Simple deprotection of acetal type protecting groups under neutral conditions

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Simple chemoselective deprotection of acetal type protecting groups under neutral conditions.

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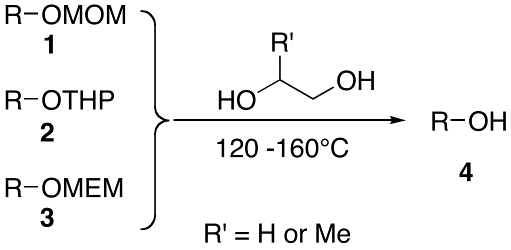
Abstract—When acetals such as MOM ethers, MEM ethers, and THP ethers were heated in ethylene glycol or propylene glycol, solvolysis proceeded smoothly to produce alcohols in excellent yield. This reaction is a very promising method for chemoselective deprotection of acetal type protecting groups.

Keywords: deprotection; acetal; ethylene glycol; propylene glycol.

Selective protection and deprotection of hydroxyl groups are very important procedures in multi-step syntheses of complicated molecules. Acetal type protecting groups such as methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), and tetrahydropyranyl (THP) are commonly used for alcohols and phenols. Although many methods to deprotect them have already been reported,1) most were accomplished under acidic conditions, which often causes adverse reactions. Recently, Lee et al. are reported on the deprotection of MOM and MEM protecting groups by reactions with CBr_4 and *i*-PrOH.2) Seemingly, this reaction proceeded under neutral conditions. However, HBr, generated from CBr_4 and *i*-PrOH *in situ*, causes deprotection. In this paper, we report on a very simple method for the deprotection of acetal type protecting groups under neutral conditions.



Scheme 1.

Our method is simple and inexpensive: heating acetals with ethylene glycol (EG) or propylene glycol (PG)(Scheme 1). The deprotection of acetals (**1-3**) proceeded smoothly under these conditions to give alcohols (**4**) in excellent yield. Not only MOM ethers (**1**) of alcohols (primary, secondary, and tertiary), but phenols also reacted smoothly under similar conditions. The

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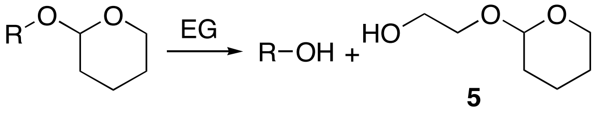
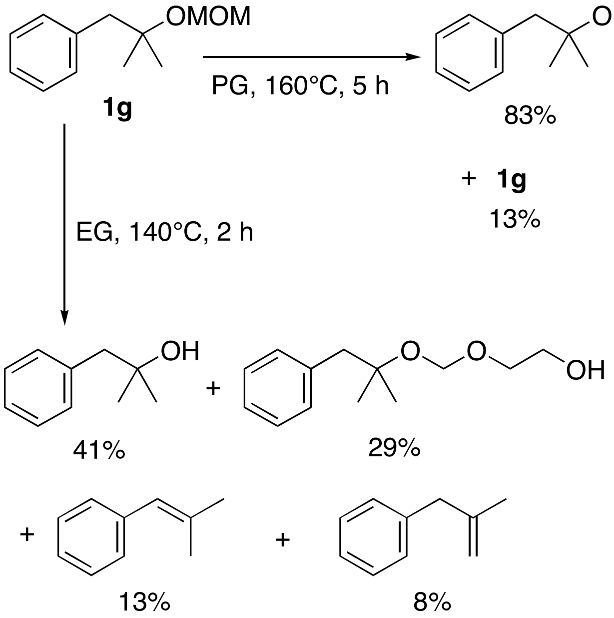
deprotection of THP ether (**2**) and MEM ether (**3**) also proceeded. However, the deprotection of MEM ether required somewhat higher temperatures. In the case of THP ethers, 2-(2-hydroxyethoxy)-1-oxacyclohexane(**5**) was isolated. For example, the deprotection of THP ether **2a** and **2b** gave **5** in 75% and 57% yield, respectively. Results are summarized in Table 1.



Scheme 2.

