analyses using nonlinear regression were obtained on an IBM 370/168 computer with the NLIN procedure of the SAS data package (Gauss-Newton method).

2,6-Pyrido-18-crown-6 (8).[12] A suspension of NaH (3.14 g, 61% oil suspension, 80.0 mmol) in THF (300 mL) was heated to reflux. Separate solutions of 2,6-bis(bromomethyl)pyridine (**5**;[12] 5.25 g, 19.8 mmol) in pyridine (150 mL) and tetraethylene glycol (3.85 g, 19.8 mmol) in THF (150 mL) were simultaneously added dropwise over a 3-h period. The mixture was cooled and evaporated in vacuo and the resulting solid was dissolved in CH_2Cl_2 (10 mL). Residual NaH was decomposed by careful addition of H_2O (5 mL). The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to a viscous brown oil. Elution of the oil through neutral alumina (60 mesh) with EtOAc and trituration from cold Et_2O (-78 °C) yielded the crown ether (1.69 g, 28%) as fluffy white crystals: mp 40.0-41.5 °C (lit.[12] mp 40-41 °C); ^1H NMR (250 MHz, $CDCl_3$) δ 3.57-3.63 (8 H, m), 3.64-3.79 (8 H, m), 4.76 (4 H, s), 7.24 (2 H, d, J = 7.7 Hz), 7.66 (1 H, t, J = 7.7 Hz); IR (KBr pellet) 3040, 2830, 1589, 1570, 1453, 1343, 1242, 1100 cm^{-1}.

2,6-Pyrido-18-crown-6 *N*-Oxide (1).[5] 2,6-Pyrido-18-crown-6 (**2**; 200 mg, 0.673 mmol), Na_2CO_3 (1.00 g, 4.92 mmol), and 4,4'-thiobis(6-*tert*-butyl-*m*-cresol) (30 mg, 1% wt of peracid) were stirred into 1,2-dichloroethane (20 mL). 3,5-Dinitroperoxybenzoic acid[13] (521 mg, 2.46 mmol of active oxygen) was added and stirred at room temperature for 2.5 h. Filtration through sintered glass and evaporation in vacuo gave a yellow oil, which was chromatographed through basic alumina with THF to yield oxidized product **1** (110 mg, 52%) as a light-yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 3.41 (8 H, s), 3.59-3.62 (4 H, m), 4.96 (4 H, s), 7.29-7.48 (3 H, m); IR (NaCl) 2860, 1440, 1405, 1350, 1295, 1245, 1108, 1020, 940, 780 cm^{-1}.

2,6-Bis(methoxymethyl)pyridine *N*-Oxide (3). Compound **3** was prepared as slightly colored crystals (mp 51.5-52.0 °C) in 70% yield by oxidation of **4**[12] as described for the preparation of crown ether **1** (vide supra). Data for **3**: ^1H NMR (250 MHz, $CDCl_3$) δ 3.49 (6 H, s), 4.66 (4 H, s), 7.25-7.39 (3 H, m); IR (CCl_4) 2990, 2925, 2820, 1590, 1535, 1400, 1370, 1242, 1194, 995, 968 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.23; H, 7.43; N, 7.63.

Potassium Tri-*sec*-butylborodeuteride (8).[17] The oil was removed from potassium deuteride (1.0 g, 20-25% suspension by repeated washings with Et_2O) under a nitrogen atmosphere. To the dry KD was added tri-*sec*-butylborane (18 mL, 1 M in THF) with water bath cooling. The mixture was stirred 1 h and transferred via cannula to a septum-capped flame-dried tube. This solution showed no appreciable loss of reducing power when stored under nitrogen at room temperature for several months.

Preparation and Attempted Reduction of Complex 6. A flame-dried 5-mL flask was fitted with a magnetic stir bar and sealed under nitrogen with a rubber septum. A solution of **1** (10 μL, 0.366 M, 3.66 μmol) in benzene was charged into the flask. After the contents were cooled to 0 °C in an ice-water bath, tri-*sec*-butylborane (3.7 μL, 1.0 M, 3.70 μmol) was added. After an additional 2 h of stirring, an aliquot was removed and quenched into 0.1 mL of CH_3OH. LC analysis showed no reduced crown products to be present in the reaction mixture. Cyclohexanone (10.3 mg, 10.5 μmol, 3 equiv) was added to the reaction mixture. After 30 min, GLC analysis revealed 33% reduction of cyclohexanone to cyclohexanol. An identical procedure was used with identical results for the attempted reduction of complex **7**.

Reduction of 2,6-Pyrido-18-crown-6 *N*-Oxide (1) by Potassium Tri-*sec*-butylborodeuteride. Crown ether **1** (24.5 mg, 72.0 μmol) was dissolved in benzene-d_6 (0.5 mL, sieve-dried) and cooled to 0 °C in an ice-water bath. Reducing agent (72 μL of a 1 M THF solution) was added and the mixture was concentrated in vacuo. Chromatography (basic alumina, THF) yielded 9.1 mg (42%) of reduced product: ^1H NMR, same as that reported for crown ether **2**; mass spectrum, m/e 297 (M^+ for **2**).

