2-Polyfluoroalkylchromones
14.* Synthesis of 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles

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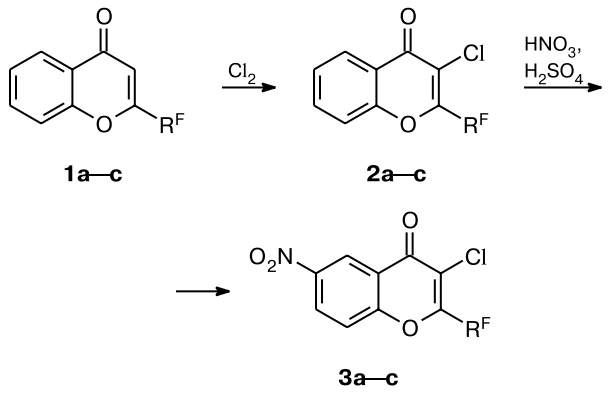
3-Chloro-2-polyfluoroalkyl- and 3-chloro-6-nitro-2-polyfluoroalkylchromones were synthesized. These compounds react with $N_2H_4 \cdot 2HCl$ on boiling in ethanol to form 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles.

Key words: 3-chloro-2-polyfluoroalkylchromones, hydrazine dihydrochloride, 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles.

Chromones represent an important class of oxygen-containing heterocycles, many of which are found in nature and well studied. However, data on the chemical properties of 3-halochromones are scarce. It is known that the reaction of 3-bromochromone with secondary amines affords 3-aminochromones.[2] The reactions of 3-bromochromone with primary amines[2] and of 3-iodochromone with secondary amines[3] are accompanied by the γ-pyrone ring contraction to form 2-aminomethylene-1-benzofuran-3-ones, *i.e.*, 3-halochromones react with amines in different way and give products containing no halogen atom. Published data on the interaction of 3-halochromones with hydrazine and its derivatives are lacking.

Scheme 1



R^F = CF_3 (**a**), $(CF_2)_2H$ (**b**), CF_2H (**c**)

Results and Discussion

Radical chlorination of 2-trifluoromethylchromone (**1a**) produced[4] 3-chloro-2-trifluoromethylchromone (**2a**), whose nitration resulted in 3-chloro-6-nitro-2-trifluoromethylchromone (**3a**) (Scheme 1). In this work we extended these reactions to chromones **1b,c** with the 1,1,2,2-tetrafluoroethyl and difluoromethyl groups and studied the reactions of 2-R^F-3-chlorochromones **2a—c** and **3a—c** with hydrazine dihydrochloride.

It has previously been shown that chromones **1** react smoothly with hydrazine hydrate, ammonia, primary amines, ethylenediamine, and diethylenetriamine to form the corresponding R^F-containing pyrazoles,[5] aminoenones,[6,7] 2-aminochromanones,[6] chromene-4-imines,[7] 2,3-dihydro-1*H*-1,4-diazepines,[8] and 1,4,8-triazabicyclo[5.3.0]dec-4-enes.[9] In this work we found that the replacement of the hydrogen atom in position 3 of the chromone system by the chlorine atom dramatically changes the reactivity of 2-R^F-3-chlorochromones toward N-nucleophiles, resulting in fast resinification of the reaction mixture. It is established that for 3-chlorochromones **2** and **3** a decrease in the pH of the reaction medium prevents resinification but considerably decreases the rate of reactions involving these compounds.

