First example of regioselective nucleophilic 1,6-addition of trimethyl(trifluoromethyl)silane to 4*H*-chromene derivatives

V. Ya. Sosnovskikh,[a] B. I. Usachev,[a] M. N. Permyakov,[a] D. V. Sevenard,[b] and G.-V. Röschenthaler[b]*

[a]A. M. Gor´kii Ural State University,
51 prosp. Lenina, 620083 Ekaterinburg, Russian Federation.
Fax: +7 (343) 261 5978. E-mail: Vyacheslav.Sosnovskikh@usu.ru
[b]Institute of Inorganic and Physical Chemistry, University of Bremen,
Leobener Strasse, 28334 Bremen, Germany

Condensation of 2-trifluoromethylchromone with diethyl malonate, ethyl cyanoacetate, and Meldrum´s acid gave the corresponding methylidene derivatives of 2-trifluoromethyl-4*H*-chromene. Nucleophilic 1,6-addition of an excess of Me_3SiCF_3 in the presence of Me_4NF to those obtained from the former two compounds afforded 4-substituted 2,2-bis(trifluoromethyl)-2*H*-chromenes.

Key words: the Knoevenagel condensation, methylidene derivatives of 4*H*-chromene, trimethyl(trifluoromethyl)silane, nucleophilic 1,6-addition, 2,2-bis(trifluoromethyl)-2*H*-chromenes.

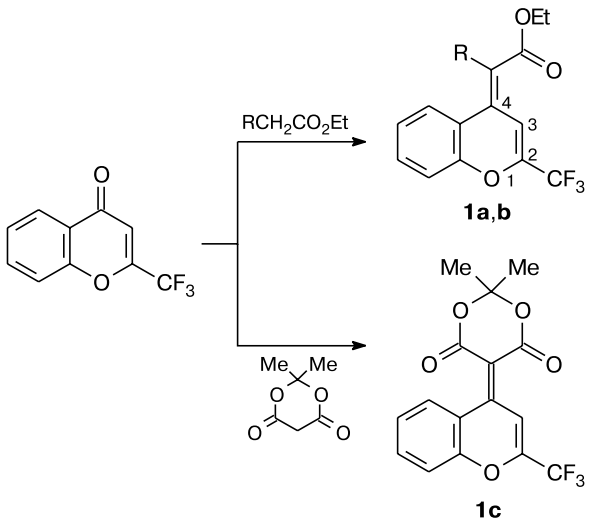
Nucleophilic trifluoromethylation of organic compounds is complicated due to the instability of the free trifluoromethyl anion, which easily decomposes into the fluoride anion and difluorocarbene.[1] The use of Me_3SiCF_3 (Ruppert´s reagent) in the presence of the fluoride anion as an initiator allows one to avoid this undesirable reaction and effect direct introduction of the CF_3 group into organic substrates (saturated and α,β-unsaturated carbonyl compounds) by 1,2-nucleophilic addition leading to the corresponding trifluoromethylated alcohols.[2—4] Reactions of Me_3SiCF_3 with 2-trifluoromethylchromones in the presence of catalytic amounts of Me_4NF represent the first example of 1,4-addition to the α,β-enone system we have discovered; these highly regioselective reactions give 2,2-bis(trifluoromethyl)chroman-4-ones in good yields.[5—8]

In the present work, using the Knoevenagel condensation of 2-trifluoromethylchromone with compounds containing an active methylene group (diethyl malonate, ethyl cyanoacetate, and Meldrum´s acid), we synthesized the corresponding methylidene derivatives and studied their reactions with Ruppert´s reagent with the aim of collecting new data on the possibility of nucleophilic trifluoromethylation of conjugated systems.

Results and Discussion

2-Methylchromone is known to react as a carbonyl compound with hippuric acid on heating in Ac_2O (see Ref. 9) and with ethyl cyanoacetate in the presence of piperidine in boiling benzene.[10] We found that 2-trifluoromethylchromone is inert toward active methylene compounds under these conditions, but reacts with diethyl malonate, ethyl cyanoacetate, and Meldrum´s acid in the presence of $TiCl_4$ and pyridine to give methylidene derivatives of 4*H*-chromene **1a—c** in 51—96% yields (Scheme 1). Earlier,[11] this method has been proposed for the Knoevenagel condensation with poorly reactive aromatic ketones. In the ^1H NMR spectra of com-

