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PERFLUOROALKYLATION OF 2-THIOPYRIMIDINE DERIVATIVES

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The method of perfluoroalkylation of heterocyclic thiols and disulfides by thermolytic reaction with xenon(II) bisperfluoroalkylcarboxylates has been extended to sulfur-containing pyrimidines, including 2-mercaptopyrimidines, symmetrical disulfides, and S-trifluoroacetyl derivatives obtained from the corresponding thiols. The main reaction products are 2-SC_nF_{2n+1} (n = 1, 2)-substituted pyrimidines. Their formation proceeds only via disulfides into which the initial thiols and S-trifluoroacetyl derivatives are converted in the reaction medium. Side reactions occurred in the case of trifluoromethylation linked with the perfluoroalkylation of the pyrimidine nucleus at the free 5 position (in the case of the 4,6-dimethyl derivative), or at position 4 or 4 and 5 (for unsubstituted pyrimidine). In addition, the introduction of the CF_3 group at one of the methyl substituents was confirmed by the formation of CH_2CF_3 fragment.

Keywords: 4,6-dimethyl-2-perfluoroalkylthiopyrimidines, 4,6-dimethyl-5-trifluoromethyl-2-trifluoromethylthiopyrimidine, 4-methyl-6-(2,2,2-trifluoroethyl)-2-trifluoromethylthiopyrimidine, 2-perfluoroalkylthiopyrimidines, 4-trifluoromethyl-2-trifluoromethylthiopyrimidine, and 4,5-bistrifluoromethyl-2-trifluoromethylthiopyrimidine, perfluoroalkylation of heterocyclic thiols and disulfides.

We recently developed a method of perfluoroalkylating sulfur-containing derivatives of heterocyclic compounds by thermolytic reaction with xenon(II) bisperfluoroalkylcarboxylates [1-3]. The method enables working with available starting materials, such as thiols and disulfides, inserting SC_nF_{2n+1} (when n = 1-3) fragments in fairly high yield, carrying out the synthesis under mild conditions, and isolating the desired compounds relatively easily.

In the present work the method is successfully extended to sulfur-containing pyrimidines. Starting materials taken were derivatives of 2-mercaptopyrimidines (previously subjected to trifluoromethylation in the presence of CF_3Br/NaH [4] and CF_3I/NH_3 [5], in the latter case with UV irradiation), their S-trifluoroacetyl derivatives, obtained *in situ* in the presence of trifluoroacetic anhydride, and also symmetrical disulfides obtained by the oxidation of the corresponding thiols [6]. Generation of xenon bisperfluoroalkylcarboxylates was effected either beforehand (method A) or *in situ* (method B). On thermolysis of the xenon compounds in the presence of thiopyrimidine derivatives perfluoroalkylation of the latter occurs. It was discovered that the main reaction products are 2-SC_nF_{2n+1} (n = 1, 2)-substituted pyrimidines, while their formation occurs only *via* disulfides. Conversion of the initial thiols **1** and S-trifluoroacetyl derivatives **2** into disulfides occurs in the reaction medium, as established by TLC. On trifluoromethylation of compounds **1-3** (by methods A and B) 4,6-dimethyl-2-trifluoromethylthiopyrimidine (**4a**), 4,6-dimethyl-5-trifluoromethyl-2-trifluoromethylthiopyrimidine (**5**), and 4-methyl-6-(2,2,2-trifluoroethyl)-2-trifluoromethylthiopyrimidine (**6**) were formed in molar ratios 1.0:0.48:0.13.

