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Optimization and Scaling up of the Azaindole Derivatives Synthesis

Abstract

In this study, an optimized method for the synthesis of azaindoles was developed and successfully scaled up to a 100 g batch. Improved yields were observed when using electron-deficient azaheterocycles and substrates bearing electron-withdrawing substituents. 6-Chloro-1*H*-pyrrolo[3,2-*c*]pyridine was selected for further functionalization using a carbonylation protocol involving carbon monoxide. As a result, novel and promising building blocks for medicinal chemistry were obtained.

Keywords: azaindoles; Sonogashira coupling; Larock synthesis; carbonylation

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Оптимізація та масштабування методу синтезу похідних азаіндолу

Анотація

У цьому дослідженні було розроблено оптимізований метод синтезу азаіндолів, який успішно масштабовано для одержання до 100 г цільової сполуки. Кращі виходи спостерігали в разі використання електронодефіцитних азагетероциклів та замісників з електронно-акцепторними властивостями. Для подальшої функціоналізації було обрано 6-хлоро-1*H*-піроло[3,2-*c*]піридин шляхом його карбонілювання дією карбон(II) оксиду. Внаслідок цього було одержано нові перспективні будівельні блоки для потреб медичної хімії.

Ключові слова: азаіндоли; реакція Соногашіри; синтез Ларока; карбонілювання

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Supporting information: Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of the synthesized compounds.
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■ Introduction

Azaindoles are compounds composed of fused azaheterocyclic and pyrrole rings, forming aromatic frameworks that serve as bioisosteres of indoles and are structurally similar to purine bases. This structural similarity contributes to their broad spectrum of biological activities, making them valuable in pharmaceuticals, industrial applications, and natural product chemistry [1–4].

According to the SciFinder® database, azaindoles have increasingly attracted research attention since 2000 (**Figure 1**). Since 2004, due to their recognized antiviral properties and influenced by global health crises, the number of publications on azaindoles has nearly doubled.

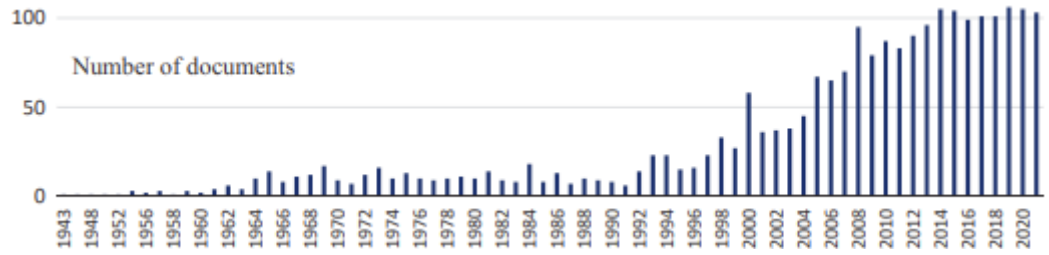


Figure 1. The published papers dedicated to azaindoles

Currently, over 100 articles related to azaindoles are published annually [5].

Numerous synthetic approaches have been developed for azaindole formation, predominantly involving the assembly of a pyrrole ring onto existing azaheterocyclic frameworks. However, methods assembling azaheterocycles onto a pyrrole core have also been documented (**Figure 2**) [5, 6].

■ Results and discussions

Taking into account the significant range of biological activities exhibited by azaindoles discovered over the past two decades, optimizing synthetic routes remains critically important. This study aimed to validate and optimize synthetic methods across various electron-deficient azaheterocycles, such as pyridine, pyrazine, and pyrimidine.

