2-Polyfluoroalkylchromones
6.* Synthesis of substituted 2-morpholino-2-trifluoromethylchroman-4-ones

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Morpholine adds smoothly at the double bond of substituted 5- and 8-nitro-2-trifluoromethylchromones to form the corresponding 2-morpholino-2-trifluoromethylchroman-4-ones. 6-Methoxy-5-nitro-2-trifluoromethylchromone adds also benzylamine, whereas 7-methoxy-8-nitro-2-trifluoromethylchromone undergoes ring opening under the action of benzylamine to give 3-benzylamino-4,4,4-trifluoro-1-(2-hydroxy-4-methoxy-3-nitrophenyl)but-2-en-1-one.

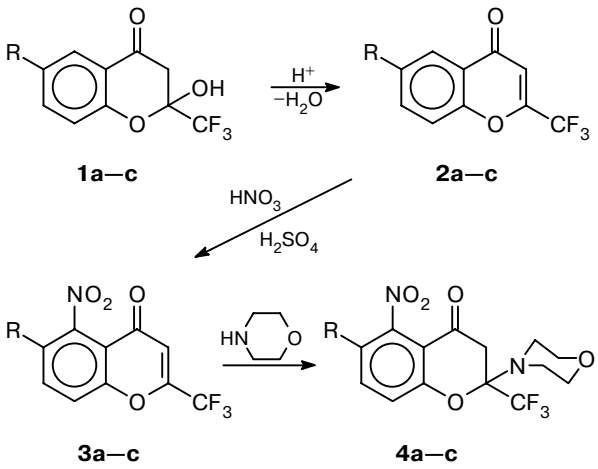
Key words: 2-morpholino- and 2-benzylamino-2-trifluoromethylchroman-4-ones, synthesis; substituted 5- and 8-nitro-2-trifluoromethylchromones, reactions with morpholine and benzylamine.

It is known[2] that ammonia or primary amines react with 2-trifluoromethylchromones at the C(2) atom primarily with the pyrone-ring opening. However, the reactions with compounds containing the methyl group at position 5 of the chromone system are terminated at the stage of nucleophilic addition to form 2-amino and 2-alkylaminochroman-4-ones, respectively. Unlike piperidine, which reacts with 2-trifluoromethylchromones to give unstable adducts, morpholine readily adds at the activated double bond of 2-trifluoromethyl- and 6-nitro-2-trifluoromethylchromones to form the corresponding 2-morpholinochromanones. This reaction appears to be typical only of 2-trifluoromethylchromones and does not proceed when the CF_3 group is replaced by other polyfluoroalkyl substituents.

In the present work, we studied the reactions of substituted 2-trifluoromethylchromones with morpholine. The condensation reactions of 5-methoxy-, 5-methyl-, and 5-chloro-2-hydroxyacetophenones with ethyl trifluoroacetate in the presence of LiH in THF afforded the corresponding 6-substituted 2-hydroxy-2-trifluoromethylchroman-4-ones (**1a—c**) in 73—87% yields.[3,4] The latter were dehydrated upon refluxing in alcohol[3] or acetic acid in the presence of catalytic amounts of HCl to form 6-methoxy-, 6-methyl-,[3] or 6-chloro-2-trifluoromethylchromones (**2a—c**), respectively. It appeared that these compounds did not react with morpholine in the conditions under study, whereas 6-methoxy-5-nitro-2-trifluoromethylchromone (**3a**), which has been prepared by us previously[1] by nitration of chromone **2a**, readily gave the expected 2-morpholinochromanone **4a** (Scheme 1).

In this connection, we performed nitration of chromones **2b,c** with a nitrating mixture at 40 and 75 °C, respectively, and found that these compounds, like chromone **2a**, were selectively nitrated at position 5 to form nitrochromones **3b,c**, respectively. The latter, in turn, smoothly added morpholine to yield 2-morpholinochromanones **4b,c**, respectively (Scheme 1).

Scheme 1



R = MeO (**a**), Me (**b**), Cl (**c**)

Unlike unstable 2-piperidino-2-trifluoromethylchroman-4-ones,[5] compounds **4a—c** occur as colorless crystals stable upon storage. Their spectral data agree well with the structures of 2-morpholinochromanones **4a—c**. The IR spectra of these compounds have an intense absorption band ν(C=O) at 1715—1720 cm^{-1}. The ^1H NMR spectra have a characteristic AB system of the chromanone CH_2 group with the centers at δ 3.17—3.20 and with J_{AB} = 16.5—16.8 Hz along with signals for the protons of the morpholine and aromatic moieties.

