Brief Communications

2-Polyfluoroalkylchromones
7.* Reactions of 6-substituted 2-tetra- and 2-pentafluoroethylchromones with 2-aminoethanol

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The reactions of 2-aminoethanol with 6-methyl-2-tetra- and 6-methyl-2-pentafluoroethylchromones involve the carbonyl group to give imines; the reactions with 6-nitro-2-tetra- and 6-nitro-2-pentafluoroethylchromones involve the C(2) atom, resulting in the pyrone ring opening. This also occurs in the reactions of 2-(1,1,2,2-tetrafluoroethyl)chromone with ammonia and benzylamine.

Key words: 2-tetra- and 2-pentafluoroethylchromones, 2-aminoethanol, ammonia, benzylamine, 4-[*N*-(2-hydroxyethyl)imino]-6-methyl-2-tetra- and pentafluoroethyl-4*H*-chromenes, 3-(2-hydroxyethylamino)-1-(2-hydroxy-5-nitrophenyl)-4,4,5,5-tetra- and 4,4,5,5,5-pentafluoropent-2-en-1-ones, 3-amino- and 3-benzylamino-1-(2-hydroxyphenyl)-4,4,5,5-tetrafluoropent-2-en-1-ones.

It is known[2] that chromone easily reacts with 2-aminoethanol involving the C(2) atom to give 3-(2-hydroxyethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one. Recently, we have shown that the reactions of 2-polyfluoroalkylchromones with 2-aminoethanol also mainly occur as the pyrone ring opening.[3] However, tetra- and pentafluoroethylchromones **1a**,**b** behave differently to yield imines **2a**,**b**.

Results and Discussion

This reaction was examined in more detail for chromones **1c**—**f**. It was found that the reaction outcome depends on the nature of the substituent in position 6. Thus the compounds with the electron-donating methyl group (**1c**,**d**) are converted into imines (**2c**,**d**), while 6-nitro derivatives (**1e**,**f**) undergo ring opening to give enamino ketones **3e**,**f** (~20 °C, 2 h) (Scheme 1). Note that the reaction with imine **2c** is completed in a week and with imine **2d** in a day. Different reaction rates were also observed for unsubstituted chromones **1a**,**b**.[3] 5,7-Dimethyl-2-(1,1,2,2-tetrafluoroethyl)chromone does not react with 2-aminoethanol, which is most probably due to steric hindrances at the C(4) atom.

The reactions of chromone **1a** with ammonia and benzylamine involve the C(2) atom, which are accompanied by the ring opening to give 3-amino- and 3-benzylamino-1-(2-hydroxyphenyl)-4,4,5,5-tetrafluoropent-2-en-1-ones **4a** and **4b**, respectively (Scheme 2).

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* For Part 6, see Ref. 1.

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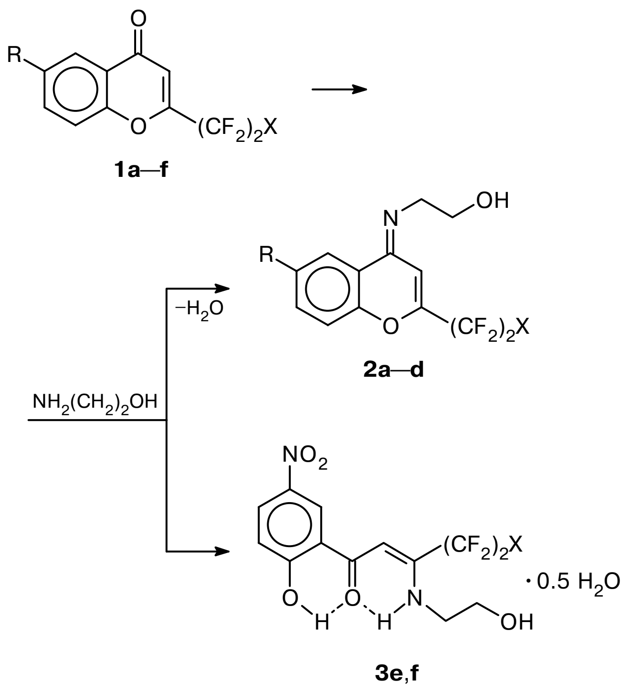
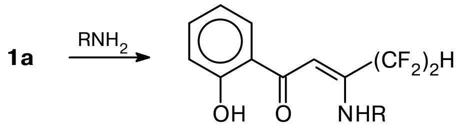
Scheme 1



	a	b	c	d	e	f
R	H	H	Me	Me	NO$_2$	NO$_2$
X	H	F	H	F	H	F

Scheme 2



R = H (**4a**), CH$_2$Ph (**4b**)

