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Solution and Solid Phase p-Alkoxybenzylation of Alcohols under Neutral Conditions

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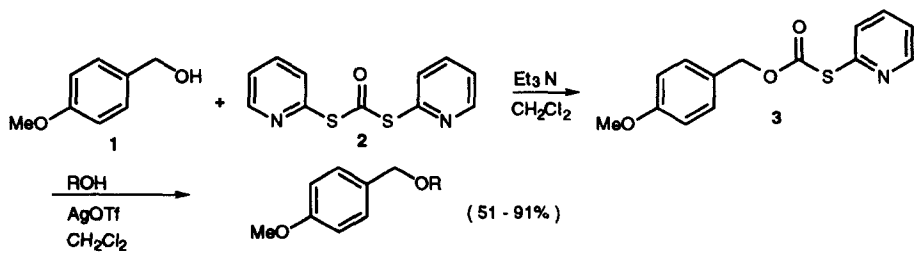
Abstract: Primary, secondary, and tertiary alcohols can be converted to p-methoxybenzyl ethers under neutral conditions in the presence of a variety of commonly used functional and protective groups. The method can be adapted to solid phase on a Wang resin.

Keywords: p-Methoxybenzyl (PMB) ether, pyridylthiocarbonate, solid phase alkylation

p-Methoxybenzyl (PMB) ethers[1] play an important role as protective groups in organic synthesis,[1] especially in oligosaccharide synthesis, in peptide coupling, and in nucleoside chemistry. The versatility of the PMB ether group is reflected in its selective deprotection by oxidative cleavage with DDQ[1,2] in the presence of other compatible protective groups such as benzyl, allyl and silyl ethers for example. Like the benzyl ether group, the PMB group is traditionally introduced under strongly basic conditions[3] (NaH, DMF, benzylic halide) or under protic or Lewis acidic conditions[4] ($BF_3.Et_2O$, PPTS, TfOH, CSA, $TrClO_4$, and benzylic trichloroacetimidate[5]). Especially noteworthy is the compatibility of a variety of functional groups (ester, ketone, silyl ether, sulfonate, etc.) under these reaction conditions.[5]

In this paper, we report the use of the readily prepared 4-methoxybenzyl-2-pyridylthio carbonate **3** (PMB-TOPCAT)[6] as a new reagent to convert alcohols into the corresponding PMB ethers in solution and on solid phase.[7] The particular attributes of the method are that the reaction conditions are neutral, hence the compatibility of a large cross-section of other protective groups and functionalities (Scheme 1).

Scheme 1



As seen from Table 1, yields are excellent for a variety of alcohols, including amino sugar, amino acid and nucleoside derivatives, which have not been studied under Lewis acid/imidate conditions.[5]

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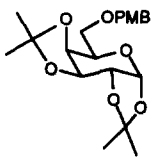
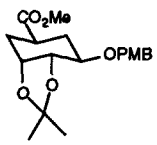
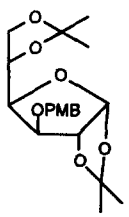
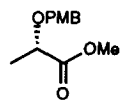
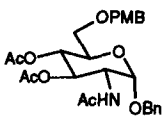
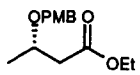
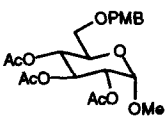
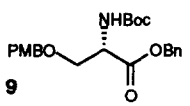
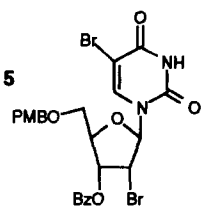
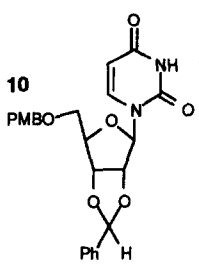
The protection of primary, secondary, and tertiary alcohols takes place under mild conditions and in excellent yields. No *N*-alkylation was observed with amides, carbamates and pyrimidine-type nitrogens (Table 1, entries 3, 8, 9, 10 respectively). Under the conditions of the reaction, no ester migration, β-elimination, or epimerization were observed (Table 1, entries 3, 4, 7, 9 respectively).

Table 1

Alcohol[a]	Time(min.)	Yield(%)[b]	Alcohol[a]	Time(min.)	Yield(%)[b]
1 	30	85	6 	50	70
2 	60	72	7 	40	79
3 	30	92	8 	40	88
4 	30	82	9 	30	83
5 	50	80	10 	50	71

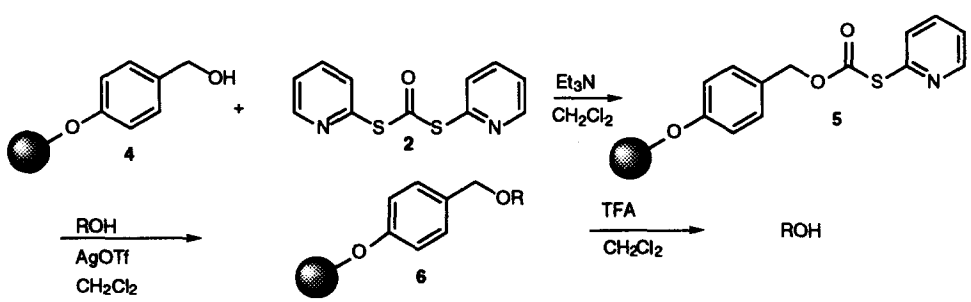
a. Yield of isolated, chromatographically pure product. b. Products compared to authentic samples when Otherwise they were characterized by routine spectroscopic techniques (^1H, ^{13}C, mass).

