Reduction of Symmetric and Mixed Anhydrides of Carboxylic Acids by Sodium Borohydride with Dropwise Addition of Methanol

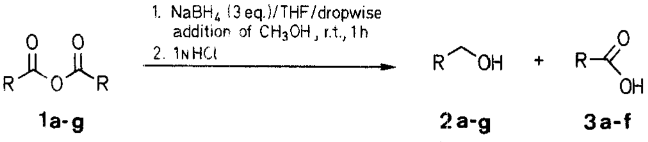
Kenso Soai,* Shuji Yokoyama, Katsuko Mochida

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Shinjuku, Tokyo 162, Japan

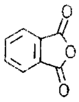
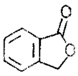
Symmetric and mixed anhydrides of carboxylic acids are reduced in high yields with sodium borohydride in tetrahydrofuran with dropwise addition of methanol.

Although several reports on the reduction of carboxylic anhydrides have been appeared, most of them deal with cyclic anhydrides.[1-7,14] The number of reports on the reduction of acyclic anhydrides is very few.[8,9] Recently lithium *n*-butylborohydride is reported to reduce benzoic anhydride to the corresponding benzyl alcohol and benzoic acid.[9]

We report a chemoselective reduction of symmetric anhydrides **1** and mixed anhydrides **4** of carboxylic acids with sodium borohydride in tetrahydrofuran with dropwise addition of methanol.

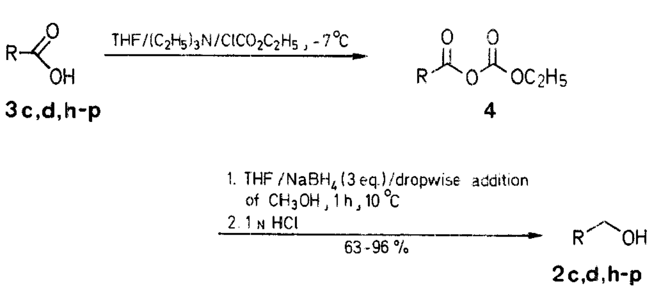


1a-g **2a-g** **3a-f**

1–3	R	1–3	R
a	n-C_6H_{13}	m	$C_6H_5(CH_2)_2$
b	n-$C_{11}H_{23}$	n	n-C_7H_{15}
c	C_6H_5	o	n-C_9H_{19}
d	4-ClC_6H_4	p	n-C_4H_9CHBr
e	3-$NO_2C_6H_4$		
f	$C_6H_5CH_2$		
h	4-$NO_2C_6H_4$	1g	
i	2-naphthyl		
j	4-$CH_3C_6H_4$		
k	4-$CH_3OC_6H_4$		
l	$C_6H_5CH{=}CH$	2g	

To a mixture of **1** and sodium borohydride in tetrahydrofuran, methanol was added dropwise over a period of 1 h at room temperature. Anhydrides **1** were reduced to the corresponding alcohols **2** and acids **3** in good to high yields. The results are shown in the Table 1. Thus, heptanoic anhydride (**1a**) was reduced to 1-heptanol (**2a**) in 88 % and heptanoic acid (**3a**) was obtained in 88 % (Table 1, entry 1). The effectiveness of the present procedure is clearly shown by the low yield of **2a** (52 %) obtained by the conventional reduction with sodium borohydride in the single solvent ethanol (Table 1, entry 3). Dropwise addition of methanol was more effective than the addition of a small amount at the beginning of the reduction (Table 1, entries 1 and 4). Room temperature gave better results than reflux temperature (Table 1, entries 1 and 5), unlike similar reductions of esters,[10], epoxides,[11] disulfides,[12] and azides.[13] It was also found that the present procedure enables the selective reduction of anhydrides containing chloro or nitro groups (Table 1, entries 8 and 9).

