Chlorolysis of β-functionalized alkyl polyfluoroalkenyl sulfides

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Chlorolysis of β-functionalized alkyl polyfluoroalkenyl sulfides giving rise to β-functionalized polyfluoroalkenesulfenyl chlorides was examined. β-Cyano-containing sulfenyl chlorides underwent intramolecular cyclization at the nitrile group to form substituted isothiazoles.

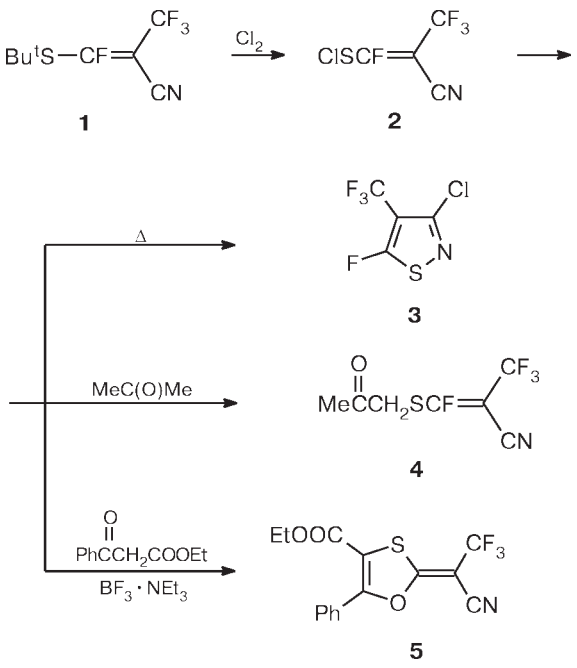
Key words: chlorolysis, alkyl polyfluoroalkenyl sulfides, polyfluoroalkenesulfenyl chlorides, sulfenylation.

Interest in the chemistry of fluorine-containing sulfenyl chlorides arises primarily from their preparative importance as convenient and sometimes unique synthons for the insertion of polyfluoroalkylthio groups into various organic compounds.[1] The presence of additional functional groups in sulfenyl chlorides makes it possible to substantially enhance their synthetic potential, particularly, for the preparation of heterocyclic compounds. Theoretical and applied aspects of the chemistry of α,β-unsaturated fluorine-containing organic derivatives of divalent sulfur, including sulfenyl chlorides, have attracted growing interest in recent years.[2] At the same time, of all functionalized derivatives of polyfluoroalkenesulfenyl chlorides, only 1,3,3,3-tetrafluoro-2-(methoxycarbonyl)propenesulfenyl chloride has been described and investigated in sufficient detail.[3—5] In the present study, we examined the possibility of the preparation of new representatives of sulfenyl chlorides of this type by chlorolysis of functionalized alkyl vinyl sulfides, which are presently readily accessible owing to a procedure developed by us previously.[6]

Results and Discussion

It appeared that *tert*-butyl 2-cyano-1,3,3,3-tetrafluoropropenyl sulfide (**1**) is inert with respect to sulfuryl chloride even upon refluxing. Its chlorolysis proceeds in excess chlorine in a sealed glass tube at 20 °C. The resulting sulfenyl chloride **2** is thermally labile and undergoes intramolecular cyclization to form substituted isothiazole **3** upon distillation. However, we detected sulfenyl chloride **2** in the reactions with CH-acids. Thus, its reaction with acetone gave rise to sulfide **4**, whereas the product of sufenylation of benzoylacetoacetic ester was isolated as substituted alkylidene-1,3-oxathiole **5** after treatment with the $BF_3 \cdot NEt_3$ complex (Scheme 1).

