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APPLICATION OF SO_3H SILICA GEL TO DEPROTECTION OF SILYL ETHERS

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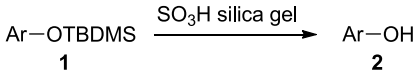
Abstract – A newly developed SO_3H silica gel cleaved the *O*-Si bonds in various aryl and alkyl silyl ethers to give the corresponding phenols and alcohols in good to excellent yield. The crude filtrates contained no silyl residues. The solid phase ^{29}Si NMR analyses of the SO_3H silica gel strongly suggested that the silyl residues were captured by silanol groups on the surface of the silica gel. The SO_3H silica gel could be recycled at least ten times without any loss of activity. The disappearance of silyl residues in the crude filtrate was observed in even the 10th repetition. Our method provides an easily handled desilylation method that requires no further purification. Our method was also applicable to a selective desilylation reaction of a derivative **5** with different siloxy groups or desilylation of an alkaloid derivative **7**.

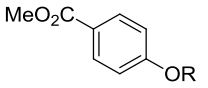
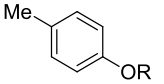
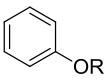
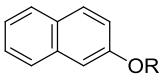
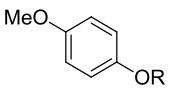
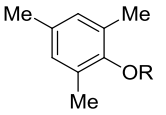
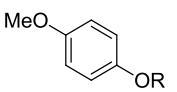
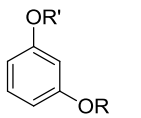
For several decades, solid-supported reagents have been widely used in organic synthesis.[1] The solid-supported reagents are expected to reduce waste products and to provide efficient and environmentally benign processes. Indeed, solid catalysts can not only be easily separated from the reaction products by simple filtration, but are also recyclable. We recently developed a silica gel whose surface was modified by alkylsulfonic acid groups (SO_3H silica gel)[2] for the purpose of scavenging amines or purifying acidic materials. Some applications of aryl sulfonic acid immobilized on silica gel have been reported: cleavage of Bn, *i*-Pr, *t*-Bu, allyl, or MOM groups[3] in aromatic ethers; an efficient preparation of *o*-quinone methides for hetero Diels-Alder reaction;[4] and for scavenging isocyanides.[5] Reactions in the presence of

silica sulfuric acid[6] or silica gel supported $NaHSO_4$[7] has also been reported. However, to the best of our knowledge, there has been no application in organic synthesis of a SO_3H silica gel on which alkylsulfonic acid groups are immobilized. Herein, we report the first application of a SO_3H silica gel to deprotection of aryl or alkyl silyl ethers.

We attempted the cleavage of various aryl TBDMS ethers **1** (Table 1).[8,9] The electron rich aryl silyl ether was cleaved under milder reaction conditions (entry 3), whereas the reaction of the electron deficient aryl silyl ether progressed more slowly (entry 1). The deprotections of all the tested TBDMS ethers **1** were completed at 50 ºC or lower reaction temperature within 60 min to provide the corresponding phenolic derivatives **2** in excellent yields except for **1b** (entry 2). The sublimation property of phenol **2b** may account for the low isolated yield. Under the reaction conditions, benzoate was tolerate (entry 1), but aryl acetate was labile (entry 8). This procedure was applicable to a large scale reaction (entry 4). It is noteworthy that no signals stemming from silyl residues were observed in the ^{1}H NMR analyses of the crude products. This result indicates that this procedure can achieve the desilylation process without need for additional purification.

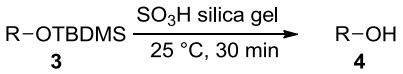
Table 1. Desilylation of aryl TBDMS ethers **1**

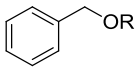
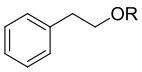
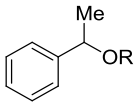
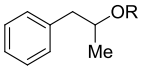
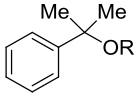
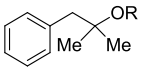


