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

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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,^{1,2,3} 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 ketones⁵ 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 dimethylsulfide 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, when *B*-H oxazaborolidines are 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, 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,5e} 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

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

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 elaborated reagents, and moreover, the complete removal of water is extremely difficult.

Herein, we describe a novel approach for 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

In our previous work,¹⁴ we observed an unprecedented *B*-alkylation of the oxazaborolidine **1** derived from (1*R*, 2*S*)-(–)-norephedrine by the *n*-butyllithium addition, forming the corresponding cyclic borohydride **2**, as illustrated in scheme 2. After an aqueous work-up, the boronic acid derivative **3b** was isolated in 91% crude yield, as clear oil, and identified by ¹¹B, ¹H, ¹³C 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**, used by Garcia and coworkers,^{5d} the formation of this compound was successfully completed by heating **3b**, obtaining a 75% yield of the distilled product with more than 95% purity by GC/MS, ¹H and ¹³C NMR.¹⁶

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 ¹¹B and ¹³C 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 sulphate, produced the crude boronic acid intermediate **3** with good purity (> 85% by GC/MS) and excellent yield, as illustrated in Table 1.

In the case of analogues **3a,c** and **d**, the yields of the pure *B*-alkyl-oxazaborolidines obtained by the previous dehydration method were modest because the boronic acid intermediate **3** co-distilled 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 4Å 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, ¹¹B, ¹H and ¹³C NMR.¹⁶ The boiling points and ¹¹B NMR signals of *B*-methyl and *n*-butyl substituted oxazaborolidines **4**, and the isolated yields of the analytical pure compounds prepared by the aqueous and dry methods, are shown in table 2.

Typical experimental procedure

To a solution of Borane-THF (43 mmol, 43 mL, 1.0 M) at room temperature was added drop-wise 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 hr at room temperature, the solvents were 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 ¹¹B, ¹H and ¹³C NMR was similar to the *B*-H-1,3,2-oxazaborolidine reported by Quallich.¹⁷ A solution of *n*-BuLi (18.6 mmol, 8.0 mL, 2.32 M in hexanes) was added in 15 min to the previous obtained solid dissolved in anhydrous ether (30 mL) and cooled at –78°C. The mixture was stirred overnight at 25°C. The pale rose mixture with a fine

suspension was cooled at 0°C and then allowed to react with solid ammonium chloride (4.4g, 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 obtaining 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); ¹¹B NMR (500 MHz), δ (CDCl₃, ppm) 35; ¹H 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); ¹³C 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⁺), 202 (100%).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. (a) NMR in CDCl_3 (δ ppm): ^{11}B 9.2; ^1H 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 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 (70ev, m/z) 217 ($\text{M}^+ - \text{H}_2\text{O}$), 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 by Rico AR, Tlahuextl M, Flores-Parra A, Contreras R. *J Organomet Chem* 1999;581:122–128.
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Scheme 1.

Scheme 2.

Table 1

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

Compound 3	Bp. (°C/mmHg)	¹¹ B-NMR ^a
3a	95/0.7	7.

Compound 3	Bp. (°C/mmHg)	¹¹ B-NMR ^a
<p>3c</p>	120/0.5	8.
<p>3d</p>	110/0.1	8.

^aChemical displacements using BF₃-OEt₂ as internal standard.

^bYield of crude product based on the corresponding amino alcohol.

^cPure compounds were not obtained due to partial dehydration during distillation.

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

Compound 4	Bp. (°C/mmHg)	¹¹ B-NMR ^a
4a	42/0.12	32

Compound 4	Bp. (°C/mmHg)	¹¹ B-NMR ^a
4b	82/0.1	35
4c	80/2.0	34
4d	84/0.55	34

^aChemical displacements using BF₃-OEt₂ as internal standard.

^bYield based on the corresponding amino alcohol by treatment of **2** with anhydrous ammonium chloride followed by fractional distillation.

^cBy treatment of **2** with aqueous ammonium chloride and calculated from crude product **3**.