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SYNTHESIS OF 4-(TRIFLUOROMETHYL)-2*H*-THIOCHROMENES

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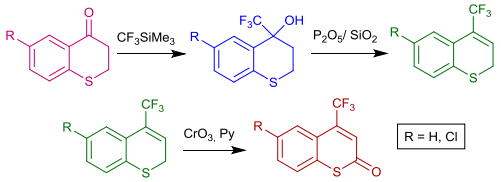
Abstract

The dehydration of 4-CF_3-thiochroman-4-ols under the action of phosphorus pentoxide on silica gel afforded previously unknown 4-CF_3-2H-thiochromenes, which appeared to be convenient precursors for 4-CF_3-thiocoumarins.



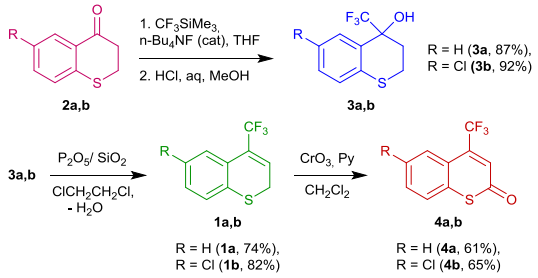
Key words: 4-trifluoromethyl-2*H*-thiochromenes, 4-(trifluoromethyl)thiocoumarins, 1-thiochroman-4-ones.

Introduction

Substituted 2*H*-thiochromenes (2*H*-1-benzothiopyran derivatives) amount to an important class of heterocyclic compounds [1, 2]. These heterocycles are thioanalogs of chromenes and exhibit a broad spectrum of biological activity [3–5]. At the same time, 2*H*-thiochromenes are much less studied compared to chromene derivatives. Only recently the first natural representative of this class of heterocycles has been isolated, which represents a luciferin with a tricyclic thieno[3,2-*f*]thiochromene structure and is responsible for bioluminescence of the marine worm *Odontosyllis undecimdonta* [6]. The synthetic derivatives of 2*H*-thiochromenes are also not widely explored unlike the analogous chromene structures. Thus, 4-trifluoromethyl-2*H*-thiochromenes have not been described in the literature, while 4-trifluoromethyl-2*H*-chromenes have been well studied [7].

Results and discussion

We developed a convenient synthetic route to previously unknown 4-trifluoromethyl-2*H*-thiochromenes **1a,b** starting from readily available 1-thiochroman-4-ones **2a,b** (Scheme 1). According to the suggested approach, at the first stage 4-(trifluoromethyl)thiochroman-4-ols **3a,b** were obtained in high yields by the reaction of compounds **2a,b** with CF_3SiMe_3 (the Ruppert–Prakash reagent) [8]. The key stage was the dehydration of carbinols **3a,b** to form target 4-trifluoromethyl-2*H*-thiochromenes **1a,b**. After a series of experiments, thiochromenes **1a,b** were obtained in good yields by refluxing carbinols **3a,b** in 1,2-dichloroethane with phosphorus pentoxide on silica gel (SICAPENT® reagent) used as a dehydrating agent. Compared to P_2O_5, SICAPENT® can be readily dosed and is well separated from the liquid phase by filtration after completion of the reaction. The structures and identities of compounds **1a,b** were confirmed by ^1H, ^{19}F and ^{13}C NMR spectroscopy, mass spectrometry, as well as elemental analyses. The thiochromene nature of compounds **1a,b** was also evidenced by the oxidation of a methylene unit of the thiopyran ring, resulting in the formation of known 4-CF_3-thiocoumarins **4a,b** (using as an oxidizing agent CrO_3 in the presence of pyridine [9]). Thiocoumarins **4a,b** were earlier obtained by our research group using an alternative method starting from 1-[2-(*tert*-butylthio)phenyl]-2,2,2-trifluoroethanones [10].



Scheme 1. Synthesis of 4-CF_3-2*H*-thiochromenes **1a,b**.