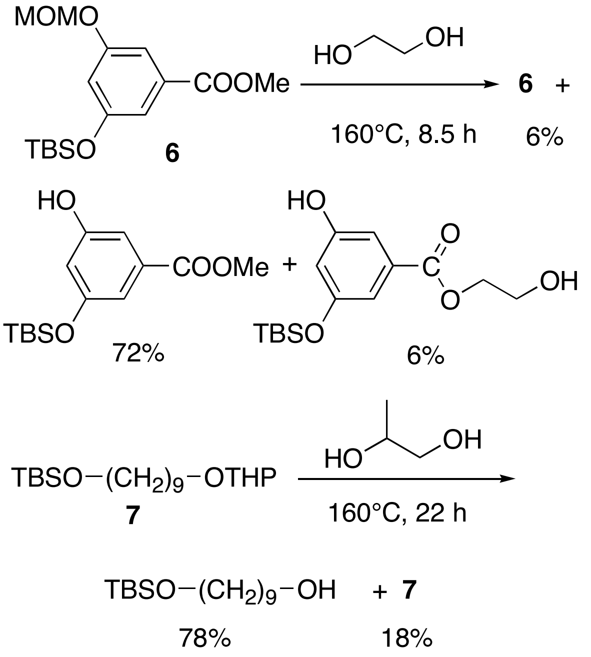
Although the deprotection of **1d** and **3d** proceeded without destruction of ester groups, solvolysis of the ester group of **1e** occurred to some extent under the similar conditions. The diastereoisomeric ratio of **1c** did not change during the deprotection. Both of the MOM groups of **1f** were removed in excellent yield in EG at 120 °C.

However, in the case of **1g**, a considerable amount of alkenes was obtained (Scheme 3), probably because of insufficient solubility of **1g** to EG. To increase the solubility of **1g**, we used PG instead of EG, and the yield of **4g** was successfully improved to 83%, recovering 13% of **1g**.



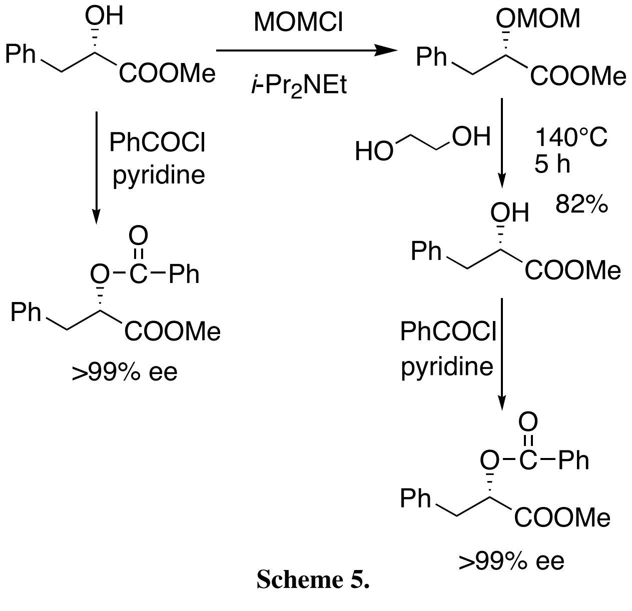
Scheme 3.

The chemoselective deprotection of the MOM group in the presence of *t*-butyldimethylsilyl (TBS) group can be accomplished. The TBS group was not removed under similar conditions. Results are summarized in Scheme 4.



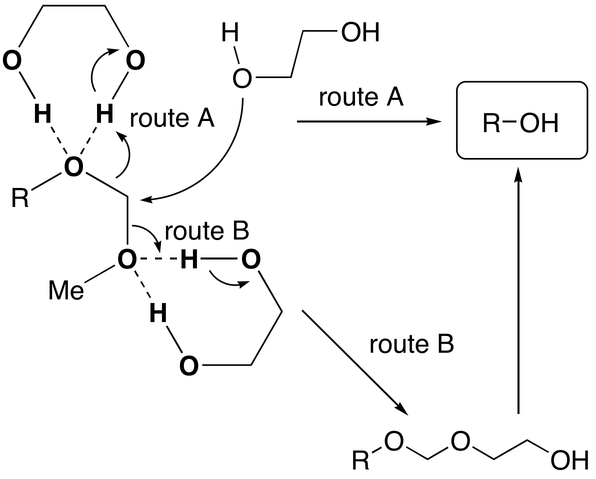
Scheme 4.

The deprotection of the MOM ether of chiral methyl (*S*)-3-phenyl-2-hydroxypropanoate proceeded with retention of the configuration of the asymmetric carbon; the enantiomeric excess was determined as benzoate. Results are summarized in Scheme 5. The enantiomeric ratio of (*S*)-3-phenyl-2-hydroxypropanoate did not change during the course of protection, deprotection, or benzoylation.



Scheme 5.

The plausible mechanism of these reactions is shown in Scheme 6. Hydroxyl groups of the glycol make hydrogen bonds with oxygen atoms of acetals, and facilitate the cleavage of the carbon-oxygen bond of acetals. Then, a nucleophilic attack of a hydroxyl group of another glycol cleaves from the carbon-oxygen bond to give alcohols and acetal (route A). The alternative stepwise deprotection route B is also plausible.



Scheme 6.

General procedures. About 10% solution of acetal (**1-3**) in EG or PG was heated (conditions are summarized in Table 1). After the usual workup, the following purification with column chromatography on silica gel gave alcohol (or phenol) (**4**).

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