

Short Note

2-(2-(4-Methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic Acid

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Abstract: For the first time, we describe a new approach towards the synthesis of previously unknown 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic acid. The presented method is based on the multicomponent condensation of 5-hydroxy-4,7-dimethyl-2H-chromen-2-one, 4-methoxyphenylglyoxal and Meldrum's acid. It was shown that the studied reaction proceeds in two steps including the initial interaction of starting materials in MeCN and the final formation of furylacetic acid moiety in acidic media. The structures of the obtained compound were established by ^1H , ^{13}C -NMR spectroscopy and high-resolution mass spectrometry.

Keywords: multicomponent reaction; furocoumarin; Meldrum's acid; arylglyoxals



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1. Introduction

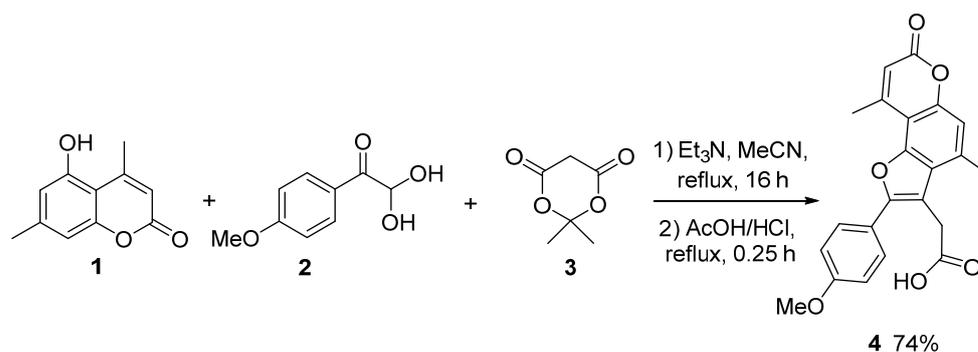
Furocoumarin derivatives are an important class of heterocyclic compounds widely presented in various natural products [1–7]. Numerous representatives of furocoumarins possess significant biological activity [8–14]. Generally, products of this type are used as active photosensitizers in psoralen and UVA (PUVA) therapy. Thus, furocoumarins can be employed in treatment of various skin diseases [15–22]. In this regard, the development of new methods for the synthesis of products containing the furocoumarin moiety is of considerable interest.

In most cases, furocoumarins can be prepared on the basis of substituted hydroxy-coumarins. α -Halogen ketones are generally employed as the second component for the formation of the furocoumarin moiety [23–28]. Wherein, the use of the methodology of multicomponent reactions can open access to a wide range of products containing the furocoumarin fragment. A significant advantage of this approach is the ability to obtain target products in one synthetic stage [29–33]. It should be noted that we previously proposed a general approach to the synthesis of condensed furylacetic acids based on the multicomponent reaction of various hydroxyl derivatives with arylglyoxals and Meldrum's acid [34–38]. We assumed that this approach could be used to synthesize substituted furo[2,3-f]coumarins.

