Stereoselective synthesis of cis-2-(polyfluoroalkyl)chroman-4-ols and trans-4-acylamino-2-(polyfluoroalkyl)chromans

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Dedicated to Professor Alexander F. Pozharskii on his 70th birthday

Abstract
trans-4-Acylamino-2-(polyfluoroalkyl)chromans were synthesized using a Ritter reaction between cis-2-(polyfluoroalkyl)chroman-4-ols and various nitriles.

Keywords: 2-(Polyfluoroalkyl)chromans, reduction, oxidation, dehydration, Ritter reaction

Introduction

The biological activity of many of the naturally occurring compounds which incorporate a chroman ring system has resulted in several applications of chromans of various levels of saturation and oxidation in synthesis. The powerful electron-withdrawing ability of polyfluoroalkyl substituents, especially as potentially useful pesticides and drug candidates in the field of potassium channel openers. On the other hand, the polyfluoroalkyl groups are highly important substituents in the field of organic chemistry. The introduction of these groups into organic molecules can bring about some remarkable changes in the physical properties, chemical reactivity, and biological activity of the derived fluorinated compounds. In particular, due to the powerful electron-withdrawing ability of polyfluoroalkyl substituents 2-RF-chromones, 3-RFCO-chromones and 3-nitro-2-RF-chromenes have attracted our attention as highly reactive compounds, which can serve as the starting substances in the synthesis of a whole series of heterocycles with interesting properties.

However, to the best of our knowledge, very little is known about the synthesis and properties of partially fluorinated chroman derivatives. We have recently shown that the reaction of 2-RF-chromones with CF3SiMe3 proceeded as a 1,4-addition and provided an access to 2,2-bis(polyfluoroalkyl)chroman-4-ones and their derivatives. Earlier 2,2-bis(trifluoromethyl)-6-nitrochroman-4-one, which is a key structural element of the fluorinated analogues of an
important class of potassium channel openers, benzopyran-4-amide derivatives, was prepared by treating 2-fluoro-5-nitroacetophenone with hexafluoroacetone trihydrate. Also, 2,2,6-tris(trifluoromethyl)-2H-chromene, a key intermediate for the preparation of the fluorinated analogues of cromakalim, a highly potent antihypertensive drug, and 6,7-dimethoxy-2-methyl-2-(trifluoromethyl)-2H-chromene, a trifluoromethyl analogue of the natural insect antijuvenile hormone precocene II, were described. There has been only one paper on the synthesis of chroman-4-one with a trifluoromethyl group at the 2-position. In view of the unique biological properties displayed by chromans on one hand and by many CF₃-containing heterocycles on the other hand, it was of interest to obtain novel fluorine-containing chroman derivatives from 2-RF-chromones.

Results and Discussion

Chromones and chromanones can be reduced with different reagents but also undergo ring opening, hydrogenolysis and other side reactions which lower the yields of chroman-4-ols. Attempted reduction of chromones using hydride donors such as NaBH₄ or hydrogenation using noble metal catalysts has been reported to lead to complex mixtures from over-reduction. We found that 2-RF-chromones 1a–c smoothly reacted with sodium borohydride in methanol to afford cis-2-(polyfluoroalkyl)chroman-4-ols 2a–c in good yields (65–83%). The corresponding chromanone 3, intermediate of the reaction, is in situ reduced to chromanol 2 because the reduction of 3 is faster than that of 1 due to double bond conjugation in the latter. Reduction of 1 to 2 exhibits high stereoselectivity and the cis-structure of chromanols 2 is evident from the coupling constants. In the ¹H NMR spectra, the axial H-3 proton manifests itself at δ 2.03–2.10 as a doublet of triplets or a doublet of doublets of triplets with the geminal constant ²J = 12.8–13.4 Hz and the vicinal constants ³JH₃,H₂ = 9.9–12.1 Hz and ³JH₃,H₄ = 8.9–10.8 Hz, which indicate the axial arrangement of the H-2 and H-4 atoms. Therefore, chromanols 2 in CDCl₃ are in the half-chair conformation with cis-diequatorial arrangement of the substituents. Initial attack at the carbonyl group of 3 by sodium borohydride might be expected to occur from the side opposite to the R² group leading to the cis-2. Note that reduction of flavones and chromones with NaBH₄/NiCl₂ in methanol also yields cis-flavan-4-ols and cis-chroman-4-ols.

