Reactions of 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylsulfenyl chloride with aromatic and heterocyclic compounds

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1,3,3,3-Tetrafluoro-2-methoxycarbonylpropenylsulfenyl chloride readily reacts with activated aromatic and heterocyclic compounds to form *C*-sulfenylation products as *E* isomers. In some cases, its reactions with phenolic compounds are accompanied by cyclization giving rise to fused 2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-oxathioles.

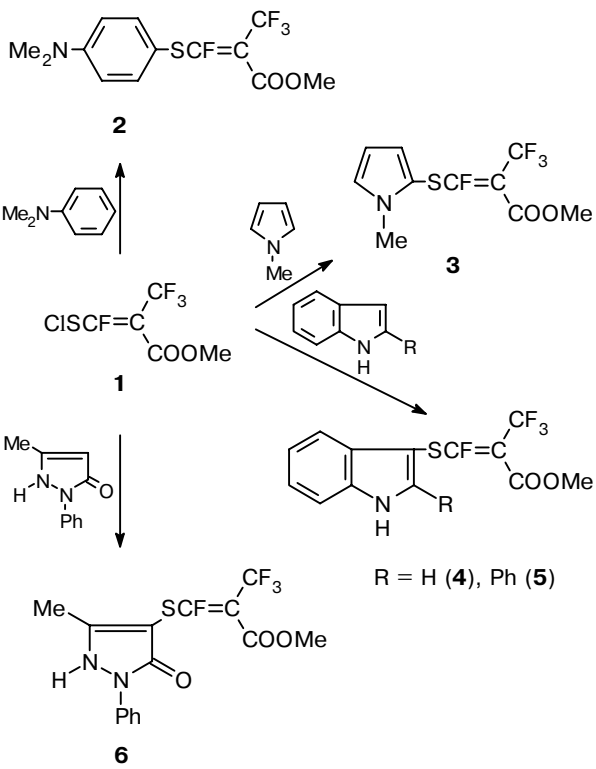
Key words: 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylsulfenyl chloride, sulfenylation, aromatic and heterocyclic compounds, 2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-oxathioles.

C-Sulfenylation of aromatic and heterocyclic compounds with polyfluoroalkylsulfenyl chlorides has been well studied.[1] Nevertheless, these reactions still attract considerable attention as a promising approach to the synthesis of biologically active compounds. However, analogous reactions involving polyfluoroalkenylsulfenyl chlorides have not been performed. Recently, we have demonstrated that the reactions of α-fluoro-α,β-unsaturated sulfenyl chlorides with enolizable carbonyl compounds gave rise to products which underwent cyclization to form substituted 1,3-oxathioles due to high anionoid lability of the vinylic fluorine atom.[2] In this connection, it was of interest to study the reactions of 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylsulfenyl chloride (**1**) with activated aromatic and heterocyclic compounds and to examine the possibility of heterocyclization of the reaction products in the case of hydroxy derivatives.

Results and Discussion

We demonstrated that sulfenyl chloride **1**, like saturated polyfluorinated sulfenyl chlorides, readily formed *C*-sulfenylation products **2—6** in the reactions with *N*,*N*-dimethylaniline, *N*-methylpyrrole, indole, 2-phenylindole, and 3-methyl-1-phenyl-2,5-dihydropyrazol-5-one, respectively (Scheme 1).

Scheme 1



The reactions of sulfenyl chloride **1** with phenol and *ortho*- and *meta*-cresols afforded *para*-substitution products (with respect to the OH group) **7—10**, whereas the reactions of **1** with compounds containing a substituent in the *para* position with respect to the OH group underwent sulfenylation at the *ortho* position. The exception is 2,3-dimethylphenol whose reaction with **1** gave rise to a mixture of the *ortho*- and *para*-substitution products. Attempts to isolate the *ortho*-sulfenylation products in individual form failed because even under mild reaction conditions they underwent spontaneous cyclization to form substituted benzooxathioles **11—15** (Scheme 2). Cyclization of these compounds was completed on heating (for example, on refluxing in chloroform) or in the presence of the complex $BF_3 \cdot NEt_3$. Naturally, the reaction of sulfenyl chloride **1** with resorcinol proceeded analogously.

