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Short Note

6-Chloro-2-hydroxy-2-trifluoromethyl-2*H*-chromene-3-carboxylic acid (5-allylsulfanyl-[1,3,4]thiadiazol-2-yl)-amide

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Abstract: A new chromene containing 1,3,4-thiadiazole and trifluoromethyl(CF_3), 6-chloro-2-hydroxy-2-trifluoromethyl-2*H*-chromene-3-carboxylic acid (5-allylsulfanyl-[1,3,4]thiadiazol-2-yl)-amide was synthesized and its structure was characterized by IR, ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and HRMS.

Keywords: chromene; 6-chloro-2-hydroxy-2-trifluoromethyl-2*H*-chromene-3-carboxylic acid (5-allylsulfanyl-[1,3,4]thiadiazol-2-yl)-amide; synthesis

1. Introduction

Many compounds containing chromene ring moiety display broad spectrum of biological activity [1–4]. 2*H*-Chromenes have gained much attention because of various biological activities such as antiviral, anti-tumor, anti-bacterial, fungicidal, antiflamatory, antioxidative and activator of potassium channels effects [5–9]. Recently, introduction of fluorine atoms into organic compounds has been regarded as one of the best ways for the enhancement or modification of their original biological activities [10,11]. It was found and verified that the trifluoromethyl(CF_3) group, regarded as a pseudo-halogen, imparted unique biological activity [12,13].

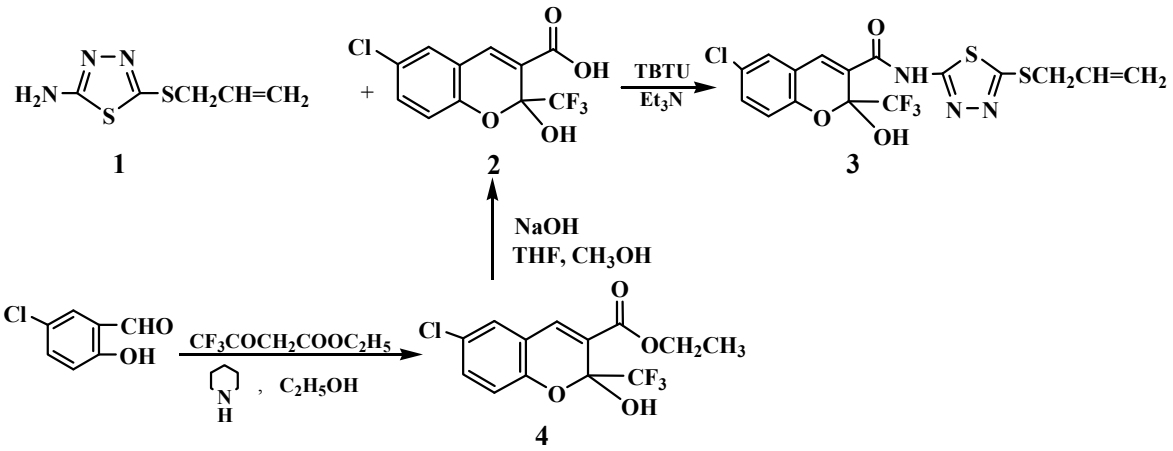
On the other hand, thiadiazoles are organic heterocyclic compounds having been reported to have a wide application in pharmaceuticals and pesticides due to their good and extensive biological activities [14–16]. Introduction of a thiadiazole ring into the chromene may improve the biological activities. As a continuation of our previous work for synthesis of heterocyclic compounds with chromene skeleton [17–19], we report here another new 2*H*-chromene, 6-chloro-2-hydroxy-2-

trifluoromethyl-2*H*-chromene-3-carboxylic acid (5-allylsulfanyl-[1,3,4]thiadiazol-2-yl)-amide, and it was fully characterized.

Synthesis

The title compound **3** was prepared from dehydration of 6-chloro-2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylic acid **2**, obtained by hydrolysis of ethyl 6-chloro-2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylate **4** [19], with an equimolar amount of 5-allylsulfanyl-[1,3,4]thiadiazol-2-ylamine **1** in acetonitrile for 24 h in the presence of *N,N,N′,N′*-tetramethyluranium-*O*-(benzotriazol-1-yl)tetrafluoroborate (TBTU) and triethyl amine. This new chromene was fully characterized by IR, ^{1}H-NMR, ^{13}C-NMR and HRMS data. As shown in Scheme 1.

Scheme 1. The synthesis of 6-chloro-2-hydroxy-2-trifluoromethyl-2*H*-chromene-3-carboxylic acid (5-allylsulfanyl-[1,3,4]thiadiazol-2-yl)-amide, **3**.



Experimental

All reagents were purchased from commercial sources and used without further purification. Infrared spectra were recorded with a Nicolet IS10 Fourier Transform Infrared Spectrophotometer (4000–400 cm^{-1}) (KBr pellets). ^{1}H and ^{13}C-NMR spectra of $CDCl_3$ solutions were obtained by a Bruker DPX-400 Spectrometer, respectively. ^{19}F-NMR spectra were recorded in $CDCl_3$ by instrument calibration. High resolution mass spectrometry data were measured on a Waters Q-Tof micro™ instrument with an electrospray ionization source (ESIMS). Melting points were determined on an X-5 digital microscopic melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and are uncorrected.

To a solution of 6-chloro-2-hydroxy-2-(trifluoromethyl)-2*H*-chromene-3-carboxylic acid (**2**) (2.20 g, 7.5 mmol) and 5-allylsulfanyl-[1,3,4]thiadiazol-2-ylamine (**1**) (1.30 g, 7.5 mmol), in dry acetonitrile (100 mL), TBTU (4.81 g, 15 mmol) and Et_3N (3.1 mL, 22.5 mmol) were added. The mixture was stirred for 24 h at 40 °C with TLC monitoring using ethyl acetate: ethylene dichloride (1:1) as eluent. After completion of the reaction, the solvent was removed by reduced pressure distillation. The residue was chromatographed on silica gel using ethyl acetate:ethylene dichloride (1:3~1:1) as the eluent, to make the title compound **3** a white solid.

Yield: 56%; m.p.: 205.2~206.1 °C.

IR, (ν, cm^{-1}): 3457 (-OH), 3128 (N-H), 1654 (C=O), 1611, 1563, 1488 (Ar), 1281 (C-N), 1186 (C-O-C).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 4.00 (d, *J* = 6.4 Hz, 2H, CH_2S), 5.36 (d, *J* = 10 Hz, 1H, -CH=), 5.53 (d, *J* = 16.8 Hz, 1H, Allyl-H), 5.97–6.08 (m, 2H, Allyl-H, Ar-H), 7.11 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.45 (d, *J* = 7.6 Hz, Ar-H), 8.64 (s, 1H, H-4).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 36.00, 69.95(q, $^2J_{C,\,F}$ = 33.5 Hz, *C*CF_3), 105.14, 114.50, 119.03, 120.96, 123.45(q, $^1J_{C,\,F}$ = 286.6 Hz, CF_3), 127.57, 128.28, 130.14, 133.95, 138.64, 153.85, 158.25, 163.33, 164.73.

^{19}F-NMR ($CDCl_3$, 376.5 MHz): −76.68 (-CF_3).

HRMS: calcd for *m/z* $(C_{16}H_{11}ClF_3N_3O_3S_2\text{-}OH)^+$: 431.9855; found: 431.9854.

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Conflicts of Interest

The authors declare no conflict of interest.

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