The Larock's synthetic approach was selected to achieve the research purposes due to its versatility and potential for structural diversity. This methodology involves a two-step process: the Sonogashira coupling using TMS-acetylene, followed by the heterocyclization mediated by KO*t*Bu [7–11]. Seven azaindole derivatives were chosen for the synthesis, including compounds (**3a**, **3c**, **3g**) previously described to establish a more convenient and efficient method. For example, the synthesis of 5*H*-pyrrolo[2,3-*b*]pyrazine derivative (**3a**) *via* *N*-mesyl amino pyrazine reported earlier faced difficulties at the initial stage, resulting in low overall yields [12]. Similarly, the synthesis of 6-chloro-1*H*-pyrrolo[3,2-*c*]pyridine (**3c**) involved a complicated multi-step catalytic oxidation [13]. Additionally, the synthesis of 7-methyl-1*H*-pyrrolo[3,2-*b*]pyridine (**3g**) was previously achieved through the Bartoli method with only 18% yield [14] or a multistep Suzuki coupling [15]. Derivatives **3b**, **3d**, **3e**, and **3f** have not been previously reported.

Commercially available amines were utilized for synthesizing **3a**, **3c**, **3f**, and **3g** derivatives, namely 3-chloropyrazin-2-amine (**1a**), 5-bromo-2-chloropyridin-4-amine (**1c**), 2-chloro-5-(trifluoromethyl)pyridin-3-amine (**1f**), and 2-bromo-4-methylpyridin-3-amine (**1g**). 5-Bromo-2-methylpyrimidin-4-amine (**1b**) was obtained with a high yield *via* the halogen reduction using Pd/C followed by the bromination (**Scheme 1**) [16, 17]. 3-Iodo-2-methoxypyridin-4-amine (**1d**) was prepared by the iodination using NIS in acetonitrile at reflux conditions [18]. For 2-bromo-6-(trifluoromethyl)pyridin-3-amine (**1e**), the bromination with NBS was conducted in acetonitrile instead of $CHCl_3$, significantly reducing the formation of regioisomers [19].

The Sonogashira reaction was scaled up to 100 g for each amine, and intermediates **2a–g** were purified by flash chromatography, resulting in excellent yields (**Scheme 2**). The lowest yield (64.3%) was noted for alkyne **2c** due to side reactions employing chlorine atoms. The optimal cyclization conditions involved the use of 1.2 equiv.

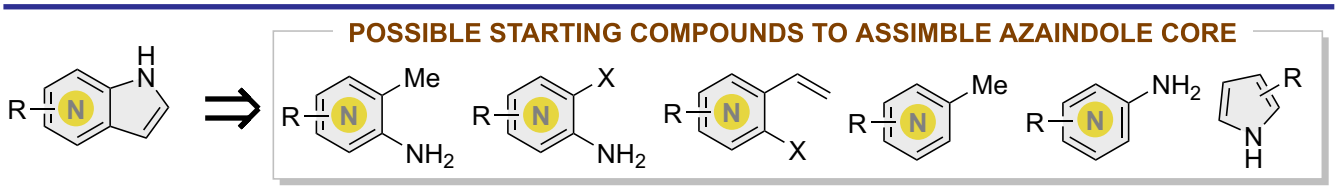
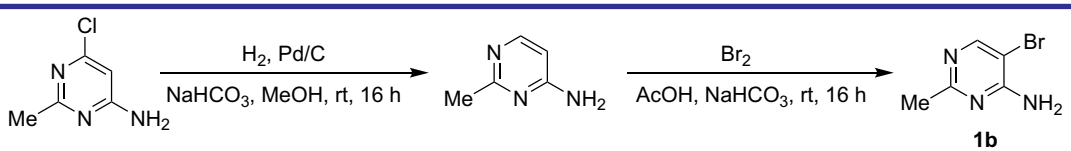


