Hydroboration. 78. Reinvestigation of the Hydroboration of N-Substituted-3-pyrrolines. Preparation of *N*-Benzyl-3-pyrrolidinol and (*N*-Benzyl-3-pyrrolidinyl)boronate of Very High Enantiomeric Purity

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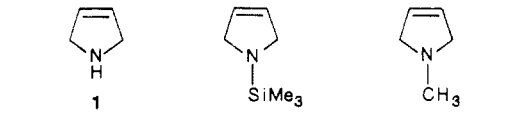
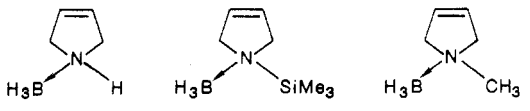
We have described the hydroboration of various heterocyclic olefins with representative hydroborating agents, such as borane–methyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane (9-BBN), dicyclohexylborane (Chx_2BH), and disiamylborane (Sia_2BH), providing a highly convenient and efficient method for the synthesis of heterocyclic alcohols.[2-4] Although β-substituted organoboranes readily undergo elimination,[5,6] we were able to avoid such elimination and ring cleavage by careful selection of the reagent and reaction conditions.

Recently we reported a failure to achieve the hydroboration of 3-pyrroline (**1**) and its *N*-trimethylsilyl (**2**) and *N*-methyl (**3**) derivatives.[2] Presumably coordination of the hydroborating agent with the nitrogen atom (**4**, **5**, **6**) so deactivates the neighboring double bond in the ring that hydroboration does not occur under the usual hydroborating conditions.

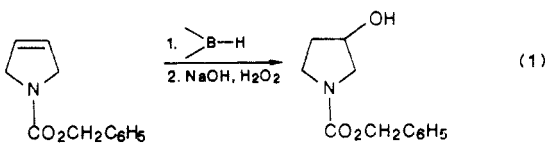


1 **2** **3**



4 **5** **6**

Success was achieved by protecting the nitrogen atom with the carbobenzyloxy group.[2,7] Indeed, *N*-carbobenzyloxy-3-pyrroline (**7**), on treatment wth representative hydroborating agents, does not form amine–borane complexes. It undergoes ready hydroboration to give the corresponding organoboranes, readily converted by the usual oxidation to *N*-carbobenzyloxy-3-pyrrolidinol in good yield (eq 1).



(1)

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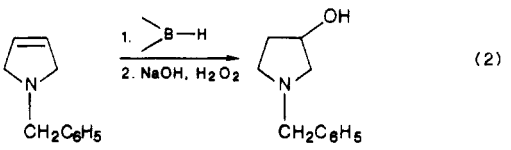
Recently, Joullié and co-workers[8] reported the successful hydroboration of *N*-benzyl-3-pyrroline (**8**) with borane–tetrahydrofuran. We were startled by this apparent difference in the reaction of *N*-methyl- and *N*-benzyl-3-pyrroline. Consequently, we undertook to restudy the hydroboration of this heterocyclic amine with representative hydroborating agents.

Results and Discussion

Compound **8**, upon treatment with BMS (1:1 mol ratio), formed an amine–borane complex, **9** (as evidenced by the ^{11}B NMR signal at δ −8.3). No hydroboration was observed. However, the hydroboration of **8** could be achieved by treatment of **8** with excess borane. The reaction could not be detected by ^{11}B NMR but could be readily followed by analysis for residual hydride. The organoboranes thus obtained, upon oxidation with alkaline hydrogen peroxide, gave *N*-benzyl-3-pyrrolidinol in quantitative yields. The hydroboration of compound **8** with 9-BBN (1:1 mol ratio) could also be achieved with or without the use of excess reagent, even though it forms an amine–borane complex. The trialkylborane thus obtained (as evidenced by a ^{11}B NMR signal at δ 84.4) underwent oxidation to *N*-benzyl-3-pyrrolidinol in quantitative yield (eq 2). Similarly, the



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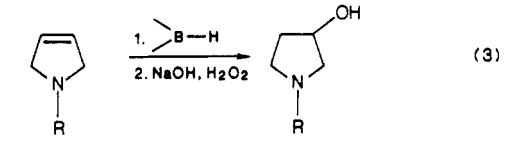
(2)

8

hydroboration of **8** could be achieved with Sia_2BH, with or without excess, converted upon oxidation to *N*-benzyl-3-pyrrolidinol in quantitative yield. The results are summarized in Table I.

