Aminoborohydrides. 10. The Synthesis of Tertiary Amine−Boranes from Various Benzyl Halides and Lithium *N,N*-Dialkylaminoborohydrides

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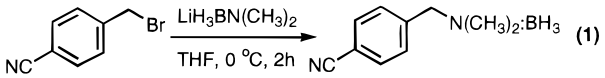
Carbanions with a negative charge alpha to nitrogen are valuable intermediates in organic synthesis.[1] Deprotonation of tertiary benzylic amine−borane complexes with *n*-BuLi is an excellent method of regioselectively lithiating benzylamines alpha to nitrogen.[2] The borane moiety provides protection of the amine lone pair and stabilizes the generated carbanion due to its Lewis acidic character. These carbanions react with electrophiles and provide a useful method for synthesizing α-substituted benzylamines. Usually, these tertiary amine−borane complexes are formed from reaction of BH_3−THF with the corresponding tertiary amine.

We now report a method for the direct synthesis of tertiary amine−borane complexes by alkylation of lithium *N,N*-dialkylaminoborohydride (LAB) reagents. There is some precedent for our observations; sodium *N,N*-dimethylaminoborohydride (NaAB) was reported[3a] to react with 1-iodododecane to give *N,N*-dimethyldodecylamine. This result suggests an S_N2 reaction of NaAB with 1-iodododecane. Vedejs[3b] utilized this reaction to synthesize *N*-methylaziridine−borane complexes by quenching the corresponding aminoborohydrides with methyl iodide. These results indicate that LAB reagents, which can be viewed as borane complexes of lithium *N,N*-dialkylamides,[4] react with benzylic and alkyl halides in a much different manner than lithium *N,N*-dialkylamides, which generally react with these species to form products resulting from carbene, radical (electron transfer), and carbanion pathways and not tertiary amine products resulting from nucleophilic displacement processes.[5]

In our recent study of the competitive reduction of aldehydes, ketones, esters, and epoxides in the presence of a nitrile using LAB,[6] the reduction of the C−Br bond in 4-cyanobenzyl bromide was attempted. The reaction did not give the expected *p*-tolunitrile, but instead gave *N,N*-dimethyl-4-cyanobenzylamine−borane as the sole product (eq 1).

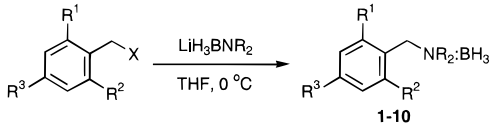


(1)

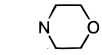
No quaternary ammonium salt was obtained in the reaction due to the interaction of the amine lone pair with the borane moiety. The fact that the alkylation occurred is quite intriguing since LAB reagents are known to reduce benzyl halides to hydrocarbons at 25 °C.[7] Obviously, LAB reagents react with benzyl halides via a different pathway at 0 °C. To check the generality of this reaction, we studied the interactions of various benzyl halides with LAB reagents at 0 °C. Herein, we report the results of this study.

LAB reagents containing various amine moieties were found to react with both unsubstituted and substituted benzyl halides to give the corresponding tertiary amine−borane complexes (Table 1). This reaction is very general, and even the sterically bulky substrate, 1,3,5-triisopropylbenzyl chloride,[8] when allowed to react with LiH_3BNMe_2, gave an excellent yield (95%) of the corresponding amine−borane **5**. The free amines can be liberated

Table 1. Direct Amination of Benzyl Halides with Lithium *N,N*-Dialkylaminoborohydrides



1-10

R^1	R^2	R^3	X	amine (NR_2)	product	reaction time (h)	yield, %[a,b]
H	H	CN	Br	NMe_2	**1**	2	78
H	H	H	Br	NMe_2	**2**	2	75
H	H	H	Br	NMe_2	**3**	2	62[c]
Cl	Cl	H	Cl	NMe_2	**4**	0.5	72
i-Pr	*i*-Pr	*i*-Pr	Cl	NMe_2	**5**	0.5	95
H	H	H	Br		**6**	2	76
H	H	H	Br		**7**	2	72
Cl	Cl	H	Cl		**8**	0.5	43[c]
H	H	H	Br		**9**	2	55
H	H	H	Br	NMeBn	**10**	2	95

[a]Isolated overall yields. [b]Product purity determined by ^1H, ^{13}C, and ^{11}B NMR and mp/bp. [c]Isolated as the free amine after quenching the reaction mixture with 12 M hydrochloric acid, removing the neutral product (2,6-dichlorotoluene) by extraction with diethyl ether, and making the acid layer strongly basic with 50% sodium hydroxide.

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(1) (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *25*, 471. (b) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 65.

(2) Ebden, M. R.; Simpkins, N. S.; Fox, D. N. *Tetrahedron Lett.* **1996**, *36*, 8697.

