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α-Oxosulfines Part 3.[1] Generation and Trapping of α -Oxothioaldehyde *S*-Oxides

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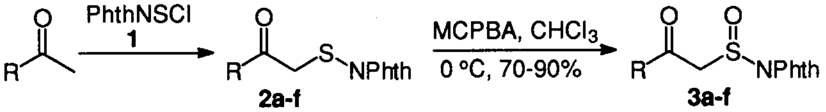
***Abstract*:** α-Oxothioaldehyde *S*-oxides **4a-f** can be generated under very mild conditions from the corresponding sulfinyl compounds **3a-f**, which in turn are obtained by *m*-chloroperoxybenzoic acid (MCPBA) oxidation of α-oxothiophthalimides **2a-f**. The reactive sulfine intermediates can be trapped as electron-poor dienophiles as well as electron-poor dienes with formation of dihydrothiopyran *S*-oxides **5a-e** or 1,4-oxathiin *S*-oxides **6a-f**, respectively. © 1997 Published by Elsevier Science Ltd.

α-Oxothioaldehyde *S*-oxides represent an interesting class of heterocumulenes which has found relatively few applications. These reactive intermediates have been obtained by the reaction of thionyl chloride with silyl enol ethers[2] or by retro Diels-Alder reactions of anthracene derived dihydrothiopyran *S*-oxides[3] and have been trapped as electron-poor dienophiles.

In the last few years we have shown that by exploiting the reactivity of the phthalimidesulfenyl chloride **1** (PhthNSCl, Phth = phthaloyl) it is possible to obtain the precursors of a number of carbon-sulfur double bond containing reagents such as α-oxothiones,[4] α,α'-dioxothiones[5] and *ortho*-thioquinones.[6] In this paper we report the oxidation of N-thiophthalimide derivatives **2a-f** to give the precursors of α-oxothioaldehyde *S*-oxides, namely the sulfinyl derivatives **3a-f**, and the trapping experiments of the transient α-acyl sulfines **4a-e**.

The α-oxothiophthalimide derivatives **2a-f** were prepared reacting the phthalimidesulfenyl chloride **1** with the corresponding methyl ketones[7] (Scheme 1).



2a: R = Me　**2d**: R = 2-Naphthyl　**2e**: R = 1-Thienyl
2b: R = Ph　**2c**: R = 1-Naphthyl　**2f**: R = MeOCO

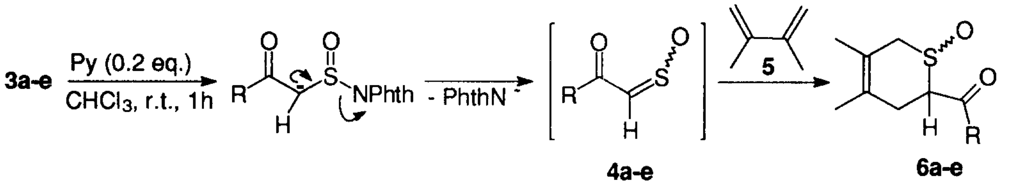
Scheme 1

Among the methods reported in the literature for the oxidation of sulfenamides,[8] we found that, in the case of compounds **2**, the protocol described by Harpp[9] and co-workers, i.e. *m*-chloroperoxybenzoic acid (MCPBA) in chloroform at 0 °C, gives good results affording N-phthalimidesulfinamides **3a-f** in reasonable yields (Scheme 1).

Derivatives **3** are quite sensitive to hydrolysis and were used as obtained by trituration with diethyl ether since, the usual work-up required for MCPBA oxidation, causes extensive decomposition.

The reaction of compounds **3a-e** with 2,3-dimethyl-1,3-butadiene (**5**) carried out in chloroform at room temperature in the presence of 0.2 equivalents of pyridine gave the dihydrothiopyran *S*-oxides **6a-e** which were isolated in good yields as mixtures of diastereoisomers[10] (Scheme 2).

The formation of derivatives **6** can be explained with the formation of the transient thioaldehydes **4** "via" deprotonation and base catalysed 1,2 elimination at sulfur, followed by a classical [4+2] cycloaddition reaction of the very efficient electron-poor dienophilic sulfines **4** to the diene **5** (Scheme 2).



