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Short Note

4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine

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Abstract

A novel nitrogen-containing heterocyclic compound, 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine, was designed and synthesized using 6-chloropyridin-3-aldehyde and cyclopropyl methyl ketone as starting materials. The structure of the target compound was characterized by ^{1}H NMR, ^{13}C NMR and HRMS, and the spectral data were consistent with the expected structure, confirming the correctness of the product.

Keywords: nitrogen-containing heterocycles; pyrimidine amine compounds; Michael addition

1. Introduction

In recent decades, nitrogen-containing heterocyclic compounds have played a crucial role in fields such as organic chemistry, medicinal chemistry, and materials science. Their structural diversity and excellent biological activities have been a research hotspot [1]. Many key biological macromolecules in living systems contain nitrogen-containing heterocyclic structures. For example, pyrimidine compounds are one of the important bases in nucleic acids, widely present in the structures of DNA and RNA [2]. Based on the importance of such scaffolds, pyrimidines and their derivatives have gradually become significant research objects in medicinal chemistry [3]. Among them, the 2-amino-pyrimidine structure unit has received extensive attention due to its unique electronic properties and good structural modifiability. Numerous studies have confirmed that compounds containing the 2-amino-pyrimidine scaffold exhibit significant inhibitory effects in areas such as anti-inflammatory, anti-cancer, anti-bacterial, anti-viral, and anti-HIV treatments [4–6].

From a synthetic perspective, many mature synthetic strategies have been established for 2-amino-pyrimidines. Among them, the method of constructing the pyrimidine ring by condensation between β-dicarbonyl compounds and guanidine derivatives is the most classic and widely used [7]. Typically, β-dicarbonyl compounds (such as β-diketones or β-ketoesters) react with guanidine or substituted guanidine salts in an alkaline environment to form the 2-amino-pyrimidine scaffold. This reaction usually occurs in alcohol solvents (such as ethanol or methanol), with common bases including sodium carbonate, potassium carbonate, or sodium ethanol. The reaction temperature is often controlled under reflux conditions (approximately 70–100 °C), and the reaction time is typically 4–12 h [8]. Under alkaline conditions, the β-dicarbonyl compound first undergoes nucleophilic addition with guanidine to form an intermediate, followed by intramolecular cyclization and dehydration to form the pyrimidine ring structure, ultimately yielding the target product, 2-amino-pyrimidine or its substituted derivatives. This method has advantages such as

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easy availability of raw materials, relatively mild reaction conditions, and high yields, making it of great value in both laboratory synthesis and industrial production [9,10].

In this study, a classical heterocyclic construction strategy was employed using reactive α,β-unsaturated ketones as key intermediates to build the pyrimidine scaffold. First, 6-chloropyridin-3-aldehyde and cyclopropyl methyl ketone were used as raw materials to undergo a hydroxy aldehyde condensation reaction under strong alkaline conditions, forming an intermediate compound with an α, β-unsaturated ketone structure [11]. Due to the conjugated system of such compounds, they have excellent reactivity and are often used as important synthetic platforms to build various nitrogen-containing heterocycles. On this basis, the α, β-unsaturated ketone compound reacted with guanidine hydrochloride under alkaline conditions to undergo a condensation cyclization reaction, constructing the pyrimidine ring scaffold. The reaction was conducted using methanol as the solvent, and under alkaline conditions, guanidine reagents underwent nucleophilic addition, cyclization, and dehydration to form the pyrimidine ring structure. The new compound 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine was successfully synthesized (Figure 1).

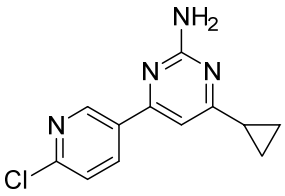
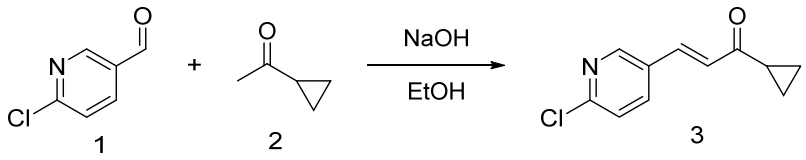