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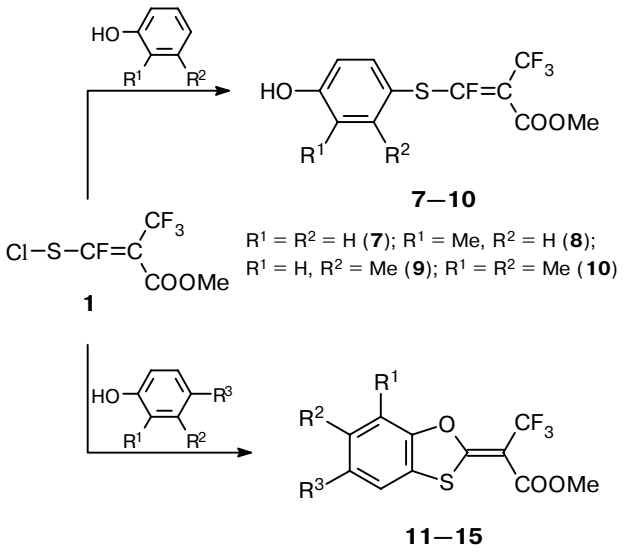
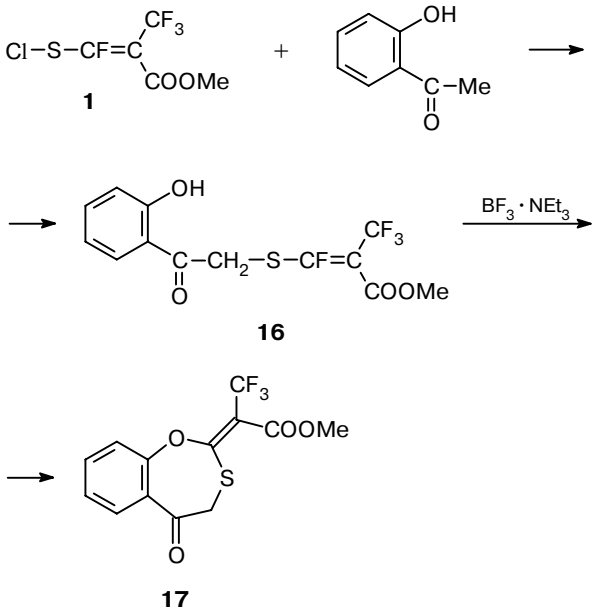
Scheme 2



$R^1 = R^2 = H$, $R^3 = Me$ (**11**); $R^1 = R^3 = Me$, $R^2 = H$ (**12**); $R^1 = R^2 = Me$, $R^3 = H$ (**13**); $R^1 = H$, $R^2 = R^3 = OCH_2O$ (**14**); $R^1 = R^3 = H$, $R^2 = OH$ (**15**)

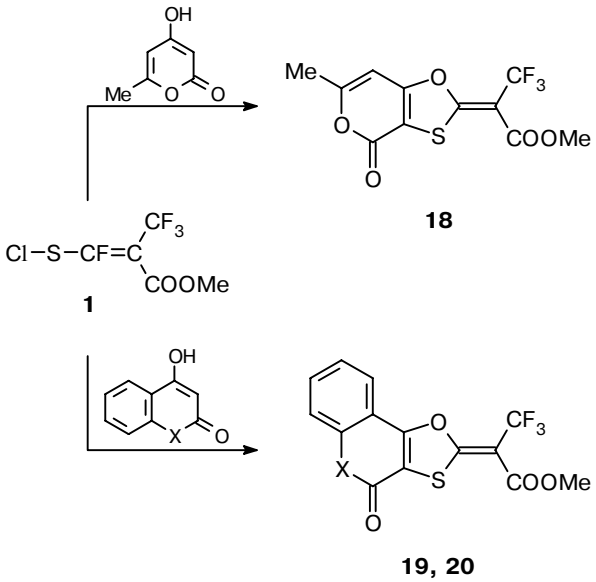
Due to deactivation of the aromatic nucleus, 2-acetylphenol reacted with **1** analogously to other methyl ketones.[1] When heated with the complex $BF_3 \cdot NEt_3$, the resulting product **16** underwent heterocyclization to form compound **17** containing a seven-membered heterocyclic fragment (Scheme 3).

