Reaction of Sodium Cyanoaluminum Hydride with Selected Organic Compounds Containing Representative Functional Groups

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Sodium cyanoaluminum hydride (**SCAH**) was prepared by the reaction of aluminum hydride and sodium cyanide in tetrahydrofuran at room temperature, and the approximate rates and stoichiometry of the reaction with selected organic compounds containing representative functional groups under the standardized conditions (tetrahydrofuran, 0 °C) were studied in order to define the reducing characteristics of the reagent for selective reductions. The reducing ability of **SCAH** was also compared with that of the parent sodium aluminum hydride (**SAH**). Generally the reducing power of **SCAH** appears to be weaker than that of the parent **SAH**. However, the reduction patterns of both reagents are quite similar. Thus, the reagent readily reduces carbonyl compounds, epoxides, amides, nitriles, carboxylic acids and their acyl derivatives to the corresponding alcohols or amines.

Key Words : Sodium cyanoaluminum hydride, Selective reduction, Organic functional groups, Systematic reduction study

Introduction

The remarkable stability and selectivity of sodium cyanoborohydride, $NaBH_3CN$, induced by the strong electron-withdrawing cyanide group establish it as one of the more useful hydride reagents.[1-5] In fact, sodium cyanoborohydride is such an extremely mild reducing agent that even readily reducible groups, such as aldehydes and ketones, are effectively reduced only when the electrophilicity of the carbonyl is increased by protonation.[1,6] Thus, the reducing power of sodium cyanoborohydride appears to be much milder than that of sodium borohydride itself.[7]

In this connection, our recent research activity has been concerned with the exploration of sodium cyanoaluminum hydride (**SCAH**). In this article, we wish to report the preparation and general reducing characteristics of **SCAH**.

Results and Discussion

Preparation of a Solution of Sodium Cyanoaluminum Hydride (SCAH) in THF. Sodium cyanoaluminum hydride (**SCAH**) was prepared by reacting AlH_3 in THF with NaCN as a solid. The solid NaCN is slowly disappeared as cyanide ion adds to AlH_3 in THF. The formation of $NaAlH_3CN$ was completed in 3 h at room temperature (Eq. 1).

$$AlH_3 + NaCN \xrightarrow[\text{RT, 3 h}]{\text{THF}} \underset{\textbf{SCAH}}{NaAlH_3CN} \qquad (1)$$
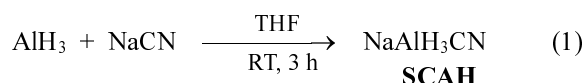
The ^{27}Al NMR spectrum of **SCAH**[8] in THF showed a broad singlet at δ 96 ppm relative to $Al(H_2O)_6^{3+}$.

Aldehydes and Ketone (Table 1). All of the aldehydes and ketones examined were reduced cleanly to the alcohol stage within 0.5 h at 0 °C. There was no reactivity difference in the structure of carbonyl compounds under the experimental conditions. Sodium aluminum hydride (**SAH**) shows the same trend.[9,10]

α,β-Unsaturated Aldehydes and Ketones (Table 2). α,β-Unsaturated aldehydes, such as crotonaldehyde and cinnamaldehyde, readily reacted with 0.34 equiv of the reagent (*ie.*, 1.0 equiv of hydride) to produce the corresponding allylic alcohols in an essentially 100% purity. However, the reaction with excess hydride of the reagent involves the carbon-carbon double bond. For example, the reaction of cinnamaldehyde with 1 equiv of **SCAH** (*ie.*, 3 equiv of hydride) produced a mixture of cinnamyl alcohol (20%) and hydrocinnamyl alcohol (80%). Further, the reaction of isophorone, a α,β-unsaturated ketone, even with a limited amount of the reagent (*ie.*, 1 equiv of hydride) afforded a mixture of both 1,2- and 1,4-reduction products.

