Reaction of Lithium Cyanoaluminum Hydride with Selected Organic Compounds Containing Representative Functional Groups. Comparison of Reducing Characteristics between Lithium and Sodium Cyanoaluminum Hydrides

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Received April 9, 2009, Accepted May 28, 2009

Lithium cyanoaluminum hydride (**LCAH**) was prepared by the metal cation exchange reaction of sodium cyanoaluminum hydride with lithium chloride in tetrahydrofuran. The reducing characteristics of **LCAH** were explored systematically by the reaction with selected organic compounds containing representative functional groups under the standardized conditions (tetrahydrofuran, 0 °C). The reducing ability of **LCAH** was also compared with of the sodium derivative, sodium cyanoaluminum hydride (**SCAH**). Generally, the reducing behavior of **LCAH** resembles that of SCAH closely, but the reactivity of **LCAH** toward representative organic functional groups appeared to be stronger than that of **SCAH**. Thus, the regent reduces carbonyl compounds, epoxides, amides, nitriles, disulfides, carboxylic acids and their acyl derivatives to the corresponding alcohols or amines, at a relatively faster rate than that of **SCAH**. The cyano substitution, a strong election-withdrawing group, diminishes the reducing power of the parent metal aluminum hydrides and hence effects the alteration of their reducing characteristics.
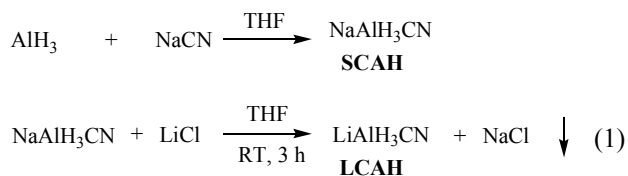
Key Words : Lithium cyanoaluminum hydride, Sodium aluminum hydride, Selective reduction organic functional groups, Systematic reduction study, Comparison of reducing characteristics

Introduction

Very recently, we reported the systematic study on the approximate rates of reaction of sodium cyanoaluminum hydride (**SCAH**)[1] with selected organic compounds and the comparison of it reducing characteristics with those of the parent sodium aluminum hydride (**SAH**).[2] The reagent possesses a unique reducing characteristics, showing a milder reactivity toward organic functional groups than that of **SAH**, apparently due to the electron-withdrawing cyano group. This intrigued us. It seems desirable to explore the reducing characteristics of lithium cyanoaluminum hydride (**LCAH**) and compare its reduction pattern with that of sodium derivative (**SCAH**)[1] and others.[3] In this article, we wish to report the preparation and general reducing characteristics of **LCAH**.

Results and Discussion

Preparation of a Solution of Lithium Cyanoaluminum Hydride (LCAH) in THF. Lithium cyanoaluminum hydride (**LCAH**) was prepared by reacting sodium cyanoaluminum hydride (**SCAH**) in THF with LiCl *via* metal cation exchange reaction. As NaCl precipitates out from the reaction mixture, a solution of **LCAH** in THF forms. The formation of LiAlH₃CN was completed in 3 h at room temperature (Eq.1). The ^{27}Al NMR spectrum of **LCAH** in THF showed a broad singlet at δ 103 ppm relative to Al(H₂O)₆.[39]

$$AlH_3 \quad + \quad NaCN \quad \xrightarrow{THF} \quad \underset{\textbf{SCAH}}{NaAlH_3CN}$$

$$NaAlH_3CN + LiCl \xrightarrow[RT,\ 3\ h]{THF} \underset{\textbf{LCAH}}{LiAlH_3CN} + NaCl \downarrow \quad (1)$$

Aldehydes and Ketones (Table 1). All of the aldehydes and ketones examined were reduced clearly to the alcohol stage within 0.5 h at 0 °C. There was no reactivity difference in the structure of carbonyls under the experimental conditions. As **SCAH** also readily reduces such simple carbonyl compounds to the corresponding alcohols, no significant difference in the reactivity owing to the metal cation exchange can be recognizable in these reactions.

