A Simple and Efficient Synthesis of 2-Methyl-2-trifluoromethylchroman-4-ones from 2-Trifluoromethyl-4H-chromen-4-imines and Malonic Acid

Vyacheslav Ya. Sosnovskikh,* Boris I. Usachev
Department of Chemistry, Ural State University, 620083 Ekaterinburg, Russia
Fax +7(3432)615978; E-mail: Vyacheslav.Sosnovskikh@usu.ru
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Abstract: N-Benzyl-2-trifluoromethyl-4H-chromen-4-imines and malonic acid on heating in anhydrous dioxane afford 2-trifluoromethyl-2-methylchroman-4-ones in ~60% yield. 2-Methyl-2-trifluoromethyl-4-oxochromane-6-carbaldehyde and 2-methyl-2-trifluoromethyl-4-oxochromane-6-carboxylic acid, the fluorinated analogues of natural lactarochromal and the corresponding acid, were obtained by the oxidation of 2,6-dimethyl-2-trifluoromethylchroman-4-one with K2S2O8.

Key words: N-benzyl-2-trifluoromethyl-4H-chromen-4-imines, malonic acid, 2-methyl-2-trifluoromethylchroman-4-ones, oxidation, fluorinated analogues of natural compounds

In continuation of our studies on the chemical properties of 2-polyfluoroalkylchromones,1 we recently developed the method for the synthesis of 2-polyfluoroalkyl-4H-chromene-4-imines2 and showed that in an acidic medium these compounds exceed 2-RF-chromones in reactivity due to the formation of the chromen-iminium cation. This fact allowed us to apply 2-trifluoromethyl-4H-chromen-4-imines and sodium azide for the preparation of vicinal triazoles with electron-donating groups in the 2-hydroxyaryl substituent, since the attempts to prepare the latter from 2-trifluoromethylchromones failed.3 Recognizing the possibility that appropriate 2-trifluoromethylchromen-4-imines might serve as an attractive building blocks for the synthesis of various CF3-containing heterocyclic compounds, we decided to investigate their reactions with other nucleophilic reagents.

In this work we wish to report that malonic acid demonstrated an unusual behavior in the reaction with N-benzyl-2-trifluoromethylchromene-4-imines 1a,b. By boiling equimolar amounts of 1a,b and malonic acid in anhydrous dioxane, 2-methyl-2-trifluoromethylchroman-4-ones, 2a,b, were obtained in ~60% yield. Malonic acid acts as methylating agent in this reaction. Note that methylmalonic and phenylacetic acids do not react, under similar conditions with 2-trifluoromethylchromen-4-imines, and malonic acid in the presence of pyridine does not methylate 2-trifluoromethylchromones. Earlier4 methylation of non-fluorinated chromones at C-2 was realized under the action of lithium dimethylcuprate.

We believe that the starting substances are mutually activated at the first stage of the reaction: malonic acid protonates chromen-imine 1 to the iminium cation, which increases electrophilicity of C-2, and 1, being a sufficiently strong base, deprotonates the activated CH2 group of the acid, thus enhancing its nucleophilicity. The result of this catalysis is the addition of malonic acid at C-2 to form intermediate A, which decarboxylates to give B. The easy decarboxylation of the second CO2H group is associated, most likely, with the pyrone cycle opening to intermediate C, whose subsequent cyclization and hydrolysis in the presence of HCl results in chromanones 2 (Scheme 1).

The described reaction probably represents the best overall route to partially fluorinated analogues of natural chromanones, chromanes and chromenes with the gem-

![Scheme 1](image-url)
dimethyl group at C-2, which are widespread in nature and exhibit different kinds of biological activities.\(^5\) For example, 2-methyl-4-oxo-2-trifuoromethylchroman-6-carbaldehyde (3), the analog of natural lactarochromal, a metabolite of the fungus *Lactarius deliciosus*\(^6\) in which the CH\(_3\) group is replaced by the CF\(_3\) group, was synthesized by the oxidation of the 6-Me group of chromanone 2b with a mixture of K\(_2\)S\(_2\)O\(_8\) and CuSO\(_4\) in aqueous acetonitrile\(^7\) in 41% yield. In addition to trifluorolactarochromal 3, this reaction gives the corresponding trifluoroacid 4 (yield 15%), which is also a fluorinated analog of the natural acid isolated from *Chrysothamnus viscidiflorus*\(^8\) (Scheme 2).

