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Efficient Synthesis of *B*-Alkylated Oxazaborolidines Derived from Ephedrine and Norephedrine

Margarita Ortiz-Marciales,* Eduvigis González, Melvin De Jesús, Sandraliz Espinosa, Wildeliz Correa, Johanna Martínez, and Ruth Figueroa

Department of Chemistry, University of Puerto Rico−Humacao, CUH Station, Humacao, Puerto Rico 00791

mr_ortiz@webmail.uprh.edu

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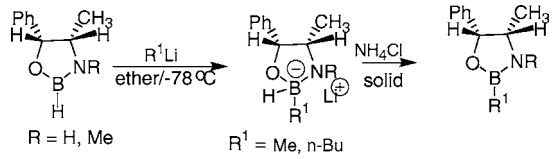
ABSTRACT



Representative *B*-butyl- and *B*-methyl-1,3,2-oxazaborolidines derived from ephedrine and norephedrine were prepared in good yield and excellent purity by one-pot treatment of *B*-H oxazaborolidines with the corresponding organolithium reagent and subsequent hydrolysis of the cyclic borohydride intermediate with anhydrous ammonium chloride.

Chiral 1,3,2-oxazaborolidines have been well studied and regarded as important catalysts for the enantioselective reduction of prochiral ketones, imines, and oximes[1−3] and in other stereoselective transformations.[4] The development of oxazaborolidines has been limited mainly by the availability of suitable chiral amino alcohols. Norephedrine and ephedrine are commercially available and relatively inexpensive in their two enantiomeric forms. Consequently, their derived oxazaborolidines, and particularly the *B*-alkyl-substituted systems, have been widely investigated and reported as highly efficient chiral templates for the borane reduction of prochiral ketones[5] and C═N double bonds,[6] in catalytic hydroboration,[7] as well as in addition of diethylzinc to aldehydes.[8]

B-H oxazaborolidines are usually prepared by the reaction of norephedrine or ephedrine with borane−THF or borane

(1) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, Y. *J. Chem. Soc., Chem. Commun.* **1981**, 315−317.

(2) (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. (b) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763−784. (c) Singh, V. K. *Synthesis* **1992**, 605−617. (d) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475−1504.

(3) (a) Nakagawa, M.; Kawate, T.; Kakikawa, T.; Yamada, H.; Matsui, T.; Hino, T. *Tetrahedron* **1993**, *49*, 1739−1748. (b) Fontaine, E.; Namane, C.; Meneyrol, J.; Geslin, M.; Serva, L.; Roussey, E.; Tissandie, S.; Maftouh, M.; Roger, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2185−2189. (c) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902−7911.

(4) (a) Seerden, J.-P. G.; Boeren, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843−11852. (b) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151−3152. (c) Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551−5554. (d) Brown, J. M.; Lloyd-Jones, G. C. *Tetrahedron: Asymmetry* **1990**, *1*, 869−872.

(5) (a) Caze, C.; El-Moualij, N.; Hodge, P.; Lock, C. J.; Ma, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 345−349. (b) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 1539−1542. (c) Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron: Asymmetry* **1994**, *5*, 165−168. (d) Bach, J.; Berenguer, R.; Jordi Garcia, J.; Loscertales, T.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021−9025. (e) Quallich, G. J.; Blake, J. F.; Woodall, T. M. Diphenyloxazaborolidines for Enantioselective Reduction of Ketones. In *Reductions in Organic Synthesis*; Abdel-Magid, A. F., Ed. American Chemical Society: Washington, DC, 1996; Chapter 7, pp 112−126. (f) Quallich, G. J. B.; James F.; Woodall, Teresa M. *J. Am. Chem. Soc.* **1994**, *116*, 8516−8525. (g) Compound **4b** was prepared following the procedure given in ref 5a for the condensation reaction of butylboronic acid with norephedrine in toluene. We were able to obtain only a 41% yield of distilled **4b** with impurities of butyl boronic acid and amino boronic intermediate **3b**, as observed by ^{11}B NMR.

