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Short Note

2-(2-(4-Methoxyphenyl)furo[3,2-*h*]quinolin-3-yl)acetic Acid

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Abstract: A simple and efficient protocol for the synthesis of the previously unknown 2-(2-(4-methoxyphenyl)furo[3,2-*h*]quinolin-3-yl)acetic acid was elaborated. The suggested method is based on the telescoped multicomponent reaction of 8-hydroxyquinoline, 4-methylglyoxal, and Meldrum's acid. The studied process includes the initial interaction of the starting compounds in MeCN followed by intramolecular cyclization to the target product in refluxing acetic acid. The advantage of this approach is the application of readily available starting materials, atom economy, and a simple work-up procedure. The structure of the synthesized furylacetic acid derivative was proven by ^{1}H, ^{13}C, 2D-NMR, IR spectroscopy, and high-resolution mass spectrometry.

Keywords: 8-hydroxyquinoline; arylglyoxals; Meldrum's acid; telescoped process

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1. Introduction

8-Hydroxyquinoline (8HQ) and its derivatives have huge and diverse biological activities [1–6]. 8HQ is one of the oldest antibacterial agents used by mankind, dating back to before the age of modern antibiotics. The interest in the antibacterial agents of this class has not decreased in the present time [7–11]. Further, the various compounds containing 8HQ moiety possess antiproliferative [12–15] and antifungal [9,16–18] properties, and some derivatives of 8HQ have been tested as neuroprotective agents [19–21] and botulinum neurotoxin inhibitors [22]. The structures of some important bioactive derivatives of 8-hydroxyquinoline are shown in Figure 1. Along with pharmacological applications, chelates of 8HQ are used in organic light-emitting diodes (OLEDs) and as fluorescent chemosensors [23,24].

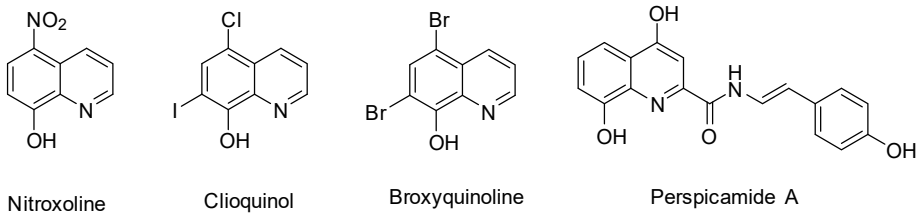
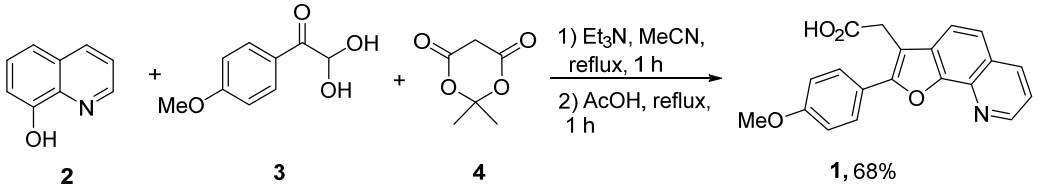


Figure 1. Bioactive 8-hydroxyquinoline derivatives.

A convenient approach to the synthesis of various derivatives of 8-hydroxyquinoline is the use of the methodology of multicomponent reactions [25–27]. The undoubted advantage of these processes is the possibility of one-step synthesis of the target products [28–32]. At the present time, multicomponent reactions employing arylglyoxals as starting compounds have attracted considerable attention [33,34]. The presence of two functional groups in the molecule of these substances allows one to create a wide variety of heterocyclic systems. However, it should be noted that there are no examples in the literature of the joint use of arylglyoxals and 8-hydroxyquinoline in multicomponent reactions. Therefore, the elaboration of novel synthetic methods based on the multicomponent reaction of arylglyoxals and 8HQ is of great interest.

