Dimethylethylamine–Alane and *N*-Methylpyrrolidine–Alane. A Convenient Synthesis of Alane, a Useful Selective Reducing Agent in Organic Synthesis†

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The simple procedure for the synthesis of alane in tetrahydrofuran (THF) originally developed by Brown and Yoon[1,2] has been used for more than two decades in numerous applications in organic synthesis.[3] The procedure involves treatment of a standardized solution of lithium aluminum hydride in THF with the theoretical quantity of 100% sulfuric acid (eq 1). However, use of alane as a

$$2LiAlH_4 + H_2SO_4 \rightarrow 2AlH_3 + Li_2SO_4 + 2H_2 \quad (1)$$

reagent or as a starting material for other reagents is still considered to be difficult and expensive.[4] This is probably due to the cumbersome procedure of preparing standardized THF solutions of lithium aluminum hydride and making 100% sulfuric acid and the difficulty of precisely controlling the theoretical quantity of 100% sulfuric acid added to the lithium aluminum hydride solution. Moreover, the alane in THF effects a slow THF celavage reaction.[1] Consequently, there has been a need for a more convenient preparation of alane reagent suitable for applications in organic synthesis. We report a new and convenient procedure for synthesizing alane as the tertiary amine–alane adduct with no comparable problem and its use in organic synthesis with high efficiency and effectiveness essentially identical with that of alane in THF.

Some years ago, Dilts and Ashby[5] reported that treatment of trimethylamine with lithium aluminum hydride in benzene produced bis(trimethylamine)–alane and trilithium aluminum hexahydride (eq 2). The reaction was

$$3LiAlH_4 + 4(CH_3)_3N \rightarrow Li_3AlH_6 + 2AlH_3{\cdot}[N(CH_3)_3]_2 \quad (2)$$

complete after 3 days but no interaction was observed in THF. On the other hand, the interaction of triethylamine with lithium aluminum hydride in benzene yielded a stable, soluble triethylamine–lithium aluminum hydride adduct (eq 3).[5,6] Thus, it appears that the extraction of alane

$$LiAlH_4 + Et_3N \rightarrow LiAlH_4{\cdot}NEt_3 \quad (3)$$

from lithium aluminum hydride with tertiary amines takes place depending on the nature of the alkyl substituents of these amines. Accordingly, we studied the alane extraction from lithium aluminum hydride (eq 4) systematically using a series of methyl- and ethyl-substituted tertiary amines such as trimethylamine, dimethylethylamine, diethylmethylamine, and triethylamine as well as *N*-methylpyrrolidine. We found that the extraction reaction carried out at 25 °C for 16 h in toluene produced amine–alane in yields depending on the tertiary amine used, as shown in the following equation:[7]

$$3LiAlH_4 + 2nNR_3 \rightarrow 2AlH_3{\cdot}(NR_3)_n + Li_3AlH_6 \quad (4)$$

n = 2 for Me_3N, n = 1 for others

$$\underset{90\%}{Me_2EtN} > \underset{83\%}{MeN(CH_2)_4} > \underset{48\%}{Me_3N} > \underset{12\%}{MeEt_2N} \gg \underset{<1\%}{Et_3N}$$

Consequently, dimethylethylamine and *N*-methylpyrrolidine, which are liquids at room temperature, represent the two most efficient and convenient tertiary amines for extraction of dimethylethylamine–alane (DMEA–alane) and *N*-methylpyrrolidine–alane (NMP–alane), respectively, from lithium aluminum hydride.

We selected DMEA-alane for the application study in selective reduction of organic compounds. The reagent was prepared simply by stirring anhydrous dimethylethylamine with commercial grade lithium aluminum hydride in toluene at room temperature for 16 h and filtering off the insoluble material. Analysis of the insoluble solids by X-ray powder diffraction showed only trilithium aluminum hexahydride. The amine–alane reagent in toluene thus prepared was analyzed and found to have an Al:H ratio of 1.00:3.08 and could be stored as a clear solution in a tightly capped bottle in a drybox at room temperature for months without a significant decrease of soluble aluminum or hydride. ^{27}Al NMR of the solution detected only a single species exhibiting an unsplit broad singlet at δ 108.7. The ^1H NMR spectrum of DMEA–alane in C_6D_6 showed a 1:1 complex between AlH_3 and NMe_2Et.

