Synthesis of 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c] pyridin-2-one

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ABSTRACT: 1-(4-Bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (1) is an important intermediate for the synthesis of many biologically active compounds. It was synthesized from pyridin-4-ol (7) and 4-bromo-2-fluoroaniline through five steps including nitration, chlorination, *N*-alkylation, reduction and condensation. The structures of the compound 8 was confirmed by ^{1}H NMR spectrums and target compound 1 confirmed by Mass spectra.
KEYWORD: 1-(4-Bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one; Pyridin-4-ol; Synthesis

1 INTRODUCTION

Cancer is a disease caused by normal cells changing so that they grow in an uncontrolled way. Although many anti-tumor drugs and surgeries are available, the slow efficacy of the anti-tumor drugs and the cancer recurrence are still problems [1-2]. In recent years, there were many small molecule anticancer drugs had been reported. Among them, 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (**1**) is an significant intermediate for the synthesis of many biologically active compounds. Therefore, design and synthesis of 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (**1**) derivative as small molecule inhibitors played a essential role in the study of anticancer.

Many 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (**1**) derivatives which exhibited potential biological activities, such as 1-methyl-3-phenyl-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one(**2**)[3], 1,8-dimethyl-1,3-dihydro-2*H*-imidazo[4,5-b]quinolin-2-one(**3**)[4], 8-bromo-1-(2-chlorophenyl)-3-methyl-1,3-dihydro-2*H*-imidazo[4,5-c]quinolin-2-one(**4**)[5], 4-(mesityloxy)-3,6-dimethyl-1-(pentan-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one(**5**)[6], 1-(4-(2-isocyanopropan-2-yl)phenyl)-3-methyl-8-(quinolin-3-yl)-1,3-dihydro-2*H*-imidazo[4,5-c]quinolin-2-one (6)[7], these 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (**1**) derivatives showed biological activity.

Most of the synthetic methods of 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (1) which reported in the literature have the drawbacks, such as complicated reaction conditions [8]. Pyridin-4-ol (7) is a key intermediate for synthesizing 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (1). The synthesis of the target compound is necessary. The structures of representative compounds were shown in Fig. 1 and Fig 2.

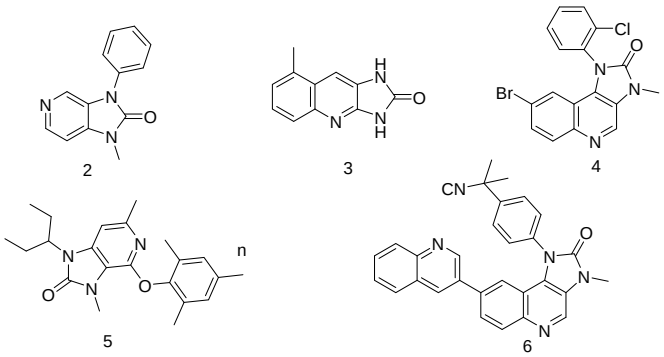


Fig.1 Structures of some drugs or active compounds containing 1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one

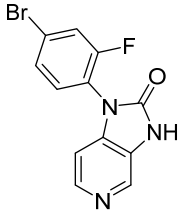


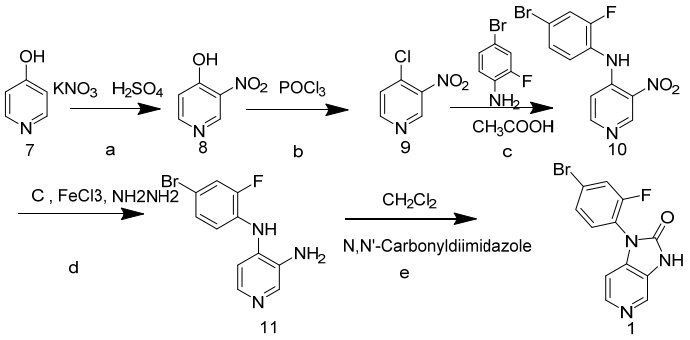
Fig.2 Structure of the target compound 1

2 MATERIALS AND METHODS

NMR spectrum were performed using Bruker 500 MHz spectrometers (Bruker Bioscience, Billerica,MA, USA) with TMS as an internal standard.Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA).All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical).

3 SYNTHESIS OF COMPOUNDS

The structures and the synthetic route were shown in Scheme 1.



Scheme 1. The synthetic route of Compound 1

Reagents and conditions:(a) KNO_3, H_2SO_4, 110℃, 10 h (b) $POCl_3$, 110 ℃, 3 h (c) 4-Bromo-2-fluoroaniline, 25 ℃, 10 h(d) C, $FeCl_3$, NH_2NH_2, 1 h; (e) N,N'-Carbonyldiimidazole, CH_2Cl_2, .

