Reaction of Lithium Tris(diethylamino)aluminum Hydride in Tetrahydrofuran with Selected Organic Compounds Containing Representative Functional Groups

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Received February 24, 1993

The approximate rates and stoichiometry of the reaction of excess lithium tris(diethylamino)aluminum hydride (LTDEA) with selected organic compounds containing representative functional groups under standardized condition (tetrahydrofuran, 0℃) were examined in order to define the characteristics of the reagent for selective reductions. The reducing ability of LTDEA was also compared with those of the parent lithium aluminum hydride (LAH) and lithium tris(dibutylamino)aluminum hydride (LTDBA). In general, the reactivity toward organic functionalities is in order of LAH≫LTDEA≥LTDBA. LTDEA shows a unique reducing characteristics. Thus, benzyl alcohol and phenol evolve hydrogen slowly. The rate of hydrogen evolution of primary, secondary, and tertiary alcohols is distinctive: 1-hexanol evolves hydrogen completely in 6 h, whereas 3-hexanol evolves hydrogen very slowly. However, 3-ethyl-3-pentanol does not evolve any hydrogen under these reaction conditions. Primary amine, such as *n*-hexylamine, evolves only 1 equivalent of hydrogen. On the other hand, thiols examined are absolutely inert to this reagent. LTDEA reduces aldehydes, ketones, esters, acid chlorides, and epoxides readily to the corresponding alcohols. Quinones, such as *p*-benzoquinone and anthraquinone, are reduced to the corresponding diols without hydrogen evolution. However, carboxylic acids, anhydrides, nitriles, and primary amides are reduced slowly, whereas tertiary amides are readily reduced. Finally, sulfides and sulfoxides are reduced to thiols and sulfides, respectively, without evolution of hydrogen. In addition to that, the reagent appears to be an excellent partial reducing agent to convert esters, primary carboxamides, and aromatic nitriles into the corresponding aldehydes. Free carboxylic acids are also converted into aldehydes through treatment of acyloxy-9-BBN with this reagent in excellent yields.

Introduction

Lithium tris(dialkylamino)aluminum hydrides appeared to be attractive selective reducing agents, especially in the conversion of carboxylic acid derivatives into the corresponding aldehydes.[1-10] Among them, lithium tris(diethylamino)aluminum hydride (LTDEA) is proved to be the most valuable for such transformation: it transforms free carboxylic acids,[4] carboxylic esters,[7,9] carboxamides,[1,3,9] and aromatic nitriles[8,9] into the corresponding aldehydes in high yields.

Although LTDEA appeared as a promising reducing agent, there was a limitation to use the reagent in the selective conversion of such functionalities in a complex molecule and a full investigation of the reagent was not available. Accordingly, we undertook to study the appoximate rates and stoichiometry of the reaction under standardized conditions (tetrahydrofuran, 0℃) of excess LTDEA with our standard list of organic compounds containing representative functional groups. In this paper, a full scope of the reducing characteristics of LTDEA is described. In addition to that, the reducing ability of the reagent is compared with those of the parent LAH[11] and lithium tris(dibutylamino)aluminum hydride (LTDBA).[2]

Results and Discussion

The reagent, LTDEA, can be easily prepared in pure form by treatment of lithium aluminum hydride (LAH) with three equivalents or excess diethylamine both at 0℃ or room temperature (Eq. 1).

$$LiAlH_4 + 3Et_2NH \xrightarrow[0 \text{ or } 25℃]{THF} Li(Et_2N)_3AlH + 3H_2\uparrow \quad (1)$$

LTDEA is very stable at ambient temperature or below. No sign of disproportionation and hydride loss is observed while the reagent is kept under a static pressure of dry nitrogen. The ^{27}Al-NMR spectrum of LTDEA in THF showed a broad singlet at δ 120 ppm relative to $Al(H_2O)_6^{3+}$. The procedure used involved preparation of a reaction mixture of LTDEA (1.0 M) and the compound (0.25 M) in THF at 0℃. The solution was maintained at 0℃. Hydrogen evolution following addition of the compound to the reagent was measured. A blank reaction was run under identical condition without addition of the compound. From time to time, aliquots were taken from the reaction mixture and analyzed for the remaining hydride by hydrolysis. From the difference in yields of hydrogen in the two cases, the hydride used by the compounds for reaction was calculated. In this way, it was possible to calculate the number of moles of hydride used by the compound for hydrogen evolution and the number of moles of hydride utilized for reduction.

