Steric factor in reactions of substituted 2-trifluoromethylchromones with ammonia and primary amines

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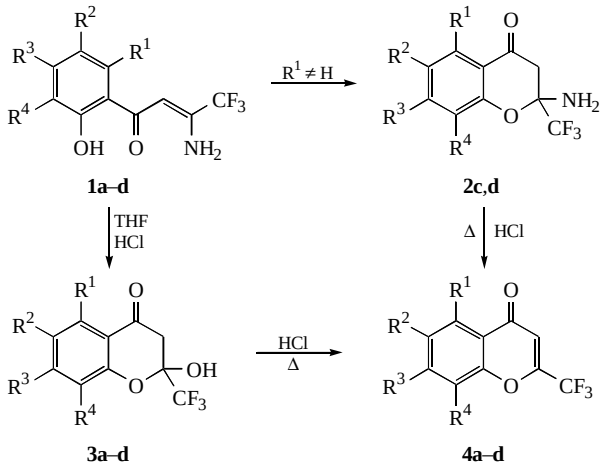
Substituted 2-trifluoromethylchromones react with ammonia and primary amines at the activated double bond to form 3-amino- and 3-alkylamino-4,4,4-trifluoro-1-(2-hydroxyaryl)but-2-en-1-ones or 2-amino- and 2-alkylamino-2-trifluoromethylchroman-4-ones depending on the substituent in the 5-position of the chromone system.

Previously,[1–3] it was found that condensation of substituted 2-hydroxyacetophenones with trifluoroacetonitrile results in either hydroxy oxo enamines **1a**,**b** or, in the presence of a substituent in the 6-position of the benzene ring, mixtures of hydroxy oxo enamines **1c**,**d** and 2-amino-2-trifluoromethylchromanones **2c**,**d**. Subsequently, compounds **1c**,**d** were found (unpublished data) to undergo irreversible transformation in alcoholic solutions in the presence of ethylenediamine at room temperature with the formation of cyclic species **2c**,**d**. The latter are stable substances and do not exhibit ring–chain tautomerization in solvents such as $CDCl_3$ and [$^2H_6$]DMSO at room temperature (^{1}H NMR data). Thus, with a CF_3 group at the C(2) atom and $R^1 \neq H$, the chromanone structure of **2** is energetically more favourable than aminoenone species **1**.

Hydrolysis of compounds **1a–d** under mild conditions[1] gives 2-hydroxy-2-trifluoromethylchroman-4-ones **3a–d**, which can also be prepared on condensation of corresponding methyl ketones with ethyl trifluoroacetate,[4] and boiling of chromanones **2c**,**d** and **3a–d** in ethanol with catalytic amounts of HCl results in 2-trifluoromethylchromones **4a–d**.[4]

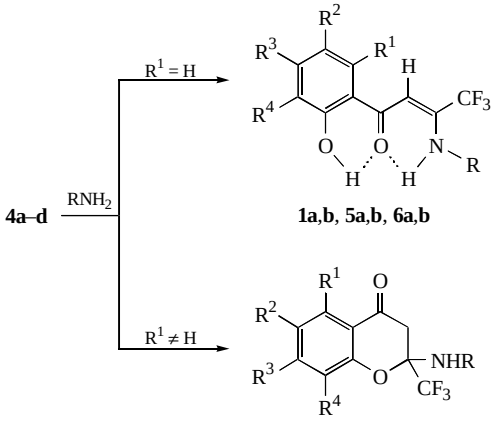


1a–d **2c**,**d** **3a–d** **4a–d**

a $R^1 = R^2 = R^3 = R^4 = H$
b $R^1 = R^2 = H$, $R^3 + R^4$ = benzo
c $R^1 = R^3 = Me$, $R^2 = R^4 = H$
d $R^1 + R^2$ = benzo, $R^3 = R^4 = H$

The aim of this study was to examine the reactions of substituted 2-trifluoromethylchromones **4a–d** with ammonia and primary amines. It is well known[5–7] that 2-methylchromones undergo ring opening under the action of amines to form corresponding aminoenones with a 2-hydroxyaryl substituent at the carbonyl group. In this connection, taking into account published data,[1–3] it is believed that 2-trifluoromethylchromones **4a–d** will either exhibit a similar behaviour or, because of high electron-withdrawing capability of the CF_3 group (at $R^1 \neq H$), give products of amine addition to the double bond without opening the pyrone ring.

