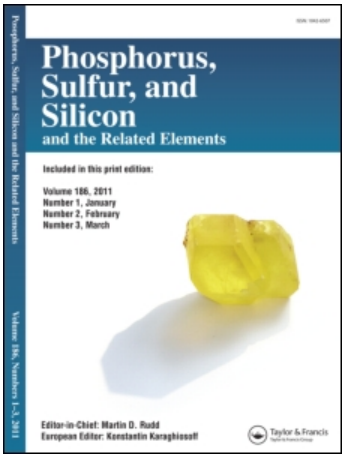

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SULFINIC ACIDS AND RELATED COMPOUNDS. 15. CONVENIENT METHODS FOR ESTERIFYING SENSITIVE SULFINIC ACID SALTS[1]

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In a study of conversions of sensitive sulfinate salts to esters, a trisulfide bissulfinate, $[NaO_2S(CH_2)_4S]_2S$ (**1**), was esterified with trialkyloxonium fluorborates. This procedure (Method A) was better for ethylation than use of ROH-HCl/$BF_3 \cdot (C_2H_5)_2O$ (Method B), but Method B was better for methylation. Disodium 3-sulfinopropanoate (**7**) was best dimethylated with $CH_3OH/BF_3 \cdot (C_2H_5)_2O$ without HCl (Method C). Method B or C gave satisfactory results with sodium *p*-toluenesulfinate (**3**), but ROH/$BF_3 \cdot (C_2H_5)_2O$ with the free acid was better than either (Method D). *p*-Tolylsulfonyldiazomethane did not esterify *p*-toluenesulfinic acid; only the sulfonate was isolated (**10**; 15–20% yield).

INTRODUCTION

Di- or trisulfide sulfinate salts are promising antiradiation drugs.[2a-f] Among these, the trisulfide bissulfinate **1** is of special interest.[2f]

$$\underset{\mathbf{1}}{NaO_2S(CH_2)_4SSS(CH_2)_4SO_2Na} \rightarrow \underset{\mathbf{2a},\ R=C_2H_5;\ \mathbf{2b},\ R=CH_3}{ROS(CH_2)_4SSS(CH_2)_4SOR} \qquad (1)$$

Such salts show variable hydration and present analytical problems,[2b] however, which might be alleviated by use of the esters (e.g. **2** in eq. 1). Furthermore, esters should be easier to handle and purify, and (being lipophilic) they should pass through membranes and be more active orally. Although the dimethyl ester **2b** was prepared earlier from **1** by the use of HCl in CH_3OH and then of diazomethane,[3] the diethyl ester **2a** also was needed for biological tests. We therefore sought mild and more convenient methods for preparing both **2a** and **2b**, using sodium *p*-toluenesulfinate (**3**) as a model, as well as for esterifying a carboxyalkanesulfinate as a model for sensitive synthons useful in convergent syntheses of di- and trisulfide sulfinates.[1]

RESULTS AND DISCUSSION

Methods reported for the preparation of sulfinic esters were considered unpromising for application to **1**,[4-6] which is sensitive to many reagents. Another possibility,

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trimethylsulfonium hydroxide, has been used for methylation of various acidic compounds,[7] but the NaOH produced would be expected to saponify esters; an alternative, the reaction of trimethylsulfonium iodide (**4**) with sodium *p*-toluenesulfinate (**3**), was tried in hot CH_3OH or DMF but gave only *p*-tolyl *p*-toluenethiolsulfonate, *p*-$CH_3C_6H_4SO_2SC_6H_4$-*p*-CH_3, and unchanged **3**; none of the ester **5** could be isolated.

p-$CH_3C_6H_4SO_2Na$ $(CH_3)_3SI$ *p*-$CH_3C_6H_4S(O)OCH_3$

3 **4** **5**

Many alkylations of sulfinic acid salts take place on the sulfur atom and result in the formation of sulfones rather than esters (such reactions occur with "soft" alkylating agents in the HSAB sense, in contrast to O-alkylation with "hard" agents).[8] Since triethyloxonium tetrafluoroborate (**6a**) is a "hard" agent which ethylates the arenesulfinate salt **3** in high yields,[9] **6** was tried with the alkanesulfinate salt **1**. Previously, only **6a** has been used and only with relatively stable arenesulfinates.[9] The salt **1** with three equivalents of **6a** afforded the ethyl ester **2a** in 80–90% yield (eq. 2, R = C_2H_5). However, washing the product (**2a**) with H_2O to remove