Application of DMEA–alane as a selective reducing agent was tested by reaction with several different organic compounds containing representative functional groups. These reactions enabled a comparison of the reducing characteristics of this reagent in THF–toluene to be made with alane in THF (Table I). Reductions of carboxylic acid derivatives such as caproic acid, ethyl 3-chloropropionate, and *p*-nitrobenzoyl chloride with DMEA–alane at 0 or 25 °C gave 1-hexanol, 3-chloro-1-propanol, and *p*-nitrobenzyl alcohol in <1 h in 99, 99, and 90% yields, respectively. Reductions of benzonitrile and *N,N*-dimethylbenzamide under similar conditions gave benzylamine and dimethylbenzylamine, both in 98% yield. Thus, DMEA–alane, like alane in THF, is highly effective in selectively reducing the carboxylic acid derivatives to the corresponding alcohol without significant attack on halide or nitro groups and in reducing nitriles and amides to amines.

In conclusion, a new and convenient synthesis of DMEA-alane and NMP-alane has been demonstrated. It also has been shown that the DMEA-alane reagent can be used in selective reduction of organic compounds with high efficiency and effectiveness essentially identical with that of alane in THF. We hope the present development provides an easier access to an alane reagent suitable for use in organic synthesis. Should any large-scale uses result, commercial quantities could be produced by the alternative $NaAlH_4/AlCl_3$/tertiary amine process.[9]

† This work has been presented at an IUPAC symposium, OMCOS-V (Florence, Italy, Oct 1-6, 1989).

‡ Recently retired from Ethyl Corp.

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(7) See Experimental Section for determination of yields of amine–alanes and $LiAlH_4$–amine complexes.

(8) The yield of $AlH_3{\cdot}(NMe_3)_2$ after 20 days was 87%.

(9) Marlett, E. M. U.S. Patent 4474743, 1984, to Ethyl Corp.

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Table I. Reduction of Selected Organic Compounds with $AlH_3 \cdot NMe_2Et$[a]

compd	temp, °C	[$AlH_3 \cdot NMe_2Et$]/[compd]	time, h	product	$AlH_3 \cdot NMe_2Et$ yield, %	$AlH_3 \cdot THF$ yield, %	ref
caproic acid	0	1.33	3.0	1-hexanol	99[b]	98.5[c]	1
ethyl 3-chloropropionate	0	1.00	0.25	3-chloro-1-propanol	99[d]	100[d]	2
p-nitrobenzoyl chloride	0	1.00	0.5	*p*-nitrobenzyl alcohol	90[e]	92[e]	2
N,N-dimethylbenzamide	25	1.33	0.5	dimethylbenzylamine	98[e]	98[f]	2
benzonitrile	25	1.33	1.0	benzylamine	98[f]	96.8[f]	2

[a] Reactions were in THF–toluene, 0.25 M in compound. Compounds were added to the reagent solution. [b] Yield was determined by ^1H NMR using methylenecyclohexane as an internal standard. [c] Calculated from the number of millimoles of hydride used for reduction reported in the reference. [d] Yields were determined by GC analysis. [e] Isolated yields. [f] Yields were estimated by titration.

Experimental Section

A Perkin-Elmer Plasma II emission spectrometer was used for ICP spectroscopic determination of Al and Li. Active hydride contents were determined by measuring H_2 evolution upon hydrolysis of solutions using a standard gas buret technique.[10] ^1H NMR spectra were recorded on a Varian EM-390 90-MHz NMR spectrometer, and ^{27}Al NMR spectra were recorded on a GE-Nicolet NT 360-MHz NMR spectrometer. The X-ray diffraction pattern was recorded on a Scintag PAD V automated X-ray powder diffractometer.

Preparation of DMEA–Alane. The following procedure for the synthesis of $AlH_3 \cdot NMe_2Et$ in toluene is representative for amine–alane extraction from $LiAlH_4$. All operations were performed under a nitrogen atmosphere. To a slurry of $LiAlH_4$ (7.6 g, 200 mmol) suspended in toluene (200 mL, distilled from $NaAlH_4$) was added dimethylethylamine (50 mL, distilled from $NaAlH_4$ after stirring overnight), and the mixture was magnetically stirred for 16 h. The resulting insoluble solid (3.59 g, corresponding to 66.7 mmol of Li_3AlH_6) was filtered off using a fritted-glass funnel and washed with a small amount of toluene. The combined filtrate (127.9 g) analyzed as 2.77 wt % Al and 0.06 wt % Li by ICP spectroscopy. The total soluble Al (3.54 g, 131.2 mmol) corrected for soluble Li (0.077 g, 10.96 mmol) corresponded to 90% yield of the amine–alane (120.24 mmol). Analysis of the filtered solids by X-ray powder diffraction showed only Li_3AlH_6; no $LiAlH_4$ was detected. An aliquot of the filtrate analyzed as 3.16 mmol of active H per gram of filtrate upon hydrolysis (404.2 mmol total, Al:H = 1.00:3.08). ^1H NMR in C_6D_6: δ 3.94 (s, 3 H, AlH_3), 2.27 (q, 2 H, NCH_2CH_3), 1.96 (s, 6 H, CH_3), 0.76 (t, 3 H, NCH_2CH_3). ^{27}Al NMR in toluene: δ 108.7 (br s). The yields of other amine–alanes were also determined by analysis of total soluble aluminum corrected for the soluble lithium using ICP spectroscopy. The soluble lithium amounted to about 8% of the theoretical yield of amine–alane with dimethylethylamine, to 10–12% with *N*-methylpyrrolidine and trimethylamine, but to 75% with diethylmethylamine and 92% with triethylamine.

