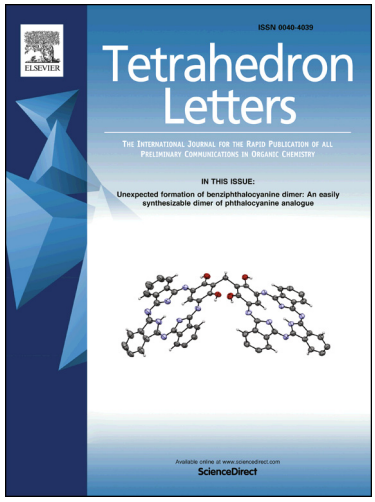


# Diisobutylaluminum Borohydride: an efficient reagent for the reduction of tertiary amides to the corresponding amines under ambient conditions

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# Diisobutylaluminum Borohydride: an efficient reagent for the reduction of tertiary amides to the corresponding amines under ambient conditions

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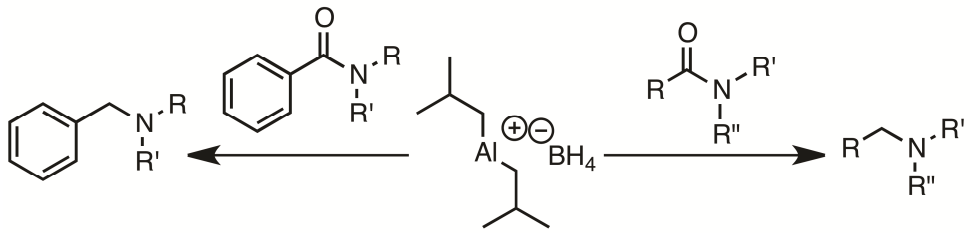



**Abstract**

A synthetically simple mixed metal hydride, diisobutylaluminum borohydride [$(i\text{Bu})_2\text{AlBH}_4$], is easily generated from a 1:1 mixture of borane-dimethylsulfide (BMS) and diisobutylaluminum hydride (DIBAL). The reduction of tertiary amides using $(i\text{Bu})_2\text{AlBH}_4$ is complete within five minutes under ambient conditions and the product tertiary amines were isolated in 70 to 99% yields by a simple acid-base extraction. This new methodology, reported herein, works well for reduction of tertiary aliphatic and aromatic amides as well as lactams to the corresponding amines and product isolation and purification does not require column chromatography.

**Keywords**

Aluminum, Boron, Borohydride, Ambient, Amide, Amine, Hydride, Reduction

## 1. Introduction

Reduction of amides to the corresponding amines is an important process in organic chemistry for the synthesis of amines.[1] These reductions are typically difficult due to the low electrophilicity of the carbonyl carbon and use pyrophoric reducing agents, high reaction temperatures, and/or long reaction times.[2] Extensive use of amines as starting materials for plastics,[3] agrochemicals,[4] and dyes[5] in industry make amide reduction an important functional group transformation in organic chemistry. Amines also play an important role in biological processes and are key functionalities found in many pharmaceuticals in wide use today,[6] such as central nervous system (CNS) drugs,[7-10] Thus, the growing interest in and use of amines has necessitated novel and efficient methods for their synthesis, including amide reduction. A major challenge in the synthesis of amines from the corresponding amides is the reduction of the least electrophilic amide functionalities, which are often difficult functional groups to reduce.

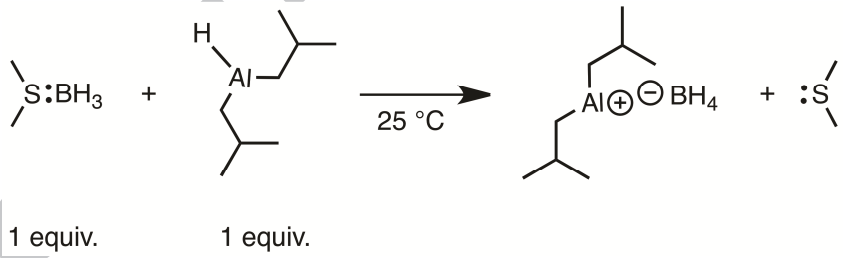
Common reducing reagents employed for these reductions include lithium aluminum hydride ($LiAlH_4$)[11] and borane-tetrahydrofuran ($BH_3$:THF)[12] which are pyrophoric or require refluxing conditions or extended reaction times. Borane-dimethylsulfide (BMS) can reduce tertiary amides to amines, however, this procedure requires refluxing conditions as well as continuously distilling off dimethylsulfide.[13] It has been reported that diisobutylaluminum hydride (DIBAL) reduces tertiary amides to the corresponding amines but the reaction needs to be carried out at 200 ºC.[14] Non-pyrophoric lithium aminoborohydride (LAB) reagents can reduce tertiary amides to the corresponding alcohols or amines depending on the steric requirements of the LAB reagent.[15] Tertiary amides can also be reduced to the corresponding amines using silane

