chem. Commun.* **1997**, 229.

(3) For application of this approach in the synthesis of chiral "proton sponges", see: (a) Charmant, J. P. H.; Lloyd-Jones, G. C.; Peakman, T. M.; Woodward, R. L. *Tetrahedron Lett.* **1998**, *39*, 4733. (b) Charmant, J. P. H.; Lloyd-Jones, G. C.; Peakman, T. M.; Woodward, R. L. *Eur. J. Org. Chem.* **1999**, 2501. (c) Lloyd-Jones, G. C. *Synlett* **2001**, 161.

(4) Bar Haim, G.; Kol, M. *Tetrahedron Lett.* **1998**, *39*, 2643.

(5) For the selective monoacylation of symmetrical diamines via prior complexation with 9-BBN, see: Zhang, Z. X.; Yin, Z. W.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2003**, *5*, 3399.

(6) For selective N-alkylation employing cesium bases, see: Salvatore, R. N.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 674.

(7) For selective monomethylation of substituted anilines by dimethyl carbonate in the presence of a zeolite catalyst, see: Selva, M.; Tundo, P.; Perosa, A. *J. Org. Chem.* **2003**, *68*, 7374.

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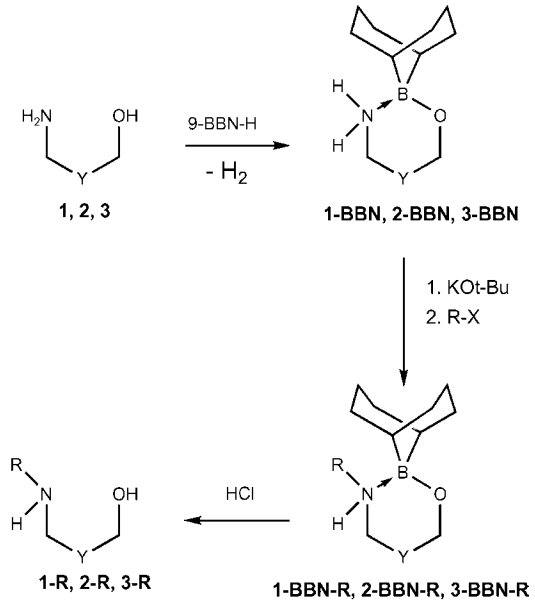
Scheme 1. General Alkylation Scheme of Amino Alcohols via Chelation to 9-BBN



R = Me, Et, n-Pr, Bn.

should consist of an oxygen−boron covalent bond and a strong nitrogen−boron coordinative bond. In this neutral form, the amine functionality is, at the same time, protected from alkylation as well as being more acidic since the nitrogen lone pair is coordinating to the Lewis acidic boron center. Facile removal of a single proton by a relatively mild base should lead to formation of an anionic nucleophile that can react with a single equivalent of an alkyl halide giving the mono-*N*-alkyl product that is protected from further alkylation by coordination to the boron. Finally, a mild acidic hydrolysis of 9-BBN should release the mono-N-alkylated amine (Scheme 1).

Therefore, the first substrate we chose was 2-hydroxybenzylamine (**1**),[8] which is expected to bind to 9-BBN by a strong oxygen−boron covalent bond and a strong nitrogen−boron coordinative bond, thus completing a six-membered chelate ring. *N*-Alkyl derivatives of 2-hydroxybenzylamine, which are intermediates in the synthesis of several biologically active compounds, have previously been prepared by amine condensation with salicylaldehyde followed by reduction,[9] since a direct reaction of 2-hydroxybenzylamine with alkyl halides is expected to yield a mixture of alkylation products. Adding 1.0 equiv of 9-BBN−H to 2-hydroxybenzylamine in ether resulted in evolution of hydrogen gas and formation of the chelate **1-BBN**, which was isolated by removal of the solvent in quantitative yield. Alternatively, **1-BBN** can be synthesized from methoxy-9-BBN and 2-hydroxybenzylamine with formation of methanol. **1-BBN** is a white, air-sensitive crystalline compound. The spectral properties of **1-BBN** support its proposed structure (see Supporting Information for full spectroscopic characterization of **1-BBN**). In particular, the formation of an O−B−N chelate is supported by the ^{11}B NMR chemical shift, which is consistent with a tetracoordinate boron atom (Table 1).

