



Selective Deprotection of the Diphenylmethylsilyl (DPMS) Hydroxyl Protecting Group under Environmentally Responsible, Aqueous Conditions

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Two new methods for selective deprotection of diphenylmethylsilyl (DPMS) ethers are described. Unmasking can be achieved with either catalytic amounts of perfluoro-1-butanefluoride (a SuFEx reagent) under mild, aqueous micellar conditions, or using stoichiometric amounts of 18-crown-6 ether in aqueous ethanol.

Protecting group chemistry as used in organic synthesis has been developed to address specific needs associated with numerous transformations.^[1] It is a response to synthetic chemistry that originates from the traditional world of organic chemistry associated with a petroleum-based discipline; one that has and continues to depend upon organic solvents as reaction medium. Hence, it is not the least surprising that most, if not all methodologies for the removal of protecting groups, for alcohols in particular, rely on the same type of reaction media: organic solvents. Even hydrolysis reactions almost invariably involve an organic co-solvent required for solubilization purposes, which, by definition, creates an immediate waste water stream upon workup, not to mention organic waste that is predominantly from the solvent. As organic synthesis begins to build the toolbox of technologies enabling some of the most commonly utilized reactions to be run using nanoparticle technology in water,^[2] this raises the question as to whether protecting groups are even required under such circumstances.

However, until more of the new rules are manifested under which chemistry in water is operating,^[3] protecting groups still have a place in synthetic chemistry. In this report, therefore, we describe two new sets of conditions under which the less frequently chosen diphenylmethylsilyl (DPMS) hydroxyl protecting group can be selectively removed, *both of which are environmentally friendly and rely on water as the reaction medium* (Figure 1).

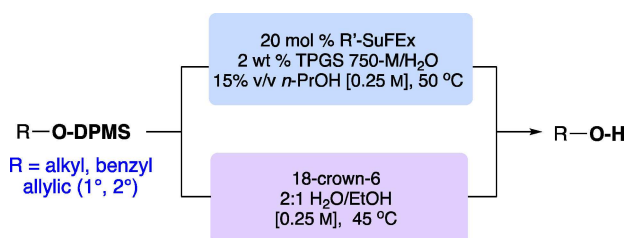


Figure 1. General reaction protocols for the selective deprotection of the DPMS protecting group.

Since the diphenylmethylsilyl (DPMS) hydroxyl protecting group was introduced,^[4] its use has been limited relative to other silyl ether derivatives. Unmasking by fluoride ion, akin to several alternative silicon-based analogs, affords the corresponding free alcohol quickly in THF at room temperature in the presence of TBAF. Hence, while the protection step is high-yielding, the *selectivity* of DPMS ether deprotection is usually the key factor that lies behind use of other more common silyl ethers (TMS, TBS, TIPS and TBDPS).^[5–6] There is one report illustrating preferential removal of the DPMS residue is achievable in the presence of the TBS and TBDPS groups using NaN_3 in warm DMF.^[7] However, the substrate scope in this study was modest, and relied on dipolar, aprotic DMF, a solvent to be avoided given its health hazard. Under more modern, “green” conditions, and with newly discovered elements of selectivity to its credit, the DPMS protecting group may well today become a valued addition to organic synthesis (*vide infra*).

An initial observation revealed that cleavage of a DPMS protected alcohol takes place upon exposure to catalytic amounts of benzyloxy carbonyl fluoride within a mixture of water and CH_3CN (2:1) at 50 °C. Several additional sulfonyl fluorides were also screened in an alcohol/water mixture to evaluate each as alternatives for deprotection (Table 1). While the original Sharpless conditions employing SuFEx (sulfur(VI)

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Table 1. Deprotection of citronellyldiphenylmethylsilyl ether **1a** using sulfonyl fluorides.