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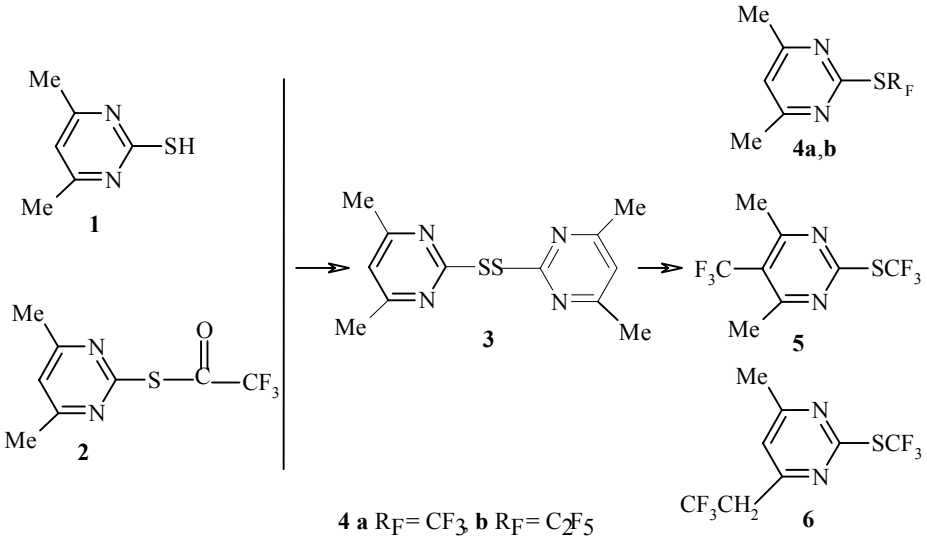
Selective perfluoroalkylation of the sulfur-containing groups occurs in the presence of xenon bisperfluoroethylcarboxylate with the formation of only 4,6-dimethyl-2-pentafluoroethylthiopyrimidine (**4b**) (see Scheme), which is probably caused by the effect of steric factors on the process of inserting a pentafluoroethyl radical into the heteroaromatic nucleus.



4 a R_F= CF_3, **b** R_F= C_2F_5

Compounds **4a,b**, **5**, and **6** were readily identified by NMR spectra. In the ^{1}H NMR spectrum of the first two compounds singlets were present for the methyl groups at 2.44 and 2.45 ppm and also singlets for the pyrimidine ring protons at 6.86 and 6.81 ppm respectively. In the spectrum of derivative **5** only a quadruplet appeared for the methyl protons at 2.66 ppm with $^5J_{CH3\text{-}CF3}$ = 2.7 Hz. In the case of compound **6** three signals were observed: a singlet for methyl group at 2.53 ppm, a quadruplet for CH_2 group of the trifluoroethyl fragment at 3.52 ppm with J = 10.3 Hz, and also a singlet for the pyrimidine ring proton at 7.05 ppm. The fluorine homologs **4a** and **4b** were readily distinguished by the ^{19}F NMR spectra. In the case of compound **4a** one signal was observed for the SCF_3 group at -44.28 ppm and for compound **4b** there were two peaks at -93.09 and -83.20 ppm corresponding to the SCF_2 and CF_3 fragments. The spectra of pyrimidines **5** and **6** were characterized by the presence of pairs of signals for the various CF_3 groups, belonging both to the SCF_3 fragment at -41.34 and -41.37 ppm and to the CF_3 substituent in the pyrimidine ring at -55.85 ppm or to the trifluoroethyl group at -61.29 ppm.

The maximum yields of compounds **4a,b** were 28 and 19% respectively, achieved at molar ratios of reactants **1-3** to R_FCOOH to XeF_2 of 1:6:3. Overall the process of perfluoroalkylating compound **3** may be represented as follows.

$$RSSR + (R_FCOO)_2Xe \longrightarrow RSSR^{\bullet+} + (R_FCOO)_2Xe^{\bullet-}$$

$$(R_FCOO)_2Xe^{\bullet-} \longrightarrow R_FCOO^{\bullet} + R_FCOO^{-} + Xe$$

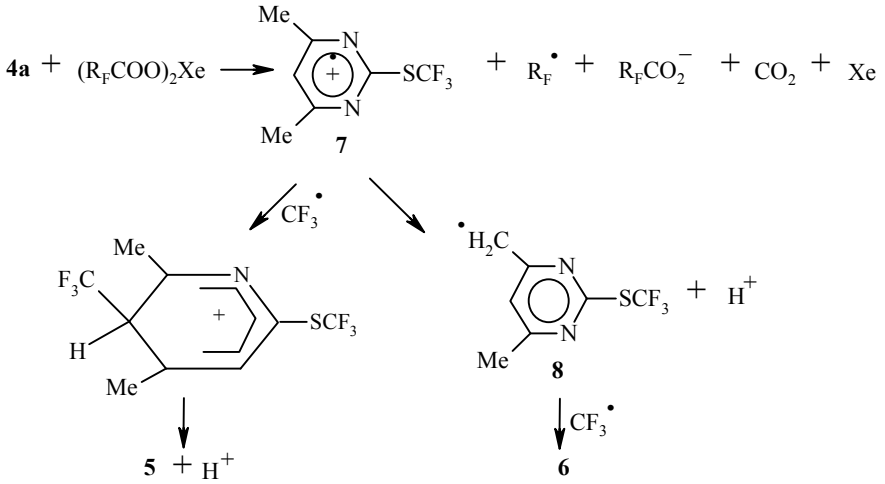
$$R_FCOO^{\bullet} \longrightarrow R_F^{\bullet} + CO_2$$