2. Results and Discussion

Herein, we develop a highly efficient approach to synthesize 2-(2-(4-methoxyphenyl)furo [3,2-*h*]quinolin-3-yl)acetic acid **1** on the basis of the multicomponent reaction (MCR) of 8-hydroxyquinoline **2**, 4-methoxyphenylglyoxal **3,** and Meldrum's acid **4** (Scheme 1). Previously, we have demonstrated that similar syntheses of condensed furylacetic acids are achieved through a two-stage telescoped process [35–39]. This approach includes the initial condensation of the starting compounds in acetonitrile (MeCN) and subsequent acid treatment, leading to the target products. It should be noted that the interaction of 8-hydroxyquinoline **2**, 4-methoxyphenylglyoxal **3,** and Meldrum's acid **4** in the presence of Et_3N in MeCN followed by reflux in acetic acid (AcOH) for 1 h resulted in furylacetic acid **1**. As a result of the above-mentioned one-pot telescopic process, the target product was obtained in a 68% yield.



Scheme 1. Synthesis of 2-(2-(4-methoxyphenyl)furo[3,2-*h*]quinolin-3-yl)acetic acid **1**.

The assumed reaction pathway for the formation of 2-(2-(4-methoxyphenyl)furo quinolin-3-yl)acetic acid **1** is depicted in Scheme 2. Initially, base-catalyzed condensation of arylglyoxal **2** with Meldrum's acid **3** leads to unstable aroylmethylene derivative **A**. Next, the addition of 8-hydroxyquinoline anion **B** to intermediate **A** results in the formation of adduct **D**. Further acid treatment of intermediate **D** leads to the cleavage of Meldrum's acid moiety accompanied by the liberation of acetone and CO_2 molecules. As a result, unstable γ-ketoacid **F** was formed. Finally, the cyclization of intermediate **F** with the elimination of water molecules leads to the target furylacetic acid **1**.

For synthesized compound **1,** a series of 2D-NMR (HSQC, HMBC, COSY) experiments were carried out (Figures S5–S7). The key HMBC correlations are presented in Figure 2. The methylene group protons have four main correlations: H_2-1 to C-2 of the carboxyl group, C-3, C-4, and C-5 of a furan moiety. These correlations indicated the presence of an acetic acid unit attached to a furan fragment.

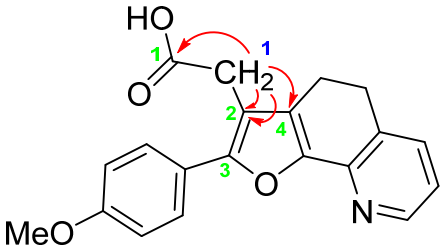
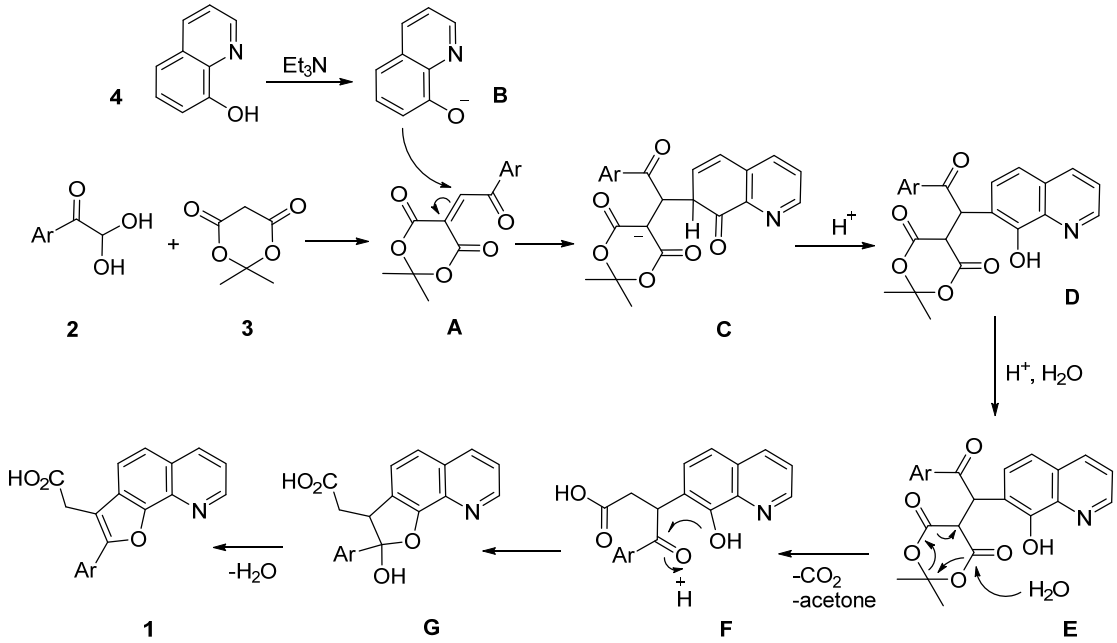


Figure 2. The key HMBC correlations in compound **1**.

