Structure of diethyl (polyfluorobenzoyl)malonates and their thermal intramolecular cyclization*

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The reaction of the C-ethoxymagnesium derivative of diethyl malonate with polyfluorobenzoyl chlorides affords the corresponding (polyfluorobenzoyl)malonates prone to thermal cyclization into coumarin derivatives. The compounds obtained are inherent in keto—enol tautomerism.

Key words: malonates, coumarins, heterocyclization, keto—enol tautomerism, organofluorine compounds.

Diethyl (polyfluorobenzoyl)malonates are key intermediates in the synthesis of polyfluorine-containing quinolones[1—4] and benzothiazines[5] exhibiting antiviral,[6] antibacterial,[7] and antitumor[8] activity. Fluoroquinolones represent a particular group of modern antibiotics, such as ofloxacin, levofloxacin, and others. Polyfluorobenzoylmalonates are not often obtained in the pure form and are generally used *in situ* for the synthesis of the corresponding 3-oxoesters.[9—11] No data were found on other transformations of this type of compounds.

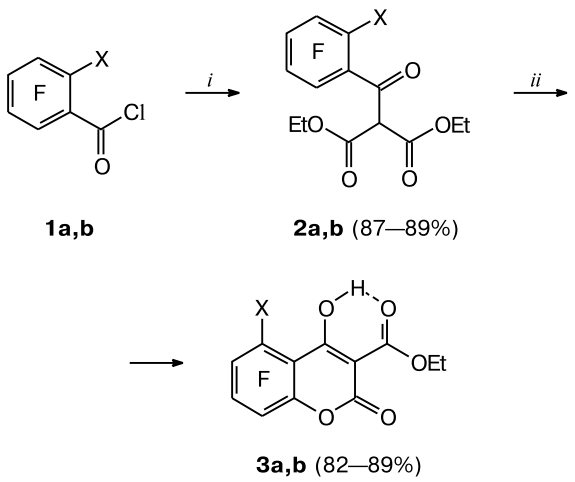
The purpose of the present work is to obtain diethyl (polyfluorobenzoyl)malonates and to study their structures and further chemical transformations.

The reactions of 2,3,4,5-tetrafluorobenzoyl (**1a**) and pentafluorobenzoyl (**1b**) chlorides with malonic ester under the action of magnesium ethoxide afforded diethyl (polyfluorobenzoyl)malonates (**2a**,**b**) (Scheme 1) similarly to earlier works.[11—13]

The structures of isolated (polyfluorobenzoyl)malonates **2a,b** (Scheme 2) were studied in detail. Their individual character was confirmed by TLC, the quantitative composition was established using elemental analysis, and structural features and tautomeric composition were studied by IR spectroscopy and ^1H and ^{19}F NMR spectroscopy.

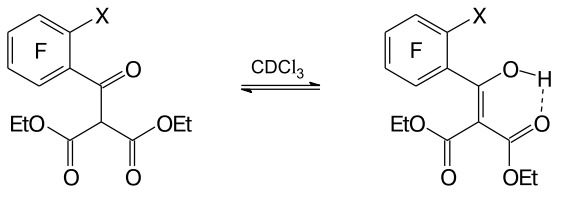
Compounds **2a,b** are prototropic systems and, according to the data of NMR spectroscopy, in $CDCl_3$ solutions they exist as a mixture of tautomeric forms **A** and **B**. The presence of the enol form in the spectra is indicated by the signal of the proton of the hydroxyl group at δ 13.82—13.96, and keto form **A** can easily be identified by the signal of the methine proton at δ 5.10—5.42. The sig-

Scheme 1



X = H (**a**), F (**b**)
i. $EtOMgCH(CO_2Et)_2$, toluene, 0 °C; *ii*. 150—200 °C.

