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Novel Regiocontrolled Protection of 1,2- and 1,3-Diols via Mild Cleavage of Methylene Acetals

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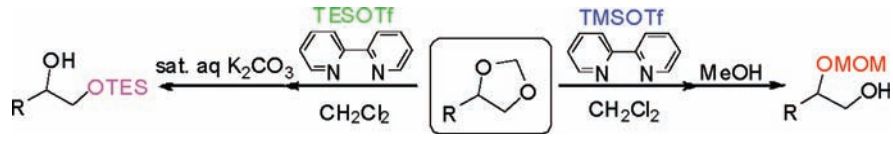
ABSTRACT



The regiocontrolled protection of unsymmetrical 1,2- and 1,3-diols has been developed. Different types of protected diols are available from the methylene acetal in a one-pot procedure. Highly regioselective protection of diols with a silyl group at the less hindered hydroxy group as well as with a MOM group at the more hindered one were achieved. The reaction conditions are mild without affecting other functional groups including acid-labile function.

1,2- and 1,3-diols are the basic structures of polyhydroxy compounds, and the protection of diols is essential for the construction of such molecules. A variety of protective groups for diols have been developed, and dioxolanes and dioxanes are well-known as common protective groups.[1] However, the regioselective monoprotection of unsymmetrical diols is still a challenging theme in organic syntheses. Such transformations are classified into two types of protections, i.e., the protection of the less hindered hydroxy group and protection of the more hindered one. Although a number of monoprotections of the less hindered hydroxy group in unsymmetrical diols has been developed,[1,2] the selective protection of the more hindered hydroxy group is rather difficult. Conversion of cyclic acetals from diols to monoprotected diols is one of the effective methods for the regioselective protection at the more hindered hydroxy group. For example, the reaction of benzylidene acetals of unsymmetrical diols with a Lewis acid and reducing agent is a representative method for the mono-Bn protection at the more hindered hydroxy group.[1] Yamamoto and co-workers reported that the use of trimethyl orthoformate and DIBAL via the formation of the ortho ester produced monomethoxymethyl (MOM)-protected diols at the more hindered site.[3] A similar protection from trimethyl orthoformate to the monoester in the absence of a reducing reagent has also been reported using $Yb(OTf)_3$, but the selectivitiy was not satisfactory.[4] Other selective monoprotections at the more hindered site, such as cyclic acetals−MeMgI,[5] cyclic silylene−*n*-BuLi[6] or BF_3•SMe_2−allyltrimethylsilane,[7] ben-

(1) (a) Wuts, P. G. W.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2006. (b) Kocieński, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2005.

(2) For selected reports, see: (a) Posner, G. H.; Oda, M. *Tetrahedron Lett.* **1981**, *22*, 5003. (b) Rana, S. S.; Barlow, J. J.; Matta, K. L. *Tetrahedron Lett.* **1981**, *22*, 5007. (c) Takano, S.; Ohkawa, T.; Ogasawara, K. *Tetrahedron Lett.* **1988**, *29*, 1823. (d) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791. (e) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 2420. (f) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447. (g) Srinivas, K. V. N. S.; Mahender, I.; Das, B. *Synlett* **2003**, 2419.

(3) Takasu, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 1947.

(4) Ikejiri, M.; Miyashita, K.; Tsunemi, T.; Imanishi, T. *Tetrahedron Lett.* **2004**, *45*, 1243.

(5) Cheng, W.-L.; Yeh, S.-M.; Luh, T.-Y. *J. Org. Chem.* **1993**, *58*, 5576.

(6) Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422.

