Heteroatom Chemistry
Volume 5, Number 5/6, 1994

Methanolysis of 1,3-Oxathiolane-2-thione: A Stereospecific Preparation of Episulfides

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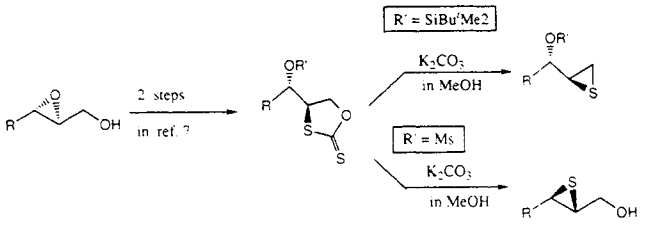
Received 25 August 1994

ABSTRACT

Potassium carbonate mediated methanolysis of optically active 1,3-oxathiolane-2-thiones (5-membered cyclic xanthates) took place under very mild conditions to give optically pure 1,2-episulfides. Also, methanolysis of 4-[1-(methanesulfonyloxy)alkyl]-1,3-oxathiolane-2-thiones and 2,4-dialkyl substituted 1,3-oxathiolane-2-thione gave 2,3-episulfides, stereospecifically.

INTRODUCTION

The episulfide group is an attractive functional group for synthesis of organic compounds, and this subject has recently been reviewed by Fokin et al. [1]. Direct preparations of episulfides (thiiranes) from epoxides (oxiranes) have been performed by reactions with Ph_3PS [2], KSCN [3], a combination of thiourea and KSCN [4], or cyclic dithiourethane [5]. However, these reactions have not been studied from the point of view of asymmetric syntheses of optically active thiiranes. However, it should be mentioned that Sharpless has described the transformation of an asymmetric oxirane to an optically active thiirane by reaction with thiourea and titanium tetraisopropoxide [6]. We have recently reported asymmetric preparations of 4-alkyl substituted 1,3-oxathiolane-2-thiones (5-membered cyclic xanthates) from optically pure 2,3-epoxy alcohols [7]. In an extension of the chemistry of 5-membered cyclic xanthates, we herein report a new and reliable access to either optically active 1,2-episulfides or 2,3-episulfides by methanolysis of asymmetric 4-alkyl 1,3-oxathiolane-2-thiones under basic conditions. A typical reaction sequence starting with an optically active 2,3-epoxy alcohol is depicted in Scheme 1.



SCHEME 1

Regio and Stereospecific Formation of 1,2- and/or 2,3-Episulfides

α-Hydroxy xanthate **1** [7] was silylated with TBDMSOTf in the presence of 2,6-lutidine to give silyl ether **2** in 96% yield, which, upon treatment with anhydrous potassium carbonate in methanol, gave episulfide **3** in 97% yield. The structure of **3** was confirmed by its mass and proton NMR spectra. The M + 1 positive ion peak was observed in the FAB mass spectrum at 309 (*m/z*), and the M-57 peak appeared at 251 (*m/z*) due to the typical fragmentation of *tert*-butyldimethylsilyl ether in the electron impact mass spectrum. In the proton NMR spectrum, typical terminal episulfide protons appeared at δ 2.54 and 2.31, each as double doublets, whose coupling constants were 6.2 and 1.1 Hz and 5.5 and 1.1 Hz, respectively. Alternatively, **1** was mesylated to give **4**, and the mesylate was then treated with anhydrous potassium carbonate in

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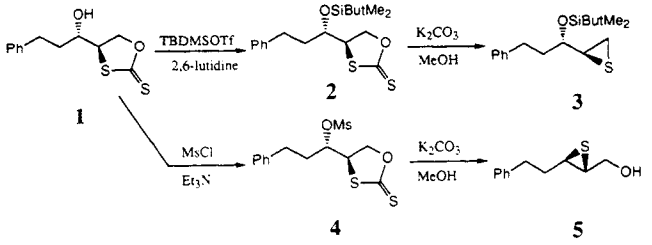