![Scheme 2](image)

**Scheme 2**

In conclusion, the reaction of 2-trifluoromethylchromen-4-imines 1 with malonic acid is a simple and efficient method for synthesis of analogues of 2,2-dimethylchroman-4-ones in which one of the methyl groups in the gemdimethyl moiety is replaced by the CF\(_3\) group. This approach can be used for the preparation of partially fluorinated analogues of natural compounds, which are of interest because of their potential biological activity.

\(^1\)H NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400.13 MHz with TMS as the internal standard. The IR spectra were measured on an IKS-29 instrument as suspensions in Nujol. Melting points are uncorrected. All solvents used were dried and distilled per standard procedures. The starting aminoenones, 4-(Benzylamino)-1,1,1-trifluoro-4-(2-hydroxyaryl)but-3-en-2-ones, and distilled per standard procedures. The starting aminoenones, 4-(Benzylamino)-1,1,1-trifluoro-4-(2-hydroxyaryl)but-3-en-2-ones, and distilled per standard procedures.

**N-Benzyl-6-methyl-2-trifluoromethyl-4H-chromen-4-imine (1b)**

This compound was obtained similarly to 1a in 77% yield as a colorless solid; mp 98–99 °C.

IR (Nujol): 1670 (C=O), 1610, 1575, 1495 cm\(^{-1}\) (C=C, Ar).

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) = 4.56 (s, 2 H, CH\(_2\)), 2.83 (s, 3 H, CH\(_3\)), 7.27–7.44 (m, 7 H, H-6, H-8, C\(_6\)H\(_5\)), 7.52 (ddd, 1 H, H-7, J\(_m\) = 8.4, 7.3 Hz, J\(_p\) = 1.6 Hz), 8.34 (d, 1 H, H-5, J\(_m\) = 7.7 Hz).


**2-Methyl-2-trifluoromethylchroman-4-one (2a); Typical Procedure**

A mixture of chromene-imine 1a (7.0 g, 0.023 mol) and malonic acid (2.6 g, 0.025 mol) was refluxed in anhyd dioxane (20 ml) for 3 h. After the reaction mixture had cooled to r.t., 50% EtOH (20 ml) and conc. HCl (5 ml) were added. The resulting solution was left to stand at 20 °C for 10 min, after which it was diluted with H\(_2\)O (500 ml). The product was extracted with hexane (3 x 30 ml), the combined hexane extracts were dried (K\(_2\)CO\(_3\)) and distilled under reduced pressure to give the title compound 2a (3.1 g, 58%) as a light yellow oil; bp 112–116 °C/17 Torr; n\(_D\) = 1.4965, d\(_4\) = 1.3275 g/cm\(^3\).

IR (neat): 1705 (C=O), 1615, 1590 cm\(^{-1}\) (Ar).

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) = 1.59 (m, 3 H, CH\(_3\)), 2.78 (dq, 1 H, CH\(_2\)), 4.76 (s, 2 H, CH\(_2\)), 5.41 (s, 1 H, H-5), 7.07 (ddd, 1 H, H-8, J\(_m\) = 8.4 Hz, J\(_p\) = 0.4 Hz), 7.21 (ddd, 1 H, H-6, J\(_m\) = 7.9, 7.2 Hz, J\(_p\) = 1.0 Hz), 5.33 (ddd, 1 H, H-7, J\(_m\) = 8.4, 7.2 Hz, J\(_p\) = 0.6 Hz), 8.12 (s, 1 H, H-5).

