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Fluoroaryl containing β,β′-dioxoesters in the synthesis of fluorobenzopyran-4(2)-ones

S.P. Kisil', Ya.V. Burgart, V.I. Saloutin*, O.N. Chupakhin

Institute of Organic Synthesis, Urals Division, Russian Academy of Sciences, 620219, GSP-147 Ekaterinburg, Russia

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Abstract

Fluoroaryl containing β,β′-dioxoesters and their copper(II) chelates have been prepared by acylation of ethyl acetoacetate with 2,6-dimethoxy-3,4,5-trifluorobenzoyl, 2-methoxy-3,4,5,6-tetrafluorobenzoyl and pentafluorobenzoyl chlorides. Cyclization of these β,β′-dioxoesters leads to formation of substituted fluorochromones. Depending on conditions, 2-methyl-5-methoxy-6,7,8-trifluoro-3-ethoxycarbonylchromone hydrolyzed to 5-hydroxy-2-methyl-6,7,8-trifluorochromone or 5-hydroxy-2-methyl-6,7,8-trifluorochromone-3-carboxylic acid. The same chromone reacts with morpholine to form a seven-substituted product and ammonium hydroxide to give 3-iminoacetyl-4-hydroxy-5-methoxy-6,7,8-trifluorocoumarin. Hydrolysis of the latter affords 3-acetyl-4-hydroxy-5-methoxy-6,7,8-trifluorocoumarin. Ethyl-2-(2,6-dimethoxy-3,4,5-trifluorobenzoyl)-3-oxobutanoates undergoes ketone-splitting to 1-(2,6-dimethoxy-3,4,5-trifluorophenyl)-1,3-butandione.

Keywords: Acylation; β,β′-Dioxoesters; Copper(II) chelate; Trifluorochromone; Trifluorocoumarin

1. Introduction

Chromone and coumarin fragments enter into the structures of both natural and synthetic biologically active compounds, therefore creation of new representatives of this class of compounds is potentially useful. One of the methods for synthesis of fluorine containing benzopyran-2(4)-ones is acylation of various β-oxoesters by pentafluorobenzoyl chloride [1–4]. We previously developed a method of selective *o*-methoxylation of pentafluorobenzoic acids allowing us to obtain 2-methoxy-3,4,5,6-tetrafluorobenzoic acids and 2,6-dimethoxy-3,4,5-trifluorobenzoic acids depending on the conditions [5].

In this paper, acylation of ethyl acetoacetate by these fluorobenzoyl chlorides and synthesis of novel fluorobenzopyran-2(4)-ones are described.

2. Results and discussion

2.1. Acylation of ethyl acetoacetate by fluorobenzoyl chlorides

2,6-Dimethoxy-3,4,5-trifluorobenzoyl and 2-methoxy-3,4,5,6-tetrafluorobenzoyl chlorides **2a,b** were obtained by heating the corresponding acids **1a,b** with an excess of phosphorus pentachloride (Scheme 1). These fluorobenzoyl chlorides were used for acylation of ethyl acetoacetate.

It is known that acylation of ethyl acetoacetate by pentafluorobenzoyl chloride leads to formation of 3-ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluorochromone instead of expected β,β′-dioxoester [1,2]. In the present work, it has been found that interaction of fluorobenzoyl chlorides **2a,b** with ethyl acetoacetate in the presence of magnesium ethoxide results in β,β′-dioxoesters **3a,b** (Scheme 1). The treatment of these β,β′-dioxoesters **3a,b** with copper(II) acetate gives copper(II) chelates **4a,b**. The same chelates can be obtained directly from the reaction of ethyl acetoacetate with fluorobenzoyl chlorides **2a,b** without intermediate isolation of β,β′-dioxoesters **3a,b** when the reaction mass was treated with copper(II) acetate. The decomposition of copper chelates **4a,b** with hydrochloric acid affords free ligands **3a,b**.

We obtained the copper(II) chelate of ethyl-2-pentafluorobenzoyl-3-oxobutanoate **4c** (Scheme 2) from the reaction of ethyl acetoacetate with pentafluorobenzoyl chloride **3c** when the reaction mass was treated with copper(II) acetate. Decomposition of the latter by hydrogen chloride gives the corresponding β,β′-dioxoester **3c**. Previous attempts to isolate β,β′-dioxoester **3c** failed because of instability and intramolecular cyclization into 3-ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluorochromone **5b** [1].

* Corresponding author. Fax: +7-3432-745954.
E-mail address: saloutin@ios.uran.ru (V.I. Saloutin).

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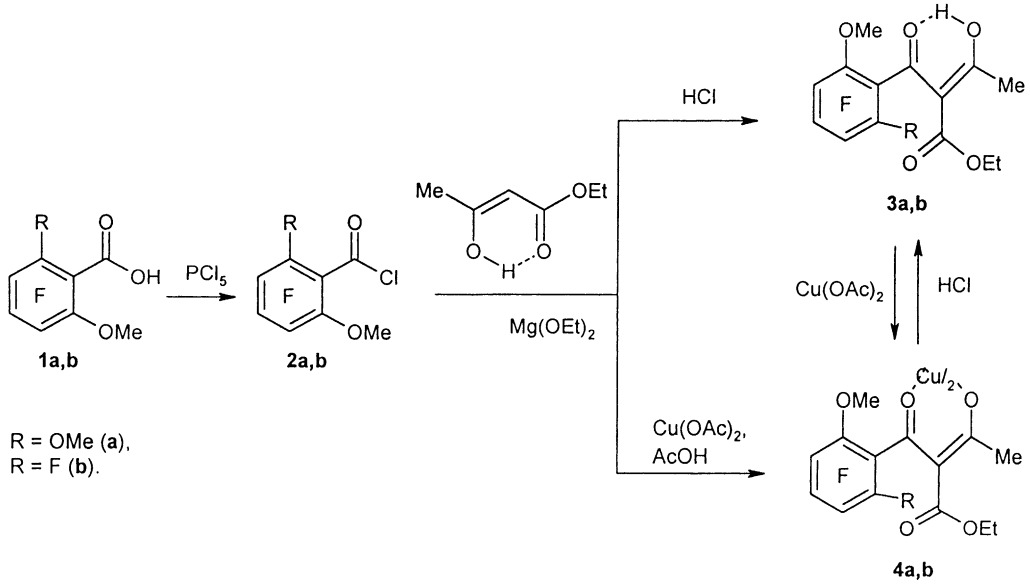


