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Christopher G. Andrews[a]; Richard F. Langler[a]
[a] Department of Chemistry, Mount Allison University, Sackville, New Brunswick, Canada

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Reactions of α-sulfone disulfides with sulfinate anions

Christopher G. Andrews and Richard F. Langler*

Department of Chemistry, Mount Allison University, Sackville, New Brunswick, Canada

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Degenerate substitution reactions (at carbon) between the appropriate sulfinic acid salts and tosylmethyl methyl or mesylmethyl methyl disulfides have formed symmetrical disulfone disulfides in moderate yields. These products form in a redox process involving sulfinate anions following partial skeletal disassembly arising from rupture of the SS bond. The reaction of mesylmethyl methyl disulfide and sodium methanesulfinate provides a natural product, dysoxysulfone, in low yield.

Keywords: α-sulfone disulfides; SS bond rupture; mesylmethyl disulfide; dysoxysulfone; α-benzoate disulfide

1. Introduction

Recently (*1*), we have described the first example of substitution reactions in which RSO_2 groups [R = CH_3 or *p*-$CH_3(C_6H_4)$] were displaced from tetrahedral carbon (see Scheme 1).

The focus of the initial report, once the reactions were shown to be viable, was establishing the equilibrium amounts of **1** and **2**. Equilibrium was established after 96 h at 50 °C (aqueous acetone) at which point a modest amount of an unidentified product (showed, *inter alia*, a singlet at δ 4.3 in the ^{1}H NMR) had formed. In attempting to isolate/identify the unknown compound(s), the chemistry in the current report was simplified by examining degenerate substitution reactions (at carbon, as shown in Scheme 2) on α-sulfone disulfides **3**.

Our mechanistic proposal for the Scheme 1 chemistry featured S_N2 substitution at carbon. An alternative proposal, suggested by a referee of the earlier paper (*1*), assumed nucleophilic attack by sulfinate anions at the disulfide linkage of **1** or **2** producing α-sulfonylmethyl mercaptide anions **4** which, in the referee's proposal, would dissociate reversibly, as shown in Scheme 3.

Thioformaldehyde is efficiently trapped by mercaptide anions (*2*, *3*). Consequently, Scheme 3 leads to the expectation that an assortment of thioformaldehyde homologues of **4** (see **5**) should have formed and products derived from them should have been isolated. No such products were observed.

$$RSO_2(CH_2S)_nCH_2S^{\ominus}$$

5

*Corresponding author. Email: langler.rick@gmail.com

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$$p\text{-}CH_3(C_6H_4)SO_2CH_2SSCH_3 \ (\mathbf{1}) + CH_3SO_2Na \rightleftharpoons p\text{-}CH_3(C_6H_4)SO_2Na + CH_3SO_2CH_2SSCH_3 \ (\mathbf{2})$$

Scheme 1.

$$RSO_2CH_2SSCH_3 \ (\mathbf{3}) + RSO_2Na \rightleftharpoons RSO_2Na + RSO_2CH_2SSCH_3 \ (\mathbf{3})$$

R = CH_3 or p-$CH_3(C_6H_4)$

Scheme 2.

$$RSO_2CH_2S^{\ominus} \ (\mathbf{4}) \rightleftharpoons CH_2S + RSO_2^{\ominus}$$

Scheme 3.

Hence, a second goal for the current examination of simpler degenerate substitutions (see Scheme 2) was to enhance the opportunity to observe modest yields of chain-extended products (derived from **5**).

2. Results and discussion

Results, from the first experiment in the present series, are presented in Scheme 4.

In accord with our earlier report (*1*), the reaction produced a significant amount of unchanged sulfone disulfide **1** along with a very modest amount of methyl *p*-toluenethiosulfonate **7**. A previously unknown compound was isolated, in pure form, from column fractions. Spectroscopic characterization revealed, *inter alia*, ^{1}H NMR signals appropriate for the tosyl group along with a methylene signal at δ 4.31 and a molecular ion at m/e 402 in the mass spectrum along with daughter ions associated with the tosyl group. The spectroscopic data, *inter alia*, supports the disulfone disulfide structure **6** (Scheme 4) which was assigned to the new compound. This report establishes the identity (*i.e.* **6** in Scheme 4) of the previously unidentified minor product in our earlier work (see Scheme 1 and Duffy and Langler (*1*)).

