2-Polyfluoroalkylchromones
5.* Nitration and chlorination of 2-trifluoromethylchromones

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Electrophilic nitration of 2-trifluoromethylchromone and its 6- and 7-methoxy derivatives affords 6-, 5-, and 8-nitro derivatives, respectively, while 5,7-dimethyl-2-trifluoromethylchromone yields a 6,8-dinitro derivative. Radical chlorination results in 3-chloro derivatives.

Key words: 2-trifluoromethylchromones, electrophilic nitration, radical chlorination.

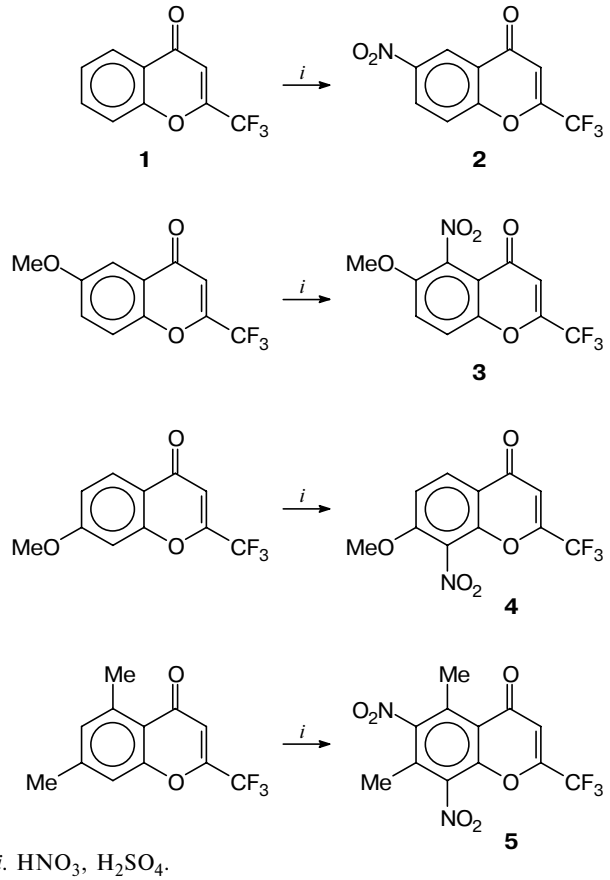
Chromones are an important class of oxygen-containing heterocyclic compounds. Unlike the properties of 2-alkylchromones,[2] numerous representatives of which occur in nature and are well studied, those of 2-polyfluoroalkylchromones have been little studied.

Recently, we have described the reactions of 2-polyfluoroalkylchromones with ammonia, primary amines,[3] ethylenediamine, trimethylenediamine,[4] and diethylenetriamine[5] which revealed significant differences in the reactivities of 2-alkyl- and 2-polyfluoroalkylchromones with respect to N-nucleophiles. In the present work, we report for the first time the behavior of 2-trifluoromethylchromones in the reactions of electrophilic nitration and radical chlorination, which are best studied for their nonfluorinated analogs.

Nitrochromones are accessible intermediates in the synthesis of biologically active aminochromones.[2] It is well known[6] that chromone, 2- and 3-alkyl-, 2-alkoxycarbonyl-, and 2,3-dialkylchromones with non-substituted benzene rings are easily nitrated at position 6 at 0—20 °C; dinitration of the benzene ring is not observed. We found that 2-trifluoromethylchromone (**1**),[7] despite the presence of the electron-withdrawing CF_3 group, is also easily nitrated at ambient temperature to give 6-nitro-2-trifluoromethylchromone (**2**) in 67% yield (Scheme 1). Nitration in 20% oleum with 95% HNO_3 at 110 °C did not result in a dinitro derivative (TLC). The maximum yield of chromone **2** (96%) was attained when the nitration was carried out at 75 °C for 1 h.

Previously, it was shown that the nitration of 6- and 7-methoxychromones with a nitrating mixture at 0 °C gives 5- and 8-nitro derivatives, respectively,[8] while 7-methoxy-2-methylchromone transforms into 7-methoxy-8-nitro-2-methylchromone at 0 °C and into 6,8-dinitro-7-methoxy-2-methylchromone at 30 °C.[9] We found that 6- and 7-methoxy-2-trifluoromethylchromones[10] afford only mononitrated products **3** and **4**, with no dinitro derivatives (TLC) even under more drastic conditions (75 °C). The relatively low yields of chromones **3** and **4** (41 and 34%, respectively) are probably due to the destabilization effect of the electron-donor MeO group on the chromone system, which causes undesirable destruction. It is of note that, under the same condi-

Scheme 1



i. HNO_3, H_2SO_4.

* For Part 4, see Ref. 1.