Scheme 1



Unlike sulfide **1**, *tert*-butyl 2-cyano-1,2-difluorovinyl sulfide (**6**) readily reacted with sulfuryl chloride. As a result, the product of cyclization and simultaneous chlorination, *viz.*, isothiazoline **7**, was isolated in 15% yield (Scheme 2). The major portion of the reaction products is a complex higher-boiling mixture, which presumably

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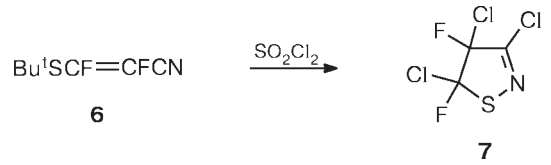
consists of polysulfides and intermolecular cyclization products.

Scheme 2

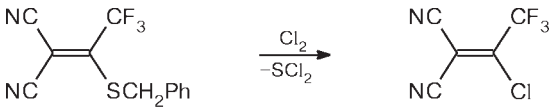


6 **7**

Isothiazole **5** and isothiazoline **7** are colorless labile liquids. Their structures were confirmed by ^{19}F NMR spectroscopy, mass spectrometry, and elemental analysis. Examples of intramolecular heterocyclization of sulfenyl chlorides at the nitrile group of nonfluorinated compounds were reported in the literature (see, for example, Ref. 7).

Even in the cold, chlorolysis of 2-benzylthio-1,1-dicyano-3,3,3-trifluoropropene (**8**) led to the cleavage of the C—S bonds yielding sulfur dichloride and 2-chloro-1,1-dicyano-3,3,3-trifluoropropene (**9**) (Scheme 3).

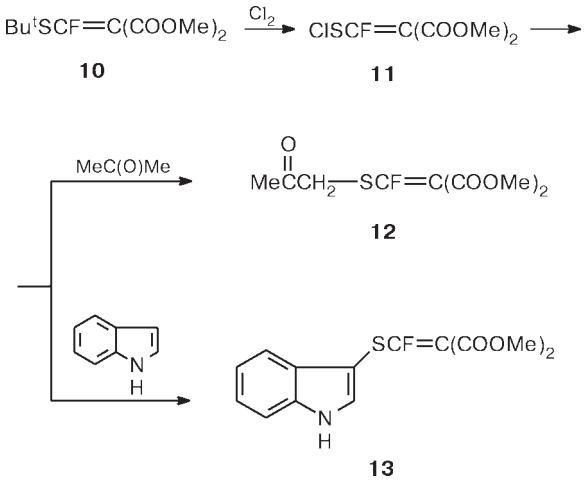
Scheme 3



8 **9**

The reaction of *tert*-butyl 1-fluoro-2,2-di(methoxycarbonyl)vinyl sulfide (**10**) with chlorine afforded crystalline sulfenyl chloride **11**, which reacted with acetone and indole to give the expected products **12** and **13**, respectively (Scheme 4).

