Formation of 2,2-difluoro-3-hydroxymethylbenzo-1,4-oxathianes from 2-(α-trifluoromethylvinylthio)phenols

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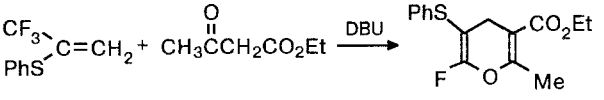
It is shown that 2,2-difluoro-3-hydroxymethylbenzo-1,4-oxathianes are formed together with 3-trifluoromethylbenzo-1,4-oxathianes when *ortho*-(α-trifluoromethyl-β-chloroethylthio)-phenols are boiled with excess aqueous alkali. The mechanism of the reaction is discussed.

Key words: *ortho*-(α-trifluoromethyl-β-chloroethylthio)phenols, *ortho*-(α-trifluoromethylvinylthio)phenols, 3-trifluoromethylbenzo-1,4-oxathianes, 2,2-difluoro-3-oxymethylbenzo-1,4-oxathianes.

In the preceding paper[1] it was shown that when *ortho*-(α-trifluoromethylvinylthio)phenols are heated with aqueous alkali (70—80 °C), they are converted to 3-trifluoromethylbenzo-1,4-oxathianes as a result of intramolecular heterocyclization. Analogous products were also obtained from 2-(α-trifluoromethyl-β-chloroethylthio)phenols that readily eliminate HCl when heated (~70 °C) with excess alkali. On the other hand, it is known that the heterocyclization of phenyl-α-trifluoromethylvinyl sulfide with ethyl acetoacetate in the presence of diazabicycloundecene (DBU) involves defluorination of the intermediate carbanion.[2]

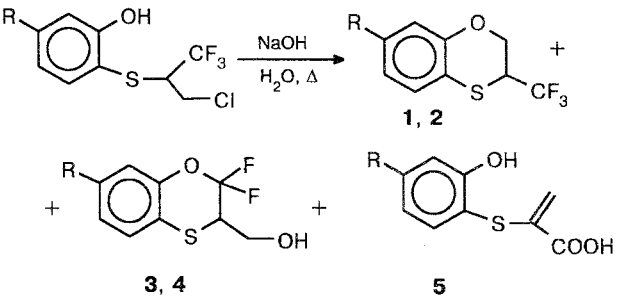


In the present work we considered the possible analogous transformations of 2-(α-trifluoromethylvinylthio)-phenols.

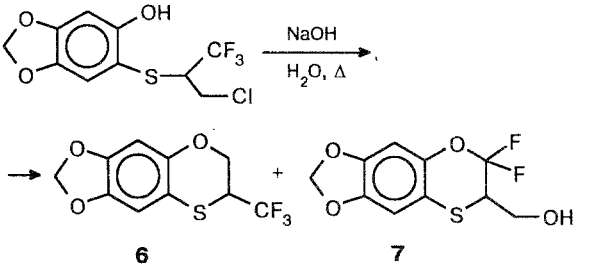
It has been shown that boiling 5-fluoro- and 5-methoxy-2-(α-trifluoromethyl-β-chloroethylthio)-phenols with excess alkali not only yields the corresponding 3-fluoromethylbenzo-1,4-oxathianes (**1**, **2**), but also affords 2,2-difluoro-3-hydroxymethylbenzo-1,4-oxathianes (**3**, **4**) in yields up to 30 %. In the case of 5-methoxy-2-(α-trifluoromethyl-β-chloroethylthio)-phenol, 2-(α-carboxyvinylthio)-5-methoxyphenol (**5**) was also isolated in low yield.

Analogously, in a boiling alkali solution, 4,5-methylenedioxy-2-(α-trifluoromethyl-β-chloroethylthio)phenol forms tricycic compounds **6** and **7** in 33 % and 21 % yields, respectively.

The mixture of 2- and 4-(α-trifluoromethyl-β-chloroethylthio)-1-naphthols that was obtained from



R = F (**1**, **3**); MeO (**2**, **4**, **5**)



1-trifluoromethyl-2-chloroethylsulfenylchloride and 1-naphthol, resulted in oxathianes **8** and **9** under the same conditions.

Therefore, the formation of 2,2-difluoro-3-hydroxymethylbenzo-1,4-oxathianes from 2-(α-trifluoromethylvinylthio)phenols in boiling alkali solution has a general character. It is most probable that the reaction mechanism involves the primary attack of a hydroxy-anion at the C=C bond of the starting compound, stabilization of

