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Addition of silanethiols to aldehydes and ketones: a simple route to homochiral α-siloxyalkanethiols

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Abstract—In the presence of imidazole as a catalyst, silanethiols R_3SiSH react by addition with aldehydes and with ketones that carry electron-withdrawing substituents to give α-siloxyalkanethiols $R^1R^2C(SH)OSiR_3$. Diastereoselective addition of a silanethiol to an enantiopure aldehyde or ketone provides a convenient route to a homochiral α-siloxyalkanethiol $R^1R^2C^*(SH)OSiR_3$.
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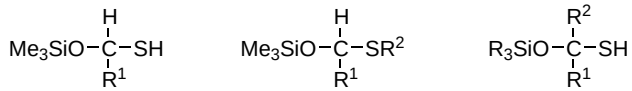
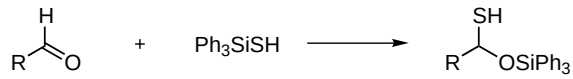
The only previously reported examples of α-siloxyalkanethiols appear to be compounds of the type **1** that were first described by Harpp and co-workers in 1981.[1] These thiols were prepared by the reaction of aldehydes with hydrogen sulphide and trimethylchlorosilane, in the presence of pyridine, and were readily oxidised to the corresponding disulphides. Subsequently, Harpp and Kobayashi[2] showed that *S*-alkylation of **1** to give the α-siloxyalkyl sulphide **2**, followed by desilylation of the latter and loss of aldehyde from the unstable hemithioacetal produced, offers a route to alkanethiols R^2SH under very mild conditions. Thioethers of the type **2** have also been prepared by the addition of alkylthiosilanes Me_3SiSR^2 to aldehydes and analogous addition to ketones has been described.[3,4]



1 **2** **3**

In the present paper we report that the imidazole-catalysed reaction of silanethiols[5] R_3SiSH with aldehydes and with ketones that carry electron-withdrawing α-substituents provides a convenient method for the preparation of α-siloxyalkanethiols of the type **3**.

A solution of 2,2-dimethylpropanal (2.0 mmol), triphenylsilanethiol (TPST, 2.0 mmol) and imidazole (0.2 mmol) in dichloromethane (4 cm^3) was stirred for 2.5 h at room temperature under argon. The solvent was removed by rotary evaporation and the residue was examined by ^1H NMR spectroscopy, which showed that essentially complete conversion of the silanethiol and aldehyde to the α-siloxyalkanethiol **4** had taken place (Eq. (1)); in the absence of imidazole no addition product was formed. Analytically pure **4** was isolated in 80% yield by chromatography on silica gel (light petroleum–CH_2Cl_2 eluent, 10:1). TPST also added readily to butanal under the same conditions in the presence of imidazole, with essentially complete consumption of the aldehyde, and the thiol **5** was isolated in 70% yield.



4 R = Bu^t
5 R = Pr^n (1)

The imidazole-catalysed addition reactions of a number of other silanethiols with 2,2-dimethylpropanal and with butanal were also investigated and the results are summarised in Table 1; yields obtained from the primary aldehyde were somewhat lower and by-products were present before purification. The yields of α-siloxyalkanethiols from silanethiols of similar Brønsted acidity decrease dramatically as the bulk of the substituents at silicon increases, suggesting that nucleophilic substitution at silicon is of key importance in the overall addition process. Thus, in contrast to TPST, tri-*o*-tolylsilanethiol is unreactive (entry 2). Although Bu^tPh_2SiSH does not add to either aldehyde (entry 4), good yields of α-siloxyalkanethiol are obtained when the *t*-butyl group is exchanged for the smaller methyl group (entry 3) or for a *t*-butoxy substituent in which

Keywords: silicon and compounds; thiols; aldehydes; ketones; asymmetry.

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Table 1. α-Siloxyalkanethiols prepared by the imidazole-catalysed reactions of silanethiols with 2,2-dimethylpropanal and with butanal[a]

Entry	Silanethiol	Isolated yield (%) of α-siloxyalkanethiol[b]	
		$Bu^tCH(SH)OSiR_3$	$PrCH(SH)OSiR_3$
1	Ph_3SiSH	80	70
2	$(o\text{-}MeC_6H_4)_3SiSH$	0[c]	0[c]
3	$MePh_2SiSH$	85	69
4	Bu^tPh_2SiSH	0[c]	0[c]
5	Bu^tOPh_2SiSH	82	66

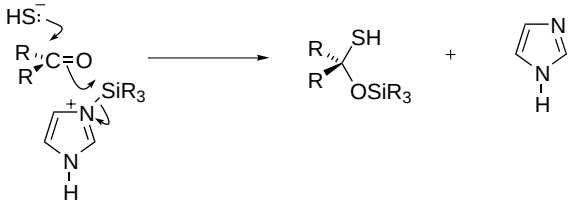
[a] A solution of the silanethiol (2.0 mmol), the aldehyde (2.0 mmol) and imidazole (0.2 mmol) in dichloromethane (4 cm^3) was stirred at room temperature for 2.5 h.

