Synthesis of Ethyl 4-(4-Nitrophenoxy) Picolinate

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Abstract. Ethyl 4-(4-nitrophenoxy) picolinate 4 is an important intermediate for the synthesis of many biologically active compounds. The compound ethyl 4-(4-nitrophenoxy) picolinate was obtained by three simple steps to synthesis from 2-picolinic acid. In this paper, three novel chloropicolinoyl chloride derivatives were prepared. The structure was confirmed by MS and 1H NMR. Furthermore, the synthetic method was optimized. The total yield of the target product was 78.57%.

1. Introduction

Due to factors such as life stress, cancer has become the most common and scary disease in modern times and has become the second leading cause of death after cardiovascular disease. According to statistics, in 2015, a total of 8.8 million people worldwide died of cancer [1]. Traditional cancer treatments include surgery, chemotherapy, and radiation therapy. Among them, surgery is only suitable for early treatment; chemotherapy and radiotherapy can effectively inhibit advanced cancer, but it has serious side effects on normal human cells [4-6]. Seeking more effective and safe treatment has become a hot topic of research [7]. With the in-depth study of the pathogenesis, molecular targeted therapy has gradually become a research hotspot. The toxic side effects of its highly targeted treatments on patients have decreased significantly, and many small molecule inhibitors have been developed and entered preclinical studies. Part of the highly potent and selective small molecule inhibitors are shown in Figure 1 [10-13], and those compounds containing a pyridylamide fragment have a good inhibitory effect. Our synthetic ethyl 4-(4-nitrophenoxy) pyridinecarboxylate 4 derivatives are an integral part of many similar small molecule inhibitors. There are many reported synthetic methods, most of which have the disadvantages of long synthetic routes, low yields, and harmful to the environment [14-16]. In order to solve these problems, this study designed and optimized the synthetic route and method of ethyl 4-(4-nitrophenoxy) pyridinecarboxylate derivative. Ethyl 4-(4-nitrophenoxy) picolinate 4 was synthesized from 4-chloropicolinic acid mainly by a nucleophilic substitution reaction. Make it more suitable for industrial production.
2. Materials and Methods
NMR spectra were performed using Bruker 400 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, China).

3. Synthesis of Compounds
The structures and the synthetic route were shown in Scheme 1.

4. Synthesis of 4-chloropicolinoyl Chloride 2
The commercially available 2-picoliniacid (5.00 g, 0.04 mol) was dissolved in thionyl chloride (40 mL) at room temperature and the mixture was heated to 85 °C after addition of DMF (2d). One hour later, NaBr (0.42 g, 0.004 mol) was added portionwise. Continue stirring until the reaction is over. Reaction was complete by TLC analysis. The filtrate was concentrated under reduced pressure to afford product as a yellow viscous oil and was used for next step without further purification. Yield 97.0 %. MS (ESI): m/z [M+H] + 174.96.

5. Synthesis of 2-((4-chloropicolinoyl)oxy)ethan-1-ylium 3
The CH2Cl2 (30 mL) was poured into a beaker and mixed with triethylamine (26.3 g, 0.260 mol) and ethanol (9.20 g, 0.200 mol) stirred for 0.5 hour at 0 °C. Then 4-chloropicolinyl chloride (3.00 g, 0.017 mol) was slowly added in the mixture and stirring at 0 °C for 20 minutes. The reaction was completed...
by TLC analysis. The reaction mixture was extracted with suitable water and Ethyl acetate of twice the amount. The combined organic layer was dried over anhydrous Na$_2$SO$_4$. Concentrate organic layer under vacuum to afford to brown oil. Yield 90.0 %. MS (ESI): m/z [M + H]$^+$ 185.02.

6. Synthesis of ethyl 4-(4-nitrophenoxy)pollinate 4

Compound 3 (5 g, 0.0270 mol) and p-nitrophenol (7.5 g, 0.0540 mol) were dissolved in chlorobenzene (50 mL) and then the temperature was raised to 135 °C. Stirring is continued until the reaction is complete. The reaction was completed by TLC analysis. The reaction solution was extracted with a suitable water and dichloromethane. The organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated. Obtained a white solid, yield 90.0 %. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.75 (d, $J$ = 5.0 Hz, 1H), 8.40 (d, $J$ = 8.4 Hz, 2H), 7.71 (s, 1H), 7.51 (d, $J$ = 8.4 Hz, 2H), 7.44 (d, $J$ = 2.8 Hz, 1H), 4.39 (dd, $J$ = 13.1, 6.2 Hz, 2H), 1.37 (t, $J$ = 6.7 Hz, 3H). MS (ESI): m/z [M + H]$^+$ 288.07.

7. Conclusion

In conclusion, the compound ethyl 4-(4-nitrophenoxy) picolinate was prepared by nucleophilic substitution reaction through three steps. The synthetic method and the reaction’s conditions was optimized, the yield of the product was higher than others, and making it more suitable for industrial production. It structure was confirmed by MS and $^1$H NMR spectrum.

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