Compounds **3e**,**f** form hemihydrates; both in the crystalline state and in a chloroform solution they exist in the acyclic form with *Z*-configuration of the C=C bond and *s-cis*-conformation stabilized by two intramolecular hydrogen bonds (IMHB).[3] When the NO$_2$ group is *para* relative to the phenolic OH group, the O—H...O hydrogen bond becomes stronger, as evidenced by a downfield shift of a distinct singlet for the phenolic proton in the ^{1}H NMR spectrum (δ 13.65 for **3e** and 13.45 for **3f**) compared to a broadened singlet for 5-unsubstituted analogs (δ 12.63—12.85).[3] A very narrow signal for the phenolic OH group indicates that intermolecular exchange of the phenolic proton decelerates owing to a strong IMHB involving this group.[4]

The ^{1}H NMR spectra of imines **2c**,**d** contain only one set of signals, suggesting a high reaction stereoselectivity and the formation of a sterically less strained *anti*-isomer in which the *peri*-H atom and 2-hydroxyethyl group are the most distant from each other.[3]

Thus, we demonstrated, with the reactions of chromones **1c**—**f** with 2-aminoethanol, a subtle influence of the remote substituent on the reactivities of the C(2) and C(4) atoms. The change in the reaction pathway in the case of chromones **1e**,**f** is probably due to the fact that the attack on the C(2) atom is accompanied by the cleavage of the C—O bond, and the electron-withdrawing nitro group favors stabilization of the leaving phenolate anion, thus facilitating the pyrone ring opening. By contrast, the electron-donating methyl group destabilizes the resulting phenolate anion, making the steric factor of the polyfluoroethyl group dominant in the case of chromones **1c**,**d**. This explanation correlates well with the results of the MNDO,[5,6] AM1,[7] and PM3 [8] semiempirical calculations of the energies of anion formation in the reactions of chromones **1c**,**e** with 2-aminoethanol.

Earlier, we have shown that the reactions of chromone **1a** with ethylenediamine and diethylenetriamine afford 5-(2-hydroxyphenyl)-7-(1,1,2,2-tetrafluoroethyl)-2,3-dihydro-1*H*-1,4-diazepine[9] and 5-(2-hydroxyphenyl)-7-(1,1,2,2-tetrafluoroethyl)-1,4,8-triazabicyclo[5.3.0]dec-4-ene,[10] respectively. Trimethylenediamine brings about the decomposition of chromone **1a** into 2-hydroxyacetophenone. Considering these data and the fact that *tert*-butylamine and aniline do not react with chromone **1a** at all, one can conclude that the formation of imines **2a**—**d** discovered in the present study is unique to 2-aminoethanol and some 5-unsubstituted 2-polyfluoroalkylchromones containing no electron-withdrawing substituents in positions 6 and, probably, 8 of the chromone system.

Experimental

IR spectra were recorded on an IKS-29 instrument (Vaseline oil). ^{1}H NMR spectra were recorded on Tesla BS-567A (100 MHz) and Bruker WM-250 spectrometers (in CDCl$_3$ with Me$_4$Si as the internal standard). Compounds **2a**,**b** were characterized earlier.[3]

4-[*N*-(2-Hydroxyethyl)imino]-6-methyl-2-(1,1,2,2-tetrafluoroethyl)-4*H*-chromene (2c). Chromone **1c** (250 mg, 0.96 mmol) was dissolved in 2-aminoethanol (500 mg, 8.2 mmol), and the reaction mixture was left at ~20 °C for a week. Trituration with 5 mL of water gave a solid product, which was filtered off, washed with water, and recrystallized from hexane. The yield was 200 mg (69%), m.p. 103—104 °C. Found (%): C, 55.22; H, 4.28; N, 4.58. $C_{14}H_{13}F_4NO_2$. Calculated (%): C, 55.45; H, 4.32; N, 4.62. IR, ν/cm^{-1}: 1670 (C=N); 1600 (C=C). ^{1}H NMR, δ: 2.42 (s, 3 H, Me); 2.87 (br.s, 1 H, OH); 3.62 (t, 2 H, CH$_2$N, J = 5.2 Hz); 3.97 (t, 2 H, CH$_2$O, J = 5.2 Hz); 6.11 (tt, 1 H, CF$_2$CF$_2$H, $^2J_{H,F}$ = 53.1 Hz, $^3J_{H,F}$ = 4.2 Hz); 6.73 (s, 1 H, =CH); 7.18 (d, 1 H, H(8), J_o = 8.5 Hz); 7.34 (dd, 1 H, H(7), J_o = 8.5 Hz, J_m = 1.6 Hz); 8.13 (br.s, 1 H, H(5)).

