Synthesis of ethyl 3-oxo-2-(3,4,5-trifluoro-2,6-dimethoxybenzoyl)butyrate

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Ethyl acetoacetate was acylated with 3,4,5-trifluoro-2,6-dimethoxybenzoyl chloride to give, for the first time, ethyl 3-oxo-2-(3,4,5-trifluoro-2,6-dimethoxybenzoyl)butyrate and its copper chelate. The title compound was used for the synthesis of 6,7,8-trifluoro-5-hydroxy-2-methylchromone, 1-(3,4,5-trifluoro-2,6-dimethoxyphenyl)butane-1,3-dione, and its copper chelate.

Key words: acylation, β,β'-dioxo ester, β-diketone, Cu^{II} chelate, chromone.

Fluoroaryl-containing β,β'-tricarbonyl compounds are valuable starting reagents for the synthesis of various β-oxo esters, β-diketones, and fluorinated benzopyrones (chromones and flavones).[1—4] At present, only their pentafluorobenzoyl derivatives are known, because β-dicarbonyl compounds were acylated only with pentafluorobenzoyl chloride.[2—5]

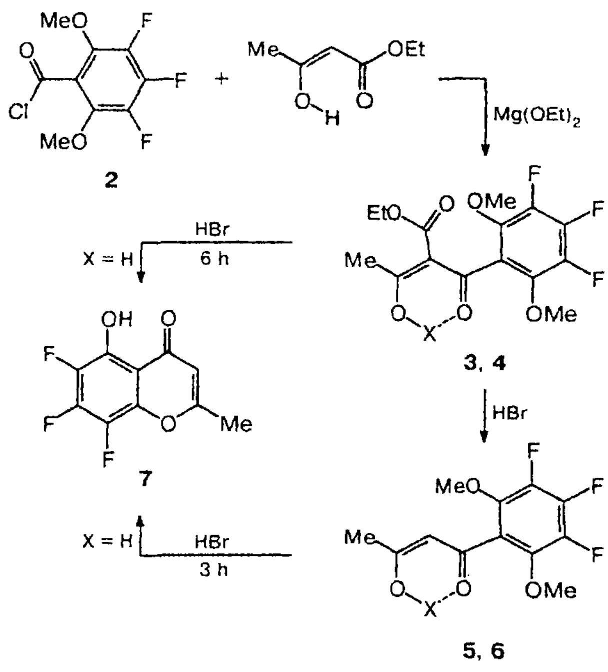
Recently, we have developed a preparative method for the synthesis of 3,4,5-trifluoro-2,6-dimethoxybenzoic acid (**1**) by selective *ortho*-methoxylation of pentafluorobenzoic acid.[6] The reaction of acid **1** with PCl_5 resulted in 3,4,5-trifluoro-2,6-dimethoxybenzoyl chloride (**2**), which further was used to acylate ethyl acetoacetate. It is known that ethyl acetoacetate reacts with C_6F_5COCl to give 3-ethoxycarbonyl-5,6,7,8-tetrafluoro-2-methylchromone.[2,3,7] Acylation of ethyl acetoacetate with chloride **2** (containing no *ortho*-fluorine atoms) in the presence of $(EtO)_2Mg$ affords ethyl 3-oxo-2-(3,4,5-trifluoro-2,6-dimethoxybenzoyl)butyrate (**3**). When treated with copper acetate, β,β'-dioxo ester **3** yields copper chelate (**4**) (Scheme 1).

β,β'-Dioxo ester **3** is virtually completely enolized and exists as one of the theoretically possible tautomers (its ^1H and ^{19}F NMR spectra recorded in $CDCl_3$ show only one set of signals). Thus the ^1H NMR spectrum contains no signal from the methine proton of a ketone form and exhibits a broadened low-field singlet from the enolic proton at δ 17.63 (Table 1). The chemical shift value for the latter indicates a strong intramolecular hydrogen bond in this β,β'-dioxo ester. Its IR spectrum shows only one high-frequency absorption band at 1720 cm^{-1} corresponding to the stretching vibrations of a free keto group; in addition, two absorption bands from the enolized β-dicarbonyl fragment appear at 1625 and 1485 cm^{-1}.

