

Lithium Diisobutylmorpholinoaluminum Hydride (LDBMOA) as an Effective Partial Reducing Agent for Tertiary Amides and Nitriles

Yu Ri Kim and Duk Keun An*

Department of Chemistry, Kangwon National University and Institute for Molecular Science and Fusion Technology, Chunchon 200-701, Korea. *E-mail: dkan@kangwon.ac.kr
 Received August 11, 2012, Accepted September 4, 2012

Key Words : Lithium diisobutylmorpholinoaluminum hydride (LDBMOA), Partial reduction, Aldehyde, Tertiary amide, Nitrile

Reduction of carboxylic acid derivatives directly to aldehydes is useful tool in organic synthesis. Many synthetic methods have been reported for preparation of aldehydes from carboxylic acid derivatives such as acid chlorides, esters, amides, and nitriles. We developed and reported that a new class of partial reducing agents simply prepared from diisobutylaluminum hydride (DIBALH) smoothly reduced carboxylic acid derivatives to aldehydes in useful yields at mild reaction condition.¹ The direct synthetic method of aldehydes from carboxylic acid derivatives without oxidation step is important and valuable tool in organic synthesis.

As a part of our research program directed toward the discovery of new reducing agents through simple modification of commercial DIBALH, we very recently found that lithium diisobutylmorpholinoaluminum hydride (LDBMOA) was easily prepared by reacting an equimolar amount of lithium morpholide with DIBALH in THF at room temperature (Scheme 1).


Previously, we have evaluated a reducing property of this reagent for the partial reduction of representative carboxylic acid derivatives to aldehydes (Table 1). Fortunately, we found possibility of partial reduction of tertiary amides and nitriles to aldehydes in very good yields at 0 °C.

We tried to decide optimization of reaction conditions for partial reduction of amides and nitriles to aldehydes through reaction of *N,N*-dimethylbenzamide and benzonitrile as a model compounds with LDBMOA (Table 2). And then we immediately carried out the partial reduction of various tertiary amides and nitriles to the corresponding aldehydes using the verified reaction conditions with LDBMOA.

As shown in Table 3, aromatic tertiary amides of electron-withdrawing substituents were smoothly reduced to the corresponding aldehydes in almost quantitative yields (entries 2-6 in Table 3). And aromatic tertiary amides including electron-donating substituents were smoothly reduced to the corre-

sponding aldehydes in 80-97% (entries 7-12 in Table 3). Similarly, reduction of *N,N*-dimethyl-2-furoamide and *N,N*-dimethyl-2-naphthamide gave the corresponding aldehydes in 75% and 99% yield, respectively (entries 13 and 14 in Table 3). Furthermore, aliphatic amides such as *N,N*-dimethylcaproamide and *N,N*-dimethyldodecanoamide were


Table 1. Evaluation of LDBMOA as partial reducing agents for carboxylic acid derivatives^a



Entry	Compound	LDBMOA (eq)	Time (h)	Yield of aldehyde (%)
1	ethyl benzoate	1.3	1	80
2	ethyl caproate	1.3	1	32
3	benzoyl chloride	1.3	1	42
4	caproyl chloride	1.3	1	56
5	<i>N,N</i> -dimethylbenzamide	1.3	1	95
6	<i>N,N</i> -dimethylcaproamide	1.3	1	89
7	benzonitrile	1.3	1	95
8	capronitrile	1.3	1	no reaction

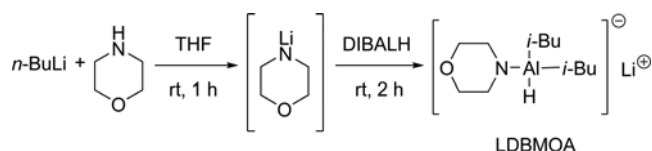
^aYields were determined by GC.