4 3-NITROPYRIDIN-4-OL **(**8**)**

Pyridin-4-ol (10 g, 0.105 mol) is dissolved in conc. H_2SO_4 (60 mL) at 0 ℃. KNO_3 (15 g, 0.149 mol) was added in portions over 10 minutes to the above solution and the reaction mixture is sequentially stirred for 10 hours at 110 ℃. The mixture is poured into 300 mL ice-water. The resulting precipitate is collected and washed with water thoroughly, dried and recrystallized from ether to give the pure product (9 g, yield 61%). M.p. 274-276℃. MS: 141.3 $[M+H]^+$, 163.1 $[M+Na]^+$. ^1H NMR (400 MHz,DMSO) δ 12.39 (s, 1H), 8.89 (s, 1H), 7.87 (s, 1H), 6.57 (s, 1H).

5 4-CHLORO-3-NITROPYRIDINE **(**9**)**

3-Nitropyridin-4-ol (8) (5.5 g, 0.0393 mol) was added to toluene (16 mL). The reaction flask was cooled to 0 degree and phosphoryl chloride (25 mL, 0.27 mol) was added dropwise. The mixture was blanketed with argon and heated to 110 degree for 2 h. Upon complete consumption of the precursor, as indicated by TLC, the mixture was cooled to room temperature and 100 mL of H_2O was added. The mixture was then cooled to 0 degree, and the resulting brown solid was filtered. Recrystallization from ethanol gave yellow crystals (4.8 g, 0.21 mol, 77% yield). M.p. 32℃; MS: 159.2 [M+H]+, 181.1 [M+Na]+.

6 *N*-(4-BROMO-2-FLUOROPHENYL)-3-NITROPYRIDIN-4-AMINE **(**10**)**

4-Bromo-2-fluoroaniline(2 g, 0.0105 mol) (**9**) and 4-bromo-2-fluoroaniline was dissolved in Acetic acid (7 mL) at room temperature. The reaction mixture was sequentially stirred for 10 hours at 25 ℃.After the completion of the reaction (monitored by TLC). Adjusting the pH to 8.5, the precipitated solid was filtered. The filter cake was washed with water and then obtained a yellow product (3 g, 91.7%). MS: 312.1, 314.1 $[M+H]^+$, 334.1, 336.1 $[M+Na]^+$.

7 *N*-4-(4-BROMO-2-FLUOROPHENYL) PYRIDINE-3,4-DIAMINE **(**11**)**

N-(4-bromo-2-fluorophenyl)-3-nitropyridin-4-amine (1 g, 0.0032 mol) (**10**) was dissolved in ethanol (60 mL) at room temperature. The reaction mixture was heated to 50℃ and activated carbon (1 g, 0.083 mol), ferric chloride (0.5 g, 0.00308 mol), hydrazine hydrate (0.2 g, 0.004 mol) was added and stir for 4 h at 80℃. After the completion of the reaction (monitored by TLC). Cooled to room temperature, the precipitated solid was filtered. The filtrate was evaporated to dryness and washed with water and then obtained a scream product (0.7 g, 83.4%). MS: 282, 284 $[M+H]^+$, 304.1, 306.1 $[M+Na]^+$.

8 1-(4-BROMO-2-FLUOROPHENYL)-1,3-DIHYDRO-2*H*-IMIDAZO[4,5-C]PYRIDIN-2-ONE**(**1**)**

To a solution of *N*-4-(4-bromo-2-fluorophenyl)pyridine-3,4-diamine (1 g, 0.0036 moL) and triethylamine (0.1 g, 1 mmol) in 30 mL of THF was added CDI (1 g, 0.006 mol) at room temperature . The mixture was stirred at that temperature for 20 h and then the reaction mixture was poured into water (100 mL) and filtered. The filter cake was purified by washing with ether to afford 0.7 g of 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (1) (63.1 % yield) MS: 308.1, 310.1 $[M+H]^+$; 332.1, 330.2 $[M+Na]^+$.

9 CONCLUSIONS

In conclusion,1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2H-imidazo[4,5-c]pyridin-2-one (**1**) was synthesized from pyridin-4-ol and *N*-(4-bromo-2-fluorophenyl)-3-nitropyridin-4-aminethrough fjive steps including Nitration, chlorination, *N*-alkylation, reduction and condensation. The synthetic method of the target compound (**1**) was optimized by changing conditions of the reaction so that can improve the yield. So the synthetic method can be used to synthesize 1-(4-bromo-2-fluorophenyl)-1,3-dihydro-2*H*-imidazo[4,5-c]pyridin-2-one (**1**) derivatives.

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