2-Polyfluoroalkylchromones
8.* 2-Trifluoromethyl- and 6-nitro-2-trifluoromethylchromones in reactions with amines

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The reactions of 6-nitro-2-trifluoromethylchromone with benzylamine, ethanolamine, and aniline afforded 3-benzyl(2-hydroxyethyl,phenyl)amino-4,4,4-trifluoro-1-(2-hydroxy-5-nitrophenyl)but-2-en-1-ones, respectively, whereas the reactions with ethylenediamine and diethylenetriamine gave rise to 5-(2-hydroxy-5-nitrophenyl)-7-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepine and 5-(2-hydroxy-5-nitrophenyl)-7-trifluoromethyl-1,4,8-triazabicyclo[5.3.0]dec-4-ene, respectively. Morpholine added at the double bond of 2-trifluoromethyl- and 6-nitro-2-trifluoromethylchromones to form 2-morpholino-2-trifluoromethylchroman-4-one and its 6-nitro-substituted analog, respectively, whereas piperidine reacted only with 2-trifluoromethylchromone to yield 2-piperidino-2-trifluoromethylchroman-4-one.

Key words: 2-trifluoromethylchromones, primary and secondary amines, β-amino-β-trifluoromethyl vinyl ketones, 2,3-dihydro-1*H*-1,4-diazepine derivatives, 2-morpholino- and 2-piperidino-2-trifluoromethylchroman-4-ones.

The replacement of the methyl group in 2-methylchromones by the trifluoromethyl group leads to an increase in electrophilicity of the C(2) atom and affects substantially the reactivity of the pyrone ring with respect to N-nucleophiles.[2—4] Previously,[5] we have described nitration of 2-trifluoromethylchromone (**1a**) giving rise to 6-nitro-2-trifluoromethylchromone (**1b**).

In the present study, we compared the reactivities of chromones **1a** and **1b** in reactions with primary, secondary, and aromatic amines.

Results and Discussion

Earlier, we have demonstrated that the pyrone ring of chromone **1a** was readily cleaved under the action of benzylamine[2] and ethanolamine[6] to form the corresponding aminoenones **2a** and **3a**. The reactions of chromone **1a** with ethylenediamine[3] and diethylenetriamine[4] afforded dihydrodiazepine **4a** and the 1,4,8-triazabicyclo[5.3.0]dec-4-ene derivative (**5a**), respectively (Scheme 1).

In the present study, we found that analogous products **2b—5b** were formed also in the reactions of chromone **1b** with the above-mentioned mono-, di-, and triamines. It should be noted that, in spite of the high acidity of the phenol hydroxyl group, no formation of inner salts was observed in the case of compounds **4b** and **5b** as evidenced by the data from ^{1}H NMR spectroscopy (see the Experimental section). Therefore, we revealed no fundamental differences in the reactivity of chromones **1a** and **1b** with respect to N-nucleophiles in this series of compounds.

In this connection, we extended the range of the amines under study and examined the reactions of chromones **1a,b** with *tert*-butylamine, piperidine, morpholine, aniline, and *m*-trifluoromethylaniline (Scheme 2).

It appeared that treatment of chromones **1a,b** with *tert*-butylamine at ~20 °C was accompanied by resinification of the reaction mixture and no individual reactions products were isolated. The reactions of piperidine with chromones **1a,b** proceeded reversibly to give unstable adducts **6a,b**, respectively. We succeeded in isolating and analyzing only compound **6a**, which decomposed to the initial components in a period of a few days. Previously,[7] an analogous result has been obtained in the reaction of piperidine with 6-methyl-2-trifluoromethylchromone.

It was also found that morpholine added at the double bond of chromone **1a** upon heating to 80 °C for 7 h, whereas chromone **1b** reacted smoothly with morpholine even at ~20 °C during 20 min. These reactions gave rise to 2-morpholinochromanones **7a** and **7b** in 85 and 90% yields, respectively. It should be noted that chromone as such was cleaved under the action of morpholine to form 1-(2-hydroxyphenyl)-3-morpholinoprop-2-en-1-one,[8] whereas the reaction of 2-methylchromone with morpholine (according to the results of out study) did not proceed. Thus, we discovered the

