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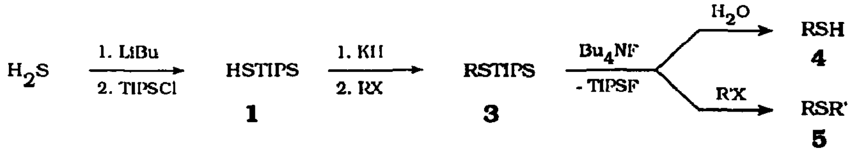
# THIOLS, UNSYMMETRICAL SULFIDES AND THIOACETALS FROM THE NEW REAGENT: TRIISOPROPYLSILANETHIOL

Edgar I. Miranda,[1] Michael J. Díaz,[2] Izander Rosado[3] and John A. Soderquist*
Department of Chemistry, University of Puerto Rico
Río Piedras, Puerto Rico 00931

**Abstract**. *Triisopropylsilanethiol (HSTIPS, **1**), easily prepared in 98% yield from $H_2S$ and TIPSCl, is efficiently alkylated in a selective manner with 1° and 2° alkyl halides or tosylates through its potassium thiolate (**2c**) to provide RSTIPS (**3**) in excellent yields. Compound **3** provides a convenient source of alkanethiols (**4**), unsymmetrical dialkyl sulfides (**5**) and thioacetals (**6**).*

As an important functionality, alkanethiols (mercaptans) are available from numerous synthetic routes, the simplest being from the reaction of metal hydrosulfides with alkyl halides.[4] Unfortunately, sulfides or disulfides as well as elimination products are also normally observed in this process. These problems can be overcome using a variety of reagents which convert alkyl halides, tosylates, mesylates and even alcohols to the corresponding thiols. As an attractive alternative to such methods, we envisaged that through the simple conversion of $H_2S$ to its triisopropylsilyl (TIPS) derivative **1**, one of its reactive sites would be effectively blocked resulting in its clean monoalkylation. Subsequently, the intermediate alkyl silyl sulfides (*e.g.* **3**) could be converted either to alkanethiols (**4**) or to unsymmetrical dialkyl sulfides (**5**). While literature precedence exists for each of the above steps, the overall reaction sequence has not been achieved.[5-7]



Recently, we have found that the triisopropyl substitution on silicon not only retards nucleophilic reactions at silicon, but also, greatly impedes reactions at adjacent centers.[8] Consequently, we anticipated that TIPSCl, rather than less convenient silanethiol precursors ($R_3SiH$, $R_3SiNH_2$), could be used to prepare **1** because the steric bulk of the TIPS group would prevent disilathiane formation.[6] Moreover, **1** and **3** were expected to have greater hydrolytic stabilities than their less bulky counterparts, thereby facilitating the overall process,[6,9] while still permitting the desilylation of **3** with fluoride ion.[5c] The simple preparation of **4** or **5** by this deprotonation/alkylation methodology presented an attractive alternative to the existing methods.[5]

Silanethiol **1** is available from LiSH and TIPSCl in essentially quantitative yield (98%). It is stable to both an aqueous work-up and distillation and even chromatography ($Al_2O_3$ or $SiO_2$).[10] By contrast, other conditions ($R_3SiCl$, $NEt_3$, $H_2S$)[6,7b,c] result in no reaction (5 d, 25 °C).

**Table 1**. The Preparation of **3** from Alkyl Halides and Tosylates and **2**.

| entry | R | M | X | time (h) | **3** | yield |
|---|---|---|---|---|---|---|
| 1 | Et | Li | Br | 24 | a | 100[a] |
| 2 | Et | Na | Br | 6 | a | 94[a] |
| 3 | Et | K | Br | 6 | a | 91(100[a]) |
| 4 | Et | K | I | 5 | a | 85[a] |
| 5 | Et | K | OTs | 22 | a | 91[a] |
| 6 | *n*-Bu | K | Br[b] | 3 | b | 90 |
| 7 | *n*-Oct | K | Br | 6 | c | 91 |
| 8 | $PhCH_2$ | K | Cl | 1 | d | 83 |
| 9 | $PhCH_2$ | K | Br | 0.25 | d | 88(100[a]) |
| 10 | $CH_2{=}CHCH_2$ | K | Br | 1 | e | 86 |
| 11[c] | $Br(CH_2)_2$ | K | Br | 8 | f | 73 |
| 12[d] | $-(CH_2)_2-$ | K | Br | 4 | g | 82 |
| 13 | $MeCHBr(CH_2)_2-$ | K | Br | 3 | h | 92 |
| 14 | *i*-Pr | K | OTs | 4 | i | 75 |
| 15 | $-CHMe(CH_2)_2-$ | K | OTs | 76 | j | 89 |
| 16[e] | $-CHMe(CH_2)_2-$ | K | Br | 3 | j | 95 |
| 17[f] | $-CHMeCH_2MeCH-$ | K | OTs | 24 | k | 16 |
| 18[e,g] | $-CHMeCH_2MeCH-$ | K | OTs | 24 | k | 74 |

[a] GC yield, ± 5%. [b] BuBr was added at 25 °C. [c] 2 equiv of 1,2-dibromoethane were used. [d] 2.4 equiv of TIPSSK were used. [e] DMF rather than THF was used as the reaction solvent in these cases. [f] A 1:1 *meso/dl* mixture was employed which produced only the *meso* product. [g] A 72:28 *meso/dl* mixture produced **3k** as a 90:10 *meso/dl* mixture.

