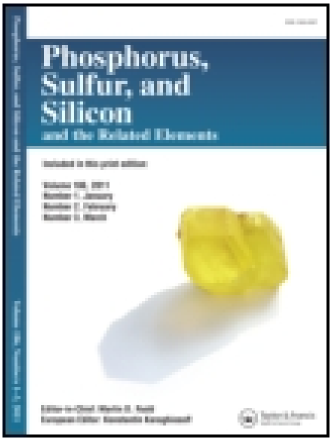

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A Novel and Simple Synthesis of 2-(Trifluoromethyl)-4H-thiochromen-4-ones

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A Novel and Simple Synthesis of 2-(Trifluoromethyl)-4*H*-thiochromen-4-ones

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*Alkyl 2-mercaptophenyl ketones react with trifluoroacetic anhydride in the presence of triethylamine to give 2-(trifluoromethyl)-4*H*-thiochromen-4-ones, which are transformed into the corresponding pyrazoles by treatment with hydrazine hydrate and into 1,1-dioxides by oxidation with H_2O_2 in AcOH.*

Keywords 2-(Trifluoromethyl)-4*H*-thiochromen-4-one and their 1,1-dioxides; alkyl 2-mercaptophenyl ketones; pyrazoles

INTRODUCTION

Chromones are one of the most widely distributed classes of natural compounds occurring in the plant kingdom. Many natural and synthetic chromone derivatives exhibit various types of biological activities and are used as substrates in the preparation of a variety of rearranged products and new heterocyclic systems.[1,2] The widespread occurrence of the chromone system in a variety of biologically active products has stimulated considerable interest in the development of new synthetic methods for the construction of chromones and their thio

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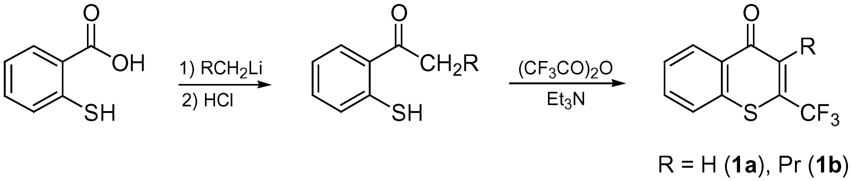
analogues.[3–6] We report a facile, new procedure for the preparation of 2-trifluoromethyl- and 2-trifluoromethyl-3-propyl-1-thiochromones from readily available alkyl 2-mercaptophenyl ketones.[7]

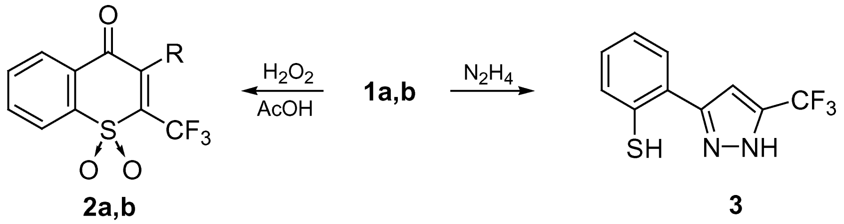
RESULTS AND DISCUSSION

The chemistry of the 1-thiochromones is well known.[4–6] However, there has been only one paper on the synthesis of 1-thiochromones with a polyfluoroalkyl group at the 2 position.[8] To the best of our knowledge, no reports of the synthesis of 3-alkyl-2-polyfluoroalkyl-1-thiochromones have appeared in the literature. In continuation of our studies on the synthesis and chemical properties of 2-polyfluoroalkylchromones, which turned out to be highly reactive compounds in the reactions with N-, S-, and C-nucleophiles,[2] we now report our results on the preparation and reactivity of 2-trifluoromethyl-1-thiochromones **1a**,**b**. These compounds were synthesized as shown in Scheme 1.



SCHEME 1

We found that the modified Baker–Venkataraman reaction of alkyl 2-mercaptophenyl ketones, prepared from thiosalicylic acid and the corresponding alkyllithium, with trifluoroacetic anhydride in the presence of triethylamine in boiling THF, produced 1-thiochromones **1a**,**b**, which are of much interest because of their synthetic potential. Compounds **1a**,**b** were smoothly oxidized by treatment with H_2O_2 in glacial acetic acid and gave thiochromone 1,1-dioxides **2a**,**b** in high yields. The reaction of **1a** with hydrazine hydrate at room temperature yields the expected pyrazole **3** (Scheme 2).



