Lewis Acid-Catalyzed Deprotection of *p*-Methoxybenzyl Ether

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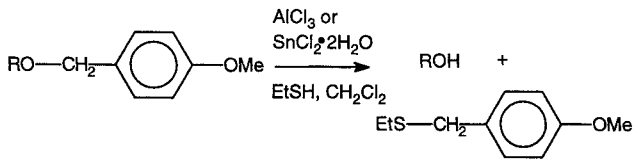
Abstract: The *p*-methoxybenzyl protecting group was readily removed from alcohols and phenols using catalytic amounts of $AlCl_3$ or $SnCl_2 \cdot 2H_2O$ in the presence of EtSH at room temperature. Under these mild conditions other protecting groups such as methyl and benzyl ethers, *p*-nitrobenzoyl esters, TBDPS ethers and isopropylidene acetal were unchanged.

Selective protection and deprotection of hydroxyl groups is essential for multi-step synthesis of carbohydrates and polyhydroxylated natural products.[2] The *p*-methoxybenzyl (PMB) group is one of the most useful groups for alcohol protection because it can be selectively cleaved in the presence of benzyl ethers. Some methods for selectively removing the PMB group include oxidation by ceric ammonium nitrate (CAN)[3] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[4] as well as Lewis acid catalyzed cleavage with Me_2BBr,[5] $BF_3 \cdot OEt_2$-$NaCNBH_3$,[6] and a combination of TMSCl-$SnCl_2$-anisole.[7] To date, no catalytic method for PMB deprotection has been reported and stoichiometric or excess amount of cleavage reagent is typically required.

We now report that the combination of a catalytic amount of a Lewis acid, aluminum chloride ($AlCl_3$)[8] or tin (II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) with a soft nucleophile (EtSH) is an efficient approach to cleave selectively the *p*-methoxybenzyl protecting group of alcohols and phenols in the presence of benzyl ether and other sensitive functional groups.



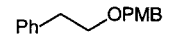
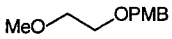
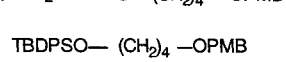
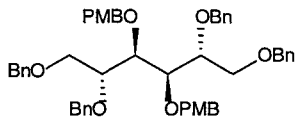
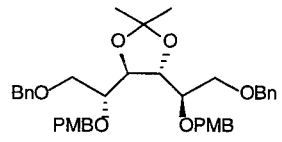
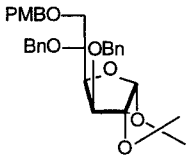
Scheme 1

Treatment of PMB ether **1**[9] (Table 1, entry 2) with 0.2 equiv of $AlCl_3$ in the presence of EtSH (4 equiv) in CH_2Cl_2 at room temperature gave 2-phenyl-1-ethanol in a high yield (95%) after flash chromatography to remove the sulfide byproduct EtSPMB (R_f = 0.3 in hexane). In the absence of EtSH, the alcohol was isolated in 82% yield contaminated by impurities (entry 1). The generality of this approach was tested on various PMB ethers. The complex $AlCl_3$-EtSH cleaved selectively PMB ethers in the presence of linear and cyclic ethers (entries 3 and 4). Treatment of benzyl *p*-methoxybenzyl ether **4** with $AlCl_3$-EtSH gave only the benzyl alcohol without a trace of *p*-methoxybenzyl alcohol (entry 5, Scheme 2). PMB ethers were also selectively cleaved in the presence of *p*-nitrobenzoyl esters and TBDPS ethers (entries 6 and 7). Deprotection of bisPMB ethers **7** (entry 8) and **8** (entry 9) gave the corresponding diols in good yields. When the carbohydrate derivative **9**, which contains an isopropylidene acetal, benzyl ether and glycosidic function, was subjected to the action of $AlCl_3$-EtSH, the parent alcohol was obtained in 73% yield (entry 10), and 80% by replacement of $AlCl_3$ with $SnCl_2 \cdot 2H_2O$ (entry 11).

Having established the conditions for the selective cleavage of PMB ether of various alcohols and polyols, we turned our attention to the

Table 1. Cleavage of PMB ether of alcohols and

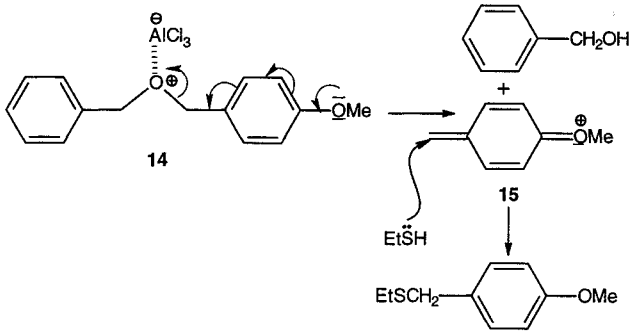
ROPMB —A, B or C→ ROH

Entry	ROPMB Structure	ROPMB No.	Conditions[a] / equiv of LA[b] / time	Yield[c] ROH
1		1	**A** / 0.2 / 1 h	82%
2			**B** / 0.2 / 40 min	95%
3		2	**B** / 0.3 / 3 h	73%
4		3	**B** / 0.1 / 5 h	93%
5		4	**B** / 0.2 / 30 min	93%
6		5	**B** / 0.3 / 35 min	89%
7		6	**B** / 0.3 / 90 min	84%
8		7	**B** / 0.6 / 90 min	97%
9		8	**B** / 0.6 / 30 min	76%
10		9	**B** / 0.2 / 30 min	73%
11			**C** / 0.3 / 3 h	80%

a) **A** : $AlCl_3$, CH_2Cl_2; **B** : $AlCl_3$, EtSH (4 equiv), CH_2Cl_2; **C** : $SnCl_2 \cdot 2H_2O$, EtSH (4 equiv), CH_2Cl_2