Scheme 1.

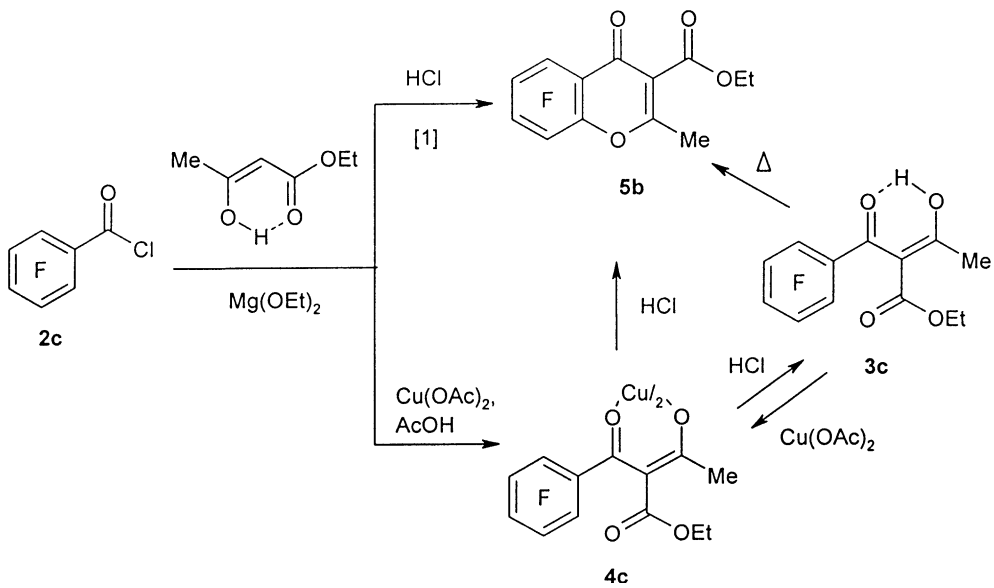
β,β′-Dioxoesters **3b,c** readily cyclized into chromone **5a,b** on heating in the absence of solvents or in DMSO (Schemes 2 and 3). The same chromones can be obtained from chelates **4b,c** by heating in DMSO. The cyclization proceeds through intramolecular substitution of the *o*-fluorine atom in the fluorophenyl substituent.

In contrast, β,β′-dioxoester **3a** and its chelate **4a** are stable compounds. Attempts to subject the β,β′-dioxoester to cyclization failed. Heating β,β′-dioxoester **3a** in hydrogen bromide results in chromone **6** or β-diketone **7** depending on the reaction time and temperature (Scheme 4). Treatment of the latter with copper(II) acetate gives chelate **8**. Chromone **6** can be obtained by heating β-diketone **7** in hydrogen bromide also.

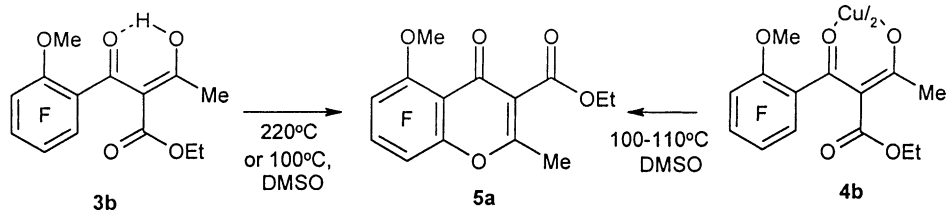
The difficulty of cyclization of β,β′-dioxoester **3a** into a chromone is explained by the absence of readily leaving *o*-fluorine atoms unlike its pentafluorophenyl and tetrafluorophenylsubstituted analogues **3b,c**.

