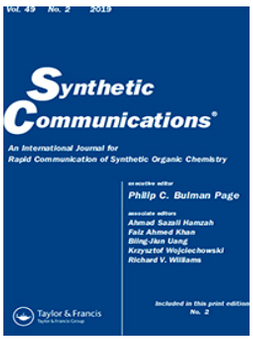

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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Fumika Karaki, Miki Kuwada, Saki Tajiri, Misaki Kanda, Mari Yanai, Mitsuhiro Kamimura, Kennosuke Itoh & Hideaki Fujii (2019) A deprotection procedure using SO_3H silica gel to remove non-silyl protecting groups, Synthetic Communications, 49:2, 212-220, DOI: 10.1080/00397911.2018.1548023

To link to this article: https://doi.org/10.1080/00397911.2018.1548023

SYNTHETIC COMMUNICATIONS®
2019, VOL. 49, NO. 2, 212–220
https://doi.org/10.1080/00397911.2018.1548023

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A deprotection procedure using SO_3H silica gel to remove non-silyl protecting groups

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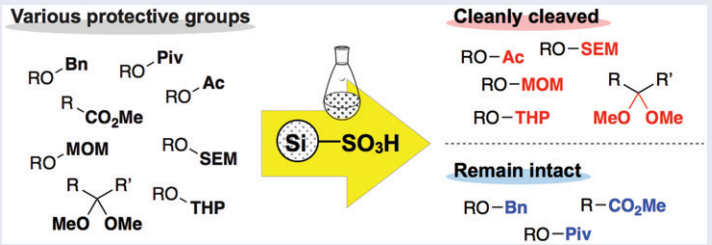
ABSTRACT

Protecting groups are indispensable in organic synthesis and there is a great need for a variety of deprotection methods. Here, we investigated the scope of the application of a deprotection procedure using SO_3H silica gel, which we have previously reported as a desilylation procedure. Under these conditions, -OMOM, -OSEM, -OTHP, and -OAc groups and dimethyl acetal were cleaved. Pivaloyloxy, benzyloxy and methoxy carbonyl groups remained intact and selective deprotection of TBS groups in the presence of other protecting groups was accomplished. We succeeded in cleaving an acetyl group on a secondary alcohol in a highly polar nortropine derivative. Our findings here provide another deprotection option and would be helpful in the synthesis of multifunctional compounds.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 26 September 2018

KEYWORDS
SO_3H silica gel; solid-supported catalyst; acid-catalyzed deprotection

Introduction

Protection and deprotection sequences are indispensable in organic synthesis, even in the 21st century.[1,2] As the number of reactive functional groups increases in proportion to the complexity of the molecules, selective protection and deprotection methods have been adopted in synthesizing these molecules.[3–7] However, only a limited number of methods to cleave protecting groups are available in the arsenal of the chemist: acidic,[8,9] basic,[10,11] oxidative and reductive conditions,[12–15] nucleophilic

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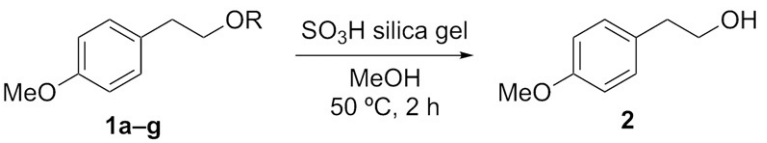
substitutions,[16–18] etc. With this limited number of procedures, we must selectively cleave the desired groups.

We have previously reported a desilylation method using SO_3H silica gel, an alkylsulfonic acid-functionalized silica gel.[19,20] This procedure is environmentally friendly since the SO_3H silica gel could be reused for deprotection without pretreatment. Moreover, simple filtration and elution processes were sufficient to obtain the crude product. No aqueous workup was required. As the obtained crude products contained no silyl residues in almost all cases, no additional purification processes were needed. These features allowed us to reduce the usage of organic solvent and to limit the emission of polluted water. Although this method has been applied only to the cleavage of silyl ethers thus far, it has the potential to cleave a wider variety of protecting groups by extending the scope of application. Also, information on the tolerance of various functional groups toward SO_3H silica gel would be useful in achieving selective deprotection of a desired protecting group in the construction of highly functionalized complex molecules. In this report, we explored the tolerance and lability of various protecting groups to our deprotection procedure using SO_3H silica gel.

