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Stereoselective synthesis of 2,5-disubstituted-1,4-oxathiane *S*-oxides

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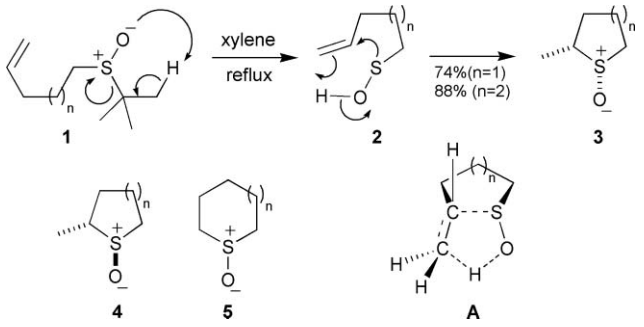
β-Allyloxy and β-propargyloxy *tert*-butyl sulfoxides undergo tandem sulfoxide elimininationintramolecular sulfenic acid addition reactions to produce 1,4-oxathiane *S*-oxides.

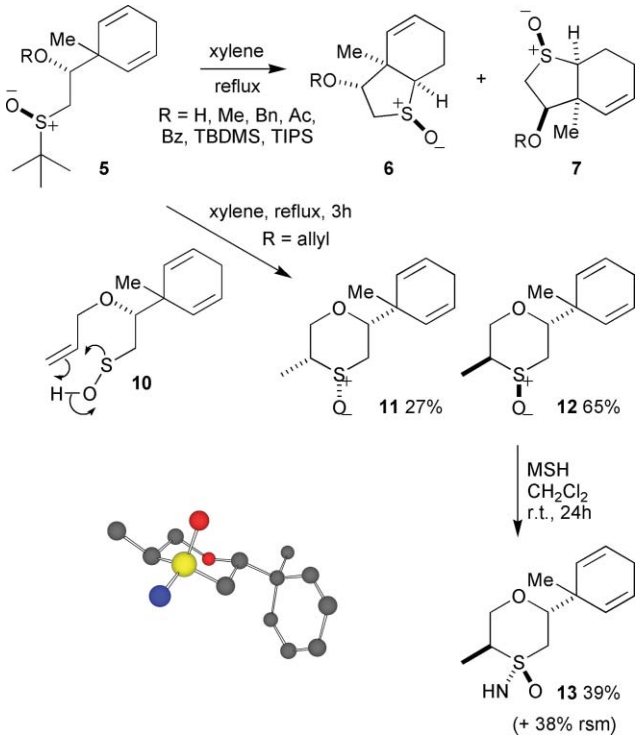
The thermolysis of sulfoxides containing a β-hydrogen atom is a venerable approach to alkene synthesis.[1] The reverse reaction, the addition of a sulfenic acid to an alkene, is also known, and is subject to the same constraints in the transition state *i.e.* the need for the five participating atoms to achieve coplanarity in a concerted *syn* addition.[2] Intramolecularly this can lead to high levels of regio- and diastereochemical control, elegantly demonstrated by Jones and coworkers in the 1970's in a tandem sulfoxide elimination–sulfenic acid addition approach to cyclic sulfoxides (Scheme 1).[3] Thermolysis of *tert*-butyl sulfoxide **1** generates a sulfenic acid intermediate **2** which adds to the terminal alkene *via* planar transition state **A** to give *cis*-sulfoxide **3** as the sole product. Cyclic transition states leading to the *trans*-sulfoxide **4** or the sulfoxide **5** that might arise from addition of the sulfur atom to the terminus of the alkene are sterically impossible.



Scheme 1 Jones' tandem sulfoxide elimination–sulfenic acid addition.

We recently reported an extension of this methodology to a novel diastereotopic group selective sulfenic acid addition reaction (Scheme 2).[4] The ratio of diastereomeric perhydrobenzothiophene *S*-oxides **6** and **7** was found to depend on the nature of the group attached to oxygen in the connecting chain, with selectivities ranging from 1 : 1 in the case of R = H, to 4.9 : 1 in the case of R = TBDMS. In the course of this work we investigated the case of the alcohol protected as an allylic ether (**5**, R = allyl). Thermolysis in this case did not give rise to a mixture **6** and **7**, but rather to a mixture of two 1,4-oxathiane *S*-oxides **11** and **12**. Clearly in this case the intermediate sulfenic acid **10** chemoselectively adds to the terminal alkene rather than the diene to form a 6-membered oxathiane ring in preference to a fused 5-membered ring.[5]

