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Silver(I) Oxide Mediated Highly Selective Monotosylation of Symmetrical Diols. Application to the Synthesis of Polysubstituted Cyclic Ethers

Abderrahim Bouzide*,† and Gilles Sauvé

Pharmacor Inc., 535 Boulevard Cartier Ouest, Laval, QC, Canada H7V 3S8, and INRS–Institut Armand Frappier, 531 Boulevard des prairies, Laval, QC, Canada H7V 1B7

abouzide@invenux.com

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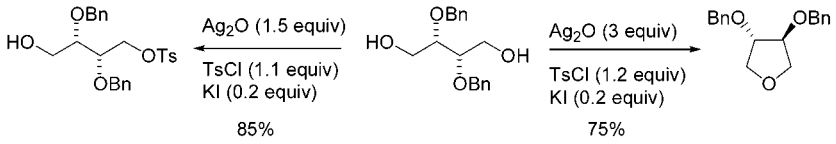
ABSTRACT



The reaction of symmetrical diols and oligo(ethylene glycol)s with a stoichiometric amount of *p*-toluenesulfonyl chloride in the presence of silver(I) oxide and a catalytic amount of potassium iodide led selectively to the monotosylate derivatives in high yields. Polysubstituted cyclic ethers were obtained readily upon treatment of the corresponding diols with an excess of silver oxide. The high selectivity was explained on the basis of the difference in acidity between the two hydroxy groups, which undergo an intramolecular hydrogen bonding.

Monofunctionalization of symmetrical diols has been of considerable interest in organic synthesis. While selective monosulfonylation of a primary alcohol in the presence of a secondary or tertiary alcohol is well established,[1] the monosulfonylation of symmetrical diols can still present a synthetic problem. To monotosylate 1,4-butanediol, Ahlberg and Wu have added an excess of diol in the presence of triethylamine without solvent.[2] Those authors found that the utilization of solvent favors the formation of the ditosylate, due the high solubility of the monotosylate compared to the diol. Choudary et al. have recently reported a monotosylation of diol mediated by metal-exchanged montmorillonite clay catalyst, employing *p*-toluenesulfonic acid as tosylation agent.[3] A strong base such as BuLi was also used to achieve the monotosylation of diols.[4] All these methods suffer from the use of an excess of diol, which is difficult to remove from the reaction mixture, or from harsh conditions, not often compatible with acid- or base-sensitive functional groups.

Recently, we reported a new practical sulfonylation of alcohols in the presence of silver oxide (Ag_2O) and a catalytic amount of potassium iodide (KI).[5] This method has proven to be an excellent protocol to mediate monotosylation of symmetrical diols and oligo(ethylene glycol)s (OEGs) under neutral conditions using a stoichiometric amount of tosylating agent (Scheme 1).

For example, a solution of 1,4-butanediol in dichloromethane treated with Ag_2O (1.5 equiv) and TsCl (1.1 equiv) in the presence of KI (0.2 equiv) at room temperature yielded

† Present address: Invenux, Inc., 6840 N. Broadway, Suite F, Denver, CO 80221.

(1) (a) O'Donnell, C. J.; Burke, S. D. *J. Org. Chem.* **1998**, *63*, 8614−8616. (b) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447−450. (c) Bucher, B.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 9617−9621. (d) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V. Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578−3585.

(2) Ahlberg, P.; Wu, Y. *J. Org. Chem.* **1994**, *59*, 5076−5077.

(3) Choudhary, B. M.; Chowdary, N. S.; Kantam, M. *Tetrahedron* **2000**, *56*, 7291−7298.

(4) (a) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 3999−4000. (b) Marshall, J. A.; Hinkle, K. *J. Org. Chem.* **1997**, *62*, 5989−5995.

(5) Bouzide, A.; LeBerre, N.; Sauvé, G. *Tetrahedron Lett.* **2001**, *42*, 8781−8783.