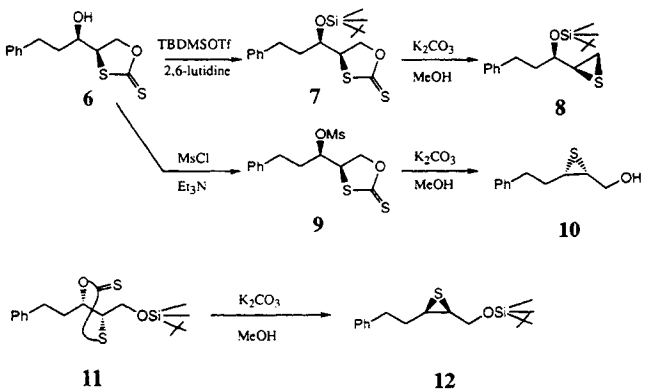
SCHEME 2

methanol. None of the corresponding 1,2-episulfide and mercapto alcohol was obtained, but 2,3-episulfide **5** was formed in 46% yield. In both reactions, only a single steroisomer was isolated, and none of the mercapto alcohol was found in the crude reaction mixture.

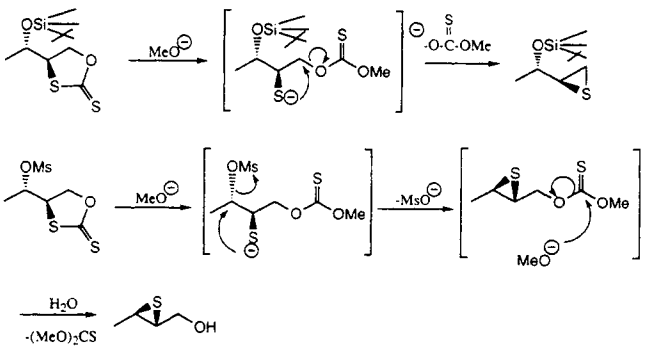
Similar reaction processes were observed in the case of **6**, the diastereomer of **1**, as shown in Scheme 3. Compound **6** was transformed to episulfides **8** and **10** stereospecifically. When xanthate **7** [7] was subjected to potassium carbonate mediated methanolysis conditions, 3-(*tert*-butyldimethylsilyl)oxy 1,2-episulfide **8** was obtained in 95% yield as a single stereoisomer. On the other hand, mesylate **9**, obtained in 94% yield from **6**, when treated under the same conditions, gave cis-2,3-epoxy alcohol **10** in 53% yield. None of the corresponding 1,2-episulfide was detected in this reaction. The corresponding reaction of the 4,5-dialkyl substituted 1,3-oxathiolane-2-thione **11** [7], also proceeded stereospecifically to give cis-2,3-episulfide **12** in 80% yield. The compound **12** was found to be the enantiomer of the *tert*-butyldimethylsilyl ether of **10**.

DISCUSSION

Probable reaction mechanisms are proposed in Scheme 4. First, the methoxide anion attacks the thiocarbonyl carbon atom in the cyclic xanthate and opens the ring to form the thiolate anion. An intramolecular nucleophilic displacement on the



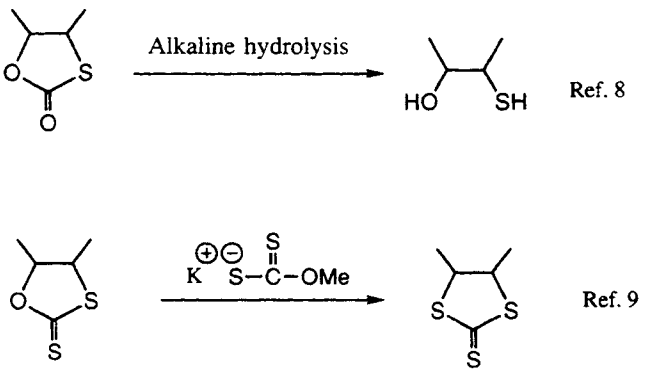
SCHEME 3



SCHEME 4

adjacent carbon with departure of the thionocarbonate ion gives the episulfide. On the other hand, when the C-OMs group is present adjacent to the cyclic xanthate, thiolate anion, once formed by methanolysis of the xanthate, attacks the mesylate carbon from the back side with inversion to produce the 2,3-episulfide, and the methyl thionocarbonate may then undergo hydrolysis to afford the 2,3-epithio alcohol. All the reactions take place stereospecifically.

