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Reactions of Ketene Dithioacetals with Bis-nucleophiles: Synthesis of Novel Heterocyclic Thiols

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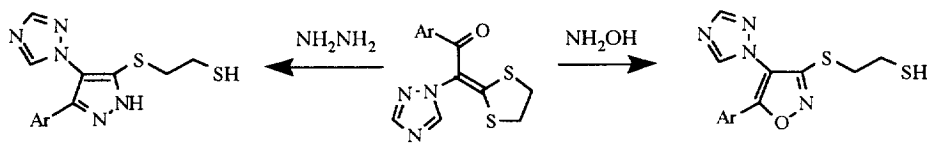
Abstract: The reactions of hydroxylamine, hydrazines, thiourea and guanidines with ketene dithioacetals are reported. The chemo- and regioselective aspects of the synthesis of the heterocyclic thiol products are contrasted with recently described processes based on related alkene substrates.

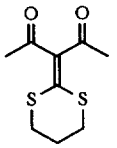
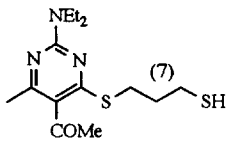
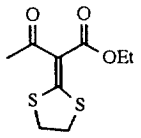
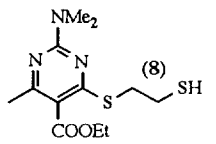
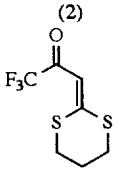
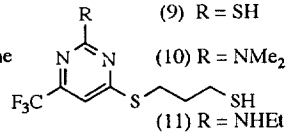
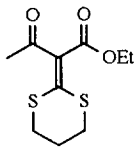
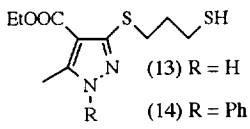
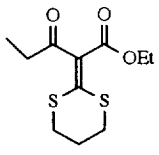
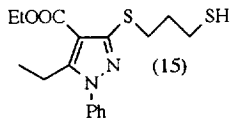
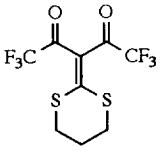
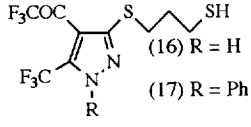
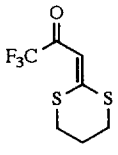
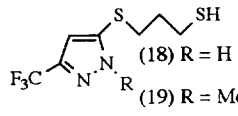
Heterocyclic thiols have an important place in medicinal chemistry. Some thiols, for example captopril[1], have been extensively used in the treatment of hypertension. Nucleophilic substitutions have been widely used for construction of medicinally important heterocyclic sulfides, for example cimetidine and ranitidine[2], from thiols. Two recent papers[3,4] describe the synthesis of heterocyclic thiols by elaboration of α-oxoketenedithioacetals with bisnucleophiles. Reaction of a series of dithioacetals with hydrazine hydrate[3,4] and hydroxylamine hydrochloride[4] afforded pyrazoles and isoxazoles respectively (see Scheme). Earlier it had been shown[5] that alcohols, which are side-chain substituted pyrimidines, can be prepared by reaction of α-oxoketeneacetals with guanidines and amidines. Here we describe the reaction of such bisnucleophiles with α-oxoketenedithioacetals to permit the efficient synthesis of pyrimidines carrying a remote thiol group. In view of the present interest in construction of fluorosubstituted heterocycles[6] and the need to generalise the access to thiols based on five membered heterocycles, we also report that the readily available α-oxoketenedithioacetals react with hydrazines to afford efficiently both fluorinated and non-fluorinated pyrazoles.



SCHEME

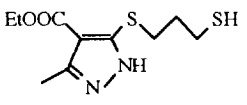
The routes to α-oxoketenedithioacetals have been reviewed[7] and the synthesis of the required acetals are described in the experimental section of the preceding paper[8]. All are available in one or two steps from readily