3a, 4a, 6a: R = Me; 65%; *Trans/Cis*=53/47 **3c, 4c, 6c**: R = 1-Naphthyl; 98%; *Trans/Cis*=79/21

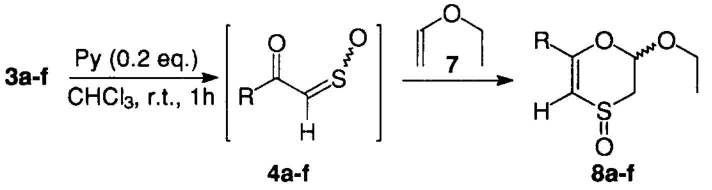
3b, 4b, 6b: R = Ph; 61%; *Trans/Cis*=54/46 **3d, 4d, 6d**: R = 2-Naphthyl; 84%; *Trans/Cis*=80/20

3e, 4e, 6e: R = 1-Thienyl; 56%; *Trans/Cis*=90/10

Scheme 2

The use of α-oxosulfines as electron-poor dienes in inverse electron demand Diels-Alder reactions has been described by us[1,11,12] as well as by other authors,[2] however this reaction has not yet been reported for α-acylthioaldehyde *S*-oxides. Due to the mildness of the reaction conditions required to generate sulfines **6** we verified the possibility to trap the transient thioaldehyde *S*-oxides as dienes using ethyl vinyl ether (**7**) as model electron-rich dienophile.

By generating the sulfines **4** in the presence of two moles of **7**, 1,4-oxathiin *S*-oxides **8a-f** were isolated as mixtures of diastereiosomers[13] which were separated by flash chromatography (Scheme 3).



3a, 4a, 8a: R = Me; 44%; *Trans/Cis*=28/72 **3d, 4d, 8d**: R = 2-Naphthyl; 71%; *Trans/Cis*=16/84
3b, 4b, 8b: R = Ph; 49%; *Trans/Cis*=18/82 **3e, 4e, 6e**: R = 1-Thienyl; 36%; *Trans/Cis*=14/86
3c, 4c, 8c: R = 1-Naphthyl; 77%; *Trans/Cis*=15/85 **3f, 4f, 8f**: R = MeOCO; 31%; *Trans/Cis*=6/94

Scheme 3

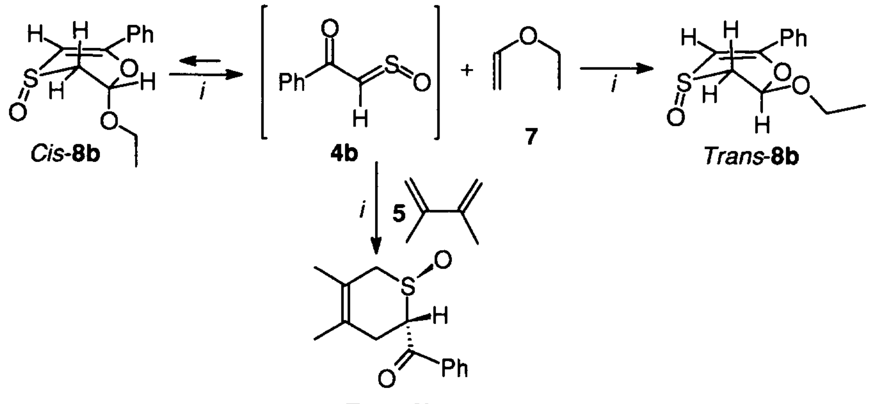
The yields reported in Scheme 3 refer to the combined weight of both diastereoisomers isolated after column chromatography, while the *trans/cis* ratio has been measured by ^{1}H n.m.r. on the crude reaction mixture after 1 hour at room temperature, just before the quench (Scheme 3).

Indeed we observed that the *trans/cis* ratio depends upon a number of factors such as the reaction time, the temperature and the amount of pyridine used to generate the thioaldehyde *S*-oxides. Moreover, work-up procedures and chromatographic purification alter the *trans/cis* ratio in favour of the *trans*-isomers.

For example when we generated the sulfine **4b** at -18 °C using 0.2 equivalents of pyridine, in the presence of **7**, we could monitored by ^{1}H n.m.r. the formation of *cis* cycloadduct **8b** as the sole product. However appreciable amounts (45%) of *trans*-**8b** were also isolated after work-up and purification. On the other hand using 2 equivalents of base the *trans/cis* ratio measured after 12 hours at room temperature was 50/50.

A reasonable explanation for these observations involves an easy retro Diels-Alder process[1,11] operative for 1,4-oxathiin *S*-oxides **8** which, even at room temperature, can generate the sulfine **4** and the vinyl ether **7**. This process seems to be easier for the *cis* adduct (which is the kinetically favoured isomer) than for the *trans* isomer (thermodynamically favoured). Moreover the pyridine must also play a role in the rate of the retro Diels-Alder reaction.[4] Indeed when the pure *cis*-**8b** derivative was kept at room temperature in $CDCl_3$ its transformation into the *trans* isomer ($t_{1/2}$ = 8 days) **4** was observed. When 0.5 equivalent of pyridine was added to the pure *cis*-**8b** the "isomerization" was sensibly faster ($t_{1/2}$ = 4 days) and the complete transformation into the *trans*-**8b** was obtained in about 12 days.

