Novel fluorinated chromones

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Abstract

The self-condensation of ethyl pentafluorobenzoylacetate leads to the formation of 3-pentafluorophenyl-1*H*-isopyrono[2,3-*b*]-6,7,8,9-tetrafluorochromone in 37% yield. On hydrolysis, this gave 2-pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone. Other routes for preparing some new fluorinated chromones have been confirmed via intramolecular cyclization of ethyl pentafluorobenzoylpyruvate and also from the 2-ethoxymethylene pentafluorobenzoylacetic ester.

Introduction

During recent years attention has increasingly been focused on the synthesis of fluorine-containing quinolone antibacterials. Hence, fluorine-containing chromone carboxylic acids are also very interesting being their oxygen analogues. Monofluorinated chromones have been prepared from monofluoro-substituted phenols [1, 2]. Dicarbonyl pentafluorobenzene derivatives are known to be useful in this area because the nucleophilic replacement of their *ortho*-fluorine atom leads to the formation of chromone structures. Such behaviour has been found in the reactions of pentafluoroaromatic 1,3-keto esters [3] and 1,3-diketones [3, 4] and also in the synthesis of 3-ethoxycarbonyl-2-methyl-5,6,7,8-tetrafluorochromone through the reaction of pentafluorobenzoyl chloride with ethoxy magnesium acetoacetic ester [3, 5, 6]. For the syntheses of other fluorine-containing chromone derivatives, however, different approaches are needed, and moreover, the use of the magnesium–organic compounds described previously [3, 5–7] is not convenient. Herein we wish to report an effective synthesis of some new fluorochromones based on the reactions of pentafluorobenzoylacetic ester and also pentafluorobenzoylpyruvic ester.

Experimental

Melting points were measured in open capillaries and are reported uncorrected. Infrared spectra were measured on a Specord 75 IR spectrometer. ^{1}H NMR spectra were recorded on a Tesla BS-567 A instrument (^{1}H: 100 MHz) using TMS as an external standard. ^{19}F NMR spectra were recorded on a Tesla BS-587 instrument (^{19}F: 75 MHz) using $CFCl_3$ as an external standard. All chemical shifts are reported in ppm and wavenumbers in cm^{-1}. Mass-spectral data were obtained using a MAT-311a mass spectrometer.

Compound **1** was prepared according to literature methods [8]. Compound **11** was prepared from pentafluorobenzoylacetic ester as described in the literature [9].

*Synthesis of 3-pentafluorophenyl-1*H*-isopyrono[2,3-*b*]-6,7,8,9-tetrafluorochromone (3) (nc)*

Compound **1** [8] (5.0 g, 17.7 mmol) was heated under reflux for 50 min. After cooling, 30 ml of hexane was added to the reaction mixture. The resulting precipitate was collected and recrystallized from acetonitrile to give 1.5 g of **3** (yield, 37%; m.p. 255–260 °C). ^{1}H NMR (DMFA-d_7) δ: 7.45 (1H, t, CH, J(H–F) = 0.94 Hz) ppm. ^{19}F NMR (CD_3COCD_3) δ: −160.99 (2F, m, C_6F_5); −160.28 (1F, t, C_6F_4); −158.28 (1F, d–d, C_6F_4); −148.96 (1F, t–t, C_6F_5); −147.61 (1F, d–t, C_6F_4); −142.61 (1F, d–t, C_6F_4); −138.58 (2F, m, C_6F_5) ppm. IR (cm^{-1}): 1760 (C=O, pyrone); 1645 (C=O, chromone); 1550, 1520, 1500 (C=C). MS *m/e* (relative intensity, ion): 452 (100.0%, M); 433 (37.7%, M−F); 424 (34.8%, M−CO); 285 (25.3%, M−C_6F_5); 195 (85.0%, C_6F_5CO); 193 (12.0%); 192 (18.1%); 167 (21.6%, C_6F_5); 117 (9.7%). Analysis: Found: C, 47.56; H, 0.46; F, 37.78%. Calc. for $C_{18}HF_9O_4$: C, 47.81; H, 0.22; F, 37.81%.