Selective reduction of the double bond in chromone 1a can be achieved by using of diisobutylaluminium hydride (1 equiv.) in THF–toluene solution at –78 °C. In this case, chroman-4-one 3a was obtained as a sole product in 56% yield. This is not surprising since reduction of isoﬂavones to isoﬂavan-4-ones under the same reaction conditions has been described previously. In addition, homoisoﬂavones has been converted into homoisoﬂavanones by subjecting to catalytic hydrogenation. The oxidation of chromanols 2a,b to chromanones 3a,b in 74–79% yields was performed with chromic acid (from sodium dichromate and sulfuric acid) in ethyl ether. Dehydration of chromanol 2a was effected by a trace of p-toluene sulfonic acid.
acid in boiling benzene for 5 h and subsequent distillation of the reaction mixture gave 2-(trifluoromethyl)-2H-chromene 4 in 70% yield, which was sensitive to oxygen of air.

Surprisingly, as in the case of 2-(trifluoromethyl)chroman-4-one 3a, whose isolation and characterization had not been reported prior to our work,12 none of these simple compounds was recorded in the literature. We regarded these compounds as desirable targets because of their relationship to naturally occurring benzopyran derivatives and usefulness as R\textsuperscript{F}-containing building blocks for the preparation of more complex partially fluorinated heterocycles.

![Scheme 1](image-url)

**Scheme 1.** Synthesis of 2-R\textsuperscript{F}-chroman-4-ols 2a–c, 2-R\textsuperscript{F}-chroman-4-ones 3a,b and 2-CF\textsubscript{3}-2H-chromene 4.

Application of the Ritter reaction conditions to 2-(polyfluoroalkyl)chroman-4-ols 2a–c gave the new compounds 4-acylamino-2-(polyfluoroalkyl)chromans 5a–f. This reaction proceeded smoothly for all substrates and analytically pure products can be isolated by simple filtration in excellent yields (ca. 95%). The Ritter reaction was stereoselective and chromans 5a–f were obtained as mixtures of trans- and cis-isomers (trans/cis = 84/16 – 94/6) without the formation of any side products. The determination of the isomers ratio can easily be performed by \textsuperscript{1}H and \textsuperscript{19}F NMR spectroscopic analysis. The hydrolysis of 5a (trans/cis = 92/8) as a representative example with concentrated hydrochloric acid led to the pure trans-4-amino-2-(trifluoromethyl)chroman hydrochloride 6, which was converted into trans-4-benzamido-2-(trifluoromethyl)chroman 5f under the action of sodium hydroxide and benzoyl chloride (Scheme 2).

The configurations of 5 were assigned from their \textsuperscript{1}H NMR spectra, in which two sets of signals showed the presence of two diastereomers. In the major isomer, \(J_{H2a,H3a} = 10.8–12.5\) Hz and \(J_{H4e,H3a} \approx J_{H4e,H3e} \approx 3.7\) Hz; in the minor isomer, axial H-3 proton appeared as a quartet with \(J_{H3a,H3e} \approx J_{H3a,H4a} \approx J_{H3a,H2a} = 12.0–12.2\) Hz. The size of the coupling constants suggests a 2-
equatorial-4-axial arrangement for the 2 and 4 substituents in the major (*trans*) isomer and a diequatorial arrangement in the minor (*cis*) isomer. Thus, in this series of chromans, *cis*-isomer is destabilized by repulsion between the 4-equatorial acylamino group and the peri-hydrogen. In the $^{19}$F NMR spectra of 5a,d–f, the CF$_3$ group of *trans* - and *cis*-isomers manifests itself as a doublet at 85.2–85.6 and 84.3–84.7 ppm with $^3$J$_{F,H}$ = 6.6–6.7 and 6.4–6.5 Hz, respectively.

![Scheme 2](image)

<table>
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<th>Ratio of <em>trans/cis</em> 5</th>
<th>Yield (%)</th>
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<td>b</td>
<td>CF$_2$H</td>
<td>Me</td>
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<tr>
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Scheme 2. Synthesis of 4-acylamino-2-(polyfluoroalkyl)chromans 5a–f.

