Synthesis of 6-bromo-4-iodoquinoline

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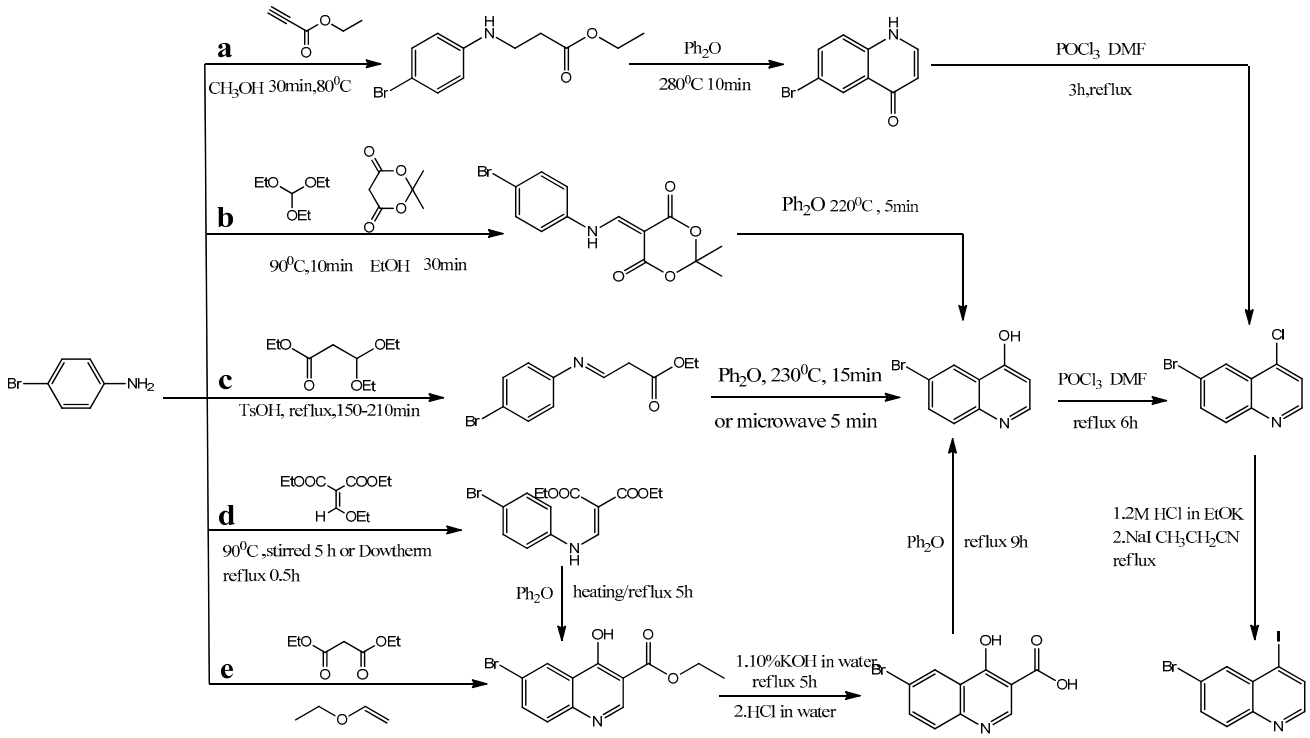
Abstract. 6-Bromo-4-iodoquinoline is an important intermediate for the synthesis of many biologically active compounds, such as GSK2126458. It was synthesized from 2,2-dimethyl-1,3-dioxane-4,6-dione and 4-bromoaniline through five steps including cyclization reaction and substitution reaction. And the structures of 6-bromoquinolin-4-ol and 6-bromo-4-iodoquinoline were confirmed by ^{1}H NMR spectrum.