Figure 2. Main strategies toward azaindoles



Scheme 1. The synthesis of starting pyrimidine **1b**

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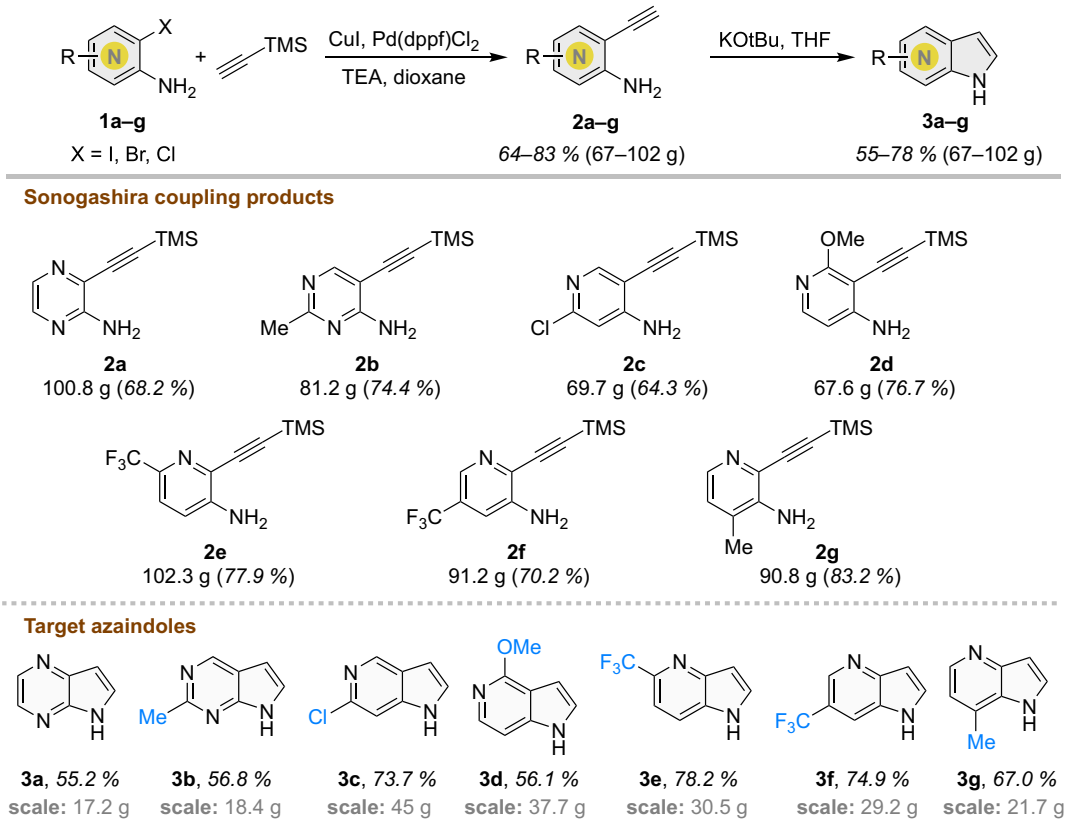


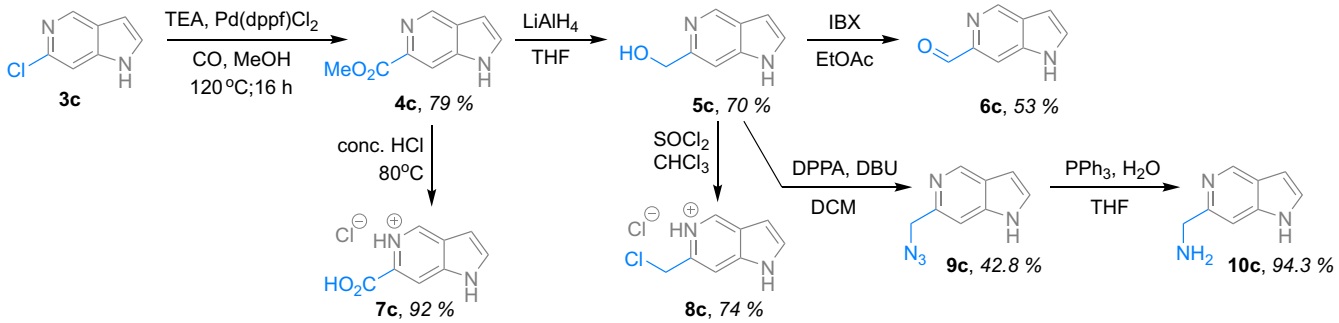
Scheme 2. The synthesis of the target azaindoles: scales and yields

of KO*t*Bu in THF. Compounds **2** with electron-withdrawing substituents, such as CF_3 (**2e**, **2f**) and chlorine (**2c**), along with a weakly electron-donating methyl group (**2g**), secured higher yields of the target azaindoles **3** of about 70%. At the same time, pyrazine and pyrimidine derivatives (**3a**, **3b**) were obtained with 55–57% yields similar to the methoxy derivative **3d** (56.1%).

