

A One-Step Conversion of *p*-Methoxybenzyl Ethers into Methoxymethyl Ethers by the Action of Dimethoxymethane in the Presence of Tin(II) Bromide and Bromomethyl Methyl Ether

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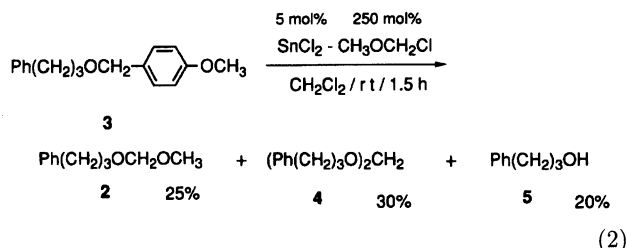
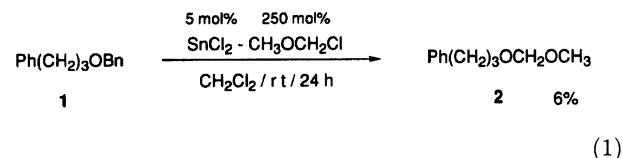
Synopsis. The combined use of dimethoxymethane with catalytic amounts of tin(II) bromide and bromomethyl methyl ether cleaves *p*-methoxybenzyl ethers to give methoxymethyl ethers in good yields. The chemoselective conversion of *p*-methoxybenzyl ethers in the presence of the benzyl ether function into methoxymethyl ethers has also occurred successfully.

A great number of protective groups for the hydroxyl function¹⁾ have played important roles in organic synthesis, particularly in the degradation or transformation of natural products and in the synthesis of polyfunctional molecules. Various types of protective groups for the hydroxyl function have been exploited and are classified mostly into alkyl ether-, silyl ether-, acetal-, and ester-types.

Transferring from one protective group into another²⁾ is frequently employed during the course of the total synthesis of complex natural products, such as carbohydrates and macrolide antibiotics. A two-step transformation is generally needed for this purpose; deprotection and consecutive introduction of another protecting group of choice. If the transformation can be effectively performed in a one-step procedure, the merit in a reduced product loss as well as in experimental convenience will be quite rewarding. Based on this point of view, we previously demonstrated a direct conversion of benzyl protected alcohols into the corresponding acetates,³⁾ effected by the action of an excessive amount of acetyl bromide (AcBr) along with a catalytic amount of SnBr₂.⁴⁾ Herein, we wish to report on a novel and efficient procedure for the direct conversion of *p*-methoxybenzyl (PMB) ethers into the corresponding methoxymethyl (MOM) ethers.

Our previous investigation concerning the direct transformation of benzyl protected alcohols to the corresponding acetates effected by the AcBr/SnBr₂ reagent system⁵⁾ suggested that MOMX/SnX₂ would provide an efficient reagent for the direct conversion of benzyl ethers into methoxymethyl ethers. We first examined the direct conversion of benzyl ether into methoxymethyl ether by employing chloromethyl methyl ether instead of acetyl chloride according to a procedure reported in a previous paper.³⁾ The treatment of 1-benzyloxy-3-phenylpropane (**1**) with SnCl₂ and MOMCl in 0.05 and 2.5 molar ratios, respectively, to the substrate at room temperature for 24 h in CH₂Cl₂ gave 1-methoxymethoxy-3-phenylpropane (**2**) in only

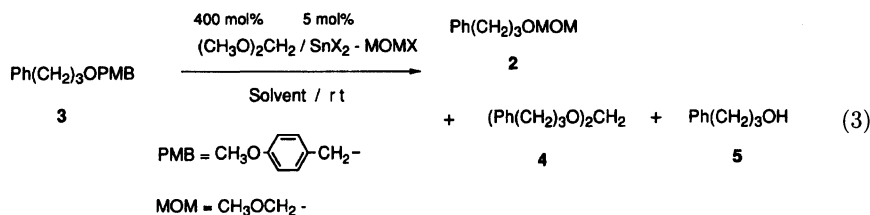
6% yield (Eq. 1). A similar reaction starting from 1-(4-methoxybenzyloxy)-3-phenylpropane (**3**) gave 1-methoxymethoxy-3-phenylpropane (**2**), bis(3-phenylpropoxy)methane (**4**), and 3-phenylpropanol (**5**) in 25, 30, and 20% yield, respectively (Eq. 2).⁶⁾



After a screening of various reaction conditions, we found that employing an excessive amount of dimethoxymethane as the methoxymethyl source and 1,2-dichloroethane as a solvent gave the desired MOM ether in a higher yield (Table 1). We have chosen a combination system of SnBr₂, MOMBr, and (CH₃O)₂CH₂ (molar ratio of PMB ether:SnBr₂:MOMBr:(CH₃O)₂CH₂ = 1.0:0.05:0.5:10) in 1,2-dichloroethane as the tentative optimum reaction conditions (Run 7).