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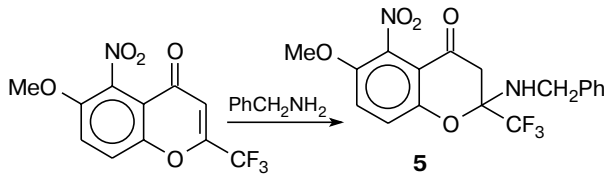
As mentioned above, the reactions of 2-trifluoromethylchromones containing the CH_3 group at position 5 with primary amines are terminated at the stage of nucleophilic addition at the C(2) atom.[2] This fact was attributable to the destabilizing effect of the *ortho*-CH_3 group on the open aminoenone form. The effect consists in the appearance of unfavorable steric interactions between this group and the vinyl hydrogen atom and hinders the formation of a planar conformation, which can be stabilized through intramolecular hydrogen bonds. Taking this fact into account, one would expect that primary amines will also react with 5-nitrochromones **3a—c** without the opening of the pyrone ring. Actually, we found that the presence of the 5-NO_2 group in chromone **3a** is favorable for the addition not only of morpholine, but also of benzylamine at the C(2) atom giving rise to compound **5** (Scheme 2), whereas 6-nitro-2-trifluoromethylchromone added morpholine, but underwent ring opening under the action of benzylamine. To the contrary, 5,7-dimethyl-2-trifluoromethylchromone added benzylamine but did not react with morpholine.

Scheme 2



These data allow the conclusion that a combination of steric and electronic effects in 5-nitro-2-trifluoromethylchromones proves to be most favorable for the synthesis of 2-aminochromanone derivatives. The NO_2 group at position 5 of the chromone system, like any other bulky substituent, hinders the opening of the pyrone ring. At the same time, NO_2 is a strong electron-withdrawing group resulting in an increase in the electrophilicity of the C(2) atom, which makes possible the addition not only of primary amines but also of less reactive secondary amines at this atom.

To confirm the above-mentioned considerations, we studied the reactions of 7-methoxy-8-nitro-2-trifluoromethylchromone (**3d**), which we have prepared previously[1] by nitration of 7-methoxy-2-trifluoromethylchromone (**2d**),[3] with morpholine and benzylamine. It was found that the reactions of chromone **3d** with morpholine and benzylamine afforded 2-morpholinochromanone **4d** and aminoenone **6**, respectively (Scheme 3).

Therefore, the reactions of 2-trifluoromethylchromones with morpholine are not accompanied by the opening of the chromone system, but are sensitive to the nature of the substituents in the benzene ring. The reactions proceed successfully either if the benzene ring of chromone does not contain substituents[2] or if this ring contains at least one nitro group. More reactive primary amines add at the C(2) atom without opening of the pyrone ring only if chromones contain a bulky substituent at position 5; otherwise the corresponding aminoenones containing the 2-hydroxyaryl substituent at the carbonyl group are formed.

Experimental

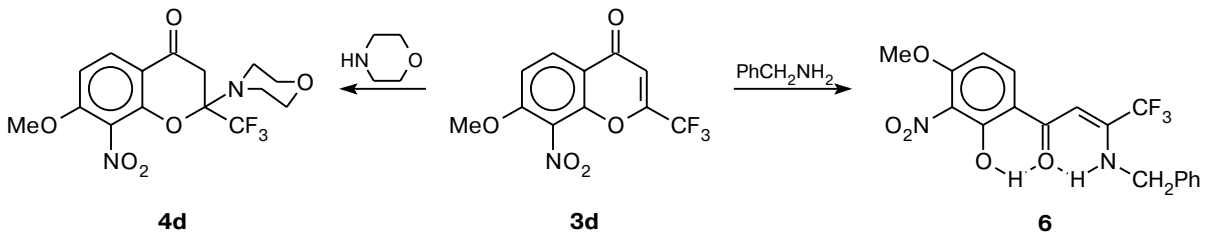
The IR spectra were measured on an IKS-29 instrument in Nujol mulls. The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ with Me_4Si as the internal standard.

