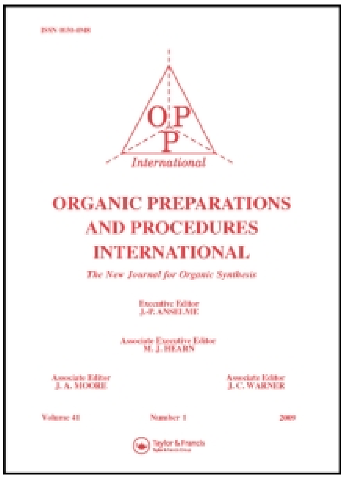

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REDUCTION OF ORGANIC COMPOUNDS WITH SODIUM ALUMINUM HYDRIDE IN THEORETICAL AMOUNT

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REDUCTION OF ORGANIC COMPOUNDS WITH SODIUM ALUMINUM HYDRIDE IN THEORETICAL AMOUNT

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Very recently, the approximate rate and stoichiometry of the reduction of organic compounds with excess sodium aluminum hydride (SAH)[1] have shown its reducing characteristics to be very similar to that observed for LAH.[2] Thus, although SAH reduces many organic functional group nearly as readily as LAH does,[3] it is much less reactive toward some functionalities. However, a reexamination of the reactions with use of the reagent in *theoretical* amount instead of using excess reagent, seemed to be more desirable for practical purposes. Accordingly, we undertook a study to examine the possibility for *quantitative* reductions of representative organic compounds in the absence of excess reagent.

All aldehydes and ketones listed in Table 1 were cleanly reduced to the corresponding alcohols with the stoichiometric amount of SAH. In the case of cinnamaldehyde, the nature of the product

TABLE 1. Reaction of SAH with Representative Aldehydes and Ketones in THF at 0°[a]

Cmpd	Time	Ratio of SAH/cmpd	Hydride[b]	Product	Yield[c] (%)
Caproaldehyde	5 min	0.25	1.00	1-Hexanol	100
Benzaldehyde	5 min	0.25	1.00	Benzyl alcohol	100
2-Heptanone	5 min	0.25	1.00	2-Heptanol	99
Pinacolone	5 min	0.25	1.00	Pinacol	100
Norcamphor	1.0 hr	0.25	1.00	Norborneol	>99
Acetophenone	0.5 hr	0.25	1.00	1-Phenylethanol	100
Benzophenone	1.0 hr	0.25	1.00	Benzhydrol	99
Cinnamaldehyde	0.5 hr	0.25	1.00	Cinnamyl alcohol	93
	0.5 hr	0.50	2.00	Hydrocinnamyl alcohol	100

a) 0.4 Equivalent of the reagent and 2.0 equivalent of compound both in THF were utilized for reactions. b) Mmoles of hydride per mmol of compound. c) Determined by GC analysis with an internal standard and authentic samples.

depends on the amount of hydride utilized; thus, only cinnamyl alcohol was obtained with a quarter equivalent of SAH, while a quantitative reduction to the *saturated* alcohol was realized when a half equivalent of the reagent was utilized.

Carboxylic acids and their derivatives were studied with a half equivalent of SAH at 0° or room temperature. With the exception of sodium benzoate, all of the compounds were reduced to the corresponding alcohols in nearly quantitative yields. The reaction of sodium benzoate was quite slow and the yield was only 65% at room temperature in 72 hrs. The results are summarized in Table 2. All of the esters and lactones examined were reduced cleanly to the corresponding alcohols with a half equivalent of SAH at 0° within 3 hrs in essentially quantitative yields as summarized in Table 3.

TABLE 2. Reaction of SAH with Carboxylic Acids and Their Derivatives in THF[a]

Cmpd	Temp. (°C)	Time, (hrs)	Ratio of SAH/cmpd	Hydride[b]	Product	Yield[c] (%)
Caproic acid	rt	12.0	0.75	2.00[d]	1-Hexanol	98
Benzoic acid	rt	12.0	0.75	2.00[d]	Benzyl alcohol	100
Sodium caproate	rt	72.0	0.50	2.00	1-Hexanol	98
Sodium benzoate	rt	72.0	0.50	1.45	Benzyl alcohol	65
Caproyl chloride	0	1.0	0.50	2.00	1-Hexanol	100
Benzoyl chloride	0	1.0	0.50	2.00	Benzyl alcohol	100

a-c) See corresponding footnotes of Table 1. d) Along with immediate evolution of 1 equivalent of hydrogen.

TABLE 3. Reaction of SAH with Esters and Lactones in THF at 0°[a]

Cmpd	Time (hrs)	Ratio of SAH/cmpd	Hydride[b]	Product	Yield[c] (%)
Ethyl caproate	3.0	0.50	2.00	1-Hexanol	100
Ethyl benzoate	3.0	0.50	2.00	Benzyl alcohol	100
γ-Butyrolactone	0.25	0.50	2.00	1,4-Butanediol	>99
Phthalide	1.0	0.50	2.00	1,2-Benzenedimethanol	98[d]

a-c) See corresponding footnotes of Table 1. d) An isolated yield.

