New derivatives of dehydroacetic acid: synthesis of 2-polyfluoroalkyl-7-methylpyrano[4,3-*b*]pyran-4,5-diones

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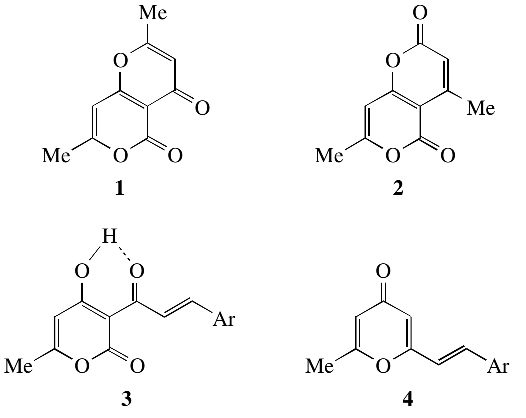
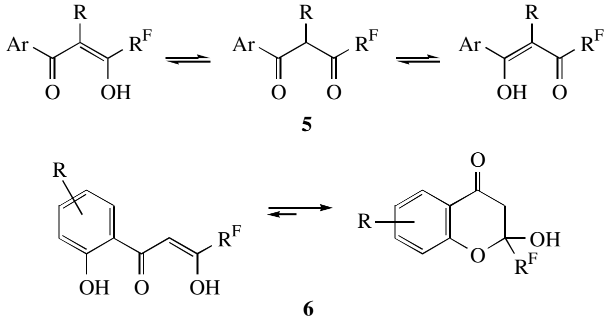
The condensation of dehydroacetic acid with $\mathrm{R^FCO_2Et}$ in the presence of LiH in THF afforded fluorine-containing 3-acetoacetyl-4-hydroxy-6-methylpyrones, which underwent cyclization to 2-polyfluoroalkyl-7-methylpyrano[4,3-*b*]pyran-4,5-diones on treatment with concentrated sulfuric acid at room temperature.

Previously,[1–4] it was found that triacetic lactone and dehydroacetic acid react with acetoacetic acid esters to form pyranopyranediones **1** and **2**, which are highly reactive molecules with several reaction centres.[5] It is also known[6–8] that aromatic aldehydes react with dehydroacetic acid, which can be considered as a heterocyclic analogue of 2-hydroxyacetophenone, to afford styrene derivatives **3**, which can be transformed into γ-pyrones **4** in acidic media. However, there is no published data on the reactions of dehydroacetic acid with carboxylic acid esters.



Scheme 1

To extend our studies concerning 2,3-dihydro-6-trifluoromethyl-4-pyrones[9–11] and 2-polyfluoroalkylchromones,[12–14] we examined the reactions of dehydroacetic acid with the esters of fluorinated carboxylic acids for the synthesis of fluorinated analogues of 2,7-dimethylpyrano[4,3-*b*]pyran-4,6-dione (Praill's α,γ-bispyrone) **1**. It is well known that the presence of fluorine atoms in the γ-position of β-diketones increases the degree of enolization.[15,16] As a rule, the methylene group in fluorine-containing β-diketones **5** (R = H) cannot be detected in the ^{1}H NMR spectra, and the diketo form appears only in the presence of a substituent at the α-position (**5**, R = Me or Br).[17] The condensation products of 2-hydroxyacetophenones with $\mathrm{R^FCO_2Et}$ (**6**, $\mathrm{R^F = CF_3}$) exist only in a cyclic semiketal form[18] both in solutions and in a crystalline state, whereas at $\mathrm{R^F = (CF_2)_2H}$ or $\mathrm{C_2F_5}$ they exist as a mixture of open-chain completely enolised (20%) and cyclic (80%) forms in a $\mathrm{CDCl_3}$ solution.[19]



Scheme 2

We found that the condensation of dehydroacetic acid with $\mathrm{R^FCO_2Et}$ in the presence of LiH in THF afforded 3-polyfluoroacetoacetyl-2-pyrones **7a–c** in 70–77% yields.† Under these conditions, ethyl acetate, ethyl dichloroacetate, and ethyl trichloroacetate did not enter into this reaction. The starting dehydroacetic acid was isolated in the case of ethyl acetate, whereas resinification of the reaction mixture due to the haloform cleavage and carbene formation was observed with the other two esters.[20]

