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[(*tert*-Butyldimethylsilyl)oxy]methanethiol and [(*tert*-butyldiphenylsilyl)oxy]methanethiol—nucleophilic protected H_2S equivalents

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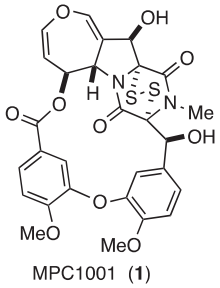
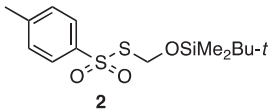
ABSTRACT

[(*tert*-Butyldimethylsilyl)oxy]methanethiol [$HSCH_2OSiMe_2Bu$-*t*] is a nucleophilic reagent for introduction of a protected bivalent sulfur; this reagent is complementary to the electrophilic reagent *p*-$MeC_6H_4SO_2SCH_2OSiMe_2Bu$-*t*. The thiol is prepared by the action of HSLi on *tert*-butyl(chloromethoxy) dimethylsilane [$ClCH_2OSiMe_2Bu$-*t*] and it reacts with alkyl bromides to give protected thiols.

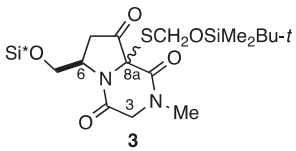
During model studies related to the synthesis of MPC1001 (**1**) the sulfonothioic ester **2** was designed as an *electrophilic* reagent for introducing sulfur masked with a [(*t*-butyldimethyl)siloxy] methyl group.[1,2] The structure of the protecting group allows its removal under mild conditions by exposure either to fluoride ion or to a sulfenyl halide. The SCH_2OSiMe_2Bu-*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 Eqs. 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 $HSCH_2OSiMe_2Bu$-*t* and its use to make protected thiols by reaction with alkyl halides.



MPC1001 (**1**)

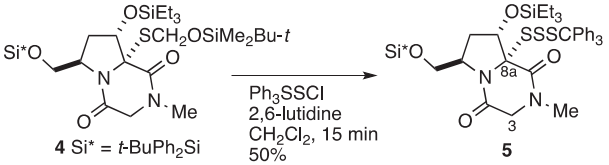


2

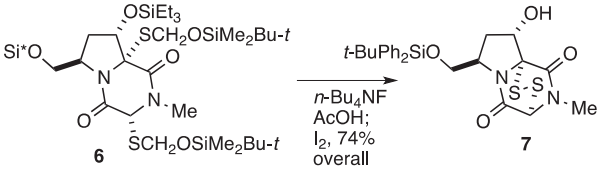


3

A few (siloxyalkyl) thiols, $RCH(OSiMe_3)SH$, were first reported in 1981[5] by reaction of H_2S with anhydrous *n*-C_3H_7CHO, EtCHO, *i*-PrCHO, *c*-$C_6H_{11}CHO$, *t*-BuCHO, PhCHO, and crotonaldehyde in the presence of Me_3SiCl and, more recently, several examples of the type $RCH(OSiPh_3)SH$ 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



4 Si* = *t*-$BuPh_2Si$ — Ph_3SSCl, 2,6-lutidine, CH_2Cl_2, 15 min, 50% — **5** (1)



6 — *n*-Bu_4NF, AcOH; I_2, 74% overall — **7** (2)

reagent $HSCH_2OSiMe_2Bu$-*t* for two reasons: it was clear from prior work[4] that the protecting group behaved nicely and, secondly, this reagent, unlike homologs reported in the literature, avoids the introduction of diastereoisomers.

The synthesis of $HSCH_2OSiMe_2Bu$-*t* is shown in Scheme 1. The sequence **8** → **11** is known[7] 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

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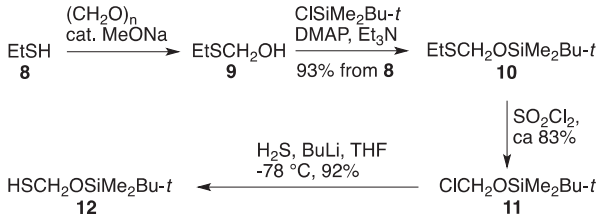


Scheme 1. Synthesis of $HSCH_2OSiMe_2Bu$-*t*.