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Synthesis of 2-pentafluorobenzoylmethyl-5,6,7,8-tetrafluorochromone (4) (nc)

A mixture of **3** (1.0 g, 2.2 mmol) and concentrated HCl (5 ml) in 20 ml of acetic acid was heated under reflux for 20 h. The reaction mixture was poured into water (100 ml). The resulting precipitate was collected and dried. The residue was chromatographed on silica gel with CH_2Cl_2 to give 0.4 g (43%) of **4** (m.p. 125–126 °C). ^{1}H NMR (CD_3COCD_3) δ: 4.58 (2H, t, CH_2, J(H–F) = 1.4 Hz); 6.42 (1H, s, CH) ppm. ^{19}F NMR (CD_3COCD_3) δ: −162.28 (1F, t, C_6F_4); −161.07 (2F, m, C_6F_5); −158.77 (1F, d–d, C_6F_4); −149.44 (1F, d–t, C_6F_4); −148.90 (1F, t–t, C_6F_5); −143.43 (1F, d–d–d, C_6F_4); −139.88 (2F, m, C_6F_5) ppm. IR (cm^{-1}): 1690 (C=O, C_6F_5CO); 1650 (C=O, chromone); 1510 (C=C). MS *m/e* (relative intensity, ion): 426 (13.5%, M); 195 (100.0%, C_6F_5CO); 167 (39.0%, C_6F_5). Analysis: Found: C, 47.96; H, 1.02; F, 40.12%. Calc. for $C_{17}H_3F_9O_3$: C, 47.91; H, 0.71; F, 40.12%.

Synthesis of bis(ethyl-2-hydroxy-4-oxo-4-pentafluorophenylbut-2-enoato)copper(II) (8) (nc)

A mixture of pentafluoroacetophenone (**5**) (60.6 g, 0.29 mol) and 81.1 g (0.56 mol) of diethyloxalate (**6**) and 2.46 g (0.31 mol) of ground LiH was heated carefully until the exothermal reaction had begun. After cooling to room temperature, the unreacted LiH was filtered off. An aqueous solution of copper(II) acetate was added to the filtrate until the aqueous layer became permanently sky-blue in colour. The resulting precipitate was collected by filtration and purified by recrystallization from ether/hexane to give 51.0 g (52%) of **8** (m.p. 230 °C). IR (cm^{-1}): 1735, 1720 (C=O, ester); 1655 (C=O); 1590 (C=C). Analysis: Found: C, 42.34; H, 1.97; F, 27.40%. Calc. for $C_{24}H_{12}F_{10}O_8Cu$: C, 42.27; H, 1.77; F, 27.86%.

Synthesis of ethyl-2-hydroxy-4-oxo-4-pentafluorophenylbut-2-enoate (7) (nc)

A mixture of **8** (10.0 g, 14.7 mmol) and 100 ml of 10% HCl in 150 ml of CH_2Cl_2 was shaken until the organic layer became colourless. The lower organic layer was isolated and the solvent removed under reduced pressure. The residue obtained after distillation was pure **7** (8.0 g, yield 89%). ^{1}H NMR ($CDCl_3$) δ: 1.43 (3H, t, J = 7 Hz, CH_2CH_3); 4.42 (2H, q, J = 7 Hz, CH_2CH_3); 6.75 (1H, w s, CH) ppm. ^{19}F NMR ($CDCl_3$; A, B, C-isomers, ratio A/B/C = 3:1:1) δ: −161.78 (C, 2F, *meta* fluorines, m); −160.56 to −161.31 (A, 2F, *meta* fluorines and B, 2F, *meta* fluorines, m); −151.26 (C, 1F, *para* fluorine, t–t); −149.46 (B, 1F, *para* fluorine, t–t); −148.76 (A, 1F, *para* fluorine, t–t); −143.13 (C, 2F, *ortho* fluorines, m); −141.17 (B, 2F, *ortho* fluorines, m); −139.96 (A, 2F, *ortho* fluorines, m) ppm. IR (cm^{-1}): 3450, 2700 (OH); 1750, 1730 (C=O, ester); 1640, 1620 (C=O); 1580 (C=C). Analysis: Found: C, 46.72; H, 2.26; F, 30.48%. Calc. for $C_{12}H_7F_5O_4$: C, 46.47; H, 2.28; F, 30.62%.