Derivative **3c**, known for its biological activity [20, 21], offered the additional synthetic flexibility due to its halogen substituent. The catalytic carbonylation with CO in the methanol medium provided the corresponding ester **4c** with a high yield, which after the acidic hydrolysis yielded carboxylic acid **7c** (**Scheme 3**). At the same time, the reduction of the ester with $LiAlH_4$ yielded alcohol **5c**, which was likely to be a valuable intermediate for MedChem research. The reaction of **5c** with $SOCl_2$ produced chloromethyl derivative **8c**, while the oxidation with IBX in EtOAc yielded aldehyde **6c** in a moderate 53% yield. The corresponding amine **10c** was also synthesized *via* azide intermediate **9c**, formed using DPPA-DBU conditions, followed by the Staudinger reduction, without the intermediate purification.

■ Conclusion

In this study, an optimized method for the azaindole synthesis was reviewed and successfully scaled up to a 100 g batch size. Higher yields were achieved with electron-deficient azaheterocycles bearing electron-withdrawing substituents. Additionally, 6-chloro-1H-pyrrolo[3,2-c]pyridine was selected for further functionalization, leading



Scheme 3. The functionalization of product **3c**

to the preparation of novel and promising building blocks suitable for applications in medicinal chemistry.

■ Experimental part

^{1}H and ^{19}F NMR spectra were recorded on a Varian Unity Plus 400 instrument (400 and 376 MHz, respectively), ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 instrument (500 and 126 MHz, respectively), ^{13}C NMR spectra were also recorded on an Agilent ProPulse 600 (151 MHz) spectrometer. The NMR chemical shifts were referenced using the solvent signals at 7.26 and 77.1 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$ and 2.48 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6; C_6F_6 was used as the internal standard for ^{19}F NMR spectra. Mass spectra were obtained on an Agilent LC/MSD SL 1100 instrument (the atmospheric pressure electrospray ionization (ES-API)) or an Agilent 5890 Series II 5972 GCMS instrument (the electron impact (EI) ionization (70eV)). HRMS experiments were performed on an Agilent 6224 TOF LC/MS instrument using the electrospray ionization. The composition of hydrochloride salts was determined by the acid-base titration method. Melting points were measured in open capillary tubes and were given uncorrected. All starting compounds and solvents were obtained from Enamine Ltd. and used without additional purification.

The general procedure for the Sonogashira reaction (compounds 2a–g)

To the solution of **1a–g** (100 g) in 1.0 L dioxane, TMS-acetylene (1.2 equiv.) and TEA (4.0 equiv.) were was added. Then the mixture was degassed under argon and stirred for 10 min, CuI (0.05 equiv.) and Pd(dppf)Cl_2 (0.03 equiv.) were added in one portion under the argon atmosphere, the resulting mixture was stirred at 90 °C for 16 h. Upon completion of the reaction, the mixture was filtered through a celite pad and concentrated under vacuum. The crude mixture was purified by flash column chromatography in the corresponding eluent described below to give pure **2a–g**.

3-((Trimethylsilyl)ethynyl)pyrazin-2-amine (**2a**)

Flash chromatography purification using $CHCl_3$–MeCN mixture (9:1) as an eluent.

A yellow solid. Yield – 100.8 g (68.2%). M. p. 115 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.24 (9H, s), 6.48 (2H, s), 7.72 (1H, d, J = 2.5Hz), 7.93 (1H, d, J = 2.2Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: -0.4, 100.1, 100.8, 122.9, 132.5, 142.2, 156.3. LCMS (ES-API), m/z 192 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_9H_{13}N_3Si$ 191.0879, found 191.0875.

2-Methyl-5-((trimethylsilyl)ethynyl)pyrimidin-4-amine (**2b**)

Flash chromatography purification using $CHCl_3$ as an eluent.

