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p-Methoxybenzyl Ether Cleavage by Polymer-Supported Sulfonamides

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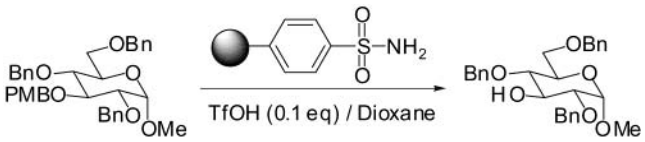
ABSTRACT



***p*-Methoxybenzyl ethers have been found to transfer from alcohols to sulfonamides in the presence of catalytic trifluoromethanesulfonic acid. This process for protecting group removal can be performed in solution with yields >94%. Through the use of sulfonamide-functionalized ("safety-catch") resins, *p*-methoxybenzyl ethers can be cleaved in excellent yields with minimal purification.**

The *p*-methoxybenzyl (PMB) protecting group is used widely. Its utility stems, in part, from its propensity to undergo cleavage under conditions orthogonal to those employed for benzyl group removal. PMB groups are generally removed through the use of oxidizing agents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ceric ammonium nitrate (CAN).[1] PMB groups may also be cleaved in the presence of strong acids, but they are stable to many acidic conditions.[2] For example, PMB ethers are used as protecting groups in many glycosylation reactions promoted by catalytic acids.[3] Consequently, we were surprised to observe quantitative removal of a PMB ether group during the attempted glycosylation of **1**, in which catalytic trifluoromethanesulfonic acid (TfOH)[4] was employed as a promoter (Figure 1). Upon isolation of the byproducts, it was found that the PMB group had been transferred to the sulfonamide intermediate to yield **3** in 94%. We hypothesized

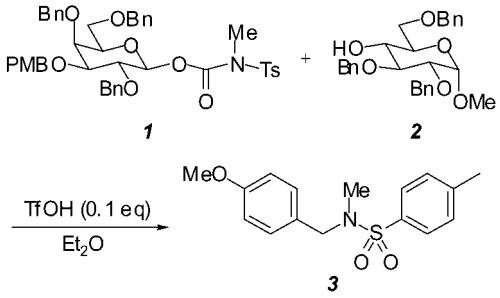


Figure 1. Initial observation of PMB ether cleavage in the presence of catalytic triflic acid.

that this process might constitute a new method for the selective removal of PMB ethers.

To determine if the process is general, compound **4**[5] was treated with 0.1 equiv of TfOH in the presence of *N*-methyl-

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(1) (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999. (b) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885−888. (c) Classon, B.; Garegg, P. J.; Samuelsson, B. *Acta Chem. Scand., Ser. B* **1984**, *B38*, 419−422.

(2) (a) Hodgetts, K. J.; Wallace, T. W. *Synth. Commun.* **1994**, *24*, 1151−1155. (b) Jenkins, D. J.; Riley, A. M.; Potter, B. V. L. *J. Org. Chem.* **1996**, *61*, 7719−7726. (c) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524. (d) De Medeiros, E. F.; Herbert, J. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2725.

(3) For examples, see: (a) Sanders, W. J.; Manning, D. D.; Koeller, K. M.; Kiessling, L. L. *Tetrahedron* **1997**, *53*, 16391−16422. (b) Zhang, Z.; Ollmann, I.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (c) Morales, J.; Zurita, D.; Penades, S. *J. Org. Chem.* **1998**, *63*, 9212−9222.

(4) Hinklin, R. J.; Kiessling, L. L. *J. Am. Chem. Soc.* **2001**, *123*, 3379−3380.

(5) Sharma, G. V. M.; Mahahngam, A. K. *J. Org. Chem.* **1999**, *64*, 8943−8944.

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p-toluenesulfonamide (**5**)[6] (Figure 2). Complete removal of the PMB group was observed, and sulfonamide **3** and menthol (**6**) were generated. Importantly, PMB removal was

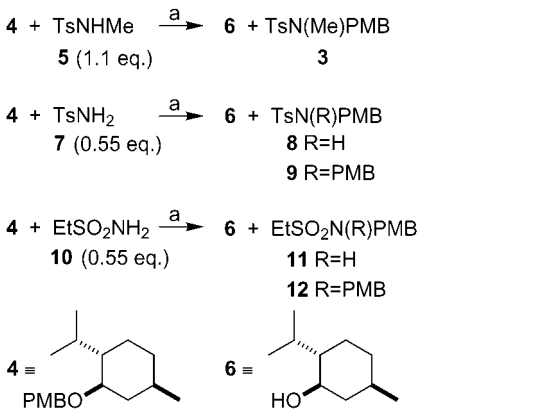


Figure 2. The effect of sulfonamide structure on the deprotection of PMB ether **4**. (a) 0.1 equiv of TfOH in Et_2O.