Compounds **1b** and **2b,d** were prepared according to a procedure reported previously.[3] Compounds **3a,d** were synthesized according to a known procedure.[1]

Anhydrous THF was prepared by refluxing a mixture of THF (1 L), anthracene (3—4 g), and metallic sodium for 2 days followed by distillation. 2-Hydroxy-5-methoxyacetophenone was prepared according to a known procedure.[6]

2-Hydroxy-6-methoxy-2-trifluoromethylchroman-4-one (1a). Anhydrous THF (15 mL) and finely dispersed LiH (0.68 g, 0.086 mol) were placed in a round-bottom three-neck flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. The reaction mixture was brought to reflux and a solution of 2-hydroxy-5-methoxyacetophenone (4.15 g, 0.025 mol) and CF_3CO_2Et (4.26 g, 0.030 mol) in anhydrous THF (10 mL) was added dropwise with stirring. Then the reaction mixture was refluxed with stirring for 3 h and concentrated to dryness on a water bath under reduced pressure. The residue was treated with an aqueous solution of AcOH (7 mL of AcOH in 50 mL of water). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from hexane. The yield was 4.8 g (73%), m.p. 130—131 °C. Found (%): C, 50.40; H, 3.66. $C_{11}H_9F_3O_4$. Calculated (%): C, 50.39; H, 3.46. IR, ν/cm^{-1}: 3265 (OH), 1675 (C=O), 1615, 1490 (arom.). ^{1}H NMR, δ: 3.03 (s, 2 H, CH_2); 3.80 (s, 3 H, MeO); 3.97 (s, 1 H, OH); 6.96 (d, 1 H, H(8), J_o = 8.8 Hz);

Scheme 3



7.13 (dd, 1 H, H(7), J_o = 8.8 Hz, J_m = 3.0 Hz); 7.32 (d, 1 H, H(5), J_m = 3.0 Hz).

6-Chloro-2-hydroxy-2-trifluoromethylchroman-4-one (1c) was prepared analogously to chromanone **1a** in 87% yield, m.p. 144—145 °C. Found (%): C, 45.18; H, 2.39. $C_{10}H_6ClF_3O_3$. Calculated (%): C, 45.05; H, 2.27. IR, ν/cm^{-1}: 3320 (OH), 1695 (C=O), 1610 (arom.). ^{1}H NMR, δ: 3.06 (s, 2 H, CH_2); 3.81 (s, 1 H, OH); 7.04 (d, 1 H, H(8), J_o = 8.7 Hz); 7.52 (dd, 1 H, H(7), J_o = 8.7 Hz, J_m = 2.7 Hz); 7.87 (d, 1 H, H(5), J_m = 2.7 Hz).

6-Methoxy-2-trifluoromethylchromone (2a). Acetic acid (1.0 mL) and one drop of concentrated HCl were added to chromanone **1a** (1.0 g, 3.8 mmol). The mixture was refluxed for 3 min, cooled, and diluted with water. The crystalline product was filtered off, washed with water, dried, and recrystallized from aqueous methanol. The yield was 0.85 g (91%), m.p. 84 °C. Found (%): C, 53.92; H, 3.04. $C_{11}H_7F_3O_3$. Calculated (%): C, 54.11; H, 2.89. IR, ν/cm^{-1}: 3075 (=CH), 1680 (C=O), 1660 (C=C), 1620 (arom.). ^{1}H NMR, δ: 3.91 (s, 3 H, MeO); 6.70 (s, 1 H, =CH); 7.34 (dd, 1 H, H(7), J_o = 9.1 Hz, J_m = 2.8 Hz); 7.48 (d, 1 H, H(8), J_o = 9.1 Hz); 7.55 (d, 1 H, H(5), J_m = 2.8 Hz).

6-Chloro-2-trifluoromethylchromone (2c) was prepared analogously to chromone **2a** in 97% yield, m.p. 57 °C. Found (%): C, 48.45; H, 1.74. $C_{10}H_4ClF_3O_2$. Calculated (%): C, 48.32; H, 1.62. IR, ν/cm^{-1}: 1680 (C=O), 1665 (C=C), 1650, 1610 (arom.). ^{1}H NMR, δ: 6.74 (s, 1 H, =CH); 7.52 (d, 1 H, H(8), J_o = 8.9 Hz); 7.72 (d, 1 H, H(7), J_o = 8.9 Hz, J_m = 2.5 Hz); 8.16 (d, 1 H, H(5), J_m = 2.5 Hz).