Scheme 4

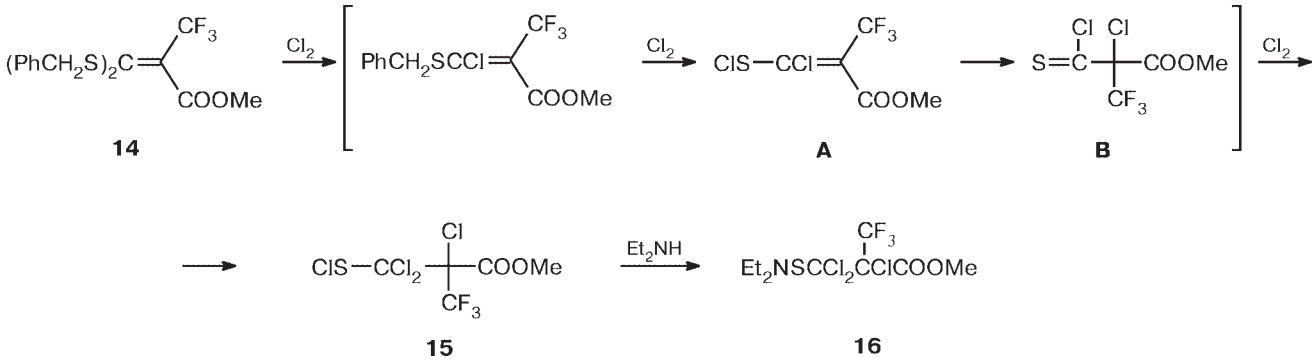


10 **11** **12** **13**

Under the conditions typical of chlorolysis of benzyl sulfides, the reaction of methyl β,β-bis(benzylthio)trifluoromethacrylate (**14**) with chlorine afforded a complex mixture inseparable by fractionation. According to the data from GLC-mass spectrometry, this mixture contained 1,1,2-trichloro-3,3,3-trifluoro-2-(methoxycarbonyl)propanesulfenyl chloride (**15**) (*m/z*: 326 [M^+]). The fact that the double bond in vinyl sulfide **14** is chlorinated (which is untypical of such compounds) as well as the mass spectra of other products suggest that the reaction involves the 1,3-migration of chlorine from the S atom of sulfenyl chloride **A** (*m/z*: 254 [M^+], two isomers) to the C_β atom to form thiocarbonyl compound **B** (*m/z*: 254 [M^+]). Chlorination of the latter gave rise to sulfenyl chloride **15** (Scheme 5). Chlorotropism in the carbon—carbon—sulfur triad was exemplified by perfluoro-2-methyl-2-pent-3-enesulfenyl chloride.[8]

Sulfenyl chloride **15** was prepared in the individual form by the reaction performed with an excess of chlo-

Scheme 5



14 **A** **B** **15** **16**

rine in a sealed tube at 50 °C and was detected in the reaction with diethylamine (see Scheme 5).

Experimental

The ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer (188.31 MHz). The ^{1}H NMR spectra were measured on a Bruker AC-300SF instrument (300.13 MHz). The chemical shifts (δ) are given relative to CF_3COOH (^{19}F, external standard) and Me_4Si (^{1}H, internal standard). The mass spectra (EI) of the reaction products were obtained on an HP-5890 gas chromatograph equipped with an HP-5972 mass-selective detector; the energy of ionizing electrons was 70 eV.

The starting β-functionalized alkyl polyfluoroalkenyl sulfides were prepared according to a procedure described previously.[6]

2-Cyano-1,3,3,3-tetrafluoropropenesulfenyl chloride (2). Sulfide **1** (4.55 g, 0.02 mol) was placed in a glass tube and chlorine (2.1 g, 0.03 mol) was condensed into the tube at −78 °C. Then the tube was sealed, slowly (3 h) heated to 20 °C, kept for 5 h, and opened. Volatile products were removed *in vacuo* (50 Torr) and the remaining sulfenyl chloride **2** was used in subsequent reactions without additional purification. ^{19}F NMR ($CDCl_3$): 18.3 (m, 3 F, CF_3); 33.8 (m, 1 F, CF).

3-Chloro-5-fluoro-4-(trifluoromethyl)isothiazole (3). Sulfenyl chloride **2** (4.1 g, 0.02 mol) was fractionated *in vacuo* (50 Torr). Repeated distillation afforded isothiazole **3** in a yield of 2.2 g (54%), b.p. 55—57 °C (50 Torr). Found (%): C, 23.48. C_4ClF_3NS. Calculated (%): C, 23.36. ^{19}F NMR ($CDCl_3$): −24.4 (q, 1 F, CF, $J_{F,F}$ = 18 Hz); 17.3 (d, 3 F, CF_3, $J_{F,F}$ = 18 Hz). MS, *m/z*: 205 $[M]^+$.