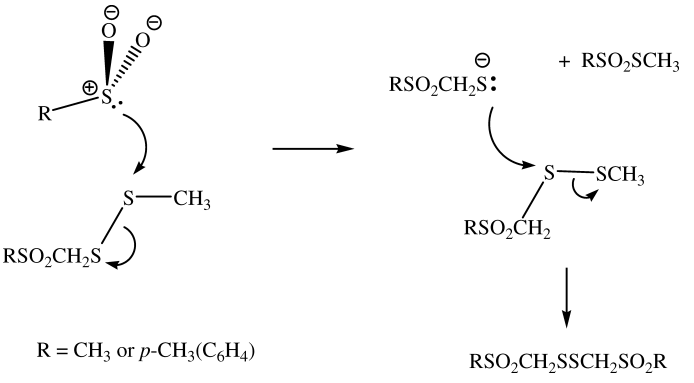
The formation of the disulfone disulfide **6** raises an interesting problem. An apparently straightforward explanation for the formation of **6** would invoke nucleophilic attack by sulfinate anions at the thiomethyl-bearing sulfenyl sulfur (see Scheme 5) in the final step.

$$p\text{-}CH_3(C_6H_4)SO_2CH_2SSCH_3 \ (\mathbf{1}) + p\text{-}CH_3(C_6H_4)SO_2^{\ominus}$$

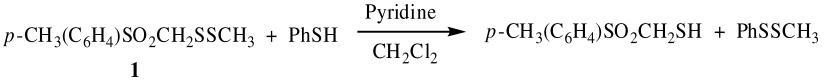
Acetone / Water; Δ, 22 h

$$(p\text{-}CH_3(C_6H_4)SO_2CH_2S)_2 \ (\mathbf{6}) \ (17\%) + p\text{-}CH_3(C_6H_4)SO_2SCH_3 \ (\mathbf{7}) \ (2\%) + \mathbf{1} \ (59\%)$$

Scheme 4.



Scheme 5.



1

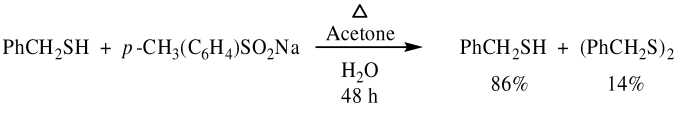
Scheme 6.

The problem with the proposal in Scheme 5 is that available evidence suggests that mercaptide anions attack exclusively at methyl-bearing sulfenyl sulfur. An earlier example (*4*) is provided in Scheme 6.

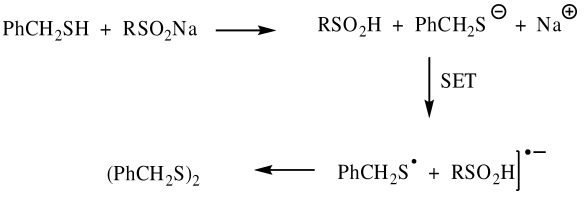
Previous exploration of reactions involving sulfonate esters and mercaptide anions (*5*) uncovered unexpectedly facile redox reactions, in which selected aryl sulfonate esters appear to act as single-electron acceptors (SET mechanism). An experiment, intended to assess a related possibility for the reaction shown in Scheme 4, is presented in Scheme 7 (relative yields shown therein).

Included in a number of mechanisms which may be entertained for Scheme 7, is the possibility that low concentrations of benzyl mercaptide anions and *p*-toluenesulfinic acid might produce disulfide product by SET (see Scheme 8 for a proposal).

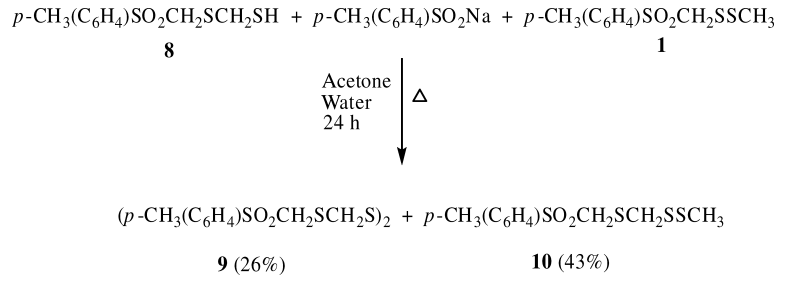
Another test of the mechanistic alternatives in Schemes 5 and 8 was carried out (see Scheme 9). Consistent with the foregoing discussion, **1** served exclusively as a thiomethylating agent and **8** was converted cleanly to the symmetrical disulfide **9** and the disulfide **10**.



