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Synthesis of 1,3,2-Dioxathiolane-4-Methylene-2-Oxides: Potential Allene Oxide Equivalents

Michael Shipman*

School of Chemistry, University of Exeter, Stocker Road, Exeter, Devon, EX4 4QD, U.K.

Heidi R. Thorpe

Department of Chemistry, Loughborough University, Loughborough, Leics., LE11 3TU, U.K.

Ian R. Clemens

Glaxo Wellcome Research & Development Ltd, Glaxo Wellcome Medicines Research Centre, Stevenage, Herts, SG1 2NY, U.K.

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Abstract: Two complementary approaches to 1,3,2-dioxathiolane-4-methylene-2-oxides are described. For example, treatment of 2-hydroxy-2-methylbutan-3-one with thionyl chloride (Et_3N, CH_2Cl_2, -78°C) yields 5,5-dimethyl-1,3,2-dioxathiolane-4-methylene-2-oxide **5** in 58% yield. Alternatively, cyclic sulfite **11**, bearing a 4-(2-nitrophenylseleno)methyl substituent, can be induced to undergo oxidative elimination (30% H_2O_2, THF then $CDCl_3$, Δ) to **5** in 28% yield.

INTRODUCTION

Allene oxides (*eg* **1**, Figure 1) are an unusual class of heterocyclic compound which have been shown to participate in a number of interesting chemical conversions including various cycloaddition and ring opening reactions.[1,2] However, the inherent reactivity of this highly strained ring system means that allene oxides are difficult to produce and handle, and consequently most useful chemistry involves their generation and further transformation *via* one pot processes. As part of our own work centred on developing new synthetic transformations using allene oxides,[3] we repeatedly became frustrated by this limitation as it restricts the types of novel reaction sequences that can be devised. As a potential solution to this problem, we sought to devise more stable heterocyclic systems that might be chemically equivalent to allene oxides. Since it is well known that the cyclic sulfite or sulfate ring reacts with nucleophiles in a similar way to epoxides,[4] we wondered whether 1,3,2-dioxathiolane-4-methylene-2-oxides **2** or 1,3,2-dioxathiolane-4-methylene-2,2-dioxides **3** might behave as allene oxide equivalents. Furthermore, we reasoned that compounds such as **2** or **3** would contain less angular strain than the corresponding allene oxide and therefore may be sufficiently stable for routine isolation. While one cyclic sulfite **2** ($R^1 = R^2 = Me$) has been made by the treatment of 2,2-dimethylcyclopropanone with sulfur dioxide,[5] this approach is impractical for the development of a general route to such systems. In this paper, we describe for the first time, our efforts to develop general approaches to heterocyclic ring systems **2** and **3**.