This reaction is a simple and effective method for the preparation of protected 4-amino-2-(polyfluoroalkyl)chromans 5. It should be noted that 4-amino-2,2-dimethyl-6-halogenochromans (non-fluorinated analogues of 5) are the key intermediates of the synthetic process, giving, in the last step, access to compounds structurally related to the potassium channel opener cromakalim. These 2,2-dimethylchromans are much more selective for insulin-secreting cells over vascular tissue than the reference molecule, cromakalim.
Conclusions

Reduction of 2-(polyfluoroalkyl)chromones with sodium borohydride and diisobutylaluminium hydride provides a simple and convenient preparative procedure from readily available starting materials to cis-2-(polyfluoroalkyl)chroman-4-ols and 2-(polyfluoroalkyl)chroman-4-ones, which may be considered as new precursors in the synthesis of other highly functionalized biologically and medicinally important products. Ritter reaction between cis-2-(polyfluoroalkyl)chroman-4-ols and nitriles represents a stereoselective approach to the synthesis of a variety of trans-4-acylamino-2-(polyfluoroalkyl)chromans and trans-4-amino-2-(polyfluoroalkyl)chromans.

Experimental Section

General Procedures. $^1$H (400 MHz) and $^{19}$F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in CDCl$_3$ or DMSO-$d_6$ with TMS and C$_6$F$_6$ as internal standards, respectively. IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled as per standard procedures. The starting chromones 1a–c were prepared according to described procedure.

General procedure for the synthesis of cis-2-(polyfluoroalkyl)chroman-4-ols (2a–c)

Sodium borohydride (285 mg, 7.5 mmol) was added to a cooled (with ice water) solution of chromone 1 (5.0 mmol) in 5 ml of methanol. The mixture was stirred at 5–10 °C for 0.5 h and diluted with water (10 ml). The colorless crystals that formed were filtered, washed with water, dried, and recrystallized from hexane or heptane–ethyl ether (5:1).

cis-2-(Trifluoromethyl)chroman-4-ol (2a). Yield 83%, mp 127–128 °C. IR (KBr) 3462, 1613, 1581, 1488, 1462 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.93 (d, 1H, OH, $J$ = 8.4 Hz), 2.03 (ddd, 1H, H-3a, $J_{H3a,H3e}$ = 12.9 Hz, $J_{H3a,H2a}$ = 12.1 Hz, $J_{H3a,H4a}$ = 10.8 Hz), 2.53 (ddd, 1H, H-3e, $J_{H3e,H3a}$ = 12.9 Hz, $J_{H3e,H4a}$ = 6.2 Hz, $J_{H3e,H2a}$ = 2.3 Hz), 4.50 (dqd, 1H, H-2a, $J_{H2a,H3a}$ = 12.1 Hz, $J_{H2a,CF3}$ = 6.0 Hz, $J_{H2a,H3e}$ = 2.3 Hz), 5.01 (m, 1H, H-4a), 6.91 (dd, 1H, H-8, $J$ = 8.2, 1.1 Hz), 7.03 (td, 1H, H-6, $J$ = 7.5, 1.1 Hz), 7.22 (ddd, 1H, H-7, $J$ = 8.2, 7.3, 1.6 Hz, $^6J_{H7,H4a}$ = 0.7 Hz), 7.49 (dt, 1H, H-5, $J$ = 7.7, 1.2 Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) δ 82.82 (d, CF$_3$, $J$ = 6.0 Hz). Anal. Calcd for C$_{10}$H$_9$F$_3$O$_2$: C, 55.05; H, 4.16. Found: C, 54.96; H, 4.18.

cis-2-(Difluoromethyl)chroman-4-ol (2b). Yield 70%, mp 79–80 °C. IR (KBr) 3445, 1613, 1581, 1487, 1461 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.70 (bs, 1H, OH), 2.05 (dt, 1H, H-3a, $J_{H3a,H3e}$ = 13.4 Hz, $J_{H3a,H2a}$ = $J_{H3a,H4a}$ = 9.5 Hz), 2.43 (ddd, 1H, H-3e, $J_{H3e,H3a}$ = 13.4 Hz, $J_{H3e,H4a}$ = 5.7 Hz, $J_{H3e,H2a}$ = 3.0 Hz), 4.37 (qdd, 1H, H-2a, $J_{H2a,H3a}$ = $J_{H2a,CF2}$ = 9.9 Hz, $J_{H2a,CHF2}$ = 4.5 Hz, $J_{H2a,H3e}$ = 3.0 Hz), 4.98 (dd, 1H, H-4a, $J_{H4a,H3a}$ = 8.9 Hz, $J_{H4a,H3e}$ = 5.7 Hz), 5.99 (ddd, 1H, CHF$_2$, H
cis-2-(Perfluoroethyl)chroman-4-ol (2c). Yield 65%, mp 120–121 °C. IR (KBr) 3344, 3253, 1614, 1588, 1489, 1460 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.90 (d, 1H, OH, \(J = 8.5\) Hz), 2.10 (td, 1H, H-3a, \(J_{H3a,H3c} = J_{H3a,H2a} = 12.6\) Hz, \(J_{H3a,H4a} = 10.8\) Hz), 2.55 (ddt, 1H, H-3e, \(J_{H3e,H3a} = 12.8\) Hz, \(J_{H3e,H4a} = 6.2\) Hz, \(J_{H3e,H2a} = J_{H3c,CFF} = 2.0\) Hz), 4.62 (dddd, 1H, H-2a, \(J_{H2a,CFF} = 17.0\) Hz, \(J_{H2a,H3a} = 12.0\) Hz, \(J_{H2a,CFF} = 5.0\) Hz, \(J_{H2a,H3e} = 2.0\) Hz), 5.04 (dt, 1H, H-4a, \(J_{H4a,H3a} = 10.0\) Hz, \(J_{H4a,H3e} = J_{H4a,OH} = 7.5\) Hz), 6.88 (dd, 1H, H-8, \(J = 8.2, 1.0\) Hz), 7.03 (td, 1H, H-6, \(J = 7.5, 1.0\) Hz), 7.22 (ddd, 1H, H-7, \(J = 8.3, 7.3, 1.3\) Hz), 7.49 (dt, 1H, H-5, \(J = 7.7, 1.0\) Hz). Anal. Caled for C\(_{10}\)H\(_{10}\)F\(_2\)O\(_2\): C, 58.50; H, 3.88. Found: C, 58.42; H, 3.83.