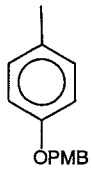
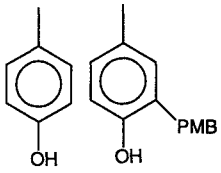
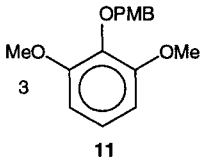
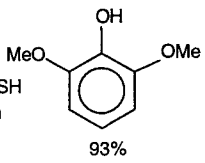
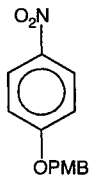
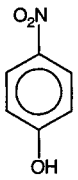
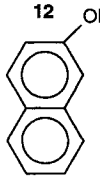
b) Lewis acid

c) Isolated yield



Scheme 2

Table 2. Cleavage of Aryl PMB ethers

Entry	PMB ether	Conditions[a]	Products / Yields[b]
1	 **10**	$AlCl_3$-EtSH 0.1 equiv / 2 min	 32% 62%[c]
2		$SnCl_2 \cdot 2H_2O$-EtSH 0.2 equiv / 30 min	76% 12%
3	 **11**	$SnCl_2 \cdot 2H_2O$-EtSH 0.1equiv / 2 min	 93%
4	 **12**	$AlCl_3$-EtSH 0.3 equiv / 30 min	 91%
5	 **13**	$SnCl_2 \cdot 2H_2O$-EtSH 0.2 equiv / 30 min	Alkylated products

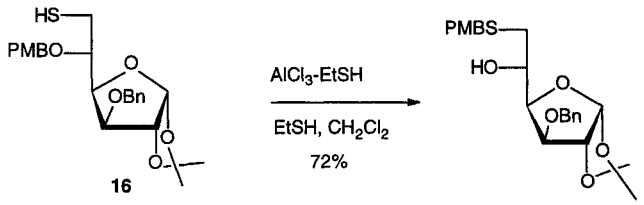
a) 4 equiv of EtSH were used. b) Isolated yield

cleavage of aryl PMB ethers. The results are summarized in Table 2. The PMB ether of *p*-cresol **10** on reaction with $AlCl_3$-EtSH in CH_2Cl_2 at room temperature for 2 min gave the desired product in only 32% yield contaminated with 62% of product from *ortho*-alkylation.[10] The use of $SnCl_2 \cdot 2H_2O$-EtSH gave the *p*-cresol in 76% yield and reduced the amount of *ortho*-alkyaltion to 12%. No *ortho*-alkylated product was detected in the case of **11** in which the two *ortho* positions were occupied by methoxy moieties, nor in the case of *p*-nitrophenyl PMB ether **12**. On the other hand, the treatment of PMB ether of 2-naphthol **13** afforded only alkylation products.[6, 10]

Cleavage of the PMB ether is presumed to proceed by the same mechanism as described for debenzylation of benzyl ethers in the presence in stoichiometric amount of Lewis acid.[7,11] Lewis acid coordination of the PMB ether oxygen to form a complexed oxygen species **14** triggers an electronic delocalisation that liberates the parent alcohol and the oxonium **15** which is trapped by nucleophilic attack of EtSH to afford the PMB ethyl sulfide (Scheme 2).

In the case of PMB ether **16**,[13] the SH group served as a trapping agent to give only the *S*-alkylated product in 72% yield (Scheme 3).

A typical procedure for the cleavage of **1** is as follows: to a stirred solution of **1** (240 mg, 1.0 mmol) in dichloromethane (10 mL) was added EtSH (300 (L, 4.05 mmol) followed by $AlCl_3$ (27 mg, 0.20 mmol). The reaction was stirred at room temperature for 40 min and



Scheme 3

then quenched with saturated aqueous $NaHCO_3$ solution. The organic material was extracted into EtOAc, and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the crude residue was purified by column chromatography on silica gel with EtOAc/hexanes as eluant to afford 2-phenyl-1-ethanol in 95% yield, accompanied with 77% of EtSPMB.[14]

In conclusion, we have found that a combination of catalytic amounts of either $AlCl_3$ or $SnCl_2 \cdot 2H_2O$ and EtSH is an effective method for cleaving PMB ethers of alcohols and phenols. The present method should have wide application in view of the common use of the PMB in organic synthesis. The significant feature of the reaction is that the cleavage is catalytic and consequently other functionalities are resistant to the mild reaction conditions of the deprotection.

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References and Notes

1. To whom correspondence should be addressed.
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7. Akiyama, T.; Shima, H.; Ozaki, S. *Synlett* **1992**, 415.
8. The use of an excess of $AlCl_3$-EtSH is a well known method for the cleavage of benzyl ether[11] and methyl ether.[12]
9. PMB ether were prepared using the standard procedures employing PMBCl and either NaH in DMF at room temperature (for alcohols) or K_2CO_3 in refluxing acetone (for phenols).
10. Hart, L. S.; Waddington, C. R. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 1607.
11. Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.
12. Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E.; *Chem. Lett.* **1979**, 97.
13. The thiol **16** (Scheme 3) was prepared from the commercially available diacetone-D-glucose: a) NaH, BnBr, DMF, 5 h (92%), b) aq. 50% AcOH, rt, 24 h (99%), c) NaH, DMF, PMBCl (41%), d) Ph_3P, DIAD, AcSH (88%), e) NaOH (70%).
14. All compounds were characterized by ^1H, ^{13}C-NMR, IR and HRMS.