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Aminoborohydrides. 3. A Facile Reduction of Tertiary Amides to the Corresponding Amines and Alcohols in High Purity Using Lithium Aminoborohydrides. Sterically Controlled Selective C-N or C-O Bond Cleavage

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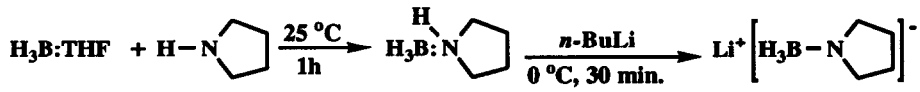
Summary: *Lithium aminoborohydrides ($LiABH_3$), obtained by the reaction of n-BuLi with amine-boranes, are powerful reducing agents for the reduction of tertiary amides to the corresponding amines or alcohols. Lithium pyrrolidinoborohydride ($LiPyrrBH_3$) and lithium diisopropylaminoborohydride ($LiH_3BN(i\text{-}Pr)_2$) reduce both aliphatic and aromatic tertiary amides to give either the corresponding alcohol or amine, depending on the steric requirement of the tertiary amide and the $LiABH_3$ used. The yields of amines and alcohols from this procedure range from very good to essentially quantitative.*

Recently,[2] we demonstrated that lithium aminoborohydrides ($LiABH_3$) are powerful yet stable reducing agents, comparable in power to lithium aluminum hydride ($LiAlH_4$), while possessing none of the dangerous properties of $LiAlH_4$. $LiABH_3$'s are non-pyrophoric and thermally stable as evidenced by melting points in excess of 200 °C. $LiABH_3$'s can be prepared readily in large scale and in quantitative yield from *n*-BuLi and any amine-borane complex (eq.1).



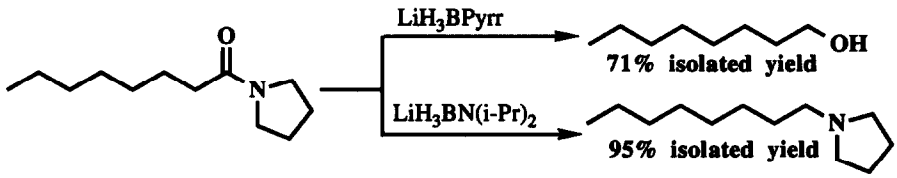
(1)

Currently, there are few good methods for reducing tertiary amides cleanly.[3] A sampling of organic chemistry texts shows that the $LiAlH_4$ reduction of amides is virtually the only methodology mentioned,[4] even though a general method for the reduction of tertiary amides with BH_3·THF has been available for nearly 30 years.[3e-h] However, this latter method suffers from the need to rigorously exclude air and water during the reduction.

After the serendipitous discovery of the reducing power of $LiABH_3$'s, we initiated a systematic study of the reducing properties of $LiABH_3$'s on 52 test compounds encompassing all major functional groups.[2] The initial work with amides indicated that, not only do $LiABH_3$'s readily reduce tertiary amides, but selective reduction to the corresponding alcohol[2,5a,b] or amine[2,5b] could be achieved by varying the steric environment of the $LiABH_3$ or the amide. These results led us to conduct a detailed study of the reduction of tertiary amides with lithium pyrrolidinoborohydride ($LiPyrrBH_3$) and lithium diisopropylaminoborohydride ($LiH_3BN(i\text{-}Pr)_2$). The results of this study are discussed below.

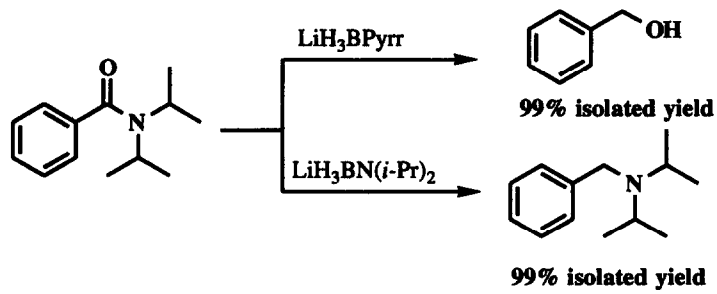
The results summarized in **Table 1** and **Table 2** indicate that the reduction of tertiary amides with $LiPyrrBH_3$ or $LiH_3BN(i\text{-}Pr)_2$ to the the corresponding amine or alcohol is a method of general applicability and represents a substantial improvement over other reducing agents currently available for carrying out these