2-(Trifluoromethyl)chroman-4-one (3a) from chromanol 2a. Ethyl ether (350 ml) and chromanol 2a (35.6 g, 0.163 mol) were placed in a round-bottom flask fitted with a stirrer, dropping funnel, and a condenser. The chromic acid solution, prepared from sodium dichromate dihydrate (24.4 g, 0.082 mol) and 20.0 ml of concentrated sulfuric acid diluted to 120 ml, was added drop-wise to the stirred solution over 1 h, maintaining the temperature at 5–10 °C. The reaction mixture was stirred for 4 h at room temperature and allowed to stand overnight. Then the upper ether layer was separated, and the aqueous phase extracted with ether (25 ml). The combined extracts were washed with a 5% solution of sodium carbonate (2 x 50 ml), then water (50 ml), dried over anhydrous calcium chloride, and concentrated to afford the chromanone 3a as colorless crystals, 27.8 g (yield 79%), crystallized from hexane, mp 85–86 °C (ref.\(^{12}\); mp 84–85 °C). IR (KBr) 1704, 1614, 1604, 1578, 1475, 1464 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.92 (dd, 1H, CHH, \(J = 16.9, 3.9\) Hz), 3.01 (dd, 1H, CHH, \(J = 16.9, 12.3\) Hz), 4.82 (qd, 1H, CH, \(J = 12.3, 5.8, 3.9\) Hz), 7.09 (dd, 1H, H-8, \(J = 8.4, 1.0\) Hz), 7.12 (ddd, 1H, H-6, \(J = 7.9, 7.3, 1.0\) Hz), 7.56 (ddd, 1H, H-7, \(J = 8.4, 7.3, 1.8\) Hz), 7.91 (dd, 1H, H-5, \(J = 7.9, 1.8\) Hz); \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) 83.83 (d, CF\(_3\), \(J = 5.8\) Hz). Anal. Caled for C\(_{13}\)H\(_{12}\)F\(_2\): C, 55.56; H, 3.26. Found: C, 55.57; H, 3.12.