TABLE Synthesis of Heterocyclic Thiols

Substrate	Nucleophile	Product	Yield[a] (%)
 (1)	*N,N*-Diethylguanidine sulfate	 (7)	58
 (2)	*N,N*-Dimethylguanidine sulfate	 (8)	32
 (3)	Thiourea	 (9) R = SH	65
	N,N-Dimethylguanidine sulfate	(10) R = NMe_2	58
	N-Ethylguanidine sulfate	(11) R = NHEt	61
	N,N-Diethylguanidine sulfate	(12) R = NEt_2	70
 (4)	Hydrazine hydrate	 (13) R = H	52
	Phenylhydrazine	(14) R = Ph	59
 (5)	Phenylhydrazine	 (15)	72
 (6)	Hydrazine hydrate	 (16) R = H	52
	Phenylhydrazine	(17) R = Ph	63
 (3)	Hydrazine hydrate	 (18) R = H	46
	Methylhydrazine	(19) R = Me	75

a Yield of isolated product after chromatography

available carbonyl compounds. In the Table we report thirteen examples of the formation of heterocyclic thiols by reaction of bisnucleophiles with the ketenedithioacetals (1-6). In the seven examples of the preparation of pyrazoles using hydrazine hydrate, methylhydrazine and phenylhydrazine, a simple heating of the substrates in ethanol affords the fluorinated and non-fluorinated pyrazoles in comparable yields. Formation of fluorinated and non-fluorinated pyrimidines requires higher temperatures and reactions are conveniently achieved at 140°C. In the case of reaction of the diketone (1) with diethylguanidine sulfate the disulfide was observed as a minor product. By reaction under nitrogen disulfides were not obtained in the other reactions and the thiols are in all cases easily isolated by column chromatography. For the products (7-12) obtained by reaction of the guanidines and thiourea there are no structural ambiguities assuming that reaction occurs by ring opening of the dithioacetal by 1,4-addition of the nucleophile followed by further reaction with the more reactive carbonyl centre. In contrast in formation of the products (13-19) by reaction with hydrazine hydrate and methyl- or phenyl-hydrazine, literature precedent indicates that in each case isomeric pyrazoles might be obtained. One ambiguity applies to the products of reaction with hydrazine hydrate, where each of the products (13, 16 and 18) might exist as the alternative pyrazoles (20, 21 and 22). Similarly in reaction with substituted hydrazines distinction is needed between the proposed structures (14, 15, 17 and 19) or the alternative isomers (23-26). The former ambiguity is resolved by observation in the case of pyrazole (13) of a significant nOe between the methyl group and the proximate NH. In the recent papers reporting the formation of pyrazoles from ketene dithioacetals no indication is



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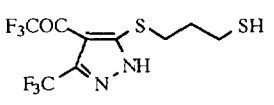
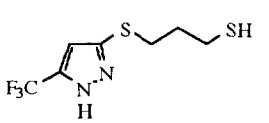
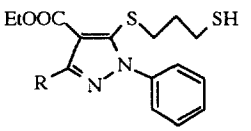


(21)

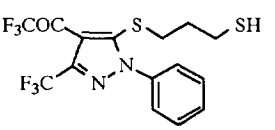


(22)



(23) R = Me

(24) R = Et



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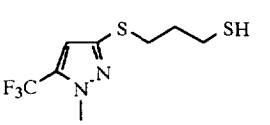

(26)

given of the regiochemical outcome in reactions with hydrazine. Literature precedents for reactions of methyl- and phenyl-hydrazine are conflicting. Katritzky et al[9] have suggested that in reaction of mono-substituted hydrazines the less hindered non-substituted site is the preferred site of initial attack with electrophiles. With ketoamides methylhydrazine reacts[10] first through the NH_2 group. With α-oxovinyl ethers[11] initial attack of methylhydrazine and also phenylhydrazine is 1,4- by the NH_2 group. With enaminones[12] both methyl- and phenylhydrazine react in the same manner by 1,4-reaction of the NH_2 group. In contrast to these results there are a number of instances[13,14,15] where different regioisomers are obtained in reactions of methyl- and phenyl-hydrazine. In each of these cases a 1,4-addition is followed by a cyclisation to give a pyrazole. In a further example[16] the two