These results are interesting in comparison with the cases for cyclic thiol carbonates. Scharf reported that hydrolysis of a 1,3-oxathiolane-2-one in alkaline media afforded a 1,2-mercapto alcohol exclusively [8]. In such a case, a thiolate anion would be produced as an intermediate, but due to a low ability to eliminate methyl carbonate, it might not give the corresponding episulfide but instead a simple hydrolyzed product. This represents a conspicuous difference between methyl carbonate and methyl thionocarbonate, which exhibits an excellent leaving character against an attack of a thiolate anion. Moreover, the reaction of 1,3-oxathiolane-2-one with the sodium or potassium salt of methyl xanthate (Na or KSCSOMe) gave 1,3-dithiolane-2-thione. This reaction was proposed to take place through a thiolate intermediate, but the mechanism seems to be rather complicated [9].



SCHEME 5

CONCLUSION

Potassium carbonate mediated methanolysis of a cyclic xanthate takes place stereospecifically to give an episulfide, and a 5-membered cyclic xanthate can be regarded as an excellent precursor for an episulfide.

EXPERIMENTAL

Spectra were measured by use of the following instruments; for ^1H and ^{13}C NMR, JEOL-GX400 (400 and 100 MHz) and Varian Gemini 300 (300 and 75 MHz); for low- and high-resolution mass spectra (LRMS and HRMS), JEOL-JMS-303HF; for IR, JASCO IRA-1; for optical rotation angle, JASCO DIP-370. NMR spectra were obtained in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were measured by the electron impact (EI) method at 70 eV or by the fast atom bombardment (FAB) method. Only strong and/or structurally important peaks are reported here for MS and IR spectra. Thin-layer chromatography was carried out on 0.25 mm E. I. Merck precoated silica-gel plates (60F-254). Wako gel (C-200) was used for silica-gel column chromatography.

Typical Reaction for Methanolysis. To a solution of a cyclic xanthate (1 mmol) in methanol (5 mL) was added anhydrous K_2CO_3 (240 mg), and the mixture was stirred for 0.5 to 2 hours at room temperature. Then, the mixture was diluted with ethyl acetate (60 mL) and washed with water (5mL × 2) and brine (5 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel and eluted with an appropriate solvent (a mixture of ethyl acetate and hexane) to give the episulfide. The yields, eluents, and physical and spectroscopic data are described as follows.

(2R - 3S)-3-[(tert-Butyldimethylsilyl)oxy]-1,2-epithio-5-phenylpentan-1-ol (**3**) Yield 97%. Eluent, hexane; R_f = 0.40 (2.5% EtOAc in hexane); $[\alpha]_D^{24}$ −15.7° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 7.36–7.31 (2H, m), 7.27–7.21 (3H, m), 3.34 (1H, dt, *J* = 7.3 and 5.3 Hz), 3.01 (1H, ddd, *J* = 7.3, 6.2 and 5.5 Hz), 2.87 (1H, m), 2.78 (1H, m), 2.54 (1H, dd, *J* = 6.2 and 1.1 Hz), 2.31 (1H, dd, *J* = 5.5 and 1.1 Hz), 2.55–2.02 (2H, m), 0.98 (9H, s), 0.13 (3H, s), 0.12 (3H, s). ^{13}C NMR ($CDCl_3$) δ = 142.18, 128.35, 128.33, 125.76, 76.54, 39.66, 38.12, 31.29, 25.87, 24.22, 18.17, −4.00, −4.47; LRMS (EI) *m/z* (rel intensity %) 251 (M − 57, 34), 219 (77), 143 (41), 91 (57), 75 (base). LRMS (FAB) *m/z* 309 (M + 1). HRMS (FAB) found: 309.1736. Calcd for $C_{17}H_{29}OSSi$ (M + 1): 309.1709.