Scheme 7.



Scheme 8.



Scheme 9.

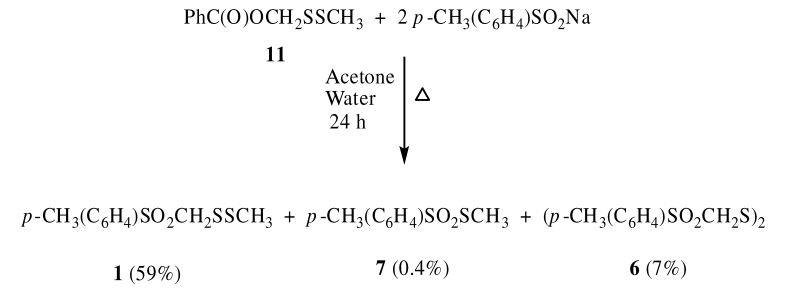
Regardless which redox mechanism is operating, the mechanism in Scheme 5 is inconsistent with available information. The symmetrical disulfides **6** (Scheme 4) and **9** (Scheme 9) likely form by means of a redox pathway involving sulfinate anions and not, in the case of **6**, by nucleophilic attack at the less electrophilic (more hindered, poorer leaving group) sulfenyl sulfur in **1**.

In a reaction designed to provide more efficient access to product mixtures like the one shown in Scheme 4, the benzoate disulfide **11** (synthetic precursor for **1**) was treated with two equivalents of sulfinate anions (see Scheme 10).

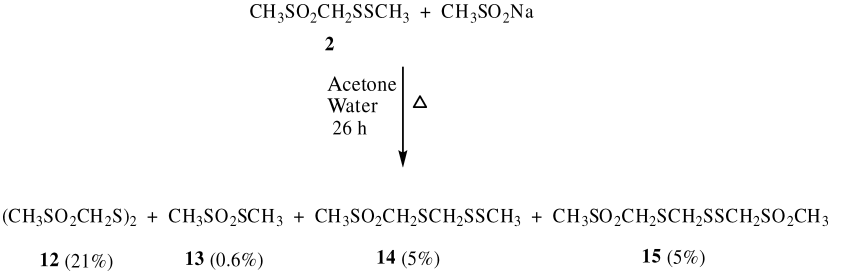
Previous results (*1*) support the view that *p*-toluenesulfinate anions are superior (somewhat softer) thiophiles than are methanesulfinate anions. Current results are consistent with that view.

Methanesulfinate anions converted the α-sulfone disulfide **2** into the expected disulfone disulfide **12** and a pair of chain-extended products (see Scheme 11).

The results in Scheme 11 conform to the view that methanesulfinate anions (somewhat harder bases) attack at the disulfide linkage a little less efficiently than *p*-toluenesulfinate anions do and that α-mesylmethyl mercaptide anions dissociate to furnish thioformaldehyde (Scheme 3) more readily, thus leading to chain-extended products with greater facility.



Scheme 10.



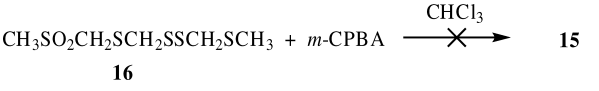
Scheme 11.

The disulfone disulfide **12** is a known natural product (*6*, *7*). The chemistry presented in Scheme 11 shows the final reaction of a three-step synthesis of **12** from dimethyl disulfide [$(CH_3S)_2 \rightarrow$ **11** $\rightarrow$ **12**] which is comparable to a published synthesis (*8*).

The disulfone disulfide **15** (dysoxysulfone) has been isolated from Fijian mahogany plants (*9*). Thereafter, Block *et al.* (*3*) published a four-step synthesis of dysoxysulfone **15**. Our attempts to obtain dysoxysulfone from dideoxydysoxysulfone **16** with several peroxide-based redox systems were unsuccessful (*10*) (see Scheme 12 for the last of our attempts).

