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[[(*tert*-Butyl)dimethylsilyl]oxy]-methyl Group for Sulfur Protection

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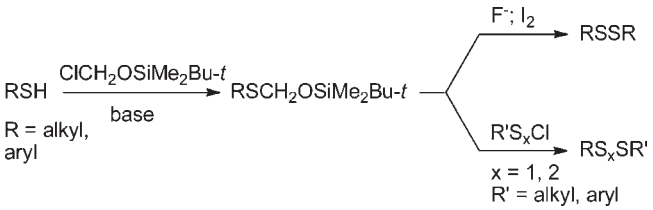
ABSTRACT



Aromatic and aliphatic thiols can be protected by reaction with *t*-BuMe$_2$SiOCH$_2$Cl in DMF in the presence of a base (2,6-lutidine or proton sponge); the resulting *t*-BuMe$_2$SiOCH$_2$SR or *t*-BuMe$_2$SiOCH$_2$SAr are deprotected by sequential treatment with Bu$_4$NF and I$_2$ to give symmetrical disulfides. Another mode of deprotection involves reaction with a sulfenyl chloride; this process gives an unsymmetrical disulfide and was examined with Me(CH$_2$)$_{11}$SCH$_2$OSiMe$_2$Bu-*t* and three sulfenyl chlorides.

In connection with work on the synthesis of the antitumor agent MPC1001 (**1**, Figure 1), we needed to introduce sulfur in a temporarily protected form by reaction of a carbanion with a sulfenylating reagent. For initial studies, reagent **3** was used[1] (Scheme 1) because it gave a satisfactory yield and stereoselectivity, but it subsequently proved to be unsuitable as the sulfur protecting group could not be removed from a more advanced intermediate under sufficiently mild conditions (Bu$_4$NF[2] or ArSCl[3]). The excessive robustness of the CH$_2$CH$_2$SiMe$_3$ group forced us to devise a sulfenylating reagent in which the sulfur is protected in such a way that the protecting group can be removed under mild conditions, and we were led to consider reagent **5** as a suitable candidate for evaluation. Our experience had shown that arylsulfonothioic acid esters (such as **6**) (Figure 2) are able to deliver a protected sulfur to carbanions derived from **2**, and we expected that the choice of a silyl ether, as in **5**, would allow fine control, if necessary, of the conditions required for deprotecting the oxygen; such control would be exercised by changing the alkyl groups on

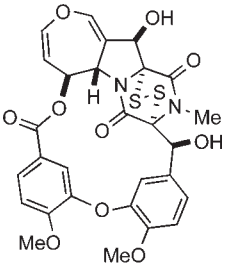


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Figure 1. Antitumor agent MPC1001.

silicon. We would also require that the released alcohol (or alkoxide **8**) would collapse as shown (Scheme 2). A number of hydroxymethyl sulfides (RSCH$_2$OH, R = alkyl or aryl) are known and are isolable, but there are indications[4] that, under appropriate conditions, they do fragment to release

(1) Peng, J.; Clive, D. L. J. *J. Org. Chem.* **2009**, *74*, 513–519.

(2) Cf. (a) Koreeda, M.; Yang, W. *J. Am. Chem. Soc.* **1994**, *116*, 10793–10794. (b) Wang, Y.; Koreeda, M.; Chatterji, T.; Gates, K. S. *J. Org. Chem.* **1998**, *63*, 8644–8645. (c) Hamm, M. L.; Cholera, R.; Hoey, C. L.; Gill, T. J. *Org. Lett.* **2004**, *6*, 3817–3820.

(3) Cf. Gerland, B.; Désiré, J.; Lepoivre, M.; Décout, J.-L. *Org. Lett.* **2007**, *9*, 3021–3023.

(4) (a) Classon, B.; Garegg, P. J.; Liu, Z.; Samuelsson, B. *Carbohydr. Res.* **1988**, *174*, 369–374. (b) Schwartz, B.; Vogel, K. W.; Drueckhammer, D. G. *J. Org. Chem.* **1996**, *61*, 9356–9361. (c) For higher aldehydes than formaldehyde, see: Harpp, D. N.; Kobayashi, M. *Tetrahedron Lett.* **1986**, *27*, 3975–3978. (d) Gong, Y.; Ma, M.; Luo, Y.; Bong, D. *J. Am. Chem. Soc.* **2008**, *130*, 6196–6205. (e) Horner, L.; Jürgens, E. *Annalen* **1957**, *602*, 135–153.

