Preparation of 4-Substituted 1,3-Oxathiolan-5-ones *via* the Sulphenium Ion Intermediate Generated by the Pummerer Rearrangement

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4-Substituted 1,3-oxathiolan-5-ones have been synthesized *via* the Pummerer rearrangement from the *S*-oxide of the parent molecule. The 4,5-dione is obtained in the presence of pyridine *N*-oxide.

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We have previously reported that 2,2-diphenyl-2-mercaptoacetic acid forms a *cis*-dioxo molybdenum (**VI**) complex $MoO_2(Ph_2C(S)COO)_2^{-2}$ which reacts with different substrates acting as a model compound for active sites of oxo-transfer Molybdoenzymes [1]. It is possible to obtain also another stable monomeric Mo(V) complex $MoO(Ph_2C(S)-COO)_2^{-1}$ [2] whose paramagnetic parameters are the most promising mimics of the epr spectrum of sulphite oxidase and nitrate reductase [3].

These results stimulated us to study the preparation of new 2-mercaptoacids. The acetalization of α-thioglycolic acid with aldehydes [4] or ketones [5] affords 1,3-oxathiolan-5-ones. Furthermore α-thioglycolic acids derivatives can be prepared by hydrolysis of 1,3-oxathiolan-5-ones [6] or selective cleavage of the carbon-sulphur bond [7].

Although several synthesis of substituted oxathiolanones have been reported by alkylation [8] or aldol condensation [9] of the corresponding enolates, the C_4 carbonyl or aryl oxathiolanone derivatives cannot be prepared by these methods.

As a part of our investigations on the α-thioglycolic acids, we wish to report here the preparation of 4-carbonyl and 4-aryl derivatives of 1,3-oxathiolan-5-ones by the Pummerer rearrangement.

The starting oxathiolanone was prepared by refluxing for 4 hours a benzene solution of thioglycolic acid and cyclohexanone in the presence of *p*-toluenesulphonic acid with azeotropic removal of the water formed to obtain **1** in 80% yield.

When the oxathiolanone **1** was treated with hydrogen peroxide in acetic acid a single *S*-oxide **2** [10] was obtained in 80% yield. The *S*-oxide **2** reacts with *p*-toluenesulphonic acid to obtain an α-thiocarbocation **3** derived formally by elimination of OH^- group from the sulphoxide [11].

On the assumption that the sulphenium ion intermediate can give electrophilic aromatic substitution on aromatic rings [12] we have prepared compounds **4** *via* the Pummerer rearrangement of *S*-oxide **2**. McIntosch *et al.* [13] reported that the same reaction using a mixture of TFA and TFAA as catalyst was unsuccessful. However C_4 substitution could be achieved easily in the presence of *p*-toluenesulphonic acid in an excess of electron-rich arenes.

We found that the ion **3** is captured intermolecularly by anisole, 1,3,5-trimethoxybenzene or thiophene to obtain compounds **4**. The aromatic compounds, used as trapping agents, act as mild nucleophiles to give electrophilic aromatic substitution products. The completion of the reaction was performed by azeotropic removal of water under an argon atmosphere in the presence of an excess of aromatic compound. Yields of crystallized products are summarized in the Table 1.

Table 1

Yields of C_4 derivatives of 1,3-oxathiolan-5-one **1**

AROMATIC COMPOUND	PRODUCT	YIELD
Anisole	**4a**	60%
1,3,5-trimethoxybenzene	**4b**	30%
Thiophene	**4c**	48%
Benzene	**4d**	10%
Pyridine N-oxide	**5**	60%

It is important to point out that anisole and thiophene affords only substitution at C_4 and C_2, respectively, and no other constitutional isomers can be found. Moreover considering that steric effects imparted by methoxy groups may be responsible for the decrease in yield observed in the reaction with 1,3,5-trimethoxybenzene, the present results suggests that the electrophilic aromatic substitution is, under these reaction conditions, very sensitive to steric hindrance and also to the orientation of electrophiles on substituted aromatic rings.

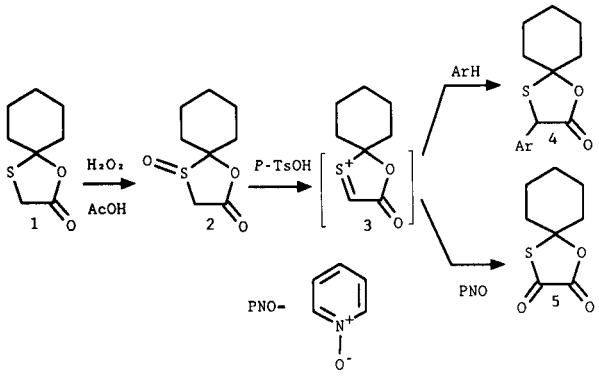
Although the reaction with benzene gave a 10% yield, most of the sulphoxide **2** could be recovered unchanged in

this reaction. This demonstrates that the concentration of sulphenium ion is very low under these reaction conditions. Therefore when very poor nucleophiles, such as benzene, were used to withdraw the ion intermediate, the yields of the reaction generally decreases. Furthermore this suggests the stability of the oxathiolanone ring under the acidic reaction conditions employed herein.

