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Reactions of 3-(polyfluoroacyl)chromones with indole and *N*-methylindole

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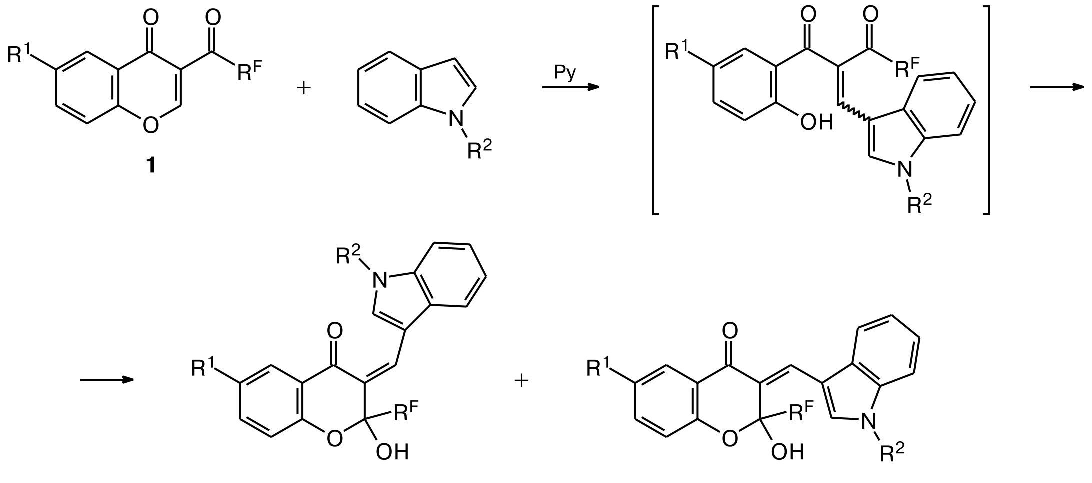
Unlike well studied 3-formylchromones[1,2] and 3-acylchromones,[3—6] data on the chemical properties of 3-(polyfluoroacyl)chromones **1** are scarce. It is only known that their reactions with primary aliphatic and aromatic amines proceed *via* the mechanism of nucleophilic 1,4-addition followed by pyrone ring opening and ring closure involving the phenolic hydroxyl and R^FCO group in 3-alkyl(aryl)aminomethylene-2-hydroxy-2-polyfluoroalkylchroman-4-ones.[7,8]

Taking into account that the indole ring is an important structural fragment of many natural and biologically active substances,[9] we studied the reactions of 3-(polyfluoroacyl)chromones **1** with indole and *N*-methylindole. In this reaction indoles behave exclusively as C-nucleophiles, and the reaction proceeds at position 2 of the chromone system, which is further recyclized to form 2-hydroxy-3-(indol-3-ylmethylene)-2-polyfluoroalkylchroman-4-ones (**2a—d**) in 42—67% yields (Scheme 1). When the reaction occurs in boiling pyridine for 3 h, compounds **2a—d** are formed as a mixture of *Z*- and *E*-isomers (*Z*/*E* = 88/12—96/4), whose structures were confirmed by the data of elemental analysis and ^1H, ^{19}F, and ^{13}C NMR spectroscopy. In the spectra of the *Z*-isomers a singlet of the olefinic proton and a doublet of the indolic proton H(2) ($J_{H,NH}$ = 3.1 Hz) are observed at 7.95—8.05 and 9.34—9.39 ppm, respectively; whereas for the *E*-isomers they are observed at δ 8.63—8.70 and 8.42—8.43 because of the deshielding effect of the carbonyl group.[10] Due to this, signals of other protons were assigned and the composition of the formed mixture of geometric isomers was calculated.

Note that in the reaction with 3-iodochromone indoles act as *N*-nucleophiles yielding 2-(*N*-indolyl)chromones in a mixture of aurone derivatives.[11] No other published data for the reactions of chromones with indoles are available.

