A VERSATILE SYNTHESIS OF FUNCTIONALIZED THIOLS

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Summary: The reaction of trimer 6 and an alkyl lithium afforded thiolate 7 which reacted with primary halides to produce silyl thioethers in good to excellent yields. The silyl thioethers could be hydrolyzed to the thiols using HF in acetonitrile.

The preparation of thiols is often plagued by a number of competing side reactions such as disulfide formation, thioether formation and oxidation of the thiol.^{1.} These side reactions can significantly attenuate the yield of thiol, particularly when oxygen is not excluded from the reaction. We recently required a reliable preparation of highly functionalized thiols. While there were a few often-cited synthetic methods for the generation of simple thiols, these methods failed to provide acceptable yields of the thiol 1. For example, the allylic thioester 2 could



readily be prepared using KSAc; however, the hydrolysis of 2 under acidic or mildly basic conditions (NaCN, MeOH 25°C) afforded several products.² Direct reaction of bromide 3 with NaSH also generated several products.³ Additionally, the reaction of the bromide 4 with KSAc and then KOH or HCl produced thiolactone 5. We, therefore, examined the little-studied trimer 6⁴ as a general precursor to silvl thiolates 7, which we expected to be excellent nucleophiles in anhydrous media.



The reaction of methyl lithium with 6 in ether rapidly and cleanly generated thiolate 7a which reacted with bromide 3 to produce 8. Unexpectedly, the reaction of bromide 4 with 7a provided 5 instead of 9 as the major product. Because of this result and the ease by which thioether 8 decomposed upon attempted distillation or chromatography, we prepared thiolate 7b by reaction of 6 with *tert*-butyl lithium. As expected, thiolate 7b reacted efficiently with bromides 3 and 4 to afford, after Florisil chromatography, thioethers 10 and 11 in 99% and 92% yields, respectively. The reactions of thiolates 7a and 7b are collated in Table 1. The reactions in Table 1 demonstrate the

RX	thiolate	T (°C)	time	solvent	% yield
	TBSSLi	$0 \rightarrow 25$	6 hrs	Et ₂ O	92
MeÓ	TMSSLi	$0 \rightarrow 25$	6 hrs	THF	mostly 5
	TBSSLi	$0 \rightarrow 25$	$20 \ hrs$	Et ₂ O	83
	TBSSLi	$0 \rightarrow 25$	48 hrs	Et ₂ O	75 ^a
Br	TBSSLi	$0 \rightarrow 25$	2 hrs	Et ₂ O	99
℃O ₂ Et	TMSSLi	0°	5 min.	THF	
	TBSSLi	$25 \rightarrow 40$	168 hrs	Et ₂ O	79
Br	TBSSLi	25-40	168 hrs	Et ₂ O	
	TMSSLi	$0 \rightarrow 25$	48 hrs	Et ₂ O	90-95
Dr Dr	TMSSLi	$0 \rightarrow 25$	24 hrs	THF	85b

Table 1.	The Reactions	of	Thiolates	with	Alkyl	Halides
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RX +	Me ₂ RSiSLi	->	R-S-SiRMe ₂
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^aSome sulfide and/or disulfide formed, decreasing the yield.

^bThe product was a 3:1:1 mixture of silyl thioether:sulfide:disulfide.

compatibility of unsaturated esters, ethers and alkenes with the reaction conditions. A representative reaction was conducted as follows: to a solution of hexamethyl cyclotrisilathiane (1 eq) in ether at 0°C under an argon atmosphere was added dropwise *tert*-butyl lithium (3 eq). The resulting light yellow solution was allowed to warm to 25°C over 1.5 h. The colorless solution was then cooled to 0°C and the halide (0.90 eq) was added. The solution was then warmed to the temperature shown in Table 1 for the time indicated in Table 1. The reaction was worked up by addition of three volumes of hexane, filtration through Celite and concentration in vacuo. The resulting silyl thioether was purified by chromatography⁵.

We were also able to generate alkoxide 12a by the reaction of trimer 13 with *tert*-butyl lithium. This alkoxide reacted with bromide 4 to produce silyl ether 14 in 100% yield. The reactions of alkoxide 12b with esters had previously been reported.⁶



Hydrolysis of the silvl thioethers 10 using mild acid (THF, H₂O, HOAc) or base (K₂CO₃, MeOH) gave low yields of the desired thiol. Fortunately, hydrolysis using the reaction conditions developed by Newton and Roberts⁷ for the hydrolysis of TBS ethers of alcohols afforded thiol 1 in excellent yield as the only isolated product. For simple silvl thioethers, such as PhCH₂SSit-BuMe₂, the mild acid conditions are very effective.

$$10 \frac{\text{HF}}{\text{MeCN}} 1$$

Trimer 6 reacts rapidly with alkyl lithium reagents. However, the vinyl thiolate could not be prepared from the reaction of 6 with vinyl magnesium bromide. The reactions of trimer 6 with other Grignard reagents were also complicated.

In summary, the reactions of organolithium reagents with trimer 6 provides a convenient and high-yield preparation of silvl thiolates. These reagents react with functionalized halides to generate silvl sulfides in high yield. The corresponding thiols can be produced by reaction of the silvl sulfides with HF in acetonitrile. This method has the advantage of introducing a protected thiol directly into a complex molecule, thus avoiding undesired intermolecular or intramolecular cyclization reactions. <u>Acknowledgement</u>. We thank the National Institutes of Health (Grant GM 33604) for generous financial support. We also thank Professor Thomas Barton and Dr. Chong-Bok Kim for helpful discussions.

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- 5. Sulfide 11: NMR (CDCl₃) δ 0.31 (s, 6 H), 0.96 (s, 9 H), 1.27 (t, 3 H, J = 7.1 Hz), 3.675 (s, 3 H), 3.85 (s, 2 H), 4.15 (q, 2 H, J = 7.1 Hz), 5.02 (s, 1 H); IR (film) 2950, 2920, 2850, 1710, 1620, 1460, 1440, 1420, 1370, 1290, 1250, 1160, 1130, 1050, 820, 800, 770 cm⁻¹; MS: m/e 275.1, 233.1, 205.0, 159.0, 131.0, 103.1, 89.0, 75.0, 59.0; HRMS: m/e for C₁₃H₂₆O₃SSi, calde. 290.13720, measured 290.13647, error = -2.49 ppm; CMR (CDCl₃) δ -3.67, 14.25, 18.81, 24.85, 26.22, 55.62, 59.44, 91.11, 166.68, 172.95; TLC (10% EtOAc/Hexanc) R_f = 0.50, decomposes to two spots, 0.50, 0.44; colorless oil. TBS Ether of Geranyl thiol: NMR (CDCl₃) δ 5.295 (m, 1 H), (5.09 (m, 1 H), 3.15 (d, 2 H, J = 7.7 Hz), 2.03 (m, 4 H), 1.68 (d, 3 H, J = 0.7 Hz), 1.66 (s, 3 H), 1.60 (s, 3 H), 0.96 (s, 9 H), 0.275 (s, 6 H); IR (film) 2950, 2920, 2850, 1470, 1460, 1360, 1245, 1005, 835, 820, 805, 675 cm⁻¹; MS: m/e 284.2, 227.1, 193.1, 137.1, 121.1, 93.1, 81.1, 69.1, 57.1; HRMS: calcd. 284.19940, measured 284.19922, error 1.63 ppm; CMR (CDCl₃) δ 137.08, 131.32, 123.94, 123.01, 39.48, 26.35, 25.62, 23.84, 18.87, 17.62, 15.95, 3.55.
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