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Reactions of 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenesulfenyl chloride with enamines

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1,3,3,3-Tetrafluoro-2-methoxycarbonylpropenesulfenyl chloride readily reacts with enamines (derivatives of β-oxo acids) to give sulfenylation products. The reactions with *N*-aryl-substituted enamines are accompanied by cyclization to form *N*-aryl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazoles.

Key words: enamines, 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenesulfenyl chloride, sulfenylation, cyclization, *N*-aryl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazoles.

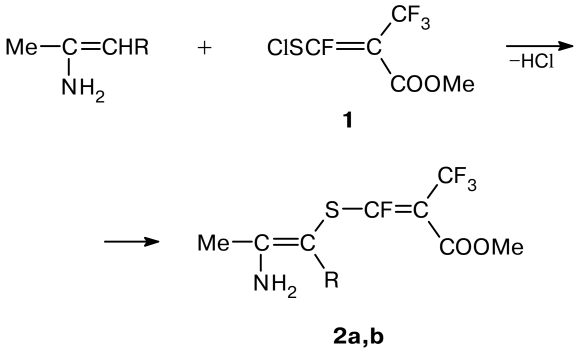
C-Sulfenylation of enolyzable carbonyl compounds and enamines under the action of fluoroaliphatic sulfenyl chlorides has been extensively investigated. This provides a convenient method for the synthesis of fluorine-containing functionally substituted sulfides, including α-fluorovinyl derivatives.[1,2] The latter, in turn, can serve as precursors of sulfur-containing cyclic compounds. In particular, we have demonstrated that the reaction products of α-fluoro-α,β-unsaturated sulfenyl chlorides with enols readily underwent intramolecular cyclization to form substituted 1,3-oxathioles.[2]

In the present study, we examined the reactions of 1,3,3,3-tetrafluoro-2-methoxycarbonylpropenesulfenyl chloride (**1**) with enamines derived from β-oxo acids and also explored the possibilities of heterocyclization of the resulting products.

Results and Discussion

Methyl 3-aminocrotonate and 3-aminocrotononitrile readily reacted with sulfenyl chloride **1** to form sulfenylation products **2a,b** in high yields (Scheme 1).

Scheme 1

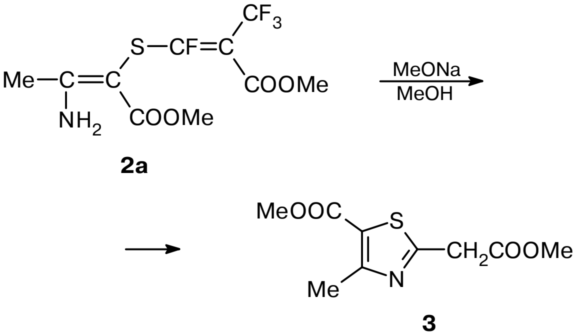


R = COOMe (**a**), CN (**b**)

The reactions were carried out in chloroform with the use of the reagents taken in an equimolar ratio, the reaction product acting as an acceptor of hydrogen chloride. According to the NMR spectroscopic data, sulfenylation proceeded stereospecifically to form exclusively the *E* isomer ($J_{F,F}$ = 30 Hz), which is typical of these reactions.[2,3] The ^{1}H NMR spectrum of compound **2a** shows that the H atoms of the amino group are nonequivalent due apparently to the involvement in hydrogen bonding with the ester group. The absence of hydrogen bonds in the case of compound **2b** gives rise to the *E,Z* isomerism with respect to the double bond of the enamine fragment.

Attempts to perform intramolecular cyclization of compounds **2a** and **2b** in the presence of the $BF_3 \cdot NEt_3$ complex failed. Thus after refluxing in a chloroform solution, we isolated the starting compounds. Cyclization of compound **2a** was performed on boiling in methanol in the pesence of such strong base as sodium methoxide; however, this reaction was accompanied by saponification of the trifluoromethyl group and decarboxylation to form substituted thiazole **3** in 44% yield (Scheme 2).