The formation of sulfine **4**, from retro Diels-Alder process of *cis* derivatives **8**, was further demonstrated adding 4 equivalents of diene **5** to a 82/18 mixture of *cis*-**8b** and *trans*-**8b**. In this case it was possible to observe by ^{1}H nmr the release of ethyl vinyl ether **7** and the formation of derivative **6b**, as single *trans* isomer.[14] The consumption of *cis*-**8b** was complete in about 72 hours, when the *trans*-**6b**/*trans*-**8b** ratio was 77/23, and no further changes were detected in the reaction mixture for prolonged reaction times (Scheme 4).



i: $CHCl_3$, r.t.

Scheme 4

The geometry of the *cis* and *trans* cycloadducts **8** was determined by ^{1}H n.m.r. analysis[15] which indicates that in both isomers the sulfoxide oxygen lays in a pseudo-axial position and the ethoxy group is pseudo-axial in the kinetic favoured *cis* isomer and pseudo-equatorial in the more stable *trans* isomer (Scheme 4).

This attribution is in perfect agreement with the geometry observed in similar 1,4-oxathiin *S*-oxide systems[1,11] and was also supported by ab-initio calculations[16] which showed that derivative *cis*-**8a** is 2 kcal/mol less stable than *trans*-**8a**, while this difference is almost 6 kcal/mol for compound **8b**. Moreover, the calculation showed that for both isomers the conformation with the sulfoxide oxygen in a pseudo-axial position, as reported in Scheme 4, is the favoured one (ca. 2 kcal/mol for *cis*-**8a** and 0.3 kcal/mol for *trans*-**8a**).

In conclusion, we have shown that the oxidation of α-oxothiophthalimides represents a simple method to obtain precursors of α-oxothioaldehyde *S*-oxide. The transient sulfines, which can be generated under very mild conditions, can be trapped both by electron-rich dienes and by electron-rich dienophiles. The latter result represents, at the best of our knowledge, the first example of α-oxothioaldehyde *S*-oxides involved as electron-poor dienes in inverse electron demand Diels-Alder reactions.

New possibilities offered by N-thiophthalimide derivatives for the access to new classes of hetero-dienophiles and hetero-dienes are under investigation in this laboratory.

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7. Derivatives **2e** and **2f** were obtained reacting **1** with the appropriate silyl enol ether in dichloromethane at -18 °C.
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9. a) Harpp, D. N. ; Back, T. G. *Tetrahedron Lett.*, **1972**, *52*, 5313-5316. b) Harpp, D. N.; Back, T. G. *J. Org. Chem.*, **1973**, 38, 4328-4334.
10. The attribution of the structure to both stereoisomers of compounds **6a-e** has been obtained by means of their spectroscopic data which are in perfect agreement with those reported by Zwanenburg and coworkers[2b] who described a number of similar dihydrothiopyran derivatives including **6b** and **6d**.
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13. Independent oxidation of *cis* and *trans* cycloadduct **8a** gave the same sulfone indicating that *cis*-**8a** and *trans*-**8a** must be stereoisomers at sulfoxide sulfur.
14. A similar stereoselectivity was not observed in the retro Diels-Alder reactions of 3-oxo-substituted-1,4-oxathiin *S*-oxides which, at 60 °C in the presence of **5**, gave *cis*/*trans* mixtures of dihydrothiopyran *S*-oxides.[11]
15. All compounds were fully characterised and gave satisfactory elemental analysis. Selected data for cycloadduct *cis*-**8b** and *trans*-**8b** are as it follows: *Cis*-**8b**. I.R.: 3064, 2983, 1675 + 1602, 1047 cm^{-1}; ^{1}H-n.m.r.: 1.29 (t, 3H, J = 6.8 Hz), 3.13 (dd, 1H, J = 14.4, 2.6 Hz), 3.43 (ddd, 1H, J = 14.4, 4.0, 1.4 Hz), 3.67÷3.85 (m, 1H), 3.89÷4.05 (m, 1H), 5.69 (dd, 1H, J = 4.2, 2.2 Hz), 6.40 (d, 1H, J = 1.6 Hz) 7.35÷7.48 (m, 3H), 7.63÷7.73 (m, 2H) δ; **M.S.**: *m/z* (rel. int. %): 236 (M$^{+\cdot}$, 0.2), 105 (100), 77 (69). *Trans*-**8b**. ^{1}H-n.m.r.: 1.37 (t, 3H, J = 7.0 Hz), 2.76 (dd, 1H, J = 14.0, 10.2 Hz), 3.21 (bdt, 1H, J = 14.0, 1.6 Hz), 3.80÷3.98 (m, 1H), 4.14÷4.30 (m, 1H), 5.60 (dd, 1H, J = 10.2, 1.6 Hz), 6.32 (d, 1H, J = 1.8 Hz), 7.35÷7.48 (m, 3H), 7.63÷7.73 (m.2H) δ. Anal: Calcd. for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92. Found: C, 60.00; H, 6.03.
16. Ab initio calculations were obtained using a 3-21G* basis set with a geometry optimisation implemented via a Spartan program running on a IBM-RISC 6000 work station.

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