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Superacidified Reaction of Sulfides and Esters for the Direct Synthesis of Sulfonium Derivatives

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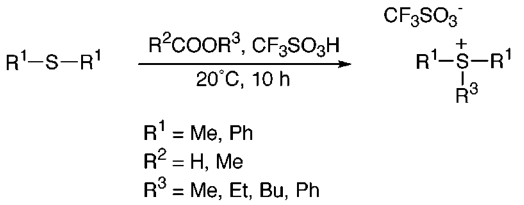
Interest in sulfonium compounds has been stimulated by their useful application as raw materials for the synthesis of drugs and sulfur-containing natural compounds,[1] and a convenient source of carbon radicals via a one-electron reduction.[2] In addition, aryl sulfonium salts are highly photosensitive and can be utilized as efficient photochemical sources of strong Brønsted acids for cationic polymerization of olefins or epoxides and chemically amplified photoresists.[3] In view of the important role of these compounds, there is a real need for a mild and versatile synthetic method. Among a number of synthetic methods described in the literature,[4] the direct synthesis from the corresponding sulfides is preferable due to the simple overall procedure. Many applicable alkylating or arylating reagents for sulfides have been reported such as alkyl iodides,[5] diaryliodonium salts,[6] trialkyloxonium salts,[7] and alcohols or ethers with strong acids employed in excess.[8] Methyl triflate also shows a good reactivity to sulfides, while phenyl triflate does not.[9] Quite recently, a synthetic method for aryl sulfonium salts has been developed by the oxidative coupling of aryl sulfides through a two-electron-transfer process.[10] These routes, however, are deemed unsatisfactory due to the general lack of applicability to a wide variety of symmetrical and unsymmetrical, alkyl and aryl sulfonium salts. There have been few reports on the synthesis of triarylsulfonium salts by the direct arylation of sulfides. We report herein a novel, general, and high-yield preparative method that gives a variety of sulfonium compounds bearing alkyl and/or aryl groups by the acid-promoted reaction of sulfides with esters (Scheme 1).

Scheme 1



Dimethyl sulfide was reacted with 2 equiv of methyl formate in acidic solution at 20 °C to give the trimethylsulfonium salt. The reaction proceeds rapidly and is completed within 2 h. A strong acid with an H_o (Hammett acidity function) below −7.0, such as methanesulfonic acid (−7.9) and sulfuric acid (−11.9), is required for the quantitative formation of the sulfonium product. In particular, trifluoromethanesulfonic acid (−14.1) was the most effective and provided trimethylsulfonium triflate in 93% yield.

Table 1 summarizes the results of the reaction of several other sulfides with esters and shows the wide utility for this transformation. This reaction also proceeds for diaryl sulfides. Diphenyl sulfide was reacted with methyl triflate to produce a diphenylmethylsulfonium triflate as a white crystalline powder in 85% yield (entry 2). Dibenzothiophene and thianthrene could be quantitatively methylated to the corresponding cyclic sulfonium salts under the same conditions (entries 9 and 10).[11] The reaction is also applicable to other chalcogen derivatives such as diphenyl selenide for the preparation of the selenonium salt (entry 11).

The product yield depends on the ester used, with methyl formate (R^2 = H, R^3 = Me) being the most appropriate for the methylation of diphenyl sulfide. The use of acetate esters (R^2 = Me) resulted in a significant decrease in the product yield (entry 4), although R^3 of an ester does not show a significant effect on it; the reaction of diphenyl sulfide with ethyl formate or butyl formate gives diphenylethylsulfonium triflate in 80% yield (entry 3) or diphenylbutylsulfonium triflate in 82% yield (entry 5), respectively. It should be pointed out that, contrary to the classical nucleophilic reaction of sulfides with alkyl halide, the reaction does not give diphenyl *sec*-butylsulfonium triflate; carbon-skeleton rearrangement or chain-branching did not take place. A possible mechanism for this alkylation is shown in Scheme 2 where the superacidified ester would produce the butyloxonium cation as the active alkylating species.[12] The reaction of the butyloxonium cation with sulfide substrates should give the sulfonium product

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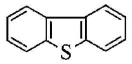
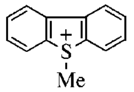
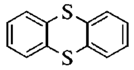
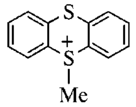
(11) A dimethylated product, *S,S′*-dimethylthianthrenium bistriflate, was not formed under these conditions.