Entry	R	Yield ^[a] [%]
1	$n\text{-C}_4\text{H}_9\text{-}$	0
2	$\text{PhCH}_2\text{-}$	86
3	Ph-	17
4	4-propylphenyl-	0
5	perfluorobutyl-	94
6	4-nitrophenyl-	90

[a] Isolated Yields. 0.5 mmol scale reaction.

fluoride exchange) reagents in click chemistry called for a 1:1 mixture of acetonitrile/water as reaction medium,^[8] *n*-propanol was selected due to its relatively benign nature and lower cost relative to acetonitrile. Benzylsulfonyl fluoride (entry 2), as well as sulfonyl fluorides bearing electron-withdrawing groups, such as 4-nitrobenzenesulfonyl fluoride (entry 6), led to very efficient desilylation of model substrate **1a**. Another especially effective SuFEx reagent is perfluorobutanesulfonyl fluoride (entry 5). By contrast, the typical alkyl or aryl analogs (entries 1, 3, and 4) were either sluggish or gave little-to-no conversion after 16 h under otherwise identical conditions. From this study, perfluorobutanesulfonyl fluoride was chosen for its high reactivity as well as its substantially lower cost compared to its 4-nitrophenyl- or benzyl- analogs.

Notwithstanding the effectiveness of a SuFEx reagent to desilylate a DPMS ether, the main question surrounding selectivity remained. As illustrated in Tables 2a and 2b, the

Table 2. (a) Chemoselectivity of perfluorobutanesulfonyl fluoride towards alkyl silyl ethers.

entry	Silyl ether [SiR ₃]	Yield ^[a] [%]
1	TMS	95
2	TIPS	0 (86) ^[b]
3	DPMS	91
4	TBS	0 (89) ^[b]
5	TBDPS	0 (84) ^[b]

*R-SuFEx = $n\text{-C}_4\text{F}_9\text{SO}_2\text{F}$; [a] Isolated yields. [b] Isolated yields after 72 h. 0.5 mmol scale.

(b) Chemoselectivity of perfluorobutanesulfonyl fluoride towards allylic silyl ethers.

Entry	Silyl ether [SiR ₃]	Yield ^[a] [%]
1	TIPS	0
2	DPMS	83
3	TBS	trace

*R-SuFEx = $n\text{-C}_4\text{F}_9\text{SO}_2\text{F}$; [a] Isolated yields; 0.5 mmol scale.

chemoselectivity associated with these deprotections, while unexpected, is noteworthy. Complete removal of the DPMS residue in **2a** could be achieved within 4 h at a concentration of 0.25 M with virtually no deprotection of the TBS, TIPS, or TBDPS ethers (entries 2, 4 and 5) under identical reaction conditions (entry 3). As expected, the TMS ether is especially labile and is hydrolyzed. Deprotections of the other silyl ethers did eventually take place, requiring 72 h to reach completion. Similar results were obtained in the case of allylic educt **4a**. On the other hand, phenolic DPMS ethers do not participate in this deprotection chemistry, perhaps adding to the selectivity of this method.^[9] However, all types of silyl protected propargylic alcohols underwent facile deprotection upon treatment with SuFEx reagents.

As part of our ongoing efforts to assist with the “switch” of organic synthesis from an organic solvent to a water-based discipline using nanoreactors derived from newly engineered and benign surfactants,^[10] it has been found that fluoride ion is reluctant towards entering the hydrophobic micellar inner core, thereby all but eliminating the option to cleave silyl ethers in this manner “in water.” This was attributed to the highly favorable status of hydrated fluoride ion, and hence, silyl ether cleavage appeared to require a “dry” source of this ion to be available in an aqueous micellar medium. This led us to examine a lipophilic SuFEx reagent in the presence of nanomicelles, where a water-stable sulfonyl fluoride might release fluoride in return for the oxygen in an alcohol, all taking place within the inner hydrophobic core of a micellar environment.^[11] Hence, as an alternative set of reaction conditions, we investigated the effectiveness of a SuFEx reagent within micelles derived from TPGS-750-M (Figure 2).^[12] Use of this

