An Improved Synthesis of Cyclohexenothioxanthenones

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An improved synthesis of cyclohexanothioxanthenones in high yield (70-90%) by treatment of thiosalicylic acid (**4**) or 2,2′-dithiosalicylic acid with 1,2,3,4-tetrahydronaphthalene (**5**) in the presence of concentrated sulfuric acid or a mixture of 95% sulfuric acid with 27-30% fuming sulfuric acid (in 5:1 to 2:1 v/v ratio) was described. The crude product consisted of three isomers which were isolated and identified. These isomers are 1,2-, 2,3- and 3,4-cyclohexanothioxantenone (**1**, **2**, and **3**).

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Thioxanthenone and many substituted thioxanthenones have been prepared by different methods [1-17]. The synthesis of 2,3-cyclohexenothioxanthenone (**2**) by a cyclo-aromatization of 3-(phenylthio)-5,6,7,8-tetrahydronaphalene-2-carboxylic acid was reported [18]. However, the synthesis of cyclohexenothioxanthenone isomers have not been reported to the best of our knowledge. Herein, we describe an improved preparation, isolation and identification of cyclohexenothioxanthenones including 1,2-cyclohexenothioxanthenone (**1**), 2,3-cyclohexenothioxanthenone (**2**), and 3,4-cyclohexenothioxanthenone (**3**). These compounds might be useful photoinitiators as are other thioxanthenone derivatives, such as 2-chlorothioxanthenone, 2-aminothioxanthenone, and 2-isopropylthioxanthenone [2-5].

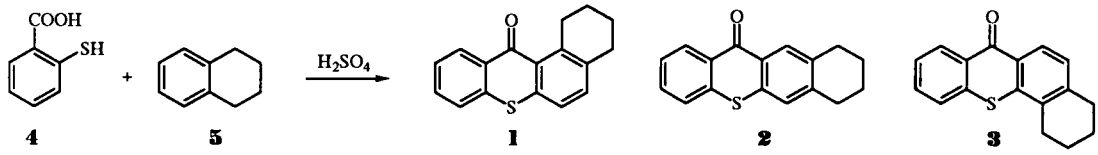
Results and Discussion.

The cyclohexenothioxanthenones were synthesized in 69-80% (isolated) yields by treatment of thiosalicylic acid (**4**) with 1,2,3,4-tetrahydronaphthalene (**5**) (mole ratio: **5**/**4** = 4-7) in the presence of concentrated sulfuric acid (95-98%) at 85° for 2 hours (equation 1). Replacing **4** with 2,2′-dithiosalicylic acid (DTSA) in this synthesis gave 60-75% yields. Even higher yields (85-90%) were obtained in both methods by mixing 95% sulfuric acid with 27-30% fuming sulfuric acid (in 5:1 to 2:1 v/v ratios) and keeping the molar ratio of (sulfuric acid + sulfur trioxide)/**4** at 30 or higher. Analysis, gc and tlc, showed that the crude product consisted of three compounds with relative yields of 73%, 18%, and 8.1% (about 9:2:1). Analysis (gc-ms) of the crude product indicated that all three had a molecular weight of 266, suggesting they must be structural isomers.

Analysis (tlc) on silica gel using toluene as eluant gave R_f values of 0.617, 0.367, and 0.308 for **1** through **3**, respectively. The pure isomers were separated by column chromatography over silica gel (70-230 mesh) upon eluting with hexane. They exhibited melting points of 107.5-108.0° (isomer **1**, light-yellow needles), 180.0-181.0° (isomer **2**, light-yellow needles), and 198.0-199.0° (isomer **3**, light-yellow cotton-like crystals), respectively. The purity of each isolated isomer was at least 98-99% (gc analysis).