Scheme 2



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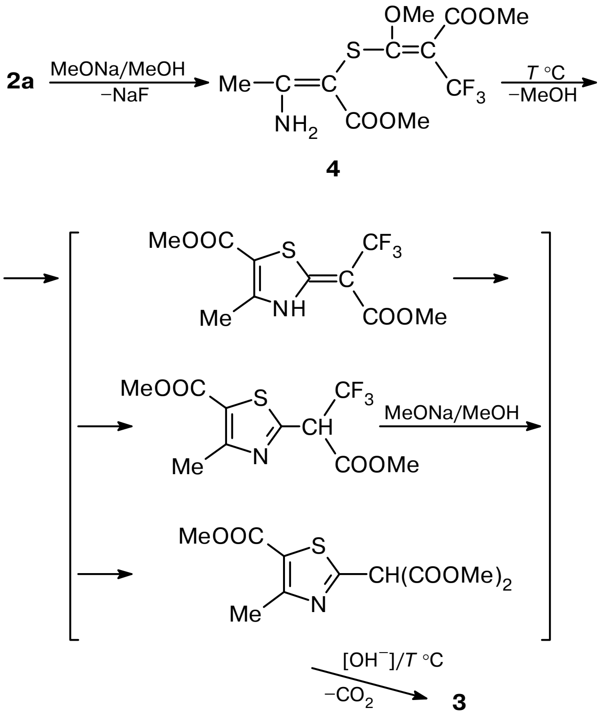
α-Methoxy-substituted sulfide **4**, which formed even at 20 °C (this fact was confirmed by a special experiment), was obtained as the primary reaction product. The latter underwent cyclization upon subsequent heating. The assumed reaction pathway (Scheme 3) involves the conversion of the α-CF_3-CH acid resulting from the N→C migration of the proton into a thiazolyl-substituted malonate. The latter is, apparently, the direct precursor of thiazole **3**.

Scheme 3

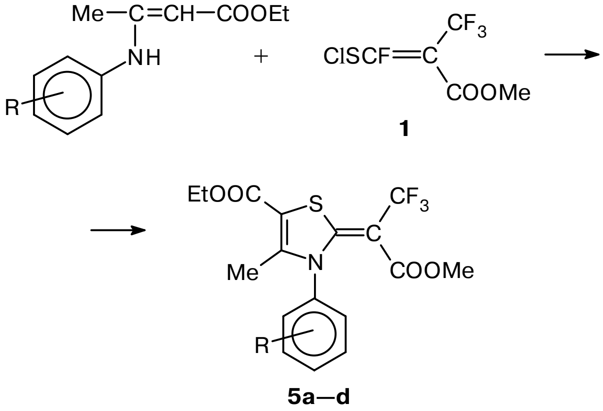


Unlike enamines with a free amino group, *N*-aryl-substituted enamines react with sulfenyl chloride **1** under mild conditions to form substituted *N*-aryl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazoles (**5a—d**) in one step (Scheme 4).

Judging from the NMR spectroscopic data, compounds **5a—d** exist as mixtures of *Z* and *E* isomers; however, their ratios in solutions varied with time. For example, the ratio of the isomers of compound **5a** in dimethyl sulfoxide changed from 5 : 1 to 1 : 2 after 2 weeks. Apparently, this is associated with the ρ-π-π conjugation between the lone electron pair of the nitrogen atom, the double bond, and the carbonyl group, which allows one isomer to be converted into another (apparently, into a thermodynamically more stable isomer) through a zwitterionic transition state (Scheme 5).

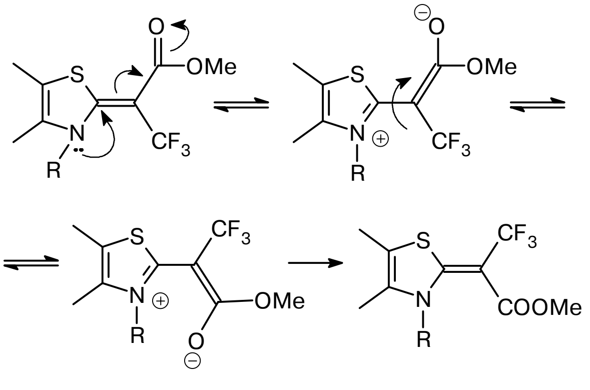
Previously, it has been suggested that ρ-π-π conjugation is responsible for stereoselectivity of the formation of *O*-alkyl-*N*,*N*-dialkylaminoacetals of (fluorocarbonyl)-[4] and (dialkylamido)trifluoromethylketenes.[5]

Scheme 4



R = H (**a**), 4-Et (**b**) 4-F (**c**), 2-OMe (**d**)

Scheme 5



Experimental

The ^{19}F NMR spectra were recorded on a Bruker AC-200F spectrometer operating at 188.31 MHz. The ^{1}H NMR spectra were measured on a Bruker AC-300SF spectrometer operating at 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 course of the reactions and the purities of the resulting compounds were monitored by TLC on Merck 60F-254 plates in an acetone—CCl_4 system.

