

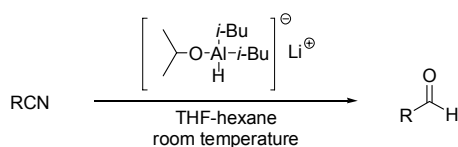
A New Method of Partial and Chemoselective Reduction of Nitriles to Aldehydes by Lithium Diisobutyl-*iso*-propoxyaluminum Hydride (LDBIPA)

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We recently reported the results of studied on the partial reducing character of esters, tertiary amides, acid chlorides, and nitriles to aldehydes, referring in particular to a new class of reducing agents comprising lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA), and potassium diisobutyl-*t*-butoxyaluminum hydride (PDBBA). Among these, LDBBA showed the best results for partial reduction of nitriles in high yield (67 - 98%) at 0 °C.¹ Also, we very recently have reported that one reducing agents, lithium diisobutyl-*iso*-propoxyaluminum hydride (LDBIPA),² the *iso*-propoxy derivatives of DIBALH, is a new effective partial reducing agents which can reduce various tertiary amides to aldehydes in excellent yields at 0 °C. Accordingly, we applied new types of lithium diisobutylalkoxyaluminum hydrides, including LDBIPA, to find useful reducing agent having better partial reducing ability for nitriles to aldehydes than LDBBA (Scheme 1) because partial reduction of nitriles into aldehydes is one of the important and highly desirable methods in organic synthesis, and a large number of reducing agents for this purpose have been reported.³ Herein, we wish to introduce an excellent new method of partial reduction of nitriles to aldehydes by a new reducing agent.



Scheme 1

Results and Discussion

As shown in Table 1, we first tried to evaluate the partial reducing ability in the partial reduction of 4-chlorobenzonitrile as a model compound to corresponding aldehyde with LDBMA (lithium diisobutylmethoxyaluminum hydride), LDBEA (lithium diisobutylethoxyaluminum hydride), and LDBIPA in THF at room temperature, respectively. We thus quantitatively obtained 4-chlorobenzaldehyde by reaction of 4-chlorobenzonitrile with LDBIPA for 1 h at room temperature.

Because we found optimum reaction conditions and also that LDBIPA was the best reducing agent for partial reduction of nitriles, among the new reducing agents, through investigation on the model compound, we immediately carried out the

partial reduction of other aromatic and aliphatic nitriles to the corresponding aldehydes using the verified methodology with LDBIPA. The results for representative nitriles are summarized in Table 2.

Table 1. Reduction of 4-chlorobenzonitrile with lithium diisobutylalkoxyaluminum hydrides at room temperature

compound	hydride	reaction condition		yield (%) ^a	
		H/nitrile	time (h)	aldehyde	nitrile
4-chlorobenzonitrile	LDBMA	1.2	1	90	8
			3	91	7
		1.5	1	87	0
	LDBEA		3	89	0
		1.2	1	93	5
			3	95	5
LDBIPA	1.5	1	81	0	
		3	84	0	
	1.2	1	99	0	

^aYields were determined by GC.

As shown in Table 2, various aromatic nitriles with electron-withdrawing and electron-donating substituents were smoothly reduced to the corresponding aldehydes in almost quantitative yields (entries 1-13 in Table 2). Among these, all aromatic nitriles having electron-donating groups required a longer reaction time and/or a larger amount of hydride than the other aromatic nitriles (entries 7-13 in Table 2). A remarkable feature in these results was the production of the corresponding aldehyde with benzaldehyde as a minor product through debromination of the starting ester and/or the produced aldehyde in the reaction of 4-bromobenzonitrile with LDBIPA (entry 6 in Table 2). In contrast, aliphatic nitriles, such as capronitrile and dodecanenitrile are totally resistant to LDBIPA (entries 14 and 15 in Table 2). The results indicate that LDBIPA can selectively reduce aromatic nitriles in the presence of aliphatic nitriles. Indeed, when LDBIPA was reacted with a 1:1 mixture of benzonitrile and capronitrile at room temperature, the reaction afforded only benzaldehyde with essentially no reduction of the capronitrile (Table 3).

These results show that LDBIPA is a new partial reducing agent for the direct transformation of aromatic nitriles to the corresponding aldehydes in excellent yields at room temperature. Furthermore, LDBIPA has good chemoselectivity in that LDBIPA does not react with aliphatic nitriles at all. Therefore,

Table 2. Yields of aldehydes in the reduction of representative nitriles with LDBIPA at room temperature

entry	nitrile	reaction condition		yield of aldehyde (%) ^a
		H/nitrile	time (h)	
1	benzointrile	1.2	1	99
2	4-fluorobenzointrile	1.2	1	99
3	2-chlorobenzointrile	1.2	3	99
4	3-chlorobenzointrile	1.2	1	99
5	4-chlorobenzointrile	1.2	1	99
6	4-bromobenzointrile	1.2	1	76
7	2-tolunitrile	1.2	12	98
8	3-tolunitrile	1.2	6	99
9	4-tolunitrile	1.2	6	99
10	2,5-dimethylbenzointrile	1.2	12	94
11	2-methoxybenzointrile	2.0	12	86
12	4-methoxybenzointrile	1.2	6	99
13	1-cyanonaphthalene	1.2	6	91
14	capronitrile	1.2	1	no reaction
15	dodecanenitrile	1.2	1	no reaction

^aYields were determined by GC.**Table 3.** Selective reduction of benzointrile in the presence of capronitrile with LDBIPA at room temperature^{a,b}

compound	product	yield (%) ^c
benzointrile and capronitrile	benzaldehyde	99
	benzointrile	0
	caproaldehyde	0
	capronitrile	99

^aThe reduction of a 1:1 mixture of benzointrile and capronitrile using 1.2 equiv of LDBIPA was carried out. ^bReacted for 1 h. ^cYields were determined by GC.

the LDBIPA is believed to be an alternative reagent for reducing aromatic nitriles to the corresponding aldehydes, without affecting aliphatic nitriles in quantitative yields under mild reaction conditions.

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 reaction 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 purified further by standard methods before use. THF was dried over sodium-benzophenone and distilled. DIBALH and *n*-butyllithium were purchased from Aldrich Chemical Company. GC analyses were performed on a Donam DS 6200 FID or Younglin Acme 6000M FID chromatograph, using a HP-1 (crosslinked methyl siloxane) 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 new hydrides. The LDBMA, LDBEA and LD-BIPA solutions were stable in the refrigerator for 6 months without any appreciable loss of hydride content.

Reduction of nitriles to aldehydes. The following procedure for the reduction of benzointrile with LDBBA is representative. To a solution of benzointrile (0.051 mL, 0.5 mmol) in THF (5 mL) containing naphthalene as an internal standard was added LDBIPA (1.3 mL, 0.46 M in THF-hexane, 0.6 mmol) at room temperature. 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.

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