In contrast to β-diketones **5** (R = H), the ^{1}H NMR spectra of compounds **7a–c** in a $\mathrm{CDCl_3}$ solution exhibited two sets of signals; one of them corresponds to ketodienol form **A**, and the other, to two diketoenol forms **B** and **C**, which are indistin-

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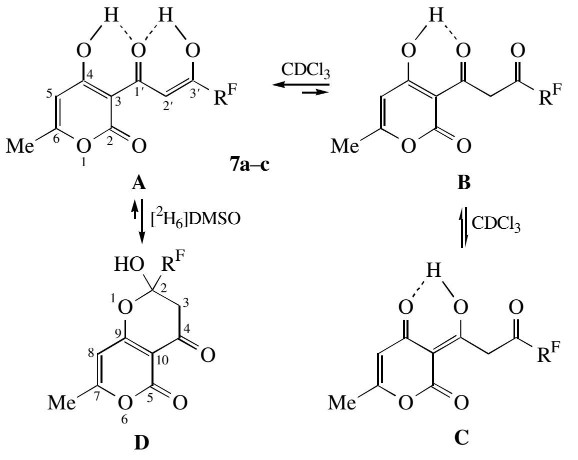
† *4-Hydroxy-6-methyl-3-(4,4-difluoroacetoacetyl)-2-pyrone* **7a**: yield 77%, mp 133–134 °C (ethanol). ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$) δ: **A** (70%): 2.30 (d, 3H, Me, ^4J 0.6 Hz), 5.98 [q, 1H, =CH(5), ^4J 0.6 Hz], 6.07 (t, 1H, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 53.7 Hz), 7.38 [s, 1H, =CH(2′)], 13.41 [br. s, 1H, HO–C(3′)], 15.42 [s, 1H, HO–C(4)]; **B** (30%): 2.30 (s, 3H, Me), 4.20 (s, 1H, $\mathrm{CH_2}$), 6.02 (s, 1H, =CH), 6.03 (t, 1H, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 53.8 Hz), 15.46 (s, 1H, OH). ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$ + [$^2\mathrm{H_6}$]DMSO) δ: **D** (100%): 2.29 (d, 3H, Me, ^4J 0.7 Hz), 2.87 (AB system, $\Delta\delta$ 0.39 ppm, 2H, $\mathrm{CH_2}$, J_{AB} 16.1 Hz), 6.05 (t, 1H, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 54.5 Hz), 6.20 (s, 1H, =CH), 8.71 (br. s, 1H, OH). ^{19}F NMR (75.3 MHz, $\mathrm{C_6F_6}$, $\mathrm{CDCl_3}$) δ: **A** (70%): 36.32 (d, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 53.9 Hz); **B** (30%): 33.09 (d, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 53.9 Hz). IR (Vaseline oil, ν/cm^{-1}): 3315 (OH), 3105 (=CH), 1760 (O–C=O), 1645 (C=O), 1530 (C=C). Found (%): C, 48.80; H, 3.30. Calc. for $\mathrm{C_{10}H_8F_2O_5}$ (%): C, 48.79; H, 3.28.

4-Hydroxy-6-methyl-3-(4,4,4-trifluoroacetoacetyl)-2-pyrone **7b**: yield 76%, mp 130–131 °C (ethanol). ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$) δ: **A** (80%): 2.31 (s, 3H, Me), 6.00 [s, 1H, =CH(5)], 7.53 [s, 1H, =CH(2′)], 13.47 [br. s, 1H, HO–C(3′)], 15.18 [s, 1H, HO–C(4)]; **B** (20%): 2.31 (s, 3H, Me), 4.32 (s, 1H, $\mathrm{CH_2}$), 6.03 (s, 1H, =CH), 15.30 (s, 1H, OH). ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$ + [$^2\mathrm{H_6}$]DMSO) δ: **D** (100%): 2.32 (s, 3H, Me), 2.98 (AB system, $\Delta\delta$ 0.26 ppm, 2H, $\mathrm{CH_2}$, J_{AB} 16.3 Hz), 6.19 (s, 1H, =CH), 9.29 (br. s, 1H, OH). ^{13}C NMR (100 MHz, $\mathrm{CDCl_3}$ + [$^2\mathrm{H_6}$]DMSO) δ: 20.13 (Me), 40.94 (C–3), 98.70 (C–10), 98.88 (q, C–2, $^2J_{\mathrm{C,F}}$ 34.6 Hz), 99.20 (C–8), 120.72 (q, $\mathrm{CF_3}$, $^1J_{\mathrm{C,F}}$ 285.56 Hz), 156.14 (C–7), 169.66 (C–9), 171.88 (C–5), 181.75 (C–4). IR (Vaseline oil, ν/cm^{-1}): 3310 (OH), 3100 (=CH), 1760 (O–C=O), 1645 (C=O), 1550, 1530 (C=C). Found (%): C, 45.44; H, 2.69. Calc. for $\mathrm{C_{10}H_7F_3O_5}$ (%): C, 45.47; H, 2.67.