We also examined the reduction of mixed anhydrides **4** of carboxylic and carbonic acids with our new method. Anhydrides **4** were prepared *in situ* from carboxylic acids **3** and ethyl chloroformate.[14] Then, sodium borohydride was added to **4** and methanol was added dropwise to the mixture over a period of 1 h at 10 °C. By this procedure, benzyl alcohol (**2c**) was obtained from benzoic acid (**3c**) in 96 % yield (Table 2, entry 1). The yields of the reduction of aromatic carboxylic acids are higher than those by the conventional method.[14] Moreover, this reducing system is chemoselective, and carboxylic acids were reduced to the corresponding alcohols in the presence of chloro, bromo or



3c,d,h-p **4** **2c,d,h-p**

Table 1. Reduction of Carboxylic Acid Anhydrides **1a**–**g** to **2a**–**g** and **3a**–**f**

Entry	Anhydride **1**	Product **2**			Product **3**		
		Yield[a] (%)	m.p. (°C) or b.p. (°C)/Torr[b] found	reported[c]	Yield[a] (%)	m.p. (°C) or b.p. (°C)/Torr[b] found	reported[c]
1[d]	a	88	120/91	176	88	130–135/94	223
2[e]	a	84			78		
3[d,f]	a	52			–		
4[d,g]	a	73			70		
5[d,h]	a	79			78		
6[e]	b	81	151/86	255–259	80	150/3	131/1
7[e]	c	85	154/85	205	80	151/3	249
8[d]	d	94	67–68	75	100	235–236	243
9[d]	e	82	–	–	84	138–139	140–142
10[d]	f	97	–	–	94	77	77
11[d]	g	75[i]	69–70	75	–		

[a] Yields of isolated pure products. Purities were checked by IR, ^1H-NMR and TLC analyses. The IR and ^1H-NMR spectra were in accord with those of authentic samples. See Ref. 15.

[b] Bath temperature during Kugelrohr distillation.

[c] See Ref. 16.

[d] Small scale reduction (1 mmol).

[e] Preparative scale reduction (20 mmol).

[f] Reduction run in ethanol without the addition of methanol.

[g] A small amount of methanol (1.5 mmol) was added at once at the beginning of the reduction.

[h] At refluxing temperature.

[i] Phthalide.

nitro groups. For example, *p*-chlorobenzoic acid (**3d**) was reduced to *p*-chlorobenzyl alcohol (**2d**) in 82% yield (Table 2, entry 3). Thus the procedure provides convenient method for the selective conversion of carboxylic acids **3** to alcohols **2**.

Table 2. Reduction of Carboxylic Carbonic Anhydrides **4c**, **d**, **h–p** to **2c**, **d**, **h – p**

Entry	Product	Yield[a] (%)	m.p. (°C) or b.p. (°C)/Torr[b]	Lit. m.p. (°C) or Lit. b.p. (°C)/Torr[c]
1[d]	**2c**	96	–	–
2[e]	**2c**	76	138–139/19	205
3[d]	**2d**	82	69–70	75
4[d]	**2h**	83	92–93	96–97
5[d]	**2i**	93	78–79	81
6[d]	**2j**	88	58	61–62
7[d]	**2k**	90	–	–
8[d]	**2l**	86	–	–
9[d]	**2m**	85	–	–
10[d]	**2n**	63	–	–
11[d]	**2o**	71	–	–
12[d]	**2p**	71	–	–

[a–e] See the corresponding footnotes in Table 1.

1-Heptanol (2a) and Heptanoic acid (3a); Typical Procedure for Preparative Scale Reductions of Carboxylic Acid Anhydrides:
Methanol (10.0 ml) is added dropwise to the mixture of heptanoic anhydride (**1a**; 4.92 g, 20.3 mmol) and sodium borohydride (2.30 g, 60.7 mmol) in tetrahydrofuran (40 ml) over a period of 1 h at room temperature. Then, 1 normal hydrochloric acid (40 ml) is added, and the resultant aqueous layer is made alkaline (pH 11) with concentrated aqueous sodium hydroxide. The mixture is extracted with diethyl ether (6 × 30 ml). The aqueous layer is acidified (pH 1) with 6 normal hydrochloric acid and the mixture is extracted with dichloromethane (4 × 40 ml). The extracts are dried with sodium sulfate, and the solvent is evaporated under reduced pressure. The crude product is purified by Kugelrohr distillation to give **2a**; yield: 2.00 g (84%) and **3a**; 2.06 g (78%) (Table 1, entry 2).

2-Naphthalenemethanol (2i); Typical Procedure for Small Scale Reductions of Carboxylic Carbonic Anhydrides:
To a mixture of 2-naphthoic acid (**3i**; 0.186 g, 1.08 mmol), tetrahydrofuran (3.0 ml) and triethylamine (0.11 ml, 1.08 mmol), ethyl chloroformate (0.12 ml, 1.08 mmol) is added over a period of 5 min at – 7 °C. After stirring for an additional 30 min at same temperature, the mixture is filtered with suction, and the cake is washed with tetrahydrofuran (3 × 2 ml).

