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A Convenient Trimethylsilylthioxy-Dehalogenation Reaction for the Preparation of Functionalized Thiols

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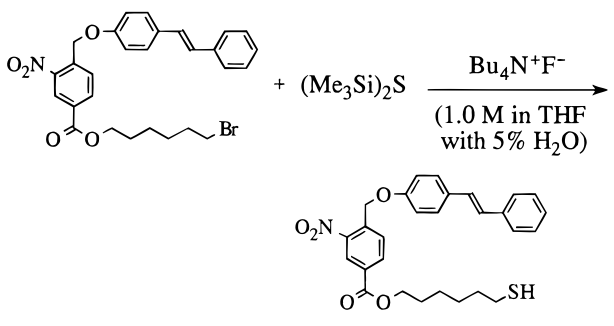
We report a new synthetic method for thiol synthesis and its application in the in situ generation of self-assembled thiolate monolayers on noble metals. Thiols are versatile synthetic intermediates and are considered crucial in many biological processes.[1] Long-standing interest in thiol-containing compounds has recently been stimulated by their utility in the formation of self-assembled monolayers (SAMs) of alkanethiolates on noble metal surfaces.[2] Synthesis and characterization of functionalized SAMs is becoming increasingly important as a vehicle for preparing well-ordered thin films and for using such SAMs in interfacial design and in materials fabrication.[3] For some time, our group has been interested in the photochemical properties of SAMs,[3g,4] and the ability to prepare the required thiols and monolayers in situ would simplify the preparation methods now being used.[5]

Accordingly, we sought a new synthetic method for generating functionalized thiols. It is well-known that methods for direct mercapto-dehalogenation of alkyl halides usually suffer from secondary alkylations to form dialkyl sulfide byproducts. An ideal procedure for thiol synthesis should thus involve an efficient transformation to form a protected but easily activated thiol derivative and should have a subsequent deprotection step that can be achieved without the strongly acidic or basic conditions associated with more conventional methods.[6] We have found that tetrabutylammonium trimethylsilylthiolate ($\mathrm{Me_3SiS^-Bu_4N^+}$, **1**),[7] generated in situ by adding a solution of tetrabutylammonium fluoride (TBAF) to hexamethyldisilathiane in THF, reacts rapidly with a variety of alkyl bromides and chlorides at ambient temperature (eq 1). Upon aqueous workup or filtration through a silica gel column, the corresponding thiols are produced in excellent yields (Table 1).

$$(\mathrm{Me_3Si})_2\mathrm{S} \xrightarrow[-\mathrm{Me_3SiF}]{\mathrm{TBAF}} \underset{\mathbf{1}}{\mathrm{Me_3SiS^-Bu_4N^+}} \xrightarrow[-\mathrm{Br^-Bu_4N^+}]{\mathrm{RBr}}$$

$$\mathrm{RSSiMe_3} \xrightarrow[-(\mathrm{Me_3Si})_2\mathrm{O}]{\mathrm{H_2O}} \mathrm{RSH} \qquad (1)$$

To the best of our knowledge, this procedure represents the mildest available method for thiol synthesis. In addition, it can be conveniently carried out with common synthetic reagents in about 1 h of operation. Because the reaction is conducted under near neutral reaction conditions for a short period of time, autoxidation of thiol products to disulfides and/or sulfonic acids becomes less severe compared to the methodologies that require basic hydrolysis. Furthermore, we found that this procedure can be used to generate highly electron deficient thiol derivatives, which are particularly difficult to synthesize because of the strong tendencies for intramolecular single electron-transfer oxidation of key thiolate intermediates in the reactions.[8] For example, we have been able to apply this method to generate the highly functionalized thiol **2** (eq 2) without the complications encountered using currently prevalent methods that involve thiolate intermediates, e.g., decomposition of the substrate in basic conditions presumably initiated by reduction of the nitrobenzene group. The synthesis takes place efficiently here because the intended substitution by $\mathrm{Me_3SiS^-}$ competes favorably with the reduction of the electron deficient nitrobenzene group.