Alcohol, Phenol, Amines, and Thiols (Active Hydrogen Compounds). 1-Hexanol, a primary alcohol, evolved hydrogen relatively fast, but benzyl alcohol only slowly. The reaction with 3-hexanol, a secondary alcohol, evolved hydrogen very sluggishly, whereas 3-ethyl-3-pentanol, a tertiary alcohol, did not react with this reagent at all. Phenol also evolved hydrogen slowly. *n*-Hexylamine liberated only one equivalent of hydrogen rapidly within 1 h at 0℃. However, both the thiols examined were inert toward reagent under

Table 1. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Active Hydrogen Compounds in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
1-Hexanol	0.5	0.72	0.72	0.00
	1.0	0.81	0.81	0.00
	3.0	1.00	1.00	0.00
Benzyl alcohol	0.5	0.34	0.34	0.00
	3.0	0.50	0.50	0.00
	6.0	0.63	0.63	0.00
	12.0	0.78	0.78	0.00
	24.0	0.96	0.96	0.00
	48.0	1.01	1.01	0.00
3-Hexanol	0.5	0.08	0.08	0.00
	3.0	0.10	0.10	0.00
	6.0	0.11	0.11	0.00
	24.0	0.19	0.19	0.00
3-Ethyl-3-pentanol	24.0	0.00	0.00	0.00
Phenol	0.5	0.23	0.23	0.00
	1.0	0.35	0.35	0.00
	12.0	0.71	0.71	0.00
	48.0	0.89	0.89	0.00
	120.0	1.00	1.00	0.00
n-Hexylamine	0.5	0.90	0.90	0.00
	1.0	1.00	1.00	0.00
	3.0	1.00	1.00	0.00
1-Hexanethiol	3.0	0.00	0.00	0.00
Benzenethiol	3.0	0.00	0.00	0.00

[a] 5.0 mmol of compound was added to 20 mmol of the reagent (0.25 M in compound and 1.0 M in hydride). [b] Mmol per mmol of compound.

these conditions. These results are summarized in Table 1.

Similarly, LTDBA did not react with benzyl alcohol, phenol and thiols, whereas tertiary alcohol and amine evolved hydrogen slowly.[2] On the other hand, the parent LAH evolved hydrogen immediately from the reaction with these active hydrogen compounds.[11]

Aldehydes and Ketones. All the saturated aldehydes and ketones examined consumed one equivalent of hydride rapidly for reduction to the corresponding alcohol within 1 h at 0℃. Cinnamaldehyde utilized two equivalents of hydride rapidly, indicating a ready involvement of the double bond. Consequently, in this case the reduction goes cleanly to the hydrocinnamyl alcohol stage. The same behavior was realized with LAH.[11] However, the reaction with LTDBA utilized one equivalent of hydride rapidly with further reduction being very slow.[2] The results are summarized in Table 2.

The stereochemistry of the reagent in the reduction of typical cyclic ketones was also examined, and the results and those of LAH and LTDBA for comparison are summarized in Table 3. The introduction of dialkylamino group enhances the stereoselectivity to a large extent. Thus, the stereoselectivity increases with increasing the bulkiness of dialkylamino group. For example, the parent LAH reduces 3,3,5-trimethylcyclohexanone to the corresponding less stable isomer(*trans* alcohol) in a ratio of 52% at 0℃,[11] whereas LTDEA and LTDBA[2] reduce it in ratios of 87 and 93%, respectively.

Table 2. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Aldehydes and Ketones in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Caproaldehyde	0.5	0.01	1.00	0.99
	1.0	0.01	1.00	1.99
Benzaldehyde	0.5	0.00	1.00	1.00
	1.0	0.00	1.00	1.00
2-Heptanone	0.5	0.00	1.01	1.01
	1.0	0.00	1.01	1.01
Norcamphor	0.5	0.00	0.99	0.99
	1.0	0.00	1.01	1.00
Acetophenone	0.5	0.00	1.00	1.00
	1.0	0.00	1.00	1.00
Benzophenone	0.5	0.00	0.99	0.99
	1.0	0.00	1.00	1.00
Cinnamaldehyde	0.5	0.00	1.99	1.99
	6.0	0.00	2.01	2.01

[a, b] See the corresponding footnotes in Table 1.

Table 3. Stereochemistry in the Reduction of Cyclic Ketones with Lithium Aluminum Hydride, Lithium Tris(diethylamino)aluminum Hydride, and Lithium Tris(dibutylamino)aluminum Hydride in Tetrahydrofuran at 0℃

Compound	Less stable isomer (%)[a,b]		
	$LiAlH_4$[c]	$Li(Et_2N)_3AlH$	$Li(Bu_2N)_3AlH$[d]
Cyclohexanone			
2-methyl-	24	52	56
3-methyl-	16	19	28
4-methyl-	19	25	28
4-*t*-butyl-	9	43	49
3,3,5-trimethyl-	52	87	93
Norcamphor	89	91	91
Camphor	92	93	94

[a] Excess reagent utilized. [b] Quantitative yields of alcohols. [c] Data taken from ref. 11. [d] Data taken from ref. 2.

