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Controlled Reduction of Tertiary Amides to The Corresponding Aldehydes or Amines Using Dialkylboranes†

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Abstract: Several tertiary amides were reduced using one or two equivalents of various dialkylboranes, such as 9-borabicyclo[3.3.1] nonane (9-BBN), dicyclohexylborane (Chx_2BH), or disiamylborane (Sia_2BH). The reduction of tertiary amides having alkyl substituents of varying steric requirement at the nitrogen atom, required two equivalents of 9-BBN for complete reduction and gave the corresponding tertiary amines. However, sterically more hindered dialkylboranes such as Chx_2BH and Sia_2BH, reacted in 1:1 stoichiometry with tertiary amides and partially reduced them to the corresponding aldehydes. © 1997 Elsevier Science Ltd. All rights reserved.

The reduction of amides to the corresponding amines has been studied with many complex metal hydrides such as lithium aluminum hydride, trimethoxyaluminohydride, and aluminum hydride.[1] Lithium aluminum hydride is a powerful reducing agent capable of reducing almost all functional groups.. Consequently, it is a synthetic challenge to reduce only a single functional group in a multi-functional molecule. The reduction of amides has also been studied with borane in tetrahydrofuran (BH_3•THF).[2] Borane is a milder reducing agent than lithium aluminum hydride, and excess BH_3:THF is required to reduce amides, since the product amine forms a 1:1 complex with borane.[2] It has been reported that 9-borabicyclo[3.3.1] nonane (9-BBN) reduces *N,N*-dimethylbenzamide to benzyl alcohol.[3] However, the generality of this reaction has not been studied. Another powerful, yet selective class of reducing agents that reduce amides to amines are the lithium aminoborohydrides ($LiAlBH_3$) that have been developed in our laboratories.[4] $LiAlBH_3$'s reduce tertiary amides to amines or alcohols depending upon the steric requirement of the amine moiety in the reducing agent.

Partial reduction of amides to aldehydes is an important transformation in organic syntheses. There are few methods[5] available for this challenging transformation. Many of the partial reductions have been studied with aluminum and boron hydrides.[6] Recently, Buchwald and co-workers[7] have developed a one-pot conversion of amides to amines using stoichiometric amounts of Ti(O-*i*Pr)$_4$ and Ph_2SiH_2 at room temperature. However, use of alkyl substituted boranes for the partial reduction of amides has not been reported as a synthetic procedure. There is one example of the reduction of *N,N*-dimethylbenzamide with disiamylborane (Sia_2BH) to benzaldehyde.[5d] Even though disiamylborane has been shown to be an excellent hydroborating reagent,[8] it has not been used extensively as a reducing agent. In this paper we report the reduction of tertiary amides with dialkylboranes. For our study we selected aliphatic, alicyclic, and aromatic tertiary amides and different dialkylboranes, such as 9-BBN, Sia_2BH and dicyclohexylborane (Chx_2BH).

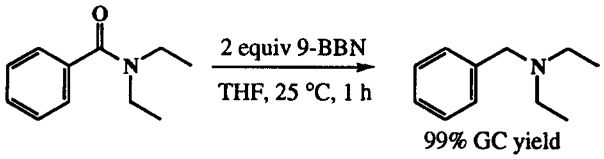
We first studied the reduction of various tertiary amides with the commercially available dialkylborane, 9-BBN. Reduction of *N,N*-dimethylbenzamide using one equivalent of 9-BBN gave some alcohol and mostly unreacted amide. However, the reduction of *N,N*-dimethylbenzamide using two equivalents of 9-BBN gave benzyl alcohol as reported in the literature.[3] Unfortunatelly, this reaction is not general as all other amides used in our study gave the corresponding amines as the sole product. 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. The reduction of amides with 9-BBN was usually rapid, very clean, and essentially quantitative (**Table 1**).[9]

Table 1. Reduction of Tertiary Amides with 9-BBN

Entry	Amide	Product^{a}	yield^{b,c}
1	*N,N*-diethylcyclohexanecarboxamide	*N,N*-diethylcyclohexylamine	87 (76)
2	*N,N*-diethylbenzamide	*N,N*-diethylbenzylamine	99 (80)
3	*N,N*-diethyl-*m*-toluamide	*N,N*-diethyl-*m*-toluidine	83
4	*N,N*-dimethyldecanamide	*N,N*-dimethyldecylamine	88
5	*N*-pyrrolidinocyclohexanecarboxamide	*N*-pyrrolidinocyclohexylamine	82
6	*N*-pyrrolidinobenzamide	*N*-pyrrolidinobenzylamine	99 (79)

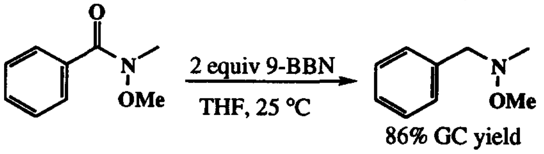
[a] Characterized by ^{1}H and ^{13}C NMR spectroscopy, and capillary GC (methyl silicate column); [b] GC yield, dodecane was used as an internal standard; [c] isolated yields are given in parenthesis

Reduction of *N,N*-diethylbenzamide with 9-BBN gave 99% yield of the corresponding amine in one hour at 25 °C (eq. 1).