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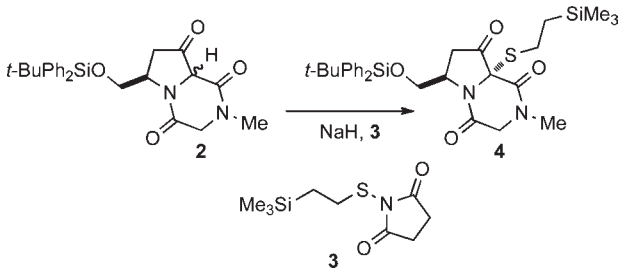
Scheme 1. Original Sulfenylation



a thiol and an aldehyde (cf. **8**→**9**), although the fragmentation occurs less readily with derivatives of formaldehyde (cf. **8**) than with derivatives of higher aldehydes. In the event, the fragmentation step was not problematic.

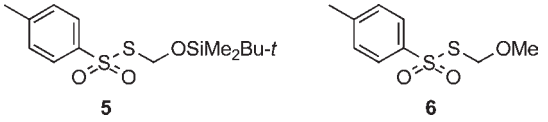
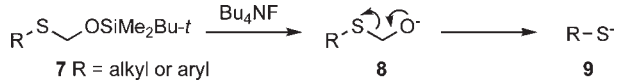


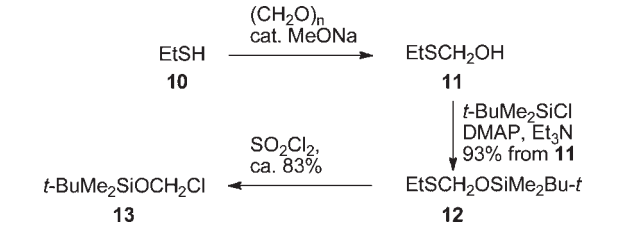
Figure 2. Aryl sulfonothioic acid esters.

Scheme 2. Protecting Group Design



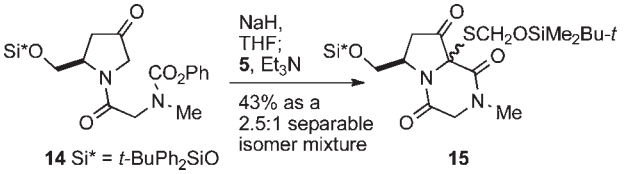
The obvious way to prepare reagents of type **5**, a structure that appears to represent a new compound class,[5] is by reaction of $TolSO_2SNa$ with *t*-$BuMe_2SiOCH_2Cl$ (**13**), a compound that is easily prepared by the reported method,[6] which is summarized in Scheme 3; several chloromethoxysilanes

Scheme 3. Formation of *t*-$BuMe_2SiOCH_2Cl$



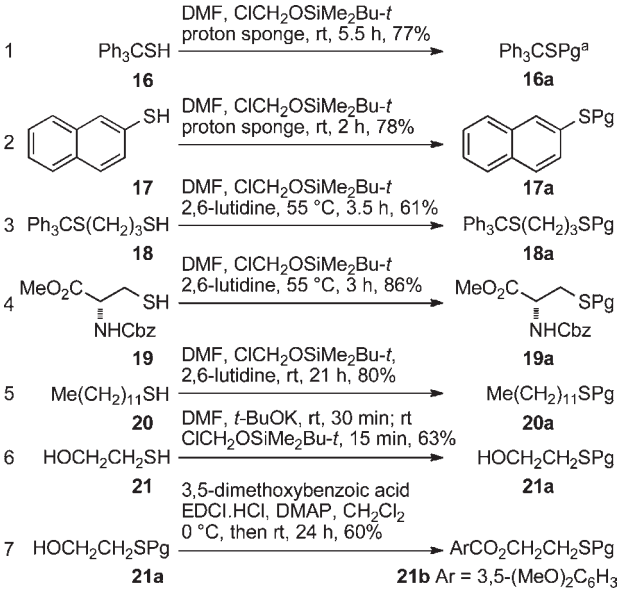
(one is commercially available[7]) have been used before for *O*-protection of alcohols[8,9] and protection of *N*-1 of pyrimidines.[6] Reaction of **13** with $TolSO_2SNa$ in MeCN gave **5** (53%), which was used for the sulfenylation shown in Scheme 4. Reagent **13** can be kept in a freezer (−20 °C) for 1−2 days; likewise, reagent **5** should be stored in a freezer and can be kept in this manner for several months; both reagents are most conveniently generated just before use, and we have made them on a 1−3 g scale.