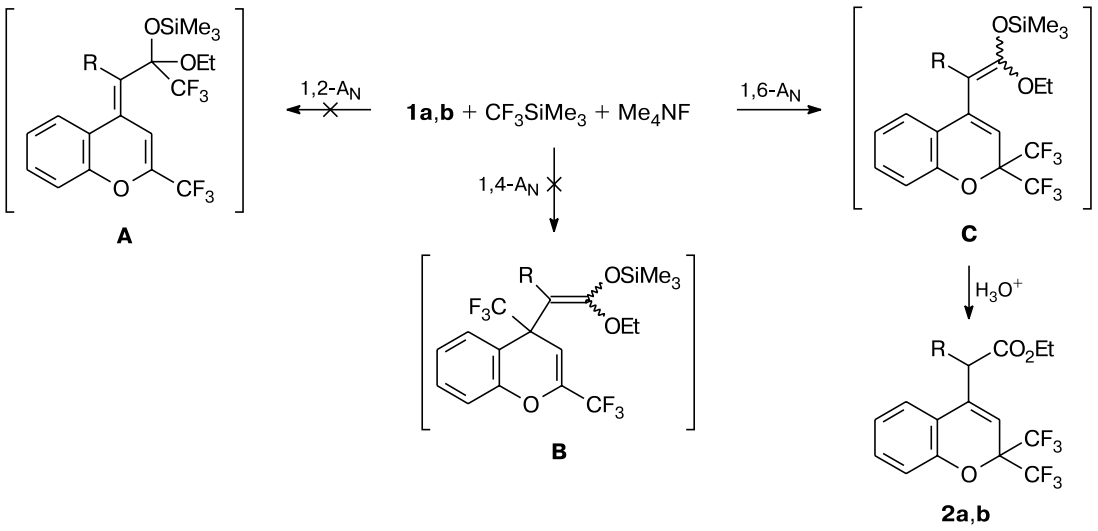
Scheme 1



R = CO_2Et (**a**), CN (**b**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1628—1630, September, 2006.
1066-5285/06/5509-1687

Scheme 2



pounds **1a—c**, a singlet for the H(3) proton is strongly shifted downfield (δ 8.22—8.95 versus δ 6.74 for the starting 2-trifluoromethylchromone) because of its deshielding by the carbonyl O atom, which suggests the preferred s-*cis*-conformation of the exocyclic fragment. The chemical shift of the CF_3 group remains virtually unchanged: δ_F 90.3—91.2 in products **1a—c** and δ_F 90.7 in 2-trifluoromethylchromone.

The structural features of 4*H*-chromenes **1a—c** allow three possible pathways in their reactions with Me_3SiCF_3 (Scheme 2): 1,2-addition to the ester group (product **A**), 1,4-addition (**B**), and 1,6-addition (**C**). We found that the reactions of compounds **1a,b** with Me_3SiCF_3 (2 equiv.) in the presence of Me_4NF (1.5 equiv.) occur as the nucleophilic 1,6-addition to the conjugated systems of 4*H*-chromenes **1a,b**. This proceeds *via* intermediate **C** to give, following acid hydrolysis, 2,2-bis(trifluoromethyl)-2*H*-chromenes **2a,b** in 80 and 71% yields, respectively. Under analogous conditions, compound **1c** reacted less unambiguously.

The ^1H NMR spectrum of compound **2a** shows, apart from the signals for the ester groups and for the aromatic protons, singlets at δ 4.73 and 5.84 for the methine and vinylic protons; in the spectrum of compound **2b**, these protons resonate as a doublet (δ 4.76, $J_{CH,H(3)}$ = 0.8 Hz) and a slightly broadened singlet (line width 2.5 Hz) at δ 5.99, respectively, due to additional splitting at the fluorine atoms of the CF_3 groups. The methylene protons of the CO_2Et groups in chromenes **2a,b** are diastereotopic;[12] however, only in compound **2a** do they resonate as doublets of quartets with J = 10.8 and 7.1 Hz.

The discovered reaction is the first example of nucleophilic 1,6-addition of trimethyl(trifluoromethyl)silane and may be of interest for the synthesis of partially fluorinated analogs of natural derivatives of 2,2-dimethyl-2*H*-chromene.

Experimental

IR spectra were recorded on a Perkin-Elmer Spectrum BX-II instrument (in KBr pellets or thin film). ^1H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400.1 (^1H) and 376.5 MHz (^{19}F)) in $CDCl_3$ with Me_4Si and C_6F_6 as internal standards, respectively. The mass spectrum of compound **2a** was recorded on a Bruker MAT 8200 instrument (EI, 70 eV). The starting 2-trifluoromethylchromone was prepared according to a known procedure;[13] all other reagents were commercial chemicals.