Repetition of the hydroboration of compounds **1–3** led to mixed results. We confirmed our earlier failure to achieve hydroboration with **1** and **2**. However, the use of excess borane readily achieves the hydroboration of compound **3**. The product was readily oxidized to *N*-methyl-3-pyrrolidinol in almost quantitative yield (eq 3, R = CH_3). *n*-Butyl-3-pyrroline (**10**) behaved similarly (eq 3, R = *n*-Bu).



(3)

3, R = Me
10, R = *n*-Bu

The difficulty in our earlier failure to recognize that we had achieved hydroboration with the *N*-methyl- and *N*-butyl derivatives arose from our failure to detect reaction by observing the ^{11}B NMR spectra. These did not show the changes we had anticipated for a successful hydroboration.

It should be pointed out that a valuable property of both the *N*-benzyl and *N*-carbobenzyloxy protecting groups is their ready removal by hydrogenolysis over Pd on charcoal.[7,8] Consequently, through this deprotection reaction, we can realize the parent 3-pyrrolidinols.

We previously reported the asymmetric hydroboration of *N*-carbobenzyloxy-3-pyrroline by diisopinocampheylborane.[9] The trialkylborane intermediate, upon oxidation,

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(2) Brown, H. C.; Vara Prasad, J. V. N.; Zee, S.-H. *J. Org. Chem.* **1985**, *50*, 1582.
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(4) Brown, H. C.; Ramachandran, P. V.; Vara Prasad, J. V. N. *J. Org. Chem.* **1985**, *50*, 5583.
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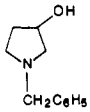
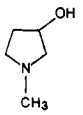
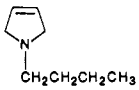
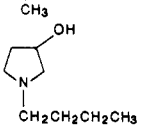
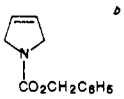
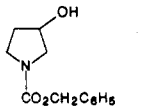
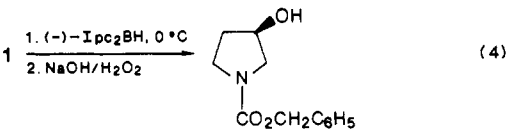
Table I. Hydroboration of N-Substituted-3-pyrrolines at 25 °C

olefin	product	hydroborating agent	olefin to hydroborating agent ratio	reactn time, h	yield,[a] %
		$BH_3{\cdot}SMe_2$	1:1	24	0
			1:1.33	1	30
				2	97
			1:1.66	1	65
				2	97
			1:2	1	100
		9-BBN	1:1	1	96
			1:2	0.5	98
		Sia_2BH	1:1	3	99
			1:2	1	100
		$BH_3{\cdot}SMe_2$	1:1	48	0
			1:1.33	36	94
		9-BBN	1:2	24	97
		Sia_2BH	1:2	24	98
		$BH_3{\cdot}SMe_2$	1:1	48	0
			1:1.33	36	95
		9-BBN	1:2	24	93
		Sia_2BH	1:2	24	99
 [b]		$BH_3{\cdot}SMe_2$	1:1.33	1	88
		9-BBN	1:1	1	92
		Sia_2BH	1:1	3	84

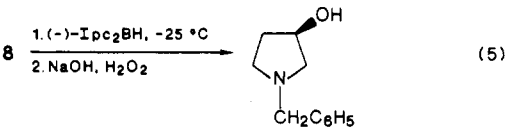
[a] By GC analysis. [b] Reference 2. Results included to permit ready comparison.

gives *N*-carbobenzyloxy-3(*S*)-pyrrolidinol of 89% ee (eq 4). The lower asymmetric induction, compared to other


(4)

five-membered ring heterocycles (essentially 100% ee), may be attributed to the higher temperature (0 °C vs. −25 °C) required for the hydroboration stage. Fortunately, the hydroboration of *N*-benzyl-3-pyrroline with diisopinocampheylborane proceeds readily at −25 °C.