$NaSH.xH_2O$, 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 conditions[8] 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, ^{13}C 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.

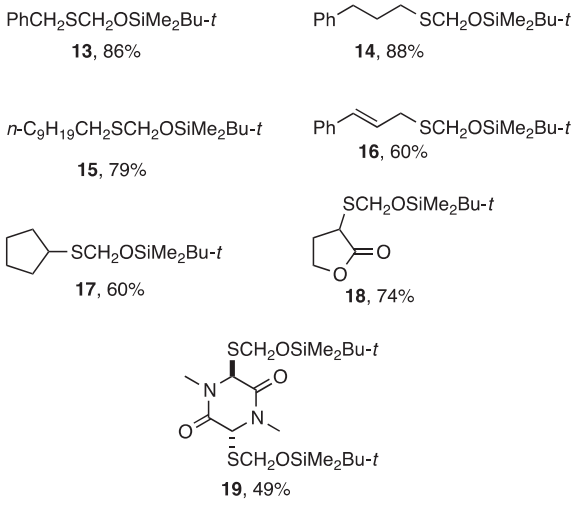
As expected, the protected thiol can be deprotonated and then alkylated with bromides, and our results are shown in Table 1. For compounds **13** to **16** the experimental procedure involved adding the thiol **12** to a mixture of NaH (1 equiv) and the starting bromide in DMF at 0 °C. In the case of **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 °C, followed by BnBr, but the NaH method was just as effective.

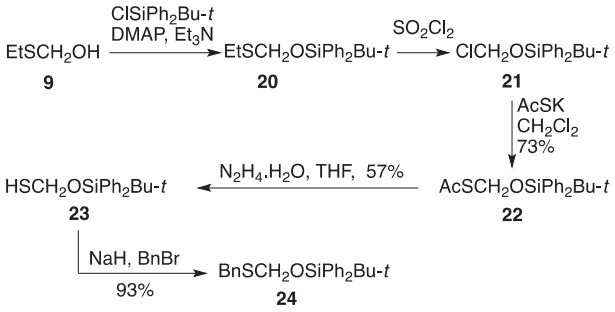
As shown by the Table, primary and activated bromides give yields between 60% and 88%. Cyclopentyl bromide also reacted, but experiments with cyclohexyl bromide were unsuccessful.

Under our experimental conditions we did not notice the formation of vinyl sulfides, which are formed readily from RCH($OSiMe_3$)SH (R ≠ H), NaH and alkyl halides *if* the RCH($OSiMe_3$)SH/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 $HSCH_2OSiPh_2Bu$-*t* in an exactly analogous manner, using $ClCH_2OSiPh_2Bu$-*t*. This is also a known[14] compound available in high yield (99%) from

Table 1
S-Protected thiols

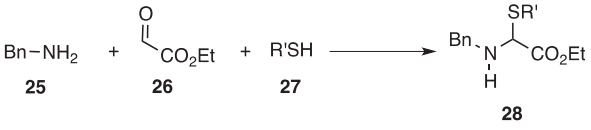




Scheme 2. Synthesis and alkylation of $HSCH_2OSiPh_2Bu$-*t*.

$EtSCH_2OSiPh_2Bu$-*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 $HSCH_2OSiPh_2Bu$-*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 $HSCH_2OSiPh_2Bu$-*t* in 57% yield. As expected, thiol **23** can be alkylated, as shown by the single example we studied (**23** → **24**).

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 EtO_2CCHO, followed by addition of a thiol (*p*-$MeOC_6H_4CH_2SH$ 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′ = SCH_2OSiMe_2Bu-*t*) in 86% yield.



(3)

Conclusion

The CH_2OSiR_3 protecting group for bivalent sulfur has proven useful in model studies[1] related to MPC1001; with appropriate substrates the unit SCH_2OSiR_3 can be introduced either by use of the electrophilic reagent **2** or the complementary nucleophilic reagent **12**.

Acknowledgments

We thank NSERC for financial support, the China Scholarship Council for an Award to D. S., and Professor W. B. Motherwell and Dr. S. T. Hilton for experimental details of their route to α-(alkylthio) glycine esters.

Supplementary data

Supplementary data (experimental procedures and copies of ^1H and ^{13}C NMR spectra for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.079.

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