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Addition of thiols to ethyl 4,4,4-trifluorocrotonate

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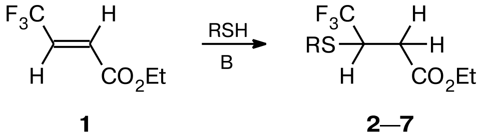
Ethyl 4,4,4-trifluorocrotonate **1** readily adds aliphatic and aromatic thiols and aminothiols at the double bond in the presence of catalytic amounts of alkylamines and ammonia to give 3-thiolation products. Thiolacetic acid reacts with ester **1** in the absence of a catalyst at 100 °C.

Key words: ethyl 4,4,4-trifluorocrotonate, thiols, aminothiols, thiolacetic acid, thiolation.

The addition of thiols at the C=C bond of trifluoromethyl-containing acrylic acids has been studied insufficiently. Earlier,[1] it has been demonstrated that 4,4,4-trifluorocrotonic acid reacts with thiols on heating and in the presence of trifluoromethanesulfonic acid as a catalyst. The reactions of thiols with 4,4,4-trifluorocrotonates have not been investigated earlier. In the present study, we investigated the addition of thiols to ethyl 4,4,4-trifluorocrotonate (**1**) under conditions of base catalysis.



R = Ac (**2**), Et (**3**), Bn (**4**), Ph (**5**), $H_2N(CH_2)_2$ (**6**), *o*-$H_2NC_6H_4$ (**7**)
B is alkylamine, ammonia

We found that ethyl (*E*)-4,4,4-trifluorocrotonate (**1**), like the parent acid,[1] regiospecifically added AcSH on heating in the absence of a catalyst to form ethyl 3-acetylthio-4,4,4-trifluorobutyrate (**2**). Thiols do not react with ester **1** even upon prolonged heating at 150 °C under conditions of acid catalysis (*p*-toluene- or trifluoromethanesulfonic acids). By contrast, thiols readily add to crotonate **1** in the presence of catalytic amounts of alkylamines (primary, secondary, or tertiary) or ammonia at 20 °C. Benzenethiol reacts with ester **1** exothermally. The reaction of ester **1** with 2-aminoethanethiol does not require a catalyst because the reaction is catalyzed by the amino group of the reagent, whereas the reaction of **1** with 2-aminoethanethiol hydrochloride (amino group is protected) proceeds only in the presence of a base. The reaction of ester **1** with aminobenzenethiol does not proceed even upon heating to 100 °C for 10 h. However, this reaction in the presence of triethylamine is completed in a few minutes. Apparently, the basicity of the aromatic amino group is insufficient for activation of the thiol group and catalysis of the reaction.

All reactions afford exclusively 3-thiolation products as evidenced by the ^{19}F NMR spectra. These spectra have single signals of the CF_3 group as doublets, whereas in the spectra of alternative 2-thiolation products, this signal should represent a triplet.

To summarize, the addition of thiols at the double bond of ethyl (*E*)-4,4,4-trifluorocrotonate (**1**) catalyzed by ammonia or organic bases would be expected to be of considerable preparative importance.

Experimental

The ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AC-200 P spectrometer using $CDCl_3$ as the solvent (unless otherwise mentioned) with Me_4Si or $CFCl_3$ as the internal standards. The course of the reactions was monitored by TLC on Silufol in a 1 : 12 ethyl acetate—light petroleum mixture and also by iodometric titration of the thiol group.

Ethyl (*E*)-4,4,4-trifluorocrotonate (1) was synthesized from ethyl trifluoroacetate according to a known procedure.[2] The yield was 80%, b.p. 112—115 °C.