For the reaction of 3-chlorochromones **2a—c** and **3a—c** with hydrazine, we found that the reaction with the $N_2H_4 \cdot 2HCl$ salt instead of the hydrazine hydrate itself on boiling in ethanol with an additive of concentrated HCl produces previously unknown 4-chloropyrazoles **4a—c** and **5a—c** in high yields (Scheme 2). In the presence of AcONa, the reaction mixture almost immediately becomes dark red and resinifies upon boiling for 10—15 min. It is important that the reactivity of 3-chlorochromones decreases in the series **2a** > **2b** > **2c** and increases substantially when the nitro group is introduced into position 6. For example, 2-trifluoromethylchromones **2a** and **3a** react with $N_2H_4 \cdot 2HCl$ within 24 and 4 h, respectively, while this reaction for chromones **2b**,**c** and **3b**,**c** takes 48 and 8 h, respectively. Thus, unlike the reactions of 3-bromo- and 3-iodochromones with amines,[2,3] 3-chloro-

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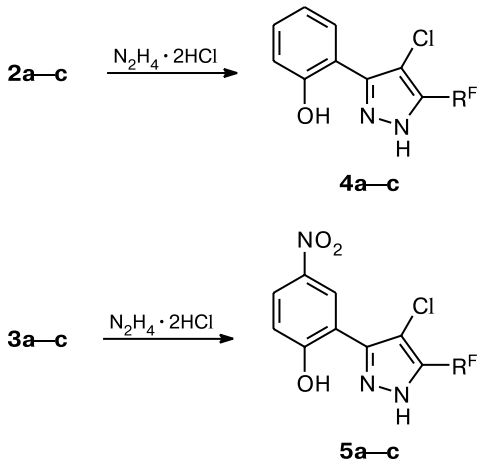
chromones **2a—c** and **3a—c** react with hydrazine with retention of the chlorine atom in the product. Note that the synthesis of 4-chloropyrazoles **4a—c** and **5a—c** does not seem obvious against the background of various transformations of haloalkenes with the geminal electron-withdrawing group (all of them occur with halogen atom substitution, see the review[10]).

Scheme 2



R^F = CF_3 (**a**), $(CF_2)_2H$ (**b**), CF_2H (**c**)

We have previously[5] described the synthesis of 3(5)-2-hydroxyaryl-5(3)-polyfluoroalkylpyrazoles and presented the data concerning their tautomeric and conformational structure in solutions of $CDCl_3$ and DMSO-d_6. It was shown that in both $CDCl_3$ and DMSO-d_6, in spite of the fact that intramolecular hydrogen bonds (IMHB) between O—H and N= are cleaved and the prototropic equilibrium shifts to the 1*H*-3-R^F-tautomer on going from one solvent to another, *N*-unsubstituted pyrazoles are planar, *i.e.*, the torsion angle between the 2-hydroxyaryl group and pyrazole ring is small. One of the criteria for this conclusion is the upfield shift of the signal from the aromatic H(6) proton on going from planar to nonplanar molecules by ~0.5 ppm.[11] Taking into account these data, it is of interest to compare the ^{1}H NMR spectra of pyrazoles **4b** and **5b** in which the signal from the H(6) proton on going from $CDCl_3$ to DMSO-d_6 exhibits the upfield shift by 0.75 ppm for **4b** and by 0.87 ppm for **5b**, while the signals of other protons shift insignificantly. It is likely that in $CDCl_3$ solutions 4-chloropyrazoles retain the planar conformation, although the introduction of the Cl atom diminishes the basicity of the pyrazole ring and weakens the IMHB strength, while in DMSO-d_6 unfavorable interactions between the H(6) and Cl atoms become predominant and result in the shift of the 2-hydroxyaryl substituent from the plane of the pyrazole cycle.

Thus, 3-chloro-2-polyfluoroalkylchromones react with $N_2H_4 \cdot 2HCl$ with retention of the chlorine atom and formation of 4-chloro-3(5)-(2-hydroxyaryl)-5(3)-polyfluoroalkylpyrazoles, which are difficult to be synthesized by other methods.

Experimental

IR spectra were recorded on an IKS-29 instrument in Nujol. ^{1}H NMR spectra were obtained on a Bruker DRX-400 spectrometer in $CDCl_3$ or DMSO-d_6 (working frequency 400.13 MHz, internal standard Me_4Si). The starting chromones **1a—c** have been described in the works,[12,13] and for 3-chlorochromones **2a** and **3a**, see Ref. 4.

