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A mild method for the protection of alcohols using a *para*-methoxybenzylthio tetrazole (PMB-ST) under dual acid–base activation

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ABSTRACT

With a view to expand the repertoire of chemoselective methods applicable to sensitive and multifunctional substrates, the *p*-methoxybenzylation of alcohols under essentially neutral conditions is reported. This was achieved by the silver triflate (AgOTf) activation of 5-(*p*-methoxybenzylthio)-1-phenyl-1*H*-tetrazole (PMB-ST) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP).

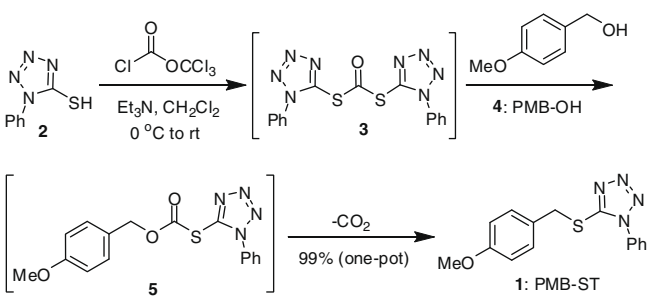
The majority of organic chemists would appreciate making multifunctional molecules without the need for any protecting groups.[1] Yet most complex molecules are only accessible in a practical fashion with the assistance of protecting groups. Typically, a protection–deprotection strategy will influence the length, efficiency[2] and even the success[3] of a synthesis. As a consequence, a plethora of protecting group reagents and deprotection methods has been deployed for a wide range of functionalities.[4]

In a chemoselective context, new methods to introduce protecting groups are just as important as methods to remove protecting groups. This is particularly true when modulating the reactivity and stability of advanced intermediates during the developmental stages of a synthesis. Indeed, subtle changes in the chosen protecting groups, stemming from steric, electronic and anchimeric effects, can often control the efficiency or even the success of a key step. New methods should therefore be compatible with a multitude of sensitive functionality. Ideally, these methods should also meet the challenging demands (steric or electronic) presented by advanced intermediates, particularly in complex total synthesis.[1–3,5]

The *para*-methoxybenzyl (PMB) ether is a frequently employed hydroxy-protecting group in organic synthesis, which offers modular lability[3,6] over benzyl (Bn) and 2-naphthyl (NAP) ethers, for example, by using DDQ, CAN or TFA.[7] The introduction of PMB ethers can, however, be problematic under basic conditions (NaH, DMF, PMB-halide) or acidic conditions ($BF_3{\cdot}Et_2O$, CSA, TfOH, PMB-trichloroacetimidate).[8] Noteworthy recent advances in arylmethyl etherification have been developed by the Dudley group, for example, the benzyl (Bn) or PMB protection of alcohols by pyridinium-derived reagents.[9]

In 1999, Hanessian and Huynh reported *p*-methoxybenzyl-2-pyridyl thiocarbonate (PMB-TOPCAT),[10] a reagent that provides PMB ethers upon reacting alcohols in the presence of silver triflate (AgOTf). In the same year, Marcune et al. reported a methoxymethyl (MOM) 2-pyridyl thioether[11] for the MOM protection of alcohols in conjunction with AgOTf and NaOAc. Inspired by these reports and the success of our Ag(I)-activation of 2-deoxythioglycosides in a complex total synthesis setting,[12,13] we report herein a new thiotetrazole-based system to transfer PMB groups onto alcohols in a mild fashion. Notably, we demonstrate the virtues of the complementary activation of both the electrophile and the nucleophile by combining compatible Lewis acids with non-nucleophilic Brønsted bases.

We initially targeted the PMB-thiocarbonyl tetrazole **5** akin to Hanessian's PMB-TOPCAT reagent (Scheme 1).[10] Although the thiocarbonate **5** was too unstable to be investigated systematically, it conveniently underwent decarboxylation to a new PMB-transfer reagent, 5-(*p*-methoxybenzylthio)-1-phenyl-1*H*-tetrazole (PMB-ST, **1**).[14] By modification of reported procedures,[15] the PMB-ST reagent **1** could be prepared quantitatively in one-pot.[16] Diphosgene was first reacted with 1-phenyl-1*H*-tetrazole-5-thiol (**2**) to give the *S*,*S*′-bis(1-phenyl-1*H*-tetrazol-5-yl)dithiocarbonate (**3**). Upon addition of *p*-methoxybenzyl alcohol (**4**), the mono-thiocarbonate that formed **5** decarboxylated spontaneously.[17] The PMB transfer reagent (PMB-ST, **1**) is stable for use in air, at room



Scheme 1. One-pot synthesis of PMB-ST reagent **1**.