Synthesis of methylidene derivatives 1a—c (general procedure). A solution of $TiCl_4$ (0.53 g, 2.8 mmol) in CCl_4 (0.7 mL) was added at 0 °C to THF (6 mL) and the mixture was stirred for 10 min. Then 2-trifluoromethylchromone (0.30 g, 1.4 mmol) and a compound with an active methylene group (1.4 mmol) were successively added. The reaction mixture was stirred with cooling for 20 min, pyridine (0.44 g, 5.6 mmol) was added, and stirring was continued at ~20 °C for 12 h. The resulting mixture was treated with water (20 mL) and reaction products were extracted with ether (10 mL). The organic layer was separated, washed with a saturated solution of $NaHCO_3$, and concentrated. The residue was recrystallized from ethanol.

4-Diethoxycarbonylmethylidene-2-trifluoromethyl-4*H*-chromene (1a). Yield 96%, colorless crystals, m.p. 93—94 °C. Found (%): C, 57.36; H, 4.27. $C_{17}H_{15}F_3O_5$. Calculated (%): C, 57.31; H, 4.24. IR (KBr), ν/cm^{-1}: 3125, 2979, 1728, 1702, 1670, 1610, 1564. ^1H NMR ($CDCl_3$), δ: 1.32 (t, 6 H, 2 Me, J = 7.1 Hz); 4.28 (q, 2 H, CH_2, J = 7.1 Hz); 4.35 (q, 2 H, CH_2, J = 7.1 Hz); 7.25 (ddd, 1 H, H(6), J_o = 8.3 and 7.3 Hz, J_m = 1.1 Hz); 7.33 (dd, 1 H, H(8), J_o = 8.4 Hz, J_m = 1.1 Hz); 7.53 (ddd, 1 H, H(7), J_o = 8.4 and 7.3 Hz, J_m = 1.4 Hz); 7.64 (dd, 1 H, H(5), J_o = 8.3 Hz, J_m = 1.3 Hz); 8.22 (s, 1 H, H(3)). ^{19}F NMR ($CDCl_3$), δ: 90.3 (s, CF_3).

4-Cyano(ethoxycarbonyl)methylidene-2-trifluoromethyl-4*H*-chromene (1b). Yield 51%, yellow crystals, m.p. 102—103 °C. Found (%): C, 58.22; H, 3.28; N, 4.29. $C_{15}H_{10}F_3NO_3$. Calculated (%): C, 58.26; H, 3.26; N, 4.53. IR (KBr), ν/cm^{-1}: 3128, 2986, 2207, 1704, 1660, 1611, 1527. ^{1}H NMR ($CDCl_3$), δ: 1.41 (t, 3 H, Me, J = 7.1 Hz); 4.36 (q, 2 H, CH_2, J = 7.1 Hz); 7.47—7.52 (m, 2 H, H(6), H(8)); 7.73 (ddd, 1 H, H(7), J_o = 8.5 and 7.3 Hz, J_m = 1.4 Hz); 8.68 (s, 1 H, H(3)); 9.07—9.10 (m, 1 H, H(5)). ^{19}F NMR ($CDCl_3$), δ: 90.6 (s, CF_3).

2,2-Dimethyl-5-(2-trifluoromethyl-4*H*-chromen-4-ylidene)-1,3-dioxane-4,6-dione (1c). Yield 55%, orange crystals, m.p. 192—193 °C. Found (%): C, 56.49; H, 3.38. $C_{16}H_{11}F_3O_5$. Calculated (%): C, 56.48; H, 3.26. IR (KBr), ν/cm^{-1}: 3125, 3003, 1728, 1696, 1641, 1610, 1563, 1510. ^{1}H NMR ($CDCl_3$), δ: 1.89 (s, 6 H, 2 Me); 7.41 (ddd, 1 H, H(6), J_o = 8.3 and 7.3 Hz, J_m = 1.0 Hz); 7.56 (dd, 1 H, H(8), J_o = 8.5 Hz, J_m = 1.0 Hz); 7.76 (ddd, 1 H, H(7), J_o = 8.5 and 7.3 Hz, J_m = 1.3 Hz); 7.88 (dd, 1 H, H(5), J_o = 8.3 Hz, J_m = 1.3 Hz); 8.95 (s, 1 H, H(3)). ^{19}F NMR ($CDCl_3$), δ: 91.2 (s, CF_3).

Reactions of chromenes 1a,b with Me_3SiCF_3. Trimethyl(trifluoromethyl)silane (0.28 g, 2.0 mmol) was added under nitrogen to a solution of chromene **1a** or **1b** (1.0 mmol) in anhydrous THF (5 mL). The mixture was cooled to −30 °C and anhydrous Me_4NF (0.14 g, 1.5 mmol) was added in small portions with vigorous stirring. The reaction mixture was stirred at −30 °C for 24 h, two drops of 20% HCl were added at 0 °C, and the solvent was removed under reduced pressure without heating. The residue was triturated with pentane (10 mL) and the solution was passed through a short column with silica gel (30—60 mesh) and concentrated. Chromenes **2a,b** were obtained as viscous liquids and dried *in vacuo* over P_2O_5.