Synthesis of 3-chlorochromones (2) (general procedure). The Cl_2 flow was passed for 0.5 h through a solution of chromone **1** (0.015 mol) in CCl_4 (15 mL) along with irradiation by an incandescent lamp (60 W). After the solvent was evaporated, a liquid residue (~5 mL) was boiled in EtOH (10 mL) for 15 min. Then the mixture was cooled, and the formed crystalline product was filtered off, washed with cold EtOH, and dried.

3-Chloro-2-(1,1,2,2-tetrafluoroethyl)chromone (2b) was synthesized in 76% yield, m.p. 75—76 °C, colorless needle-like crystals. Found (%): C, 47.01; H, 1.65. $C_{11}H_5ClF_4O_2$. Calculated (%): C, 47.08; H, 1.80. IR, ν/cm^{-1}: 1665 (C=O), 1620 (C=C), 1575 (arom.). ^{1}H NMR ($CDCl_3$), δ: 6.33 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 52.8 Hz, $^3J_{H,F}$ = 4.4 Hz); 7.53 (ddd, 1 H, H(6), J_o = 8.1 Hz, J_o = 7.2 Hz, J_m = 1.0 Hz); 7.56 (d, 1 H, H(8), J_o = 8.6 Hz); 7.80 (ddd, 1 H, H(7), J_o = 8.7 Hz, J_o = 7.2 Hz, J_m = 1.7 Hz); 8.27 (dd, 1 H, H(5), J_o = 8.0 Hz, J_m = 1.7 Hz).

3-Chloro-2-difluoromethylchromone (2c). The yield was 56%, m.p. 122—123 °C (EtOH), colorless needle-like crystals. Found (%): C, 52.14; H, 2.09. $C_{10}H_5ClF_2O_2$. Calculated (%): C, 52.09; H, 2.19. IR, ν/cm^{-1}: 1665 (C=O), 1625 (C=C), 1610, 1580 (arom.). ^{1}H NMR ($CDCl_3$), δ: 7.02 (t, 1 H, CF_2H, $^2J_{H,F}$ = 52.2 Hz); 7.51 (ddd, 1 H, H(6), J_o = 8.1 Hz, J_o = 7.2 Hz, J_m = 1.0 Hz); 7.60 (dt, 1 H, H(8), J_o = 8.6 Hz, $J_m \approx J_p \approx$ 0.5 Hz); 7.79 (ddd, 1 H, H(7), J_o = 8.7 Hz, J_o = 7.2 Hz, J_m = 1.7 Hz); 8.27 (dd, 1 H, H(5), J_o = 8.0 Hz, J_m = 1.7 Hz).

Synthesis of 3-chloro-6-nitrochromones (3) (general procedure). Concentrated HNO_3 (2 mL) and concentrated H_2SO_4 (1 mL) were added to a solution of 3-chlorochromone **2** (3.6 mmol) in concentrated H_2SO_4 (2 mL). The resulting mixture was stored at 45 °C for 1.5 h and diluted with cold water (100 mL). The precipitated product was filtered off and recrystallized from EtOH.

3-Chloro-6-nitro-2-(1,1,2,2-tetrafluoroethyl)chromone (3b). The yield was 70%, m.p. 127—128 °C, colorless crystals. Found (%): C, 40.54; H, 1.19; N, 4.22. $C_{11}H_4ClF_4NO_4$. Calculated (%): C, 40.58; H, 1.24; N, 4.30. IR, ν/cm^{-1}: 1675 (C=O), 1630 (C=C), 1610, 1580 (arom.), 1530 (NO_2). ^{1}H NMR ($CDCl_3$), δ: 6.31 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 52.7 Hz, $^3J_{H,F}$ = 3.9 Hz); 7.76 (d, 1 H, H(8), J_o = 9.2 Hz); 8.63 (dd, 1 H, H(7), J_o = 9.2 Hz, J_m = 2.7 Hz); 9.13 (d, 1 H, H(5), J_m = 2.7 Hz).

