Synthesis of 2-Alkylthio-3-chloro- and 2,3-Bis(alkylthio)propanals

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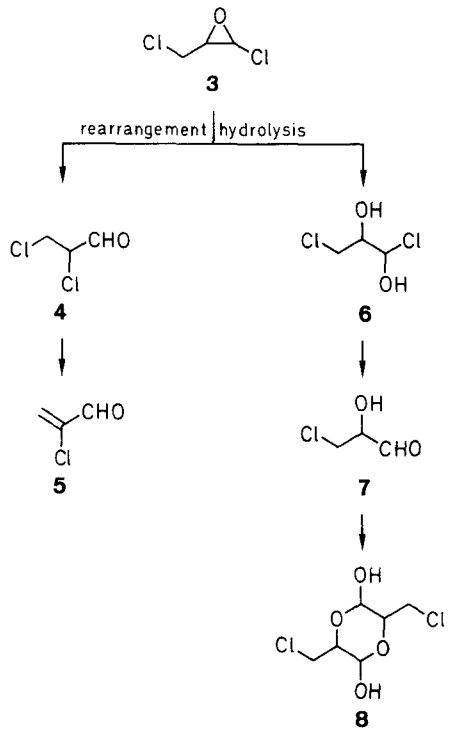
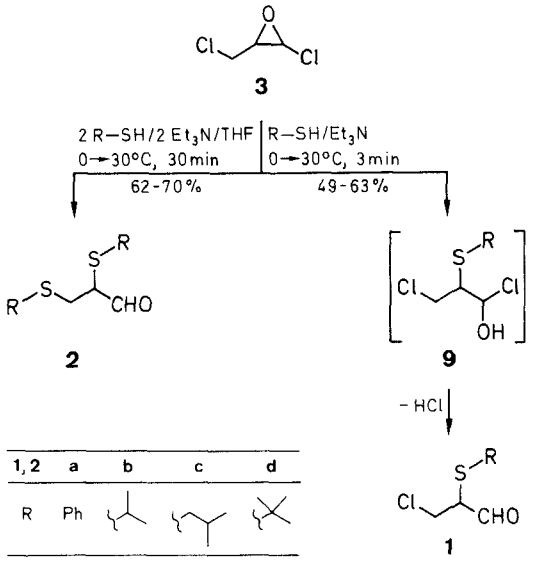
A general synthesis of 2-alkylthio-3-chloro- and 2,3-bis(alkylthio)propanals consists of the tertiary amine catalysed regiospecific ring opening of 2-chloro-3-chloromethyloxirane (1,3-dichloropropene oxide) with alkanethiols.

In a programme of synthetic work with the objective of finding new agents for the control of male fertility,[1] various derivatives of (alkylthio)- and (arylthio)-propanals (e.g., **1** and **2**) were required, not only for biological testing but also for use as building blocks in further synthetic work. These molecules bear three reactive groups positioned along the C_3 chain, which require careful synthetic manipulation. Of the several approaches tested, we chose to study the novel ring-opening reaction of 2-chloro-3-chloromethyloxirane (1,3-dichloropropene oxide, **3**) with sulfur nucleophiles under mild conditions.

It had originally been reported[2] that under hydrolytic conditions oxirane **3** is converted into 2-chloropropenal (**5**). However, re-investigation revealed that the reaction can take two different paths.[3] The facile thermal rearrangement of **3** leads to 2,3-dichloropropanal (**4**) which readily eliminates hydrogen chloride to give 2-chloropropenal (**5**). At lower temperatures, however, compound **3** is hydrolysed to **6** which looses hydrogen chloride to give **7**, which then dimerizes and is isolated as the cyclic dimer **8**.



The latter reaction sequence (**3** → **6** → **7**) appeared to present an interesting and direct route to compounds such as **1** and **2**, based on the speculation that epoxide ring opening with a sulfur nucleophile could be faster than the competing rearrangement of **3**, and dimerization (e.g., **7** → **8**) would not occur. However, it was noted that, unlike the conversion of **3** → **6** where indiscriminate attack of hydroxide ion at either C-1 or C-2 would yield the same product, only regiospecific ring opening at the apparently less hindered C-2 site would lead to the target compounds **1** and **2**. We now report on the success of this reaction, which provides a simple and straightforward method for the synthesis of the title compounds.