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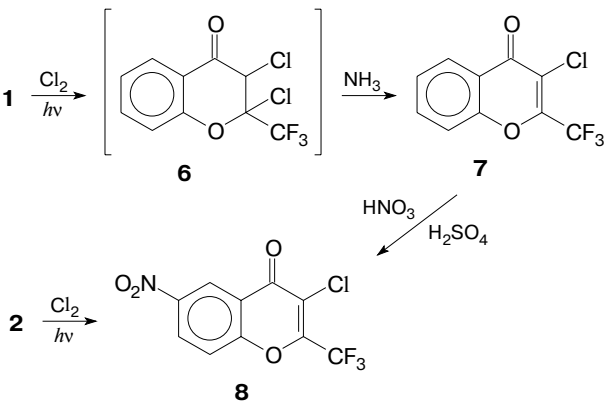
tions, 5,7-dimethyl-2-trifluoromethylchromone[10,11] gives dinitro derivative **5** in virtually quantitative yield.

The structures of chromones **2**—**5** were unambiguously determined by ^{1}H NMR spectroscopy (see Experimental). Thus the ^{1}H NMR spectrum of chromone **2** shows a doublet with J_m = 2.7 Hz at δ 9.06 for the most deshielded HC(5) proton (owing to an anisotropic effect of the carbonyl and nitro groups). The proton at the C(7) atom affected only by the nitro group manifests itself as a doublet of doublets with J_o = 9.1 Hz and J_m = 2.7 Hz at δ 8.60, while the HC(8) proton, as a doublet with J_o = 9.1 Hz at δ 7.75. A singlet for the vinylic proton in chromone **2** appears at δ 6.82, *i.e.*, is shifted downfield by 0.1 ppm compared to that for non-substituted chromone **1** (see Ref. 7).

Halogenation of chromones at the C(3) atom is usually a more difficult problem than halogenation in the benzene ring.[2] Examples of both electrophilic and radical chlorination of the chromone system in position 3 are documented. Treatment of a solution of chromone-3-carbaldehyde and chromone-3-carboxylic acid in AcOH with NaOCl at ~20 °C gave[12] 3-chlorochromone in 86 and 41% yields, respectively. When refluxed in SO_2Cl_2 in the presence of benzoyl peroxide for 10 h, ethyl chromone-2-carboxylate afforded a mixture of three products in nearly equal amounts; one of them is ethyl 3-chlorochromone-2-carboxylate.[13]

The reaction of 2-trifluoromethylchromone (**1**) with chlorine in the light in CCl_4 at 60 °C for 1 h yields an unstable compound, which is likely to be a product of radical addition of Cl_2 to the double bond (**6**) (*cf.* Ref. 13). The latter was treated with ammonium hydroxide at ~20 °C to give 3-chloro-2-trifluoromethylchromone (**7**). Chlorination of chromone **2** for 8 h under similar conditions results in 3-chloro-6-nitro-2-trifluoromethylchromone (**8**), which was alternatively obtained by the nitration of chromone **7** (Scheme 2).

Scheme 2



Hence, unlike the reactions with N-nucleophiles, the reactions of 2-trifluoromethylchromones with electrophilic and radical reagents do not differ from those involving 2-alkyl- and 2-alkoxycarbonylchromones.

Experimental

IR spectra were recorded on an IKS-29 instrument (Nujol mulls). ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ with Me_4Si as the internal standard. The starting 2-trifluoromethylchromones were prepared as described in Refs. 7, 10, and 11.

6-Nitro-2-trifluoromethylchromone (2). A mixture of conc. H_2SO_4 (0.5 mL) and 70% HNO_3 (0.5 mL, 7.8 mmol) was added to a solution of chromone **1** (0.50 g, 2.33 mmol) in 2.0 mL of conc. H_2SO_4. The reaction mixture was heated at 75 °C for 1 h, cooled, and poured with stirring onto crushed ice. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 0.58 g (96%), m.p. 155—156 °C. Found (%): C, 46.50; H, 1.64; N, 5.34. $C_{10}H_4F_3NO_4$. Calculated (%): C, 46.35; H, 1.56; N, 5.41. IR, ν/cm^{-1}: 1675 (C=O); 1625, 1580 (C=C, arom.); 1535 (NO_2). ^{1}H NMR, δ: 6.82 (s, 1 H, =CH); 7.75 (d, 1 H, H(8), J_o = 9.1 Hz); 8.60 (dd, 1 H, H(7), J_o = 9.1 Hz, J_m = 2.7 Hz); 9.06 (d, 1 H, H(5), J_m = 2.7 Hz).

The same nitrating mixture was used for the preparation of compounds **3**—**5** and **8**.