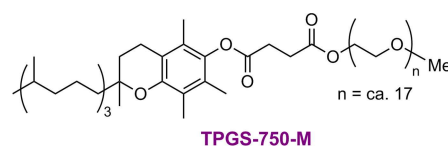
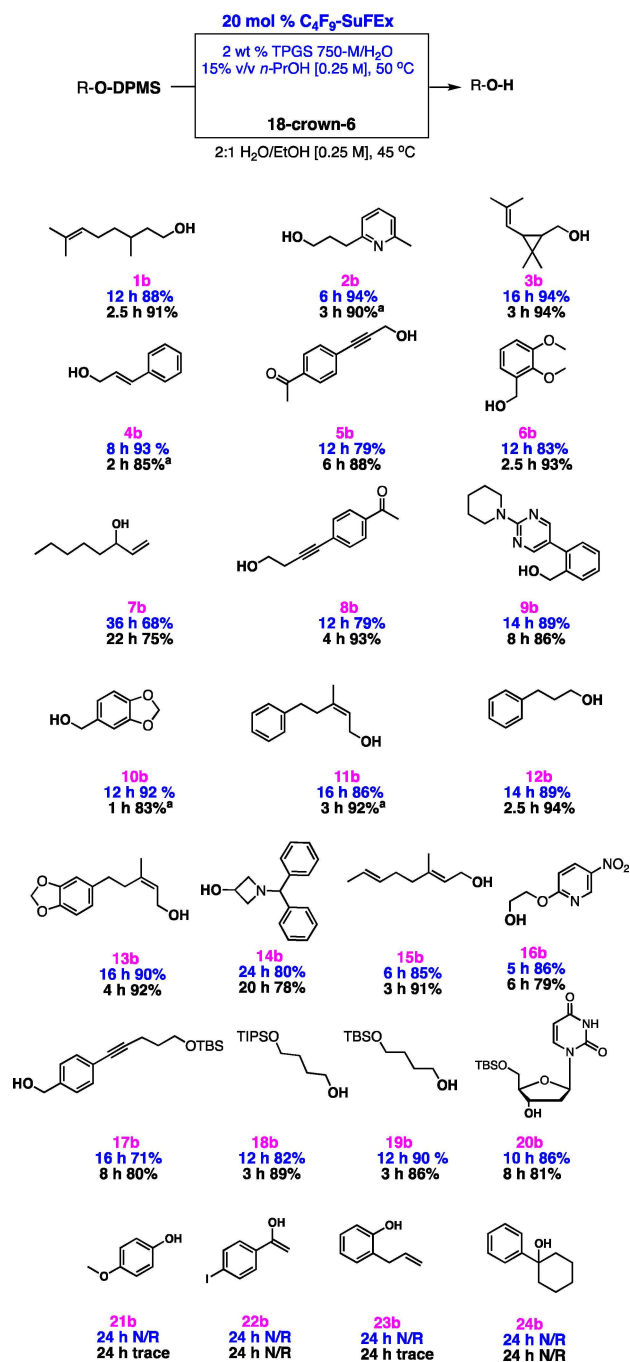


Figure 2. Structure of designer surfactant TPGS-750-M.

surfactant medium may broaden the scope of substrates, in particular those with solubility and/or reactivity issues in water/alcohol mixtures.

As shown in Scheme 1 (results in blue), various primary alcohols derived from DPMS ethers containing a wide variety of functional groups are amenable, leading to good-to-excellent yields of deprotected alcohols. These include nitro (**16b**), benzylic (**6b**, **9b**, **10b**) propargylic (**5b**), allylic (**4b**, **7b**, **11b**, **13b**, **15b**) heteroaromatic (**2b**, **9b**, **16b**), and alkyl (**1–3b**, **12b**, **17–19b**). Notable cases include the tolerance exhibited by several basic nitrogen-containing educts affording product alcohols **2**, **9**, **14** and **16**, as well as an allylic cyclopropane leading to product **3**. Secondary alcohols were also deprotected, although there was a noticeable increase in reaction time, likely a steric effect. Diol-containing substrates also exhibited selectivity towards the DPMS ether, as both TBS and

