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α-Benzoyloxylation of dimethyl trisulfide and a novel reaction of the resultant trisulfide benzoate

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α-Benzoyloxylation of dimethyl trisulfide and a novel reaction of the resultant trisulfide benzoate

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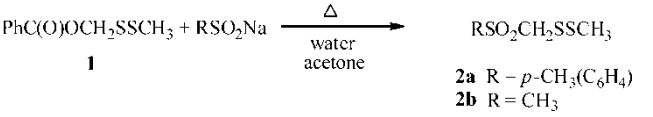
Reaction between sulfinate anions and α-benzoate of dimethyl disulfide produces a novel α-thiolbenzoate disulfide. Thiolbenzoate appears to arise from the reaction of a contaminant, α-benzoate of dimethyl trisulfide, present in benzoate disulfide. Benzoate trisulfide is formed by the reaction of benzoic anhydride with dimethyl trisulfide, a contaminant in commercial dimethyl disulfide.

Keywords: α-thiolester disulfides; trisulfide acyloxylation; α-sulfone disulfides

1. Introduction

Some time ago, we selected α-sulfone disulfides as synthetic targets on the grounds that they showed interesting and potentially useful results in various biological screening programs. Initially, our newly developed synthesis deployed α-propionoxy dimethyl disulfide as a precursor for α-sulfone disulfides. More recently, α-benzoyloxy dimethyl disulfide **1** has been deployed (Scheme 1). A review of this chemistry has been published (*1*).



Scheme 1.

Early efforts (*2*) produced clean benzoate disulfide **1** by means of a particularly cumbersome purification procedure. The work, described in the current report, began with the goal of dramatically streamlining the chromatographic part of our procedure.

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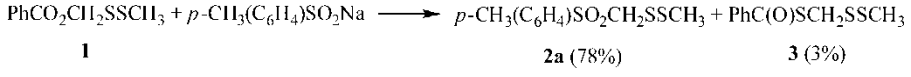
2. Results and discussion

Conventional column chromatography on **1** led to some material loss (apparent decomposition) and, subsequently, the development of an apparatus for bundled chromatography (*3*). Preparation of **1** followed up with bundled column chromatography and reduced pressure distillation (4) provided material of satisfactory purity, albeit in somewhat reduced yield (19%).

Benzoate disulfide **1**, prepared in this manner, provided α-sulfone disulfide, *p*-toluenesulfonylmethyl methyl disulfide **2a**, in the usual yield. Conventional column chromatography furnished **2a** and a new product, benzoylthiomethyl methyl disulfide **3** (Scheme 2).

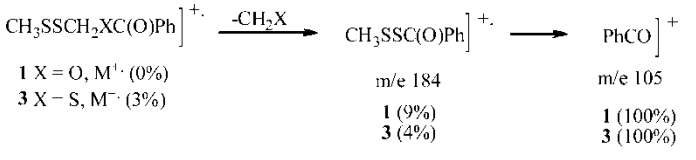


Scheme 2.

Given the reaction conditions and the reactants, neither the structure of **3** nor a reasonable pathway for its formation is immediately obvious. Evidence gathered to elucidate its structure included IR, ^{1}H NMR, ^{13}C NMR, and GC-MS. The IR spectrum of the benzoate disulfide **1** features a strong carbonyl absorption at 1710 cm^{-1} whereas the IR spectrum of **3** shows a strong carbonyl absorption at 1667 cm^{-1}. Thiolacetate carbonyl bands are typically observed near 1680 cm^{-1} (*5*), hence 1667 cm^{-1} is appropriate for an aryl thiolester carbonyl band position.

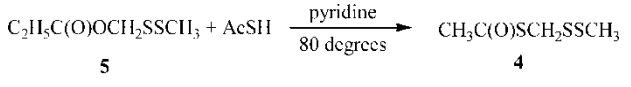
The key aspect of the proton NMR spectrum offers further support for the assignment of a thiolester structure to **3**. Benzoate disulfide **1** shows the methylene singlet at δ 5.55, whereas the thiolbenzoate disulfide **3** has the corresponding signal at δ 4.37. Methylene carbon resonances are observed at δ_C 73.5 for **1** and δ_C 37.6 in support of the thiolester structure proposed for **3**. Moreover, the carbonyl carbon signal for **1** is observed at δ_C 165.8 in contrast to that for **3**, which is observed at δ_C 190.1.