Results and discussion

To determine the relative lability of protected alcohols and ketones to SO_3H silica gel, we treated them with the TBS-cleaving conditions in our previous report[19,20] (Tables 1 and 2). Although we identified heptane as an optimal solvent in that report, undesired dimers contaminated the product when the procedure was applied to MOM or SEM protected alcohols **1a** and **1 b**.[1] To circumvent this problem, we employed another condition: 50 °C, 2 h in methanol. Under these conditions, production of dimer was com-

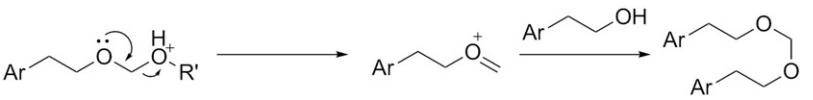
Table 1. Deprotection of protected alcohols.



Entry	Starting material	*R*	Yield (%)[a]
1	**1a**	MOM	88
2	**1b**	SEM	81[b]
3	**1c**	THP	93[b]
4	**1d**	Bn	0
5[c]	**1e**	Tr	28[d] (21)[e]
6	**1f**	Ac	93
7	**1g**	Piv	1 (51)[f]

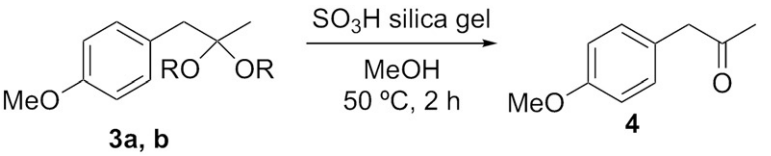
[a]Isolated yields; [b]No purification process was needed; [c]Toluene was used as a solvent instead of methanol; [d]3 h; [e]24 h; [f]120 °C, 24 h.

[1]This dimer may be produced through the elimination of the protonated alkoxide moiety and the subsequent addition of the deprotected alcohol to the resulting oxonium cation (see Scheme 1). Methanol used in these reaction was not dehydrated grade and contained several amounts of water. It is possible that this water hydrolyzed the oxonium cation intermediate and suppressed the formation of the dimers.



Scheme 1. Proposed mechanism for the production of the dimers. R = Me or $CH_2CH_2SiMe_3$.

Table 2. Deprotection of protected ketones.



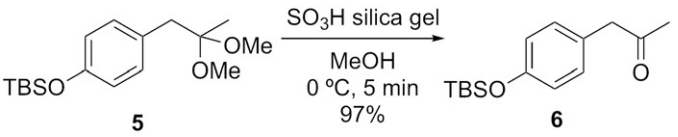
Entry	Starting material	*R*	Yield (%)[a]
1	**3a**	Me	92[b]
2	**3b**	—$(CH_2)_2$—	29 (0)[c]

[a]Isolated yields; [b]No purification process was needed; [c]8 h. The reaction gave a complex mixture.

pletely suppressed in the case of SEM-protected alcohol **1 b** (Table 1, entry 2). On the other hand, the crude product was contaminated with *ca.* 4% of dimer in the case of MOM ether **1a**, and column chromatography was required to obtain pure alcohol **2** (Table 1, entry 1). Tetrahydropyranyl groups were cleanly cleaved in methanol and no purification was needed in this case (Table 1, entry 3). The benzyl group, another ether protecting group, remained completely intact (entry 4). Our attempt to test more acid-labile trityl-protected alcohol **1e** failed due to the poor solubility of the compound in methanol. Instead, we used toluene as a solvent and treated with SO_3H silica gel for 3 h, which is another TBS-cleaving condition we have reported earlier[19] (entry 5). The deprotected alcohol **2** was obtained in 28% yield in 3 h. However, even after 24 h, the starting material **1e** did not disappear and product yield was not improved. As the formed trityl cation is stable, this should rebind to the hydroxy group of the product **2**. As for acyl protecting groups, while the acetyl group was deprotected cleanly (entry 6), the more bulky pivaloyl group was almost intact under this condition (entry 7). Although pivaloyl-protected **1 g** was consumed under harsh conditions (120 °C, 24 h), the yield of **2** was not satisfactory.[2] We next applied our procedure to protected ketones (Table 2). Dimethyl acetal was deprotected efficiently to furnish the ketone **4** (entry 1). In the case of more acid-resistant 1,3-dioxolane (entry 2), a large portion of the starting material remained in the crude mixture. Complete consumption of **3 b** was accomplished after 8 h, but this condition gave a complex mixture.