In addition when pyridine *N*-oxide is used as the trapping agent, we only obtain product **5** (Scheme 1). We must note that the pyridine *N*-oxide shows a quite different behaviour compared to that of other aromatic compounds assayed. Indeed, no electrophilic aromatic substitution was observed rather a regioselective oxidation of the carbonyl at C_4 to give the unusual dione **5** which may be used as the precursor of the thiooxalic acid.

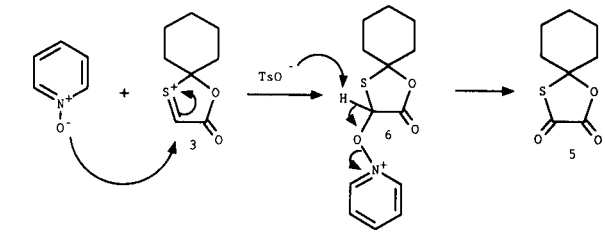
Scheme 1

Outline of Pummerer Reaction Sequence of 1,3-oxathiolan-5-one **1**



This reaction could be considered as a real Pummerer rearrangement, but the fact that product **5** only appears when pyridine *N*-oxide is present in the reaction medium, suggests an intermolecular mechanism involving an oxygen atom transfer reaction from pyridine *N*-oxide to **3**. We feel that under these experimental conditions, the observed product **5** can best be explained *via* the adduct **6** followed by elimination of the pyridinium salt (see Scheme 2).

Scheme 2



EXPERIMENTAL

General.

All solvents and reagents were purified and dried where necessary using standard procedures. All melting points were determined with a Reichert apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 281. The nmr spectra were recorded on either a Bruker AC-200 (200 MHz), a Varian Unity (400 MHz), or a Unity (300 MHz) spectrometer. Chemical shifts in the ^1H nmr are denoted in δ units (ppm) relative to tetramethylsilane as an internal standard at $\delta = 0$ and chemical shifts in the ^{13}C nmr are denoted in δ units (ppm) relative to deuteriochloroform ($\delta = 76.9$). Splitting patterns are designated as follows: s, singlet; d, doublet; m, multiplet. Mass spectra were observed on a Hewlett Packard 5988A 70 eV I.Q. mass spectrometer. All compounds were purified by bulb to bulb distillation or by column chromatography on Merck Silica gel 60 (0.06-0.20 mm.) and had spectral data in accord with the proposed structures.

Cyclohexanespiro-2'-1',3'-oxathiolan-5'-one **1**.

A mixture of thioglycolic acid (3.8 mmoles), anhydrous *p*-toluenesulphonic acid (4 mmoles), and cyclohexanone (4.4 mmoles) in dry benzene (20 ml) were heated under reflux for 4 hours with continuous azeotropic removal of water under an argon atmosphere. Work-up in the usual way and bulb to bulb distillation under reduced pressure gave one main fraction bp 131-133° at 10 mm Hg (3.0 mmoles, 80%). Crystallization from hexane gave white solid crystals of mp 26-27°; ir (film): ν 1772 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.5 (4H, m), 1.75 (2H, m), 1.92 (4H, m), 3.66 (2H, s); ^{13}C nmr (deuteriochloroform): δ 22.95, 23.83, 31.36, 38.96, 171.62; ms: m/z (% relative intensity) 172 (M^+, 12.3), 99 (100), 81 (70.4).

Cyclohexanespiro-2'-*S*-oxide-1',3'-oxathiolan-5'-one **2**.

A solution of **1** (6 mmoles) in acetic acid was treated with hydrogen peroxide (9 mmoles) at 0°, poured into cool water and then extracted with dichloromethane (4 x 25 ml). The extract was washed with saturated sodium bicarbonate solution and brine. Removal of the solvent yielded **2** as a solid material which was recrystallized from hexane/dichloromethane to give pure white solid crystals of **2** (4.8 mmoles, 80% yield), mp 90-92°; ir (potassium bromide): ν 1780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.4-2.2 (10H, m), 3.6 (1H, d, J = 17.7 Hz), 3.8 (1H, d, J = 17.7 Hz); ^{13}C nmr (deuteriochloroform): δ 22.18, 22.67, 24.07, 28.57, 32.56, 51.87, 101.47, 169.32; ms: m/z (% relative intensity) 188 (M^+, 0.78), 99 (67.5), 81 (51.1), 42 (100).

Anal. Calcd. for $C_8H_{12}O_3S$: C, 51.06; H, 6.38; S, 17.02. Found: C, 50.98; H, 6.52; S, 16.8.

