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A mild and efficient approach for the deprotection of silyl ethers by sodium periodate

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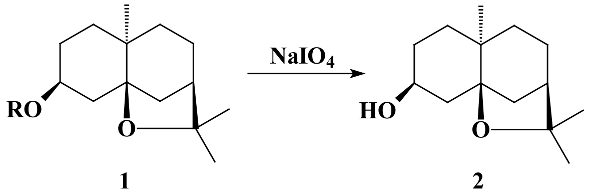
Abstract—A mild and efficient method for the deprotection of silyl ethers is reported. The most often used silyl protecting groups, such as TBDMS, TIPS, TMS, TES, TIBS, TPS can be cleaved by $NaIO_4$ furnishing the corresponding alcohol in high yields. This method can be used for a wide range of substrates. © 2002 Elsevier Science Ltd. All rights reserved.

Silyl ethers are the most widely used hydroxyl protecting groups in organic synthesis. Among silylating reagents, triethylsilyl chloride (TESCl) and *tert*-butyldimethylsilyl chloride (TBDMSCl) are often used as the corresponding silyl ethers are stable towards various reagents and conditions. The deprotection of silyl ethers is usually carried out with tetrabutylammonium fluoride (TBAF),[1] aqueous acid,[2] aqueous HF–CH_3CN[3] or various Lewis acids.[4] Many other methods have also been reported including catalytic transfer hydrogenation using Pd,[5] reductive cleavage by DIBAL-H,[6] oxidative cleavage by DDQ[7] and ultrasonic cleavage in MeOH/CCl_4,[8] together with the use of $PdCl_2(CH_3CN)_2$,[9] I_2,[10] K_2CO_3 in aqueous ethanol,[11] and chloride ions.[12] Herein we report a new mild and efficient method for the deprotection of silyl ethers.

We have serendipitously found that TES can be cleaved by $NaIO_4$ in THF. Because commercial $NaIO_4$ is somewhat acidic, we wondered whether the cleavage of the Si–O bond was caused by the acidity of the periodate. However, when the pH of the reaction was adjusted to neutral or slightly basic, the TES and TBDMS groups were still cleaved. In further investigations, alcohol **2** was used as a model substrate for silyl ether protection and deprotection because its axial hydroxyl is somewhat hindered and this kind of molecule is so sensitive to the vanillin/H_2SO_4 coloring agent that trace amounts of starting material, product or by-product can easily be detected on TLC (Scheme 1). The TMS, TES, TBDMS, TIPS, TIBS, TPS, TBDPS groups were used as protecting groups to investigate the scope of the silyl ether deprotection. The protection of alcohol **2** with various silylating reagents afforded the corresponding silyl ethers **1** using conventional methods. Silyl ethers **1** were treated with $NaIO_4$ in THF at room temperature and the reactions were monitored by TLC. After the usual work-up and chromatography, alcohol **2** (Table 1, entries 1–6) was obtained in high yields.[13] However, the TBDPS groups (Table 1, entries 7 and 8) could not be removed at room temperature, and gave only low yields at elevated temperatures after longer reaction times. The reaction can be performed in either THF/H_2O or aqueous EtOH (Table 1, entry 9; Table 2, entry 6).



Scheme 1.

In order to investigate the applicability of this method to different kinds of substrates, we selected a variety of substrates. Taxanes and a β-lactam (Table 2, entries 1–3) were chosen because they are very sensitive to acidic conditions. Taxanes and *O*-TES-*N*-benzoylphenylisoserine methyl ester (Table 2, entries 2 and 4) were selected to see if α-hydroxy carbonyl groups can endure such conditions, as well as phenolic and *p*-nitrobenzyl alcohols. The results show that the reac-

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Keywords: silyl ether; deprotection; sodium periodate.

