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Lithium diisobutyl-*t*-butoxyaluminum hydride, a new and efficient reducing agent for the conversion of esters to aldehydes

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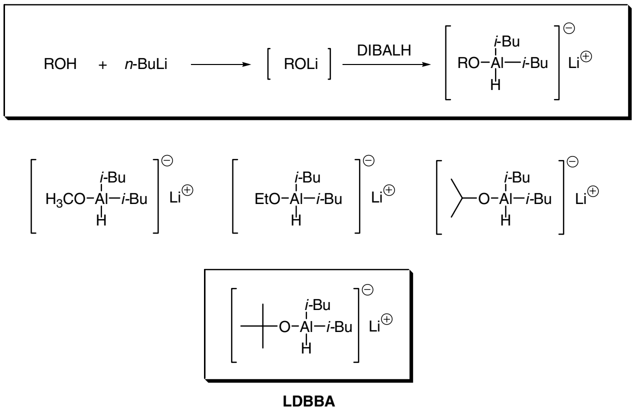
Abstract—Lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), easily prepared by reaction of lithium *t*-butoxide with DIBALH, readily reacts with common aromatic and aliphatic esters to give the corresponding aldehydes in 74–88% yield at 0 °C. Especially, this reagent proved to be the most effective partial reducing agent for conversion of isopropyl esters to aldehydes, in most cases, with >90% yield under the same reaction temperature.

Partial reduction of ester to aldehyde is one of the most important and highly desirable methods in organic synthesis, and a large number of reducing agents for this purpose have been reported.[1] Among them, diisobutylaluminum hydride (DIBALH),[2] which is commercially available, is used as the most popular reducing agent, although this reagent provides moderate yields (48–88%) and requires a very low temperature (−78 °C). It has also been reported that several other reducing agents for partial reduction of esters, such as lithium tri-*t*-butoxyaluminum hydride (LTBA),[3] bis(4-methyl-1-piperazinyl)aluminum hydride,[4] lithium tris(diethylamino)aluminum hydride ($LiAlH(NEt_2)_3$),[5] and sodium diethylpiperidinohydroaluminate (SDPA),[6] can be used. However, these reagents cannot achieve very general reduction of both aliphatic and aromatic esters, and additionally sodium diethyldihydroaluminate (SDDA), which is the precursor for synthesis of SDPA, is not commercially available. Recently, we have reported that lithium diisobutyldialkylaminohydroaluminates, the amino derivatives of DIBALH, are new partial reducing agents which can reduce various esters to aldehydes. Among them, lithium diisobutylpiperidinohydroaluminate (LDBPA) was the most effective for partial reduction of esters to aldehydes in moderate to good yields at 0 °C,[7a] and also LDBPA was effective for partial reduction of aromatic nitriles and tertiary amides in almost quantitative yield.[7b,c] In the course of our program for developing a new selective reducing agent, we found that lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA) prepared from DIBALH smoothly reduced esters to aldehydes in very good yields at 0 °C. Herein, we wish to report a new alternative and efficient method for partial reduction of esters to aldehydes by LDBBA under mild conditions.

Scheme 1 outlines the preparation of lithium diisobutylalkoxyaluminum hydrides from DIBALH. Thus, when an equimolar amount of easily preparable lithium alkoxide derived from common alcohols and *n*-butyllithium was reacted with DIBALH in THF at 0 °C or room temperature, these reagents such as lithium diisobutylmethoxyaluminum hydride (LDBMA), lithium diisobutylethoxyaluminum hydride (LDBEA), lithium



Scheme 1. Preparation of lithium diisobutylalkoxyaluminum hydrides.

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Table 1. Reduction of representative aromatic and aliphatic esters with lithium diisobutylalkoxyaluminum hydrides at 0 °C[a,b]

Compound	Product	LDBMA (%)	LDBEA (%)	LDBIPA (%)	LDBBA (%)
Ethyl benzoate[c]	Benzaldehyde	7	9	23	74
Ethyl caproate[d]	Caproaldehyde	19	29	31	87

[a] Reduction of esters by using 1.2 equiv of lithium diisobutylalkoxyaluminum hydrides.

[b] Yields were determined by GC.

[c] Reacted for 3 h.

[d] Reacted for 1 h.

diisobutylisopropoxyaluminum hydride (LDBIPA), and LDBBA[8] were obtained quantitatively.[9] Next, we examined partial reduction of representative aromatic and aliphatic esters to aldehydes by using these hydride reagents in THF at 0 °C. The results are summarized in Table 1.