Ethyl 3-acetylthio-4,4,4-trifluorobutyrate (2). A mixture of crotonate **1** (3.36 g, 20 mmol) and AcSH (1.60 g, 21 mmol) was heated in a sealed tube under argon at 100 °C for 12 h. The reaction mixture was distilled. Compound **2** was obtained in a yield of 3.46 g (71%), b.p. 115 °C (15 Torr), n_D^{21} 1.4230. Found (%): C, 39.11; H, 4.40; F, 23.27; S, 13.36. $C_8H_{11}F_3O_3S$. Calculated (%): C, 39.34; H, 4.50; F, 23.36; S, 13.12. ^1H NMR, δ: 1.2 (t, 3 H, Me, J = 7.76 Hz); 2.35 (s, 3 H, Ac); 2.77 (AB portion of the $ABMX_3$ spectrum, δ_A = 2.62, δ_B = 2.92, 2 H, CH_2, $J_{A,B}$ = 14.91 Hz, $J_{A(B),H}$ = 9.32 Hz, $J_{B(A),H}$ = 4.66 Hz);

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4.12 (q, 2 H, CH_2O, J = 7.76 Hz); 4.59 (m, 1 H, CH). ^{13}C NMR, δ: 13.12 (q, Me, $^1J_{C,H}$ = 126.83 Hz); 28.95 (q, Ac, $^1J_{C,H}$ = 130.28 Hz); 32.98 (t, CH_2CO, $^1J_{C,H}$ = 134.4 Hz); 40.81 (dq, CH, $^1J_{C,H}$ = 145.53 Hz, $^2J_{C,F}$ = 31.45 Hz); 60.6 (t, CH_2O, $^1J_{C,H}$ = 147.71 Hz); 125.20 (q, CF_3, $^1J_{C,F}$ = 278.64 Hz); 167.86 (s, COO); 190.06 (s, COS). ^{19}F NMR, δ: 70.5 (d, CF_3, J = 9.15 Hz).

Ethyl 3-ethylthio-4,4,4-trifluorobutyrate (3). A mixture of ester **1** (1.68 g, 10 mmol), EtSH (0.7 g, 11.3 mmol), and Et_3N (0.1 g, 1 mmol) was kept in an atmosphere of argon at 25 °C for 20 days, diluted with Et_2O (20 mL), washed with 5% HCl (2×5 mL), and dried with $MgSO_4$. After distillation, compound **3** was obtained in a yield of 1.56 g (68%), b.p. 90 °C (20 Torr), n_D^{20} 1.4125. Found (%): C, 41.72; H, 5.53; F, 25.05; S, 13.75. $C_8H_{13}F_3O_2S$. Calculated (%): C, 41.74; H, 5.65; F, 24.78; S, 13.91. ^1H NMR, δ: 1.10 (t, 6 H, Me, J = 7.14 Hz); 2.52 (AB portion of the $ABMX_3$ spectrum, δ_A = 2.35, δ_B = 2.67, 2 H, CH_2, $J_{A,B}$ = 16.40 Hz, $J_{A(B),H}$ = 10.57 Hz, $J_{B(A),H}$ = 3.90 Hz); 2.57 (AB spectrum, δ_A = 2.54, δ_B = 2.60, 2 H, CH_2S, $J_{A,B}$ = 7.37 Hz); 3.45 (m, 1 H, CH); 4.03 (q, 2 H, CH_2O, J = 7.14 Hz). ^{13}C NMR, δ: 13.96 and 14.13 (both q, 2 Me each, $^1J_{C,H}$ = 118.96 Hz); 27.07 (t, CH_2CO, $^1J_{C,H}$ = 140.60 Hz); 34.66 (t, CH_2S, $^1J_{C,H}$ = 131.33 Hz); 43.67 (dq, CH, $^1J_{C,H}$ = 142.25 Hz, $^2J_{C,F}$ = 30.0 Hz); 61.2 (t, CH_2O, $^1J_{C,H}$ = 147.63 Hz); 126.62 (q, CF_3, $^1J_{C,F}$ = 278.20 Hz); 169.4 (s, CO). ^{19}F NMR, δ: 71.30 (d, CF_3, J = 9.17 Hz).