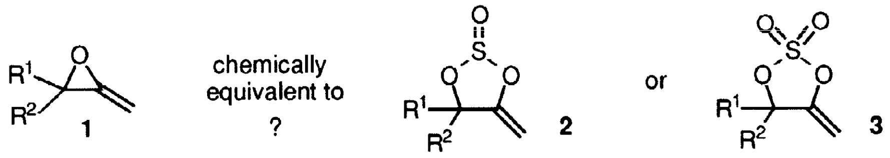

Figure 1

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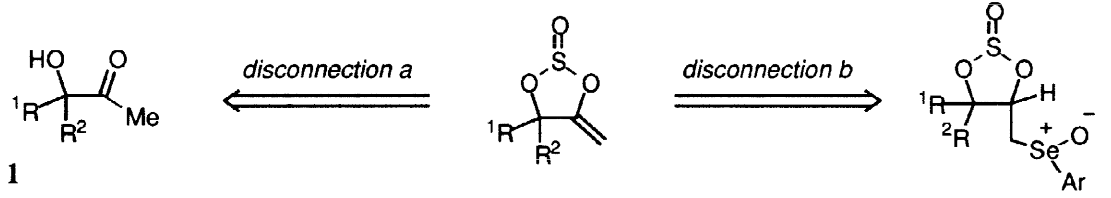
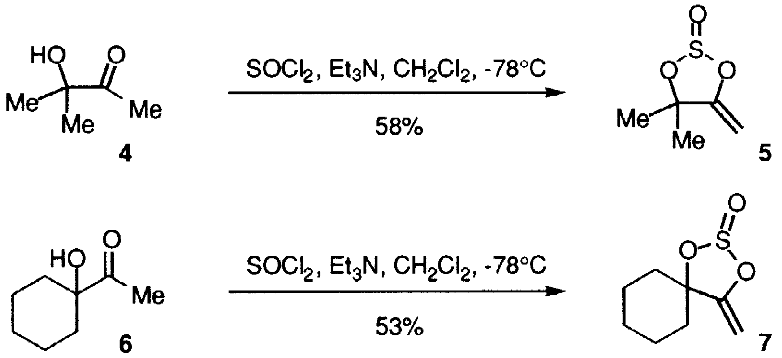
RESULTS AND DISCUSSION

We have explored two different routes to 1,3,2-dioxathiolane-4-methylene-2-oxides as depicted in Scheme 1. We imagined that reaction of thionyl chloride with α-hydroxyketones *via* the corresponding enol form might provide a direct route to such compounds (*ie* disconnection a). Alternatively, we considered an approach based upon construction of the cyclic sulfite ring followed by introduction of the exocyclic double bond by an elimination reaction (*ie* disconnection b) might lead to the desired compounds. To ensure such eliminations could be effected under very mild reaction conditions, we proposed a selenoxide based elimination reaction. Both of these approaches have been evaluated and our findings are presented in the following sections.



Scheme 1

Preparation of 4-Methylene Cyclic Sulfites from α-Hydroxyketones. As discussed above, we reasoned that methylene cyclic sulfites might be prepared by the treatment of an α-hydroxyketone with thionyl chloride. In order to attempt this transformation we chose, in the first instance, to use 2-hydroxy-2-methylbutan-3-one **4** as the corresponding methylene cyclic sulfite **5** is a known compound (*vide supra*). Treatment of **4** with thionyl chloride at room temperature in dichloromethane containing two equivalents of triethylamine for 1 hour followed by aqueous work-up gave a black residue. Comparisons with the ^{1}H NMR spectroscopic data reported by Turro *et al.*[5] indicated that the mixture was predominently 5,5-dimethyl-4-methylene-1,3,2-dioxathiolane-2-oxide **5**. The yield of cyclic sulfite **5** was improved to 58%, by lowering the reaction temperature to -78°C and quenching the reaction at this temperature (Scheme 2). In a similar manner, 1-acetyl cyclohexanol **6** was transformed into methylene cyclic sulfite **7** in 53% yield after column chromatography (Scheme 2).



Scheme 2

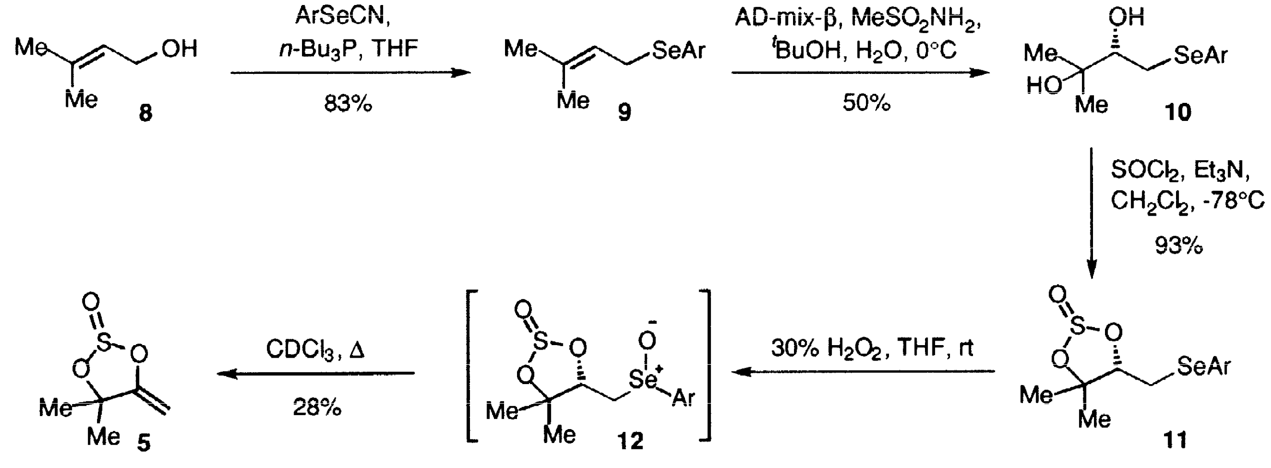
Efforts to effect similar transformations using α-hydroxy ketones in which the carbon bearing the hydroxyl group is not fully substituted have been unsuccessful. Both 3-hydroxy-2-butanone and 1-hydroxy-2-butanone did not undergo conversion to the corresponding cyclic sulfites upon treatment with thionyl chloride (-78°C, Et_3N).