Sodium borohydride (0.129 g, 3.40 mmol) is added to the filtrate in one portion. Then, methanol (0.68 ml) is added dropwise to the mixture over a period of 1 h at 10 °C. After the reaction mixture is quenched with 1 normal hydrochloric acid (7 ml), the organic layer is separated, and the aqueous layer extracted with dichloromethane (3 x 10 ml). The combined organic layer is dried with sodium sulfate, and the solvent is removed under reduced pressure. The residue is purified with TLC on silica gel (eluent: ethyl acetate/hexane, 2:1) to afford **2i**; yield: 0.159 g (93%) (Table 2, entry 5).

Benzyl alcohol (2); Procedure for the Preparative Scale Reduction of Carboxylic Carbonic Anhydrides:
Ethyl chloroformate (1.91 ml, 19.9 mmol) is added to a mixture of benzoic acid (**3c**; 2.43 g, 19.9 mmol), tetrahydrofuran (30 ml) and triethylamine (2.98 ml, 19.9 mmol) over a period of 30 min at – 7 °C. After stirring for an additional 30 min at same temperature, the mixture is filtered with suction, and the cake is washed with tetrahydrofuran (4 x 7 ml). Sodium borohydride (2.70 g, 76.0 mmol) is added to the filtrate in one portion. Then, methanol (12.0 ml) is added dropwise to the mixture over a period of 1 h at 10 °C. After the reaction mixture is quenched with 6 normal hydrochloric acid (30 ml), and the organic layer is separated, and the aqueous layer extracted with dichloromethane (3 x 50 ml). The combined organic layer is dried with sodium sulfate, and the solvent is evaporated under reduced pressure. The residue is purified by Kugelrohr distillation to afford **2c**; yield: 1.65 g (76%) (Table 2, entry 2).

Received: 5 January 1987

(1) Vaughan, W.R., Goetschel, C.T., Goodrow, M.H., Warren, C.L. *J. Am. Chem. Soc.* **1963**, *85*, 2282.
(2) Bailey, D.M., Johnson, R.E. *J. Org. Chem.* **1970**, *35*, 3574.
(3) Cross, B.E., Stewart, J.C. *Tetrahedron Lett.* **1968**, *32*, 3589.
(4) Bloomfield, J.J., Lee, S.L. *J. Org. Chem.* **1967**, *32*, 3919.
(5) Bazant, V., Capka, M., Cerny, M., Chvalovsky, V., Kochloefl, K., Kraus, M., Malek, J. *Tetrahedron Lett.* **1968**, *29*, 3303.
(6) Brown, H.C., Weissman, P.M., Yoon, N.M. *J. Am. Chem. Soc.* **1966**, *88*, 1458.
(7) Brown, H.C., Yoon, N.M. *J. Am. Chem. Soc.* **1966**, *88*, 1464.
(8) Nystrom, R.F., Brown, W.G. *J. Am. Chem. Soc.* **1947**, *69*, 1197.
(9) Kim, S., Moon, Y.C., Ahn, K.H. *J. Org. Chem.* **1982**, *47*, 3311.
(10) Soai, K., Oyamada, H., Ookawa, A. *Synth. Commun.* **1982**, *12*, 463.
Soai, K., Oyamada, H., Takase, M., Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.
Soai, K., Oyamada, H., Takase, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2327.
Soai, K., Oyamada, H. *Synthesis* **1984**, 605.
(11) Soai, K., Ookawa, A., Oyamada, H., Takase, M. *Heterocycles* **1982**, *19*, 1371.
(12) Ookawa, A., Yokoyama, S., Soai, K. *Synth. Commun.* **1986**, *16*, 819.
(13) Soai, K., Yokoyama, S., Ookawa, A. *Synthesis* **1987**, 48.
(14) Ishizumi, K., Koga, K., Yamada, S. *Chem. Pharm. Bull.* **1968**, **16**, 492.
(15) *The Aldrich Library of NMR Spectra*, Pouchert, C.J., Campbell, J.R. (eds.), Aldrich Chemical Co., Milwaukee, 1974.
The Aldrich Library of Infrared Spectra, Pouchert, C.J. (ed.), Aldrich Chemical Co., Milwaukee, 1975.
(16) *CRC Handbook of Data on Organic Compounds*, Weast, R.C., Astle, M.J. (eds.), CRC Press Inc., Florida, 1985.