Experimental section

General remarks

The ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Bruker Avance 400 spectrometer with the operating frequencies of 400 (^1H) and 101 MHz (^{13}C)). The chemical shifts of ^{13}C nuclei were determined relative to the $CDCl_3$ signal (δ_C = 77.0 ppm) and recalculated to the signal of $SiMe_4$. The $^{19}F\{^1H\}$ NMR spectra were recorded on a Bruker Avance 300 spectrometer with an operating frequency of 282 MHz for ^{19}F nuclei. The chemical shifts of ^{19}F nuclei were determined relative to CF_3CO_2H as an external standard and recalculated to the signal of $CFCl_3$. The NMR spectra were obtained in $CDCl_3$. The Mass spectra were obtained on a Finnigan Polaris Q instrument (ion trap, ionizing voltage energy 70 eV) by chromatography–mass spectrometry.

(Trifluoromethyl)trimethylsilane CF_3SiMe_3 was purchased from P&M. SICAPENT® (P_2O_5 on an inert carrier, ~75% P_2O_5 by mass) was purchased from Merck. 1-Thiochroman-4-ones **2a,b** were obtained according to the published procedure [11].

Syntheses

Synthesis of 4-CF_3-2*H*-thiochroman-4-ols. CF_3SiMe_3 (5.33 g, 37.5 mmol) was added to a solution of 1-thiochroman-4-one **2a** (4.1 g, 25.0 mmol) in 70 mL of THF. The mixture was cooled to 10 °C. Then 1 M solution of Bu_4NF (1 mL) in THF was added, and the resulting mixture was stirred at 20 °C for 16 h. THF was evaporated under vacuum. The residue was dissolved in 50 mL of methanol and treated with 10 mL of 10% aq. HCl. The desilylation was carried out for 24 h. Methanol was evaporated under vacuum, and the residue obtained was dissolved in CH_2Cl_2 (100 mL). The organic layer was separated, washed with a saturated aq. solution of NaCl, dried over anhydrous $MgSO_4$, and concentrated on a rotary evaporator. The residue obtained was crystallized from PE to give 5.1 g of **4-(trifluoromethyl)thiochroman-4-ol** (**3a**) as white crystals. Yield: 87%. Mp: 64–65 °C (PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.0 Hz, 1H), 7.28–7.23 (m, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 3.27–3.17 (m, 1H), 3.12–3.03 (m, 1H), 2.60 (ddd, J = 14.0, 7.2, 3.3 Hz, 1H), 2.51 (s, 1H), 2.46–2.34 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.0, 129.7, 129.3, 128.1 (q, J = 2.2 Hz), 126.9, 125.7 (q, J = 286.7 Hz), 124.5, 71.9 (q, J = 28.4 Hz), 31.9, 22.1 (q, J = 1.8 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –77.41 (s) ppm. Anal. Calcd for $C_{10}H_9F_3OS$: C 51.28; H 3.87. Found: C 51.30; H 4.00%.

6-Chloro-4-(trifluoromethyl)thiochroman-4-ol (**3b**) was obtained as white crystals in the analogous manner. Yield: 92%. Mp: 44–45 °C (PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.23 (dd, J = 8.5, 2.2 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 3.34–3.18 (m, 1H), 3.13–2.99 (m, 1H), 2.61 (ddd, J = 14.1, 6.7, 3.3 Hz, 1H), 2.49 (s, 1H), 2.42–2.27 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.6, 131.0, 130.1, 130.0, 128.3 (q, J = 2.2 Hz), 128.0, 125.4 (q, J = 286.7 Hz), 71.8 (q, J = 28.7 Hz), 31.6, 22.1 (q, J = 2.0 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –77.57 (s) ppm. Anal. Calcd for $C_{10}H_8ClF_3OS$: C 44.70; H 3.00. Found: C 44.61; H 3.12%.

