Trifluoroacetylation of ethyl 2,4-dioxopentanoate. The first synthesis of 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylic acid and its derivatives

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Condensation of ethyl 2,4-dioxopentanoate with ethyl trifluoroacetate in the presence of NaOEt leads to ethyl 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylate, from which the corresponding acid and its amide, as well as 4-hydroxy-6-(trifluoromethyl)pyridine-2-carboxamide were obtained.

Key words: trifluoroacetylation, ethyl 2,4-dioxopentanoate, ethyl 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylate, organofluorine compounds, heterocyclization, γ-pyranones, pyridines.

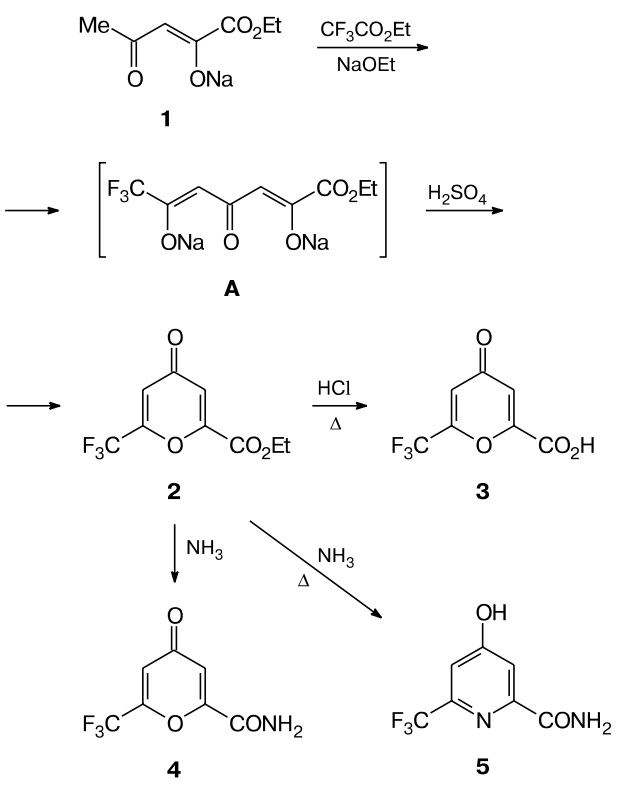
In recent years, a great interest is taken in synthesis of fluorine-containing heterocyclic compounds, many of which are used as agrochemical and medical preparations.[1] Some trifluoromethylated γ-pyranones are known[2—6] as starting materials in synthesis of pyridines with one or two CF_3 groups. Nevertheless, the fluorinated analog of 4-oxo-4*H*-pyran-2,6-dicarboxylic (chelidonic) acid, namely 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylic (6-trifluoromethylcomanic) acid, was not described so far.

Results and Discussion

In the present work we have shown that treatment of sodium derivative of ethyl 2,4-dioxopentanoate (**1**), obtained in turn from acetone and diethyl oxalate,[7] with ethyl trifluoroacetate in the presence of NaOEt followed by acidic hydrolysis leads to ethyl 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylate (**2**) in 47% yield (Scheme 1). This ester is smoothly hydrolyzed to 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylic acid (**3**) by reflux in 20% aq. HCl, whereas its treatment with 20% aq. ammonia depending on conditions applied (see Experimental) affords amides **4** or **5** in high yields, which are of interest in synthesis of new CF_3-containing derivatives of γ-pyranone and γ-pyridone (4-hydroxypyridine).

Structures of all compounds synthesized are in good agreement with analytical and IR spectroscopic data, as well as with ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectroscopic data. The characteristic feature of the ^{1}H NMR spectra consists in two doublets of H(3) and H(5) protons with ^4J = 2.2—2.3 Hz.

Scheme 1



In conclusion, trifluoroacetylation of compound **1** under studied conditions takes place at the methyl group, which leads to the disodium salt **A**, which on acidification

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is predisposed to heterocyclization into ethyl 6-trifluoromethylcomanate.

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum BX-II spectrometer in KBr pellets. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer with operating frequencies of 400.1 MHz (^{1}H), 100.6 MHz (^{13}C), and 376.5 MHz (^{19}F), internal standards, Me_4Si (^{1}H, ^{13}C) and C_6F_6 (^{19}F).