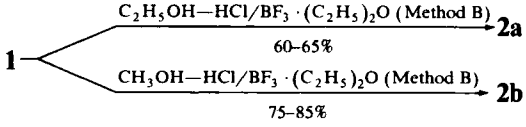
$$\mathbf{1} + R_3O^+BF_4^- (\mathbf{6a}, R = C_2H_5; \mathbf{6b}, R = CH_3) \xrightarrow{CH_2Cl_2, 0\text{–}5^\circ C (\text{Method A})} \mathbf{2a} \text{ or } \mathbf{2b} \quad (2)$$

inorganic acid lowered the yield and led to contamination of the **2a** (presumably by the sulfinic acid); a qualitative experiment in aqueous CH_3OH confirmed that **2a** is readily hydrolyzed, since the pH dropped rapidly during about an hour and became constant after about three hours. Fortunately, washing the solution of **2a** in CH_2Cl_2 with chilled saturated brine remarkably enhanced the yield and purity; this procedure also was important in other preparations. Trimethyloxonium tetrafluoroborate (**6b**) converted **1** into the methyl ester (**2b**; eq. 2, R = CH_3, 77% yield); rigorously pure **2b** could not be obtained (NMR), although the IR spectrum was identical with that of **2b** reported earlier.[3]

Since an alcohol with boron trifluoride etherate [$BF_3 \cdot (C_2H_5)_2O$] will esterify carboxylic acids[10] and sulfinamides,[11] this approach was explored with the toluenesulfinate **3** as a model. When the salt **3** was treated with one equivalent of $CH_3OH \cdot HCl$ and two equivalents of $BF_3 \cdot (C_2H_5)_2O$, the ester **5** was obtained in 71% yield (Method B). It is noteworthy that the salt **3** also reacted with three equivalents of $BF_3 \cdot (C_2H_5)_2O$ in CH_3OH, even in the absence of CH_3OH—HCl to afford **5** in 64% yield (Method C); use of only two equivalents reduced the yield significantly. The free acid with $BF_3 \cdot (C_2H_5)_2O$ in CH_3OH gave still better results (81%; Method D) and probably would be the method of choice in rare instances when a sulfinic acid is readily accessible and relatively stable.

Esterification of the salt **1** then was sought with CH_3OH—$HCl/BF_3 \cdot (C_2H_5)_2O$ (Method B). Reaction of **1** with two equivalents of CH_3OH—HCl and two of $BF_3 \cdot (C_2H_5)O$ afforded the dimethyl ester **2b** in good yield and purity (eq. 4). Method B seems superior to A for preparing the methyl ester **2b**. Method B also converted **1** to the ethyl ester **2a** (eq. 3), but here use of the triethyloxonium salt **6a** seems superior (Method A). Method C, the use of $CH_3OH/BF_3 \cdot (C_2H_5)_2O$ without HCl, was unsatisfactory with **1**, and no methyl ester (**2b**) could be isolated.

Derivatives of carboxyalkanesulfinates, such as **7**,[12] are of interest for flexible convergent syntheses in which di- and trisulfides may be connected with sulfinates by ester linkages formed between a hydroxyl function on one molecule and a carboxyl function on another.[1] The disodium salt **7** could be converted by Method C to the dimethyl ester **8** (eq. 5), which was synthesized earlier from the diacid dichloride;[1] use of HCl with **7** led to considerable decomposition and poor results (Method B).



(3)

(4)

$$NaO_2S(CH_2)_2CO_2Na \xrightarrow[66\%]{CH_3OH/BF_3 \cdot (C_2H_5)_2O\ (Method\ C)} CH_3OS(CH_2)_2COCH_3 \quad (5)$$

7 **8**

It is worth adding that distillation of **8** results in large losses and no improvement in purity,[1] owing to the thermal instability common to many sulfinic esters.