Scheme 3



On heating, heterocyclic compounds, such as 4-hydroxy-6-methyl-2-pyrone, 4-hydroxycoumarin, and 2,4-dihydroxyquinoline, underwent sulfenylation simultaneously with cyclization giving rise to compounds **18—20**, respectively (Scheme 4).

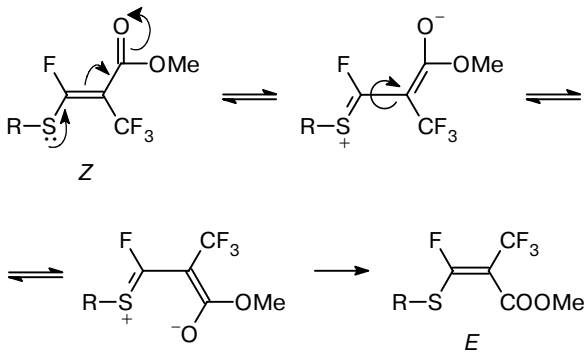
Scheme 4



X = O (**19**), NH (**20**)

The NMR spectral data for compounds **2—10** and **16** (Table 1) indicate that sulfenylation proceeded stereospecifically because only the *E* isomers (the *cis* arrangement of the trifluoromethyl group and the F atom, $J_{F,F} = 30$ Hz) were formed in all reactions, whereas the starting sulfenyl chloride **1** contained up to 15% of the *Z* isomer. Analogous results have been obtained previously in the reactions of sulfenyl chloride **1** with carbonyl compounds.[2,3] Conceivably, this phenomenon is attributable to p—π—π conjugation between the lone electron pairs of the S atom with the multiple bond and the carbonyl group as a result of which the *Z* isomer was converted into the thermodynamically more stable *E* isomer in the course of the reaction (Scheme 5).

Scheme 5



Conceivably, the high rate of isomerization is also favored by high stability of the sulfonium ion due to the