transformations. Particularly significant is that many aromatic or aliphatic tertiary amides can be converted to either the corresponding alcohol or amine by simply varying the steric environment of the amide or the $LiABH_3$. Thus, for 1-pyrrolidinooctanamide, reduction at 25 °C with $LiPyrrBH_3$ yields 1-octanol in 71% isolated yield; reduction of the same amide with $LiH_3BN(i\text{-}Pr)_2$ yields 1-pyrrolidinooctane in 95% isolated yield (eq. 2, **Table 1**).



(2)

Similar results were obtained for *N,N*-diisopropylbenzamide (eq. 3, **Table 2**).



(3)

Although earlier work with sodium aminoborohydrides reports similar results for the reductions of tertiary amides, mixtures of products were often obtained and the steric environment of both the amide and the sodium aminoborohydride required careful balancing to achieve the desired product.[5] Since sodium borohydrides are much less reactive than the corresponding lithium borohydrides, rather drastic conditions were also required.

Another significant advantage of $LiABH_3$'s over other amide reducing agents is that, once the $LiABH_3$ has been generated *in situ, no precautions to exclude air need be taken when the reduction is done.* Further, reductions with $LiABH_3$'s are complete in 2-3 hours at ambient temperature, although some very hindered tertiary amides require refluxing for 2-3 hours to achieve a reasonable yield of the corresponding amine. The crude products obtained in $LiABH_3$ reductions of tertiary amides are often of nearly analytical purity and require no further purification, particularly when $LiH_3BN(i\text{-}Pr)_2$ is used as the reducing agent.

The following procedure for the reduction of 1-pyrrolidinooctanamide to 1-pyrrolidinooctane, using $LiH_3BN(i\text{-}Pr)_2$, is representative (*in situ* generation of $LiH_3BN(i\text{-}Pr)_2$ was carried out under nitrogen in oven-dried glassware; *no precautions to exclude air were taken during the actual reduction)*: a 50-mL serum vial equipped with a magnetic stirring bar was sealed with a rubber septum, cooled under nitrogen, and charged with diisopropylamine (1.2 g, 1.7 mL, 12 mmol) and BH_3·THF (1M, 12 mL, 12 mmol) was added with stirring. The reaction mixture was stirred for 1h at 25 °C, cooled to 0 °C, and *n*-butyllithium (2.5 M, 4.8 mL, 12 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min. 1-pyrrolidinooctanamide (1.4g, 6.9 mmol) was

Table 1. Reduction of Aliphatic Tertiary Amides With Lithium Aminoborohydrides[a,b,c]

amide	$LiABH_3$(eq)	Product[d]	Yield, %[e]	BP (Torr)[f]
1-pyrrolidinooctanamide	Li[H_3BPyrr](1.2)	1-octanol	71	129-131 (0.3)
1-pyrrolidinooctanamide	Li[H_3BN(*i*-Pr)$_2$](1.7)	1-pyrrolidinooctane	95	44-45 (0.3)
N,N-diethyldodecanamide	Li[H_3BPyrr](1.2)	*N,N*-diethyldodecanamine	71	99-100 (0.5)
N,N-diethyldodecanamide	Li[H_3BN(*i*-Pr)$_2$](1.2)	*N,N*-diethyldodecanamine	98	99-100 (0.5)
N,N-diisopropylcyclohex-amide	Li[H_3BN(*i*-Pr)$_2$](1.7)[g]	*N,N*-diisopropyl-*N*-methylenecyclohexane	64[h]	45-47 (0.6)
N,N-diethylnipecotamide	Li[H_3BN(*i*-Pr)$_2$](2.0)[i]	3-[(*N,N*-diethylamino) methyl]piperidine	87	97-99 (8)