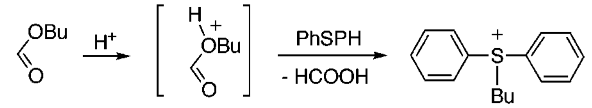
(12) The related oxonium cation, RO^+H_2, appears to form in perchloric acid−alcohol mixtures. In such mixtures, alkyl sulfides are converted into trialkylsulfonium perchlorates without any rearrangement of the alkyl substituents. See: Milligan, T. W.; Minor, B. C. *J. Org. Chem.* **1963**, *28*, 235.

Table 1. Synthesis of Sulfonium Derivatives from Sulfides and Esters[a]

	substrate				
entry	R^1	R^2	R^3	product[b]	yield[c] (%)
1	Me	H	Me	$\mathrm{Me{-}\underset{Me}{\overset{+}{S}}{-}Me}$	93
2	Ph	H	Me	$\mathrm{Ph{-}\underset{Me}{\overset{+}{S}}{-}Ph}$	85
3	Ph	H	Et	$\mathrm{Ph{-}\underset{Et}{\overset{+}{S}}{-}Ph}$	80
4	Ph	Me	Et	$\mathrm{Ph{-}\underset{Et}{\overset{+}{S}}{-}Ph}$	13
5	Ph	H	n-Bu	$\mathrm{Ph{-}\underset{n\text{-}Bu}{\overset{+}{S}}{-}Ph}$	82
6[d]	Ph	Me	Ph	$\mathrm{Ph{-}\underset{Ph}{\overset{+}{S}}{-}Ph}$[e]	36
7[d]	Ph	H	Ph	$\mathrm{Ph{-}\underset{Ph}{\overset{+}{S}}{-}Ph}$	45
8[d]	Ph	Ph	Ph	—	0
9		H	Me		86
10		H	Me		94
11[f]	Ph	H	Me	$\mathrm{Ph{-}\underset{Me}{\overset{+}{Se}}{-}Ph}$	98

[a] Standard reaction conditions: 10 mmol of sulfide and 20 mmol of ester in 5mL of trifluoromethanesulfonic acid, 20 °C, 10 h. [b] As triflate. [c] Isolated yields. [d] A 1:10 (w/v) solution of phosphorus pentoxide in trifluoromethanesulfonic acid was used. [e] Isolated as hexafluoroantimonate after metathesis with $NaSbF_6$. [f] Diphenyl selenide was used as substrate.

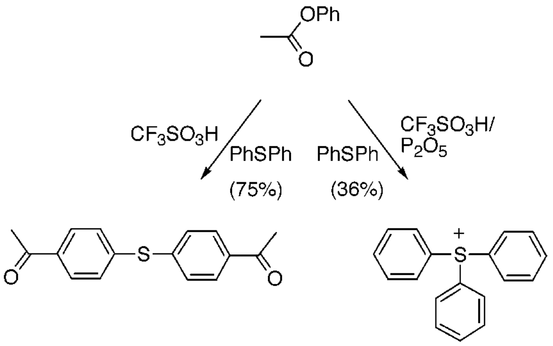
Scheme 2



without the rearrangement of the alkyl substituents. The increased yields with formates instead of acetates probably reflects the stability of the oxonium cations, where those from the acetate are more stabilized by hyperconjugative interactions from the methyl group. Since under the reaction conditions the esters are all protonated the differences in ion stability get translated into leaving group efficiency, the protonated formate being the more reactive species relative to the protonated acetates.