(6) (a) Cho, T. B.; Ryu, M. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 191−192. (b) Cho, B. T.; Ryu, M. H.; Chun, Y. S.; Dauelsberg, C.; Wallbaum, S.; Martens, J. *Bull. Korean Chem. Soc.* **1994**, *15*, 53−57. (c) Dougherty, J. T.; Flisak, J. R.; Hayes, J.; Lantos, I.; Liu, L.; Tucker, L. *Tetrahedron:* Asymmetry **1997**, *8*, 497−500.

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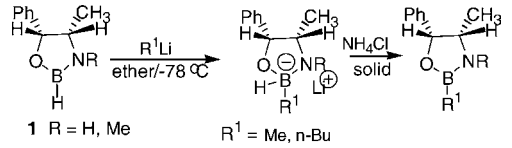
dimethyl sulfide complex.[4c] Their extreme sensitivity to air and moisture make these reagents difficult to purify by distillation or recrystallization, and therefore, they are commonly prepared in situ for subsequent reactions.[9] However, side products present with the unpurified *B*-H heterocyclic catalysts or reagents cause a detrimental effect on the enantiomeric purity of desired chiral products.[10] Furthermore, *B*-H oxazaborolidines left over a period of time can form dimers or oligomers that alter the nature of the chiral catalyst.[4d,11] On the contrary, *B*-alkylated compounds are more stable and easier to purify and handle than the nonsubstituted counterparts and produce similar enantioselectivities.[5e] *B*-Substituted 1,3,2-oxazaborolidines are typically prepared by condensation of the amino alcohols with boronic acids,[5a] boroxines,[5d,e] or their boronate esters,[4c] removing water and boronic acid, or boronic ester residues, by azeotropic distillation in toluene.[5d] The treatment of chiral amino alcohols with organo-bis(diisopropylamino)borane for the synthesis of *B*-alkyl and phenyl oxazaborolidines has also been reported.[12] However, these methods require expensive and elaborate reagents, and moreover, the complete removal of water and boronic acid is extremely difficult.

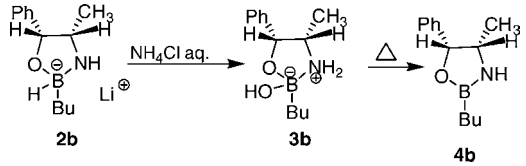
Herein, we describe a novel approach for the one-pot synthesis of pure *B*-alkyl-1,3,2-oxazaborolidines derived from ephedrine and norephedrine via alkylation of the parent boraheterocyclic compound **1**, as indicated in Scheme 1.[13]

Scheme 1



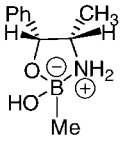
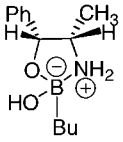
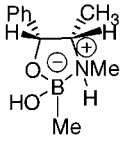
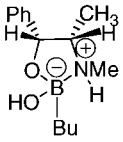
In our previous work,[14] we observed an unprecedented *B*-alkylation of the oxazaborolidine **1** derived from (1*R*,2*S*)-(−)-norephedrine by *n*-butyllithium addition, forming the corresponding cyclic borohydride **2**, as illustrated in Scheme 2. After an aqueous workup, the boronic acid derivative **3b** was isolated in 91% crude yield as a clear oil and identified by ^{11}B, ^{1}H, and ^{13}C NMR and IR spectral data.[15] Intermediate **3b** was observed to be stable to acid and base hydrolysis and can be potentially valuable as a suitable source for the heterocyclic catalyst **4b**. Contrary to the butylboronic acid condensation procedure to prepare **4b** reported by Garcia and co-workers,[5d,g] the formation of this compound was successfully completed by heating **3b**, affording a 75% yield of the distilled product with more than 95% purity by GC/MS and ^{1}H and ^{13}C NMR.[16]

Scheme 2



The approach given in Scheme 2 was then investigated for the synthesis of other common *B*-alkyl-1,3,2-oxazaborolidines derived from (1*R*,2*S*)-(−)-norephedrine and (1*R*,2*S*)-(−)-ephedrine. Initially, the *B*-H oxazaborolidines were synthesized by a modification of the established condensation reaction of the corresponding chiral 1,2-amino alcohol with borane−THF[4c,d] and characterized by ^{11}B and ^{13}C NMR spectroscopy.[4d,17] The boron alkylation with *n*-butyl- or methyllithium of the in situ-prepared *B*-H oxazaborolidine took place readily at −78 °C, forming the lithium borohydride salt **2**. Upon treatment with an aqueous ammonium chloride solution, extraction with ether or dichloromethane, and drying the organic phase with sodium sulfate, the crude boronic acid intermediate **3** was produced with good purity (>85% by GC/MS) and excellent yield, as illustrated in Table 1.

