Preliminary Communication

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Efficient three-component synthesis of 5-(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-5,12-dihydrobenzo[*b*]-pyrimido[5,4-*g*][1,8]naphthyridine-2,4(1*H*,3*H*)-dione<https://doi.org/10.1515/hc-2017-0265>

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Abstract: 1,8-Naphthyridine derivatives are important heterocyclic compounds. A facile and efficient one-pot procedure for the synthesis of 5-(6-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-5,12-dihydrobenzo[*b*]pyrimido[5,4-*g*][1,8]naphthyridine-2,4(1*H*,3*H*)-dione (**3**) via a three-component reaction of barbituric acid, 2-chloro-3-formylquinoline and ammonia under basic conditions is described.

Keywords: barbituric acid; benzo[*b*][1,8]naphthyridine; 2-chloro-3-formylquinoline.

1,8-Naphthyridine derivatives show a broad range of interesting physiological activities including anti-inflammatory [1], analgesic [2], antiaggressive [3], anticancer [4], antibacterial [5], antitumor [6], antihypertensive [7] and antiallergic [8] properties. Several synthetic routes to this

class of compounds have been reported [9–14]. Interesting procedures involve one-pot condensations [15–17]. Here, we report the synthesis of a new 1,8-naphthyridine derivative **3** by a one-pot three-component reaction of barbituric acid, ammonia and 2-chloro-3-formylquinoline (Scheme 1).

The proposed mechanism is shown in Scheme 2. The first step involves the attack of the enol form of barbituric acid (**1**) on 2-chloro-3-formylquinoline (**2**) to form the corresponding intermediate product **4** by the loss of a molecule of water. A subsequent addition of **4** with a second molecule of barbituric acid (**1**) in its enol form generates the intermediate product **5**, the final reaction of which with ammonia yields the observed product **3** following the loss of H₂O and HCl molecules.

In conclusion, a simple and efficient method for the synthesis of a benzo[*b*][1,8]naphthyridine derivative by a three-component reaction of 2-chloro-3-formylquinoline, barbituric acid and ammonia was developed. Currently, we are studying the scope and limitations of this new reaction using analogues of barbituric acid.

Scheme 1

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Scheme 2

Experimental

5-(6-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-5,12-dihydrobenzo[*b*]pyrimido [5,4-*g*][1,8]naphthyridine-2,4(1*H*,3*H*)-dione (3)

A mixture of barbituric acid (256 mg, 2 mmol) and aqueous ammonia (35%, 5 mL) was stirred at room temperature for 15 min, then treated with 2-chloro-3-formylquinoline (191.5 mg, 1 mmol) and heated under reflux for an additional 50 min. After cooling to room temperature, the resulting precipitate was collected to give **3** as a creamy solid: yield 333 mg (85%); mp 280°C (decomp.); proton nuclear magnetic resonance (¹H NMR) (DMSO-*d*₆, 300 MHz): δ 3.37 (1H, br s, NH), 5.19 (1H, s), 7.41 (1H, t, *J*=8.2 Hz), 7.5 (2H, br s, NH), 7.60 (1H, t, *J*=8.2 Hz), 7.73 (1H, d, *J*=8.4 Hz), 7.84 (1H, d, *J*=8.4 Hz), 8.09 (1H, s), 9.14 (2H, br s, NH), 10.82 (1H, br s, OH); carbon-13 nuclear magnetic resonance (¹³C NMR) (DMSO-*d*₆, 75 MHz): δ 27.7; 88.8; 93.4; 125.2; 125.7; 127.5; 127.7; 127.9; 129.8; 137.4; 144.6; 150.3; 152.6; 154.7; 155.2; 163.7; 163.9; Fourier-transform infrared spectroscopy (FT-IR) (KBr): ν 3432; 3218; 3018; 2855; 1685; 1648; 1493; 1350; 1270; 1101; 757 cm⁻¹; electron ionization mass spectrometry (EI-MS): *m/z* 392 (5, M⁺), 313 (8), 181 (29), 83 (42), 69 (60), 57 (97), 43 (100%). Anal. Calcd for C₁₈H₁₂N₆O₅: C, 55.11; H, 3.08; N, 21.95. Found: C, 55.24; H, 3.17; N, 22.34.

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