3-(2-Cyano-1,3,3,3-tetrafluoropropenylthio)propan-2-one (4). Acetone (2.9 g, 0.05 mol) was added with stirring to sulfenyl chloride **2** (2.05 g, 0.01 mol). The reaction mixture became colorless and hydrogen chloride was evolved. The mixture was kept at 20 °C for 2 h and then fractionated. Compound **4** was obtained in a yield of 1.2 g (53%), b.p. 91—94 °C (3 Torr). Found (%): C, 37.07; H, 2.21. $C_7H_5F_4NOS$. Calculated (%): C, 37.00; H, 2.20. ^{1}H NMR (DMSO-d_6): 2.29 (s, 3 H, Me); 4.38 (s, 2 H, CH_2). MS, *m/z*: 227 $[M]^+$.

2-(1-Cyanotrifluoroethylidene)-4-ethoxycarbonyl-5-phenyl-1,3-oxathiole (5). A mixture of sulfenyl chloride **2** (2.05 g, 0.01 mol) and ehtyl benzoylacetate (1.9 g, 0.01 mol) was kept at 20 °C until evolution of hydrogen chloride ceased (24 h) and then dissolved in ether (20 mL). Then the $BF_3 \cdot NEt_3$ complex (3.4 g, 0.02 mol) was added and the reaction mixture was stirred for 3 h. The precipitate that formed was filtered off and the filtrate was washed with 5% HCl (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. Compound **5** was obtained in a yield of 1.6 g (48%), m.p. 68—70 °C. Found (%): C, 52.90; H, 2.91. $C_{15}H_{10}F_3NO_3S$. Calculated (%): C, 52.79; H, 2.93. ^{1}H NMR (DMSO-d_6): 1.31 (t, 3 H, Me, J = 7 Hz); 4.30 (q, 2 H, CH_2, J = 7 Hz); 7.56 and 7.87 (both m, 3 H and 2 H, Ph). ^{19}F (DMSO-d_6): 24.6 and 25.9 (both s, ratio was 2 : 1, CF_3). MS, *m/z*: 341 $[M]^+$.

3,4,5-Trichloro-4,5-difluoroisothiazoline (7). Sulfuryl chloride (8.0 g, 0.06 mol) was added dropwise with stirring and cooling (5—10 °C) to sulfide **6** (3.5 g, 0.02 mol). The reaction mixture was kept at 20 °C until gas evolution ceased (3 h) and then fractionated. Compound **7** was obtained in a yield of 0.7 g (15%), b.p. 65—66 °C (50 Torr). Found (%): C, 15.97. $C_3Cl_3F_2NS$. Calculated (%): C, 15.89. ^{19}F NMR ($CDCl_3$): −57.8 and −16.6 (both d, 2 CF, $J_{F,F}$ = 5 Hz); −32.2 and −7.5 (both d, 2 CF, $J_{F,F}$ = 17 Hz), the ratio of the isomers was 1 : 1. MS, *m/z*: 225 $[M]^+$.

Chlorolysis of 2-benzylthio-1,1-dicyano-3,3,3-trifluoropropylene. Dry chlorine (1.4 g, 0.02 mol) was condensed with cooling to −78 °C into a flask containing compound **8** (2.7 g, 0.01 mol). The reaction mixture was slowly heated with stirring to 20 °C and then fractionated. As a result, SCl_2 and 2-chloro-1,1-dicyano-3,3,3-trifluoropropylene (**9**) were obtained whose physicochemical and spectroscopic characteristics correspond to the published data.[9]

1-Fluoro-2,2-di(methoxycarbonyl)ethenesulfenyl chloride (11). An excess of dry chlorine was bubbled with stirring through sulfide **10** (25.0 g, 0.1 mol), the temperature being maintained at no higher than 20 °C. The reaction was accompanied by the formation of a precipitate. After completion of the exothermic reaction, the mixture was diluted with an equal volume of hexane and the precipitate was filtered off. Compound **11** was obtained in a yield of 19.0 g (83%), m.p. 34—36 °C. Found (%): C, 31.64; H, 2.67. $C_6H_6ClFO_4S$. Calculated (%): C, 31.51; H, 2.63. ^{1}H NMR ($CDCl_3$): 3.80 (s, 2 OMe). ^{19}F NMR ($CDCl_3$): 14.9 (s, CF).