Sulfenyl chloride **1** was prepared according to a known procedure.[3]

Reactions of sulfenyl chloride 1 with enamines (general procedure). A solution of sulfenyl chloride **1** (0.01 mol) in $CHCl_3$ (15 mL) was added dropwise with stirring to a solution of enamine (0.01 mol) in $CHCl_3$ (15 mL) at a temperature from 0 to +5 °C. The reaction mixture was kept at 20—25 °C for 20 h and then washed with a 10% $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, the solvent was removed *in vacuo*, and the residue was extracted with hot hexane. The crystals that precipitated upon cooling were filtered off.

Methyl 3-amino-2-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)crotonate (2a), the yield was 89%, m.p. 103—105 °C, R_f 0.31 (1 : 9). ^{1}H NMR ($CDCl_3$), δ: 2.26 (s, 3 H, Me); 3.71 (s, 3 H, OMe); 3.85 (s, 3 H, OMe); 5.52 and 9.32 (both br.s, 1 H each, NH_2). ^{19}F NMR (DMSO-d_6), δ: 19.3 (q, 1 F, CF, J = 30.0 Hz); 27.0 (d, 3 F, CF_3, J = 30.0 Hz). Found (%): C, 37.71; H, 3.44. $C_{10}H_{11}F_4NO_4S$. Calculated (%): C, 37.85; H, 3.47.

3-Amino-2-(1,3,3,3-tetrafluoro-2-methoxycarbonylpropenylthio)crotononitrile (2b), yield 82%, m.p. 73—75 °C, R_f 0.51 (1 : 3). ^{1}H NMR ($CDCl_3$), δ: 2.21 and 2.34 (both s, 3 H, Me, the ratio is 1 : 5); 3.85 and 3.86 (both s, 3 H, OMe, the ratio is 1 : 5); 5.50 (br.s, 2 H, NH_2). ^{19}F NMR (DMSO-d_6), δ: 17.9 and 18.1 (both q, the ratio is 5 : 1, 1 F, CF, J = 30.0 Hz); 26.4 and 26.5 (both d, the ratio is 5 : 1, 3 F, CF_3, J = 30.0 Hz). MS, m/z: 284 $[M]^+$. Found (%): C, 38.17; H, 2.84. $C_9H_8F_4N_2O_2S$. Calculated (%): C, 38.03; H, 2.82.

Ethyl 4-methyl-3-phenyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazole-5-carboxylate (5a), yield 65%, m.p. 93—95 °C, R_f 0.68 (1 : 9). ^{1}H NMR (DMSO-d_6), δ: 1.30 (m, 3 H, Me); 2.17 and 2.21 (both s, 3 H, Me, the ratio is 5 : 1); 3.52 and 3.60 (both s, 3 H, OMe, the ratio is 5 : 1); 4.30 (m, 2 H, CH_2); 7.30—7.70 (m, 5 H, Ph). MS, m/z: 387 $[M]^+$. Found (%): C, 52.89; H, 4.19. $C_{17}H_{16}F_3NO_4S$. Calculated (%): C, 52.71; H, 4.13.

Ethyl 3-(4-ethylphenyl)-4-methyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazole-5-carboxylate (5b), yield 63%, m.p. 81—83 °C, R_f 0.55 (1 : 9). ^{1}H NMR ($CDCl_3$), δ: 1.25 (m, 3 H, Me); 1.35 (m, 3 H, Me); 2.20 and 2.25 (both s, 3 H, Me, the ratio is 1 : 2); 2.72 (m, 2 H, CH_2); 3.66 and 3.72 (both s, 3 H, OMe, the ratio is 1 : 2); 4.30 (m, 2 H, OCH_2); 7.10 and 7.35 (both m, 2 H each, C_6H_4). ^{19}F NMR (CCl_4), δ: 14.8 and 25.7 (both s, CF_3, the ratio is 1 : 2). Found (%): C, 54.79; H, 4.87. $C_{19}H_{20}F_3NO_4S$. Calculated (%): C, 54.94; H, 4.82.