3-Chloro-2-difluoromethyl-6-nitrochromone (3c). The yield was 69%, m.p. 120—121 °C, colorless crystals. Found (%): C, 43.58; H, 1.50; N, 5.09. $C_{10}H_4ClF_2NO_4$. Calculated (%): C, 43.58; H, 1.46; N, 5.08. IR, ν/cm^{-1}: 1670 (C=O), 1630 (C=C), 1580 (arom.), 1530 (NO_2). ^{1}H NMR ($CDCl_3$), δ: 7.04 (t, 1 H, CF_2H, $^2J_{H,F}$ = 51.9 Hz); 7.79 (d, 1 H, H(8), J_o =

9.2 Hz); 8.62 (dd, 1 H, H(7), J_o = 9.2 Hz, J_m = 2.8 Hz); 9.12 (d, 1 H, H(5), J_m = 2.8 Hz).

Synthesis of 4-chloropyrazoles (4, 5) (general procedure). A solution of chromone **2** or **3** (0.92 mmol) in EtOH (4 mL) was added by $N_2H_4 \cdot 2HCl$ (0.16 g, 1.5 mmol) and 1 droplet of concentrated HCl. The resulting mixture was boiled, cooled, and diluted with water (10 mL). Colorless crystals of the product were filtered off, washed with water, dried, and recrystallized.

4-Chloro-3(5)-(2-hydroxyphenyl)-5(3)-trifluoromethylpyrazole (4a). The duration of the reaction was 24 h, the yield was 66%, m.p. 168—169 °C (toluene). Found (%): C, 45.73; H, 2.04; N, 10.66. $C_{10}H_6ClF_3N_2O$. Calculated (%): C, 45.74; H, 2.30; N, 10.67. IR, ν/cm^{-1}: 3390, 3220 (NH, OH), 1675, 1615, 1595, 1570, 1530, 1510. ^{1}H NMR ($CDCl_3$), δ: 6.30 (br.s, 1 H, OH); 6.96 (dd, 1 H, H(3), J_o = 8.2 Hz, J_m = 0.8 Hz); 7.10 (ddd, 1 H, H(5), J_o = 7.9 Hz, J_o = 7.4 Hz, J_m = 1.0 Hz); 7.33 (ddd, 1 H, H(4), J_o = 8.2 Hz, J_o = 7.4 Hz, J_m = 1.6 Hz); 8.15 (dd, 1 H, H(6), J_o = 7.9 Hz, J_m = 1.6 Hz); 11.3 (br.s, 1 H, NH).

4-Chloro-3(5)-(2-hydroxyphenyl)-5(3)-(1,1,2,2-tetrafluoroethyl)pyrazole (4b). The duration of the reaction was 48 h, the yield was 62%, m.p. 87—88 °C (twice from a hexane—toluene mixture). Found (%): C, 44.87; H, 2.40; N, 9.62. $C_{11}H_7ClF_4N_2O$. Calculated (%): C, 44.84; H, 2.39; N, 9.51. IR, ν/cm^{-1}: 3430, 3200 (NH, OH), 1675, 1660, 1620, 1590, 1580. ^{1}H NMR ($CDCl_3$), δ: 6.23 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.2 Hz, $^3J_{H,F}$ = 4.1 Hz); 7.0 (br.s, 1 H, OH); 6.98 (d, 1 H, H(3), J_o = 8.2 Hz); 7.07 (t, 1 H, H(5), J_o = 7.6 Hz); 7.31 (ddd, 1 H, H(4), J_o = 8.2 Hz, J_o = 7.2 Hz, J_m = 1.5 Hz); 8.14 (dd, 1 H, H(6), J_o = 7.9 Hz, J_m = 1.4 Hz); 11.4 (br.s, 1 H, NH). ^{1}H NMR (DMSO-d_6), δ: 6.90 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 51.9 Hz, $^3J_{H,F}$ = 5.1 Hz); 6.94 (t, 1 H, H(5), J_o = 7.5 Hz); 7.02 (d, 1 H, H(3), J_o = 8.2 Hz); 7.33 (ddd, 1 H, H(4), J_o = 8.2 Hz, J_o = 7.3 Hz, J_m = 1.6 Hz); 7.39 (dd, 1 H, H(6), J_o = 7.6 Hz, J_m = 1.5 Hz); 10.2 (br.s, 1 H, OH); 13.9 (br.s, 1 H, NH).