2. Results

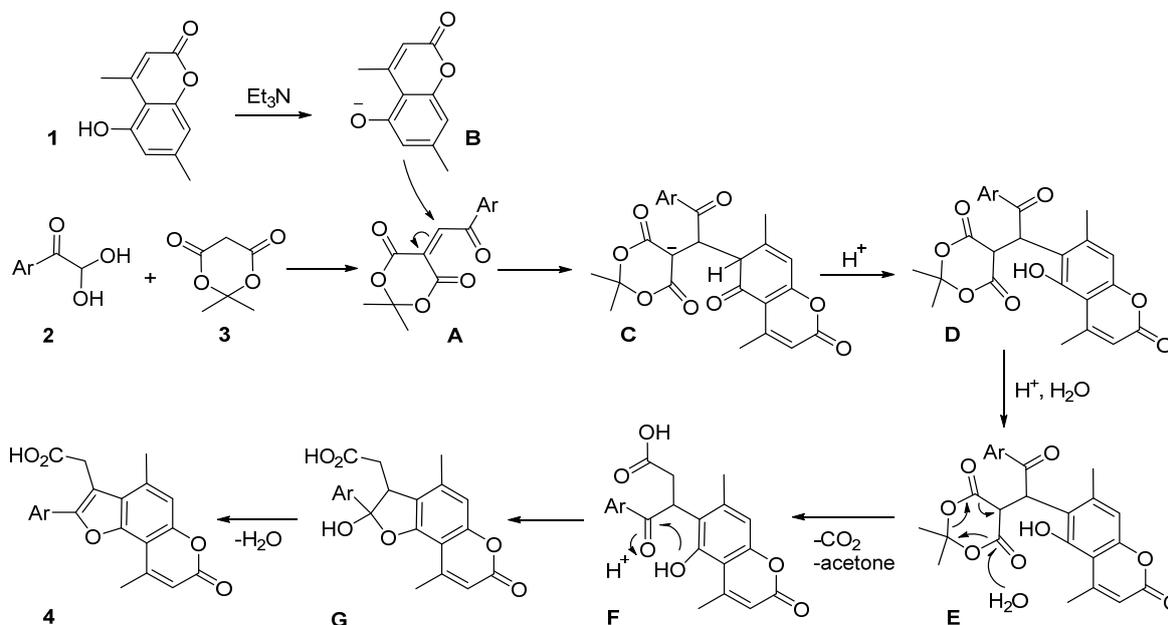
In the present communication, we report that a multicomponent reaction of 5-hydroxy-4,7-dimethyl-2H-chromen-2-one **1**, 4-methoxyphenylglyoxal **2** and Meldrum's acid **3** in the presence of Et_3N leads to previously unknown 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic acid **4** (Scheme 1). Earlier, it was demonstrated that this type of reaction is a two-step cascade process. Herein, the interaction of components in acetonitrile (MeCN) proceeds at the first stage, and the final acid-catalyzed cyclization leads to the target product. It is important to note that in the considered case prolonged reflux (16 h) in MeCN is necessary for the synthesis of furocoumarin derivative **4**. At the same time, it is necessary to use a 6-fold excess of arylglyoxal **2**, Meldrum's acid **3**, and Et_3N for the complete conversion of coumarin **1** to target product **4**. It should be

noted that the starting compound **1** remains as an impurity in the resulting product **2** if a smaller excess of the above-mentioned reagents is used. Apparently, this difference is due to the low reactivity of the coumarin **1** compared with those of the previously studied hydroxyl derivatives. Wherein, a mixture of hydrochloric and acetic acids is used for the final cyclization similar to the previous works [34–38]. The presented method allows one to synthesize the target 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic acid **4** with a 74% yield.



Scheme 1. Synthesis of 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic acid **4**.

The proposed reaction mechanism is presented in Scheme 2. At the first step, interaction of Meldrum's acid **3** with arylglyoxal **2** leads to intermediate **A**. Next, the addition of coumarin anion **B** to Michael acceptor **A** results in the formation of adduct **D**. The further acid-catalyzed cleavage of Meldrum's acid moiety is followed by the elimination of CO_2 and acetone-produced γ -ketoacid **F**. Finally, intermediate **F** is transformed to the target product **4** via cyclodehydration including the hydroxyl group of the coumarin fragment and the carbonyl unit.



Scheme 2. Proposed reaction mechanism for the formation of 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic acid **4**.

In summary, a convenient one-pot cascade method for the synthesis of previously unknown 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic

acid based on the multicomponent condensation of 5-hydroxy-4,7-dimethyl-2H-chromen-2-one, 4-methoxyphenylglyoxal and Meldrum's acid was elaborated. The advantages of this approach are the application of readily available starting compounds, atom economy, and easy work-up procedures, which can avoid chromatographic purification. The structure of the synthesized furocoumarin was confirmed by ^1H , ^{13}C -NMR spectroscopy and high-resolution mass spectrometry.

