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Aminoborohydrides. 11. Facile Reduction of *N*-Alkyl Lactams to the Corresponding Amines Using Lithium Aminoborohydrides

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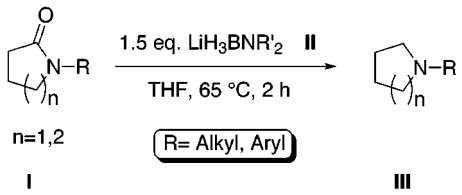
ABSTRACT



Various five- and six-membered *N*-alkyl lactams were reduced to the corresponding cyclic amines using lithium *N,N*-dialkylaminoborohydrides (LAB). Most of the reductions were essentially complete after refluxing in THF for 2 h. The cyclic amine products were easily isolated after an aqueous workup in very good to excellent yields. It is possible to selectively reduce most functional groups, such as esters, in the presence of a lactam using LAB reagents.

The reduction of lactams to the corresponding cyclic amines is of interest in both natural products[1,2] and synthetic organic chemistry.[3,4] Lithium aluminum hydride[5] ($LiAlH_4$) has been the most commonly used reducing agent for this transformation. Chemoselective methods for the reduction of lactams to amines have also been developed using diisobutylaluminum hydride (DIBAL),[6] borane,[7,8] sodium borohydride,[9] and rhodium-catalyzed hydrosilation.[10]

Lithium aminoborohydrides (LAB) **2** are a new, powerful class of reducing agents that can reproduce, in air, virtually all of the transformations[11] now carried out with $LiAlH_4$. Our research group has recently reported the facile and chemoselective reduction of both tertiary amides[12] and *N*-alkyl lactams[13] to amines using 9-borabicyclo[3.3.1]nonane (9-BBN). In continuation of our amide reduction study with LAB reagents **2**,[14] we decided to investigate the reduction of *N*-alkyl lactams **1** to cyclic amines **3** using lithium dimethylaminoborohydride (LiH_3BNMe_2) **2a**. We now report the results of our study as outlined in Scheme 1.

For our study, we selected various five- and six-membered lactams. Reduction of 1-benzyl-2-pyrrolidinone **1a** with 1 equiv of lithium dimethylaminoborohydride (LiH_3BNMe_2) **2a** at 25 °C was sluggish and gave *N*-benzyl pyrrolidine **3a** as the major product and some unreacted starting material.

(1) Ikotta, N.; Hanaki, A. *Chem. Pharm. Bull.* **1990**, *38*, 2712.
(2) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10526.
(3) Ramsden, N. G.; Fleet, G. W.; Namgoong, S. K. *J. Chem. Soc., Perkin Trans. II* **1991**, 1991.
(4) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; pp 432−434.
(5) Brown, H. C.; Weissman, P. M.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1458.
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(10) Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017.
(11) Fisher, G. B.; Harrison, J.; Fuller, J. C.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1992**, *33*, 4533.
(12) Godjoian, G.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 1717.
(13) Collins, C. J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673.
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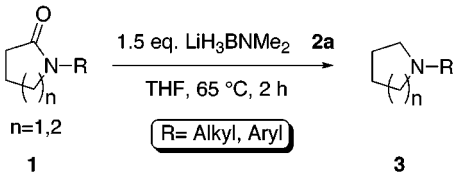
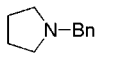
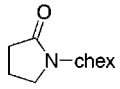
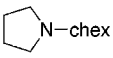
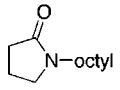
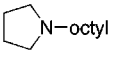
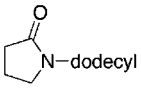
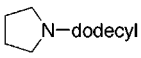
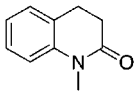
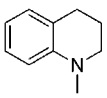
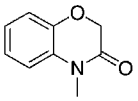
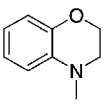
Scheme 1



Refluxing 1-benzyl-2-pyrrolidinone **1a** in THF for 2 h with 1.5 equiv of LiH_3BNMe_2 **2a** gave *N*-benzylpyrrolidine **3a** (Table 1, entry 1) as the sole product. The progress of the reactions was monitored using FTIR by the disappearance of the lactam carbonyl at 1660−1705 cm^{-1}. Most of the reductions were essentially complete after 2 h.