In the hope that use of the group p-$CH_3C_6H_4SO_2CH_2$ would lead to crystalline esters, p-toluenesulfinic acid (as a model) was treated with p-tolylsulfonyldiazomethane (p-$CH_3C_6H_4SO_2CHN_2$, **9**).[13] Instead of the desired ester, p-$CH_3C_6H_4SO_2CH_2OS(O)C_6H_4$-$p$-$CH_3$, however, only the corresponding sulfonate was obtained [p-$CH_3C_6H_4SO_2CH_2OS(O)_2C_6H_4$-$p$-$CH_3$, **10**; 15–20% yield]; this **10** was identical with **10** synthesized independently.[14] Since benzoic acid also was not esterified by **9**, we conclude that both benzoic and p-toluenesulfinic acid are too weakly acidic, unlike p-toluenesulfonic acid which is esterified;[14] the sulfonate **10** probably was formed by esterification of the sulfonic acid, which arose from oxidation or disproportionation of p-toluenesulfinic acid.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra, reported in parts per million (δ), are ^1H spectra obtained with a JEOL Model JNM-MH-100 spectrometer with $(CH_3)_4Si$ as an internal standard [or, in D_2O, with $(CH_3)_3Si(CH_2)_3SO_3Na$]. IR spectra were obtained with a Perkin-Elmer Model 727 spectrometer and KBr pellets or neat liquids. Elemental analyses were done by Galbraith Laboratories. Moist extracts usually were dried by using anhydrous $MgSO_4$, and solvents then were removed with a rotary-flask evaporator under reduced pressure. TLC was performed on Eastman Chromagram silica gel plates (catalog no. 13181), with 1 : 1 ethyl acetate-hexane, with visualization by I_2 vapor or UV; preparative TLC was done on 1000-μM Whatman PK6F silica gel plates. Methanolic HCl solutions were prepared by passing HCl gas into CH_3OH; the molarity was determined by titrating an aliquot in H_2O with standard NaOH and phenolphthalein. The boron trifluoride etherate [$BF_3 \cdot (C_2H_5)_2O$] was from Eastman Kodak (Yellow Label). The trisulfide bissulfinate **1** monohydrate was prepared as described earlier.[2c]

Use of Trialkyloxonium Tetrafluoroborates (Method A).

a. Diethyl 4,4'-trithiobis(butanesulfinate) (**2a**). A suspension of the trisulfide monohydrate **1** (1.00 g, 2.50 mmol) in CH_2Cl_2 (100 mL) was cooled to 0–5°C, and triethyloxonium tetrafluoroborate (**6a**; 1.42 g, 7.50 mmol) dissolved in CH_2Cl_2 (10 mL) was added during 30 min with good stirring. Inorganic precipitate was removed by filtration, and the CH_2Cl_2 solution was washed twice with 10 mL of chilled saturated brine. The organic layer then was dried, and the solvent was removed. Purification was achieved best by redissolving the semisolid ester in a minimum amount of CH_2Cl_2 and adding pentane to slight turbidity. This mixture was centrifuged, and the clear solution was diluted with sufficient pentane (ca. 300 mL) to

precipitate the ester. Decantation and drying at 2 torr for 24 h gave 0.80 g (81%) of **2a** as an oil: $n^{25}D$, 1.5493; NMR ($CDCl_3$) δ:4.20 (q,2 H), 2.96 (m,4 H), 1.96 (m,4 H), 1.40 (t,3 H); IR (neat): 2950, 1620, 1440, 1400, 1380, 1320, 1220, 1120, 1020, 1000, 890, 720 cm^{-1}. TLC showed one somewhat elongated spot (R_f 0.31; 1 : 1 ethyl acetate-hexane).

Anal. Calcd for $C_{12}H_{26}O_4S_5$: C, 36.54; H, 6.59; S, 40.60. Found: C, 35.85; H, 6.51; S, 41.00.