Table 1. Boronic Acid Derivatives Prepared by Alkylation of the *B*-H Oxazaborolidine **1**

	compound **3**	bp (°C/mmHg)	^{11}B-NMR[a] (δ, ppm)	yield[b,c] (%)
3a		95/0.7	7.1	80
3b		-	8.0	91
3c		120/0.5	8.1	75
3d		110/0.1	8.5	97

[a] Chemical shifts using BF_3-OEt_2 as an internal standard. [b] Yield of crude product based on the corresponding amino alcohol. [c] Pure compounds were not obtained due to partial dehydration during distillation.

In the case of analogues **3a**,**c**,**d**, the yields of the pure *B*-alkyl-oxazaborolidines obtained by the previous dehydration method were modest because the boronic acid interme-

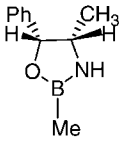
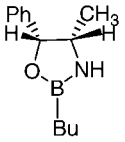
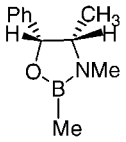
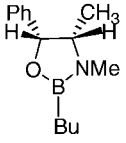
(9) Sakito, Y.; Yoneyoshi, Y.; Suzukamo, G. *Tetrahedron Lett.* **1988**, *29*, 223−224.

(10) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880−2888.

diate **3** codistilled with the oxazaborolidine. The yields of the desired heterocyclic products were only slightly improved by azeotropic distillation of the water using toluene or xylene and 4 Å molecular sieves.[5d] In addition, other side products were observed by GC/MS.

After attempting to find a better alternative to prepare the *B*-alkylated oxazaborolidine from the borohydride intermediate **2** by treatment with MeI or TMSCl, the use of anhydrous ammonium chloride provided the expected oxazaborolidines in good yield and with excellent purity as indicated by GC/MS and ^{11}B, ^{1}H, and ^{13}C NMR.[16,18] The boiling points and ^{11}B NMR signals of *B*-methyl and *n*-butyl-substituted oxazaborolidines **4** and the isolated yields of the analytically pure compounds prepared by the aqueous and dry methods are shown in Table 2.

Table 2. *B*-Alkyl Oxazaborolidines Prepared by *B*-Alkylation of the Parent Heterocyclic Compound

compound **4**	bp (°C/mmHg)	^{11}B-NMR[a] (δ, ppm)	yield[b] (%)
4a 	42/0.12	32	65 48[c]
4b 	82/0.1	35	56 75[c]
4c 	80/2.0	34	58 45[c]
4d 	84/0.55	34	70 50[c]

[a] Chemical shifts using BF_3-OEt_2 as an internal standard. [b] Yield based on the corresponding amino alcohol by treatment of **2** with anhydrous ammonium chloride followed by fractional distillation. [c] By treatment of **2** with aqueous ammonium chloride and calculated from crude product **3**.

In summary, we have achieved the first efficient and direct approach to *B*-alkylated oxazaborolidines derived from ephedrine and norephedrine via alkylation of the *B*-H precursors, opening a new avenue for the preparation of other important *B*-substituted oxazaborolidines, which are presently under study.

Acknowledgment. Financial support by the National Institutes of Health through their MBRS (GM 08216) and NIH-AREA (GM 59829) grants is greatly appreciated. The NIH-MARC, DOD-ONR, and NSF-AMP undergraduate support is also gratefully acknowledged. From the University of Puerto Rico, Río Piedras, we thank Professor John A. Soderquist for his helpful discussions and Mr. José Martínez for obtaining the NMR spectra.

Supporting Information Available: Spectroscopic data from *B*-alkylated oxazaborolidines. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Brown, J. M.; Lloyd-Jones, G. C.; Layzell, T. P. *Tetrahedron: Asymmetry* **1993**, *4*, 2151−2154. (b) Nevalainen, V. *Tetrahedron: Asymmetry* **1994**, *5*, 387−394. (c) Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255−2260.