(2S-3R)-2,3-Epithio-5-phenyl-1-pentanol (**5**) Yield 46%. Eluent, 20% ethyl acetate in hexane; mp 57.5–58.5°C recrystallized from methylene chloride; R_f = 0.41 (30% EtOAc in hexane); $[\alpha]_D^{24}$ + 119.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 7.32–7.19 (5H, m), 3.78 (1H, dd, *J* = 11.7 and 4.0 Hz), 3.57 (1H, dd, *J* = 11.7 and 1.5 Hz), 2.88 (2H, ddd, *J* = 15.9, 8.1 and 5.5 Hz), 2.82–2.72 (2H, m), 2.13 (1H, ddt, *J* = 13.9, 8.1, and 5.9 Hz), 1.86 (1H, ddt, *J* = 13.9, 7.3, and 5.5 Hz), 1.68 (1H, br s); ^{13}C NMR ($CDCl_3$) δ = 140.84, 128.50, 128.50, 126.19, 63.67, 44.79, 40.06, 37.27, 35.37; IR (film) 3400 cm^{-1} (OH); MS (EI) *m/z* (rel intensity) 194 (M^+, base), 177 (10), 152 (12), 150 (11), 146 (15), 139 (14). Found: C, 67.83; H, 7.56%. Calcd for $C_{11}H_{14}OS$: C, 68.00; H, 7.26%.

(2R, 3R)-3-[(tert-Butyldimethylsilyl)oxy]-1, 2-epithio-5-phenylpentane (**8**) Yield 95%. Eluent 2.5% EtOAc in hexane; R_f = 0.47 (2.5% EtOAc in hexane); $[\alpha]_D^{24}$ −1.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 7.32–7.25 (2H, m), 7.21–7.17 (3H, m), 3.33 (1H, ddd, *J* = 12.5, 7.1, and 5.1 Hz), 2.99 (1H, ddd, *J* = 12.5, 6.6, and 5.5 Hz), 2.80 (1H, ddd, *J* = 10.3, 6.4, and 2.9 Hz), 2.69 (1H, dd, *J* = 5.5 and 1.5 Hz), 2.45 (1H, dd, *J* = 6.6 and 1.5 Hz), 2.20 (1H, dd, *J* = 5.5 and 1.5 Hz), 1.99–1.90 (2H, m), 0.92 (9H, s), 0.14 (3H, s), 0.08 (3H, s); ^{13}C NMR ($CDCl_3$) δ = 141.97, 128.41, 128.25, 125.87, 76.97, 39.93, 39.66, 31.67, 25.45, 22.28, 18.18, −3.60, −4.61; MS (EI) *m/z* (rel intensity) 251 (M − 57, 78), 219 (28), 217 (55), 143 (56), 121 (21), 91 (base), 75 (93). HRMS (FAB) found: 309.1727. Calcd for $C_{17}H_{29}OSSi$ (M + 1): 309.1709.

(2R,3S)-2,3-Epithio-5-phenyl-1-pentanol (**10**) Yield 46%. Eluent 2.5% EtOAc in hexane; R_f = 0.38 (30% EtOAc in hexane); $[\alpha]_D^{24}$ −21.8 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 7.31–7.25 (2H, m), 7.23–7.19 (3H, m), 3.78 (2H, d, *J* = 6.6 Hz), 3.20 (1H, td, *J* = 6.6 and 5.8 Hz), 3.03 (1H, ddd, *J* = 8.4, 5.8, and 3.3 Hz), 2.91 (1H, ddd, *J* = 13.9, 8.4, and 5.5 Hz), 2.80 (1H, ddd, *J* = 13.9, 7.5, and 5.5 Hz), 2.20 (1H, dddd, *J* = 13.9, 8.4, 7.5, and 5.5 Hz), 1.95–1.86 (1H, dddd, *J* = 13.9, 8.4, 5.5, and 3.3 Hz), 1.60 (1H, br s); ^{13}C NMR ($CDCl_3$) δ = 140.92, 128.51, 128.51, 126.21, 96.12, 62.28, 41.48, 40.90, 35.85, 32.41; IR (film) 3400 cm^{-1} (OH); MS (EI) *m/z* (rel intensity) 194 (M^+, 17), 143 (5), 123 (21), 91 (23). HRMS (EI) found: 194.0745. Calcd for $C_{11}H_{14}OS$ (M^+): 194.0765.