In order to gain insight into the ease of hydrolysis of the diethyl ester (**2a**), 1 g was dissolved in CH_3OH, and H_2O was added to a slight turbidity (ca 2 mL). The solution was stirred while the pH was monitored to assess the formation of the sulfinic acid. The values of pH at various times (min) were: 6.8 (initial), 6.2 (15), 5.8 (30), 4.8 (60), 4.3 (90), 3.9 (120), 3.6 (150), 3.5 (180), 3.6 (240).

(b) Dimethyl 4,4'-Trithiobis(butanesulfinate) (**2b**). Much as in (a), salt **1** · H_2O (1.00 g, 2.50 mmol), suspended in CH_2Cl_2 with cooling at 0–5°C, when treated with trimethyloxonium fluoroborate (**6b**, 1.10 g, 7.50 mmol) partially dissolved in CH_2Cl_2 (150 mL), with stirring for 1 h, with isolation as for **2a**, afforded **2b** as a viscous oil (0.70 g; 77%): $n^{25}D$ 1.5564 (lit.[3] $n^{25}D$ 1.5575). The ^1H-NMR spectrum of this **2b** agreed with a previous report,[3] although there was indication of a little impurity that could not be removed by TLC or column chromatography (where only 1,2-dithiane 1,1-dioxide was isolated, as a decomposition product). The IR spectrum of the ester was congruent with that of **2b** prepared using diazomethane.[3]

Use of Boron Trifluoride Etherate in Alcohols. Methods B, C, and D.

a. Methyl p-toluenesulfinate (**5**). In Method B, sodium *p*-toluenesulfinate (**3**, 1.50 g, 8.4 mmol), used as a model sulfinate, was dissolved in CH_3OH (25 mL) and CH_3OH—HCl (0.7640 M, 11.0 mL, 8.40 mmol) was added, followed by $BF_3 \cdot (C_2H_5)_2O$ solution (2.3 g, 16.8 mmol). The reaction mixture was stirred for 2 h at ca. 25°C, after which most of the CH_3OH was removed and 100 mL of H_2O added. An oil separated, which was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with a cold aqueous solution of $NaHCO_3$. Drying and removal of solvent gave **5** as an oil (1.00 g, 71%): $n^{25}D$, 1.5380 (lit.[15], 1.5370). The IR and NMR spectra were identical with those of authentic **5** prepared earlier,[15] and TLC gave a single clean spot.

By means of Method C, **5** also was obtained from the salt **3** by stirring **3** (1.50 g, 8.4 mmol) in CH_3OH (25 mL) containing $BF_3 \cdot (C_2H_5)_2O$ (3.5 g, 25.2 mmol) for 2 h at ca. 25°C. Isolation as described above led to 0.90 g (64%) of the ester **5**: $n^{25}D$ 1.5382. When the ratio of $BF_3 \cdot (C_2H_5)_2O$ to **3** was reduced from 3 : 1 to 2 : 1, the yield decreased by ca. 20%.

In Method D, **5** also was formed when free *p*-toluenesulfinic acid (1.50 g, 9.6 mmol) dissolved in CH_3OH (25 mL) was allowed to react with $BF_3 \cdot (C_2H_5)_2O$ (2.70 g, 19.2 mmol) for 2 h at ca 25°C. Isolation as before gave 1.30 g (81%) of **5**: $n^{25}D$ 1.5376.