The stereochemistry of the two products was tentatively assigned as shown on the basis of the following rationale. By



Scheme 2 Discovery of a 1,4-oxathiane *S*-oxide synthesis and X-ray crystal structure of sulfoximine **13**.

analogy to the Jones system (Scheme 1), only oxathianes with a *cis*-stereochemical relationship between the sulfinyl oxygen and adjacent methyl group are possible as a consequence of the stereochemical requirements of the transition state for addition of a sulfenic acid to an alkene. Hence the two diastereomers should differ only in the relative configuration at position 2 of the 1,4-oxathiane ring. The relative stereochemistry of the major compound was ultimately attained by X-ray analysis of the sulfoximine **13**, obtained by treatment of the major isomer **12** with *O*-mesitylenesulfonylhydroxylamine (MSH).‡ The conversion of sulfoxides to sulfoximines with this reagent is known to occur with retention of configuration.[6]

The cyclisation in Scheme 2 constitutes a novel and potentially general approach to 1,4-oxathiane *S*-oxide ring synthesis if it is, as it would appear to be, independent of the diene ring system.[7] In order to investigate the scope this chemistry, we have prepared a number of related cyclisation precursors bearing phenyl and *tert*-butyl groups in place of the diene in combination with a range of alkene and alkyne coupling partners. These compounds were readily prepared by the simple four step procedure shown in Scheme 3. Addition of two equivalents of the anion of *tert*-butyl methyl sulfoxide **14** to ethyl benzoate or ethyl pivaloate gave the β-ketosulfoxide **15a** and **15b** respectively, which were reduced stereoselectively with DIBAL-H at low temperature to give the β-hydroxysulfoxides **16a** and **16b**.[8] Alkylation of these

† Author to whom correspondence regarding X-ray crystal structures should be addressed.

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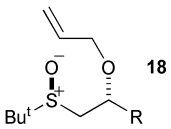
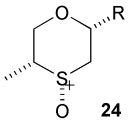
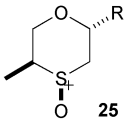
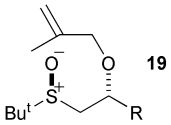
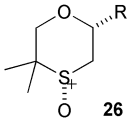
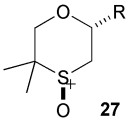
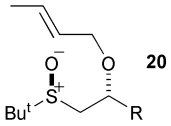
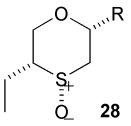
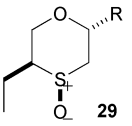
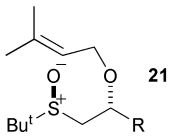
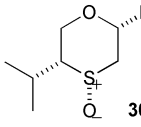
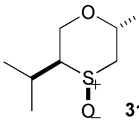
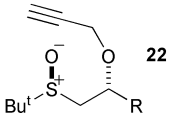
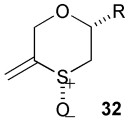
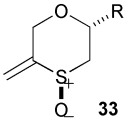
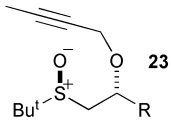
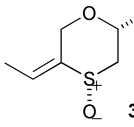
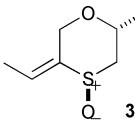
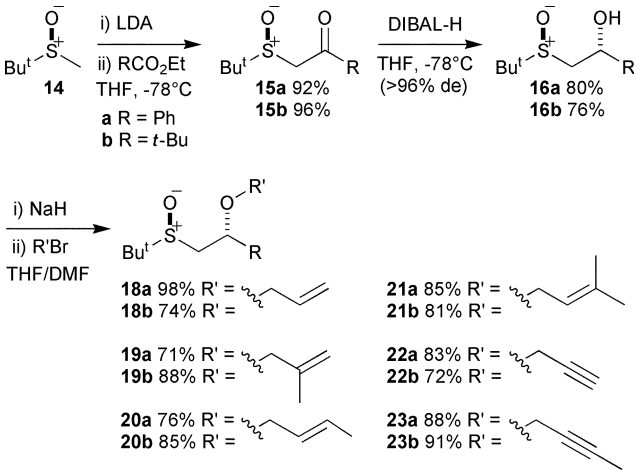
Table 1 Synthesis of oxathianes[a]