Table 1. Data from ^1H and ^{19}F NMR spectroscopy* for compounds **2—20**

Compound	δ_F ($J_{F,F}$/Hz)	δ_H ($J_{H,H}$/Hz)
2	22.0 (d, 3 F, CF_3, J = 30); 16.7 (q, 1 F, CF, J = 30)	2.98 (s, 6 H, 2 NMe); 3.84 (s, 3 H, OMe); 6.75, 7.38 (both d, 2 H each, C_6H_4, J = 9)
3	—	3.65 (s, 3 H, NMe); 3.87 (s, 3 H, OMe); 6.20, 6.62, 7.05 (all m, 1 H each, 3 CH)
4	—	3.91 (s, 3 H, OMe); 7.15, 7.48 (both m, 2 H each, C_6H_4); 7.62 (d, 1 H, CH, J = 3); 11.70 (br.s, 1 H, NH)
5	22.6 (d, 3 F, CF_3, J = 30); 17.0 (q, 1 F, CF, J = 30)	3.96 (s, 3 H, OMe); 7.22 (m, 2 H, 2 CH); 7.54 (m, 5 H, 5 CH); 7.80 (m, 2 H, 2 CH); 12.20 (br.s, 1 H, NH)
6	—	2.23 (s, 3 H, Me); 3.86 (s, 3 H, OMe); 7.26 (m, 3 H, 3 CH); 7.54 (d, 2 H, 2 CH, J = 7)
7	—	3.82 (s, 3 H, OMe); 6.87, 7.48 (both d, 2 H each, C_6H_4, J = 9); 10.20 (br.s, 1 H, OH)
8	24.4 (d, 3 F, CF_3, J = 30); 19.8 (q, 1 F, CF, J = 30)	2.11 (s, 3 H, Me); 3.80 (s, 3 H, OMe); 6.88, 7.28 (both d, 1 H each, 2 CH, J = 8); 7.35 (s, 1 H, CH); 10.02 (br.s, 1 H, OH)
9	—	2.30 (s, 3 H, Me); 3.83 (s, 3 H, OMe); 6.70 (d, 1 H, CH, J = 8); 6.83 (s, 1 H, CH); 7.41 (d, 1 H, CH, J = 8); 10.00 (br.s, 1 H, OH)
10	—	2.10, 2.30 (both s, 3 H each, 2 Me); 3.84 (s, 3 H, OMe); 6.78, 7.30 (both d, 1 H each, 2 CH, J = 8); 9.95 (br.s, 1 H, OH)
11	24.1 (s, CF_3)	2.36 (s, 3 H, Me); 3.81 (s, 3 H, OMe); 7.23, 7.50 (both d, 1 H each, 2 CH, J = 8); 7.70 (s, 1 H, CH)
12	—	2.36, 2.42 (both s, 3 H each, 2 Me); 3.88 (s, 3 H, OMe); 6.97, 7.13 (both s, 1 H each, 2 CH)
13	—	2.30 (s, 6 H, 2 Me), 3.81 (s, 3 H, OMe); 7.20, 7.56 (both d, 1 H each, 2 CH, J = 8)
14	—	3.84 (s, 3 H, OMe); 6.14 (s, 2 H, CH_2); 7.16, 7.27 (both s, 1 H each, 2 CH)
15	25.5 (s, CF_3)	4.80 (s, 3 H, OMe); 6.80 (d, 1 H, CH, J = 8); 6.98 (s, 1 H, CH); 7.62 (d, 1 H, CH, J = 8); 10.10 (s, 1 H, OH)
16	23.8 (d, 3 F, CF_3, J = 30); 17.9 (q, 1 F, CF, J = 30)	3.85 (s, 3 H, OMe); 4.70 (s, 2 H, CH_2); 6.95 (m, 2 H, 2 CH); 7.48 (t, 1 H, CH, J = 7); 7.86 (d, 1 H, CH, J = 7); 11.18 (s, 1 H, OH)
17	24.5 (s, CF_3)	3.82 (s, 3 H, OMe); 4.03 (s, 2 H, CH_2); 7.40 (d, 1 H, CH, J = 8); 7.52 (t, 1 H, CH, J = 8); 7.78 (t, 1 H, CH, J = 8); 8.05 (d, 1 H, CH, J = 8)
18	21.7 (s, CF_3)	2.47 (s, 3 H, Me); 3.88 (s, 3 H, OMe); 6.40 (s, 1 H, CH)
19	21.2 (s, CF_3)	3.92 (s, 3 H, OMe); 7.45 (m, 2 H, 2 CH); 7.66 (t, 1 H, CH, J = 9); 7.80 (d, 1 H, CH, J = 9)
20	28.0 (s, CF_3)	3.87 (s, 3 H, OMe); 7.40 (t, 1 H, CH, J = 7); 7.51 (d, 1 H, CH, J = 7); 7.67 (t, 1 H, CH, J = 7); 7.78 (d, 1 H, CH, J = 7); 12.30 (br.s, 1 H, OH)

* Solvents: DMSO-d_6 for compounds **2—5**, **7—11**, **13—17**, and **20** and $CDCl_3$ for compounds **6**, **12**, **18**, and **19**.

presence of the aromatic substituent at the S atom responsible for the charge stabilization.

Experimental

The ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer operating at 188.31 MHz. The ^1H NMR spectra were measured on a Bruker AC-300SF instrument operating at 300.13 MHz. The chemical shifts (δ) are given relative to CF_3COOH (^{19}F, the external standard) and Me_4Si (^1H, the internal standard). The course of the reactions and the purities of the resulting compounds were monitored by TLC on Merck 60F-254 plates in an acetone—CCl_4 system. The physicochemical constants and the data from elemental analyses for compounds **2—20** are given in Table 2.

Sulfenyl chloride **1** was prepared according to a known procedure.[3]

***N,N*-Dimethyl-4-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)aniline (2).** A solution of sulfenyl chloride **1** (2.4 g, 10 mmol) in chloroform (5 mL) was added dropwise with stirring to a solution of *N,N*-dimethylaniline (2.4 g, 20 mmol) in chloroform (20 mL) at 0—5 °C. The reaction mixture was kept at 20 °C for 24 h and then washed with water (3×50 mL). The organic layer was separated and dried with Na_2SO_4. The solvent was removed *in vacuo* and the residue was recrystallized from hexane.