Synthesis of 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (9) (nc)

A solution of **8** (41.0 g, 60.0 mmol) in 150 ml of DMSO was heated for 20 min. at 100 °C. After cooling to room temperature, 300 ml of water was added to the reaction mixture. The resulting precipitate was collected by filtration, washed with 20 ml of 10% HCl and water, and dried under reduced pressure to give 33.0 g (95%) of **9** (m.p. 124–125 °C). ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, J = 7 Hz, CH_2CH_3); 4.48 (2H, q, J = 7 Hz, CH_2CH_3); 7.04 (1H, s, CH) ppm. ^{19}F NMR ($CDCl_3$) δ: −158.83 (1F, t); −155.90 (1F, d–d); −145.49 (1F, d–t); −141.42 (1F, m) ppm. IR (cm^{-1}): 1745 (C=O, ester); 1665 (C=O); 3070, 1620 (C=C). Analysis: Found: C, 49.48; H, 2.27; F, 26.10%. Calc. for $C_{12}H_6F_4O_4$: C, 49.67; H, 2.08; F, 26.19%.

Synthesis of ethyl-2-ethoxymethylene-3-oxo-3-pentafluorophenylpropionate (11) [9]

A mixture of pentafluorobenzoylacetic ester (**1**) (20.0 g, 71.0 mmol) and ethyl orthoformate (**10**) (50.0 g, 340.0 mmol) was refluxed for 5 h with removal of the resulting EtOH. The solution was distilled under reduced pressure to give 19.5 g (81%) of **11** (b.p. 160–162 °C/1–2 mmHg). ^{1}H NMR δ: 1.41 (3H, t, J = 11 Hz, $CO_2CH_2CH_3$); 1.47 (3H, t, J = 11 Hz, $CO_2CH_2CH_3$); 1.20 (3H; d–t, J = 12 Hz, J = 2.2 Hz, $CHOCH_2CH_3$); 4.35 (2H, q, J = 11 Hz, $CO_2CH_2CH_3$); 4.37 (2H, q, J = 11 Hz, $CO_2CH_2CH_3$); 4.14 (2H, q, J = 12 Hz, $CHOCH_2CH_3$); 7.80 (1H, d, J = 2.2 Hz, CH) ppm. IR (cm^{-1}): 1720, 1700 (C=O, ester); 1665 (C=O); 1610, 1570 (C=C). Analysis: Found: C, 49.37; H, 3.24; F, 27.68%. Calc. for $C_{14}H_{11}F_5O_4$: C, 49.71; H, 3.28; F, 28.09%.

Synthesis of 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (12) (nc)

A mixture of **11** (3.0 g, 8.9 mmol) and 10 ml of water was refluxed for 15–20 min. After cooling, the precipitate was collected by filtration, washed with 20 ml of water, then with 20 ml of hexane and dried to give 1.6 g (62%) of **12** (m.p. 104–105 °C). ^{1}H NMR ($CDCl_3$) δ: 1.40 (3H, t, J = 7.5 Hz, CH_2CH_3); 4.40 (2H, q, J = 7.5 Hz, CH_2CH_3); 8.60 (1H, s, CH) ppm. ^{19}F NMR (CD_3COOD) δ: −159.82 (1F, t); −158.01 (1F, d–d); −147.49 (1F, d–t); −141.65 (1F, m) ppm. IR (cm^{-1}): 1730 (C=O, ester); 1670, 1645 (C=O); 1585 (C=C). Analysis: Found: C, 49.43; H, 2.08; F, 26.35%. Calc. for $C_{12}H_6F_4O_4$: C, 49.67; H, 2.08; F, 26.19%.