Thus, compound **8**, on hydroboration with diisopinocampheylborane (derived from (+)-α-pinene) (1:2 mol ratio) at −25 °C, followed by oxidation with alkaline hydrogen peroxide, provided *N*-benzyl-3(*S*)-pyrrolidinol ($[\alpha]_D$ −3.145°, lit.[10] −2.47°, 84% ee) in excellent yield (eq 5). On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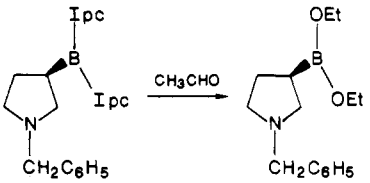
the basis of the literature rotation, the optical purity of the alcohol is 107% ee. Presumably, the literature value is low and our *N*-benzyl-3-pyrrolidinol is optically purer than any material previously prepared, probably close to 100% ee. From this derivatives, the parent alcohol, 3-(*S*)-pyrrolidinol can be prepared by debenzylation using Pd on carbon.[10] However, we did not attempt to do so. Since both (+)- and (−)-α-pinene are readily available, both enantiomers of pyrrolidinol can be easily synthesized. The optically active 3-pyrroldinols are precursors to depsipeptides and some substituted pyrrolidinols are biologically active.[10] Therefore, hydroboration–oxidation of **8** to yield *N*-benzyl-3-pyrrolidinol in high enantiomeric purity constitutes a simple procedure to achieve optically active pyrrolidinols.

Chiral alkylboronic esters containing only one alkyl group attached to boron are highly promising intermediates for asymmetric synthesis proceeding through boron chemistry.[11-13] Previously, we have shown that heterocyclic diisopinocampheylborane, upon treatment with acetaldehyde, liberates α-pinene quantitatively, providing optically active diethyl heterocyclic boronates.[9] By adopting a similar procedure, diethyl (*N*-benzyl-3(*S*)-pyrrolidinyl)boronate was prepared (eq 6). It was further


(6)

purified by treatment with dry hydrochloric acid in ethyl ether, followed by regeneration with diisopropylamine. The ready availability of the five-membered nitrogen heterocyclic boronate of high enantiomeric excess should make possible the ready synthesis of many other related compounds in high enantiomeric excess by use of known organoborane chemistry.

Experimental Section

The reaction flasks and other glass equipment were stored in an oven at 150 °C overnight and assembled in a stream of dry nitrogen gas. Syringes were assembled and fitted with needles while hot and cooled in a stream of dry nitrogen gas. Special techniques used in handling air-sensitive materials are described in detail elsewhere.[14]

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Spectra. ^{11}B NMR spectra were recorded on a Varian FT-80A instrument. The chemical shifts are in δ relative to $BF_3 \cdot OEt_2$. ^1H NMR (60 MHz), IR, and mass spectra were recorded on Varian T-60, Perkin-Elmer 137, and Finnegan GC/mass spectrometers, respectively.

GC Analyses. All GC analyses were carried out with a Hewlett-Packard 5890 chromatography using 9 ft × 12 ft × 0.125 in. columns packed with 10% Carbowax 20M on Chromosorb W (100–120 mesh).

Materials. Borane–methyl sulfide (BMS) and 9-borabicycl-9[3.3.1]nonane (9-BBN) in THF were purchased from Aldrich Chemical Company and were estimated according to the standard procedure.[14] Tetrahydrofuran (THF) was distilled over benzophenone ketyl and stored under nitrogen atmosphere in an ampule. *N*-Benzyl-3-pyrroline and *N*-(*n*-butyl)-3-pyrroline were prepared from *cis*-1,4-dichloro-2-butene according to the literature procedures.[8,15] *N*-Methyl-3-pyrroline and *N*-(trimethylsilyl)-pyrroline (contains 25% of the corresponding pyrrolidine) were prepared from 3-pyrroline (containing 25% of the corresponding pyrrolidine) by similar literature procedure.[16] The internal standard, hexadecane (Phillips) was kept over 4-Å molecular sieves under atmosphere and used as such.

Disiamylborane[3] and diisopinocampheylborane[17] were prepared as described in the literature.

Hydroboration with BMS. A typical experiment is as follows. In a 25-mL flask equipped with a septum inlet, magnetic stirring bar, and connecting tube leading to a mercury bubbler was placed 0.32 g (2 mmol) of *N*-benzyl-3-pyrroline in 1.3 mL of THF. To it was added 0.05 g (0.2 mmol) of hexadecane. The reaction flask was cooled to 0 °C. To it was added 0.28 mL (2.66 mmol) of BMS (9.7 M) via syringe. The reaction mixture was kept at room temperature under stirring. The reaction was followed by taking 0.1-mL aliquots and hydrolyzing by adding them to a solution of THF/glycerol/3 N HCl (1:1:1) medium. The hydrogen evolved was measured and the residual hydride was calculated. After the completion of the reaction, the reaction mixture was oxidized by using 6 N sodium hydroxide and 30% hydrogen peroxide. After 5 h, the aqueous phase was saturated with anhydrous K_2CO_3 and was extracted with 3 × 5 mL of ethyl acetate. The crude reaction mixture was dried over anhydrous Na_2SO_4 and analyzed by GC. The percentage of the products was calculated by using a correction factor. The results are summarized in Table I.

