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First synthesis of 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid and its derivatives

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Treatment of 6-trifluoromethylcomanic acid with sodium hydrosulfide afforded for the first time 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid (6-trifluoromethylthiocomanic acid). When heated or treated with H_2SO_4, this acid easily underwent decarboxylation leading to 2-trifluoromethyl-4*H*-thiopyran-4-one. Because of this, both ethyl and methyl 6-trifluoromethylthiocomanates were obtained in low yields (15—23%). Decarboxylation of 6-tri(di)fluoromethylcomanic acids gave 2-tri(di)fluoromethyl-4*H*-pyran-4-ones in 77—80% yields.

Key words: 6-tri(di)fluoromethylcomanic acid, 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid, decarboxylation, 2-trifluoromethyl-4*H*-thiopyran-4-one, 2-tri(di)fluoromethyl-4*H*-pyran-4-ones.

Being highly reactive cyclic enones, fluoroalkylated γ-pyrones are of interest as starting materials for the synthesis of various partially fluorinated heterocyclic compounds with a wide spectrum of useful properties.[1] However, only a few representatives of this class of compounds have been documented. The methods of their synthesis include fluoroacylation of acetyloxiranes,[2] 2-alkoxyvinyl methyl ketone,[2] and 2-dimethylaminovinyl methyl ketone[3] and cyclization of bis(polyfluoroalkyl)-1,3,5-triketones.[4] The chemical properties of γ-pyrones containing polyfluoroalkyl substituents are poorly studied,[3—6] mainly because these highly reactive compounds with three electrophilic sites are not easily accessible. Recently,[7] we have demonstrated that ethyl 4-oxo-6-trifluoromethyl-4*H*-pyran-2-carboxylate (**1a**) can easily be obtained by trifluoroacetylation of a sodium salt of ethyl 2,4-dioxopentanoate with ethyl trifluoroacetate and used for the synthesis of a number of new trifluoromethylated γ-pyrones.

In the present work, 6-trifluoromethylcomanic acid (**2a**) obtained by acid hydrolysis of ester **1a** (see Ref. 7) was employed for the synthesis of 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid (6-trifluoromethylthiocomanic acid, **3a**) and its derivatives, including 2-trifluoromethyl-4*H*-thiopyran-4-one (**4a**), a first representative of trifluoromethylated γ-thiopyrones.

Results and Discussion

A reaction of acid **2a** with aqueous NaSH at 50 °C for 20 min afforded for the first time acid **3a** in 42% yield (Scheme 1). This is the first and so far sole example of a direct transformation of the γ-pyrone ring into the γ-thiopyrone one, because we failed with 6-difluoromethylcomanic acid (**2b**), the nearest analog of acid **2a**. A reaction of acid **2b** (obtained in 88% yield from ester **1b** as described earlier[7] for compound **2a**) with NaSH under similar conditions did not give 6-difluoromethylthiocomanic acid. Only a small amount of the starting acid **2b** was recovered from the reaction mixture; the application of more drastic conditions (90 °C, 1 h) resulted in resinification. Note that key intermediates in the synthesis of nonfluorinated γ-thiopyrones are thiacyclohexanones, which are oxidized under drastic conditions, and not easily accessible diacetylenic ketones.[8—10] In addition, 2,6-diaryl-4*H*-thiopyran-4-ones can be obtained by the thio-Claisen condensation of dialkyl ketones with aromatic dithio esters.[11]

When acid **3a** was distilled or heated in 70% H_2SO_4, not yet described 2-trifluoromethyl-4*H*-thiopyran-4-one (**4a**) was obtained in high yield (see Scheme 1). The tendency of acid **3a** toward decarboxylation presents certain problems in the synthesis of some of its derivatives. For instance, in an attempt to obtain ethyl 6-trifluoromethylthiocomanate (**5**) by esterification of acid **3a** in hot ethanol in the presence of H_2SO_4, we isolated a mixture of ester **5** and thiopyrone **4a** (~25%). In the individual state, we obtained this ester only in low yield (15%) when keeping acid **3a** in HCl-saturated anhydrous ethanol at ~20 °C for 48 h. Methyl 6-trifluoromethylthiocomanate (**6**) was synthesized in 23% yield by methylation