This methodology was applied to 1-cyclohexyl-2-pyrrolidinone **1b** (Table 1, entry 2), 1-octyl-2-pyrolidinone **1c** (Table 1, entry 3), and 1-dodecyl-2-pyrrolidinone **1d** (Table 1, entry 4), and all of these substrates give the corresponding cyclic amine products **3b**−**d** in very good to excellent yields. This method was also general for six-membered lactams and may have applications in alkaloid chemistry. Reduction of 1-methyl-3,4-dihydroquinolone **1e** (Table 1, entry 5) gave *N*-methyl-1,2,3,4-tetrahydroquinoline **3e** in 96% yield. Also, 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one **1f** (Table 1, entry 5) gave *N*-methyl benzomorpholine **3f** in 75% yield.

Table 1. Reduction of *N*-Alkyl Lactams **1** with LiH_3BNMe_2 **2a** to the Corresponding Amine **3**

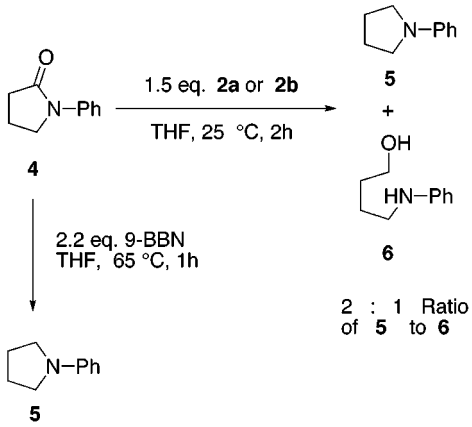
entry	lactam[a]	cyclic amine	yield (%)[b]
1	 **1a**	 **3a**	86
2	 **1b**	 **3b**	80
3	 **1c**	 **3c**	89
4	 **1d**	 **3d**	96
5	 **1e**	 **3e**	96[c]
6	 **1f**	 **3f**	75[c]

[a] All reactions were carried out on 10 mmol scale unless otherwise noted.[15] [b] Isolated yields. [c] A 5 mmol scale reaction.

LAB reagents can perform a reagent-controlled reduction of amides. For example, 1-pyrrolidooctanamide can be reduced to either 1-octanol with lithium dimethylaminoborohydride **2a** or 1-pyrrolidinooctane with the sterically bulky lithium diisopropylaminoborohydride ($LiH_3BN(^iPr)_2$) **2b**. On the basis of our amide reduction study with LAB reagents,[14] we speculated that we could reduce lactams to either the cyclic amine or the ring-opened amino alcohol depending upon the steric requirement of the LAB reagent used.

However, we found that 1-phenyl-2-pyrrolidinone **4** was the only substrate that gave any ring-opened product. Reduction of **4** at 25 °C with both LiH_3BNMe_2 **2a** and $LiH_3BN(^iPr)_2$ **2b** gave *N*-phenylpyrrolidine **5** and *N*-phenylaminobutanol **6** in 2:1 ratio in 95% yield (Scheme 2). It should be pointed out that reduction of 1-phenyl-2-pyrrolidinone with 9-BBN gave *N*-phenylpyrrolidine **5** as the sole product in 95% yield.[16]

Scheme 2

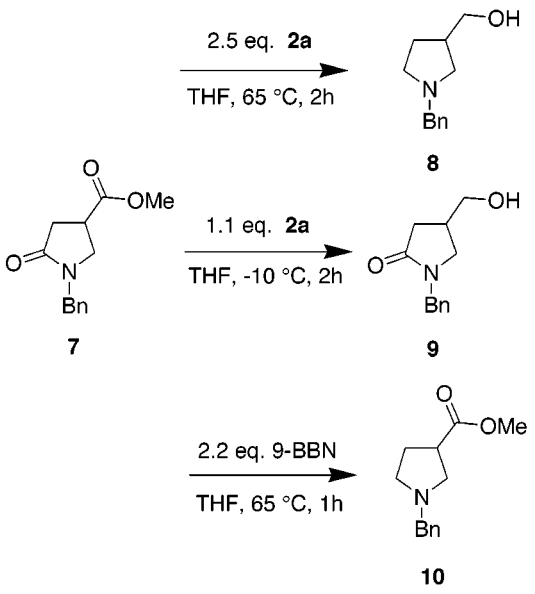


A possible explanation for the ring opening of 1-phenyl-2-pyrrolidinone **4** with LAB reagents is the stabilization of the negatively charged nitrogen nucleofuge by delocalization