2-(Trifluoromethyl)chroman-4-one (3a) from chromone 1a. To a solution of the chromone 1a (1.5 g, 7.0 mmol) in dry tetrahydrofuran (30 ml), a solution of DIBAL in toluene (7.5 mmol) was added at –78 °C under a nitrogen atmosphere. After 3 h, the mixture was quenched with water (5 ml) and allowed to warm to room temperature. After the addition of KOH (3 g in 5 ml of water) and ether (30 ml), the organic phase was separated, and the aqueous phase extracted with ether (10 ml). The combined extracts were washed with saturated sodium chloride, dried, and evaporated to give chromanone 3a as colorless crystals, 850 mg (yield 56%), mp 85–86 °C. 2-(Difluoromethyl)chroman-4-one (3b). This compound was prepared from chromanol 2b analogously to 3a; yield 74% (5.9 g from 8.0 g chromanol 2b), colorless crystals, mp 57–58 °C (heptane–ethyl ether). IR (KBr) 1698, 1606, 1577, 1474, 1463 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.83 (dd, 1H, CHH, \(J = 16.9, 3.6\) Hz), 2.94 (dd, 1H, CHH, \(J = 16.9, 12.7\) Hz), 4.82 (t, d, 1H, H-4, \(J = 16.9, 12.7\) Hz), 7.13 (d, 1H, H-6, \(J = 8.0, 1.0\) Hz), 7.29 (d, 1H, H-7, \(J = 8.0, 1.0\) Hz), 7.52 (dd, 1H, H-5, \(J = 8.0, 1.0\) Hz).
1H, CH, J = 12.7, 7.8, 3.5 Hz), 6.04 (dd, 1H, CHF, 2J_H,F = 55.6, 54.2 Hz, J = 3.3 Hz), 7.04 (dd, 1H, H-8, J = 8.4, 1.1 Hz), 7.08 (ddd, 1H, H-6, J = 7.9, 7.3, 1.1 Hz), 7.53 (ddd, 1H, H-7, J = 8.4, 7.3, 1.8 Hz), 7.90 (dd, 1H, H-5, J = 7.9, 1.8 Hz). 19F NMR (376 MHz, CDCl3) δ 29.82 (ddd, CFF, 2J_F,F = 294.9 Hz, 2J_F,H = 55.6 Hz, 3J_F,H = 12.7 Hz), 33.26 (ddd, CFF, 2J_F,F = 294.9 Hz, 2J_F,H = 54.2 Hz, 3J_F,H = 7.8 Hz). Anal. Calcd for C10H8F2O2: C, 60.61; H, 4.07. Found: C, 60.60; H, 3.99.

2-(Trifluoromethyl)-2H-chromene (4). A solution of chromanol 2a (5.5 g, 0.025 mol) in benzene (50 ml), along with a catalytic amount of p-toluene sulfonic acid, was refluxed for 5 h with a Dean-Stark trap under an atmosphere of nitrogen. After cooling, the reaction mixture was washed with 40% solution of KOH and dried over KOH and the benzene was removed under vacuum. Distillation afforded 3.5 g (yield 70%) of chromene 4 as a colorless oil, bp 80–81 °C at 15 mm. IR (neat) 1650, 1608, 1488, 1459 cm−1; 1H NMR (400 MHz, DMSO-d6) δ 5.23 (qdd, 1H, H-2, 3J_H,F = 6.6 Hz, J = 3.8, 1.8 Hz), 5.65 (dd, 1H, H-3, J = 10.0, 3.8 Hz), 6.66 (dd, 1H, H-4, J = 10.0, 1.2 Hz), 6.86 (d, 1H, H-8, J = 8.1 Hz), 6.91 (td, 1H, H-6, J = 7.4, 1.1 Hz), 7.01 (dd, 1H, H-5, J = 7.5, 1.7 Hz), 7.16 (td, 1H, H-7, J = 7.6, 1.7 Hz); 19F NMR (376 MHz, CDCl3) δ 82.04 (d, CF3, J = 6.6 Hz). Anal. Calcd for C10H7F3O: C, 60.01; H, 4.07. Found: C, 59.75; H, 3.32.

**General procedure for the synthesis of compounds 5a–c**

A solution of chromanol 2 (1.8 mmol) in 5 ml of acetonitrile, containing 0.3 ml of 98% sulfuric acid, was allowed to stand for 1 day at room temperature. Then the reaction mixture was poured into cold water (40 ml) and the white precipitate collected by filtration, washed with water and dried.

4-Acetamido-2-(trifluoromethyl)chroman (5a). Yield 95%, mp 181–182 °C. IR (KBr) 3308, 1648, 1587, 1527, 1489, 1459 cm−1; 1H NMR (400 MHz, DMSO-d6) trans-isomer (92%) δ 1.86 (s, 3H, Me), 2.07–2.12 (m, 2H, CH2), 4.80 (dqd, 1H, H-2, J = 12.5, 6.6, 1.5 Hz), 5.07 (dt, 1H, H-4, J = 7.9, 3.8 Hz), 6.96 (dd, 1H, H-8, J = 8.4, 1.2 Hz), 7.00 (td, 1H, H-6, J = 7.6, 1.2 Hz), 7.23–7.28 (m, 2H, H-5, H-7), 8.43 (d, 1H, NH, J = 7.9 Hz), cis-isomer (8%) δ 1.83 (q, 1H, CHF, J = 12.0 Hz), 1.93 (s, 3H, Me), 2.28 (ddd, 1H, CHH, J = 12.5, 6.0, 2.0 Hz), 5.10–5.16 (m, 1H, H-2), 5.27–5.34 (m, 1H, H-4), 6.89 (dd, 1H, H-8, J = 8.2, 1.2 Hz), 6.99 (m, 1H, H-6), 7.16 (dt, 1H, H-5, J = 7.7, 1.2), 7.20 (ddddd, 1H, H-7, J = 8.2, 7.3, 1.7, 0.9), 8.32 (d, 1H, NH, J = 8.5 Hz); 19F NMR (376 MHz, DMSO-d6) trans-isomer (92%) δ 85.51 (d, CF3, 3J_H,F = 6.6 Hz), cis-isomer (8%) δ 84.61 (d, CF3, 3J_H,F = 6.5 Hz). Anal. Calcd for C12H12F3NO2: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.44; H, 4.51; N, 5.19.