4-Hydroxy-6-methyl-3-[2-(2,2,3,3-tetrafluoropropionyl)acetyl]-2-pyrone **7c**: yield 70%, mp 113–114 °C (ethanol). ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$) δ: **A** (80%): 2.31 (d, 3H, Me, ^4J 0.8 Hz), 5.99 [q, 1H, =CH(5), ^4J 0.8 Hz], 6.04 [tt, 1H, $\mathrm{(CF_2)_2H}$, $^2J_{\mathrm{H,F}}$ 52.9 Hz, $^3J_{\mathrm{H,F}}$ 4.7 Hz], 7.55 [s, 1H, =CH(2′)], 13.63 [br. s, 1H, HO–C(3′)], 15.21 [s, 1H, HO–C(4)]; **B** (20%): 2.31 (s, 3H, Me), 4.34 (s, 1H, $\mathrm{CH_2}$), 6.02 (s, 1H, =CH), 6.10 [tt, 1H, $\mathrm{(CF_2)_2H}$, $^2J_{\mathrm{H,F}}$ 52.5 Hz, $^3J_{\mathrm{H,F}}$ 5.2 Hz], 15.37 (s, 1H, OH). ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$ + [$^2\mathrm{H_6}$]DMSO) δ: **D** (70%): 2.31 (s, 3H, Me), 3.00 (AB system, $\Delta\delta$ 0.36 ppm, 2H, $\mathrm{CH_2}$, J_{AB} 16.3 Hz), 6.24 (s, 1H, =CH), 6.54 (tt, 1H, $\mathrm{CF_2CF_2H}$, $^2J_{\mathrm{H,F}}$ 51.9 Hz, $^3J_{\mathrm{H,F}}$ 5.8 Hz), 9.38 (br. s, 1H, OH); **A** (30%): 2.29 (s, 3H, Me), 6.17 [s, 1H, =CH(5)], 6.54 (tt, 1H, $\mathrm{CF_2CF_2H}$, $^2J_{\mathrm{H,F}}$ 51.9 Hz, $^3J_{\mathrm{H,F}}$ 5.8 Hz), 7.30 [s, 1H, =CH(2′)]. ^{19}F NMR (75.3 MHz, $\mathrm{C_6F_6}$, $\mathrm{CDCl_3}$) δ: **A** (80%): 24.35 (dt, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 52.9 Hz, $^3J_{\mathrm{F,F}}$ 6.9 Hz), 37.05 (dt, $\mathrm{CF_2H}$, $^3J_{\mathrm{H,F}}$ 4.8 Hz, $^3J_{\mathrm{F,F}}$ 6.9 Hz); **B** (20%): 24.15 (dt, $\mathrm{CF_2H}$, $^2J_{\mathrm{H,F}}$ 52.7 Hz, $^3J_{\mathrm{F,F}}$ 7.2 Hz), 36.88 (q, $\mathrm{CF_2}$, $^3J_{\mathrm{H,F}} \approx {}^3J_{\mathrm{F,F}}$ 6.5 Hz). IR (Vaseline oil, ν/cm^{-1}): 3315 (OH), 3105 (=CH), 1760 (O–C=O), 1645 (C=O), 1530 (C=C). Found (%): C, 44.70; H, 2.64. Calc. for $\mathrm{C_{11}H_8F_4O_5}$ (%): C, 44.61; H, 2.72.