The imposing nature of the TIPS substitution can be appreciated by examining the MMX-generated structure for **1** (Figure 1).

To explore the chemical behavior of **1**, the Li (**2a**), Na (**2b**) and K (**2c**) salts were prepared from Li(*n*-Bu), NaH and KH, respectively,[11] and allowed to react with EtBr in THF (*cf.* Table 1, entries 1-3). These reactions were all very clean, producing TIPSSEt (**3a**) as the only detectable product. The potassium salt (**2c**), which proved to be particularly effective, was isolated as a pure crystalline material (96%). Its reaction with representative alkyl halides and tosylates was found to produce **3** in excellent yields for the systems examined (Table 1).[12]

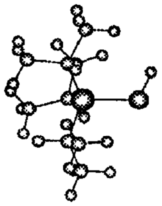
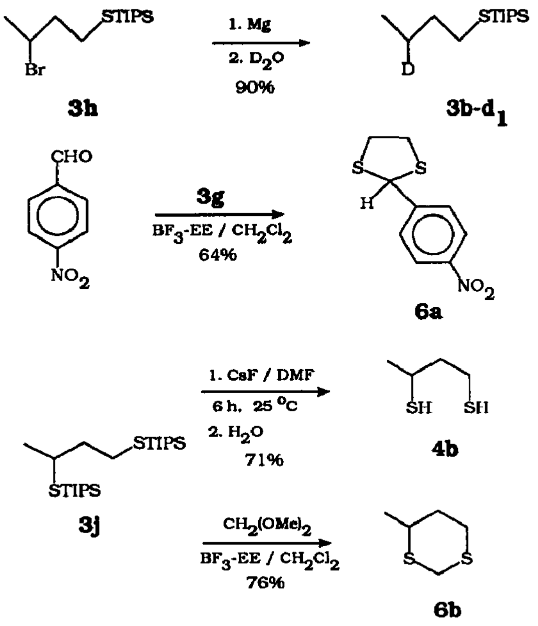


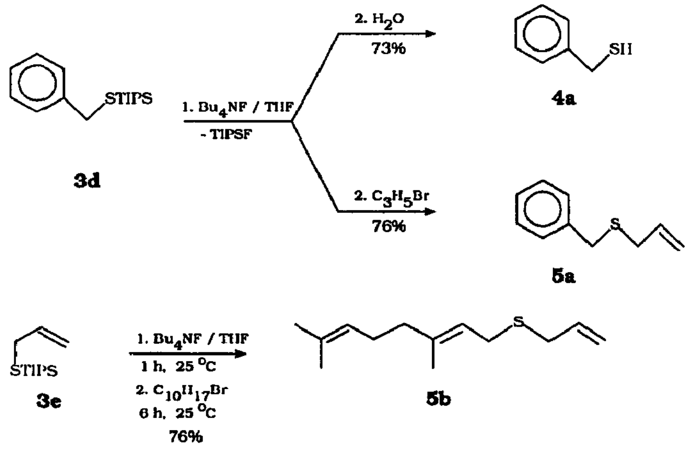
**Figure 1.** $(i\text{-}Pr)_3SiSH$ (MMX).

Allylic, benzylic and both 1° and 2° halides and tosylates are smoothly converted to **3**. We can contrast the rapid reaction of the potassium silanethiolate **2c** with benzyl bromide (25 °C, 15 min) to the slower reactions reported for this substrate with related



lithium trialkylsilanethiolates[5b] (25 °C, 48 h). Moreover, by limiting the stoichiometry to ≤1 equiv of **2c**, a difunctional substrate is selectively monothiolated (entries 11 and 13), with 1°-X groups reacting exclusively in the presence of their 2° counterparts (entry 13). Neither elimination nor disubstitution is observed. DMF proved superior to THF for the disubstitution of the reactants which contained one or more 2°-X sites. The disubstitution of the *meso* ditosylate of 2,4-pentanediol is faster than its *dl* counterpart (entries 17,18).