2 (2)

Although reactions of hexamethyldisilathiane with alkyl halides have been studied previously, the use of this reagent for thiol sythesis is unprecedented. Abel et al.[9] reported that dialkyl sulfides are produced when hexamethyldisilathiane is allowed to react with activated alkyl halides. They also demonstrated that alkyl tri-

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(1) Wardell, J. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: London, 1974; p 179.

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(6) (a) The thiourea method: Frank, R.; Smith, P. V. *J. Am. Chem. Soc.* **1946**, *68*, 2103. (b) The thiol ester method: see ref 1. (c) The thiocyanate method: *The Chemistry of Cyanates and Their Thio Derivatives*; Patai, S., Ed.; Wiley: New York, 1977; p 819.

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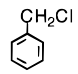
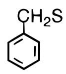
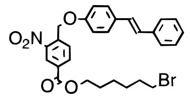
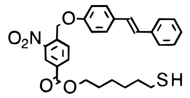
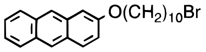
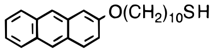
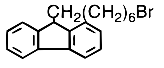
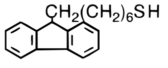
Table 1. Trimethylsilylthioxy-Dehalogenation of Bromides and Chlorides with Tetrabutylammonium Fluoride and Hexamethyldisilathiane

entry	substrate	product	Yield
1	$CH_3(CH_2)_9Br$	$CH_3(CH_2)_9SH$	94[a]
2	$HO(CH_2)_6Br$	$HO(CH_2)_6SH$	87[a]
3	$Br(CH_2)_4Br$	$HS(CH_2)_4SH$	77[a]
4	$Cl(CH_2)_4Br$	$Cl(CH_2)_4SH$	82[a]
5	$HO(CH_2)_4Cl$	$HO(CH_2)_4SH$	79[a]
6			90[a]
7			74[b]
8			80[b]
9			68[b]

[a] GC yield. [b] Isolated yield.

methylsilathiane is an intermediate in this reaction by allowing it to react with an excess of alkyl halide. Shiao et al. also reported a procedure for in situ generation of sodium trimethylsilylthiolate ($Me_3SiS^-Na^+$).[10] This reagent reacts with alkyl halides to produce exclusively dialkyl sulfides although it also reduces nitrobenzene derivatives to aromatic amines quite effectively.[10] We found that the use of TBAF in generating the trimethylsilylthiolate anion greatly improves the nucleophilicity of the reagent so that it reacts rapidly even at low temperatures, effecting a significant improvement in selectivity. If the reaction is carried out using a suspension of sodium methoxide in THF as the initial desilylation agent, a mixture of thiol and dialkyl sulfide may be produced (for 1-bromodecane, a roughly 3:2 mixture of thiol and sulfide by gas−liquid chromatography (GLC)).

In a typical preparation (eq 1), a stirred solution of alkyl bromide (about 0.5 M in freshly distilled THF) was cooled to −10 °C, and hexamethyldisilathiane (1.2 equiv, Aldrich) and TBAF (1.1 equiv, 1.0 M solution in THF with 5% water, Aldrich) were added. The resulting reaction mixture was allowed to warm to room temperature while being stirred. For bromides bearing highly electron-withdrawing groups, the reaction was shielded from room light in order to avoid photoinduced side reactions. After the disappearance of the bromide (about 20 min at ambient temperature, as observed by thin-layer chromatography (TLC) or GLC monitoring), the reaction mixture was diluted with a common organic solvent such as diethyl ether or methylene chloride and washed with aqueous ammonium chloride (sat.). A reasonably clean thiol sample can be obtained by evaporating the solvent.[11] Vacuum distillation or flash column chromatography can be performed, depending on the stability of the thiol product, to further purify the crude product.

