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PAPER

A mild and efficient method for the selective deprotection of silyl ethers using KF in the presence of tetraethylene glycol†

Hailong Yan,[a] Joong-Suk Oh[a] and Choong Eui Song*[a,b]

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A mild and efficient protocol for the deprotection of silyl ethers using KF in tetraethylene glycol is reported. A wide range of alcoholic silyl ethers can be selectively cleaved in high yield in the presence of certain acid- and base-labile functional groups. Moreover, the phenolic silyl ethers were cleaved exclusively, without affecting the alcoholic silyl ethers, at room temperature.

Introduction

Protection/deprotection protocols using silyl protecting groups are among the most widely used methods of temporarily masking alcohols and phenols.[1] With the increasing complexity of the synthetic targets, methods of selectively removing one such silyl group in the presence of another are required. Generally, fluoride compounds, inorganic bases and inorganic acids are used to cleave silyl ethers.[1] Tetrabutylammonium fluoride (TBAF) is the most typical desilylating reagent, but it has possible side-reactions caused by the nucleophilicity of the fluoride ion.[2] Furthermore, cleavage using fluoride is often associated with poor selectivity in the case of compounds having two different siloxy groups, which can give rise to unwanted side reactions such as silyl migration.[3] Moreover, commercial TBAF is known to contain water which makes it difficult to achieve anhydrous conditions.

Recently, we found that bis-terminal hydroxyl polyethers such as tetraethylene glycol and their chiral variants can serve as powerful multifunctional organic promoters *via* a cooperative activation mechanism in a range of fluoride-promoted reactions such as nucleophilic substitution and enantioselective desilylative kinetic resolution of silyl ethers of racemic secondary alcohols.[4] As shown in Fig. 1, the ether groups act as a Lewis base toward K^+, "freeing" the counter anion, as well as "enhancing" the solubility of the alkali metal salts. On the other hand, one of the two terminal OH groups forms controlled H-bonding with the fluoride anion, decreasing the basicity of the nucleophile, whereas the other -OH group is able to simultaneously activate the electrophile by hydrogen bonding, thereby stabilizing the transition state.

To demonstrate that our concept is generally applicable to other fluoride-promoted organic reactions, we also examined the deprotection of silyl ethers with KF in tetraethylene glycol and report herein an efficient and chemoselective desilylation protocol.

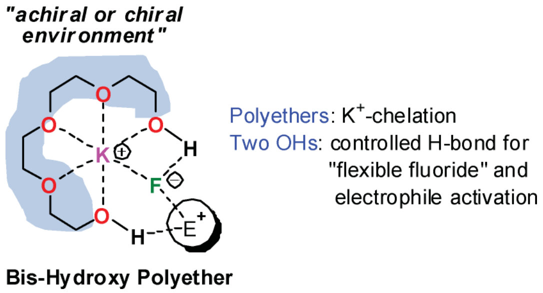

Fig. 1 Bis-terminal hydroxy polyethers (*e.g.*, tetraethylene glycol) as multifunctional promoters.

Results and discussion

As shown in Table 1, a wide range of silyl-protected hydroxy groups were cleaved in high to excellent yields under our reaction conditions using KF in tetraethylene glycol. The trimethylsilyl (TMS) and triethylsilyl (TES) groups of primary, secondary and tertiary alcohols can be rapidly and cleanly removed at room temperature (entries 1–9). The sterically more bulky *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS) and triisopropylsilyl (TIPS) ethers of alcohols were cleaved at elevated temperature (80 °C) (entries 10–13).