$$RSSR^{\bullet+} \longrightarrow RS^{\bullet} + RS^{+}$$

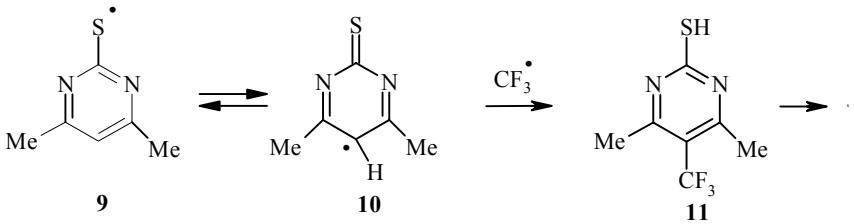
R = 2-pyrimidinyl; 4,6-dimethyl-2-pyrimidinyl

Reaction may be initiated by the transfer of an electron from disulfide RSSR to molecule of xenon bisperfluoroalkylcarboxylate with the formation of a cation radical and an anion radical [7]. The latter is converted into a mixture of perfluoroalkyl radical, perfluoroalkanoate, carbon dioxide, and xenon, while the cation radical may decompose into two particles $RS^{\cdot}$ and RS^{+}. Recombination of the radicals $RS^{\cdot}$ and $RF^{\cdot}$ leads to the formation of the expected compounds **4a** or **4b**.

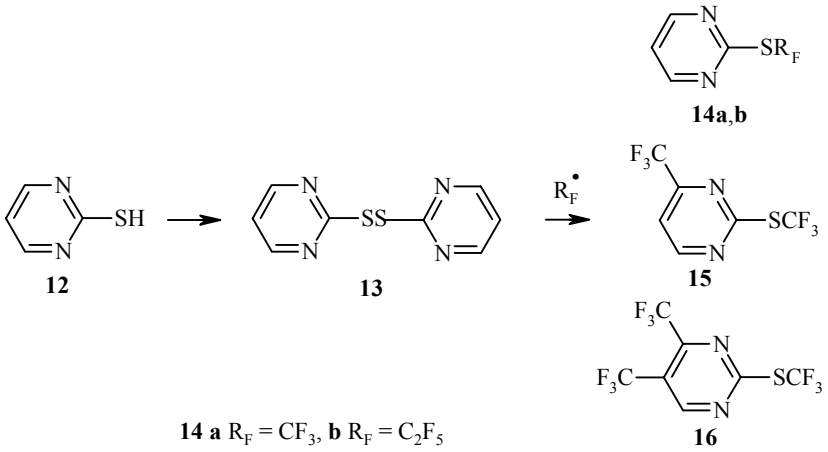
The main side processes are related to the introduction of a second CF_3 group either at position 5 of pyrimidine ring with the formation of compound **5** or at one of the methyl substituents with the formation of CH_2CF_3 group as a result of conversion of the intermediate cation radical **7** into benzyl radical **8**.