4-Acetamido-2-(trifluoromethyl)chroman (5b). Yield 72%, mp 164–165 °C. IR (KBr) 3317, 1639, 1587, 1533, 1489, 1459 cm−1; 1H NMR (400 MHz, DMSO-d6) trans-isomer (90%) δ 1.84 (s, 3H, Me), 1.90–2.01 (m, 2H, CH2), 4.41 (qt, 1H, H-2, J = 10.8, 3.5 Hz), 5.01 (dt, 1H, H-4, J = 7.7, 3.6 Hz), 6.32 (td, 1H, CF2H, 2J_H,F = 54.5 Hz, 3J_H,H = 3.3 Hz), 6.90 (dd, 1H, H-8, J = 8.2, 1.0 Hz), 6.95 (td, 1H, H-6, J = 7.5, 1.1 Hz), 7.20–7.25 (m, 2H, H-5, H-7), 8.44 (d, 1H, NH, J = 7.7 Hz), cis-isomer (10%) δ 1.76 (q, 1H, CHH, J = 12.0 Hz), 1.93 (s, 3H, Me), 2.16 (ddd, 1H, CHH, J = 12.7, 5.8, 1.8 Hz), 4.57–4.68 (m, 1H, H-2), 5.19–5.27 (m, 1H, H-4), 6.26 (td, 1H, CF2H, 2J_H,F
= 54.5 Hz, $^2J_{H,H} = 3.2$ Hz), 6.84 (dd, 1H, H-8, $J = 8.2, 1.1$ Hz), 6.94 (td, 1H, H-6, $J = 7.6, 1.1$ Hz), 7.12–7.20 (m, 2H, H-5, H-7), 8.29 (d, 1H, NH, $J = 8.5$ Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) trans-isomer (90%) $\delta$ 32.56 (dd, CF$_2$H, $^2J_{F,H} = 54.5$ Hz, $^1J_{F,H} = 11.4$ Hz), cis-isomer (10%) $\delta$ 31.72 (dd, CF$_2$H, $^2J_{F,H} = 54.5$ Hz, $^3J_{F,H} = 11.4$ Hz). Anal. Calcd for C$_{12}$H$_{13}$F$_2$NO$_2$: C, 59.75; H, 5.43; N, 5.81. Found: C, 59.88; H, 5.66; N, 5.80. 

4-Acetamido-2-(perfluoroethyl)chroman (5c). Yield 95%, mp 129–130 °C. IR (KBr) 3310, 1650, 1586, 1459, 1485 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) trans-isomer (86%) $\delta$ 1.85 (s, 3H, Me), 2.05–2.22 (m, 2H, CH$_2$), 4.87–4.97 (m, 1H, H-2), 5.12 (ddd, 1H, H-4, $J = 7.7, 4.0, 2.7$ Hz), 6.90 (dd, 1H, H-8, $J = 8.3, 1.1$ Hz), 7.01 (td, 1H, H-6, $J = 7.5, 1.1$ Hz), 7.23–7.28 (m, 2H, H-5, H-7), 8.48 (d, 1H, NH, $J = 7.9$ Hz), cis-isomer (14%) $\delta$ 1.90 (q, 1H, CHH, $J = 12.0$ Hz), 1.94 (s, 3H, Me), 2.25–2.31 (m, 1H, CHH), 5.23–5.39 (m, 2H, H-2, H-4), 6.84 (dd, 1H, H-8, $J = 8.2, 1.0$ Hz), 6.99 (td, 1H, H-6, $J = 7.6, 1.0$ Hz), 7.15–7.22 (m, 2H, H-5, H-7), 8.33 (d, 1H, NH, $J = 8.6$ Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) trans-isomer (86%) $\delta$ 33.04 (dd, 1F, CFF, $^2J_{F,F} = 276.6$ Hz, $^3J_{F,H} = 18.2$ Hz), 39.40 (dd, 1F, CFF, $^2J_{F,F} = 276.6$ Hz, $^3J_{F,H} = 5.1$ Hz), 81.56 (s, 3F, CF$_3$), cis-isomer (14%) $\delta$ 32.81 (dd, 1F, CFF, $^2J_{F,F} = 276.6$ Hz, $^3J_{F,H} = 17.0$ Hz), 39.07 (dd, 1F, CFF, $^2J_{F,F} = 276.6$ Hz, $^3J_{F,H} = 5.1$ Hz), 81.73 (s, 3F, CF$_3$). Anal. Calcd for C$_{13}$H$_{12}$F$_2$NO$_2$: C, 50.49; H, 3.91; N, 4.53. Found: C, 50.59; H, 3.99; N, 4.40. 