mediated reactions.[16-29] This methodology often requires transition metal catalysts, increased temperatures, or longer reaction times and chromatographic purification. A procedure for the complete reduction of tertiary amides to the corresponding amines at ambient temperature that does not involve chromatographic purification techniques for isolation of the product is still elusive. Herein, we report a new reagent that successfully reduces tertiary amides to the corresponding amines, is relatively safe to handle, and allows product isolation without use of chromatography.

## 2. Results and Discussion

### 2.1 Synthesis of diisobutylaluminum borohydride

As a part of our interest in generating binary hydride systems,[30] we investigated the reaction of BMS with DIBAL to generate a new binary hydride reagent, diisobutylaluminum borohydride ($i$Bu$_2$AlBH$_4$). The $^{11}$B NMR spectral analysis of a (1:1) reaction mixture displayed a quintet at -37 ppm (J=83 Hz) indicating the clean formation of $i$Bu$_2$AlBH$_4$ (Scheme 1).




**Scheme 1** Synthesis of diisobutylaluminum borohydride[31]

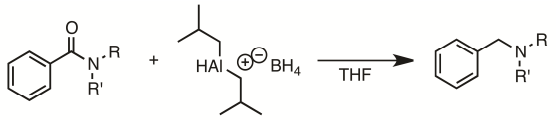
The starting BMS reagent usually displays a quartet at -20 ppm with a coupling constant of 103 Hz in the $^{11}$B NMR spectrum. When DIBAL is added to BMS, the quartet at -20 ppm disappears and a new quintet is observed at -37 ppm with a coupling constant of 83 Hz, indicative of formation of a borohydride. Interestingly, while DIBAL and BMS are

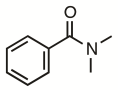
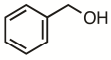
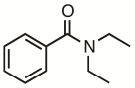
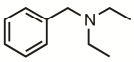
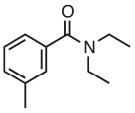
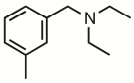
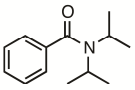
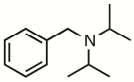
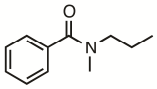
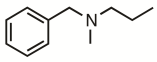
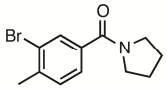
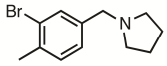
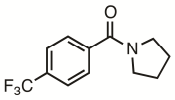
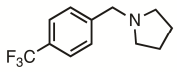
both Lewis acids, BMS is a stronger Lewis acid and accepts a hydride from DIBAL, which is the weaker Lewis acid of the two reagents. We tried the reactions of a variety of other common Lewis acidic hydrides, such as, pinacolborane (HBPin), chloromagnesium hydride (HMgCl), and $HInCl_2$ with BMS. Unfortunately these Lewis acid-BMS interactions did not generate pure binary hydrides as observed with DIBAL.

### 2.1 Reduction of aromatic tertiary amides

Most of the known hydrides are capable of reducing carbonyl functional groups present in aldehydes, ketones and esters. Preliminary screening showed that $i$Bu$_2$AlBH$_4$ behaved like other hydride reagents and reduced most electrophilic functional groups. However, we were interested in the reduction of tertiary amides, as they are difficult to reduce at ambient temperatures due to the low electrophilicity of the carbonyl functionality. Consequently, we studied the reduction of a wide variety of aromatic amides and found that the majority of the tertiary amides tested were rapidly reduced using $i$Bu$_2$AlBH$_4$ at ambient temperature to the corresponding tertiary amines.[32] The results are summarized in Table 1.

