Unexpected influence of tetra- and pentafluoroethyl groups on the direction of reactions of 2-polyfluoroalkylchromones with 2-aminoethanol

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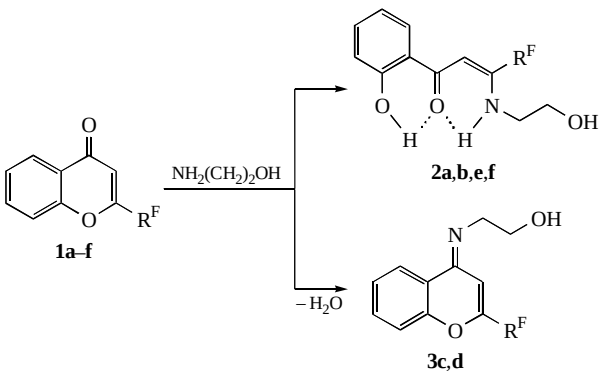
10.1070/MC2000v010n06ABEH001310

2-Polyfluoroalkylchromones react with 2-aminoethanol at room temperature to give either 3-(2-hydroxyethylamino)-1-(2-hydroxyphenyl)-3-polyfluoroalkylprop-2-en-1-ones [$R^F = CF_2H$, CF_3, $(CF_2)_2OCF_3$ or $(CF_2)_3CF_3$] or *N*-(2-hydroxyethyl)-2-polyfluoroalkyl-4*H*-chromene-4-imines [$R^F = (CF_2)_2H$ or C_2F_5].

It is well known that a pyrone ring in chromone[1] or 2-methylchromone[2] can be easily opened under the action of primary amines with the formation of β-aminovinyl ketones with a 2-hydroxyphenyl substituent at the carbonyl group. Previously,[3] it was found that 2-trifluoromethylchromones react with ammonia, methylamine and benzylamine at the C-2 atom primarily with the opening of a pyrone ring to form corresponding aminoenones. However, in the presence of a substituent at the 5-position of a chromone system, the reaction was stopped at the step of nucleophilic addition and afforded 2-amino- and 2-alkylaminochroman-4-ones.[3]

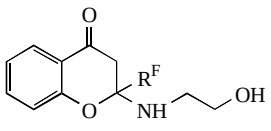
In this work, we examined the interaction of 2-polyfluoroalkylchromones **1a**–**f** with 2-aminoethanol. In addition to a well-known attack on the C-2 atom, which affords compounds **2a**,**b**,**e**,**f**, we found a new direction of this reaction at R^F = = $(CF_2)_2H$ or C_2F_5, namely, an attack at the carbonyl carbon atom to form imines **3c**,**d**.



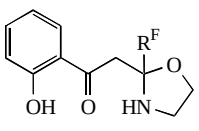
a $R^F = CF_2H$ **d** $R^F = C_2F_5$
b $R^F = CF_3$ **e** $R^F = (CF_2)_2OCF_3$
c $R^F = (CF_2)_2H$ **f** $R^F = (CF_2)_3CF_3$

Scheme 1

Compounds **2a**,**b**,**e**,**f** were prepared in 67–90% yields on dissolution of 2-polyfluoroalkylchromones **1a**,**b**,**e**,**f** in a small excess of 2-aminoethanol at room temperature for 10–15 min. These compounds are of interest as new reactive functionalised R^F-containing synthons. Theoretically, because of the presence of phenol and alcohol hydroxyl groups, these products can undergo ring–chain tautomerization and exist as both open aminoenone form **2** and cyclic species (chromanones **2′** or oxazolidines **2′′**).



2′



2′′

Previously,[4] the transamination of aromatic β-aminovinyl β-trifluoromethyl ketones under the action of 2-aminoethanol was studied, and aminoenones with a 2-hydroxyethyl group at the nitrogen atom were found to be the reaction products. Only in the case of 3-amino-1-(2-thienyl)-4,4,4-trifluorobut-2-en-1-one, a product existing as 2-(2-thenoylmethyl)-2-trifluoromethyloxazolidine in both a crystalline state and $CDCl_3$ or [$^2H_6$]DMSO solutions was obtained.