Kinetic Experiments. A flame-dried flask equipped with a magnetic stir bar was capped with a rubber septum and flushed with dry nitrogen. Into the flask was syringed a solution of **1** (9 μL, 0.370 M, 34 μmol) in dry benzene, additional dry benzene (124 μL), and dry THF (114 μL). After the contents were cooled to 0 °C in an ice-water bath, K-Selectride (17.5 μL, 1.0 M in THF, 17.5 μmol) was added. The final mixture was 0.1 M in **1** and 0.05 M in K-Selectride. The solution quickly became yellow. Aliquots (2 μL) were periodically removed and quenched into CH_3OH (100 μL). LC analyses of the quenched aliquots were carried out as outlined (vide supra). An identical procedure was used for the kinetic analyses of **3**. The competitive reductions were conducted in this manner also, except that 95 μL of a 0.370 M solution of analogue **3** (in dry benzene) was substituted for 95 μL of benzene in the reaction mixture.

Spectroscopic Determination of Association Constants (K_a). All association constants were determined with potassium picrate solution, using the method reported by Cram.[25]

Acknowledgment is made to the National Cancer Institute (Grant No. 2 R01 CA-20574) and the Alfred P. Sloan Foundation for support of this work. We thank Dr. William Rand for his assistance with the computer modelling studies and Ms. Toni Chancellor for obtaining high-field ^1H NMR spectra.

Registry No. 1, 69928-23-0; 1 potassium picrate complex (1:1), 69942-89-8; **2**, 53914-89-9; **2** potassium picrate complex (1:1), 69942-98-9; **3**, 84051-59-2; **4**, 64726-18-7; **6**, 84051-60-5; **7**, 84051-61-6; K^+, 24203-36-9; 2,6-bis(bromomethyl)pyridine, 7703-74-4; tetraethylene glycol, 112-60-7; tri-*sec*-butylborane, 1113-78-6.

Sulfenylation of Ortho Esters. A Novel Preparation of 2-[(Trihalomethyl)thio]alkanoic Acids[1]

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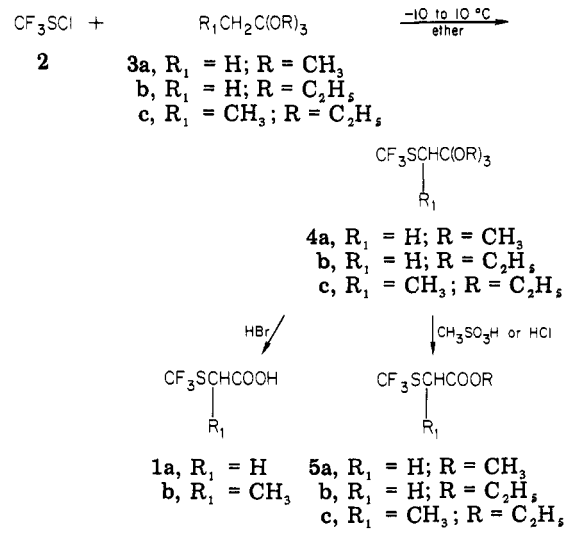
Trifluoromethanesulfenyl chloride reacts readily with ortho esters of acetic acid as well as ortho esters of higher aliphatic carboxylic acids to yield 1,1,1-trialkoxy-2-[(trifluoromethyl)thio]alkanes **4a-c**. In the presence of an excess of trifluoromethanesulfenyl chloride, disubstitution of triethyl orthoacetate was observed, giving 1,1,1-triethoxy-2,2-bis[(trifluoromethyl)thio]ethane (**6**), which underwent facile thermal elimination to yield 1,1-diethoxy-2,2-bis[(trifluoromethyl)thio]ethene (**8**). The trialkoxyethanes **4a-c** are easily transformed into the corresponding [(trihalomethyl)thio]alkanoic acids and lower alkyl esters. Trichloromethanesulfenyl chloride, a less reactive sulfenyl halide, reacts at elevated temperature in a similar manner with trimethyl and triethyl orthoacetate to furnish 1,1,1-trialkoxy-2-[(trichloromethyl)thio]ethanes **10a** and **10b**. A radical chain mechanism is proposed for the formation of **10a** and **10b**.

As a consequence of the physical and chemical properties of trifluoromethanethiol[2] (bp -37 °C), rather tedious methods are utilized for the introduction of the (trifluoromethyl)thio moiety into aliphatic compounds.

0022-3263/83/1948-0298$01.50/0

Scheme I

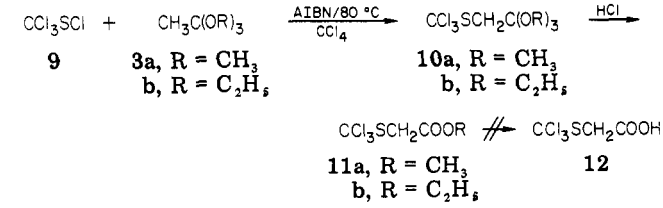


Heavy-metal salts such as bis[(trifluoromethyl)thio]mercury[3] and [(trifluoromethyl)thio]silver[4] react with aliphatic halides; however, these reagents are costly and cause severe burns on skin contact. Harris[5] has prepared methyl α-[(trifluoromethyl)thio]-β-chloropropanoate by the addition of **2** to methyl acrylate, while Trost[6] has used sulfenylation of the dianions of carboxylic acids to produce the α-methylthio derivatives that serve as acyl anion equivalents in natural product syntheses.

In an effort to develop a new synthesis of [(trifluoromethyl)thio]acetic acid (**1a**),[7] the acyl side chain of the cephalosporin antibiotic cefazaflur,[8] we studied the chemistry of trifluoromethanesulfenyl chloride (**2**).[9] It has been reported that **2** undergoes addition reactions with ketene[10] as well as radical-initiated substitution reactions with toluene.[11] Saturated hydrocarbons[11] and acetone[12] are known to participate in substitution reactions with **2**; however, we have found that acetonitrile[13] and esters of acetic acid, logical precursors of **1a**, did not react. We now report a novel sulfenylation of aliphatic ortho esters by trihalomethanesulfenyl chlorides that achieves a direct and efficient synthesis of **1a** as well as variety of 2-[(trihalomethyl)thio]alkanoic acids and esters.