(3) (a) Hutchins, R. O.; Learn, K.; El-Telbany, F. Stercho, Y. P. *J. Org. Chem.* **1984**, *49*, 2438. (b) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941.

(4) (a) Pross, A.; Radom, L. *Tetrahedron* **1980**, *36*, 673. (b) Armstrong, D. R.; Perkins, P. G.; Walker, G. T. J. *Mol. Structure (THEOCHEM)* **1985**, *122*, 189.

(5) (a) Creary, X. *J. Am. Chem. Soc.* **1977**, *99*, 7632. (b) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424.

(6) Collins, C. J.; Fisher, G. B.; Reem, A.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 529.

(7) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378.

(8) (a) Barclay, L. R. C.; Sonaware, H. R. Huson, J. C. *Can. J. Chem.* **1972**, *50*, 2318. (b) Dozeman, G. J.; Fiore, P. J.; Puls, T. P.; Walker, J. C. *Org. Process Res. Dev.* **1997**, *1*, 137.

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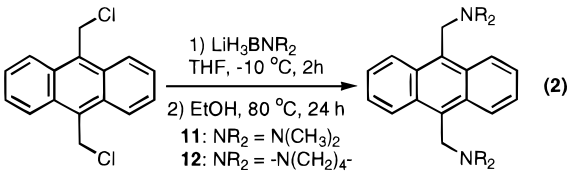
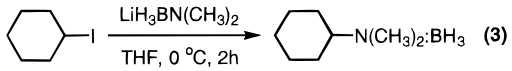
from the amine−borane complexes by methanolysis under acidic conditions. Some halides do give mixtures of the tertiary amine−borane and the hydrocarbon reduction product. The product distribution can be controlled by the reaction temperature and the steric requirements of the LAB reagent used. The reaction of benzyl halides with LAB reagents gives mainly the reduction product when carried out at 25 °C. Similarly, LAB reagents containing sterically demanding amine groups reduce benzyl halides. Thus, benzyl bromide was reduced to toluene at 0 °C by both lithium *N,N*-diisopropylaminoborohydride and lithium *N,N*-dicyclohexylaminoborohydride. Tertiary amine−boranes were also synthesized from 9,10-bis(chloromethyl)anthracene and LAB (eq 2).



(2)

The corresponding tertiary amines were obtained in almost quantitative yields by ethanolysis of the amine−borane complexes. This class of amines has recently become of great interest for the sensing of sugars in combination with boronic acids.[9] Our method is also applicable to the synthesis of aliphatic amine−boranes which gave the amination products in moderate yields (eq 3).



(3)

13
59% yield

LAB reagents are known to form dimers at ambient temperatures and higher aggregates at lower temperatures in THF solutions.[10] At lower temperatures, the nitrogen substitution reaction may be entropically favored due to a higher aggregation state of the LAB reagents, which in turn may change the reagent's reactivity to give exclusively amine−boranes from alkyl and benzyl halides. On the other hand, reduction reactions are known to have a high enthalpy of activation. Apparently, the nitrogen substitution reaction has a lower enthalpy of activation compared to the reduction reaction. Consequently, the amination reaction is the kinetically favored reaction at lower temperatures.[11]

LAB reagents are powerful, non-pyrophoric reducing agents that reproduce, in air, virtually all of the transformations for which lithium aluminum hydride is now used.[12] The results reported in the present study extend the synthetic utility of the LABs to the preparation of a wide variety of tertiary amine−boranes and tertiary amines from alkyl or benzyl halides and an appropriate LAB.

Experimental Section

General. All melting points and boiling points are uncorrected. All operations were performed under nitrogen.

Representative Experimental Procedure for Tertiary Amine−Borane Synthesis. 1-Benzylpyrrolidine−Borane (6). A solution of 5 mmol of lithium pyrrolidinoborohydride was prepared from pyrrolidine/borane complex (0.42 g, 5 mmol) and *n*-butyllithium in hexane (2.5 M, 2 mL) in anhydrous THF (3 mL). A previously dried and nitrogen flushed 50 mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was charged with freshly distilled benzyl bromide (0.86 g, 5 mmol) and anhydrous THF (5 mL). The resulting solution was cooled to 0 °C, and the THF solution of lithium pyrrolidinoborohydride was added dropwise at such a rate that the temperature of the reaction mixture remained below 5 °C. After the addition was complete, the reaction was stirred at 0 °C for 2 h. The reaction mixture was concentrated in vacuo (35 °C, 30 Torr) to afford a white solid. The solid was then quenched with deionized water (10 mL) and the slurry allowed to stir at room temperature for 1 h. The quenched reaction mixture was then cooled to 0 °C and vacuum filtered through a sintered glass funnel. The precipitate was washed with deionized water (5 mL) and hexanes (5 mL) to give 1-benzylpyrrolidine−borane (**6**) as a white crystalline solid (0.67 g, 76% yield), mp 76−77 °C.