Sodium aluminum hydride,[9,10] like lithium aluminum hydride,[11,12] also shows a similar trend. Thus, the reaction of cinnamaldehyde with the calculated amount of **SAH** (*ie.*, 0.25 equiv of **SAH**: 1 equiv of hydride) afforded cinnamyl alcohol exclusively.
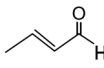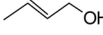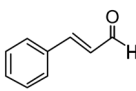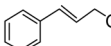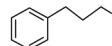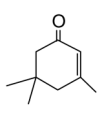
Stereochemistry in the Reduction of Cyclic Ketones

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

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

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

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

Compound	Reagent/compd	Temp. (°C)	Time (h)	Total yield (%)	Product[c]
	0.34	0	0.5	98	100% + 0%
			6	98	
	0.34	0	0.5	100	100% + 0%
	1	0	24	100	20% 80%
	0.34		1	38	25% + 75%
			6	41	

[a]A 0.5 M Concentration. [b]Analyzed by GC with a suitable internal standard. [c]Normalized.

Table 3. Stereochemistry in the Reduction of Representative Cyclic Ketone with Sodium Cyanoaluminum Hydride in Tetrahydrofuran at 0 °C[a]

Compound	Time (h)	Total yield of alcohol (%)[b]	Ratio of less stable isomer (%)[c]
2-methylcyclohexanone	0.5	99.9	43[d]
3-methylcyclohexanone	0.5	100	23[e]
4-methylcyclohexanone	0.5	99.9	22[d]
2-*t*-butylcyclohexanone	3	86	53[d]
	12	99	54[d]
4-*t*-butylcyclohexanone	6	95	
	12	100	20[d]
3,3,5-trimethylcyclohexanone	0.5	99.9	79[d]
norcamphor	0.5	100	99.9[f,h]
camphor	24	95	91[g]

[a]A 0.34 equivalent of reagent utilized. [b]Analyzed GC. [c]Normalized. [d]*Cis* isomer. [e]*Trans* isomer. [f]*Endo* isomer. [g]*Exo* isomer. [h]A 88% of *endo* isomer formed with NaAlH₄[9].

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

Compound	Temp. (°C)	Time (h)	Yield of aldehyde (%)[b]	Yield of alcohol (%)[b]
caproic acid	0	6	2	35[c]
		24	2	38
	25	3	3	96[d]
		6	3	97
benzoic acid	0	6	2	33[e]
		24	3	41
	25	6	1	49[f]
		24	2	86
		48	0	100
caproyl chloride	0	0.5	4	96
		3	3	96
benzoyl chloride	0	0.5	2	98
		3	2	98

[a]A 1.1 equiv of reagent utilized; 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]A 0.90 equiv of hydrogen evolved. [d]A 0.96 equiv of hydrogen evolved. [e]A 0.67 equiv of hydrogen evolved. [f]A 0.94 equiv of hydrogen evolved.

(Table 3). The stereoselectivity of the reagent toward cyclic ketones was also examined. All of the cyclic ketones examined were readily reduced even with a limited amout of **SCAH**. The reduction of cyclic ketones shows a general pattern of stereoselectivity which is usually obtained in the reduction with alkoxy-,[13,15] amino-[16] or thioxy-[17] substituted metal aluminum hydrides.

Carboxylic Acids and Acyl Derivatives (Table 4). The reaction of carboxylic acids evolved only partial hydrogen at 0 °C, and the subsequent reduction also proceeded very slowly. However, warming the reaction mixture to 25 °C accelerated the rate of reaction, showing the *ca.* 1 equiv of hydrogen evolution and the complete reduction to the alcohols. The rate of reaction of **SCAH** appears to be relatively shower than that of **SAH** itself.[9,10]

On the contrary, **SCAH** reduced acid chlorides examined within 0.5 h at 0 °C, in a similar rate to that of **SAH**.