We also examined the desilylation of TES ethers containing acid and base labile groups. As shown in entries 14 and 15 in Table 1, the silyl ethers **1n** and **1o** were cleanly deprotected to give the corresponding alcohols in high yield, while acid-sensitive functional groups such as tetrahydropyranyl (THP) and furanyl groups were unscathed under these conditions. The base-sensitive silyl ether **1p** can also be selectively deprotected without racemization (entry 16). It is also noteworthy that a highly base-sensitive acetate of phenol was also well-preserved (entry 17). As mentioned previously, tetra-n-butylammonium fluoride (TBAF) is inappropriate for base sensitive substrates, due to the strong basicity of the fluoride anion.[5]

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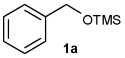
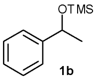
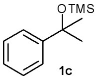
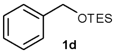
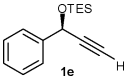
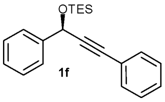
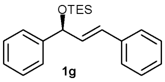
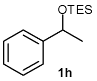
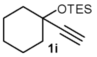
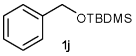
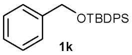
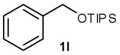
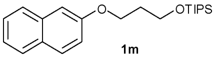
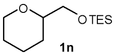
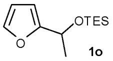
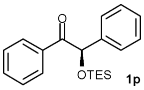
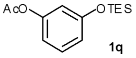
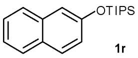
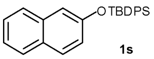
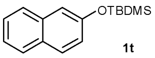
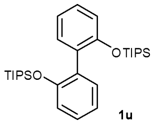
[a] *Department of Chemistry, Sungkyunkwan University, 300 Cheoncheon, Jangan, Suwon, Gyeonggi, 440-746, (Korea). E-mail: s1673@skku.edu; Fax: (+82) 31-290-7075*
[b] *Department of Energy Science, Sungkyunkwan University, 300 Cheoncheon, Jangan, Suwon, Gyeonggi, 440-746, (Korea)*

† Electronic supplementary information (ESI) available: HPLC Spectra for entry 16 of Table 1 and characterization data, 1H and 13 C NMR spectra for Table 2. See DOI: 10.1039/c1ob06300f

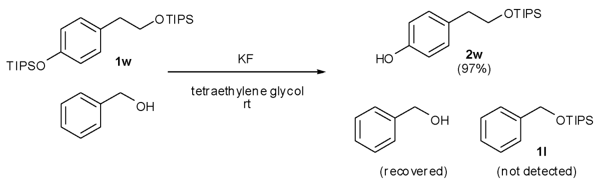
Table 1 Deprotection of silyl ethers using KF in presence of tetraethylene glycol[a]

Entry	Substrate	Time	t (°C)	Yield/%[b]
1	 1a	5 min	rt	99
2	 1b	10 min	rt	94
3	 1c	20 h	rt	80
4	 1d	30 min	rt	98
5	 1e	30 min	rt	95
6	 1f	30 min	rt	98
7	 1g	2.5 h	rt	91
8	 1h	3 h	rt	99
9	 1i	24 h	rt	82
10	 1j	3 h 5 h	70 80	94 92
11	 1k	3.5 h	80	99
12	 1l	1.5 h	80	95
13	 1m	5 h	80	97
14	 1n	2.5 h	rt	98
15	 1o	4 h	rt	99
16[c]	 1p	2 h	rt	93
17	 1q	20 min	rt	98
18	 1r	15 min	rt	98
19	 1s	30 min	rt	96
20	 1t	30 min	rt	98
21[d]	 1u	30 min	rt	96

[a] All reactions were carried out with 0.1 mmol of the substrate and 1.5 equiv of KF in tetraethylene glycol (1.0 mL). [b] Isolated yields. [c] The enantiopurity of the obtained alcohol was determined by chiral HPLC analysis using a chiral stationary phase (See ESI†). [d] The reaction was carried out with 3.0 equiv KF.

