Synthesis of 1-methyl-3-(5-nitropyridin-2-yl) urea

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Abstract. 1-methyl-3-(5-nitropyridin-2-yl) urea (8) is an important intermediate for small molecule anticancer drugs. A rapid and high yield synthetic method for 1-methyl-3-(5-nitropyridin-2-yl) urea (8) was established in this work. The target compound was synthesized from the commercially available 2-chloro-5-nitropyridine (5) through multi-step nucleophilic reactions. The structure of the target product was confirmed by 1H NMR. In addition, the synthetic method was optimized. The total yield of the four steps was high up to 92%.

1. Introduction

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/the mammalian target of rapamycin (mTOR) signaling pathway plays a critical role in a diverse set of cellular functions, including cell growth, proliferation, motility, differentiation, and survival, which have been identified as promising targets for the treatment of cancer, providing validated therapeutic targets associated with malignancies[1-3]. The use of tyrosine kinase inhibitors has acquired resistance through secondary mutations or by amplification of genes [4-5]. Although a lot of antitumor drugs have been developed, effective drugs that can overcome this resistance problem have not been discovered so far and have not yet reached clinical trials [6-7]. Therefore we need to continue developing and optimizing antitumor inhibitors [8-9]. Indeed, many small molecule anticancer drugs have been reported in recent years. Among them, many molecules contain the structure of 1-methyl-3-(5-nitropyridin-2-yl) urea (8). The structures of these compounds are shown in Fig.1. For example, 1-(4-(3-chloro-2-fluorophenoxy)-5-(2,4-dimethoxyphenyl)pyridin-2-yl)-3-methylurea(1)([10], 1-(4-bromo-3-(5-methoxypyridin-3-yl)oxy)phenyl)-3-methylurea(2) [11], (E)-1-(4-(4-((1-(4-chlorobenzyl)-5-ethyl-4,6-dioxo-1,3,5-triazinan-2-ylidene)amino)phenoxy)pyridin-2-yl)-3-methylurea(3)[12], 3-[[1,1′-biphenyl]-4-yl]-1-(1-(5-bromopyridin-2-yl)piperidin-4-yl)-1-methylurea(4)[13]. Among them, compound 1 can also be used to effectively improve glucokinase activator, and compound 3 is a potential analgesic.

![Fig. 1 Intermediates containing the active compound](image-url)
Therefore, design and synthesis of 1-methyl-3-(5-nitropyridin-2-yl)urea(8) derivative as small molecule inhibitors play a great role in the study of anticancer drugs. In this paper, we have found a fast and high yield synthesized route to 1-methyl-3-(5-nitropyridin-2-yl)urea(8). In the step of the whole route, compound 5 rapidly synthesized target compound 8 through multi-step nucleophilic reactions, which made it more suitable for industrial production. Structures of the raw materials, intermediate compounds of the reaction and target compound were shown in Scheme 1.

2. Materials and methods

NMR spectra were performed using Bruker 300 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).

3. Synthesis of compounds

The structures and the synthetic route were shown in Scheme 1.

![Scheme 1](image)

Reagents and conditions: (a) Ammonium hydroxide, 80 °C; (b) DMAP, DIPEA, 1,4-dioxane, r.t.; (c) Methylamine, DMAP, 70 °C;

4. Preparation for 5-nitropyridin-2-amine(6)

Compound 5 (2 g, 10.5 mmol) were dissolved in ammonium hydroxide and stirred at 80 °C for 2 hours. The mixture was concentrated and suction-filtered to give the target compound 6 (95% yield).

5. Preparation for phenyl (5-nitropyridin-2-yl)carbamate (7)

DMAP (0.2 g, 1.8 mmol) was added to a solution of Compound 6 (1.5 g, 8.67 mmol) in 1, 4-dioxane (30 mL). The mixture was cooled to 0 °C, then phenylchloroformate (1.561 g, 9.97 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. The precipitate was collected by filtration and was washed with water and dried under suction to give the target compound 7 (98% yield).

6. Preparation for 1-methyl-3-(5-nitropyridin-2-yl)urea (8)

Compound 5 (0.1 g, 0.34 mmol) and methylamine (0.2 g, 6.4 mmol) were dissolved in acetonitrile and stirred at 50 °C for 6 hours. The reaction mixture was concentrated under vacuum, and the residue was dissolved in dichloromethane and then washed with sodium hydroxide solution. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford the title compound 8 (92% yield). 1H NMR (400 MHz, DMSO-d6) δ 9.65 (s, 1H), 9.19 (s, 1H), 8.21 (s, 1H), 7.89 (d, J = 3.6 Hz, 1H), 7.09 (d, J = 3.5 Hz, 1H), 2.65 (d, J = 4.1 Hz, 3H).
7. Conclusions
In conclusion, reactive intermediate compound 8 was synthesized from 5-bromo-2-chloropyridine through four steps. The purity of the product was much higher than before. Its structure was confirmed by $^1$H NMR spectrum.

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