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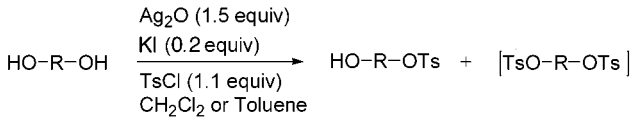
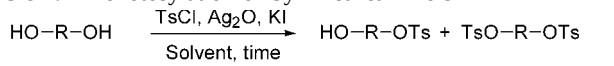
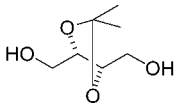
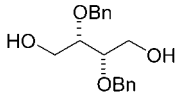
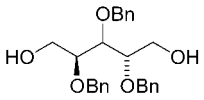
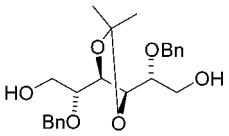
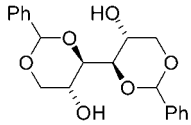
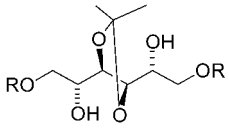
Scheme 1



within 40 min the monosulfonate ester in 91% yield, while the ditosylate byproduct was isolated in only 6% yield (Table 1, entry 2).

Table 1. Monotosylation of Symmetrical Diols



no	diol	solvent, time	Monotosyle/ Ditosylate (%)[a]	
1	1,3-Propanediol	CH_2Cl_2, 1h	75	10
2	1,4-Butanediol	CH_2Cl_2, 40 min	91	6
3	1,5-Pentanediol	CH_2Cl_2, 4h	81	8
4	1,6-Hexanediol	CH_2Cl_2, 4h	75	10
5		CH_2Cl_2, 40 min	92	4
6[7]		Toluene, 2h	85	3
7[8]		Toluene, 3h	79	5
8[9]		Toluene, 2h	85	7
9		Toluene, 2h	90	3
10[10]	 R= Ph	Toluene, 6h	84	5
11[11]	R= 4F-Bn	Toluene, 6h	93	2

[a] Isolated yield.

As illustrated in Table 1, other primary as well as secondary symmetrical diols underwent selective monotosylation in high yields.[6]

Monosulfonation of OEGs, which is often the first step in the preparation of crown ether type derivatives,[12] hydrophilic tethers for linkage of bio-molecules,[13] and spacers in solid-phase synthesis,[14] was undertaken. Thus, treatment of di(ethylene glycol) **13** under the conditions described above yielded 79% of the monotosylate along with 15% of the ditosylate. The reaction was slightly exothermic and complete within 5 min. When the reaction was achieved at 0 °C, the monotosylate was obtained in 92% accompanied with only 5% of the ditosylate[15] (Table 2). Note that in both **3** and **13** the hydoxy groups are separated by five atom units; however, better selectivity was achieved in the case of **13** (vide infra). Other commercially available OEGs (**12**, **14**−**17**) were subjected to the described conditions and gave good to excellent yields of the monotosylate ester except for **12**, which afforded moderate selectivity. Remarkably, treatment of the synthetic glycol derivatives **18**, where the two hydroxy groups are separated by 20 atom units, gave a good yield of the corresponding monotosylate (Table 2). Moderate selectivity, however, was obtained in the case of **19** and **20**.

We next took advantage of this reaction to prepare in one step polysubstituted cyclic ethers from the corresponding diols. For example, when diol **6**[7] was treated with TsCl (1.2 equiv) and an excess of Ag_2O (3 equiv) for 15 h (Table 3, conditions A), disubstituted tetrahydrofuran **23** was obtained in 75% yield. Treatment of diol **21**[16] under similar conditions