We found that the structure of products strictly depends on the substituent in the 5-position of the chromone system: at $R^1 \neq H$, reactions of chromones **4** with ammonia and primary



4a–d **1a**,**b**, **5a**,**b**, **6a**,**b** **2c**,**d**, **7c**,**d**, **8c**,**d**

1,**2** R = H
5,**7** R = Me
6,**8** R = CH_2Ph

a $R^1 = R^2 = R^3 = R^4 = H$
b $R^1 = R^2 = H$, $R^3 + R^4$ = benzo
c $R^1 = R^3 = Me$, $R^2 = R^4 = H$
d $R^1 + R^2$ = benzo, $R^3 = R^4 = H$

amines are arrested at the step of nucleophilic addition and at $R^1 = H$ proceed further and are accompanied by opening of the pyrone ring to form corresponding aminoenones. Thus, the reactions of ammonia, methylamine (25% aqueous solutions) and benzylamine with alcoholic solutions of chromones **4a**,**b** proceed at room temperature in 1–3 h and result in yellow hydroxy oxo enamines **1a**,**b**, **5a**,**b** and **6a**,**b**, respectively,† in 58–88% yields. At the same time, chromones **4c**,**d** having substituents in the 5-position ($R^1 \neq H$) react with the above amines under the same conditions to form chromanones **2c**,**d**, **7c**,**d** and **8c**,**d** (25–76% yields)‡ in 0.5 h (NH_3 and $MeNH_2$) or 7 h ($PhCH_2NH_2$).

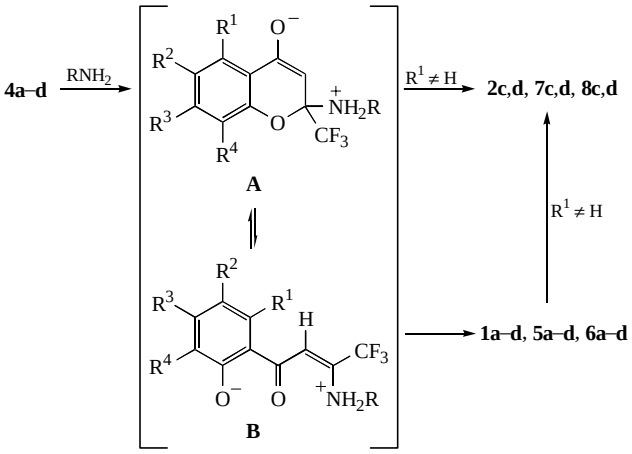
To explain the structural difference between the products, it is reasonable to suggest that, regardless of the position of a substituent in the aromatic ring, the reaction proceeds *via* pyrone ring opening to form intermediate **B** being in the equilibrium with cyclic intermediate **A**, the primary product of nucleophilic addition.

At $R^1 \neq H$, intermediate **B** is destabilised because of steric hindrances that occur between the substituent R^1 and vinyl hydrogen of the enamine unit and hinder the formation of a planar conformation. Interactions that are inevitable in the structure of **B** at $R^1 \neq H$ render the open species energetically less favourable and shift the equilibrium towards intermediate **A**. The latter intermediate leads to chromanones **2c**,**d**, **7c**,**d** and **8c**,**d**, which are incapable of ring–chain tautomerization.

At $R^1 = H$, the equilibrium is shifted towards intermediate **B**, which forms aminoenones **1a**,**b**, **5a**,**b** and **6a**,**b** upon proton transfer. These aminoenones exhibit planar conformations stabilised by two intramolecular hydrogen bonds and, because of this, are not prone to cyclization.§ Taking into account that aminoenones **1c**,**d** easily convert to chromanones **2c**,**d**, the possibility of intermediate **B** converting into aminoenones with $R^1 \neq H$, which undergo irreversible cyclization to chromanones

2c,**d**, **7c**,**d** and **8c**,**d** under the reaction conditions, cannot also be excluded.