It should be noted that alkyl 2-(fluoroacyl)acetoacetates are also completely enolized,[8] but, unlike compound **3**, they exist as a mixture of two enol forms with a tautomer having a chelated ester group predominant.

When heated with 40% HBr at 100 °C for 3 h, β,β'-dioxo ester **3** undergoes ketone splitting to give β-diketone (**5**), from which copper chelate (**6**) was obtained. Longer heating yields chromone (**7**). The latter

Scheme 1



X = H (**3**, **5**); Cu (**4**, **6**)

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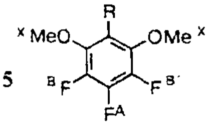
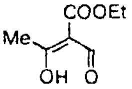
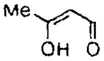
Table 1. ^{1}H and ^{19}F NMR spectral data for compounds **1**—**3** and **5**



Compound	R	δ (CDCl$_3$)				
		^{19}F			^{1}H	
		A	B,B′	*J*/Hz	X,X′	R
1	COOH	8.64 t	5.78 dq	$J_{AB} = J_{AB'} = 19.8$, $J_{BX} = J_{B'X'} = 1.6$	4.01 d	11.22 (s, COOH)
2	COCl	9.98 t	5.90 dq	$J_{AB} = J_{AB'} = 19.6$, $J_{BX} = J_{B'X'} = 2.2$	4.04 d	—
3	 COOEt Me OH O	5.91 t	4.42 dq	$J_{AB} = J_{AB'} = 19.7$, $J_{BX} = J_{B'X'} = 1.7$	3.90	17.63 (s, OH); 4.02 (q, OCH$_2$, *J* = 7.2); 2.51 (s, MeCO); 1.01 (t, Me, *J* = 7.2)
5	 Me OH O	6.96 t	5.38 dq	$J_{AB} = J_{AB'} = 20.0$, $J_{BX} = J_{B'X'} = 1.4$	3.91	15.23 (s, OH); 5.67 (s, CH); 2.14 (s, Me)

was also obtained from β-diketone **5** upon heating with HBr at 120 °C for 3 h. ^{1}H and ^{19}F NMR and IR spectroscopic data for β-diketone **5** suggest its virtually complete enolization.

Experimental

IR spectra were recorded on a Specord 75IR spectrometer. ^{1}H (80 MHz, relative to SiMe$_4$) and ^{19}F (75 MHz, relative to C$_6$F$_6$) NMR spectra were recorded on a Tesla BS-587 A spectrometer. Elemental analysis was performed with the use of a Carlo Erba CHNS-O EA 1108 analyzer.

^{19}F NMR spectral parameters for compounds **3** and **5** were determined using the PC-adapted LAOCOON-III iterative program.[9]

3,4,5-Trifluoro-2,6-dimethoxybenzoyl chloride (2). A mixture of acid **1** (3 g, 12.7 mmol) and PCl$_5$ (3 g, 14.4 mmol) was shaken until liquefaction, refluxed for 1 h, and left at 20 °C for 16 h. Distillation gave compound **2** (2.25 g, 70%), b.p. 98—100 °C (4 Torr). Found (%): C, 42.30; H, 2.37; F, 22.35. C$_9$H$_6$ClF$_3$O$_3$. Calculated (%): C, 42.46; H, 2.38; F, 22.39. IR (thin film), ν/cm^{-1}: 2950 (CH); 2845 (OMe); 1790 (COCl); 1500 (C=C$_{ar}$); 1125, 1120, 1040 (CF).

Ethyl 3-oxo-2-(3,4,5-trifluoro-2,6-dimethoxybenzoyl)-butyrate (3). Ethyl acetoacetate (4.7 g, 36.1 mmol) was added dropwise to a solution of Mg(OEt)$_2$ prepared from Mg (39.1 mg-at.). The reaction mixture was stirred at 50 °C for 1 h; then a solution of chloride **2** (7.8 g, 30.6 mmol) in 10 mL of benzene was added and stirring was continued at 20 °C for 1 h and at 50 °C for 15 min. After cooling, a solution of conc. HCl (7.8 mL) in 12 mL of water was added. The benzene layer was separated and the aqueous layer was extracted with benzene. The benzene extracts were combined, dried with MgSO$_4$, and concentrated to give product **3** (8.5 g, 80%), b.p. 154—155 °C (3 Torr). Found (%): C, 51.93; H, 4.35; F, 16.83. C$_{15}$H$_{15}$F$_3$O$_6$. Calculated (%): C, 51.73; H, 4.34; F, 16.36. IR (thin film), ν/cm^{-1}: 3450 (OH); 1720 (C=O); 1625 (C=O); 1485 (C=C); 1035 (CF).