Ethyl 3-benzylthio-4,4,4-trifluorobutyrate (4). Product **4** was prepared from ester **1** (1.68 g, 10 mmol), BnSH (1.30 g, 10.5 mmol), and Et_3N (0.1 g, 1 mmol) in a yield of 2.48 g (85%), b.p. 130 °C (2 Torr). Found (%): C, 53.28; H, 4.99; F, 19.39; S, 11.17. $C_{13}H_{15}F_3O_2S$. Calculated (%): C, 53.40; H, 5.10; F, 19.52; S, 10.96. ^1H NMR, δ: 1.23 (t, 3 H, Me, J = 7.75 Hz); 2.70 (AB portion of the $ABMX_3$ spectrum, δ_A = 2.55, δ_B = 2.84, 2 H, $CH_2C{=}O$, $J_{A,B}$ = 15.24 Hz, $J_{A(B),H}$ = 9.38 Hz, $J_{B(A),H}$ = 3.52 Hz); 3.44 (m, 1 H, CH); 3.94 (s, 2 H, CH_2S); 4.16 (q, 2 H, CH_2O, J = 7.75 Hz); 7.35 (m, 5 H, Ph). ^{13}C NMR, δ: 13.46 (q, Me, $^1J_{C,H}$ = 128.16 Hz); 34.10 (t, CH_2CO, $^1J_{C,H}$ = 128.97 Hz); 36.73 (t, CH_2S, $^1J_{C,H}$ = 141.51 Hz); 42.79 (dq, CH, $^1J_{C,H}$ = 142.05 Hz, $^2J_{C,F}$ = 30.74 Hz); 60.71 (t, CH_2S, $^1J_{C,H}$ = 148.29 Hz); 126.5—129.20 (m, Ph); 168.5 (s, CO). ^{19}F NMR, δ: 69.60 (d, CF_3, J = 8.5 Hz).

Ethyl 4,4,4-trifluoro-3-phenylthiobutyrate (5). ***A.*** A solution of PhSH (1.2 g, 10.9 mmol) in CH_2Cl_2 (5 mL) was added to a solution of ester **1** (1.68 g, 10 mmol) and Et_3N (0.1 g, 1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After completion of the exothermic reaction, the mixture was kept at 20 °C for 2 h, washed with 5% HCl (2×2 mL), and dried with $MgSO_4$. After distillation, compound **5** was obtained in a yield of 2.17 g (78%), b.p. 140 °C (5 Torr), n_D^{20} 1.4845. Found (%): C, 51.83; H, 4.69; F, 20.49; S, 11.35. $C_{12}H_{13}F_3O_2S$. Calculated (%): C, 51.80; H, 4.68; F, 20.50; S 11.51. ^1H NMR, δ: 1.17 (t, 3 H, Me, J = 6.16 Hz); 2.67 (AB portion of the $ABMX_3$ spectrum, δ_A = 2.56, δ_B = 2.77, 2 H, CH_2, $J_{A,B}$ = 16.4 Hz, $J_{A(B),H}$ = 9.8 Hz, $J_{B(A),H}$ = 3.36 Hz); 3.96 (m, 1 H, CH); 4.08 (t, 2 H, CH_2O, J = 6.16 Hz); 7.20 and 7.56 (both m, 5 H, Ph). ^{13}C NMR, δ: 9.59 (q, Me, $^1J_{C,H}$ = 126.35 Hz); 30.02 (t, CH_2CO, $^1J_{C,H}$ = 131.0 Hz); 44.55 (dq, CH, $^1J_{C,H}$ = 144.0 Hz, $^2J_{C,F}$ = 29.7 Hz); 56.99 (t, CH_2O, $^1J_{C,H}$ = 147.0 Hz); 122.0 (q, CF_3, $^1J_{C,F}$ = 277.0 Hz); 124.0—130.0 (m, Ph); 164.81 (s, CO). ^{19}F NMR, δ: 64.66 (d, CF_3, J = 8.4 Hz).