hydrazines react with an α-cyanoketone to give pyrazoles with a different regiochemical outcome. Hence in considering the regiochemical problem of formation of (14, 15, 17 and 19) or the alternative isomers (23-26) there is little guidance from preceding results. In the cases of discrimination between (14) and (23) and of (15) and (24) we were able to resolve matters by nOe experiments. A significant nOe between the ortho protons of the phenyl group and the proximate alkyl group established the formation of isomers (14) and (15). The structure of isomer (17) is assigned by analogy with formation of isomer (15). Finally the structure of isomer (19) is established by observation of the nOe between the methyl group and the methylene group next to sulfur in the side chain. Our results therefore further illustrate the difficulty in predicting the regiochemical outcome in formation of substituted pyrazoles by reactions with mono-substituted hydrazines. In contrast to the complexity of the regiochemical results, the chemoselectivity observed in the series shown in the Table is easily understood. In every case the preferred mode of initial attack is by 1,4-addition. In those cases where there is a subsequent choice between further reaction at a ketonic site or with an ester, the cyclisation is always by attack at the ketone. Hence the results establish an efficient route to both fluorinated pyrimidines and pyrazoles having a remote thiol group. The products are in all cases available in three steps from commercial materials, and the preparation of an extensive range of possible thiols can be envisaged by variation of the dicarbonyl moity and the bisnucleophile, and the use of different dithiols. The selection of target thiols as possible pharmaceutical intermediates in the pyrimidine series may be effected without regiochemical concerns and in the pyrazole series chemoselection, if not regioselection, is unambiguous.

Experimental

5-Acetyl-2-(*N*,*N*-diethylamino)-4-(3-mercaptoprop-1-yl)thio-6-methylpyrimidine (7)

To a stirred solution of sodium carbonate (1.59g) in xylene (40ml) in a flask fitted with a Dean and Stark water separator was added *N*,*N*-diethylguanidine sulfate (8.86g). The mixture was heated at 120°C for 20min. before the dione (**1**) (2.16g) in xylene (5ml) was added dropwise. The temperature was raised to 140°C and the mixture was stirred under reflux for 4h. The mixture was then cooled and the xylene was removed by azeotropic distillation. After the addition of water (150ml) the cold solution was extracted with dichloromethane (3 x 25ml). The combined organic extracts were dried and the solvent removed *in vacuo* . The crude product was purified by column chromatography [silica gel, with light petroleum and ethyl acetate (9:1) as eluent]. The title compound (**7**) was prepared as a green oil in 58% yield; δH 1.19 (6H, t J 7, CH_3), 1.37 (1H, t J 8.1, SH), 2.01 (2H, m, CH_2), 2.36 (3H, s, $COCH_3$), 2.53 (3H, s, $ArCH_3$), 2.65 (2H, m, SCH_2), 3.21 (2H, t J 7 SCH_2) and 3.65 (4H, q J 7, NCH_2); δC 13.41 (NCH_2CH_3), 23.87 (CH_2), 24.53 ($ArCH_3$), 28.46 (CH_2SH), 32.32 ($COCH_3$), 33.56 (SCH_2), 42.09 (NCH_2), 120.92, 158.34, 164.63 and 167.72 (aromatic) and 201.55 (CO); $\nu_{max.}$ 2975, 2317, 1683 and 1543 $cm.^{-1}$; found M^+ 313.128 $C_{14}H_{23}N_3OS_2$ requires 313.128 m/z 313 (100), 280 (59), 241 (29) and 208 (73). A minor (4% yield) product was the disulfide of the above thiol (**7**).

5-Carboethoxy-2-(*N*,*N*-diethylamino)-4-(2-mercaptoeth-1-yl)thio-6-methylpyrimidine (8)

Following the above procedure using a water separator with *N*,*N*-dimethylguanidine sulfate and the ester (**2**) the title compound (**8**) was obtained in 32% yield as a yellow oil; δH 1.25 (1H, t J 9.5, SH), 1.35 (2H, t J 7.4, SCH_2), 1.39 (3H, t J 7, OCH_2CH_3), 2.51 (3H, s, CH_3), 3.09 (2H, m, SCH_2), 3.23 (6H, s, NCH_3) and 4.34 (2H, q J 7, OCH_2); δC 14.19 ($ArCH_3$), 14.48 (OCH_2CH_3), 24.80 (CH_2), 25.41 (CH_2), 37.00 (NCH_3), 60.91 (OCH_2), 119.94, 147.82, 156.21 and 162.39 (aromatic) and 165.83 (CO); $\nu_{max.}$3018, 2360, and 1700 $cm.^{-1}$; found M^+ 301.095 $C_{12}H_{19}N_3O_2S_2$ requires 301.095 m/z 301 (57), 286 (41), 257 (100), 228 (57) and 208 (81).