[b] Purified by flash chromatography on silica gel (light petroleum–CH_2Cl_2 eluent, 10:1). Satisfactory spectroscopic data and elemental analyses were obtained for all compounds.

[c] No identifiable product was detected by NMR spectroscopic analysis of the crude reaction mixture.

the bulky group is further removed from silicon (entry 5).

Silanethiols are more acidic than alkanethiols and can also act as sources of electrophilic silicon such that in the presence of a catalytic amount of imidazole (ImH) a number of potentially reactive species will be produced. Thus, ImH_2^+, $ImSiR_3$, $Im(SiR_3)H^+$, HS^-, R_3SiS^- and H_2S could all be present in low, equilibrium, concentrations. One plausible mechanism for the overall addition of silanethiols to aldehydes and ketones, consistent with the experimental observations, is shown in Scheme 1. Here nucleophilic attack by HS^- at the carbonyl–carbon atom is assisted by transfer of a siliconium ion from $Im(SiR_3)H^+$ to the carbonyl–oxygen atom. A feasible alternative, less direct, mechanism for product formation could involve nucleophilic addition of R_3SiS^- to the carbonyl–carbon, followed by a 1,3-migration of the silyl group from S to O and proton

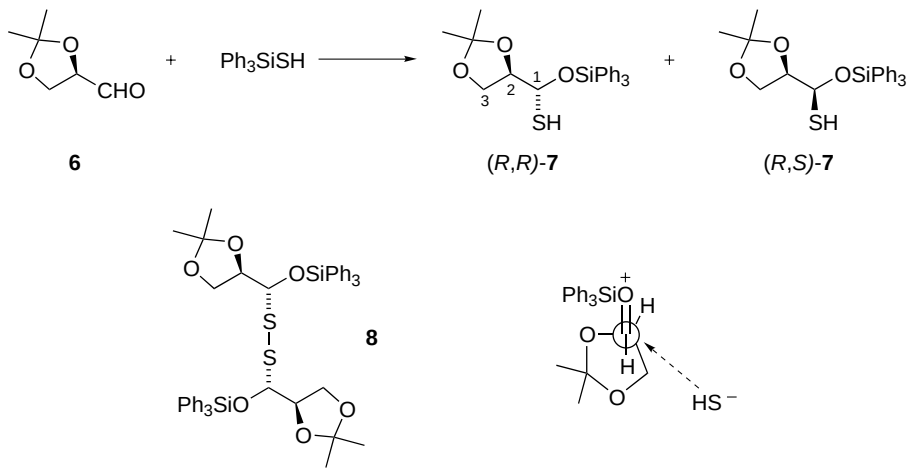


Scheme 1.

transfer from ImH_2^+ to give the product and regenerate the catalyst.

The carbonyl carbon atom in (*R*)-glyceraldehyde acetonide[6] **6** is more electrophilic than that in a simple alkyl aldehyde, because of the presence of the α- and β-oxygen atoms, and the reaction between TPST and **6** in dichloromethane in the presence of imidazole, initially at room temperature, was noticeably exothermic. Under conditions similar to those described above (5 mol% imidazole, stirring for 2.5 h), but with cooling in an ice–water bath, the addition reaction took place quantitatively to give an 87:13 mixture of (*R*,*R*)-**7** and (*R*,*S*)-**7** (Scheme 2). The diastereoisomeric mixture was isolated in 85% yield and the major isomer was separated by further chromatography on silica gel.[7] The structure of this isomer was determined after oxidation (using nickel peroxide in benzene) to the crystalline disulphide **8**[8] which was shown by X-ray diffraction[9] to be the (*R*,*R*,*R*,*R*)-compound. When (*R*,*R*)-**7** in dichloromethane was stirred at 0°C for 2.5 h in the presence of imidazole and TPST (5 mol% of each) only ca. 1% isomerisation to the (*R*,*S*)-diastereoisomer took place, implying that the original isomeric ratio is kinetically determined. When this control experiment was conducted at 40°C (bath temperature), a 95:5 mixture of (*R*,*R*)-**7** and (*R*,*S*)-**7** resulted, indicating that some reversion of **7** to aldehyde and TPST occurs under these conditions.