(2S, 3R)-1-[(tert-Butyldimethylsilyl)oxy]-2, 3-epithio-5-phenylpentane (**12**) Yield 85%. Eluent 2.5% EtOAc in hexane; R_f = 0.48 (5% EtOAc in hexane); $[\alpha]_D^{24}$ +32.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ = 7.32–7.26 (2H, m), 7.32–7.17 (3H, m), 4.00 (1H, dd, *J* = 11.4 and 5.6 Hz), 3.60 (1H, dd, *J* = 11.4 and 8.4 Hz), 3.12 (1H, ddd, *J* = 8.4, 6.0, and 5.5 Hz), 2.98 (1H, dt *J* = 8.4 and 6.6 Hz), 2.92–2.81 (2H, m), 2.17 (1H, ddt, *J* = 14.3, 6.6, and 5.9 Hz), 1.84 (1H, ddt, *J* = 14.3, 8.4, and 6.2 Hz), 0.90 (9H, s), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR ($CDCl_3$) δ = 141.23, 128.48, 128.41, 126.63, 63.59, 40.61, 40.01, 35.67, 32.28, 25.88, 18.27, −5.15, −5.30; MS (EI) *m/z* (rel

intensity) 251 (M − 57, 85), 219 (68), 218 (41), 217 (94), 143 (92), 133 (56), 121 (97), 117 (base), 91 (88), 75 (86). HRMS (FAB) found: 309.1736. Calcd for $C_{17}H_{29}OSSi$ (M + 1): 309.1709.

Preparation of (R)-4-[(S)-1-[(tert-Butyldimethylsilyl)oxy]-3-phenylpropyl] -1,3-oxathiolane-2-thione (**2**) To a mixture of alcohol (500 mg, 1.36 mmol) and 2,6-lutidine (1 mL, 8.6 mmol) in methylene chloride (25 mL) was added TBDMSOTf (0.7 mL, 3.05 mmol) at room temperature. The mixture was stirred for 25 minutes at the same temperature. Ether (25 mL) was added to the mixture, and it was washed with water (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$ and evaporated. The residual oil was purified by column chromatography on silica gel and eluted with 20% EtOAc in hexane to give silyl ether **2** (690 mg) in 96% yield, Mp 37.0–38.5°C recrystallized from ethanol. R_f = 0.41 (2.5% EtOAc in hexane); $[\alpha]_D^{24}$ −24.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 7.32–7.09 (5H, m), 4.95 (1H, dd, *J* = 9.9 and 4.1 Hz), 4.80 (1H, dd, *J* = 9.9 and 6.9 Hz), 4.05 (1H, dt, *J* = 6.9 and 4.1 Hz), 3.93 (1H, ddd, *J* = 6.9, 5.0, and 4.1 Hz), 2.69–2.63 (2H, m), 1.99–1.83 (2H, m), 0.93 (9H, s), 0.13 (3H, s), 0.13 (3H, s); ^{13}C NMR ($CDCl_3$) δ = 211.83, 140.97, 128.59, 128.16, 126.19, 78.85, 71.04, 55.14, 36.51, 30.24, 25.71, −4.18, −4.66; IR (film) 1200 cm^{-1} (C=S); MS (EI) *m/z* (rel intensity) 311 (M − 57, 18), 251 (12), 235 (29), 219 (83), 147 (33), 143 (34), 91 (80), 75 (base). Found: C, 58.69; H, 7.76%. Calcd for $C_{18}H_{28}O_2S_2Si$: C, 58.65; H, 7.66%.