A white solid. Yield – 81.2 g (74.4%). M. p. 125 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.21 (9H, s), 2.31 (3H, s), 7.46 (2H, br. s), 8.12 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: -0.2, 25.5, 97.5, 98.0, 102.2, 157.9, 162.9, 166.1. LCMS (ES-API), m/z 206 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_{10}H_{15}N_3Si$ 205.1030, found 205.1035.

2-Chloro-5-((trimethylsilyl)ethynyl)pyridin-4-amine (**2c**)

Flash chromatography purification using $CHCl_3$ as an eluent.

A yellow solid. Yield – 69.7 g (64.3%). M. p. 108 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.93 (1H, s), 6.63 (1H, s), 6.58 (2H, br. s), 0.22 (9H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 0.4, 98.5, 103.1, 103.5, 106.8, 150.6, 152.4, 157.0. LCMS (ES-API), m/z: 225 $[M+H]^+$.

2-Methoxy-3-((trimethylsilyl)ethynyl)pyridin-4-amine (**2d**)

The reaction mixture was stirred at 60° C for 16 h. Flash chromatography purification using $CHCl_3$ as an eluent.

A yellow solid. Yield – 67.6g (76.7%). M. p. 72 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.20 (9H, s), 3.77 (3H, s), 6.09 (2H, br. s), 6.32 (1H, d, J = 6.0 Hz), 7.60 (1H, d, J = 6.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 0.6, 53.6, 88.0, 98.1, 104.0, 104.5, 145.9, 157.8, 164.6. LCMS (ES-API), m/z: 221 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_{11}H_{16}N_2OSi$ 220.1032, found 220.1026.

6-(Trifluoromethyl)-2-((trimethylsilyl)ethynyl)pyridin-3-amine (**2e**)

Flash chromatography purification using $CHCl_3$ as an eluent.

A white solid. Yield – 102.3 g (77.9%). M. p. 110 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.25 (9H, s), 6.16 (2H, s), 7.21 (1H, d, J = 8.5Hz), 7.49 (1H, d, J = 8.5Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: -0.3, 99.8, 100.6, 120.4, 121.4, 125.5, 133.7, 134.0, 148.5. ^{19}F NMR (376 MHz, DMSO-d_6), δ, ppm: -65.35. LCMS (ES-API), m/z: 259 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_{11}H_{13}F_3N_2Si$ 258.0798, found 258.0800.

5-(Trifluoromethyl)-2-((trimethylsilyl)ethynyl)pyridin-3-amine **(2f)**

Flash chromatography purification using $CHCl_3$ as an eluent.

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A white solid. Yield – 91.2 g (70.2%). M. p. 132 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.26 (9H, s), 5.94 (2H, s), 7.37 (1H, s), 8.01 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: -0.4, 100.2, 101.7, 116.6, 122.5, 124.7, 129.4, 132.9, 146.0. ^{19}F NMR (376 MHz DMSO-d_6), δ, ppm: -61.99. LCMS (ES-API), *m/z*: 259 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_{11}H_{13}F_3N_2Si$ 258.0804, found 258.0800.

4-Methyl-2-((trimethylsilyl)ethynyl)pyridin-3-amine **(2g)**

The crude mixture was treated with MTBE.

A gray solid. Yield – 90.8 g (83.2%). M. p. 121 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 0.24 (9H, s), 5.13 (2H, s), 6.97 (1H, d, J = 4.6 Hz), 7.66 (1H, d, J = 4.3 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: -0.2, 17.0, 98.7, 102.0, 125.3, 125.7, 129.7, 138.0, 144.8. LCMS (ES-API), *m/z*: 205 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_{11}H_{16}N_2Si$ 204.1083, found 204.1089.

The general procedure for heterocyclization 3a–g

KO*t*Bu (1.2 equiv.) was added in one portion to a stirring solution of compound **2a–g** (1 equiv., 50 g) in 1.0 L THF at 0 °C. The temperature was brought to reflux, and the resulting mixture was stirred for 15 h. After that, the solvent was evaporated to dryness, the residue was poured into the mixture of the concentrated HCl and water (100 mL–400 mL), the mixture was stirred for 30 min and filtered through celite; the mother liquid was neutralized with ammonia to pH = 10, stirred for another 30 min. Then the precipitate was collected *via* the vacuum filtration. In case if the precipitate was not formed, the mixture was extracted with DCM (3×200 mL), combined organic layers were dried with the anhydrous Na_2SO_4 and concentrated. Compounds **3a–g** required no additional purification.