The mass spectrum of **3** is particularly helpful. CO-linked α-ester disulfides show characteristic $M^{+\cdot}-CH_2O$ ions (*6*). The mass spectrum of **3** shows both the molecular ion and an $M^{+\cdot}-CH_2S$ ion in complete accord with the assigned structure (Scheme 3).



Scheme 3.

The unambiguous synthesis of α-thiolester disulfide, acetylthiomethyl methyl disulfide **4**, was carried out as depicted in Scheme 4.

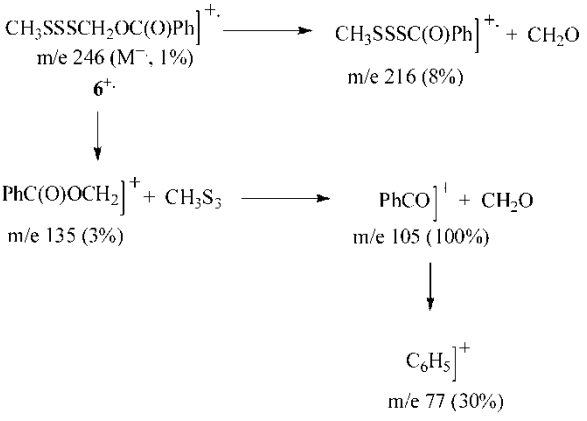


Scheme 4.

The spectra of **4** offer firm support for the structural assignment for **3**: IR ν_{CO} 1685 cm^{-1}; δ_H 4.17 (CH_2); δ_C 37.2 (CH_2), and 194.0 (CO); $M^{+\cdot}$ (9%), $M^{+\cdot}-CH_2S$ (13%).

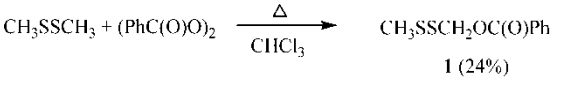
Even with the structure of disulfide thiolbenzoate **3** firmly established, it was not obvious how it could have arisen from the putative precursor **1** which has only two sulfenyl sulfur atoms. The GC-MS of disulfide benzoate **1** ($R_t = 8.5$ min), purified as described at the outset of this section, shows a minor component (about 3%, $R_t = 10.3$ min). An examination of the various spectra led to the conclusion that it was trisulfide benzoate, α-benzoyloxy dimethyl trisulfide **6**.

A particularly slow, careful distillation of a disulfide benzoate **1** sample provided a small sample which was enriched in **6** (ca 6%). The ^{1}H NMR showed appropriate signals in the aromatic region along with a pair of singlets at δ_H 5.62 (2H) and 2.56 (3H). The carbon spectrum showed important signals at δ_C 23.0 and 72.1. A complete rationale for the major ions in the mass spectrum of the minor contaminant, **6**, is presented in Scheme 5.



Scheme 5.

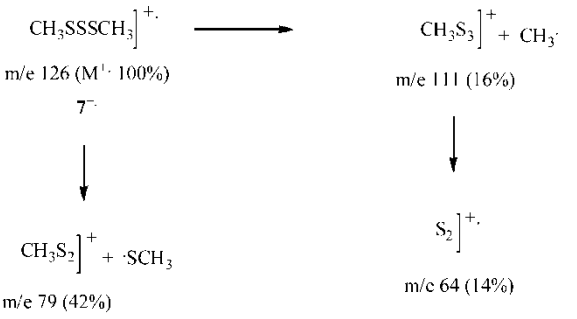
Given the structural assignment for **6** (three sulfur atoms), it begins to seem possible that the very modest amount of trisulfide benzoate **6** in purified disulfide benzoate **1** could serve as the precursor for the very modest amount of disulfide thiolbenzoate **3** (3 sulfur atoms) produced in Scheme 2 reaction. However, a new problem arises. It is by no means obvious how a reaction between dibenzoyl peroxide and dimethyl disulfide (*2*) (Scheme 6) could produce **6**.