\(^1\)F NMR (75 MHz, CDCl\(_3\)); \(\delta\) = 79.54 (m, CF\(_3\)).


**2,6-Dimethyl-2-trifluoromethylchroman-4-one (2b)**

This compound was obtained similarly to 2a in 55% yield as a yellow oil; bp 127–128 °C/15 Torr; n\(_D\) = 1.4976, d\(_4\) = 1.2885 g/cm\(^3\).

IR (neat): 1700 (C=O), 1620, 1580 cm\(^{-1}\) (Ar).

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) = 1.57 (m, 3 H, CH\(_3\)), 2.31 (s, 3 H, 6-CH\(_3\)), 2.75 (dq, 1 H, CH\(_2\)), 4.69 (s, 2 H, CH\(_2\)), 6.92 (d, 1 H, H-8, J\(_m\) = 8.5 Hz), 7.34 (ddd, 1 H, H-7, J\(_m\) = 8.5 Hz, J\(_p\) = 2.3 Hz, J\(_{\text{Me}}\) = 0.6 Hz), 7.66 (dq, 1 H, H-5, J\(_m\) = 2.3 Hz, J\(_{\text{Me}}\) = 0.4 Hz).


**N-Benzyl-6-methyl-2-trifluoromethyl-4H-chromen-4-imine (1b)**

This compound was obtained similarly to 1a in 77% yield as a colorless solid; mp 98–99 °C.

IR (Nujol): 1670 (C=O), 1610, 1575, 1495 cm\(^{-1}\) (C=C, Ar).

\(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta\) = 3.46 (s, 2 H, CH\(_2\)), 6.83 (s, 1 H, H-3), 7.27–7.44 (m, 7 H, H-6, H-8, C\(_6\)H\(_5\)), 7.52 (ddd, 1 H, H-7, J\(_m\) = 8.4, 7.3 Hz, J\(_p\) = 1.6 Hz), 8.34 (d, 1 H, H-5, J\(_m\) = 7.7 Hz).

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IR (Nujol): 1700 (C=O), 1620, 1580 cm⁻¹ (Ar).

1H NMR (400 MHz, DMSO-d₆): δ = 1.63 (s, 3 H, CH₃), 3.27 (s, 2 H, CH₂), 7.25 (d, 1 H, H-8, J = 8.7 Hz), 8.14 (dd, 1 H, H-7, J = 8.7 Hz, J₆ = 2.2 Hz), 8.31 (d, 1 H, H-5, J₆ = 2.2 Hz), 13.15 (br s, 1 H, OH).


The CHCl₃ layer was dried (K₂CO₃), filtered, the CHCl₃ was distilled off, and aldehyde 3 was extracted from the residue with hot hexane (50 mL). The hexane extract was passed through a silica gel column (d = 10 mm, l = 5 mm), and the excess hexane was distilled off until the volume of the mixture reached ~20 mL. The remaining solution was gradually cooled to −10 °C with vigorous stirring to prevent phase separation. The resulting precipitate was collected, washed with cold hexane and dried to give aldehyde 3 as a colorless solid (0.44 g, 41%); mp 70–71 °C.

IR (Nujol): 1710 (C=O), 1620, 1580 cm⁻¹ (Ar).

1H NMR (400 MHz, CDCl₃): δ = 1.64 (s, 3 H, CH₃), 2.89 (dq, 1 H, CH₂H₂H, J = 16.9 Hz, J₄ = 0.4 Hz), 3.19 (dq, 1 H, CHH₂, J = 16.9 Hz, J₄ = 0.5 Hz), 7.19 (d, 1 H, H-8, J = 8.7 Hz), 8.10 (dd, 1 H, H-7, J = 8.7 Hz, J₆ = 2.1 Hz), 8.39 (d, 1 H, H-5, J₆ = 2.1 Hz), 9.96 (s, 1 H, CHO).


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References