Reduction of Azides to Amines with Sodium Borohydride in Tetrahydrofuran with Dropwise Addition of Methanol

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Azidoalkanes, azidoarenes, and tosyl azide are reduced to the corresponding amines or *p*-toluenesulfonamide, respectively, by reaction with sodium borohydride in tetrahydrofuran with dropwise addition of small amounts of methanol.

Reduction of azides to amines is an important reaction in organic synthesis, especially in carbohydrate and nucleoside chemistry.[1] There are many reports on this reduction describing the use of, for example, lithium aluminum hydride,[2] catalytic hydrogenation,[3] triphenylphosphine,[4] triethyl phosphite,[5] sodium borohydride/phase-transfer catalyst,[6] transfer hydrogenation,[7] and sodium hydrogen telluride.[8] However, some of these methods are not chemoselective and/or require drastic reaction conditions. Reduction of azides with sodium borohydride usually gives poor yields,[1,9] except for the reduction of azidobenzene, and for the use of a phase-transfer catalyst.[6]

We have earlier demonstrated that the reducing power of sodium borohydride increases in tetrahydrofuran (or *t*-butyl alcohol) when methanol is added dropwise during the reaction and that chemoselective reductions of carboxylic esters,[10] *β*-ketoesters,[11] peptide esters,[12] oxiranes,[13] and disulfides[14] can be performed with sodium borohydride under the above reaction conditions. Sodium borohydride in tetrahydrofuran/methanol at room temperature has also been used for the reductions of conjugated ketones[15] and nitro compounds.[16]

We report here the chemoselective reduction of azidoalkanes, azidoarenes, and a sulfonyl azide (**1**) to amines (**2**) or the sulfonamide, respectively, with sodium borohydride in tetrahydrofuran with dropwise addition of methanol. The effectiveness of this tetrahydrofuran/methanol system in sodium borohydride reductions is clearly shown by the results summarized in the Table. Thus, the reduction of 1-azidooctane (**1a**) in this system affords octanamine (**2a**) in 52% yield whereas the yield dropped to 37% in a conventional solvent[9] (isopropyl alcohol). Azidoarenes and *p*-toluenesulfonyl azide, even with nitro and chloro substituents, are reduced to the corresponding amines or sulfonamide respectively, in high yields by the present chemoselective procedure. On the other hand, reduction of a *sec*-alkyl azide was rather slow. Thus, the reduction of azidobenzene (**1b**) in the presence of 2-azidooctane (**1h**) afforded aniline (**2b**) in 86% yield whereas 76% of **1h** was recovered together with small amount of **2h**. As to the effect of temperature, only 4% of octanamine (**2a**) were obtained in the reduction of 1-azidooctane (**1a**) at room temperature with sodium borohydride in the tetrahydrofuran/methanol system. On the other hand, azidoarenes (**1b**, **d**) were reduced in high yields (89–91%) even at room temperature. Since esters are also reduced by the present procedure,[10] the chemoselectivity of our procedure differs from that of the sodium borohydride reduction under phase-transfer conditions in which the ester group is hydrolyzed during the reaction.[6]

$$\underset{\textbf{1a-h}}{R{-}N_3} \xrightarrow[31-98\%]{\text{with dropwise addition of } CH_3OH/THF/NaBH_4/THF, \Delta} \underset{\textbf{2a-h}}{R{-}NH_2}$$

1, 2	R	**1, 2**	R
a	*n*-C_8H_{17}	**e**	1-naphthyl
b	C_6H_5	**f**	$C_6H_4CH_2$
c	4-ClC_6H_4	**g**	4-$CH_3C_6H_4SO_2$
d	2-$NO_2C_6H_4$	**h**	$CH_3(CH_2)_5CH(CH_3)$