4-Chloro-5(3)-difluoromethyl-3(5)-(2-hydroxyphenyl)pyrazole (4c). The duration of the reaction was 48 h, the yield was 34%, m.p. 132—133 °C (twice from a hexane—toluene mixture). Found (%): C, 49.09; H, 2.88; N, 11.49. $C_{10}H_7ClF_2N_2O$. Calculated (%): C, 49.10; H, 2.88; N, 11.45. IR, ν/cm^{-1}: 3380 (NH), 1655, 1610, 1580, 1560. ^{1}H NMR ($CDCl_3$), δ: 6.84 (t, 1 H, CF_2H, $^2J_{H,F}$ = 53.5 Hz); 7.01—7.04 (m, 2 H, H(3), H(5)); 7.30 (ddd, 1 H, H(4), J_o = 8.2 Hz, J_o = 7.3 Hz, J_m = 1.6 Hz); 8.15 (dd, 1 H, H(6), J_o = 8.1 Hz, J_m = 1.6 Hz); 8.7 (br.s, 1 H, OH); 11.3 (br.s, 1 H, NH).

4-Chloro-3(5)-(2-hydroxy-5-nitrophenyl)-5(3)-trifluoromethylpyrazole (5a). The duration of the reaction was 4 h, the yield was 67%, m.p. 213—214 °C (toluene), light yellow crystals. Found (%): C, 38.89; H, 1.52; N, 13.65. $C_{10}H_5ClF_3N_3O_3$. Calculated (%): C, 39.04; H, 1.64; N, 13.66. IR, ν/cm^{-1}: 3190, 3130 (NH, OH), 1680, 1630, 1590, 1570, 1515. ^{1}H NMR (DMSO-d_6), δ: 7.20 (d, 1 H, H(3), J_o = 9.1 Hz); 8.28 (dd, 1 H, H(4), J_o = 9.1 Hz, J_m = 2.9 Hz); 8.37 (d, 1 H, H(6), J_m = 2.9 Hz); 12.0 (br.s, 1 H, OH); 14.2 (br.s, 1 H, NH).

4-Chloro-3(5)-(2-hydroxy-5-nitrophenyl)-5(3)-(1,1,2,2-tetrafluoroethyl)pyrazole (5b). The duration of the reaction was 8 h, the yield was 83%, m.p. 209—210 °C (toluene), yellow crystals. Found (%): C, 38.91; H, 1.60; N, 12.35. $C_{11}H_6ClF_4N_3O_3$. Calculated (%): C, 38.90; H, 1.78; N, 12.37. IR, ν/cm^{-1}: 3190, 3120 (NH, OH), 1680, 1630, 1590, 1530. ^{1}H NMR (DMSO-d_6), δ: 6.93 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 51.9 Hz, $^3J_{H,F}$ = 5.0 Hz); 7.20 (d, 1 H, H(3), J_o = 9.1 Hz); 8.27 (dd, 1 H, H(4), J_o = 9.1 Hz, J_m = 2.9 Hz); 8.35 (d, 1 H, H(6), J_m = 2.9 Hz); 12.0 (br.s, 1 H, OH); 14.2 (br.s, 1 H, NH). ^{1}H NMR ($CDCl_3$), δ: 6.21 (tt, 1 H, CF_2CF_2H, $^2J_{H,F}$ = 53.3 Hz, $^3J_{H,F}$ = 3.0 Hz); 7.14 (d, 1 H, H(3), J_o = 9.1 Hz); 8.22 (dd, 1 H, H(4), J_o = 9.1 Hz, J_m = 2.7 Hz); 9.22 (d, 1 H, H(6), J_m = 2.7 Hz); 10.7 (br.s, 2 H, OH, NH).