Synthesis of compounds 2a—d (general procedure). A solution of 3-(polyfluoroacyl)chromone **1** (1.0 mmol) and indole or *N*-methylindole (1.4 mmol) in anhydrous pyridine (4 mL) was refluxed for 3 h. The resulting reaction mixture was cooled down

Scheme 1



Z-**2a—d** *E*-**2a—d**

	a	**b**	**c**	**d**
R^F	CF_2H	CF_3	$(CF_2)_2H$	CF_3
R^1	Cl	Me	H	H
R^2	H	H	H	Me

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and poured into dilute AcOH (1 : 3). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from toluene.

6-Chloro-2-difluoromethyl-2-hydroxy-3-(indol-3-ylmethylene)chroman-4-one (2a). The yield was 42%, m.p. 211—212 °C, orange crystals. Found (%): C, 60.83; H, 3.29; N, 3.73. $C_{19}H_{12}ClF_2NO_3$. Calculated (%): C, 60.73; H, 3.22; N, 3.73. IR (KBr, ν/cm^{-1}): 3424, 3288, 1625, 1601, 1541, 1488. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: *Z*-isomer (88%), 6.20 (t, 1 H, CF_2H, $^2J_{H,F}$ = 55.0 Hz); 7.14 (d, 1 H, H(8), J_o = 8.8 Hz); 7.24—7.30 (m, 2 H, indole); 7.53—7.57 (m, 1 H, indole); 7.60 (dd, 1 H, H(7), J_o = 8.8 Hz, J_m = 2.7 Hz); 7.78—7.81 (m, 1 H, indole); 7.82 (d, 1 H, H(5), J_m = 2.7 Hz); 7.95 (s, 1 H, =CH); 8.84 (s, 1 H, OH); 9.34 (d, 1 H, =CHN, $^3J_{H,NH}$ = 3.1 Hz); 12.26 (s, 1 H, NH); *E*-isomer (12%), 6.30 (t, 1 H, CF_2H, $^2J_{H,F}$ = 54.5 Hz); 7.24—7.30 (m, 2 H, indole); 7.53—7.57 (m, 1 H, indole), 7.63 (dd, 1 H, H(7), J_o = 8.7 Hz, J_m = 2.7 Hz); 7.78—7.81 (m, 1 H, indole); 8.43 (d, 1 H, =CHN, $^3J_{H,NH}$ = 3.1 Hz); 8.63 (s, 1 H, =CH); 9.19 (s, 1 H, OH); 12.26 (s, 1 H, NH); other protons are not detected because of superposition of the signals.

2-Hydroxy-3-(indol-3-ylmethylene)-6-methyl-2-trifluoromethylchroman-4-one (2b). The yield was 60%, m.p. 217—218 °C, orange crystals. Found (%): C, 64.29; H, 3.41; N, 3.79. $C_{20}H_{14}F_3NO_3$. Calculated (%): C, 64.34; H, 3.78; N, 3.75. IR (KBr, ν/cm^{-1}): 3384, 3281, 1629, 1610, 1541, 1491. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: *Z*-isomer (94%), 2.32 (s, 3 H, Me); 7.03 (d, 1 H, H(8), J_o = 8.3 Hz); 7.24—7.30 (m, 2 H, indole); 7.41 (dd, 1 H, H(7), J_o = 8.4 Hz, J_m = 2.0 Hz); 7.54—7.58 (m, 1 H, indole); 7.71 (br.s, 1 H, H(5)); 7.76—7.79 (m, 1 H,); 8.05 (s, 1 H, =CH); 9.36 (d, 1 H, =CHN, $^3J_{H,NH}$ = 3.1 Hz); 9.37 (s, 1 H, OH); 12.29 (s, 1 H, NH); *E*-isomer (6%), 7.69 (br.s, 1 H, H(5)); 8.43 (d, 1 H, =CHN, $^3J_{H,NH}$ = 3.1 Hz); 8.69 (s, 1 H, =CH); 9.68 (s, 1 H, OH); other protons are not detected because of superposition of the signals. ^{19}F NMR (376 MHz, DMSO-d$_6$, C_6F_6), δ: *Z*-isomer (93%), 79.72 (s, CF_3); *E*-isomer (7%), 80.60 (s, CF_3). ^{13}C NMR (100 MHz, DMSO-d$_6$), δ: *Z*-isomer, 20.06, 99.37 (q, $^2J_{C,F}$ = 31.7 Hz); 110.81, 112.69, 116.52, 117.37, 118.11, 120.53, 121.48, 122.95, 122.99 (q, $^1J_{C,F}$ = 291.4 Hz); 126.25, 128.85, 131.36, 135.00, 136.07, 136.42, 136.79, 154.13, 179.48; *E*-isomer, 20.05, 98.05 (q, $^2J_{C,F}$ = 32.9 Hz); 108.74, 116.67, 117.23, 118.02, 118.80, 121.64, 122.77, 126.68, 127.33, 129.40, 131.49, 134.49, 135.67, 136.82, 137.51, 154.92, 179.60, no carbon atom of the CF_3 group was detected.