Scheme 2



A **B**

2a, 67% **2a**, 33%
2b, 20% **2b**, 80%

X = H (**a**), F (**b**)

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nals of protons of the ethoxy group of form **B** are observed as two different signals because of their nonequivalence caused by the formation of an intramolecular hydrogen bond between the proton of the hydroxyl group and the oxygen atom of one of the ester fragments (see Scheme 2). It should be mentioned that tetrafluorine-containing benzoylmalonate **2a** is characterized by the difference in signals of protons of the tetrafluorophenyl groups of the enol and keto forms detected at δ 7.16 and 7.80, respectively.

Based on the assignment of the signals of protons to two forms and comparison of their integral intensities for tetrafluorobenzoylmalonate **2a**, we observed the predomination of the keto form (67%) over the enol form (33%), due to which compound **2a** is close to polyfluoroalkyl analogs.[14] Unlike **2a**, pentafluorinated analog **2b** was enolized by 80%. Evidently, its higher susceptibility to enolization is due to the additive action of the negative inductive effect of two *ortho*-fluorine atoms.

The IR spectra of benzoylmalonates **2a,b** recorded in thin layer contain two absorption bands of the ethoxycarbonyl groups at ν 1741—1739 cm^{-1} and 1705—1703 cm^{-1}. The first of them is close in value to the absorption of the isolated ester group and is caused by vibrations of two equivalent ethoxycarbonyl groups of keto form **A**. The band at ν 1705—1703 cm^{-1} corresponds to vibrations of the unbound ester group of enol form **B**. The low-frequency shift of the band of this group is caused by its conjugation with the C=C bond. These data indicate the existence of diesters **2a,b** in a mixture of keto and enol forms (**A** and **B**) without a solvent.

We found that the distillation of diesters **2a**,**b** produces by-products identified as 4-hydroxypolyfluorocoumarins (**3a**,**b**). Obviously, this heterocyclization is caused by heating. Heating of neat benzoylmalonates **2a**,**b** to 150—200 °C results in their complete conversion to products **3a**,**b** in high yields 82—89% (see Scheme 1).

The substitution of the fluorine atom by the action of diverse nucleophiles is an important property characteristic of polyfluorinated aromatic compounds.[15—19] Transformation **2**→**3** is a particular case of intramolecular substitution of the fluorine atom in the *ortho*-position under the action of the nucleophilic center to form the six-membered cycle.[10,20]

The thermal transformation of diethyl (polyfluorobenzoyl)malonates **2a**,**b** found in this work is a convenient route for the synthesis of fluorine-containing 4-hydroxypolyfluorocoumarins. The chromone—coumarin rearrangement of 3-ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluorochromone has earlier[21] been used for the synthesis of 3-substituted 4-hydroxy-5,6,7,8-tetrafluorocoumarins. This chromone was obtained by the one-step acylation of acetoacetic ester with pentafluorobenzoyl chloride in the presence of magnesium ethoxide and without isolation of intermediately formed β,β′-dioxo ester.[22]

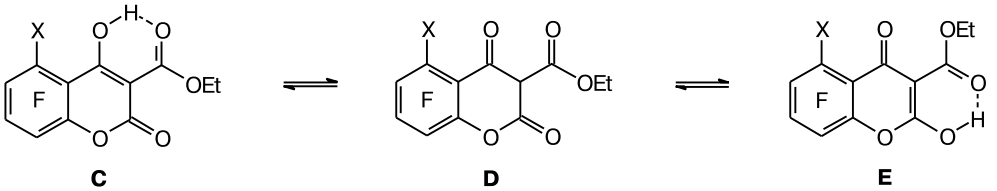
A distinctive feature of thermal cyclization of compounds **2a,b** is the participation of the oxygen atom of the ester group as a nucleophilic center. The formation of 4-hydroxypolyfluorocoumarins **3a,b** proceeds without catalysts and in the absence of bases and solvent, while the intramolecular cyclization of 2-(2-acetoxybenzoyl)-malonate to 4-hydroxy-3-ethoxycarbonylcoumarin described in the literature[23] occurs only under acidic conditions.[23]

The obtained coumarin derivatives **3a**,**b** can also be susceptible to keto—enol transformations and, therefore, it is reasonable to assume for them the existence of three tautomeric forms **C**, **D**, and **E** (Scheme 3).