Table 2. Optimization of reaction conditions for synthesis of aldehydes from tertiary amides and nitriles^a

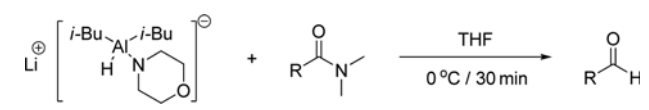


Entry	Amide or Nitrile	LDBMOA (eq)	Time (min)	Yields of aldehyde (%)	
1	<i>N,N</i> -dimethylbenzamide	1.1	10	92	
			30	92	
			10	97	
			30	99	
2	benzonitrile	1.2	60	99	
			30	90	
			1.3	30	98
				30	98

^aYields were determined by GC.



Scheme 1. Preparation of LDBMOA.

Table 3. Partial reduction of representative tertiary amides with LDBMOA^{a,b}


Entry	Amide	Hydride (eq)	Yields of aldehyde (%)
1	<i>N,N</i> -dimethylbenzamide	1.2	99 (97)
2	<i>N,N</i> -dimethyl-4-fluorobenzamide	1.2	99
3	<i>N,N</i> -dimethyl-4-chlorobenzamide	1.2	99 (99)
4	<i>N,N</i> -dimethyl-3-chlorobenzamide	1.2	99
5	<i>N,N</i> -dimethyl-2-chlorobenzamide	1.2	97
6	<i>N,N</i> -dimethyl-4-bromobenzamide	1.2	99
7	<i>N,N</i> -dimethyl-4-methoxybenzamide	1.2	90
8	<i>N,N</i> -dimethyl-4-toluamide	1.2	94
9	<i>N,N</i> -dimethyl-3-toluamide	1.2	97
10	<i>N,N</i> -dimethyl-2-toluamide	1.2	92
11	<i>N,N</i> -dimethyl-4-nitrobenzamide	1.2	91
12	<i>N,N</i> -dimethyl-3-nitrobenzamide	1.2	80
13	<i>N,N</i> -dimethyl-2-furoamide	1.2	75
14	<i>N,N</i> -dimethyl-2-naphthamide	1.2	99
15	<i>N,N</i> -dimethylcaproamide	1.2	91
16	<i>N,N</i> -dimethyldodecanoamide	1.3	89

^aYields were determined by GC. ^bIn parentheses, isolated yields after silica column chromatography.

Table 4. Partial reduction of representative nitriles with LDBMOA at 0 °C^{a,b}

Entry	Nitrile	Hydride (eq)	Yields of aldehyde (%)
1	benzotrile	1.3	98
2	4-fluorobenzotrile	1.3	99
3	4-chlorobenzotrile	1.3	98
4	3-chlorobenzotrile	1.3	97
5	2-chlorobenzotrile	1.3	96
6	4-bromobenzotrile	1.3	97 (95)
7	2,6-dichlorobenzotrile	1.3	97
8	4-tolunitrile	1.3	98 (97)
9	3-tolunitrile	1.3	98
10	2-tolunitrile	1.3	99
11	2-methoxybenzotrile	1.4	97
12	4-methoxybenzotrile	1.4	96
13	capronitrile	1.3	no reaction

^aYields were determined by GC. ^bIn parentheses, isolated yields after silica column chromatography.

smoothly reduced to the corresponding aldehydes in 90% and 89% yield (entries 15 and 16 in Table 3).

Next, we applied LDBMOA for the synthesis of aldehydes from various nitriles. The results for representative nitriles are summarized in Table 4.

Various aromatic benzonitriles of electron withdrawing and donating substituents were smoothly reduced to the corresponding aldehydes in almost quantitative yields (entries 1-12 in Table 4). In contrast, aliphatic nitrile such as capro-

nitrile is resistant to LDBMOA (entries 13 in Table 4). The results indicate that LDBMOA could selectively reduce aromatic nitriles in the presence of aliphatic nitriles.

In summary, we easily prepared new and useful LDBMOA by reacting commercially available DIBALH with lithium morpholide. Furthermore, we established a convenient method for the conversion of tertiary amides and aromatic nitriles to corresponding aldehydes in very good yield using the LDBMOA. Also, we found that this reagent did not reduce aliphatic nitriles, thus allowing chemoselective partial reduction of tertiary amides or aromatic nitriles in the presence of aliphatic nitriles. Therefore, LDBMOA is believed to be an alternative new reagent for reducing tertiary amides and aromatic nitriles to the corresponding aldehydes without affecting aliphatic nitriles.

