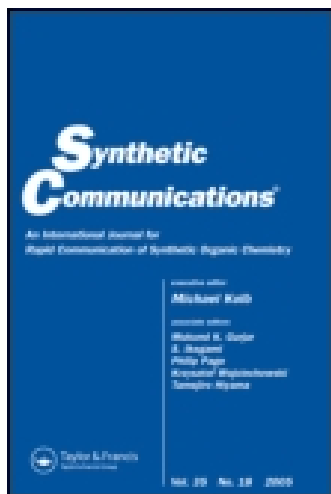


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## An Efficient and Selective Deprotecting Method for Methoxymethyl Ethers

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### ABSTRACT

Methoxymethyl ethers were selectively deprotected to the corresponding phenols in high yields by  $\text{CBr}_4$  and  $\text{PPh}_3$  in aprotic solvent ( $\text{ClCH}_2\text{CH}_2\text{Cl}$ ) under slightly thermal reaction conditions.

*Key Words:* Deprotecting; Methoxymethyl; Selectively.

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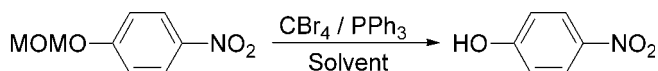
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Selective introduction and removal of protective groups is an important tool in organic synthesis.<sup>[1]</sup> Among various hydroxyl protecting groups, the methoxymethyl (MOM) ether is one of the most commonly used.<sup>[2,3]</sup> Acidic reaction is the typically used hydrolyzing method for protected hydroxyl functionality. MOM ether is generally hydrolyzed in protic solvent by acids such as HCl,<sup>[4–6]</sup> catechol boron bromide (CBB)/HOAc,<sup>[7]</sup> and pridium *p*-toluenesulfonate<sup>[8]</sup> or hydrolyzed by Lewis acid such as LiBF<sub>4</sub>,<sup>[9]</sup> Me<sub>2</sub>BBr,<sup>[10]</sup> Ph<sub>2</sub>BBr,<sup>[11]</sup> (*i*-PrS)<sub>2</sub>BBr,<sup>[12]</sup> catechol boron bromide (CBB),<sup>[13]</sup> Me<sub>3</sub>SiBr,<sup>[14]</sup> and TiCl<sub>4</sub>. In spite of their potential utility, some of the methods suffer from drawbacks, like the use of strong acid, which has somewhat restricted its utilization in molecules containing other acid-sensitive functionality, lack of selectivity, and unsatisfactory yield. Although the use of CBr<sub>4</sub> in *i*-PrOH for deprotecting MOM ether was reported,<sup>[15]</sup> the success of such deprotections relies on the in situ generation of HBr, which provides an anhydrous acidic reaction condition. The combination of CBr<sub>4</sub> and PPh<sub>3</sub> in aprotic solvent can assist in avoiding the production of HBr, although use its for the deprotection of MOM ethers has not been reported. Herewith, we wish to report the efficient and selective deprotecting method for MOM ethers.

Our study started with 4-nitrophenolic MOM ether as a test substrate (Scheme 1), in order to find the best reaction conditions, several reaction parameters had to be optimized (Table 1). A series of solvents including CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, CCl<sub>4</sub>, ClCH<sub>2</sub>CH<sub>2</sub>Cl (DCE), C<sub>6</sub>H<sub>6</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>, THF, and Et<sub>2</sub>O were screened. Although the CHCl<sub>3</sub>, C<sub>6</sub>H<sub>6</sub>, DCE showed just the same good results when used 40% catalyst amount (Table 1, entries 6, 8, 11), but the yields dropped sharply in CHCl<sub>3</sub>, C<sub>6</sub>H<sub>6</sub> when the catalyst loads decreased (Table 1, entries 7, 9). The yield still kept up with 92% in DCE (Table 1, entry 12). And, the best solvent was found to be DCE. The optimum reaction temperature was found to be 40°C. We also found that a catalytic amount of CBr<sub>4</sub> (0.2 equiv.) and PPh<sub>3</sub> (0.2 equiv.) were sufficiently enough for the reaction.

The reaction of deprotection of MOM group did not proceed when used 40% of CBr<sub>4</sub> or PPh<sub>3</sub> independently as catalyst in CH<sub>2</sub>Cl<sub>2</sub> under reflux. After combination of CBr<sub>4</sub> and PPh<sub>3</sub> as catalyst, the reaction proceeded smoothly. With use of only 20% (CBr<sub>4</sub>/PPh<sub>3</sub>) catalyst amount in anhydrous ClCH<sub>2</sub>CH<sub>2</sub>Cl, a yield up to 92% was obtained. And so the possible mechanism and catalytic cycle may be assumed as shown in Scheme 2. We have not obtained more definite evidence to prove it.

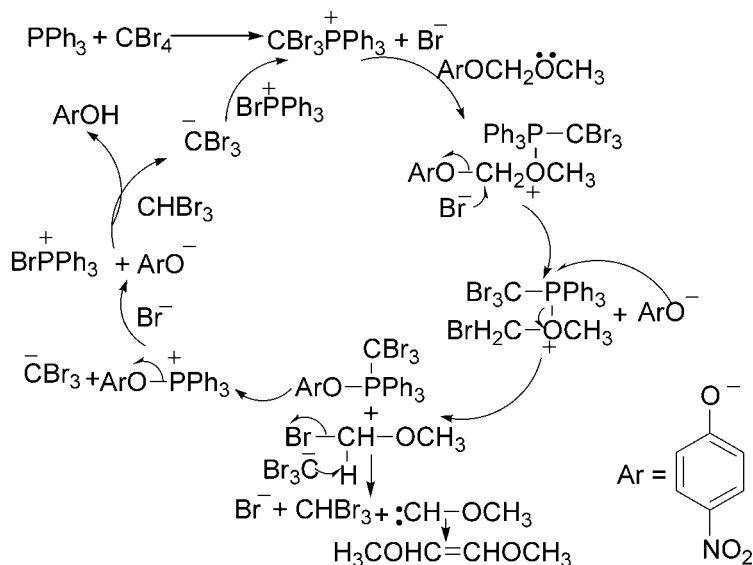


*Scheme 1.*

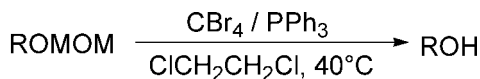
Table 1. The influence of conditions on the reaction.