2-Hydroxy-3-(indol-3-ylmethylene)-2-(1,1,2,2-tetrafluoroethyl)chroman-4-one (2c). The yield was 67%, m.p. 195—196 °C, orange crystals. Found (%): C, 61.17; H, 3.25; N, 3.57. $C_{20}H_{13}F_4NO_3$. Calculated (%): C, 61.39; H, 3.35; N, 3.58. IR (KBr, ν/cm^{-1}): 3278, 1614, 1605, 1586, 1535, 1488. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: *Z*-isomer (91%), 6.76 (tdd, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 52.2 Hz, $^3J_{H,F}$ = 8.2, 4.6 Hz); 7.07 (d, 1 H, H(8), J_o = 8.1 Hz); 7.15 (t, 1 H, H(6), J_o = 7.5 Hz); 7.24—7.30 (m, 2 H, indole); 7.54—7.61 (m, 2 H, H(7), indole); 7.76—7.80 (m, 1 H, indole); 7.91 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.5 Hz); 7.99 (s, 1 H, =CH); 9.34 (d, 1 H, =CHN, $^3J_{H,NH}$ = 3.2 Hz); 9.36 (d, 1 H, OH, J = 4.5 Hz); 12.24 (s, 1 H, NH); *E*-isomer (9%), 8.42 (br.s, 1 H, =CHN); 8.70 (s, 1 H, =CH); 9.64 (d, 1 H, OH, J = 5.0 Hz); other protons are not detected because of superposition of the signals.

2-Hydroxy-3-(1-methylindol-3-ylmethylene)-2-trifluoromethylchroman-4-one (2d). The yield was 44%, m.p. 215—216 °C, red crystals. Found (%): C, 64.24; H, 3.99; N, 3.72. $C_{20}H_{14}F_3NO_3$. Calculated (%): C, 64.34; H, 3.78; N, 3.75. IR (KBr, ν/cm^{-1}): 3398, 1655, 1634, 1609, 1587, 1539, 1494. ^{1}H NMR (400 MHz, DMSO-d$_6$), δ: *Z*-isomer (96%), 4.00 (s, 3 H, Me); 7.14 (d, 1 H, H(8), J_o = 8.2 Hz); 7.18 (ddd, 1 H, H(6), J_o = 7.8, 7.0 Hz, J_m = 1.0 Hz); 7.30—7.39 (m, 2 H, indole); 7.61 (ddd, 1 H, H(7), J_o = 8.3, 7.3 Hz, J_m = 1.6 Hz); 7.62—7.65 (m, 1 H, indole); 7.80—7.83 (m, 1 H, indole); 7.94 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.6 Hz); 8.05 (s, 1 H, =CH); 9.39 (s, 1 H, =CHN); 9.44 (s, 1 H, OH); *E*-isomer (4%), 3.98 (s, 3 H, Me); 7.84—7.87 (m, 1 H, indole); 7.91 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.6 Hz); 8.42 (s, 1 H, =CHN); 8.68 (s, 1 H, =CH); 9.75 (s, 1 H, OH); other protons are not detected because of superposition of the signals.

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