Studies to determine if cyclic sulfite **5** can be transformed into the corresponding cyclic sulfate (*ie* **3**, Figure 1, $R^1 = R^2 = Me$) by selective oxidation of the sulfur atom have been undertaken. For simple cyclic sulfites, conversion to the corresponding cyclic sulfate can be achieved using ruthenium (III) chloride and sodium periodate.[6] However, subjection of **5** to these reaction conditions resulted in the formation of complex mixtures of products. Furthermore, treatment of α-hydroxyketone **4** with sulfuryl chloride under a variety of conditions also failed to produce the desired product. Thus, it appears that this method is useful only for the preparation of methylene cyclic sulfites bearing dialkyl substituents at C-5 (*eg* **2**, Figure 1, R^1 and $R^2 \neq H$).

Preparation of 4-Methylene Cyclic Sulfites by Selenoxide Elimination. In order to develop a more general method for the preparation of methylene cyclic sulfites, the possibility of a selenoxide elimination to generate the exocyclic double bond of the cyclic sulfite ring was investigated (Scheme 1, disconnection b).

Allylselenide **9** was prepared from allylic alcohol **8** by reaction with (2-nitrophenyl)selenocyanate in tetrahydrofuran containing tri-*n*-butylphosphine in 83% yield (Scheme 3).[7] This selenide was successfully converted to the corresponding diol **10** using a Sharpless asymmetric dihydroxylation protocol,[8] albeit in rather modest 50% yield. The modest yield for this dihydroxylation reaction is probably due to competitive oxidation on selenium, although no by-products could be isolated. This supposition is supported by the fact when 3-methyl-1-(phenylseleno)-2-butene, bearing a more nucleophilic selenium centre, was dihydroxylated under similar conditions, the corresponding diol was obtained in just 12% yield. It is notable that at the time we undertook this work, asymmetric dihydroxylations of allylaryl selenides were unknown although one article concerning this topic has very recently been published.[9] Diol **10** was assigned the (2*S*)-configuration on the basis of the Sharpless mnemonic model,[8] although since this chiral centre is subsequently removed, no attempts were made to determine its enantiomeric excess. Next, diol **10** was converted into cyclic sulfite **11** in excellent yield using standard conditions.

With selenide **11** in hand, we were now in a position to evaluate the viability of the selenoxide elimination approach to 4-methylene cyclic sulfites. This material was oxidised to the corresponding selenoxide **12** using hydrogen peroxide in THF. Not surprisingly, selenoxide **11** was unstable and began to decompose almost immediately. Thermolysis of this selenoxide in *d*-chloroform resulted in complete consumption of selenoxide **12** as monitored by ^{1}H NMR spectroscopy after 4 hours. After silica gel chromatography, cyclic sulfite **5** was isolated in 28% yield over the two steps. This compound was found to be identical with the material produced in Scheme 2. While the efficency of this unoptimised oxidation-elimination sequence is rather modest, it does demonstrate that this approach to 1,3,2-dioxathiolane-4-methylene-2-oxides is feasible. The low yield may, in part, be due to the fact that this selenoxide elimination involves elimination towards an oxygen atom, a process which is known to be disfavoured.[10] We have determined that the 2-nitro substituent on the aromatic ring is essential in this oxidation-elimination sequence. The corresponding phenyl selenide (*ie* **11**, Ar = Ph) could not be induced to undergo the same process.[11]



