Chemistry of Heterocyclic Compounds, Vol. 45, No. 10, 2009

LETTERS TO THE EDITOR

SYNTHESES OF SOME 3-SUBSTITUTED ISOTHIOCHROMEN-1-ONES

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Keywords: dicarboxylic acid, isothiochromen-1-one, intramolecular cyclization.

Isocoumarins and their derivatives such as dihydroisocoumarins are secondary metabolites of a wide variety of microbial plant and insect sources and can be used in the synthesis of other medicinal compounds [1-4]. A number of substituted thioisocoumarins has been prepared [5]. They also occur as mycotoxins, fungal metabolites, and a principal sweetness component of the Japanese sweet tea [6–8]. Most methods available for the construction of the thioisocoumarin and thiocoumarin nucleus suffer from one or more drawbacks, such as a multi-step procedure, low yields [9, 10], and long reaction time required to obtain a good yield of the desired product, or the use of expensive and hazardous reagents and solvents. For example, 3-arylisocoumarins were transformed into 3-aryl-1-thioisocoumarins by the reaction with phosphorus pentasulfide, which were converted first into 3-aryldithioisocoumarins in a few steps, and then oxidized to 3-aryl-2-thioisocoumarins by potassium permanganate [11, 12].

Monolkyl and dialkyl homophthalates can be converted into 3-alkoxy- or 3-(alkylthio)dithioisocoumarins, which are readily oxidized to the corresponding 2-thioisocoumarins by potassium permanganate or benzonitrile N-oxide [13].

Finding an efficient method for the synthesis of isothiochromen-2-one is still a challenge.

In continuity of our interest [14–18] we have developed a new method for the synthesis of 3-substituted isothiochromen-2-ones from 2-(mercaptocarbonylmethyl)benzothioic acid and various aromatic or aliphatic acid chlorides. Homophthalic acid **1** was treated with thionyl chloride to give 2-(chlorocarbonylmethyl)benzoyl chloride **2**. Its reaction with potassium hydrogen sulfide followed by hydrolysis gave 2-(mercaptocarbonylmethyl)benzothioic S-acid **3**. The treatment of product **3** with different acid chlorides **4** gave 3-substituted 1H-isothiochromen-1-ones **5**.

The elaborated route to 2-thioisocoumarins is a simple method proceeding without formation of any side products such as dithioisocoumarins with the additional advantage of easy isolation of products.

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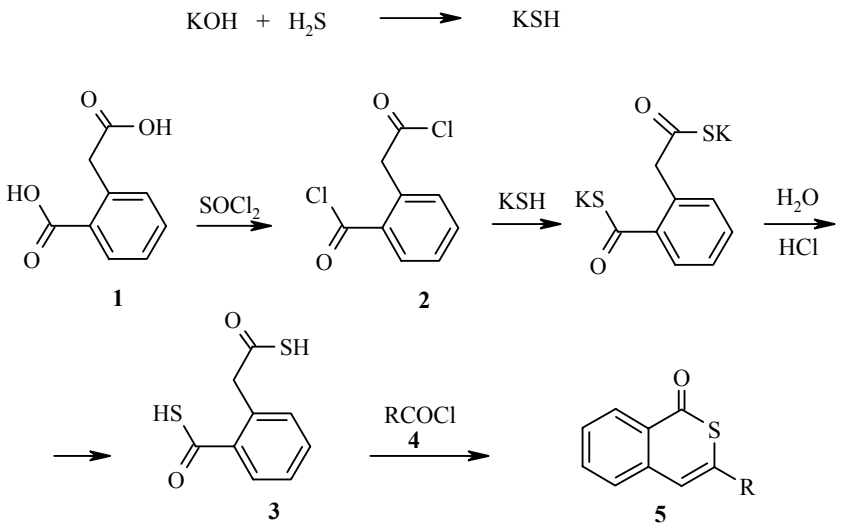
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1586-1588, September, 2009. Original article received November 9, 2008. In revised form September 21, 2009.

 0009-3122/09/4510-1276

The ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ (TMS as an internal reference). GC/MS analyses were performed with Agilent GC/MS-5973 Inert MSD series.