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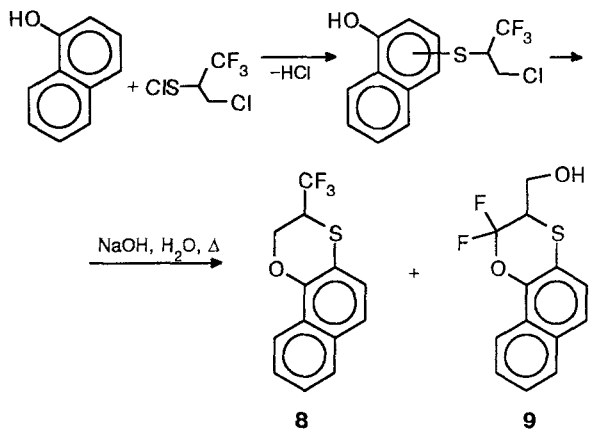
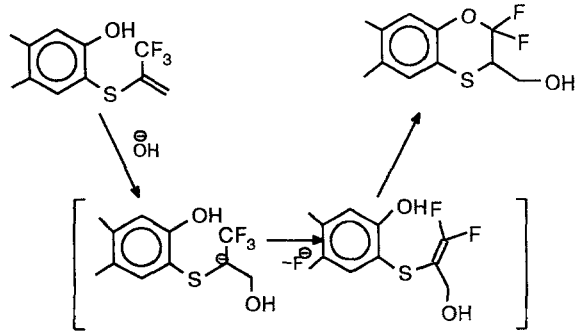
Table 1. Yields, characteristics, and elemental analysis data of compounds **1**, **3**—**5** and **7**—**9**

Compound	Yield (%)	M.p./°C B.p./°C (*p* / Torr)	R_f (CCl_4:acetone)	n_D^{20}	Found (%) Calculated			Molecular formula
					C	H	F(S)	
1	58	62—63	0.49 (CCl_4)	—	45.50 45.38	2.53 2.52	31.79 31.93	$C_9H_6F_4OS$
3	30	93—95 (1)	0.61 (4:1)	1.4817	45.81 45.76	2.96 2.97	24.07 24.15	$C_9H_7F_3O_2S$
4	17	142—143 (1)	0.51 (4:1)	1.4856	48.54 48.39	4.04 4.03	15.25 15.32	$C_{10}H_{10}F_2O_3S$
5	6	140 (decomp.)	0.30 (3:1)	—	52.85 53.09	4.28 4.42	(13.90) (14.16)	$C_{10}H_{10}O_4S$
7	21	69—70	0.44 (4:1)	—	45.92 45.80	3.08 3.05	14.34 14.50	$C_{10}H_8F_2O_4S$
8	20	60—61	0.34 (5:1)	—	57.49 57.77	3.30 3.33	21.02 21.11	$C_{13}H_9F_3OS$
9	13	67—68	0.52 (4:1)	—	58.32 58.21	3.74 3.73	14.12 14.18	$C_{13}H_{10}F_2O_2S$



8 **9**

the generated carbanion by elimination of the fluoride ion, and cyclization of the intermediate difluoromethylene compound.



The formation of compound **5** can be explained by dehydrofluorination of oxathiane **2**, which has a high CH-acidity, to 3-oxycarbonyl-7-methoxybenzo-1,4-oxathiane and by the recyclization of the latter.

The structure of oxathianes **3**, **4**, **7**, and **9** was established according to their spectral data. For example, the ^1H NMR spectra of these compounds exhibit signals for the OH group at 4.50 ppm in $(CD_3)_2CO$ or 3.10 ppm in CD_3CN. The ^{19}F NMR spectra are also informative and have specific signals for two non-equivalent fluorine atoms at −13.7 to −14.4 and −3.6 to −3.9 ppm with the spin-spin coupling constant ~152 Hz.

Experimental

The ^1H and ^{19}F NMR spectra were recorded on a Bruker WR-200SY spectrometer with working frequencies 200.12 and 188.31 MHz, respectively. Chemical shifts were determined using TMS (^1H, internal standard) and CF_3COOH (^{19}F, external standard) as references. The R_f values of the obtained compounds are reported for Silufol UV-254 plates in a CCl_4—acetone system. For the column chromatography, silica gel L 40—100 mm (Chemapol) was used.

The yields, properties, elemental analysis data, and spectral characteristics for compounds **1**, **3**—**5**, and **7**—**9** are given in Tables 1 and 2. The corresponding data for compounds **2** and **6** were described earlier.[1]

7-Fluoro-3-trifluoromethyl-benzo-1,4-oxathiane (1) and 2,2-difluoro-3-hydroxymethyl-7-methoxybenzo-1,4-oxathiane (3). 5-Fluoro-2-(α-trifluoromethyl-β-chloroethylthio)phenol (13.7 g) was added to 30 mL of a 20 % aqueous solution of NaOH at 10 °C. The mixture was heated for 2 h at 100 °C and cooled to ~20 °C. The oil that separated was extracted with ether and dried with $MgSO_4$. The fraction with b.p. 70—75 °C (1 Torr) was obtained by distillation and recrystallized from hexane. 6.9 g of oxathiane **1** and 3.5 g of oxathiane **3** were obtained.