Next, we attempted to convert esters to carboxylic acids using SO_3H silica gel.[21] When the procedure was applied to benzyl 4-methoxyphenylacetate or *tert*-butyl 4-methoxyphenylacetate, a *ca.* 6:4 mixture of the desired 4-methoxyphenylacetic acid and

[2]By adding methanol solutions of the substrates to SO_3H silica gel, we obtained fluffy powder of silica gel. Then the powder was heated at the indicated temperatures. Thus the reactions could be performed above the boiling points of the solvents.



Scheme 2. Selective deprotection of dimethyl acetal in the presence of TBS group.

undesired methyl 4-methoxyphenylacetate was furnished after consumption of the starting materials. Production of methyl ester could not be suppressed even when the reaction was performed in toluene (benzyl ester: 120 °C, 24 h, *tert*-butyl ester: 50 °C, 3 h) and the crude product was eluted with 1% acetic acid in chloroform, i.e. under the conditions in the absence of methanol.[3] We applied this procedure to the methyl 4-methoxyphenylacetate (methanol, 50 °C, 2 h), and found that this group was almost intact under these conditions.

With information on lability and tolerance of various functional groups to SO_3H silica gel in hand, we next attempted selective deprotection of highly acid-labile protecting groups in the presence of the TBS group. At 0 °C, the TBS group remained intact for 5 min and selective conversion of dimethyl acetal to ketone was accomplished (Scheme 2). This result encouraged us to apply the procedure to the selective deprotection of acid-cleavable alcohol protecting groups (Table 3). Unfortunately, acetyl, SEM, and MOM groups remained unchanged under these conditions (entries 1–3). Although the selective deprotection of the THP group in **7d** partially progressed under the condition (5 min), prolonged reaction time did not give pure mono-protected alcohol **8** due to the concomitant production of diol **9** (entry 4).

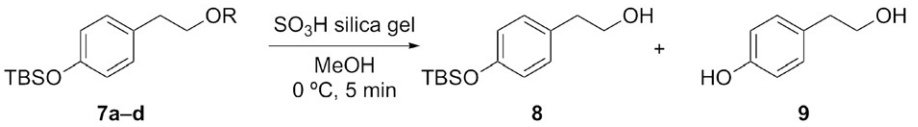
We turned our attention to the selective deprotection of TBS groups in the presence of other protecting groups (Table 4). In the presence of pivaloyloxy, benzyloxy, and methoxy carbonyl groups, the TBS groups were cleaved cleanly (entries 1–3).

To show the utility of our deprotection procedure in constructing multi-functional molecules, we applied this procedure to the selective deprotection of the TBS group in the presence of *N*-Fmoc and methoxycarbonyl groups (Scheme 3). Tetrabutylammonium fluoride, the gold standard to cleave silyl ethers, was not considered as an option due to the lability of the Fmoc group.[1] Basic aqueous conditions and Lewis acid conditions were not applicable either due to the presence of methoxycarbonyl group. By using SO_3H silica gel, the desired product **13** was obtained in excellent yield although column purification was needed to remove the silyl residue. Contamination of the silyl residue could not be supressed by using twice as much SO_3H silica gel as the standard procedure. Although we have reported that some amount of silyl residue remained in the crude product in the case of the desilylation of compounds possessing basic nitrogens,[19,20] the substrate **12** has no basic nitrogen. It is now difficult to make out the cause of this contamination.

