Mild Deprotection of Methylene Acetals in Combination with Trimethylsilyl Triflate–2,2′-Bipyridyl

Hiromichi Fujioka,* Kento Senami, Ozora Kubo, Kenzo Yahata, Yutaka Minamitsuji, and Tomohiro Maegawa

Graduate School of Pharmaceutical Sciences, Osaka University; 1–6 Yamada-oka, Suita, Osaka 565–0871, Japan.
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The facile deprotection of methylene acetal protection of diols under mild conditions is established. The combination of trimethylsilyl triflate (TMSOTf) and 2,2′-bipyridyl followed by a weakly acidic hydrolysis was effective and the substrates having acid sensitive functional groups can be tolerated under the stated conditions. The selective deprotection between methylene acetal and benzophenone ketal was achieved.

Key words deprotection; methylene acetal; diol; 2,2′-bipyridyl; pyridinium intermediate

The protection of functional groups is essential for organic syntheses. The choice of the appropriate protective group is important for the total synthesis of complex molecules and a number of protective groups for various functional groups have been developed to date.[1,2] The diol is a basic structure of polyhydroxy molecules and many protective groups for it have been developed.[1,2] Dioxolanes and dioxanes are common protective groups for diols, especially, isopropylidene ketal is the most common protective group which can be tolerated under strong basic conditions and cleaved under weakly acidic conditions. Other dioxolanes and dioxanes are also used, but some of them, which are prepared from diols and aldehydes, such as benzylidene acetal, generate a new stereogenic center which affords a diastereo mixture and may cause complex handling, separation and NMR analysis concerns. To prevent these problems, the cyclic carbonates or boronates are employed for the diol protection although the deprotection of carbonates requires strong basic conditions, while the less steric hindered boronates are unstable toward hydrolysis.[1,2]

The methylene acetal function is one of the protective groups for the 1,2- or 1,3-diols and its dioxolanes or dioxanes form a single isomer. However, the difficulty of deprotection of the methylene acetal is a common recognition and there are significant issues in its use. Because strong acidic conditions or harsh reaction conditions are required to cleave the methylene acetals,[3—15] the methylene acetal function is rarely used for the protection of diols.[1,2] Therefore, the development of a mild and convenient deprotection method would open up the utility of methylene acetal and provide a novel alternative for the diol protection because it tolerates not only basic conditions, but also mild acidic conditions. We now describe the facile deprotection of methylene acetal under mild conditions in combination with trimethylsilyl triflate (TMSOTf) and 2,2′-bipyridyl.

We have reported that the facile deprotection of THP ethers[16,17] as well as MOM ethers[18] using the combination of TESOTf–2,4,6-collidine or 2,2′-bipyridyl *via* a pyridinium intermediate (Chart 1). A slightly excess amount of 2,2′-bipyridyl was used over Lewis acid in this reaction, which made the reaction conditions mild, and an acid-labile function can be tolerated under these conditions.

Further development of this method, the regiocontrolled protection of diols from methylene acetals under mild conditions has been accomplished (Chart 2).[19] Different types of protected diols, such as the more hindered hydroxy group protected diol and less hindered one, can be obtained by a one-pot procedure.

During this study, we found that it is important for the syntheses of different types of protected diols to modify the successive treatment of the pyridinium intermediate generated in the reaction. During an initial attempt for the deprotection of methylene acetal, the hydrolysis of the pyridinium intermediate of 4-octyl-1,3-dioxolane (**1a**) with H_2O (neutral conditions) gave a mixture of the free diol (**2a**) and mono-silylated diol (**3**) (Table 1, entry 1). Further investigation of the hy-

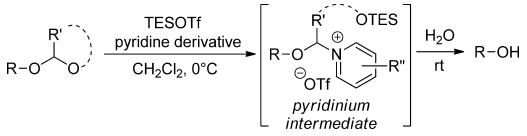


Chart 1. Mild Deprotection of THP Ether or MOM Ether in the Combination of the TESOTf–Pyridine Derivatives

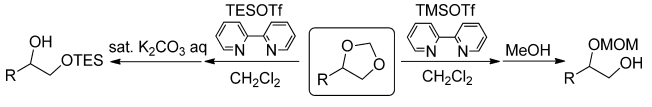
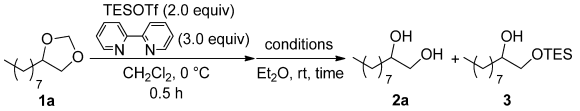