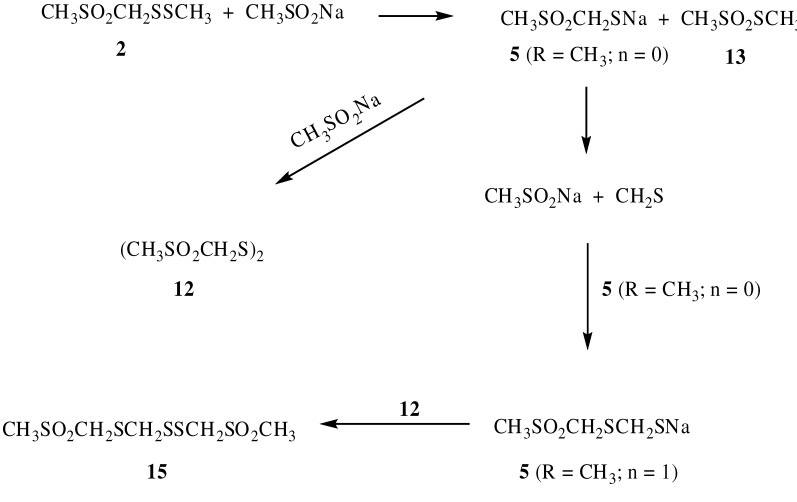
Dysoxysulfone **15** formation, in Scheme 11, must proceed in a multistep fashion. A proposed pathway is provided in Scheme 13.

As an aside, **14** (Scheme 11) could form by attack on **2** or **13** to thiomethylate **5** ($R = CH_3$; $n = 1$).

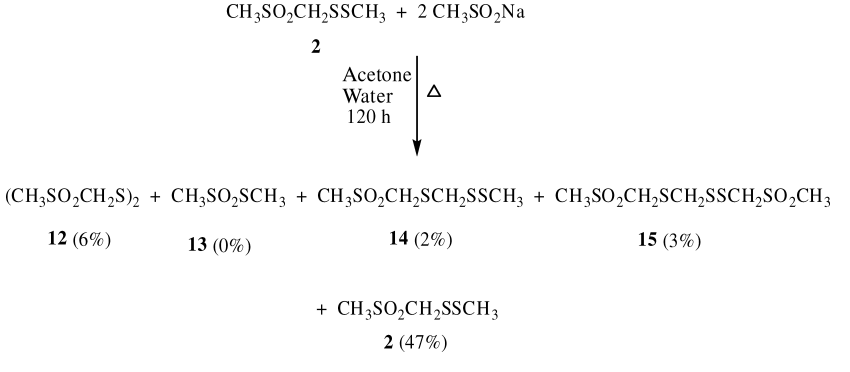


16

Scheme 12.



Scheme 13.



Scheme 14.

In an unsuccessful effort to increase the yield of dysoxysulfone **15**, the α-sulfone disulfide **2** was subjected to a pair of reactions in which both reaction time and the amount of sodium methanesulfinate were increased. Results from the second attempt are shown in Scheme 14.

3. Conclusions

An examination of degenerate substitutions (at carbon) involving α-sulfone disulfides and sulfinate anions has revealed the formation of previously unrecognized symmetrical disulfone disulfides (*i.e.* **6** in Scheme 4 and **12** in Scheme 11). A mechanistic proposal featuring SET has been advanced (see Scheme 8).

Consistent with past experience (*1*), reactions employing softer toluenesulfinate anions and α-sulfone disulfides give fewer products in higher yields (*c.f.* Schemes 4 and 11). Substitutions employing harder methanesulfinate anions and α-sulfone disulfides give more complex product arrays which feature chain-extended thioformaldehyde homologues (see Scheme 11).

Reactions of α-mesylmethyl disulfide **2** with methanesulfinate anions in warm aqueous acetone produce, *inter alia*, the natural product dysoxysulfone **15**, in very modest yield ($\leq$5%, see Scheme 11). A complete pathway proposal for the formation of **15** is provided in Scheme 13.

4. Experimental

4.1. *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. Melting point determinations were done with a Gallenkamp MFB-595 capillary melting point apparatus and are uncorrected.

4.2. *Reaction of* p-*toluenesulfonylmethyl methyl disulfide 1 with sodium* p-*toluenesulfinate*