Quinones. Like LTDBA[2], LTDEA also shows a unique reducing characteristics on the reaction of quinones examined. Thus, the reaction of both benzoquinone and antraquinone evolved no hydrogen and utilized two equivalents of hydride for reduction within 3 h at 0℃. Typical reduction of a quinone to hydroquinone uses two equivalents of hydride per mole of the quinone, one mole being used for reduction and the second mole to give hydrogen. For the reduction of a quinone to the corresponding 1,4-dihydroxycyclohexadiene, two equivalents of hydride should be used with no hydrogen formation. Therefore, these reactions must follow the path to proceed to the 1,4-dihydroxy stage. Unlike LTDEA and LTDBA, the parent LAH reduces the quinones with partial evolution of hydrogen to give a mixture of the

Table 4. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Quinones in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
p-Benzoquinone[c]	0.5[d]	0.00	1.82	1.82
	1.0	0.00	1.97	1.97
	30.	0.00	2.01	2.01
Anthraquinone[c]	0.5[e]	0.00	1.84	1.84
	1.0	0.00	1.99	1.99
	3.0	0.00	2.00	2.00

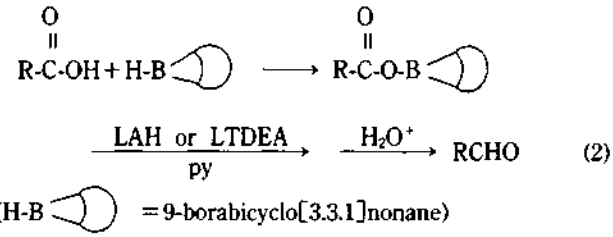
[a,b] See the corresponding footnotes in Table 1. [c] Batch reaction. [d] Color changed to dark green immediately, and a precipitate was formed and then color changed to violet. [e] Color changed to dark brown immediately.

corresponding hydroquinone and 1,4-dihydroxycyclohexadiene.[11] These experimental results are summarized in Table 4.

Carboxylic Acids and Acyl Derivatives. Carboxylic acids examined evolved one equivalent of hydrogen slowly when reacted with LTDEA at 0℃. Moreover, the reduction of the acids was also slow, requiring 3 days to be reduced to the corresponding alcohols. Acid anhydrides consumed two equivalents of hydride relatively fast, but the further hydride consumption was slow. Reduction of acid chlorides with this reagent was completed readily to the corresponding alcohols at 0℃. These results are summarized in Table 5.

The reaction of LTDBA with carboxylic acids evolved only a partial equivalent of hydrogen, whereas the reduction was faster than that with LTDEA. However, in general, LTDEA appeared to be reactive than LTDBA toward acid anhydrides and acid chlorides. LAH reduced these functionalities rapidly.[11]

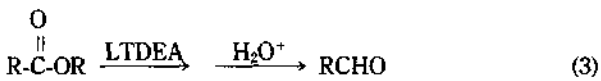
It is noteworthy that free carboxylic acids are readily transformed into the corresponding aldehydes in high yields through treatment of acyloxy-9-borabicyclo[3.3.1]nonane with LAH or LTDEA in the presence of excess pyridine[4,9] (Eq. 2).



(H-B = 9-borabicyclo[3.3.1]nonane) (2)

Because LTDEA is milder and hence more selective than LAH, LTDEA seems to be more feasible for such transformation.

Esters and Lactones. All of the esters examined consumed two equivalents of hydride readily to be reduced to alcohol stage. However, the reagent with a limiting amount transformed esters into aldehydes at −78℃ in good yields (Eq. 3).



(3)

Table 5. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Carboxylic Acids and Acyl Derivatives in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Caproic acid	0.5	0.42	1.20	0.78
	3.0	0.65	1.88	1.23
	24.0	0.82	2.35	1.53
	72.0	1.00	3.00	2.00
Benzoic acid	0.5	0.33	0.96	0.63
	1.0	0.60	1.73	1.13
	6.0	0.81	2.34	1.53
	24.0	0.98	2.82	1.84
	72.0	1.00	3.01	2.01
Acetic anhydride[c]	0.5	0.00	1.57	1.57
	1.0	0.00	2.37	2.37
	6.0	0.00	3.06	3.06
	24.0	0.00	3.62	3.62
	72.0	0.00	4.01	4.01
Succinic	0.5	0.00	1.65	1.65
anhydride[c]	6.0	0.00	1.96	1.96
	24.0	0.00	2.52	2.52
	72.0	0.00	3.15	3.15
	120.0	0.00	3.81	3.81
Phthalic	0.5	0.00	1.46	1.46
anhydride[c]	3.0	0.00	1.80	1.80
	24.0	0.00	2.70	2.70
	72.0	0.00	3.29	3.29
	168.0	0.00	4.00	4.00
Caproyl chloride	0.5	0.02	1.62	1.60
	1.0	0.02	1.97	1.95
	3.0	0.02	2.02	2.00
Benzoyl chloride	0.5	0.00	1.76	1.76
	1.0	0.00	1.94	1.94
	3.0	0.00	2.01	2.01

[a,b] See the corresponding footnotes in Table 1. [c] Hydride to compound ratio is 6 : 1.