6-Methyl-5-nitro-2-trifluoromethylchromone (3b) was prepared analogously to chromone **3a** described previously[1] by nitration of compound **2b** at 40 °C for 35 min. The yield was 39%, m.p. 164—165 °C (ethanol). Found (%): C, 48.21; H, 2.34; N, 5.10. $C_{11}H_6F_3NO_4$. Calculated (%): C, 48.37; H, 2.21; N, 5.13. IR, ν/cm^{-1}: 1680 (C=O), 1625 (C=C), 1550 (NO_2). ^{1}H NMR, δ: 2.39 (s, 3 H, Me); 6.74 (s, 1 H, =CH); 7.64 (d, 1 H, H(7), J_o = 8.8 Hz); 7.72 (d, 1 H, H(8), J_o = 8.8 Hz).

6-Chloro-5-nitro-2-trifluoromethylchromone (3c) was prepared analogously to chromone **3a** described previously[1] by nitration of compound **2c** at 75 °C for 10 min. The yield was 25%, m.p. 191—192 °C (ethanol). Found (%): C, 41.12; H, 0.97; N, 4.61. $C_{10}H_3ClF_3NO_4$. Calculated (%): C, 40.91; H, 1.03; N, 4.77. IR, ν/cm^{-1}: 1675 (C=O), 1620 (C=C), 1570 (NO_2). ^{1}H NMR, δ: 6.77 (s, 1 H, =CH); 7.70 (d, 1 H, H(8), J_o = 9.2 Hz); 7.89 (d, 1 H, H(7), J_o = 9.2 Hz).

6-Methoxy-2-morpholino-5-nitro-2-trifluoromethylchroman-4-one (4a). A mixture of chromone **3a** (0.1 g, 0.35 mmol) and morpholine (0.2 g, 2.3 mmol) was thoroughly stirred for 20 min and then triturated with water (5 mL). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from a toluene—cyclohexane mixture. The yield was 0.1 g (77%), m.p. 172—173 °C. Found (%): C, 47.90; H, 4.07; N, 7.34. $C_{15}H_{15}F_3N_2O_6$. Calculated (%): C, 47.88; H, 4.02; N, 7.44. IR, ν/cm^{-1}: 1720 (C=O), 1625 (arom.), 1540 (NO_2). ^{1}H NMR, δ: 2.75—3.00 (m, 4 H, 2 CH_2N); 3.17 (AB system, Δδ 0.04, 2 H, CH_2, J_{AB} = 16.5 Hz); 3.31—3.50 (m, 4 H, 2 CH_2O); 3.91 (s, 3 H, MeO); 7.17 (d, 1 H, H(8), J_o = 9.1 Hz); 7.31 (d, 1 H, H(7), J_o = 9.1 Hz).

6-Methyl-2-morpholino-5-nitro-2-trifluoromethylchroman-4-one (4b) was prepared analogously to compound **4a** in 95% yield, m.p. 180—181 °C. Found (%): C, 49.98; H, 4.06; N, 7.77. $C_{15}H_{15}F_3N_2O_5$. Calculated (%): C, 50.01; H, 4.20; N, 7.78. IR, ν/cm^{-1}: 1715 (C=O), 1625, 1585 w (arom.), 1540 (NO_2). ^{1}H NMR, δ: 2.26 (s, 3 H, Me); 2.77—3.00 (m, 4 H, 2 CH_2N); 3.18 (AB system, Δδ 0.06, 2 H, CH_2, J_{AB} = 16.6 Hz); 3.32—3.51 (m, 4 H, 2 CH_2O); 7.11 (d, 1 H, H(8), J_o = 8.6 Hz); 7.49 (d, 1 H, H(7), J_o = 8.6 Hz).

6-Chloro-2-morpholino-5-nitro-2-trifluoromethylchroman-4-one (4c) was prepared analogously to compound **4a** in 85% yield, m.p. 172—173 °C. Found (%): C, 44.32; H, 3.09; N, 7.40. $C_{14}H_{12}ClF_3N_2O_5$. Calculated (%): C, 44.17; H, 3.18; N, 7.36. IR, ν/cm^{-1}: 1715 (C=O), 1610 (arom.), 1540 (NO_2). ^{1}H NMR, δ: 2.77—3.00 (m, 4 H, 2 CH_2N); 3.20 (AB system, Δδ 0.01, 2 H, CH_2, J_{AB} = 16.8 Hz); 3.33—3.51 (m, 4 H, 2 CH_2O); 7.18 (d, 1 H, H(8), J_o = 9.3 Hz); 7.66 (d, 1 H, H(7), J_o = 9.3 Hz).

