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Facile Reduction of Tertiary Lactams to Cyclic Amines With 9-Borabicyclo[3.3.1]nonane (9-BBN)

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Abstract: Various 5- and 6-membered tertiary lactams were reduced to the corresponding cyclic tertiary amines using 2.2 to 2.5 equivalents of 9-borabicyclo[3.3.1]nonane (9-BBN). This method is highly chemoselective and it is easy to reduce a lactam in the presence of an ester. © 1999 Elsevier Science Ltd. All rights reserved.

The reduction of tertiary lactams to the corresponding cyclic tertiary amines is of interest in both natural products[1,2] and synthetic chemistry.[3,4] Lithium aluminum hydride ($LiAlH_4$)[5] has been the most commonly used reagent for this transformation, but its use is strongly limited due to its lack of chemoselectivity. Chemoselective methods for the reduction of lactams to amines have been developed with diisobutylaluminum hydride (DIBAL),[6] borane,[7,8] sodium borohydride[9] and rhodium catalyzed hydrosilylation.[10] Borane has been shown to selectively reduce lactams to amines in the presence of an ester.[7,8] However, an excess of BH_3-THF is required in the reduction of both lactams and amides as the borane is known to coordinate strongly with the amine products. Catalytic hydrosilylation selectively reduces amides to amines in the presence of epoxides, esters and aryl halides.[10]

9-Borabicyclo[3.3.1]nonane (9-BBN) is a mild and selective reducing agent that reduces aldehydes, ketones, acid chlorides, alkenes and slowly reduces nitriles.[11] We recently reported that 9-BBN also reduces tertiary amides to amines.[12] Unlike borane, 9-BBN generally does not form a complex with the tertiary amine products. Consequently, a stoichiometric quantity of 9-BBN is usually sufficient to carry out complete reduction of amides. In continuation of our amide reduction study, we became interested in the reduction of lactams to cyclic amines. After a survey of the literature, we found the generality of the reduction of tertiary lactams to the corresponding cyclic amines with 9-BBN had not been studied. We did find one example of lactam reduction with 9-BBN where ten equivalents of the reagent were used instead of the stoichiometric amount.[13] In this paper, we describe the results of our study on the reduction of *N*-alkyl lactams with 9-BBN.

For our study we selected various commercially available 5- and 6-membered lactams. Initially, we needed up to 3.0 equivalents of 9-BBN to entirely reduce the lactam substrates. We were quite puzzled by the necessity of an additional equivalent of reagent for complete reduction, since theoretically only two equivalents of reagent are needed for this reduction. Attempted reduction of 1-phenyl-2-pyrrolidinone with two equivalents of 9-BBN in THF at 25 °C was sluggish and gave a mixture of the expected product, *N*-phenyl-pyrrolidine (major), and the unreacted starting material (minor). We found that the varying amounts of water present in the commercial lactam samples necessitated the use of excess of 9-BBN in these reductions.[14] After some experimentation with reaction conditions, we found that drying the lactams over calcium hydride and the use of a slight excess of 9-BBN (2.2 equivalents) in refluxing THF (65 °C) gave the amine as the only product. These

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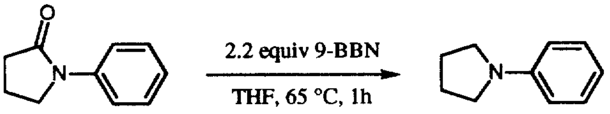
reaction conditions gave *N*-phenyl-pyrrolidine as the exclusive product from 1-phenyl-2-pyrrolidine in quantitative yield (eq. 1).

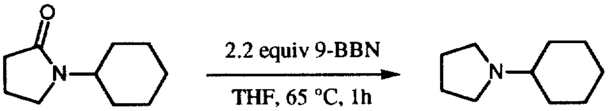


(1)

>99% Isolated Yield

The progress of the reactions was monitored by ^{11}B-NMR spectroscopy by following the disappearance of the signal at δ +27 due to the 9-BBN dimer and/or by the disappearance of the carbonyl stretch of the lactam ν=1705-1660 cm^{-1} by FTIR spectroscopy. Most of the reductions carried out in refluxing THF (65 °C) were essentially complete after one hour.

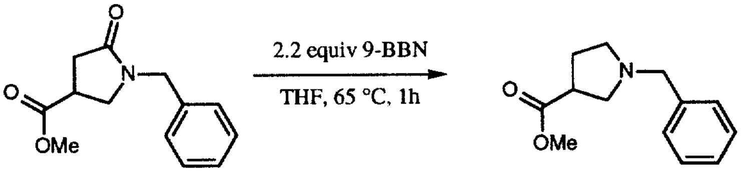
Even the substrate, 1-cyclohexyl-2-pyrrolidinone, containing the sterically bulky cyclohexyl group, required only 2.2 equivalents of 9-BBN for reduction to *N*-cyclohexyl-pyrrolidine (eq. 2).