The X-ray diffraction analysis carried out for a crystal of compound **3a** (Fig. 1) unambiguously showed that this substance is ethyl 4-hydroxy-2-oxo-6,7,8-trifluorobenzopyran(2*H*)-3-carboxylate (form **C**). The coumarin ring of the molecule is planar. An intramolecular hydrogen bond between the atoms O(2) and H(4) has the following characteristics: the intramolecular distance O(2)...H(4) is 1.61(2) Å and the angles C(7)O(4)H(4) and H(4)O(2)C(10) are 102(1) and 99.0(6)°, respectively.

A comparative analysis of the IR spectra of compounds **3a,b** revealed no substantial difference between them. These compounds have the characteristic absorption band at ν 2642—2640 cm^{-1} corresponding to vibrations of the hydroxyl group bound by the intramolecular hydrogen bond, the strong absorption band at ν 1736—1735 cm^{-1} caused by vibrations of the carbonyl group of the lactone fragment, and the absorption band at ν 1644—1643 cm^{-1} due to vibrations of the ester group bound by the intramolecular hydrogen bond. Thus, the data of IR spectroscopy indicate that compounds **3a**,**b** exist as enol form **C**.

Scheme 3



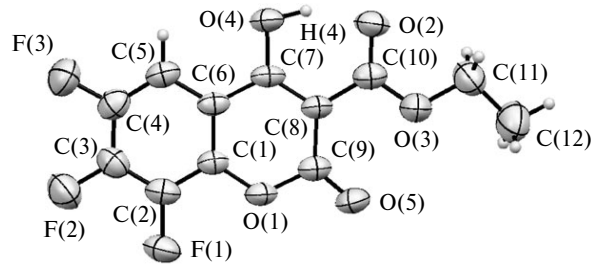


Fig. 1. General view of a molecule of compound **3a**.

The ^{1}H NMR spectra of 4-hydroxypolyfluorocoumarins **3a,b** detected in DMSO-d_6 exhibit the single set of signals corresponding to the enol form. The signal of the proton of the hydroxyl group is observed in a weak field (δ 10.36) due to its deshielding because of the formation of an intramolecular hydrogen bond with the oxygen atom of the ester substituent.

Generalizing the data obtained in this work, note that diethyl (polyfluorobenzoyl)malonates are convenient synthones for the synthesis of fluoroaromatic β-oxo esters and also fluorine-containing heterocycles. In addition, our work showed that the desired purity and high yield of (polyfluorobenzoyl)malonates used as key intermediates in the synthesis of antibiotics of the fluoroquinolone series can be achieved by a decrease in the distillation temperature due to the pressure drop.

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum One B FT-IR spectrometer in the range from 4000 to 400 cm^{-1} in thin layer on KBr plates (compounds **2a,b**) or with a DRA diffuse reflectance attachment (products **3a,b**). ^{1}H and ^{19}F NMR spectra were measured on a Bruker DRX 400 spectrometer with working frequencies of 400.1 MHz (^{1}H) and 376.5 MHz (^{19}F) using Me_4Si and C_6F_6 as internal standard, respectively. Elemental analysis was carried out on a Perkin—Elmer CHN PE 2400 automated analyzer. Melting points were measured in open capillaries on a Stuart SMP30 instrument.

Single crystals of compounds **3a** were obtained by crystallization from toluene. The X-ray diffraction experiment was carried out on an Xcalibur 3 diffractometer with a CCD detector (graphite monochromator, λ(Mo-Kα) 0.71073 Å, temperature 295(2) K, ω scan mode). An absorption correction was applied analytically by the multifacet crystal model using the CrysAlis RED 1.171.29.9 program. The crystal structure was solved and refined using the SHELXS-97 and SHELXL-97 program packages.[24]