N-Substituted-3-pyrrolidinols were isolated on doing the reaction on a 15-mmol scale.

Hydroboration with 9-BBN, Chx_2BH, and Sia_2BH. The reactions were done as described above for BMS.

Asymmetric Hydroboration of *N*-Benzyl-3-pyrroline. Diisopinocampheylborane [(−)-Ipc_2BH, derived from (+)-α-pinene, 50 mmol] in THF was cooled to −25 °C. To it was added 4 g (25 mmol) of *N*-benzyl-3-pyrroline via syringe. The reaction mixture was kept under stirring. After 24 h, the solid Ipc_2BH dissolves. The trialkylborane thus obtained was treated with 25 mL of 6 N sodium hydroxide, followed by 7.5 mL of 30% hydrogen peroxide at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The aqueous layer was saturated with anhydrous potassium carbonate. The organic layer was separated and the aqueous layer was extracted with 3 × 25 mL of ethyl acetate. The combined organic extracts were mixed and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was subjected to column chromatography using silica gel; ether/pentane (1:1) eluents removed α-pinene and isopinocampheol, whereas, ether eluents yielded the required alcohol. It was further distilled to obtain GC pure material: bp 88–90 °C/1 mm [lit.[7] bp 83–84 °C/0.23 mm]; yield 3.9 g, 89%; $[\alpha]^{23}_D$ − 3.145° (*c* 1.2, chloroform), ~100% ee [lit.[10] $[\alpha]^{25}_D$ − 2.47° (*c* 1.175, chloroform, 84% ee]. IR, ^1H NMR, and mass spectra are in agreement with the structure.

Isolation of Diethyl (*N*-Benzyl-3-pyrrolidinyl)boronate. Ethyl (*N*-benzyl-3-pyrrolidinyl)boronate was prepared by the reaction of diisopinocampheyl(*N*-benzyl-3-pyrrolindinyl)borane (10 mmol) with 100% excess (2.3 mL, 40 mmol) of CH_3CHO. The reaction mixture was stirred at 25 °C for 24 h. The excess acetaldehyde and the solvent were pumped off under reduced pressure. The residue was taken in 10 mL of ether and cooled to 0 °C. To it was added 3 mL of dry HCl in ether (4 M), and the solution was stirred for 0.5 h. The solid obtained was filtered and washed with 2 × 10 mL of ether. The solid was suspended in 10 mL of ether and to it was added 1 mL of isopropylamine, the solution was stirred at room temperature for 3 h. The solid was filtered. The filtrate was concentrated to obtain boronate.

Acknowledgment. We gratefully acknowledge support from the National Institutes of Health (Grant GM 10937-23) in this research. We also acknowledge Professor M. M. Joullié calling to our attention the apparent discrepancy between her successful hydroboration of *N*-benzyl-3-pyrroline and our reported unsuccessful hydroboration of *N*-methyl-3-pyrroline.

Registry No. **3**, 554-15-4; **7**, 31970-04-4; **8**, 6913-92-4; **10**, 6831-60-3; 9-BBN, 280-64-8; $(CH_3)_2S \cdot BH_3$, 13292-87-0; *N*-benzyl-3-pyrrolidinol, 775-15-5; *N*-methyl-3-pyrrolidinol, 13220-33-2; *N*-butyl-3-pyrrolidinol, 51045-30-8; *N*-carbobenzyloxy-3-pyrrolidinol, 95656-88-5; diisiamylborane, 1069-54-1; diisopinocampheylborane, 64234-27-1; *N*-benzyl-3(*S*)-pyrrolidinol, 101385-90-4; diethyl (*N*-benzyl-3-pyrrolidinyl)boronate, 104351-33-9; diisopinocampheyl(*N*-benzyl-3-pyrrolidinyl)borane, 104351-84-0; dicyclohexylborane, 1568-65-6.

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A More Efficient Synthesis of DMPO-Type (Nitrone) Spin Traps

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Ever since its inception, the spin-trapping technique[1] has employed nitrones extensively[2] to detect and identify a wide range of reactive free radicals generated from a variety of chemical environments. The cyclic nitrone, 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO), introduced as a spin trap in the early seventies,[3] has been shown kinetically to be an effective scavenger of alkyl,[4] hydroxyalkyl,[5] as well as alkoxy[6] radicals. The marked ability of DMPO to intercept hydroxyl[7] and superoxide radicals,[7a,c]

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