5H-Pyrrolo[2,3-b]pyrazine (**3a**)

A white solid. Yield – 17.2 g (55.2%). M. p. 153 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.61 (1H, dd, J = 3.5, 1.7 Hz), 7.85 (1H, t, J = 3.2 Hz), 8.21 (1H, d, J = 2.6 Hz), 8.36 (1H, d, J = 2.3 Hz), 12.03 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 100.8, 131.5, 137.1, 138.5, 139.6, 141.7. LCMS (ES-API), *m/z*: 120 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_6H_5N_3Si$ 119.0492, found 119.0483.

2-Methyl-7H-pyrrolo[2,3-d]pyrimidine (**3b**)

A white solid. Yield – 18.4 g (56.8%). M. p. 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.60 (3H, s), 6.49 (1H, d, J = 2.6Hz), 7.42 (1H, s), 8.85 (1H, s), 11.88 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 25.9, 99.6, 116.0, 126.8, 149.2, 152.4, 159.73. LCMS (ES-API), *m/z*: 134 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_7H_7N_3$ 133.0644, found 133.0640.

6-Chloro-1H-pyrrolo[3,2-c]pyridine (**3c**)

A brown solid. Yield – 45 g (73.7%). M. p. 189 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.59 (1H, m), 7.42 (1H, s), 7.48 (1H, m), 8.60 (1H, s), 11.62 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 101.0, 106.4, 125.0, 128.7, 141.7, 141.8, 142.5. LCMS (ES-API), *m/z*: 153 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_7H_5ClN_2$ 152.0139, found 152.0141.

4-Methoxy-1H-pyrrolo[3,2-c]pyridine (**3d**)

A brown solid. Yield – 37.7 g (56.1%). M. p. 139 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 4.10 (3H, s), 6.66 (1H, d, J = 2.3Hz), 6.97 (1H, d, J = 5.7 Hz), 7.13 (1H, m), 7.84 (1H, d, J = 5.7 Hz), 8.59 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 52.9, 99.5, 103.2, 112.1, 124.7, 137.4, 141.5, 157.7. LCMS (ES-API), *m/z*: 149 $[M+H]^+$. HRMS (APCI) *m/z*: calcd for $C_8H_8N_2O$ 148.0637, found 148.0637.

5-(Trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**3e**)

A white solid. Yield – 30.5 g (78.2%). M. p. 213 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.7 (1H, s), 7.54 (1H d, J = 8.2 Hz), 7.88 (1H, s), 7.99 (1H, d, J = 8.5 Hz), 11.76 (1H, br). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 102.0, 112.5, 119.4, 121.7–123.8 (q, J = 265 Hz, CF_3), 129.6, 132.3, 139.4, 145.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -64.47 LCMS (ES-API), *m/z*: 187 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_8H_5F_3N_2$ 186.0402, found 186.0405.

6-(trifluoromethyl)-1H-pyrrolo[3,2-b]pyridine (**3f**)

A white solid. Yield – 29.2 g (74.9%). M. p. 190 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.71 (1H, s), 7.95 (1H, s), 8.16 (1H, s), 8.65 (1H, s), 11.85 (1H, br). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 101.9, 117.3, 117.4, 124.5–126.3 (q, J = 227 Hz, CF_3), 128.1, 134.7, 138.4, 147.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ -58.81. LCMS (ES-API), *m/z*: 187 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_8H_5F_3N_2$ 186.0406, found 186.0405.

Methyl-1H-pyrrolo[3,2-b]pyridine (**3g**)

A brown solid. Yield – 21.7 g (67.0%) M. p. 189 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.48 (3H, s), 6.51 (1H, s), 6.89 (1H, s), 7.57 (1H, s), 8.17 (1H, s), 11.35 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 16.2, 101.8, 117.4, 128.3, 128.9, 142.3, 145.2, 145.6. LCMS (ES-API) *m/z*: 133 $[M+H]^+$. HRMS (APCI), *m/z*: calcd for $C_8H_8N_2$ 132.0685, found 132.0687.