Chart 2. Regiocontrolled Protection of Diols from Methylene Acetals

Table 1. The Effect of Hydrolysis Conditions



Entry	Conditions	Time (h)	Yield (%)	
			2a	**3**
1	H_2O	5	54	40
2	Sat. K_2CO_3 aq.	12	0	90
3	1 N HCl	2	78	Trace
4[a]	1 N HCl	1.5	83	0
5[b]	1 N HCl	24	13	Trace
6[c]	1 N HCl	24	—[d]	—[d]

a) TMSOTf was used instead of TESOTf. *b*) The reaction was performed in the absence of 2,2′-bipyridyl. *c*) The reaction was performed in the absence of TESOTf and 2,2′-bipyridyl. *d*) No reaction.

* To whom correspondence should be addressed. e-mail: fujioka@phs.osaka-u.ac.jp

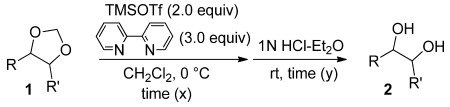
drolysis conditions revealed that the treatment with saturated K_2CO_3 aq. (basic conditions) only afforded **3** (entry 2), but the treatment with 1 N HCl (weakly acidic conditions) gave **2a** in good yield as a single product (entry 3). The use of TMSOTf instead of TESOTf improved the yield of **2a** up to 83% (entry 4). The reaction of **1a** with TESOTf only afforded **2a**, but in low yield (13%), and the formation of the pyridinium intermediate is important for the efficient deprotection (entry 5). The deprotection did not proceed without TESOTf and 2,2′-bipyridyl (entry 6). The hydrolysis was promoted by 2,2′-bipyridyl which may help H_2O access to the cationic acetal carbon in the pyridinium intermediate.[18)]

We applied the optimized conditions to various methylene acetals of the 1,2-diols and 1,3-diol. The formations of the pyridinium salts were complete within 2.5 h in each substrate and the hydrolysis of the intermediates gave the corresponding diols **2** in good to high yields (Table 2). A variety of functional groups, such as benzyl, benzoyl and TBS, were tolerated under these conditions (entries 3—5). It should be noted that the trityl group, an acid-labile functional group, survived under these conditions (entry 6). The methylene acetals of the inner 1,2-diols were also deprotected within 1.5 h (entries 8 and 9). 1,3-Dioxane was also converted to a 1,3-diol under the same conditions (entry 10). However, the methylene acetal of catechol did not form any pyridinium salt and no deprotected product was observed (entry 11).

The chemoselective deprotection between methylene acetal and benzophenone ketal within the same molecule was also examined. It is known that benzophenone ketal is deprotected by a weak acid such as AcOH or a diluted HCl solution.[1,2)] The key to the selective deprotection by our method is dependent on the steric environment in which the Lewis acid coordinates the less hindered oxygen with discrimination. Consequently, the selective deprotection of methylene acetal in **4** proceeded under the conditions affording the diol **5** with the benzophenone ketal intact (Chart 3).

In conclusion, the facile and mild deprotection of methylene acetals using TMSOTf and 2,2′-bipyridyl has been developed. The weakly acidic hydrolysis promoted the deprotection of methylene acetals to afford the free diols in good to high yields. The present method is so mild that various functional groups including the trityl group can be tolerated under the established conditions. This method is also applicable to the selective deprotection of methylene acetal in the presence of benzophenone ketal.

Table 2. Mild Deprotection of Methylene Acetals of 1,2- and 1,3-Diols in Combination of TMSOTf–2,2′-Bipyridyl



Entry	Substrate	Product	Time (x/y) (h)	Yield (%)
1	**1a**	**2a**	0.3/1.5	83
2	**1b**	**2b**	2.5/1	82
3	(R=Bn) **1c**	**2c**	0.5/3	72
4	(R=Bz) **1d**	**2d**	0.5/3	75
5[a)]	(R=TBS) **1e**	**2e**	0.5/6.5	72
6	(R=Tr) **1f**	**2f**	1/4.5	86
7[b)]	**1g**	**2g**	0.3/1	95
8[b,c)]	**1h**	**2h**	1.5/1.5	56
9	**1i**	**2i**	0.5/0.5	86
10[b,c)]	**1j**	**2j**	2/1.5	84
11	**1k**	—	—	N. R.[d)]

a) Sat. NH_4Cl aq. was used instead of 1 N HCl. *b*) 4.0 eq of TMSOTf and 6.0 eq of 2,2′-bipyridyl were used. *c*) The reaction with TMSOTf and 2,2′-bipyridyl was conducted at rt. *d*) No reaction.