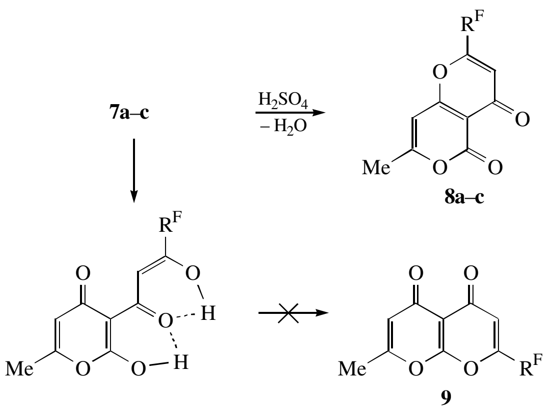


a $R^F = CF_2H$, **A**:(**B** + **C**) = 70:30
b $R^F = CF_3$, **A**:(**B** + **C**) = 80:20
c $R^F = (CF_2)_2H$, **A**:(**B** + **C**) = 80:20

Scheme 3

guishable on an NMR time scale because of rapid intrachelate tautomerization.

It is interesting that an increase from two to three fluorine atoms in a polyfluoroacyl substituent resulted in an increase in the ketodienol **A** content from 70 to 80%, whereas an increase from three to four fluorine atoms left the composition of the tautomer mixture unchanged (according to ^{1}H and ^{19}F NMR spectra). Note that the ^{1}H NMR spectra of compounds **7a–c** exhibit no signals due to cyclic form **D**, which is typical of products **6** obtained from 2-hydroxyacetophenones.[18,19] We believe that the observed differences in the structure of compounds **5**,**6** on the one hand and compounds **7a–c** on the other hand (the presence of a singlet due to a CH_2 group at 4.20–4.34 ppm and the absence of signals due to cyclic form **D**) result from the keto–enol equilibrium **B** $\rightleftharpoons$ **C**. The rapid [1,5]H sigmatropic shift between the *endo* and *exo* cyclic enol fragments of tautomers **B** and **C** results in partial enolization of the carbonyl group attached to the α-pyrone ring and hence in a decrease in the electron-acceptor effect. Thus, an increase in the electron-acceptor effect of one carbonyl group (by the introduction of fluorine atoms) is compensated by a loss at the other carbonyl group (because of the participation in tautomerization); finally, this resulted in only 70–80% enolization, as is the case in acetylacetone.[15] At the same time, the equilibrium **B** $\rightleftharpoons$ **C** is responsible for a decrease in the nucleophilicity of the OH group, and a strong intramolecular hydrogen bond (a narrow singlet at 15.30–15.46 ppm) hinders the conformational flexibility of the molecule. As a result, in contrast to compounds **6**, cyclic form **D** was not detected in a $CDCl_3$ solution. However, as judged from the appearance of a typical AB system of a CH_2 group with J_{AB} 16.1–16.3 Hz at 2.87–3.00 ppm, the equilibrium is almost completely shifted towards form **D** on the addition of dimethyl sulfoxide to solutions of compounds **7a**,**b** in $CDCl_3$. This is likely due to the rupture of intramolecular hydrogen bonds, which stabilise open forms **A**–**C**, under the action of basic dimethyl sulfoxide molecules. In the case of compound **7c**, ketodienol form **A** (30%) was present along with cyclic form **D** (70%); this fact indicated that the $(CF_2)_2H$ group is less capable of stabilising semiketal **D**.[9,19] Thus, polyfluoroacyl derivatives **7a–c** of dehydroacetic acid exist as either open-chain forms **A**–**C** or semiketal form **D** depending on the nature of solvent.



Scheme 4

We also found that compounds **7a–c** undergo dehydration on dissolution in concentrated sulfuric acid at room temperature to form a pyranopyranedione system, which can be described by isomeric structures **8** and **9** depending on the direction of enolization in the ring.