The procedure for the preparation of methyl 1*H*-pyrrolo[3,2-*c*]pyridine-6-carboxylate (4c)

To the solution of compound **3c** (30 g, 0,196 mol) and TEA (32.9 mL, 0.234 mol) in 400 mL MeOH in 500 mL autoclave, $Pd(dppf)Cl_2$ (4.75 g, 0.006 mol) was added. The reaction vessel was flushed three times with CO gas and stirred under 20 atm at 120 °C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, and the precipitate was collected *via* the vacuum filtration, washed with water and MTBE, then dried in air to obtain a pure product **4c** (27.3 g, 78.9%).

A yellow solid. Yield – 27.3 g (78.9%). M. p. 183 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 3.85 (3H, s), 6.70 (1H, d, J = 3.2 Hz), 7.62–7.73 (1H, m), 8.15 (1H, s), 8.89 (1H, s), 11.94 (1H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 52.4, 101.5, 110.0, 127.3, 130.4, 138.6, 139.2, 143.0, 166.8. LCMS (ES), m/z: 177 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_9H_8N_2O_2$ 176.0586, found 176.0581.

The procedure for the preparation of methyl 1*H*-pyrrolo[3,2-*c*]pyridine-6-carboxylate (5c)

To a cooled solution of $LiAlH_4$ (14.25 g, 1.25 equiv.) in THF (1 L) at 0 °C, **4c** (53.0 g, 0.30 mol) was added portionwise, keeping temperature bellow 0 °C. Then mixture was stirred at room temperature for 15 h. Upon completion, the reaction mixture was cooled to 0 °C and carefully neutralized with the water-NaOH solution and water. The mixture was stirred for 1 h at room temperature, and the precipitate was filtered through celite, washed with MTBE, then the mother liquid was evaporated *in vacuo* to give a pure product **5c** (31.3 g, 70.2%)

A yellow solid. Yield 31.3 g (70.2%). M. p. 132 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 4.26 (s, 2H), 5.27 (1H, br. s), 6.51 (1H, s), 7.37 (1H, s), 7.42 (1H, s), 8.69 (1H, s), 11.44 (1H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 65.0, 100.6, 103.1, 123.9, 126.7, 140.7, 142.2, 153.1; LCMS (ES), m/z: 149 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_8H_8N_2O$ 148.0637, found 148.0635.

The procedure for the preparation of 1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)methanol (6c)

To the mixture of **5c** (20.0 g, 0.135 mol) in 400 mL of EtOAc, IBX (1.5 equiv.) was added in one portion. Then the mixture was stirred at reflux for 15 h. Upon completion, the reaction mixture was filtered hot through celite, washed with EtOAc, then the mother liquid was washed with the K_2CO_3 water solution (20 g in 500 mL of water), the organic phase was dried and evaporated *in vacuo* to give a pure product **6c** (10.4 g, 52.7%).

A yellow solid. Yield – 10.4 g (52.7%). M. p. 162 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 6.73 (1H, d, J = 2.5 Hz), 7.75 (1H, d, J = 3Hz), 8.01 (1H, s), 9.01 (1H, s), 10.05 (1H, s), 12.08 (1H, s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 101.3, 106.6, 127.9, 131.0, 138.6, 143.2, 144.8, 193.6. GCMS, m/z: 146 $[M]^+$; HRMS (APCI), m/z: calcd for $C_8H_6N_2O$ 146.0476, found 146.0480.

The procedure for the preparation of 1*H*-pyrrolo[3,2-*c*]pyridine-6-carboxylic acid hydrochloride (7c)

To the solution of compound **4c** (1.0 g, 0.0057 mol), the conc. HCl (10 mL) was added. The resulting mixture was stirred at 80 °C for 15 h. Upon completion, the reaction mixture was evaporated to dryness to obtain a yellow solid product **7c** in the form of HCl salt (1.04 g, 92.0%).