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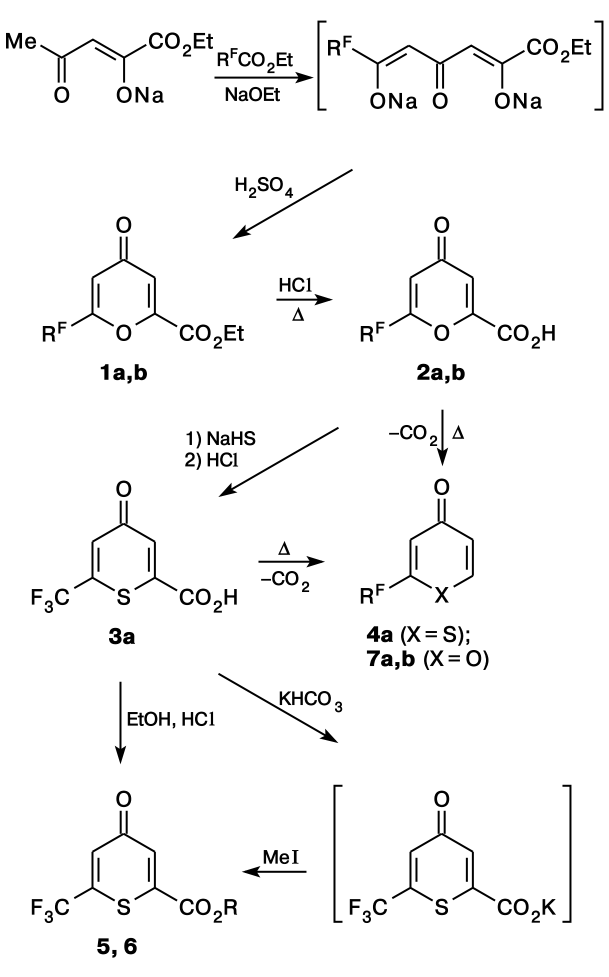
Scheme 1



R = Et (**5**), Me (**6**); $R^F = CF_3$ (**a**), CF_2H (**b**)

of a potassium salt of acid **3a** with methyl iodide in aqueous acetone.

We also found that 6-R^F-comanic acids **2a** and **2b** smoothly undergo decarboxylation at 250—260 °C to give the corresponding 4*H*-pyran-4-ones **7a** and **7b** in 80 and 77% yields, respectively. The resulting pyrones can easily be distilled off the reaction mixture and no additional purification is required. Compared to the sole alternative synthesis described earlier[2] for compound **7a**, this method involves more steps but employs less expensive and easily accessible starting reagents.

The structures of the compounds obtained agree well with elemental analysis data and IR, ^{1}H and ^{19}F NMR, and mass spectra. The characteristic feature of the ^{1}H NMR spectra of all the γ-thiopyrones obtained is the downfield shifts of the signals for the H(3) and H(5) protons compared to the signals for the corresponding protons in the spectra of γ-pyrones.

To sum up, using fluoromethylated comanic acids as starting materials, we obtained for the first time 6-trifluoromethylthiocomanic acid and its esters and developed a new method for the synthesis of tri(di)fluoromethylated γ-pyrones and 2-trifluoromethyl-γ-thiopyrone.

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum BX-II instrument in KBr pellets. ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 and 376 MHz, respectively) in $CDCl_3$ or DMSO-d_6 with Me_4Si and CCl_3F as the internal standards. The mass spectra of compounds **3a** and **4a** were measured on a MAT 8200 instrument (EI, 70 eV). Elemental analysis was carried out on a PE 2400 Series II automatic analyzer. Compounds **1a** and **2a** have been characterized earlier.[7]

Ethyl 6-difluoromethyl-4-oxo-4*H*-pyran-2-carboxylate (1b) was obtained as described for compound **1a**.[7] A sodium salt of ethyl 2,4-dioxovalerate (35.5 g, 0.2 mol) and CF_3CO_2Et (42.6 g, 0.3 mol) were added to an ethanolic solution of NaOEt prepared from metallic Na (6.9 g, 0.3 mol) and anhydrous ethanol (100 mL). The reaction mixture was refluxed for 12 h. The excess of the solvents were removed on a water bath in a water aspirator vacuum (10—12 Torr). The residue was thoroughly mixed with a mixture of ice (500 g) and conc. H_2SO_4 (25 mL). The resulting organic product was extracted with toluene—ether (2 : 1, 150 mL). The extract was distilled first under an atmospheric pressure and then in a water aspirator vacuum, while collecting a fraction with b.p. 140—150 °C (10—12 Torr). The collected liquid was mixed with ethanol (50 mL) and cooled to −25 °C. The crystallized product was filtered off, washed with cold ethanol, and dried. The yield was 22.7 g (52%), colorless crystals, m.p. 77—78 °C. Found (%): C, 49.48; H, 3.66. $C_9H_8F_2O_4$. Calculated (%): C, 49.55; H, 3.70. IR, ν/cm^{-1}: 3074, 1737, 1667, 1639, 1603. ^{1}H NMR ($CDCl_3$), δ: 1.41 (t, 3 H, Me, J = 7.1 Hz); 4.44 (q, 2 H, OCH_2, J = 7.1 Hz); 6.45 (td, 1 H, CF_2H, $^2J_{H,F}$ = 53.6 Hz, $^4J_{H,H}$ = 0.4 Hz); 6.70 (dd, 1 H, H(5), $^4J_{H,H}$ = 2.4 Hz, $^4J_{H,F}$ = 0.5 Hz); 7.13 (d, 1 H, H(3), J = 2.4 Hz). ^{19}F NMR ($CDCl_3$), δ: −124.7 (dd, CHF_2, $^2J_{H,F}$ = 53.6 Hz, $^4J_{H,F}$ = 0.5 Hz).