(1)

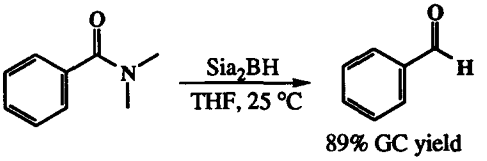
N,N-Dimethyldecanamide was reduced to the amine in 88% yield in 6 h, but cyclic amide reduction was slower requiring 12 h for the completion of the reduction (**Table 1**, entry 4 and 5). *N*-Methoxy-*N*-methylbenzamide was reduced to *N*-methoxy-*N*-methylbenzylamine in 86% yield. It should be mentioned that Weinreb amides usually undergo partial reduction to the corresponding aldehydes.[10] However, we only obtained the corresponding amine in the reduction of *N*-methoxy-*N*-methylbenzamide with 9-BBN (eq 2).



(2)

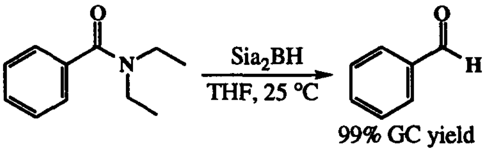
We then studied the reduction of tertiary amides by using Chx_2BH. Unlike 9-BBN, Chx_2BH reduces *N,N*-dimethylbenzamide to benzaldehyde. However, the yield of benzaldehyde was only 54% and the rest of the product was unreacted starting material; reduction of other amides showed the same trend. Reduction of tertiary amides using Chx_2BH, generally gave the corresponding aldehydes along with unreacted starting materials. We did not detect any alcohols or amines in the product. **Table 2** summarizes the results of our Chx_2BH reductions.

We then turned our attention to the reduction of tertiary amides with one equivalent of Sia_2BH, prepared freshly from hydroboration of 2-methyl-2-butene in THF.[5d] The reduction of *N*,*N*-dimethylbenzamide with Sia_2BH gave 89% benzaldehyde as reported earlier (eq. 3).[5d]

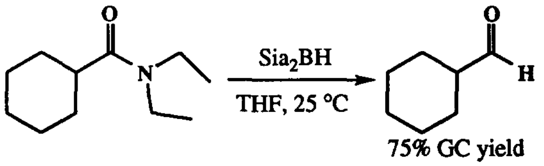


(3)

N,*N*-Diethylbenzamide was cleanly reduced to benzaldehyde in essential quantitative yield. However, the reduction of *N*,*N*-diethylcyclohexanecarboxamide gave 75% yield of the corresponding aldehyde and some unreacted amide (eq. 4 and 5).



(4)



(5)

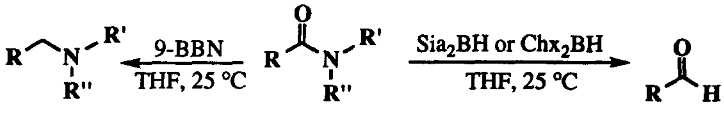
We also reduced various substituted benzamides with one equivalent of disiamylborane, and the results are summarized in **Table 2**. Our study has confirmed that earlier result and demonstrated that the Sia_2BH reductions are general, very clean, and produce only the corresponding aldehydes.[11]

Table 2. Reduction of Tertiary Amides with Dicyclohexylborane and Disiamylborane

Amide	Product[a]	Chx_2BH[b]	Sia_2BH[b]
N,*N*-dimethylbenzamide	benzaldehyde	54	89
N,*N*-dimethyl-*p*-toluamide	*p*-tolualdehyde	44	68
N,*N*-dimethyl-*p*-chlorobenzamide	*p*-chlorobenzaldehyde	32	70
N,*N*-dimethyl-*p*-methoxybenzamide	*p*-methoxybenzaldehyde	55	77
N,*N*-dimethyldecanamide	decyl aldehyde	45	85
N,*N*-diethylbenzamide	benzaldehyde	59	99
N-ethyl-*N*-phenylbenzamide	benzaldehyde	56	93

[a] Characterized by capillary GC (methyl silicate column).; [b] GC yield, dodecane was used as an internal standard

In summary, we found that the steric requirement of dialkylboranes play a major role in the reductions of tertiary amides. The reductions are independent of the steric bulk of the amides. Thus, tertiary amides can be reduced to either the corresponding amines or to the corresponding aldehydes, at will, depending on the choice of dialkylborane.



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† Dedicated to Professor H. C. Brown on the occasion of his 85th birthday.

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9. **Reduction of amide with 9-BBN.** A 50-mL round bottom flask was cooled under nitrogen and charged with 9-BBN (1.26g, 10.4 mmol). The 9-BBN was dissolved in THF (15 mL) and the solution was added to a THF (10 mL) solution containing of *N*-pyrrolidinocyclohexanecarboxamide (0.91g, 5 mmol) and dodecane (0.39g, 2.3 mmol). The progress of the reaction was monitored by ^{11}B NMR spectroscopy. The reaction was complete after stirring for 12 h. After oxidative work-up (NaOH and H_2O_2), the organic layer was seperated from the aqueous layer, washed with distilled water, and dried over anhydrous magnesium sulfate. GC analysis showed that the 9-BBN reduction of *N*-pyrrolidinocyclohexanecarboxamide gave 82% of the corresponding amine.
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11. **Reduction of amide with Disiamylborane.** A 50-mL round bottom flask was cooled under nitrogen, and the flask was charged with THF solution (5 mL) containing *N,N*-diethylbenzamide (0.88g, 4.96 mmol) and dodecane (0.18g, 1.0 mmol), as an internal standard. Freshly prepared disiamylborane[5d] solution (8 mL, 6 mmol) was added dropwise via syringe to the amide and dodecane solution. The progress of the reaction was monitored by ^{11}B NMR spectroscopy. The reaction was complete after stirring for 12 h. After oxidative work-up (NaOH and H_2O_2), the organic layer was seperated from the aqueous layer, washed with distilled water, and dried over anhydrous magnesium sulfate. GC analysis showed that disiamylborane reduced *N,N*-diethylbenzamide to benzaldehyde in 99% yield.

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