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A facile chemoselective deprotection of the *p*-methoxybenzyl group

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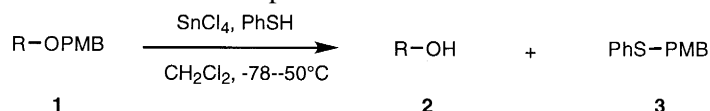
Abstract

The *p*-methoxybenzyl (PMB) group can be chemoselectively cleaved at low temperature in the presence of SnCl₄ and thiophenol. This method is especially useful in the cases where oxidative reagents such as DDQ and CAN need to be avoided. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: *p*-methoxybenzyl group; thioglycosides; orthoganol deprotection.

The *p*-methoxybenzyl (PMB) group is a very useful protecting group and has been employed widely in the synthesis of complex natural products and carbohydrate chemistry.¹ Its utility lies in the fact that it is more readily cleaved oxidatively than unsubstituted benzyl ethers. The oxidants that are used most frequently are 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)² and ceric ammonium nitrate (CAN).³ One problem associated with these oxidative conditions is that other moieties, such as thio groups can also be easily oxidized in the presence of DDQ or CAN. To solve this problem, many other deprotection methods have been developed.¹ One attractive strategy employs the combination of a Lewis acid and a soft nucleophile to remove the PMB group chemo-selectively.⁴ However, these methods often suffer from slow reaction rates and low yields.

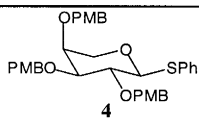
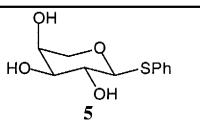
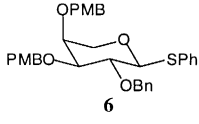
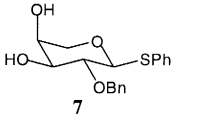
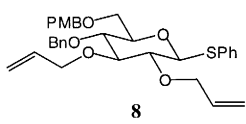
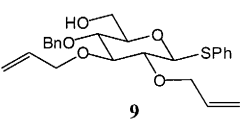
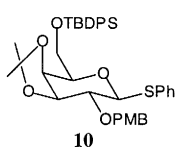
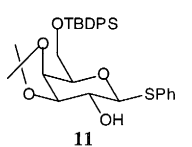
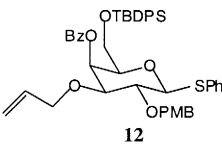
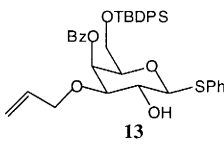
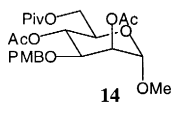
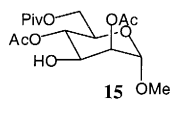
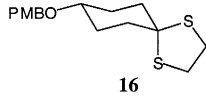
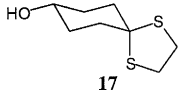
It has been reported that SnCl₄ is an efficient reagent for the selective deprotection of the PMB group in carbohydrates.⁵ However, thioglycosides failed to react with SnCl₄ under the reported conditions.⁵ We have discovered that the combination of SnCl₄/PhSH was able to cleave the PMB group in carbohydrates including thioglycosides in a highly chemo- and regioselective manner at low temperature. The reaction was quite clean and fast and the yields were uniformly superb. Furthermore, a variety of functionalities and protecting groups were found to be compatible with these mild reaction conditions.



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The results of cleavage of the PMB group in various substrates under our conditions are summarized in Table 1. Three PMB groups of compound **1** were removed under our conditions at -78°C in 5 minutes (entry 1) and the yield was excellent. Two PMB groups were successfully chemoselectively cleaved in the presence of a benzyl group (entry 2). Many other protecting groups including allyl, acetonide, *t*-butyldiphenylsilyl (TBDPS), esters, and acetal remained intact under the reaction conditions (entries 3–6). Chemoselective deprotection of the PMB group in the presence of 1,3-dithiolane was also possible (entry 7).

Table 1
Selective cleavage of *p*-methoxybenzyl (PMB) ethers

Entry	Substrates ^{a, c}	Conditions ^b	Products ^c	Yield ^d
1		SnCl ₄ (3.1 equiv) PhSH (3.6 equiv) -78°C , 5 min		90%
2		SnCl ₄ (2.1 equiv) PhSH (2.4 equiv) -78°C , 5 min		91%
3		SnCl ₄ (1.05 equiv) PhSH (1.2 equiv) -78°C – -50°C 1 h		93%
4		SnCl ₄ (1.05 equiv) PhSH (1.2 equiv) -78°C , 5 min		88%
5		SnCl ₄ (1.05 equiv) PhSH (1.2 equiv) -78°C – -50°C 1 h		91%
6		SnCl ₄ (1.05 equiv) PhSH (1.2 equiv) -78°C – -50°C 1 h		94%
7		SnCl ₄ (1.05 equiv) PhSH (1.2 equiv) -78°C , 5 min		92%

^a *p*-Methoxybenzyl ethers were prepared by conventional methods. ^b The reaction solvent is CH₂Cl₂. ^c All products were fully characterized by ¹H NMR, ¹³C NMR, and HRMS. ^d Isolated yields.

A typical procedure used in the above deprotection reactions follows: To a solution of *p*-methoxybenzyl ether (1.0 equiv.) and thiophenol (1.2 equiv.) in anhydrous CH₂Cl₂ at -78°C was added SnCl₄ (1.05 equiv.) under nitrogen. The resulting mixture was stirred at -78°C, and the reaction was monitored by TLC. In some cases (entries 3, 5, and 6) prolonged reaction times and higher temperatures were required. After the reaction was complete, aqueous NaHCO₃ was added, and the reaction mixture was extracted with CH₂Cl₂ three times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and concentrated by rotary evaporation. The product was purified by flash column chromatography.

In conclusion, we have developed a highly efficient and chemoselective reaction for the deprotection of the PMB group. Our method is particularly useful in the cases where oxidative reagents such as DDQ and CAN need to be avoided. Compared to SnCl₄ conditions,⁵ the combination of SnCl₄/PhSH has shown the same substituent tolerance, but has demonstrated its distinctive advantage in thioglycosides. This method should provide a new orthogonal deprotection approach for the removal of the PMB group in carbohydrates and other complex molecules.

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