7-Methoxy-2-morpholino-8-nitro-2-trifluoromethylchroman-4-one (4d) was prepared analogously to compound **4a** in 77% yield, m.p. 171—172 °C. Found (%): C, 47.80; H, 4.08; N, 7.40. $C_{15}H_{15}F_3N_2O_6$. Calculated (%): C, 47.88; H, 4.02; N, 7.44. IR, ν/cm^{-1}: 1700 (C=O), 1620, 1585, 1510 (arom.), 1540 (NO_2). ^{1}H NMR, δ: 2.76—2.89 (m, 2 H, CH_2N); 2.96—3.08 (m, 2 H, CH_2N); 3.16 (AB system, Δδ 0.05, 2 H, CH_2, J_{AB} = 16.9 Hz); 3.35—3.52 (m, 4 H, 2 CH_2O); 4.00 (s, 3 H, MeO); 6.81 (d, 1 H, H(6), J_o = 9.1 Hz); 7.99 (d, 1 H, H(5), J_o = 9.1 Hz).

2-Benzylamino-6-methoxy-5-nitro-2-trifluoromethylchroman-4-one (5). A solution of chromone **3a** (0.1 g, 0.35 mmol) and benzylamine (0.2 g, 1.9 mmol) in ethanol (1 mL) was brought to reflux and then cooled. Water (10 mL) and AcOH (0.5 mL) were added to the reaction mixture. The viscous product was triturated under water until it crystallized. The precipitate that formed was filtered off, dried, and recrystallized from a toluene—cyclohexane mixture. The yield was 0.08 g (58%), m.p. 151—152 °C. Found (%): C, 54.35; H, 3.73; N, 6.99. $C_{18}H_{15}F_3N_2O_5$. Calculated (%): C, 54.55; H, 3.82; N, 7.07. IR, ν/cm^{-1}: 3445 (NH), 1700 (C=O), 1630, 1580 w (arom.), 1540 (NO_2). ^{1}H NMR, δ: 2.39 (br.s, 1 H, NH); 3.04 (AB system, Δδ 0.30, 2 H, CH_2, J_{AB} = 16.7 Hz); 3.85—4.02 (m, 2 H, CH_2N); 3.88 (s, 3 H, MeO); 7.02—7.29 (m, 6 H, H(7), Ph); 7.11 (d, 1 H, H(8), J_o = 9.2 Hz).

3-Benzylamino-4,4,4-trifluoro-1-(2-hydroxy-4-methoxy-3-nitrophenyl)but-2-en-1-one (6) was prepared analogously to compound **5** from chromone **3d** in 73% yield, m.p. 155—156 °C. Found (%): C, 54.75; H, 3.85; N, 7.09. $C_{18}H_{15}F_3N_2O_5$. Calculated (%): C, 54.55; H, 3.82; N, 7.07. IR, ν/cm^{-1}: 3180 (NH), 1620 (C=O), 1575, 1530, 1495 (C=C, NH, arom.). ^{1}H NMR, δ: 3.93 (s, 3 H, MeO); 4.63 (d, 2 H, CH_2, J = 6.2 Hz); 6.13 (s, 1 H, =CH); 6.51 (d, 1 H, H(5), J_o = 9.1 Hz); 7.30—7.45 (m, 5 H, Ph); 7.73 (d, 1 H, H(6), J_o = 9.1 Hz); 10.50 (br.s, 1 H, NH); 13.56 (s, 1 H, OH).

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References

1. V. Ya. Sosnovskikh and B. I. Usachev, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 2109 [*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 2074].
2. V. Ya. Sosnovskikh, V. A. Kutsenko, and D. S. Yachevskii, *Mendeleev Commun.*, 1999, 204.
3. W. B. Whalley, *J. Chem. Soc.*, 1951, 3235.
4. E. Morera and G. Ortar, *Tetrahedron Lett.*, 1981, **22**, 1273.
5. D. S. Kemp and G. Hanson, *J. Org. Chem.*, 1981, **46**, 4971.
6. *Organic Syntheses*, J. Wiley and Sons Inc., New York—London—Sydney, Coll. vol. **4**, 836.

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