Copper chelate of ethyl 3-oxo-2-(3,4,5-trifluoro-2,6-dimethoxybenzoyl)butyrate (4). A saturated aqueous solution of Cu(OAc)$_2$ (10 mL) was added to a solution of compound **3** (0.27 g, 0.78 mmol) in 1 mL of MeOH. The bright blue precipitate that formed was filtered off and dried at 100 °C to give chelate **4** (0.23 g, 80%), m.p. 198—200 °C (from EtOH). Found (%): C, 47.44; H, 3.79; F, 14.96. C$_{30}$H$_{28}$CuF$_6$O$_{12}$. Calculated (%): C, 47.53; H, 3.72; F, 15.04. IR (suspension in Vaseline oil), ν/cm^{-1}: 1680 (C=O); 1560 (C=O); 1480 (C=C); 1030 (CF).

1-(3,4,5-Trifluoro-2,6-dimethoxyphenyl)butane-1,3-dione (5). A mixture of compound **3** (4.9 g, 19.4 mmol) and 10 mL of 40% HBr was heated with stirring at 100 °C for 2 h, cooled to 20 °C, and left for 3 days. The precipitate that formed was filtered off to give product **5** (1.4 g, 22%), m.p. 42.5—43.5 °C (from hexane). Found (%): C, 52.07; H, 3.93; F, 20.82. C$_{12}$H$_{11}$F$_3$O$_4$. Calculated (%): C, 52.18; H, 4.01; F, 20.63. IR (suspension in Vaseline oil), ν/cm^{-1}: 1620 (C=O); 1485 (C=C); 1025 (CF).

Copper chelate of 1-(3,4,5-trifluoro-2,6-dimethoxyphenyl)-butane-1,3-dione (6). Chelate **6** was obtained from compound **5** (0.25 g, 0.78 mmol) under the conditions described for the synthesis of chelate **4**. Yield 0.24 g (85%), m.p. 194—195 °C (from ethanol). Found (%): C, 46.53; H, 3.30; F, 18.54. C$_{24}$H$_{20}$CuF$_6$O$_8$. Calculated (%): C, 46.95; H, 3.28; F, 18.57. IR (suspension in Vaseline oil), ν/cm^{-1}: 1640 (C=O); 1485 (C=C); 1035 (CF).

6,7,8-Trifluoro-5-hydroxy-2-methylchromone (7). *A.* A mixture of compound **3** (0.1 g, 0.286 mmol) and 0.1 mL of 40% HBr was heated at 120 °C for 6 h and then cooled to 20 °C. The precipitate that formed was filtered off and recrystallized from hexane to give chromone **7** (0.05 g, 76%), m.p. 125—127 °C. Found (%): C, 52.12; H, 2.08; F, 24.78. C$_{10}$H$_5$F$_3$O$_3$. Calculated (%): C, 52.19; H, 2.19; F, 24.76. IR (suspension in Vaseline oil), ν/cm^{-1}: 3340 (OH); 1670 (C=O); 1645 (C=O); 1610, 1520 (C=C); 990 (CF). ^{1}H NMR (acetone-d$_6$), δ: 2.46 (s, 3 H, Me); 6.13 (s, 1 H, CH); 12.42 (s, 1 H, OH). ^{19}F NMR (acetone-d$_6$), δ: −5.88 (dd, F(6), *J* = 20.5 Hz, 4.6 Hz); −1.48 (dd, F(8), *J* = 20.5 Hz, 4.6 Hz); 14.34 (t, F(7), *J* = 20.5 Hz).

B. Chromone **7** (0.05 g, 40%) was also obtained from compound **5** (0.15 g, 0.543 mmol) upon heating with HBr for

3 h. Its physicochemical characteristics coincide with those for the sample prepared according to procedure *A*.

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