6-Difluoromethyl-4-oxo-4*H*-pyran-2-carboxylic acid (2b) was obtained as described for compound **2a**.[7] Ester **1b** (4.0 g, 18.3 mmol) was heated in vigorously stirred 20% HCl (20 mL) at 100 °C for 1 h. Then the solution was cooled to −10 °C and the crystalline product was filtered off, washed with 20% HCl, and dried. The yield was 3.06 g (88%), colorless crystals, m.p. 202—203 °C. Recrystallization from water did not change the melting point. Found (%): C, 44.22; H, 2.07. $C_7H_4F_2O_4$. Calculated (%): C, 44.23; H, 2.12. IR, ν/cm^{-1}: 3082, 2850—2450, 1735, 1656, 1614, 1589. ^{1}H NMR (DMSO-d_6), δ: 6.81 (br.d, 1 H, H(5), J = 2.4 Hz); 6.95 (d, 1 H, H(3), J = 2.4 Hz); 7.00 (t, 1 H, CF_2H, $^2J_{H,F}$ = 52.5 Hz); 12.0—16.0 (br.s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −123.9 (dd, CHF_2, $^2J_{H,F}$ = 52.5 Hz, $^4J_{H,F}$ = 0.5 Hz).

4-Oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylic acid (3a). A cooled solution of glacial acetic acid (6.58 g, 0.11 mol) in water (20 mL) was added at 0 °C to a solution of $Na_2S \cdot 9H_2O$ (29.21 g, 0.12 mol) in water (200 mL). The resulting solution of NaSH was vigorously stirred and cooled on an ice bath while adding acid **2a** (8.43 g, 0.04 mol). The reaction mixture was heated on a water bath at 50 °C for 20 min, cooled to 0 °C, and mixed with conc. HCl (100 mL). The precipitate that formed was filtered off, washed with conc. HCl, dried, and recrystallized from toluene. The yield was 3.78 g (42%), light gray crystals, m.p. 157 °C. Found (%): C, 37.54; H, 1.24. $C_7H_3F_3O_3S$. Calculated (%): C, 37.51; H, 1.35. IR, ν/cm^{-1}: 1718, 1609, 1562, 1422. ^1H NMR (DMSO-d_6), δ: 3.00—7.00 (br.s, 1 H, OH); 7.53 (d, 1 H, H(3), J = 1.6 Hz); 7.57 (quint, 1 H, H(5), J = 1.0 Hz). ^{19}F NMR (DMSO-d_6), δ: –62.9 (d, CF_3, $^4J_{H,F}$ = 0.9 Hz). MS, m/z (I_{rel} (%)): 224 $[M]^+$ (100), 196 $[M - CO]^+$ (47), 179 $[M - COOH]^+$ (98). Found: m/z 223.97516 $[M]^+$. $C_7H_3F_3O_3S$. Calculated: M = 223.97550.

2-Trifluoromethyl-4*H*-thiopyran-4-one (4a). ***A*** (solvent-free thermal decarboxylation). Acid **3a** (1.0 g, 4.5 mmol) was heated on a Wood´s alloy bath (260 °C) in a Würtz flask. The distilled product was collected as an oily liquid solidifying into colorless crystals upon cooling. The yield was 0.66 g (82%), m.p. 38—39 °C.