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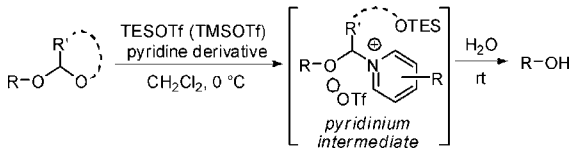
zoyl peroxide−PPh_3,[8] silica gel−AcCl,[9] etc., have also been reported. However, the reagents used in these methods are reactive and may affect other functions within a molecule, and most of them showed moderate to good selectivity, but not complete. On the other hand, the further development of differential protections of both hydroxy groups of diols with different protective groups have also been reported. Most of them were applied to sugar derivatives,[1] and there are a few methods for the nonsugar type diol protection, for example, using acyl chloride and silyl chloride via a dibutylstannylene acetal intermediate to give the regioselectively acyl and silyl protected diol.[10] Bailey and co-workers developed the selective protection of diols from methylene acetal using $ZnCl_2$ and AcCl which regiospecifically afforded the acetyl and MOM-protected diols.[11] However, the use of organotin compound or acyl chloride is unfavorable in view of its toxicity and reactivity. Therefore, the development of a mild and regiocontrolled protection method of diols has been strongly desired. We have developed the chemoselective deprotection of acetals in the presence of ketals in combination with TESOTf (triethylsilyl trifluoromethanesulfonate)-2,4,6-collidine.[12] The reaction proceeded under mild conditions via the formation of pyridinium intermediates. Recently, we demonstrated the application of this method to the mild and selective cleavage of acetal type protective groups for hydroxy groups such as tetrahydropyranyl (THP)[13] and methoxymethyl (MOM)[14] ethers. The key to the successful cleavage is the formation of the pyridinium intermediates followed by hydrolysis of the intermediates (Scheme 1).

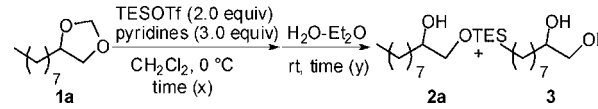
Scheme 1. Mild Cleavage of Acetal-Type Protective Groups in Combination with Silyl Triflate and Pyridine Derivative



During the course of our study on the mild cleavage of other acetal protective groups, we found the regioselective protection of 1,2-diols from methylene acetals and that the protection process is controllable. We now describe the mild and regiocontrolled protection of unsymmetrical diols using TMSOTf or TESOTf and 2,2′-bipyridyl and the successive proper treatment leading to the selective synthesis of different types of protected diols in a one-pot procedure.

As an ongoing study for the mild cleavage of acetal type protections, we examined the deprotection of methylene acetals using 4-octyl-1,3-dioxolane **1a** as a substrate with TESOTf and 2,4,6-collidine as the standard conditions. However, no deprotection of the methylene acetal was observed, but the pyridinium intermediate from **1a** and 2,4,6-collidine was formed (Table 1, entry 1). In our previous study, the structure of pyridine was found to be important not only for the formation of the intermediate but also for the hydrolysis of the intermediate.[14,15] We then investigated the effect of the pyridine derivatives. Although 2,6-dichloropyridine did not give the pyridinium intermediate at all (entry 2), the cleavage of the methylene acetal proceeded by the use of 2-bromopyridine and unexpectedly afforded a mixture of the monosilylated diol **2a** and free 1,2-diol **3** (entry 3). It is noteworthy that silylation occurred only at the less hindered hydroxy group, and no protection at the more hindered hydroxy group was observed. Based on the results, we examined the highly chemo- and regioselective silylation of an unsymmetrical diol. Other 2-substituted pyridines were also examined, and 2,2′-bipyridyl was found to be the most effective pyridine to give **2a** and **3** in high yield, but the selectivity is moderate (entry 5). We assumed that the silylated product **2a** was first generated in the reaction, followed by H_2O treatment that caused acidic conditions from the residual TESOTf, and desilylation occurred to give the 1,2-diol **3a**. Alkaline hydrolysis, as expected, significantly improved the selectivity. To our surprise, the silylated **2a** was obtained as the sole product in 90% yield by the treatment with a saturated aqueous K_2CO_3 solution (entry 6).