Synthesis of 2-carboxy-5,6,7,8-tetrafluorochromone (13) (nc)

A mixture of **9** (10.0 g, 34.5 mmol) and 10 ml of concentrated HCl in 150 ml of acetic acid was refluxed for 6 h. The acetic acid was removed to leave a crude product, which was collected by filtration, washed twice with ice–water and dried to give 7.2 g (80%) of **13** (m.p. 209–210 °C). ^{1}H NMR (CD_3COCD_3) δ: 6.75 (1H, w s, OH); 6.80 (1H, s, CH) ppm. ^{19}F NMR (D_2O) δ: −159.96 (1F, t); −156.77 (1F, d–d); −145.75 (1F, d–t); −141.42 (1F, m) ppm. IR (cm^{-1}): 1735 (C=O, ester); 1645, 1660 (C=O); 3090, 1610 (C=C). Analysis: Found: C, 45.70; H, 0.50; F, 29.20%. Calc. for $C_{10}H_2F_4O_4$: C, 45.82; H, 0.77; F, 28.99%.

Synthesis of 3-carboxy-5,6,7,8-tetrafluorochromone (14) (nc)

A mixture of **12** (4.0 g, 13.8 mmol) and 10 ml of HCl in 50 ml of acetic acid was heated for 20 h at 40–45 °C. The solvent was removed under reduced pressure to afford a precipitate which was collected by filtration, washed with CCl_4, recrystallized from AcOH/H_2O and dried under reduced pressure at 50 °C to give 2.5 g (69%) of **14** (m.p. 172–173 °C). ^{1}H NMR (CD_3COCD_3) δ: 9.17 (1H, s, CH); 12.58 (1H, w s, OH) ppm. ^{19}F NMR (CD_3COCD_3) δ: −158.97 (1F, t); −157.45 (1F, d–d); −145.50 (1F, d–t); −140.50 (1F, m) ppm. IR (cm^{-1}): 1735 (C=O, carboxy); 1660, 1645 (C=O); 1610 (C=C). Analysis: Found: C, 45.94; H, 0.61; F, 29.40%. Calc. for $C_{10}H_2F_4O_4$: C, 45.82; H, 0.77; F, 28.99%.

Synthesis of 5,6,7,8-tetrafluorochromone (15) (nc)

Method A

Compound **13** (5.0 g, 19.0 mmol) was sublimed at 230–250 °C to give 3.0 g (72%) of **15** (m.p. 95–96 °C). ^{1}H NMR (CD_3COCD_3) δ: 8.25 (1H, d, J=6.25 Hz, CH); 6.26 (1H, d, J=6.26 Hz, CH) ppm. ^{19}F NMR ($CHCl_3$) δ: −161.46 (1F, t); −158.50 (1F, d–d); −148.49 (1F, d–t); −142.77 (1F, m) ppm. IR (cm^{-1}): 1670, 1650 (C=O); 3050, 1595, 1630 (C=C). Analysis: Found: C, 49.37; H, 1.22; F, 34.99%. Calc. for $C_9H_2F_4O_2$: C, 49.56; H, 0.92; F, 34.84%.

Method B

A mixture of **12** (2.0 g, 6.9 mmol) and 10 ml of concentrated HCl in 50 ml of acetic acid was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure to leave a precipitate, which was collected by filtration, washed with water, dried and sublimed at 200 °C to give 1.1 g (73%) of **15** (m.p. 95–96 °C). The ^{1}H NMR and IR spectra were identical to those previously reported for the compound obtained by method A.

Method C

Compound **14** (0.5 g, 1.9 mmol) was sublimed at 190–200 °C to give 0.33 g (79%) of **15** (m.p. 95–96 °C). The ^{1}H NMR and IR spectra were identical to those previously reported for the compound obtained by method A.