In attempts to prepare triarylsulfonium salts, the reaction of diphenyl sulfide with phenyl acetate in trifluoromethanesulfonic acid did not yield triphenylsulfonium triflate, but bis(4-acetylphenyl) sulfide in 75% yield (Scheme 3). When the reaction is conducted in a

Scheme 3



1:10 (w/v) solution of phosphorus pentoxide in trifluoromethanesulfonic acid, triphenylsulfonium hexafluoroantimonate was obtained in 36% yield after metathesis with $NaSbF_6$ (entry 6). As a main byproduct, phenol was identified in the phenylation reaction. The reaction also proceeds for phenyl formate to give triphenylsulfonium triflate in 45% yield (entry 7). The reaction of phenyl benzoate with diphenyl sulfide, however, did not give the sulfonium product (entry 8).

In conclusion, we have developed a new valuable methodology for the preparation of arylsulfonium compounds as well as alkylsulfonium and selenonium derivatives by a simple procedure. The selective transformation of sulfides to sulfonium derivatives should be well suited for the synthesis of natural products containing sensitive subunits. Mechanistic studies and the use of this synthetic methodology to develop other alkylation/arylation reactions are currently in progress.

Experimental Section

IR spectra were obtained using a FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts are referenced downfield from TMS. All chemicals used were commercially available reagent grade, which were checked for purity by boiling point and/or IR and NMR spectroscopies. Solids were recrystallized and liquids were distilled before use.

General Procedures for the Reaction of Sulfides with Esters. Four examples of the reaction of sulfides with esters for the preparation of sulfonium derivatives are given which typify the general synthetic methods used during the course of this work.

Trimethylsulfonium Triflate. To a stirred mixture of 0.62 g (10 mmol) of dimethyl sulfide and 1.20 g (20 mmol) of methyl formate was added 5 mL of trifluoromethanesulfonic acid, and the mixture was held at 0 °C in an ice bath. The reaction mixture was stirred for 10 h while it warmed to 20 °C. The progress of the reaction was followed by TLC analysis ($CHCl_3$). After the reaction, the mixture was poured into 100 mL of diethyl ether causing precipitation of a white powder. The product was isolated by filtration, washed with ether, and dried at 20 °C in a vacuum to give trimethylsulfonium triflate (93% yield): IR (KBr) 3030 (ν_{CH_3}), 1272, 1093 (ν_{SO}), 1263, 1161, 634 (ν_{CF}) cm^{-1}; ^1H NMR (D_2O) δ 2.89 (s, 9H); ^{13}C NMR (D_2O) δ 26.7. Anal. Calcd for $C_4H_9F_3O_3S_2$: C, 21.24; H, 4.01; S, 28.35. Found: C, 21.51; H, 4.22; S, 28.07.

Diphenylmethylsulfonium Triflate. To a stirred mixture of 1.86 g (10 mmol) of diphenyl sulfide and 1.20 g (20 mmol) of methyl formate was added 5 mL of trifluoromethanesulfonic acid, and the mixture was held at 0 °C in an ice bath. The reaction mixture was stirred for 10 h while it warmed to 20 °C. The progress of the reaction was followed by TLC analysis ($CHCl_3$). After the reaction, the mixture was poured into 100 mL of distilled water. The resulting white suspension was extracted with three 100 mL portions of dichloromethane. The combined dichloromethane solution was evaporated to 10 mL and then poured into 200 mL of diethyl ether causing precipitation of a white powder. The product was isolated by filtration, washed with ether, and dried at 20 °C in a vacuum to give diphenylmethylsulfonium triflate (85% yield): IR (KBr) 3098 (ν_{CH}), 1271, 1092 (ν_{SO}), 1258, 1159, 637 (ν_{CF}) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.99 (s, 3H), 7.78−8.16 (m, 10H); ^{13}C NMR (acetone-d_6) δ 28.0, 128.0, 130.9, 132.0, 135.1. Anal. Calcd for $C_{14}H_{13}F_3O_3S_2$: C, 47.99; H, 3.74; S, 18.30. Found: C, 48.06; H, 3.98; S, 18.13.

