



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*Bu)₂AlBH₄], is easily generated from a 1:1 mixture of borane-dimethylsulfide (BMS) and diisobutylaluminum hydride (DIBAL). The reduction of tertiary amides using (*i*Bu)₂AlBH₄ is complete within five minutes under ambient conditions and the product tertiary amines were isolated in 70–99% 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.

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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 dyes⁵ 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 (LiAlH₄)¹¹ and borane-tetrahydrofuran (BH₃: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 °C.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.

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Results and discussion

Synthesis of diisobutylaluminum borohydride

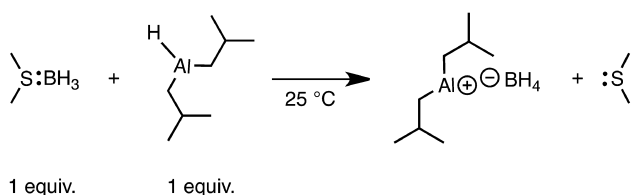
As a part of our interest in generating binary hydride systems,³⁰ we investigated the reaction of BMS with DIBAL to generate a new binary hydride reagent, diisobutylaluminum borohydride ($i\text{Bu}_2\text{AlBH}_4$). The ^{11}B NMR spectral analysis of a (1:1) reaction mixture displayed a quintet at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

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.

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 $i\text{Bu}_2\text{AlBH}_4$ 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 $i\text{Bu}_2\text{AlBH}_4$ at ambient temperature to the corresponding tertiary amines.³² The results are summarized in Table 1.

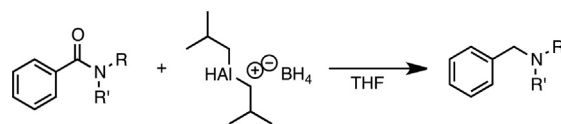
N,N -Diethylbenzamide and N,N -diethyl-*m*-toluamide (DEET) were reduced to N,N -diethylbenzylamine and N,N -diethyl-(3-methylbenzyl)amine and isolated in 80% and 99% yields respectively (Table 1, entries 1 and 2). These reductions were followed by IR spectral analysis of aliquots withdrawn periodically 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 suc-



Scheme 1. Synthesis of diisobutylaluminum borohydride.³¹

Table 1

Reduction of aromatic tertiary amides using $i\text{Bu}_2\text{AlBH}_4$.



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 °C for 1 h on a 5 mmol scale with 1 equivalent of amide and 1.1 equivalent of $i\text{Bu}_2\text{AlBH}_4$. $i\text{Bu}_2\text{AlBH}_4$ was added at 0 °C 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.

cessfully 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.

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).

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