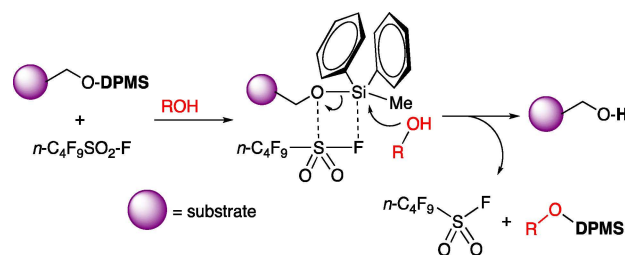


Scheme 1. Scope of DPMS ether deprotection. Reaction times and yields using SuFEx reagent $n\text{-C}_4\text{F}_9\text{SO}_2\text{F}$ (blue) or 18-crown-6 ether (black). Isolated yields [a] H₂O/EtOH as solvent system; 0.5 mmol scale.

TIPS ethers remained intact (17–19b). The case of nucleoside 20b is especially noteworthy in that a DPMS derivative of a secondary alcohol is deprotected in the presence of a primary TBS ether. Aryl and silyl enol ethers were nonresponsive to these conditions (21–23b). Tertiary alcohols showed no reactivity whatsoever towards conversion to the corresponding free alcohols (24b). The Z-olefin-containing product 11 derived from the corresponding Z-silyl ether indicated, along with the examples cited above, that an explanation for the observed

reactivity may not be based simply on the presence of adventitious acid.

A number of mechanisms have been proposed in the literature to account for cleavage of silyl ethers.^[13] Both steric and electronic effects at silicon have been studied, and it has been determined that the substitution around this atom plays a crucial role in determining the reactivity and mechanistic pathways followed.^[14–15] While fluoride ion is typically crucial in chemoselective deprotections of silyl ethers,^[16–17] in this case it is unlikely to be acting as the active species as the sulfonyl fluoride can be reclaimed intact upon completion of the reaction. Krutak et al. described decades ago the remarkable stability of alkyl sulfonyl fluorides under aqueous conditions in their generation and subsequent use of SuFEx derivatives.^[18] They showed that the weak reactivity of the $-\text{SO}_2\text{F}$ moiety tolerates a wide array of reaction conditions. Sulfonyl fluorides have also been known to possess high reactivity towards silicon under basic conditions, as Gembus has described in the interconversion of silyl ethers to tosylates.^[19] With respect to selective deprotection of DPMS ethers, a similar mechanism as described by Gembus may be operating here (Scheme 2). Thus,



Scheme 2. Proposed mechanism for SuFEx-catalyzed deprotections.

the sulfonyl fluoride is acting as both a strong Lewis acid and weak Lewis base, coordinating to the silicon-oxygen bond in a Negishi-like 2+2 fashion. This, in turn, leads to a more electrophilic silicon, susceptible to nucleophilic attack by alcohol at a far greater rate than that of other trisubstituted silyl groups.

The electron-poor nature of the DPMS ether, which may account for its susceptibility, in general, leads to the free alcohol along with the intact (albeit volatile) sulfonyl fluoride for further use. While evaluating the effectiveness of a variety of water/solvent mixtures for deprotections of DPMS ethers, we serendipitously came across the ability of crown ethers to effect the same cleavage of the Si–O bond in the total absence of a SuFEx reagent. In again testing model substrate 1a, complete deprotection occurred after only 1.5 hours at 50 °C when using a 1:1 mixture of water and 18-crown-6 (Table 3). Crown ether-like solvents (e.g., PEG 200 or 400; entries 2, 3) were notably ineffective. Smaller crown ethers (entries 4, 5) afforded the desired free alcohol 2, albeit at a slower rate. Several solvents alone (entries 7–9) led to recovery of starting material. Further evaluation of 1a (Table 4) indicated that the amount of 18-crown-6 was pivotal.

Table 3. Screening various co-solvents and crown ethers.