Results and discussion

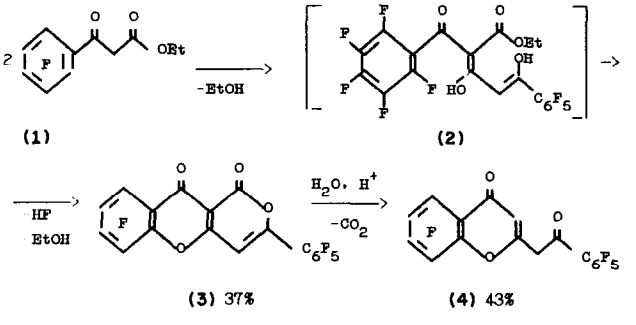
Self-condensation of pentafluorobenzoylacetic ester

It is well known that trifluoroacetoacetates (also non-fluorinated β-keto esters) when subjected to a Lewis acid (acid and alkali for acetoacetates) catalyzed self-condensation gave pyrone derivatives [7]. It has been reported that treatment of ethyl trifluoroacetoacetate with phosphorus pentoxide causes dealkoxylation, then dimerization of the intermediate, thereby leading to the formation of a pyrone structure [10].

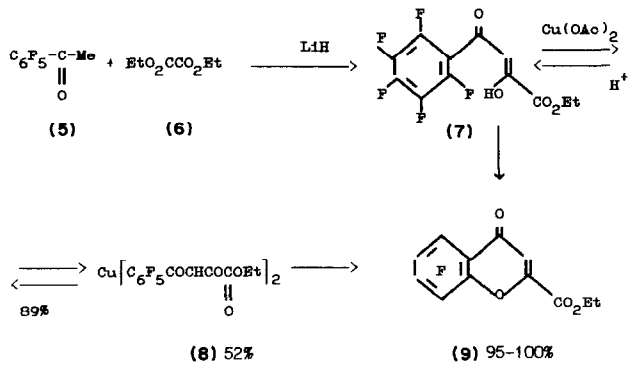
In the present work, it has been found that ethyl pentafluorobenzoylacetate (**1**) forms 3-pentafluorophenyl-1*H*-isopyrono[2,3-*b*]-6,7,8,9-tetrafluorochromone (**3**) on refluxing without any catalyst, obviously through the formation of intermediate **2** (Scheme 1). Further, acid hydrolysis of **3** gave the chromone derivative **4** in moderate yield (Scheme 1).

The ^{1}H NMR spectrum of **3** exhibited only a vinylic proton as a triplet at 7.45 ppm with a coupling constant of 0.94 Hz between the CH hydrogen and the C_6F_5 fluorines. The chemical shift of this proton corresponds to that reported for α-pyrone [11]. The ^{1}H NMR spectrum of **4** exhibited a similar type of coupling between the CH_2 group and the C_6F_5 fluorines (4.58 ppm, J=1.4 Hz). In compound **4**, a resonance at 6.42 ppm was found for the C-3 proton of γ-chromone [12]. In the ^{19}F NMR spectra of compounds **3** and **4**, seven resonance signals in the expected ratio were attributed to the fluorine atoms of the C_6F_4 and the C_6F_5 groups. In support of the structures assigned to **3** and **4**, molecular ion peaks were detected for each compound.

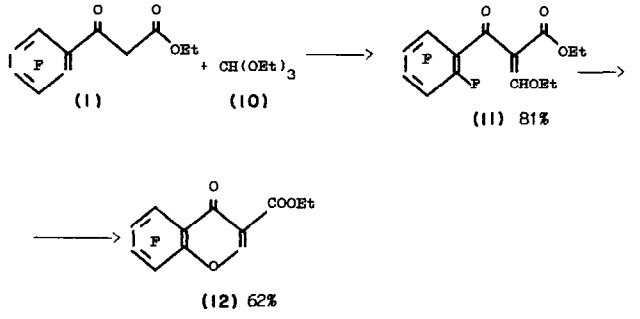
Interestingly, when ethyl acetoacetate was heated with **1**, only product **3** was obtained. This difference in reactivity between aliphatic and polyfluoroaromatic



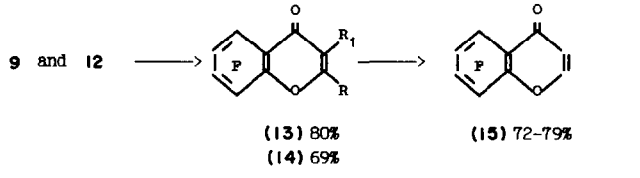
Scheme 1.



