

[*tert*-Butyldimethylsilyl]oxy]methanethiol and [*tert*-Butyldiphenylsilyl]oxy]- methanethiol—Nucleophilic Protected H₂S Equivalents

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Abstract

[*tert*-Butyldimethylsilyl]oxy]methanethiol [HSCH₂OSiMe₂Bu-*t*] is a nucleophilic reagent for

introduction of a protected bivalent sulfur; this reagent is complementary to the electrophilic reagent *p*-MeC₆H₄SO₂SCH₂OSiMe₂Bu-*t*. The thiol is prepared by the action of HSLi on *tert*-butyl(chloromethoxy)dimethylsilane [ClCH₂OSiMe₂Bu-*t*] and it reacts with alkyl bromides to give protected thiols.

Keywords:

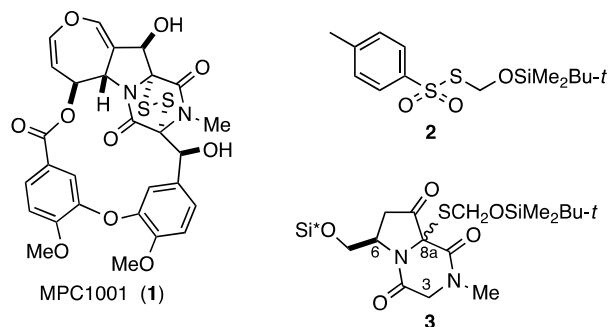
sulfur protection

protection of sulfur

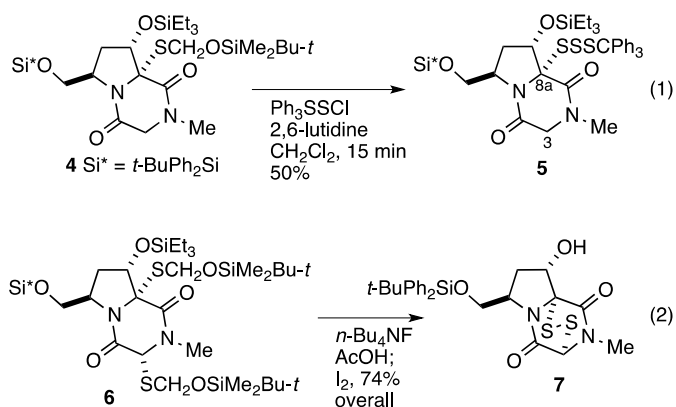
thiol

hydrogen sulfide equivalent

During model studies related to the synthesis of MPC1001 (**1**) the sulfonothioic ester **2** was designed as an *electrophilic* reagent for introducing sulfur masked with a [(*t*-butyldimethyl)siloxy]methyl group.^{1,2} The structure of the protecting group allows its removal under mild conditions by exposure either to fluoride ion or to a sulfenyl halide. The SCH₂OSiMe₂Bu-*t* unit was shown to be stable to a wide range of conditions,^{1,3} and its deprotection was illustrated by the conversion of **4** to **5** and of **6** to **7** (see eq 1 and 2).⁴ In connection with further work in the MPC series we needed a complementary reagent that would introduce the same protected sulfur unit but by means of a *nucleophilic* reagent, and we here report the preparation of HSCH₂OSiMe₂Bu-*t* and its use to make protected thiols by reaction with alkyl halides.

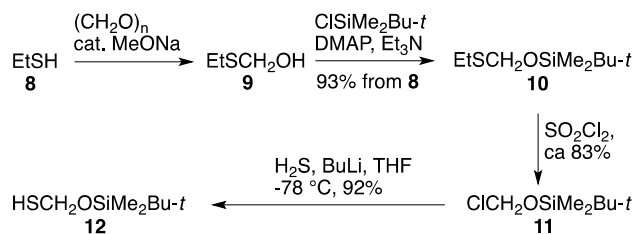


A few (siloxyalkyl) thiols, $\text{RCH}(\text{OSiMe}_3)\text{SH}$, were first reported in 1981⁵ by reaction of H_2S with anhydrous $n\text{-C}_3\text{H}_7\text{CHO}$, EtCHO , $i\text{-PrCHO}$, $c\text{-C}_6\text{H}_{11}\text{CHO}$, $t\text{-BuCHO}$, PhCHO and crotonaldehyde in the presence of Me_3SiCl and, more recently, several examples of the type $\text{RCH}(\text{OSiPh}_3)\text{SH}$ have been described,⁶ but the parent series—the one formally derived from monomeric formaldehyde—has not been reported. It was important for us to use the specific



reagent $\text{HSCH}_2\text{OSiMe}_2\text{Bu-}t$ for two reasons: it was clear from prior work⁴ that the protecting group behaved nicely and, secondly, this reagent, unlike homologs reported in the literature, avoids the introduction of diastereoisomers.