Table 2. ^1H and ^{19}F NMR spectral data of compounds **1, 3—5,** and **7—9**

Compound	^{19}F NMR δ, ppm (*J*/ Hz)	^1H NMR δ, ppm (*J*/ Hz)
1	−8.6 d.d (3 F, 2.0 and 8.6); 37.5 p (1 F, 4.5)	7.18 d.d (1 H, 6.4 and 9.3); 6.80 m (2 H); 4.93 d.d (1 H, 2.7 and 12.0); 4.38 m (2H)
3	−13.8 d (1 F, 152.5); —3.6 d.d (1 F, 8.7 and 152.5); 37.3 p (1 F, 4.5)	7.33 d.d (1 H, 8.5 and 6.2); 6.97 m (2 H); 4.52 br.s (1 H); 4.10 m (1H); 3.84 m (2 H)
4	−13.7 d (1 F, 152.5); —3.7 d.d (1 F, 8.8 and 152.5	7.04 d (1 H, 8.5); 6.58 m (2 H); 4.05 m (1 H); 3.75 m (2 H); 3.70 s (3 H); 3.10 br.s (1 H)
5	—	7.62 d (1 H, 7.9); 6.83 m (2 H); 6.45 s (1 H); 5.25 s (1 H); 4.08 s (3 H)
7	−14.4 d (1 F, 152.0); −3.8 d.d (1 F, 9.0 and 152.0)	6.78 s (1 H); 6.69 s (1 H); 6.05 s (2 H); 4.06 m (1 H); 3.73 m (2 H); 3.08 br.s (1 H)
8	−8.7 d.d (3 F, 1.8 and 8.5)	8.23 d (1 H, 7.4); 8.05 d (1 H, 7.4); 7.52 m (3 H); 7.31 d (1 H, 8.5); 5.25 m (1 H); 4.53 m (2 H)
9	−13.7 d (1 F, 152.0); −3.9 d.d (1 F, 9.0 and 152.0)	8.21 d (1 H, 7.3); 8.05 d (1 H, 7.3); 7.61 m (3 H); 7.37 d (1 H, 8.2); 4.53 t (1 H, 6.1); 4.24 m (1 H); 4.13 m (1 H); 3.97 m (1 H)

*Solvent: $(CD_3)_2CO$ for compounds **1**, **3**, **5**, **8**, **9**, CD_3CN for compounds **4**, **7**.

3-Trifluoromethyl-7-methoxybenzo-1,4-oxathiane (2), 2,2-difluoro-3-hydroxymethyl-7-methoxybenzo-1,4-oxathiane (4), and 2-(α-carboxyvinylthio)-5-methoxyphenol (5). 5-Methoxy-2-(α-trifluoromethyl-β-chloroethylthio)phenol (13.3 g) was added to 30 mL of a 20 % aqueous solution of NaOH at 10 °C. The mixture was heated for 2 h at 100 °C and cooled to ~20 °C. The oil that separated was extracted with ether and dried with $MgSO_4$. The ether was removed *in vacuo*, and the residue was inserted into a column with 150 g of silica gel and eluted with a CCl_4—acetone (10:1) mixture. 3.3 g of compound **2** and 2.1 g of compound **4** were obtained. The aqueous solution was acidified with hydrochloric acid. The oil that separated was extracted with ether and dried with $MgSO_4$. The ether was removed *in vacuo*, and the residue was extracted with hot hexane to obtain 0.7 g of compound **5**.

3-Trifluoromethyl-6,7-methylenedioxybenzo-1,4-oxathiane (6) and 2,2-difluoro-3-hydroxymethyl-6,7-methylenedioxybenzo-1,4-oxathiane (7). 4,5-Methylenedioxy-2-(α-trifluoromethyl-β-chloroethylthio)phenol (15 g) was added to 30 mL of a 20 % aqueous solution of NaOH at 10 °C. The mixture was heated for 2 h at 100 °C and cooled to ~20 °C. The oil that separated was extracted with ether. The ether solution was dried with $MgSO_4$ and the ether was removed *in vacuo*. The residue was inserted into a column with 150 g of silica gel and eluted with a CCl_4—acetone (10:1) mixture to obtain 4.4 g of oxathiane **6** and 2.8 g of oxathiane **7**.

3-Trifluoromethylnaphto[1,2-*b*]-1,4-oxathiane (8) and 2,2-difluoro-3-hydroxymethylnaphto[1,2-*b*]-1,4-oxathiane (9). 1-Trifluoromethyl-2-chloroethylsulfphenyl chloride (19.9 g) was added to a solution of 1-naphthol (14.4 g) in chloroform (50 mL) with stirring at ~0 °C. The mixture was heated to ~20 °C and stored for 20 h until no HCl was liberated. The solvent was removed *in vacuo*. The residue was added to 60 mL of a 20 % aqueous solution of NaOH at 10 °C. The mixture was heated for 2 h at 100 °C and cooled to ~20 °C. The oil that separated was extracted with ether. The ether solution was dried with $MgSO_4$ and the solvent was removed *in vacuo*. The residue was inserted into a column with 150 g of silica gel and eluted with a CCl_4—acetone (15:1) mixture to obtain 5.4 g of oxathiane **8** and 3.5 g of oxathiane **9**.

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