where Ar = 2-NO$_2$Ph

Scheme 3

In summary, we have established the viability of two new routes to 1,3,2-dioxathiolane-4-methylene-2-oxides. Work to further develop these synthetic methods and to ascertain whether these heterocycles will serve as allene oxide equivalents in a variety of transformations is ongoing and this work will be disclosed in due course.

EXPERIMENTAL

General. Dichloromethane (DCM) was distilled from phosphorus pentoxide prior to use. Anhydrous tetrahydrofuran (THF) and diethyl ether were prepared by distillation from sodium benzophenone ketyl under nitrogen immediately prior to use, or alternatively, purchased from Aldrich in Sure/Seal™ bottles. All reactions were performed using oven dried glassware under an atmosphere of nitrogen unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded at 250 MHz and 62.9 MHz respectively on a Bruker AC-250 instrument or at 400 MHz and 100 MHz respectively on a Bruker DPX-400 instrument. Spectra were recorded in deuterochloroform unless otherwise stated and residual protic solvent (7.26 ppm) was used as the internal standard. Infra-red spectra were recorded on a Nicolet FT-205 spectrometer or a Perkin-Elmer Paragon 1000 spectrometer with internal calibration. High and low resolution mass spectra were recorded on a Kratos 80 mass spectrometer under EI conditions unless otherwise stated. High resolution CI spectra were performed at the EPSRC Mass Spectrometry Centre, Swansea.

5,5-Dimethyl-4-methylene-1,3,2-dioxathiolane-2-oxide (5).[5] To 3-hydroxy-3-methylbutan-2-one **4** (510 mg, 5.00 mmol) dissolved in dichloromethane (8 ml) containing triethylamine (1.39 ml, 9.98 mmol) at -78°C was added dropwise thionyl chloride (0.44 ml, 6.03 mmol) dissolved in dichloromethane (2 ml). The solution was stirred at -78°C for 3 h then saturated $NaHCO_3$ solution (5 ml) was added and the solution was allowed to warm to room temperature. The solution was poured into water and the layers separated. The aqueous layer was extracted with dichloromethane (2 x 10 ml) and the combined organic extracts washed with brine (20 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **5** (427 mg, 58%) as a pale coloured oil which can be further purified by column chromatography (10% ethyl acetate / light petroleum); ν_{max} (film) 2989, 2934, 1670 (C=C), 1458, 1372, 1227, 1159, 939, 837, 795 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 4.74 (1H, d, 3.3 Hz), 4.34 (1H, d, 3.3 Hz), 1.79 (3H, s), 1.56 (3H, s); δ_C (100 MHz, $CDCl_3$) 160.7 (s), 89.1 (s), 85.8 (t), 30.6 (q), 28.8 (q). Data consistent with those reported by Turro *et al.*[5]