Triphenylsulfonium Hexafluoroantimonate. To a stirred mixture of 1.86 g (10 mmol) of diphenyl sulfide and 2.72 g (20 mmol) of phenyl acetate was added 5 mL of freshly prepared 1:10 solution of phosphorus pentoxide (0.50 g) in trifluoromethanesulfonic acid, and the mixture was held at 0 °C in an ice bath. The reaction mixture was stirred for 10 h while it warmed to 20 °C. The progress of the reaction was followed by TLC analysis ($CHCl_3$). The color of the reaction gradually became dark red. After the reaction, the mixture was poured into 100 mL of distilled water. To the slightly turbid solution there was then added 7.76 g (30 mmol) of sodium hexafluoroantimonate, and a pale brown oil separated. The oil was extracted with three 100 mL portions of dichloromethane. The combined dichloromethane solution was evaporated to 10 mL and then poured into 200 mL of diethyl ether to precipitate a powder. The product was recrystallized from ethanol/2-propanol to give triphenylsulfonium hexafluoroantimonate (36% yield): IR (KBr) 3058 (ν_{CH}), 1679, 1580 ($\nu_{C=C}$) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67−7.72 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 126.6, 131.5, 131.9, 133.8. Anal. Calcd for $C_{18}H_{15}F_6SSb$: C, 43.32; H, 3.03; S, 6.42. Found: C, 43.15; H, 3.33; S, 6.35.

Triphenylsulfonium Triflate. To a stirred mixture of 1.86 g (10 mmol) of diphenyl sulfide and 2.44 g (20 mmol) of phenyl formate was added 5 mL of freshly prepared 1:10 solution of phosphorus pentoxide (0.50 g) in trifluoromethanesulfonic acid, and the mixture was held at 0 °C in an ice bath. The reaction mixture was stirred for 10 h while it warmed to 20 °C. The progress of the reaction was followed by TLC analysis ($CHCl_3$). The color of the reaction gradually became dark purple. After the reaction, the mixture was poured into 100 mL of distilled water. The slightly turbid solution was extracted with three 100 mL portions of dichloromethane. The combined dichloromethane solution was evaporated to 10 mL and then poured into 200 mL of diethyl ether, causing precipitation of a pale red powder. The crude product was washed with water and recrystallized twice from ethyl acetate to give triphenylsulfonium triflate (45% yield): IR (KBr) 3060 (ν_{CH}), 1273, 1066 (ν_{SO}), 1258, 1156, 639 (ν_{CF}) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.61−7.70 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 124.6, 131.4, 131.6, 135.1. Anal. Calcd for $C_{19}H_{15}F_3O_3S_2$: C, 55.33; H, 3.67; S, 15.55. Found: C, 55.74; H, 3.99; S, 15.13.

Diphenylethylsulfonium Triflate. See the preparation of diphenylmethysulfonium triflate for details. Compounds used were diphenyl sulfide (1.86 g, 10 mmol), ethyl formate (1.48 g, 20 mmol), and trifluoromethanesulfonic acid (5 mL). The extraction/precipitation solvents were dichloromethane/diethyl ether to afford 2.80 g (80%) of the title compound: IR (KBr) 3063 (ν_{CH}), 1269, 1092 (ν_{SO}), 1260, 1161, 637 (ν_{CF}) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 1.40 (t, 3H, J = 7.2 Hz), 4.40 (q, 2H, J = 7.2 Hz), 7.76−8.18 (m, 10H); ^{13}C NMR (acetone-d_6) δ 8.2, 38.5, 124.3, 130.0, 130.6, 133.7. Anal. Calcd for $C_{15}H_{15}F_3O_3S_2$: C, 49.44; H, 4.15; S, 17.60. Found: C, 49.76; H, 4.45; S, 17.29.