Entry	Compound	Temp (ºC)	Time (min)	Conversion[a] (%)	Yield[b] (%)	Entry	Compound	Temp (ºC)	Time (min)	Conversion[a] (%)	Yield[b] (%)
1	 **1a**: R=TBDMS **2a**: R=H	50	60	99	82	5	 **1d**: R=TBDMS **2d**: R=H	50	30	99	96
2	 **1b**: R=TBDMS **2b**: R=H	50	30	99	47	6	 **1e**: R=TBDMS **2e**: R=H	50	30	98	98
3	 **1c**: R=TBDMS **2c**: R=H	25	10	quant.	quant.	7	 **1f**: R=TBDMS **2f**: R=H	50	30	99	93
4[c]	 **1c**: R=TBDMS **2c**: R=H	25	30	quant.	96	8	 **1g**: R=TBDMS, R'=Ac **2g**: R=R'=H	50	30	quant.	95

[a] Conversion (%) was determined by the integral ratio of the ^{1}H NMR of the crude product.
[b] Isolated yield.
[c] In this run, compound **1c** (2.38g, 10 mmol) was used.

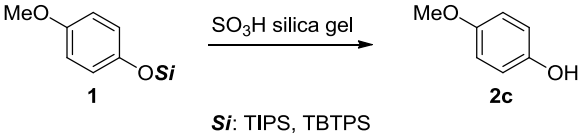
Table 2. Desilylation of alkyl TBDMS ethers **3**

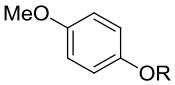
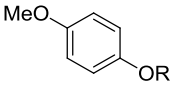


Entry	Compound	Conversion[a] (%)	Yield[b] (%)	Entry	Compound	Conversion[a] (%)	Yield[b] (%)
1	 **3a**: R=TBDMS **4a**: R=H	quant.	73[c]	4	 **3d**: R=TBDMS **4d**: R=H	97	88
2	 **3b**: R=TBDMS **4b**: R=H	quant.	72[c]	5	 **3e**: R=TBDMS **4e**: R=H	quant.	quant.
3	 **3c**: R=TBDMS **4c**: R=H	96	-[d]	6	 **3f**: R=TBDMS **4f**: R=H	99	97

[a] Conversion (%) was determined by the integral ratio of the ^{1}H NMR of the crude product.
[b] Isolated yield.
[c] The ^{1}H NMR spectra of the crude product indicated only the alcohol **4**.
[d] The ratio of alcohol **4c**/styrene derivative was 1/8.

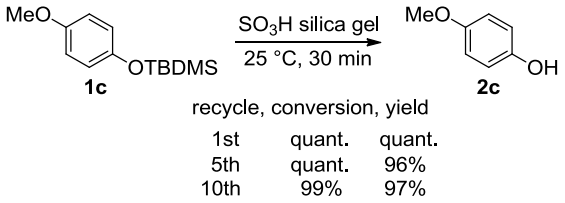
Table 3. Desilylation of *p*-methoxyphenyl silyl ethers **1**



Entry	Compound	Temp (ºC)	Time (min)	Conversion[a] (%)	Yield[b] (%)	Entry	Compound	Temp (ºC)	Time (min)	Conversion[a] (%)	Yield[b] (%)
1		50	30	87	ND[c]	3		50	120	42	ND[c]
2	**1h**: R=TIPS **2c**: R=H	50	120	quant.	79	4	**1i**: R=TBDPS **2c**: R=H	100	120	quant.	91

[a] Conversion (%) was determined by the integral ratio of the ^{1}H NMR of the crude product.
[b] Isolated yield.
[c] not determined. The isolated yield was not determined because the reaction was not complete.

We next applied the procedure to the deprotection of alkyl TBDMS ethers **3** (Table 2). All the tested alkyl TBDMS ethers **3** were smoothly desilylated at 25 ºC to give the corresponding alcohols in good to excellent yield except for **3c** (entry 3), regardless of the structural feature; primary, secondary, or tertiary ethers were all highly reactive. As we expected, the *O*-Si bonds of alkyl silyl ethers **3** were more easily cleaved and the desilylation of alkyl silyl ethers **3** was completed under milder reaction conditions compared to aryl silyl ethers **1**.[10] The reaction of silyl ether **3c** provided a styrene derivative as the main product due to the



Scheme 1. Recycling of the SO_3H silica gel for the desilylation of **1c**

(a) (b)