In addition, another direction for the formation of compound **5** is possible. Isomerization of the hetarylthiyl radicals $RS^{\cdot}$ **9** into the carbon-centered radical **10** with localization of the radical center at position 5 of the pyrimidine ring, subsequent recombination with CF_3 radical with the formation of 2-mercapto-4,6-dimethyl-5-trifluoromethylthiopyrimidine (**11**), oxidation of the latter with xenon bistrifluoromethylcarboxylate into the corresponding disulfide, and finally conversion into trifluoromethylthio derivative **5** according to the following scheme:

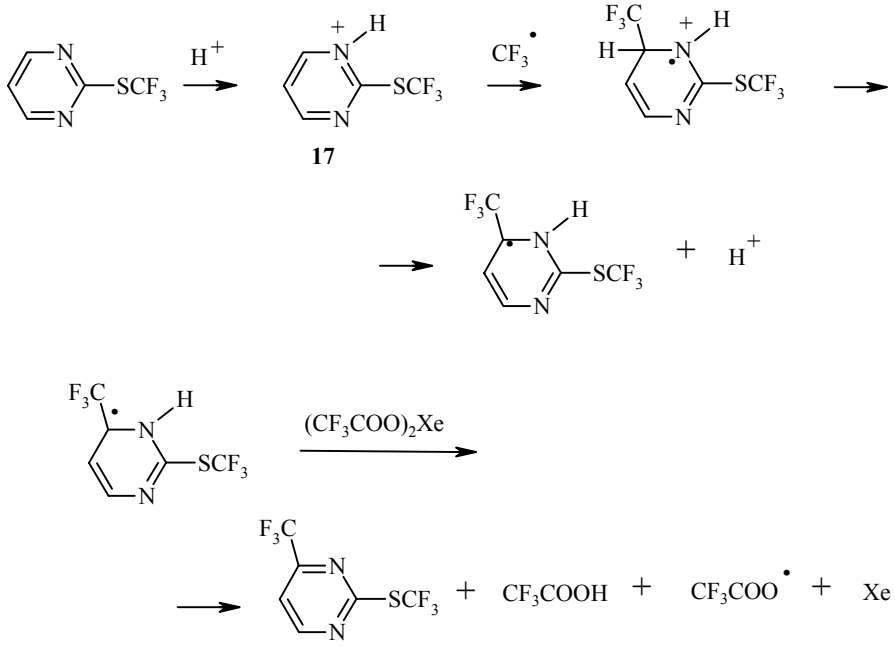


Three compounds were isolated from the reaction mixture after trifluoromethylation of compound **12**. These were 2-trifluoromethylthiopyrimidine (**14a**), 4-trifluoromethyl-2-trifluoromethylthiopyrimidine (**15**), and 4,5-bistrifluoromethyl-2-trifluoromethylthiopyrimidine (**16**) in molar ratios 1.0:2.1:0.4. Under analogous conditions the single reaction product formed on pentafluoroethylation was 2-pentafluoroethylthiopyrimidine.



The ^{1}H NMR spectra of the fluorine homologs **14a,b** were characterized by the presence of a doublet for the two protons at positions 4 and 6 of the pyrimidine ring at 8.65 ppm and also a doublet for the 5-H proton at 7.19 and 7.22 ppm respectively with coupling constant of 4.8 Hz. In the spectrum of compound **15** two doublets were present with the same intensity at 7.51 and 8.91 ppm corresponding to the pyrimidine 5- and 6-H protons with coupling constants equal to 5.0 and 4.8 Hz respectively. In the case of pyrimidine **16** only one singlet was observed for the 5-H proton at 9.14 ppm. In all the ^{19}F NMR spectra of compounds **14a**, **15**, and **16** a singlet was present at -41.3 to -41.6 ppm for the SCF_3 group. Signals for the trifluoromethyl groups bound to the pyrimidine ring were observed at -70.73 ppm (**15**) and also -60.21 and -67.14 ppm (**16**). The SC_2F_5 substituent of compound **14b** was displayed in the ^{19}F NMR spectra as two signals at -93.20 (SCF_2) and -83.32 ppm (CF_3). Maximum yields of compounds **14a** and **14b** of 7 and 26% were obtained on using molar reactant ratios of thiol **12** to R_FCOOH to XeF_2 of 1:20:3. On using lower quantities of acid and XeF_2 the initial thiol **12** did not react completely and a lower yield of the desired compounds **14a,b** was observed.

The selective trifluoromethylation of compound **14a** at position 4 of the pyrimidine ring may be explained by the presence in the reaction mixture of the protonated form **17** predominantly, and as a result the radical attack proceeds at the more positively charged carbon atom [8, 9].