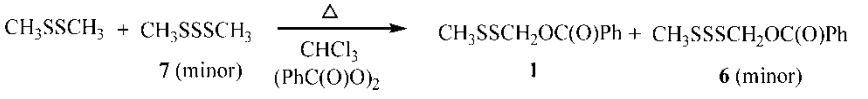
Scheme 6.

When our commercially produced dimethyl disulfide (98%, Fluka) was carefully examined by GC-MS, a minor contaminant (<1%) was detected ($R_t = 2.3$ min). The mass spectrum requires three sulfur atoms ($M^{+\cdot}$ 100%; $M^{+\cdot}$+1, 4.6%; $M^{+\cdot}$+2, 14%) which supports dimethyl trisulfide **7** as its structural assignment. Furthermore, the obvious alternative possibility, methyl thiomethanesulfonate, shows major ions at m/e 81 and 63 in its mass spectrum. These ions are absent in the spectrum of the contaminant in our commercial dimethyl disulfide. Scheme 7 presents a fragmentation scheme for the minor component on the basis that it is dimethyl trisulfide **7**.

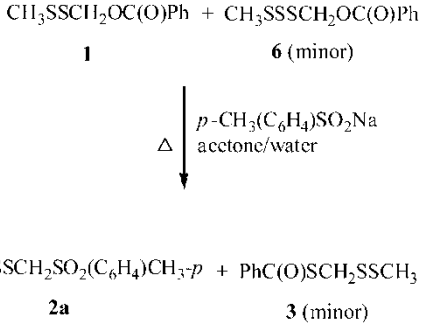
It is now possible to rationalize the presence of benzoate trisulfide **6** in distilled disulfide benzoate **1** (Scheme 8).



Scheme 7.



Scheme 8.



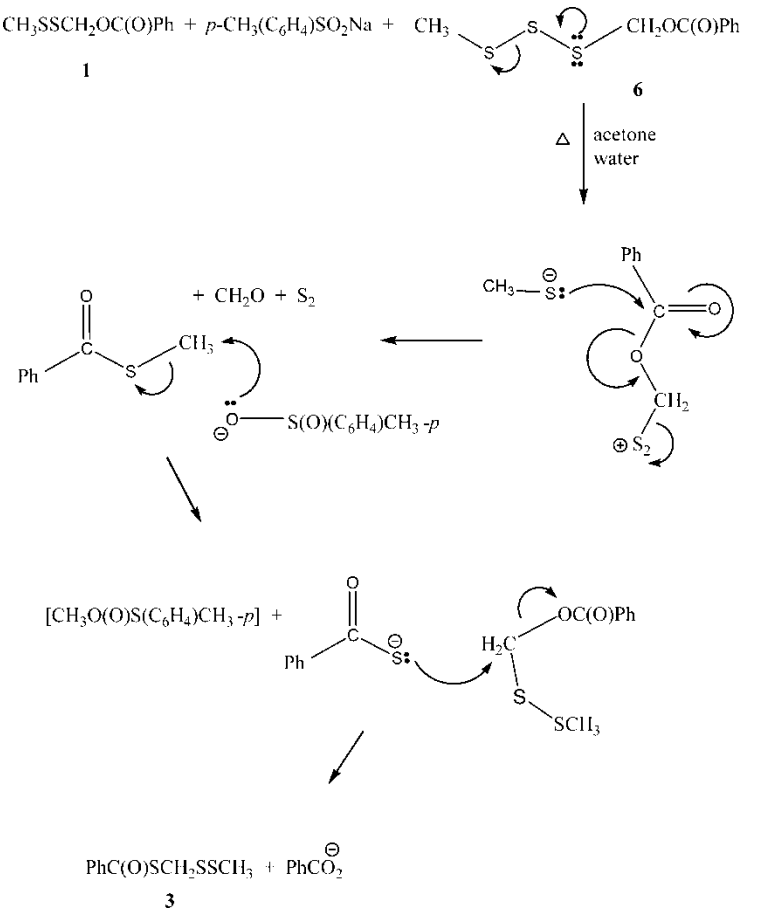
Scheme 9.

Thereafter, disulfide thiolbenzoate **3** (Scheme 2) may form from benzoate trisulfide **6** (Scheme 9).