B. Under analogous conditions, the reaction with the use of cyclohexylamine or Et_2NH as the catalyst afforded compound **5** in 75—80% yield.

C. A mixture of ester **1** (1.68 g, 10 mmol) and PhSH (1.2 g, 10.9 mmol) was dissolved in a 5% methanolic NH_3 (5 mL) at 0 °C. Then the reaction mixture was kept at 20 °C for 24 h, concentrated, and distilled to give ester **5** in 85% yield.

Ethyl 3-(2-aminoethyl)thio-4,4,4-trifluorobutyrate hydrochloride (6). ***A.*** The reaction of equimolar amounts of crotonate **1** and 2-aminoethanethiol in anhydrous MeOH performed at 20 °C for 24 h afforded ethyl 3-(2-aminoethyl)thio-4,4,4-trifluorobutyrate, which was transformed into its hydrochloride by passing dry HCl through the reaction mixture. Then the reaction mixture was concentrated to dryness and the residue was recrystallized from anhydrous EtOH. Compound **6** was obtained in 80% yield, m.p. 98—100 °C. Found (%): C, 33.91; H, 5.46; N, 5.09. $C_8H_{15}ClF_3NO_2S$. Calculated (%): C, 34.10; H, 5.33; N, 4.97. ^1H NMR (CD_3OD), δ: 1.17 (t, 3 H, Me, J = 7.08 Hz); 2.71 (AB portion of the $ABMX_3$ mixture, δ_A = 2.49, δ_B = 2.93, 2 H, CH_2CO, $J_{A,B}$ = 17.2 Hz, $J_{A(B),H}$ = 11.6 Hz, $J_{B(A),H}$ = 3.55 Hz); 2.82—3.19 (m, 4 H, $(CH_2)_2$); 3.76 (m, 1 H, CH); 4.10 (q, 2 H, CH_2O, J = 7.08 Hz). ^{19}F NMR, δ: 72.17 (d, CF_3, J = 8.37 Hz).

B. A mixture of equimolar amounts of ester **1** and 2-aminoethanethiol hydrochloride in anhydrous MeOH was heated in a sealed tube under an argon atmosphere at 100 °C for 10 h. Iodometric titration of an aliquot withdrawn from the reaction mixture demonstrated that the number of thiol groups remained unchanged. The reaction mixture was cooled to 0 °C, Et_3N (10 mol.%) was added dropwise, and the mixture was kept at 20 °C for 24 h. The solvent was evaporated and the residue was recrystallized from EtOH to give hydrochloride **6** in 88% yield.

Ethyl 3-(2-aminophenyl)thio-4,4,4-trifluorobutyrate (7). A mixture of equimolar amounts of crotonate **1** and *o*-aminobenzenethiol in anhydrous CH_2Cl_2 did not react when heated in a sealed tube under argon at 100 °C for 5 h. After the addition of Et_3N (10 mol.%), the reaction was brought to completion at 20 °C during 24 h. After removal of the solvent, ester **7** was obtained in 95% yield as an oil, which crystallized on cooling. M.p. 35 °C. Found (%): C, 49.11; H, 4.81; N, 4.74. $C_{12}H_{14}F_3NO_2S$. Calculated (%): C, 49.15; H, 4.78; N, 4.78. ^1H NMR, δ: 1.3 (t, 3 H, Me, J = 7.15 Hz); 2.77 (AB portion of the $ABMX_3$ spectrum, δ_A = 2.64, δ_B = 2.90, 2 H, CH_2, $J_{A,B}$ = 16.8 Hz, $J_{A(B),H}$ = 11.1 Hz, $J_{B(A),H}$ = 3.0 Hz); 3.92 (m, 1 H, CH); 4.23 (q, 2 CH, CH_2O, J = 7.15 Hz); 4.69 (s, 2 H, NH_2); 6.7—7.5 (5 H, Ph). ^{19}F NMR, δ: 69.38 (d, CF_3, J = 8.8 Hz).

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