Reaction of Trifluoromethanesulfenyl Chloride with Ortho Esters. Ortho esters of acetic acid (**3a, 3b**) were found to react with **2** to yield novel orthoacetates, 1,1,1-trialkoxy-2-[(trifluoromethyl)thio]ethanes (**4a, 4b**). The reaction of trifluoromethanesulfenyl chloride with trimethyl orthoacetate or triethyl orthoacetate was very

Scheme II



rapid. When a stream of trifluoromethanesulfenyl chloride[14] (bp −4 to 2 °C) was bubbled into an ether (or methyl acetate) solution containing an excess of **3a** or **3b** at −5 °C, the yellow color, indicative of the presence of the sulfenyl chloride, was discharged within seconds.[15] Vacuum distillation of the crude reaction product gave the colorless ortho esters **4a** or **4b** in 75–80% yield. These compounds were hydrolyzed by 48% hydrobromic acid to [(trifluoromethyl)thio]acetic acid (**1a**) in overall yields of 60–65% or converted by anhydrous hydrogen chloride or methanesulfonic acid to their corresponding esters **5a** or **5b** (Scheme I).

The reaction is general for higher aliphatic ortho esters. Thus treatment of triethyl orthopropanoate (**3c**) with **2** gave the ortho ester **4c** (yield 55%), which on treatment with 48% hydrobromic acid was converted in 70% yield to 2-[(trifluoromethyl)thio]propanoic acid (**1b**). On treatment with concentrated hydrochloric acid, **4c** was converted to the ethyl ester **5c** (24% yield). The ready availability of a large variety of substituted ortho esters[16] increases the utility of this method for the preparation of various 2-[(trifluoromethyl)thio]alkanoic acids and esters. Even sulfenylation of α-disubstituted ortho esters such as 1,1,1-trialkoxy-2-methylpropane to produce 1,1,1-trialkoxy-2,2-dialkyl-2-[(trifluoromethyl)thio]ethane is feasible since reactions of **2** do not appear to be greatly affected by steric factors (e.g., the reaction of **2** with isobutane[11] and the ready formation of **6**). In addition, reaction of other electrophilic sulfenyl halides (e.g., chlorodifluoromethanesulfenyl chloride)[12] with ortho esters is within the scope of this method.[17]

The reaction can be modified to produce bis[(trihalomethyl)thio] derivatives. When the orthoacetate **3b** was added to a large excess of **2** and the reaction time extended to 16 h, the orthoacetate reacted with 2 equiv of **2** to give 1,1,1-triethoxy-2,2-bis[(trifluoromethyl)thio]ethane (**6**) in a yield of 75%. Distillation of crude **6** resulted in 1,2-elimination to give 1,1-diethoxy-2,2-bis[(trifluoromethyl)thio]ethene (**8**). This compound was characterized spectroscopically by the absence of a methine proton in the ^{1}H NMR and the presence of two weak vinyl carbons, δ 63.13 and 174.34 (^{13}C NMR). This Δδ value for the vinyl carbon atoms in **8**, 111.21 ppm, is greater than the Δδ values for many other polarized ethylenes such as 1,1-dichloro-2,2-dicyanoethylene (Δδ = 66.6 ppm)[18] and points to the polar nature of this ketene acetal. We have assigned the upfield signal to the bis[(trifluoromethyl)thio]-substituted vinyl carbon. (A discussion of this assignment is included in the Experimental Section.) Treatment of **6**

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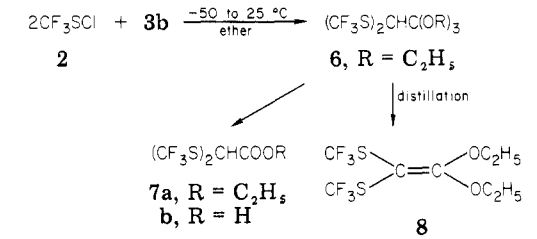
(8) DeMarinis, R. M.; Hoover, J. R. E.; Dunn, G. L.; Actor, P.; Uri, J. V.; Weisbach, J. A. *J. Antibiot.* **1975**, *28*, 463.
(9) Tullock, C. W.; Coffman, D. D. *J. Org. Chem.* **1960**, *25*, 2016.
(10) Harris, J. F. *J. Org. Chem.* **1972**, *37*, 1340.
(11) Harris, J. F. *J. Org. Chem.* **1966**, *31*, 931.
(12) Bayreuther, H.; Haas, A. *Chem. Ber.* **1973**, *106*, 1418.
(13) However, **2** is reported to add to the C≡N bond in cyanoethylenes: Hartzler, W. D. *J. Org. Chem.* **1964**, *29*, 1194.
(14) Commercial supplier Armageddon Chemical Co.; see ref 9.
(15) The rapid consumption of highly toxic trifluoromethanesulfenyl chloride minimized any laboratory exposure. Toxicity data have been reported for this volatile fluorocarbon: Stump, E. C. *Chem. Eng. News* **1967**, *45*, 44.
(16) The chemistry of ortho esters is treated in detail: DeWolfe, R. H. "Carboxylic Ortho Acid Derivatives"; Academic Press, New York, 1970.
(17) The sulfenyl chlorides C_3F_7SCl, CHF_2CF_2SCl, $CClF_2SCl$, and CCl_2FSCl are reported to give reactions analogous to CF_3SCl with toluene and alkanes: Harris, J. F. *J. Org. Chem.* **1979**, *44*, 563.
(18) Gansow, O. A.; Burke, A. R.; King, R. B.; Saran, M. S. *Inorg. Nucl. Chem. Lett.* **1974**, *10*, 291.

with 48% hydrobromic acid (20 h, reflux) gave the novel 2,2-bis[(trifluoromethyl)thio]acetic acid (**7b**) in 51% yield.