Table 1. 9-BBN Chelates, ^{11}B NMR Chemical Shifts, and Yields of Final N-Alkylated Products

9-BBN chelate	^{11}B NMR (ppm, vs $BF_3{\cdot}OEt_2$)	isolated product	total yield
1-BBN	−0.6		100%
1-BBN−Me	0.8	**1-Me**	95%
1-BBN−Et	1.3	**1-Et**	95%
1-BBN−Pr	1.4	**1-Pr**	95%
1-BBN−Bn	1.8	**1-Bn**	95%
2-BBN	3.0		100%
2-BBN−Me	4.3	**2-Me**·HCl	100%
2-BBN−Et	5.0	**2-Et**·HCl	100%
2-BBN−Pr	5.2	**2-Pr**·HCl	100%
2-BBN−Bn	5.6	**2-Bn**·HCl	100%
3-BBN	13.5		100%
3-BBN−Me	9.2	**3-Me**	90%
3-BBN−Et	23.1	**3-Et**	90%
3-BBN−Pr	31.6	**3-Pr**	90%
3-BBN−Bn	41.0	**3-Bn**	90%

As expected, **1-BBN** did not react with electrophiles such as methyl iodide at room temperature. However, on addition of potassium *tert*-butoxide at room temperature to **1-BBN** dissolved in THF followed by a primary alkyl halide R−X namely, iodomethane, iodoethane, 1-bromopropane, or benzyl chloride, an immediate reaction took place, as was evident from the precipitation of a white solid (potassium halide). Filtration and removal of the solvent gave the mono-*N*-alkyl derivatives **1-BBN−R** quantitatively. ^{1}H NMR spectra of the crude products indicated that alkylation took place only on the nitrogen atom and that polyalkylation did not occur. In analogy to **1-BBN**, the mono-*N*-alkyl derivatives **1-BBN−R** are also chelating according to ^{11}B NMR (Table 1). An acidic hydrolysis of the 9-BBN group at room temperature followed by a basic workup gave the four mono-N-substituted 2-hydroxybenzylamines **1-R** (R = Me, Et, Pr, Bn) in very high yields (Table 1).

The second prototypical amino alcohol we investigated was the aliphatic 3-aminopropanol (**2**), whose tendency to form a six-membered chelate with 9-BBN may be somewhat diminished due to loss of entropic conformational freedom. A previous synthesis of N-substituted 3-amino alcohol relied on a Michael addition between a primary amine and ethyl acrylate followed by reduction.[10] In addition, the *N*-benzyl derivative was synthesized by a nucleophilic substitution employing a large excess of the amine to avoid over-

(8) Holly, F. W.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 1875. (b) Zaugg, H. E.; Schaefer, A. D. *J. Org. Chem.* **1963**, *28*, 2925.

(9) (a) Neuvonen, K.; Pihlaja, K. *J. Chem. Soc., Perkin Trans. 2* **1988**, 461. (b) Yoshikawa, H.; Fuchigami, K.; Shono, T. *J. Pesticide Sci.* **1986**, *11*, 631. (c) Neuvonen, K.; Pihlaja, K. *Magn. Reson. Chem.* **1990**, *28*, 239. (d) Clark, J. S.; Middleton, M. D. *Org. Lett.* **2002**, *4*, 765.

(10) (a) Le Lann, M.; Saba, S.; Shoja, M. *J. Heterocycl. Chem.* **1991**, *28*, 1789. (b) Jones, R. A. Y.; Katritzky, A. R.; Trepanier, D. L. *J. Chem. Soc. B* **1971**, 1300. (c) Israeli, H. Z.; Derel, J. M.; Cunningham, R. F.; Dayton, P. G.; Yü, T. F.; Gutman, A. B.; Long, K. R.; Long, R. C.; Goldstein, J. H. *J. Med. Chem.* **1972**, *15*, 709.

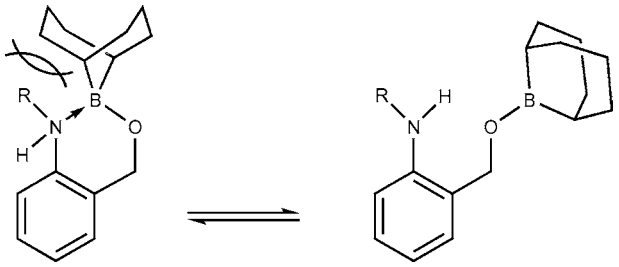
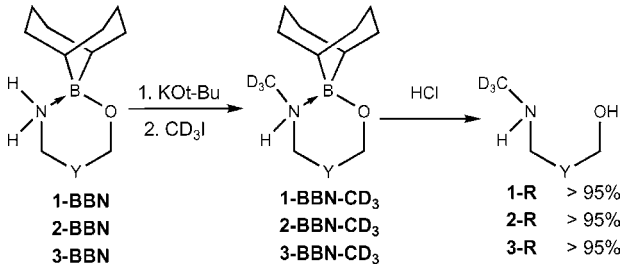