Esters (Table 5). All of the esters examined in this study were reduced rapidly with 1.1 equiv of **SCAH** within 3 h at

0 °C to give quantitative yields of the corresponding alcohols, which are similar to the cases with **SAH**.[9,10]

Epoxides (Table 6). The reaction of **SCAH** with epoxides examined proved much slower than that of **SAH**, requiring 24-48 h at 0 °C to complete the reduction to alcohols.

The selectivity toward unsymmetrical epoxides appears to be somewhat embarrassing. Thus, 1,2-butylene oxide yielded 100% of the secondary alcohol as expected. However, in the case of styrene oxide, some tendency to open at the more substituted position was noted, the product consisting of a mixture of 84% 1- and 16% 2-phenylethanol. In this case **SAH** gives a cleaner product, 97% 1-, 3% 2-,[9] with AlH₃ being less selective, 76% 1-, 24% 2-.[18]

Amides and Nitriles (Table 7). Primary amides such as caproamide and benzamide, evolved 1.5-1.9 equiv of hydrogen at 25 °C with the first equiv of hydrogen evolving rapidly and the second slowly. However, in both cases, the

Table 5. Reaction of Representative Esters with Sodium Cyano-aluminum Hydride in Tetrahydrofuran at 0 °C[a]

Compound	Reagent/compd	Time (h)	Yield of alcohol (%)[b]
ethyl caproate	0.34	6	21
		24	25
	1.1	0.5	80
		1	98
		3	99.9
ethyl benzoate	0.34	6	24
		24	27
	1.1	0.5	97
		1	99
		3	99.9
phenyl acetate	1.1	0.5	100
isopropenyl acetate	1.1	0.5	100

[a]A 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard.

Table 6. Reaction of Representative Epoxides with Sodium Cyano-aluminum Hydride in Tetrahydrofuran at 0 °C[a]

Compound	Time (h)	Yield of alcohol (%)[b]
1,2-butylene oxide	6	42
	12	75
	24	100[c]
styrene oxide	6	54
	12	78
	24	96
	48	99.9[d]

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

reduction proceeded at a relatively fast rate (72 h at 25 °C) to produce the corresponding amines. **SAH** also reduces them readily to the amines within 24 h under the similar reaction conditions.[9]

On the other hand, tertiary amides reacted readily with this reagent to produce the corresponding tertiary amines. Finally, capronitrile reacted slowly, requiring 72 h at 25 °C to complete the reduction to *n*-hexylamine, but benzonitrile was reduced readily by the reagent to benzylamine within 12 h even at 0 °C.

It is noteworthy that **SAH** is excellent for the trans-formation of tertiary amides to aldehydes.[9,10] In the present study we also examined **SCAH** for such possibility. However, this reagent failed to effect such an aldehyde formation.

In the case of capronitrile, *ca.* 0.08 equiv of hydrogen was evolved immediately at 25 °C and 0.14 equiv at 0 °C, presumably by reaction of the reagent with the active α-hydrogen of the nitrile. **SAH** also partially evolves hydrogen (0.37 equiv at 0 °C),[9] but the quantity of hydrogen is larger than that by **SCAH**.

Sulfur Compounds (Table 8). Both disulfides examined reacted with this reagent to afford 2 mole of thiol per mole of disulfide. In this reaction *ca.* 1 equiv of hydrogen was evolved, apparently by reacting with the thiol *in situ* formed

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

Compound	Reagent /compd	Temp. (°C)	Time (h)	Product	Yield (%)[b]
caproamide	2	25	6	*n*-hexylamine	89[c]
			24		94
			72		98
			12		98
benzamide	2	25	6	benzylamine	90[d]
			24		92
			72		99
			120		99
N,N-dimethyl-caproamide	1	0	0.5	*N,N*-dimethyl-hexylamine	100
N,N-dimethyl-benzamide	1	0	0.5	*N,N*-dimethyl-benzyl-amine	100[e]
capronitrile	1	25	3	*n*-hexylamine	47
			24		73
			48		95
			72		99.9
benzonitrile	1	0	3	benzylamine	47
			6		91
			12		98
			24		98

[a]A 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]A 1.92 equiv of hydrogen evolved. [d]A 1.51 equiv of hydrogen evolved. [e]A 0.08 equiv of hydrogen evolved.

