

Lithium Aluminum Hydride에 의한 삼차아미드로부터 알코올의 합성

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(1991. 1. 9 접수)

A Convenient Procedure for the Conversion of Tertiary Amides to the Corresponding Alcohols with Lithium Aluminum Hydride

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(Received January 9, 1991)

INTRODUCTION

Reduction of tertiary amides with various metal hydrides¹, such as lithium aluminum hydride^{1c} and borane², is reported to proceed mainly with carbon-oxygen bond fission to give the corresponding tertiary amines. And the reduction to the corresponding alcohols is rather unusual. Such reductions were achieved only with lithium triethylborohydride³, sodium dimethylaminoborohydride⁴, and borane⁵. However, these reagents were reported to be useful only for less hindered tertiary amides such as N,N-dimethylamides. Although lithium aluminum hydride has also been reported occasionally for the reduction of tertiary amides to the corresponding alcohols⁶, good yields were obtained only with some tertiary amides such as N-benzoylpyrrol, N-benzoylindole, and N-benzoyl-carbazole⁷. Now we wish to report a general reduction of tertiary amides with lithium aluminum hydride to the corresponding alcohols.

RESULTS AND DISCUSSION

Contrary to our general understanding¹, our preliminary study of the reaction of lithium aluminum hydride with N,N-dimethylhexanamide and N,N-dimethylbenzamide revealed that the major

products were the corresponding aldehydes and/or alcohols (products of carbon-nitrogen bond fission), instead of amines, especially when the reaction was carried out at 0°C with limited amount of hydride in a short period of time (Table 1). In the case of reaction at 0°C with 2 mole ratio of hydride to compound, both amides gave the corresponding aldehydes and alcohols as major products (88%) along with a small amount of corresponding amines (11%). And the corresponding alcohols were obtained in the yields of 85% and 88% respectively upon quenching the reaction mixture with sodium borohydride solution. However, the yields of amines increase with increasing reaction time or increasing the ratio of hydride to compound. Thus, at 67°C, both amides were reduced to the corresponding tertiary amines almost exclusively, and the tertiary amines became the major product by increasing the amount of hydride, and reaction time (Table 1). This prompted us to develop a general procedure for the selective reduction of tertiary amides to the corresponding alcohols by reducing with lithium aluminum hydride and quenching the reaction mixture with aqueous sodium borohydride solution.

We have tested the generality of this procedure with 15 representative tertiary amides. Reductions

Table 1. Reaction of N,N-dimethylhexanamide and N,N-dimethylbenzamide with lithium aluminum hydride

Tertiary amide	Temp °C	Hydride/ comp. ^a	Time hr	Product, % ^b		
				aldehyde	alcohol	amine
N,N-dimethylhexanamide	0	2	0.5	76	12	11
	0	2	0.5 ^c	0	85	11
	0	4	0.5	30	13	57
	0	4	3.0	17	10	73
	25	4	0.5	15	7	78
	67	4	0.5	3	10	87
	67	4	3.0	0	0	91
	67	4	3.0	0	0	96
N,N-dimethylbenzamide	0	2	0.5	65	23	11
	0	2	0.5 ^c	0	88	11
	0	4	0.5	42	31	26
	0	4	0.5 ^d	35	36	29
	0	4	3.0	25	30	45
	25	4	0.5	15	17	68
	67	4	0.5	2	7	91
	67	4	3.0	0	0	96

^a Mole of hydride per mole of compound. ^b Products were estimated by GLPC analysis after quenching the mixture with water. ^c The reaction mixture was quenched with aqueous sodium borohydride solution. ^d Reverse addition.

were carried out at 0°C for a shorter period of time (usually 0.5 h) with limited amount of hydride, and the amount of hydride was increased when the reaction was slow. The reaction appears to be quite general, proceeding satisfactorily for both aliphatic and aromatic derivatives examined. Thus, N,N-dimethylamides of both aliphatic and aromatic acids were reduced to the corresponding alcohols in the yields of 80~90%. And acyl derivatives of pyrrolidine and piperidine were also reduced to alcohols in very good yields. Even N,N-dimethylamides of hindered acids such as cyclohexanecarboxylic acid and pivalic acid gave fairly good yields (75~76%). Furthermore bulkier N-substituted amides such as N,N-diethylhexanamide and N,N-diisopropylbenzamide gave the corresponding alcohols in the yields of 78~83%. Even N,N-diethylpivalamide, a highly hindered amide, gave a 81% yield of pivalyl alcohol in 1 h at 0°C using 3.5 equiv of hydride. Therefore it is rather puzzling that the reduction of N,N-di-

Table 2. Selective reduction of tertiary amides to the corresponding alcohols with lithium aluminum hydride in THF at 0°C

