Synthesis of 4-Chloro-N, N-Dimethyl Pyridine Car Box Amide

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Keywords: 4-chloro-N; N-dimethyl pyridine car box amide; Synthesis; Process optimization

Abstract. Sorafenib (1) in the medical field to show the potential biological activity. Literature on the majority of tumor cells have a high biological activity, such as lymphoma, breast cancer, prostate cancer. However, some synthetic route of Sorafeni has disadvantages, such as low product yield and complicated post-treatment. Therefore, in this paper, the main purpose is to optimize the Sorafeni part of the synthesis route. The effects of reaction reagent, feed and temperature on the yield of the reaction were discussed. The optimized reaction conditions were as follows $SOCl_2$: $POCl_3$=5:1 and use K_2CO_3 instead of triethylamine. The structures were confirmed by ^1H NMR.

Introduction

The incidence of liver cancer is about 20/10000, due to early symptoms of liver cancer is not obvious[1], nearly 80% of patients is already advanced, half of the world's liver cancer occurred in China, and in China the primary factor in liver cancer Among them, hepatitis B in the first place[2-5], the causative factor with liver cancer in Europe and the United States are very different.4-Chloro-N, N-dimethyl pyridine car box amide is part of the key intermediate in sorafenib, and largely affects the activity of sorafenib, which is a novel multi-targeted oral drug for the treatment of tumors and Sorafenib is a new multi-target anti-tumor drugs[6-10], developed by the German Bayer Pharmaceutical Company, which can act on both tumor cells and tumor blood vessels. It has a dual antitumor effect by inhibiting RAF / MEK / ERK-mediated cell signaling pathways directly by inhibiting tumor cell proliferation[11-12], But also by blocking angiogenin and platelet-derived growth factor receptor block tumor neovascularization formation, and indirectly inhibit tumor cell growth.

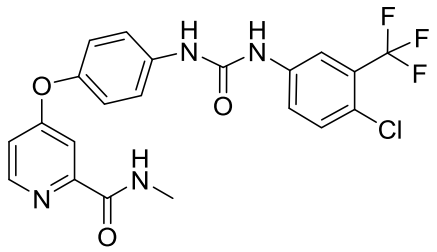


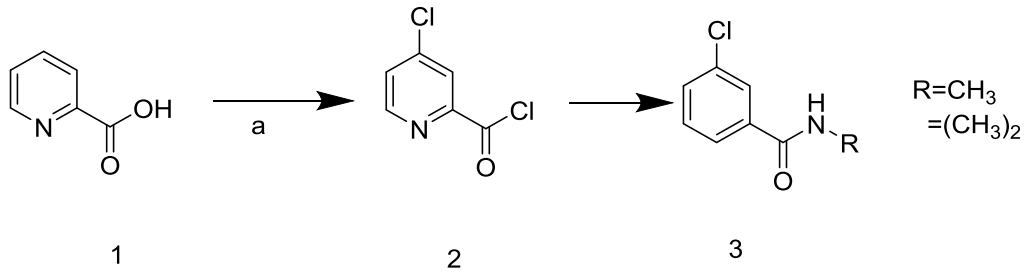
Figure 1. Structures of Sorafenib

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). 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 synthetic route were shown in Scheme 1.



Scheme 1. The synthetic route of compounds 3a-3b

Reagents And Conditions: (a)SOCl2 and POCl3, ,NaBr, chlorobenzene:, 85℃, 15 h; (b) THF, K2CO3, r. t, 4 h.

Synthesis of 4 - Chloropicolinoyl Chloride(2). To the mixture of NaBr(0.023 g,0.0015 mol) and picolinic acid (10.0 g , 0.167 mol), in chlorobenzene (75 mL). After stirring for 0.5 h at 50℃, tdilute $SOCl_2$ and Phosphorus oxychloride was added slowly with stirring maintaining the temperature 50 ℃, Raise the temperaturethe to 85 ℃. reaction was complete by TLC analysis, 20Filtration, take filtrate, 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 93.2%. MS (ESI): m/z $[M+H]^+$ 177.96.

Synthesis of 4-chloro-N, N-dimethylpicolinamide(3a-3b). The CH_2Cl_2 (80 mL) was transferred to a beaker and 4-chloropicolinoyl chloride (1.34 g, 0.357 mol) was slowly added with stirring for 15 minutes at a temperature below 0℃, then 30% dimethylamine was dropping at room temperature and the reaction was maintained at 0 ℃ for 4.5 hours. The reaction was complete by TLC analysis. The reaction mixture was poured onto Ethyl acetate The organic phase was separated ,then concentrated it under reduced pressure to afford product as a yellow viscous oil,Yield : 86%. ^{1}H NMR (400 MHz, DMSO) δ 8.52 (d, *J* = 5.4 Hz, 1H), 7.65 (d, *J* = 1.3 Hz, 1H), 7.53 (m, 1H), 2.97 (s, 3H), 2.89 (d, *J* = 8.0 Hz, 3H).MS (ESI): m/z $[M+H]^+$ 181.3

4-chloro-N-methylpicolinamide(3b). Yellow Oily liquid. Yield 87%. MS (ESI): m/z $[M+H]^+$ 171.5

Results and Discussion

Effect of Solvent Type on Yield of Compound 2. Synthesis of 4 - chloropicolinoyl chloride, the reagents used $SOCl_2$ in the literature, but the reaction there are some shortcomings, such as long reaction time, high temperature, and the yield is not high. Therefore, the authors intend to use $SOCl_2$ and Phosphorus oxychloride in combination as reagents. The data are shown in Table 1.

Table 1 Effect of solvent type

reagent	reaction time	temperature	yield
$SOCl_2$	28h	100° C,	76%
$SOCl_2$: $POCl_3$=5:1	15h	85° C,	93.2%

Effect of Reagent on Yield in Synthetic Route of Compounds 3. Synthesis of 4-chloro-N, N-dimethyl picolinic acid amide in the literature used for the triethylamine triethylamine, but the use of more triethylamine, resulting in waste of reagents, a long reaction time, the temperature is difficult to control, Not high shortcomings. Therefore, the authors intend to use K_2CO_3 instead of triethylamine. The experimental results are shown in Table 2.

Table 2 Effect of reagent

reagent	reaction time	yield
$N(C_2H_5)_3$	28h	78.2%
K_2CO_3	4.5h	8%

Conclusions

In general, 4-chloro-N, N-dimethylpyridinecarboxamide is synthesized by including chlorination, nucleophilic substitution. Through the synthesis method optimization, shorten the reaction time, the temperature is relatively mild, less by-products, the target compound yield higher. The structure was confirmed by 1H NMR.

Acknowledgments

We gratefully acknowledge the generous support provided by The National Natural Science Funds of Jiangxi Science & Technology Normal University (2016XJZD007)

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