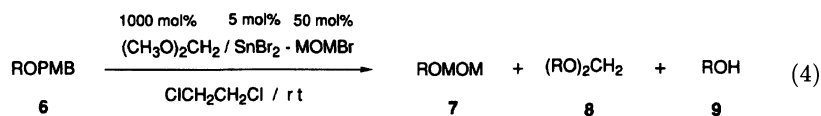
The reaction was conducted with various PMB ethers, including those of primary, secondary, and phenolic alcohols; the results are summarized in Table 2. By using this method, PMB ethers were transformed into the corresponding MOM ethers in good yields. However, the reaction of PMB ether of phenolic alcohol gave mainly the parent alcohol (Run 8). PMB ethers were cleaved chemoselectively in the presence of the benzyl ether function within the same molecule (Runs 1 and 4). In the case of the PMB ether of oleyl alcohol the cis carbon-carbon double bond, of which is incompatible with acidic conditions, the conversion of PMB ether into MOM ether has been efficiently achieved and without any detectable stereomutation (Run 5). Concerning the reaction mechanism first, MOM ether is supposed to be formed directly from PMB ether along with a concomitant elimination of PMBX (X = Br and/or MeO), similar to the case of the direct conversion of benzyl ethers into acetates.³⁾ The subsequent disproportionation of MOM ether via an acetal-exchange is present

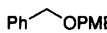
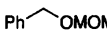
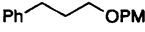
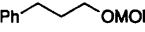
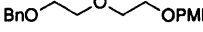
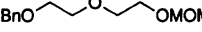
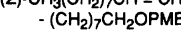
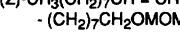
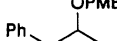
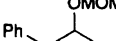
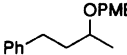
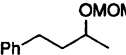
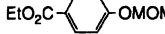
Table 1. The Effect of Reagent System of Direct Conversion of PMB Ether into MOM Ether



Run	SnX ₂ -MOMX (mol%)	Solvent	Time h	Yield/% ^{a)}		
				2	4	5
1	SnCl ₂	CH ₂ Cl ₂	20	5	0	11
2	SnCl ₂ -MOMCl(20)	CH ₂ Cl ₂	24	28	4	11
3	SnCl ₂ -MOMCl(50)	CH ₂ Cl ₂	10	58	9	13
4	SnCl ₂ -MOMCl(50)	ClCH ₂ CH ₂ Cl	5	64	10	7
5	SnBr ₂ -MOMBr(50)	CH ₂ Cl ₂	8	69	8	6
6 ^{b)}	SnBr ₂ -MOMBr(50)	ClCH ₂ CH ₂ Cl	5	73	5	6
7 ^{b)}	SnBr ₂ -MOMBr(50)	ClCH ₂ CH ₂ Cl	24	77	3	5

a) Isolated yield from PMB ether. b) 1000 mol% of (CH₃O)₂CH₂ was used.

Table 2. Synthesis of Various MOM Ethers from PMB Ethers^{a)}

Run	ROPMB	ROMOM	Time h	Yield/% ^{b)}		
				7	8	9
1			6	77	3	3
2			24	80	2	5
3			24	77	3	5
4			6	81	0	0
5			4	68	0	12
6			24	57	9	17
7			24	72	2	13
8			24	13	0	80

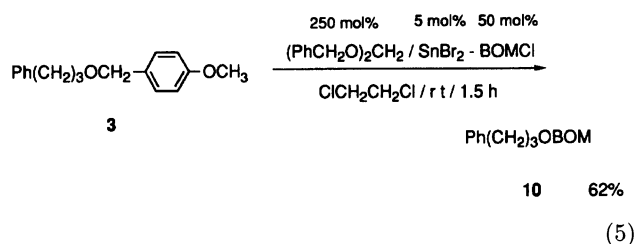
a) All the products gave satisfactory ¹H, ¹³C NMR and IR spectra. b) Isolated yield from PMB ether.

under the reaction conditions.⁶⁾

Next, we examined the direct conversion of PMB ether **3** into benzyloxymethyl (BOM) ether **10** us-

ing dibenzyloxymethane and benzyl chloromethyl ether (BOMCl) instead of dimethoxymethane and bromomethyl methyl ether; again, the result was satisfactory,

as shown in Eq. 5.



The direct conversion of PMB ethers into MOM ethers provides a new and convenient method for the synthesis of methoxymethyl ethers from *p*-methoxybenzyl ethers. Further synthetic investigations concerning other useful direct conversions of the protective group are now in progress.

Experimental

General Procedure. To a suspension of anhydrous SnBr_2 (6.2 mg, 0.022 mmol) and 1-(4-methoxybenzyloxy)-3-phenylpropane (115 mg, 0.449 mmol) in 1,2-dichloroethane (1.5 ml) was added dropwise dimethoxymethane (342 mg, 4.49 mmol) in 1,2-dichloroethane (1.5 ml) and bromomethyl methyl ether (32.1 mg, 0.25 mmol) in 1,2-dichloroethane (1 ml) successively at room temperature under an argon atmosphere. The reaction mixture was stirred for 24 h at this temperature and then quenched with a phosphate buffer (pH 7). The organic materials were extracted with dichloromethane and dried over Na_2SO_4 . The solvent was evaporated and 1-methoxymethoxy-3-phenylpropane (62.0 mg, 77%) was isolated by thin-layer chromatography on silica gel.

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- 6) The acetal-exchange is supposed to be occurred under the reaction conditions, since treatment of 1-methoxymethoxy-3-phenylpropane (**2**) with a mixture of SnCl_2 (5 mol%) and MOMCl (250 mol%) gave bis(3-phenylpropoxy)methane (**4**), 3-phenylpropanol (**5**), and recovered 1-methoxymethoxy-3-phenylpropane (**2**) in 42, 19, and 21% yield, respectively.