SCHEME 2

In conclusion, the reaction of alkyl 2-mercaptophenyl ketones with trifluoroacetic anhydride provides a simple process from readily available starting materials to 2-trifluoromethyl-1-thiochromones, which may be considered as useful R^F-containing substrates for the synthesis of a wide variety of heterocyclic compounds with potential biological activity.

EXPERIMENTAL

^{1}H (200 or 400 MHz) and ^{19}F (188 MHz) NMR spectra were recorded on a Bruker DPS-200 and Bruker DRX-400 spectrometers in $CDCl_3$ solution with TMS as the internal standard. Mass spectra were obtained at 70 eV, 200°C on a MAT 8200 spectrometer. The IR spectra were measured on an IKS-29 instrument as suspensions in Nujol. *o*-Mercaptoacetophenone was obtained from thiosalicylic acid and methyllithium according to known method.[7]

1-(2-Sulfanylphenyl)pentan-1-one

A mixture of thiosalicylic acid (6.0 g, 0.039 mol) and finely dispersed LiH (0.80 g, 0.10 mol) in anhydrous THF (20 ml) was refluxed for 0.5 h. Then the mixture was cooled to rt and 100 ml of 1 M (0.10 mol) butyllithium in Et_2O was added under a nitrogen atmosphere. The mixture was allowed to stand at rt for 4 h. It was then poured into water (100 ml), the aqueous layer was saturated with ammonium chloride, and the organic phase was separated. After removal of the solvent under reduced pressure, the residual oil was distilled to give the fraction with bp 153–165°C (11 Torr). The crude product was treated with 15 ml of pentane at −30°C and the crystalline material was isolated by filtration to give the title compound as colorless crystals. Yield 5.05 g (67%), mp 46–47°C; IR (Nujol) 1665 (C=O), 1585, 1550 cm^{-1} (Ar); ^{1}H NMR (400 MHz, $CDCl_3$, J/Hz) δ 0.95 (t, 3H, Me, $J = 7.3$), 1.41 (sext, 2H, CH_2, $J = 7.4$), 1.73 (quint, 2H, CH_2, $J = 7.5$), 2.97 (t, 2H, CH_2, $J = 7.4$), 4.36 (s, 1H, SH), 7.18–7.22 (m, 1H, Ar), 7.29–7.32 (m, 2H, Ar), 7.88 (d, 1H, H-6, $J_o = 7.8$). Anal. calcd. for $C_{11}H_{14}OS$: C, 68.00; H, 7.26. Found: C, 67.91; H, 7.17.

2-(Trifluoromethyl)-4*H*-thiochromen-4-one (1a)

Triethylamine (11.1 g, 0.11 mol) was added to a solution of *o*-mercaptoacetophenone (4.0 g, 0.026 mol) and trifluoroacetic anhydride (8.0 g, 0.038 mol) in anhydrous THF (15 ml). After the initial exothermic reaction had subsided (approximately 10 min), the reaction mixture was refluxed for 10 min. Then, diluted HCl (3 ml of water and 9 ml of concentrated HCl) was added at heating and the resulting solution was refluxed for an additional 15 min. The cooled mixture was quenched by addition of water (100 ml) and extracted with pentane (3 × 20). After removal of the solvent under reduced pressure, the residual oil was distilled to give the fraction with bp 90–95°C (0.5 Torr). The crude product was treated with 15 ml of 70% ethanol at −30°C and the crystalline material was isolated by filtration, washed with aqueous ethanol, and dried to give the title compound as colorless crystals. Yield 2.65 g (44%), mp 52–53°C (lit.[8] mp 50–52°C); MS m/z [I_{rel} (%)] 230 $[\mathrm{M}]^+$ (89), 202 (100), 183 (34), 136 (61), 108 (44), 69 (29), 28 (50).

3-Propyl-2-(trifluoromethyl)-4*H*-thiochromen-4-one (1b)

This compound was obtained in a similar way to **1a** in 23% yield as a colorless solid; mp 73–74°C; IR (Nujol) 1625 (C=O), 1590, 1550 cm^{-1} (C=C, Ar); ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$, J/Hz) δ 1.04 (t, 3H, Me, $J = 7.4$), 1.51–1.61 (m, 2H, $\mathrm{CH_2}$), 2.83 (tq, 2H, $\mathrm{CH_2}$, $J = 8.0$, $^5J_{\mathrm{H,F}} = 1.7$), 7.58 (ddd, 1H, H-6, $J_o = 8.1, 6.7$, $J_m = 1.6$), 7.62 (ddd, 1H, H-8, $J_o = 8.1$, $J_m = 1.6$, $J_p = 0.6$), 7.66 (ddd, 1H, H-7, $J_o = 8.1, 6.7$, $J_m = 1.5$), 8.50 (ddd, 1H, H-5, $J_o = 8.1$, $J_m = 1.5$, $J_p = 0.6$). Anal. calcd. for $\mathrm{C_{13}H_{11}F_3OS}$: C, 57.34; H, 4.07. Found: C, 57.63; H, 4.41.