**Table 1 Reduction of aromatic tertiary amides using $i$Bu$_2$AlBH$_4$**




| Entry | Amide[a] | Product | Yield (%)[b] |
|---|---|---|---|
| 1 |  |  | 98 |
| 2 |  |  | 80 |
| 3 |  |  | 99 |
| 4 |  |  | 99 |
| 5 |  |  | 92 |
| 6 |  |  | 89 |
| 7 |  |  | 84 |

[a]Reductions carried out at 25 ºC for 1 hour on a 5 mmol scale with 1 equivalent of amide and 1.1 equivalent of *i*$Bu_2AlBH_4$. *i*$Bu_2AlBH_4$ was added at 0 ºC and the ice bath was removed after all the hydride was added to the reaction mixture. Product was isolated through acid-base extraction; no further purification was required. [b]Isolated yield.

*N*,*N*-Diethylbenzamide and *N*,*N*-diethyl-m-toluamide (DEET) were reduced to *N*,*N*-diethylbenzylamine and *N*,*N*-diethyl-(3-methylbenzyl)amine and isolated in 80% and 99% yields respectively (Table 1, entries 1 and 2). These reductions were followed by IR spectral analysis of aliquots withdrawn periodically from the reaction mixture; the reduction was considered complete when the carbonyl stretch was no longer visible in the

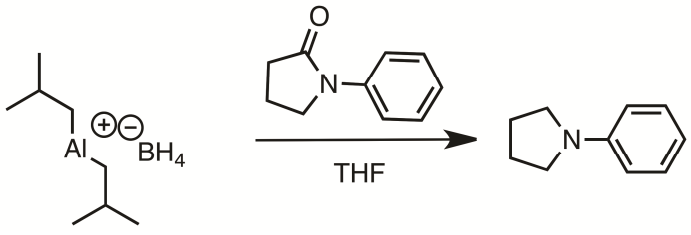
IR spectrum. The reaction was quenched with methanol. The aluminum-containing compounds formed a solid polymer that was easily removed by simple filtration followed by a methanol wash. The combined filtrate was concentrated and the product amine was isolated by simple acid-base extraction, without the need for column chromatographic purification techniques.[33] Sterically hindered *N*,*N*-diisopropylbenzylamine was isolated from the reduction of *N*,*N*-diisopropylbenzamide in 99% yield (Table 1, entry 3). The unsymmetrical aromatic amide *N*-methyl-*N*-propylbenzamide was reduced to *N*-methyl-*N*-propylbenzylamine and isolated in 92% yield (Table 1, entry 4). Since tertiary benzamides were successfully reduced in overall good yields, the influence of both electron-donating and electron-withdrawing groups was investigated. Benzamides with electron-withdrawing groups, such as bromo or trifluoromethyl substituents, were successfully reduced. (3-Bromo-4-methylphenyl)(pyrrolidin-1-yl)methanone and pyrrolidin-1-yl(4-(trifluoromethyl)phenyl)methanone were reduced to the corresponding amines in 89% and 84% yields, respectively (Table 1, entries 5 and 6). Since our initial functional group screening showed $i\text{Bu}_2\text{AlBH}_4$ can reduce most electrophilic compounds, bifunctional aromatic compounds were not tested for the chemoselective reduction of amides.

**2.2 Reduction of aliphatic tertiary amides and tertiary lactams**

Two different substrates, *N*,*N*-dimethylhexamide and 1-(pyrrolidin-1-yl)hexan-1-one, were chosen as preliminary examples for the reduction of aliphatic tertiary amides and tertiary lactams, respectively. Substrates that have a long *N*-alkyl chain on the amide were selected to facilitate the isolation of the reduction products by using a simple acid-base extraction. The reduction products, *N*,*N*-dimethylhexylamine and 1-

hexylpyrrolidine were isolated in yields of 84% and 88%, respectively (Table 2, entries 1 and 2). Similarly, 2-(2-bromophenyl)-1-(pyrrolidin-1-yl)ethanone was reduced to 1-(2-bromophenethyl)pyrrolidine in an isolated yield of 83% (Table 2, entry 7).