Addition of an equimolecular amount of epoxide **3**[2] to a solution of thiophenol and triethylamine in tetrahydrofuran at room temperature afforded a mixture of **1a** and **2a** in 19% and 27% yields, respectively. Isolation of such a mixture revealed that epoxide ring opening of **3** does indeed take place favourably at C-2 as anticipated, but that chloroaldehyde **1**, once formed, competes successfully with the parent epoxide for the thiol nucleophile to give **2**. The obvious task was to find suitable reaction conditions. This we accomplished by adding oxirane **3** to a solidified equimolecular mixture of thiophenol and triethylamine at 0 °C without solvent, with good stirring using an oversized magnetic bar, followed by quickly raising the temperature to 30 °C, which resulted in an instant and vigorous reaction. Rapid conventional workup gave a residue which was shown by ^{1}H-NMR analysis to consist almost entirely of the aldehyde **1a**. On the other hand, the use of excess (> 2 equivalents) thiophenol and triethylamine under similar conditions, with or without solvent (THF), gave exclusively **2a** in high yield.

Aliphatic sulfur nucleophiles behaved in the same manner as thiophenol. Thus, various compounds **1** and **2** could be prepared.

Compounds **1** and **2** are not very stable; for example, aldehydes **1** decompose upon contact with silica gel and react quickly with nucleophilic solvents, such as ethanol, to yield complex mixtures, while aldehydes **2** decompose on prolonged heating under vacuum distillation con-

Table. Aldehydes **1** and **2** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	MS (70 eV) *m/z* (%)	IR (Film) ν(cm^{-1})	^{1}H-NMR (CCl_4/TMS) δ, *J*(Hz)
1a	63	C_9H_9ClOS (200.7)	200.5 (M^+, 3.4), 165 (9.4), 123 (34.5), 110 (100), 109 (54.2)	1736, 1585, 1485, 1440, 745, 695	3.18 (dd, 1H, *J* = 14, 7), 3.46 (dd, 1H, *J* = 14, 7), 4.14 (dt, 1H, *J* = 7, 3), 7.30 (s, 5H), 9.41 (d, 1H, *J* = 3)
1b	62	$C_6H_{11}ClOS$ (166.6)	166.5 (M^+, 15.4), 131 (12), 76 (51.6), 75 (29.4), 43 (100)	1735, 1460, 1365	1.29 (d, 6H, *J* = 7), 2.88 (dd, 1H, *J* = 15, 7), 3.00 (m, 1H), 3.14 (dd, 1H, *J* = 15, 7), 4.22 (dt, 1H, *J* = 7, 3), 9.50 (d, 1H, *J* = 3)
1c	49	$C_7H_{13}ClOS$ (180.6)	180.5 (M^+, 20.8), 145 (9.5), 90 (63), 89 (16), 57 (66.8), 56 (100)	1738, 1465, 1385, 1365	1.20 (d, 6H, *J* = 7), 1.80 (m, 1H), 2.49 (d, 2H, *J* = 7), 2.94 (dd, 1H, *J* = 14, 7), 3.14 (dd, 1H, *J* = 14, 7), 4.23 (dt, 1H, *J* = 7, 3), 9.46 (d, 1H, *J* = 3)
1d	54	$C_7H_{13}ClOS$ (180.6)	180.5 (M^+, 19), 145 (7.4), 90 (54.5), 89 (11.3), 57 (81.7), 56 (100)	1738, 1460, 1365	1.35 (s, 9H), 2.82 (dd, 1H, *J* = 14, 7), 3.11 (dd, 1H, *J* = 14, 7), 4.17 (dt, 1H, *J* = 7, 3), 9.40 (d, 1H, *J* = 3)
2a	70	$C_{15}H_{14}OS_2$ (274.3)	274 (M^+, 29.2), 165 (56.4), 164 (19), 110 (70.4), 109 (100)	1720, 1580, 1480, 1440, 740, 690	3.02 (dd, 1H, *J* = 15, 7), 3.25 (dd, 1H, *J* = 15, 7), 3.60 (dt, 1H, *J* = 7, 3), 7.25 (s, 10H), 9.42 (d, 1H, *J* = 3)
2b	64	$C_9H_{18}OS_2$ (206.25)	206 (M^+, 28), 131 (9.5), 130 (12.2), 76 (25), 75 (19.1), 43 (100)	1720, 1460, 1385, 1365	1.27 (d, 6H, *J* = 7), 1.29 (d, 6H, *J* = 7), 2.65 (dd, 1H, *J* = 15, 7), 2.90 (dd, 1H, *J* = 15, 7), 2.94 (m, 2H), 3.14 (dt, 1H, *J* = 7, 4.5), 9.12 (d, 1H, *J* = 4.5)
2c	62	$C_{11}H_{22}OS_2$ (234.3)	234 (M^+, 35.9), 145 (12.3), 144 (10), 90 (11.3), 89 (10.9), 57 (100)	1718, 1465, 1385, 1365	1.00 (d, 12H, *J* = 7), 1.78 (m, 2H), 2.27 (d, 2H, *J* = 7), 2.42 (d, 2H, *J* = 7), 2.64 (dd, 1H, *J* = 13, 7), 2.85 (dd, 1H, *J* = 13, 7), 3.22 (dt, 1H, *J* = 7, 4), 9.16 (d, 1H, *J* = 4)
2d	67	$C_{11}H_{22}OS_2$ (234.3)	234 (M^+, 9.2), 144 (2), 90 (4.5), 89 (2.4), 57 (100)	1720, 1460, 1365	1.36 (s, 18H), 2.54 (dd, 1H, *J* = 15, 7), 2.89 (dd, 1H, *J* = 15, 7), 3.28 (dt, 1H, *J* = 7, 4), 9.22 (d, 1H, *J* = 4)