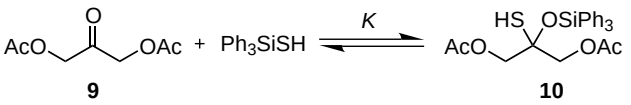
According to the Felkin–Anh transition-state model[10] for carbonyl addition, nucleophilic attack by HS^- on



Scheme 2.

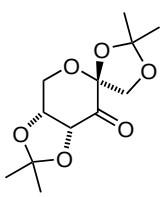
the preferred conformation of the free aldehyde **6**, along the least hindered trajectory at the Bürgi–Dunitz angle, should take place at the *Si*-face of the aldehyde and lead to (*R*,*S*)-**7**. However, if the bulky Ph_3Si group is closely associated with the carbonyl oxygen atom in the transition state, attack at the *Re*-face could become preferred, leading to the observed kinetic preference for formation of the (*R*,*R*)-diastereoisomer, as illustrated in Scheme 2.

TPST failed to add to simple dialkyl ketones, such as cyclopentanone, methyl neopentyl ketone and norcamphor, in the presence of imidazole at room temperature. However, addition to 1,3-diacetoxypropan-2-one **9** took place readily to give the α-siloxyalkanethiol **10** (Eq. (2)). Thus, in the presence of 10 mol% imidazole in dichloromethane at room temperature, as described for the reactions of aldehydes, 75% of **9** was converted to **10**, as judged by ^{1}H NMR spectroscopy immediately after rapid removal of the solvent by rotary evaporation at room temperature. Essentially the same extent of conversion of **9** to **10** was observed when the reaction time was extended to 4 h. Conversion was substantially less (ca. 30%) when the reaction was carried out at 40°C, while reaction at −15°C for 4 h resulted in 93% conversion of **9** to **10**. Under the latter conditions, analytically-pure **10** was isolated as an oil in 76% yield by chromatography on silica gel (light petroleum–CH_2Cl_2 eluent, 10:1).

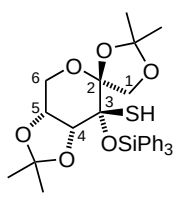


9 **10** (2)

These results imply that **10** is in quasi-equilibrium with **9** and TPST under the reaction conditions. The addition is presumably exothermic ($\Delta_r H$ negative) and hence the equilibrium constant K will decrease with increasing temperature. However, the addition process will be associated with a large negative entropy change such that $\Delta_r G$ is significantly less negative than $\Delta_r H$, leading to reversibility under the conditions employed. In support of this interpretation, when a sample of pure adduct **10** was heated at 40°C in the presence of imidazole (10 mol%) in dichloromethane, examination by NMR spectroscopy after removal of the solvent showed reversion to the ketone such that the ratio **9**:**10** was 44:56. When subjected to similar treatment in the absence of imidazole, the α-siloxyalkanethiol **10** was completely unchanged.



11



12

The fructose-derived ketone **11**[11,12] and related electrophilic ketones[13] have been employed successfully by Shi and co-workers as catalysts for the asymmetric dioxirane-mediated epoxidation of alkenes, using oxone as the stoichiometric oxidant. By analogy with the comparative ease of silanethiol addition to the electrophilic ketone **9**, we anticipated that TPST would undergo diastereoselective addition to **11** to give a homochiral α-siloxyalkanethiol. This type of thiol would provide an SH group in a chiral, conformationally-defined environment and has the potential to mediate efficient enantioselective hydrogen-atom transfer to a prochiral carbon-centred radical.[14]

A dichloromethane solution containing the ketone **11**, TPST (1.0 equiv.) and imidazole (5 mol%) was stirred under argon at 0°C for 4 h. After removal of the solvent and purification of the residue by flash chromatography on silica gel (light petroleum–diethyl ether eluent, 5:1), followed by recrystallisation from hexane–diethyl ether at −18°C, the α-siloxyalkanethiol **12** was obtained in 66% yield.[15] The structure of **12** was confirmed by single-crystal X-ray diffraction[9] and shows that attack by HS^- has taken place at the less hindered face of the carbonyl group; no conclusive evidence for formation of any of the other diastereoisomer could be obtained from NMR spectroscopic analysis of the crude reaction mixture.