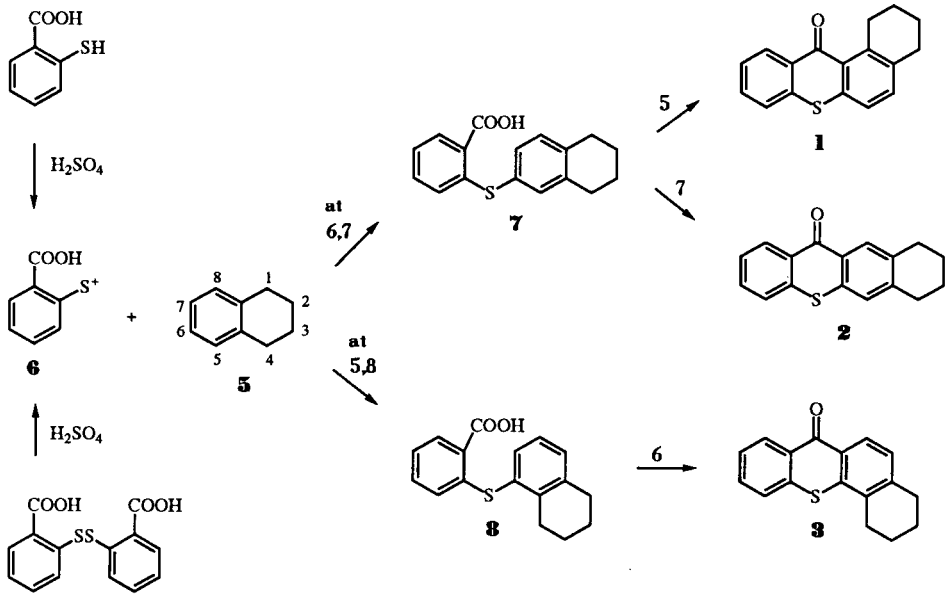
Structural identification was performed by ^1H nmr, ^{13}C nmr and uv spectroscopy. Proton nmr analysis confirmed the first isomer eluted was 1,2-cyclohexenothioxanthenone (**1**) the second isomer was 2,3-cyclohexenothioxanthenone (**2**) and the third isomer was 3,4-cyclohexenothioxanthenone (**3**), respectively. The absorption maximum in the uv spectra of the three isomers were **1** λ max = 375 nm, **2** λ max = 380 nm, and **3** λ max 370 nm. Each gave a C=O stretch at 1630-1640 cm^{-1}. A possible mechanism for this reaction is shown in Scheme 1 below.

The mercapto group of **4** (or DTSA upon cleavage) is oxidized to a sulfenic acid which immediately decomposes to a sulfenium ion [8]. Electrophilic substitution by this ion onto 1,2,3,4-tetrahydronaphthalene **5**, occurred more rapidly at the 6 or 7 position to give the major intermediate **7**, (about 92%) and slower at the 5 position to give **8**. Cyclization of **7** occurred at either the 5 or the 7 position to give the isomer **1**, (73%) or isomer **2**, (19%). Cyclization of **8** resulted in the isomer **3**, (8.1%). Thioxanthenone yields depended directly upon the sulfuric acid concentration and mole ratio of **5**/**4** (or **5**/DTSA), because sulfonation of **5** (equation 2) competes with the generation of sulfenium ion, **6**, and subsequent electrophilic substitution. A high sulfuric acid concentration increased the rate of sulfonation but concentrations above 92% are required for rapid generation of **6** followed by electrophilic substitution. Thus, a careful balance between these two competing processes was essential.



4 **5** **1** **2** **3** (1)