(12) Chavant, P. Y.; Vaultier, M. *J. Organomet. Chem.* **1993**, *455*, 37−46.

(13) Ortiz-Marciales, M.; De Jesús, M.; González, E.; Espinosa, S.; Correa, W. U.S. Patent Application 60/445,743, Feb 2003.

(14) Ortiz-Marciales, M.; González, E.; Figueroa, R.; Martínez, J.; Muñoz, X.; Espinosa, S.; Correa W. Presentation 820, *Abstracts of Papers*, 223rd National Meeting of the American Chemical Society, Orlando, FL, Apr 7−11, 2002; American Chemical Society: Washington, DC, 2002; CHED.

(15) (a) NMR in $CDCl_3$ (ppm): ^{11}B δ 9.2; ^{1}H δ 7.3−6.9 (m, Ph), 4.9 (d, J = 5.2, PhCH−O), 4.4 (s, br, OH), 3.4 (m, CH−N), 3.0 (s, br, NH_2), 1.2−1.1 (m, CH_2), 0.87−0.79 (m, CH_2 , CH_3), 0.67 (d, J = 5.3, CH_3); ^{13}C δ 140.9 (C_{para}), 128−126, 77.4 (PhCH−O), 53.1 (CH−N), 27.2, 26.7, 20.6, 14.3. IR (ν cm^{-1}): 3352 (br, OH, NH_2) 1603 (br, NH_2). GC/MS (70 ev, *m*/*z*): 217 ($M^{+\bullet} - H_2O$), 202 (100%). (b) This compound is new; however, no analytical sample could be obtained due to its partial dehydration on purification. (c) *B*-phenyl boronic acid intermediates formed by the addition of water to oxazaborolidines were reported: Rico, A. R.; Tlahuextl, M.; Flores-Parra, A.; Contreras, R. *J. Organomet. Chem.* **1999**, *581*, 122−128.

(16) See Supporting Information.

(17) Quallich, G. J. U.S. Patent 6,037,505, May 14, 2000.

(18) **Typical Experimental Procedure.** To a solution of borane−THF (43 mmol, 43 mL, 1.0 M) at room temperature was added dropwise a solution of (1*R*,2*S*)-(−)norephedrine (2.5 g, 15.5 mmol) in THF (25 mL). After the clear reaction mixture was stirred for 12 h at room temperature, the solvent was removed under vacuum (20 mmHg) and the white foamy residue was gradually heated in an oil bath to 130 °C and maintained at this temperature for 30 min. A clear crystalline solid compound was obtained, which by ^{11}B, ^{1}H, and ^{13}C NMR was similar to the *B*-H-1,3,2-oxazaborolidine reported by Quallich. A solution of *n*-BuLi (18.6 mmol, 8.0 mL, 2.32 M in hexanes) was added in 15 min to the previously obtained solid dissolved in anhydrous ether (30 mL) and cooled at −78 °C. The mixture was stirred overnight at 25 °C. The pale rose-colored mixture with a fine suspension was cooled at 0 °C and then allowed to react with solid ammonium chloride (4.4 g, 82.5 mmol) for 4 h at room temperature. The solid was removed by filtration using a Schlenk filter under nitrogen flow and vacuum (15 mmHg). The filtrate was concentrated using a vacuum pump and heated at 40 °C, affording the crude product (3.9 g, 99% yield). A short path distillation at reduced pressure furnished the pure ***B*-butyl-1,3,2-oxazaborolidine 4b** as a clear oil (2.0 g, 56%, 98% purity by GC/MS): bp 82 °C/0.1 mmHg. IR (ν cm^{-1}): 3219 (NH). NMR in $CDCl_3$ (500 MHz, ppm): ^{11}B δ 35; ^{1}H δ 7.3 (m, 5H), 7.50 (d, J = 6 Hz, 1H), 3.9 (m, 1H), 3.5 (br s, 1H, NH), 1.5 (m, 4H), 0.9 (m, 5H), 0.6 (d, J = 6 Hz, 3H); ^{13}C δ 139.6, 127.7, 127.2, 126.7, 126.1, 82.1, 53.8, 27.3, 25.4, 20.4, 13.8, 11.3 (br). MS (*m*/*z*): 216.9 ($M^{+\bullet}$), 202 (100%).