

Partial Reduction of Tertiary Amides to Aldehydes Using a New Reducing Agent, Lithium Diisobutyl-*iso*-propoxyaluminum Hydride (LDBIPA)

Young Mi Choi, Min Eai Kim, and Duk Keun An*

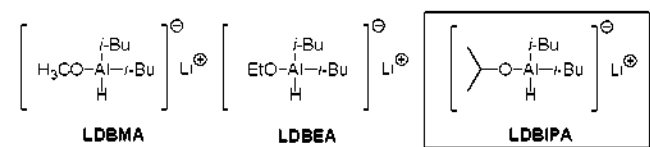
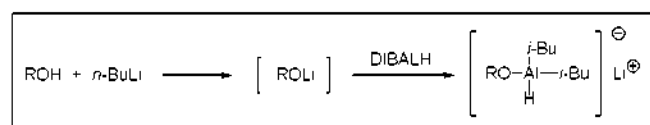
Department of Chemistry, Kangwon National University, Chuncheon 200-701, and
Institute for Molecular Science and Fusion Technology, Korea. *E-mail: dkan@kangwon.ac.kr

Received July 23, 2009, Accepted September 23, 2009

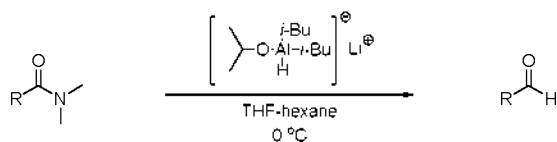
Key Words: Lithium diisobutyl-*iso*-propoxyaluminum hydride. Aldehyde. Tertiary amide. Partial reduction

Partial reduction of carboxylic acid derivatives to aldehydes with efficient reducing agents is one of the important techniques in organic synthesis; hence, large numbers of useful reducing agents for this purpose have been reported over a long time. Recently, we have found and reported that a new class of reducing agents including lithium diisobutylpiperidinoaluminum hydride (LDBPA), lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA) and sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA) showed effective partial reducing characteristics for various esters and acid chlorides.¹ However, these reducing agents were not very effective for tertiary amides and nitriles, that are usually easier targets than esters for partial reduction.² Therefore, we decided to develop new and effective reducing agents that can achieve partial reduction of tertiary amides with excellent yields in the course of our development work in the area of partial reduction of carboxylic acid derivatives.

Previously, we easily prepared new reducing agents by reaction of methanol, ethanol or *iso*-propanol with DIBALH. Scheme 1 outlines the preparation of new-type lithium diisobutylalkoxyaluminum hydrides. Lithium diisobutylmethoxyaluminum hydride (LDBMA), lithium diisobutylethoxyaluminum hydride (LDBEA) and lithium diisobutyl-*iso*-propoxyaluminum hydride (LDBIPA) were successfully prepared by reacting an equimolar amount of lithium alkoxide with DIBALH in THF-hexane at 0 °C.



Scheme 1



Scheme 2

Also, the reducing properties of these lithium diisobutylalkoxyaluminum hydrides (LDBMA, LDBEA and LDBIPA) for partial reduction of tertiary amides were studied. We wish to report herein our results for partial reduction of tertiary amides to aldehydes with the new reducing agents.

Results and Discussion

We first examined the partial reduction of *N,N*-dimethylbenzamide as a model compound with the new reducing agents to evaluate the reducing characteristics and reaction conditions. As shown in Table 1, the partial reduction of the tertiary amide with LDBMA, LDBEA and LDBIPA was performed in THF at 0 °C. We found that we could obtain the best result with LDBIPA in terms of quantitative yield in 1 h.

Therefore, we used LDBIPA for synthesis of aldehydes from various tertiary amides at 0 °C (Scheme 2). The results for representative tertiary amides are summarized in Table 2.

As shown in Table 2, tertiary amides with electron-withdrawing substituents, such as *N,N*-dimethyl-4-chlorobenzamide, *N,N*-dimethyl-3-bromobenzamide and *N,N*-dimethyl-4-bromobenzamide, and electron-donating substituents, such as *N,N*-dimethyl-3-nitrobenzamide, *N,N*-dimethyl-3-toluamide and *N,N*-dimethyl-4-methoxybenzamide, were readily reduced to the corresponding aldehydes in 95 ~ 99% yield (entries 2-7). Similarly, reduction of *N,N*-dimethyl-2-naphthylamide and *N,N*-dimethyl-2-furoamide gave the corresponding aldehydes in 97% and 92% yield, respectively (entries 8 and 9). Furthermore, aliphatic amides such as *N,N*-dimethylcaproamide and *N,N*-dimethyldodecanoamide were smoothly reduced to the corresponding aldehydes in 89% and 90% yield (entries 10 and 11).