2-Mercapto-4-(3-mercaptoprop-1-yl)thio-6-trifluoromethylpyrimidine (9)

Following the above procedure using a water separator with thiourea and the ketone (**3**) the title compound (**9**) was obtained in 65% yield as a yellow oil; δH 1.45 (1H, t J 8.1, SH), 2.03 (2H, m, CH_2), 2.68 (2H, m, SCH_2), 3.34 (2H, t J 7, SCH_2), 4.58 (1H, bs, SH) and 7.14 (1H, s, ArH); δC 23.53 (CH_2), 28.16 (CH_2), 32.77, SCH_2), 111.02, 121.47 (CF_3), 153.96, 171.11 and 173.38 (aromatic); $\nu_{max.}$2935, 2359, and 1574 $cm.^{-1}$; found M^+ 285.988 $C_8H_9F_3N_2S_3$ requires 285.988 m/z 285 (100), 253 (48), 220 (73), 217 (65) and 184 (25).

2-(*N*,*N*-Dimethylamino)-4-(3-mercaptoprop-1-yl)thio-6-trifluoromethylpyrimidine (10)

Following the above procedure using a water separator with *N*,*N*-dimethylguanidine sulfate and the ketone (**3**) the title compound (**10**) was obtained in 58% yield as a yellow oil; δH 1.46 (1H, t J 8.1, SH), 2.01 (2H, m, CH_2), 2.65 (2H, m, SCH_2), 3.25 (6H, s, NCH_3), 3.37 (2H, t J 7, SCH_2) and 7.06 (1H, s, ArH); δC 22.61 (CH_2), 29.46 (CH_2), 33.31 (CH_2), 38.41 (NCH_3), 114.61, 119.46 (CF_3), 150.61, 169.41 and 173.31 (aromatic); $\nu_{max.}$3115, 2527, and 1522 $cm.^{-1}$; found M^+ 297.058 $C_{10}H_{14}F_3N_3S_2$ requires 297.058 m/z 297 (61), 253 (100), 228 (41), 222 (27) and 190 (64).

2-(*N*-Ethylamino)-4-(3-mercaptoprop-1-yl)thio-6-trifluoromethylpyrimidine (11)

Following the above procedure using a water separator with *N*-ethylguanidine sulfate and the ketone (**3**) the title compound (**11**) was obtained in 61% yield as a yellow oil; δH 1.18 (3H, t J 7, CH_3), 1.44 (1H, t J 8.1, SH), 2.00 (2H, m, CH_2), 2.63 (2H, m, SCH_2), 3.44 (2H, q J 7.1, NCH_2), 3.37 (2H, t J 7, SCH_2), 6.18 (1H, bs, NH) and 7.09 (1H, s, ArH); δC 14.87 (CH_3), 22.61 (CH_2), 28.88 (CH_2), 33.93 (CH_2), 35.98 (NCH_2), 115.21, 119.82 (CF_3), 150.25, 168.90 and 172.62 (aromatic); $\nu_{max.}$3434, 3105, 2496, and 1534 $cm.^{-1}$; found M^+ 297.058 $C_{10}H_{14}F_3N_3S_2$ requires 297.058 m/z 297 (100), 253 (75), 228 (34) and 220 (64).

2-(*N*,*N*-Diethylamino)-4-(3-mercaptoprop-1-yl)thio-6-trifluoromethylpyrimidine (12)

Following the above procedure using a water separator with *N*,*N*-diethylguanidine sulfate and the ketone (**3**) the title compound (**12**) was obtained in 70% yield as a yellow oil; δH 1.19 (6H, t J 7, CH_3), 1.37 (1H, t J 8.1, SH), 1.99 (2H, m, CH_2), 2.67 (2H, m, SCH_2), 3.37 (2H, t J 7, SCH_2), 3.65 (4H, q J 7, NCH_2),and 7.11

(1H, s, ArH); δC 13.55 (CH_3), 21.66 (CH_2), 29.22 (CH_2), 34.73 (CH_2), 42.16 (NCH_2), 114.23, 118.94 (CF_3), 151.64, 170.41 and 173.39 (aromatic); $\nu_{max.}$ 3106, 2533, and 1553 $cm.^{-1}$; found M^+ 325.088 $C_{12}H_{18}F_3N_3S_2$ requires 325.089 m/z 325 (75), 256 (23), 253 (100) and 184 (35).

