Reduction of Acid Chlorides to Hydroxy Compounds by Sodium Borohydride Adsorbed on Alumina

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Heterogeneous organic reactions which can occur at alumina surfaces have been recently reviewed[1a,b]. Here, it has been pointed out that, in comparison to the homogeneous reactions, heterogeneous reactions offer a few distinct advantages such as selectivity, mildness, and operational simplicity. In addition to several examples of reactions at alumina surface, we have recently shown that sodium borohydride impregnated on neutral alumina ($NaBH_4$ Alox) is able to reduce a wide variety of carbonyl compounds to the corresponding hydroxy derivatives[2].

In the present communication we report that $NaBH_4$ Alox in anhydrous diethyl ether smoothly reduces acyl and aroyl chlorides **1** into the corresponding hydroxy compounds **2**.

$$R-CO-Cl \xrightarrow{NaBH_4-Alox} R-CH_2-OH$$

1a-i **2a-i**

1,2	R	1,2	R
a	C_6H_5	**e**	$4-H_3CO-C_6H_4$
b	$n-C_3H_7$	**f**	$n-C_7H_{15}$
c	$H_3CO-CO-(CH_2)_2-$	**g**	$4-Br-C_6H_4$
d	$C_6H_5-\underset{\substack{\vert \\ O-CHO}}{CH}-$	**h**	$4-O_2N-C_6H_4$
		i	$C_6H_5-CH=CH-$

Acid chlorides cannot be reduced to alcohols by sodium borohydride in hydroxylic media, since they mainly react with the solvents[3]. On the other hand, it has been reported that acid chlorides are reduced by sodium borohydride in inert solvents and good yields are indicated for simple chlorides[4].

However, by this procedure the results for unsaturated and other polyfunctional acid chlorides seem to be less clear-cut. For example, reduction of 4-methoxy-4-oxobutanoyl chloride (**1c**) by means of sodium borohydride in dioxan afforded γ-butyrolactone in only 40% yield[4]. By the same method, cinnamoyl chloride (**1i**) undergoes reaction at the carbon-carbon double bond, as shown by the isolation of 12% of 3-phenyl-1-propanol and the fact that no cinnamyl alcohol (**2i**) could be recovered[4].

In contrast, $NaBH_4$ Alox reduction of acid chlorides in dry diethyl ether affords the corresponding alcohol, also in those cases where previous methods were less successful or failed. In fact, methyl 4-hydroxybutanoate (**2c**) could be prepared in 80% yields[5] from **1c** and 90% of cinnamyl alcohol (**2i**) was easily obtained from **1i**.

The mildness and effectiveness of our method is further illustrated by the clean reduction of (*R*)(−)-1-formyloxyphenylacetyl chloride (**1d**) to (*R*)(−)-1-formyl-1-phenyl-1,2-ethanediol (**2d**) in 82% yield.

Reductions take place within a few hours (2–4 h) at ambient temperature, also in the case of aroyl chlorides which require more forcing conditions by the usual procedures[4]. Filtration of the solid and a few washings with diethyl ether afford the hydroxy compounds in the yields summarized in Table.

Table. Reduction[a] of Acid Chlorides with $NaBH_4$ Alox

Product[b,c]	Yield [%][d]	m.p. or b.p./torr	Lit. m.p. or b.p./torr
2a	90	203–205°/760	205°/760[6]
2b	82	115–117°/760	117°/760[6]
2c	80	50°/0.5	45–46°/0.2[5]
2d	82	158–160°/0.5	—[e]
2e	88	134–135°/12	135°/12[6]
2f	90	192–194°/760	194°/760[6]
2g	85	76–77°	77°[6]
2h	88	92–93°	92–94°[6]
2i	90	127°/10	127–128°/10[6]

[a] Ratio $NaBH_4$ Alox/substrate = 1 g/mmol; reaction time 2–4 h at ambient temperature.

[b] Liquid alcohols were bulb-to-bulb distilled in a Glass tube oven, Büchi GKR 500.

[c] Analysis of compounds were within the range of error: C ±0.30, H ±0.25, N ±0.10%.

[d] Yields of isolated compounds.

[e] New compound; $[\alpha]_D$: −77.2° (c 1.4, $CHCl_3$);

$C_9H_{10}O_3$	calc.	C 65.05	H 6.07
(166.2)	found	65.15	6.08

I.R. (film): $\nu = 3400$; 1730 cm^{-1}.

^1H-N.M.R. ($CDCl_3$/TMS): $\delta = 3.65$ (t, 1H); 4.25 (t, 1H); 4.80 (m, 1H); 5.35 (s, 1H); 7.30 (m, 5H); 7.92 ppm (s, 1H).

Preparation of $NaBH_4$ Alox:

The reagent is prepared as described[2], except that it is kept in a dessiccator over phosphorus pentoxide in vacuo (0.5–1 torr) for 3–4 days.

Reduction of Acid Chlorides; General Procedure:

A solution of the acyl or aroyl chloride **1** (10 mmol) in anhydrous diethyl ether (10 ml) is added to a mixture of freshly prepared $NaBH_4$ Alox (10 g) in anhydrous diethyl ether (30 ml) under stirring. The reaction is complete within a few hours (2–4 h) at ambient temperature and the work-up consists of a filtration and washing with reagent grade diethyl ether (3 × 30 ml). Evaporation of the solvent to dryness affords the hydroxy compounds which are distilled or crystallized; yields are summarized in the Table. T.L.C. (silica gel plates, benzene/ethyl acetate, 9:1 V:V eluent), G.L.C., I.R., ^1H-N.M.R. and microanalysis of products showed a purity of >98% (G.L.C. conditions: 1% SE 30 on 100–120 mesh Gas Chrom Q).

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[5] 4-Hydroxybutanoic acid esters are quite difficult to synthesize; for example, **2c** has been prepared in 13% yield by acidic methanolysis of γ-butyrolactone; H. C. Brown, K. A. Keblys, *J. Org. Chem.* **31**, 485 (1966).

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