2.2. Reactions of 3-ethoxycarbonyl-2-methyl-5-methoxy-6,7,8-trifluoro-4H-1,4-dihydrobenzopyran-4-one 5a

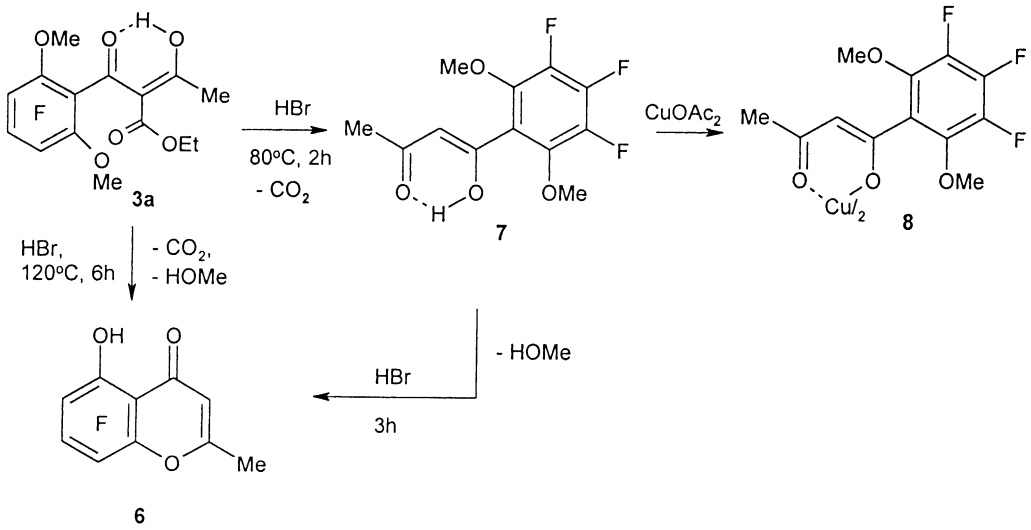
Reactions of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone and 3-ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluoro-



Scheme 2.



Scheme 3.

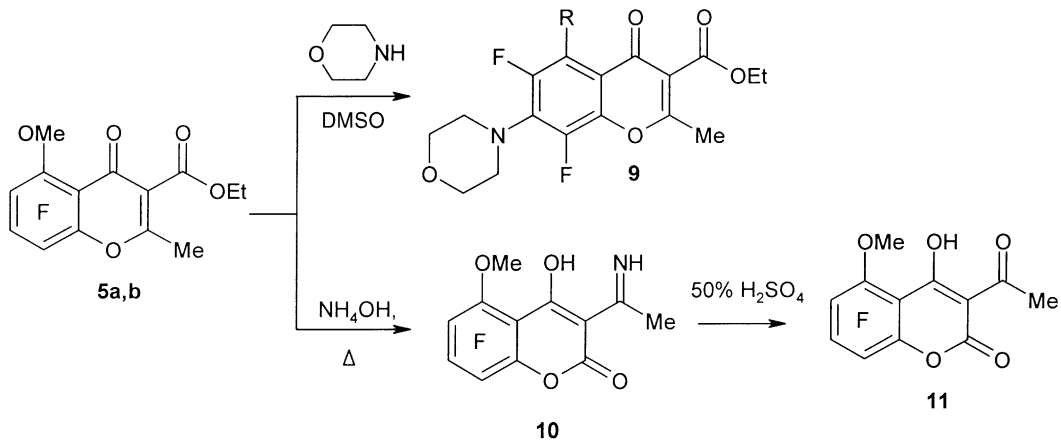


Scheme 4.

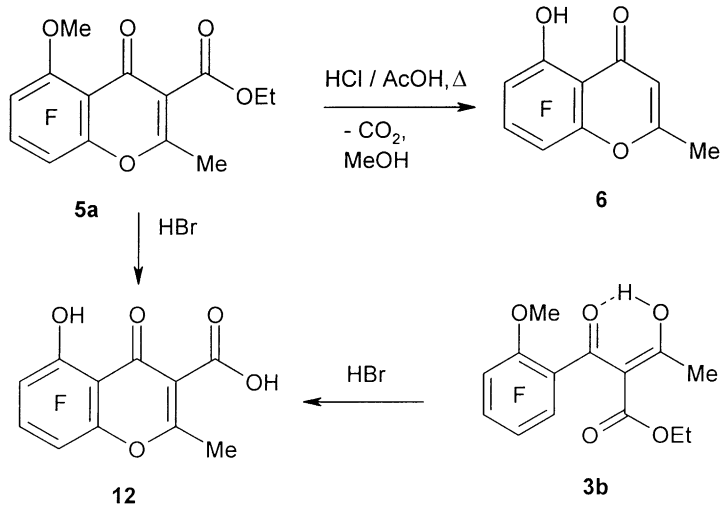
chromone with secondary amines is known to give seven-substituted heterocycles [6,7]. Chromone **5a** acts with morpholine in DMSO to yield seven-substituted chromone **9** also (Scheme 5). Thus, the substituent at the position five of chromone cycle does not change the direction of the reaction with secondary amines.

Chromone **5a** on boiling in aqueous ammonia undergoes an acyl-lactone rearrangement to form 3-iminoacetyl-4-hydroxy-5-methoxy-6,7,8-trifluorocoumarin **10** (Scheme 5) like chromone **5b** described previously [7]. Heating 3-iminoacetylcoumarin **10** in dilute sulfuric acid affords 3-acetylcoumarin. Under these conditions, the methoxy group does not hydrolyze.

Hydrolysis of chromone **5b** in an acid medium at room temperature is known to afford the corresponding chromone-3-carboxylic acid, moreover the reaction is accompanied by partial rearrangement of chromone **5b** into 3-acetyl-5,6,7,8-tetrafluorochromone [7]. In contrast to transformations of chromone **5b**, the 5-methoxysubstituted analogue **5a** is not hydrolyzed under these conditions. Under



Scheme 5.



Scheme 6.

more severe conditions on boiling in an acid medium, chromone **5a** gives chromone **6** as a result of decarboxylation and hydrolysis of methyl-phenyl ether (Scheme 6).

Heating chromone **5a** in hydrogen bromide yields chromone-3-carboxylic acid **12** (Scheme 6). The same product may be obtained from β,β′-dioxoester **3b**.