Figure 2. Possible equilibrium between chelate and open-form isomers in **3-BBN-R**.

alkylation,[11] as well as by copper-catalyzed coupling of iodobenzyl alcohol with benzylamine.[12] Adding 1.0 equiv of 9-BBN-H to **2** resulted in evolution of hydrogen gas and quantitative formation of the desired six-membered chelate **2-BBN**, as supported by spectroscopic data and especially ^{11}B NMR. Following the same deprotonation and alkylation as above led to the mono-N-alkylated products **2-BBN−R** in quantitative yields whose ^{11}B NMR indicated that they, too, were chelating. Finally, a mild acidic hydrolysis procedure led to the four mono-*N*-alkyl 3-hydroxypropylamines **2-R** (R = Me, Et, Pr, Bn) isolated as the hydrochloride salts in quantitative yields.

We found that this alkylation method is successful even for six-membered chelates featuring a weak donor, namely, 2-aminobenzyl alcohol (**3**). Previous syntheses of alkyl derivatives of this amino alcohol relied on various combinations of condensation followed by reduction.[13] Reacting **3** with 9-BBN-H led to the air-sensitive chelate **3-BBN** in quantitative yield. Even though this chelate is expected to be less stable due to formation of a weak aromatic nitrogen−boron coordinative bond, the sequence of deprotonation−alkylation led selectively to the formation of the respective alkylated chelates **3-BBN−R**, quantitatively. Interestingly, the ^{11}B NMR chemical shifts of the alkylated chelates featured a substantial downfield shift as a function of the bulk of the *N*-alkyl groups (a similar but much less apparent trend may be observed for the former series). This trend may result from equilibrium between a chelate (having a typical ^{11}B NMR chemical shift of ca. 0 ppm) and its relatively stable open-form isomer in which the nitrogen lone pair is donated to the aromatic ring (having a typical ^{11}B NMR chemical shift of ca. 50 ppm)[2,14] that favors the latter as the bulk of the N-substituents increases (Figure 2). Again, a facile acidic hydrolysis gave the four alkylated products **3-R** in very high yields (Table 1).

Scheme 2. Synthesis of *N*-Deuteriomethyl Derivatives of Amino Alcohols **1**−**3**



Preliminary experiments indicated that the chelation to 9-BBN approach is not successful for 1,2-amino alcohols. Thus, even though the reaction of norephedrine with 9-BBN−H led to a five membered chelate,[14] the following deprotonation and alkylation sequence led to a mixture of alkylation products. It is possible that the monoalkylated chelate is too strained and reacts further with an alkyl halide via its neutral open-form isomer. It is possible that given an appropriate Lewis acid-chelating center, the selective alkylation of these important substrates may be achieved.

The advantage of the chelation to 9-BBN method over the common reductive amination procedure may be appreciated by the selective and essentially quantitative formation of the CD_3-derivatives of all these prototypical amino alcohols by employing CD_3I as the alkylating agent (Scheme 2). Obviously, a classical approach to these compounds would have required a less economical use of deuterated agents.

In conclusion, we have shown that the "chelation to 9-BBN" is a straightforward, mild, and efficient method for selective mono-N-alkylation of several prototypical 3-amino alcohols.[15] This approach can clearly be extended to various substrates featuring a 1,3-relationship between an amine and an alcohol group.

Acknowledgment. We thank the Israel Science Foundation for financial support.

Supporting Information Available: Synthetic procedures and analytical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048554K

(11) (a) Ravina, E.; Ramos, R. G.; Masaguer, C. F.; Garcia Mera, G. *Synth. Commun.* **1994**, *24*, 321. (b) Ali, Sk. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917.

(12) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

(13) (a) Yamakawa, T.; Matsukura, H.; Nomura, Y.; Yoshioka, M.; Masaki, M.; Igata, H.; Okabe, S. *Chem. Pharm. Bull.* **1991**, *39*, 1746. (b) Coppola, G. M. *J. Heterocycl. Chem.* **1986**, *23*, 223.

(14) Parent compound, 2-aminoethanol, is known to form a five-membered chelate with 9-BBN: (a) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197. (b) Brown, H. C.; Prasad, J. V. N. V. *J. Org. Chem.* **1986**, *51*, 4526.

(15) Attempted extension of this methodology to secondary alkyl halides (e.g., isopropyl bromide) failed, apparently due to a competing elimination reaction.