The reduction of lactones, such as γ-butyrolactone and phthalide, utilized one hydride rapidly, with a second equivalent of hydride being taken up slowly. However, in this case, the yield of aldehyde estimated by hydrazine analysis appeared not to be satisfactory. Isopropenyl acetate utilized two equivalents of hydride fast, and a third hydride was consumed slowly. Apparently the reaction involves the attack on the double bond. These results are summarized in Table 6.

The reactivity of LTDEA toward esters and lactones appeared to be a little stronger than of LTDBA. However, the parent LAH reduced esters and lactones exceedingly rapidly.[11]

Epoxides. The reaction of epoxides examined proved very fast, an uptake of equivalent of hydride per mole of epoxide being realized in 1 h or less, at a rate comparable to that with LAH.[11] The same behavior was previously noted with the di-*n*-butylamino derivative. The reaction also proved

Table 6. Reaction of Lithium Tris(diethylamino)aluminum Hyride with Representative Esters and Lactones in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Ethyl caproate	0.5	0.00	1.81	1.81
	1.0[c]	0.00	1.91	1.91
	3.0	0.00	2.00	2.00
Ethyl benzoate	0.5	0.00	1.83	1.83
	1.0	0.00	1.91	1.91
	3.0[d]	0.00	2.00	2.00
Phenyl acetate	0.5	0.00	1.43	1.43
	3.0	0.00	1.90	1.90
	6.0	0.00	2.01	2.01
γ-Butyrolactone	0.5	0.00	1.08	1.08
	3.0	0.00	1.38	1.38
	24.0	0.00	1.79	1.79
	48.0	0.00	1.98	1.98
Phthalide	0.5	0.00	1.05	1.05
	3.0	0.00	1.15	1.15
	12.0	0.00	1.21	1.21
Isopropenyl	0.5	0.00	1.85	1.85
acetate	0.3	0.00	2.01	2.01
	6.0	0.00	2.03	2.03
	24.0	0.00	2.32	2.32
	72.0	0.00	2.54	2.54

[a,b] See the corresponding footnotes in Table 1. [c] 67% of caproaldehyde was obtained when treated with 1 equivalent of reagent at −78℃. [d] 79% of benzaldehtde was formed with 10% excess reagent at −78℃.

Table 7. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Epoxides in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[a]	Hydride used[b]	Hydride used for reduction[b]
1,2-Butylene oxide[c]	0.5	0.00	1.00	1.00
	1.0	0.00	1.00	1.00
Styrene oxide[d]	0.5	0.00	1.01	1.01
	1.0	0.00	1.00	1.00
Cyclohexene oxide	0.5	0.00	1.00	1.00
	1.0	0.00	1.00	1.00
1-Methylcyclohexene	0.5	0.00	1.01	1.01
oxide[e]	1.0	0.00	1.01	1.01

[a,b] See the corresponding footnotes in Table 1. [c] Only 2-butanol was detected. [d] 1-Phenylethanol (99%) and trace of 2-phenylethanol. [e] Only 1-methylcyclohexanol was detected.

to be quite selective, with hydride undergoing transfer to less substituted of the two carbon atoms of the epoxide ring. Thus, the reagent attacks the epoxides exclusively in a S_N2-type ring opening. The results are summarized in Table 7.

Amides and Nitriles. Excess LTDEA reduced primary carboxamides, such as capromide and benzamide slowly with concurrent slow evolution of hydrogen in an amount of less than one equivalent. However, tertiary carboxamides were reduced rapidly to the corresponding tertiary amines within 1 h at 0℃. The reaction of aliphatic nitrile, such as capronitrile, was slow, whereas aromatic nitrile, such as benzonitrile, was reduced readily to primary amine. These results are summarized in Table 8.