b. Dimethyl 4,4'-trithiobis(butanesulfinate) (**2b**). Method B. The salt **1** · H_2O (8.0 g, 20.0 mmol) was dissolved in CH_3OH (150 mL), the solution was cooled to 0–5° C, and CH_3OH—HCl (52.3 mL, 0.764 M, 40.0 mmol) was added gradually. Then $BF_3 \cdot (C_2H_5)_2O$ (5.6 g, 40 mmol) was added dropwise at ca. 25°C, and the mixture was stirred for 2 h. CH_3OH was removed, and the residue was diluted with cold saturated brine (100 ml). An oil separated, which was extracted with CH_2Cl_2. Washing with two 50 mL portions of cold brine, drying, removal of solvent, and drying under vacuum afforded 6.2 g (85%) of the diester **2b** as a relatively pure viscous oil: $n^{25}D$ 1.5569. Considerable losses occurred when **2b** was chromatographed on silica gel, especially if as much moisture as possible was not removed from the silica gel beforehand. Thus 4 g of the oil (**2b**) was chromatographed on 150 g of silica gel (dried at 115–120°C for 4 h and cooled in a desiccator) in a column 30 mm in diameter by the use of 1 : 1 ethyl acetate-hexane; 1.0 g of **2b** was obtained (there was still considerable loss due to decomposition on the column). The IR and ^1H NMR spectra of this **2b** were congruent with those of **2b** prepared using diazomethane:[3] $n^{25}D$, 1.5581.

c. Diethyl 4,4'-trithiobis(butanesulfinate) (**2a**). Method B. The **1** · H_2O (500 mg, 1.25 mmol) was dissolved in 10 mL of C_2H_5OH, after which essentially the procedure of (b) was followed, with use of 3.8 mL (2.45 mmol) of 0.6450 M C_2H_5OH—HCl and 0.35 g (2.50 mmol) of $BF_3 \cdot (C_2H_5)_2O$. After the stirring period (4 h), removal of most of the C_2H_5OH, and dilution with cold brine (50 mL), **2a** separated as an oil. The methylene chloride extract was washed twice with 10 ml of cold brine and dried. Removal of solvent and drying under vacuum afforded 0.30 g (60%) of the diester **2a** as viscous oil: $n^{25}D$ 1.5483. TLC gave a somewhat elongated single spot. The IR and NMR spectra were congruent with those of **2a** prepared using the triethyloxonium salt as described above.

d. Dimethyl 3-sulfinopropanoate (**8**). (Method C). Disodium 3-sulfinopropanoate[12] (**7**, 1.00 g, 5.49 mmol) was suspended in CH_3OH (20 mL). This solution was cooled to 0°C and $BF_3 \cdot (C_2H_5)_2O$ (2.30 g, 16.47 mmol) was added dropwise at ca. 25°C with constant stirring during 2 h. Most of the CH_3OH was removed, the residue was diluted with cold saturated brine, and the oil that separated was extracted with

CH_2Cl_2. Removal of solvent and drying under vacuum afforded 0.60 g (66%) of the diester **8** as an oil: $n^{25}D$ 1.4612; lit.[1] $n^{23}D$ 1.4605. TLC gave a single spot (with a small amount of tailing indicating decomposition). The IR and NMR spectra of the ester **8** thus obtained were congruent with those of **8** as reported.[1]

Attempted Esterification with p-Tolylsulfonyldiazomethane (**9**). A solution of **9** (1.30 g, 6.63 mmol)[13] and *p*-toluenesulfinic acid (1.03 g, 6.63 mmol) in $(C_2H_5)_2O$ (100 mL) was stirred at ca. 25°C overnight. The color changed from bright yellow to almost colorless. Removal of $(C_2H_5)_2O$ and recrystallization of the residue from CH_3OH afforded *p*-tolylsulfonylmethyl *p*-toluenesulfonate (**10**) as a colorless solid (0.40 g, 18%): mp 112–114°C (no analysis previously reported, or physical constants except lit.[14] mp 109°–112°C); IR (KBr): 2930, 1920, 1720, 1600, 1490, 1440, 1370, 1330, 1300, 1180, 1150, 1080, 1010, 920, 800, 740 cm^{-1}; NMR ($CDCl_3$) δ: 7.7 – 7.3 (m, 8 H), 4.9 (s, 2 H), 2.4 (s, 6 H). The mp, IR, and NMR spectra of **10** were identical with those of **10** obtained by the reported reaction of *p*-toluenesulfonic acid and **9**.[14].

Anal. Calcd for $C_{15}H_{16}O_5S_2$: C, 52.92; H, 4.74; S, 18.84. Found: C, 52.83; H, 4.50; S, 18.81.

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