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A PRACTICAL, ONE-STEP SYNTHESIS OF PRIMARY THIOLS UNDER MILD AND NEUTRAL CONDITIONS USING BIS(TRIORGANOTIN) SULFIDES[1]

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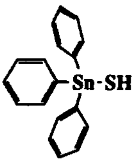
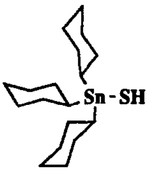
Abstract: *Thiols are obtained from primary organic halides and bis(triaryl/alkyltin) sulfides in the presence of fluoride ion in CH_3CN/H_2O at 20°C. This simple one-step methodology involving fluorodestannylation is carried out under mild and neutral conditions, in sharp contrast to virtually all known methods. Some attempts at utilizing triorganotin and triorganogermanium mercaptans for the same purpose are reported.*

The thiol functionality is of prime importance in organic chemistry as well as in biochemistry[2]. Starting materials for the preparation of primary alkylthiols include: organic halides,[3] alcohols or alcohol derivatives (mesylates, etc.),[4] amines,[5] disulfides,[6] sulfonic acids and their derivatives[7]. S_N2-type displacements are commonly involved with various nucleophilic sulfur reagents including: thioacetic acid[4b,d] and its salts, H_2S,[3h] NaSH,[3a] thiocyanate salts, pyridine-2-thione compounds,[3d,e,g] thioamides,[3f] thiourea[3b] and the salts of dithiocarbamoic[4a] or dithiocarbonic acid.[2c,4e] The procedures using these functionalities usually require several steps for the preparation of the sulfur reagent itself or for the production of the thiol group. Very often, severe basic conditions or strong heating are employed where sensitive functionalities would not survive (*e.g.* the thiourea[3b] or thiolester methodologies[4b,d]).

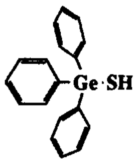
We investigated the use of triorganotin mercaptans **1** and **2** and triphenylgermanium mercaptan (**3**) as potential new sulfhydryl transfer agents in a mild one-step reaction with some primary alkyl halides employing recent fluorodestannylation or fluorodegermanylation techniques.[8]



(1)



(2)



(3)

$Bu_3Sn\text{-}S\text{-}SnBu_3$

(4)

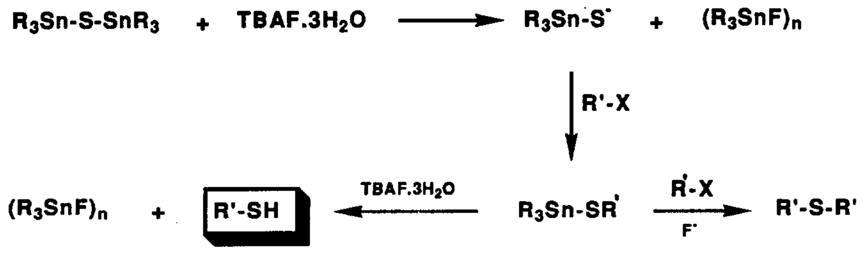
$Ph_3Sn\text{-}S\text{-}SnPh_3$

(5)

We attempted to prepare the bulky organotin compounds **1** and **2** from the corresponding organotin chloride and $NaSH.XH_2O$ or H_2S/Et_3N in benzene at 20°C under nitrogen atmosphere without any success. The products obtained rapidly decomposed to produce the corresponding organotin sulfides with release of H_2S. In an effort to synthesize triphenylgermanium mercaptan,[9] we bubbled H_2S into a solution of triphenylgermanium chloride and triethylamine in benzene affording **3** as a slightly more stable compound than **1** or **2**. However, all attempts to utilize fluoride ion in order to release the sulfhydryl anion in the presence of benzyl bromide led to starting material, formation of bis(triphenylgermanium) sulfide and the release of H_2S.