Reaction of Trichloromethanesulfenyl Chloride with Ortho Esters. The chemistry of trichloromethanesulfenyl chloride (**9**) has been studied extensively;[19] however, neither [(trichloromethyl)thio]acetic acid (**12**) or its esters have appeared in the literature.[20] Since the acid **12** would be a novel chemical intermediate, we undertook its preparation via ortho ester sulfenylation.

Trichloromethanesulfenyl chloride was found to be less reactive than its fluorine counterpart. Forcing conditions, i.e., refluxing **9** and ortho ester **3a** in carbon tetrachloride with 2,2′-azobis(2-methylpropionitrile) (AIBN), were necessary to form **10a** (yield 55%; Scheme II). Ortho ester **10a** could not be distilled due to extensive decomposition; however, treatment of the original reaction mixture with hydrogen chloride or methanesulfonic acid followed by distillation gave methyl [(trichloromethyl)thio]acetate (**11a**) free from any impurities.

Owing to their sensitivity, attempts to hydrolyze **11a** and **11b** to **12** have been unsuccessful; these esters are rapidly decomposed by dilute alkali, e.g., sodium carbonate in aqueous tetrahydrofuran at 25 °C. Acid hydrolysis (e.g., boron tribromide, trimethylsilyl iodide, etc.) should be more suitable. This conversion as well as other reactions of these esters are currently under investigation.

Mechanism of the Sulfenylation of Ortho Esters. The reaction of trichloromethanesulfenyl chloride (**9**) with **3a** and **3b** requires periodic introduction of 2,2′-azobis(2-methylpropionitrile) (AIBN) in refluxing carbon tetrachloride for conversion to **10**. On the basis of this finding and the work of Kloosterziel,[21] we feel a priori that a radical chain mechanism, initiated by AIBN, best explains this process (Scheme III).

Scheme III

$$CCl_3SCl \xrightarrow[\Delta]{AIBN} CCl_3S\cdot + Cl\cdot \quad (1)$$

$$Cl\cdot + CH_3C(OR)_3 \rightarrow \cdot CH_2C(OR)_3 + HCl \quad (2)$$

$$CCl_3SCl + \cdot CH_2C(OR)_3 \rightarrow CCl_3SCH_2C(OR)_3 + Cl\cdot \quad (3)$$

$$CCl_3S\cdot + \cdot CH_2C(OR)_3 \rightarrow CCl_3SCH_2C(OR)_3 \quad (4)$$

No such mechanistic implications can be deduced from the sulfenylation of **3a** or **3b** by trifluoromethanesulfenyl chloride (**2**). Carrying out the reaction at −10 °C in the presence of hydroquinone in a flask protected from laboratory light did not appear to retard the reaction; thus, we were unable to determine any agent present initiating a radical sequence corresponding to Scheme III.

We did find, however, that 1,1-dimethoxyethylene (**13**; ketene dimethyl acetal) also reacted with **2** under very mild conditions. Thus reaction of **2** with a 2-fold excess of **13** and methanol (ether, −10 °C) and stirring at 10 °C produced **4a** as the only product.

$$2 + \underset{\mathbf{13}}{CH_2{=}C(OCH_3)_2} + CH_3OH \xrightarrow[\text{ether}]{-10 \text{ to } 10\ ^\circ C} \underset{\mathbf{4a}}{CF_3SCH_2C(OCH_3)_3}$$

The mechanistic consequence of this finding will only be understood after further studies.

Experimental Section

^1H NMR and ^{19}F NMR spectra were recorded on a Perkin-Elmer Model R32 spectrometer operating at 90 MHz and are reported in δ, with use of tetramethylsilane and Freon-11, respectively, as the internal standards. ^{13}C NMR spectra were recorded with a Varian Model CFT-20 operating at 20 MHz with tetramethylsilane as an internal reference. Mass spectra were run on a Perkin-Elmer Hitachi RMU-6E spectrometer at 70 eV. Infrared spectra were obtained with a Perkin-Elmer Model 457 grating instrument. Assignment of absorption bands attributed to CF_3S and C–F were based on the work of Harris.[5] GC–mass spectra were obtained on a Finnigan 3600 gas chromatograph mass spectrometer instrument using a 4 ft × 2 mm 3% OV-17 column. The refractive indices were determined on an Abbé refractometer. C and H analyses were determined on a Perkin-Elmer 240 C,H,N analyzer; halogen and sulfur were analyzed by the Schoniger combustion method. Except where otherwise noted, a short-path distillation apparatus with a 5-cm vigreaux column was used to carry out all distillations. The Waters Associates Prep 500 using a PrePak-500/silica column with 4:1 hexane–ethyl ether as the mobile phase was used for preparative-scale high-pressure liquid chromatography.