General Procedure for preparation of pyrazoles

To a stirred solution of the substrate (10mmol) in ethanol (20ml) at room temperature was added the appropriate bisnucleophile (10mmol). The solution was then heated under reflux, cooled, poured into brine (20ml) and extracted with diethyl ether (3 x 25ml). The combined organic extracts were dried and the solvent removed *in vacuo*.The crude product was purified by column chromatography [silica gel, light petroleum and ethyl acetate (7:3) as eluent]. Solid products were recrystallised from ethanol.
Using the above procedure the following thiols were prepared:

4-Carbethoxy-5(3)-(3-mercaptoprop-1-yl)thio-3(5)-methyl-1*H*-pyrazole (13) by reaction of the ester (**4**) with hydrazine under reflux for 30min. and purification to afford in 52% yield the title compound as white crystals m. p. 71-73°C; δH 1.37 (3H, t J 7.2, OCH_2CH_3), 1.40 (1H, t J 8.1, SH), 2.04 (2H, m, CH_2), 2.52 (3H, s, CH_3), 2.67 (2H, m, SCH_2), 3.19 (2H, t J 7 SCH_2), 4.32 (2h, q J 7.2, OCH_2) and 8.10 (1H, bs, NH); δC 12.35 (CH_3), 14.55 (CH_3), 23.73 (CH_2), 29.23 (CH_2SH), 33.31 (SCH_2), 60.37 (OCH_2), 109.52, 146.37 and 150.11 (aromatic) and 163.87 (CO); $\nu_{max.}$ 3164, 2946, 2414 and 1692$cm.^{-1}$; found M^+ 260.370 $C_{10}H_{16}N_2O_2S_2$ requires 260.371, m/z 260 (100), 214 (53) and 181 (37).

4-Carbethoxy-3-(3-mercaptoprop-1-yl)thio-5-methyl-1phenylpyrazole (14) by reaction of the ester (**4**) with phenylhydrazine under reflux for 3 hours and purification to afford in 59% yield the title compound as a red oil; δH 1.28 (3H, t J 7.1, OCH_2CH_3), 1.34 (1H, t J 7.3, SH), 1.98 (3H, s, CH_3), 2.17 (2H, m, CH_2), 2.84 (2H, m, SCH_2), 2.99 (2H, t J 7.1 SCH_2), 4.23 (2H, q J 7.1, OCH_2) and 6.85-7.25 (5H, aromatic); δC 14.45 (CH_3), 15.45 (CH_3), 24.17 (CH_2), 29.30 (CH_2SH), 29.66 (SCH_2), 60.70 (OCH_2), 113.25, 120.33, 126.08, 129.29, 140.37, 145.05 and 159.91 (aromatic) and 165.08 (CO); $\nu_{max.}$ 2965, 2426 and 1694$cm.^{-1}$; found M^+ 336.101 $C_{16}H_{20}N_2O_2S_2$ requires 336.100 m/z 336 (78), 290 (47), 257 (45), 246 (91), 231 (100), 216 (95) and 159 (61).

4-Carbethoxy-5-ethyl-3-(3-mercaptoprop-1-yl)thio-5-methyl-1phenylpyrazole (15) by reaction of the ester (**5**) with phenylhydrazine under reflux for 3 hours and purification to afford in 72% yield the title compound as a golden oil; δH 1.17 (3H, t J 7, CH_3),1.39 (3H, t J 7, OCH_2CH_3), 1.44 (1H, t J 8.1, SH), 2.07 (2H, m, CH_2), 2.69 (2H, m, SCH_2), 2.89 (2H, q J 7.4, CH_2), 3.23 (2H, t J 7.1 SCH_2), 4.35 (2H, q J 7, OCH_2) and 7.37-7.46 (5H, aromatic); δC 13.85 (CH_3), 14.56 (CH_3), 19.39 (CH_2), 23.92 (CH_2), 28.96 (SCH_2), 33.57 ($ArSCH_2$), 60.43 (OCH_2), 109.60, 126.06, 129.00, 129.45, 139.01, 150.42 and 151.18 (aromatic) and 163.59 (CO); $\nu_{max.}$ 2966, 2443 and 1695$cm.^{-1}$; found M^+ 350.113 $C_{17}H_{22}N_2O_2S_2$ requires

350.112 m/z 350 (92), 317 (100), 273 (24) and 240 (62).

