An Unusual Reduction of Tertiary Amides with Carbon-Nitrogen Fission

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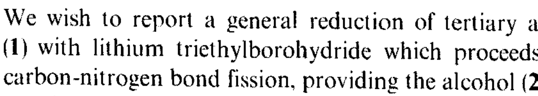
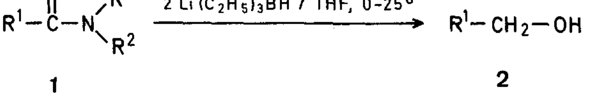
Reductions of tertiary amides with various metal hydride reducing agents, such as lithium aluminum hydride[1] and diborane[2], proceed with carbon-oxygen bond fission to give the corresponding tertiary amines.



$$R^1-CO-N(R^2)_2 \xrightarrow{BH_3\ /\ THF,\ 0-25°} R^1-CH_2-N(R^2)_2$$

We wish to report a general reduction of tertiary amides (**1**) with lithium triethylborohydride which proceeds with carbon-nitrogen bond fission, providing the alcohol (**2**), and not the amine, as the reaction product.



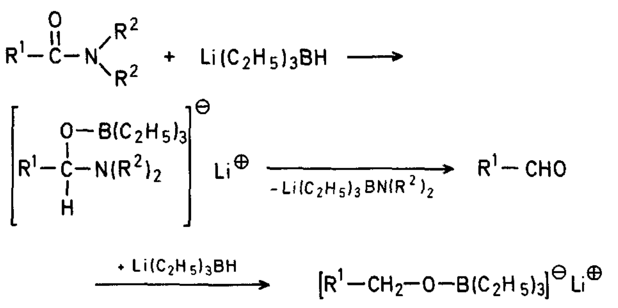
$$R^1-CO-N(R^2)_2 \xrightarrow{2\ Li(C_2H_5)_3BH\ /\ THF,\ 0-25°} R^1-CH_2-OH$$

1 **2**

The reaction appears to be quite general, proceeding satisfactorily in the case of the representative aliphatic and aromatic derivatives examined. Thus, the dimethylamide of benzoic acid is quantitatively converted into benzyl alcohol. The dimethylamides of simple linear aliphatic acids, such as butanoic acid and hexanoic acid, are reduced to the corresponding alcohols in yields of 80–90%. Branched chain derivatives, such as *N*,*N*-dimethyl-2-methylpropanamide, are converted to alcohols in comparable yields. Finally, even the hindered derivative, *N*,*N*-dimethyl-2,2-dimethylpropanamide, is reduced to the alcohol in a yield of 95%. These results are summarized in the Table.

For the dimethylamides the rates are quite fast, the reactions being completed in 1–7 h at 0°. However, the rate of reduction decreases as the steric requirements of the amide grouping increase. Thus, the pyrrolidide of butanoic acid requires 32 h at 0° and the *N*,*N*-diethyl derivative requires 24 h at 25°. The yields for these relatively hindered derivatives are somewhat lower. The steric effect becomes dominant in the case of the *N*,*N*-diisopropylamide (Table). Here no reduction is observed even after 24 h at 25° and the starting material is readily recovered in essentially quantitative amounts. Thus, the *N*,*N*-diisopropylamide grouping could be used to protect the carboxylic acid group toward reduction by lithium triethylborohydride.

The reaction presumably proceeds through the formation of the aldehyde as an intermediate.



The aldehyde is then rapidly reduced by the reagent to the alcohol stage. The triethylborane adduct of lithium dialkylamide must retain strongly basic properties. Presumably, some condensation of aldehyde under the influence of this basic intermediate is responsible for the modest decrease in yield observed for derivatives containing hydrogen *alpha* to the carbonyl group (Table).

Finally, we should mention that lithium triethylborohydride evolves one equivalent of hydrogen from primary and secondary amides without any significant reduction taking place for 24 h at 25°. These amides can be easily recovered in quantitative yields by simple hydrolysis. Consequently, the reagent is capable of reducing selectively relatively unhindered tertiary amide groups in the presence of primary or secondary amide groups as well as of the *N*,*N*-diisopropylamide group.