Experimental Section

General. All glassware used was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior 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 were commercial products of the highest pure which were further purified by standard methods before use. THF was dried over sodium-benzophenone and distilled. DIBALH and *n*-BuLi were purchased from Aldrich Chemical Company. Tertiary amides were prepared by the method of Brown and Tsukamoto.² GC analyses were performed on a Yonglin, Acme 6000M FID chromatograph using a HP-5 (5%-diphenyl-95%-dimethylsiloxane copolymer, 30 m) capillary column. All GC yields were determined with the use of a suitable internal standard and authentic mixture.

Preparation of LDBMOA. To a solution of morpholine (4.4 mL, 50 mmol) in THF (25.6 mL), *n*-BuLi (20 mL, 2.5 M soln. in hexanes, 50 mmol) was slowly added at 0 °C. After being stirred for at 1 h at room temperature, DIBALH (1.0 M soln. in hexanes, 50 mmol) was dropwise to the reaction mixture at 0 °C and the mixture was stirred for 2 h at room temperature to give a LDBMOA.

Partial Reduction of Tertiary Amides and Aromatic Nitriles to Aldehydes with LDBMOA. The following procedure for reduction of *N,N*-dimethylbenzamide with LDBMOA is representative. To a solution of *N,N*-dimethylbenzamide (0.149 g, 1.0 mmol) in THF (10.0 mL) containing naphthalene as an internal standard was added LDBMOA (2.4 mL, 0.5 M in THF-hexanes, 1.2 mmol) at 0 °C. After 30 min, the reaction mixture was hydrolyzed with 1 *N* aq HCl (10 mL) and extracted with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, and filtered. After the removal of solvents in vacuum and purification of residue by column chromatography on silica gel gave benzaldehyde (0.103 g, 97%).

Acknowledgments. This work was supported by a National Research Foundation of Korean Grant funded by the Korean Government (2012R1A1B6000451). We are also grateful

for the support of Brain Korea 21.

References

- (a) Partial reduction of acid chlorides: Choi, S. J.; Lee, S. D.; An, D. K. *Bull. Korean Chem. Soc.* **2008**, *29*, 1449. (b) Partial reduction of esters: Ahn, J. H.; Song, J. I.; Ahn, J. E.; An, D. K. *Bull. Korean Chem. Soc.* **2005**, *26*, 377; Chae, M. J.; Song, J. I.; An, D. K. *Bull. Korean Chem. Soc.* **2007**, *28*, 2517; Kim, M. S.; Choi, Y. M.; An, D. K. *Tetrahedron Lett.* **2007**, *48*, 5061; Song, J. I.; An, D. K. *Chem. Lett.* **2007**, *36*, 886. (c) Partial reduction of tertiary amides : Woo, S. M.; Kim, M. E.; An, D. K. *Bull. Korean Chem. Soc.* **2006**, *27*, 1913; Choi, S. J.; Lee, K. J.; Lee, G. B.; An, D. K. *Bull. Korean Chem. Soc.* **2008**, *29*, 1407; Choi, Y. M.; Kim, M. E.; An, D. K. *Bull. Korean Chem. Soc.* **2009**, *30*, 2825. (d) Partial reduction of nitriles: Ha, J. H.; Ahn, J. H.; An, D. K. *Bull. Korean Chem. Soc.* **2006**, *27*, 121; Choi, S. J.; Eom, K. Y.; Hwang, H. S. *Bull. Korean Chem. Soc.* **2008**, *29*, 2303; Choi, Y. M.; Yoo, M.; An, D. K. *Bull. Korean Chem. Soc.* **2010**, *31*, 473.
 - Brown, H. C.; Tsukamoto, T. *J. Am. Chem. Soc.* **1964**, *86*, 1089.
-