Scheme 4. Sulfenylation with **5**



As we would later need to deprotect the sulfur in a more advanced intermediate than **15**, and have now actually done so (88% yield), we next examined the deprotection step of our plans. For this purpose, the thiols listed in Scheme 5 were converted into the corresponding com-

Scheme 5. Preparation of $RSCH_2OSiMe_2Bu$-*t*[a]

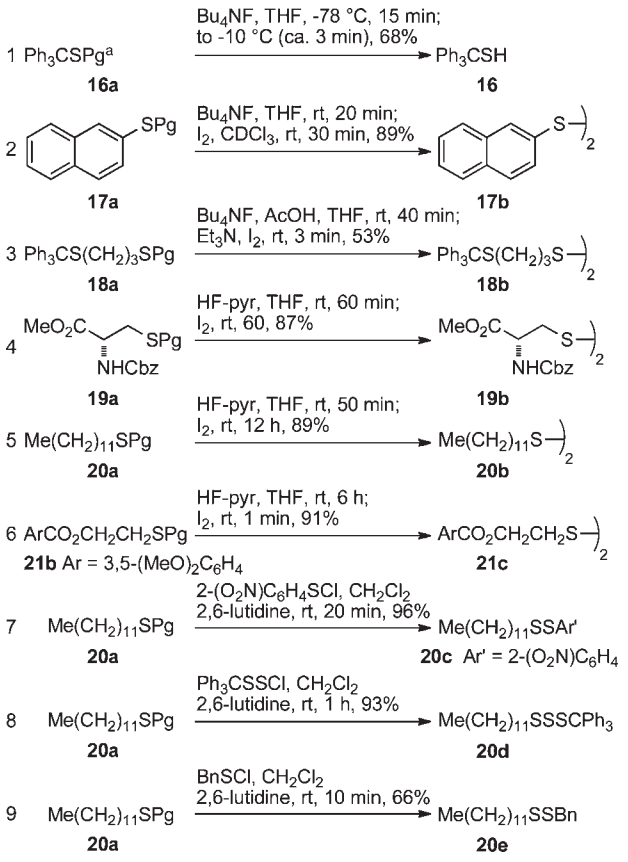


[a] Pg = CH_2OSiMe_2Bu-*t*.

pounds in which the sulfur is protected with a [[(*tert*-butyl)dimethylsilyl]oxy]methyl group. In each case, the thiol was treated with **13** in the presence of a base. DMF

(5) Numerous *O*-*C*, as opposed to *O*-*Si*, analogues are known.
(6) Benneche, T.; Gundersen, L.-L.; Undheim, K. *Acta Chem. Scand.* **1988**, *42B*, 384–389.
(7) *i*-Pr_3SiOCH_2Cl is commercially available.
(8) (a) Gundersen, L.-L.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 706–709. (b) Hunziger, J.; Hall, J.; Martin, P. European Patent 1565479B1, 2006.
(9) Pitsch, S.; Weiss, P. A.; Jenny, L.; Stutz, A.; Wu, X. *Helv. Chim. Acta* **2001**, *84*, 3773–3795.