A solution of sodium *p*-toluenesulfinate (0.21 g, 1.19 mmol) in acetone (4 mL) and water (1 mL) was added to sulfone disulfide **1** (0.26 g, 1.19 mmol). The reaction mixture was swirled gently and immersed into a preheated oil bath (50°C) for 22 h. Chloroform (100 mL) was added and the resultant mixture washed with water (50 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated, affording a yellow oil. Crude product was chromatographed on silica gel (26 g) using 3:1 petroleum ether/chloroform (30– 25 mL fractions), followed by 1:1 petroleum ether/chloroform (25 mL fractions). Fractions 41–42 were combined and concentrated giving methyl *p*-toluenethiosulfonate **7** (3 mg, 14 μmol, 1%) which had the properties described elsewhere (*11*). Fraction 43 contained unchanged sulfone disulfide **1** (4 mg) and thiosulfonate **7** (2 mg, 10 μmol, 0.8%). Fractions 44–47 were combined and concentrated to afford unchanged sulfone disulfide **1** (*2*, *4*)(134 mg). Fraction 48 provided the sulfone disulfide **1** (21 mg) and di(*p*-toluenesulfonylmethyl) disulfide **6** (16 mg, 52 μmol, 4%). Fractions 50–55 were combined and concentrated yielding clean disulfone disulfide **6** (60 mg, 144 μmol, 12.5%). The sulfone disulfide **6** (total yield: 17%) was recrystallized from methanol (mp 156.2–156.4 °C). $C_{16}H_{18}O_4S_4$ requires C, 47.7; H 4.5. Found: C, 47.4; H 4.6. **6** had IR 1311, 1149 cm^{-1}. ^{1}H NMR (270 MHz) δ 2.45 (s, 6H), 4.31 (s, 4H), 7.38 (*d*, $J = 7.9$ Hz, 4H), 7.80 (*d*, $J = 7.9$ Hz, 4H). ^{13}C NMR

δ 21.8, 63.6, 129.0, 130.1, 134.5, 145.6. MS (DIP): 402 ($M^{+\cdot}$, 2%), 247 (27%), 155 (22%), 139 (100%), 91 (79%).

4.3. *Reaction of benzyl thiol with sodium* p-*toluenesulfinate*

A solution of benzyl thiol (0.18 g, 1.48 mmol, homogeneous by GCMS and ^{1}H NMR) in acetone (4 mL) was added to a solution of sodium *p*-toluenesulfinate (0.27 g, 1.49 mmol) in water (1 mL). The reaction mixture was warmed (50 °C) for 48 h. Water (50 mL) was added and the resultant mixture washed with chloroform (3–100 mL aliquots). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product (0.19 g) contained benzyl thiol and dibenzyl disulfide as indicated by ^{1}H NMR (270 MHz) and GCMS. After integration of the ^{1}H NMR, a calculation using a previously-published equation (*12*) established the yield of the disulfide as 14% (26 mg, 0.10 mmol).

4.4. *Reaction of* p-*toluenesulfonylmethyl mercaptomethyl sulfide 8 with* p-*toluenesulfonylmethyl methyl disulfide 1 and sodium* p-*toluenesulfinate*

p-Toluenesulfonylmethyl mercaptomethyl sulfide **8** (0.27 g, 1.20 mmol) (*13*), sodium *p*-toluenesulfinate (0.21 g, 1.20 mmol) and *p*-toluenesulfonylmethyl methyl disulfide **1** (*2,4*) (0.27 g, 1.19 mmol) were added to acetone (4 mL) and water (1 mL). The reaction mixture was swirled and warmed (50 °C) for 24 h. Water (100 mL) was added and the resultant mixture extracted with chloroform (2–50 mL aliquots). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated, affording a pale yellow oil (0.54 g). Crude product was chromatographed on silica gel (55 g) employing chloroform (50 mL fractions) for elution. Fractions 6-8 were combined and concentrated to give sulfone sulfide disulfide **10** (0.15 g, 0.51 mmol, 43%). The disulfide **10** has been fully characterized elsewhere (*13*). Fractions 9–11 were combined and concentrated to provide unchanged mercaptan **8** (31 mg, 9%). Fractions 13–14 provided impure disulfone bissulfide disulfide **9** (0.223 g). Recrystallization from methanol (13 mL) afforded **9** (77 mg, 0.15 mmol, 26%, mp 117–118 °C). $C_{18}H_{22}O_4S_6$ requires C, 43.7; H, 4.5. Found: C, 43.8; H, 4.3. **9** had IR 1299, 1190 cm^{-1}. ^{1}H NMR (270 MHz) δ 2.45 (s, 6H), 4.10 (s, 4H), 4.16 (s, 4H), 7.36 (*d*, $J = 8.1$ Hz, 4H), 7.81 (*d*, $J = 8.1$ Hz, 4H). ^{13}C NMR δ 21.7, 42.1, 53.5, 128.9, 130.0, 134.6, 145.5. MS (DIP): 293 (M^+-$TsCH_2S$, 3%), 215 ($TsCH_2SCH_2$, 31%), 155 (15%), 139 (100%), 91 (43%).

