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

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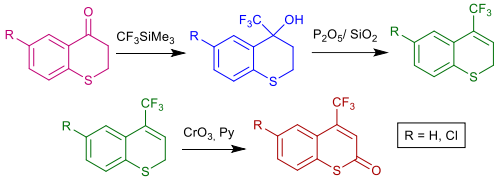
Abstract

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.



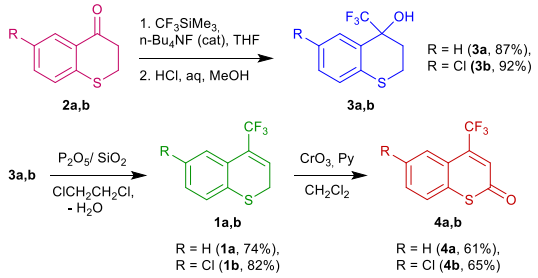
Key words: 4-trifluoromethyl-2*H*-thiochromenes, 4-(trifluoromethyl)thiocoumarins, 1-thiochroman-4-ones.

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** (4.10 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 5.10 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 (1.50 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

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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/ioXXXXx.

References

1. S. Murugappan, P. V. Kuthe, K. V. G. C. Sekhar, M. Sankaranarayanan, *Org. Biomol. Chem.*, **2024**, *22*, 6045–6079. DOI: 10.1039/d4ob00690a
2. S. S. Sajadikhah, M. Nassiri, *Chem. Heterocycl. Compd.*, **2021**, *57*, 1073–1075. DOI: 10.1007/s10593-021-03026-x
3. C. Ortiz, F. Echeverri, S. Robledo, D. Lanari, M. Curini, W. Quiñones, E. Vargas, *Molecules*, **2020**, *25*, 800. DOI: 10.3390/molecules25040800
4. R. Roy, S. Rakshit, T. Bhowmik, S. Khan, A. Ghatak, S. Bhar, *J. Org. Chem.*, **2014**, *79*, 6603–6614. DOI: 10.1021/jo5011125
5. V. Luque-Agudo, J. Albarrán-Velo, J. G. Fernández-Bolaños, O. López, M. E. Light, J. M. Padrón, I. Lagunes, E. Román, J. A. Serrano, M. V. Gil, *New J. Chem.*, **2017**, *41*, 3154–3162. DOI: 10.1039/C6NJ03940E

6. A. A. Kotlobay, M. A. Dubinnyi, K. V. Purtov, E. B. Guglya, N. S. Rodionova, V. N. Petushkov, Y. V. Bolt, V. S. Kublitski, Z. M. Kaskova, R. H. Ziganshin, Y. V. Nelyubina, P. V. Dorovatovskii, I. E. Eliseev, B. R. Branchini, G. Bourenkov, I. A. Ivanov, Y. Oba, I. V. Yampolsky, A. S. Tsarkova, *Proc. Natl. Acad. Sci. U. S. A.*, **2019**, *116*, 18911–18916. DOI: 10.1073/pnas.1902095116
7. A. S. Golubev, P. N. Ostapchuk, T. V. Strelkova, N. D. Kagramanov, K. Yu. Suponitsky, R. U. Takazova, N. D. Chkanikov, *Org. Biomol. Chem.*, **2022**, *20*, 6809–6820. DOI: 10.1039/d2ob01177h
8. G. K. S. Prakash, R. Krishnamurti, G. A. Olah, *J. Am. Chem. Soc.*, **1989**, *111*, 393–395. DOI: 10.1021/ja00183a073
9. A. Ruwet, M. Renson, *Bull. Soc. Chim. Belg.*, **1968**, *77*, 465–466. DOI: 10.1002/bscb.19680770711
10. A. S. Golubev, I. M. Golubev, P. N. Ostapchuk, T. V. Strelkova, K. Yu. Suponitsky, N. D. Chkanikov, *Russ. Chem. Bull.*, **2024**, *73*, 3045–3054. DOI: 10.1007/s11172-024-4421-5
11. C. D. Hurd, S. Hayao, *J. Am. Chem. Soc.*, **1954**, *76*, 5065–5069. DOI: 10.1021/ja01649a016