Scheme 6. Deprotection of $RSCH_2OSiMe_2Bu\text{-}t$[a]



[a] Pg = $CH_2OSiMe_2Bu\text{-}t$.

is a satisfactory solvent and proton sponge or 2,6-lutidine are suitable bases, but the optimum conditions are sensitive to the structure of the starting thiol. For entries 1 and 2, proton sponge gave a satisfactory result, but for entry 3 the yield with 2,6-lutidine was a little better than with proton sponge (61% versus 55%). In these three cases, we also tried NaH in THF; for entries 1 and 2, the yields were comparable to those obtained with proton sponge, but the aliphatic thiol of entry 3 did not react cleanly under these (NaH) conditions. In the case of the amino acid (entry 4), use of 2,6-lutidine gave a better yield (86%) than proton sponge (76%), but Hünig's base led to a poor yield (ca. 25%). The case of dodecanethiol (entry 5) was examined in detail: several combinations of solvent (CH_2Cl_2, PhMe, MeCN, DMF, THF, EtOAc, and Et_2O) and base (Hünig's base, 2,6-lutidine, DMAP, *t*-BuOK, DBU) were tried; the DMF/2,6-lutidine combination emerged from these experiments as likely to be generally satisfactory. Monoprotection of the hydroxy thiol **21** (entry 6) was best done with *t*-BuOK in DMF, using a slight excess of the hydroxy thiol (1.3 equiv); the yield was much lower with BuLi/THF or with 2,6-lutidine/DMF or proton sponge/DMF. Entry 7 of Scheme 5 does not involve sulfur protection, the hydroxyl group being acylated by a standard method to give **21b**, the desired substrate for deprotection studies. In each case, the

Table 1. Stability Tests of **20a**

	reagent	solvent	temp (°C)	time	**20a** decomp (%)
1	H_2, Pd/C	MeOH−CH_2Cl_2[a]	rt	5.5 h	0
2	H_2, Rh/Al_2O_3	EtOAc	rt	4 h	0
3	Zn dust	AcOH-Et_2O (1:2)[b]	rt	1 h	3
4	$NaBH_4$	THF-H_2O (8:1)	0	1 h	0
5	$LiAlH_4$	THF	rt	1 h	7
6	DIBAL	CH_2Cl_2	−78	1 h	3
7	LDA	THF	−78	45 min	10
8	EtMgBr	THF	0	1 h	7
9	BuLi[c]	THF	−78	15 min	4
10	piperidine[d]	CH_2Cl_2	rt	20 min	0
11	CF_3CO_2H[e]	CH_2Cl_2	0	30 min	100
12	$TsOH.H_2O$	CH_2Cl_2	rt	4.5 h	94
13	PPTS[f]	MeOH	rt	4.7 h	47
14	PPTS	CH_2Cl_2	rt	4.5 h	2
15	$BF_3.Et_2O$	CH_2Cl_2	0	1 h	100
16	CBr_3/Ph_3P[g]	CH_2Cl_2	0	30 min	7
17	PCC[h]	CH_2Cl_2	rt	40 min	100
18	Dess-Martin	CH_2Cl_2	rt	2 h	100
19	IBX[i]	DMSO	rt	2 h	10
20	Swern	CH_2Cl_2	[j]		100
21	Et_3SiOTf[k]	CH_2Cl_2	−78	25 min	5

[a] A small amount of CH_2Cl_2 was used to solubilize **20a**. When the experiment was repeated using 2:3 MeOH−CH_2Cl_2 at rt for 40 min in the presence of [2-(2-bromophenyl)ethoxy]triethylsilane the Et_3Si group was completely removed (ref 13) and **20a** was unchanged. [b] These are conditions for removal of a Troc group (ref 14). [c] Experiment done in the presence of $(PhS)_2CH_2$, and the mixture was quenched with D_2O; all the dithioketal had been converted into $(PhS)_2CHD$, and **20a** was unchanged. [d] Piperidine/CH_2Cl_2 = 1:4 by volume. When done in the presence of Fmoc-Pro-OMe, the Fmoc group was removed (cf. ref 15), but **20a** was unchanged. [e] CF_3CO_2H/CH_2Cl_2 = 1:2 by volume; these are standard conditions for Boc removal (ref 16). [f] Under these conditions, *O*-$SiMe_2Bu\text{-}t$ groups are desilylated (ref 17). [g] Done in the presence of 2-(2-bromophenyl)ethanol; all of the alcohol was converted into the corresponding bromide, and 93% of **20a** remained. [h] Oxidation of a secondary alcohol in the presence of a methylthiomethyl ether is known (cf. ref 18). [i] A hydroxyl can be oxidized in the presence of a sulfide (ref 19). [j] Standard Swern procedure. [k] The experiment was done in the presence of 2-(2-bromophenyl)ethanol and 2,6-lutidine; after 25 min, 50% of the alcohol had been silylated and 95% of **20a** remained.