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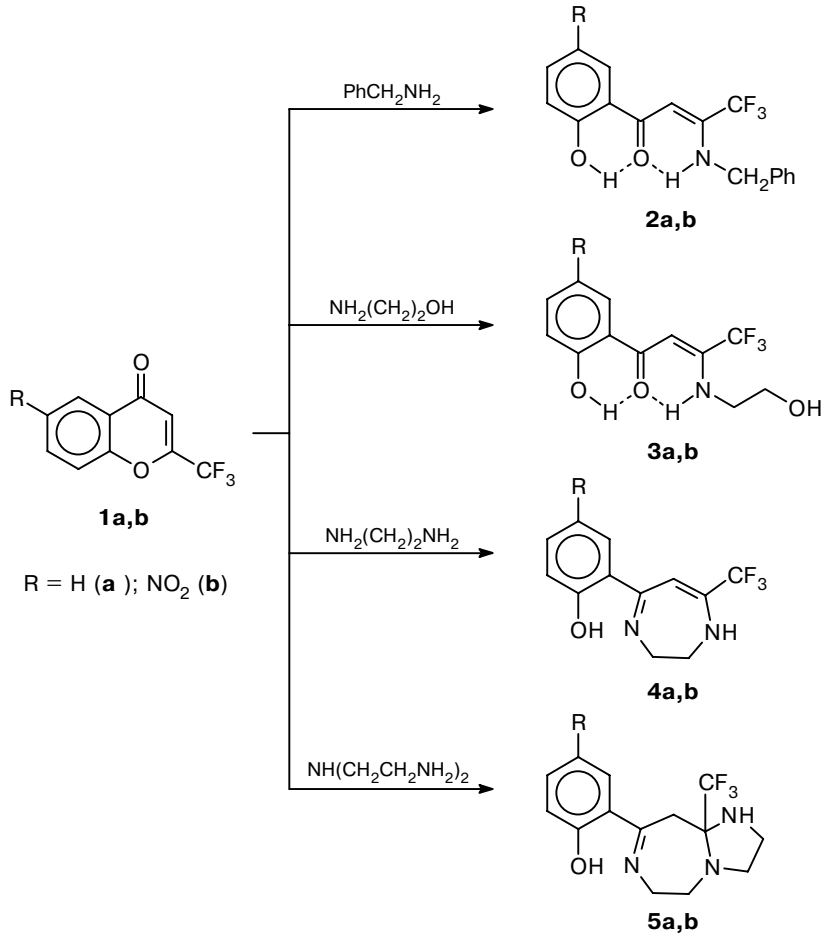
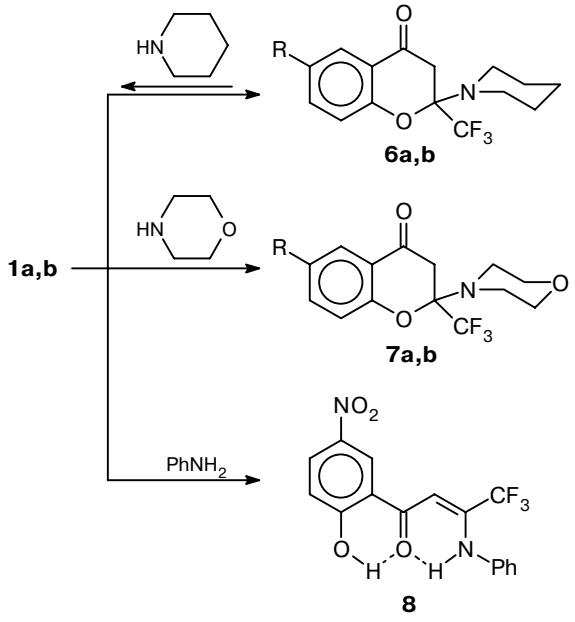
Scheme 1



Scheme 2



reaction giving rise to compounds **7a,b**, which provides the first example of the nucleophilic addition of secondary amines to the chromone system. Apparently, this reaction is favored by the electron-withdrawing CF_3 group, which not only increases the electrophilicity of the C(2) atom, but also stabilizes[9] the aminoketal fragment in 2-morpholinochromanones **7a,b**. The replacement of the CF_3 group by the CF_2H, $(CF_2)_2H$, or C_2F_5 groups has no success in the reactions with morpholine, which, on the one hand, reduces the synthetic possibilities of these reaction, but, on the other hand, underlines the unique ability of the CF_3 group to stabilize systems analogous to compounds **7a,b**.