Formation of Methanesulfonates **4** *and* **9** To a mixture of secondary alcohol **1** or **2** (800 mg, 3.14 mmol) and triethylamine (7.0 mL, 5 mmol) in methylene chloride (10 mL) was added methanesulfonyl chloride (3.6 mL, 4.7 mmol) at 0°C. The mixture was stirred for 10 minutes, and then it was poured into ice water (10 mL) and extracted with ether (70 mL). The ethereal extract was washed with water (4 mL × 2) and brine (4 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel with elution by methylene chloride to give the mesylate **4** or **9**.

(R)-4-[(S)-1-(methanesulfonyloxy)-3-phenylpropyl]-1,3-oxathiolane-2-thione (**4**) Yield 96%. Mp 57.5°C recrystalized from methanol. R_f = 0.64 (methylene chloride); $[\alpha]_D^{24}$ −64.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 7.33–7.27 (2H, m), 7.24–7.19 (3H, m), 4.95 (1H, ddm, *J* = 10.6 and 2.7 Hz), 4.93–4.87 (1H, m), 4.83 (1H, dd, *J* = 10.6 and 7.0 Hz), 4.25 (1H, ddd, *J* = 7.0, 5.9, and 2.9 Hz), 3.10 (3H, s), 2.85 (1H, ddd, *J* = 14.3, 9.5, and 5.9 Hz), 2.75 (1H, ddd, *J* = 14.3, 9.2, and 7.0 Hz), 2.21 (1H, m), 2.05 (1H, m); ^{13}C NMR ($CDCl_3$) δ = 209.58, 139.63, 128.80, 128.34, 126.65, 80.06, 78.10, 53.78, 38.84, 33.74, 30.86; IR (film) 1250 cm^{-1} (C=S), 1325 and 1170 cm^{-1} (SO_2); MS (EI) *m/z* (rel intensity) 332 (M^+, base), 316 (11), 280 (16), 257 (19), 239 (12), 223 (18), 176 (50). Found: C, 47.10; H, 4.92%. Calcd for $C_{13}H_{16}O_4S_3$: C, 46.97; H, 4.85%.

(R)-4-[(R)-1-(Methanesulfonyloxy)-3-phenylpropyl]-1,3-oxathiolane-2-thione (**9**) Yield 94%, oil; R_f = 0.45 (CH_2Cl_2); $[\alpha]_D^{24}$ −43.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ = 7.38–7.17 (5H, m), 5.14 (1H, dd, *J* = 10.3 and 1.8 Hz), 4.96 (1H, dt, *J* = 8.6 and 3.7 Hz), 4.83 (1H, dd, *J* = 10.3 and 7.0 Hz), 4.20 (1H, ddd, *J* = 8.6, 7.0, and 1.8 Hz), 3.09 (3H, s), 2.86 (1H, ddd, *J* = 14.3, 8.8, and 5.5 Hz), 2.71 (1H, ddd, *J* = 14.3, 8.4, and 7.3 Hz), 2.15 (1H, dddd, *J* = 12.8, 7.3, 5.5, and 3.7 Hz), 2.01 (1H, dddd, *J* = 12.8, 8.8, 8.4, and 3.7 Hz); ^{13}C NMR ($CDCl_3$) δ = 210.24, 139.50, 128.67, 128.27, 126.51, 79.29, 78.96, 54.20, 38.57, 33.00, 31.14; IR (KBr) 1205 cm^{-1} (C=S), 1330 and 1170 (SO_2); MS (EI) *m/z* (rel intensity) 332 (M^+, base), 280 (11), 257 (7), 237 (23), 206 (7), 179 (12), 143 (84). HRMS (FAB) found: 332.0235. Calcd for $C_{13}H_{16}O_4S_3$ (M^+): 332.0211.

ACKNOWLEDGMENT

We thank Dr. Shigeru Oae (Institute of Heteroatom Chemistry) for discussing the reaction mechanisms and for his warm encouragement.

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