Thus, for the first time, the fluoroaryl containing β,β′-dioxoesters are obtained and their use for the synthesis of fluorobenzopyran-2(4)-ones is established.

3. Experimental details

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured on a Specord 75 IR spectrometer (using vaseline oil as solvent). ^{1}H and ^{19}F NMR spectra were recorded on a Tesla BS-587A instrument (^{1}H: 80 MHz, using TMS as an internal standard, ^{19}F: 75 MHz, using C_6F_6 as an internal standard). Microanalyses were performed with a Carlo Erba CHNS-O EA 1108 elemental analyzer.

3.1. Materials

Acids **1a,b** were prepared by the method described previously [5].

3.2. Acylation of ethyl acetoacetate by fluorobenzoyl chlorides

3.2.1. 2,6-Dimethoxy-3,4,5-trifluorobenzoylchloride (2a)

Phosphorus pentachloride (3 g, 14.4 mmol) was added to acid **1a** (3 g, 12.7 mmol). The mixture was refluxed for 1 h and stored for 12 h at 20°C. After distillation in vacuum, compound **2a** (2.25 g, 70%) was obtained. A bp of 98–100°C (4 Torr). ^{1}H NMR ($CDCl_3$) δ: 4.04 (6H, d, $2OCH_3$, $J_{H-F} = 2.2$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 9.98 (1F, t, F-4, $J_{(4\text{-}3)} = J_{(4\text{-}5)} = 19.6$ Hz), 5.90 (2F, dq, F-3, F-5, $J_{(3\text{-}4)} = J_{(5\text{-}4)} = 19.6$, $J_{F3-H} = J_{F5-H} = 2.2$ Hz) ppm. IR: 2950 (CH); 1790 (COCl); 1500 (C=C); 1125, 1120, 1040 (C–F) cm^{-1}. Analysis: Found: C, 42.30; H, 2.37; F, 22.35. Calc. for $C_9H_6ClF_3O_3$: C, 42.46; H, 2.38; F, 22.39%.

3.2.2. 2-Methoxy-3,4,5,6-tetrafluorobenzoylchloride (2b)

In a similar manner, compound **2b** (26 g, 88%) was obtained from acid **1b** (27.36 g, 0.12 mol). A bp of −90°C (3 Torr). ^{1}H NMR ($CDCl_3$) δ: 4.13 (3H, d, OCH_3, $J_{H-F} = 2.4$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 21.6 (1F, ddd, F-6, $J_{(6\text{-}5)} = 22.0$, $J_{(6\text{-}3)} = 9.3$, $J_{(6\text{-}4)} = 4.9$ Hz), 13.37 (1F, dt, F-4, $J_{(4\text{-}6)} = 4.9$, $J_{(4\text{-}5)} = J_{(4\text{-}3)} = 20.0$ Hz); 8.99 (1F, ddq, F-3, $J_{(3\text{-}6)} = 9.3$, $J_{(3\text{-}4)} = 20.0$, $J_{(3\text{-}5)} = 0$; $J_{F3-H} = 2.4$ Hz); 0.25 (1F, dd, F-5, $J_{(5\text{-}6)} = 22.0$, $J_{(5\text{-}4)} = 20.0$, $J_{(5\text{-}3)} = 0$ Hz) ppm. IR: 1770 (COCl); 1630, 1510, 1490 (C=C); 1020 (C–F) cm^{-1}. Analysis: Found: C, 39.81; H, 1.34; F, 30.70. Calc. for $C_8H_3ClF_4O_2$: C, 39.76; H, 1.25; F, 31.45%.

3.2.3. Ethyl-2-(2,6-dimethoxy-3,4,5-trifluorobenzoyl)-3-oxobutanoate (3a)

Ethyl acetoacetate (4.7 g, 36.1 mmol) was added to a solution of $Mg(OEt)_2$ prepared from Mg chips (9.36 g, 39.1 mmol). The reaction mixture was stirred for 1 h at 50°C. A solution of benzoyl chloride **2a** (7.8 g, 30.6 mmol) in 10 ml of benzene was added. The reaction mixture was stirred for 1 h at 20°C and 15 min at 50°C, cooled to 20°C and poured into a solution of conc. HCl (7.8 ml) in 12 ml of water. The benzene layer was separated. The aqueous solution was extracted with benzene (2 × 20 ml). The benzene layers were combined and dried under $MgSO_4$. After distillation under reduced pressure, compound **3a** (8.5 g, 80%) was obtained. A bp of 154–155°C (3 Torr). ^{1}H NMR ($CDCl_3$, a mixture of two tautomers in a ratio of 11:1) δ: 17.63, 14.59 (1H, br.s, OH); 4.02, 4.05 (2H, q, $O\underline{CH_2}CH_3$, $^{3}J = 7.1$ Hz); 3.90, 3.86 (3H, d, OCH_3, $J_{H-F3} = 1.7$ Hz); 2.51, 2.48 (3H, s, CH_3); 1.01, 1.08 (3H, t, $OCH_2\underline{CH_3}$, $^{3}J =$

7.1 Hz) ppm. ^{19}F NMR ($CDCl_3$, a mixture of two tautomers in a ratio of 11:1) δ: 5.91 (1F, t, F-4, $J_{(4\text{-}3)} = J_{(4\text{-}5)} =$ 19.7 Hz), 4.42 (2F, dq, F-3, F-5, $J_{(3\text{-}4)} = J_{(5\text{-}4)} = 19.7$, $J_{F3-H} = J_{F5-H} = 1.7$ Hz) ppm. IR: 3450 (OH); 1720 (C=O); 1625 (C=O); 1485 (C=C); 1035 (C–F) cm^{-1}. Analysis: Found: C, 51.93; H, 4.35; F, 16.83. Calc. for $C_{15}H_{15}F_3O_6$: C, 51.73; H, 4.34; F, 16.36%.