A yellow solid. Yield – 1.04 g (92%). M. p. 280 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 7.15 (1H, s), 8.12 (1H, s), 8.49 (1H, s), 9.29 (1H, s), 13.81 (1H, s), 14.80 (1H, br). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 105.9, 111.3, 126.0, 130.9, 135.2, 137.8, 141.6, 162.3. LCMS (ES), m/z: 163 $[M+H]^+$. HRMS (APCI) m/z: calcd for $C_8H_6N_2O_2$ 162.0428, found 162.0429.

The procedure for the preparation of 6-(chloromethyl)-1*H*-pyrrolo[3,2-*c*]pyridine hydrochloride (8c)

To the solution of $SOCl_2$ (1.5 equiv.) in 400 mL of $CHCl_3$, alcohol **5c** (30 g, 0.20 mol) was added dropwise at 0 °C. Then the mixture was stirred at room temperature for 16 h. Upon completion, the precipitate was collected *via* vacuum filtration, washed with $CHCl_3$, then dried to obtain pure product **8c** (30.5 g, 74.2%, hydrochloride salt).

A yellow solid. Yield – 30.5 g (74.2%). M. p. 209 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 5.20 (2H, s), 7.01 (1H, d, J = 0.5 Hz), 7.96 (1H, d, J = 2.2Hz), 8.12 (1H, s), 9.27 (1H, s), 13.37 (1H, s), 15.86 (1H, br. s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 41.5, 104.8, 110.1, 124.1, 133.6, 136.8, 139.7, 142.4. LCMS (ES), m/z: 167 $[M+H]^+$. HRMS (APCI) m/z: calcd for $C_8H_7ClN_2$ 166.0297, found 166.0298.

The procedure for the preparation of 6-(azidomethyl)-1H-pyrrolo[3,2-c]pyridine (9c)

To a cooled to 0 °C solution of DBU (1.2 equiv.) and **5c** (5.0 g, 0.03 mol) in 200 mL of THF, DPPA (1.2 equiv.) was added portionwise keeping temperature bellow 0 °C. Then the mixture was

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stirred at room temperature for 15 h. Upon completion, the reaction mixture was evaporated to dryness. The crude mixture was purified by column chromatography using the $CHCl_3$-MeCN system as an eluent to give **9c** (2.5 g, 42.8%) as a yellow solid with 80% purity. The product was used in the next step without any purification due to stability issues.

Yield – 2.5 g (42.8%). Purity 80%. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 4.50 (2H, s), 6.58 (1H, d, J = 2.8 Hz), 7.41–7.52 (2H, m), 8.82 (1H, s), 11.66 (1H, s).

The procedure for the preparation of (1*H*-pyrrolo[3,2-*c*]pyridin-6-yl)methanamine (10c)

To the solution of crude **9c** (2.5 g, 0.01 mol) in 50 mL of THF, PPh_3 (1.2 equiv.) was added in one portion and H_2O (1.5 equiv.) in 30 min. The resulting mixture was stirred at room temperature for 15 h. Upon completion, a diluted HCl (2 equiv.) was added, the water solution was extracted twice with $CHCl_3$ (for PPh_3 and Ph_3PO separation), and then the water solution was neutralized with K_2CO_3. The precipitate was collected *via* the vacuum filtration, washed with THF, then dried to obtain a pure product **10c** (2.0 g, 94.3%).

A white solid. Yield – 2.0 g (94.3 %). M. p. 190 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.96–2.40 (1H, br. s), 3.85 (2H, s), 6.52 (1H, d, J = 2.3 Hz), 7.37 (1H, d, J = 2.0 Hz), 7.39 (1H, s), 8.72 (1H, s), 11.45 (1H, br. s). ^{13}C NMR (151 MHz, DMSO-d_6), δ, ppm: 48.0, 100.5, 103.6, 123.8, 126.6, 140.7, 142.3, 154.0. LCMS (ES), m/z: 148 $[M+H]^+$. HRMS (APCI), m/z: calcd for $C_8H_9N_3$ 147.0794, found 147.0796.

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