Table 8. Reaction of Representative Sulfur Compounds with Sodium Cyanoaluminum Hydride in Tetrahydrofuran[a]

Compound	Temp (°C)	Time (h)	Product	Yield (%)[b]
diphenyl disulfide	0	0.5	benzenethiol	190
		1		198
		3		200[c]
di-*n*-butyl disulfide	0	0.5	butanethiol	182
		1		198
		3		200[d]
phenyl *n*-propyl sulfide	0	3		0
dimethyl sulfoxide	25	0.5	dimethyl sulfide	100[e]
diphenyl sulfone	25	24		0

[a]A 1.1 equiv of reagent utilized; 0.5 M concentration. [b]Analyzed by GC with a suitable internal standard. [c]A 0.98 equiv of hydrogen evolved. [d]A 0.99 equiv of hydrogen evolved. [e]A 1.0 equiv of hydrogen evolved.

during the reaction. On the other hand, sulfides proved to be stable to the reagent under the experimental conditions. Dimethyl sulfoxide evolved 1 equiv of hydrogen readily and was reduced to the sulfide in 0.5 h at 25 °C. Finally, diphenyl sulfone was stable even at 25 °C. **SAH** shows a quite similar trend to **SCAH** in the reaction of sulfur compounds, but the rate of reaction of **SAH** appears to be faster than that of **SCAH**.

Conclusion

To our knowledge, the present study first reports a con-

venient procedure for preparing sodium cyanoaluminum hydride (**SCAH**) and its general reducing characteristics in the reaction of organic compounds containing representative functional groups. Generally the reducing power of **SCAH** appears to be weaker than that of the parent sodium aluminum hydride (**SAH**). However, the reduction pattern of both reagents is quite similar. It is our hope that, as a more detailed exploration for better understanding the reagent proceeds, this reagent should find its usefulness in selective reduction of organic functional groups in connection with the usefulness shown by the Meerwein-Ponndorf-Verley (**MPV**) type reducing agents.[19]

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.[20]

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 Aluminum Hydride in THF. An oven-dried, 1-L, round-bottom flask with side arm equipped with a magnetic stirring bar and an adaptor was attached to a mercury bubbler. The flask was flushed with dry nitrogen and then maintained under a static pressure of nitrogen. To this flask was added 400 mL of a 1.10 M solution of LiAlH$_4$ in THF and the flask was immersed into an ice-water both. To this solution 43.6 g of methanesulfonic acid (451 mmol, 2.5% excess) was added slowly with stirring. After the hydrogen evolution was completed the slurry was allowed to stand at 0 °C to permit the undissolved material to settle. The ^{27}Al NMR spectrum of the resulting clear solution showed a broad singlet at δ 104 ppm (relative to Al(H$_2$O)$_6^{3+}$) and the concentration analyzed by measuring the hydrogen evolved upon hydrolysis with 2 N H$_2$SO$_4$-THF (1:1) appeared to be 0.90 M.

Preparation of a Solution of Sodium Cyanoaluminum Hydride (SCAH) in THF. In an usual set-up were placed 10.0 g of predried sodium cyanide (198 mmol, 10% excess) and 10 mL of THF. To this slurry 200 mL of a solution of AlH$_3$ (180 mmol) in THF thus prepared was added slowly via a double-ended needle with vigorous stirring at room temperature. The slurry was stirred until the solid was disappeared for 3 h. The ^{27}Al NMR spectrum of the clear

solution showed a broad singlet at δ 96 ppm (relative to Al(H$_2$0)$_6^{3+}$) and the concentration analyzed by measuring the hydrogen evolved upon hydrolysis with 2 N H$_2$SO$_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-bottom 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 benz-aldehyde (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$_2$CO$_3$ 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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