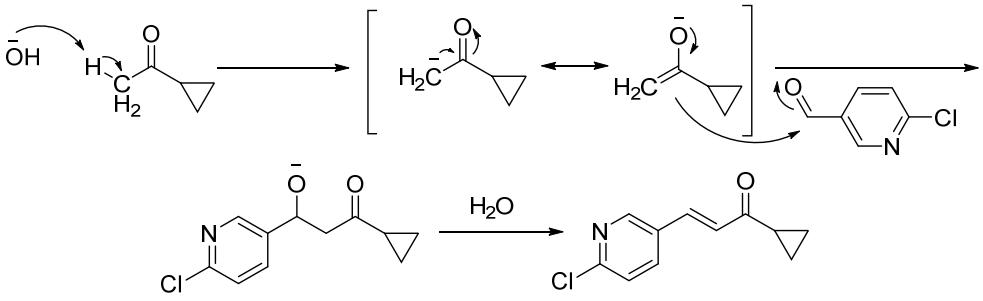
Figure 1. 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine.

2. Results and Discussion

To synthesize the target compound 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine, we first synthesized the intermediate compound containing an α, β-unsaturated ketone structure [12]. Using 6-Chloropyridin-3-aldehyde and cyclopropyl methyl ketone as raw materials, we used sodium hydroxide to provide an alkaline environment and ethanol as the solvent to synthesize (*E*)-3-(6-Chloropyridin-3-yl)-1-cyclopropylprop-2-en-1-one (Scheme 1). This reaction is a typical hydroxy aldehyde condensation reaction [13], and under the sodium hydroxide ethanol solution, the α-hydrogen of cyclopropyl methyl ketone was attacked by hydroxide ions, transferring electrons to form a carbon–carbon double bond. The carbonyl oxygen then accepted the electron pair from the carbonyl π-bond to form an enolate anion. This enolate anion then attacked the carbonyl carbon of 6-chloropyridin-3-aldehyde, completing the nucleophilic addition. After protonation, a β-hydroxy ketone intermediate was formed. Subsequently, under basic conditions and heating, hydroxide ions again abstracted the hydrogen from the α-carbon, leading to the elimination of the hydroxyl group and the formation of the intermediate (*E*)-3-(6-Chloropyridin-3-yl)-1-cyclopropylprop-2-en-1-one (Scheme 2).

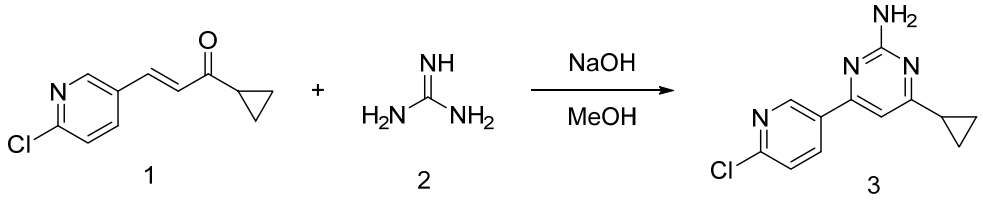


Scheme 1. Synthesis of (*E*)-3-(6-Chloropyridin-3-yl)-1-cyclopropylprop-2-en-1-one.

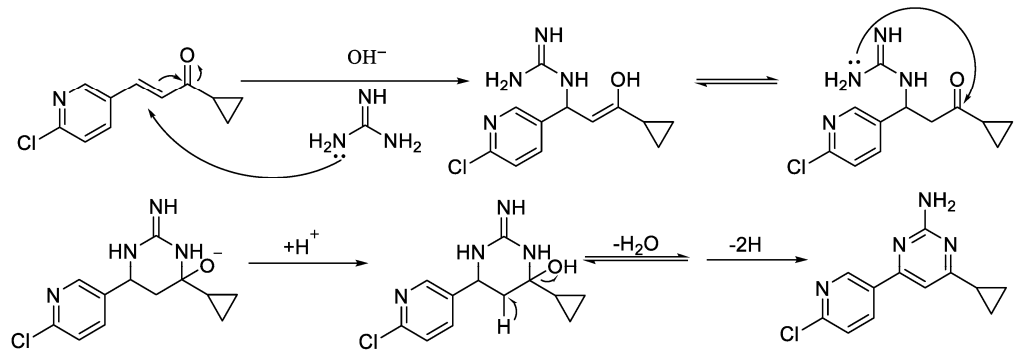


Scheme 2. Reaction mechanism for the synthesis of (*E*)-3-(6-Chloropyridin-3-yl)-1-cyclopropylprop-2-en-1-one.