(6) (a) **General Procedure for the Monotosylation of Symmetrical Diols.** To a stirred solution of diol (1 mmol) in CH_2Cl_2 or toluene (10 mL) were added fresh Ag_2O (350 mg, 1.5 mmol), TsCl (210 mg, 1.1 mmol), and KI (33 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for alkanediols and at 0 °C for OEGs for 5 min to 8 h and then filtered through a small pad of silica gel and washed with EtOAc. Evaporation of the solvent, followed by column chromatography, gave the desired monotosylate product. (b) The use of fresh Ag_2O is recommended because on standing for a few months on bench, Ag_2O became less active due to its oxidation to AgO and its decomposition to metallic silver: L'vov, B. V. *Thermochim. Acta* **1999**, *333*, 13−19. (c) Ag_2O can be easily prepared by reacting $AgNO_3$ with NaOH, Tanabe, M.; Peters, R. H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 386−392.

(7) (a) Nemoto, H.; Takamatsu, S.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 1321−1322. (b) Kalinovski, H. O.; Crass, G.; Seebach, D. *Chem. Ber.* **1981**, *114*, 477. We found that diol **6** can be prepared readily in good yield from dimethyl L-tartrate without isolating the intermediate. Reaction of dimethyl L-tartrate with Ag_2O in the presence of BnBr at reflux of CH_2Cl_2; after filtration and evaporation of the solvent, the crude was treated with $LiAlH_4$ in THF to afford **6** in 88% overall yield after purification.

(8) (a) Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1991**, *32*, 5701−5704. (b) Burgess, K.; Chaplin, D. A.; Henderson, I. *J. Org. Chem.* **1992**, *57*, 1103−1109.

(9) **8** was prepared in three steps from commercially available 3,4-*O*-isopropylidene-D-mannitol: (i) Bu_2SnO, CsF, *p*-methoxybenzyl chloride (PMBCl), (ii) BnBr, NaH, DMF, (iii) $SnCl_2$, EtSH, CH_2Cl_2.

(10) Zuccarello, G.; Bouzide, A.; Kvarnström, I.; Niklasson, G.; Svensson, S. C. T.; Brisander, M.; Danielsson, H.; Nillroth, U.; Karlén, A.; Hallberg, A.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1998**, *63*, 4898−4906.

(11) **11** was prepared readily from commercially available 3,4-*O*-isopropylidene-D-mannitol: (i) Bu_2SnO, Toluene, (ii) 4F−BnBr, CsF, DMF.

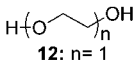
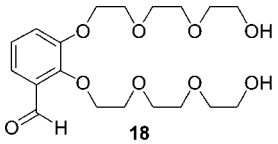
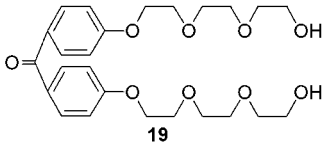
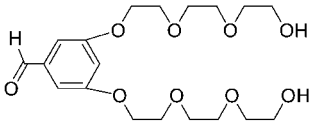
(12) (a) Dietrich, B.; Viout, P.; Lehn, J.-M. *Macrocyclic Chemistry*; VCH: Weinheim, 1993. (b) Pederson, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017−7036. (c) Izzat, R. M.; Pawlak, K.; Bradshaw, J. S. *Chem. Rev.* **1995**, *95*, 2529−2586 and references therein.

(13) (a) Roberts, C.; Chen, C. S.; Mrksich, M.; Martinochonok, V.; Ingeber, D. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1998**, *120*, 6548−6555. (b) Wittman, V.; Takayama, S.; Gong, K. W.; Weitz-Schmidt, G.; Wong, C.-H. *J. Org. Chem.* **1998**, *63*, 5137−5143. (c) Valiokas, R.; Svedhem, S.; Svensson, S. C. T.; Lieberg, B. *Langmuir* **1999**, *15*, 3390−3394.

(14) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509. (b) Houseman, B.; Mrksich, M. *J. Org. Chem.* **1998**, *63*, 7552−7555. (c) Bettinger, T.; Remy, J.-S.; Erbacher, P.; Behr, J.-P. *Bioconjugate Chem.* **1998**, *9*, 842−846.