Entry	Solvent	Catalyst (equiv.)	Temp. (°C)	Yield (%) <sup>a</sup>
1	CH <sub>2</sub> Cl <sub>2</sub>	0.4	40°C	74
2	THF	0.4	40°C	47
3	CCl <sub>4</sub>	0.4	40°C	26
4	Et <sub>2</sub> O	0.4	40°C	56
5	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	0.4	40°C	75
6	CHCl <sub>3</sub>	0.4	40°C	90
7	CHCl <sub>3</sub>	0.1	40°C	32
8	C <sub>6</sub> H <sub>6</sub>	0.4	40°C	98
9	C <sub>6</sub> H <sub>6</sub>	0.2	40°C	19
10	C <sub>6</sub> H <sub>6</sub>	0.1	40°C	4
11	ClCH <sub>2</sub> CH <sub>2</sub> Cl	0.4	40°C	93
12	ClCH <sub>2</sub> CH <sub>2</sub> Cl	0.2	40°C	92
13	ClCH <sub>2</sub> CH <sub>2</sub> Cl	0.15	40°C	74
14	ClCH <sub>2</sub> CH <sub>2</sub> Cl	0.1	40°C	58
15	ClCH <sub>2</sub> CH <sub>2</sub> Cl	0.2	25°C	65

<sup>a</sup>The yields were determined after chromatographic purification.

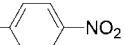
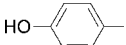
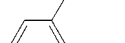
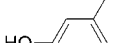
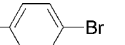
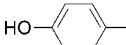
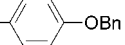
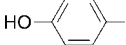
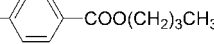
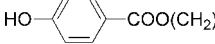
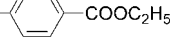
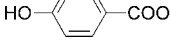
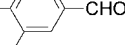
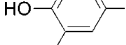
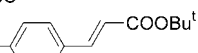
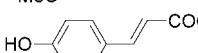
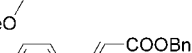
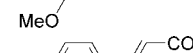


Scheme 2.

*Scheme 3.*

To further explore the potential of this catalyst system, we examined the selective removal of MOM group from other substrates in the presence of various functional groups under the optimized condition (Scheme 3). MOM ethers were cleaved selectively. The results are summarized in Table 2. The deprotection proceeds smoothly by treatment of the ethers with 20% catalyst loads in  $\text{CH}_2\text{ClCH}_2\text{Cl}$  at  $40^\circ\text{C}$ . A series of MOM ethers were deprotected to their corresponding phenols with high yields (90–99%), Table 2 (entries 1–9). The functional groups, just as esters, methyl and benzyl

**Table 2.** Cleavage of MOM ethers by  $\text{CBr}_4/\text{PPh}_3$ .

Entry	Substrate	Product	Yield (%) <sup>a</sup>
1	MOMO-  -NO <sub>2</sub>	HO-  -NO <sub>2</sub>	92
2	MOMO-  -	HO-  -	92
3	MOMO-  -Br	HO-  -Br	91
4	MOMO-  -OBn	HO-  -OBn	90
5	MOMO-  -COO(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	HO-  -COO(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	91
6	MOMO-  -COOC <sub>2</sub> H <sub>5</sub>	HO-  -COOC <sub>2</sub> H <sub>5</sub>	94
7	MOMO-  -CHO	HO-  -CHO	97
8	MOMO-  -COOBu <sup>t</sup>	HO-  -COOBu <sup>t</sup>	99
9	MOMO-  -COOBn	HO-  -COOBn	96

<sup>a</sup>The yields were determined after chromatographic purification.

ethers were found to be stable under the conditions (entries 4, 5, 6, 7, 8, 9). Excellent chemoselectivity was also observed in the presence of aldehyde and *t*-Bu ester groups (entries 7, 8). It is well known that the combination of CBr<sub>4</sub> and PPh<sub>3</sub> is the olefinic reagent of aldehyde. In this system, no olefin was observed. It is indicated that the reaction of CBr<sub>4</sub> and PPh<sub>3</sub> with aldehyde was suppressed. This method is also compatible with other function groups, just as are the nitro and olefin groups (entries 1, 8, 9).

The procedure for deprotection of the MOM group is simple. A mixture of MOM ether (0.5 mmol), CBr<sub>4</sub> (0.1 mmol), and PPh<sub>3</sub> (0.1 mmol) in anhydrous CH<sub>2</sub>ClCH<sub>2</sub>Cl (2.5 mL) was heated at 40°C for an appropriate time to complete the reaction. After complete conversion as monitored by TLC, the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether.

In conclusion, we set up a mild and efficient method for the selective removal of MOM ether group in the presence of other protective groups using CBr<sub>4</sub> and PPh<sub>3</sub> in an aprotic solvent (CH<sub>2</sub>ClCH<sub>2</sub>Cl) at 40°C. The adopted procedure is simple, inexpensive, and high yield that makes it a useful addition to the existing methods.

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