In the second step, the intermediate compound was reacted with guanidine hydrochloride under alkaline conditions, completing the condensation cyclization to form the pyrimidine scaffold (Scheme 3). This reaction is a typical Michael addition reaction, and under alkaline methanol solution, guanidine hydrochloride lost a proton under sodium hydroxide to form free guanidine. The imine nitrogen of guanidine then attacked the β-carbon of the α, β-unsaturated ketone (Michael addition receptor), resulting in the formation of an enolate anion intermediate. This intermediate underwent intramolecular cyclization, forming a six-membered dihydropyrimidine intermediate, with the carbonyl bond breaking and oxygen remaining as a hydroxyl group on the ring. Under basic conditions, this hydroxyl group underwent elimination and dehydration, forming a carbon–nitrogen double bond and restoring the aromaticity of the pyrimidine ring. Finally, proton transfer led to the formation of the target product 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine (Scheme 4).



Scheme 3. Synthesis of 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine.



Scheme 4. Reaction mechanism for the synthesis of 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine.

The structural integrity of the target compound was confirmed through ^{1}H NMR and ^{13}C NMR spectra (Supplementary Materials), ensuring an accurate description of the synthetic pathway and molecular structure. According to the analysis of the ^{1}H NMR spectrum, the J-values reflect the coupling interactions between hydrogen atoms. The

signal at δ 9.06 (d, J = 2.4 Hz, 1H) corresponds to the hydrogen at position 2 of the pyridine ring, with the chemical shift in the downfield region, which is characteristic of the hydrogen adjacent to the nitrogen atom. The signals at δ 8.45 (dd, J_1 = 8.4 Hz, J_2 = 2.5 Hz, 1H) and δ 7.66 (d, J = 8.3 Hz, 1H) correspond to the hydrogens at positions 4 and 5 of the pyridine ring, respectively. These two signals show typical ortho-coupling splitting patterns, and the chemical shifts and splitting patterns of these three hydrogen signals closely match the theoretical peak positions for a chlorinated pyridine ring. The singlet signal at δ 7.18 (s, 1H) corresponds to the hydrogen at position 5 of the pyrimidine ring, while the singlet at δ 6.61 (s, 2H) corresponds to the two active hydrogens on the amino group at position 2 of the pyrimidine ring. Additionally, the multiple signal at δ 2.01–1.92 (m, 1H) belongs to the methylene hydrogen directly attached to the pyrimidine ring in the cyclopropyl group. The multiple at δ 1.04–0.95 (m, 4H) corresponds to the four hydrogens of the methylene group in the cyclopropyl group.

Based on the analysis of the ^{13}C NMR spectrum, the signals at δ 174.02 and δ 164.17 correspond to the carbon atoms at positions 2 and 6 of the pyrimidine ring. These carbons are attached to nitrogen atoms and are in an electron-deficient environment, resulting in significant downfield chemical shifts. The five signals at δ 159.99, 152.05, 148.79, 138.17, and 132.80 correspond to the five carbon atoms in the pyridine ring. Specifically, δ 159.99 and δ 152.05 correspond to the carbons at positions 2 and 6 adjacent to the nitrogen atom, δ 148.79 corresponds to the carbon at position 3 connected to the chlorine substituent, and δ 138.17 and δ 132.80 correspond to the carbons at positions 4 and 5. The signal at δ 124.79 corresponds to the carbon at position 4 of the pyrimidine ring, which is directly connected to the pyridine ring and appears in a relatively low-field region due to the anisotropic effect of the aromatic ring. The signal at δ 104.27 corresponds to the carbon at position 5 of the pyrimidine ring, which exhibits a high-field shift, consistent with the characteristics of an sp^2 hybridized carbon adjacent to two nitrogen atoms. Furthermore, the two signals at δ 17.26 and δ 10.39 correspond to the methylene carbon attached to the pyrimidine ring and the two equivalent methylene carbons in the cyclopropyl group, with δ 17.26 corresponding to the methylene carbon and δ 10.39 corresponding to the two equivalent methylene carbons. These data accurately describe the structure of the target compound, ensuring the correctness of the compound.