Table 1. Effect of Pyridine Derivatives[a]



entry	pyridines	time (*x*/*y*) (h)	yield (%)	ratio (**2a**:**3**)
1	2,4,6-collidine	1.0/−	*b*	
2	2,6-dichloropyridine	−/−	N.R.[c]	
3	2-bromopyridine	0.5/0.5	73	59:41
4	2-phenylpyridine	1.0/72	69	17:83
5	2,2′-bipyridyl	0.5/5	94	57:43
6[d]	2,2′-bipyridyl	0.5/12	90	100:0

[a] The reaction of **1a** was conducted with TESOTf and a base in CH_2Cl_2 followed by hydrolysis after the formation of the intermediate. [b] The hydrolysis of the intermediate did not proceed. [c] No reaction. [d] Saturated aq K_2CO_3 was used instead of H_2O during the hydrolysis.

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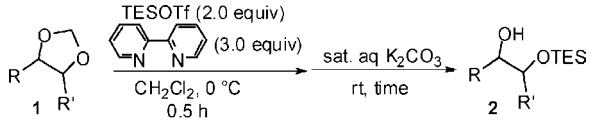
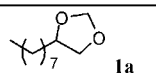
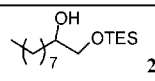
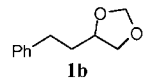
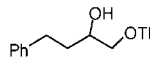
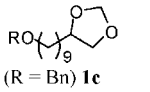
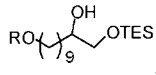
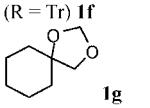
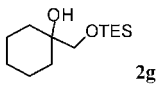
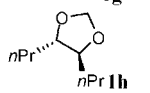
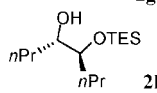
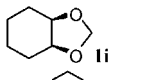
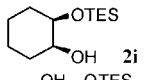
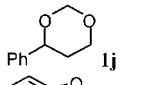
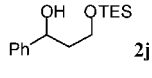
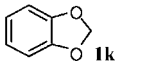
(9) Ogawa, H.; Ide, Y.; Honda, R.; Chihara, T. *J. Phys. Org. Chem.* **2003**, *16*, 355.
(10) (a) Ricci, A.; Roelens, S.; Vannucchi, A. *J. Chem. Soc., Chem. Commun.* **1985**, 1457. (b) Reginato, G.; Ricci, A.; Roelens, S.; Scapecchi, S. *J. Org. Chem.* **1990**, *55*, 5132. (c) Roelens, S. *J. Org. Chem.* **1996**, *61*, 5257.
(11) (a) Bailey, W. F.; Rivera, A. D. *J. Org. Chem.* **1984**, *49*, 4958. (b) Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532. (c) Bailey, W. F.; Carson, M. W.; Zarcone, L. M. J. *Organic Syntheses*; Wiley: New York, 2004; Collect. Vol. 10, p 492.
(12) (a) Fujioka, H.; Sawama, Y.; Murata, N.; Okitsu, T.; Kubo, O.; Matsuda, S.; Kita, Y. *J. Am. Chem. Soc.* **2004**, *126*, 11800. (b) Fujioka, H.; Okitsu, T.; Sawama, Y.; Murata, N.; Li, R.; Kita, Y. *J. Am. Chem. Soc.* **2006**, *128*, 5930.
(13) (a) Fujioka, H.; Okitsu, T.; Ohnaka, T.; Sawama, Y.; Kubo, O.; Okamoto, K.; Kita, Y. *Adv. Synth. Catal.* **2007**, *349*, 636. (b) Fujioka, H.; Kubo, O.; Okamoto, K.; Senami, K.; Okitsu, T.; Ohnaka, T.; Sawama, Y.; Kita, Y. *Heterocycles* **2009**, *77*, 1089.
(14) Fujioka, H.; Kubo, O.; Senami, K.; Minamitsuji, Y.; Maegawa, T. *Chem. Commun.* **2009**, 4429.
(15) The addition of Et_2O was necessary to prevent the undesirable side reaction. See ref 14.