In summary, we easily prepared new and useful lithium diisobutylalkoxyaluminum hydrides (LDBMA, LDBEA and LDBIPA) from commercially available DIBALH. We also applied these reagents for partial reduction of tertiary amides to aldehydes. Among these hydrides, LDBIPA appeared to be an excellent reagent for partial reduction of tertiary amides under mild conditions (0 °C). Therefore, LDBIPA is believed to be an alternative reagent for the synthesis of aldehydes from tertiary amides in organic synthesis.

Experimental Section

General. All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior

Table 1. Reduction of *N,N*-dimethylbenzamide with lithium diisobutylalkoxyaluminum hydrides at 0 °C.

Compound	Hydride	Reaction condition		Yield (%) ^a	
		H ⁺ /amide	time (h)	aldehyde	amide
<i>N,N</i> -dimethylbenzamide	LDBMA	1.2	1	92	7
			3	94	6
			6	94	6
	LDBEA	1.2	1	94	5
			3	95	4
			6	97	3
LDBIPA	1.2	1	99	0	

^aYields were determined by GC.**Table 2.** Partial reduction of representative tertiary amides with LDBIPA at 0 °C.

Entry	Compound	Reaction condition		Yield of aldehyde (%) ^a
		H ⁺ /amide	Time (h)	
1	<i>N,N</i> -dimethylbenzamide	1.2	1	99
2	<i>N,N</i> -dimethyl-4-chlorobenzamide	1.2	1	99
3	<i>N,N</i> -dimethyl-3-bromobenzamide	1.2	1	96
4	<i>N,N</i> -dimethyl-4-bromobenzamide	1.2	1	97
5	<i>N,N</i> -dimethyl-3-nitrobenzamide	1.2	1	96
6	<i>N,N</i> -dimethyl-3-toluamide	1.2	1	99
7	<i>N,N</i> -dimethyl-4-methoxybenzamide	1.2	1	95
8	<i>N,N</i> -dimethyl-2-naphthylamide	1.2	1	97
9	<i>N,N</i> -dimethyl-2-furoamide	1.2	1	92
10	<i>N,N</i> -dimethylcaproamide	2.0	3	89
11	<i>N,N</i> -dimethyldodecanoamide	2.0	3	90

^aYields were determined by GC.

to use. All reactions and manipulation of air- and moisture-sensitive materials were carried out using standard techniques for handling air-sensitive materials. All chemicals except tertiary amides were commercial products of the highest purity which were further purified by standard methods before use. THF was dried over sodium-benzophenone and distilled. DIBALH and *n*-butyllithium were purchased from Aldrich Chemical Company. Tertiary amides were prepared by the method of Brown and Tsukamoto.^{1c} GC analyses were performed on a Donam DS 6200 FID or Younglin Acme 6000M FID chromatograph, using a HP-1 (crosslinked methylsiloxane) capillary column (30 m). All GC yields were determined with the use of a suitable internal standard and authentic mixture. The concentration of LDBIPA solution in THF-hexane was measured gasometrically by hydrolysis of an aliquot of the solution with a hydrolyzing mixture of *t*-butyl alcohol-THF (1:1) at 0 °C.

Preparation of LDBIPA. To a solution of *iso*-propanol (4.21 mL, 55 mmol) in THF (25 mL) was added *n*-butyllithium (20 mL, 2.5 M in hexane, 50 mmol) at 0 °C. After being stirred for 1 h at room temperature, DIBALH (50 mL, 1.0 M in hexane, 50 mmol) was added dropwise to the reaction mixture at 0 °C and the mixture was stirred for 2 h at room temperature to give a colorless homogeneous solution.

Stability of the new hydrides. The LDBMA, LDBEA and LDBIPA solutions were stable in a refrigerator for 6 months

without any appreciable loss of hydride content.

Reduction of tertiary amides to aldehydes. The following procedure for the reduction of *N,N*-dimethylbenzamide with LDBIPA is representative. To a solution of *N,N*-dimethylbenzamide (0.075 g, 0.5 mmol) in THF (5 mL) containing naphthalene as an internal standard was added LDBIPA (1.36 mL, 0.44 M in THF-hexane, 0.6 mmol) at 0 °C. After 1 h, the reaction mixture was hydrolyzed with 5 mL of 1 N HCl (aq) and the product was extracted with 10 mL of diethyl ether. The ether layer was dried over anhydrous magnesium sulfate. GC analysis showed a 99% yield of benzaldehyde.

Acknowledgments. This work was supported by the Korea Science and Engineering Foundation (2009-0066035). We are also grateful for the support of Brain Korea 21.

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