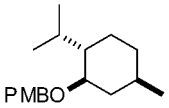
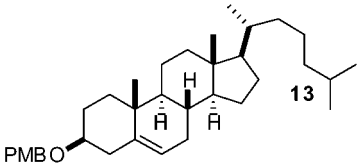
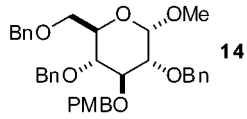
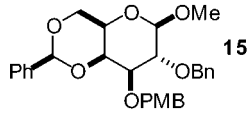
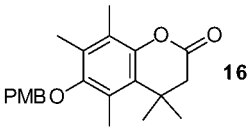
not observed when sulfonamide **5** was omitted from the reaction. Silver triflate also promoted PMB group cleavage; however, >1 equiv was required to obtain cleavage kinetics similar to those observed with 0.1 equiv of triflic acid. Attempts to effect PMB removal using weaker acids[2] have not been successful.

With this initial success, we explored the effect of sulfonamide structure on the reaction. A primary sulfonamide was tested in place of **5** to determine whether two PMB groups could be transferred to one sulfonamide. The reaction of **4** in the presence of 0.1 equiv of TfOH with 0.55 equiv of *p*-toluenesulfonamide (**7**) resulted in complete removal of the PMB group. Two sulfonamide byproducts (**8** and **9**) were generated. The utility of an alkyl sulfonamide, ethanesulfonamide (**10**), also was explored. It, too, was effective, generating **6** in high yield along with the expected sulfonamides **11** and **12**. The rate of the reaction with the more nucleophilic alkyl sulfonamide was not enhanced significantly; consequently, we employed aryl sulfonamides in subsequent studies.

The scope of the deprotection process was evaluated using several PMB ethers, **13**−**16**[7] (Table 1). These were generated from the corresponding alcohols via standard transformations. Compounds **4**, **13**, and **14** all can be cleaved to afford very high isolated yields of the product alcohols (Table 1). Most reactions can be performed with the commercially available *p*-toluenesulfonamide **7**. When the *N*-methyl derivative **5** is the acceptor, however, chromatographic separation is more facile because only one sulfonamide is produced (**3** vs. **8** and **9**).

(6) Townsend, C. A.; Theis, A. B. *J. Org. Chem.* **1980**, *45*, 1697−1699.
(7) (a) Mulard, L. A.; Kovac, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1994**, *251*, 213−232. (b) Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Vijaykumar, D. *J. Org. Chem.* **1995**, *60*, 5961−5962. (c) Wennerberg, J.; Olofsson, C.; Frejd, T. *J. Org. Chem.* **1998**, *63*, 3595−3598.

Table 1. Deprotection of PMB Ethers Using Catalytic TfOH in the Presence of a Sulfonamide[a]

substrate		% yield
	**4**	95
	**13**	98
	**14**	97
	**15**	<10[b] 94[c]
	**16**	97

[a] 0.1 M substrate in Et_2O, 0.55 equiv of $TsNH_2$ and 0.1 equiv of TfOH. [b] Low yield due to formation of TsN=CHAr. [c] 1.1 equiv of TsNHMe instead of $TsNH_2$.

Sulfonamide substitution also can influence the outcome of the deprotection reaction for some substrates. For example, treatment of benzylidene acetal **15** with tosylsulfonamide (**7**) and TfOH resulted in a mixture of products; the desired alcohol was produced in very low yield (<10%). Under these conditions, the benzylidene acetal is labile, and competitive sulfonimine formation occurs.[8] In contrast, when secondary sulfonamide **5** was employed, compound **15** was transformed into the desired alcohol in high yield (94%). The use of the secondary sulfonamide eliminates the possibility of sulfonimine formation, thereby allowing for PMB group release from substrates that contain acid-sensitive functional groups.

The method we have developed for PMB ether cleavage is complementary to others. For example, it can be applied to substrates sensitive to oxidation, as the reaction of compound **16** illustrates (Table 1). Hydroquinone derivatives are oxidized by either DDQ or CAN; treatment of **16** with CAN yielded the quinone product exclusively.[9] In contrast, the reaction of **16** in the presence of $TsNH_2$ and TfOH afforded the phenol in high yield. No unwanted quinone byproducts were observed.