1-Methyl-2-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)pyrrole (3). A solution of sulfenyl chloride **1** (2.4 g, 10 mmol) in chloroform (10 mL) was added dropwise with stirring to a solution of 1-methylpyrrole (0.8 g, 10 mmol) and pyridine (0.8 g, 10 mmol) in chloroform (10 mL) at 10 °C. The reaction mixture was refluxed for 2 h and then washed with 5% HCl and water (2×50 mL). The organic layer was separated, dried with Na_2SO_4, and fractionated.

3-(1,3,3,3-Tetrafluoro-2-methoxycarbonylpropenylthio)indole (4). Sulfenyl chloride **1** (2.4 g, 10 mmol) was added dropwise with stirring to a solution of indole (1.2 g, 10 mmol) in benzene (20 mL), during which precipitation was observed. The reaction mixture was refluxed until evolution of HCl ceased (5 h). The solvent was removed *in vacuo*, the residue was extracted with hot hexane, and the crystals that formed upon cooling were filtered off.

Analogously, **3-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)-2-phenylindole (5)** was prepared from 2-phenylindole.

3-Methyl-1-phenyl-4-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)-2,5-dihydropyrazol-5-one (6). Sulfenyl chloride **1**

Table 2. Yields, physicochemical properties, and data from elemental analyses for compounds **2—20**

Compound	R_f (system)*	M.p./°C [b.p./°C] (*p*/Torr)	Yield (%)	Found / Calculated (%) C	Found / Calculated (%) H	Molecular formula
2	0.76 (*A*)	85—87	76	48.46 / 48.30	4.05 / 4.02	$C_{13}H_{13}F_4NO_2S$
3	0.51 (*A*)	[98—99] (3)	68	42.61 / 42.40	3.22 / 3.18	$C_{10}H_9F_4NO_2S$
4	0.35 (*A*)	83—85	74	49.02 / 48.90	2.77 / 2.82	$C_{13}H_9F_4NO_2S$
5	0.59 (*A*)	90—92	82	57.88 / 57.72	3.31 / 3.29	$C_{19}H_{13}F_4NO_2S$
6	0.26 (*B*)	131—133	55	47.86 / 47.75	3.40 / 3.45	$C_{15}H_{12}F_4N_2O_3S$
7	0.44 (*A*)	51—53	64	44.72 / 44.59	2.68 / 2.70	$C_{11}H_8F_4O_3S$
8	0.42 (*A*)	71—73	78	46.50 / 46.45	3.26 / 3.23	$C_{12}H_{10}F_4O_3S$
9	0.33 (*A*)	74—76	75	46.58 / 46.45	3.20 / 3.23	$C_{12}H_{10}F_4O_3S$
10	0.39 (*A*)	108—110	46	48.27 / 48.15	3.75 / 3.70	$C_{13}H_{12}F_4O_3S$
11	0.29 (*C*)	145—147	77	49.70 / 49.66	3.06 / 3.10	$C_{12}H_9F_3O_3S$
12	0.31 (*C*)	176—178	81	51.16 / 51.32	3.55 / 3.62	$C_{13}H_{11}F_3O_3S$
13	0.67 (*A*)	133—135	23	51.22 / 51.32	3.64 / 3.62	$C_{13}H_{11}F_3O_3S$
14	0.63 (*A*)	217—219	85	45.12 / 45.00	2.25 / 2.19	$C_{12}H_7F_3O_5S$
15	0.37 (*A*)	140 (decomp.)	81	45.11 / 45.21	2.44 / 2.40	$C_{11}H_7F_3O_4S$
16	0.19 (*A*)	74—76	66	46.32 / 46.15	2.99 / 2.96	$C_{13}H_{10}F_4O_4S$
17	0.66 (*A*)	80—82	60	49.17 / 49.06	2.84 / 2.83	$C_{13}H_9F_3O_4S$
18	0.36 (*A*)	192—194	77	42.71 / 42.86	2.30 / 2.27	$C_{11}H_7F_3O_5S$
19	0.42 (*A*)	216—218	72	48.73 / 48.84	2.07 / 2.03	$C_{14}H_7F_3O_5S$
20	—	325—327	70	49.07 / 48.98	2.35 / 2.33	$C_{14}H_8F_3NO_4S$

* *A*, CCl_4—acetone (9 : 1); *B*, CCl_4—acetone (3 : 1); *C*, CCl_4.