The synthesis of HSCH₂OSiMe₂Bu-*t* is shown in Scheme 1. The sequence **8**→**11** is known⁷ and was used in the preparation of **2**, our original reagent. In the present case, replacement of the chlorine in **11** initially proved troublesome. We first used commercial NaSH.xH₂O, but that gave the desired product heavily contaminated (>50%) with other substances. Treatment of **11** with AcSNa worked well, but we were unable to effect clean hydrolysis to **12**. Oxidation of crude **12** to the disulfide, followed by hydride reduction was also unsatisfactory. Eventually, we generated HSLi in THF under anhydrous conditions⁸ and found that it reacts cleanly with **11** to afford the desired reagent **12**. Material made in this way (ca 92% yield) contains only minor impurities (¹H NMR, ¹³C NMR) and is perfectly suitable for direct use; it can be stored in a closed vessel in a freezer for several (at least 4) weeks.



Scheme 1. Synthesis of HSCH₂OSiMe₂Bu-*t*.

As expected, the protected thiol can be deprotonated and then alkylated with bromides, and our results are shown in Table 1. For compounds **13** to **16** the experimental procedure involved adding the thiol **12** to a mixture of NaH (1 equiv) and the starting bromide in DMF at 0 °C. In the case of **18** and **19**,⁹ the NaH was added to a solution of the bromide and the thiol in order to avoid premature deprotonation of the carbonyl compound. This reverse mode of addition was arbitrarily also used for **17**. In a preliminary experiment to prepare **13**, *n*-BuLi was

added to a THF solution of the thiol at $-78\text{ }^{\circ}\text{C}$, followed by BnBr, but the NaH method was just as effective.

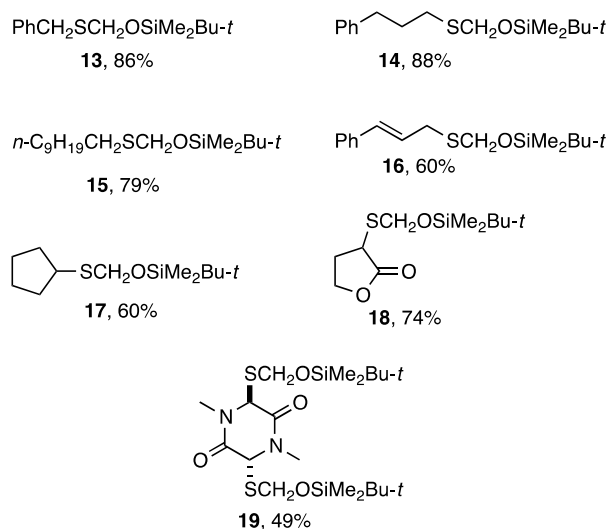


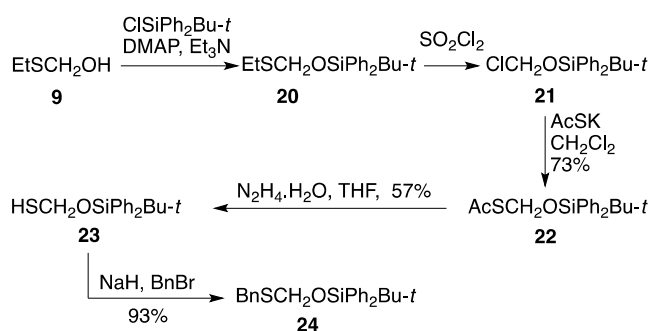
Table 1. *S*-Protected thiols.

As shown by the Table, primary and activated bromides give yields between 60 and 88%. Cyclopentyl bromide also reacted, but experiments with cyclohexyl bromide were unsuccessful.