2-(Trifluoromethyl)-1λ^6-thiochromene-1,1,4-trione (2a)

A mixture of thiochromone **1a** (0.50 g, 2.2 mmol), 33% $\mathrm{H_2O_2}$ (3 ml), and AcOH (6 ml) was heated in a water bath for 1 h and then cooled to room temperature. The reaction mixture was diluted with water (20 ml) and the crystalline product that precipitated was filtered off, washed with water, dried, and recrystallized from methylcyclopentane. Yield 0.24 g (42%) as a yellow powder; mp 135–136°C; ^{1}H NMR (200 MHz, $\mathrm{CDCl_3}$, J/Hz) δ 7.08 (s, 1H, =CH), 7.82 (td, 1H, H-6, $J_o = 7.6$, $J_m = 1.2$), 7.95 (td, 1H, H-7, $J_o = 7.6$, $J_m = 1.3$), 8.08 (dd, 1H, H-8, $J_o = 7.9$, $J_m = 1.2$), 8.19 (dd, 1H, H-5, $J_o = 7.9$, $J_m = 1.3$); ^{19}F NMR (188 MHz, $\mathrm{CDCl_3}$, $\mathrm{CFCl_3}$) δ −61.6 (d, $\mathrm{CF_3}$, $^4J_{\mathrm{F,H}} = 1.0$ Hz); MS m/z [I_{rel} (%)] 262 $[\mathrm{M}]^+$ (20), 193 $[\mathrm{M{-}CF_3}]^+$ (44), 136 (24), 104 (100), 76 (49), 50 (21); HRMS calcd. for $\mathrm{C_{10}H_5F_3O_3S}$ (M^+) 261.9912. Found: 261.9913.

3-Propyl-2-(trifluoromethyl)-1λ^6-thiochromene-1,1,4-trione (2b)

This compound was obtained in a similar way to **2a** in 89% yield as a colorless powder, mp 86–87°C; ^{1}H NMR (400 MHz, $\mathrm{CDCl_3}$, J/Hz) δ 1.04 (t, 3H, Me, $J = 7.4$), 1.56 (sext, 2H, $\mathrm{CH_2}$, $J = 7.4$), 2.74 (tq, 2H, $\mathrm{CH_2}$, $J = 8.0$, $^5J_{\mathrm{H,F}} = 1.5$), 7.79 (td, 1H, H-6, $J_o = 7.6$, $J_m = 1.2$), 7.91 (td, 1H, H-7, $J_o = 7.6$, $J_m = 1.3$), 8.06 (ddd, 1H, H-8, $J_o = 7.9$, $J_m = 1.2$, $J_p = 0.4$), 8.19 (ddd, 1H, H-5, $J_o = 7.9$, $J_m = 1.3$, $J_p = 0.4$); MS m/z [I_{rel} (%)] 304 $[\mathrm{M}]^+$ (4), 171 (45), 104 (100), 76 (63); HRMS calcd. for $C_{13}H_{11}F_3O_3S$ (M^+) 304.0381. Found: 304.0382.

3(5)-(2-Mercaptophenyl)-5(3)-trifluoromethylpyrazole (3)

A mixture of thiochromone **1a** (0.20 g, 0.87 mmol) and 80% hydrazine hydrate (0.5 ml) was stirred at room temperature for 20 min and then 20% HCl (7 ml) was added. The crystalline product that precipitated was filtered off, washed with water, dried, and recrystallized from cyclohexane. Yield 0.13 g (62%) as yellow crystals; mp 92–94°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.62 (s, 1H, SH), 6.84 (s, 1H, =CH), 7.27–7.54 (m, 4H, arom.), 11.3 (br.s, 1H, NH); ^{19}F NMR (188 MHz, $CDCl_3$, $CFCl_3$) δ −63.2 (s, CF_3); MS m/z [I_{rel} (%)] 244 $[\mathrm{M}]^+$ (100), 225 (14), 147 (39), 121 (17), 69 (14); HRMS calcd. for $C_{10}H_7F_3N_2S$ (M^+) 244.0282. Found: 244.0270.

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