Entry	Cyclisation precursor	Oxathianes	R	Time/h	Crude ratio[b]	Isolated yield
1	 **18**	 **24**  **25**	**a** Ph	3	1 : 1.8	30% **24a**, 40% **25a**
2			**b** *t*-Bu	8	1 : 2.4	68% (**24b** + **25b**)
3	 **19**	 **26**  **27**	**a** Ph	8	1 : 1.3	64% (**26a** + **27a**)
4			**b** *t*-Bu	7	1 : 1.6	61% (**26b** + **27b**)
5	 **20**	 **28**  **29**	**a** Ph	6	ND	0% **28a**, 20% **29a**
6			**b** *t*-Bu	8	ND	0% **28b**, 36% **29b**
7	 **21**	 **30**  **31**	**a** Ph	2.5	—	0
8			**b** *t*-Bu	3[c]	—	0
9	 **22**	 **32**  **33**	**a** Ph	7	1 : 1	11% **32a**, 13% **33a**
10			**b** *t*-Bu	8	1 : 1.5	27% **32b**, 47% **33b**
11	 **23**	 **34**  **35**	**a** Ph	2	2.2 : 1	0% **34a**, 25% **35a**
12			**b** *t*-Bu	5	1 : 1.4	38% **34b**, 42% **35b**

[a] Xylene, 0.14 M, reflux. [b] Ratio determined by integration in ^{1}H NMR. [c] 34% Recovered starting material.



Scheme 3 Preparation of cyclisation precursors.

alcohols with an allylic or propargylic bromide gave the ethers **18–23** in good yield.[9]

Results of the thermolysis of sulfoxides **18–23** are presented in Table 1. In every case, purification of the oxathiane *S*-oxides was achieved by direct application of the crude reaction mixture to column chromatography. The xylene eluted first, followed by the mixture of oxathiane *S*-oxides, which in many cases were separable.§

Thermolysis of allyl ether **18a** gave rise to two separable 2,5-disubstituted 1,4-oxathiane *S*-oxides **24a** and **25a** (entry 1, Table 1). Crystals suitable for X-ray analysis were obtained for both **24a** and **25a** and allowed for the unambiguous assignment of the stereochemistry of these oxathiane *S*-oxides (Fig. 1).‡

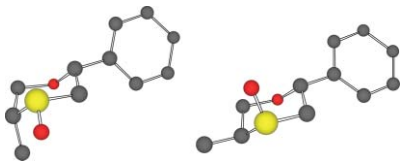


Fig. 1 X-Ray crystal structures of **24a** (left) and **25a** (right).

Both sulfoxides crystallize in chair conformations with the bulky phenyl group occupying an equatorial position, placing the sulfinyl oxygen equatorial in the case of **24a** and axial in the case of **25a**. The major compound **25a** has all substituents on the ring in a favourable position. The preference for a sulfinyl oxygen to occupy an axial position on a six-membered ring has been ascribed to an attractive van der Waals interaction with hydrogen atoms in a *syn* 1,3-diaxial relationship,[10] and indeed in the X-ray of **25a** the sulfinyl oxygen is seen to be bent towards the inside of the ring by these stabilizing interactions.

The conformations adopted by **24a** and **25a** in the solid state are also maintained in solution. A single set of signals is observed in the ^{1}H and ^{13}C NMR for both **24a** and **25a**, suggesting they exist as predominantly one conformation in solution.[11] In both cases the proton at position 2 of the ring shows a large coupling constant consistent with an axial orientation, placing the aryl group in an equatorial position. The chemical shift of this hydrogen is significantly different in the two diastereomeric oxathiane *S*-oxides as a consequence of the anisotropic effect of the sulfinyl group (4.53 ppm in **24a** *vs.* 5.17 ppm in **25a**). In **25a** H-2 is deshielded since it is in a *syn* 1,3 diaxial relationship with the sulfoxide.[12]

The above analysis allowed for a convenient method to assign the major and minor compounds in the cyclisations presented

in Table 1. In general, the oxathianes appeared in one chair conformation in solution consistent with the bulky phenyl or *tert*-butyl group in the equatorial position. Similarly, sulfoxides **11** and **12** each exist in one chair conformation in solution, with the diene ring equatorial in both cases.

The efficiency of the cyclisation is dependent on the substitution pattern on the alkene. Simple, unsubstituted terminal alkenes give good yields of 1,4-oxathiane *S*-oxides irrespective of the R group (entries 1 and 2). A methyl substituent on the internal carbon of the alkene is tolerated (entries 3 and 4), whereas substitution on the terminal carbon results in much lower yields (entries 5 and 6). A range of unidentifiable by-products were formed upon thermolysis of **20** which did not allow for the determination of the ratio of **28** and **29** in the crude NMR. Hence although only one oxathiane *S*-oxide was isolated from these reactions, it is unlikely that this is such a highly stereoselective process. The prenyl ether **21** failed to provide any of the expected cyclisation products **30** and **31**, and only decomposition was observed in these cases (entries 7 and 8).