The IR spectra of compounds **2a**,**b**,**e**,**f** in Vaseline oil exhibit an intense absorption band at 1620–1625 cm^{-1}, which is typical of the C=O group conjugated with an enamine unit. The ^1H NMR spectra of these compounds, measured immediately after dissolving in $CDCl_3$ (which reflect the structure of the substances in a crystalline state), exhibit a singlet at δ 6.01–6.25 ppm due to vinyl protons, a quartet (3.60–3.62 ppm) due to CH_2N (this quartet was transformed into a triplet on the addition of CD_3CO_2D) and a triplet (3.86–3.88 ppm) due to CH_2O groups. Moreover, the spectra exhibit the singlets of alcohol OH, NH and phenol OH at 1.90–2.10, 10.40–10.94 and 12.63–12.85 ppm, respectively. The addition of CD_3CO_2D to a solution of compound **2b** in $CDCl_3$ resulted in the disappearance of signals due to active NH and OH protons, whereas the chemical shifts of the other protons remained almost unchanged. This suggests an amide character of nitrogen and hence its low basicity. In this case, other changes associated with the cyclization, hydrolysis or degradation of aminoenone **2b** in an acidic medium were not observed. These data suggest that products of the reactions between chromones **1a**,**b**,**e**,**f** and 2-aminoethanol exist in both a crystalline state and in a $CDCl_3$ solution as open aminoenone species **2** with the (*Z*)-configuration and s-*cis*-conformation stabilised by two intramolecular hydrogen bonds.†

Unexpectedly, the reaction between 2-aminoethanol and chromones **1c**,**d** bearing tetrafluoroethyl and pentafluoroethyl substituents proceeded at the keto groups to afford imines **3c**,**d**.‡ The reactions, which were performed at ~20 °C as in the preparation of aminoenones **2a**,**b**,**e**,**f**, were completed in five days for **3c** and in a day for **3d**. That is, the formation of imines **3** is much slower than the formation of aminoenones **2**, and the terminal hydrogen atom of the $(CF_2)_2H$ group additionally decreases the rate of reaction at the C-4 atom. It is likely that the nucleophilic attack on the C-4 rather than C-2 atom is due to the fact that, on going from CF_2H to $(CF_2)_2H$ and from CF_3 to C_2F_5 groups, the electrophilicity of the C-2 atom increases insufficiently for a 2-aminoethanol molecule to overcome the increased steric hindrances. As a result of this, the reaction at the carbonyl carbon atom becomes preferable. However, with increasing chain length of a polyfluoroalkyl substituent, the electronic factor becomes predominant, and the reaction results in the formation of aminoenones **2e**,**f**.

According to the ^1H NMR spectra of compounds **3c**,**d**, which exhibit only one set of signals, the reaction is highly stereoselective and leads to imines **3c**,**d** with the *anti*-configuration at the C=N bond to minimise unfavourable spatial interactions with the *peri*-hydrogen atom. This conclusion was supported by the chemical shifts of H(5) atoms, which remained almost unchanged on going from chromones **1c**,**d** to imines **3c**,**d** (8.21 and 8.22 ppm for **1c**,**d** or 8.24 and 8.30 ppm for **3c**,**d**, respectively). In contrast to aminoenones **2**, imines **3** exhibit pronounced basic properties and react with acetic acid. Thus, imine **3c** was completely converted into the iminium cation on the addition of CD_3CO_2D to a chloroform solution of this imine. All signals in the NMR spectrum of this cation, except for those of CH_2O and $(CF_2)_2H$ groups, are downfield shifted by 0.39–0.68 ppm.

Thus, using the reaction of 2-polyfluoroalkylchromones with 2-aminoethanol as an example, we found a special effect of tetrafluoroethyl and pentafluoroethyl groups on the reaction path. The combination of steric and electronic factors is responsible for the reaction at the carbonyl group; this reaction is not typical of chromones.

This work was supported by the Russian Foundation for Basic Research (grant no. 99-03-32960).

