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Highly Selective Silver(I) Oxide Mediated Monoprotection of Symmetrical Diols

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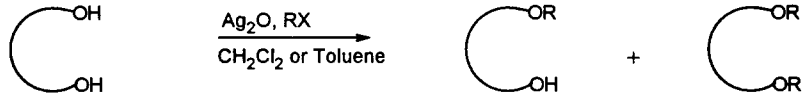
Abstract: Treatment of symmetrical diol with Ag_2O and alkyl halide gave the monoprotected derivative in good to excellent yield.

Symmetrical diols are important synthons in organic synthesis and the selective protection of only one of the two chemically-equivalent hydroxyl groups is often required.[2] Frequently, treatment of these diols with a stoichiometric equivalent of protecting reagent results in the formation of a 1/2/1 mixture of the unreacted diol, the monoprotected and the bisprotected derivative, respectively. In certain cases,[3] this statistical distribution can be overcome by employing a large excess of the starting diol relative to the protecting reagent. This process substantially reduces the amount of diprotected product, but one is then faced with the problem of separating the desired product from the bulk of unreacted diols. McDougal *et al.*[4] have reported a process involving the formation of the corresponding sodio-monoalkoxide, in which subsequent treatment by a silylating reagent delivered the monoprotected derivative in good yields. However low selectivity was observed in the case of secondary alcohols. Recently, Nishiguchi *et al.* have reported monoacetylation[5] and monotetrahydropyranylation[6] of symmetrical 1,n-diol by the means of strongly acidic ion-exchange resin. Other methods[7] using solid phase techniques have also given monoacylated products in good yields.

In this paper, we wish to report a practical methodology for the monoalkylation of symmetrical diol in the presence of silver(I) oxide and alkyl halide. This simple procedure produces monoprotected product in moderate to high yields when stoichiometric equivalents of diol and alkyl halide are used.

Scheme 1

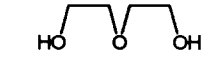
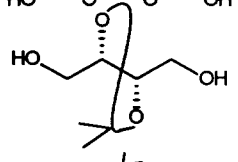
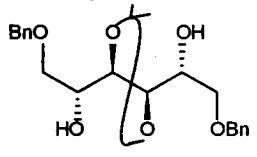
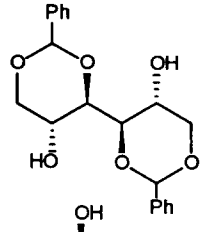
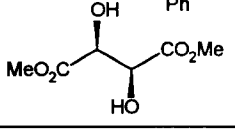


I II III

In connection with a program centered on the preparation of HIV-1 protease inhibitors,[8] we needed an efficient method for the monoprotection of the diol **11**[9] (Table 1) as the corresponding monobenzyl ether. Our preliminary attempts to monobenzylate **11** by NaH in THF, DMF or by phase transfer conditions (aqueous NaOH, BnBr, tetra-*n*-butylammonium bromide) led predominantly to the unwanted dibenzylated product. However, treatment of **11** with freshly prepared Ag_2O[10] (1.5 equiv) and BnBr (1.1 equiv) in toluene afforded the monobenzylated derivative in 93% yield with only 3% of dibenzylated derivative isolated. In an effort to explore the versatility of this reaction, we submitted various symmetrical primary as well as secondary diols to the action of Ag_2O and benzyl bromide. The results are summarized in Table 1. The treatment of commercially available 1,n-primary diols (n = 2-6, 8, 10) (**1-7**) with Ag_2O (1.5 equiv) and BnBr (1.1 equiv) yielded the monobenzyl ethers in moderate to high yields. Dichloromethane was used as solvent because of the low solubility of primary 1,n-diols in toluene. Other solvents such as chloroform, diethyl ether and ethyl acetate also gave satisfactory results. Acetonitrile was an unsuitable solvent that gave decreased rates for the alkylation and favoured the hydrolysis of BnBr to the corresponding benzyl alcohol. Tetrahydrofuran was avoided since ring-opening of THF was catalyzed by Ag_2O.[11] For example, treatment of ethylene glycol with Ag_2O and BnBr in THF gave the expected ether contaminated with the mono- and dibenzyl ethers of 1,4-butanediol. These byproducts were obtained when Ag_2O and BnBr were stirred in

THF in the absence of any diol.