Table 8. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Amides and Nitriles in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Caproamide	0.5	0.21	0.65	0.44
	3.0	0.48	1.13	0.65
	12.0[c]	0.62	1.56	0.94
	24.0	0.78	1.86	1.08
	72.0	0.92	2.20	1.28
Benzamide	0.5	0.25	0.74	0.49
	3.0	0.51	1.50	0.99
	6.0[d]	0.58	1.71	1.13
	24.0	0.83	2.46	1.63
	72.0	1.01	3.02	2.01
N,N-Dimethyl-	0.5	0.00	1.88	1.88
caproamide[e]	1.0	0.00	2.01	2.01
N,N-Dimethyl-	0.5	0.00	1.94	1.94
benzamide[f]	1.0	0.00	2.01	2.01
Capronitrile	0.5	0.00	0.70	0.70
	1.0	0.00	0.91	0.91
	3.0	0.00	1.05	1.05
	6.0	0.00	1.17	1.17
Benzonitrile[g]	0.5	0.00	1.36	1.36
	1.0	0.00	1.45	1.45
	3.0	0.00	1.67	1.67
	6.0	0.00	1.96	1.96
	12.0	0.00	2.01	2.01

[a,b] See the corresponding foortnotes in Table 1. [c] 62% of caproaldehyde was formed when treated with 2 equivalents of reagent at 25℃. [d] 91% of benzaldehyde was formed with 2 equivalents of reagent at 25℃. [e] 85% of caproaldehyde was formed with 10% excess reagent in 3 h. [f] 96% of benzaldehyde was formed with 10% excess reagent in 3 h. [g] 93% of benzaldehyde formed with 1 equivalent of reagent in 1 h at 25℃.

The reaction of primary carboxamides with LTDEA is quite interesting. In the case of utilizing two equivalents of the reagent, one reagent is consumed for hydrogen and the other is used for reduction, showing the possibility of the formation of aldehyde intermediate. This possibility was examined utilizing two equivalents of the reagent per mole of the compound. In fact, the reagent reduced various primary carboxamides to the corresponding aldehydes in good yields at room temperature[1,3,9] (Eq. 4). Although tertiary carboxamides consumed two equivalents of hydride rapidly, the controlled reaction with a limiting amount of LTDEA provided aldehydes in high yields. The reagent also achieved the aldehyde formation from the reaction of aromatic nitriles in yields of 60-90% (Eq. 5). However, LTDBA and LTDHA (the di-*n*-hexylamino derivative) appeared to be much more

Table 9. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Nitro Compounds and Their Derivatives in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
1-Nitropropane[c]	0.5	0.00	1.72	1.72
	1.0	0.00	1.96	1.96
	6.0	0.00	2.02	2.02
	24.0	0.00	2.04	2.04
Nitrobenzene[d]	3.0	0.36	2.01	1.65
	12.0	0.50	2.54	2.04
	48.0	0.73	3.10	2.37
	72.0	0.84	3.35	2.51
Azobenzene[e]	0.5	0.00	0.57	0.57
	3.0	0.00	0.88	0.88
	24.0	0.00	0.97	0.97

[a,b] See the corresponding footnotes in Table 1. [c] A brown color formed immediately. [d] A brown color formed and turned to light brown slowly. [e] Solution changed from reddish brown to dark brown.

efficient. Especially, LTDHA nicely achieved the chemoselective reduction of aromatic nitriles to the corresponding aldehydes in essentially quantitative yields in the presence of aliphatic nitriles.[6,9]

$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}NH_2 \xrightarrow{LTDEA} \xrightarrow{H_2O^+} RCHO \quad (4)$$

$$ArC{\equiv}N \xrightarrow{LTDEA} \xrightarrow{H_3O^-} RCHO \quad (5)$$

LTDBA reduced primary carboxamides to the corresponding amines readily without evolution of hydrogen.[2] Tertiary amides were also reduced rapidly with this reagent.[2] It is noteworthy that the reaction of LAH with primary carboxamides evolved two equivalents of hydrogen rapidly with slow reduction.[11] Furthermore, LAH reacted with capronitrile to evolve a partial hydrogen, by reaction of the reagent with the active hydrogen of the nitrile.[11]

Nitro Compounds and Their Derivatives. 1-Nitropropane consumed two equivalents of hydride readily without evolution of hydrogen, but no further reduction was observed. Nitrobenzene utilized two equivalents of hydride readily with slow evolution of hydrogen. The reduction of nitrobenzene by LAH to hydrazobenzene state consumed five equivalents of hydride, with two and half equivalents of hydride being utilized for reduction and two and half for hydrogen evolution. Therefore, the reaction by this reagent utilizing two and half equivalents of hydride for reduction corresponds to a reduction to the hydrazobenzene stage. The slow hydrogen evolution would be attributed to the low reactivity of this reagent toward an unknown intermediate which possesses active hydrogen. Azobenzene was also reduced slowly to the hydrazobenzene stage without evolution of hydrogen. The results are summarized in Table 9.

Other Nitrogen Compounds. Cyclohexanone oxime liberated one equivalent of hydrogen slowly, and utilized one equivalent of hydride for reduction relatively fast. But the further hydride consumption was quite slow. This stoichiometry corresponds to reduction to the N-hydroxyamine stage. Phenyl isocyanate was rapidly reduced, utilizing one equivalent of hydride for reduction, corresponding to reduction to the formanilide stage. However, the reduction to the next N-methylaniline stage was quite slow. The attack to pyridine ring was very sluggish, whereas 4-picoline N-oxide was readily reduced by this reagent. These results are summarized in Table 10.