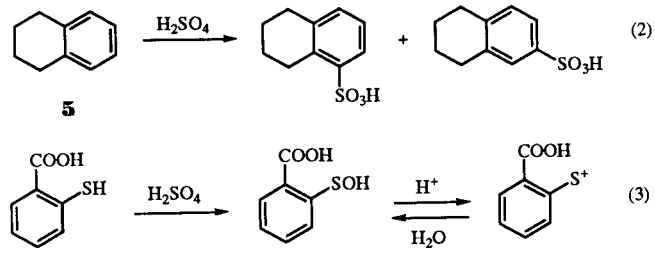
Scheme 1



Although sulfonation rates increase as the sulfuric acid concentration increases, hplc analysis (acetonitrile/water, 70/30, reverse phase, C18 column) showed that the amount of **5** that was sulfonated actually *decreased* at higher acidity. In fact, sulfonation predominates only at sulfuric acid concentrations below 92%. In 80% sulfuric acid the yield of thioxanthenones was only 5% and 85% of **5** was sulfonated after 24 hours at 25°. A similar result was obtained using 85% sulfuric acid at 80° for 2 hours. Another factor is the effect of sulfuric acid concentration on sulfenium ion **6**. Ion **6** is destroyed rapidly by water (equation 3). Hence, electrophilic substitution and cyclization to thioxanthenones occurred only when a high concentration of sulfuric acid (low water activity) was maintained. The sulfonic acid concentration must be ~93% for electrophilic substitution/cyclization to predominate.

Since a mole of water is liberated during cyclization the acid medium is increasingly diluted as the reaction proceeds. The highest yields of thioxanthenones reported in previous studies [2-17] was about 50-60%. Those studies used 95% sulfuric acid. However, dilution of the sulfuric acid took place due to liberation of water during the reaction. The increased water activity as the reaction proceeded lowered the yields. As shown here, high yields (85-90%, isolated) of thioxanthenones were generally be obtained using a mixture of 95% sulfuric acid and fuming sulfuric acid (27-30% free sulfur trioxide). Due to competing sulfonation of **5**, the mole ratio of **5** to **4** had to be higher than 2:1, the best ratio is 3:1 to 4.5:1.

The electrophilic substitution/cyclization route employing **4** with an organic substrate, as described here for cyclohexenothioxanthenones, is *generally applicable to a range of aromatic substrates* containing either electron-donating or electron-withdrawing substituents. *In all cases the sulfuric acid concentration should be kept above 90-94% throughout the reaction.* The reaction exotherm should be controlled to keep the temperature below 80-90° to reduce further competing sulfonation. However, *temperatures of 45 to 75° are advantageous.* The high acidity necessary to rapidly generate reactive sulfenium ion, **6**, and promote the electrophilic substitution/cyclization also results in a strong sulfonating medium. Since **4**, the aromatic substrate and the products were all possible targets of further sulfonation, control of temperature to give a high rate of thioxanthenone formation without further sulfonation was critical for achieving the highest yields. Careful control of acidity, temperature and TSA/substrate ratios generally leads to isolated thioxanthenone yields from 75-92%.



(2)

(3)

EXPERIMENTAL

General.

All chemicals were purchased from Aldrich Chemical Co. and used without purification. Melting points are uncorrected.

Procedure for Synthesis of Cyclohexenothioxanthones Using 95% Sulfuric Acid.

Thiosalicylic acid (98%) (3.0 g, 20 mmoles) was slowly added into a mixture of 45 ml of sulfuric acid (95%, d = 1.840), and 1,2,3,4-tetrahydronaphthalene (20 ml, 0.15 mole). During the period of addition the temperature of the reaction mixture rose automatically to 55-60°. The resulting yellow suspension was then stirred for 2 hours at 30-35° followed by heating on a water bath at 85° for 1.5 hours. The reaction mixture changed from red to dark red on heating. It was then cooled to room temperature and poured slowly into 300 ml of ice-water. The resulting yellow precipitate was filtered and washed with water (3 x 50 ml). The yellow solid was stirred in aqueous 5% sodium hydroxide (100 ml) for 30 minutes, filtered, washed with water to remove alkali and dried under vacuum at 50° overnight to yield 3.58 g of crude product, mp 92-98°, yield 69%. Analysis (gc, DB-5, 50 m column, 290°) gave three peaks (73%, 19%, and 8.1%) and gc-ms analysis showed the compounds corresponding to each peak to have the same molecular weight (266).

Synthesis of Cyclohexenothioxanthones from 2,2'-Dithiosalicylic Acid.