4-Chloro-5(3)-difluoromethyl-3(5)-(2-hydroxy-5-nitrophenyl)pyrazole (5c). The duration of the reaction was 8 h, the yield was 70%, m.p. 203—204 °C (toluene), yellow crystals. Found (%): C, 41.48; H, 2.11; N, 14.37. $C_{10}H_6ClF_2N_3O_3$. Calculated (%): C, 41.47; H, 2.09; N, 14.51. IR, ν/cm^{-1}: 3195, 3130 (NH, OH), 1670, 1630, 1610, 1590, 1575, 1525. ^{1}H NMR (DMSO-d_6), δ: 7.19 (t, 1 H, CF_2H, $^2J_{H,F}$ = 53.0 Hz); 7.19 (d, 1 H, H(3), J_o = 9.1 Hz); 8.26 (dd, 1 H, H(4), J_o = 9.1 Hz, J_m = 2.9 Hz); 8.34 (d, 1 H, H(6), J_m = 2.9 Hz); 12.0 (br.s, 1 H, OH); 13.9 (br.s, 1 H, NH).

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References

1. V. Ya. Sosnovskikh and B. I. Usachev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2002, 1801 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 1954].
2. R. B. Gammill, S. A. Nash, and S. A. Mizsak, *Tetrahedron Lett.*, 1983, **24**, 3435.
3. Y. Sugita, T. Iwaki, M. Okamoto, and I. Yokoe, *Heterocycles*, 2001, **55**, 881.
4. V. Ya. Sosnovskikh and B. I. Usachev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2000, 2109 [*Russ. Chem. Bull.*, *Int. Ed.*, 2000, **49**, 2074].
5. V. Ya. Sosnovskikh, M. A. Barabanov, and A. Yu. Sizov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2002, 1184 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 1280].
6. V. Ya. Sosnovskikh, V. A. Kutsenko, and D. S. Yachevskii, *Mendeleev Commun.*, 1999, 204.
7. V. Ya. Sosnovskikh, and B. I. Usachev, *Mendeleev Commun.*, 2000, 240.
8. V. Ya. Sosnovskikh and V. A. Kutsenko, *Izv. Akad. Nauk*, *Ser. Khim.*, 1999, 817 [*Russ. Chem. Bull.*, 1999, **48**, 812 (Engl. Transl.)].
9. V. Ya. Sosnovskikh, I. I. Vorontsov, and V. A. Kutsenko, *Izv. Akad. Nauk*, *Ser. Khim.*, 2001, 1360 [*Russ. Chem. Bull.*, *Int. Ed.*, 2001, **50**, 1430].
10. A. Yu. Rulev, *Usp. Khim.*, 1998, **67**, 317 [*Russ. Chem. Rev.*, 1998, **67** (Engl. Transl.)].
11. J. Catalán, F. Fabero, R. M. Claramunt, M. D. Santa Maria, M. C. Foces-Foces, F. H. Cano, M. Martinez-Ripoll, J. Elguero, and R. Sastre, *J. Am. Chem. Soc.*, 1992, **114**, 5039.
12. V. Ya. Sosnovskikh and I. S. Ovsyannikov, *Zh. Org. Khim.*, 1993, **29**, 89 [*Russ. J. Org. Chem.*, 1993, **29**, 74 (Engl. Transl.)].
13. V. Ya. Sosnovskikh, A. Yu. Sizov, and B. I. Usachev, *Izv. Akad. Nauk*, *Ser. Khim.*, 2002, 1175 [*Russ. Chem. Bull.*, *Int. Ed.*, 2002, **51**, 1270 (Engl. Transl.)].

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