5(3)-(3-Mercaptoprop-1-yl)thio-4-trifluoroacetyl-3(5)-trifluoromethyl-1*H*-pyrazole (16) by reaction of the dione (**6**) with hydrazine hydrate under reflux for 30 min. and purification to afford in 52% yield the title compound as a red oil; δH 1.44 (1H, t J 8.1, SH), 2.00 (2H, m, CH_2), 2.65 (2H, m, SCH_2) and 3.25 (2H, t J 7, SCH_2); δC 23.30 (CH_2), 28.76 (CH_2SH), 32.98 (SCH_2), 119.19 (CF_3), 119.57 (C_4), 121.63 ($COCF_3$), 137.26 (CCF_3) 174.37 (CF_3CO) and 185.37 (CS); $\nu_{max.}$ 3192, 2939, 2611, 1676 and 1654 $cm.^{-1}$; found M^+ 337.998 $C_9H_8F_6N_2OS_2$ requires 337.998 m/z 338 (57), 305 (100), 241 (24) and 208 (76).

3-(3-Mercaptoprop-1-yl)thio-1-phenyl-4-trifluoroacetyl-5-trifluoromethylpyrazole (17) by reaction of the dione (**6**) with phenylhydrazine under reflux for 3 hours and purification to afford in 63% yield the title compound as a yellow oil; δH 1.36 (1H, t J 8.1, SH), 2.00 (2H, m, CH_2), 2.63 (2H, m, SCH_2), 3.22 (2H, t J 7, SCH_2) and 7.0-7.3 (5H, m, aromatic); δC 23.29 (CH_2), 30.84 (CH_2SH), 33.34 (SCH_2), 114.23 (C_4), 119.27 (CF_3), 121.49 ($COCF_3$), 127.79, 129.41, 130.06 and 138.61 (aromatic), 141.39 (CCF_3) 170.29 (CF_3CO) and 184.26 (CS); $\nu_{max.}$2947, 2512, 1679 and 1649 $cm.^{-1}$; found M^+ 414.028 $C_{15}H_{12}F_6N_2OS_2$ requires 414.029 m/z 414 (59), 345 (100), 339 (46), 337 (46) and 317 (21).

5(3)-(3-Mercaptoprop-1-yl)thio-3(5)-trifluoromethyl-1*H*-pyrazole (18) by reaction of the ketone (**3**) with hydrazine hydrate under reflux for 30 min. and purification to afford in 46% yield the title compound as a pale yellow oil; δH 1.37 (1H, t J 8.1, SH), 1.89 (2H, m, CH_2), 2.65 (2H, m, SCH_2), 2.97 (2H, t J 7.4, SCH_2), 6.64 (1H, s, ArH) and 11.52 (1H, bs, NH); δC 23.01 (CH_2), 33.29 (CH_2SH), 34.49 (SCH_2), 108.66, 120.91 (CF_3), 136.24 (CCF_3) and 152.39 (CS); $\nu_{max.}$ 3142 and 2595 $cm.^{-1}$; found M^+ 242.015 $C_7H_9F_3N_2S_2$ requires 242.016 m/z 242 (100), 209 (40) and 135 (53).

5(3)-(3-Mercaptoprop-1-yl)thio-1-methyl-3-trifluoromethylpyrazole (19) by reaction of the ketone (**3**) with methylhydrazine under reflux for 30 min. and purification to afford in 75% yield the title compound as a colourless oil; δH 1.35 (1H, t J 8.1, SH), 1.89 (2H, m, CH_2), 2.65 (2H, m, SCH_2), 2.93 (2H, t J 7, SCH_2), 3.95 (3H, s, CH_3) and 6.59 (1H, s, ArH); δC 23.11 (CH_2), 33.04 (CH_2SH), 34.25 (SCH_2), 37.43 (NCH_3), 109.24, 121.47 (CF_3), 141.36 (CCF_3) and 151.46 (CS); $\nu_{max.}$ 2572 $cm.^{-1}$; found M^+ 256.031 $C_8H_{11}F_3N_2S_2$ requires 256.032 m/z 256 (100), 241 (72), 223 (47) and 208 (32).

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