Diphenylbutylsulfonium Triflate. See the preparation of diphenylmethysulfonium triflate for details. Compounds used were diphenyl sulfide (1.86 g, 10 mmol), butyl formate (2.04 g, 20 mmol), and trifluoromethanesulfonic acid (5 mL). The extraction/precipitation solvents were dichloromethane/diethyl ether to afford 3.22 g (82%) of the title compound: IR (KBr) 3073 (ν_{CH}), 1267, 1094 (ν_{SO}), 1155, 637 (ν_{CF}) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 0.93 (t, 3H, J = 7.3 Hz), 1.56−1.65 (m, 2H), 1.77−1.85 (m, 2H), 4.47 (t, 2H, J = 7.5 Hz), 7.76−8.22 (m, 10H); ^{13}C NMR (acetone-d_6) δ 13.6, 21.9, 27.2, 44.6, 126.3, 131.7, 132.2, 135.3. Anal. Calcd for $C_{17}H_{19}F_3O_3S_2$: C, 52.03; H, 4.88; S, 16.34. Found: C, 52.00; H, 5.11; S, 16.02.

***S*-Methyldibenzothiophenium Triflate.** See the preparation of diphenylmethysulfonium triflate for details. Compounds used were dibenzothiophene (1.84 g, 10 mmol), methyl formate (1.20 g, 20 mmol), and trifluoromethanesulfonic acid (5 mL). The extraction/precipitation solvents were dichloromethane/diethyl ether to afford 3.00 g (86%) of the title compound: IR (KBr) 3053, 3010 (ν_{CH}), 1260, 1092 (ν_{SO}), 1159, 637 (ν_{CF}) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.70 (s, 3H), 7.82−8.02 (m, 4H), 8.47 (d, 2H, J = 7.9 Hz), 8.57 (d, 2H, J = 8.3 Hz); ^{13}C NMR (acetone-d_6) δ 35.2, 125.1, 128.9, 132.0, 132.5, 134.8, 140.3. Anal. Calcd for $C_{14}H_{11}F_3O_3S_2$: C, 48.27; H, 3.18; S, 18.41. Found: C, 48.50; H, 3.34; S, 18.35.

***S*-Methylthianthrenium Triflate.** See the preparation of diphenylmethysulfonium triflate for details. Compounds used were thianthrene (2.16 g, 10 mmol), methyl formate (1.20 g, 20 mmol), and trifluoromethanesulfonic acid (5 mL). The extraction/precipitation solvents were dichloromethane/diethyl ether to afford 3.58 g (94%) of the title compound: IR (KBr) 3083 (ν_{CH}), 1272, 1069 (ν_{SO}), 1263, 1159, 637 (ν_{CF}) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.50 (s, 3H), 7.76−8.36 (m, 8H); ^{13}C NMR (acetone-d_6) δ 25.5, 120.3, 130.6, 131.1, 134.7, 135.3, 136.6. Anal. Calcd for $C_{14}H_{11}F_3O_3S_3$: C, 44.20; H, 2.91; S, 25.29. Found: C, 44.28; H, 3.03; S, 25.03.

Diphenylmethylselenonium Triflate. See the preparation of diphenylmethysulfonium triflate for details. Compounds used were diphenyl selenide (2.33 g, 10 mmol), methyl formate (1.20 g, 20 mmol), and trifluoromethanesulfonic acid (5 mL). The extraction/precipitation solvents were dichloromethane/diethyl ether to afford 3.89 g (98%) of the title compound: IR (KBr) 3048 (ν_{CH}), 1271, 1073 (ν_{SO}), 1258, 1175, 637 (ν_{CF}) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3H), 7.58−7.72 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 26.8, 127.3, 130.3, 131.3, 133.2. Anal. Calcd for $C_{14}H_{13}F_3O_3SSe$: C, 42.33; H, 3.30; S, 8.07. Found: C, 42.47; H, 3.02; S, 8.40.

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