Ethyl 4-oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylate (2). Anhydrous THF (30 mL), Bu^{t}OH (0.25 mL), sodium derivative of ethyl 2,4-dioxopentanoate (**1**)[7] (35.5 g, 0.2 mol), and CF_3CO_2Et (42.6 g, 0.3 mol) were added to an alcoholic solution of NaOEt obtained by dissolution of sodium (6.9 g, 0.3 mol) in anhydrous EtOH (100 mL). The resulting reaction mixture was refluxed for 12 h and then concentrated *in vacuo* (10—12 Torr). The residue was thoroughly stirred with a mixture of ice (500 g) and conc. H_2SO_4 (25 mL), the organic product thus obtained was extracted with a toluene—ether (2 : 1) mixture (150 mL). The extract was first distilled at atmospheric pressure and then *in vacuo* and the fraction with b.p. 140—150 °C (10—12 Torr) was collected. The distillate was mixed with EtOH (50 mL) and cooled down to −25 °C, the crystallized product was filtered off, washed with cold EtOH, and dried. The yield was 22.1 g (47%), colorless crystals, m.p. 43—44 °C. Found (%): C, 45.64; H, 3.16. $C_9H_7F_3O_4$. Calculated (%): C, 45.78; H, 2.99. IR, ν/cm^{-1}: 3076, 1752, 1672, 1639, 1610. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, Me, J = 7.1 Hz); 4.46 (q, 2 H, OCH_2, J = 7.1 Hz); 6.80 (d, 1 H, H(5), J = 2.3 Hz); 7.16 (d, 1 H, H(3), J = 2.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 13.90 (Me); 63.40 (CH_2); 115.93 (q, C(5), $^3J_{C,F}$ = 2.6 Hz); 118.04 (q, CF_3, $^1J_{C,F}$ = 274.2 Hz); 119.97 (C(3)); 152.88 (q, C(6), $^2J_{C,F}$ = 40.1 Hz); 152.90 (C(2)); 158.68 (O—C=O); 177.42 (C=O). ^{19}F NMR ($CDCl_3$), δ: 90.50 (s, CF_3).

4-Oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxylic acid (3). Ester **2** (2.0 g, 8.5 mmol) was refluxed in 20% aq. HCl (20 mL) for 2 h. Then the reaction mixture was cooled down to 0 °C, the crystalline product was filtered off, washed with 20% aq. HCl, and dried. The yield was 1.54 g (88%), colorless crystals, m.p. 171—172 °C. Recrystallization from water does not lead to a change in its melting points. Found (%): C, 40.44; H, 1.16. $C_7H_3F_3O_4$. Calculated (%): C, 40.40; H, 1.45. ^{1}H NMR (DMSO-d_6), δ: 7.01 (d, 1 H, H(5), J = 2.3 Hz); 7.18 (d, 1 H, H(3), J = 2.3 Hz); 11.0—17.0 (br.s, 1 H, OH).

4-Oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxamide (4). Ester **2** (5.0 g, 21.2 mmol) was vigorously stirred with 25% aq. NH_3 (50 mL) at 0 °C for 1 h, the precipitate that formed was filtered off, washed with water, and dried. Recrystallization from aq. EtOH (1 : 1) does not lead to a change in its melting points. The yield was 3.07 g (70%), m.p. 250—252 °C (subl.). Found (%): C, 40.61; H, 1.91; N, 6.71. $C_7H_4F_3NO_3$. Calculated (%): C, 40.59; H, 1.95; N, 6.76. IR, ν/cm^{-1}: 3381, 3244, 3189, 1719, 1663, 1640, 1610. ^{1}H NMR (DMSO-d_6), δ: 7.00 (d, 1 H, H(5), J = 2.3 Hz); 7.13 (d, 1 H, H(3), J = 2.3 Hz); 8.19, 8.37 (both s, 1 H each, NH).

4-Hydroxy-6-(trifluoromethyl)pyridine-2-carboxamide (5). Ester **2** (3.0 g, 12.7 mmol) was gradually added to a stirred solution of 20% aq. NH_3 (15 mL). The reaction mixture was brought to boiling temperature in an open flask, while the formed homogeneous solution was concentrated to ~5 mL in volume. After the reaction mixture was cooled down, the formed crystals were filtered off and washed with water (10 mL), the filtrate was separated and again concentrated to ~5 mL in volume. After the mixture was cooled down, the new crop of the product was filtered off and washed with water (10 mL) again. The procedure with the filtrate was repeated two more times. The yield was 2.46 g (94%), colorless crystals, m.p. 202—204 °C. Recrystallization from water does not lead to a change in its melting points. Found (%): C, 40.83; H, 2.23; N, 13.74. $C_9H_5F_3N_2O_2$. Calculated (%): 40.79; H, 2.45; N, 13.59. IR, ν/cm^{-1}: 3415, 3347, 3200, 1700, 1617, 1587. ^{1}H NMR (DMSO-d_6), δ: 7.34 (d, 1 H, H(5), J = 2.2 Hz); 7.62 (d, 1 H, H(3), J = 2.2 Hz); 7.81, 7.91 (both s, 1 H each, CONH); 11.87 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 95.91 (s, CF_3).

References

1. T. Hiyama, *Organofluorine Compounds. Chemistry and Application*, Springer-Verlag, Berlin, 2000.
2. S. Babu and M. J. Pozzo, *J. Heterocycl. Chem.*, 1991, **28**, 819.
3. V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, W. Aelterman, and N. De Kimpe, *Tetrahedron*, 2000, **56**, 7313.
4. V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, K. A. Tehrani, and N. De Kimpe, *Tetrahedron*, 2001, **57**, 2051.
5. V. I. Tyvorskii, D. N. Bobrov, and O. G. Kulinkovich, *Tetrahedron*, 1998, **54**, 2819.
6. D. S. Yachevskii, D. L. Chizhov, K. I. Pashkevich, and V. N. Charushin, *Arkivoc*, 2004, **9**, 71.
7. J.-M. Becht, S. D. L. Marin, M. Maruani, A. Wagner, and C. Mioskowski, *Tetrahedron*, 2006, **62**, 4430.

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