Tertiary amide ^a	Hydride/ comp.	Time hr	Alcohol % ^b
N,N-dimethylhexanamide	2.0	0.5	85
1-hexanoylpyrrolidine	3.0	1.0	82(73)
1-hexanoylpiperidine	3.0	0.5	92
N,N-diethylhexanamide	3.5	1.0 ^c	78
N,N-diisopropylhexanamide	5.0	5.0 ^d	2
N,N-dimethylcyclohexanecarboxamide	3.5	0.5	(76)
N,N-dimethylpivalamide	2.0	0.5	73
N,N-diethylpivalamide	3.5	1.0	81
N,N-dimethylbenzamide	2.0	0.5	88
1-benzoylpyrrolidine	2.0	0.5	92
1-benzoylpiperidine	3.0	0.5	97(93)
N,N-diethylbenzamide	2.5	1.0	89
N,N-diisopropylbenzamide	5.0	3.0	83
N,N-dimethyl- <i>p</i> -toluamide	3.0	0.5	(86)
N,N-dimethyl- <i>p</i> -anisamide	2.5	0.5	(88)

^a One mmol of compound in THF was added to the limited amount of LAH, and the reaction mixture was quenched with aqueous NaBH₄. ^b Yields were estimated by GLPC analysis. Figures in the parenthesis are isolated yields (5 mmol scale). ^c Reaction at 25°C. ^d Unreacted amide (51%) and tertiary amine (47%) were observed by GLPC.

isopropylhexanamide proceeded only 50% in 5 h at room temperature, the product being the corresponding tertiary amine almost exclusively. The results are summarized in Table 2.

N,N-diethylamides of aliphatic acid is reported to be reduced to the corresponding alcohols in 50% yield with LiEt₃BH³ in 24 h at room temperature, and in only 26% yield with sodium dimethylaminoborohydride⁴. And hindered tertiary amides such as N,N-dimethylpivalamide and N,N-diethylbenzamide also gave poor yields of alcohols (37% and 4% respectively) with borane⁵. Therefore this simple procedure seems to provide a general method for the selective reduction of tertiary amides to the corresponding alcohols.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from so-

dium-benzophenone ketyl and stored under dry nitrogen atmosphere. The lithium aluminum hydride-THF solution was standardized by hydrolyzing a known aliquot of the solution with 2 N H₂SO₄-THF mixture and measuring the hydrogen gas evolved. Most of the organic compounds utilized in this study were the commercial products of the highest purity. They were further purified immediately prior to use when necessary according to the standard procedures⁸. Tertiary amides were prepared by the method of Brown and Tsukamoto⁹.

Reduction of Tertiary Amides with Lithium Aluminum Hydride. The reduction of N,N-dimethylbenzamide with lithium aluminum hydride is typical of the procedure followed. An oven dried flask with a septum inlet and a magnetic stirring bar, was connected to a mercury bubbler, and cooled down to 0°C in an ice bath under a stream of dry nitrogen. To the flask was added 2.2 ml (2 mmol) of lithium aluminum hydride (0.91 M in hydride) solution in THF and 0.8 ml of THF. Reaction was started by adding 1 ml (1 mmol) of a 1.0 M solution of N,N-dimethylbenzamide and *n*-dodecane (as an internal standard) in THF at 0°C. After 30 min reaction, 3~4 drops of aqueous NaBH₄ (~4 M in hydride) solution was added to 1 ml aliquot of the reaction mixture. The solution was dried with anhydrous potassium carbonate and the organic layer was subjected to GLPC analysis (5% Carbowax 20 M on KOH treated Chromosorb T column). The analysis showed that 88% of benzyl alcohol and 11% of N,N-dimethylbenzylamine.

Preparative Procedure of Reduction of Tertiary Amides to Alcohols. The following preparative procedure for the reduction of N,N-dimethyl-*p*-anisamide to 4-methoxybenzyl alcohol is representative. To the flask, typically equipped as above, 10 ml (12.5 mmol in hydride) of lithium aluminum hydride (1.25 M in hydride) solution in THF and 5 ml of THF were introduced. Then 0.90 g of N,N-dimethyl-*p*-anisamide (5 mmol) in THF (5 ml) was added over 2 min at 0°C. After 30 min reaction, 3 ml of aqueous NaBH₄ (~4 M in hydride)

solution was added. After additional 30 min stirring, 20 ml of 2 M HCl solution was added while cooling the solution with ice bath. The alcohol product was extracted with ether (3×30 ml) and dried over anhydrous magnesium sulphate. The ether solution was concentrated on a rotary evaporator, and the solvent was thoroughly removed under vacuum to give 0.61 g (88%) of anise alcohol, n_D^{20} 1.5436 (lit.¹⁰ n_D^{20} 1.5442), >97% pure by GLPC.

ACKNOWLEDGEMENT

We are grateful to the Ministry of Education for supporting this work.

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