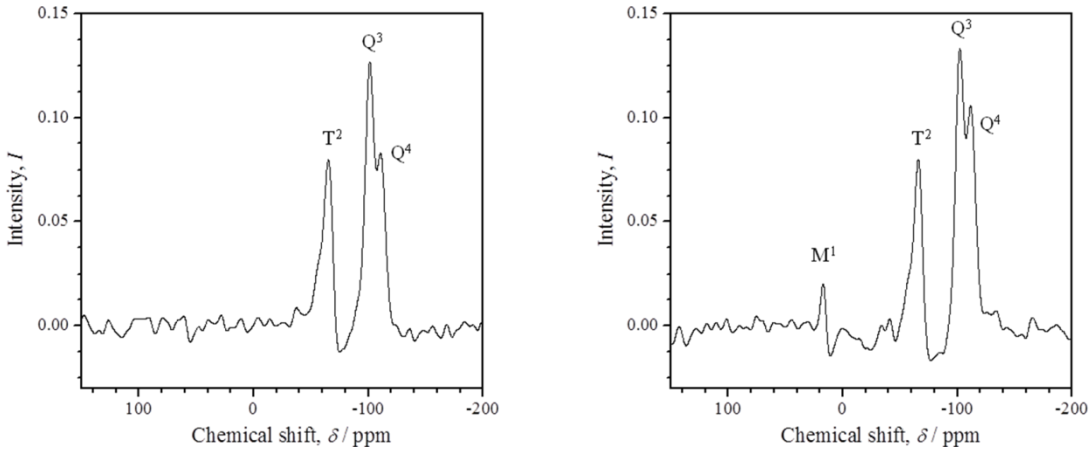
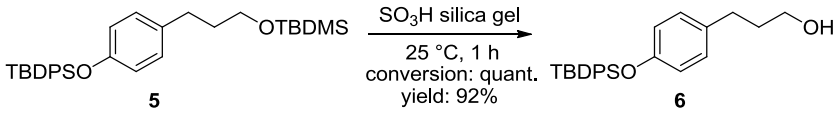


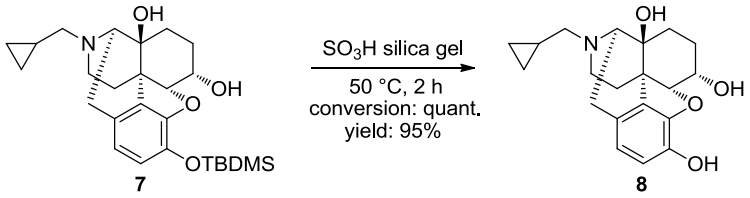
Figure 1. Solid phase ^{29}Si NMR spectra (500 MHz). (a) Unused SO_3H silica gel, (b) SO_3H silica gel used ten-times for the desilylation reaction. The signals at 18 ppm, -65 ppm, -100 ppm, and -111 ppm were assigned to ***Si***(O-Si)C_3 (M^1), ***Si***(O-Si)$_2$(OH)C (T^2), ***Si***(O-Si)$_3$(OH) (Q^3), and ***Si***(O-Si)$_4$ (Q^4), respectively.

occurrence of an elimination reaction *via* the stable tertiary benzylic cation (entry 3). In the case of alkyl TBDMS ethers, no silyl residues were also observed in the crude product. Although Das *et al.* reported the deprotection of alkyl TBDMS ethers using silica gel supported $NaHSO_4$, there was no description about the silyl residues in the crude product.[7k,11] Other aryl silyl ethers with silyl groups bulkier than TBDMS group were applied to this procedure (Table 3). The TIPS or *t*-butyldiphenylsilyl (TBDPS) ethers are reported to be 35- or 250-fold more stable toward acid than the TBDMS ethers.[10] These bulky and stable silyl ethers required higher reaction temperatures and/or longer reaction times for cleavage of their *O*-Si bonds as compared to TBDMS ethers (entries 2 and 4). In contrast to the case of TBDMS ethers in which no silyl residues were observed in the crude product, TIPS or TBDPS ethers provided crude product mixtures that included TIPS or TBDPS residues. However, the use of far longer reaction times and/or higher reaction temperatures decreased the amount of silyl residues in the crude products and, ultimately, almost no silyl residues were detected.[12]