The appearance of a doublet of quartets of the N–Me group is the characteristic feature of the ^{1}H NMR spectra of aminoenones **5a** and **5b**, which have the *Z*-configuration of the double bond.[2] This is due to the splitting at the NH proton (*J* 5.8 Hz), which participates in the formation of the intramolecular hydrogen bond, and the spin–spin interaction (*J* 1.3–1.4 Hz), which is typical of ^{1}H and ^{19}F nuclei and results from the spatial proximity of the methyl and trifluoromethyl groups.[8] For chromanones **8c** and **8d**, in addition to the AB system of the CH_2(3) group, we observed a multiplet due to the benzyl methylene group whose diastereotopic protons are split because of the spin–spin interaction with the NH proton.



Thus, depending on the substituent in the 5-position of the chromone system, the interaction of 2-trifluoromethylchromones **4a–d** with ammonia and primary amines results in either the products of addition at the C(2) atom or the pyrone ring opening to form an aminoenone system. This fact is of interest with respect to both a new approach to the preparation of 2-amino- and 2-alkylamino-2-trifluoromethylchromanones and the synthesis of fluorine-containing N-substituted hydroxy oxo enamines, which cannot be obtained by direct condensation of nitriles with ketones.[1–3]

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† Compounds **1a**,**b** were described in refs. 1 and 2.

4,4,4-Trifluoro-1-(2-hydroxyphenyl)-3-methylaminobut-2-en-1-one **5a**: yield 78%, mp 118–119 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 3.15 (dq, 3H, MeN, *J* 5.8, 1.4 Hz), 6.22 (s, 1H, =CH), 6.85 [td, 1H, H(5), *J* 8.0, 1.4 Hz], 6.95 [dd, 1H, H(3)], 7.40 [td, 1H, H(4)], 7.66 [dd, 1H, H(6)], 10.4 (br. s, 1H, NH), 12.69 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3190 (br., NH), 1625 (C=O), 1580, 1570 (C=C, NH). Found (%): C, 53.87; H, 4.22; N, 5.76. Calc. for $C_{11}H_{10}F_3NO_2$ (%): C, 53.88; H, 4.11; N, 5.71.

4,4,4-Trifluoro-1-(1-hydroxynaphth-2-yl)-3-methylaminobut-2-en-1-one **5b**: yield 88%, mp 138–139 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 3.13 (dq, 3H, MeN, *J* 5.8, 1.3 Hz), 6.27 (s, 1H, =CH), 7.15–7.78 (m, 5H, H_{arom}), 8.36–8.48 (m, 1H, peri-H), 10.3 (br. s, 1H, NH), 14.37 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3180 (br., NH), 1620 (C=O), 1600, 1575, 1500 (C=C, NH). Found (%): C, 61.13; H, 4.24; N, 4.82. Calc. for $C_{15}H_{12}F_3NO_2$ (%): C, 61.02; H, 4.10; N, 4.74.

3-Benzylamino-4,4,4-trifluoro-1-(2-hydroxyphenyl)but-2-en-1-one **6a**: yield 58%, mp 98–99 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 4.60 (d, 2H, CH_2, *J* 6.3 Hz), 6.28 (s, 1H, =CH), 6.75–6.96 [m, 2H, H(5), H(3)], 7.30–7.47 [m, 6H, H(4), Ph], 7.66 [dd, 1H, H(6), *J* 8.0, 1.4 Hz], 10.6 (br. s, 1H, NH), 12.61 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3190 (br., NH), 3080, 3050 (=CH arom.), 1630 (C=O), 1580, 1530 (C=C, NH). Found (%): C, 63.47; H, 4.52; N, 4.36. Calc. for $C_{17}H_{14}F_3NO_2$ (%): C, 63.55; H, 4.39; N, 4.36.

3-Benzylamino-4,4,4-trifluoro-1-(1-hydroxynaphth-2-yl)but-2-en-1-one **6b**: yield 65%, mp 84–85 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 4.63 (d, 2H, CH_2, *J* 6.5 Hz), 6.34 (s, 1H, =CH), 7.17–7.86 (m, 10H, H_{arom}), 8.36–8.48 (m, 1H, peri-H), 10.6 (br. s, 1H, NH), 14.31 (s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3180 (br., NH), 1620 (C=O), 1575, 1500 (C=C, NH). Found (%): C, 67.74; H, 4.57; N, 3.80. Calc. for $C_{21}H_{16}F_3NO_2$ (%): C, 67.92; H, 4.34; N, 3.77.