Table 10. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Other Nitrogen Compounds in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Cyclohexanone	0.5	0.23	0.60	0.37
oxime	3.0	0.50	1.01	0.51
	24.0	1.02	1.73	0.71
	72.0	1.02	2.03	1.01
	168.0	1.02	2.48	1.46
Phenyl isocyanate	0.5	0.00	0.96	0.96
	1.0	0.00	1.04	1.04
	6.0	0.00	1.20	1.20
	24.0	0.00	1.35	1.35
	48.0	0.00	1.60	1.60
Pyridine	0.5	0.00	0.02	0.02
	6.0	0.00	0.10	0.10
	24.0	0.00	0.16	0.16
4-Picoline	0.5	0.00	1.48	1.48
N-oxide	1.0	0.00	1.86	1.86
	3.0	0.00	2.01	2.01

[a,b] See the corresponding footnotes in Table 1.

LTDBA also reduced cyclohexanone oxime to the N-hydroxyamine stage and phenyl isocyanate to the formanilide stage readily.[2] On the other hand, LAH reduced cyclohexanone oxime to cyclohexylamine and phenyl isocyanate to N-methylaniline rapidly.[11]

Sulfur Compounds. LTDEA shows a very interesting characteristics in the reduction of disulfides: the reagent reduced disulfides to thiols at an exceedingly fast rate at 0℃ without evolution of any hydrogen. Every metal hydride reducing agent appeared in the literature[12] evolves hydrogen during the reduction of disulfides. Therefore, excess reagent should be utilized for complete reduction. However, it is now possible to reduce disulfides under the practical conditions with only the calculated amount of reagent. LTDEA with one equivalent readily reduced both aliphatic and aromatic disulfides to the corresponding thiols in quantitative yields at 0℃ or 25℃ within 6 h (Eq. 6).[10] LTDBA also showed an identical phenomenon, but the rate of reduction was slower, requiring an elevated reaction temperature (25℃ or reflux) or a longer reaction time (12 h at 0℃).[10] Dimethyl sulfoxide was reduced slowly to dimethyl sulfide with LTDEA. LAH also reduced these compounds rapidly, but evolved one equivalent hydrogen concurrently. Methanesulfonic acid and *p*-toluenesulfonic acid monohydrate liberated hydrogen relatively fast: the former evolved one equivalent of hydrogen

Table 11. Reaction of Lithium Tris(diethylamino)aluminum Hydride with Representative Sulfur Derivatives in Tetrahydrofuran at 0℃

Compound[a]	Time, h	Hydrogen evolved[b]	Hydride used[b]	Hydride used for reduction[b]
Di-*n*-butyl	0.5	0.00	1.00	1.00
disulfide[c]	1.0	0.00	1.00	1.00
Diphenyl	0.5	0.00	1.01	1.01
disulfide[d]	1.0	0.00	1.01	1.01
Dimethyl	0.5	0.00	0.51	0.51
sulfoxide	1.0	0.00	0.63	0.63
	3.0	0.00	0.86	0.86
	6.0	0.00	1.01	1.01
Diphenyl sulfone	0.5	0.00	0.04	0.04
	1.0	0.00	0.12	0.12
	6.0	0.00	0.23	0.23
Methanesulfonic	0.5	0.76	0.76	0.00
acid	1.0	0.88	0.88	0.00
	3.0	0.95	0.95	0.00
	6.0	1.00	1.00	0.00
p-Toluenesulfonic	0.5	1.47	1.47	0.00
acid monohydrate	3.0	2.02	2.02	0.00
	12.0	2.56	2.56	0.00
	24.0	3.01	3.01	0.00

[a,b] See the corresponding footnotes in Table 1. [c] 99% of 1-butanethiol was formed with 1 equivalent of reagent in 6 at 0℃. [d] 98% of benzenethiol formed with 1 equivalent of reagent in 6 h at 0℃.

within 6 h and the latter evolved three equivalents of hydrogen within 24 h at 0℃. LAH evolved one equivalent hydrogen rapidly,[11] whereas LTDBA evolved only a partial hydrogen.[2] These results are summarized in Table 11.

$$\text{R-S-S-R} \xrightarrow{\text{LTDEA}} \xrightarrow{H_3O^+} 2\,\text{RSH} \qquad (6)$$

Conclusion

The reducing properties of LTDEA in tetrahydrofuran are now fully characterized and also compared with those of lithium aluminum hydride (LAH) and lithium tris(dibutylamino)aluminum hydride (LTDBA). The reducing power of the reagent appears to be much weaker than LAH, but a little stronger than LTDBA. LTDEA is a mild selective reducing agent, especially in the conversion of free carboxylic acid (through treatment of acyloxy-9-BBN), esters, primary carboxamides, and aromatic nitriles into the corresponding aldehydes in good yields. Furthermore, LTDEA with a calculated amount reduces disulfides to the corresponding thiols without evolution of hydrogen in quantitative yields. Consequently, this reagent should find a variety of application in organic synthesis.