4-[*N*-(2-Hydroxyethyl)imino]-6-methyl-2-perfluoroethyl-4*H*-chromene (2d) was obtained analogously from chromone **1d** (100 mg, 0.36 mmol) and 2-aminoethanol (200 mg, 3.3 mmol), with the exception that the reaction was completed in a day. The yield was 70 mg (61%), m.p. 91—92 °C.

Found (%): C, 52.38; H, 3.81; N, 4.28. $C_{14}H_{12}F_5NO_2$. Calculated (%): C, 52.34; H, 3.77; N, 4.36. IR, ν/cm^{-1}: 1665 (C=N), 1605 (C=C). ^{1}H NMR, δ: 2.42 (s, 3 H, Me); 2.63 (br.s, 1 H, OH); 3.61 (t, 2 H, CH_2N, J = 5.3 Hz), 3.96 (t, 2 H, CH_2O, J = 5.3 Hz); 6.74 (s, 1 H, =CH); 7.19 (d, 1 H, H(8), J_o = 8.5 Hz); 7.33 (dd, 1 H, H(7), J_o = 8.5 Hz, J_m = 1.9 Hz); 8.07 (br.s, 1 H, H(5)).

1-(2-Hydroxy-5-nitrophenyl)-3-(2-hydroxyethylamino)-4,4,5,5-tetrafluoropent-2-en-1-one (3e). A mixture of chromone **1e** (100 mg, 0.34 mmol) and 2-aminoethanol (100 mg, 1.6 mmol) was left at ~20 °C for 2 h. The resulting homogeneous solution was diluted with 5 mL of water and acidified with 0.3 mL of AcOH. The precipitate that formed was filtered off, washed with water, and recrystallized from hexane—toluene (1 : 1). The yield was 90 mg (73%), m.p. 121—122 °C. Found (%): C, 43.45; H, 3.77; N, 7.65. $C_{13}H_{12}F_4N_2O_5 \cdot 0.5H_2O$. Calculated (%): C, 43.22; H, 3.63; N, 7.75. IR, ν/cm^{-1}: 3270—3670 (NH, OH, H_2O); 1615 (C=O); 1590 (C=C); 1565, 1350 (NO_2). ^{1}H NMR, δ: 2.06 (br.s, 1 H, OH); 3.71 (q, 2 H, CH_2N, J = 5.2 Hz); 3.92 (t, 2 H, CH_2O, J = 5.1 Hz); 6.07 (tt, CF_2CF_2H, $^2J_{H,F}$ = 53.2 Hz, $^3J_{H,F}$ = 3.3 Hz); 6.10 (s, 1 H, =CH); 7.00 (d, 1 H, H(3), J_o = 9.1 Hz); 8.25 (dd, 1 H, H(4), J_o = 9.1 Hz, J_m = 2.6 Hz); 8.55 (d, 1 H, H(6), J_m = 2.6 Hz); 11.18 (br.s, 1 H, NH); 13.65 (s, 1 H, OH).

1-(2-Hydroxy-5-nitrophenyl)-3-(2-hydroxyethylamino)-4,4,5,5,5-pentafluoropent-2-en-1-one (3f) was obtained analogously from chromone **1f** (100 mg, 0.32 mmol) and 2-aminoethanol (100 mg, 1.6 mmol). The yield was 90 mg (73%), m.p. 150—151 °C. Found (%): C, 41.27; H, 3.15; N, 7.30. $C_{13}H_{11}F_5N_2O_5 \cdot 0.5H_2O$. Calculated (%): C, 41.17; H, 3.19; N, 7.39. IR, ν/cm^{-1}: 3270—3690 (NH, OH, H_2O); 1620 (C=O); 1590 (C=C); 1565, 1355 (NO_2). ^{1}H NMR, δ: 1.75 (br.s, 2 H, OH, 0.5 H_2O); 3.68 (q, 2 H, CH_2N, J = 5.4 Hz); 3.91 (t, 2 H, CH_2O, J = 4.9 Hz); 6.17 (s, 1 H, =CH); 7.02 (d, 1 H, H(3), J_o = 9.1 Hz); 8.26 (dd, 1 H, H(4), J_o = 9.1 Hz, J_m = 2.5 Hz); 8.57 (d, 1 H, H(6), J_m = 2.5 Hz); 11.13 (br.s, 1 H, NH); 13.45 (s, 1 H, OH).