***α,β*-Unsaturated Aldehydes and Ketones (Table 2).** *α,β*-Unsaturated aldehydes examined, such as crotonaldehyde and cinnamaldehyde, were readily reduced by a limited amount of the reagent (0.34 equiv of **LCAH** : *i.e.* 1.0 equiv of hydride) to the corresponding allylic alcohols in an essentially 100% yield. However, excess hydride of the reagent (*i.e.* 1 equiv of **LCAH** : 3 equiv of hydride) attacked the carbon-carbon double bond. For instance, the reaction of cinnamaldehyde with 1 equiv of **LCAH** produced a mixture of cinnamyl alcohol (54%) and hydrocinnamyl alcohol (46%). Further, the reaction of isophorone,

Table 1. Reaction of Representative Aldehydes and Ketones with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran at 0 °C[a]

Compound	Time (h)	Yields of alcohol (%)[b]	
		LiAlH₃CN	NaAlH₃CN[c]
caproaldehyde	0.5	100	100
benzaldehyde	0.5	100	100
2-heptanone	0.5	100	100
acetophenone	0.5	100	100
benzophenone	0.5	100	100
norcamphor	0.5	100[c]	100[d]

[a]An equivalent of reagent utilized; 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]Data takrn from ref. 1. [d]A 0.34 equivalent of reagent utilized.

Table 2. Reaction of Representative α,β-Unsaturated Aldehydes and Ketones with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran[a]

Compound	Reagent/Compd	Temp. (°C)	Time (h)	LiAlH$_3$CN		NaAlH$_3$CN[b]	
				Total yield (%)[c]	Product[d] 1,2-: 1,4-	Total yield (%)[c]	Product[d] 1,2-: 1,4-
crotonaldehyde	0.34	0	0.5	100	100:0	98	100:0
			6	100	100:0	98	100:0
cinnamaldehyde	0.34	0	0.5	100	100:0	100	100:0
	1	0	24	100	54:46	100	20:80
isophorone	0.34	25	1			38	
			6	78	14:86	41	25:75
			12	89	15:85		
			24	99.6	15:85	52	48:62
	1	0	12	99.9	2:98		
			24	99.8	2:98		

[a]A 0.5 M concentration. [b]Data taken from ref. 1. [c]Analyzed by GC with a suitable internal standard. [d]1,2-Product corresponds to allylic alcohol; 1,4-product corresponds to saturated alcohol. Normalized ratio.

a α,β-unsaturated ketone, even with a limited amount of the reagent produced a mixture of both 1,2- and 1,4-reduction products. Finally, the reaction with excess hydride of **LCAH** afforded the 1,4-reduction product (the saturated alcohol), 3,3,5-trimethylcyclohexanol, exclusively. The sodium derivative, **SCAH**, also shows a similar trend.[1] Thus, the reaction of cinnamaldehyde with a limited amount of **SCAH** afforded cinnamyl alcohol exclusively, however excess amount of the reagent produced both products. Similarly, the reaction of isophorone even with a limited amount of **SCAH** afforded a mixture of both products.[1] The rate difference between **LCAH** and **SCAH**[1] was first observed in the reduction of isophorone. Thus, **LCAH** reduced isophorone in 24 h at room temperature, but **SCAH** reduced only ca. 50% in that reaction period.[1] Further, excess **LCAH** can reduce isophorone within 12 h even at 0 °C.

Stereochemistry in the Reduction of Cyclic Ketones (Table 3). The stereoselectivity of the reagent toward representative mono- and bicyclic ketones were also examined. The stereochemistry of **LCAH** showed a quite similar trend to that of **SCAH**,[1] which is usually obtained in the reaction with other

Table 3. Stereochemistry in the Reduction of Representative Cyclic Ketones with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran at 0 °C[a]

Compound	Time (h)	Ratio of less stable isomer (%)[b]	
		LiAlH$_3$CN	NaAlH$_3$CN[g]
2-methylcyclohexanone		39[c]	43[c]
3-methylcyclohexanone		20[d]	23[d]
4-methylcyclohexanone		16[c]	22[c]
2-t-buthylcyclohexanone		61[c]	53[c]
4-t-buthylcyclohexanone		9[c]	20[c]
3,3,5-trimethyllcyclohexanone		79[c]	79[c]
norcamphor		91[e]	99.9[e]
camphor		92[f]	91[f]

[a]Total yields of alcohols are higher than 95%, analyzed by GC. [b]Normalized. [c]Cis isomer. [d]Trans isomer. [e]Endo isomer. [f]Exo isomer. [g]Data taken from ref. 1.

substituted metal aluminum hydrides.[2]

Carboxylic Acids and Acyl Derivatives (Table 4). The reaction of carboxylic acids with the reagent evolved only partial hydrogen at 0 °C, and the subsequent reduction also proceed very slowly. However, warming the reaction mixture to 25 °C enhanced the reaction rate, achieving a quantitative hydrogen evolution and a rapid reduction to the alcohol stage. This reaction pattern is quite similar to that with **SCAH**, that the rate of reaction with **LCAH** appears to be relatively faster than that with **SCAH**.[1]