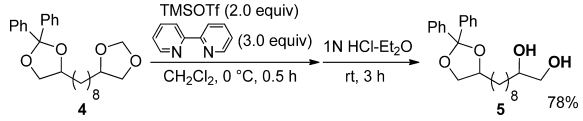


Chart 3. Selective Deprotection of Methylene Acetal in the Presence of Benzophenone Ketal

Experimental

General Procedure. *n*-Decane-1,2-diol (2a)[20)] (Table 1, Entry 4) TMSOTf (73.2 μl, 0.405 mmol) was added to a solution of methylene acetal **1a** (37.3 mg, 0.202 mmol) and 2,2′-bipyridyl (94.8 mg, 0.607 mmol) in CH_2Cl_2 (0.4 ml) at 0 °C under N_2. The reaction mixture was stirred for 30 min at 0 °C. After disappearance of **1a** on TLC, Et_2O (2 ml) and 1 N HCl (2 ml) was added to the reaction mixture. The resulting solution was stirred until disappearance of the pyridinium salt (highly polar compound). The mixture was extracted with CH_2Cl_2 (or AcOEt). The combined organic layer was washed with saturated $NaHCO_3$ aq. then dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash SiO_2 column chromatography (hexanes/AcOEt=1/1) to give a diol **2a** (29.1 mg, 83%).

4-Phenylbutane-1,2-diol (2b)[21)] (Table 2, Entry 2) According to the general procedure, the treatment of **1b** (34.6 mg, 0.194 mmol) with 2,2′-bipyridyl (90.9 mg, 0.582 mmol) and TMSOTf (70.0 μl, 0.387 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 1 h gave **2b** (26.6 mg, 82%). Eluent; hexanes/AcOEt (2/1) to hexanes/AcOEt (1/1).

11-Benzyloxy-undecane-1,2-diol (2c)[22)] (Table 2, Entry 3) According to the general procedure, the treatment of **1c** (61.0 mg, 0.199 mmol) with 2,2′-bipyridyl (93.3 mg, 0.597 mmol) and TMSOTf (72.0 μl, 0.398 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 3 h gave **2c** (42.3 mg, 72%). Eluent; hexanes/AcOEt (1/1) to AcOEt.

11-Benzoyloxy-undecane-1,2-diol (2d) (Table 2, Entry 4) According to the general procedure, the treatment of **1d** (63.4 mg, 0.199 mmol) with 2,2′-bipyridyl (93.3 mg, 0.597 mmol) and TMSOTf (72.0 μl, 0.398 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 3 h gave **2d** (46.1 mg, 75%). Eluent; hexanes/AcOEt (1/1) to AcOEt. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30—1.80 (16H, m), 2.61—2.65 (2H, m), 3.43—3.45 (1H, m), 3.63—3.69 (2H, m), 4.31 (2H, t, J=6.4 Hz), 7.42—7.46 (2H, m), 7.54—7.57 (1H, m), 8.03—8.05 (2H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ:

25.4, 25.9, 28.6, 29.2, 29.4 (3×C), 29.5, 33.1, 65.1, 66.8, 72.3, 128.3, 129.5, 130.5, 132.8, 166.7; HR-MS (FAB) Calcd for $C_{18}H_{29}O_4$ (M^++H) 309.2066, Found 309.2050.

11-*tert*-Butyldimethylsilyloxy-undecane-1,2-diol (2e) (Table 2, Entry 5) According to the general procedure, the treatment of **1e** (66.4 mg, 0.201 mmol) with 2,2′-bipyridyl (94.8 mg, 0.607 mmol) and TMSOTf (73.1 μl, 0.404 mmol), then treatment of Et_2O (2 ml) and saturated NH_4Cl aq. (2 ml) for 6.5 h gave **2e** (46.2 mg, 72%). Eluent; hexanes/AcOEt (1/1) to AcOEt. White solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.00 (6H, s), 0.85 (9H, s), 1.23—1.46 (16H, m), 2.41 (2H, s), 3.36—3.40 (1H, m), 3.53—3.65 (4H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: −5.3, 18.4, 25.5, 25.8, 26.0, 29.4, 29.5 (2×C), 29.6, 32.8, 33.1, 63.3, 66.8, 72.3; HR-MS (FAB) Calcd for $C_{17}H_{39}O_3Si$ (M^++H) 319.2668, Found 319.2669.