As our deprotection procedure does not need aqueous workup, it would be applicable to highly hydrophilic compounds. Therefore, we applied this procedure to nortropine derivative **14**. The product **15** is so polar (cLogP = −1.79[4]) that it is difficult to extract from water. As expected, standard solvolysis and extraction from the aqueous layer using

[3] SO_3H silica gel is produced by modifying the surface of silica gel using a trimethoxy-type silane coupling agent. The residual methoxy group may cause the conversion.
[4] The cLogP value was calculated using ChemDraw Professional version 16.0.

Table 3. Attempt to selective deprotection of protected alcohols in the presence of TBS group.

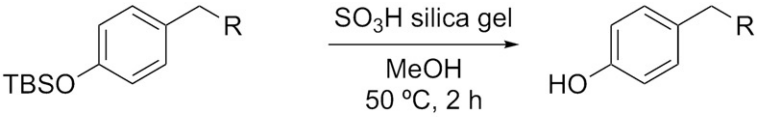


7a–d **8** **9**

Entry	Starting material	*R*	**7:8:9**[a]
1	**7a**	Ac	100:0:0
2	**7b**	SEM	100:0:0
3[b]	**7c**	MOM	100:0:0
4	**7d**	THP	73:27:0 (26:42:31)[c]

[a]The composition ratio was determined from ^{1}H NMR of the crude products; [b]20 min; [c]2 h.

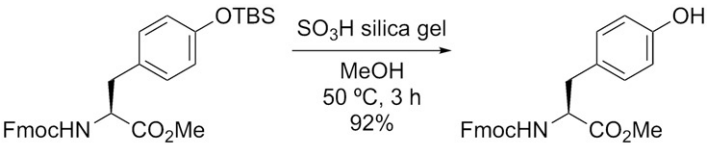
Table 4. Selective deprotection of TBS group in the presence of acid-resistant groups.



10a–c **11a–c**

Entry	Starting material	*R*	Yield (%)[a]
1	**10a**	CH_2OPiv	96
2	**10b**	CH_2OBn	98
3	**10c**	CO_2Me	100

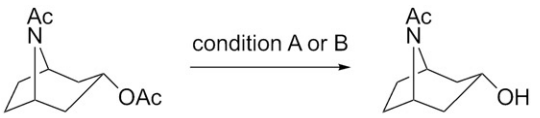
[a]Isolated yields.



12 **13**

Scheme 3. Selective deprotection of TBS group in the presence of other functional groups.

Table 5. Comparison of two *O*-deacetylation protocols.



14 **15**

Condition		Yield (%)[a]
A	K_2CO_3, MeOH, rt, 3 h	33
B	SO_3H silica gel, MeOH, 100 °C, 6 h	75

[a]No purification process was needed.

dichloromethane gave only low yield of **15** (Table 5, condition A). In sharp contrast, our deprotection procedure gave a moderate yield of **15,** although rather harsh condition was needed to deprotect the acetyl group on a secondary alcohol moiety (condition B).

Conclusions

We have explored the scope of application of a deprotection procedure using SO_3H silica gel to remove non-silyl protecting groups. Conventional protecting groups for alcohols (MOM, SEM, THP and acetyl groups) and dimethyl acetal were cleaved cleanly. *O*-Pivaloyl, *O*-benzyl, and methoxycarbonyl groups, on the other hand, remained intact. Based on these findings, selective deprotection was accomplished. In addition, the superiority of this procedure in synthesizing polar compounds was shown. Our finding here will present SO_3H silica gel as a choice in the development of synthetic strategies for complex multi-functional compounds.

Experimental

General information

All reagents and solvents were obtained from commercial suppliers and were used without further purification. IR spectra were recorded on a JASCO FT/IR-460Plus. NMR spectra were recorded on an Agilent Technologies VXR-400NMR for ^{1}H- and ^{13}C-NMR. Chemical shifts were reported as δ values (ppm) referenced to tetramethylsilane. MS were obtained on a JEOL JMS-100LP or JMS-AX505HA by applying an electrospray ionization (ESI) or electron impact (EI) method. The progress of the reaction was determined on Merck Silica Gel Art. 5715 (TLC). Column chromatographies were carried out using CHROMATOREX® PSQ 60B (Fuji Silysia) or Hi-Flash™ Column M or L (Yamazen Cooperation). SCAVENGER SO_3H SILICA (Fuji Silysia), which contains 5%wt of water, was used for the deprotection reactions. The reactions were performed under an argon atmosphere unless otherwise noted.