Entry	Co-solvent	t [h]	Yield ^[a] [%]
1	none	24	0
2	PEG 200	24	0
3	PEG 400	24	0
4	12-crown-4	24	71
5	15-crown-5	24	56
6	18-crown-6	1.5	97
7	<i>t</i> -butanol	24	0
8	<i>n</i> -propanol	24	0
9	ethanol	24	0

[a] Isolated yields; 0.5 mmol scale.

Table 4. Preliminary screening of 18-crown-6.

Entry	Crown [equiv]	H ₂ O/EtOH [x:y]	T [°C]	t	Yield ^[a] [%]
1	10	100:0	45	75 min	91
2	5	100:0	45	45 h	90
3	2	100:0	45	45 h	20
4	5	2:1	45	90 min	98
5	2	2:1	45	2 h	90
6	1	100:0	45	45 h	18
7	1	2:1	45	4 h	94
8	1	2:1	25	16 h	5
9	0.5	2:1	45	26 h	90
10	0.2	2:1	45	16 h	6

[a] Isolated yields; 0.5 mmol scale.

Upon introduction of a co-solvent, in this case ethanol in a 2:1 ratio to water (with 5 equiv. of crown ether present), rates of reactions increased significantly (e.g., entry 2 vs. entry 4). When a stoichiometric amount of crown was present in combination with a 2:1 ratio of water/ethanol, complete deprotection was observed in only four hours (entry 7). Further reducing the quantity of crown ether, however, increased reaction times, presumably due to a drop in the solubilizing properties of the reaction medium. The reaction appears to essentially stop when run at room temperature (entry 8).

The observed selectivity under these crown ether conditions was similar to that observed using the SuFEx reagent (Table 5a, 5b). Alkyl and allylic DPMS ethers are cleaved preferentially over their TBS, TIPS, and TBDPS ether counterparts. After 24 h, the TIPS and TBDPS ethers remained untouched (Table 5a, entries 2 and 5; Table 5b, entries 1 and 3) while only minimal conversion was observed with the TBS ether (entry 4). These conditions, as noted previously, do not discriminate between the TMS and DPMS groups (entries 1 and 3). As with SuFEx conditions (vide supra), both aryl and enol silyl ethers are unreactive.

As shown by the examples in Scheme 1 (results in black), 18-crown-6 ether is equally as effective as the SuFEx reagent for DPMS ether deprotections. These comparisons also revealed

Table 5. (a) Selectivity for deprotection of an alkyl silyl ether mediated by 18-crown-6.

Entry	Silyl ether (SiR ₃)	Yield ^[a] [%]
1	TMS	92
2	TIPS	0 (0) ^[b]
3	DPMS	89
4	TBS	0 (5) ^[b]
5	TBDPS	0 (0) ^[b]

[a] Isolated yields, [b] Isolated yields after 24 h. 0.5 mmol scale.

(b) Selectivity for deprotection of allylic silyl ethers mediated by 18-crown-6.

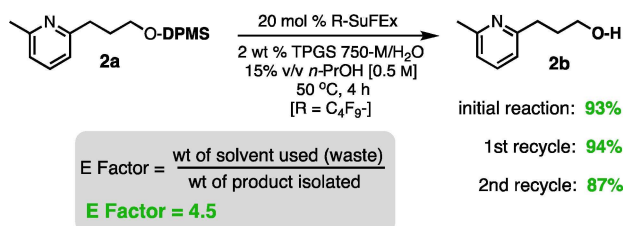
Entry	Silyl ether (SiR ₃)	Yield ^[a] [%]
1	TIPS	0
2	DPMS	90
3	TBS	trace

[a] Isolated yields.

that the former leads to faster rates of Si–O bond cleavage, at an even somewhat lower temperature.