Synthesis of 4-CF_3-2*H*-thiochromenes. SICAPENT® reagent (4.0 g, ~20 mmol P_2O_5) was added to a solution of compound **3a** (2.3 g, 10 mmol) in 70 mL of dry 1,2-dichloroethane. The reaction mixture was refluxed for 2 h and, after cooling to room temperature, filtered. The filtrate was treated with ice water. The organic layer was separated, washed with a saturated aq. solution of NaCl, dried over anhydrous $MgSO_4$, and concentrated on a rotary evaporator. **4-(Trifluoromethyl)-2*H*-thiochromene** (**1a**) was purified by column chromatography on silica gel (eluent: PE–AcOEt, 7:1). Yield: 1.6 g (74%). The crude product was additionally purified by distillation and isolated as a light-yellow liquid. Bp: 75–76 °C (2 Tor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.49 (m, 1H), 7.42–7.35 (m, 1H), 7.27–7.15 (m, 2H), 6.72 (t, J = 5.8 Hz, 1H), 3.44 (dq, J = 5.8, 1.9 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 133.5, 130.1 (q, J = 29.5 Hz), 128.9, 128.0, 127.7, 126.1, 126.0 (q, J = 6.2 Hz), 125.9 (q, J = 2.8 Hz), 123.4 (q, J = 273.5 Hz), 24.0 ppm. ^{19}F (282 MHz, $CDCl_3$): δ –63.30 (s) ppm. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 216 $[M]^+$ (22), 215 $[M–H]^+$ (12), 165 $[M–HCF_2]^+$ (15), 147 $[M–CF_3]^+$ (100). Anal. Calcd for $C_{10}H_7F_3S$: C 55.55; H 3.26. Found: C 55.30; H 3.30%.

6-Chloro-4-(trifluoromethyl)-2*H*-thiochromene (**1b**) was obtained as white crystals in the analogous manner. Yield: 82%. Mp: 35–36 °C (PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 8.4, 2.1 Hz, 1H), 6.76 (t, J = 5.8 Hz, 1H), 3.43 (dd, J = 5.8, 1.8 Hz, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 131.9, 131.8, 129.6 (q, J = 29.9 Hz), 129.0, 128.9, 128.8, 127.2 (q, J = 6.3 Hz), 125.9 (q, J = 2.7 Hz), 123.1 (q, J = 273.5 Hz), 24.0 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –63.43 (s) ppm. MS (EI, 70 eV), *m/z* (I_{rel} (%)): 250 $[M]^+$ (23), 249 $[M–H]^+$ (14), 181 $[M–CF_3]^+$ (100), 146 [M–CF_3–Cl]+ (21), 145 $[M–HCF_3–Cl]^+$ (24). Anal. Calcd for $C_{10}H_6ClF_3S$: C 47.92; H 2.41. Found: C 47.97; H 2.43%.

Synthesis of 4-CF_3-2*H*-thiocoumarins. A solution of pyridine (1.90 g, 24 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a suspension of finely ground CrO_3 (1.5 g, 15 mmol) in CH_2Cl_2 (40 mL). The resulting red-brown solution was stirred for 30 min and cooled to 5 °C. Then a solution of thiochromene **1a** (0.22 g, 1 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at 20 °C for 24 h. The workup was accomplished according to the published procedure [7]. **4-(Trifluoromethyl)-2*H*-thiochromen-2-one** (**4a**) was isolated by column chromatography on silica gel (eluent: PE–AcOEt, 7:1). Yield 0.14 g (61%). Mp: 78 °C (PE). **4-(Trifluoromethyl)-6-chloro-2*H*-thiochromen-2-one** (**4b**) was obtained analogously. Yield: 65%. Mp: 120 °C (PE–EA). The physicochemical and spectral characteristics of compounds **4a,b** were in good agreement with the literature data [10].

Conclusions

In summary, we developed a convenient synthetic route to 4-(trifluoromethyl)-2*H*-chromenes that involves the reaction of 1-thiochroman-4-ones with trifluoromethyltrimethylsilane and subsequent dehydration of 4-CF_3-thiochroman-4-ols with phosphorus pentoxide on silica gel.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: the NMR and mass spectra of the compounds under consideration. For ESI, see DOI: 10.32931/io2531a.

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