Acknowledgements

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7. *Representative procedure*: Under an atmosphere of argon, imidazole (34 mg, 0.50 mmol) was added to a stirred solution of 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde[6] **6** (1.30 g, 10.0 mmol) and triphenylsilanethiol (2.92 g, 10.0 mmol) in dry dichloromethane (20 cm^3) cooled in an ice–water bath. The mixture was stirred for a further 2.5 h at 0°C, the solvent was removed by rotary evaporation at room temperature and the residue was subjected to flash chromatography on silica gel, eluting with light petroleum (bp 40–60°C)–diethyl ether (10:1), to give **7** (3.59 g, 85%) as a colourless oil consisting of two diastereoisomers in the ratio 87:13. A pure sample of the major product (*R*,*R*)-**7** could be obtained by further careful chromatography, eluting with light petroleum–

CH_2Cl_2–diethyl ether (23:1:1), $[\alpha]_D^{21}$ −39.5 ($c=2.1$, $CHCl_3$). NMR (500 MHz for ^1H, 125.7 MHz for ^{13}C, $CDCl_3$ solvent, J in Hz); δ_H 1.35 (3H, s, Me), 1.36 (3H, s, Me), 2.04 (1H, d, J 8.6, SH), 3.88 (1H, dd, J 8.9 and 6.0, 3-H^A), 4.08 (1H, dd, J 8.9 and 6.8, 3-H^B), 4.31 (1H, apparent q, <J> 6.4, 2-H), 4.98 (1H, dd, J 8.6 and 6.4, 1-H), 7.37–7.71 (15H, m, 3Ph); δ_C 25.4, 26.4, 66.6, 76.7, 80.9, 110.4, 127.9, 130.3, 133.4, 135.7. MS (EI, 70 eV) 422 (M^+, 3), 199 (100%). IR (liq. film) 2557 cm^{-1} (SH str.). Found: C, 67.9; H, 6.2. $C_{24}H_{26}O_3SiS$ requires C, 68.2; H, 6.2%.

8. A solution of the thiol (0.62 g, 1.47 mmol) in benzene (2 cm^3) was stirred vigorously with an excess of suspended nickel peroxide hydrate (Aldrich, 1.33 g) at room temperature for 4 h. The reaction mixture was filtered through Celite and the filter cake was washed thoroughly with CH_2Cl_2. Solvents were removed from the filtrate under reduced pressure and the residue was purified by flash chromatography on silica gel, using light petroleum–CH_2Cl_2–diethyl ether (21:2:2) as eluent, to give the disulphide **8** (0.54 g, 87%) as a white foam, which was recrystallised from diethyl ether–hexane; mp 110–112°C, $[\alpha]_D^{23}$+32.9 ($c=1.0$, $CHCl_3$). NMR (500 MHz for ^1H, 125.7 Hz for ^{13}C, $CDCl_3$ solvent, J in Hz); δ_H 1.24(8) (6H, s, 2Me), 1.25(3) (6H, s, 2Me), 3.52 (2H, dd, J 8.6 and 6.5, 3-H^A), 3.66 (2H, dd, J 8.6 and 6.7, 3-H^B), 4.42 (2H, apparent q, <J> 6.3, 2-H), 4.63 (2H, d, J 5.8, 1-H), 7.31–7.63 (30H, m, 6Ph); δ_C 25.4, 26.3, 66.2, 78.8, 86.4, 110.1, 127.8, 130.2, 133.4, 135.8. Found: C, 68.3; H, 6.0. $C_{48}H_{50}O_6S_2Si_2$ requires C, 68.4; H, 6.0%.
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15. Physical data for **12**: mp 136–138°C, $[\alpha]_D^{20}$ −6.5 ($c=2.1$, $CHCl_3$). NMR (500 MHz for ^1H, 125.7 MHz for ^{13}C, $CDCl_3$ solvent, J in Hz); δ_H 1.05 (3H, s, Me), 1.48 (3H, s, Me), 1.49 (3H, s, Me), 1.55 (3H, s, Me), 3.12 (1H, s, SH), 3.65 (1H, dd, J 12.7 and 4.6, 6-H^A), 3.98 (1H, d, J 6.3, 4-H), 4.11 (1H, dt, J 6.3 and 4.7, 5-H), 4.14 (1H, d, J 9.4, 1-H^A), 4.24 (1H, dd, J 12.7 and 4.7, 6-H^B), 4.63 (1H, d, J 9.4, 1-H^B), 7.35–7.79 (15H, m, 3 Ph); δ_C 25.2, 26.2, 26.4, 27.3, 63.8, 70.7, 72.1, 79.0, 84.6, 105.8, 110.1, 110.4, 127.7, 130.0, 134.8, 136.0. MS (EI, 70 eV) 550 (M^+, 1), 517 (7), 259 (100%). IR (KBr disc) 2600 cm^{-1} (SH str.). Found: C, 65.3; H, 6.1. $C_{30}H_{34}O_6SiS$ requires C, 65.4; H, 6.2%.