A Chemoselective One-Step Reduction of β-Ketoesters to 1,3-Diols

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The reduction of β-ketoesters to the corresponding 1,3-diols by complex metal hydrides requires two steps[1], involving first the reduction to β-hydroxyesters by sodium borohydride and subsequent reduction of the β-hydroxyester formed to the corresponding 1,3-diols using lithium aluminium hydride. Due to the overwhelming reducing power of lithium aluminium hydride[2], the second step cannot be carried out in a chemoselective manner in the presence of other reducable groups, such as nitro, amide, etc. The direct reduction of β-ketoesters to 1,3-diols by lithium aluminium hydride is known to give only very low yield with formation of by-products[3,4].

The reduction of an α-acetylamino-β-ketoester to the corresponding 1,3-diol by lithium borohydride formed *in situ* has been reported[5]. Although sodium borohydride reduces β-ketoesters to 1,3-diols to some extent[6], to the best of our knowledge, no method has been reported for the synthetically useful one-step chemoselective reduction of β-ketoesters by sodium borohydride to the corresponding 1,3-diols.

We recently reported the chemoselective reduction of simple carboxylic esters[7] and oxiranes[8] by sodium borohydride in the mixed solvent system *t*-butyl alcohol/methanol. We now

Table. Reduction of β-Ketoesters **1** to 1,3-Diols **2**

Substrate	R^1	R^2	R^3	Mixed solvent A / B	Product	Yield [%]	b.p.[a] [°C]/torr	Molecular formula or b.p. [°C]/torr reported
1a	$-(CH_2)_4-$		C_2H_5	t-C_4H_9OH/H_3C-OH	**2a**	88[b]	–	$C_7H_{14}O_2$ (130.4)[c]
				t-C_4H_9OH/C_2H_5OH	**2a**	80[b]	–	–
				THF/H_3C-OH	**2a**	94[b] (85)[d]	170°/2	104–105/0.7[9]
1b	CH_3	H	CH_3	t-C_4H_9OH/H_3C-OH	**2b**	73[e]	150°/20	207°/760[10]
				THF/H_3C-OH	**2b**	85[e] (73)[d]	150°/20	
1b′	CH_3	H	C_2H_5	t-C_4H_9OH/H_3C-OH	**2b**	79[e]	150°/20	
				THF/H_3C-OH	**2b**	78[e]	150°/20	
1b″	CH_3	H	n-C_4H_9	t-C_4H_9OH/H_3C-OH	**2b**	76[e]	150°/20	
1c	C_6H_5	H	C_2H_5	THF/H_3C-OH	**2c**	96[b] (86)[d]	150–155°/3	126°/2[10]

[a] Kugelrohr distillation, bath temperatures are given.

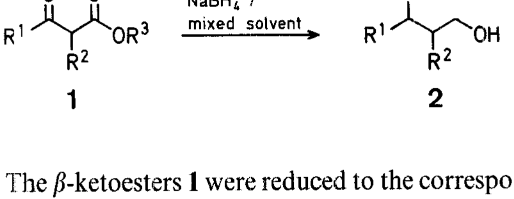
[b] Yield of isolated product purified by chromatography in small scale (1 mmol) reaction.

[c] calc. C 64.58 H 10.84
found 64.50 11.13
I.R. (neat): $\nu = 3400, 2931, 1482, 1420, 1352, 1327, 1273, 1199\ cm^{-1}$.
^1H-N.M.R. ($CDCl_3$): $\delta = 0.60$–3.20 (m, 11H), 3.25–4.66 ppm (m, 3H)
^{13}C-N.M.R. ($CDCl_3$): $\delta = 20.17, 23.73, 24.17, 24.31, 24.90, 26.12, 31.43, 33.28, 36.11, 42.25, 66.81, 67.88, 70.90, 76.36$ ppm.
Ratio of *cis* : *trans* is 1.15 ± 0.15 : 1 as determined by ^{13}C-N.M.R.

[d] Yield of isolated product purified by distilation in preparative scale (20 mmol) reaction.

[e] Yield of isolated product purified by distillation in small scale (1 mmol) reaction.

describe a one-step chemoselective reduction of β-ketoesters to the corresponding 1,3-diols by sodium borohydride in a mixed solvent system containing alcohol.



The β-ketoesters **1** were reduced to the corresponding diols **2** in good yields when methanol was added dropwise to a refluxing mixture of **1** and sodium borohydride in tetrahydrofuran (Table). Purity and structure of products **2** were confirmed by microanalysis, I.R. ^1H-, and ^{13}C-N.M.R. spectra. The ^{13}C-N.M.R. spectra showed fourteen sets of singlets, indicating a mixture of *cis*- and *trans*-isomers. As seen from the Table, both mixed solvents system of tetrahydrofuran/methanol and *t*-butyl alcohol/methanol are suitable for the reduction. Ethanol was slightly less effective as cosolvent than methanol.