6-Methoxy-5-nitro-2-trifluoromethylchromone (3) was obtained by the nitration of 6-methoxy-2-trifluoromethylchromone at 45 °C for 30 min. Yield 41%, m.p. 191—192 °C (ethanol). Found (%): C, 45.78; H, 2.17; N, 4.83. $C_{11}H_6F_3NO_5$. Calculated (%): C, 45.69; H, 2.09; N, 4.84. IR, ν/cm^{-1}: 1680 (C=O); 1630 (C=C); 1560 (NO_2). ^{1}H NMR, δ: 4.00 (s, 3 H, MeO); 6.69 (s, 1 H, =CH); 7.55 (d, 1 H, H(7), J_o = 9.5 Hz); 7.72 (d, 1 H, H(8), J_o = 9.5 Hz).

7-Methoxy-8-nitro-2-trifluoromethylchromone (4) was obtained by the nitration of 7-methoxy-2-trifluoromethylchromone at 65 °C for 30 min. Yield 34%, m.p. 193—194 °C (ethanol). Found (%): C, 45.69; H, 1.83; N, 4.91. $C_{11}H_6F_3NO_5$. Calculated (%): C, 45.69; H, 2.09; N, 4.84. IR, ν/cm^{-1}: 1680 (C=O); 1620 (C=C); 1550 (NO_2). ^{1}H NMR, δ: 4.09 (s, 3 H, MeO); 6.73 (s, 1 H, =CH); 7.22 (d, 1 H, H(6), J_o = 9.2 Hz); 8.29 (d, 1 H, H(5), J_o = 9.2 Hz).

5,7-Dimethyl-6,8-dinitro-2-trifluoromethylchromone (5) was obtained by the nitration of 5,7-dimethyl-2-trifluoromethylchromone as described for compound **2**. Yield 95%, m.p. 171—172 °C (ethanol). Found (%): C, 43.59; H, 2.27; N, 8.55. $C_{12}H_7F_3N_2O_6$. Calculated (%): C, 43.39; H, 2.12; N, 8.43. IR, ν/cm^{-1}: 1690 (C=O); 1620 (C=C); 1550 (NO_2). ^{1}H NMR, δ: 2.39 (s, 3 H, Me(7)); 2.79 (s, 3 H, Me(5)); 6.76 (s, 1 H, =CH).

3-Chloro-2-trifluoromethylchromone (7). A flow of Cl_2 was passed at ~60 °C through a solution of chromone **1** (4.0 g, 18.7 mmol) in 50 mL of CCl_4 with irradiation with a 60-W lamp. After 1 h, the solution was concentrated, and the liquid residue was dissolved in 20 mL of ethanol and mixed with 200 mL of 1% aqueous solution of NH_3. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 2.2 g (47%), m.p. 137 °C. Found (%): C, 48.58; H, 1.72. $C_{10}H_4ClF_3O_2$. Calculated (%): C, 48.32; H, 1.62. IR, ν/cm^{-1}: 1665 (C=O); 1630, 1615, 1580 (C=C, arom.). ^{1}H NMR, δ: 7.53 (td, 1 H, H(6), J_o = 7.9 Hz, J_m = 1.4 Hz); 7.58 (dd, 1 H, H(8), J_o = 7.9 Hz, J_m = 1.4 Hz); 7.81 (td, 1 H, H(7), J_o = 7.9 Hz, J_m = 1.8 Hz); 8.27 (dd, 1 H, H(5), J_o = 7.9 Hz, J_m = 1.8 Hz).

3-Chloro-6-nitro-2-trifluoromethylchromone (8). *A.* Chromone **7** was nitrated at 45 °C for 40 min. The yield of compound **8** was 37%, m.p. 142—143 °C (ethanol). Found (%): C, 40.98; H, 1.06; N, 4.68. $C_{10}H_3ClF_3NO_4$. Calculated (%): C, 40.91; H, 1.03; N, 4.77. IR, ν/cm^{-1}: 1680 (C=O); 1630,

1580 (C=C, arom.); 1540 (NO_2). ^{1}H NMR, δ: 7.78 (d, 1 H, H(8), J_o = 9.1 Hz); 8.64 (dd, 1 H, H(7), J_o = 9.1 Hz, J_m = 2.8 Hz); 9.12 (d, 1 H, H(5), J_m = 2.8 Hz).

B. A solution of chromone **2** (0.43 g, 1.7 mmol) in 5 mL of CCl_4 was saturated with Cl_2 at ~20 °C. Then, the reaction vessel was hermetically sealed and irradiated with the light of a 60-W lamp at 60 °C for 8 h. The solution was concentrated, and the residue was dissolved in 15 mL of EtOH and refluxed for 5 min. After cooling, the precipitate that formed was filtered off, washed with ethanol, dried, and recrystallized from ethanol. The yield of compound **8** was 0.15 g (31%), m.p. 142—143 °C (ethanol).

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