2-(Mercaptocarbonylmethyl)benzothioic acid (3). Homophthalic acid **1** (0.1 mol) was converted to its chloride **2** by stirring with $SOCl_2$ (0.15 mol) and then mixed with a solution containing ethanol/KOH, then stirred under 10°C by passing H_2S gas continuously overnight. The resulting solution was filtered off, and the filtrate was distilled and evaporated to dryness. The residue was then mixed with cold water and extracted using benzene to remove any neutral material. The aqueous solution was finally acidified, and the solid formed was separated and extracted with ether. The ether was distilled under vacuum to give compound **3** (95%); mp 183-185°C. ^1H NMR spectrum, δ, ppm: 2.56 (2H, s); 3.56 (2H, s); 7.24-7.22 (2H, m); 7.74 (1H, d); 7.35 (1H, m). GC/MS, *m/z*: 212.1128. $C_9H_8O_2S_2$ (212.28).

3-Substituted isothiochromen-1-ones 5a–d were synthesized from benzothioic acid **3** (1 mmol) and acid chloride **4a–d** (4 mmol) by heating under reflux at 200°C in an oil bath. The products obtained were recrystallized from ether using activated charcoal and identified by NMR spectroscopy.

3-Phenyl-1H-isothiochromen-1-one (5a) was synthesized using benzoyl chloride in 95% yield; mp 105°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.1 (1H, s, H-4); 7.2-7.3 (4H, m, Ar); 7.41-7.42 (2H, d, *J* = 6.3, Ar); 7.58-7.60 (2H, d, *J* = 8, Ar); 7.7 (1H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 102.58 (C=CR); 120.30, 125.36, 127.06, 128.71, 129.06, 129.33, 129.50, 129.71, 130.49, 132.08, 135.85, 137.75 (C=CR); 152.89, 161.78 (C=O). GC/MS, *m/z*: 239 [M^+]. Found, %: C 75.47; H 4.32; O 6.67; S 13.34. $C_{15}H_{10}OS$. Calculated, %: C 75.60; H 4.23; O 6.71; S 13.46.

3-Methyl-1H-isothiochromen-1-one (5b) was synthesized using acetyl chloride in 95% yield; mp 110°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.7 (3H, s, Ar); 6.7 (1H, s, H-4); 7.3 (1H, m, Ar); 7.41-7.50 (2H, m, Ar); 7.93-7.95 (1H, d, *J* = 8, Ar). ^{13}C NMR spectrum, δ, ppm: 9.64 (CH_3); 103.53 (C=CCH_3); 119.94, 124.84, 127.55, 129.53, 134.73, 137.65 (C=CCH_3); 154.57, 163.01 (–C=O). GC/MS, *m/z*: 177 [M^+]. Found, %: C 68.27; H 4.51; O 9.19; S 18.03. $C_{10}H_8OS$. Calculated, %: C 68.15; H 4.58; O 9.08; S 18.19.

3-(4-Chlorophenyl)-1H-isothiochromen-1-one (5c) was synthesized using *p*-chloro- benzoyl chloride in 94% yield; mp 145°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.2 (1H, s, H-4); 7.25 (2H, m, Ar); 7.28 (1H, m, Ar); 7.3 (2H, m, Ar); 7.5 (1H, m, Ar); 7.6 (1H, m, Ar); 7.94-7.92 (1H, d, *J* = 7.6, Ar). ^{13}C NMR spectrum, δ, ppm: 102.09 (C=CR); 120.58, 126.04, 126.51, 2×(128.42); 129.13, 129.76, 130.47, 2×(134.99); 136.02, 137.27

(C=CR); 152.58, 162.05 (C=O). GC/MS, *m/z*: 258.24 [M+2]. Found, %: C 66.17; H 3.27; O 5.76; S 11.71. $C_{15}H_9ClOS$ (256.68). Calculated, %: C 66.05; H 3.33; Cl 13.00; O 5.87; S 11.76.

3-*p*-Tolyl-1H-isothiochromen-1-one (5d) was synthesized using *p*-methylbenzoyl chloride in 85% yield; mp 160°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, CH_3); 7.12 (2H, m, Ar); 7.2 (1H, s, H-4); 7.28–7.31 (2H, m, Ar); 7.5 (1H, m, Ar); 7.6 (2H, m, Ar); 7.9 (1H, s, Ar). ^{13}C NMR spectrum, δ, ppm: 21.39 (CH_3); 101.08 (C=CR); 120.42, 125.19, 2×(125.84); 127.91, 129.20, 2×(129.55); 129.65, 134.82, 137.73 (C=CR); 140.28, 153.86, 162.45 (C=O). GC/MS, *m/z*: 256.18 [M^+]. Found, %: C 76.27; H 4.67; O 6.41; S 12.79. $C_{16}H_{12}OS$ (256.26). Calculated, %: C 76.16; H 4.79; O 6.34; S 12.71.

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