We cannot unambiguously choose between structures **8** and **9** based on the ^{1}H NMR spectra of dehydrated products, which exhibit a singlet or doublet of the Me group (2.37–2.39 ppm), a singlet or quartet (6.23–6.27 ppm) and a singlet (6.62–6.76 ppm) of vinyl protons. The ^{13}C NMR spectrum of a product obtained from **7a** exhibits two downfield signals at 171.80 and 168.96 ppm, which are also inadequate for deciding between α- and γ-pyrone carbonyls. However, the IR spectra of compounds formed from **7a–c** under exposure to H_2SO_4 exhibit an intense absorption band at 1740–1755 cm^{-1}, which is typical of α-pyrones;[21] thus, structure **8** analogous to Praill's α,γ-bispyrone **1**[1] can be suggested.‡

Thus, we described the condensation of dehydroacetic acid with R^FCO_2Et, which is characteristic of only polyfluorinated carboxylic acid esters, as the first example of dehydroacetic acid reactions with esters. Compounds **8** are promising highly reactive R^F-containing synthons.

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‡ *2-Difluoromethyl-7-methylpyrano[4,3-*b*]pyran-4,5-dione* **8a**: yield 65%, mp 188–189 °C (ethanol). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.37 (d, 3H, Me, ^4J 0.5 Hz), 6.23 [q, 1H, =CH(8), ^4J 0.5 Hz], 6.41 (t, 1H, CF_2H, $^2J_{H,F}$ 53.4 Hz), 6.62 [s, 1H, =CH(3)]. ^{19}F NMR (75.3 MHz, C_6F_6, $CDCl_3$) δ: 37.78 (d, CF_2H, $^2J_{H,F}$ 53.1 Hz). IR (Vaseline oil, ν/cm^{-1}): 3090–3130 (=CH), 1755 (O–C=O), 1685, 1645, 1555 (C=O, C=C). Found (%): C, 52.77; H, 2.46. Calc. for $C_{10}H_6F_2O_4$ (%): C, 52.65; H, 2.65.

*2-Trifluoromethyl-7-methylpyrano[4,3-*b*]pyran-4,5-dione* **8b**: yield 82%, mp 245–246 °C (ethanol). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.39 (s, 3H, Me), 6.27 [s, 1H, =CH(8)], 6.76 [s, 1H, =CH(3)]. ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 2.35 (s, 3H, Me), 6.68 [s, 1H, =CH(8)], 6.99 [s, 1H, =CH(3)]. ^{13}C NMR (100 MHz, $CDCl_3$ + [$^2H_6$]DMSO) δ: 19.97 (Me), 97.99 (C-8), 105.78 (C-10), 116.27 (C-3), 117.83 (q, CF_3, $^1J_{C,F}$ 273.4 Hz), 148.83 (q, C-2, $^2J_{C,F}$ 39.2 Hz), 155.90 (C-7), 168.84 (C-9), 168.96 (C-5), 171.80 (C-4). IR (Vaseline oil, ν/cm^{-1}): 3070 (=CH), 1755 (O–C=O), 1685, 1650, 1550 (C=O, C=C). Found (%): C, 48.71; H, 1.92. Calc. for $C_{10}H_5F_3O_4$ (%): C, 48.80; H, 2.05.

*2-(2,2,3,3-Tetrafluoroethyl)-7-methylpyrano[4,3-*b*]pyran-4,5-dione* **8c**: yield 94%, mp 196–197 °C (ethanol). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.38 (d, 3H, Me, ^4J 0.5 Hz), 6.08 [tt, 1H, $(CF_2)_2H$, $^2J_{H,F}$ 52.9 Hz, $^3J_{H,F}$ 2.8 Hz], 6.26 [q, 1H, =CH(8), ^4J 0.5 Hz], 6.75 [s, 1H, =CH(3)]. ^{19}F NMR (75.3 MHz, C_6F_6, $CDCl_3$) δ: 27.02 (dt, CF_2H, $^2J_{H,F}$ 52.9 Hz, $^3J_{F,F}$ 3.9 Hz), 41.08 (q, CF_2, $^3J_{H,F} \approx {}^3J_{F,F}$ 3.4 Hz). IR (Vaseline oil, ν/cm^{-1}): 3090 (=CH), 1740 (O–C=O), 1680, 1640, 1555 (C=O, C=C). Found (%): C, 47.57; H, 2.18. Calc. for $C_{11}H_6F_4O_4$ (%): C, 47.50; H, 2.17.

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