(15) Only 54% of the monotosylate was obtained when stoichiometric amount of TsCl and pyridine were employed; see: MacMahon, S.; Fong, R., II; Baran, P. S.; Safonov, I.; Wilson, S. R.; Schuster, D. I. *J. Org. Chem.* **2001**, *66*, 5449−5455. Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1991**, *56*, 4326−4329.

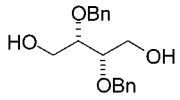
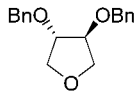
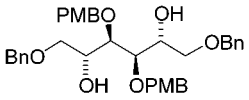
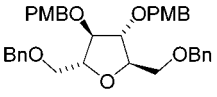
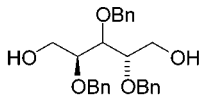
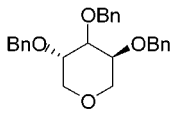
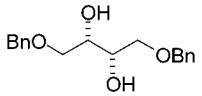
Table 2. Monotosylation of OEGs

OEG	time, temp (°C)	Monotosylate/ Ditosylate (%)[a]
		
12: n= 1	25 min, 0	61 : 23
13: n= 2	5 min, 0	92 : 5
14: n= 3	10 min, 0	92 : 4
15: n= 4	15 min, 0	85 : 7
16: n= 5	15 min, 0	78 : 11
17: n= 6	15 min, 0	85 : 7
 **18**	45 min, 0	84[b] : 5
 **19**	8 h, 25	68 : 24
 **20**	8 h, 25	69 : 21

[a] Isolated yield. [b] 1:1 regiosiomers were obtained (^{1}H, ^{13}C NMR).

yielded the *C*-glycosyl **24** in 70% yield. The trisubstituted tetrahydropyran **25** and the oxirane **26**[17] were obtained in

Table 3. Synthesis of Cyclic Ethers from Symmetrical Diols

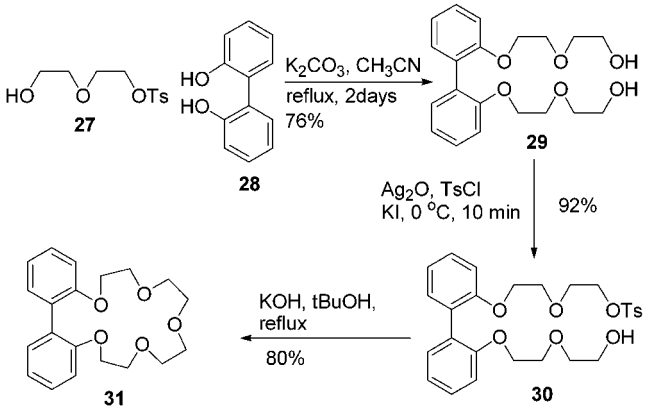
diol	conditions[a]	cyclic ether	yield(%)
 **6**	A	 **23**	75
	B		81
 **21**	A	 **24**	70
	B		88
 **7**	A	 **25**	42
	B		67
 **22**	A	 **26**	61

[a] Conditions A: Ag_2O (3 equiv), KI (0.2 equiv), TsCl (1.2 equiv), CH_2Cl_2, 15 h. Conditions B: (i) Ag_2O (1.5 equiv), KI (0.2 equiv), TsCl (1.2 equiv), CH_2Cl_2, 2−4 h, (ii) K_2CO_3 (2 equiv), MeOH.

moderate yields when tribenzyl L-arabitol **7**[8] and dibenzyl L-threitol **23**, respectively, were treated under the same conditions. On the other hand, the yields of cyclic ethers were significantly increased when the reaction were performed under the previously described conditions, followed by treatment of the crude product with potassium carbonate in methanol (Table 3, conditions B).

