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Synthesis of Diethyl 2-(2-chloronicotinoyl)malonate

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Abstract: Diethyl 2-(2-chloronicotinoyl)malonate 3 is a nitrogen-containing water-soluble carboxylic acid as an important intermediates of small molecule anticancer drugs. In this study, this paper explored a faster and celerity method to synthesize compound 3. By using 2-chloronicotinic acid as a kind of easily available compound through two steps to made the target compound. The structure was confirmed by MS and ^{1}HNMR. Furthermore, the synthetic method was optimized. The total yield of the two steps was 83.3 %.

Introduction

As we all know, cancer become more and more complex, the traditional treatment methods such as surgery, chemotherapy and radiotherapy is not enough to treat completely. The advent of small molecule targeted inhibitors has led to a new advance in anticancer drugs. Small molecule target inhibitors mainly act on the signaling pathways involved in cancer cell growth, further hindering cell growth and promoting apoptosis [1-3]. The structure of diethyl 2-(2-chloronicotinoyl)malonate have been found in many small molecule kinase inhibitors. The structures of representative compound derivatives were shown in Fig. 1 [4-6].

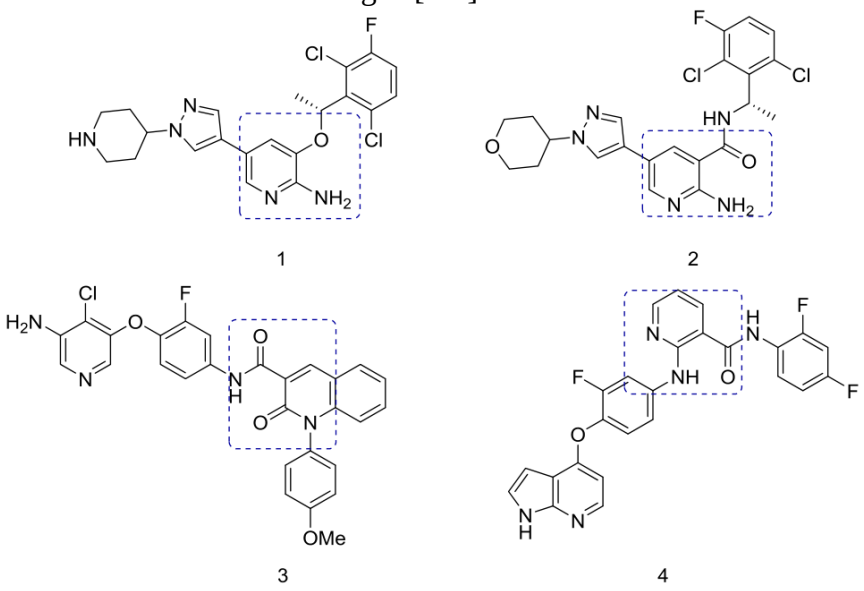

Fig.1. Structure of representative 4-Chloropyridine derivatives.

As have been reported, diethyl 2-(2-chloronicotinoyl)malonate derivations was an important intermediate for synthesis those active compounds. In this paper, a new

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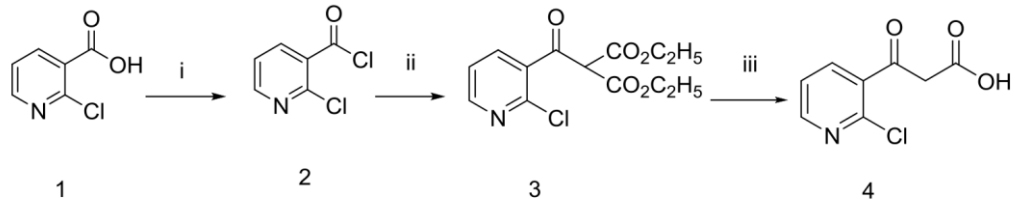
series of diethyl 2-(2-chloronicotinoyl)malonate 3 was synthesized. Our synthetic method of 3 was optimized based on the previous study. In the second step, we replaced diethyl 2-(2-chloronicotinoyl)malonate with 4-chloropicolinoyl chloride, giving a yield of 96%, make it more suitable for industrial production.

Materials and Methods

All melting points were obtained on a Büchi Melting Point B-540 apparatus and were uncorrected. NMR spectra were performed using Bruker 400 MHz spectrometers with TMS 210 as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS. 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.

Synthesis of Compounds

The structures and the synthetic route were shown in Scheme 1 [7-11].



Scheme.1. The synthetic route of compound 2-3

Reagents and conditions: (i) $SOCl_2$, DMF, 85 ℃, reflux, 1 h; (ii) $CH_2(CH_2NH_2)_2$, $MgCl_2$, toluene; (iii) CH_3CH_2OH, KOH, H_2O, 80 ℃, reflux.

Synthesis of 4 – chloropicolinoyl Chloride 2

2-Chloronicotinic acid (5.00 g, 0.041 mol) was added at 60 ° C, and the mixture was heated to 85 ℃ after addition of DMF (2d), and stirring was continued for 1 hour. The reaction was completed by TLC analysis. The reaction solution was added appropriate amount of toluene 2-3 times to give a pale yellow liquid product, yield: 92.5 % MS (ESI): m/z $[M+H]^+$ 174.96.

Synthesis of Diethyl 2-(2-chloronicotinoyl)malonate 3

Diethyl malonate(2.99 g, 0.019 mol), triethylamine(10 mL) and toluene were stirred at room temperature for 0.5 h, then magnesium chloride was added and stirring continued for 1.5 h. After the time, 2-chloronicotinoyl chloride (3.00 g, 0.017 mol) was slowly added to the reaction vessel and stirred at room temperature for 2-3 h. The reaction was monitored by thin-layer chromatography (TLC). The reaction solution was added to saturate NaCl and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under a reduced pressure to afford diethyl 2-(2-chloronicotinoyl)malonate 3 as yellow liquid, yield: 90.0%, MS (ESI): m/z $[M+H]^+$ 299.06.

Synthesis of 3-(2-chloropyridin-3-yl)-3-oxopropanoic Acid 4

Diethyl 2-(2-chloronicotinoyl)malonate 3 (3.105 g, 0.010 mol) was dissolved in ethanol and added KOH(0.80 g, 0.02 mol) and a little H_2O (3 mL), Stirring at 80 ℃. The reaction was completed by TLC analysis. The PH value of solution was adjusted to the 2-3, then use ethyl acetate extraction 2-3 times,combined the organic layer and

dried it by moderatesanhydrous Na_2SO_4. In the end, remaining solution was swirled off the final product, yield: 85.5%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.58 (d, *J* = 3.2 Hz, 1H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.57 (dt, *J* = 10.5, 5.3 Hz, 1H), 3.60 – 3.55 (m, 2H).MS (ESI): m/z [M+H] + 199.00.

Conclusions

In conclusion, diethyl 2-(2-chloronicotinoyl)malonate 3 were synthesized from the commercially available 2-chloronicotinic acid through two steps main content about nucleophilic substitution. Through the optimization of the synthesis conditions of the target compound 3, the purity and yield of the product was higher. Its structure was confirmed by ^{1}HNMR spectrum.

Acknowledgments

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