1-[1-Fluoro-2,2-di(methoxycarbonyl)vinylthio]propan-2-one (12) was prepared analogously to compound **4** from sulfenyl chloride **11** and acetone. The yield was 91%, m.p. 45—47 °C. Found (%): C, 43.33; H, 4.38. $C_9H_{11}FO_5S$. Calculated (%): C, 43.20; H, 4.40. ^{1}H NMR (DMSO-d_6): 2.25 (s, 3 H, Me); 3.78 (s, 6 H, 2 OMe); 4.07 (s, 2 H, CH_2). MS, *m/z*: 250 $[M]^+$.

3-[1-Fluoro-2,2-di(methoxycarbonyl)vinylthio]indole (13). A solution of sulfenyl chloride **11** (2.3 g, 0.01 mol) in benzene (10 mL) was added dropwise with stirring and cooling to 10 °C to a solution of indole (1.2 g, 0.01 mol) in benzene (20 mL), the formation of an abundant precipitate taking place. The reaction mixture was refluxed until evolution of HCl ceased (6 h). Then the solvent was removed *in vacuo*, the product was extracted from the residue with hot hexane, and the crystals that formed upon cooling were filtered off. Compound **13** was obtained in a yield of 1.6 g (53%), m.p. 74—76 °C. Found (%): C, 54.49; H, 3.86. $C_{14}H_{12}FNO_4S$. Calculated (%): C, 54.37; H, 3.88. ^{1}H NMR (DMSO-d_6): 3.70 and 3.81 (both s, 3 H each, OMe); 7.18 and 7.52 (both m, 2 H each, C_6H_4); 7.79 (s, 1 H, CH); 11.80 (br.s, 1 H, NH). MS, *m/z*: 309 $[M]^+$.

1,1,2-Trichloro-3,3,3-trifluoro-2-(methoxycarbonyl)propanesulfenyl chloride (15). Sulfide **14** (4.0 g, 0.01 mol) was placed in a glass tube and chlorine (2.1 g, 0.03 mol) was condensed into the tube at −78 °C. The tube was sealed, slowly (3 h) warmed to 20 °C, kept for 24 h, heated at 50 °C for 2 h, and opened. The mixture was fractionated to obtain sulfenyl chloride **15** in a yield of 1.6 g (49%), b.p. 65—67 °C (2 Torr). Found (%): C, 18.56; H, 1.01. $C_5H_3Cl_4F_3O_2S$. Calculated (%): C, 18.40; H, 0.92. ^{1}H NMR ($CDCl_3$): 3.83 (s, OMe). MS, *m/z*: 326 $[M]^+$.

***N,N*-Diethyl-[1,1,2-trichloro-3,3,3-trifluoro-2-(methoxycarbonyl)propane]sulfenylamide (16).** A solution of diethylamine (1.5 g, 0.02 mol) in ether (10 mL) was added dropwise with stirring to a solution of sulfenyl chloride **15** (3.3 g, 0.01 mol) in ether (20 mL) at 0 °C. The reaction mixture was kept at 20 °C for 3 h, the precipitate that formed was filtered off, and the

filtrate was fractionated. Sulfenylamide **16** was obtained in a yield of 1.9 g (52%), b.p. 92—94 °C (1 Torr). Found (%): C, 29.61; H, 3.55. $C_9H_{13}Cl_3F_3NO_2S$. Calculated (%): C, 29.79; H, 3.59. ^{1}H NMR (DMSO-d_6): 1.20 (t, 6 H, 2 Me, J = 7 Hz); 3.30 and 3.45 (both sept, 2 H each, 2 CH_2, J = 7 Hz); 3.96 (s, 3 H, OMe). ^{19}F NMR (DMSO-d_6): 12.6 (s, CF_3).

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