On the other hand, all of the acid chlorides examined were

Table 4. Reaction of Representative Carboxylic Acids and Acyl Derivatives with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran[a]

Compound	Temp (°C)	Time (h)	Yield of alcohol (%)[b]	
			LiAlH$_3$CN	NaAlH$_3$CN[c]
caproic acid	0	24	52[d]	38[e]
	25	3	99[f]	96[g]
		6	99.7	97
benzoic acid	0	6	42[h]	33[i]
		24	54	41
	25	3	85	
		6	95	49[k]
		24	97	86
		48	97	98
caproyl chloride	0	0.5	100	96[m]
		3	100	96
benzoyl chloride	0	0.5	100	98[n]
		3	100	98

[a]A 1.1 equiv of reagent utilized; 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]Data taken from ref. 1. [d]A 0.92 equiv of hydrogen evolved. [e]A 0.90 equiv of hydrogen evolved. [f]A 1.02 equiv of hydrogen evolved and no aldehyde detected. [g]A 0.96 equiv of hydrogen evolved and 3% of caproaldehyde formed. [h]A 0.72 equiv of hydrogen evolved. [i]A 0.67 equiv of hydrogen evolved and 2% of benzaldehyde formed. [j]A 1.03 equiv of hydrogen evolved. [k]A 0.94 equiv of hydrogen evolved. [l]3% of benzaldehyde formed. [m]4% of caproaldehyde formed. [n]2% of benzaldehyde formed.

Table 5. Reaction of Representative Esters with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrafuran at 0 °C[a]

Compound	Reagent/ Compd	Time (h)	Yield of alcohol (%)[b]	
			LiAlH$_3$CN	NaAlH$_3$CN[c]
ethyl caproate	0.34	6	23	21
		24	28	25
	1.1	0.5	99	97
		1	99.9	99
		3		99.9
ethyl benzoate	0.34	6	25	24
		24	31	27
	1.1	0.5	90	80
		1	99.9	98
		3		99.9
phenyl acetate	1.1	0.5	100	100
isoprophenyl acetate	1.1	0.5	100	100

[a]A 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]Data taken from ref. 1.

rapidly reduced to the corresponding alcohols by the reagent within 0.5 h at 0 °C, which appears exactly same as that by **SCAH**.[1]

Esters (Table 5). The reaction of esters, such as ethyl caproate and ethyl benzoate, with a calculated amount of

Table 6. Reaction of Representative Epoxides with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran at 0 °C[a]

Compound	Time (h)	Yield of alcohol (%)[b]	
		LiAlH$_3$CN	NaAlH$_3$CN[c]
1,2-butylene oxide	3	86	35
	6	92	42
	12	99	75
	24	99[d]	100[d]
styrene oxide	3	58	52
	6	82	54
	12	98	78
	24	99.9[e]	96
	48		99.9[f]

[a]An equivalent of reagent utilized; 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]Data taken from ref. 1. [d]One hundred % of 2-butanol. [e]A mixture of 1-phenylethanol (93%) and 2-phenylethanol (7%). [f]A mixture of 1-phenylethanol (84%) and 2-phenylethanol (16%).

LCAH (*i.e.* 1 equiv of hydride) at 0 °C failed to produce the corresponding aldehydes, showing a slow further reduction to the alcohol stages. All of the esters examined in this study were rapidly reduced with 1.1 equiv of the reagent (*i.e.* 3.3 equiv of hydride) within 1 h at 0 °C to give quantitative yields of the corresponding alcohols. In this case, the rate of reaction with **LCAH** also appears to be faster than that with **SCAH**.[1]

Table 7. Reaction of Representative Amides and Nitriles with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran[a]

Compound	Reagent/ Compd	Temp. (0 °C)	Time (h)	Product	Yield (%)[b]	
					LiAlH$_3$CN	NaAlH$_3$CN[c]
caproamide	2	25	6	*n*-hexylamine	91[d]	89[e]
			24		96	94
			48		99	98
			72		99	98
			120			
	2	reflux	3		96	
			6		96	
			24		98	
benzamide	2	25	6	benzylamine	91[f]	90[g]
			24		97	92
			48		99	
			72		99	99
N,N-methylcaproamide	2	0	0.5	*N,N*-dimethylhexylamine	100	100
N,N-dimethylbenzamide	1	0	0.5	*N,N*-dimethylbezylamine	100	100
capronitrile	1	25	3	*n*-hexylamine	57[h]	47[i]
			24		93	73
			48		99.9	95
			72		99.9	99.9
benzonitrile	1	0	3	benzylamine	65	47
			6		93	91
			12		99.9	98
			24		99.9	98