We also examined the desilylation of silyl protected phenols, as shown in Table 1 (entries 17–21), and found that even sterically bulky silyl groups such as TIPS, TBDMS and TBDPS could be completely removed within 30 min at room temperature in nearly quantitative yield. The significantly different desilylation conditions of sterically bulky silyl ethers of phenols (entries 18–21) and alcohols (entries 10–13) prompted us to examine the possibility of the chemoselective deprotection of phenolic silyl ethers in the presence of the alcoholic silyl ethers.

Because many biologically significant natural products such as vancomycin, teicoplanian, novobiocin, and phenolic glycoconjugates possess both phenol and alcohol functional groups, the chemoselective removal of phenolic silyl protection in the presence of aliphatic silyl ethers is of considerable interest.[6] However, relatively few options are available for the selective removal of aryl silyl ethers in the presence of alcoholic silyl ethers.[7,8] In this context, we were pleased to find that phenolic silyl ethers of **1v–1z** were cleaved exclusively, without affecting the aliphatic silyl ethers, at room temperature (Table 2). The chemoselectivity is higher than 99%. Compared to the protocols reported to date, our method is remarkably mild and selective. We then conducted the deprotection of bis-TIPS-protected 4-(2-hydroxyethyl)phenol **1w** in the presence of excess benzyl alcohol to confirm that the retaining of the alkyl silyl ethers was not the result of possible silyl exchange or migration (Scheme 1).[9] The absence of formation of benzyl TIPS ether **1l** excludes the possibility of silyl redistribution.

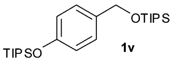
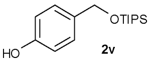
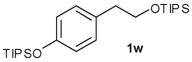
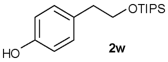
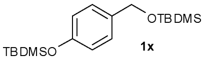
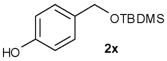
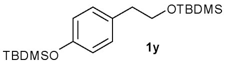
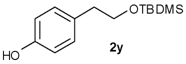
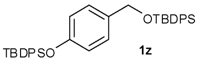
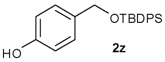


Scheme 1

Conclusion

In summary, we developed a mild and efficient protocol for the deprotection of silyl ethers (TMS, TES, TBDMS, TBDPS, TIPS ethers) using KF in tetraethylene glycol. A wide range of alcoholic

Table 2 Selective desilylation of phenolic silyl ethers in the presence of alcoholic silyl ethers[a]

Entry	Substrate	Product	Time/h	t (°C)	Yield/%[b]
1	 1v	 2v	3	rt	93
2	 1w	 2w	4	rt	92
3	 1x	 2x	3	rt	94
4	 1y	 2y	3	rt	98
5	 1z	 2z	4	rt	99

[a] All reactions were carried out with 0.1 mmol of the substrate and 1.5 equiv KF in tetraethylene glycol (1.0 mL) at room temperature. [b] Isolated yields.

silyl ethers can be selectively cleaved in high yield in the presence of certain acid- and base-labile functional groups. Moreover, the phenolic silyl ethers were cleaved exclusively, without affecting the alcoholic silyl ethers, at room temperature. The advantages of this procedure over the previously reported processes include its simplicity and the clean and rapid reactions it promotes. Therefore, we believe that this protocol will find wide applications in the synthesis of complex molecules.

Experimental

General procedures for the desilylation reactions

Spray dried potassium fluoride (8.7 mg, 0.15 mmol) and dried tetraethylene glycol (1.0 mL) were added to a vial and stirred with a magnetic stirring bar. The silyl protected substrate (0.1 mmol) was then added and the reaction mixture stirred at room temperature or 80 °C. The reaction was followed by TLC (EtOAc : hexanes = 1 : 4) until the starting materials were no longer detected. After the reaction was completely finished, the reaction mixture was quenched with water (10 mL) and extracted with diethyl ether (10 mL X 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and purified by short silica column chromatography (EtOAc : hexane = 1 : 4) to afford the desilylated alcohol product as a colorless oil or solid.

Acknowledgements

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