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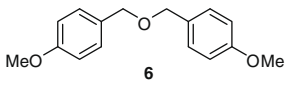
temperature, and can be stored in a refrigerator for several months without decomposition.

In order to design functional group tolerance in our reagent system, we envisaged the concerted action of a compatible Lewis acid/Brønsted base pairing, the concept being to both activate the thioether (in **1**) and facilitate deprotonation of the alcohol.[18] We further selected 1-phenyl-1*H*-tetrazole thiol **2** for two reasons: its leaving group potential and its lack of odour.[17,19] Table 1 shows an optimization study for the PMB protection of cyclohexanol by using AgOTf/DTBMP. Equimolar amounts of PMB-ST **1** and AgOTf were found optimal (entries 2 and 3). The presence of at least one equivalent of DTBMP was found to be essential in achieving a good yield (entries 1, 3, 7 and 8). Trace amounts of water were removed with activated molecular sieves (4 Å MS), which improved the yields and minimized the generation of the bis-PMB ether **6**.



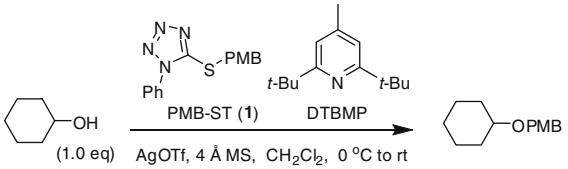
6

Amongst the various thiophilic activators and solvents evaluated (Table 2), silver triflate (AgOTf) and dichloromethane gave optimal results (entry 2). The use of highly polar solvents such as acetonitrile (entry 9) and dimethylformamide (Table 2, entry 10) gave no reaction or only a trace amount of product. α,α,α-Trifluorotoluene was found to be inferior as a substitute for dichloromethane (entry 11).

Under the established protocol,[20] primary, secondary, tertiary, phenolic and propargylic alcohols were found to give the corresponding PMB ethers in moderate to good yields (Table 3). Both acid and base labile functionalities were tolerated (entries 3, 4 and 6–11); for example, the successful PMB protection of the acid/base-sensitive[21] β-hydroxy silane (entry 11) is noteworthy (the yield reflects the purity of the starting material). Neither α-epimerization nor β-elimination was observed after *p*-methoxybenzylation of the Roche ester, as indicated by chiral HPLC analysis (entry 15).

Interestingly, the regioselective protection of a diol functionality within carbohydrates could be addressed with this procedure; for example, allyl-4,6-*O*-benzylidene-α-D-mannopyranoside and allyl-2,3-di-*O*-carbonyl-α-D-mannopyranoside (entries 12 and 13)

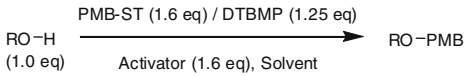
Table 1
Optimization of PMB-etherification with PMB-ST **1**



Entry	PMB-ST (equiv)	AgOTf[a] (equiv)	DTBMP (equiv)	Yield[b] (%)
1	1.2	1.5	—	N.R.[c]
2	1.4	1.6	1.25	75
3	1.6	1.6	1.25	89
4	2.0	2.0	1.25	79
5	1.6	1.6	2.0	72
6	1.6	1.6	1.5	74
7	1.6	1.6	1.0	77
8	1.6	1.6	0.5	43

[a] Activator added at 0 °C, then reaction mixture was allowed to warm to rt over 12 h. Reagents are relative to 1 equiv of the alcohol.
[b] Isolated yields. Unreacted alcohol was fully recovered.
[c] No reaction.

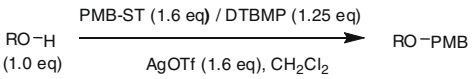
Table 2
Thiophilic activator and solvent screening



Entry	Activator	Solvent	Time[a] (h)	Yield[b] (%)
1	$AgPF_6$	CH_2Cl_2	4	68
2	AgOTf	CH_2Cl_2	4	89
3	$AgBF_4$	CH_2Cl_2	12	43
4	$AgSbF_6$	CH_2Cl_2	12	41
5	CuOTf	CH_2Cl_2	12	65
6	$ZnCl_2$	CH_2Cl_2	12	N.R.[c]
7	AgOTf	THF	12	35
8	AgOTf	$ClCH_2CH_2Cl$	12	30
9	AgOTf	CH_3CN	12	N.R.
10	AgOTf	DMF	12	Trace
11	AgOTf	CF_3Ph	12	38

[a] Activator added at 0 °C, then reaction mixture was allowed to warm to rt. Reagents are relative to 1 equiv of the alcohol.
[b] Isolated yields. Unreacted alcohol was fully recovered.
[c] No reaction.