[a]A 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]Data taken from ref. 1. [d]A 1.94 equiv of hydrogen evolved. [e]A 1.92 equiv of hydrogen evolved. [f]A 1.61 equiv of hydrogen evolved. [g]A 1.51 equiv of hydrogen evolved. [h]A 0.07 equiv of hydrogen evolved. [i]A 0.08 equiv of hydrogen evolved.

Table 8. Reaction of Representative Sulfur Compounds with Lithium and Sodium Cyanoaluminum Hydrides in Tetrahydrofuran[a]
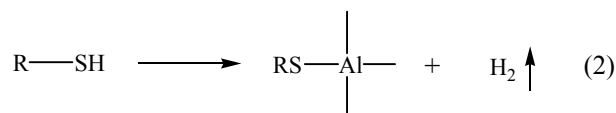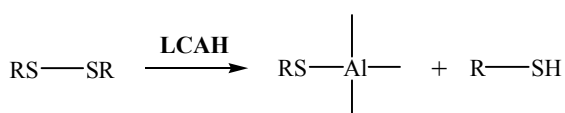
Compound	Temp. (°C)	Time (h)	Product	Yield (%)[b]	
				LiAlH$_3$CN	NaAlH$_3$CN[c]
diphenyl disulfide	0	0.5	benzenethiol	200[d]	190
		1		200	198
		3			200[e]
di-*n*-butyl disulfide	0	0.5	butanethiol	201[f]	182
		1		200	198
		3			200[g]
phenyl-*n*-propyl sulfide	0	3		0	0
dimethyl sulfoxide	25	0.5	dimethyl sulfide	100[h]	100[i]
diphenyl sulfone	25	24		0	0

[a]A 1.1 equiv of reagent utilized; 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]Data taken from ref. 1. [d]A 0.98 equiv of hydrogen evolved. [e]A 0.98 equiv of hydrogen evolved. [f]A 1.01 equiv of hydrogen evolved. [g]A 0.99 equiv of hydrogen evolved. [h]A 0.99 equiv of hydrogen evolved. [i]A 1.00 equiv of hydrogen evolved.

Epoxides (Table 6). The reaction of **LCAH** with epoxides examined appeared faster than that of **SCAH**,[1] requiring 12 ~ 24 h at 0 °C to complete the reduction to alcohols. The reaction toward 1,2-butylene oxide showed a 100% regioselectivity to yield only 2-butanol, whereas the reaction toward styrene oxide yielded a mixture of 93% 1- and 7% 2-phenylethanol. **SCAH** also showed a 100% selectivity in the reduction of 1,2-butylene oxide to give pure 2-butanol, but the selectivity appeared in the reduction of styrene oxide was somewhat lower than that with **LCAH**, the product consisting of 84% 1- and 16% 2-phenylethanol.

Amides and Nitrides (Table 7). Primary amides, such as caproamide and benzamide, evolved 1.6 ~ 1.9 equiv of hydrogen at 25 °C with the first equiv of hydrogen evolving rapidly and the second slowly. However, in both cases, the reduction proceeded at a relatively fast rate (48 h at 25 °C) to produce the corresponding primary amines, the reaction is quite similar to that with **SCAH**. On the other hand, the reaction of tertiary amides proceeded readily to the corresponding tertiary amines even at 0 °C. Capronitrile reacted slowly, requiring 48 h at 25 °C to complete the reduction to *n*-hexylamine, but benzonitrile was reduced at a relatively faster rate to benzylamine within 12 h even at 0 °C. In general, the reaction of nitriles with **LCAH** proceeded at a faster rate than that with **SCAH**.[1] In addition to that, the quantity of hydrogen evolution due to the reaction of the acidic α-hydrogen of capronitrile with LCAH also appeared to be quite similar to that with **SCAH**.