As shown in Table 1, the bulky *t*-butanol derivative was most effective the reduction of esters to aldehydes. Of these hydrides examined, we found that LDBBA provided the best results. So, we applied LDBBA for the synthesis of aldehydes from various esters at 0 °C. The results for representative esters are summarized in Table 2.

As shown in Table 2, ethyl benzoate was smoothly reduced to produce benzaldehyde in 74% yield. Under identical conditions, reduction with DIBALH itself provided only benzyl alcohol. The case of *t*-butyl benzoate showed very slow reduction, in rather lower yield (63% and 69%), presumably due to the bulk of the *t*-butyl group. Also, benzoates with an electron-withdrawing substituents such as ethyl 4-fluorobenzoate, methyl 3-chlorobenzoate, ethyl 4-chlorobenzoate, ethyl 2-bromobenzoate, ethyl 4-bromobenzoate, and ethyl 4-nitrobenzoate, and electron-donating substituent such as ethyl 2-toluate were readily reduced to the corresponding aldehydes in 81–85% yields. Similarly, reduction of other aromatic esters such as ethyl 2-naphthoate and ethyl 2-furoate gave the corresponding aldehydes in 80% and 81% yield, respectively. Furthermore, aliphatic esters such as ethyl caproate, ethyl undecanoate, and ethyl cyclohexanecarboxylate were smoothly reduced to the corresponding aldehydes in 81–88% yields. Especially, LDBBA showed much improved yields for isopropyl esters such as isopropyl benzoate and isopropyl caproate. Therefore, we tested the aldehyde synthesis from the representative isopropyl esters with LDBBA. The results are summarized in Table 3.

As shown in Table 3, LDBBA reduced various aliphatic and aromatic isopropyl esters[10] to aldehydes, in most cases, with >90% yield at 0 °C. However, isopropyl 4-methoxybenzoate under the same conditions was reduced somewhat slowly and gave 85% yield of 4-methoxybenzaldehyde after 24 h. This is attributable to its lower reactivity than that of the other esters, because methoxy is a very good electron-donating substituent. Furthermore, isopropyl cinnamate, an α,β-unsaturated isopropyl ester, gave 79% yield.

In summary, we easily prepared a series of lithium diisobutylalkoxyaluminum hydrides by the reaction of commercially available DIBALH with lithium alkoxides. Among them, LDBBA was the most effective for reduction of esters to aldehydes in good yield. As a substrate for the reaction with LDBBA, the isopropyl esters were more effective than the methyl and ethyl esters. Another great advantage of this reagent is that this aldehyde synthesis can be carried out at 0 °C instead of a very low temperature (−78 °C) or a very high

Table 2. Yields of aldehydes in the reduction of representative esters with LDBBA at 0 °C

Entry	Compound	Reaction conditions		Yield of aldehyde[a] (%)
		H$^-$/ester	Time (h)	
1	Ethyl benzoate	1.2	3	74
2		(1.2)	(3)	(0)[b]
3	Isopropyl benzoate	1.3	3	89
4	*t*-Butyl benzoate	3.0	3	63
5		4.0	3	69
6	Ethyl 4-fluorobenzoate	1.2	3	83
7	Methyl 3-chlorobenzoate	1.2	3	81
8	Ethyl 4-chlorobenzoate	1.2	3	83
9	Ethyl 2-bromobenzoate	1.2	3	85
10	Ethyl 4-bromobenzoate	1.2	3	83
11	Ethyl 4-nitrobenzoate	1.2	3	85
12	Ethyl 2-toluate	1.2	3	82
13	Ethyl 2-naphthoate	1.2	3	80
14	Ethyl 2-furoate	1.2	1	81
15	Ethyl caproate	1.2	1	87
16	Isopropyl caproate	1.3	1	98
17	Ethyl undecanoate	1.2	1	88
18	Ethyl cyclohexanecarboxylate	1.2	1	81

[a] Yields were determined by GC.

[b] Yield obtained by DIBALH alone is shown in parentheses.