The spectral data agree well with the structures of 2-morpholinochromanones **7a,b**. The IR spectra of these compounds have intense absorption bands ν(C=O) at 1710 and 1725 cm^{-1}. The ^1H NMR spectra have a characteristic AB system of the chromanone CH_2 group with the centers at δ 3.14 and 3.24, respectively, (J_{AB} ~16.5 Hz) along with signals for the protons of the morpholine and aromatic fragments.

It is known that 2-methylchromone, unlike chromone,[8] does not react with aniline.[10] We found that

2-trifluoromethylchromone (**1a**) also did not react with aniline. However, 6-nitro-2-trifluoromethylchromone (**1b**) was cleaved upon heating with aniline (80 °C, 4 h) to yield aminoenone **8**. Aniline did not react with 6-nitro-2-difluoromethyl- and 6-nitro-2-(1,1,2,2-tetrafluoroethyl)chromones, while *m*-trifluoromethylaniline is insufficiently nucleophilic to be involved in the reaction with chromone **1b**. The difference in the reactivity of chromones **1a** and **1b** was exemplified only by conversion **1b** → **8**, excluding the milder conditions of the reaction of compound **1b** with morpholine.

Hence, the introduction of the nitro group at position 6 of 2-trifluoromethylchromone leads to an increase in the reactivity of the pyrone ring with respect to N-nucleophiles and makes possible the reaction with aniline.

Experimental

The IR spectra were recorded on an IKS-29 instrument in Nujol mulls. The ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer in $CDCl_3$ with Me_4Si as the internal standard.

The reagents from Aldrich were used. 6-Nitro-2-trifluoromethylchromone (**1b**) was prepared according to a procedure reported previously.[5]

3-Benzylamino-4,4,4-trifluoro-1-(2-hydroxy-5-nitrophenyl)but-2-en-1-one (2b). A solution of chromone **1b** (0.25 g, 1.0 mmol) and benzylamine (0.25 g, 2.3 mmol) in EtOH (3 mL) was heated to boiling and kept at ~20 °C for 24 h. Then H_2O (5 mL) was added to the reaction mixture. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from EtOH. The yield was 0.22 g (62%), m.p. 123—124 °C. Found (%): C, 55.76; H, 3.59; N, 7.62. $C_{17}H_{13}F_3N_2O_4$. Calculated (%): C, 55.74; H, 3.58; N, 7.65. IR, ν/cm^{-1}: 1615 (C=O), 1580, 1515 (C=C, arom.). ^{1}H NMR, δ: 4.69 (d, 2 H, CH_2, J = 6.2 Hz); 6.31 (s, 1 H, =CH); 7.02 (d, 1 H, H(3), J_o = 9.2 Hz); 7.33—7.48 (m, 5 H, Ph); 8.27 (dd, 1 H, H(4), J_o = 9.2 Hz, J_m = 2.6 Hz); 8.63 (d, 1 H, H(6), J_m = 2.6 Hz); 10.72 (br.s, 1 H, NH); 13.45 (s, 1 H, OH).

4,4,4-Trifluoro-3-(2-hydroxyethylamino)-1-(2-hydroxy-5-nitrophenyl)but-2-en-1-one (3b). A mixture of chromone **1b** (0.10 g, 0.4 mmol), ethanolamine (0.10 g, 1.6 mmol), and EtOH (1 mL) was stirred for 10 min until the chromone was completely dissolved. Then H_2O (5 mL) and AcOH (0.3 mL) were added. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from a 1 : 1 toluene—hexane mixture. The yield was 0.11 g (89%), m.p. 170—171 °C. Found (%): C, 45.14; H, 3.55; N, 8.62. $C_{12}H_{11}F_3N_2O_5$. Calculated (%): C, 45.01; H, 3.46; N, 8.75. IR, ν/cm^{-1}: 3550 (OH), 3180 (NH), 1620 (C=O), 1585 (C=C). ^{1}H NMR, δ: 1.88 (br.s, 1 H, OH); 3.67 (q, 2 H, CH_2N, J = 5.3 Hz); 3.91 (br.s, 2 H, CH_2O); 6.26 (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 = 2.6 Hz); 8.59 (d, 1 H, H(6), J_m = 2.6 Hz); 10.73 (br.s, 1 H, NH); 13.49 (s, 1 H, OH).

