Synthesis of 2-Chloronicotinic Acid Derivatives

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Abstract. 2-Chloronicotinic acid and its derivatives are important intermediates for the synthesis of medical antibiotics, anti-cardiovascular drugs, insecticides and herbicides, and they used in the synthesis pranoprofen and diflufenican. In this work, a rapid synthetic method for 2-morpholinonicotinic acid was established. The 2-morpholinonicotinic acid was synthesized from the commercially available dichloro-hydrochloric acid through three steps including esterification, nucleophilic substitution and hydrolysis. The structures were confirmed by MS. Furthermore, the synthetic method was optimized, and the total yield of the three steps was 93 %.

Introduction

2-Chloronicotinic acid is a derivative of nicotinic acid which is an important pharmaceutical intermediates[1-7]. 2-Chloronicotinic acid and its derivatives are commonly used in the synthesis of pranoprofen and diflufenican[8-9].With the domestic and foreign scientific research institutions effort to niacin derivatives, the application of the product is now not limited to the field of medicine, and in the food, feed, dyeslight, heat additives and other field also has application. Therefore, the development of nicotinic acid derivatives with better bioactivity has become a hotspot in the field of medicine[10-14].

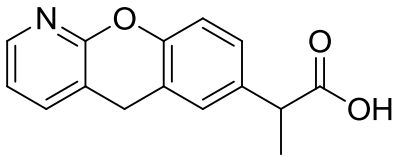


Figure 1. Sructures of pranoprofen

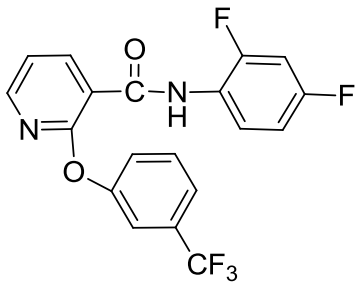


Figure 2. Sructures of diflufenican

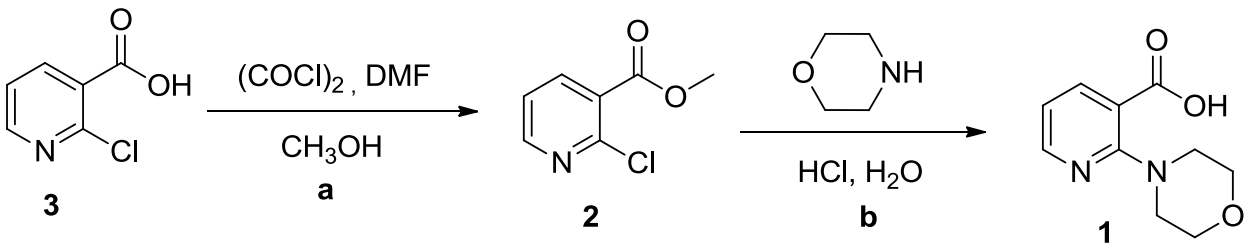
In this study, we synthesized 2-morpholinonicotinic acid, taking 2-chloronicotinic acid as a starting material. The final product was obtained by acylation, nucleophilic substitution and reduction, and make it more suitable for industrial production. The reaction have simple steps, mild conditions, simple post-treatment application prospects. The structures of pranoprofen and diflufenican were shown in Fig. 1 and Fig. 2, respectively.

Materials and Methods

Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106. Elemental analysis instrument (Carlo Erba, Milan, Italy). 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 1



Scheme 1. The synthetic route of 2-morpholinonicotinic acid

Reagents and Conditions: (a) $(COCl)_2$, DMF (N,N-Dimethylformamide), Triethylamine, CH_3OH, 40 ℃. (b) Morpholine, HCl, H_2O, 100 ℃.

Methyl 2-chloronicotinate 2. A solution of 2-chloronicotinic acid (5.0 g, 31.7 mmol) and DMF (Catalytic amount) in DCM (dichloromethane) (50 mL) was stirred at r.t. $(COCl)_2$ (3.94 g, 31.26 mmol) was added to the mixture slowly. The progress of the reaction was monitored by TLC. After completion of the reaction. The above untreated mixture was added to a solution of CH_3OH and triethylamine at 0 - 5 ℃ in an ice/water bath, and then stirreing for 30 min. Diluted with water 50 mL, extracted with ethyl acetate (100 mL*3), and the organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield product (5.3 g, 97%) as a yellow solid. MS (ESI): m/z 171.0$[M+H]^+$.

2-Morpholinonicotinic acid 1. Methyl 2-chloronicotinate (5.0 g, 32.0 mmol) was added to a solution of morpholine (5.59 g, 64 mmol) in N,N-dimethylacetamide (50 mL). The mixture was heated to 100 ℃ and stirred at this temperature for 40 min. The progress of the reaction was monitored by TLC. After completion of the reaction. Diluted with water 50 mL, extracted with ethyl acetate (100 mL*3), and the organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give light yellow oily liquid. The above liquid was dissolved in ethanol (100 mL), and then NaOH (10 %) solution was added to the reaction mixture slowly, until the pH of the mixture to 10. Concentrated under reduced pressure to give white granular solid, the above solid was dissolved in ethanol (100 mL), and then HCl (37 %) solution was added to the reaction mixture slowly, until the solid precipitates. Concentrated under reduced pressure to yield product (5.8 g, 96%) as a light yellow granular solid. MS (ESI): m/z 208.1$[M+H]^+$.

Conclusions

In conclusion, 2-morpholinonicotinic acid was synthesized from the commercially available 2-chloronicotinic acid through three steps including esterification, nucleophilic substitution and hydrolysis. The synthetic method of 2-morpholinonicotinic acid and the reactions conditions were optimized, the purity of the product was much more higher. The reaction have simple steps, mild conditions, simple post-treatment and high yield. Therefore, the synthesis methods are more suitable for industrial production, and also have good a application prospects. Its structure was confirmed by MS.

Acknowledgments

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