It should be pointed out that Zakharkin and coworkers claim that a limited amount of SAH converts esters to aldehydes in good yields.[4] However, in our hands the reactions of ethyl benzoate and ethyl caproate give the corresponding aldehydes in yields of 20% or less (the reported yields are 48% and 85%, respectively).

A theoretical amount of the reagent reduced epoxides to alcohols slowly but completely in 24 hrs at room temperature. The reaction of SAH is much slower than that of LAH, but the selectivities of these two reagents for attacking the less substituted of the two carbon atom of epoxides are identical (Table 4). The results of the reduction of tertiary carboxamides and benzonitrile both with a quarter and a half equivalent of SAH at 0° and room temperature are summarized in Table 5. The reduction of both of the tertiary amides with a half equivalent of SAH gave a mixture of the corresponding tertiary amine and alcohol whereas the use of a quarter equivalent resulted in formation of the corresponding aldehydes in good yields. Zakharkin and coworkers had reported that the reduction of tertiary carboxamides with SAH gave a mixture of amine, alcohol and aldehyde, the product ratio being dependent on the reaction conditions.[5] Various dimethylcarboxamides were converted to the corresponding aldehydes in good yields.[5] These results offer a promising application for synthesis of aldehydes from tertiary carboxamides in good yields. With a half equivalent of SAH, benzonitrile was reduced to benzylamine in quantitative yield both at 0° and room temperature while the theoretical amount of hydride afforded benzaldehyde in a yield of 85% at room temperature in 1 hr.

TABLE 4. Reaction of SAH with Epoxides in THF at Room Temperature[a]

Cmpd	Time (hrs)	Ratio of SAH/cmpd	Hydride[b]	Product	Yield[c] (%)
1,2-Butylene oxide	12.0	0.25	1.00	2-Butanol	100
Cyclohexene oxide	24.0	0.25	1.00	Cyclohexanol	>99
Styrene oxide	24.0	0.25	1.00	1-Phenylethanol	94
				2-Phenylethanol	3

a-c) See corresponding footnotes of Table 1.

TABLE 5. Reaction of SAH with *tert*- Amides and Nitrile in THF[a]

Cmpd	Temp. (°C)	Time, (hrs)	Ratio of SAH/cmpd	Hydride[b]	Product	Yield[c] (%)
N,*N*-Dimethyl-caproamide	0	48.0	0.50	2.00	*N*,*N*-Dimethylhexylamine	53
					1-Hexanol	47
	0	3.0	0.25	1.00	Caproaldehyde	84
	rt	0.5	0.25	1.00	Caproaldehyde	79
N,*N*-Dimethyl-benzamide	0	48.0	0.50	2.00	*N*,*N*-Dimethylbenzylamine	33
					Benzyl alcohol	63
	0	3.0	0.25	1.00	Benzaldehyde	83[d]
	rt	0.5	0.25	1.00	Benzaldehyde	84[d]
Benzonitrile	0	12.0	0.50	2.00	Benzylamine	>99[e]
	rt	6.0	0.50	2.00	Benzylamine	98[e]
	rt	1.0	0.25	1.00	Benzaldehyde	85[d]

a-c) See corresponding footnotes of Table 1. d) Analyzed as 2,4-dinitrophenylhydrazones. e) Estimated by titration.

A three quarter-equivalent of the reagent reduced phenylisocyanate to *N*-methylaniline in a yield of 99% at 0° in 6 hrs. The reaction of nitrobenzene with excess reagent led to the slow formation of hydrazobenzene with concurrent evolution of 2.49 equiv. of hydrogen at room temperature in 24 hrs. Disulfides consumed 2 equiv. of hydride at 0°, one for hydrogen evolution and the other for reduction, providing 2 equiv. of the corresponding thiols in quantitative yields. Finally, dimethyl sulfoxide was readily reduced by a half equivalent of SAH to dimethyl sulfide with evolution of 1 equiv. of hydrogen at room temperature in 6 hrs. These results are summarized in Table 6.

TABLE 6. Reaction of SAH with Nitrogen and Sulfur Compounds in THF[a]

Cmpd	Temp. (°C)	Time, (hrs)	Ratio of SAH/cmpd	Hydride[b]	Product	Yield[c] (%)
Phenyl isocyanate	0	6.0	0.75	3.00	*N*-Methylaniline	99
Nitrobenzene	rt	24.0	1.50	2.50[e]	Hydrazobenzene	85[d]
Di-*n*-butyl disulfide	0	6.0	0.50	1.00[f]	1-Butanethiol	100
Diphenyl disulfide	0	0.25	0.50	1.00[f]	Benzenethiol	>99
Dimethyl sulfoxide	rt	6.0	0.50	1.00[f]	Dimethyl sulfide	99

a-c) See corresponding footnotes of Table 1. d) An isolated yield. e) Along with 2.49 equiv. of hydrogen evolution. f) Along with 1 equiv. of hydrogen evolution.