Experimental Section

Materials. Tetrahydrofuran (THF) was dried over a 4 Å molecular sieve and distilled from sodium-benzophenone ketyl prior to use. Most of the organic compounds utilized in this study were commercial products of the highest available purity. They were further purified by distillation or recrystallization when necessary. Some compounds, such as 1-methyl-1,2-cyclohexene oxide, tertiary amides, and cyclohexyl tosylate, were synthesized by using standard procedures. Lithium aluminum hydride (LAH, Aldrich) was dissolved in THF and the clear solution was used for the preparation of LTDEA standard solution (*vide infra*).

General Methods. All glassware was predried at 140℃ for several hours, assembled hot, dried further with a flame, and cooled under the stream of nitrogen. All reactions were carried out under the static pressure of dry nitrogen in flasks fitted with a septum-covered side arm with use a standard technique for handling air-sensitive material.[13]

Instruments. GC analyses were performed on a Hewlett-Packard 5790A FID chromatograph equipped with a Hewlett-Packard 3390A integrator/plotter, using Carbowax 20 M on 100/120 mesh Supelcoport or 15% THEED on 100/120 mesh Supelcoport (0.125 in.×12 ft. columns). All GC yields were determined with use of suitable internal standard and authentic samples. ^{27}Al-NMR spectra were recorded on a Bruker WP 80 SY spectrometer, and chemical shifts are reported relative to $Al(H_2O)_6^{3+}$. IR spectra are recorded on a Perkin-Elmer 1339 spectrophotometer.

Preparation of Lithium Tris(diethylamino)aluminum Hydride (LTDEA). An oven-dried, 500 mL, round-bottomed flask with a side arm, equipped with a condenser leading to a mercury bubbler was flushed with dry nitrogen and maintanied under a static pressure of nitrogen. To this flask was charged 100 mL of $LiAlH_4$-THF (2.0 M, 200 mmol), and followed by dropwise addition of 46.08 g of diethylamine (630 mmol) *via* a double-ended needle with vigorous stirring. The mixture was stirred for 6 h at room temperature until the hydrogen evolution was completed. The resulting clear solution was standardized by hydrolyzing an aliquot with 2 N H_2SO_4-THF mixture to be 1.50 M, and kept under nitrogen at 0℃. The THF solution of LTDEA was characterized by a characteristic absorption in the IR at around 1695 cm^{-1} (ν_{Al-H}) and by a broad singlet at δ 120 ppm in ^{27}Al-NMR.

General Procedure for Determination of Rates and Stoichiometry. To a 100 mL flask fitted with a side arm and a condenser leading to a gas buret was added 24 mL (36 mmol) of a 1.50 M THF solution of LTDEA. The flask was immersed into an ice bath and the reaction mixture was diluted with 12 mL of THF containing 9 mmol of the compound to be examined. This makes the mixture 1 M in hydride and 0.25 M in the compound under investigation. At appropriate time intervals, 4 mL of aliquots were withdrawn and quenched in a 2 N H_2SO_4-THF hydrolyzing mixture. The hydrogen evolved by the compound was collected in a gas buret and measured the volume of hydrogen.

The reaction of 2-heptanone is described as a representative. In an usual set-up was placed 24 mL of 1.50 M LTDEA in THF, and followed by addition of 12 mL of THF solution containing 1.03 g (9 mmol) of 2-heptanone at 0℃. No hydrogen was evolved. After 1 h, the analysis showed no difference in the residual hydride, which indicates that the reaction was completed. The results are summarized in Table 2.

Reduction of 1,2-Butylene Oxide. The following experiment illustrates the technique utilized in cases where the reaction mixture was subjected to identification of prod-

ucts.

Utilized the above general procedure, the reduction of 1,2-butylene oxide with LTDEA was performed for 1 h at 0℃. The reaction mixture was then hydrolyzed with 2 N HCl and the organic layer was taken up in ether. The GC analysis with 10% CW 20 M column showed only the presence of 2-butanol.

In cases where a single product in the reaction mixture was apparent, we did not perform the product identification further.

General Procedure for Stereoselectivity Study. The reduction of 3,3,5-trimethylcyclohexanone is described as representative. To a 10 mL vial capped by rubber septum was added 2 mL of a solution of LTDEA in THF (1.50 M. 3 mmol). The vial was kept at 0℃, and to this was added 1 mL of a 2 M compound (2 mmol) in THF. The reaction mixture was stirred for 3 h at that temperature and then hydrolyzed by 3 N H_2SO_4. The aqueous layer was saturated with anhydrous magnesium sulfate, and the organic layer was subjected to GC analysis to indicate 87% *trans* alcohol. The results are summarized in Table 3.