Reduction of Organic Compounds with DMEA–Alane. The following procedure for the reduction of ethyl 3-chloropropionate with $AlH_3 \cdot NMe_2Et$ is representative of the selective reduction of the organic compounds examined. All reductions were carried out under a nitrogen atmosphere. The amine–alane solution in toluene (11.4 mL, 0.88 M) was introduced to a 100-mL round-bottomed flask containing THF (20.3 mL) via a hypodermic syringe and the mixture was cooled to 0 °C. The ester, contained in dry THF (8.3 mL of 1.2 M) previously cooled to 0 °C, was added to the reagent solution with stirring at 0 °C. The formation of a white precipitate was observed immediately. After 15 min, the reaction mixture was hydrolyzed with 6 mL of THF–H_2O (1:1) mixture. 1-Octanol (0.640 g, 4.91 mmol) was added as an internal standard. The organic layer was separated, dried ($MgSO_4$), and analyzed by GC using a 60-m FFAP capillary column for 9.91 mmol of 3-chloro-1-propanol (99% yield). The yield of benzylamine was determined by titration, the yields of dimethylbenzylamine and *p*-nitrobenzyl alcohol were determined by isolation, and the yield of 1-hexanol was determined by ^1H NMR with methylenecyclohexane as an internal standard. These products were all confirmed by ^1H NMR.

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Registry No. $LiAlH_4$, 16853-85-3; Me_2NEt, 598-56-1; $MeN(CH_2)_4$, 120-94-5; Me_3N, 75-50-3; Et_2NMe, 616-39-7; Et_3N, 121-44-8; $AlH_3 \cdot Me_2EtN$, 124330-23-0; $AlH_3 \cdot MeN(CH_2)_4$, 126084-10-4; $AlH_3 \cdot (Me_3N)_2$, 17211-58-4; $AlH_3 \cdot MeEt_2N$, 123031-51-6; $AlH_3 \cdot Et_3N$, 12076-08-3; $Me(CH_2)_4CO_2H$, 142-62-1; $ClCH_2CH_2CO_2Et$, 623-71-2; *p*-$NO_2C_6H_4COCl$, 122-04-3; $PhCONMe_2$, 611-74-5; PhCN, 100-47-0; $Me(CH_2)_5OH$, 111-27-3; $Cl(CH_2)_3OH$, 627-30-5; *p*-$NO_2C_6H_4CH_2OH$, 619-73-8; $PhCH_2NMe_2$, 103-83-3; $PhCH_2NH_2$, 100-46-9.

Supplementary Material Available: ^1H and ^{27}Al NMR spectra of DMEA–alane and X-ray powder diffraction spectrum of the filtered solids (3 pages). Ordering information is given on any current masthead page.

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Novel Neutral Alkylations of Indoles and Pyrroles with Vinyl Epoxides at High Pressure[1]

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In organic synthesis, the most important reaction is alkylation. Alkylation reactions are generally catalyzed by either acid or base, but obviously, the mildest way to perform these reactions is to conduct them under neutral conditions. The high-pressure technique as one of these approaches has seen increased use in recent years.[2] As a part of our program to develop new synthetic methods in this field,[3] it has become of interest to investigate the alkylation of indoles or pyrroles. In this paper we describe an essentially noncatalyzed carbon–carbon bond formation of indoles and pyrroles with vinyl epoxides. The procedure constitutes a useful method to produce tryptophol derivatives, which are of interest as synthetic intermediates toward antibiotics such as indolmycin.[4]

Although it is known that indoles react with some epoxides with the assistance of Lewis acid catalysts or

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(2) For reviews of this area, see: (a) *Organic High Pressure Chemistry*; le Noble, W. J., Ed.; Elsevier: Amsterdam, 1988. (b) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. (c) Matsumoto, K.; Sera, A. *Ibid.* **1985**, 999.
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