After removing the eluent under reduced pressure, the used SO_3H could cleave the *O*-Si bond. The SO_3H silica gel was a reagent that was at least ten times recyclable without any loss of activity (Scheme 1). It is



Scheme 2. Selective desilylation of compound **5**



Scheme 3. Desilylation of compound **7**

worthnoting that no silyl residues were detected in the crude product, even after the 10th run.[13] We carried out a solid phase ^{29}Si NMR analysis of the SO_3H silica gel, which had been used ten times for the desilylation process (Figure 1b). In comparison with ^{29}Si NMR spectrum of unused SO_3H silica gel (Figure 1a), a signal was apparent at 18 ppm, which was assigned to ***Si***(O-Si)C3 (M^1), *i.e.* the trialkylsilyl group bound to a silanol, in the ^{29}Si NMR spectrum of the ten times used SO_3H silica gel. Moreover, the relative intensities of the signals at -65 and -100 ppm, which were assigned, respectively, to the silyl group in the side chain[14] and the silanol group on the surface of the silica gel, decreased compared to the intensity of the signal at -111 ppm, which was thought to be unchanged because the signal arose from the structure of the silica gel itself. These observations strongly suggested that the silyl residues provided by desilylation were captured by silanol groups on the surface of the silica gel. The TBDMS group could smoothly react with the silanol groups under these desilylation conditions. On the other hand, the bulkiness of the TIPS or TBDPS groups would retard the reaction of the silyl groups with the silanol groups. As a result, the disappearance of these bulky residues would require a longer reaction time and/or higher reaction temperature.

This procedure was applicable to a selective desilylation; compound **5** with different siloxy groups was selectively converted into TBDPS ether **6** (Scheme 2). The *O*-Si bond of α-naltrexol-3*O*-TBDMS ether (**7**) was also cleaved to give α-naltrexol (**8**) (Scheme 3).[15]

In conclusion, we found that the newly developed SO_3H silica gel cleaved the *O*-Si bonds in various aryl and alkyl silyl ethers to give the corresponding phenols and alcohols in good to excellent yields. These methods provide the desilylation procedures without purification because the crude products contained no silyl residues. The solid phase ^{29}Si NMR analyses of the SO_3H silica gel strongly suggested that the silyl residues were captured by the silanol groups on the surface of the silica gel. The SO_3H silica gel could be recycled at least ten times without any loss of activity. The disappearance of silyl residues in the crude product was observed in even the 10th repetition. The methods were also applicable to a selective desilylation reaction or desilylation of an alkaloide derivative.

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T. Aoyama, T. Takido, and M. Kodomari, *Tetrahedron Lett.,* 2012, **68**, 7077.

8. General procedure: The mixture of SO_3H silica gel (2 g) and the heptane solution[9] of the silyl ether (0.4 M, 1 mL) was shaken for one min and left to stand at an appropriate temperature. The silica gel appeared to be powdered because only a small amount of solvent was used. After an appropriate reaction time, the substrates were eluted by methanol and SO_3H silica gel was removed by filtration.
9. Various solvents were applicable. See the supporting information in detail.
10. P. G. M. Wuts and T. W. Greene, 'Greene's Protective Groups in Organic Synthesis,' 4th ed. John Wiley & Sons, New Jersey, 2007, p. 164.
11. According to reference 7k, the silica gel supported $NaHSO_4$ could not cleave the bond *O*-Si bond of the phenyl TBDMS ether.
12. The ^1H NMR spectra of the crude products in the desilylation of **1i** under various reaction conditions (50 ºC, 120 min, higher reaction temperatures, and longer reaction times) are shown in the supporting information.
13. The SO_3H silica gel has silanol groups at the density of 1.8–2.3 mmol/g. Therefore, theoretically at least 1.8–2.3 mmol of silyl residue was capable to be captured when the 1 g of the SO_3H silica gel was used.
14. The SO_3H silica gel has side chains on which the SO_3H groups are attached. The side chains are bound to the silica gel through silica gel-O-C or (silica gel-O)$_2$-Si-C bonds.
15. In this reaction, some amount of silyl residue remained in the crude product. Since compound **7** has a basic nitrogen, SO_3H groups immobilized on the silica gel might be partly neutralized to retard the capture of silyl residues by silanols.