(15) **General Procedure.** An oven-dried 100-mL round-bottom flask equipped with a magnetic stirring bar was sealed with a rubber septum, cooled under nitrogen, and charged with dimethylamine−borane (0.882 g, 15 mmol) and anhydrous THF (15 mmol). At 0 °C, *n*-butyllithium (2.5 M, 6 mL, 15 mmol) was added dropwise via syringe, and the reaction mixture was stirred at 0 °C for 1 h. 1-Benzyl-2-pyrrolidinone (1.75 g, 10 mmol) was added neat via syringe. The flask was fitted with a water-cooled reflux condenser, and the reaction mixture heated to reflux under nitrogen. The progress of the reaction was monitored by FTIR. After 2 h, the reaction was cooled to 0 °C under nitrogen and quenched by the slow addition of 25 mL of 3 M HCl. (*Caution!* Hydrogen evolution!) The aqueous layer was then extracted with 4 × 20-mL portions of diethyl ether, and the organic layers were separated. At 0 °C, solid NaOH was added to aqueous layer, and the aqueous layer was extracted with 4 × 20-mL portions of diethyl ether/THF. The ethereal fractions were combined, dried over $MgSO_4$, and filtered. The solvent was removed under vacuum (35 °C, 30 Torr) and then (25 °C, 1 Torr). To give *N*-benzylpyrrolidine 1.39 g (86% yield) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 1.80−1.82 (quint, 4H), 2.52−2.56 (quint, 4H), 3.63 (s, 2H), 7.24−7.28 (t, 2H), 7.32−7.37 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.57, 54.28, 60.85, 127.0, 128.2, 128.3, 129.0, 139.4.

(16) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley and Sons: New York, 1989; p 1208.

Scheme 3



into the benzene ring which does not occur when an alkyl group is attached to the nitrogen (Table 1, entries 1−4) or electron-donating groups are attached to the phenyl ring (Table 1, entries 5 and 6). 1-Phenyl-2-pyrrolidinone was the only example where ring opening was observed. No ring-opened amine, enamine, or hemiaminal products were detected in any of the other examples.

It is possible to selectively reduce sensitive functionalities with LAB reagents in the presence of a lactam. The reduction of esters with LAB reagents is quite facile even at room or reduced temperatures.[11] However, the reduction of lactams requires elevated temperatures or extended reaction times at room temperature with LAB reagents. We used these observations to selectively reduce an ester moiety in the presence of a lactam. At −10 °C, the ester in methyl 1-benzyl-2-oxopyrrolidine-4-carboxylate **7** is reduced by stirring with 1.1 equiv of LiH_3BNMe_2 **2a** without affecting the lactam thus giving the alcohol product, 1-benzyl-4-(hydroxymethyl)-2-pyrrolidinone **9**, in 96% yield after aqueous workup (Scheme 3). Lithium borohydride ($LiBH_4$) can also perform a similar transformation as it can reduce esters and not amides. However, such a selective reduction with $LiBH_4$ requires extended refluxing conditions.[15] Reduction of an ester in the presence of an lactam with LAB reagents is complementary to 9-BBN reduction which can reduce the lactam in methyl 1-benzyl-2-oxo-pyrrolidine-4-carboxylate **7** in the presence of an ester to give methyl 1-pyrrolidinone-3-carboxylate **10**.[13] In refluxing THF (65 °C) using 2.5 equiv of **2a**, both the ester and lactam moieties are reduced in **8** to give the cyclic amino alcohol, 1-benzyl-3-(hydroxymethyl)-pyrrolidine **9**, in 88% yield. In summary, reduction of **7** at lowered temperatures with 1.1 equiv of **2a** gives **9**. Reduction of **7** with 2.5 equiv of **2a** gives **8**. Reduction of **7** with 9-BBN gives **10**.

In conclusion, reduction of lactams with lithium aminoborohydrides is facile and in most cases gives exclusively the cyclic amine product in very good to excellent yields. This method is chemoselective, and it is possible to reduce more sensitive functionalities such as aldehydes, ketones, epoxides and esters in the presence of a lactam.

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Supporting Information Available: Proton and carbon spectra for compounds **3a**−**f**, **5**, **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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