A key objective to be met in the development of new methods is to streamline product isolation and purification.[10] To this end, solid-supported reagents and scavenging resins are valuable. Our finding that sulfonamide groups can

(8) Wunsch, B.; Nerdinger, S. *Chem. Lett.* **1998**, 799−800.
(9) Amsberry, K. L.; Borchardt, R. T. *Pharm. Res.* **1991**, *8*, 323−330.

function as scavengers in PMB ether cleavage reactions prompted us to examine the utility of immobilized sulfonamides. Sulfonamide-functionalized resins are used widely in solid-phase organic synthesis.[11] We envisioned that these could facilitate PMB ether removal by trapping the PMB cation (Figure 3). Purification of the desired alcohol would

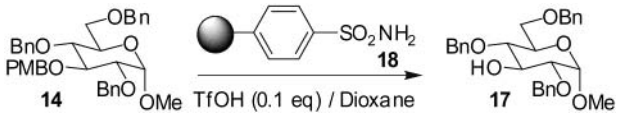


Figure 3. Example illustrating the strategy for PMB ether removal using safety-catch resins as scavengers.

involve neutralization of the triflic acid and filtration.

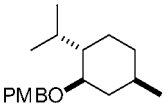
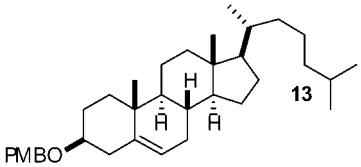
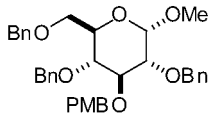
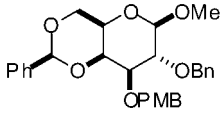
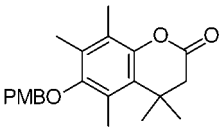
PMB ether cleavage occurred with a resin-bound sulfonamide group under conditions similar to those used for reactions in solution. The yield, however, was optimal when dioxane solvent was used instead of diethyl ether. Because the commercially available resins contain primary sulfonamide groups, only 0.5 equiv of resin is required, in principle. The loading levels can vary, however, and some reaction sites may be inaccessible; consequently, 0.7 equiv was used. These conditions gave reproducible results. After the mixture was neutralized, filtered, and concentrated, the desired alcohol could be recovered in high yield and purity without chromatography (Table 2). As anticipated, when substrate **15** was treated with resin **18** competitive sulfonimine formation led to low yields (<10%) of the target alcohol (Table 2, entry 4). The use of an immobilized secondary sulfonamide should circumvent this difficulty.

A typical procedure for the deprotection of PMB ethers using safety-catch resin **18** has been developed. The resin **18** (0.07 mmol) is allowed to swell in 1 mL of dioxane, 0.01 mmol of TfOH is added, and the mixture is agitated. The resin is filtered, rinsed with dioxane, and resuspended in 1 mL of dioxane. The PMB ether (0.1 mmol) is added, followed by TfOH (0.01 mmol). After 4−6 h, the reaction is quenched by the addition of aqueous sodium bicarbonate. The mixture is filtered through a small plug of silica gel to remove water and salts, and the resulting solution is concentrated. This procedure affords the desired alcohols in excellent yields.

(10) For a review, see: (a) Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213−1224. For recent examples, see: (b) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193−7196. (c) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, W. *J. Am. Chem. Soc.* **1997**, *119*, 4874−4881. (d) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886.

(11) (a) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055−3056. (b) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *Chem. Commun.* **1971**, 636−637.

Table 2. Deprotection of Various PMB Ethers in the Presence of Sulfonamide-Substituted Resins

substrate		% yield
	**4**	64[b]
	**13**	98
	**14**	95
	**15**	<10[c]
	**16**	97

[a] 0.1 M substrate in dioxane, 0.7 equiv of *p*-toluenesulfonamide safety-catch resin and 0.1 equiv of TfOH. [b] Reduced yield due to volatility of product. [c] Low yield due to competitive sulfonimine formation.

Our studies demonstrate that sulfonamides function as excellent scavengers in the acid-catalyzed cleavage of PMB ethers. Additionally, commercially available safety-catch resins can be used to effect PMB protecting group removal to afford target alcohols in high yields with minimal purification. This protocol is convenient, and it can be used with substrates sensitive to oxidation. Finally, our studies suggest that sulfonamide-containing compounds, either in solution or immobilized, may act to effectively capture carbocation byproducts in a wide range of reactions.

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Supporting Information Available: Experimental procedures and NMR spectral data of aromatic and aliphatic sulfonamide products (**3**, **8**, **9**, **11**, and **12**). This material is available free of charge via the Internet at http://pubs.acs.org.

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