Table 1: Selective monobenzylation of symmetrical diol[a]

n°	HO—R—OH I	Solvent	Time	HO—R—OBn / BnO—R—OBn II[b]	 III[b]
1	Ethylene glycol	CH_2Cl_2	15 h	70%	8%
2	Propane-1,3-diol	CH_2Cl_2	5 h	87%	7%
3	Butane-1,4-diol	CH_2Cl_2	3 h	91%	5%
4	Pentane-1,5-diol	CH_2Cl_2	4 h	89%	8%
5	Hexane-1,6-diol	CH_2Cl_2	4 h	82%	7%
6	Octane-1,8-diol	CH_2Cl_2	15 h	71%	12%[c]
7	Decane-1,10-diol	CH_2Cl_2	15 h	60%	16%[c]
8		CH_2Cl_2	1 h	88%	7%
9		CH_2Cl_2	1 h	90%	5%
10		Toluene	4 h	89%	5%
11[8]		Toluene	15 h	93%	3%
12		Toluene	15 h	92%	3%
13		CH_2Cl_2	15 h	77%	8%[d]

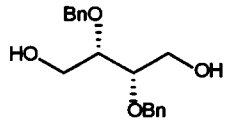
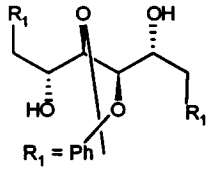
[a] Unless otherwise indicated, all reactions were carried out at RT with 1.1 equiv of BnBr and 1.5 equiv of Ag_2O .

[b] Isolated yield. [c] Not very soluble, 12 to 20% of recovered diol.[d]Catalytic amount of KI was added.

The monobenzylation of the oligoethylene glycols **8** and **9** proceeds much faster than aliphatic diols and gave excellent yields of monoprotected derivatives.[12] In comparison to the McDougal monosilylation method, we found that the monoprotection of symmetrical secondary diols gave better yield and better selectivity, and only traces of dibenzylated product were detected upon treatment of diols **11**[9] and **12** with Ag_2O and BnBr. It is noteworthy that even when the reaction was carried out in the presence of an excess of BnBr (2-4 equiv) and left for a long time, the dibenzylated product did not exceed 3-5% of the yield. The reaction of dimethyl L-tartrate (**13**) with Ag_2O was very slow and the addition of a catalytic amount of KI was required to accelerate the alkylation.[13] Other alkyl halides such as iodomethane, 4-nitrobenzyl bromide and 4-fluorobenzyl bromide were used as alkylating reagents and also gave

satisfactory results (Table 2).

Table 2: Selective monoalkylation of symmetrical diol[a]

n°	HO—R—OH (I)	RX	Solvent	Time	Yield[b]
14[14]		MeI	CH_2Cl_2	5 h	78%[c]
15[15]	 R_1 = Ph	MeI	Toluene	15 h	75%[c]
15[15]	R_1 = Ph	4-NO_2-BnBr	Toluene	15 h	63%[d]
16[16]	R_1 = OPh	4-F-BnBr	Toluene	15 h	95%
11[9]	R_1 = OBn	4-F-BnBr	Toluene	15 h	93%

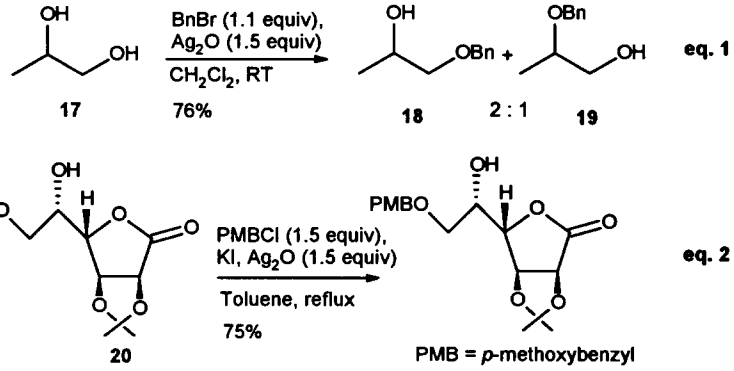
[a] All reactions were carried out at RT with 1.1 equiv of RX and 1.5 equiv of Ag_2O.

[b] Isolated yield. [c] 12-15% of dimethylated derivative were isolated.

[d] No trace of dialkylated product was detected.

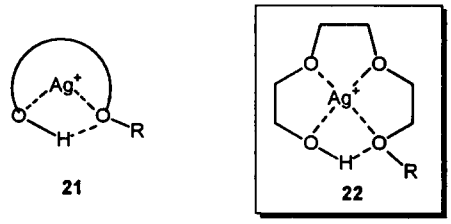
We did not observe any appreciable selectivity in the benzylation of 1,2-propanediol (**17**) with Ag_2O and BnBr (1.1 equiv) and obtained an unseparable mixture of monobenzylated derivatives in a ratio of 2:1[17,18] in favour of compound **18** (Scheme 2, eq. 1). When the secondary alcohol was more sterically hindered as in diol **20**, the alkylation occurred selectively on the primary alcohol on heating in toluene (Scheme 2, eq. 2).