Study of the influence of methods of synthesis A and B on the process of perfluoroalkylation showed that the determining factor is the solubility of disulfides **3** and **13**, which are used as starting materials or are formed in the course of the reaction in result of oxidation of the corresponding thiols. Maximum yields of perfluoroalkylation products of thiol **2** and disulfide **3** correspond to the maximum solubility of disulfide **3**, which is observed in CH_2Cl_2 (method A). In the case of thiol **12** the use of method B is optimal if perfluoroalkylcarboxylic acid is used as solvent, in which the intermediate disulfide **16** is more soluble, enabling an increase in the yield of the desired compound.

EXPERIMENTAL

Column chromatography was carried out on silica gel 60, 230-400 mesh (Merck), TLC – on plates of silica gel 60 F_{254} (Merck). The ^1H and ^{19}FNMR spectra were recorded on Bruker AM 360 (360 MHz) or AM 500 (500 MHz) spectrometers in $CDCl_3$ using TMS or $CFCl_3$ as internal standards. Chromato-mass spectral analysis was carried out on a Hewlett-Packard 5890 (70 eV) chromato-mass spectrometer using 30 m capillary column coated with HP1 oil. The high resolution mass spectra were recorded on a VG Autospec mass spectrometer.

General Procedure. A. The initial disulfide or thiol (4 mmol) was added with stirring to mixture prepared at -20°C from XeF_2 (2 g, 12.0 mmol), perfluoroalkylcarboxylic acid (1.8-2.6 ml, 24 mmol), and CH_2Cl_2 (30 ml). The reaction mixture was stirred with spontaneous heating to +5°C.

B. Xenon difluoride (2 g, 12 mmol) was added with stirring at 30°C to mixture of the initial disulfide or thiol (4 mmol) in perfluoroalkylcarboxylic acid (6.1-8.7 ml, 80 mmol). The end of the reaction was determined in both cases by the end of gas evolution. The reaction mixture obtained by methods A or B was neutralized with Na_2CO_3 solution, extracted with chloroform, the extract was dried over Na_2SO_4, and evaporated in vacuum. The residue was chromatographed on silica gel, eluent was benzene–hexane, 1:4.

4,6-Dimethyl-2-trifluoromethylthiopyrimidine (4a). Mp 45-46°C (50-51°C [5]). Yield 28%, light brown crystals. ^1H NMR spectrum, δ, ppm: 2.44 (6H, s, 2Me); 6.86 (1H, s, 5-H). ^{19}F NMR spectrum, δ, ppm: -41.27 (s, SCF_3). Mass spectrum, *m/z* (*I*, %): 208 (100) $[M]^+$, 107 (76) $[M\text{-}SCF_3]^+$, 69 (24) $[CF_3]^+$. Found, *m/z* 208.0311 $[M]^+$. $C_7H_7F_3N_2S$. Calculated: M = 208.0282.

4,6-Dimethyl-5-trifluoromethyl-2-trifluoromethylthiopyrimidine (5). Yield 14%, orange crystals; mp 47-49°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.66 (q, $^5J_{CH_3\text{-}CF_3}$ = 2.7, Me). ^{19}F NMR spectrum, δ, ppm: -41.34 (s, SCF_3); -55.85 (s, CF_3). Mass spectrum, *m/z* (*I*, %): 276 (100) $[M]^+$, 257 (15) $[M\text{-}F]^+$, 175 (65) $[M\text{-}SCF_3]^+$, 69 (59) $[CF_3]^+$. Found: *m/z* 276.0154 $[M]^+$. $C_8H_6F_6N_2S$. Calculated: M = 276.0156.

4-Methyl-6-(2′,2′,2′-trifluoroethyl)-2-trifluoromethylthiopyrimidine (6). Yield 3.2%, light brown crystals; mp 44-46°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.54 (3H, s, CH_3); 3.52 (2H, q, *J* = 10.3, CH_2); 7.05 (1H, s, 5-H). ^{19}F NMR spectrum, δ, ppm: -41.37 (s, SCF_3); -61.29 (s, CF_3). Mass spectrum, *m/z* (*I*, %): 276 (86) $[M]^+$, 175 (100) $[M\text{-}SCF_3]^+$, 69 (48) $[CF_3]^+$. Found, %; C 35.02; H 2.50; N 9.60. $C_8H_6F_6N_2S$. Calculated, %: C 34.79; H 2.19; N 10.14.