The silver oxide mediated monosulfonylation of diols has proven to be an excellent method for the straightforward synthesis of crown ether type derivatives as exemplified in the synthesis of 5-*O*-crown ether **31**[18] (Scheme 2). Reaction

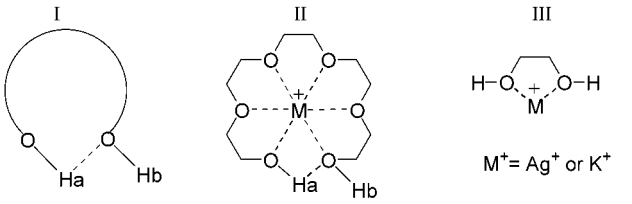
Scheme 2. Synthesis of 5-*O*-Crown Ether **31**



of the monotosylate **27**, which was obtained in excellent yield from **13** (Table 2), with 2,2′-biphenol **28** yielded diol **29** in 76% yield. Submission of **29** to the above monotosylation conditions afforded the monosulfonic ester **30** with excellent selectivity even though the two OH groups are separated by 16 atom units.[19] Treatment of **30** in the presence of base under dilute conditions afforded **31** in good yield.

Although we do not have any material evidence, one can attribute this highly selective monotosylation of symmetrical diols to an internal hydrogen bonding (IHB) (Scheme 3, I).

Scheme 3



The hydrogen atom Ha involved in the IHB becomes less acidic than Hb, which is in contrast more activated by this

(16) Compound **21** was prepared in three steps starting from commercially available 1,2,5,6-di-*O*-isopropylidene-D-mannitol: (i) PMBCl, NaH, DMF, (ii) aqueous AcOH (70%), 40 °C, (iii) Bu_2SnO, CsF, BnBr.

(17) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440−1456.

chelation, and therefore, Hb will be first deprotonated by Ag_2O. Our results are consistent with earlier work that has shown that IHB exists in 1,*n*-alkanediols ($n = 2-6$)[20] and that 1,4-butanediol has the strongest IHB despite its seven-membered ring chelate.[21] The high selectivity obtained in the sulfonylation of OEGs compared to that obtained in alkanediols may be explained by the coordination of Ag^+ (or K^+) with ether oxygen atoms in the OEGs.[22] This chelate makes the two OH groups closer to favor an IHB (Scheme 3, II). On the other hand, the moderate selectivity obtained in the case of **19** and **20** can be attributed to the remoteness of the two OH groups. In the case of ethylene glycol **12**, its low selectivity is probably due to the chelation of Ag^+ (or K^+) with the oxygen electron pairs, which can prevent any IHB (Scheme 3, III).

(18) Kohama, H.; Yoshinaga, M.; Ishizu, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3707−3708.

(19) The ditosylate byproduct was isolated in only 5% yield.

(20) Busfield, W. K.; Ennis, M. P.; McEwen, I. J. *Spectrochim. Acta* **1973**, *29A*, 1259−1264.

(21) (a) Fishman, E.; Chen, T. L. *Spectrochim. Acta* **1969**, *25A*, 1231−1242. (b) Morantz, D. J.; Waite, M. S. *Spectrochim. Acta* **1971**, *27A*, 1133−1137.

(22) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945−5948.

In summary, we report an easy method to monotosylate symmetrical diols under neutral conditions using a stoichiometric amount of tosyl chloride in the presence of Ag_2O and a catalytic amount of KI. The reaction does not require any workup, and the monotosylate esters are often isolated after filtration of insoluble material followed, if necessary, by a simple purification by column chromatography. Another key merit of the present reaction is the ease by which substituted cyclic ethers can be obtained from the corresponding diols.

Acknowledgment. We thank Dr. Gervais Berubé (University of Trois-Rivières) and Ms. Ming Chou (Invenux, Inc.) for their comments on the manuscript.

Supporting Information Available: Experimental procedures for the monotosylation of diols and for the synthesis of cyclic ether **23**−**26** and **31**. Characterization data for the monotosylation products of diols **6**, **7**, **13**, **14**, **19**, and **20**, for cyclic ethers **23**−**26**, and for compounds **29**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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