[a] Yield of isolated product.
[b] Satisfactory microanalyses: C ±0.27, H ±0.31; exception: **2c** (C −0.44).

ditions. We have found that compounds **1** are best purified by filtering their solutions in dichloromethane/hexane (1:9) through a cellulose column followed by bulb-to-bulb vacuum distillation, whereas simple column chromatography on cellulose is recommended for the purification of compounds **2**.

Reagents were purchased from either Fluka or Sigma Chemical Companies and were purified by distillation before use. Merck microcrystalline cellulose was used for column chromatography. All reactions were conducted under N_2; reagents were introduced into the reaction flasks via N_2-flushed syringes.

Microanalyses and mass spectra were performed by the Scientific and Technological Research Equipment Center, Chulalongkorn University. IR spectra were recorded on a Beckman IR 20A spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-60 or a Jeol FX 90Q spectrophotometer.

3-Chloro-2-(phenylthio)propanal (1a); Typical Procedure:
A mixture of *cis*- and *trans*-1,3-dichloropropene oxide[2] (**3**; 1.00 g, 7.87 mmol) is added in one portion to a solidified mixture of PhSH (0.87 g, 7.91 mmol) and Et_3N (0.80 g, 7.92 mmol) at 0 °C with good stirring (using an oversized egg-shaped magnetic bar). After the addition, the temperature of the mixture is quickly raised to 30 °C, whereupon a vigorous reaction ensues. After 3 min, the mixture is taken up in CH_2Cl_2 (50 mL) and this solution is rapidly washed with H_2O (5 × 15 mL), then dried (Na_2SO_4), and evaporated to dryness to give a dark-brown residue. The residue is dissolved in CH_2Cl_2/hexane (1:9; 25 mL) and this solution is passed through a short cellulose column using CH_2Cl_2/hexane (1:9) as eluent. The combined product is flash distilled (bulb-to-bulb; 80 °C (bath)/0.05 Torr) to give the pure product **1a** as a clear colorless liquid, yield: 0.99 g (63%).

C_9H_9ClOS (200.7) calc. C 53.86 H 4.52 found 53.59 4.48

2,3-Bis(phenylthio)propanal (2a); Typical Procedure:
1,3-Dichloropropene oxide (**3**; 1.00 g, 7.87 mmol) is added with stirring to a solution of PhSH (1.80 g, 16.37 mmol) and Et_3N (1.70 g, 16.83 mmol) in THF (20 mL) at 0 °C and stirring is continued at r.t. for 30 min. The mixture is then poured into CH_2Cl_2 (50 mL) and this solution washed with H_2O (5 × 15 mL), dried (Na_2SO_4), and evaporated to dryness to give a yellow liquid (1.14 g; shown by ^{1}H-NMR analysis to consist almost solely of product **2a**). Attempted flash-vacuum distillation leads to decomposition and a severe loss in yield. Purification of the crude product, if required, may be carried out by column chromatography on cellulose using CH_2Cl_2/hexane (1:9) as eluant to give the analytically pure product **2a** as a colorless viscous liquid; yield: 1.51 g (70%).

$C_{15}H_{14}OS_2$ (274.4) calc. C 65.66 H 5.14 found 65.57 5.11

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(1) A programme initiated by the International Organization for Chemical Sciences in Development (IOCD); cf. *Chem. Eng. News*. **1984**, Nov. 19, 8.
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