(2)

82% Isolated Yield

The mildness and selectivity of 9-BBN is demonstrated by its ability to selectively reduce the lactam moiety in methyl 1-benzyl-2-oxo-pyrrolidine-4-carboxylate without reducing the ester (eq. 3). This method is complementary to reduction with LiBH$_4$ that is able to reduce esters and not amides.[15]



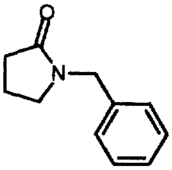
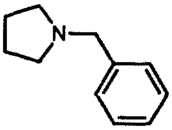
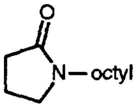
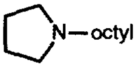
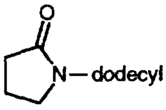
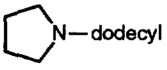
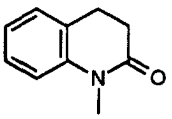
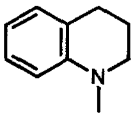
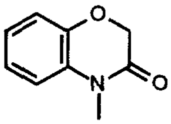
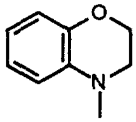
(3)

86% Isolated Yield

This methodology was also applied to 1-benzyl-2-pyrrolidinone (Table 1, Entry 1), 1-octyl-2-pyrrolidinone (Table 1, Entry 2) and 1-dodecyl-2-pyrrolidinone (Table 1, Entry 3) to give the corresponding amines. No ring opened amine, enamine or hemiaminal products were detected in the examples described in this paper. 1-Methyl-3,4-dihydroquinolone[16] was also reduced with 2.2 equivalents 9-BBN to give 1-methyl-1,2,3,4-tetrahydroquinoline in 86% yield (Table 1, Example 4). Reduction of 4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one gave 4-methyl-benzomorpholine in 93% yield (Table 1, Example 5).

The results of this study of lactam reduction with 9-BBN are summarized in **Table 1**.

Table 1. Reduction of Lactams to the Corrresponding Amines with 9-BBN.

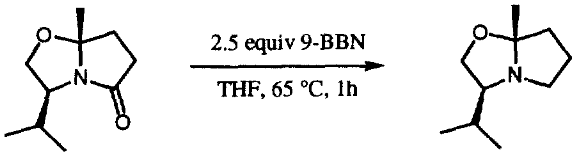
Entry	Lactam	Equiv. 9-BBN	Time, h	Product	Yield, % [a,b]
1		2.2	1		96
2		2.2	1		93
3		2.2	1		97
4		2.2	1		86[c]
5		2.2	1		93[c]

[a] Isolated yields, 10 mmol scale unless otherwise noted.

[b] Characterized by ^{1}H NMR, ^{13}C NMR and capillary GC (methylsiloxane) analysis. Products determined to be >95% pure by ^{1}H NMR and capillary GC analysis.

[c] Isolated yield, 5mmol scale.

Similarly, (3S-*cis*)-(+)-tetrahydro-3-isopropyl-7a-methylpyrrolo[2,1-*b*]oxazol-5(6*H*)-one was reduced using 2.5 equivalents of 9-BBN to give the corresponding amine in essentially quantitative yield (eq. 4)



(4)

95% Isolated Yield

The greater excess of reagent needed in this case was probably due to the two bulky substituents adjacent to the nitrogen.

In conclusion, 9-BBN is a mild and selective reducing agent useful in the reduction of *N*-alkyl lactams to the corresponding cyclic amines. The method described in this study is facile and general for 5- and 6-membered *N*-alkyl lactams. Upon completion of the reaction(s), a simple non-oxidative work-up was employed using ethanolamine to complex and precipitate the 9-BBN derivative that is formed as the by-product in this reduction. This method may be useful for the chemoselective reduction of lactams bearing functionalities not tolerated by $LiAlH_4$.

Representative Procedure: A dry 250-mL round bottom flask was charged with 9-BBN (2.68 g, 22 mmol) and 1-phenyl-2-pyrrolidinone (1.61 g, 10 mmol) in a glove bag under a nitrogen atmosphere. Anhydrous THF (44 mL) was then added *via* syringe. The reaction mixture was heated to 65 °C. The progress of the reaction was monitored by ^{11}B NMR spectroscopy and FTIR. The reaction was complete after refluxing for 1h. The solution was cooled to room temperature under nitrogen, ethanolamine (1.34 g, 1.33 mL, 22 mmol) was added and the residue concentrated *in vacuo* (100 Torr, 35 °C). The resulting solid was then triturated with pentane (100 mL) for 1h and the flask was cooled to 0 °C for 12h. The suspension was filtered over a short plug of Celite and rinsed with ice cold pentane (2x25 mL). The filtrate was concentrated *in vacuo* (100 Torr, 35 °C) then (1 Torr, 25 °C), to give *N*-phenyl-pyrrolidine (1.47 g, 99 % yield) as a light yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 2.04-2.07 (m, 4H), 3.33-3.36 (m, 4H), 6.63-6.64 (d, 2H), 6.71-6.74 (t, 1H), 7.27-7.32 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 25.59, 47.70, 111.8, 115.5, 129.2, 148.1.

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