The ortho esters and trihalomethanesulfenyl chlorides could often be used from commercial sources without further purification. Trifluoromethanesulfenyl chloride was supplied as a gas;[14] it was also commercially available as a liquid in ampules. **Extreme caution should be taken when handling this toxic compound.**[15]

General Procedures for Preparation of 1,1,1-Trialkoxy-2-[(trifluoromethyl)thio]alkanes 4a–c. A freshly prepared ethereal solution of trifluoromethanesulfenyl chloride (0.5 mol) prepared by passing **2** into ether (60 mL) chilled to −50 °C was added to the appropriate ortho ester (0.8–1.0 mol) in anhydrous ether (250 mL) cooled to −5 °C.

The addition was carried out rapidly (4–5 min) and was accompanied by evolution of gas when carried out at this scale or larger. The yellow color indicative of the sulfenyl chloride had usually disappeared within the addition period. The solution was stirred for 1–1.5 h at ambient temperature. Any solids formed were removed by filtration, and the filtrate was evaporated under reduced pressure to remove solvent and starting materials. The resultant oil was distilled (15–25 mmHg), and in most cases this was sufficient to produce the sample from which analytical data were obtained. Where indicated, additional purification methods were employed. The sulfenylation reaction was sometimes carried out in methyl acetate or in an excess of the ortho ester.

Preparation of 1,1,1-Trimethoxy-2-[(trifluoromethyl)thio]ethane (4a) from 3a. Following the general procedure, **4a** was synthesized from trimethyl orthoacetate in 77% yield based on trifluoromethanesulfenyl chloride, bp 62 °C (15 mmHg). The reference sample of **4a** was obtained by preparative high-pressure liquid chromatography. We obtained a clear oil: η^{25}_D 1.3895; IR (neat) 1450, 1280, 1110 (C–F), 885, 760 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (s, OCH_3 and CH_2); ^{13}C NMR ($CDCl_3$) δ 31.51 (s, CH_2, broadened by three-bond coupling to fluorine), 50.19, 113.43, 131.31 (q, $J_{^{13}C-^{19}F}$ = 304.5 Hz); ^{19}F NMR ($CDCl_3$) δ 42.3. Anal. Calcd for $C_6H_{11}F_3O_3S$: C, 32.73; H, 5.04; S, 14.56. Found: C, 33.20; H, 5.09; S, 14.77.

When the reaction was carried out in the dark with the addition of 0.05 equiv of hydroquinone or of 2,6-di-*tert*-butyl-4-methylphenol, **4a** was produced, and little or no rate retardation was observed.

Preparation of 4a via Reaction of Trifluoromethanesulfenyl Chloride with 1,1-Dimethoxyethylene (13) and Methanol. A solution of **13** (4.8 g, 54.5 mmol) and methyl alcohol

(19) Reviews: Sosnovsky, G. *Chem. Rev.* **1958**, *58*, 509. Senning, A. *Ibid.* **1965**, *65*, 385. Kuhle, E. *Synthesis* **1970**, 561; **1971**, 563; **1971**, 617.

(20) The homologous disulfide, ethyl [(trichloromethyl)dithio]acetate was reported earlier (see ref 7).

(21) Radical chemistry of trichloromethanesulfenyl chloride has been discussed: Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1234; **1963**, *82*, 497, 508.

(1.6 g, 50 mmol) in ether (20 mL) was cooled to −15 °C, and a cold solution (−40 °C) of **2** in ether (2 g, 14.7 mmol/10 mL) was added in one portion and the reaction stirred at 10 °C for 10 h. Evaporation of solvent gave **4a** and 1,1-dimethoxyethylene (GC–mass spectra) as the only products. The ^1H NMR and ^{13}C NMR were compatible with a mixture of **4a** and starting material in approximately equal molar quantities.

Preparation of Ethyl [(Trifluoromethyl)thio]acetate (5b). Treatment of an undistilled sample of **4b** with a stream of dry hydrogen chloride at ambient temperature for 30 min followed by distillation gave the ethyl ester **5b**, 50% yield based on **2**. Further purification was achieved by preparative-scale high-pressure liquid chromatography; bp 68 °C (35 mmHg); η^{25}_D 1.3837; IR (neat) 3000, 1750, 1310, 1120, 1030, 760 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, t, CH_3), 3.64 (2 H, s, CH_2S), 4.20 (2 H, q, CH_2O); ^{13}C NMR ($CDCl_3$) δ 14.13, 32.22 (CH_2S, q, $J_{^{13}C-^{19}F}$ = 7.8 Hz, long-range coupling), 62.60, 130.93 (q, $J_{^{13}C-^{19}F}$ = 301 Hz), 168.08; ^{19}F NMR ($CDCl_3$) δ 43.1; high-resolution mass spectrum, calcd for $C_5H_7F_3O_2S$ 188.012, found 188.013.

Preparation of [(Trifluoromethyl)thio]acetic Acid (1a). To 48% hydrobromic acid (5 mL) was added 1,1,1-trimethoxy-2-[(trifluoromethyl)thio]ethane (**4a**, 2.0 g, 9.1 mmol). The reaction was heated at 100 °C for 2 h and then stirred at room temperature for 16 h. The reaction solution was saturated with sodium chloride and extracted with dichloromethane (4 × 15 mL). The dichloromethane extracts were combined and dried over magnesium sulfate followed by decolorization with charcoal (Norit A). The solution was concentrated under reduced pressure at room temperature yielding 1.3 g (89%) of **1a**, a colorless oil. Distillation yielded 1.12 g of **1a**: bp 80 °C (10 mmHg) [lit. bp 101 °C (31 mmHg)];[4] η^{25}_D 1.3924; IR (neat) 3000 (br), 1730, 1425, 1300, 1130 (C–F), 910, 760 (CF_3S), 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (2 H, s, CH_2), 13.30 (1 H, s, OH); ^{13}C NMR ($CDCl_3$) δ 31.81, 130.36 (q, $J_{^{13}C-^{19}F}$ = 306.6 Hz), 172.89; ^{19}F NMR ($CDCl_3$) δ 42.8. Anal. Calcd for $C_3H_3F_3O_2S$: C, 22.50; H, 1.89; S, 20.03. Found: C, 22.53; H, 2.18; S, 19.63.

