Solvolysis of Benzyl Alcohols and Ethers in 1,2-Diols and Application to a Deprotection of Benzyl Ether-type Protecting Groups

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Some kinds of benzyl alcohols and ethers react with 1,2-diols, such as ethylene glycol and propylene glycol, at 130–190 °C to give 2-hydroxyethyl or 2-hydroxypropyl ethers. Application of this reaction to a deprotection of benzyl ether-type protecting groups, under neutral conditions, was also described.

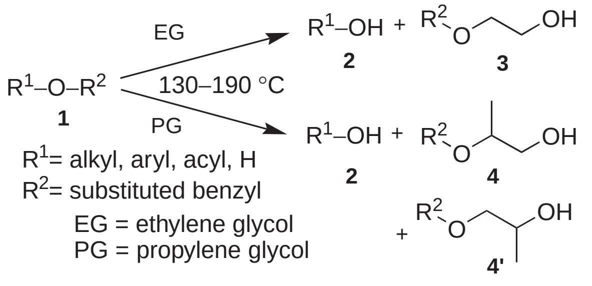
Recently, we have reported that acetal-type protecting groups, such as methoxymethyl (MOM) ethers, can be removed under neutral conditions by heating with 1,2-diols.[1] Those results suggest that some kinds of C–O bonds may cleave because of the reaction with ethylene glycol. In this paper, we wish to report the solvolysis of some benzyl ethers and benzyl alcohols in 1,2-diols. The former reaction can be used for deprotection of benzyl ether-type protecting groups under neutral conditions (Scheme 1).

Benzyl ether-type protecting groups are very popular in organic syntheses. Not only simple benzyl ethers, substituted benzyl ethers are also used to control the easiness for deprotection.[2] The deprotection of benzyl ether often accomplished with reductive method using such as H_2/Pd–C[3] or Raney Nickel,[4] and oxidative method using DDQ is also successful for some benzyl ethers such as *p*-methoxybenzyl (MPM) ethers.[4,5] However, the deprotection of MPM ether bearing a proximal hydroxyl group by DDQ is not succesful, and acetal are formed as a main product.[6]

The new method for the deprotection of benzyl ether-type protecting groups, described as follows, is quite different from those methods reported. It is neither a reductive nor an oxidative method.

When many kinds of benzyl ethers of alcohols and phenols were heated with ethylene glycol (EG) or propylene glycol (PG), the solvolysis proceeded smoothly to give alcohols or phenol. The results are summarized in Table 1. The C–O bond cleavage proceeded regioselectively, and alcohols (**2**) and ethers (**3** or **4**) were obtained.

So far as the substrate is soluble in hot EG, the solvolysis of *p*-methoxybenzyl (MPM) ethers **1a** and **1b** proceeded smoothly at 130–150 °C to give **2** in good yield. However, in the cases of less polar substrates such as **1c** and **1d**, which are not soluble in hot EG, using PG gave better results. When PG was used instead of EG, the mixture of 2-(4-methoxyphenylbenzyloxy)-1-propanol (**4a**) and 1-(4-methoxyphenylbenzyloxy)-2-propanol (**4a′**) was obtained; the ratio of them are not determined.

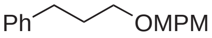
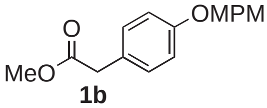
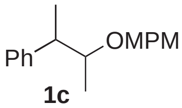
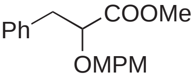
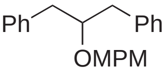
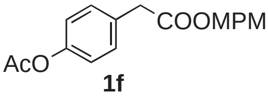
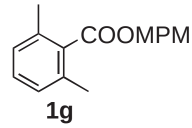
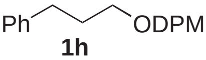
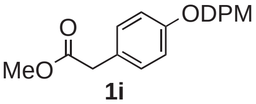


Scheme 1.

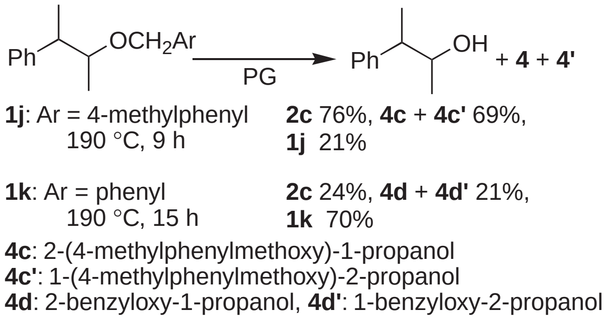
Not only MPM ethers, diphenylmethyl (DPM) ethers **1h** and **1i** also react with PG to give **2a** and **2b**, respectively.

MPM esters **1f** and **1g** also reacted with EG under similar conditions to give carboxylic acid.