3.2.4. Ethyl-2-(2-methoxy-3,4,5,6-tetrafluorobenzoyl)-3-oxobutanoate (**3b**)

In a similar manner, compound **3b** (8.5 g, 79%) was obtained from benzoylchloride **2b** (7.8 g, 31 mmol) as an oil. ^{1}H NMR ($CDCl_3$, a mixture of two tautomers in a ratio of 7:1) δ: 17.55, 14.61 (1H, br.s, OH); 4.05, 4.10 (2H, q, $O\underline{CH_2}CH_3$, $^3J = 7.1$ Hz); 3.94, 3.89 (3H, d, OCH_3, $J_{H-F3} = 2.0$ Hz); 2.54, 2.46 (3H, s, CH_3); 1.05, 1.10 (3H, t, $OCH_2\underline{CH_3}$, $^3J = 7.1$ Hz) ppm. ^{19}F NMR ($CDCl_3$, a mixture of two tautomers in a ratio of 7:1) δ: 18.82, 17.18 (1F, ddd, F-6, $J_{(6\text{-}5)} = 23.0$, $J_{(6\text{-}3)} = 8.8$; $J_{(6\text{-}4)} = 2.0$ Hz); 7.87, 6.78 (1F, td, F-4, $J_{(4\text{-}6)} = 2.0$, $J_{(4\text{-}5)} = J_{(4\text{-}3)} = 20.0$ Hz); 5.77 (1F, ddq, F-3, $J_{(3\text{-}6)} = 8.8$, $J_{(3\text{-}4)} = 20.0$, $J_{(3\text{-}5)} = 0$, $J_{F3-H} = 2.0$ Hz); −1.42 (1F, ddd, F-5, $J_{(5\text{-}4)} = 20.0$, $J_{(5\text{-}3)} = 0$ Hz) ppm. IR: 2970, 2930 (OH); 1715 (C=O); 1640, 1570 (C=O, C=C); 1510, 1485 (C=C); 1020 (C–F) cm^{-1}. Analysis: Found: C, 50.16; H, 3.86; F, 22.71. Calc. for $C_{14}H_{12}F_4O_5$: C, 50.01; H, 3.60; F, 22.60%.

To a solution of chelate **4b** (19 g, 52 mmol) in 100 ml of ether, 7 ml of HCl and 15 ml of water were added. The mixture was stirred at 20°C for 15 min. The ether layer was separated. The aqueous layer was extracted by ether (3 × 15 ml). The combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed in vacuum to give compound **3b** (16.55 g, 95%). The physical data were identical to those listed above.

3.2.5. Ethyl-2-pentafluorobenzoyl-3-oxobutanoate (**3c**)

Anhydrous gaseous hydrogen chloride was passed through a solution of chelate **4c** (0.3 g, 0.845 mmol) in 50 ml of dry ether. The resulting precipitate was filtered off. The ether was removed in vacuum at 20°C to give compound **3c** (0.27 g, 99%) as an oil. ^{1}H NMR ($CDCl_3$, a mixture of two tautomers in a ratio of 4:1) δ: 17.44, 14.65 (1H, br.s, OH); 4.10, 4.40 (2H, q, $O\underline{CH_2}CH_3$, $^3J = 7.1$ Hz); 1.12, 1.39 (3H, t, $OCH_2\underline{CH_3}$, $^3J = 7.1$ Hz); 2.57, 2.47 (3H, s, CH_3) ppm. ^{19}F NMR ($CDCl_3$, a mixture of two tautomers in a ratio of 4:1) δ: 20.21, 18.42 (2F, m); 9.95 (1F, m); 1.11, −2.93 (2F, m) ppm. IR: 2930 (OH), 1710 (C=O), 1650, 1570 (C=O, C=C), 1520, 1500 (C=C), 985 (C–F) cm^{-1}. Analysis: Found: C, 47.93; H, 2.73; F, 29.15. Calc. for $C_{13}H_9F_5O_4$: C, 48.16; H, 2.80; F, 29.30%.

3.2.6. Bis(ethyl-2-(2,5-dimethoxy-3,4,5-trifluorobenzoyl)-3-hydroxy-2-butenoate)copper(II) (**4a**)

A solution of copper(II) acetate (0.3 g, 1.6 mmol) in 10 ml of water was added to a solution of compound **3a** (0.27 g, 0.78 mmol) in 1 ml of MeOH. The resulting precipitate was filtered off and dried at 100°C to give compound **4a** (0.23 g, 80%) as a blue powder, mp of 198–200°C (from ethanol). IR: 1680 (C=O), 1560 (C=O); 1480 (C=C); 1030 (C–F) cm^{-1}. Analysis: Found: C, 47.44; H, 3.79; F, 14.96. Calc. for $C_{30}H_{28}F_6O_{12}Cu$: C, 47.53; H, 3.72; F, 15.04%.