‡ Compounds **2c**,**d** were described in refs. 2 and 3.

2-Trifluoromethyl-2-methylamino-5,7-dimethylchroman-4-one **7c**: yield 60%, mp 119–120 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 2.1 (br. s, 1H, NH), 2.32 (s, 3H, Me), 2.43 (s, 3H, MeN), 2.59 (s, 3H, Me), 2.95 (AB system, $\Delta\delta$ 0.34 ppm, 2H, CH_2, *J* 16.4 Hz), 6.69 (s, 1H, H_{arom}), 6.75 (s, 1H, H_{arom}). IR (Vaseline oil, ν/cm^{-1}): 3350 (br., NH), 1680 (C=O), 1620, 1570, 1520 (NH, arom.). Found (%): C, 57.25; H, 5.32; N, 4.99. Calc. for $C_{13}H_{14}F_3NO_2$ (%): C, 57.14; H, 5.16; N, 5.13.

2-Trifluoromethyl-2-methylaminobenzo[f]chroman-4-one **7d**: yield 76%, mp 103–104 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 2.3 (br. s, 1H, NH), 2.45 (s, 3H, MeN), 3.13 (AB system, $\Delta\delta$ 0.36 ppm, 2H, CH_2, *J* 16.4 Hz), 7.14–8.06 (m, 5H, H_{arom}), 9.38 (d, 1H, peri-H). IR (Vaseline oil, ν/cm^{-1}): 3400 (br., NH), 1660 (C=O), 1625, 1600, 1575, 1515 (NH, arom.). Found (%): C, 60.90; H, 3.98; N, 4.61. Calc. for $C_{15}H_{12}F_3NO_2$ (%): C, 61.02; H, 4.10; N, 4.74.

2-Benzylamino-2-trifluoromethyl-5,7-dimethylchroman-4-one **8c**: yield 57%, mp 93–94 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 2.3 (br. s, 1H, NH), 2.32 (s, 3H, Me), 2.59 (s, 3H, Me), 2.97 (AB system, $\Delta\delta$ 0.36 ppm, 2H, CH_2, *J* 16.4 Hz), 3.92 (m, 2H, CH_2Ph), 6.72 (s, 2H, H_{arom}), 7.0–7.3 (m, 5H, Ph). IR (Vaseline oil, ν/cm^{-1}): 3330 (br., NH), 3080, 3040 (=CH arom.), 1680 (C=O), 1620, 1575, 1515, 1500 (NH, arom.). Found (%): C, 65.38; H, 5.04; N, 4.01. Calc. for $C_{19}H_{18}F_3NO_2$ (%): C, 65.32; H, 5.19; N, 4.01.

2-Benzylamino-2-trifluoromethylbenzo[f]chroman-4-one **8d**: yield 25%, mp 122–123 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ: 2.5 (br. s, 1H, NH), 3.17 (AB system, $\Delta\delta$ 0.36 ppm, 2H, CH_2, *J* 16.5 Hz), 3.96 (m, 2H, CH_2Ph), 7.05–8.07 (m, 10H, H_{arom}), 9.38 (d, 1H, peri-H). IR (Vaseline oil, ν/cm^{-1}): 3425 (br., NH), 1680 (C=O), 1620, 1600, 1575, 1515, 1500 (NH, arom.). Found (%): C, 67.81; H, 4.28; N, 3.71. Calc. for $C_{21}H_{16}F_3NO_2$ (%): C, 67.92; H, 4.34; N, 3.77.

§ Judging from the IR spectra in Vaseline oil, in which the absorption band due to the C=O group at 1660–1680 cm^{-1} is absent, aminoenones **1a**,**b**, **5a**,**b** and **6a**,**b** with R^1 = H occur only in the open form both in the solid state and in $CDCl_3$ solutions (^{1}H NMR spectroscopy data). We assume the possibility of their cyclization to corresponding amino chromanones; however, the conditions for this transformation, which can be considered as a new example of reversible ring–chain tautomerization, remain to be found.