[a]Reactions run with $LiABH_3$ generated *in situ* at 25 °C unless otherwise noted. [b]Generated by: (1) 12 mmol amine + 12 mL 1M BH_3·THF, 1h, 25 °C; (2) 12 mmol 2.5M *n*-BuLi, 30 min., 0 °C. [c]Purity determined by ^{11}B-NMR of the THF solution of $LiABH_3$. [d]Product purity determined by 250 MHz ^{1}H- and ^{13}C-NMR and FT-IR. [e]Isolated yields. [f]BP/MP are uncorrected. [g]Quantitative recovery of starting material with $LiPyrrBH_3$ at 25 °C or 65 °C. [h]Reduction done at 65 °C for 2h. [i]85:15 ratio of amine:alcohol for reduction with $LiPyrrBH_3$ at 25 °C.

Table 2. Reduction of Aromatic Tertiary Amides With Lithium Aminoborohydrides[a,b,c]

amide	$LiABH_3$(eq)	Product[d]	Yield, %[e]	BP (Torr)[f]
N,N-dimethylbenzamide	Li[H_3BN(*i*-Pr)$_2$](1.2)	benzyl alcohol	98	50-52 (1)
N,N-diethyl-*m*-toluamide	Li[H_3BPyrr](1.2)	3-methylbenzyl alcohol	95	52-54 (0.2)
N,N-diethyl-*m*-toluamide	Li[H_3BN(*i*-Pr)$_2$](1.2)	3-methyl-*N,N*-diethyl-benzylamine	99	136-138 (100)
N,N-diisopropylbenzamide	Li[H_3BPyrr](1.2)[g,h]	benzyl alcohol	99	50-52 (1)
N,N-diisopropylbenzamide	Li[H_3BN(*i*-Pr)$_2$](1.2)	*N,N*-diisopropylbenzylamine	98	40-41 (0.1)
N,N-diethylsalicylamide	Li[H_3BPyrr](1.2)	*N,N*-diethylsalicylamine	65	59-60 (0.5)
N,N-diethylsalicylamide	Li[H_3BN(*i*-Pr)$_2$](2)[h]	*N,N*-diethylsalicylamine	67	59-60 (0.5)
N,N-diethylnicotinamide	Li[H_3BN(*i*-Pr)$_2$](1.2)[h]	*N,N*-diethylnicotinamine	86	59-60 (0.5)
N,N-diethylnicotinamide	Li[H_3BPyrr](1.2)	*N,N*-diethylnicotinamine	65	59-60 (0.5)

[a]Reactions run with $LiABH_3$ generated *in situ* at 25 °C unless otherwise noted. [b]Generated by: (1) 12 mmol amine + 12 mL 1M BH_3·THF, 1h, 25 °C; (2) 12 mmol 2.5M *n*-BuLi, 30 min., 0 °C. [c]Purity determined by ^{11}B-NMR of the THF solution of $LiABH_3$. [d]Product purity determined by 250 MHz ^{1}H- and ^{13}C-NMR and FT-IR. [e]Isolated yields. [f]BP/MP are uncorrected. [g]Quantitative recovery of starting material with $LiPyrrBH_3$ at 25 °C. [h]Reduction done at 65 °C for 2h.

added neat by syringe. The reaction mixture was stirred for 2h at 25 °C. The reaction was quenched by the *slow* addition of 3M HCl (42 mmol, 14 mL). The aqueous fraction was separated, layered with diethyl ether (~40 mL), and solid sodium hydroxide added until the reaction mixture was strongly basic to litmus. The ethereal fraction was separated, the aqueous fraction extracted with diethyl ether (4 x 15 mL), and the ethereal fractions combined and dried over $MgSO_4$. The solvent was removed *in vacuo* at 25 °C (6 torr) to yield 1-pyrrolidinooctane (95% isolated yield, BP: 44-45 °C, 0.3 Torr).

Currently, we are exploring the use of lithium aminoborohydrides for the reduction of primary and secondary amides. We are also investigating the use of $LiABH_3$'s both more hindered than $LiH_3BN(i\text{-}Pr)_2$ and less hindered than $LiPyrrBH_3$ in order to achieve total control over C-N versus C-O bond cleavage in the reduction of tertiary amides.

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