Under our experimental conditions we did not notice the formation of vinyl sulfides, which are formed readily from $\text{RCH}(\text{OSiMe}_3)\text{SH}$ ($\text{R} \neq \text{H}$), NaH and alkyl halides *if* the $\text{RCH}(\text{OSiMe}_3)\text{SH}/\text{NaH}$ mixture is stirred for 30 min at 0°C and 10 min at room temperature.¹³

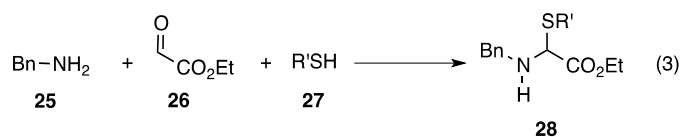
Although our main interest is in the *t*-butyldimethylsilyl group for *O*-protection, we also sought to prepare $\text{HSCH}_2\text{OSiPh}_2\text{Bu-}t$ in an exactly analogous manner, using $\text{ClCH}_2\text{OSiPh}_2\text{Bu-}t$. This is also a known¹⁴ compound available in high yield (99%) from $\text{EtSCH}_2\text{OSiPh}_2\text{Bu-}t$, itself formed very efficiently. However, when we treated the chloride with HSLi the results were erratic and in only one out of six attempts did we obtain the desired $\text{HSCH}_2\text{OSiPh}_2\text{Bu-}t$ (32%). We were unable to identify the cause(s) of this variability, but we found that reaction of the

chloride with AcSK gives the expected thioacetate (Scheme 2), and this reacts with hydrazine hydrate to liberate HSCH₂OSiPh₂Bu-*t* in 57% yield. As expected, thiol **23** can be alkylated, as shown by the single example we studied (**23**→**24**).



Scheme 2. Synthesis and alkylation of HSCH₂OSiPh₂Bu-*t*.

As stated above, our need for a nucleophilic protected thiol arose during studies on a natural product synthesis, and we were specifically interested in the generation of α -(alkylthio) glycine esters **28**. Several of these have been made (eq 3) by reaction of an amine with EtO₂CCHO, followed by addition of a thiol (*p*-MeOC₆H₄CH₂SH was used in the reported experiments).¹⁵ Our requirements were for a protecting group on sulfur that could be removed by treatment with fluoride ion or with a sulfenyl chloride; hence the design of the thiol **12**. When we used this thiol in the manner described by eq 3 we obtained **28** (R' = SCH₂OSiMe₂Bu-*t*) in 86% yield.



Conclusion

The CH₂OSiR₃ protecting group for bivalent sulfur has proven useful in model studies¹ related to MPC1001; with appropriate substrates the unit SCH₂OSiR₃ can be introduced either by use of the electrophilic reagent **2** or the complementary nucleophilic reagent **12**.

Acknowledgments.

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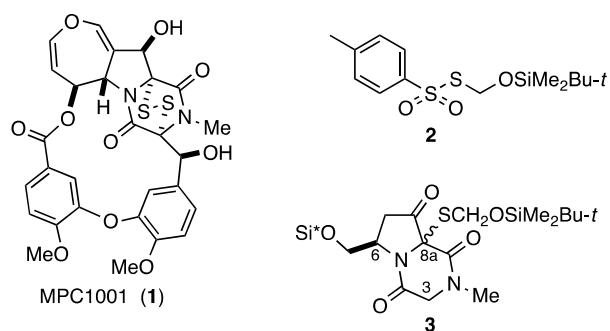
Supplementary data

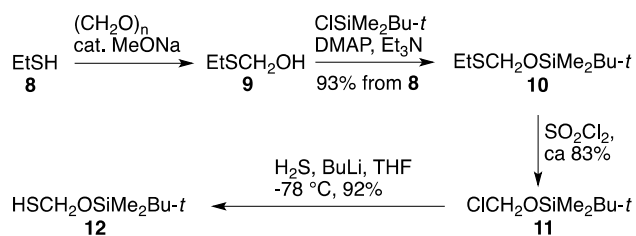
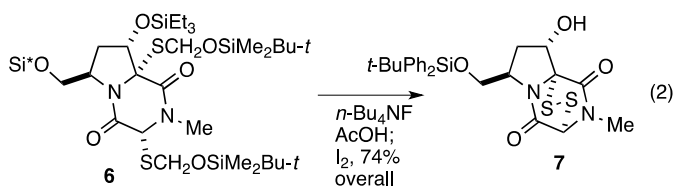
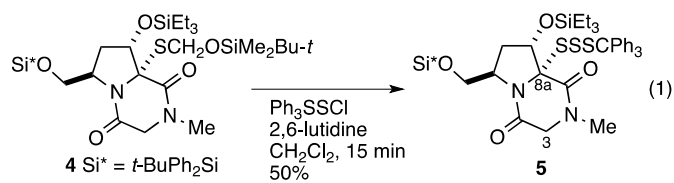
Supplementary data (experimental procedures and copies of ¹H and ¹³C NMR spectra for new compounds) associated with this letter can be found, in the online version, at doi:

References

1. Wang, L.; Clive, D. L. J. *Org. Lett.* **2011**, *13*, 1734–1737.
2. Wang, L.; Clive, D. L. J. *Org. Synth.* **2013**, *90*, 10–24.
3. Choi, J.; Park, H.; Yoo, H. J.; Kim, S.; Sorensen, E. J.; Lee, C. *J. Am. Chem. Soc.* **2014**, *136*, 9918–9921.
4. Wang, L.; Clive, D. L. J. *Tetrahedron Lett.* **2012**, *53*, 1504–1506.
5. (a) Aida, T.; Chan, T.-H.; Harpp, D. N. *Angew. Chem. Int. Edn.* **1981**, *20*, 691–692. (b) Harpp, D. N.; Kobayashi, M. *Tetrahedron Lett.* **1986**, *27*, 3975–3978.
6. Cai, Y.; Roberts, B. P. *Tetrahedron Lett.* **2001**, *42*, 8235–8238.

7. Benneche, T.; Gundersen, L.-L.; Undheim, K. *Acta. Chem. Scand.* **1988**, *42B*, 384–389.
8. Still, I. W. J.; Natividad-Preyra, R.; Toste, F. D. *Can. J. Chem.* **1999**, *77*, 113–121.
9. The stereochemical assignment to **19**, which was made from the corresponding dibromide (probably *trans*) (reference 10), is based on a comparison of its ¹H NMR spectrum with those reported for the *cis* and *trans* isomers of 1,4-dimethyl-3,6-bis(methylsulfanyl)piperazine-2,5-dione (reference 11) and 1,4-diethyl-3,6-bis(methylsulfanyl)piperazine-2,5-dione (reference 12).
10. (a) Balan, C.; Mahajan, S.; Nagavarapu, U.; Gupta, S. WO Patent 195821 A1, June 25, 2015. (b) Crooke, S.; Whitlock, C. *Molecules* **2012**, *17*, 14841–14845.
11. Poisel, H.; Schmidt, U. *Angew. Int. Edn.* **1971**, *10*, 130–131.
12. Sato, T.; Hino, T. *Chem. Pharm. Bull.* **1976**, *24*, 285–293.
13. Harpp, D. N.; Aida, T.; Chan, T. H. *Tetrahedron Lett.* **1985**, *26*, 1795–1798.
14. Gundersen, L.-L.; Benneche, T.; Undheim, K. *Acta. Chem. Scand.* **1989**, *43B*, 706–709.
15. Hilton, S. T.; Motherwell, W. B.; Selwood, D. L. *Synlett* **2004**, 2609–2611.





Scheme 1. Synthesis of $\text{HSCH}_2\text{OSiMe}_2\text{Bu-}t$.

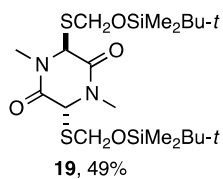
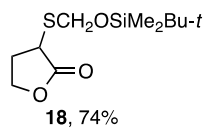
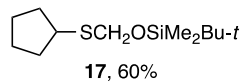
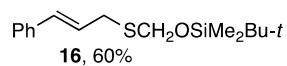
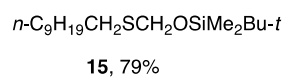
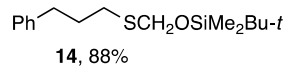
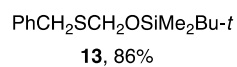
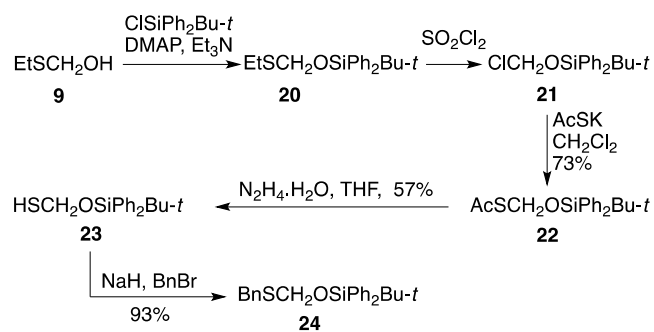


Table 1. *S*-Protected thiols.**Scheme 2.** Synthesis and alkylation of $\text{HSCH}_2\text{OSiPh}_2\text{Bu-}t$.