4.5. *Reaction of benzoate disulfide 11 with sodium* p-*toluenesulfinate*

A solution of sodium *p*-toluenesulfinate (0.42 g, 2.38 mmol) in water (1.5 mL) and acetone (6 mL) was added to benzoate disulfide **11** (*14*) (0.26 g, 1.19 mmol). The reaction mixture was warmed (50 °C) for 48 h. Water (50 mL) was added and the ensuing mixture was extracted with chloroform (2–50 mL aliquots). The combined organic layers were washed with 2.5% W/V sodium hydroxide (2–50 mL portions). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated, affording a pale yellow oil (0.194 g). The crude was chromatographed on silica gel (20 g) employing 3:1 petroleum ether/chloroform (60–20 mL fractions) followed by chloroform (20 mL) fractions. Fraction 4 was concentrated giving thiosulfonate **7** (1 mg, 0.005 mmol, 0.4%). Fractions 47–53 were combined and concentrated to provide the sulfone disulfide **1** (0.18 g, 0.71 mmol, 59%). Fractions 64–65 were concentrated and combined to furnish the disulfone disulfide **6** (16 mg, 0.040 mmol, 7%).

4.6. *Reaction of mesylmethyl methyl disulfide 2 with sodium methanesulfinate (26 h)*

Sodium methanesulfinate (0.15 g, 1.49 mmol) was dissolved in water (1 mL) and the solution added to the sulfone disulfide **2** (0.256 g, 1.49 mmol) in acetone (4 mL). The reaction mixture was warmed (50 °C) for 26 h. Water (50 mL) was added and the resultant mixture washed with chloroform (2–100 mL portions). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent evaporated to give crude product (0.198 g). The crude product was dissolved in methanol (1 mL). After 18 h, the disulfone disulfide **12** (31 mg) was filtered off and shown to be identical to authentic material (*3,8*) by ^{1}H NMR, ^{13}C NMR and mp. Solvent was evaporated from the mother liquor and the residue chromatographed on silica gel (20 g) employing chloroform (20 mL fractions) for elution. Fraction 6 gave a mixture which showed appropriate signals in the ^{1}H NMR and appropriate mass spectra in the GCMS to establish that it contained methyl methanethiosulfonate **13** (1 mg, 0.009 mmol, 0.6%) (*15*), the starting sulfone disulfide **2** (17 mg) and the sulfone sulfide disulfide **14** (8 mg, 0.035 mmol, 5%) (*10*). Fractions 7–11 were combined and concentrated affording starting sulfone disulfide **2** (0.104 g, total 0.121 g, 47%). Fractions 27–28 and 32–46 were combined and concentrated furnishing a mixture of the symmetrical disulfone disulfide **12** (8 mg, total 39 mg, 0.156 mmol, 21%) and dysoxysulfone **15** (4.6 mg). Fractions 29–31 furnished clean dysoxysulfone **15** (2 mg, total 6.6 mg, 0.22 mmol, 5%; mp 104–105 °C; lit. (*3,9*), 97–99 °C; 107–108 °C). Dysoxysulfone **15** had ^{1}H NMR (270 MHz) δ 3.02 (s, 3H), 3.05 (s, 3H), 4.02 (s, 2H), 4.16 (s, 2H), 4.40 (s, 2H). ^{13}C NMR δ 38.7, 39.3, 41.9, 51.6, 61.3. MS (DIP): 217 ($M^+ - CH_3SO_2$, 3%), 171 ($M^+ - CH_3SO_2CH_2S$, 19%), 139 ($CH_3SO_2CH_2S{=}CH_2^+$, 100%), 93 ($CH_3SO_2CH_2^+$, 24%).

4.7. *Reaction of mesylmethyl methyl disulfide 2 with sodium methanesulfinate (120 h)*

Sodium methanesulfinate (0.30 g, 2.98 mmol) and the sulfone disulfide **2** (0.26 g, 1.49 mmol) were reacted (120 h) and worked up as described in the preceding experiment. Chromatography ($CHCl_3$ elution), as above, furnished unchanged **2** (30%), the sulfone sulfide disulfide **14** (2%), dysoxysulfone **15** with persistent impurities (<3% yield **15**), and the disulfone disulfide **12** (6%).

Acknowledgement

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