Use of a primary alcohol as co-solvent proved crucial for this selective chemistry. When co-solvents such as THF or EtOAc were examined, minimal conversion was observed after 24 hours suggesting that the alcohol may play a role in these reactions. Our surfactant technology was incompatible with 18-crown-6, as its presence in the medium led to significantly slower reactions. This may be due to the hydrophilic nature of 18-crown-6, in which case it prefers to remain in the aqueous phase while the substrate would prefer the inner micellar lipophilic core. 18-Crown-6 is known to accelerate various substitution reactions.^[20] Silyl migration from one hydroxyl function to another is a phenomenon described by Friesen, where migration was observed upon treatment of a *tris*-silylated aryl glucal with base.^[21] In our case, the crown ether may be acting as a mediator for the silyl migration of the DPMS ether to the more readily available alkanol in solution. The possibility for trace acid being responsible for this selective deprotection was ruled out based on data from Davies, comparing rates of acid-catalyzed hydrolysis of varying silyl ethers. It was noted that all silyl ethers tested (TMS, TBS, DPMS, TIPS, and TBDPS) hydrolyzed in a 1% HCl/MeOH media.^[22] However, pH measurements indicated that the reaction medium involved (pH~5) in these selective deprotections is *not* acidic enough to facilitate a standard acid-catalyzed deprotection.

Recycling of the aqueous TPGS-750-M-containing reaction mixture is readily achieved by an in-flask extraction with minimal amounts of MTBE as the extraction solvent (Scheme 3). However, due to the lipophilic nature of the SuFEx catalyst, re-addition of the sulfonyl fluoride (20 mol%) is required with each recycle. The yields and reaction times of the two recycles did not vary significantly, while the E Factor^[23–24] (based on organic solvent used), as a measure of waste produced relative



Scheme 3. E Factor determination and recycling studies.

to the amount of product obtained, remained relatively low, especially when compared to other commonly used deprotection protocols.

In summary, two new methods for selective deprotection of primary and secondary alkyl DPMS ethers have been uncovered, where chemistry in water appears to be responsible for the unexpected chemoselectivities observed. Either catalytic amounts of perfluorobutanesulfonyl fluoride ($n\text{-C}_4\text{F}_9\text{SO}_2\text{F}$), or a stoichiometric amount of 18-crown-6 ether, can be used for these purposes. Both methods are technically straightforward, offer a recyclable and safe aqueous medium, and rely on reagents that are items of commerce. The precise role of 18-crown-6, in particular, awaits further elucidation. Nonetheless, an eventual understanding of exactly how both a SuFEx reagent and crown ether facilitate the highly selective deprotection of DPMS ethers may lead to related additional, environmentally responsible chemistry in water waiting to be discovered.

Experimental Section

Experimental Details can be found in the Supporting Information.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: green chemistry · selective silyl ether deprotection · SuFEx-catalyzed desilylations · aqueous micellar medium

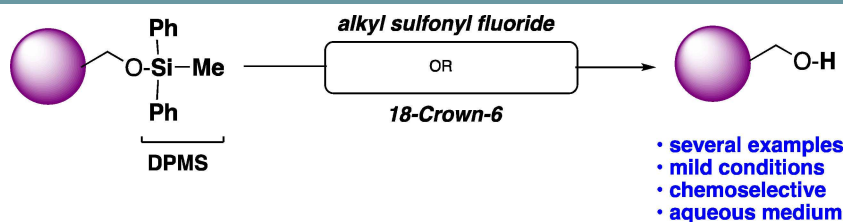
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COMMUNICATIONS



Chemistry in water; new rules. Yep, take an old silyl hydroxyl protecting group like Ph₂MeSi (DPMS), put the derived ether under either of two different aqueous conditions and “boom”; it can be removed selectively in the presence of TBS, TIPS, and

TBDPS ethers under very mild conditions. The first: cat. RSO₂F/EtOH (i.e., a SuFEx reagent) under micellar catalysis conditions. The second: 18-crown-6 (stoichiometric). That’s it. Take your pick!

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1 – 6

Selective Deprotection of the Diphenylmethylsilyl (DPMS) Hydroxyl Protecting Group under Environmentally Responsible, Aqueous Conditions