Table 3
PMB-protection of alcohols (ROH) with PMB-ST **1**



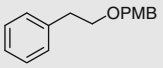
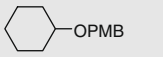
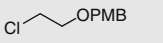
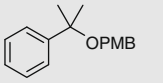
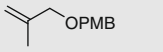
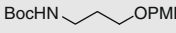
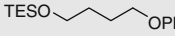
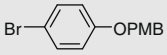
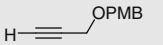
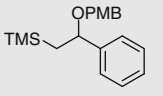
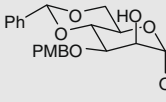
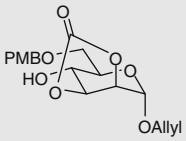
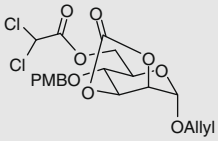
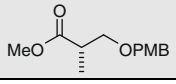
Entry[a]	ROPMB	Yield[b] (%)
1		89
2		89
3		78
4		73
5		65
6		71
7		76
8		55
9		61
10		60
11		23
12		57

Table 3 (*continued*)

Entry[a]	ROPMB	Yield[b] (%)
13		80
14		55
15		56

[a] Activator added at 0 °C, then reaction mixture was allowed to warm to rt over 4–12 h. Reagents are relative to 1 equiv of the alcohol.

[b] Isolated yields. Although yields were not optimized for each case, all unreacted alcohols were fully recovered.

gave the mono *p*-methoxybenzylated products at the 3- and 6-positions, respectively. Although this selectivity is similar to methods that employ dibutyltin oxide, the PMB-ST system is less toxic.[22] Lastly, PMB-ST **1** shows advantages over PMB-TOPCAT[10] in terms of its stability and leaving group potential, typically giving maximum yields within 24 h.

In summary, we report the synthesis and utility of 5-(*p*-methoxybenzylthio)-1-phenyl-1*H*-tetrazole (PMB-ST, **1**) as a new reagent for PMB etherification. The functional group tolerance of the reagent system was studied over a range of alcohols. Even sensitive substrates and functionality survived the PMB-ST/AgOTf/DTBMP conditions, thereby allowing full recovery of precious starting material. We thus envisage this reagent system to find utility in the PMB protection of advanced, multifunctional substrates. Improvements and application to other protecting modalities, such as to the NAP, MOM, benzyl and allyl ethers and carbonates, are ongoing.

Acknowledgements

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Supplementary data

Supplementary data (experimental procedures, characterization data and NMR spectra of selected compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.020.