General Procedure for the Pummerer Rearrangement.

A solution of **2** (2.5 mmoles) and *p*-toluenesulphonic acid (3.7 mmoles) in chloroform was poured in an excess of aromatic compound (8 mmoles), and the solution was heated under reflux for 1 hour with azeotropic removal of water under argon atmosphere. The reaction mixture was washed with water to remove *p*-toluenesulphonic acid and dried. The solvent was evaporated and the residue was crystallized from hexane/dichloromethane to give **4** or **6**. Yields of crystallized products are summarized in the Table 1.

Cyclohexanespiro-2′-4′-(*p*-methoxyphenyl)-1′,3′-oxathiolan-5′-one **4a**.

This compound had mp 74-76°; ir (potassium bromide): ν 1765 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.2-2.2 (10H, m), 3.78 (3H, s), 5.11 (1H, s), 6.87 (2H, d, J = 8.6 Hz), 7.34 (2H, d, J = 8.6 Hz); ^{13}C nmr (deuteriochloroform): δ 23.43, 23.68, 24.39, 40.08, 40.28, 50.66, 55.33, 90.53, 114.31, 127.31, 129.83, 159.72, 173.26; ms: m/z (% relative intensity) 278 (M^+, 18.0), 234 (16.7), 151 (100).

Anal. Calcd. for $C_{15}H_{18}O_3S$: C, 64.74; H, 6.47; S, 11.51. Found: C, 64.82; H, 6.51; S, 11.39.

Cyclohexanespiro-2′-4′-(2″,4″,6″-trimethoxyphenyl)-1′,3′-oxathiolan-5′-one **4b**.

This compound had ^1H nmr (deuteriochloroform): δ 1.40-2.11 (10H, m), 3.73 (3H, s), 3.76 (3H, s), 3.78 (3H, s), 5.66 (1H, s), 6.05 (1H, s), 6.09 (1H, s); ^{13}C nmr (deuteriochloroform): δ 23.48, 23.58, 24.41, 39.84, 40.56, 41.36, 55.36, 55.79, 90.14, 91.65, 92.91, 105.57, 158.70, 161.65, 174.41; ms: m/z (% relative intensity) 338 (M^+, 50.18), 294 (37.5), 211 (74.0), 179 (100).

Anal. Calcd. for $C_{17}H_{22}O_5S$: C, 60.35; H, 6.50; S, 9.46. Found: C, 59.83; H, 6.24; S, 9.33.

Cyclohexanespiro-2′-4′-(2″-thienyl)-1′,3′-oxathiolan-5′-one **4c**.

This compound had mp 86-88°; ir ν 1775 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.2-2.2 (10H, m), 5.40 (1H, s), 6.99 (1H, dd, J = 5.1 and 0.9 Hz), 7.17 (1H, dd, J = 3.5 and 0.9 Hz), 7.30 (1H, dd, J = 5.1 and 3.5 Hz); ^{13}C nmr (deuteriochloroform): δ 23.37, 23.56, 24.26, 40.11, 40.18, 46.52, 91.39, 126.41, 127.14, 127.18, 138.78, 172.31; ms: m/z (% relative intensity) 254 (M^+, 9.98), 210 (32.15), 128 (100).

Anal. Calcd. for $C_{12}H_{14}O_2S_2$: C, 56.69; H, 5.51; S, 25.21. Found: C, 56.37; H, 5.49; S, 25.54.

Cyclohexanespiro-2′-4′-phenyl-1′,3′-oxathiolan-5′-one **4d**.

This compound had mp 96-98°; ir: ν 1767 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.80-1.06 (10H, m), 4.84 (1H, s), 6.98-7.14 (5H, m); ^{13}C nmr (deuteriochloroform): δ 23.27, 23.49, 24.2, 39.94, 40.14, 50.96, 90.57, 128.30, 128.47, 128.67, 135.31, 172.77; ms: m/z (% relative intensity) 248 (M^+, 7.71), 204 (24.8), 121 (100).

Anal. Calcd. for $C_{14}H_{16}O_2S$: C, 67.74; H, 6.45; S, 12.90. Found: C, 67.80; H, 6.43; S, 12.88.

Cyclohexanespiro-2′-1′,3′-oxathiolan-4′,5′-dione **5**.

This compound had mp 72-74°; ir: ν 1782, 1700 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.20-2.20 (10H, m); ^{13}C nmr (deuteriochloroform): δ 23.05, 23.71, 40.91, 157.70, 180.89; ms: m/z (% relative intensity) 187 ($M^+ + 1$, 0.14), 114 (83.4), 81 (100).

Anal. Calcd. for $C_8H_{10}O_3S$: C, 51.61; H, 5.37; S, 17.20. Found: C, 51.68; H, 5.35; S, 17.15.

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