Preparation of 3. To a solution of p-methoxybenzyl alcohol (7.2 mmol) and di-(2-pyridyl)thiocarbonate (10.9 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (21.7 mmol). The reaction mixture was stirred at room temperature for 7h. The solution was concentrated and purified by flash chromatography on silica gel (hexanes/EtOAc 4:1) to give the desired product **3** (80%) as a yellow liquid which solidifies at 0 °C and can be stored at that temperature for several months without appreciable change; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.56-8.54 ppm (m, 1H), 7.71-7.64 (m, 2H), 7.30-7.27 (m, 2H), 7.24-7.21 (m, 1H), 6.87-6.85 (m, 2H), 5.19 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.2 ppm, 159.8, 151.6, 150.0, 137.2, 130.4, 129.3, 126.7, 123.3, 113.9, 69.4, 55.1.

p-Methoxybenzylation of Alcohols. The alcohol (1 mmol) and **3** (1.5 eq) were dissolved in CH_2Cl_2 (5 mL) at room temperature. Silver triflate (1.5 eq) was added at 0 °C, and stirring was continued at room temperature for 30 minutes to 2 h. After adding 2 drops of pyridine, the suspension was filtered through Celite. The filtrate was concentrated and purified by flash chromatography on silica gel to give the corresponding PMB ether. Yields varied from 70 to 92% (Table 2).

Solid Phase p-Alkoxybenzylation. The method was easily adaptable to solid phase.[8] Thus, treatment of a suspension of the Wang resin with reagent **2** gave the corresponding 2-pyridylthiocarbonate (TOPCAT) resin **4**.[9] (Scheme 2, Table 2). In a typical etherification on solid support, the alcohol (0.26 mmol) was added to a suspension of the resin **4** (100 mg; 0.86 mmol loading capacity) in CH_2Cl_2 and AgOTf (0.26 mmoles) was added in one portion. After 1 to 5 h, the resin was filtered, washed with CH_2Cl_2 pyridine, DMF, DMSO, MeOH, THF, CH_2Cl_2 and dried. Infrared analysis (KBr) showed the absence of a hydroxyl band. Treatment of the resin with aq. 10% v/v TFA in CH_2Cl_2 containing a drop of methanol or water released the alcohol component in excellent yield (Table 2).

Scheme 2

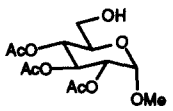
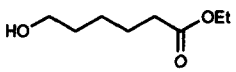
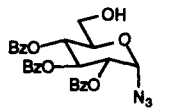
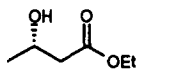
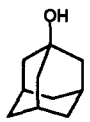
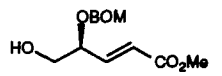


This method complements the previously reported solid phase benzylation of alcohols using the Wang trichloroacetimidate resin in the presence of Lewis acids.[7] The neutral conditions of the presently described protocol presents several advantages, particularly since a variety of functional groups are tolerated.

Although allyl ethers could also be prepared in solution using $Cu(OTf)_2$ as an activator, the yields were only modest and the reaction times longer. In contrast to **4**, benzyl

2-thiopyridyl carbonate was found to be unreactive towards alcohols under the same conditions, presumably because of the absence of a stabilizing p-methoxy group.

Table 2

ROH	Yield(%)[a]	ROH	Yield(%)[a]
	87		96
	80		98
	80		94

a. Yields based on weight of recovered alcohol after acidic cleavage chromatographic purification, and comparision with authentic material

The presently described methods for the solution and solid phase derivatization of alcohols as PMB ethers complement other methods of etherification, under basic and Lewis or protic acidic conditions, and they should further extend the scope and utility of such ethers in organic synthesis.

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[8] a. For examples of O-alkylation on solid phase, see: Moon, H.-S.; Schore, N. E.; Kurth, M.J. *Tetrahedron Lett.* **1994**, *35*, 8915; also, Crowly, T. I.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135 and the references cited therein; b. For polymer-bound tritylation using trityl chloride resin, see for an example: Chan, C.; Randall, L. A. A.; Miller, R. B.; Jones, A. D.; Kurth, M. T. *J. Am. Chem. Soc.*, **1994**, *116*, 2661; also Fyles, T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 435; c. For Mitsunobu attachment of phenols on Wang resin, see: Richter, L.; Cradek, T. R. *Tetrahedron Lett.* **1994**, *35*, 4705; d. For polymer-bound THP ethers using DHP resin, see: Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.
[9] A suspension of the Wang resin (0.8 mmol) in 20 mL CH_2Cl_2, was allowed to swell for 15 min. Et_3N (333 μL; 2.4 mmol) and reagent **2** (595 mg; 2.4 mmol) were added and the suspension was stirred gently for 24h. The resin was filtered, washed with, DMSO, THF, $CHCl_2$, then dried. IR analysis showed the absence of hydroxyl peaks. The TOPCAT resin could be stored as a dry powder at 0° without change.
[10] For diversely substituted benzyl ethers and their cleavage, see, Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172.