4-(Diethoxycarbonylmethyl)-2,2-bis(trifluoromethyl)-2*H*-chromene (2a). Yield 80%, a colorless oil. Found (%): C, 50.40; H, 3.63. $C_{18}H_{16}F_6O_5$. Calculated (%): C, 50.71; H, 3.78. IR, ν/cm^{-1}: 1740, 1661, 1610, 1493. ^{1}H NMR ($CDCl_3$), δ: 1.25 (t, 6 H, 2 Me, J = 7.1 Hz); 4.24 (dq, 2 H, 2 C<u>H</u>H, J = 10.8 and 7.1 Hz); 4.28 (dq, 2 H, 2 CH<u>H</u>, J = 10.8 Hz, J = 7.1 Hz); 4.73 (s, 1 H, CH); 5.84 (s, 1 H, H(3)); 7.01 (dd, 1 H, H(8), J_o = 8.1 Hz, J_m = 1.1 Hz); 7.02 (td, 1 H, H(6), J_o = 7.6 Hz, J_m = 1.1 Hz); 7.22 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.5 Hz); 7.29 (td, 1 H, H(7), J_o = 7.8 Hz, J_m = 1.5 Hz). ^{19}F NMR ($CDCl_3$), δ: 84.0 (s, CF_3). MS (EI, 70 eV), m/z (I_{rel} (%)): 426 $[M]^+$ (28), 357 $[M - CF_3]^+$ (100), 257 (25), 239 (42).

4-[Cyano(ethoxycarbonyl)methyl]-2,2-bis(trifluoromethyl)-2*H*-chromene (2b). Yield 71%, a colorless oil. Found (%): C, 50.37; H, 2.78; N, 3.45. $C_{16}H_{11}F_6NO_3$. Calculated (%): C, 50.67; H, 2.92; N, 3.69. IR, ν/cm^{-1}: 2226, 1732, 1664, 1605, 1578, 1482. ^{1}H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, Me, J = 7.1 Hz); 4.29 (q, 2 H, CH_2, J = 7.1 Hz); 4.76 (d, 1 H, CH, J = 0.8 Hz); 5.99 (br.s, 1 H, H(3)); 7.05 (dd, 1 H, H(8), J_o = 8.1 Hz, J_m = 1.1 Hz); 7.07 (td, 1 H, H(6), J_o = 7.6 Hz, J_m = 1.1 Hz); 7.29 (dd, 1 H, H(5), J_o = 7.8 Hz, J_m = 1.5 Hz); 7.35 (td, 1 H, H(7), J_o = 7.8 Hz, J_m = 1.5 Hz).

This work was financially supported by the German Research Society (Deutsche Forschungsgemeinschaft, Grant 436 RUS 113/758/1-1).

References

1. B. R. Langlois and T. Billard, *Synthesis*, 2003, 185.
2. G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757.
3. R. P. Singh and J. M. Shreeve, *Tetrahedron*, 2000, **56**, 7613.
4. G. K. S. Prakash and M. Mandal, *J. Fluorine Chem.*, 2001, **112**, 123.
5. V. Ya. Sosnovskikh, D. V. Sevenard, B. I. Usachev, and G.-V. Röschenthaler, *Tetrahedron Lett.*, 2003, **44**, 2097.
6. V. Ya. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Röschenthaler, *J. Org. Chem.*, 2003, **68**, 7747.
7. D. V. Sevenard, V. Ya. Sosnovskikh, A. A. Kolomeitsev, M. H. Königsmann, and G.-V. Röschenthaler, *Tetrahedron Lett.*, 2003, **44**, 7623.
8. V. Ya. Sosnovskikh, B. I. Usachev, D. V. Sevenard, and G.-V. Röschenthaler, *J. Fluorine Chem.*, 2005, **126**, 779.
9. F. Eiden and A. Engelhardt, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1967, **300**, 211.
10. I. Zeid, H. A. El-Bary, S. Yassin, and M. Zahran, *Liebigs Ann. Chem.*, 1984, 186.
11. W. Lehnert, *Tetrahedron*, 1973, **29**, 635.
12. D. W. Brown, A. J. Floyd, and M. Sainsbury, *Organic Spectroscopy*, Wiley, New York, 1988.
13. V. Ya. Sosnovskikh and B. I. Usachev, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 434 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 453 (Engl. Transl.)].

Received April 20, 2006;
in revised form July 21, 2006