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PREPARATION OF THIOLS USING α-TRIMETHYLSILOXY DERIVATIVES[1]

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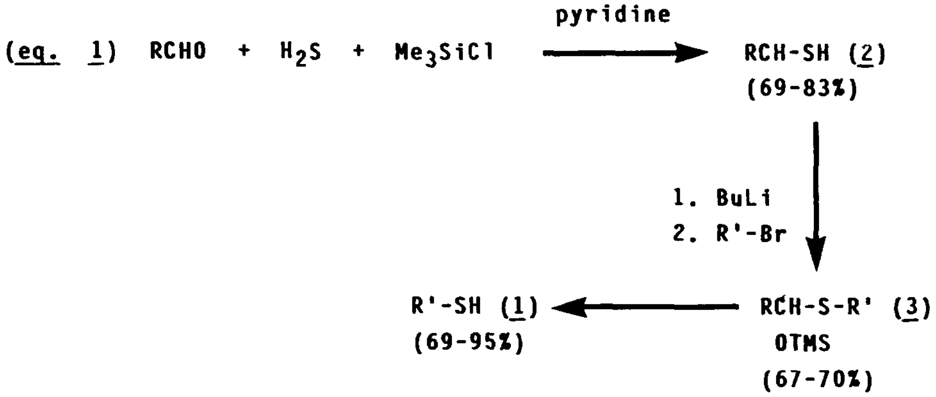
Abstract: Aliphatic thiols (1) can be prepared under the mildest conditions presently available by desilylation of the appropriate α-trimethylsiloxy sulfide (3). Sulfides 3 are generated by either alkylation of the corresponding alkyl halide or by standard literature methods.

There are a variety of procedures available for the preparation of thiols (1)[2]. Notable among these is the thiourea method[3]. It involves thioalkylation of an alkyl halide with thiourea and subsequent base hydrolysis of the isothiouronium salt. Another method[4] involves the decomposition of an alkyl halide-dimethylthioformamide adduct but in non-aqueous solvents. A recent technique[5] uses an analogous procedure permitting the breakdown of a pyridine-2-thione-alkyl halide adduct in neutral solution.

We wish to report a conversion of alkyl halides into thiols using α-trimethylsiloxy thiols(2)[6] as the mediating reagent (eq. 1). These thiols are readily available by treatment of an alkyl aldehyde, (e.g. propanal) trimethylsiloxy chloride and H_2S. Treatment of siloxythiols 2 with BuLi followed by alkylation with the appropriate alkyl halide gives sulfides 3; subsequent desilylation with KF, provides thiols in good overall yield. The following overall procedure is representative.



The α-trimethylsiloxy sulfides(3) were prepared by literature methods[7] or by direct alkylation of siloxy thiols 2. The alkylation procedure is as follows. To a solution of 0.77g (4.3 mM) of α-trimethylsiloxy-n-propyl thiol in 10 mL of DMF was added dropwise 2.6 ml of a 1.65 M solution of n-BuLi in hexane. The solution was stirred for 1.5h at -60°C; 0.73g (4.3 mM) of benzyl bromide in 3 mL of DMF was added dropwise. Stirring was continued for 2h at -60°C and warmed to RT over 1h. Addition of 10 mL of 5% NaOH solution was followed by extraction (3 x 20mL with pentane. The extracts were dried ($MgSO_4$) and the product chromatographed on silica gel (hexane/EtOAc) to give sulfide (3b) in 70% yield (identical to an authentic sample).

To a stirred solution of 0.50g (1.87 mM) of α-trimethylsiloxy-n-propylbenzyl sulfide (3b) in 10 mL of methanol was added 0.19g (2.9 mM) of anhydrous KF at room temperature; stirring was continued for 2h. After addition of a few drops of 6N HCl, yields were determined by gas chromatography using an internal standard or by preparative gas chromatography. Conventional isolation of the thiol involved evaporation of the solvent under reduced pressure followed by addition of 20 mL of H_2O. The solution was acidified and extracted with pentane (3 x 20 mL). The extracts were dried and the solvent evaporated. In all cases TLC, GLC,

^{1}Hnmr and IR spectra were identical with those of authentic samples.

The method is effective for the overall conversion of R'Br to R'SH in good yield. Advantages are the extremely mild conditions for alkylation (-60^o C) and desilylation (RT), as well as the simplicity of the experimental procedures (cf ref. 3).

DESILYLATION OF α-TRIMETHYLSILOXY SULFIDES (3)

Compound	R	R'	R'SH[a] (1)	Yield
3a	*n*-C_3H_7	C_6H_5[d]	C_6H_5SH	84[b]
3b	*n*-C_3H_7	$C_6H_5CH_2$	$C_6H_5CH_2SH$	86[b]
3c	C_2H_5	$C_6H_5CH_2$	$C_6H_5CH_2SH$	95[b]
3d	*i*-C_3H_7	C_6H_5[d]	C_6H_5SH	77[c]
3e	*n*-C_3H_7	$CH_3(CH_2)_5$	$CH_3(CH_2)_5SH$	69[c]

[a] All product thiols were pure by GLC analysis; [b] yields were determined by GLC analysis using an internal standard; [c] isolated yields; [d] prepared by ref. 7.

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3. R.L. Frank and P.V. Smith, *J. Am. Chem. Soc.*, *68*, 2103 (1946); J. Speziale, *Org. Synth.*, Coll. Vol. *4*, 401 (1963). It should be noted that this very popular method nearly always involves alkylation temperatures of 50°-80°C and work-up conditions of strong base (KOH) and hydrolysis temperatures of up to 100°C.

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