Scheme 2.



Scheme 3.



Compound	R	R_1
13	COOH	H
14	H	COOH

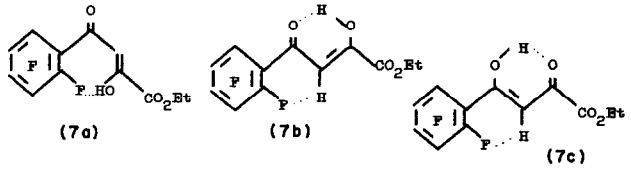
Scheme 4.

β-keto esters may result from the electron-withdrawing effect of the C_6F_5 substituent and the greater nucleophilic mobility of the *ortho*-fluorine atom of **1**. Hence, compound **1** is unstable when stored at room temperature for a long time, and is partially transformed by distillation to give the fused heterocyclic compound **3**.

Intramolecular cyclization of pentafluorobenzoylpyruvate (**7**) *and of the 2-ethoxymethylene pentafluorobenzoylacetate derivative* (**11**) *also occurred.*

Pentafluoroacetophenone (**5**) reacts with diethyloxalate (**6**) in the presence of LiH to give ethyl pentafluorobenzoylpyruvate (**7**), which can be isolated through its copper(II) chelate **8** (Scheme 2). Ester **7** is stable when stored at room temperature, but is converted by heat to give 2-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**9**) in quantitative yield. 2-Pentafluorophenylacetyl pentafluorobenzoylacetate [3] was similarly transformed to 3-ethoxycarbonyl-2-pentafluorobenzyl-5,6,7,8-tetrafluorochromone. Chelate **8** is stable when heated in water and non-polar solvents, but is destroyed by heat in dimethylsulfoxide or dimethylformamide to also give product **9** (Scheme 2).

The structure of **7** was assigned as an enol form on the basis of its ^1H NMR spectrum, as found for polyfluoroacylpyruvic esters [13]. In contrast to polyfluoroacylpyruvate, such enol formation for compound **7** may be due to H-bonding not only with the oxygen but also with the *ortho*-fluorine atom. The observation of three multiple resonance signals for each aromatic fluorine in the ^{19}F NMR spectrum and the doubling of bands in IR spectrum of **7** seems to support the presence of the following three geometrical isomers:



Displacement of the C-3 hydrogen atom of **9** with carbon dioxide or chlorocarbonate to give a carboxylic group was unsuccessful since the chromone ring is stable to electrophiles. An alternative synthetic route for this purpose was developed starting from ester **1**.

It is known that the reaction of pentafluorobenzoylacetate (**1**) with ethyl orthoformate (**10**) results in the formation of 2-ethoxymethylene pentafluorobenzoylacetate (**11**). [9]. This compound was refluxed with water to form 3-ethoxycarbonyl-5,6,7,8-tetrafluorochromone (**12**) in 62% yield (Scheme 3). The ^1H NMR spectra showed clear differences between **12** (the signal of the methine proton at C-2 appears at 9.60 ppm) and **9** (the signal of the proton at C-3 appears at 7.04 ppm).

Esters **9** and **12** were hydrolyzed under acidic conditions to give carboxylic acids **13** and **14**, respectively (Scheme 4). Sublimation of **13** and **14** produced the same product **15** (Scheme 4). Chromone **15** was derived alternatively directly from ester **12** in boiling acetic acid (this may be as a result of the lesser stability of the 3-carboxychromone **14** relative to the 2-carboxychromone **13**). Interestingly, when formic acid was used for the decarboxylation of **12**, the product of the partial reduction of the C=C bond was also obtained.

In conclusion, the reactions described demonstrate the preparation of fluorine-containing chromones from the di- and tri-carbonyl derivatives of pentafluorobenzene in good yield via a simple synthetic procedure.

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