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Received: 29th March 2000; Com. 00/1636

† *3-(2-Hydroxyethylamino)-1-(2-hydroxyphenyl)-4,4-difluorobut-2-en-1-one* **2a**. Chromone **1a** (255 mg, 1.3 mmol) was dissolved in 92 mg (1.5 mmol) of 2-aminoethanol, and the reaction mixture was kept for 15 min at room temperature. The resulting crystals of aminoenone **2a** were washed with water and recrystallised from hexane; yield 280 mg (84%), mp 101–102 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.90 (br. s, 1H, OH), 3.61 (q, 2H, CH_2N, J 5.4 Hz), 3.86 (t, 2H, CH_2O, J 5.1 Hz), 6.01 (s, 1H, =CH), 6.29 (t, 1H, CF_2H, $J_{H,F}$ 53.3 Hz), 6.83 [td, 1H, H(5), ^oJ 7.6 Hz, ^mJ 1.0 Hz], 6.93 [dd, 1H, H(3), ^oJ 8.2 Hz, ^mJ 1.0 Hz], 7.37 [td, 1H, H(4), ^oJ 7.8 Hz, ^mJ 1.5 Hz], 7.65 [dd, 1H, H(6), ^oJ 8.0 Hz, ^mJ 1.5 Hz], 10.40 (br. s, 1H, NH), 12.85 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3470 (OH), 3180 (br., NH), 1625 (C=O), 1590, 1570, 1530 (w) (C=C, NH, arom.). Found (%): C, 56.19; H, 5.03; N, 5.30. Calc. for $C_{12}H_{13}F_2NO_3$ (%): C, 56.03; H, 5.09; N, 5.45.

3-(2-Hydroxyethylamino)-1-(2-hydroxyphenyl)-4,4,4-trifluorobut-2-en-1-one **2b**: yield 67%, mp 105–106 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.85 (br. s, 1H, OH), 3.61 (q, 2H, CH_2N, J 5.5 Hz), 3.88 (t, 2H, CH_2O, J 5.2 Hz), 6.25 (s, 1H, =CH), 6.85 [td, 1H, H(5), ^oJ 7.6 Hz, ^mJ 1.0 Hz], 6.95 [dd, 1H, H(3), ^oJ 8.2 Hz, ^mJ 1.0 Hz], 7.40 [td, 1H, H(4), ^oJ 7.8 Hz, ^mJ 1.5 Hz], 7.66 [dd, 1H, H(6), ^oJ 8.0 Hz, ^mJ 1.5 Hz], 10.55 (br. s, 1H, NH), 12.65 (s, 1H, OH); after the addition of CD_3CO_2D: 3.59 (t, 2H, CH_2N, J 5.3 Hz), 3.86 (t, 2H, CH_2O, J 5.3 Hz), 6.24 (s, 1H, =CH), 6.86 [td, 1H, H(5), ^oJ 7.6 Hz, ^mJ 1.0 Hz], 6.95 [dd, 1H, H(3), ^oJ 8.2 Hz, ^mJ 1.0 Hz], 7.39 [td, 1H, H(4), ^oJ 7.8 Hz, ^mJ 1.5 Hz], 7.67 [dd, 1H, H(6), ^oJ 8.0 Hz, ^mJ 1.5 Hz]. IR (Vaseline oil, ν/cm^{-1}): 3470 (OH), 3180 (br., NH), 1625 (C=O), 1585, 1560, 1530 (w) (C=C, NH, arom.). Found (%): C, 52.45; H, 4.38; N, 5.03. Calc. for $C_{12}H_{12}F_3NO_3$ (%): C, 52.37; H, 4.39; N, 5.09.

3-(2-Hydroxyethylamino)-1-(2-hydroxyphenyl)-4,4,5,5-tetrafluoro-5-trifluoromethoxypent-2-en-1-one **2e**: yield 68%, mp 72–73 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.93 (br. s, 1H, OH), 3.62 (q, 2H, CH_2N, J 5.3 Hz), 3.87 (t, 2H, CH_2O, J 5.1 Hz), 6.16 (s, 1H, =CH), 6.86 [t, 1H, H(5), ^oJ 7.7 Hz], 6.96 [d, 1H, H(3), ^oJ 8.2 Hz], 7.40 [td, 1H, H(4), ^oJ 7.8 Hz, ^mJ 1.4 Hz], 7.64 [d, 1H, H(6), ^oJ 8.0 Hz], 10.93 (br. s, 1H, NH), 12.63 (br. s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3460 (OH), 3170 (br., NH), 1620 (C=O), 1585, 1560, 1535 (w) (C=C, NH, arom.). Found (%): C, 43.25; H, 3.20; N, 3.56. Calc. for $C_{14}H_{12}F_7NO_4$ (%): C, 42.98; H, 3.09; N, 3.58.