Preparation of Methyl [(Trifluoromethyl)thio]acetate (5a). The ester **5a** was prepared by treatment of crude **4a** with a stream of dry hydrogen chloride at ambient temperature for 30 min or by treatment with methanesulfonic acid (15% by weight of the ortho ester) for 1 h at 45 °C. The resulting product, methyl [(trifluoromethyl)thio]acetate (**5a**), was purified by distillation; yield from **2** was 50%; bp 50 °C (15 mmHg); IR (neat) 2900, 1752, 1420, 1295, 1100, 1000, 892, 755 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (2 H, s, CH_2), 3.79 (3 H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ 31.71 (CH_2S, broadened by long-range coupling to fluorine into four lines, $J_{^{13}C-^{19}F}$ = 2 Hz), 53.15, 130.35 (q, $J_{^{13}C-^{19}F}$ = 307 Hz) 168.24; mass spectrum m/e (relative intensity) 174 (M^+, 8.5), 143 (2), 115 (49), 81 (17), 76 (9), 69 (CF_3^+, 62), 59 (100).

Preparation of 1,1,1-Triethoxy-2-[(trifluoromethyl)-thio]ethane (4b). Following the general procedure, **4b** was prepared from triethyl orthoacetate in 53% yield based on **2**; bp 76–82 °C (25 mmHg); ^1H NMR ($CDCl_3$) δ 1.20 (9 H, t, CH_3), 3.27 (2 H, s, CH_2S), 3.56 (6 H, q, CH_2O), additionally δ 0.9, 1.5 (weak, impurities). Anal. Calcd for $C_9H_{17}F_3O_3S$: C, 41.21; H, 6.53; S, 12.22. Found: C, 41.07; H, 6.21; S, 12.30.

Preparation of 1,1,1-Triethoxy-2-[(trifluoromethyl)-thio]propane (4c). Following the general procedure, **4c** was prepared from triethyl orthopropanoate and purified by Podbielniak vacuum distillation on a 60-cm Heli-pak column: yield 55%; bp 94 °C (20 mmHg); η^{25}_D 1.3960; IR (neat) 2990, 1458, 1310, 1220, 1100 (C–F), 760 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (9 H, t, CH_3CH_2), 1.47 (3 H, d, CH_3CH), 3.57 (1 H, q, CH), 3.59 (6 H, q, CH_2); ^{13}C NMR ($CDCl_3$) δ 16.74, 20.00, 47.92, 60.30, 114.73, 133.32 (q, $J_{^{13}C-^{19}F}$ = 313.6 Hz); ^{19}F NMR ($CDCl_3$) δ 42.3. Anal. Calcd for $C_{10}H_{19}F_3O_3S$: C, 43.47; H, 6.93; S, 11.60. Found: C, 43.18; H, 6.72; S, 11.97.

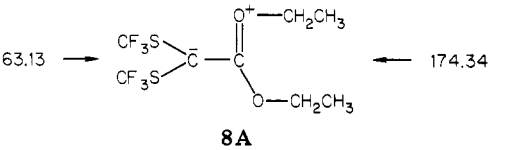
Preparation of 2-[(Trifluoromethyl)thio]propanoic Acid (1b). To a mixture of 48% hydrobromic acid (60 mL) and sodium iodide (0.05 g, 0.003 mol) was added undistilled 1,1,1-triethoxy-2-[(trifluoromethyl)thio]propane (**4c**, 8.0 g, 0.029 mol), and the solution was refluxed for 3 h. Upon cooling, the reaction mixture was saturated with sodium chloride and then extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure at 45 °C. The residual oil was distilled yielding 3.55 g (70%) of **1b**: bp 80–2 °C (33 mmHg); η^{25}_D 1.3920; IR (neat) 3000, 1725, 1460, 1420, 1130 (C–F), 760 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (3 H, d, CH_3), 3.93 (1 H, q, CH); ^{13}C NMR ($CDCl_3$) δ 17.74, 41.61, 130.22 (q, $J_{^{13}C-^{19}F}$ = 304 Hz), 178.67; ^{19}F NMR ($CDCl_3$) δ 41.5. Anal. Calcd for $C_4H_5F_3O_2S$: C, 27.59; H, 2.89; S, 18.41. Found: C, 27.65; H, 2.96; S, 18.74.

Preparation of Ethyl 2-[(Trifluoromethyl)thio]propanoate (5c). To concentrated hydrochloric acid (5 mL) was added 1,1,1-triethoxy-2-[(trifluoromethyl)thio]propane (**4c**, 5.0 g, 18 mmol). The two-phase reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with dichloromethane (3 × 25 mL). The dichloromethane extracts were combined and washed with a saturated sodium bicarbonate solution (2 × 15 mL) then with water (2 × 15 mL). The organic solution was dried over magnesium sulfate and concentrated under reduced pressure at 30 °C. The resulting pale yellow oil (1.5 g) was distilled, yielding 0.875 g (24%) of **5c**: bp 44 °C (8 mmHg); η^{25}_D 1.3847; IR (neat) 2990, 1740, 1120 (C–F), 1025, (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3 H, t, CH_3CH_2), 1.59 (3 H, d, CH_3CH), 3.89 (1 H, q, CH), 4.20 (2 H, q, CH_2); ^{13}C NMR ($CDCl_3$) δ 13.96, 18.40, 41.84, 62.15, 130.32 (q, $J_{^{13}C-^{19}F}$ = 306.6 Hz), 171.13; ^{19}F NMR ($CDCl_3$) δ 41.0. Anal. Calcd for $C_6H_9F_3O_2S$: C, 35.64; H, 4.49; S, 16.14. Found: C, 35.85; H, 4.38; S, 16.02.