4-Methylene-5,5'-spirocyclohexyl-1,3,2-dioxathiolane-2-oxide (7). To 1-acetylcyclohexan-1-ol **6** (426 mg, 3.00 mmol) dissolved in dichloromethane (6 ml) containing triethylamine (0.84 ml, 6.03 mmol) at -78°C was added thionyl chloride (0.24 ml, 3.29 mmol) dissolved in dichloromethane (1 ml) dropwise. The solution was stirred at -78°C for 2 h then saturated NH_4Cl solution (3 ml) was added and the solution allowed to warm to room temperature. The solution was poured into water and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 5 ml) and the combined organic extracts were washed with brine (10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography (30% ethyl actetate / light petroleum) to give **7** (298 mg, 53%) as a colourless oil; ν_{max} (film) 2939, 2864, 1663 (C=C), 1449, 1217, 937 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.77 (1H, d, 3.3 Hz), 4.34 (1H, d, 3.3 Hz), 2.34 (1H, m), 1.93 (1H, m), 1.79-1.28 (8H, m); δ_C (100 MHz, $CDCl_3$) 159.4 (s), 90.0 (s), 85.7 (t), 38.0 (t), 36.5 (t), 23.3 (t), 23.1 (t), 20.8 (t). The instability of this compound prevented its further characterisation.

3-Methyl-1-[(2-nitrophenyl)seleno]-2-butene (9). (2-Nitrophenyl)selenocyanate (2.73 g, 12.0 mmol) and 3-methyl-2-buten-1-ol **8** (860 mg, 9.99 mmol) were dissolved in tetrahydrofuran (32 ml) and stirred at 0°C. Freshly distilled tri-*n*-butyl phosphine (2.92 ml, 11.7 mmol) was added dropwise and the mixture allowed to warm to room temperature. After 2.5 h, the reaction was estimated, by TLC, to be complete and the solvent was removed under reduced pressure. The residue was purified by column chromatography (30% ethyl acetate / light petroleum) to give **9** (2.25 g, 83%) as an orange oil; ν_{max} (film) 3026, 2970, 2914, 1664, 1590, 1565, 1513, 1450, 1328, 1303, 1251, 1096, 1037 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.28 (1H, d, 8.5 Hz), 7.51 (2H, m), 7.31 (1H, m), 5.38 (1H, t, 7.9 Hz), 3.59 (2H, d, 7.9 Hz), 1.75 (6H, s); δ_C (100 MHz, $CDCl_3$) 147.0 (s), 138.9 (s), 135.6 (s), 133.9 (d), 129.9 (d), 126.7 (d), 125.7 (d), 117.4 (d), 26.2 (q), 25.2 (t), 18.2 (q); *m/z* 271 (M^+), 203, 186, 156, 106, 69, 41; Observed (M^+): 271.0112; $C_{11}H_{13}NO_2Se$ requires: 271.0111.

(2*S*)-3-Methyl-2,3-dihydroxy-1-[(2-nitrophenyl)seleno]butane (10). AD-mix-β (7.98 g) and methanesulfonamide (541 mg, 5.69 mmol) were dissolved in 1:1 *tert*-butanol/water (55 ml) and stirred vigorously while being cooled to 0°C. 3-Methyl-1-[(2-nitrophenyl)seleno]-2-butene **9** (1.54 g, 5.7 mmol) was added and the resulting mixture stirred for 4 days at 0°C. Sodium metabisulfite (5.7 g, 30.0 mmol) was added to the mixture in small portions and the mixture stirred for 30 min while warming to room temperature. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic extracts were washed with 1.0 M KOH, 5% HCl and brine then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by column chromatography (ethyl acetate) to give **10** (869 mg, 50%) as a yellow crystalline solid (m.p. 84-86°C); $[\alpha]^{20}_{D}$ = -30.8 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$) 3695, 3605, 3066, 2983, 1593, 1517, 1422, 1335 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.06 (1H, dd, 8.3, 1.4 Hz), 7.40 (1H, dd, 8.2, 1.3 Hz), 7.33 (1H, dt, 7.1, 1.4 Hz), 7.14 (1H, dt, 7.1, 1.4 Hz), 3.50 (1H, dd, 10.5, 2.4 Hz), 3.01 (1H, dd, 12.5, 2.4 Hz), 2.79 (1H, dd, 12.5, 10.5 Hz), 1.13 (3H, s), 1.10 (3H, s) (signals for the hydroxyl protons are very broad 2.7-1.8 ppm); δ_C (100 MHz, $CDCl_3$) 147.6 (s), 135.2 (d), 134.1 (s), 129.8 (d), 126.8 (d), 126.2 (d), 76.6 (s), 73.4 (d), 30.1 (t), 26.7 (q), 24.8 (q); *m/z* 323 (MNH_4^+); Observed (M^+): 303.0011; $C_{11}H_{15}NO_4Se$ requires: 303.0010.