B (decarboxylation in the presence of H_2SO_4). Acid **3a** (1.5 g, 6.7 mmol) was added to 70% H_2SO_4 (1 mL). The resulting mixture was refluxed with stirring for 1 h and cooled to 20 °C. The product was extracted with ether (20 mL), the extract was concentrated, and the residue was recrystallized from light petroleum. The yield was 0.85 g (71%), colorless crystals, m.p. 38.5 °C. IR, ν/cm^{-1}: 1630, 1270, 1188, 1147. ^1H NMR ($CDCl_3$), δ: 7.09 (dd, 1 H, H(5), J = 10.3 Hz, J = 1.7 Hz); 7.34 (dq, 1 H, H(3), J = 1.7 Hz, J = 0.8 Hz); 7.80 (d, 1 H, H(6), J = 10.3 Hz). ^{19}F NMR (250 MHz, $CDCl_3$), δ: –65.0 (s, CF_3). MS, m/z (I_{rel} (%)): 180 $[M]^+$ (100), 152 $[M - CO]^+$ (59), 133 $[M - 47]^+$ (30). Found: m/z 179.98529 $[M]^+$. $C_6H_3F_3OS$. Calculated: M = 179.98567.

Ethyl 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylate (5). Acid **3a** (0.15 g, 0.7 mmol) was dissolved in ethanol (5 mL) saturated with HCl. The resulting mixture was kept at 20 °C for 48 h and then diluted with water (20 mL). The product was extracted with ether (20 mL), the extract was concentrated, and the residue was recrystallized from ethanol. The yield was 0.026 g (15%), light yellow crystals, m.p. 41—42 °C. ^1H NMR ($CDCl_3$), δ: 1.43 (t, 3 H, Me, J = 7.2 Hz); 4.47 (q, 2 H, CH_2, J = 7.2 Hz); 7.37 (m, 1 H, H(5)); 7.77 (d, 1 H, H(3), J = 1.6 Hz). ^{19}F NMR ($CDCl_3$), δ: –64.8 (d, CF_3, $^4J_{H,F}$ = 0.7 Hz).

Methyl 4-oxo-6-trifluoromethyl-4*H*-thiopyran-2-carboxylate (6). Potassium bicarbonate (0.45 g, 4.46 mmol) and MeI (0.95 g, 6.69 mmol) were added to a stirred solution of acid **3a** (0.50 g, 2.23 mmol) in acetone—water (3 : 1, 8 mL). The mixture was kept at 20 °C for 24 h and then diluted with water (20 mL). The product was extracted with light petroleum (25 mL), the extract was concentrated, and the residue was recrystallized from light petroleum. The yield was 0.12 g (23%), light yellow crystals, m.p. 79 °C. Found (%): C, 40.19; H, 2.28. $C_8H_5F_3O_3S$. Calculated (%): C, 40.34; H, 2.12. IR, ν/cm^{-1}: 3080, 1740, 1656, 1602, 1576. ^1H NMR ($CDCl_3$), δ: 4.02 (s, 3 H, MeO); 7.36 (m, 1 H, H(5)); 7.77 (d, 1 H, H(3), J = 1.7 Hz). ^{19}F NMR ($CDCl_3$), δ: –64.8 (d, CF_3, $^4J_{H,F}$ = 0.7 Hz).

2-Trifluoromethyl-4*H*-pyran-4-one (7a). Acid **2a** (4.0 g, 19.2 mmol) was heated on a Wood´s alloy bath (260 °C) in a Würtz flask. The distilled product was collected as an oily liquid solidifying into large crystals upon cooling. The yield was 2.52 g (80%), colorless crystals, m.p. 21 °C (*cf.* Ref. 2: m.p. 21—22 °C). ^1H NMR ($CDCl_3$), δ: 6.46 (dd, 1 H, H(5), J = 5.9 Hz, J = 2.5 Hz); 6.75 (d, 1 H, H(3), J = 2.5 Hz); 7.84 (d, 1 H, H(6), J = 5.9 Hz).

2-Difluoromethyl-4*H*-pyran-4-one (7b) was obtained from acid **2b** (1.5 g, 7.9 mmol) as described above for pyrone **7a**. The yield was 0.88 g (77%), light yellow crystals, m.p. 33—34 °C. Found (%): C, 49.55; H, 2.69. $C_6H_4F_2O_2$. Calculated (%): C, 49.33; H, 2.76. IR, ν/cm^{-1}: 1625, 1269, 1188, 1130. ^1H NMR ($CDCl_3$), δ: 6.37 (td, 1 H, CHF_2, J = 53.6 Hz, J = 0.4 Hz); 6.40 (dd, 1 H, H(5), J = 5.9 Hz, J = 2.5 Hz); 6.61 (d, 1 H, H(3), J = 2.5 Hz); 7.80 (d, 1 H, H(6), J = 5.9 Hz). ^{19}F NMR ($CDCl_3$), δ: –124.9 (dd, CHF_2, $^2J_{H,F}$ = 53.6 Hz, $^4J_{H,F}$ = 0.4 Hz).

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