Deprotection protocol using SO_3H silica gel

Deprotection using SO_3H silica gel was conducted according to our previous reports.[19,20] A solution of substrates with protective groups (0.4 mmol) in the indicated solvent (1 mL) was treated with SO_3H silica gel (2 g, 0.2 mmol/g). After shaking for 1 min, resulting powder was left to stand at the indicated temperature. Then, the powder was put on the pad of Celite and eluted with MeOH (30 mL). The obtained eluate was concentrated under reduced pressure to yield the products. No purification process was required when compounds **1 b**, **1c**, **3a**, **10a–c** and **14** were used as starting materials. In the case of compound **12**, although 0.1 mmol/g of SO_3H silica gel was used, silyl residues were not completely trapped by silica gel and purification process was required.

Characterization of deprotected products

4 -Methoxyphenethyl alcohol (2)

The spectral data for this compound coincided with those of commercially obtained one.

4 -Methoxyphenylacetone (4)

The spectral data for this compound coincided with those of commercially obtained one.

4 -Hydroxyphenethyl pivalate (11a)

The spectral data for this compound coincided with the literature.[22]

4 -(2-(Benzyloxy)ethyl)phenol (11b)

A colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (t, $J = 7.2$ Hz, 2H), 3.65 (t, $J = 7.2$ Hz, 2H), 4.52 (s, 2H), 4.63 (s, 1H), 6.74 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.21–7.44 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.3, 71.4, 72.9, 115.2, 127.6, 127.7, 128.4, 129.9, 130.6, 138.1, 154.1. HR-MS (ESI): Calcd for $C_{15}H_{16}NaO_2$ $[M+Na]^+$: 251.1048. Found: 251.1055. IR (neat, cm^{-1}): 3348, 1613, 1515, 1453, 1230, 1075, 471.

Methyl 2-(4-hydroxyphenyl)acetate (11c)

The spectral data for this compound coincided with the literature.[23]

Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-tyrosinate (13)

The crude product was purified with column chromatography (Hi-Flash M; *n*-hexane/ethyl acetate, 62:28 to 51:49) to eliminate contaminated silyl residues. The spectral data coincided with the literature.[24]

1 -((1R,3r,5S)-3-Hydroxy-8-azabicyclo[3.2.1]octan-8-yl)ethan-1-one (15)

A colorless solid. Mp 115.0–117.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74–1.81 (m, 1H), 1.83–1.94 (m, 2H), 1.94–2.04 (m. 2H), 2.05 (s, 3H), 2.10–2.35 (m, 4H), 4.07–4.12 (m, 1H), 4.12–4.17 (m, 1H), 4.61–4.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 27.2, 28.8, 38.6, 39.9, 50.6, 54.7, 64.8, 166.0. HR-MS (ESI): Calcd for $C_9H_{15}NNaO_2$ $[M + Na]^{+:}$ 192.1000. Found: 192.0999. IR (KBr, cm^{-1}): 3361, 2945, 1609, 1467, 1090, 1045, 976, 901, 648.

Deacetylation of compound 14 by solvolysis

A suspension of **14** (83.0 mg, 0.393 mmol) and potassium carbonate (1.10 g, 7.96 mmol) in methanol (10 mL) was stirred at ambient temperature for 3 h. Then the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Water was added to the residue and the whole was extracted with dichloromethane. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure. Compound **15** (22.2 mg, 0.131 mmol, 33.3%) was obtained without purification. The yield was improved to 92.7% by using chloroform/2-propanol = 3:1 as an extraction solvent.

Acknowledgments

We are grateful to Dr. Kenichiro Nagai (Analytical Unit for Organic Chemistry of Kitasato University) for help with the structure determination of the newly synthesized compounds.

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