Introduction

6-Bromo-4-iodoquinoline is a kind of important intermediate in the synthesis of GSK2126458. Its synthetic method was reported in a large amount of literature. Liu Kun *et al.* synthesized 6-bromo-4-iodoquinoline based on triethylor thoformate, meldrum's acid and 4-bromoaniline, which were stirred together at room temperature. The product was cyclized in ether under argon at 210 ℃ to get 6-bromoquinolin-4-ol. Then reacted with $POCl_3$ to obtain 6-bromo-4-chloroquinoline which was reacted with hydrochloric acid/ethyl ether to afford the hydrochloride. The hydrochloride was replaced by NaI in acetonitrile to obtain the title compound 6-bromo-4-iodoquinoline[1]. Synthetic method of Min Wang *et al.* is slightly different. Meldrum's acid and trimethyl orthoformate were refluxed for 3 h, when the solution was cooled to 50 ℃, 4-bromoaniline in trimethyl orthoformate was added dropwise. The obtained product was added slowly to preheated Ph_2O and heated at 250 ℃ for 15 min[2]. The steps of Chlorination and Iodination was similar to Liu Kun's. In other reports such as Wenjuan Zhang *et al.* and XI Ning *et al*., triethylorthoformate, meldrum's acid and 4-bromoaniline were stirred and refluxed in ethanol which is an solvent to furnish compound 5-(((4-bromophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione. Afterwards, the compound was heated in Ph_2O at 220 ℃[3,4]. The remaining steps are similar to the previous. These synthetic route were shown in route **b** of scheme 1.

There are some other synthetic methods of quinoline using other raw materials. Mugnaini Claudia *et al.* synthesized quinoline based on ethyl propiolate and 4-bromoaniline in methanol, the compound was cyclized in Ph_2O at 280 ℃[5] (route **a** in scheme 1) . Ma,Menglin's method was started from ethyl 3,3-diethoxypropanoate and 4-bromoaniline, then cyclized in Ph_2O at 230 ℃[6] (route **c** in scheme 1). Ai Jeng Lin and REN,Pingda synthesized it from diethyl 2- (ethoxy methylene)malonate and 4-bromoaniline[7,8] (route **d** in scheme 1). Duffy,Kevin J's method was started from ethoxyethene, diethyl malonate and 4-bromoaniline[9] (route **e** in scheme 1).

In this study, Our synthetic method of 6-bromo-4-iodoquinoline was optimized based on the previous study. In the first step, the reaction was without solvent which is ethanol in other literature. Because during the reaction, ethanol was generated. And in the third step, the temperature was 190 ℃ in order to avoid the impurities. In this way, the yield was developed and the reaction time was shortened.



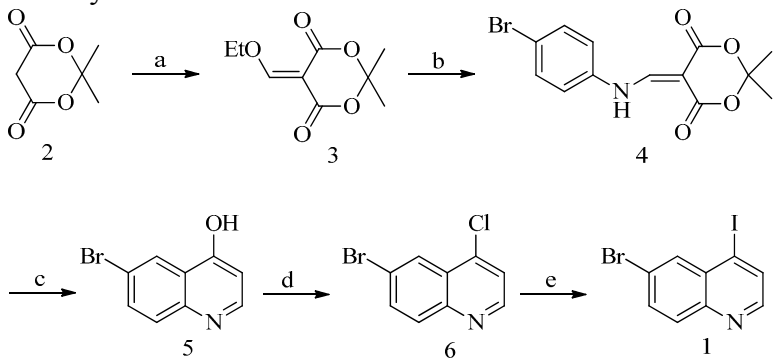
Scheme 1. The synthetic route of 6-bromo-4-iodoquinoline in other literature

Materials and methods

NMR spectra were performed using Bruker 500 MHz spectrometers (Bruker Bioscience, Billerica,MA, USA) with TMS as an internal standard.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, China).

Synthesis of compounds

The structures and the synthetic route were shown in Scheme 2.



Scheme 2. The synthetic route of Compound 1

Reagents and conditions:(a) 105 ℃, Triethylorthoformate, 3 h; (b) 4-bromoaniline, C_2H_5OH, 80 ℃, 3.5 h; (c) Ph_2O, 190 ℃, 10 min; (d) $POCl_3$, DMF, 110 ℃, 3 h; (e) THF, HCl/Et_2O, NaI, CH_3CN.