Sulfur Compounds (Table 8). Both disulfides examined reacted rapidly with this reagent to produce 2 mol of thiol per mole of disulfide. In this reaction, 1 equiv of hydrogen was evolved immediately, apparently due to the further reaction of *in situ* formed thiol (Eq. 2).

$$RS\!-\!\!-SR \xrightarrow{\text{LCAH}} RS\!-\!\!-\overset{|}{\underset{|}{Al}}\!-\!\! + R\!-\!\!-SH$$

$$R\!-\!\!-SH \longrightarrow RS\!-\!\!-\overset{|}{\underset{|}{Al}}\!-\!\! + H_2\!\uparrow \quad (2)$$

However, sulfides proved to be quite stable to the reagent under the experimental conditions. Dimethyl sulfoxide was readily reduced to the sulfide with the evolution of 1 equiv hydrogen. Finally, diphenyl sulfone was stable even at 25 °C. **SCAH** also shows a quite similar trend to **LCAH** in the reaction of sulfur compounds, but the rate of reaction appears to be slower than that of **LCAH**.

Conclusion

The approximate rate and stoichiometry of the reaction of a newly-synthesized lithium hydride (**LCAH**) with selected organic compounds containing representative functional groups was examined in order to compare the behavior of the sodium derivative (sodium cyanoaluminum hydride, **SCAH**), previously explored. In general, the behavior of **LCAH** resembles that of **SCAH** closely, but the reactivity of **LCAH** toward functional groups appears to be stronger than that of **SCAH**. However, the reducing characteristics of both derivatives are significant different from there of the parent lithium and sodium aluminum hydrides, apparently due to the presence of cyano substituent. The cyano substituent, a strong electron-withdrawing group, diminishes the reducing power of the parent metal aluminum hydrides and hence effects the alteration of their reducing characteristics. As a more detailed exploration on these cyano derivatives, these reagents should find their usefulness is selective reduction of organic compounds.

Experimental Section

General. The reaction flasks and other glassware used in the experiments were predried at 140 °C for several hours,

assembled hot, and cooled under a stream of nitrogen. Syringes were cooled under a stream of nitrogen and assembled. All reactions were carried out under a static pressure of nitrogen in flasks fitted with septum-covered side arms with use of standard techniques for handling air-sensitive materials.[5]

Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl and stored under dry nitrogen. Lithium aluminum hydride (**LAH**) was obtained from Aldrich Chemical Co. and used directly without further purification.

Gas chromatographic analysis for products were carried out using a gas chromatograph equipped with 30 m × 0.25 mm in capillary column of DB-Wax and 25 m × 0.2 mm in capillary column of HP-FFAP. All GC yields were determined with use of a suitable internal standard and authentic mixture.

Preparation of a Solution of Lithium Cyanoaluminum Hydride (LCAH) in THF. Into an oven-dried, 500 mL, round-bottomed flask with side arm equipped with a magnetic stirrer, was changed 7.63 g of predried LiCl (180 mmol) and the flask was attached to mercury bubbler. The flask was then further dried with a flame under a stream of dry nitrogen. To this flask was added 200 mL of a 0.85 M solution of sodium cyanoaluminum hydride (170 mmol) in THF,[1,4] and the mixture was stirred vigorously until all the NaCl precipitated out for 3 h at room temperature. The ^{27}Al NMR spectrum of the clean solution showed a broad singlet at σ 103 ppm (relative to $Al(H_2O)_6^{3+}$) and the concentration analyzed by measuring the hydrogen evolved upon hydrolysis with 2 *N* H_2SO_4-THF(1:1) appeared to be 0.85 M.

General Procedure for Determination of Rate and Identification of Product. The reaction of benzaldehyde is described to examplify the reduction procedure. A 50 mL, oven-dried, round-bottomed flask, equipped with a side arm and reflux condenser connected to a gas meter, was placed in an ice-water bath and cooled under dry nitrogen. To this flask were added 0.5 mL of a 0.85 M **SCAH** solution (5.0 mmol), 5 mmol of tridecane as an internal standard and 1 mL of THF. Two and a half mL of 2.0 M solution of benzaldehyde (5.0 mmol) in THF was injected into the reagent solution rapidly. This made the mixture 0.5 M both in the reagent and the compound. After 0.5 h, an aliquot of the reaction mixture was withdrawn and hydrolyzed with 2 *N* HCl. The aqueous layer was saturated with K_2CO_3 and the organic layer was dried with anhydrous $MgSO_4$. GC analysis of the organic layer showed the presence of 100% benzyl alcohol. In cases where a maximum yield of the reduction product was apparent, no further analysis of the product was performed.

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