3.2.7. Bis(ethyl-2-(2-methoxy-3,4,5,6-tetrafluorobenzoyl)-3-hydroxy-2-butenoate)copper(II) (**4b**)

In a similar manner, compound **4b** (0.23 g, 78%) was obtained from compound **3b** (0.27 g, 0.8 mmol) as a blue powder, mp 135–139°C (from ethanol). IR: 1700 (C=O); 1615, 1590 (C=O, C=C); 1490, 1450, 1400 (C=C); 1025 (C–F) cm^{-1}. Analysis: Found: C, 46.06; H, 3.15; F, 20.56. Calc. for $C_{28}H_{22}F_8O_{10}Cu$: C, 45.81; H, 3.02; F, 20.71%.

Ethyl acetoacetate (23.4 g, 0.18 mol) was added to solution of $Mg(OEt)_2$ prepared from Mg chips (3.51 g, 0.15 mol). The reaction mixture was stirred for 1 h at 50°C. A solution of benzoyl chloride **2b** (25 g, 0.1 mol) in 45 ml of benzene was added. The reaction mixture was stirred for 1 h at 20°C and 15 min at 50°C. After cooling, a solution of copper(II) acetate (12.95 g) and acetic acid (5.9 g) in 40 ml of water was added. The organic layer was separated. The aqueous layer was extracted with ether (3 × 30 ml). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuum at 20°C. The residue was reprecipitated from MeOH by water to give compound **4b** (33.5 g, 89%). The physical data were identical to those listed above.

3.2.8. Bis(ethyl-2-pentafluorobenzoyl-3-hydroxy-2-butenoato)copper(II) (**4c**)

Ethyl acetoacetate (11.7 g, 0.09 mol) was added to solution of $Mg(OEt)_2$ prepared from Mg chips (1.87 g, 0.08 mol). The reaction mixture was stirred for 1 h at 50°C. A solution of benzoyl chloride **2c** (18.4 g, 0.08 mol) in 30 ml of benzene was added. The reaction mixture was stirred for 1 h at 20°C and 15 min at 50°C. After cooling, a solution of copper(II) acetate (6.7 g) and acetic acid (2.9 g) in 30 ml of water was added. The organic layer was separated. The aqueous layer was extracted with ether (3 × 20 ml). The organic layer was dried over $MgSO_4$. The solvent was removed in vacuum at 20°C. The residue was reprecipitated from MeOH by water to give compound **4c** (8.3 g, 29%) as a green powder, mp 162–164°C (from ethanol). IR: 1680 (C=O); 1630, 1580 (C=O C=C); 1495, 1450, 1430 (C=C); 980 (C–F) cm^{-1}. Analysis: Found: C, 43.89; H, 2.22; F, 26.70. Calc. for $C_{26}H_{16}F_{10}O_8Cu$: C, 43.99; H, 2.27; F, 26.76%.

3.2.9. 3-Ethoxycarbonyl-2-methyl-5-methoxy-6,7,8-trifluoro-4H-1,4-dihydrobenzopyrane-4-one (**5a**)

Compound **3b** (16.5 g, 49 mmol) was distilled at 225–226°C in vacuum. After cooling, the distillate was crystallized (mp = 50–60°C). Recrystallization from hexane gave product **5a** (6 g, 39%) as white crystals (mp 66–68°C). ^{1}H NMR (CD_3COCD_3) δ: 4.35 (2H, q, $O\underline{CH_2}CH_3$,

$^3J = 7.1$ Hz); 3.96 (3H, d, OCH_3, $J_{H-F6} = 0.8$ Hz); 2.47 (3H, s, CH_3); 1.35 (3H, t, $OCH_2\underline{CH}_3$, $^3J = 7.1$ Hz) ppm. ^{19}F NMR (CD_3COCD_3) δ: 12.51 (1F, dd, F-7, $J_{(7-6)} = 21.0$; $J_{(7-8)} = 20.0$ Hz), 6.64 (1F, d, F-6, $J_{(6-7)} = 21.0$, $J_{(6-8)} = 0$ Hz), 3.42 (1F, d, F-8, $J_{(8-7)} = 20.0$, $J_{(8-6)} = 0$ Hz) ppm. IR: 1735 (CO_2Et); 1660 (C=O); 1630 (C=C); 1485, 1115 (C=C); 1020 (C–F) cm^{-1}. Analysis: Found: C, 53.11; H, 3.49; F, 17.99. Calc. for $C_{14}H_{11}F_3O_5$: C, 53.17; H, 3.51; F, 18.02%.

A solution of chelate **4b** (4.1 g, 11.1 mmol) in 15 ml of DMSO was heated at 80°C for 3 h. After cooling, a mixture of conc. HCl (15 ml) and water (30 ml) was added. The resulting precipitate was collected by filtration and recrystallized from hexane to give product **5a** (0.6 g, 18%). The physical data were identical to those listed above.

*3.2.10. 3-Ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluoro-4H-1,4-dihydrobenzopyrane-4-one (**5b**)*

Compound **3c** (6.48 g, 0.02 mol) was heated at 100–110°C for 1 h. The resulting solid was recrystallized from a mixture of CCl_4–hexane (1:2) to give product **5b** (5.6 g, 92%) as a light yellow crystals (mp 91–92°C (lit. mp 90°C [1]). The physical data were identical to those listed [1].

A solution of chelate **4c** (0.5 g, 1.41 mmol) in 12 ml of DMSO was heated at 80°C for 3 h and stored at 20°C for 24 h. A mixture of conc. HCl (12 ml) and water (12 ml) was added. The mixture was extracted with ether (3 × 15 ml). The extract was washed with water and dried under $MgSO_4$. The solvent was removed in vacuum. The residue was recrystallized from a mixture of CCl_4–hexane (1:2) to give product **5b** (0.2 g, 47%) as light yellow crystals, mp 91–92°C. The physical data were identical to those listed [1].