4-Carbethoxyacetamido-2-(trifluoromethyl)chroman (5d). This compound was prepared from chromanol 2a and ethyl cyanoacetate analogously to 5a–c. Yield 94%, mp 138–139 °C. IR (KBr) 3318, 1736, 1644, 1589, 1524, 1491, 1463 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) trans-isomer (91%) $\delta$ 1.18 (t, 3H, Me, $J = 7.1$ Hz), 2.08–2.18 (m, 2H, 3-CH$_2$), 3.24 (AB-system, 2H, CH$_2$, $J = 15.2$ Hz), 4.08 (q, 2H, OCH$_2$, $J = 7.1$ Hz), 4.74–4.83 (m, 1H, H-2), 5.06 (dt, 1H, H-4, $J = 7.6, 3.8$ Hz), 6.97 (d, 1H, H-8, $J = 8.2$ Hz), 7.02 (td, 1H, H-6, $J = 7.5, 1.1$ Hz), 7.25–7.30 (m, 2H, H-5, H-7), 8.71 (d, 1H, NH, $J = 7.6$ Hz), cis-isomer (9%) $\delta$ 1.22 (t, 3H, Me, $J = 7.1$ Hz), 1.85 (q, 1H, 3-CHH, $J = 12.2$ Hz), 2.27–2.34 (m, 1H, 3-CHH), 3.33 (AB-system, 2H, CH$_2$, $J = 15.2$ Hz), 4.13 (q, 2H, OCH$_2$, $J = 7.1$ Hz), 5.10–5.20 (m, 1H, H-2), 5.29–5.37 (m, 1H, H-4), 6.90 (dd, 1H, H-8, $J = 8.2, 1.0$ Hz), 6.98 (m, 1H, H-6), 7.19–7.26 (m, 2H, H-5, H-7), 8.62 (d, 1H, NH, $J = 9.0$ Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) trans-isomer (91%) $\delta$ 85.18 (d, CF$_3$, $^3J_{H,F} = 6.6$ Hz), cis-isomer (9%) $\delta$ 84.29 (d, CF$_3$, $^3J_{H,F} = 6.4$ Hz). Anal. Calcd for C$_{15}$H$_{14}$F$_3$NO$_4$: C, 54.38; H, 4.87; N, 4.23. Found: C, 54.33; H, 4.54; N, 4.12. 

4-Acrylamido-2-(trifluoromethyl)chroman (5e). This compound was prepared from chromanol 2a and acrylonitrile analogously to 5a–c. Yield 92%, mp 180–181 °C. IR (KBr) 3298, 1654, 1631, 1587, 1523, 1488, 1458 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) trans-isomer (94%) $\delta$ 2.12–2.21 (m, 2H, CH$_2$), 4.77–4.86 (m, 1H, H-2), 5.17 (dt, 1H, H-4, $J = 7.7, 3.6$ Hz), 5.66 (dd, 1H, $=CH, J = 8.0, 4.3$ Hz), 6.15–6.25 (m, 2H, $=CH_2$), 6.98 (dd, 1H, H-8, $J = 8.3, 1.2$ Hz), 7.01 (td, 1H, H-6, $J = 7.5, 1.2$ Hz), 7.25–7.30 (m, 2H, H-5, H-7), 8.68 (d, 1H, NH, $J = 7.7$ Hz), cis-isomer (6%) $\delta$ 1.89 (q, 1H, CHH, $J = 12.2$ Hz), 2.31–2.37 (m, 1H, CHH), 5.14–5.20 (m, 1H, H-2), 5.37–5.45 (m, 1H, H-4), 5.70 (dd, 1H, $=CH, J = 9.8, 2.8$ Hz), 6.22–6.32 (m, 2H, $=CH_2$), 6.91 (dd, 1H, H-8, $J = 8.3, 1.0$ Hz), 6.98 (m, 1H, H-6), 7.11–7.24 (m, 2H, H-5, H-7), 8.60 (d, 1H, NH, $J = 8.5$ Hz); $^{19}$F NMR (376 MHz, DMSO-$d_6$) trans-isomer (94%) $\delta$ 85.51 (d, CF$_3$, $^3J_{H,F} = 6.6$ Hz).
Hz), cis-isomer (6%) δ 84.65 (d, CF₃, JT₃H,F = 6.5 Hz). Anal. Calcd for C₁₃H₁₂F₃NO₂: C, 57.57; H, 4.46; N, 5.16. Found: C, 57.66; H, 4.39; N, 5.09.