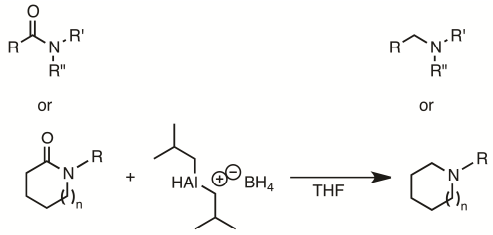
When $BH_3$:THF is used for reduction of amides, excess of the expensive borane reagent is required for the complete amide reduction due to the coordination of $BH_3$ to the amine products.[34a,b] When lactams are reduced using DIBAL, a mixture of the amino-alcohol and cyclic amine products are observed.[35] Methyl-LAB can reduce 1-phenyl-2-pyrrolidinone to give a mixture of *N*-phenylpyrrolidine and *N*-phenylaminobutanol.[36] However, $i\text{Bu}_2\text{AlBH}_4$ reduced lactams to the corresponding cyclic amines in very good yields. The alkyl lactam, 1-octyl-2-pyrrolidone, was reduced to 1-octylpyrrolidine in 87% isolated yield (Table 2, entry 3). Most notably, 1-phenyl-2-pyrrolidone was reduced to 1-phenylpyrrolidine in a 71% isolated yield (Table 2, entry 4). Reduction of this lactam with other reducing agents typically gives the ring opened product, 4-(phenylamino)butan-1-ol. The lactam nitrogen can coordinate to a Lewis acid making the *N*-atom a good leaving group, to give an aldehyde intermediate that gets further reduced to the amino alcohol product. However this product was not observed when 1-phenyl-2-pyrrolidone was reduced with $i\text{Bu}_2\text{AlBH}_4$. Reductions using $i\text{Bu}_2\text{AlBH}_4$ most likely go through an imine intermediate, ultimately resulting in the cyclic amine product (Scheme 2).

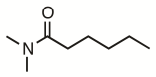
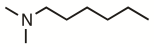
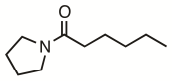
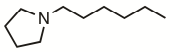
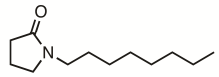
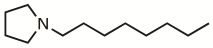
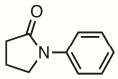
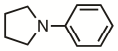
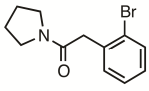
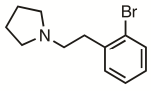



**Scheme 2** Reduction of 1-phenyl-2-pyrrolidone using $i\text{Bu}_2\text{AlBH}_4$

*N*-Methyl-2-piperidone and *N*-methylcaprolactam were reduced to give the 1-methylpiperidine-borane complex and 1-methylazepane-borane complex, respectively (Table 2, entries 5 and 6). Long *N*-alkyl chain lactams were reduced to the corresponding cyclic amines and isolated in pure form free from amino-alcohol side products.