Scheme 2



Alcohol alkylation with silver(I) oxide has been reported, but to our knowledge no mechanism has been proposed for this reaction. In order to explain the selectivity of monobenzylation of diols in the presence of silver(I) oxide, we propose that it is the result of the complexation of the diol's oxygens with the silver atom, a Lewis acid, giving the complex **21** (Scheme 3). The coordination increases the lability (acidity) of the diols' hydrogen,[19] especially the one (R=H) not involved in intramolecular hydrogen bonding, thus favoring benzylation. The effect is more significant if more oxygen atoms are present to complex with the silver atom, as shown with complex **22** which contains two additional oxygens (ether) compared to complex **21**. This hypothesis is supported by the different selectivity of **6** and **9**. In both diols, the two hydroxyl groups are separated by 8 atoms, however **9** reacted more rapidly and provided higher selectivity, a result that can be explained by the chelation of the oxygen atoms of **9** by Ag^+ (see complex **22**, Scheme 3).

Scheme 3



R= H, Bn, Alkyl

In conclusion, we have found a convenient and efficient method[20] for the selective monoalkylation of primary as well as secondary diols. Due to its simplicity and its mild conditions, this reaction will find wide application in organic synthesis.

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References and notes

1. To whom correspondence should be addressed. Fax: (514) 686-5619; Email: sauveg@accent.net.
2. See for example: (a) Börjesson, L.; Csöregh, I.; Welch, C. J. *J. Org. Chem.* **1995**, *60*, 2989. (b) Nicolaou, K. C.; Hwang, C. -K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040. (c) Marshall, J. A.; Beaudoin, S.; Lewinski, K. *J. Org. Chem.* **1993**, *58*, 5876. (d) Raederstorff, D.; Shu, A. Y. L.; Thompson, J. E.; Djerassi, C. *J. Org. Chem.* **1987**, *52*, 2337. (e) Jones, G. B.; Hubert, R. S. *Synlett* **1993**, 367.
3. Ikeda, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5177 and references therein.
4. McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
5. Nishiguchi, T.; Fujisaki, S.; Ishii, Y.; Yano, Y.; Nishida, A. *J. Org. Chem.* **1994**, *59*, 1191.
6. Nishiguchi, T.; Kuroda, M.; Saitoh, M.; Nishida, A.; Fujisaki, S. *J. Chem. Soc. Chem. Commun.* **1995**, 2491.
7. Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327 and references therein.
8. Bouzide, A.; Yelle, J.; Sauvé, G. Unpublished results.
9. The diol **11** was obtained in 71% yield by selective 1,6-di-*O*-benzylation (Bu_2SnO, toluene, then CsF, BnBr) of commercially available 3,4-*O*-isopropylidene-D-mannitol.
10. Tanabe, M.; Peters, R. H. *Org. Syn., Coll. Vol. VII*, **1990**, p. 386.
11. Marshall *et al.* have also observed the ring opening of THF by Ag_2O: Marshall, J. A.; Seletsky, B. M.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 3413.
12. Large excess of oligoethylene glycols *vs* BnBr in aqueous NaOH were used for the preparation of monoprotected oligoethylene glycols. Selve, C.; Achilefu, S.; Mansuy, L. *Synth. Commun.* **1990**, *20*, 799.
13. For another method to prepare monobenzylated dialkyl tartrate see: Guindon, Y.; Girard, Y.; Berthiaume, S.; Gorys, V.; Lemieux, R.; Yoakim, C. *Can. J. Chem.* **1990**, *68*, 897.
14. Nemto, H.; Takamatsu, S.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 1321.
15. Hultén, J.; Bonham, M. N.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Aqvist, J.; Classon, B.; Danielson, U. H.; Karlen, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885.
16. Ghosh, A. K.; Mckee, S. P.; Thomson, W. J. *Tetrahedron Lett.* **1991**, *32*, 5729.
17. For an example of selective monobenzylation of unsymmetrical diols with Ag_2O, see Walkup, R. D.; Cunningham, R. T. *Tetrahedron Lett.* **1987**, *28*, 4019.
18. Determined by NMR.
19. Carey, F. A.; Sundberg, R. J. *Chimie Organique Avancée*. 3ème Édition. DeBoeck Université. 1996; p.230.
20. General procedure for the monoalkylation of symmetrical diols: To a stirred solution of diol (1 mmol) in toluene or CH_2Cl_2 was added freshly prepared Ag_2O[10] (1.5 mmol) and alkyl halide (1.1 mmol). The reaction was stirred for 1 to 15 h and filtered through a silica gel pad. Evaporation of the solvent followed by flash chromatography gave the monoalkylated product. All compounds were characterized by NMR, IR and high resolution MS.

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