Representative Experimental Procedure for Tertiary Amine Synthesis. *N,N*-Dimethylbenzylamine (3). A solution of 20 mmol of lithium *N,N*-dimethylaminoborohydride was prepared from 1.18 g (20 mmol) of dimethylamine/borane complex (1.18 g, 20 mmol) and *n*-butyllithium in hexane (2.5 M, 8 mL) in anhydrous THF (12 mL). A previously dried and nitrogen flushed 50 mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum was charged with freshly distilled benzyl bromide (3.42 g, 20 mmol) and anhydrous THF (20 mL). The resulting solution was cooled to 0 °C, and the solution of lithium *N,N*-dimethylaminoborohydride solution was added at such a rate that the temperature of the reaction mixture remained below 5 °C. After the addition was complete, the reaction was stirred at 0 °C for 2 h. The reaction mixture was concentrated in vacuo (35 °C, 30 Torr) to afford a white solid. The reaction was then quenched with 20 mL of 1 M methanolic hydrochloric acid and heated at reflux for 12 h (***CAUTION***: Hydrogen evolution!). The solution was cooled to room temperature under nitrogen and concentrated in vacuo (35 °C, 30 Torr). The flask was placed in an ice−water bath, and to the flask was added deionized water (20 mL) and then solid KOH until the solution was strongly basic (pH = 12). The contents of the flask and the rinsings (deionized water (10 mL) and diethyl ether (10 mL)) were transferred to a separatory funnel and the aqueous layer extracted with 3 × 20 mL portions of diethyl ether. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo (35 °C, 30 Torr) to give *N,N*-dimethylbenzylamine (**3**) as a light yellow oil (1.66 g, 63% yield), bp = 183−184 °C (760 Torr).

4-Cyano-*N,N*-dimethylbenzylamine−borane (1): white, crystalline powder, mp 92−94 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 2.50−2.60 (s, 6H), 4.00−4.10 (s, 2H), 7.65−7.95 (m, 4H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 51.5, 68.0, 114.0, 119.5, 133.0, 135.0, 139.0; ^{11}B NMR (80.2 MHz, THF) δ −6.44 (q, J = 93 Hz); IR (Nujol, cm^{-1}) 2272.0, 2321.0, 2371.2 (st B−H).

***N,N*-Dimethylbenzylamine−borane (2)**: white, crystalline powder, mp 98−101 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 2.40−2.60 (s, 6H), 3.90−4.00 (s, 2H), 7.35−7.55 (m, 5H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 51.0, 69.0, 129.5, 130.0, 133.5, 134.0; ^{11}B NMR (80.2 MHz, THF) δ −2.67 (q, J = 98 Hz); IR (Nujol, cm^{-1}) 2272.7, 2319.4, 2364.8 (st B−H).

***N,N*-Dimethylbenzylamine (3)**: light yellow oil, bp 183−184 °C (760 Torr); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.20−2.30 (s, 6H), 3.40−3.50 (s, 2H), 7.20−7.40 (m, 5H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 45.3, 64.4, 127.0, 128.2, 129.1, 138.8.

(9) James, T. D.; Sandanayake, K. R. A. S.; Iguchi, R.; Shinkai, S. *J. Am. Chem. Soc.* **1995**, *117*, 8982.

(10) Noth, H.; Thomas, S.; Schmidt, M. *Chem. Ber.* **1996**, *129*, 451.

(11) According to the Eyring equation, the rate of a reaction can be expressed as $\ln k = \ln(k/h) + \ln T - \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R$. The negative, temperature-dependent term $\Delta H^{\ddagger}/RT$ will cause a reaction to be kinetically slow if $\Delta H^{\ddagger}$ is a large, positive number and T is a small number. See: Weissberg, A. *Investigations of Rates and Mechanisms of Reactions*, 4th ed.; Bernasconi, C. F., Ed.; Wiley and Sons: New York, 1986; pp 285−286.

(12) (a) Fisher, G. F.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533. (b) Fisher, G. F.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 1901. (c) Fisher, G. F.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 257.

2,6-Dichloro-*N*,*N*-dimethylbenzylamine−borane (4): white, crystalline powder, mp 88−90 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 2.60−2.67 (s, 6H), 4.41−4.50 (s, 2H), 7.40−7.60 (m, 3H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 51.6, 60.8, 130.8, 132.8, 133.2, 139.4; ^{11}B NMR (80.2 MHz, THF) δ −5.67 (q, J = 98 Hz); IR (Nujol, cm^{-1}) 2273.5, 2316.7, 2368.4 (st B−H).