Preparation of Ethyl 2,2-Bis[(trifluoromethyl)thio]acetate (7a) via 6. To a cold (−50 °C) solution of trifluoromethanesulfenyl chloride (54.0 g, 0.396 mol) in ether (125 mL) was added, over 10 min, a solution of triethyl orthoacetate (25.7 g, 0.158 mol) in ether (50 mL). The reaction was stirred at −50 °C for 1.5 h. The cooling bath was removed, and the reaction was stirred at ambient temperature for 16 h. The amount of mono- and bis-substituted product was determined by ^1H NMR. Absence of a methylene proton signal for CF_3SCH_2 (δ 3.6–3.7) indicated little if any mono-substituted **4b** in the reaction mixture. Workup yielded 39.4 g (75.5%) of **6** as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.65 (9 H, t, CH_3), 4.25 (6 H, q, CH_2), 5.08 (1 H, s, CH). Crude 1,1,1-triethoxy-2,2-bis[(trifluoromethyl)thio]ethane (**6**, 10.0 g, 0.028 mol) was treated with 48% hydrobromic acid (50 mL) at 100 °C for 30 min. Upon cooling to room temperature, the reaction mixture separated into two layers. The aqueous layer was removed and extracted with dichloromethane (3 × 25 mL). The dichloromethane extracts were combined with the organic layer from the reaction mixture, dried over magnesium sulfate, and concentrated under reduced pressure at 30 °C. The residual oil was distilled under aspirator pressure yielding 2.5 g (31%) of **7a**: bp 75 °C (41 mmHg); η^{25}_D 1.3832; IR (neat) 3000, 1750, 1375, 1130, 1020 (C–F); 870, 765 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, t, CH_3), 4.27 (2 H, q, CH_2), 5.11 (1 H, s, CH); ^{13}C NMR ($CDCl_3$) δ 13.77, 46.88 (SCH, broadened by three-bond coupling to fluorine), 64.10, 128.9 (q, $J_{^{13}C-^{19}F}$ = 309.7 Hz), 166.05; ^{19}F NMR ($CDCl_3$) δ 42.3. Anal. Calcd for $C_6H_6F_6O_2S_2$: C, 25.00; H, 2.10; S, 22.25. Found: C, 25.46; H, 2.16; S, 22.41.

Isolation of 1,1-Diethoxy-2,2-bis[(trifluoromethyl)thio]-ethene (8) via Distillation. The above reaction was repeated, and the residue (28 g) after evaporation at 60 °C was distilled on a Podbielniak vacuum distillation apparatus equipped with a 60-cm Heli-pak distillation column, center cut; 6.76 g; bp 82 °C (6 mmHg); η^{25}_D 1.4157; IR (neat) 3000, 1540, 1380, 1020 (C–F), 760 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3 H, t, CH_3), 4.27 (2 H, q, CH_2); ^{13}C NMR ($CDCl_3$) δ 14.81, 63.13, 69.14, 130.11 (q, $J_{^{13}C-^{19}F}$ = 300 Hz), 174.34; ^{19}F NMR ($CDCl_3$) δ 46.0; mass spectrum, m/e (relative intensity) 316 (M^+, 9), 247 ($M^+ - CF_3$,16), 219 (9), 215 ($M^+ - SCF_3$,6), 191 (13), 145 (27), 29 (100). Anal. Calcd for $C_8H_{10}F_6O_2S_2$: C, 30.38; H, 3.10; S, 20.28. Found: C, 30.91; H, 3.17; S, 20.66.

The two weak vinyl signals in the ^{13}C NMR of **8** (δ 63.13, 174.34) were enhanced by addition of 0.05 M chromium acetylacetonate. We have assigned the *upfield* signal to the bis[(trifluoromethyl)thio]-substituted carbon on the basis of resonance contribution of **8A**, which should shield this carbon as indicated.[22]



8A

The broadening of the δ 63.13 signal (ca. 10 Hz) is the result of three-bond coupling to the fluorine atoms.

Preparation of 2,2-Bis[(trifluoromethyl)thio]acetic Acid (7b). To a mixture of 48% hydrobromic acid (90 mL) and acetic acid (10 mL) was added 1,1,1-triethoxy-2,2-bis[(trifluoromethyl)thio]ethane (**6**, 14.5 g, 0.04 mol) along with sodium iodide (0.5 g, 0.003 mol). The dark solution was refluxed for 20 h. The reaction solution, after cooling to room temperature, was saturated with sodium chloride and extracted with dichloromethane (3 × 75 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure at 30 °C. The residual oil was purified by distillation yielding 5.36 g (51%) of **7b**: bp 101 °C (33 mmHg); IR (neat) 3000, 1725, 1400, 1260, 1125, 815, 760 (CF_3S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (s, CH); ^{13}C NMR ($CDCl_3$) δ 46.86, 129.78 (q, $J_{^{13}C-^{19}F}$ = 309 Hz), 173.34; ^{19}F NMR ($CDCl_3$) δ 43.4. Anal. Calcd for $C_4H_2F_6O_2S_2$: C, 18.46; H, 0.77; F, 43.81; S, 24.65. Found: C, 18.49; H, 0.89; F, 43.98; S, 24.78.