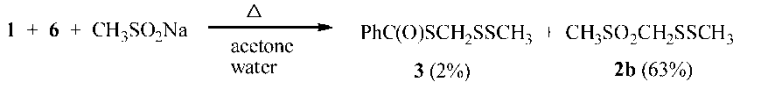
A possible mechanism for the transformation of **6** into **3** is presented in Scheme 10.

In a final experiment, distilled disulfide benzoate **1**, containing a minor amount of trisulfide benzoate **6**, was reacted with sodium methanesulfinate. In accord with the Scheme 10 proposal, thiolbenzoate disulfide **3** was formed (Scheme 11).

The initially unrecognized presence of dimethyl trisulfide **7** in commercial dimethyl disulfide has led to the formation of α-benzoate trisulfide **6** as a previously unrecognized minor contaminant in chromatographed (12 bundle), distilled disulfide benzoate **1**. Benzoyloxylation of trisulfide may well follow the mechanism we have previously proposed for the benzoyloxylation of dimethyl disulfide (1). Subsequent reaction of the benzoate mixture (**1** and **6**) with sulfinate anions produces thiolbenzoate disulfide **3**. A reasonable mechanistic proposal is presented in Scheme 10.



Scheme 10.



Scheme 11.

3. Experimental

3.1. *General*

Infrared spectra were recorded on a Thermo Nicolet 2000 spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR spectra were obtained on a JEOL JNM-GSX270 Fourier-transform NMR system. Unless otherwise specified, all NMR spectra were obtained in deuterated chloroform using tetramethyl silane as an internal standard. Mass spectra were obtained on a Hewlett-Packard 5988A gas–liquid chromatography mass spectrometer system.

3.2. *Preparation of disulfide benzoate* **1**

Dimethyl disulfide (1.27 g, 13.5 mmol) and wet commercial dibenzoyl peroxide (4 g) were added to chloroform (150 mL). A soxhlet extractor was attached to the reaction flask and a thimble charged with anhydrous $MgSO_4$ (10 g) was placed in the soxhlet. The reaction mixture was refluxed for 72 h, added to chloroform (100 mL), and the resultant solution extracted with 2.5% W/V sodium hydroxide (two 50 mL aliquots). The organic layer was dried ($MgSO_4$), filtered, and the solvent evaporated.

An additional three runs were carried out and the product from each run was combined with the others. The crude product was diluted up to 240 mL with chloroform and the resultant solution was stirred at ambient temperature for 2 h. The solution was split into 12 equal portions (burette), which were concentrated separately. The separate portions were purified simultaneously using a 12-bundle apparatus (3) and 3:1 chloroform/petroleum ether for elution.

Fractions 9–15 were combined, concentrated, and the residue was distilled (*4*) affording disulfide benzoate **1** (2.14 g, 10 mmol, 19%, bp 140–144°C/1.6 Torr). The properties of **1** have been given earlier (*2*). GC-MS showed a minor component (3%) at $R_t = 10.4$ min.

3.3. *Preparation of enriched trisulfide benzoate* **6**

A sample of chromatographed (12 bundle), distilled **1** was redistilled at reduced pressure providing several fractions. Fraction 2 (2.07 g, bp 136–140°C/1.5 Torr) was essentially unchanged. Fraction 3 (52 mg, bp 145°C/1.5 Torr) was principally **1** enriched in **6** (6%). ^{1}H NMR (270 MHz) δ 2.54 (s, 3H), 5.61 (s, 2H) along with aromatic absorption which was overlayed with signals from **1**. ^{13}C NMR (68 MHz) δ 23.0, 72.1 along with aromatic resonances very close to those signals due to **1**. Only one carbonyl resonance was observed (δ_C 165.8). The mass spectrum is detailed in Scheme 5.

3.4. *Reaction of disulfide benzoate* **1**, *containing ca 3%* **6**, *with sodium sulfinate salts*

A pair of reactions between benzoate disulfide **1** and sodium *p*-toluenesulfinate or separately **1** and sodium methanesulfinate were carried out as described below for the *p*-toluenesulfinate salt.

Sodium *p*-toluenesulfinate (1.02 g, 5.76 mmol) was dissolved in water (4 mL). A solution of benzoate disulfide **1** (1.03 g, 4.79 mmol) in acetone (16 mL) was added. The reaction mixture was immersed into a constant temperature bath (50°C) for 2 h. Chloroform (100 mL) was added and the resultant mixture was washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated to furnish yellow oil.