EXPERIMENTAL SECTION

The reaction flasks and other glassware used in the experiments were predried at 140° 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 using standard techniques for handling air-sensitive material.[6] All chemicals were commercial products of the highest purity which were further purified by standard methods before use. Tetrahydrofuran (THF) was distilled from benzophenone-sodium ketyl. Sodium aluminum hydride (SAH) was obtained from Ethyl Corporation and used directly without further purification. Hydrogen chloride in diethyl ether was purchased from the Aldrich Chemical Company or synthesized from hydrochloric acid and sulfuric acid using an automatic gasometer.[6] GC analyses were carried out on a Varian 5730A FID chromatograph equipped with a Hewlett-Packard 3390A integrator/plotter. All GC yields were determined with use of a suitable internal standard and authentic mixtures. NMR spectrometers used were a Varian Model T-60 (60 MHz) for ^{1}H NMR spectrum and a Varian FT-80A for ^{27}Al NMR.

Preparation of Sodium Aluminum Hydride (SAH) in THF.- An oven-dried, 2-L, rounded-bottomed flask with a 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. The flask was charged with *ca.* 40 g of SAH (*ca.* 750 mmol) and 600 mL of THF. The slurry was stirred for at least 48 hrs at room temperature and then allowed to stand at 0° to permit the undissolved materials to settle. The ^{27}Al NMR spectrum of the resulting solution showed a well defined quintet centered at δ 96.7 (relative to $Al(H_2O)_6^{3+}$) ($J_{Al\text{-}H}$= 175 Hz). The concentration of SAH in THF measured by hydrolysis was 1.2 M. This solution was diluted to 0.40 M for further reactions.

General Procedure Used for Hydride Reductions.- The following procedure for the reduction of caproic acid is illustrative. An oven-dried, 50-mL flask, fitted with a side-arm and a reflux condenser connected to a gas buret, was charged with 18.8 mL of 0.40 M SAH in THF (7.5 mmol). The flask was then cooled to 0° with an ice-water bath and a precooled 5 mL of a 2.0 M solution of caproic acid in THF (1.16 g, 10.0 mmol) was added dropwise at 0° with vigorous stirring. One equivalent of hydrogen gas was evolved instantly and a white gelatinous precipitate was formed. The precipitate gradually disappeared as the reaction proceeded. The rate of reaction was monitored by measuring the hydride content in a measured aliquot. After 12 hrs at 0°, the consumption of hydride was complete. The reaction mixture was then hydrolyzed with 10% sulfuric acid. Hexadecane (2.26 g, 10.0 mmol) was added as an internal standard. Gas chromatographic analysis using of a 12 ft. x 0.125 in. column of 10% Carbowax 20 M on 100-200 mesh Supelcoport showed 98% 1-hexanol.

Estimation of Amines by Titration.- The reduction of benzonitrile is representative. In the usual setup, 1.03 g of benzonitrile (10.0 mmol) was reduced with 12.5 mL of SAH (0.40 M, 5.0 mmol) for 6 hrs at room temperature. The reaction mixture was then hydrolyzed with 5 mL of water and 1 g of sodium hydroxide pellets. The clear solution was decanted and the residue was extracted with THF twice. The combined solution was diluted with water to 100 mL. To 5.0 mL of the amine solution was added 5.0 mL of 0.1 N HCl and the mixture was thoroughly shaken and titrated with 0.05 N sodium carbonate using methyl red as an indicator. Two titrations were carried out for the determination of each amine; 2.20 and 1.80 mL of 0.05 N sodium carbonate were needed, which correspond to 98% yield of benzylamine.

Isolation of Products.- The following reduction of phthalide is representative. To 10 mmol of SAH in 25 mL of THF solution was added 2.68 g of phthalide (20 mmol) in 20 mL of THF at 0° . After 1 hr, the reaction mixture was hydrolyzed with 10% sulfuric acid. The aqueous layer was then saturated with potassium carbonate and thoroughly extracted into THF. The combined THF extract was dried over anhydrous sodium sulfate. After removal of the solvent under a reduced pressure, there was obtained 1,2-benzenedimethanol, a light yellowish solid (2.71 g, 98% yield), mp 64-66°. The identity of the product was further confirmed by ^1H NMR.

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3. Actually, the use of SAH rather than LAH seems to be more desirable because of its lower cost of production and easier handling.

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