trans-4-Amino-2-(trifluoromethyl)chroman hydrochloride (6). A suspension of amide 5a (300 mg, 1.16 mmol) in 36% hydrochloric acid (4 ml) and water (2 ml) was refluxed for 7 h and allowed to stand overnight at room temperature. The solid product was collected by filtration, washed with ethyl ether and dried to give salt trans-6 as colorless needles, 250 mg (yield 85%), mp 240 °C (subl.). IR (KBr) 3408, 2890, 1613, 1598, 1586, 1515, 1491, 1463 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 2.30 (ddd, 1H, CHH, J = 14.8, 12.4, 5.2), 2.54 (dt, 1H, CHH, J = 14.8, 2.2), 4.62 (bs, 1H, H-4), 5.20 (dqd, 1H, H-2, J = 12.4, 6.4, 2.2), 7.01 (dd, 1H, H-8, J = 8.3, 1.1 Hz), 7.08 (td, 1H, H-6, J = 7.6, 1.1 Hz), 7.36 (ddd, 1H, H-7, J = 8.3, 7.3, 1.7 Hz), 7.60 (dd, 1H, H-5, J = 7.8, 1.7), 8.90 (bs, 3H, N⁺H₃); ¹⁹F NMR (376 MHz, DMSO-d₆) δ 85.25 (d, CF₃, JT₃H,F = 6.4 Hz). Anal. Calcd for C₁₀H₁₁ClF₃NO: C, 47.35; H, 4.37; N, 5.52. Found: C, 47.36; H, 4.28; N, 5.38.

trans-4-Benzamido-2-(trifluoromethyl)chroman (5f). Hydrochloride 6 (130 mg, 0.5 mmol) was treated with 3 ml of 40% aqueous sodium hydroxide and the free base was extracted with ether (2 x 5 ml). The combined extracts were evaporated, the residue was dissolved in pyridine (2 ml) and benzoyl chloride (360 mg, 2.6 mmol) was added. Then the solution was allowed to stand for 1 day at room temperature, poured into 10% hydrochloric acid (10 ml) and the white precipitate collected by filtration, washed with water and dried to give trans-5f, 120 mg (yield 73%), mp >300 °C (decomp.). IR (KBr) 3320, 1630, 1579, 1514, 1487 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) trans-isomer (100%) δ 2.20–2.25 (m, 2H, CH₂), 5.00–5.06 (m, 1H, H-2), 5.37 (dt, 1H, H-4, J = 7.9, 3.8 Hz), 6.98–7.03 (m, 2H, H-8, H-6) 7.25–7.32 (m, 2H, H-7, H-5), 7.44–7.49 (m, 2H, H-3’, H-5’), 7.54 (tt, 1H, H-4’, J = 7.3, 1.3 Hz), 7.88–7.92 (m, 2H, H-2’, H-6’), 8.92 (d, 1H, NH, J = 7.9 Hz). Anal. Calcd for C₁₇H₁₄F₃NO₂: C, 63.55; H, 4.39; N, 4.36. Found: C, 63.21; H, 4.21; N, 4.28. In addition, this compound was prepared as a 94:6 mixture of trans- and cis-isomers from chromanol 2a and benzonitrile analogously to 5a–c; ¹⁹F NMR (376 MHz, DMSO-d₆) trans-isomer (94%) δ 85.62 (d, CF₃, JT₃H,F = 6.7 Hz), cis-isomer (6%) δ 84.66 (d, CF₃, JT₃H,F = 6.4 Hz).

Acknowledgements

This work was financially supported by the RFBR (Grant 06-03-32388).

References