Preparation of Ethyl [(Trichloromethyl)thio]acetate (11b). To a solution of triethyl orthoacetate (36.6 g, 0.226 mol) in carbon tetrachloride (100 mL) was added portionwise trichloromethanesulfenyl chloride (21.3 g, 0.115 mol), and the reaction was warmed to 80 °C. While the mixture refluxed for over 4 h, 2,2′-azobis(2-methylpropionitrile) (0.4 g, 0.003 mol) was added portionwise. Volatiles formed during the course of the reaction were removed through a short-path distillation apparatus. After the mixture cooled to 60 °C, methanesulfonic acid (2–3 mL) was added and the stirring continued at 60 °C for 30 min. The reaction was cooled and then quenched in ice water (200 mL). The resultant two-phase mixture was extracted with chloroform (3 × 100 mL). The combined chloroform extracts were washed with water (until the water washings were pH 5–6) followed by saturated sodium chloride. The chloroform solution was dried over magnesium sulfate and concentrated, yielding a crude liquid which weighed 26.1 g (stench). Short-path distillation yielded 16.0 g (59%) of **11b**: bp 105 °C (0.2 mmHg); η^{25}_D 1.4992; IR (neat) 3000, 1740, 1300, 1270, 1180, 1140, 1020, 805, 765 (C–S), 715 (CCl_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, CH_3), 3.93 (2 H, s, CH_2), 4.21 (2 H, q, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 14.04, 39.00, 62.14, 97.06, 167.16; mass spectrum, *m/e* (relative intensity) 236 (M^+, 2), 201 (M^+ – Cl, 15), 163 (M^+ – $COOC_2H_5$, 10), 137 (25), 109 (15), 79 (33), 29 (100). Anal. Calcd for $C_5H_7Cl_3O_2S$: C, 25.28; H, 2.97; Cl, 44.78; S, 13.50. Found: C, 25.50; H, 3.08; Cl, 44.76; S, 13.77.

The initially formed [(trichloromethyl)thio]orthoacetate **10b** could not be obtained in pure form. As indicated, it was converted directly to the ester **11b** by heating with methanesulfonic acid or hydrogen chloride.

Preparation of 1,1,1-Trimethoxy-2-[(trichloromethyl)thio]ethane (10a). Compound **10a** was prepared by reacting trimethyl orthoacetate with trichloromethanesulfenyl chloride in carbon tetrachloride in the presence of 2,2′-azobis(2-methylpropionitrile). The reaction conditions were the same as those for preparing **11b**. However, in this case, the resulting ortho ester was isolated by quenching in ice water instead of hydrolyzing the product with methanesulfonic acid. The product was extracted into dichloromethane. The organic layer was dried (sodium sulfate) and the solvent removed to afford an oil (**10a**): IR (neat) 3000, 1450, 1260, 1210, 1150, 1075, 1050, 1010, 990, 810, 785, 710 (CCl_3) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (9 H, s, CH_3), 3.65 (2 H, s, CH_2).

Attempted purification of **10a** by vacuum distillation resulted in extensive decomposition.

Preparation of Methyl [(Trichloromethyl)thio]acetate (11a). Compound **11a** was prepared from trimethyl orthoacetate in the same manner as for the preparation of the ethyl ester **11b**. Distillation of the crude product gave a 55% yield of **11a**: bp 95 °C (0.2 mmHg); η^{25}_D 1.5136; IR (neat) 3000 (v w), 1750, 1425, 1300, 1260, 1160, 1140, 1010, 810, 770 (C–S), 720 (CCl_3) cm^{-1}; ^1H NMR δ 3.84 (2 H, s, CH_2), 4.00 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 38.69, 52.90, 97.02, 167.59; mass spectrum, *m/e* (relative intensity) 187 (M^+ – Cl, 100), 133 (74), 113 (82), 105 (M^+ – CCl_3,48), 79 (54). Anal. Calcd for $C_4H_5Cl_3O_2S$: C, 21.50; H, 2.25; Cl, 47.59; S, 14.35. Found: C, 21.70; H, 2.26; Cl, 46.16; S, 14.39.

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Equilibria and Reactions in the Systems Aluminum Chloride–Acetyl Chloride–Aromatic Hydrocarbon in Sulfur Dioxide as Solvent

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Equilibrium constants are obtained for 1:1:1 complexes of $AlCl_3$–acetyl chloride–aromatic hydrocarbon with benzene, *p*-xylene, and mesitylene. The magnetic resonance spectra suggest that these are σ complexes. The rates of Friedel–Crafts acetylation are proportional to the concentration of the σ complex.

There have been many investigations of the mechanism for the Friedel–Crafts acetylation reaction. The rate study of Brown et al. on the acetylation of benzene and toluene with $AlCl_3$ in ethylene dichloride as solvent at 0 and 25 °C showed that the rate was dependent upon the concentrations of the aromatic hydrocarbons and the 1:1 $AlCl_3$–acetyl chloride complex.[2] Complicated kinetic results on the same system at 30 °C were accounted for by the intervention of three acylating species: a 1:1 complex, a complex with two $AlCl_3$'s for each acetyl chloride, and an acetylium ion.[3]

A generalized mechanism for the Friedel–Crafts reaction proposed by Brown and Stock considers the rate-determining step to be the formation of a σ complex by the attacking reagent and the aromatic hydrocarbon.[4] Olah

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