We were also interested to see whether alkynes could be incorporated into this tandem sulfoxide elimination–sulfenic acid addition sequence with the expectation of generating exocyclic vinyl sulfoxides.[13] Both terminal (entries 9 and 10) and substituted alkynes (entries 11 and 12) have been investigated, but in contrast to the alkene series there was a clear difference between the phenyl and *tert*-butyl substituted systems, with the latter giving cleaner reactions and better yields (compare entries 9 and 10, and 11 and 12). In the case of the substituted propargyl systems, only a single double bond geometry is obtained as a consequence of the geometrical requirement for the addition of a sulfenic acid to an alkyne. Interestingly, the phenyl propargyl system **22a** appears to be the only case where the major product (as judged by ^{1}H NMR of the crude reaction mixture) appears to be the equatorial sulfoxide, although the only isomer that could be isolated from the reaction after column chromatography corresponds to the (minor) axial sulfoxide.

In summary, we describe a simple 4-step synthesis of a number of novel oxathiane oxides based on the intramolecular addition of sulfenic acids to alkenes or alkynes tethered through an ether linkage. Only two of the four possible diastereomeric 2,5-disubstituted-1,4-oxathiane *S*-oxides are formed in this reaction as a consequence of the geometrical requirements of the transition state for these additions. Although only modestly diastereoselective, this procedure is still attractive in the brevity of synthesis of the cyclisation precursors and the possibility of preparing enantiomerically pure oxathiane *S*-oxides starting from homochiral *tert*-butyl methyl sulfoxide *via* a chiral relay. Furthermore, in many instances this lack of control can be overcome with a subsequent transformation employing the rich organic chemistry of sulfur—for example, oxidation to the sulfone or reduction to the sulfide in those cases where a stereocentre is not present adjacent to the sulfoxide will result in a stereoconvergent synthesis of just one stereoisomer. Further studies along these lines are in progress and will be reported in due course.

Acknowledgements

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Notes and references

‡ *Crystal data* for **13**: $C_{12}H_{19}NO_2S$, $M = 241.34$, colourless prism, $0.40 \times 0.35 \times 0.20$ mm^3, tetragonal, space group $I4_1/a$ (no. 88), $a = b = 20.9699(9)$, $c = 11.2756(6)$ Å, $V = 4958.3(4)$ Å^3, $Z = 16$, $D_c = 1.293$ g cm^{-3}, $F_{000} = 2080$, Nonius Kappa CCD, MoKα radiation, $\lambda = 0.71073$ Å, $T = 120(2)$ K, $2\theta_{max} = 54.8°$, 3252 reflections collected, 2136 unique ($R_{int} = 0.0345$). Final GooF = 1.003, $R1 = 0.0434$, $wR2 = 0.0804$, R indices based on 1417 reflections with $I > 2\sigma(I)$ (refinement on F^2), 152 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.247$ mm^{-1}. *Crystal data* for **24a**: $C_{11}H_{14}O_2S$, $M = 210.28$, colourless plate, $0.60 \times 0.30 \times 0.10$ mm^3, monoclinic, space group $P2_1$ (no. 4), $a = 7.5387(5)$, $b = 6.0000(5)$, $c = 11.4544(8)$ Å, $\beta = 91.308(5)°$, $V = 517.97(7)$ Å^3, $Z = 2$, $D_c = 1.348$ g cm^{-3}, $F_{000} = 224$, Nonius Kappa CCD, MoKα radiation, $\lambda = 0.71073$ Å, $T = 120(2)$ K, $2\theta_{max} = 50.0°$, 1518 reflections collected, 1518 unique ($R_{int} = 0.0000$). Final GooF = 1.179, $R1 = 0.1100$, $wR2 = 0.2717$, R indices based on 1457 reflections with $I > 2\sigma(I)$ (refinement on F^2), 129 parameters, 1 restraint. Lp and absorption corrections applied, $\mu = 0.283$ mm^{-1}. *Crystal data* for **25a**: $C_{11}H_{14}O_2S$, $M = 210.28$, $0.30 \times 0.30 \times 0.20$ mm^3, monoclinic, space group $P2_1/n$ (no. 14), $a = 10.5744(4)$, $b = 9.1217(3)$, $c = 11.7111(4)$ Å, $\beta = 115.825(2)°$, $V = 1016.80(6)$ Å^3, $Z = 4$, $D_c = 1.374$ g cm^{-3}, $F_{000} = 448$, Nonius Kappa CCD, MoKα radiation, $\lambda = 0.71073$ Å, $T = 120(2)$ K, $2\theta_{max} = 55.0°$, 3828 reflections collected, 2303 unique ($R_{int} = 0.0472$). Final GooF = 1.181, $R1 = 0.0418$, $wR2 = 0.0963$, R indices based on 2052 reflections with $I > 2\sigma(I)$ (refinement on F^2), 129 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.288$ mm^{-1}. CCDC reference numbers 252383–252385. See http://www.rsc.org/suppdata/ob/b4/b415529g/ for crystallographic data in .cif or other electronic format.