3. Materials and Methods

All starting chemicals and solvents were commercially available and were used as received. NMR spectra were recorded with Bruker DRX 500 (500 MHz) spectrometers (Billerica, MA, USA) in $\text{DMSO-}d_6$. Chemical shifts (ppm) were given relative to solvent signals ($\text{DMSO-}d_6$: 2.50 ppm (^1H NMR) and 39.52 ppm (^{13}C NMR)). High-resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF II instrument (Bruker Daltonik GmbH, Bremen, Germany) using electrospray ionization (ESI). The melting points were determined on a Kofler hot stage (Dresden, Germany). IR spectra were recorded on a Bruker ALPHA (Santa Barbara, CA 93117, USA) spectrophotometer in a KBr pellet.

Experimental Procedure for the Synthesis of 2-(2-(4-methoxyphenyl)-4,9-dimethyl-7-oxo-7H-furo[2,3-f]chromen-3-yl)acetic Acid 4

A mixture of 5-hydroxy-4,7-dimethyl-2H-chromen-2-one **1** (2 mmol, 0.38 g), 4-methoxyphenylglyoxal hydrate **2** (6 mmol, 1.09 g), Meldrum's acid **3** (6 mmol, 0.86 g), and Et_3N (6 mmol, 0.84 mL) in 10 mL of MeCN was refluxed for 8 h. Then, an additional amount of 4-methoxyphenylglyoxal hydrate **2** (6 mmol, 1.09 g), Meldrum's acid **3** (6 mmol, 0.86 g), and Et_3N (6 mmol, 0.84 mL) was added, and the reaction mixture was refluxed for 8 h. Next, AcOH (5 mL) was added, and the solvent was evaporated under a reduced pressure. Then, AcOH (6 mL) and HCl_{conc} (3 mL) were added to the residue, and the solution was refluxed for 15 min. Further, the solution was cooled, and the resulting precipitate was filtered off and washed 70% aq. AcOH (3×7 mL). To remove traces of AcOH and HCl, the precipitate was kept for 24 h in water (50 mL) at room temperature, collected by filtration and washed with water (3×10 mL). Pale yellow powder; yield 74% (0.56 g, 1.5 mmol); $R_f = 0.6$ (ethyl acetate/methanol volume ratio = 4:1); mp 291–293 °C. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) (Figure S1) δ 12.63 (br.s, 1H), 7.69 (d, $J = 8.8$ Hz, 2H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.06 (d, $J = 1.1$ Hz, 1H), 6.30 (d, $J = 1.5$ Hz, 1H), 3.92 (s, 2H), 3.84 (s, 3H), 2.74 (d, $J = 1.3$ Hz, 3H), and 2.66 (s, 3H). ^{13}C NMR (126 MHz, $\text{DMSO-}d_6$) (Figure S2) δ 172.19, 159.71, 159.40, 152.90, 151.26, 150.77, 148.72, 135.41, 128.27, 124.51, 121.73, 114.45, 113.22, 113.16, 108.77, 104.39, 55.14, 30.69, 21.03, and 18.63. IR spectra (KBr) (Figure S4), ν , cm^{-1} : 3061, 3000, 2957, 2837, 2684, 2595, 2554, 2422, 2061, 1904, 1836, 1726, 1694, 1670, 1626, 1511, 1453, 1401, 1384, 1365, 1308, 1256, 1215, 1177, 1159, 1110, 1065, 1035, 992, 924. HRMS (ESI-TOF) (Figure S3) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_6$: 379.1176; Found: 379.1177.

Supplementary Materials: The following are available online: copies of ^1H , ^{13}C -NMR, mass and IR spectra for compound **4**. Figure S1: ^1H NMR spectrum (500 MHz) of **4** in $\text{DMSO-}d_6$; Figure S2: ^{13}C (^1H) NMR spectrum (126 MHz) of **4** in $\text{DMSO-}d_6$; Figure S3: HRMS for compound **4**; Figure S4: IR spectrum for compound **4**.

Author Contributions: A.N.K. performed conceptualization, synthesis, spectroscopic analysis, and the writing of the manuscript. B.V.L. performed conceptualization, synthesis, spectroscopic analysis, and the writing of the manuscript. V.G.M. performed conceptualization, synthesis, spectroscopic analysis, and the writing of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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