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Short Note

2′-Chloro-4-(1-methyl-1*H*-imidazol-2-yl)-2,4′-bipyridine

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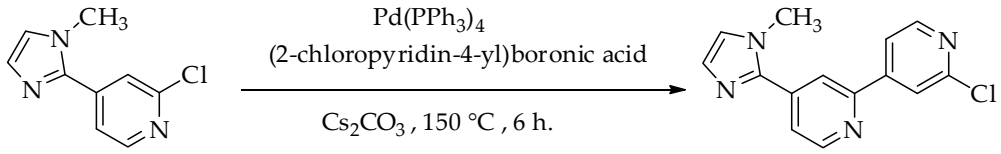
Abstract: The compound 2′-chloro-4-(1-methyl-1*H*-imidazol-2-yl)-2,4′-bipyridine was obtained with a good yield by the reaction of 2-chloro-4-(1-methyl-1*H*-imidazol-2-yl)pyridine with (2-chloropyridin-4-yl)boronic acid and structurally characterized by nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR), thin-layer chromatography–mass spectrometry (TLC–MS), HPLC, gas chromatography–mass spectrometry (GC–MS), and elemental analysis. The functionalization of the pyridine was achieved by the palladium-catalyzed Suzuki–Miyaura carbon–carbon cross-coupling reaction that afforded the target compound.

Keywords: Suzuki–Miyaura; imidazole; boronic acid; palladium-catalyzed; mass spectrometry

1. Introduction

Imidazoles are probably the most well-known heterocyclic compounds which are a common and important feature of a variety of natural products and medicinal agents [1–3]. Because of their unique antibacterial and antifungal activities, the imidazole core structure has attracted a huge interest from chemists as a significant medical scaffold [4–6]. On the other hand, it is known that bipyridines play a significant role as antibacterial and The antimicrobial activities of both these heterocyclic compounds (imidazole and bipyridine) have raised curiosity about the antimicrobial properties of organic molecules containing these two moieties [7–9]. Therefore, in this Short Note and in continuation of previous studies [10–24], a new imidazole–bipyridine derivative was synthesized for the first time by a palladium-catalyzed Suzuki–Miyaura carbon–carbon cross-coupling reaction (Scheme 1).



Scheme 1. Synthesis of 2′-chloro-4-(1-methyl-1*H*-imidazol-2-yl)-2,4′-bipyridine.

2. Results and Discussion

The 2′-chloro-4-(1-methyl-1*H*-imidazol-2-yl)-2,4′-bipyridine new imidazole–bipyridine derivative was synthesized by a one-step efficient and straightforward reaction (Scheme 1) based on palladium-catalyzed Suzuki–Miyaura carbon–carbon cross-coupling reaction. The compound 2-chloro-4-(1-methyl-1*H*-imidazol-2-yl)pyridine was reacted with (2-chloropyridin-4-yl)boronic acid. The best yield was obtained when $Pd(PPh_3)_4$ was used as the catalyst (3–5 mol%). The use of palladium acetate $Pd(OAc)_2$ in the presence of XPhos gave similar result in terms of yield.

However, the employment of $Pd(PPh_3)_4$ is significantly cheaper. Also, a chemo-selective coupling reaction proved to be important to carry out the reaction at 150 °C for 6 h to avoid by-products. Cesium carbonate was optimized as the base for the reaction. The desired compound was characterized by chemical analysis methods, which included nuclear magnetic resonance (NMR), liquid chromatography–mass spectrometry (LC–MS), gas chromatography–mass spectrometry (GC–MS), and elemental analysis. The purity of the target compound was also examined using high-performance liquid chromatography (HPLC).

3. Materials and Methods

All chemicals were purchased from commercial sources unless otherwise specified and were used without further purification. Thin-layer chromatography (TLC) controls were performed for all reactions using fluorescent silica gel 60 F254 plates (Merck, Darmstadt, Germany) and visualized under natural light and UV illumination at 254 and 366 nm. The purity of the target compound was confirmed to be >95%, as determined by reversed-phase high-performance liquid chromatography (HPLC).

Nuclear magnetic resonance (NMR) data were obtained with a Bruker ARX NMR spectrometer (Bruker BioSpin AG, Faellanden, Switzerland) at 250 MHz and on a Bruker AVANCE III HD NMR spectrometer (Bruker BioSpin AG, Faellanden, Switzerland) at 300 MHz at ambient temperature. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS). NMR spectra were calibrated against the (residual proton) peak of the deuterated solvent used. A mass spectrum was recorded on an Advion expression S electrospray ionization mass spectrometer (ESI–MS) (Shimadzu Corporation, Kyoto, Japan) with TLC interface.

Synthesis of 2′-Chloro-4-(1-methyl-1H-imidazol-2-yl)-2,4′-bipyridine

Under an argon atmosphere, a mixture of 2-chloro-4-(1-methyl-1*H*-imidazol-2-yl)pyridine (0.15 g, 0.775 mmol), (2-chloropyridin-4-yl)boronic acid (0.134 g, 0.853 mmol), and Cs_2CO_3 (0.378 g, 1.16 mmol) was added to a solution of tetrakis(triphenylphosphine)palladium $Pd(PPh_3)_4$ (40 mg, 1.16 mmol) in dioxane (5 mL) solvent. The reaction mixture was stirred and heated in a pressure vial at 150 °C for 6 h. The solvent was evaporated at reduced pressure, and the residue was purified by flash column chromatography (SiO_2, DCM/EtOH 98:02), yielding the title compound (0.127 g, 61% yield) as a yellow oil. ^{1}H-NMR (300.13 MHz, DMSO-d_6) δ = 3.94 (s, 3H), 7.12 (br. s, 1H), 7.43 (br. s, 1H), 7.84–7.86 (m, 1H), 8.14–8.22 (m, 2H), 8.40–8.41(m, 1H), 8.56 (dd, J = 5.2, 0.6 Hz, 1H) ppm, 8.83 (dd, J = 5.1, 0.7 Hz, 1H). ^{13}C-NMR (75.47 MHz, DMSO-d_6) δ = 35.3, 120.0, 120.9, 121.7, 123.4, 125.9, 129.1, 139.8, 143.9, 149.5, 150.9, 151.1, 151.8, 153.0 ppm. MS-ESI m/z: $[M + H]^+$ calculated for $C_{14}H_{11}ClN_4$: 270.7, found: 271.1; HPLC retention time (t_R): = 1.492 min. (95.9%). Analysis calculated for $C_{14}H_{11}ClN_4$: C, 62.11; H, 4.10; Cl, 13.09; N, 20.70, Found: C, 62.37; H, 4.35; Cl, 13.33; N, 20.98.

4. Conclusions

In this paper, we developed a facile and efficient chemo-selective method for the synthesis of 2′-chloro-4-(1-methyl-1*H*-imidazol-2-yl)-2,4′-bipyridine with a good yield by the Suzuki–Miyaura cross-coupling reaction and we characterized the title compound by physicochemical and spectral methods.

Supplementary Materials: The following are available online, Figure S1: HPLC, Figure S2: MS, Figure S3: ^{13}C-NMR, Figure S4: DEPT, Figure S5: ^{1}H-NMR.

Author Contributions: D.S.Z., methodology; D.L.A.-D., characterization; A.A.-A. wrote the manuscript.

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

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