major side product was the disulfide arising from adventitious oxidation of the starting thiol.

With a number of *S*-protected compounds in hand, we then examined several methods for deprotection and quickly found, as might be expected, that the most convenient procedure involves sequential deprotection and oxidation to the corresponding disulfide. Treatment of **16a** with Bu_4NF (THF, −78 to −10 °C) released the parent thiol **16**, as did similar treatment of **12** (ca. 76% conversion by ^1H NMR). If I_2 is added after removal of the silicon group then the expected symmetrical disulfides are formed in the indicated yields, which are generally well above 80%. It should be noted that we did not establish if desilylation is followed by spontaneous extrusion of formaldehyde or whether loss of formaldehyde occurs after reaction of iodine with the sulfur; while of mechanistic interest, the actual sequence is immaterial to the outcome. For removal of the silicon unit we used Bu_4NF/THF, Bu_4NF/AcOH/THF,

or HF·pyridine/THF, our experience being that Bu_4NF alone sometimes gave poorer yields than the buffered conditions.

In dealing with sulfur compounds, it is sometimes convenient to protect a thiol as an unsymmetrical disulfide from which the original thiol (or derived thiolate) can be regenerated by reduction.[10] Accordingly, we exposed **20a**, as a test case, to the action of 2-nitrophenylsulfenyl chloride and observed a very efficient conversion to unsymmetrical disulfide **20c**. This type of process would appear to be general, as the sulfenyl chlorides Ph_3CSSCl[11] and BnSCl[12] behaved analogously giving **20d** (93%) and **20e** (66%), respectively.

The experimental results summarized in Schemes 5 and 6 show that the [[(*tert*-butyl)dimethylsilyl]oxy]methyl group can serve as a protecting group for thiols in a wide range of substrates; both the protection and deprotection occur under mild conditions and several methods are available for both steps. The reactions investigated so far involve *tert*-butyldimethylsilyl compounds; we assume that the procedures would also be successful when the conditions needed for desilylation are altered by changing the substituents on silicon; however, we have not tested this possibility.

We have also evaluated the stability of the protecting group by exposing **20a** to a variety of conditions, which are summarized in Table 1. The compound is stable to H_2/Pd/C in MeOH−CH_2Cl_2 and to H_2/Rh/Al_2O_3/EtOAc. An *O*-triethylsilyl ether can be selectively deprotected in the presence of **20a**, using H_2/Pd/C in MeOH−CH_2Cl_2 (entry 1). The protecting group appears to survive typical conditions for removal of a Troc group (entry 3), and an Fmoc group can be removed in its presence by using piperidine (entry 10). Hydride reducing agents either have no effect ($NaBH_4$, entry 4) or little effect ($LiAlH_4$, DIBAL, entries 5 and 6, respectively). $(PhS)_2CH_2$ can be deprotonated with BuLi with very little decomposition (4%) of **20a** (entry 9). LDA has some effect on **20a** (entry 7).[20] Acidic reagents (entries 11−15) are not compatible with the protecting group, except for PPTS in CH_2Cl_2 (entry 14) and exposure to silica gel during chromatography. A primary alcohol can be converted into the corresponding bromide in the presence of **20a** (entry 16), but oxidizing agents (entries 17−20) damage the protecting group. A primary alcohol can be silylated with Et_3SiOTf in its presence (entry 21).

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Supporting Information Available. Experimental details for synthesis and ^1H and ^{13}C NMR spectra for the compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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(20) However, we have successfully carried out sulfenylation and acylation of an enolate containing the new protecting group.