Further, chemoselective reduction of **1c** in the presence of nitrobenzene and benzoylglycine was accomplished in *t*-butyl alcohol/methanol mixture. Compound **2c** was obtained in 99% yield and the recoveries of nitrobenzene and benzoylglycine were 61% and 100%, respectively.

As described, β-ketoesters were reduced chemoselectively in high yields in one-step by easily available sodium borohydride in mixed solvent system containing alcohol in the presence of other groups such as nitro, amide, or carboxylic acid.

2-Hydroxymethylcyclohexanol (2a); Typical Procedure for Small Scale Reduction:

Methanol (0.8 ml, solvent B) is added dropwise over a period of 1 h to a refluxing mixture of **1a** (0.166 g, 0.97 mmol) and sodium borohydride (0.093 g, 2.46 mmol) in tetrahydrofuran (4 ml, solvent A). Stirring is continued at reflux temperature for 1 h. After cooling to room temperature, 1 normal hydrochloric acid (5 ml) is added, the mixture is extracted with ether (10 × 5 ml), and the ether phase is dried with anhydrous sodium sulfate. The solvent is evaporated under reduced pressure, and the crude residue is purified by preparative T.L.C. over silica gel (eluent: ethyl acetate; R_F = ~0.5–0.6; area occupied by **2a** discerned by opaque appearance under sun light) to give **2a**; yield: 0.119 g (94%).

1,3-Butanediol (2b) and 3-Phenyl-1,3-propanediol (2c); General Procedure for Small Scale Reductions:

Methanol (0.5 ml, solvent B) is added dropwise over a period of 15 min to a refluxing mixture of β-ketoester **1b**, **1b′** or **1b″** (1 mmol) and sodium borohydride (0.095 g, 2.5 mmol) in solvent A (*t*-butyl alcohol or tetrahydrofuran, 4 ml). After the addition of methanol, the mixture is cooled to room temperature and several drops of water are added. The mixture is evaporated under reduced pressure and the residue is passed through a short silica gel column. Distillation using a Kugelrohr apparatus gives **2b**, and purification on silica gel T.L.C. (ethyl acetate) gives **2c** (Table). G.L.C. analysis (column: PEG 20 M, TCD detector) of **2b** and **2c** shown them to be more than 95% pure.

1,3-Diols from β-Ketoesters; General Procedure for Preparative Scale Reductions:

Methanol (16 ml) is added dropwise over a period of 0.5–1 h to a refluxing mixture of **1** (20 mmol) and sodium borohydride (1.89 g, 50 mmol) in tetrahydrofuran (40 ml). After cooling to room temperature, water (10 ml) is added and the mixture is acidified with 3 normal hydrochloric acid. Most of the organic solvents are evaporated under reduced pressure. For **2a** and **2c**, water layer is extracted with ethyl acetate (5 × 10 ml). For **2b**, water layer is made alkaline with aqueous potassium carbonate and evaporated under reduced pressure[11]. The residue is filtered and is washed with ethyl acetate (6 × 10 ml). The extracts and the filtrate are dried with anhydrous sodium sulfate and concentrated on a rotary evaporator. The residue is purified by Kugelrohr distillation; yield: 73–86%.

Selective Reduction of Ethyl 2-Benzoylacetate (1c) in the Presence of Nitrobenzene and Benzoylglycine:

Methanol (0.5 ml, solvent B) is added dropwise over a period of 15 min to a refluxing mixture of sodium borohydride (0.105 g, 2.78 mmol), **1c** (0.188 g, 0.98 mmol), nitrobenzene (0.115 g, 0.93 mmol), and benzoylglycine (0.175 g, 0.98 mmol) in *t*-butyl alcohol (15 ml). After the addition of methanol, the mixture is refluxed for 10 min and cooled to room temperature. Water (3 ml) is added and the mixture evaporated under reduced pressure. The residue is dissolved in 0.1 molar aqueous sodium hydroxide (10 ml) and extracted with chloroform (3 × 10 ml) followed by ethyl acetate (10 × 10 ml). The extracts are combined and dried with anhydrous sodium sulfate. Purification by column chromatography on silica gel (eluent: dichloromethane, then ethyl acetate) gives 3-phenyl-1,3-propanediol (**2c**); yield: 0.147 g, (99 %) and nitrobenzene; yield: 0.071 g (61 % recovery). Water layer is acidified to pH = ~ 1 with 6 normal hydrochloric acid, and extracted with ethyl acetate (8 × 10 ml). The extract is dried with anhydrous sodium sulfate, and evaporation under reduced pressure gives benzoylglycine; yield: 0.175 g (100 % recovery).

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[11] **2b** probably exists as chelated form with boron in acidic solutions.