5-(2-Hydroxy-5-nitrophenyl)-7-trifluoromethyl-2,3-dihydro-1*H*-1,4-diazepine (4b). A mixture of chromone **1b** (0.10 g, 0.4 mmol), ethylenediamine (0.10 g, 1.7 mmol), and EtOH (1 mL) was stirred until the chromone was completely dissolved. Then the reaction mixture was kept at ~20 °C for 30 min, diluted with H_2O (5 mL), and acidified with AcOH (0.3 mL). The precipitate that formed was filtered off, washed with water, and dried. The yield was 0.10 g (86%). Compound **4b** decomposed at ~270 °C. Found (%): C, 47.83; H, 3.31; N, 13.90. $C_{12}H_{10}F_3N_3O_3$. Calculated (%): C, 47.85; H, 3.35; N, 13.95. IR, ν/cm^{-1}: 3260 (NH), 1635 (C=N), 1560 (NO_2), 1610, 1515 (C=C, arom.). ^{1}H NMR, δ: 3.68 (br.s, 2 H, CH_2(2)); 3.94 (br.s, 2 H, CH_2(3)); 5.83 (s, 1 H, =CH); 6.55 (d, 1 H, H(3′), J_o = 9.5 Hz); 7.96 (dd, 1 H, H(4′), J_o = 9.5 Hz, J_m = 2.9 Hz); 8.52 (d, 1 H, H(6′), J_m = 2.9 Hz); 9.43 (br.s, 1 H, NH); 15.93 (br.s, 1 H, OH).

5-(2-Hydroxy-5-nitrophenyl)-7-trifluoromethyl-1,4,8-triazabicyclo[5.3.0]dec-4-ene (5b). A mixture of chromone **1b** (0.25 g, 1.0 mmol), diethylenetriamine (0.40 g, 3.9 mmol), and EtOH (1 mL) was stirred until the chromone was completely dissolved and then H_2O (7 mL) was added. After 20 min, an additional amount of H_2O (50 mL) was added to the reaction mixture and the mixture was kept at ~20 °C for 1 h. The precipitate that formed was filtered off, washed with water, and dried. The yield was 0.12 g (36%), m.p. 155—157 °C (decomp.). Found (%): C, 48.88; H, 4.57; N, 16.27. $C_{14}H_{15}F_3N_4O_3$. Calculated (%): C, 48.84; H, 4.39; N, 16.27. IR, ν/cm^{-1}: 3360 (NH), 1625 (C=N), 1560 (NO_2). ^{1}H NMR ($CDCl_3$+DMSO-d_6), δ: 3.00—3.35 (m, 6 H, CH_2(9), CH_2(10), CH_2(2)); 3.48 (br.s, 1 H, NH); 3.58 (AB system, Δδ 0.15, 2 H, CH_2(6), J_{AB} = 15.4 Hz); 3.84—4.00 (m, 1 H, C<u>H</u>H(3)); 4.13—4.31 (m, 1 H, CH<u>H</u>(3)); 6.81 (d, 1 H, H(3′), J_o = 9.4 Hz); 8.11 (dd, 1 H, H(4′), J_o = 9.4 Hz, J_m = 2.8 Hz); 8.60 (d, 1 H, H(6′), J_m = 2.8 Hz); 17.42 (s, 1 H, OH).

2-Piperidino-2-trifluoromethylchroman-4-one (6a). A mixture of chromone **1a** (0.25 g, 1.2 mmol) and piperidine (0.34 g, 4.0 mmol) was kept at ~20 °C for 1 h and then triturated with H_2O (5 mL). The product that crystallized was filtered off, washed with water, dried, and recrystallized from hexane. The yield was 0.29 g (83%), m.p. 67 °C. Found (%): C, 60.25; H, 5.44; N, 4.67. $C_{15}H_{16}F_3NO_2$. Calculated (%): C, 60.20; H, 5.39; N, 4.68. IR, ν/cm^{-1}: 1710 (C=O), 1615, 1580 (arom.). ^{1}H NMR (DMSO-d_6), δ: 0.98—1.35 (m, 6 H, 3 CH_2); 2.70—2.87 (m, 4 H, 2 CH_2N); 3.35 (AB system, Δδ 0.09, 2 H, CH_2, J_{AB} = 16.3 Hz); 7.15 (d, 1 H, H(8), J_o = 7.6 Hz); 7.16 (dd, 1 H, H(6), $J_{H(6),H(7)}$ = $J_{H(6),H(5)}$ = 7.6 Hz); 7.64 (ddd, 1 H, H(7), $J_{H(7),H(6)}$ = $J_{H(7),H(8)}$ = 8.0 Hz, $J_{H(7),H(5)}$ = 1.5 Hz); 7.77 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.5 Hz).