Ethyl 3-(4-fluorophenyl)-4-methyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazole-5-carboxylate (5c), yield 57%, m.p. 75—77 °C, R_f 0.59 (1 : 9). ^{1}H NMR (DMSO-d_6), δ: 1.39 (m, 3 H, Me); 2.18 and 2.23 (both s, 3 H, Me, the ratio is 1 : 3); 3.53 and 3.62 (both s, 3 H, OMe, the ratio is 1 : 3); 4.35 (m, 2 H, CH_2); 7.25 and 7.42 (both m, 2 H each, C_6H_4). MS, m/z: 405 $[M]^+$. Found (%): C, 50.49; H, 3.73. $C_{17}H_{15}F_4NO_4S$. Calculated (%): C, 50.37; H, 3.70.

Ethyl 3-(2-methoxyphenyl)-4-methyl-2-(2,2,2-trifluoro-1-methoxycarbonylethylidene)-2,3-dihydrothiazole-5-carboxylate (5d), yield 57%, m.p. 75—77 °C, R_f 0.45 (1 : 9). ^{1}H NMR (DMSO-d_6), δ: 1.38 (m, 3 H, Me); 2.18 and 2.23 (both s, 3 H, Me, the ratio is 1 : 3); 3.62 and 3.65 (both s, 3 H each, OMe, the ratio is 1 : 3); 3.83 and 3.80 (both s, 3 H each, OMe, the ratio is 1 : 3); 4.33 (m, 2 H, CH_2); 7.00—7.40 (m, 4 H, C_6H_4). ^{19}F NMR (CCl_4), δ: 14.7 and 25.5 (both s, CF_3, the ratio is 1 : 3). Found (%): C, 51.95; H, 4.37. $C_{18}H_{18}F_3NO_5S$. Calculated (%): C, 51.80; H, 4.32.

Methyl 2-methoxycarbonylmethyl-4-methylthiazole-5-carboxylate (3). A solution of ester **2a** (3.17 g, 0.01 mol) in MeOH (5 mL) was added with stirring and cooling to 0 °C to a solution of MeONa in MeOH (from 1.15 g (0.05 g-at.) of Na and 30 mL of MeOH). The reaction mixture was refluxed for 5 h, the solvent was removed *in vacuo*, and the residue was extracted with hot hexane. The crystals that precipitated upon cooling were filtered off. Compound **3** was obtained in a yield of 1.0 g (44%), m.p. 38—40 °C, R_f 0.47 (1 : 9). ^{1}H NMR ($CDCl_3$), δ: 2.71 (s, 3 H, Me); 3.78 and 3.86 (both s, 3 H each, 2 OMe); 4.01 (s, 2 H, CH_2). MS, m/z: 229 $[M]^+$. Found (%): C, 47.35; H, 4.73. $C_9H_{11}NO_4S$. Calculated (%): C, 47.16; H, 4.80.

Methyl 3-amino-2-(3,3,3-trifluoro-1-methoxy-2-methoxycarbonylpropenylthio)crotonate (4). A solution of ester **2a** (1.59 g, 0.005 mol) in MeOH (5 mL) was added with stirring and cooling to 0 °C to a solution of MeONa in MeOH (prepared from 0.23 g (0.01 g-at.) of Na and 10 mL of MeOH). The reaction mixture was kept at 20 °C for 3 h, poured into water, and extracted with ether. The ethereal layer was separated and dried with Na_2SO_4. The solvent was removed *in vacuo*. Compound **4** was obtained as a transparent pale-yellow oil in a yield of 1.4 g (85%), R_f 0.27 (1 : 9). ^{1}H NMR ($CDCl_3$), δ: 2.29 (s, 3 H, Me); 3.71 (s, 3 H, OMe); 3.74 (s, 3 H, OMe); 3.82 (s, 3 H, OMe); 5.35 and 9.21 (both br.s, 1 H each, NH_2). Found (%): C, 40.36; H, 4.33. $C_{11}H_{14}F_3NO_5S$. Calculated (%): C, 40.12; H, 4.26.

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