To demonstrate that the TIPS substitution provides both remarkable resistance toward hydrolysis as well as protection for the thiol moiety in Grignard reactions, **3h** was allowed to react with Mg, followed by a $D_2O$ quench, to afford **3b-d**$_1$ (90%, 91% CHD at C-3), with no accompanying elimination products nor unreacted **3h** being observable. Moreover, despite their remarkable stabilities, TIPS derivatives such as **3g** and **3j** cleanly provide 1,3-dithiolane **6a**[13] (2 h, 64% from MeOH, mp 76-79 °C) from $p$-$O_2NC_6H_4CHO$ and 1,3-dithiane **6b**[14] (3 h, 76%) from methylal, respectively ($BF_3$•EE (1.1 equiv, 25 °C)).



Desilylation of **3d** (TBAF, 1 h, 25 °C)) and **3j** (CsF, 6 h, 25 °C) followed by hydrolysis provides the corresponding mercaptans **4a** (73%) and **4b** (71%), respectively. Alternatively, the intermediate thiolate from **3d** is alkylated *in situ* with the addition of allyl bromide (3h, 25 °C) to provide TIPSF (72%) and the unsymmetrical sulfide **5a** (76%), which are easily separated ($SiO_2$, hexanes) and isolated as pure compounds. A similar process with the allyllic derivative **3e** produces isomerically pure allyl geranyl sulfide (**5b**, 76%).

These studies establish that the TIPS group imparts a unique stability to silyl sulfides preventing their hydrolysis during aqueous work-up and from attack by Grignard reagents. However, as required, it can be removed under mild conditions to provide either **4** or **5**.

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3. Graduate student supported by the NIH-MBRS Program (RR08102).

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10. To $H_2S$ (6.800 g, 199.5 mmol) in THF (300 mL) at -78 °C was added Li(*n*-Bu) (76.0 mL of 2.36 M, 177.0 mmol) dropwise. This mixture was allowed to warm to 0 °C over a period of 0.5 h, recooled to -78 °C, and TIPSCl (29.020 g, 150.75 mmol) was added dropwise. After the addition was complete, stirring was continued for 0.5 h and the mixture was allowed to warm to room temperature. Water (100 mL) and pentane (200 mL) were added. After separation, the organic phase was washed with water (3 x 100 mL), dried with $Na_2SO_4$, concentrated and distillation to give 28.120 g (98%) of **1**, bp 70-75 °C, 2.1 Torr. Anal. calcd for $C_9H_{22}SSi$: C, 56.84; H, 11.58. Found: C, 56.72; H, 11.59; $^1H$ NMR ($CDCl_3$) $\delta$ -0.56 (s, 1H), 1.07 (m, 21H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.43, 18.20; IR (neat) 2948, 2870, 2558, 1465, 1386, 1369, 882 $cm^{-1}$; GCMS *m/z* (relative intensity) 192 ($[M + 2]^{+\cdot}$, 1), 191 ($[M + 1]^{+\cdot}$, 2), 190 ($M^{+\cdot}$, 11), 148 (50), 147 (94), 146 (67), 119 (89), 105 (76), 91 (98), 77 (100), 76 (84), 75 (56), 63 (52).

11. The salts **2** were all soluble in THF. In pentane, **2a** is soluble, **2b** is partially soluble and **2c** is completely insoluble. **2c**: KH (15.736 g of 35% dispersion, 137.7 mmol) was washed with dry pentane (3 x 50 mL), pentane (150 mL) was added, and to the stirring slurry at 0 °C, **1** (25.970 g, 136.67 mmol) was slowly added. After 2 h, solvent decantation and evaporation afforded the crude salt, which was recrystallized twice from dry toluene (500 mL), to afford 29.60 g (95%) of **2c** (mp >250 °C (dec)).

12. The preparation of **3a** is representative: To **2c** (0.474 g, 2.08 mmol) in THF (5.0 mL) at -78 °C was added EtBr (0.251 g, 2.30 mmol) dropwise. The reaction mixture was allowed to warm to room temperature over a 1 h period and then stirred at room temperature for 6 h. Water (5 mL) was added, the layers were separated, and the aqueous phase was washed with pentane (3 x 5 mL). The combined organic extracts were dried over $Na_2SO_4$. Solvent evaporation, filtration through $SiO_2$ with hexane, concentration *in vacuo* gave 0.412 g of **3a** (91%). Anal. calcd for $C_{11}H_{26}SSi$: C, 60.48; H, 11.99. Found: C, 60.21; H, 11.92. $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (m, 18H), 1.18 (m, 6H) 2.47 (q, $J$ = 7.4 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 12.7, 18.3, 18.5, 20.0 ppm; IR (neat) 2960, 2940, 2860, 1460, 1380, 1365, 1260, 880 $cm^{-1}$; GCMS *m/z* (relative intensity) 220 ($[M+2]^{+\cdot}$, 2), 219 ($[M+1]^{+\cdot}$, 3), 218, ($M^{+\cdot}$, 19), 176 (29), 175 (100), 147 (50), 133 (97), 119 (50), 105 (99), 91 (48), 77 (56), 61 (29), 59 (34).

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