Treatment of 2,2'-dithiosalicylic acid (6.0 g, 19.5 mmoles) in the manner described above gave 7.25 g of crude product, yield 65%. Analysis (gc) gave three peaks (73%, 18%, and 8.5%) and gc-ms analysis showed the compound constituting each peak to have the same molecular weight (266).

Procedure for Synthesis of Cyclohexenothioxanthones Using Sulfuric Acid/Fuming Sulfuric Acid.

Thiosalicylic acid (98%, 3.0 g, 20 mmoles) and 1,2,3,4-tetrahydronaphthalene (20 ml, 0.15 mole) were slowly added into a premixed acid solution composed of 40 ml of concentrated sulfuric acid (95%) and 8 ml of fuming sulfuric acid (27% free sulfur dioxide). Then stirring was started. The temperature of the reaction mixture rose automatically to 85-90°. The resulting red solution was then stirred for 2 hours at 85° then cooled to room temperature and poured slowly into 300 ml of ice-water. A yellow precipitate was formed. It was filtered and washed with water (3 x 50 ml). The yellow solid was stirred in aqueous 5% sodium hydroxide (100 ml) for 30 minutes, filtered, washed with water until alkali-free and dried under vacuum at 50° overnight to yield 5.3 g of crude product, mp 91-98°, yield 92%. Analysis (gc, 50 m DB-5 column, 290°) gave three peaks (71%, 20%, and 9.1%) and gc-ms analysis showed each of these compounds to have the same molecular weight (266).

Synthesis of Cyclohexenothioxanthones from 2,2'-Dithiosalicylic Acid.

Treatment of 2,2'-dithiosalicylic acid 6.0 g (19.5 mmoles) in the manner described above for mixed sulfur/fuming sulfuric acid gave 9.81 g of crude product, yield 85%. Analysis (gc) gave three peaks (72%, 20%, and 8.1%). Analysis (gc-ms) showed each peak to have the same molecular weight (266).

Isolation of **1**, **2** and **3** from the Crude Product.

The crude product (1.0 g) was dissolved in chloroform (3 ml). This solution then was added slowly into a chromatographic column (30 x 600 mm) packed with silica gel (KIESELGEL 40, 70-230 mesh ASTM, EM Reagents). Hexane was used as the eluting solvent at a flow rate through the chromatographic column of 2-2.5 ml/minute. The eluting solution was collected by a autocollector, analyzed by gc and then the fractions were evaporated using a rotary evaporator to give three pure compounds (their purity are each >98% by gc) with melting points of 107.5-108.0°, 180.0-181.0°, and 198.0-199.0°, respectively; for **1**, ^{1}H nmr (deuteriochloroform, 300 MHz): δ 8.39 (1H, d, J = 5.6 Hz), 7.4 (3H, m), 7.20-7.38 (2H, m), 3.42 (2H, s), 2.83 (2H, s), 1.82 (4H, s); for **2**, δ 8.60 (1H, d, J = 5.6 Hz), 8.23 (1H, s), 7.58-7.44 (3H, m), 7.26 (1H, s), 2.94 (4H, d, J = 10.1 Hz), 1.84 (4H, s); for **3**, δ 8.58 (1H, d, J = 5.6 Hz), 8.38 (1H, d, J = 5.6 Hz), 7.34-7.60 (3H, m), 7.18 (1H, d, J = 5.5 Hz), 2.78-2.89 (4H, m), 1.80-1.99 (4H, m); ^{13}C nmr: (C1 through C-4 positions listed in order, junctions to cyclohexane ring underlined), **1**, δ 142.5, 136.5, 129.5, 123.2; **2**, δ 126.9, 137.5, 143.3, 125.9; **3**, δ 126.3, 127.4, 136.7, 142.3). The absorption maximum in the uv spectra of the three isomers were **1**, λ max = 375 nm, **2**, λ max = 380 nm, **3**, λ max = 370 nm. Each gave a C=O stretch at 1630-1640 cm^{-1} in their ir spectra.

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