*3.2.11. 5-Hydroxy-2-methyl-6,7,8-trifluoro-4H-1,4-dihydrobenzopyrane-4-one (**6**)*

A mixture of compound **3a** (0.1 g, 0.286 mmol) and 40% HBr (0.1 ml) was heated for 6 h at 120°C, then cooled to 20°C. The resulting precipitate was filtered off and recrystallized from hexane to give product **6** (0.05 g, 76%) as a white powder (mp 125–127°C). ^1H NMR (CD_3COCD_3) δ: 2.46 (3H, s, CH_3), 6.13 (1H, s, CH), 12.42 (1H, s, OH) ppm. ^{19}F NMR (CD_3COCD_3) δ: −5.88 (1F, dd, F-6, $J_{(6-7)} = 20.5$, $J_{(6-8)} = 4.6$ Hz), −1.48 (1F, dd, F-8, $J_{(8-7)} = 20.5$, $J_{(8-6)} = 4.6$ Hz), 14.34 (1F, t, F-7, $J_{(7-6)} = J_{(7-8)} = 20.5$ Hz) ppm. IR: 3340 (OH); 1670 (C=O); 1645 (C=O); 1610, 1520 (C=C); 990 (C–F) cm^{-1}. Analysis: Found: C, 52.12; H, 2.08; F, 24.78. Calc. for $C_{10}H_5F_3O_3$: C, 52.19; H, 2.19; F, 24.76%.

By analogy, product **6** (0.05 g, 40%) was obtained from compound **7** (0.15 g, 0.543 mmol) for 3 h. The physical data were identical to those listed above.

A mixture of compound **5b** (0.3 g, 0.95 mmol), conc. HCl (0.4 ml) and acetic acid (1.5 ml) was heated for 48 h. The reaction mass was poured into 10 ml of water. The resulting precipitate was filtered off, washed with water and dried to give product **6** (0.18 g, 71%). The physical data were identical to those listed above.

*3.2.12. 1-(2,6-Dimethoxy-3,4,5-trifluorophenyl)-butan-1,3-dione (**7**)*

To compound **3a** (4.9 g, 19.4 mmol) was added 10 ml of 40% HBr. The reaction mixture was heated at 100°C for 2 h, cooled to 20°C and stored for 3 days. The resulting precipitate was filtered off to give product **7** (1.4 g, 22%) as a white powder, mp 42.5–43.5°C (from hexane). ^1H NMR ($CDCl_3$) δ: 15.23 (1H, s, OH), 5.67 (1H, s, CH), 3.91 (6H, d, OCH_3, $J_{H-F3} = J_{H-F5} = 1.4$ Hz), 2.14 (1H, s, CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 6.96 (1F, d, F-4, $J_{(4-5)} = J_{(4-3)} = 20.0$ Hz), 5.38 (2F, dd, F-3, F-5, $J_{(5-3)} = J_{(3-4)} = 20.0$, $J_{(3-5)} = 0$, $J_{F3-H} = J_{F5-H} = 1.4$ Hz) ppm. IR: 1620 (C=O); 1485 (C=C); 1025 (C–F) cm^{-1}. Analysis: Found: C, 52.07; H, 3.93; F, 20.82. Calc. for $C_{12}H_{11}F_3O_4$: C, 52.18; H, 4.01; F, 20.63%.

*3.2.13. Bis(1-(2,6-dimethoxy-3,4,5-trifluorophenyl)-1-hydroxy-3-oxo-1-butenoate)cooper(II) (**8**)*

A solution of copper(II) acetate (0.15 g, 0.8 mmol) in 10 ml of water was added to a solution of compound **7** (0.25 g, 0.78 mmol) in 1 ml of MeOH. The resulting precipitate was filtered off and dried at 100°C to give compound **8** (0.24 g, 85%) as a blue powder, mp 194–195°C (from ethanol). IR: 1640 (C=O); 1485 (C=C); 1035 (C–F) cm^{-1}. Analysis: Found: C, 46.53; H, 3.30; F, 18.54. Calc. for $C_{24}H_{20}F_6O_8Cu$: C, 46.95; H, 3.28; F, 18.57%.

3.3. Reactions of 3-ethoxycarbonyl-2-methyl-5-methoxy-6,7,8-trifluoro-4H-1,4-dihydrobenzopyran-4-one

*3.3.1. 6,8-Difluoro-3-ethoxycarbonyl-2-methyl-5-methoxy-7-morpholino-4H-1,4-dihydrobenzopyran-4-one (**9**)*

A mixture of compound **5a** (0.3 g, 0.95 mmol) and morpholine (0.33 g, 3.79 mmol) in 3 ml of DMSO was stored at 20°C for 24 h. A mixture of conc. HCl (5 ml) and water (5 ml) was added. The precipitated oil was separated, washed with boiling hexane and dried to give product **9** (0.25 g, 68%) as yellow crystals (mp 90–92°C). ^1H NMR ($CDCl_3$) δ: 4.32 (2H, q, $O\underline{CH}_2CH_3$, $^3J = 7.1$ Hz); 3.87 (3H, s, OCH_3); 3.84–3.79 (4H, m, 2 CH_2); 3.44–3.38 (4H, m, 2 CH_2); 2.42 (3H, s, CH_3); 1.35 (3H, t, $OCH_2\underline{CH}_3$, $^3J = 7.1$ Hz) ppm. ^{19}F NMR ($CDCl_3$) δ: 19.92 (1F, d, F-6, $J_{(6-8)} = 4.1$ Hz), 14.83 (1F, d, F-8, $J_{(8-6)} = 4.1$ Hz) IR: 1700 (CO_2Et); IR: 1650 (C=O); 1600, 1550 (C=C); 1010 (C–F) cm^{-1}. Analysis: Found: C, 56.41; H, 5.15; F, 9.83; N, 3.64. Calc. for $C_{18}H_{19}F_2NO_6$: C, 56.40; H, 5.00; F, 9.91; N, 3.65%.