Selected crystallographic data for compound **3a**: $C_{12}H_7F_3O_5$; *M* 288.18; monoclinic crystal system with the following unit cell parameters: a = 5.2114(3), b = 24.991(2), c = 8.8377(10) Å; α = γ = 90°, β = 96.036(8)°; V = 1114.64(18) Å^3; Z = 4; d_{calc} = = 1.672 g cm^{-3}; μ = 0.161 mm^{-1}; space group $P2_1/c$. The total number of reflections was 7182, the number of independent reflections was 3215, the R_1 factor was 0.040, and the number of refined parameters was 185. The full crystallographic parameters for product **3a** are available at www.ccdc.cam.ac.uk/conts/retrieving.html (or CCDC No. 811 939, 12 Union Road, Cambridge CB2 1EZ, UK; e-mail: deposit@ccdc.cam.ac.uk).

The initial 2,3,4,5-tetrafluorobenzoyl (**1a**) and 2,3,4,5,6-pentafluorobenzoyl (**1b**) chlorides and diethyl malonate are commercially available synthones.

Diethyl (2,3,4,5-tetrafluorobenzoyl)malonate (2a). Anhydrous CCl_4 (1 mL) and absolute ethanol (>99.9%, 7 mL) and then a mixture of diethyl malonate (32 g, 0.20 mol) and absolute toluene (100 mL) were added to iodine-activated magnesium chips (4.6 g, 0.20 mol). After magnesium was dissolved, the obtained homogeneous solution was evacuated until a viscous residue was formed to which absolute ethanol (150 mL) was added. The reaction mixture was cooled to 0 °C, and a solution of tetrafluorobenzoyl chloride **1a** (40 g, 0.20 mol) in absolute toluene (70 mL) was added. The mixture was stored for 3 h. A 10% solution of H_2SO_4 (250 mL) was added, and the organic layer was separated and washed with water. The solvent was distilled off under reduced pressure, and the residue was distilled *in vacuo*. Oily yellow product **2a** was obtained in a yield of 59.81 g (89%), b.p. 140—143 °C (3 Torr). IR, ν/cm^{-1}: 3079, 2987, 2942, 2910 (O—H, C—H); 1739 (C=O); 1703 (C=O); 1632 (C=O); 1526 (C=C); 1485, 1448, 1407, 1365 (C=C^{Ar}); 1277, 1236 (C—F). ^{1}H NMR ($CDCl_3$), δ of mixture of tautomers **A—B** (67 : 33): tautomer **A**, 1.30 (t, 3 H, Me, J = 7.1 Hz); 4.30 (q, 2 H, CH_2, J = 7.1 Hz); 5.10 (d, 1 H, CH, J = 2.6 Hz); 7.80 (dddd, 1 H, C_6F_4H, J = 10.4 Hz, J = 8.4 Hz, J = 6.1 Hz, J = 2.5 Hz); tautomer **B**, 1.15 and 1.38 (both t, 6 H, 2 Me, J = 7.1 Hz); 4.12 and 4.37 (both q, 4 H, 2CH_2, J = 7.1 Hz); 7.16 (m, 1 H, C_6F_4H), 13.83 (s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: tautomer **A**, 8.83 (m, 1 F); 17.00 (m, 1 F); 25.82 (m, 1 F); 26.40 (m, 1 F); tautomer **B**, 7.46 (m, 1 F); 10.73 (m, 1 F); 23.81 (dddd, 1 F, J = 21.1 Hz, J = 12.7 Hz, J = 9.9 Hz, J = 3.2 Hz); 24.68 (tdd, 1 F, J = 18.4 Hz, J = 12.0 Hz, J = 5.9 Hz). Found (%): C, 49.87; H, 3.47; F, 22.49. $C_{14}H_{12}F_4O_5$. Calculated (%): C, 50.01; H, 3.60; F, 22.60.