11-Triphenylmethyloxy-undecane-1,2-diol (2f) (Table 2, Entry 6) According to the general procedure, the treatment of **1f** (92.5 mg, 0.202 mmol) with 2,2′-bipyridyl (94.8 mg, 0.607 mmol) and TMSOTf (73.1 μl, 0.404 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 4.5 h gave **2f** (77.5 mg, 86%). Eluent; hexanes/AcOEt (1/1). White solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.26—1.42 (16H, m), 1.58—1.66 (2H, m), 2.04 (1H, br s), 2.14 (1H, br s), 3.03 (2H, t, J=6.7 Hz), 3.40—3.44 (1H, m), 3.63—3.70 (2H, m), 7.20—7.45 (15H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 25.5, 26.4, 29.5, 29.6, 30.0, 33.2, 63.7, 66.8, 72.3, 86.2, 126.8, 127.7, 128.7, 144.5; HR-MS (FAB) Calcd for $C_{30}H_{38}O_3Na$ (M^++Na) 469.2719, Found 469.2724.

1-Hydroxymethylcyclohexanol (2g) (Table 2, Entry 7)[23] According to the general procedure, the treatment of **1g** (21.3 mg, 0.150 mmol) with 2,2′-bipyridyl (140.6 mg, 0.900 mmol) and TMSOTf (110 μl, 0.609 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 1 h gave **2g** (18.5 mg, 95%). Eluent; hexanes/AcOEt (2/1) to hexanes/AcOEt (1/1).

(±)-*trans*-Octane-4,5-diol (2h) (Table 2, Entry 8)[24] According to the general procedure, the treatment of **1h** (31.3 mg, 0.198 mmol) with 2,2′-bipyridyl (185 mg, 1.19 mmol) and TMSOTf (143 μl, 0.791 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 1.5 h gave **2h** (16.1 mg, 56%). Eluent; hexanes/AcOEt (3/1).

***cis*-1,2-Cyclohexanediol (2i) (Table 2, Entry 9)**[20] According to the general procedure, the treatment of **1i** (25.4 mg, 0.198 mmol) with 2,2′-bipyridyl (92.9 mg, 0.595 mmol) and TMSOTf (72 μl, 0.396 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 0.5 h gave **2i** (19.7 mg, 86%). Eluent; hexanes/AcOEt (1/1) to AcOEt.

3-Phenylpropane-1,3-diol (2j) (Table 2, Entry 10)[25] According to the general procedure, the treatment of **1j** (33.3 mg, 0.203 mmol) with 2,2′-bipyridyl (200 mg, 1.28 mmol) and TMSOTf (146 μl, 0.808 mmol), then treatment of Et_2O (2 ml) and 1 N HCl (2 ml) for 1.5 h gave **2j** (27.9 mg, 84%). Eluent; hexanes/AcOEt (1/1).

The Selective Deprotection of 4. 4-{9′,10′-Dihydroxydecyl}-2,2-diphenyl-1,3-dioxolane (5) (Chart 3) TMSOTf (73.1 μl, 0.404 mmol) was added to a solution of methylene acetal **4** (82.9 mg, 0.202 mmol) and 2,2′-bipyridyl (94.6 mg, 0.606 mmol) in CH_2Cl_2 (0.4 ml) at 0 °C under N_2. The reaction mixture was stirred for 30 min at 0 °C. After disappearance of **4** on TLC, Et_2O (2 ml) and 1 N HCl (2 ml) was added to the reaction mixture. The resulting solution was stirred until disappearance of the pyridinium salt (highly polar compound). The mixture was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash SiO_2 column chromatography (hexanes/AcOEt=1/1) to give a diol **5** (63.1 mg, 78%). White solid; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.24—1.74 (16H, m), 2.38 (2H, br s), 3.39—3.42 (1H, m), 3.61—3.69 (3H, m), 4.08—4.16 (2H, m), 7.24—7.34 (6H, m), 7.48—7.52 (4H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 25.5, 25.7, 29.4, 29.5 (2×C), 33.1, 33.4, 66.8, 70.0, 72.3, 76.8, 109.3, 126.2, 127.8, 127.9, 128.1, 142.8; HR-MS (EI) Calcd for $C_{25}H_{34}O_4$ (M^+) 398.2452, Found 398.2457.

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