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A NEW METHOD FOR THE REDUCTION OF SECONDARY AND TERTIARY AMIDES

Richard F. Borch
Department of Chemistry, University of Minnesota,
Minneapolis, Minnesota 55455

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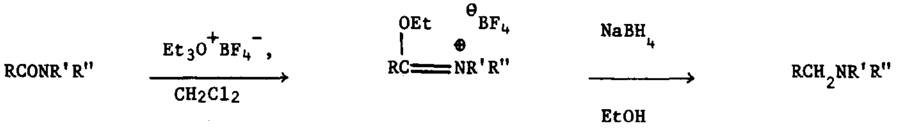
The reduction of amides with lithium aluminum hydride, aluminum hydride, lithium trimethoxyaluminum hydride, and diborane to the corresponding amines is well known (1). The non-selective nature of each of these reagents, however, precludes their use with certain other reducible groups present. We wish to report a two-step reaction sequence utilizing sodium borohydride as the reducing agent which converts secondary and tertiary amides, lactams, and urethans into the corresponding amines in excellent yields.

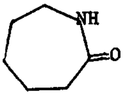
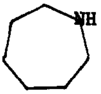
Treatment of the amide I with one equivalent of triethyloxonium fluoborate (2) in methylene chloride is known to give the imino ether fluoborate II in excellent yield (3). Replacement of the methylene chloride by absolute ethanol, followed by treatment with excess sodium borohydride at 0° or 25° gives the corresponding amine III in essentially quantitative yield.



$$\mathrm{RCONR'R''} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{Et_3O^+BF_4^-},} \mathrm{RC(OEt){=}\overset{\oplus}{N}R'R''}\ \overset{\ominus}{\mathrm{BF_4}} \xrightarrow[\mathrm{EtOH}]{\mathrm{NaBH_4}} \mathrm{RCH_2NR'R''}$$

I II III

The results are summarized in Table I.

Compound	Product	Yield[a], %
$C_6H_5CONHEt$	$C_6H_5CH_2NHEt$	92
$C_6H_5CONEt_2$	$C_6H_5CH_2NEt_2$	89 (75)[b]
$CH_3(CH_2)_3CONHEt$	$CH_3(CH_2)_3CH_2NHEt$	83
$CH_3(CH_2)_3CONEt_2$	$CH_3(CH_2)_3CH\ NEt_2$	94
$(CH_3)_3CCONHEt$	$(CH_3)_3CCH_2NHEt$	84
$(CH_3)_3CCONEt_2$	$(CH_3)_3CCH_2NEt_2$	83
p-$NO_2C_6H_4CONHEt$	p-$NO_2C_6H_4CH_2NHEt$	92
$C_6H_5CH_2NHCOOEt$	$C_6H_5CH_2NHCH_3$	81
		92

[a] Determined by gas chromatographic analysis. [b] Isolated yield.

In a typical experiment, a solution of triethyloxonium fluoborate (6.64 g., 35 mmole), and N,N-diethylbenzamide (5.73 g., 32.5 mmole) in dry methylene chloride (25 cc.) was stirred for 20 hr. at 25°. The methylene chloride was removed at reduced pressure and the residue was dissolved in 30 cc. of absolute ethanol. Sodium borohydride (3.0 g., 79 mmole) was added in portions to the stirred solution at 0°; when the addition was complete, stirring was continued for 18 hr. at 25°. The solution was poured into 250 cc. of water and extracted with 3 30-cc. portions of ether. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated. Gas chromatographic analysis: Ethyl benzoate, 2%; N,N-diethylbenzamide, 9%; N,N-diethylbenzylamine, 89%. The residue was distilled under vacuum to give 3.96 g. (75%) of gas chromatographically pure amine, b.p. 50-53° (0.3 mm.), n_D^{25} 1.5014.

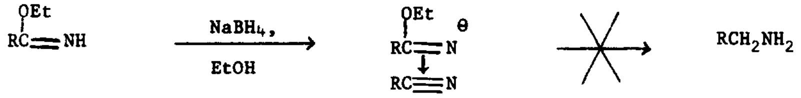
The imino ethers of the secondary amides could be isolated, if desired, by washing the methylene chloride solution with ice-cold sodium carbonate solution; reduction of the isolated imino ethers to the corresponding amines as above proceeded in quantitative yield. The fluoborate salts formed from the tertiary amides and the urethans suffered hydrolysis with water to the ethyl ester and the urethan, respectively, and thus had to be reduced directly.

We postulate a two-step mechanism for this reduction, as illustrated below for N-ethylbenzamide:

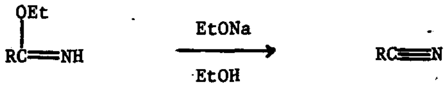
IV V VI VII

It appeared attractive to see whether we could stop the reduction at VI after consumption of one equivalent of hydride, thus ultimately leading to the aldehyde as product. Therefore, we followed the reduction of IV by NMR to see if the imine VI had a detectable lifetime under the reaction conditions. Carrying the reduction to 75% completion at 0° and at 25°, we did not observe the appearance of the imine hydrogen H_a (7.65 ppm downfield from external TMS) at either temperature. Thus, if VI is an intermediate, it must be reduced much faster than imino ether IV; our inability to isolate any trace of imine from these reductions would appear to support this conclusion.

The attempted reduction of imino ethers from primary amides did not lead to the corresponding amines. One equivalent of hydrogen was rapidly evolved (ca. 10 min.); workup of the reaction mixture after 24 hr. at 25° revealed that the new product, formed in 30-60% yield, was the corresponding nitrile, formed by elimination of ethanol as outlined below.



Further examination of this reaction indicated that the elimination could be brought about with a variety of bases, and, in fact, has provided the basis for an excellent procedure for dehydrating primary amides under non-acidic conditions in excellent yield. Thus, treatment of the imino ether of a primary amide with a catalytic quantity of dry sodium ethoxide in absolute ethanol at 60° for one hour affords the corresponding nitrile in high yield. The results are summarized in Table II.



$$\mathrm{R\overset{OEt}{\overset{|}{C}}{=}NH} \xrightarrow[\mathrm{EtOH}]{\mathrm{EtONa}} \mathrm{RC{\equiv}N}$$

TABLE II

Amide	Product	Yield, %
$C_6H_5CONH_2$	C_6H_5CN	95
$CH_3(CH_2)_3CONH_2$	$CH_3(CH_2)_3CN$	90
$(CH_3)_3CCONH_2$	$(CH_3)_3CCN$	86
$(C_6H_5)_2CHCONH_2$	$(C_6H_5)_2CHCN$	quant.

The dehydration of primary amides with sodium borohydride has been reported (4), but the milder conditions and higher yields which we have obtained should make this procedure one of considerable synthetic utility.

An attempt to find another selective reducing agent for the reduction of imino ethers derived from primary amides was unsuccessful. Lithium aluminum hydride afforded the amine in 90% yield; however, this route offers no apparent advantage over direct reduction of the amide. Lithium tri-t-butoxyaluminum hydride caused elimination to give the nitrile, although at a much slower rate than did sodium borohydride. Catalytic hydrogenation, using a variety of catalysts and solvents, gave a complex mixture of products in which the amine could not be detected by gas chromatographic analysis; the major product in each case was the ethyl ester corresponding to the starting amide, presumably arising from hydrolysis of the imino ether.

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