(*S*)-5,5-Dimethyl-4-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (11). (2*S*)-3-methyl-2,3-dihydroxy-1-[(2-nitrophenyl)seleno]butane **10** (762 mg, 2.50 mmol) was dissolved in dichloromethane (5 ml) containing triethylamine (0.70 ml, 5.0 mmol) and cooled to -78°C. Thionyl chloride (0.22 ml, 3.0 mmol) dissolved in dichloromethane (2 ml) was added dropwise to the mixture and stirring continued for 2 h at this temperature. The mixture was quenched with saturated NH_4Cl solution (5 ml) then allowed to warm to room temperature. The mixture was poured into water and the layers separated. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed successively with 2 M HCl, saturated $NaHCO_3$ and brine then dried over Na_2SO_4. Column chromatography (50% ethyl acetate / light petroleum) gave (*S*)-**11** (813 mg, 93%) as a yellow solid and as a 1:1 mixture of diastereomers (m.p. 75-85°C); ν_{max} ($CHCl_3$) 2980, 1593, 1518, 1335 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, m), 7.38 (2H, m), 7.20 (1H, m), 4.69 (0.5 H, dd, 7.8, 6.2 Hz), 4.25 (0.5 H, dd, 8.1, 5.6 Hz), 3.28 (0.5 H, dd, 12.7, 8.1 Hz), 3.10 (0.5 H, dd, 13.0, 7.8 Hz), 2.95 (0.5 H, dd, 12.7, 5.6 Hz), 2.84 (0.5 H, dd, 13.0, 6.2 Hz), 1.53 (1.5H, s), 1.49 (1.5H, s), 1.32 (1.5H, s), 1.18 (1.5H, s); δ_C (100 Hz, $CDCl_3$) 147.3 (s), 134.5 (d), 132.0 (s), 131.6 (s), 129.4 (d), 129.1 (d), 127.1 (d), 127.0 (d), 126.7 (d), 126.6 (d), 91.4 (s), 89.9 (s), 88.2 (d), 82.9 (d), 27.5 (q), 27.2 (q), 26.0 (t), 24.1 (q), 23.4 (t), 22.9 (q) (not all aromatic carbons for the two diastereomers are resolved); *m/z* 369 (MNH_4^+); Observed (MNH_4^+): 369.0023; $C_{11}H_{17}N_2O_5SSe$ requires: 369.0023.

Oxidation of (*S*)-4,4-dimethyl-5-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide (11). To (*S*)-5,5-dimethyl-4-[(2-nitrophenyl)selenomethyl]-1,3,2-dioxathiolane-2-oxide **11** (375 mg, 1.07 mmol) dissolved in tetrahydrofuran (6 ml) was added 30% aqueous hydrogen peroxide (1.80 ml) and the mixture stirred at room temperature. After 2 h the reaction was estimated, by TLC, to be complete and the mixture was diluted with water (5 ml) and extracted with ethyl acetate (3 x 5 ml). The combined organic extracts were washed with 5% ferrous sulfate solution (20 ml) and brine (20 ml) then dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was dissolved in $CDCl_3$ (3 ml) and heated to reflux. Samples were taken at 30 min intervals and analysed by TLC and ^1H NMR (250 MHz). After approximately 4 h, all of the selenoxide **12** had been consumed, so the mixture was cooled and the solvent removed under reduced pressure. Purification by column chromatography (25% ethyl acetate / light petroleum) gave 5,5-dimethyl-4-

methylene-1,3,2-dioxathiolane-2-oxide **5** (44.0 mg, 28%) as a pale yellow oil. The spectroscopic data for this material were identical with literature values[5] and those described previously.

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