3-(2-Hydroxyethylamino)-1-(2-hydroxyphenyl)-4,4,5,5,6,6,7,7,7-nonafluorohept-2-en-1-one **2f**: yield 90%, mp 86–87 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.10 (br. s, 1H, OH), 3.60 (br. s, 2H, CH_2N), 3.87 (t, 2H, CH_2O, J 5.1 Hz), 6.16 (s, 1H, =CH), 6.86 [td, 1H, H(5), ^oJ 7.6 Hz, ^mJ 1.0 Hz], 6.95 [dd, 1H, H(3), ^oJ 8.4 Hz, ^mJ 1.0 Hz], 7.40 [td, 1H, H(4), ^oJ 7.6 Hz, ^mJ 1.4 Hz], 7.65 [dd, 1H, H(6), ^oJ 8.1 Hz, ^mJ 1.4 Hz], 10.94 (br. s, 1H, NH), OH was not detected. IR (Vaseline oil, ν/cm^{-1}): 3360 (br., OH), 3180 (br., NH), 1620 (C=O), 1580, 1565, 1530 (w) (C=C, NH, arom.). Found (%): C, 42.18; H, 3.04; N, 3.58. Calc. for $C_{15}H_{12}F_9NO_3$ (%): C, 42.37; H, 2.84; N, 3.29.

‡ N-*(2-Hydroxyethyl)-2-(1,1,2,2-tetrafluoroethyl)-4*H-*chromene-4-imine* **3c**. Chromone **1c** (250 mg, 1.0 mmol) was dissolved in 122 mg (2.0 mmol) of 2-aminoethanol, and the reaction mixture was kept for 5 days at room temperature. The resulting crystals of imine **3c** were washed with water and recrystallised from hexane; yield 150 mg (52%); mp 114–115 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.54 (s, 1H, OH), 3.60 (t, 2H, CH_2N, J 5.1 Hz), 3.94 (t, 2H, CH_2O, J 5.1 Hz), 6.10 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$ 53.1 Hz, $^3J_{H,F}$ 4.0 Hz), 6.71 (s, 1H, =CH), 7.25–7.34 [m, 2H, H(8), H(6)], 7.50 [t, 1H, H(7), ^oJ 7.2 Hz], 8.24 [d, 1H, H(5), ^oJ 7.8 Hz]; after the addition of CD_3CO_2D: 4.03 (s, 2H, CH_2N), 4.06 (s, 2H, CH_2O), 6.24 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$ 52.7 Hz, $^3J_{H,F}$ 3.2 Hz), 7.39 (s, 1H, =CH), 7.64–7.71 [m, 2H, H(8), H(6)], 7.91 [t, 1H, H(7), ^oJ 7.6 Hz], 8.71 [d, 1H, H(5), ^oJ 7.4 Hz]. IR (Vaseline oil, ν/cm^{-1}): 3190 (OH), 1665 (C=N), 1625 (w), 1605, 1580 (w) (C=C, arom.). Found (%): C, 54.00; H, 3.69; N, 4.88. Calc. for $C_{13}H_{11}F_4NO_2$ (%): C, 53.99; H, 3.83; N, 4.84.

N-*(2-Hydroxyethyl)-2-perfluoroethyl-4*H-*chromene-4-imine* **3d**: yield 81%, mp 120–121 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.96 (br. s, 1H, OH), 3.63 (t, 2H, CH_2N, J 5.2 Hz), 3.97 (t, 2H, CH_2O, J 5.2 Hz), 6.78 (s, 1H, =CH), 7.30 [d, 1H, H(8), ^oJ 8.0 Hz], 7.35 [t, 1H, H(6), ^oJ 7.8 Hz], 7.55 [td, 1H, H(7), ^oJ 7.8 Hz, ^mJ 1.5 Hz], 8.30 [d, 1H, H(5), ^oJ 7.8 Hz]. IR (Vaseline oil, ν/cm^{-1}): 3220 (OH), 3100 (=CH), 1665 (C=N), 1625 (w), 1615, 1580 (w) (C=C, arom.). Found (%): C, 50.66; H, 3.48; N, 4.67. Calc. for $C_{13}H_{10}F_5NO_2$ (%): C, 50.82; H, 3.28; N, 4.56.