3. Materials and Methods

3.1. Materials

All reagents were purchased from China National Pharmaceutical Group Cor-poration (Beijing, China). We used the following: a BRUKER-600 MHz NMR spec-trometer (Rheinstetten, Germany); an SGW-X4 type melting point apparatus (Shanghai, China); a Yide Physics and Optical Instrument (Shanghai, China); a ZF-7 UV analyzer (Qingdao, China); a Hongyi Instrument Equipment (Shanghai, China); and a Heidolph rotary evaporator (Zhengzhou, China).

3.2. Synthesis of 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine

6-chloropyridin-3-aldehyde (5 mmol 0.70 g) and cyclopropyl methyl ketone (10 mmol 0.84 g) were placed in a 100 mL round-bottom flask with 50 mL ethanol containing 0.5 g sodium hydroxide as the solvent. The reaction was stirred at 30 °C for 3 h. The reaction progress was monitored by thin-layer chromatography (TLC) [V (EA):V (PE) = 1:5]. After completion, the reaction mixture was washed sequentially with ethyl acetate (150 mL) and water (100 mL) until the aqueous layer was colorless. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to obtain the crude product. It was purified using silica gel column chromatography (V

(EA):V (PE) = 1:20 to 1:5 gradient elution) to obtain the intermediate (E)-3-(6-chloropyridin-3-yl)-1-cyclopropylprop-2-en-1-one. The intermediate (5 mmol 1.03 g) was then reacted with guanidine hydrochloride (10 mmol 0.95 g) in a 100 mL round-bottom flask with 50 mL methanol containing 0.5 g sodium hydroxide as the solvent. The reaction was refluxed at 70 °C for 8 h. The reaction progress was monitored by TLC [V (EA):V (PE) = 1:2]. After completion, the reaction mixture was washed with ethyl acetate (150 mL) and water (100 mL) to remove any impurities. The organic layer was separated, dried, filtered, and concentrated to yield the target product 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine.

4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine: White solid M.P. = 188–189 °C (63% yield) ^{1}H NMR (600 MHz, DMSO) δ 9.06 (d, J = 2.4 Hz, 1H), 8.45 (dd, J_1 = 8.4, J_2 = 2.5 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.18 (s, 1H), 6.61 (s, 2H), 1.92-2.01(m, 1H), 0.95-1.04 (m, 4H) ppm. ^{13}C NMR (151 MHz, DMSO) δ 174.2, 164.1, 159.9, 152.0, 148.7, 138.1, 132.8, 124.7, 104.2, 17.2, 10.3 ppm. HRMS(ESI): $C_{12}H_{11}N_4Cl$ [M+H] $^{+}$ calcd for 247.0672, found for 247.0741.

4. Conclusions

This study successfully synthesized the novel target compound 4-(6-Chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine by a two-step reaction using 6-chloropyridin-3-aldehyde and cyclopropyl methyl ketone as raw materials. In the first step, a hydroxy aldehyde condensation reaction was used to construct the intermediate (*E*)-3-(6-Chloropyridin-3-yl)-1-cyclopropylprop-2-en-1-one. In the second step, the intermediate underwent a Michael addition reaction with guanidine hydrochloride under alkaline methanol conditions to form the pyrimidine ring. The entire reaction pathway is relatively simple, with widely available raw materials, mild reaction conditions, and clear steps, making it feasible for experimental work. The structure of the target compound was confirmed using ^{1}H NMR and ^{13}C NMR, and the spectral data confirmed the correctness of the product structure.

Supplementary Materials: The following supporting information can be downloaded online. Figure S1: ^{1}H NMR spectrum of 4-(6-chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine. Figure S2: ^{13}C NMR spectrum of 4-(6-chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine. Figure S3: HRMS analysis of 4-(6-chloropyridin-3-yl)-6-cyclopropylpyrimidin-2-amine.

Author Contributions: Y.W. synthesized the target compound and wrote the Experimental Methods and Introduction section; J.L. conceived the experimental plan; Y.Q., conducted the final review and revision of the article, and revised the Introduction, Results, and Discussion sections of the article from the scientific aspect. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The spectroscopic data presented in this study are available as Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

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