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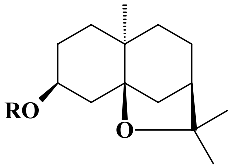
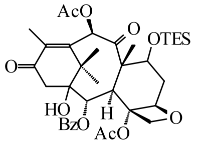
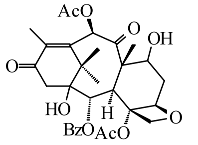
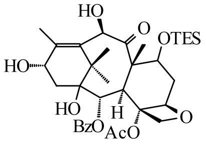
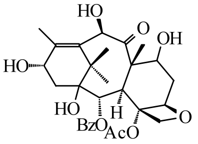
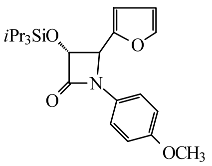
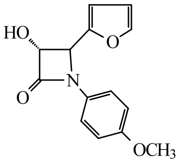
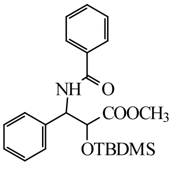
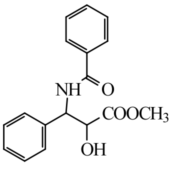
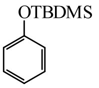
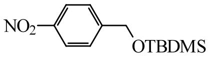
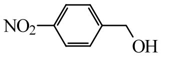
Table 1. Deprotection of silyl ethers **1** with $NaIO_4$ in THF.



1

Entry	R	Solvent	Compd **1**/ $NaIO_4$	Conditions	Yield (%)
1	TMS	THF	1:2.5	rt/1 h	98
2	TES	THF	1:2.5	rt/1 h	100
3	TIPS	THF	1:2.5	rt/1 h	94
4	TBDMS	THF	1:2.5	rt/2 h	95
5	TIBS	THF	1:2.5	rt/1 h	90
6	TPS	THF	1:2.5	rt/2 h	89
7	TBDPS	THF	1:2.5	rt–50°C/48 h	~10
8	TBDPS	THF	1:2.5	50°C/10 d	50
9	TBDMS	EtOH	1:2.5	rt/2 h	93
10	TBDMS	THF	1:1.1	rt/2 h	95
11	TBDMS	THF	1:0.15	rt/1 d	10

Table 2. Deprotection of a variety of silyl ethers

Entry	Substrate	Product	Conditions	Yield(%)
1			30-40 °C/6d, THF	82
2			30-40 °C/6 d, THF	88
3			30-40 °C/10 h, THF	91
4			rt/4 h, THF	90
5		/	THF	/
6			rt/2 h, EtOH rt/4 h, THF	94 93

tions of ethers of β-lactams and taxanes (Table 2, entries 1–3) were slower at room temperature. When the temperature was raised to 30–40°C, both reactions were complete within a few days and gave high yields. Deprotections of taxanes and *O*-TES-*N*-benzoylphenylisoserine methyl ester (Table 2, entries 2 and 4) were achieved and the vicinal hydroxyl-carbonyl group (HO–C–C=O) was stable under these conditions. It is worth noting that the phenolic silyl ether was not cleaved by $NaIO_4$.

We do not know the mechanism of the reaction at this stage. However, we are certain that this reaction is a stoichiometric one. When $NaIO_4$ was used in 1.1–2.5 mole ratio, the reaction went to completion (Table 1, entries 9 and 10), whereas 0.15 mole equivalents of $NaIO_4$ did not drive the reaction to completion (Table 1, entry 11). Therefore the reaction is not a catalytic cleavage of the Si–O bond.

In conclusion, a new, mild and facile method for the deprotection of various silyl protecting groups using $NaIO_4$ is reported, and this method is suitable for a wide range of organic compounds.

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13. General procedure for deprotection of silyl ethers: A mixture of aqueous $NaIO_4$ (2.5 mmol in 2 mL H_2O) in THF (or EtOH) (8 mL) was added to the silyl ether (1 mmol) and the mixture was stirred at the appropriate temperature until the reaction was finished. The solvent was removed under vacuum, and the residue was diluted with water (10 mL) and extracted with EtOAc (20 mL× 3). The extracts were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was chromatographed over silica gel to afford the corresponding alcohol.