Acknowledgement. The paper was supported by Organic Chemistry Research Center-KOSEF.

References

1. J. S. Cha, J. C. Lee, S. E. Lee, J. M. Kim, O. O. Kwon, H. S. Lee, and S. J. Min, *Tetrahedron Lett.*, **32**, 6903 (1991).
2. J. S. Cha, S. E. Lee, and H. S. Lee, *Bull. Korean Chem. Soc.*, **12**, 644 (1991).
3. J. S. Cha, S. E. Lee, H. S. Lee, J. M. Kim, O. O. Kwon, and S. J. Min, *Bull. Korean Chem. Soc.*, **13**, 338 (1992).
4. J. S. Cha, J. C. Lee, S. E. Lee, and H. S. Lee, *Org. Prep. Proced. Int.*, **24**, 327 (1992).
5. J. S. Cha, J. C. Lee, S. E. Lee, and H. S. Lee, *Bull. Korean Chem. Soc.*, **12**, 598 (1992).
6. J. S. Cha, S. E. Lee, and H. S. Lee, *Org. Prep. Proced. Int.*, **24**, 331 (1992).
7. J. S. Cha, S. J. Min, J. C. Lee, H. S. Lee, and S. E. Lee, *Org. Prep. Proced. Int.*, **24**, 335 (1992).
8. J. S. Cha and S. E. Lee, *Bull. Korean Chem. Soc.*, **13**, 451 (1992).
9. J. S. Cha, *Bull. Korean Chem. Soc.*, **13**, 670 (1992).
10. J. S. Cha, J. M. Kim, M. K. Jeoung, and K. D. Lee, *Bull. Korean Chem. Soc.*, **13**, 702 (1992).
11. H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1458 (1966).
12. (a) $LiAlH_4$: ref. 11; (b) $LiBH_4$: N. M. Yoon and J. S. Cha, *J. Korean Chem. Soc.*, **21**, 108 (1977); (c) Li *n*-$BuBH_3$: C. Pyun, J. C. Son, and N. M. Yoon, *Bull. Korean Chem. Soc.*, **4**, 3 (1983); (d) Li 9-BBNH: H. C. Brown, C. P. Mathew, C. Pyun, J. C. Son, and N. M. Yoon, *J. Org. Chem.*, **49**, 3091 (1984); (e) $LiEt_3BH$: H. C. Brown, S. C. Kim, and S. Krishnamurthy, *ibid.*, **45**, 1 (1980); (f) Li(*t*-BuO)$_3$AlH: H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **1**, 430 (1963); (g) K(*i*-PrO)$_3$BH: H. C. Brown, J. S. Cha, B. Nazer, S. C. Kim, S. Krishnamurthy, and C. A. Brown, *J. Org. Chem.*, **49**, 885 (1984); *Synthesis*, 498 (1984); (h) $Al(BH_4)_3$: N. M. Yoon, H. J. Lee, and J. S. Chung, *J. Korean Chem. Soc.*, **17**, 275 (1973); (i) BH_3: H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970); (j) $ThBH_2$: H. C. Brown, P. Heim, and N. M. Yoon, *J. Org. Chem.*, **37**, 2942 (1972); (k) Sia_2BH: H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 7161 (1970); (l) $ThBHCl\cdot SMe_2$: H. C. Brown, B. Nazer, J. S. Cha, and J. Sikorski, *J. Org. Chem.*, **51**, 5264 (1986); (m) AlH_3: H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966); (n) *i*-Bu_2AlH: N. M. Yoon and Y. S. Gyoung, *J. Org. Chem.*, **50**, 2443 (1985); (o) N. M. Yoon and K. E. Kim, *ibid.*, **52**, 5564 (1987); (p) $NaEt_2AlH_2$: N. M. Yoon, Y. S. Shon, and J. H. Ahn, *Bull. Korean Chem. Soc.*, **13**, 199 (1992); (q) $ThxBHBr\cdot SMe_2$: J. S. Cha, J. E. Kim, and Y. S. Oh, *ibid.*, **8**, 313 (1987); (r) K *s*-Am-9-BBNH: J. S. Cha, M. S. Yoon, K. W. Lee, and J. C. Lee, *ibid.*, **10**, 75 (1988); (s) K Thx-9-B(OR)H: J. S. Cha and S. E. Lee, *ibid.*, **13**, 531 (1992).
13. H. C. Brown, G. W. Kramer, and M. M. Midland, "Organic Synthesis *via* Boranes", Wiley-Interscience, New York, 1975.