While developing our new fluorodestannylation methodologies for making thioethers with bis(triorganotin) sulfides **4** and **5**[10] we observed the formation of thiol as a side-product in the presence of a trace amount of water in our reactions. We have been able to effectively divert this reaction in favor of thiol formation when adding more water during the reaction. Scheme 1 accounts for the results observed here. Intermediate **6**, (R_3Sn-SR') is likely trapped by water in the presence of fluoride ion to afford the thiol. We previously observed and demonstrated the existence of **6** by ^{119}Sn and ^1HMR spectroscopy when using benzyl bromide as substrate.[8]

SCHEME 1: MECHANISM FOR THE FORMATION OF THIOLS



R'= alkyl X= halide

Table 1 summarizes the various conditions attempted for thiol formation. Use of an aqueous HCl (10%) solution does not seem to improve the reaction, when comparing entries 3 and 4. We previously noted that $(Bu_3Sn)_2S$ is decomposed to some extent to H_2S and Bu_3SnF in the presence of $TBAF.3H_2O$[8]; low temperatures between 20-40°C avoid unnecessary decomposition of the reagent. Finally, CsF also seems to be useful in this procedure.

In summary, with 1-bromooctane, we found the best results with a *slow addition* (1-4 h) of the bromide (398 mg; 2.06 mmol) into a mixture containing *bis*(tributyltin)sulfide (**4**, 1.33 g.; 2.18 mmol), purified CH_3CN (CaH_2, 12 mL), $TBAF.3H_2O$ (4.52 mmol) and the addition of distilled water (0.3 mL). After completing the addition of the bromide, the mixture is stirred at 20°C for 20 h; the solvent is then evaporated and ethyl acetate is poured into the flask. Filtration through a plug of SiO_2 using EtOAc as the eluent ensures the removal of the organotin fluoride by-product[10]. Flash chromatography with 5% EtOAc/95% *n*-hexane as eluent affords pure 1-octanethiol in 71% yield. 2-Phenethyl bromide also provided the corresponding thiol in good yield (82%) under similar conditions. It should be noted here that the neutrality of these conditions discourages the possible formation of styrene by an elimination reaction of 2-phenethyl bromide in a basic medium. Finally, small amounts of thioethers were also observed as by-products but they were easily removed by the flash chromatography.

TABLE 1: FORMATION OF THIOLS

ENTRY #	SUBSTRATE	ORGANOTIN	T°C	TIME(H)	F^-	PRODUCT	YIELD%[a]
1	$CH_3(CH_2)_5Br$ (1.48 mmol)	$(Ph_3Sn)_2S$ (2.96 mmol)	50	2.5	Cs/TBAI[b] (2.23 mmol)	$CH_3(CH_2)_5SH$	36
2	$CH_3(CH_2)_7Br$ (2.09 mmol)	$(Bu_3Sn)_2S$ (2.18 mmol)	40	21.0	$TBAF.3H_2O$ (4.12 mmol)	$CH_3(CH_2)_7SH$	59
3	$CH_3(CH_2)_7Br$ (2.09 mmol)	$(Bu_3Sn)_2S$ (3.14 mmol)	20	20.0	$TBAF.3H_2O$[c] (6.18 mmol)	$CH_3(CH_2)_7SH$	52
4	$CH_3(CH_2)_7Br$[d] (2.06 mmol)	$(Bu_3Sn)_2S$ (2.18 mmol)	20	20.0	$TBAF.3H_2O$ (4.52 mmol)	$CH_3(CH_2)_7SH$	71
5	$C_6H_5CH_2CH_2Br$ (2.16 mmol)	$(Bu_3Sn)_2S$ (3.24 mmol)	20	40.0	$TBAF.3H_2O$ (6.47 mmol)	$C_6H_5CH_2CH_2SH$	82

a) isolated yields; characterized by ^{1}HNMR (200 MHz, $CDCl_3$, TMS_{int}) and compared with authentic samples by GC. All reagents were mixed together and the reaction started unless otherwise noted.
b) TBAI: tetrabutylammonium iodide (0.30 mmol)
c) 0.5 mL HCl; 10% added instead of pure H_2O
d) slow addition of the bromide with a syringe for 4h (syringe pump)

We have presented a mild and neutral methodology that not only complements the existing ones, but represents one of the mildest methods for making primary aliphatic thiols in one step from organic halides; moreover, organotin sulfides 4 and 5 are commercially available.[11] Finally, the overall yields of these reactions (71-82%) when conditions are optimized are among the best ones when considering the multi-step sequence involved in numerous other procedures.

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