The chemo- and regioselective silylation of the 1,2- and 1,3-diols is shown in Table 2. The dioxolanes of the unsymmetrical 1,2-diols were regiospecifically converted to the monosilylated alcohols in good to high yields, and no other silylated products were obtained (entries 1−9), whereas an increase in the reagents was necessary in some cases (entries 7 and 8). This method is applicable to the substrates bearing various functional groups including an acid-sensitive group (entries 3−6). Symmetrical methylene acetals **1h** and **1i** could also be converted into monosilylated diols (entries 8 and 9). Although the 1,3-dioxane derivative **1j** was less reactive toward the formation of the pyridinium salt, the treatment of **1j** at room temperature with TESOTf−2,2′-bipyridyl afforded the intermediate followed by the alkaline hydrolysis to successfully allow the regioselective formation of the monosilylated alcohol **2j** in moderate yield (53%) (entry 10). The aromatic dioxolane **1k** was inactive even at room temperature, and no pyridinium salt was formed under the reaction conditions (entry 11).

Table 2. Chemoselective and Regioselective Monosilylation of Unsymmetrical 1,2- and 1,3-Diols from Methylene Acetals

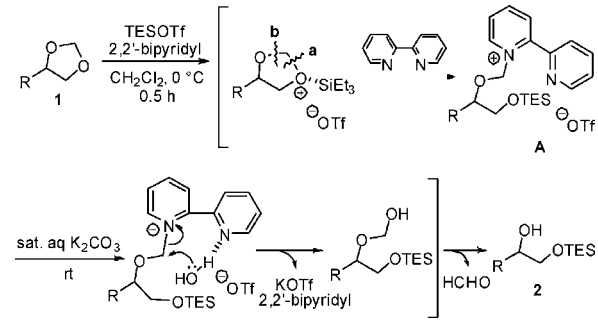


entry	substrate	product	time (h)	yield (%)
1	 **1a**	 **2a**	12	90
2	 **1b**	 **2b**	8.5 (1)[c]	93
3	 (R = Bn) **1c**	 **2c**	10	87
4	(R = Bz) **1d**	**2d**	10	92
5	(R = TBS) **1e**	**2e**	6	81
6	(R = Tr) **1f**	**2f**	7	81
7[a,b]	 **1g**	 **2g**	2.5 (7.5)[c]	90
8[a,b]	 **1h**	 **2h**	8.5 (5.5)[c]	87
9	 **1i**	 **2i**	9	80
10[b]	 **1j**	 **2j**	41 (6.5)[c]	53
11[b]	 **1k**	–	–	N.R.[d]

[a] 4.0 equiv of TESOTf and 6.0 equiv of 2,2′-bipyridyl were used. [b] The reaction with TESOTf and 2,2′-bipyridyl was conducted at rt. [c] The time indicated in parentheses was required for the formation of the pyridinium intermediate. [d] No reaction.

The chemoselective and regiospecific protection of unsymmetrical diols from methylene acetals could be explained as follows (Scheme 2). First, the methylene acetal reacted with TESOTf which regiospecifically coordinated at the less hindered oxygen atom.[16] The following attack of 2,2′-bipyridyl on the methylene carbon led to the simultaneous C−O bond cleavage at *bond* **a** to give the TES-protected pyridinium intermediate **A**. Subsequent hydrolysis of **A** afforded the monosilylated diol. The hydrolysis with H_2O might cause a weak acidic environment by generating TfOH from the residual TESOTf, which could promote the hydrolysis of the silyl group. The use of an alkaline solution could neutralize TfOH resulting in leaving the silyl group intact. The accelerating effect of 2,2′-bipyridyl on the hydrolysis may explain that the nitrogen atom on the adjacent pyridine ring helps to bring the H_2O close to the methylene carbon and promote the nucleophilic attack by H_2O.[14]