**Table 2 Reduction of aliphatic amides and lactams using *i*$Bu_2AlBH_4$[a]**

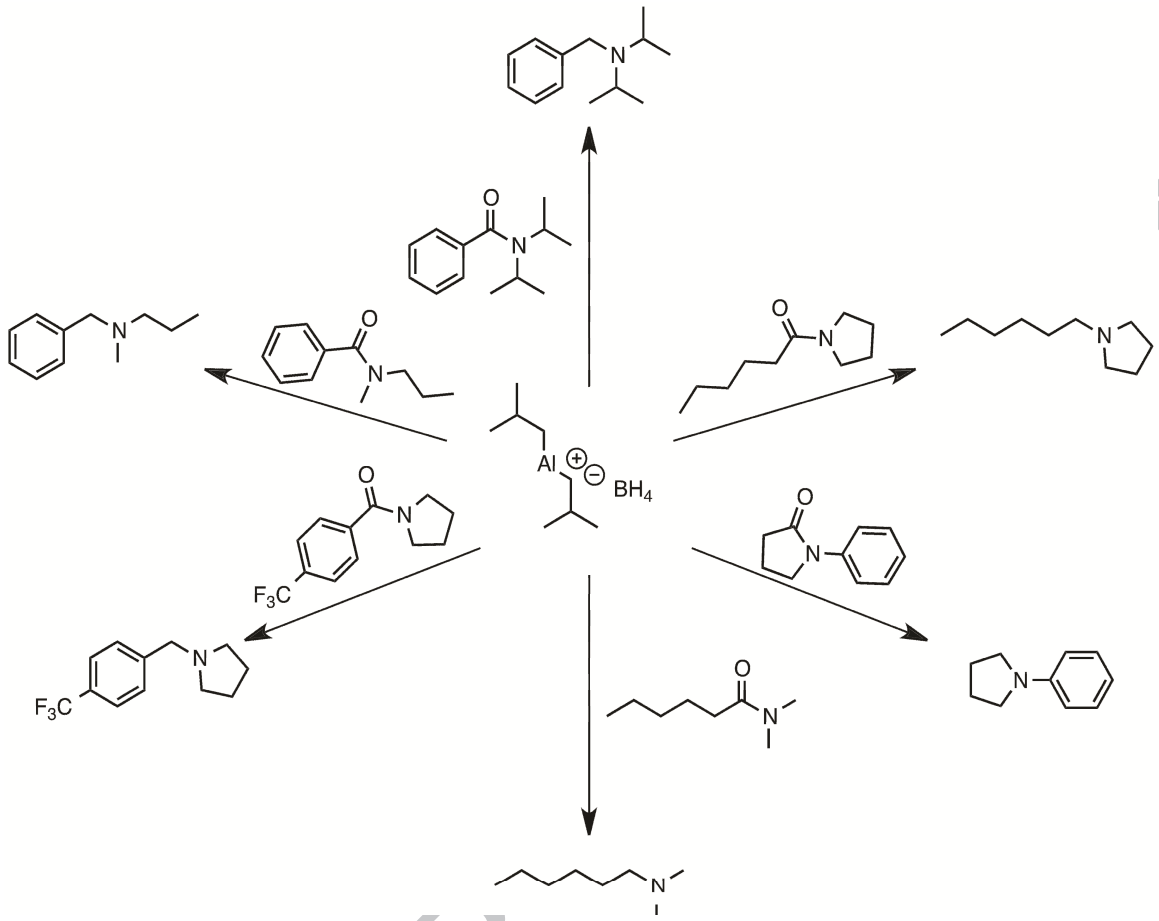



| Entry | Amide[a] | Product | Yield (%)[d,e] |
|---|---|---|---|
| 1 |  |  | 84 |
| 2 |  |  | 88 |
| 3 |  |  | 87 |
| 4 |  |  | 71 |
| 5 |  |  | X[f] |
| 6 |  |  | X[f] |
| 7 |  |  | 83 |

[a]Reductions carried out at 25 ºC for 1h on a 5 mmol scale with one equivalent of amide and 1.1 equivalent of *i*$Bu_2AlBH_4$. *i*$Bu_2AlBH_4$ was added at 0 ºC and the ice-bath was removed after all

the hydride was added to the reaction mixture. [b]Isolated yields. Product isolated through acid-base extraction and were characterized by $^1$H NMR analysis. . [c]See ref. 33.

A new, easily synthesized reducing agent has been developed for the reduction of tertiary amides. Diisobutylaluminum borohydride (*i*BuAlBH$_4$) is easily synthesized from a 1:1 mixture of BMS and DIBAL and can be stored under an inert atmosphere for at least six months. Even though this reagent can reduce other functional groups, such as aldehyde, ketones, esters, we mainly highlight the ability of this reagent to reduce tertiary amides. The reagent is relatively safe to handle and requires only ambient temperatures and a short reaction time to reduce tertiary amides. This binary hydride can reduce aromatic and aliphatic tertiary amides as well as tertiary lactams to the corresponding amines. This new reducing agent is an attractive alternative to LiAlH$_4$ or BH$_3$:THF. It should be noted that DIBAL is known to reduce tertiary amides to the corresponding aldehyde at low temperature. Borane:dimethylsulfide is not a sufficiently strong reducing agent for the reduction of tertiary amides because the reaction requires long reaction times with concurrent distillation of dimethylsulfide. Representative tertiary amides reduced by *i*Bu$_2$AlBH$_4$ are summarized in Scheme 3.