5-(Ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4)

Triethyl orthoformate (225.25 g, 1.5 mol) were added to meldrum's acid (36.028 g, 0.25 mol). Heated to 105 ℃ and stirred for 3 h. The mixture was cooled and poured into 200 mL petroleum

ether in an ice bath for 30 min, light yellow solid was precipitated, filtered off and dried to obtain the title compound **(4)** (40.521 g, 80.98%).

5-(((4-Bromophenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5)

4-Bromoaniline (28.5123 g, 0.166 mol) and 5-(ethoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **(4)** (31.8749 g, 0.098 mol) was dissolved in ethanol (480 mL). Reflux at 80 ℃ for 3 h. The reaction solution was cooled. Then the insoluble was filtered, washed with ethanol and dried to afford the title compound which was white powder **(5)** (51.8165 g, 99.73%).

6-Bromoquinolin-4-ol (6)

Ether (110.793 g, 0.65 mol) as the solvent was preheated, then 5-(((4-bromophenyl)amino) methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione **(5) (**10.110 g, 0.031 mol) was slowly added into ether. Stirred at reflux for 10 min. After the reaction was finished, the reaction solution was cooled to 50 ℃. And then the resulting mixture was added to petroleum ether slowly at room temperature, stirred for 10 min. The precipitated solid was filtered, washed with ethyl acetate and dried to get the yellowish product **(6)** (4.163 g, 59.89%). ^{1}H NMR (400MHZ, DMSO-d_6): δ8.15(d, J=2.4Hz，1H), 7.95 (m, 1H)，7.78 (m, 1H), 7.51(d, J=9.2Hz，1H), 6.0 (d，J=7.2Hz，1H).

6-Bromo-4-chloroquinoline (7)

$POCl_3$ (25 mL) was added to 6-bromoquinolin-4-ol **(6)** (2.023 g, 0.009 mol) dropwise, then two drops of DMF was added to the mixture. Stirred for 5 min at room temperature, then refluxed at 110 ℃ for 3 h. Most of $POCl_3$ was distilled off, the remaining oil was slowly added to ice water, stirred for 30 min. The solution was adjusted to pH 5-6 with $NaHCO_3$ saturated solution. Extracted with dichloromethane. The organic layer was washed twice with water, then dried with anhydrous sodium sulfate and filtered. The filtrate was distilled to afford yellowish product **(7)** (1.779 g, 81%).

6-Bromo-4-iodoquinoline (1)

6-bromo-4-chloroquinoline **(7)** (0.204 g, 0.00084 mol) was dissolved in THF(10 mL), then HCl/EtOH (3.53 g/240 mL, 80mL） was added to the solution dropwise, stirred for 30 min at room temperature. The mixture was distilled under reduced pressure to obtain the gray hydrochloride. The hydrochloride (0.100 g, 0.00036 mol) and NaI (1.638 g, 0.01 mol) was dissolved in acetonitrile (40mL), and refluxed at 100 ℃ for 32 h. The reaction liquid was cooled, distilled to get yellow powder. K_2CO_3 saturated solution (20 mL) and $NaSO_3$ saturated solution (8 mL) was added to the powder, stirred for 10 min and filtered to afford the khaki product **(1)** (0.099 g, 35.2%). ^{1}H NMR (400 MHz, DMSO) δ 8.54 (d, J = 4.5 Hz, 1H), 8.24 (d, J = 4.5 Hz, 1H), 8.16 (s, 1H), 7.98 (s, 2H).

Conclusions

In conclusion, 6-bromo-4-iodoquinoline **(1)** was synthesized from Triethyl orthoformate, meldrum's acid and 4-bromoaniline through five steps including cyclization reaction and the substitution reaction. The synthetic method of **(1)** was optimized by changing temperature and solvent of the reaction. So the synthetic method can be used to synthesize quinoline derivatives.

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