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Synthesis of 3-(1-Ethylpiperidin-2-yl) Quinolin-2(1*H*)-One

Qun-Zheng Zhang*, Ming Yuan, Yu-Hao Zhou, Si-Chang Wang, Cong-Yu Ke, Xun-Li Zhang*
Department of Chemistry, College of Chemistry and Chemical Engineering, Xi'an Shiyou University, Xi'an 710065, China

ABSTRACT Heterocycle-fused quinolinone scaffolds are important structures in drug discovery. There remain challenges for effectively synthesizing such heterocyclic compounds mainly due to the inefficient synthetic processes currently used. A simple and efficient method has been developed for the synthesis of 3-(1-ethylpiperidin-2-yl)quinolin-2(1*H*)-one using commercially available 2-chloroquinoline as starting material, through nucleophilic substitution, Suzuki coupling, catalytic reduction, and reductive amination reactions with a total yield of 24.5% for the final product. Theoretical analysis with density functional theory B3LYP has been conducted to gain insights into the possibility of the formation of the target product and its tautomer 3-(1-ethylpiperidine-2-yl) quinoline-2-ol.

KEYWORDS 3-(1-ethylpiperidin-2-yl) quinolin-2(1*H*)-one, Density functional theory analysis, Quinolinones, Synthesis method.

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INTRODUCTION

Heterocycles are present in a wide range of organic compounds which are of interest in biology, pharmaceuticals, and medicine.[1-6] Among many pharmaceutically relevant heterocycles, the heterocycle-fused quinolinone scaffold is one of the important structures in drug discovery, and its derivatives have demonstrated various biological and pharmaceutical activities, such as anti-inflammatory, anti-cancer, anti-diabetic, and anti-psychotic effects.[7-10] For example, cilostazol, dovitinib, and indacaterol have been developed for the treatment of chronic peripheral arterial occlusive disease,[11] diverse cancers,[12-15] and chronic obstructive pulmonary disease,[16,17] respectively. The biological and pharmaceutical activities of those heterocycles have been largely attributed to the inclusion of the ring structure of piperidine and/or pyridine, which are among the top 25 heterocycles that occur frequently in drug molecules.[18]

Due to the importance of quinolinone derivatives, great efforts have been made to develop efficient and sustainable synthetic procedures for the preparation of these scaffolds.[1,9] The currently reported synthetic routes to quinolinone derivatives can be mostly categorized into two groups; (i) directly using quinoline compounds as starting materials and (ii) constructing the quinoline rings. Through the first route, for example, cilostazol was synthesized with a well-established procedure starting from *N*-[(4-chlorobutyl) carbonyl]cyclohexylamine, however with challenges for effective removing the potential toxic impurities from the product.[19,20] Using readily available *N*-methoxyquinoline and ammonium tetrafluoroborate as raw materials 2-quinolinone derivatives and *N*-hydroxyquinolinone were formed through an easy-to-operate process, where, however, expensive starting materials and long reaction time were required.[21] More recently, a further simpler synthetic routed was developed to synthesize 3-alkyl quinolone compounds with a high atomic economy, but having limitations in terms of expensive starting materials and harsh reaction conditions.[7]

In the second group of synthetic routes, the synthesis involves the construction of quinoline rings. For example, 3-aryl/alkyl-2-quinolones was synthesized with a heterogeneous palladium nanoparticle-based catalyst and assisted by microwave radiation, that again required expensive starting materials with a low total yield.[22] To

*Corresponding author: Email: qzzhang@xsyu.edu.cn; xlzhang@xsyu.edu.cn

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was heated at 85°C for 5 h. The mixture was concentrated under vacuum. To the residue was added saturated aqueous $NaHCO_3$ (50 mL). The mixture was, then, extracted with EtOAc (50 mL × 3). The organic layer was combined, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography eluted with EtOAc to afford the title compound as white solid (853 mg, 80.9%). ^{1}H NMR (300 MHz, DMSO): δ 11.76 (s, 1H), 7.88 (s, 1H), 7.69 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.48–7.42 (m, 1H), 7.31–7.26 (m, 1H), 7.18–7.12 (m, 1H), 3.52–3.47 (m, 1H), 3.17–3.10 (m, 1H), 2.58–2.53 (m, 1H), 2.10–1.96 (m, 2H), 1.79–1.47 (m, 4H), 1.36–1.16 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). HRMS (EI, m/z) M^+: Calcd for $C_{16}H_{20}N_2O$: 256.1576; found: 256.1579.

CONCLUSION

A simple and efficient synthetic method has been developed for the synthesis of the pharmaceutically important quinolinone compound 3-(1-ethylpiperidin-2-yl) quinolin-2(1H)-one. 2-Chloroquinoline was introduced as a starting material followed by nucleophilic substitution, Suzuki coupling, catalytic reduction, and reductive amination reactions to yield the final product 3-(1-ethylpiperidin-2-yl) quinolin-2(1H)-one with a total yield of 24.5%. Theoretical studies with DFT B3LYP found that the HF value of the target product was 0.012664 Hartree less than that of its possible tautomer, suggesting that target product be more stable than that of its tautomer. At present, studies on the biological activity of the synthesized compound are under active investigation in our laboratories.

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