Table. Amines **2a**–**h** prepared

Product **2**	Ratio $NaBH_4$: **1** (mol : mol)	Reaction Time (h)	Yield[a] (%)	m.p. (°C) or b.p. (°C)/torr found	reported[b]
a[c]	3.0	1.0	52 (4)	–	–
a[c]	9.0	2.0	59	–	–
b[c]	0.67	1.0	93 (91)	–	–
b[d]	0.67	1.0	97	136/90[e]	184
c[c]	0.67	1.0	98	68–71	70–71
d[c]	0.67	1.0	94 (89)	68–70	72
e[c]	0.67	1.0	94	48–49	50
f[c]	3.0	2.0	84	–	–
f[d]	3.0	4.0	84	145/100[e]	185
g[c]	1.0	1.0	80	134–136	138
h[c]	9.0	8.0	31	–	–

[a] Yield of isolated pure product. Purities were checked by TLC, IR, and ^{1}H-NMR analyses. The IR and ^{1}H-NMR spectra were in accord with those of authentic samples (Lit.[17]). Yields in parentheses refer to reductions at room temperature.

[b] See Lit. [18]

[c] Small scale reduction (1 mmol).

[d] Preparative scale reduction (20 mmol).

[e] Bath temperature of Kugelrohr distillation.

2-Nitroaniline (2d); Typical Procedure for Small-Scale Reductions:
To a refluxing mixture of 1-azido-2-nitrobenzene (**1d**; 0.294 g, 1.79 mmol) and sodium borohydride (0.045 g, 1.19 mmol) in tetrahydrofuran (4 ml), methanol (0.24 ml) is added dropwise over a period of 1 h. The mixture is then allowed to cool to room temperature, 1 normal hydrochloric acid (2 ml) is added, the mixture is made alkaline (pH 11) with concentrated aqueous sodium hydroxide, and extracted with dichloromethane (4 × 5 ml). The organic extract is dried with sodium sulfate, the solvent is evaporated under reduced pressure, and the crude residue is purified by preparative TLC on alumina (eluent: hexane/chloroform 1:1) to give **2d**; yield: 0.233 g (94%).

Benzylamine (2f); Typical Procedure for Preparative-Scale Reductions:
Methanol (8.8 ml) is added dropwise to a mixture of benzyl azide (**1f**; 2.35 g, 17.6 mmol) and sodium borohydride (2.00 g, 52.8 mmol) in boiling tetrahydrofuran (40 ml) over a period of 1 h, and heating at reflux temperature is continued for 3 h. Then, 1 normal hydrochloric acid (20 ml) is added, the organic layer is separated, and the aqueous layer is washed with hexane (2 × 20 ml). The combined organic layer is extracted with 1 normal hydrochloric acid (2 × 20 ml). The aqueous layers are combined, and made alkaline (pH 11) with concentrated aqueous sodium hydroxide. This mixture is extracted with dichloromethane (3 × 50 ml) and the organic phase is dried with sodium sulfate. The solvent is evaporated under reduced pressure and the residue is purified by Kugelrohr distillation to give **2f**; yield: 1.58 g (84%); b.p. 145 °C (bath)/100 torr.

Selective Reduction of Azidobenzene (1b) in the Presence of 2-Azidooctane (1h):
To a mixture of azidobenzene (**1b**; 0.158 g, 1.33 mmol), 2-azidooctane (**1h**; 0.206 g, 1.33 mmol), sodium borohydride (0.034 g, 0.888 mmol), and tetrahydrofuran (4 ml), methanol (0.18 ml) is added dropwise over a period of 1 h at reflux temperature. The mixture is then allowed to cool to room temperature, 1 normal hydrochloric acid (2 ml) is added, the mixture is made alkaline (pH 11) with concentrated aqueous sodium hydroxide, and extracted with chloroform (4 × 5 ml). The organic extract is dried with sodium sulfate, the solvent is evaporated under reduced pressure, and the residue is purified by preparative TLC on alumina (eluent: first, hexane/chloroform 1:1, v/v, then, chloroform/methanol 20:1) to give aniline (**2b**), recovered **1h**, and a small amount of **2h**; yield of **2b**: 0.106 g (86%); yield of **2h**: 0.012 g (7%), recovery of **1h**: 0.157 g (76%).

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