2-Morpholino-2-trifluoromethylchroman-4-one (7a). A mixture of chromone **1a** (0.25 g, 1.2 mmol) and morpholine (0.35 g, 4.0 mmol) was heated at 80 °C for 7 h. Then H_2O (10 mL) was added to the cooled reaction mixture. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from hexane. The yield was 0.30 g (85%), m.p. 116—117 °C. Found (%): C, 55.74; H, 4.68; N, 4.66. $C_{14}H_{14}F_3NO_3$. Calculated (%): C, 55.82; H, 4.68; N, 4.65. IR, ν/cm^{-1}: 1710 (C=O), 1620 (arom.). ^{1}H NMR, δ: 2.80—3.00 (m, 4 H, 2 CH_2N); 3.14 (AB system, Δδ 0.05, 2 H, CH_2, J_{AB} = 16.4 Hz); 3.28—3.47 (m, 4 H, 2 CH_2O); 7.02 (dd, 1 H, H(8), $J_{H(8),H(7)}$ = 8.3 Hz, $J_{H(8),H(6)}$ = 0.8 Hz); 7.12 (ddd, 1 H, H(6) , $J_{H(6),H(5)}$ = 7.8 Hz, $J_{H(6),H(7)}$ = 7.0 Hz, $J_{H(6),H(8)}$ = 0.8 Hz); 7.55 (ddd, 1 H, H(7), $J_{H(7),H(8)}$ = 8.3 Hz, $J_{H(7),H(6)}$ = 7.0 Hz, $J_{H(7),H(5)}$ = 1.6 Hz); 7.88 (dd, 1 H, H(5), $J_{H(5),H(6)}$ = 7.8 Hz, $J_{H(5),H(7)}$ = 1.6 Hz).

2-Morpholino-6-nitro-2-trifluoromethylchroman-4-one (7b). A mixture of chromone **1b** (0.25 g, 1.0 mmol) and morpholine (0.25 g, 2.9 mmol) was thoroughly stirred for 20 min and then triturated with H_2O (5 mL). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from CCl_4. The yield was 0.30 g (90%), m.p. 135—136 °C. Found (%): C, 48.54; H, 3.61; N, 7.91. $C_{14}H_{13}F_3N_2O_5$. Calculated (%): C, 48.56; H, 3.78; N, 8.09. IR, ν/cm^{-1}: 1725 (C=O), 1625, 1590 (arom.), 1530 (NO_2). ^{1}H NMR, δ: 2.82—3.00 (m, 4 H, 2 CH_2N); 3.24 (AB system, Δδ 0.05, 2 H, CH_2, J_{AB} = 16.6 Hz); 3.30—3.50 (m, 4 H, 2 CH_2O); 7.22 (d, 1 H, H(8), J_o = 9.3 Hz);

8.45 (dd, 1 H, H(7), J_o = 9.3 Hz, J_m = 2.7 Hz); 8.78 (d, 1 H, H(5), J_m = 2.7 Hz).

3-Anilino-4,4,4-trifluoro-1-(2-hydroxy-5-nitrophenyl)but-2-en-1-one (8). A mixture of chromone **1b** (0.25 g, 1.0 mmol), aniline (0.25 g, 2.7 mmol), and three drops of Et_3N was heated at 80 °C for 4 h. Then EtOH (1 mL) was added to the cooled reaction mixture. The precipitate that formed was filtered off, washed with EtOH, dried, and recrystallized from CCl_4. The yield was 0.17 g (50 %), m.p. 156—157 °C. Found (%): C, 54.51; H, 3.29; N, 7.90. $C_{16}H_{11}F_3N_2O_4$. Calculated (%): C, 54.55; H, 3.15; N, 7.95. IR, ν/cm^{-1}: 1615 (C=O), 1600—1520 (C=C, NO_2, arom.). ^{1}H NMR, δ: 6.47 (s, 1 H, =CH); 7.08 (d, 1 H, H(3), J_o = 9.3 Hz); 7.30 (d, 2 H, Ph, J_o = 7.6 Hz); 7.39—7.49 (m, 3 H, Ph); 8.33 (dd, 1 H, H(4), J_o = 9.3 Hz, J_m = 2.5 Hz); 8.71 (d, 1 H, H(6), J_m = 2.5 Hz); 12.01 (br.s, 1 H, NH); 13.40 (s, 1 H, OH).

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