In summary, a simple and efficient multicomponent protocol for the preparation of novel 2-(2-(4-methoxyphenyl)furo[3,2-*h*]quinolin-3-yl)acetic acid on the basis of the interaction of 8-hydroxyquinoline, 4-methoxyphenylglyoxal, and Meldrum's acid was suggested. The use of readily accessible starting materials, along with atom economy and a convenient work-up process, allows one to apply the presented method for the synthesis of a wide range of similar furo[3,2-*h*]quinolinacetic acids. The structure of the obtained product was established by ^1H (Figure S1), ^{13}C (Figure S2), 2D-NMR (Figures S5–S7), IR spectroscopy (Figure S4), and high-resolution mass spectrometry (Figure S3).



Scheme 2. A plausible mechanism for the formation of compound **1**.

3. Materials and Methods

All starting chemicals and solvents were commercially available and were used as received. NMR spectra were recorded with Bruker DRX 300 (300 MHz) and Bruker AV 400 (400 MHz) spectrometers (Billerica, MA, USA) in DMSO-d_6. Chemical shifts (ppm) were given relative to solvent signals (DMSO-d_6: 2.50 ppm (^{1}H-NMR) and 39.52 ppm (^{13}C-NMR)). High-resolution mass spectra (HRMS) were obtained through a Bruker micrOTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) using electrospray ionization (ESI). The melting points were determined using 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)furo[3,2-h]quinolin-3-yl)Acetic Acid **1**

A mixture of 8-hydroxyquinoline **2** (2 mmol, 0.29 g), 4-methoxyphenylglyoxal hydrate **3** (2.4 mmol, 0.44 g), Meldrum's acid **4** (3 mmol, 0.29 g), and Et_3N (2 mmol, 0.28 mL) in 6 mL of MeCN was refluxed for 1 h. Then, the solvent was removed under reduced pressure by a rotary evaporator, AcOH (5 mL) was added to the residue, and the solution was refluxed for 1 h. Finally, the reaction mixture was evaporated in rotary, and the residue was recrystallized from MeCN (4 mL). Pale yellow powder; yield 68% (0.45 g, 1.4 mmol); mp 271–272 °C, R_f = 0.5 (ethyl acetate/methanol = 4:1). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 12.72 (br.s, 1H), 8.95 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.90–7.79 (m, 4H), 7.57 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 3.96 (s, 2H), 3.85 (s, 3H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ 171.99, 159.77, 152.71, 150.21, 147.28, 136.59, 135.90, 129.57, 128.26, 125.98, 123.23, 122.36, 120.65, 119.40, 114.63, 109.71, 55.33, 30.10. The key cross peaks (^{1}H-^{13}C) in the 2D-NMR (HMBC) spectrum: $H_1 - C_1$ (3.96; 171.99); $H_1 - C_2$ (3.96; 109.71); $H_1 - C_3$ (3.96; 152.71); $H_1 - C_4$ (3.96; 129.57). The IR spectrum (KBr), ν, cm^{-1}: 3047 (O-H), 2834 (C-H), 1715 (C=O), 1611 (C-C_{aryl}), 1572 (C-C_{aryl}), 1179 (C-O). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcld for $C_{20}H_{15}NO_4$ 334.1074; Found 334.1071.

Supplementary Materials: The following are available online: copies of ^{1}H, ^{13}C-NMR, mass, and IR spectra for compound **1**. Figure S1: ^{1}H-NMR spectrum (300 MHz) of **1** in DMSO-*d6*; Figure S2: ^{13}C{^{1}H}-NMR spectrum (75 MHz) of **1** in DMSO-*d6*; Figure S3: HRMS for compound **1**; Figure S4: IR spectrum for compound **1**; Figure S5: HSQC-NMR spectrum (400 MHz) for compound **1**; Figure S6: HMBC-NMR spectrum (400 MHz) for compound **1**; Figure S7: COSY-NMR spectrum (400 MHz) for compound **1**.

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