3-Amino-1-(2-hydroxyphenyl)-4,4,5,5-tetrafluoropent-2-en-1-one (4a). A concentrated aqueous solution of NH_3 (0.5 mL) was added to a solution of chromone **1a** (100 mg, 0.41 mmol) in 1.0 mL of ethanol. The reaction mixture was kept at ~20 °C for 2 h and diluted with 5 mL of water. After the resulting oil crystallized, the crystals were filtered off and recrystallized from hexane. The yield was 90 mg (84%), m.p. 51—52 °C. Found (%): C, 50.32; H, 3.54; N, 5.25. $C_{11}H_9F_4NO_2$. Calculated (%): C, 50.20; H, 3.45; N, 5.32. IR, ν/cm^{-1}: 3530, 3430, 3320 (NH_2); 1635 (C=O); 1590, 1535 (C=C, arom.). ^{1}H NMR (100 MHz), δ: 5.92 (tt, CF_2CF_2H, $^2J_{H,F}$ = 53.5 Hz, $^3J_{H,F}$ = 3.2 Hz); 6.12 (s, 1 H, =CH); 6.75—7.00 (m, 2 H, H(5), H(3)); 7.30—7.73 (m, 4 H, H(4), H(6), NH_2); 12.77 (s, 1 H, OH).

3-Benzylamino-1-(2-hydroxyphenyl)-4,4,5,5-tetrafluoropent-2-en-1-one (4b) was obtained analogously from chromone **1a** (250 mg, 1.0 mmol) and benzylamine (210 mg, 2.0 mmol), with the exception that the reaction was carried out without a solvent for two days. The yield was 130 mg (37%), m.p. 80—81 °C. Found (%): C, 61.10; H, 4.38; N, 4.05. $C_{18}H_{15}F_4NO_2$. Calculated (%): C, 61.19; H, 4.28; N, 3.96. IR, ν/cm^{-1}: 1605 (C=O); 1580, 1520 (C=C, arom.). ^{1}H NMR, δ: 4.64 (d, 2 H, CH_2, J = 6.3 Hz); 5.94 (tt, CF_2CF_2H, $^2J_{H,F}$ = 53.3 Hz, $^3J_{H,F}$ = 3.7 Hz); 6.15 (s, 1 H, =CH); 6.85 (td, 1 H, H(5), J_o = 7.7 Hz, J_m = 1.1 Hz); 6.94 (dd, 1 H, H(3), J_o = 8.3 Hz, J_m = 1.1 Hz); 7.30—7.44 (m, 6 H, H(4), Ph); 7.65 (dd, 1 H, H(6), J_o = 8.3 Hz, J_m = 1.5 Hz); 10.95 (br.s, 1 H, NH); 12.60 (s, 1 H, OH).

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References

1. V. Ya. Sosnovskikh and B. I. Usachev, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 434 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 453].
2. K. Kostka, *Roczn. Chem.*, 1966, **40**, 1683.
3. V. Ya. Sosnovskikh and B. I. Usachev, *Mendeleev Commun.*, 2000, 240.
4. D. C. Nonhebel, *Tetrahedron*, 1968, **24**, 1869.
5. M. J. S. Dewar and W.Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899.
6. T. Klark, *Handbook of Computational Chemistry. Practical Guide to Chemical Structure and Energy Calculations*, J. Wiley and Sons, New York, 1985.
7. M. J. S. Dewar, E. G. Zoebish, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
8. J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209.
9. V. Ya. Sosnovskikh and V. A. Kutsenko, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 817 [*Russ. Chem. Bull.*, 1999, **48**, 812 (Engl. Transl.)].
10. V. Ya. Sosnovskikh, Yu. G. Yatluk, and V. A. Kutsenko, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1825 [*Russ. Chem. Bull.*, 1999, **48**, 1800 (Engl. Transl.)].

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