Diethyl (2,3,4,5,6-pentafluorobenzoyl)malonate (2b). Yellow oil. The yield was 87%, b.p. 125—127 °C (3 Torr). IR, ν/cm^{-1}: 3078, 2988, 2942, 2911 (O—H, C—H); 1741 (C=O); 1705 (C=O); 1631 (C=O); 1524 (C=C); 1485, 1448, 1408, 1365 (C=C^{Ar}); 1276, 1237 (C—F). ^{1}H NMR ($CDCl_3$), δ of mixture of tautomers **A—B** (20 : 80): tautomer **A**, 1.28 (m, 3 H, Me); 4.29 (q, 2 H, CH_2, J = 7.1 Hz); 5.42 (s, 1 H, CH); tautomer **B**, 1.14 and 1.39 (both t, 6 H, 2 Me, J = 7.1 Hz); 4.11 and 4.40 (both q, 4 H, 2 CH_2, J = 7.1 Hz); 13.96 (s, 1 H, OH). ^{19}F NMR ($CDCl_3$), δ: tautomer **A**, 1.53 (m, 2 F); 14.39 (m, 1 F); 24.79 (m, 2 F); 26.40 (m, 1 F); tautomer **B**, 0.75 (m, 2 F); 11.03 (m, 1 F); 22.79 (m, 2 F). Found (%): C, 47.31; H, 3.01; F, 26.69. $C_{14}H_{11}F_5O_5$. Calculated (%): C, 47.47; H, 3.13; F, 26.82.

Ethyl 4-hydroxy-6,7,8-trifluoro-2-oxo-2*H*-benzopyran-3-carboxylate (3a). Diester **2a** (20 g, 0.06 mmol) was heated to 150—...200 °C, and the solid product was washed with ethanol. Product **3a** was obtained as a yellow powder in a yield of 12.1 g (89%), m.p. 169—170 °C. IR, ν/cm^{-1}: 3060, 2991, 2946, 2911 (C—H); 2642 (O—H); 1736 (C=O^{lactone}); 1644 (C=O); 1575, 1519, 1478, 1418, 1379 (C=C^{Ar}); 1046, 1024, 995 (C—F). ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3 H, Me, J = 7.1 Hz); 4.31 (q, 2 H, CH_2, J = 7.1 Hz); 7.81 (ddd, 1 H, C_6F_4H, J = 10.3 Hz, J = 8.1 Hz, J = 2.3 Hz); 10.36 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: 9.30 (td, 1 F, J = 20.4 Hz, J = 2.2 Hz); 11.54 (ddd, 1 F, J = 22.3 Hz, J = 20.4 Hz, J = 8.1 Hz); 22.91 (ddd, 1 F, J = 22.7 Hz, J = 10.4 Hz, J = 2.1 Hz). Found (%): C, 49.89; H, 2.26; F, 19.58. $C_{12}H_7F_3O_5$. Calculated (%): C, 50.01; H, 2.45; F, 19.78.

Ethyl 4-hydroxy-5,6,7,8-tetrafluoro-2-oxo-2*H*-benzopyran-3-carboxylate (3b). Yellow powder. The yield was 82%, m.p. 139—140 °C. IR, ν/cm^{-1}: 3062, 2992, 2946, 2912 (C—H); 2640 (O—H); 1735 (C=O^{lactone}); 1643 (C=O); 1575, 1521, 1478, 1419, 1383 (C=C^{Ar}); 1052, 1026, 1002 (C—F). ^{1}H NMR (DMSO-d_6), δ: 1.25 (t, 3 H, Me, J = 7.1 Hz); 4.22 (q, 2 H, CH_2, J = 7.1 Hz); 10.36 (s, 1 H, OH). ^{19}F NMR (DMSO-d_6), δ: −2.95 (t, 1 F, J = 22.2 Hz); 2.00 (ddd, 1 F, J = 22.1 Hz, J = 11.0 Hz, J = 1.9 Hz); 10.82 (t, 1 F, J = 22.3 Hz); 18.44 (br.s, 1 F). Found (%): C, 46.92; H, 1.83; F, 24.69. $C_{12}H_6F_4O_5$. Calculated (%): C, 47.08; H, 1.98; F, 24.82.

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