**Scheme 3** Summary of tertiary amides reduced using *i*$Bu_2AlBH_4$

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31. An oven-dried 100-mL round-bottom flask was equipped with a magnetic stir bar and a rubber septum, and cooled under an argon atmosphere. Borane:dimethyl sulfide (BMS, 10.6 M, 4.72 mL, 50 mmol) was added to the flask. Diisobutylaluminum hydride (DIBAL, 1M in hexane or toluene, 50 mL, 50 mmol) was added dropwise over fifteen minutes. The reaction mixture was allowed to stir for five minutes. An aliquot was taken and analyzed by $^{11}$B NMR spectroscopy. The completion was verified by the observation of a signal shift from -19.5 ppm (quartet) to -36.8 ppm (quintet) (Scheme 1). There was a change in the *J*-value from 105 Hz to 85 Hz, indicating the formation of the borohydride. Diisobutylaluminum borohydride was then transferred to an argon charged ampule and stored for no longer than three months for use. Attempting to generate diisobutylaluminum borohydride by mixing one equiv of diisobutylaluminum chloride ($i$Bu$_2$AlCl) and three equiv of sodium borohydride (NaBH$_4$) in anhydrous THF did not generate diisobutylaluminum borohydride in pure form. The generation of $i$Bu$_2$AlBH$_4$ was also attempted by dissolving one equiv of NaBH$_4$ in 1 mL *N*-methylpyrrolidone (NMP) and anhydrous THF (10 mL) followed by addition of one equiv of $i$Bu$_2$AlCl. Boron NMR analysis revealed NMP was reduced. We were unsuccessful in our attempts to obtain a X-ray quality crystal.

32. An exception is the reduction of *N*,*N*-dimethylbenzamide using $i$Bu$_2$AlBH$_4$ which gave benzyl alcohol in 98% isolated yield.

33. The following procedure is a representative. An oven-dried 50-mL round-bottom flask was equipped with a magnetic stir bar and cooled under an argon atmosphere. *N*,*N*-Diethylbenzamide (0.886 g, 5 mmol, 1 equiv) was added to the flask. The flask was fitted with a rubber septum and purged with argon and cooled to 0 °C. Anhydrous THF (5 mL) was added to the flask via a syringe. Diisobutylaluminum borohydride (6.0 mL, 5.5 mmol, 1.1 equiv) was added dropwise over 15 minutes with stirring. Upon the completion of the addition of diisobutylaluminum borohydride, the ice-bath was removed and the reaction mixture was allowed to stir at 25 °C for one hour. The reduction was complete after one hour as evidenced by the disappearance of the signal due to diisobutylaluminum borohydride (δ -36.81 p, $J$ = 85 Hz) and appearance of a signal due

to amine-borane complex (δ -7.0 q, $J$ = 96 Hz) in the $^{11}$B NMR spectral analysis of an aliquot. The reaction mixture was then concentrated under reduced pressure using a rota-vap and the reaction flask was recapped with a septum. Methanol (15 mL) was added slowly to the residue (*Caution! Hydrogen evolution*) and the mixture was stirred for one hour at 25 °C. The reaction mixture was concentrated under reduced pressure using a rota-vap to give a white solid. Methanol (15 mL) and then conc. HCl (1 mL) were added and the mixture was refluxed for 1 hour, then filtered and concentrated. Pentane (10 mL) and deionized water (5 mL) were added to the filtrate. The layers were separated and to the aqueous layer was added sodium hydroxide (NaOH pellets) until the pH of the aqueous layer was 10. The aqueous layer was then extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo (25 °C, 1 Torr). The product was essentially pure amine as evidenced by $^{1}$H, $^{13}$C and $^{11}$B NMR spectroscopic analyses. This workup procedure allowed the isolation of essentially pure amine products without the need for further purification techniques, such as column chromatography, distillation, or recrystallization.

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**Supplementary Material**

Supplementary data (general experimental details, lists of spectral data, images of $^{1}$H and $^{13}$C NMR spectra for all compounds associated with this article can be found, in the online version.

- Development of reducing agent diisobutylaluminum borohydride
- Tertiary amides reduced to the corresponding amine under ambient conditions
- No column purification technique required for isolation of amine product