The crude yellow oil from two reactions was combined and chromatographed on silica gel (200 g) employing 1:1 chloroform/petroleum ether (100 mL fractions) for elution. Fractions 12–13 were combined and concentrated to provide thiolbenzoate **3** (58 mg, 0.34 mmol, 3%). Fractions 30–44 were combined and concentrated giving sulfone disulfide **2a** (1.68 g, 7.50 mmol, 78%) (*7*).

The crude yellow oil from two reactions between disulfide benzoate **1** and sodium methanesulfinate was combined and chromatographed on silica gel (200 g) employing chloroform (100 mL fractions) for elution. Fraction 4 afforded impure thiolbenzoate **3**.

Fractions 14–23 were combined and concentrated giving sulfone disulfide **2b** (1.02 g, 5.93 mmol, 63%) (*7*). Impure **3** from fraction 4 was rechromatographed on silica gel (17 g) employing 1:1 chloroform/petroleum ether (15 mL fractions) for elution. Fractions 4–6 provided unacceptable **3** of improved purity. Impure **3** from fractions 4–6 was again chromatographed on silica gel (17 g) employing 1:3 chloroform/petroleum ether (15 mL fractions) for elution.

Fractions 34–36 were combined and concentrated furnishing clean thiolbenzoate disulfide **3** (33 mg, 0.19 mmol, 2%).

Purified thiolbenzoate disulfide **3** samples from four reactions between *p*-toluenesulfinate and **1**, and from two reactions between methanesulfinate and **1**, were combined. The entire amount of material was rectified at reduced pressure to provide **3** as pale amber oil (125 mg, 156°C/1.4 Torr). $C_9H_{10}OS_3$ requires C 46.9; H 4.4. Found: C 47.2: H 4.3. **3** had IR 1667 cm^{-1}. ^1H NMR (270 MHz) δ 2.52 (s, 3H), 4.37 (s, 2H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.98 (d, $J = 7.9$ Hz, 2H). ^{13}C NMR δ 23.6, 37.6, 127.5, 128.8, 133.9, 136.4, 190.1. MS: 232 ($M^{+\cdot}$+2, 0.5%), 231 ($M^{+\cdot}$+1, 0.4%), 230 ($M^{+\cdot}$, 3.4%), 184 ($M^{+\cdot}-CH_2S$, 4%), 151 ($M^{+\cdot}-CH_3S_2$, 13%), 105 (100%), 77 (32%).

3.5. *Preparation of disulfide thiolacetate* 4

A solution of technical grade (Aldrich) thioacetic S-acid (0.22 g) in dry pyridine (5 mL) was added to propionate disulfide **5** (0.51 g, 3.04 mmol) (*8*). The reaction mixture was immersed into a constant temperature bath (80°C) for 1.5 h. Chloroform (100 mL) was added and the resultant solution was extracted with 5% V/V hydrochloric acid (100 mL). The organic layer was washed with 2.5% sodium hydroxide (50 mL). The chloroform layer was dried ($MgSO_4$), filtered, and the solvent was evaporated.

The crude product was subjected to a filtration column using silica gel (3 g) and petroleum ether (125 mL) for elution. The solvent was distilled from the solution at atmospheric pressure. The distillation residue was rectified at reduced pressure furnishing disulfide thiolacetate **4** (113 mg, 0.67 mmol, 22%, bp 130–135°C/18 Torr). The purity of distilled **4** was about 85%. **4** had IR 1685 cm^{-1}. ^1H NMR (270 MHz) δ 2.40 (s, 3H), 2.50 (s, 3H), 4.17 (s, 2H). ^{13}C NMR δ 23.3, 30.4, 37.1, 193.8. MS: 170 ($M^{+\cdot}$ +2, 1.2%), 169 ($M^{+\cdot}$ +1, 0.6%), 168 ($M^{+\cdot}$, 8.6%), 122 ($M^{+\cdot}-CH_2S$, 13%), 89 ($M^{+\cdot}-CH_3S_2$, 11%), 43 (100%).

Acknowledgements

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