§ Representative procedure: **(2*RS*, 4*SR*, 5*RS*)-5-methyl-2-phenyl-[1,4]-oxathiane 4-oxide 24a** and **(2*RS*, 4*RS*, 5*SR*)-5-methyl-2-phenyl-[1,4]-oxathiane 4-oxide 25a** A solution of allyl ether **18a** (0.597 g, 2.24 mmol) in refluxing xylene (16 mL) was kept under argon for 3 h, following the reaction by TLC until the starting material disappeared. The crude reaction mixture was purified by column chromatography (95 : 5 diethyl ether–methanol). Diastereomer **25a** eluted first as a white solid (0.188 g, 40%); $R_f = 0.36$ (95 : 5 diethyl ether–methanol); mp = 134–136 °C; ν_{max}/cm^{-1}1044 (SO); δ_H (360 MHz, $CDCl_3$) 1.21 (3H, d, $J = 7.1$, CH_3), 2.64 (1H, dd, $J = 14.3$, $J = 11.5$, SCH_{ax}H$_{eq}$), 2.70–2.81 (1H, m, CH$_3$CH), 3.01 (1H, d,$^2J = 13.7$, SCH$_{ax}$$H_{eq}$), 3.85 (1H, dd, $J = 12.8$, $J = 3.9$, OCH$_{ax}$$H_{eq}$), 4.22 (1H, dd, $J = 12.6$, $J = 11.5$, OCH_{ax}H$_{eq}$), 5.17 (1H, dd, $J = 11.3$, $J = 1.5$, OCH), 7.29–7.42 (5H, m, ArH); δ_C (90 MHz, $CDCl_3$) 11.7 (q), 47.6 (d), 51.2 (t), 64.4 (t), 68.5 (d), 125.7 (d), 128.0 (d), 128.7 (d) and 139.9 (s); *m*/*z* (EI) 210 (M$^+$, 16%), 193 (22), 168 (39), 140 (39), 123 (100), 137 (84), 110 (63), 96 (56), 50 (44); HRMS (ESI) 233.0618 (MNa$^+$. $C_{11}H_{14}O_2S_1Na$ requires 233.0607). Diastereomer **24a** eluted second as a white solid (0.140 g, 30%); $R_f = 0.32$ (95 : 5 diethyl ether–methanol); mp = 93–95 °C; ν_{max}/cm^{-1} 1034 (SO); δ_H (360 MHz, $CDCl_3$) 1.53 (3H, d, $J = 7.0$, CH_3), 2.93 (1H, ap.t, $J = 12.2$, SCH_{ax}H$_{eq}$), 3.21 (1H, d, $J = 12.5$, SCH$_{ax}$$H_{eq}$), 3.25–3.31 (1H, m, CH$_3CH$), 3.89 (1H, dd, $J = 13.5$, $J = 1.3$, OCHH), 4.23 (1H, dd, $J = 13.5$, $J = 2.6$, OCHH), 4.53 (1H, dd, $J = 11.7$, $J = 1.6$, OCH), 7.32–7.42 (5H, m, ArH); δ_C (90 MHz, $CDCl_3$) 5.3 (q), 49.0 (d), 50.0 (t), 67.9 (t), 77.0 (d), 125.6 (d), 128.6 (d), 128.8 (d) and 139.3 (s); *m*/*z* (EI) 210 (M$^+$, 12%), 193 (20), 168 (36), 137 (71), 123 (100), 110 (45), 96 (30), 50 (33); HRMS (ESI) 233.0618 (MNa$^+$. $C_{11}H_{14}O_2S_1Na$ requires 233.0607).

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