All reactions were carried out under a dry nitrogen atmosphere. Triethylborane present in the reaction mixture may be safely removed with an aspirator under vacuum or destroyed by oxidation with alkaline peroxide, as shown in the following representative procedures.

Benzyl Alcohol:

To a 500-ml oven-dried flask fitted with a septum inlet, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, a 1.55 molar lithium triethylborohydride[3] (142 ml, 220 mmol) solution in tetrahydrofuran is added. To this vigorously stirred solution, *N*,*N*-dimethylbenzamide (14.9 g, 100 mmol) in tetrahydrofuran (50 ml) is added over 10 min at room temperature and the solution stirred for 1 h. Residual hydride is destroyed by dropwise addition of water (5 ml). Then 3 normal hydrochloric acid (110 ml) is added while cooling the solution with an ice-bath, to neutralize the base. The flask, under nitrogen, is connected to a water aspirator, and tetrahydrofuran and triethylborane are removed under vacuum. The residue is extracted with ether (3 × 150 ml), and the solution dried over anhydrous potassium carbonate. Solvent is removed and benzyl alcohol is recovered by distillation: yield: 9.77 g (90%); b.p. 95–97°/13 torr; $n_D^{20} = 1.5391$ [Lit.[4], b.p. 94°/10 torr; $n_D^{20} = 1.5404$].

Cyclohexylmethanol:

In a 1-l 3-necked flask fitted with a dropping funnel, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, a 1.55 molar lithium triethylborohydride (213 ml, 330 mmol) solution in tetrahydrofuran is introduced and cooled to 0° with an ice-bath. While vigorously stirring, *N*,*N*-dimethyl-

Table. Reduction of Tertiary Amides **1** with Lithium Triethylborohydride in Tetrahydrofuran[a] to Alcohols **2**

Amide **1** R^1	R^2	R^2	Reaction time[b]	Yield [%][c] of **2**	b.p./torr of **2**	Lit. b.p./torr of **2**
C_6H_5	CH_3	CH_3	1 h	100 (90)	95–97°/13	94°/10[4]
n-C_3H_7	CH_3	CH_3	3 h	90		
n-C_6H_{11}	CH_3	CH_3	1 h	80 (62)	93–95°/55	157°/760[6]
i-C_3H_7	CH_3	CH_3	4 h	91		
c-C_6H_{11}	CH_3	CH_3	5 h	(71)	84–85°/15	183°/760[5]
t-C_4H_9	CH_3	CH_3	7 h	95		
n-C_3H_7	$—(CH_2)_4—$		32 h	62		
n-C_3H_7	C_2H_5	C_2H_5	24 h[d]	50		
n-C_3H_7	i-C_3H_7	i-C_3H_7	24 h[d]	0[e]		

[a] Hydride/compound = 2.2/1.

[b] At 0° except where otherwise indicated.

[c] G.L.C. yield (yield of isolated product in parentheses); G.L.C. conditions: 5% Carbowax 20 M on Varaport 30, 6 ft × 0.125 in.

[d] At 25°.

[e] 97% recovery of the amide.

cyclohexanecarboxamide (23.3 g, 150 mmol) in tetrahydrofuran (50 ml) is added dropwise and the solution is stirred for 5 h at 0°. The reaction mixture is then hydrolyzed by dropwise addition of water (50 ml). Oxidation of the triethylborane formed is accomplished by the slow, careful addition of 30% hydrogen peroxide (110 ml), followed by heating at 50–60° for 1 h. The aqueous phase is saturated with potassium carbonate and the organic layer is separated. Ether (200 ml) is added to the organic layer and the solution is washed with 3 normal hydrochloric acid (2 × 100 ml), followed by saturated aqueous potassium carbonate solution (100 ml), and dried over potassium carbonate. Solvents are removed and cyclohexylmethanol is recovered by distillation; yield: 12.1 g (71%); b.p. 84–85°/15 torr; $n_D^{20} = 1.4637$ [Lit.[5], b.p. 183°/760 torr; $n_D^{20} = 1.4639$].

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[3] The reagent is available from Aldrich Chemical Co., Milwaukee, Wisconsin, U.S.A., as a 1 molar solution in tetrahydrofuran.

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