(2.4 g, 10 mmol) was added dropwise with stirring to a solution of a mixture of 3-methyl-1-phenyl-2,5-dihydropyrazol-5-one (1.75 g, 10 mmol) and pyridine (0.8 g, 10 mmol) in chloroform (20 mL). The reaction mixture was stirred for 3 h and then washed with 5% HCl and water (2×50 mL). The solvent was removed *in vacuo* and the residue was recrystallized from methanol.

4-(1,3,3,3-Tetrafluoro-2-methoxycarbonylpropenylthio)phenol (7). A mixture of phenol (0.9 g, 10 mmol) and sulfenyl chloride **1** (2.4 g, 10 mmol) was kept at 20 °C for 24 h, evolution of HCl being observed. The product was recrystallized from hot hexane.

Analogously, **2-methyl-4-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)phenol (8)** and **3-methyl-4-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)phenol (9)** were prepared from *o*- and *m*-cresol, respectively**.**

2,3-Dimethyl-4-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)phenol (10) and **6,7-dimethyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-benzooxathiole (13).** A solution of a mixture of 2,3-dimethylphenol (1.2 g, 10 mmol) and sulfenyl chloride **1** (2.4 g, 10 mmol) in chloroform (10 mL) was kept at 20 °C for 10 h and then refluxed for 2 h. The solvent was removed *in vacuo* and the residue was chromatographed on a column with silica gel (l = 1 m) using a 20 : 1 CCl_4—acetone mixture as the eluent.

5-Methyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-benzooxathiole (11). A mixture of *p*-cresol (1.1 g, 10 mmol) and sulfenyl chloride **1** (2.4 g, 10 mmol) was heated at 70 °C until evolution of HCl ceased (7 h). Then a solution of the complex $BF_3 \cdot NEt_3$ (2.2 g, 13 mmol) in ether (15 mL) was added and the reaction mixture was stirred at 20 °C for 2 h and washed with water (3×50 mL). The organic layer was separated and dried with Na_2SO_4, the solvent was removed *in vacuo*, and the residue was recrystallized from hexane.

Analogously, **5,7-dimethyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-benzooxathiole (12)** was prepared from 2,4-dimethylphenol**.**

5,6-Methylenedioxy-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-benzooxathiole (14). Sulfenyl chloride **1** (2.4 g, 10 mmol) was added with stirring to a solution of 3,4-(methylenedioxy)phenol (1.4 g, 10 mmol) in chloroform (15 mL). The reaction mixture was kept at 20 °C until elimination of HCl ceased (15 h) and then refluxed for 5 h. The crystals that precipitated upon cooling were filtered off.

Analogously, **6-hydroxy-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-1,3-benzooxathiole (15)** was prepared from resorcinol**.**

2-Hydroxyphenyl 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthiomethyl ketone (16). A mixture of 2-acetylphenol (1.3 g, 9.5 mmol) and sulfenyl chloride **1** (2.4 g, 10 mmol) was heated at 100 °C for 5 h and then cooled to 20 °C. The crystals that precipitated were recrystallized from hexane.

2-(2,2,2-Trifluoro-1-methoxycarbonylethylidene)-1,3-benzooxathiepan-5-one (17). A solution of the complex $BF_3 \cdot NEt_3$ (2.0 g, 12 mmol) in chloroform (10 mL) was added with stirring to a solution of ketone **16** (3.4 g, 10 mmol) in chloroform (10 mL). The mixture was refluxed for 0.5 h and then washed with 5% HCl and water (2×50 mL). The organic layer was separated and dried with Na_2SO_4. The solvent was removed *in vacuo* and the residue was recrystallized from hexane.

6-Methyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)oxathiolo[5,4-*c*]-2*H*-pyran-4-one (18). A suspension of 4-hydroxy-6-methyl-2-pyrone (1.25 g, 10 mmol) and sulfenyl chloride **1** (2.4 g, 10 mmol) in acetonitrile (15 mL) was refluxed with stirring for 5 h. The crystals that formed upon cooling were filtered off.

2-(2,2,2-Trifluoro-1-methoxycarbonylethylidene)oxathiolo[4,5-*c*]-2*H*-chromen-4-one (19) and **4-(2,2,2-trifluoro-1-methoxycarbonylethylidene)oxathiolo[4,5-*c*]quinolin-4-one (20)** were prepared analogously.

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