References and notes

1. (a) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193; (b) Gudmundsdottir, A. V.; Nitz, M. *Org. Lett.* **2008**, *10*, 3461; (c) Lainchbury, M. D.; Medley, M. I.; Taylor, P. M.; Hirst, P.; Dohle, W.; Booker-Milburn, K. I. *J. Org. Chem.* **2008**, *73*, 6497; (d) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404; (e) McFadden, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 7738; (f) Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Org. Lett.* **2005**, *7*, 1327.
2. (a) Hoffmann, R. W. *Synthesis* **2006**, *21*, 3531–3541; (b) Schelhaas, M.; Waldmann, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2056.
3. Choice of NAP-protection versus benzyl ethers: Inoue, M.; Uehara, H.; Maruyama, M.; Hirama, M. *Org. Lett.* **2002**, *4*, 4551.
4. (a) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley and Sons: New York, 2006; (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2005.
5. (a) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199; (b) Sharma, G. V. M.; Mahalingam, A. K. *J. Org. Chem.* **1999**, *64*, 8943.
6. (a) Wright, J. A.; Yu, J. Q.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033; (b) Plante, O. J.; Buchwald, S. L.; Seeberger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148.
7. Yan, L.; Kahne, D. *Synlett* **1995**, 523.
8. (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885; (b) Marco, J. L.; Huesorodriguez, J. A. *Tetrahedron Lett.* **1988**, *29*, 2459; (c) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
9. (a) Lopez, S. S.; Dudley, G. B. *Beilstein J. Org. Chem.* **2008**, *4*. doi:10.3762/bjoc.4.44; (b) Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436; (c) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923.
10. Hanessian, S.; Huynh, H. K. *Tetrahedron Lett.* **1999**, *40*, 671.
11. Marcune, B. F.; Karady, S.; Dolling, U. H.; Novak, T. J. *J. Org. Chem.* **1999**, *64*, 2446.
12. Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 946.
13. Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 5381.
14. In our hands, PMB-TOPCAT was found to be unstable and decarboxylated to 2-pyridyl thioethers akin to PMB-ST (**1**), which were found unreactive to mild activation methods such as AgOTf/DTBMP.
15. (a) Lee, J. I.; Park, H. *Bull. Korean Chem. Soc.* **2001**, *22*, 421; (b) Takeda, K.; Tsuboyama, K.; Takayanagi, H.; Shirokami, R.; Takeura, M.; Ogura, H. *Chem. Pharm. Bull.* **1989**, *37*, 2334; (c) (c) One-pot preparation of 5-(*p*-methoxybenzylthio)-1-phenyl-1*H*-tetrazole (**1**): Trichloromethyl chloroformate (0.6 ml, 5.00 mmol) was added dropwise to a solution of 1-phenyl-1*H*-tetrazole-5-thiol (3.6 g, 20.00 mmol) and triethylamine (3.1 ml, 22.50 mmol) in freshly distilled dichloromethane (40 ml) at 0 °C. The reaction mixture was allowed to warm up to room temperature slowly and left to stir overnight. The reaction mixture was cooled to 0 °C and *p*-methoxybenzyl alcohol (0.9 ml, 7.50 mmol) and triethylamine (3.1 ml, 22.50 mmol) were added. The reaction mixture was allowed to warm up slowly to room temperature and left to stir overnight. The reaction mixture was evaporated to dryness in vacuo, followed by precipitation from ethyl acetate. The suspension obtained was filtered through Celite and the filtrate was evaporated to dryness in vacuo. The crude product was purified by silica gel column chromatography using *n*-hexane/EtOAc (16:1) as eluent to give 5-(*p*-methoxybenzylthio)-1-phenyl-1*H*-tetrazole (2.2 g, 99%). R_f = 0.30 (hexane/EtOAc 4:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (5H, m), 7.34 (2H, d, J = 8.7 Hz), 6.84 (2H, d, J = 8.8 Hz), 4.59 (2H, s), 3.79 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.48, 153.97, 133.64, 130.50, 129.70, 127.07, 123.77, 114.20, 55.27, 37.30; MS-EI [M^+] calcd for $C_{15}H_{14}N_4OS$: 298.0888, found 298.0893.
16. PMB-ST **1** can also prepared by reacting 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions (with PMB-OH) or by halide displacement (with PMB-Cl); see Supplementary data.
17. For a proposed mechanism of decarboxylation, see: Tsuboyama, K.; Takeda, K.; Torii, K.; Ebihara, M.; Shimizu, J.; Suzuki, A.; Sato, N.; Furuhata, K.; Ogura, H. *Chem. Pharm. Bull.* **1990**, *38*, 636.
18. The dual action of both 'soft' Lewis acids or 'π-acids' and 'hard' Brønsted bases are gaining importance: (a) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5703; (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180; (c) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.
19. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
20. *General protocol for the p-methoxybenzylation of alcohols*: A solution of 5-(*p*-methoxybenzylthio)-1-phenyl-1*H*-tetrazole (PMB-ST, 0.095 g, 0.32 mmol, 1.60 equiv) and DTBMP (0.05 g, 0.25 mmol, 1.25 equiv) in freshly distilled anhydrous dichloromethane (1.5 ml) was added to the alcohol (0.20 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C and transferred to a solution of silver triflate (0.08 g, 0.32 mmol, 1.60 equiv) in freshly distilled anhydrous dichloromethane (0.5 ml). The mixture was allowed to warm up to room temperature slowly and left to stir overnight. Ethyl acetate was added to the reaction mixture and the suspension obtained was filtered through Celite. The filtrate was evaporated to dryness in vacuo. The crude product was purified by silica gel column chromatography to provide the isolated *O*-PMB product.
21. Ager, D. J. *Org. React.* **1990**, *38*, 1.
22. Wong, C. H.; Ye, X. S.; Zhang, Z. Y. *J. Am. Chem. Soc.* **1998**, *120*, 7137.