4,6-Dimethyl-2-pentafluoroethylthiopyrimidine (4b). Yield 19.4%, light brown crystals; mp 72-74°C. ^1H NMR spectrum, δ, ppm: 2.45 (6H, s, Me); 6.81 (1H, s, 5-H). ^{19}F NMR spectrum, δ, ppm: -83.20 (3F, s, CF_3); -93.09 (2F, s, SCF_2). Mass spectrum, *m/z* (*I*, %): 258 (75) $[M]^+$, 239 (7) $[M\text{-}F]^+$, 189 (7) $[M\text{-}CF_3]^+$, 139 (4) $[M\text{-}C_2F_5]^+$, 119 (12) $[C_2F_5]^+$, 107 (100) $[M\text{-}SC_2F_5]^+$. Found, %: C 37.56; H 2.85; N 10.10. $C_8H_7F_5N_2S$. Calculated, %: C 37.21; H 2.73; N 10.85.

2-Trifluoromethylthiopyrimidine (14a). Light brown oil. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.19 (1H, d t, *J* = 4.8, 5-H); 8.65 (2H, d, *J* = 4.8, 4-, 6-H). ^{19}F NMR spectrum, δ, ppm: -41.48 (s, SCF_3). Mass spectrum, *m/z* (*I*, %): 180 (88) $[M]^+$, 127 (14) $[NCSCF_3]^+$, 111 (28) $[M\text{-}CF_3]^+$, 79 (78) $[M\text{-}SCF_3]^+$, 69 (100) $[CF_3]^+$. Found, %: C 33.60; H 1.75; N 15.34. $C_5H_3F_3N_2S$. Calculated, %: C 33.34; H 1.68; N 15.55.

4-Trifluoromethyl-2-trifluoromethylthiopyrimidine (15). Light brown oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.51 (1H, d, *J* = 5.0, 5-H); 8.91 (1H, d, *J* = 5.0, 6-H). ^{19}F NMR spectrum, δ, ppm: -41.58 (s, SCF_3); -70.73 (s, CF_3). Mass spectrum, *m/z* (*I*, %): 248 (37) $[M]^+$, 229 (7) $[M-F]^+$, 179 (21) $[M-CF_3]^+$, 147 (13) $[M-SCF_3]^+$, 127 (5) $[NCSCF_3]^+$, 69 (100) $[CF_3]^+$. Found: *m/z* 247.9835. $C_6H_2F_6N_2S$. Calculated: M = 247.9843.

4,5-Bistrifluoromethyl-2-trifluoromethylthiopyrimidine (16). Light brown oil. ^{1}H NMR spectrum, δ, ppm: 9.14 (1H, s, 6-H). ^{19}F NMR spectrum, δ, ppm: -41.58 (3F, s, SCF_3); -60.21 (3F, s, 5-CF_3); -67.14 (3F, s, 4-CF_3). Mass spectrum, *m/z* (*I*, %): 316 (19) $[M]^+$, 297 (8) $[M-F]^+$, 247 (10) $[M-CF_3]^+$, 215 (3) $[M-SCF_3]^+$, 159 (10) $[M-F,-2CF_3]^+$, 127 (3) $[NCSCF_3]^+$, 69 (100) $[CF_3]^+$. Found, %: C 26.90; H 0.70; N 9.0. $C_7HF_9N_2S$. Calculated, %: C 26.59; H 0.32; N 8.86.

2-Pentafluoroethylthiopyrimidine (14b). Yield 25.2%, light brown oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.22 (1H, dd, *J* = 4.8, 5-H); 8.65 (2H, d, *J* = 4.8. 4-, 6-H). ^{19}F NMR spectrum, δ, ppm: -83.32 (3F, s, CF_3); -93.20 (2F, s, SCF_2). Mass spectrum, *m/z* (*I*, %): 230 (48) $[M]^+$, 211 (6) $[M-F]^+$, 161 (46) $[M-CF_3]^+$, 119 (25) $[C_2F_5]^+$, 84 (21) $[M-C_2F_5,-HCN]^+$, 79 (100) $[M-SC_2F_5]^+$, 69 (25) $[CF_3]^+$. Found, *m/z* 229.9963. $C_6H_3F_5N_2S$. Calculated: M = 229.9937.

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