***N*,*N*-Dimethyl-2,4,6-triisopropylbenzylamine−borane (5):** light yellow powder, mp 139−141 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.00−1.20 (d, 2H), 1.20−1.30 (d, 6H), 1.30−1.45 (d, 6H), 2.80−3.00 (sept, 1H), 3.50−3.70 (sept, 2H), 4.30−4.35 (s, 2H), 7.20−7.25 (s, 2H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 22.8, 24.5, 27.1, 35.3, 50.9, 57.1, 122.8, 124.1, 150.8, 151.7; ^{11}B NMR (80.2 MHz, THF) δ −7.11 (br d, J = 87 Hz); IR (Nujol, cm^{-1}) 2264.2, 2316.2, 2360.7 (st B−H).

1-Benzylpyrrolidine−borane (6): white, crystalline powder, mp 76−77 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.70−1.95 (m, 2H), 1.95−2.15 (m, 2H), 2.80−3.10 (m, 4H), 4.00−4.10 (s, 2H), 7.25−8.10 (m, 5H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 23.6, 60.1, 66.2, 129.1, 129.7, 131.0, 139.9; ^{11}B NMR (80.2 MHz, THF) δ −11.8 (q, J = 98 Hz); IR (Nujol, cm^{-1}) 2278.3, 2326.0, 2373.7 (st B−H).

1-Benzylpiperidine−borane (7): white, crystalline powder, mp 96−98 °C (dec); ^{1}H NMR (250 MHz, acetone-d_6) δ 1.25−1.45 (m, 2H), 1.55−1.75 (m, 2H), 2.60−2.80 (t, 2H), 2.81−3.00 (m, 2H), 4.00−4.12 (s, 2H), 7.30−7.60 (m, 5H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 22.0, 23.9, 58.1, 67.6, 128.9, 129.7, 132.9, 134.4; ^{11}B NMR (80.2 MHz, THF) δ −10.8 (q, J = 97 Hz); IR (Nujol, cm^{-1}) 2279.4, 2326.1, 2362.2, 2406.8 (st B−H).

1-(2,6-Dichlorobenzyl)pyrrolidine (8): clear, colorless liquid, bp 117−119 °C (1.3 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39−1.47 (br d, 2H), 1.48−1.60 (quint, 4H), 2.49−2.52 (t, 4H), 3.65−3.75 (s, 2H), 7.09−7.14 (t, 1H), 7.28−7.31 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 26.1, 54.5, 57.3, 128.3, 128.5, 135.2, 137.1.

4-Benzylmorpholine−borane (9): white, crystalline powder, mp 102−104 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 2.30−2.50 (t, 4H), 3.45−3.50 (m, 2H), 3.55−3.70 (t, 4H), 7.20−7.35 (m, 5H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 54.8, 64.2, 67.8, 128.2, 129.4, 130.2, 139.6; ^{11}B NMR (80.2 MHz, THF) δ −12.4 (q, J = 96 Hz); IR (Nujol, cm^{-1}) 3258.2, 3240.3, 3501.3 (st B−H).

***N*-Methyldibenzylamine−borane (10):** white, crystalline powder, mp 116−118 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 2.35−2.50 (s, 3H), 3.40−3.60 (s, 2H), 7.40−7.60 (m, 10H); ^{13}C NMR (62.8 MHz, acetone-d_6) δ 47.5, 68.0, 129.0, 130.0, 134.0, 135.0; ^{11}B NMR (80.2 MHz, THF) δ −8.83 (br d, J = 96 Hz); IR (Nujol, cm^{-1}) 2275.0, 2327.1, 2369.8, 2396.8 (st B−H).

***N*,*N*,*N*′,*N*′-Tetramethyl-9,10-bis(aminomethyl)anthracene (11):** yellow, crystalline powder, mp >300 °C (dec); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.40−2.47 (s, 12H), 4.30−4.50 (s, 4H), 7.52−7.56 (m, 4H), 8.51−8.55 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 51.5, 57.5, 105.0, 125.3, 127.0, 130.0.

9,10-Bis((1-pyrrolidino)methyl)anthracene (12): yellow, crystalline powder, mp >300 °C (dec); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.73−1.78 (br s, 8H), 2.60−2.80 (br s, 8H), 4.55−4.70 (s, 4H); 7.40−7.55 (m, 4H), 8.50−8.65 (m, 4H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 23.5, 51.2, 54.1, 107.8, 125.0, 125.4, 130.6.

***N*,*N*-Dimethylcyclohexylamine−borane (13):** light yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.25−1.50 (br s, 6H), 1.60−1.80 (br s, 4H), 2.30−2.50 (m, 1H), 3.30−3.40 (s, 6H); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 14.0, 28.9, 31.5, 47.4, 64.1; ^{11}B NMR (80.2 MHz, THF) δ −11.4 (q, J = 96 Hz).

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Supporting Information Available: Copies of the proton and carbon NMR spectra of all new compounds and infrared spectra of the borane−amine complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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