Scheme 2. Plausible Reaction Mechanism



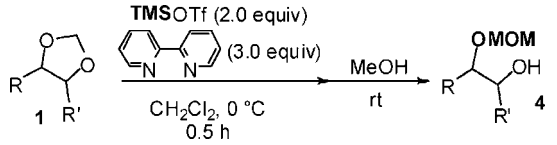
Next, we planned another type of monoprotection of the 1,2-diols. The reaction mechanism suggested that treatment of the intermediate **A** with MeOH instead of an aqueous solution would give MOM ether on the more hindered hydroxy group. Furthermore, the choice of the Lewis acid could affect the reaction, and the use of TMSOTf could undergo a concomitant deprotection of the silyl group affording the mono-MOM protected diols. As a result, the treatment of **1a** with TMSOTf−2,2′-bipyridyl[17] followed by the methanolysis exclusively led to the mono-MOM-protected diol **4a** at the more hindered hydroxy group (Table 3, entry 1). A variety of methylene acetals of 1,2- and 1,3-diols can be converted into mono-MOM-protected diols **4** (Table 3). It should be noted that the protection of the MOM ether onto the *tert*-alcohol proceeded in high yield (entry 7).

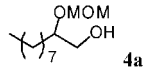
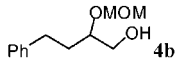
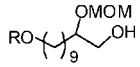
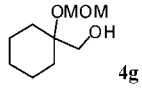
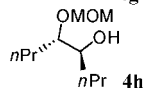
The regioselective protection of both hydroxy groups with different protective groups was also possible. The reaction of **1a** with TESOTf followed by the methanolysis with triethylamine as an additive afforded the hydroxy group

(16) The similar discrimination of two oxygen atoms by the TESOTf was observed during the selective deprotection of the acetals in the presence of ketals. We have discussed the reaction mechanism in detail. See refs 12b and 13a.

(17) No other pyridine derivatives afforded a better result than 2,2′-bipyridyl.

Table 3. Selective Mono-MOM Protection of 1,2-Diols from Methylene Acetals



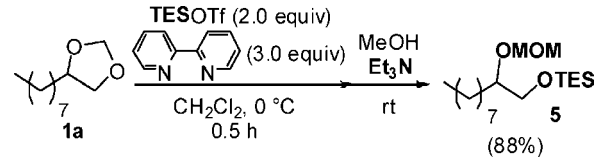
entry	substrate	product	time (h)	yiel (%)
1	**1a**	 **4a**	4.5	92
2	**1b**	 **4b**	18 (1)[b]	89
3	**1c**	 (R = Bn) **4c**	6	89
4	**1d**	(R = Bz) **4d**	4	86
5[a]	**1e**	(R = TBS) **4e**	4.5	73
6	**1f**	(R = Tr) **4f**	7	90
7	**1g**	 **4g**	1 (1)[b]	87
8[c]	**1h**	 **4h**	1.5 (1.5)[b]	41

[a] 1.0 equiv of Et_3N was used for the methanolysis. [b] The time indicated in parentheses was required for the formation of the pyridinium intermediate. [c] The reaction with TMSOTf (4.0 equiv) and 2,2′-bipyridyl (6.0 equiv) was conducted at rt.

protected diol **5** with both TES and MOM groups as a single product in high yield (88%) (Scheme 3).

In summary, we have developed the mild and regiocontrolled protection of unsymmetrical diols from methylene acetals in combination with TESOTf or TMSOTf and 2,2′-bipyridyl. This is a mild, simple, and convenient method to prepare different types of protected diols in a one-pot procedure even in the presence of acid-sensitive functions. The present method is promising for the construction of polyhydroxy compounds as well as disclosing the new utilization of methylene acetals. Further application of this method to more complex molecules is currently underway.

Scheme 3. Simultaneous Regioselective Protection of 1,2-Diol with TES and MOM Group



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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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