*3.3.2. 3-Iminoacetyl-4-hydroxy-5-methoxy-6,7,8-trifluoro-4H-1,2-dihydrobenzopyran-2-one (**10**)*

A mixture of compound **5a** (0.3 g, 0.95 mmol) and ammonium hydroxide (6 ml) was heated for 15 min. The resulting precipitate was filtered off, washed with water,

dried at 80°C to give compound **10** (0.225 g, 83%) as a white powder (mp 217–222°C). ^{1}H NMR (CD_3COCD_3) δ: 12.81 (1H, br.s, OH); 6.70 (1H, br.s NH); 4.0 (3H, d, OCH_3, $J_{H-F} = 1.2$ Hz); 2.71 (3H, s, CH_3) ppm. ^{19}F NMR (CD_3COCD_3) δ: 12.69 (1F, t, F-7, $J_{(7\text{-}6)} = J_{(7\text{-}8)} = 21$ Hz), 3.96 (1F, d, F-8, $J_{(8\text{-}7)} = 21$, $J_{(8\text{-}6)} = 0$ Hz), 2.96 (1F, d, F-6, $J_{(6\text{-}7)} = 21$, $J_{(6\text{-}8)} = 0$ Hz) ppm. IR: 3160, 2940 (NH, OH); 1650 (C=O); 1610, 1515, 1480 (C=C); 1040 (C–F) cm^{-1}. Analysis: Found: C, 50.22; H, 2.72; F, 19.85; N, 4.93. Calc. for $C_{12}H_8F_3NO_4$: C, 50.19; H, 2.81; F, 19.85; N, 4.88%.

*3.3.3. 3-Acetyl-4-hydroxy-5-methoxy-6,7,8-trifluoro-2H-1,2-dihydrobenzopyran-2-one (**11**)*

A mixture of compound **10** (0.4 g, 1.39 mmol), conc. H_2SO_4 (2 ml) and water (2 ml) was heated at 80°C for 2 h. The resulting precipitate was filtered off and dissolved in 20 ml of boiling benzene. The solution was filtered from non-dissolved impurity. Benzene was removed in vacuum to give product **11** (0.19 g, 50%) as a white powder (mp 101–102°C). ^{1}H NMR ($CDCl_3$) δ: 18.65 (1H, br.s, OH); 4.04 (3H, d, OCH_3, $J_{H-F6} = 1.5$ Hz); 2.78 (3H, s, CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 17.3 (1F, t, F-7, $J_{(7\text{-}6)} = 21.5$, $J_{(7\text{-}8)} = 21.1$ Hz), 6.08 (1F, dd, F-6, $J_{(6\text{-}7)} = 21.5$, $J_{(6\text{-}8)} = 0$; $J_{F6-H} = 1.5$ Hz), 3.82 (1F, d, F-8, $J_{(8\text{-}7)} = 21.1$, $J_{(8\text{-}6)} = 0$ Hz) ppm. IR: 3100, 2720 (OH); 1750 (CO_2H); 1665 (C=O); 1575, 1510 (C=C); 1010 (C–F) cm^{-1}. Analysis: Found: C, 50.23; H, 2.54; F, 19.56. Calc. for $C_{12}H_7F_3O_5$: C, 50.01; H, 2.45; F, 19.78%.

*3.3.4. 3-Carboxy-5-hydroxy-2-methyl-6,7,8-trifluoro-4H-1,4-dihydrobenzopyran-4-one (**12**)*

A mixture of compound **5a** (0.3 g, 0.95 mmol) and conc. HBr (0.8 ml) was heated at 130°C for 3 h. After cooling, residue was crystallized and washed with water and hexane to give product **12** (0.2 g, 77%) as a yellow crystals (mp 158–160°C). ^{1}H NMR ($CDCl_3$) δ: 12.88 (1H, br.s, OH); 11.29 (1H, s, OH); 3.1 (3H, s, CH_3) ppm. ^{19}F NMR ($CDCl_3$) δ: 20.05 (1F, t, F-7, $J_{(7\text{-}6)} = J_{(7\text{-}8)} = 20.7$ Hz), 3.18 (1F, dd, F-6, $J_{(6\text{-}7)} = 20.7$, $J_{(6\text{-}8)} = 3.0$ Hz), −2.92 (1F, dd, F-8, $J_{(8\text{-}7)} = 20.7$, $J_{(8\text{-}6)} = 3.0$ Hz) ppm. IR: 3100, 2720 (OH); 1750 (CO_2H); 1665 (C=O); 1575, 1510 (C=C); 1010 (C–F) cm^{-1}. Analysis: Found: C, 48.23; H, 1.85; F, 20.52. Calc. for $C_{11}H_5F_3O_5$: C, 48.19; H, 1.84; F, 20.79%.

By analogy, product **12** (0.12 g, 48%) was obtained from compound **3b** (0.3 g, 0.89 mmol) for 3 h. The physical data were identical to those listed above.

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