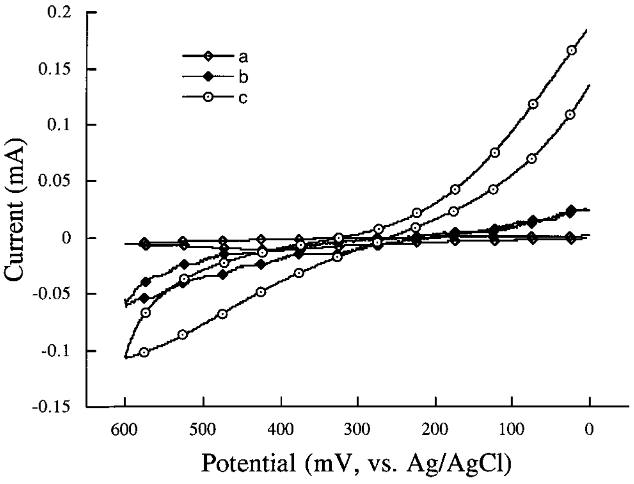
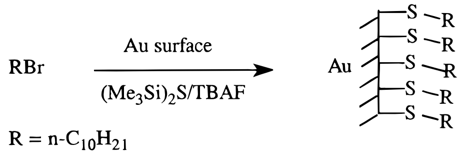


Figure 1. Cyclic voltammograms of 1.0 mM potassium ferricyanide obtained using SAM-modified gold surfaces (approximately 1.0 cm^2) as the working electrodes: (a) with a SAM electrode formed from a 1-decanethiol solution; (b) with a SAM formed from a heated mixture of 1-decanethiol and TBAF; (c) with a SAM formed from a heated synthetic mixture of 1-decanethiol starting with bromodecane. The measurements were performed in a three-electrode cell using platinum as the counter electrode and Ag/AgCl as the reference electrode. Potassium chloride (1.0 M) was used as the supporting electrolyte and the sweeping rate was 100 mV/s.

The scope of the new synthetic method was examined with several different types of electrophiles as shown in Table 1. Because most thiols are unstable toward disulfide formation, our method provides a quick and convenient access to fresh thiols. It is usually advantageous to use the thiol product in the synthetic mixture without separation and purification. This possibility was explored in the formation of self-assembled 1-decanethiol monolayer on gold (eq 3).



(3)

Indeed, as indicated by grazing angle reflectance FT-IR spectroscopy[12] and by contact angle measurements,[13] a well-ordered SAM of 1-decanethiol is formed at room temperature from a diluted synthetic mixture starting from 1-bromodecane. However, further examination of the SAM by cyclic voltammetry (CV) revealed that the faradaic current was only incompletely blocked by the decanethiolate monolayer prepared by in situ generation of the thiol, unlike a SAM prepared by treating a fresh gold surface with decanethiol solution. This result indicates the important role of surface deposition rate in accessing well-ordered SAMs.

The most likely competitor to uniform thiolate deposition is the physical adsorption of tetrabutylammonium bromide on the gold surface,[14] which blocks the chemical

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[10] Shiao, M.-J.; Lai, L.-L.; Ku, W.-S.; Lin, P.-Y.; Hwu, J. R. *J. Org. Chem.* **1993**, *58*, 4742.

[11] Disulfides are observed as impurities in the crude thiol products (3−10% for reactions of about 0.5 mmol scales). They are most likely formed by autooxidation during the workup and isolation process.

[12] Allara, D. L. In *Characterization of Organic Thin Films;* Ulman, A., Ed.; Manning Publications: Greenwich, CT, 1995; p 57.

[13] Laibinis, P. E.; Whitesides, G. M.; Allara, D. L.; Tao, Y.-T.; Parikh, A. N.; Nuzzo, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 7152. Contact angles measured by a sessile drop technique for a bare polycrystalline gold surface, for a preformed 1-decanethiol SAM, and for an in situ prepared SAM from 1-bromodecane are 58 ± 1.9°, 96.4 ± 3.7°, and 94.1 ± 1.8°, respectively.

interaction of the gold surface with a nearby incoming thiol. By preparing the SAM in situ under more rigorous conditions (under reflux for several hours), the faradaic current exhibited in the CV is greatly reduced, consistent with better packing in the monolayer and with more complete SAM coverage of the surface (Figure 1). If a SAM is generated from a reaction mixture that has been washed several times with distilled water to remove the tetrabutylammonium salt, its CV characteristics are identical to that of a well-ordered SAM deposited from a thiol solution. The above observation further supports the supposition that tetrabutylammonium salts may cause increased defects in the in situ generated SAM, but that annealing can heal these defects, at least partially.

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Supporting Information Available: Compound characterization data and copies of NMR spectra for Table 1, entries 7 and 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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