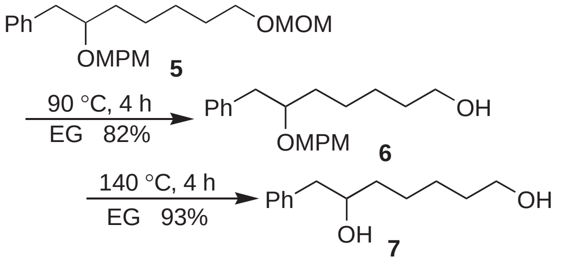
Table 1. Deprotection of benzyl ether- and ester-type protecting groups

Substrates (**1**)	Conditions	Isolated yield/%
 **1a**	EG 130 °C, 2 h	**2a** 90 (**3a** 88)
 **1b**	EG 150 °C, 4 h	**2b** 93 (**3a** 84)
 **1c**	PG 160 °C, 2 h	**2c** 92 (**4a** + **4a'** 85)
 **1d**	PG 160 °C, 2 h	**2d** 76 (**4a** + **4a'** 86)
 **1e**	PG 160 °C, 1.5 h	**2e** 97 (**4a** + **4a'** 82)
 **1f**	EG 140 °C, 4 h	**2f** 92 (**3a** 86)
 **1g**	EG 140 °C, 4 h	**2g** 96 (**3a** 93)
 **1h**	PG 150 °C, 7 h	**2a** 89 (**4b** + **4b'** 88[a])
 **1i**	PG 140 °C, 7 h	**2b** 88 (**4b** + **4b'** 92[a])

[a] **4b**: 2-(diphenylmethoxy)-1-propanol, **4b′**: 1-(diphenylmethoxy)-2-propanol.



Scheme 2.



Scheme 3.

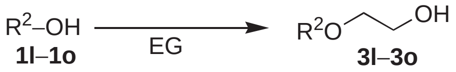
On the other hand, the corresponding solvolysis of *p*-methylbenzyl ether **1j** and benzyl ether **1k** proceeded slowly even at higher temperature. For example, when EG solution of **1j** was heated to 190 °C for 9 h, 3-phenyl-2-butanol (**2c**) was obtained in 76% yield, and 21% of **1j** was recovered. The reaction of benzyl ether **1k** is slower than that of **1j**, and 70% of **1k** was recovered after heating to 190 °C for 15 h. Results are summarized in Scheme 2. The order of the reactivity of benzyl ethers ($\mathrm{MPMOR} > p\text{-}\mathrm{MeC_6H_4CH_2OR} > \mathrm{PhCH_2OR}$) consistents with that of the stability of the benzyl cation intermediates.

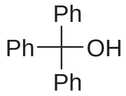
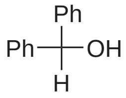
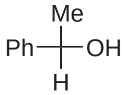
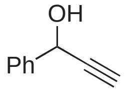
The deprotection of MPM ether needs somewhat severe conditions than that of methoxymethyl (MOM) ethers, and chemoselective deprotection of MOM group in the presence of MPM ether is possible (Scheme 3). When the substrate **5** was heated in EG to 90 °C for 4 h, the MOM group was removed chemoselectively to give alcohol **6** in 82% yield. The deprotection of the MPM group of **6** was accomplished at 140 °C to give diol **7** in 93% yield.

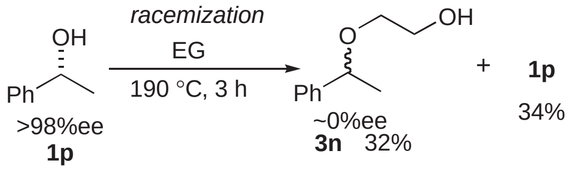
The solvolysis of some benzyl alcohols proceeded under similar conditions. Although there are some exceptions,[7] a direct replacement of a hydroxy group usually proceeds under acidic conditions. The replacement of a hydroxy group of benzylic alcohol with EG proceeded under neutral conditions. When benzylic alcohols (**1l**–**1o**) were heated in EG, 2-hydroxyethyl ethers (**3l**–**3o**) were obtained. The results are summarized in Table 2. Although the solvolysis of secondary and tertiary benzylic alcohols proceeded in good yield, that of $C_6H_5CH_2OH$ proceeded very slowly, and less than 10% of 2-benzyloxyethanol was obtained after 20 h at 190 °C.

The solvolysis of (*R*)-1-phenylethanol (**1p**) proceeded with racemization. When **1p** was heated in EG at 190 °C for 3 h, about 1:1 enantiomeric mixture[8] of **3n** was obtained (Scheme 4). It suggests that a mechanism of this reaction is not S_N2-like, but S_N1-like.

Table 2. Solvolysis of benzyl alcohols in EG



Substrates (**1**)		Conditions	Isolated yield/%	
	**1l**	190 °C, 2 h	**3l**	92
	**1m**	190 °C, 6 h	**3m**	91
	**1n**	190 °C, 8 h	**3n**	95
	**1o**	190 °C, 10 h	**3o**	62



Scheme 4.

Typical procedure is shown as follows. An ethylenglycol (8 mL) solution of **1a** (0.86 g, 3.0 mmol) was heated to 130 °C for 2 h. The solution was cooled to room temperature, and 20 mL of water was added. The mixture was extracted with ethyl acetate. After usual work up, further purification was achieved on column chromatography on silica gel (hexane–ethyl acetate), to give alcohol **2a** (0.37 g, 2.7 mmol) in 90% yield and ether **3a** (0.44 g, 2.6 mmol) in 88% yield.

References and Notes

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8 Enantiomeric ratio was determined by HPLC using Daicel Chiralcel® OD-H. However, configuration of **3n** is not determined.

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