Table 3. Yields of aldehydes in the reduction of representative isopropyl esters with LDBBA at 0 °C

Entry	Compound	Reaction conditions		Yield of aldehyde[a] (%)
		H^-/ester	Time (h)	
1	Isopropyl benzoate	1.3	3	89
2		(1.3)	(3)	(0)[b]
3	Isopropyl 4-fluorobenzoate	1.3	3	93
4	Isopropyl 4-chlorobenzoate	1.3	3	92 (77)[c]
5	Isopropyl 4-bromobenzoate	1.3	3	94
6	Isopropyl 3-nitrobenzoate	1.3	3	92 (78)[c]
7	Isopropyl 4-methoxybenzoate	1.3	24	85
8	Isopropyl 3-toluate	1.3	3	90
9	Isopropyl 2-naphthoate	1.3	3	94
10	Isopropyl 2-furoate	1.3	3	91
11	Isopropyl caproate	1.3	1	98
12	Isopropyl dodecanoate	1.3	1	94
13	Isopropyl cinnamate	1.3	1	79
14	Isopropyl cyclohexanecarboxylate	1.3	1	93

[a] Yields were determined by GC.

[b] Yield obtained by DIBALH alone is shown in parentheses.

[c] Isolated yield.

temperature (reflux). In total, we believe that the LDBBA reagent developed here is an efficient alternative to other agents for partial reduction of carboxylic esters.

Acknowledgement

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8. *Preparation of lithium diisobutyl-t-butoxyaluminum hydride (LDBBA).* To a solution of *t*-butyl alcohol (5.16 mL, 55 mmol) in THF (25 mL) was added *n*-butyllithium (20 mL, 2.5 M in hexane, 55 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. The concentration of LDBBA 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. The LDBBA solution was stable in the refrigerator for 6 months without any appreciable loss of hydride content.
9. When equimolar LDBBA and terminal acetylene such as 1-hexyne were reacted, 1 mol of hydrogen evolved rapidly. However, DIBALH could not evolve hydrogen with 1-hexyne, indicating hydroalumination of Al(III) complex.[11] Consequently, LDBBA is to be Al(IV) complex.
10. *Reduction of esters with LDBBA to aldehydes.* The following procedure for the reduction of isopropyl benzoate with LDBBA is representative. To a solution of isopropyl benzoate (0.082 mL, 0.5 mmol) in THF (5 mL) containing naphthalene as an internal standard was added LDBBA (1.3 mL, 0.5 M in THF–hexane) at 0 °C. After 3 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 an 89% yield of benzaldehyde. Isopropyl esters were prepared by methods given in the literature.[12]
    Preparation of 4-chlorobenzaldehyde from isopropyl 4-chlorobenzoate. To a solution of isopropyl 4-chlorobenzoate (1.99 g, 10 mmol) in THF (50 mL) was added LDBBA (26 mL, 0.5 M in THF–hexane) at 0 °C. After 3 h, the reaction mixture was hydrolyzed with 50 mL of 1 N HCl (aq) and the product was extracted three times with 50 mL of diethyl ether. The ether layer was dried over anhydrous magnesium sulfate. After removal of the ether, the residue was dissolved in 30 mL of ethanol, and upon addition of water, a crystalline product appeared. The solid was collected and sublimed at 55 °C under high vacuum, and pure 4-chlorobenzaldehyde (1.08 g, 77%) was obtained: mp 47 °C (lit.[13] mp 47.5 °C). The ^{1}H NMR spectrum agreed with that of an authentic sample.
    Preparation of 3-nitrobenzaldehyde from isopropyl 3-nitrobenzoate. To a solution of isopropyl 3-nitrobenzoate (2.09 g, 10 mmol) in THF (50 mL) was added LDBBA (26 mL, 0.5 M in THF–hexane) at 0 °C. After 3 h, the reaction mixture was hydrolyzed with 50 mL of 1 N HCl (aq) and the product was extracted three times with 100 mL of diethyl ether. The ether layer was poured into 150 mL of saturated sodium bisulfite (aq) solution. To this solution was added 100 mL of THF, and the mixture was stirred for 2 h. At this time the crystalline bisulfite adduct of 3-nitrobenzaldehdye was apparent. The solution was cooled in an ice bath to ensure complete crystallization of

the adduct. The adduct was collected by filtration, washed with pentane (3 × 50 mL), and dried. The adduct was placed in 100 mL of aqueous magnesium sulfate solution, 100 mL of pentane and 20 mL of a 37% formaldehyde solution was added, and the mixture was stirred for 1 h. The pentane layer was separated and dried over anhydrous magnesium sulfate. Evaporation of all volatile materials gave a pure 3-nitrobenzaldehyde (1.18 g, 78%): mp 58 °C (lit.[13] mp 58.5 °C). The ^{1}H NMR spectrum agreed with that of an authentic sample.

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