

UDC 542.06:547.83

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The Synthesis of Diverse Annulated Pyridines with 6-Membered Functionalized Saturated Cycles for Medical Chemistry Research

Abstract

The article describes a set of pyridines annulated with functionalized 6-membered saturated rings, which are attractive building blocks for the synthesis of diversified compound libraries in medical chemistry. A certain array of compounds includes pyridines with condensed cyclohexane, piperidine and tetrahydropyran cycles containing keto-, amino-, carboxylic groups, as well as fluorinated fragments. The synthesis of the compounds using the procedure previously developed by us *via* CuCl₂-catalyzed condensation of propargylamine with ketones was performed. The limits of application of this reaction were further expanded and determined in this work compared to our previous results. Condensed pyridines, which proved problematic or impossible to obtain by this method, were synthesized using other synthetic pathways. Thus, the study offers a number of new building blocks for use in drug discovery.

Keywords: organic synthesis; heterocyclic compounds; pyridines; building blocks; organofluorines; “magic methyl”; scaffold hopping

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Синтез різноманітних піридинів, анельованих функціоналізованими шестичленними насиченими циклами, для досліджень у галузі медичної хімії

Анотація

У статті окреслено набір піридинів, анельованих функціоналізованими шестичленними насиченими кільцями, які є привабливими білдинг-блоками для синтезу диверсифікованих бібліотек у медичній хімії. До визначеного масиву сполук увійшли піридини з конденсованими циклогексановим, піперидиновим та тетрагідропірановим кільцем, що містять кето-, аміно-, карбоксигрупи, фторовмісні фрагменти. Частину сполук було синтезовано за раніше розробленим нами методом – CuCl₂-каталізованою конденсацією пропаргіламіну та кетонів. У презентованій роботі було додатково розширено та визначено межі застосування цієї реакції. Конденсовані піридини, одержання яких за цим методом виявилось проблемним або неможливим, синтезовано іншими шляхами. Отже, дослідження пропонує низку нових будівельних блоків для використання в пошуку лікарських засобів.

Ключові слова: органічний синтез; гетероциклічні сполуки; піридини; фторорганічні сполуки; «чарівний метил»; скафолдне прогнозування

Citation: Yehorov, D. V.; Subota, A. I. The synthesis of diverse annulated pyridines with 6-membered functionalized saturated cycles for medical chemistry research. *Journal of Organic and Pharmaceutical Chemistry* **2023**, 21 (3), 23–30.

<https://doi.org/10.24959/ophcj.23.289263>

Supporting information: Copies of ¹H, ¹⁹F NMR and LC-MS spectra of the synthesized compounds.

Received: 15 August 2023; **Revised:** 27 September 2023; **Accepted:** 5 October 2023

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Funding: The authors received no specific funding for this work.

Conflict of interests: The authors have no conflict of interests to declare.

Introduction

Pyridines annulated to saturated cycles (PASCs) are widely used in drug discovery. Among the compounds containing this fragment there are substances demonstrating anti-HIV [1], antiretroviral [2, 3], antibacterial [4] and antimigraine [5] activity (Figure 1).

Due to such a wide spectrum of the biological activity demonstrated, chemists need convenient and cost-effective methods for the synthesis of diverse functionalized PASCs in multigram and/or even semi-industrial scales. In this research, we demonstrate our strategy for solving this problem and propose a synthetic strategy for producing a set of bicyclic building blocks containing pyridine and an annulated saturated core with various substituents and functional groups. According to the development of “magic methyl” and “magic fluorine” concepts, along with classical functions, we included compounds bearing methylmethylene (2), dimethylmethylene (3) and difluoromethylene (4) moieties in our short-list. Isomeric conformationally restricted ketones **6a–d**, carboxylic acids **7a–d**, PASCs with exocyclic amine function **8a–d** and those featuring endocyclic one **9a–d** were also treated as utility building blocks for modern combinatorial chemistry and drug discovery (Figure 2).

Reported approaches towards pyridines annulated with 6-membered saturated cycles include: (A) the partial reduction of the corresponding

aromatic compounds, (B) the construction of the saturated 6-membered ring and (C) the construction of the pyridine ring. Viable routes to implement the approaches are illustrated by a retrosynthetic analysis of compound **9c** (Figure 3).

Approach C can also be illustrated by the intermolecular Diels-Alder reaction with an inverse electron demand [6], intermolecular oxidative cyclization [7, 8] or [4+2]-cyclization. Examples of [4+2]-cyclization include reactions catalyzed by gold [9] and ruthenium [10–13]. Recently, our research group proposed a simple and scalable method *via* the condensation catalyzed by available and cheap CuCl_2 [14] (Figure 4). Thanks to our research, this approach has become cost-effective and, along with good scalability and diversity, very promising for obtaining such compounds.

In this light, we aimed to extend and determine the scope of the method and perform the synthesis of the set of diverse PASCs. In addition, in some cases of the method, we proposed other approaches for the synthesis of the target molecules.

Results and discussion

In our previous work [9], we reported on the synthesis of the parent core **1**, ketones **6a** and **6b**, carboxylic acid **7b**, amines **8a**, **9a**, **9b** and dihydropyranopyridine **10b**. The scope of the method was successfully expanded to the synthesis of

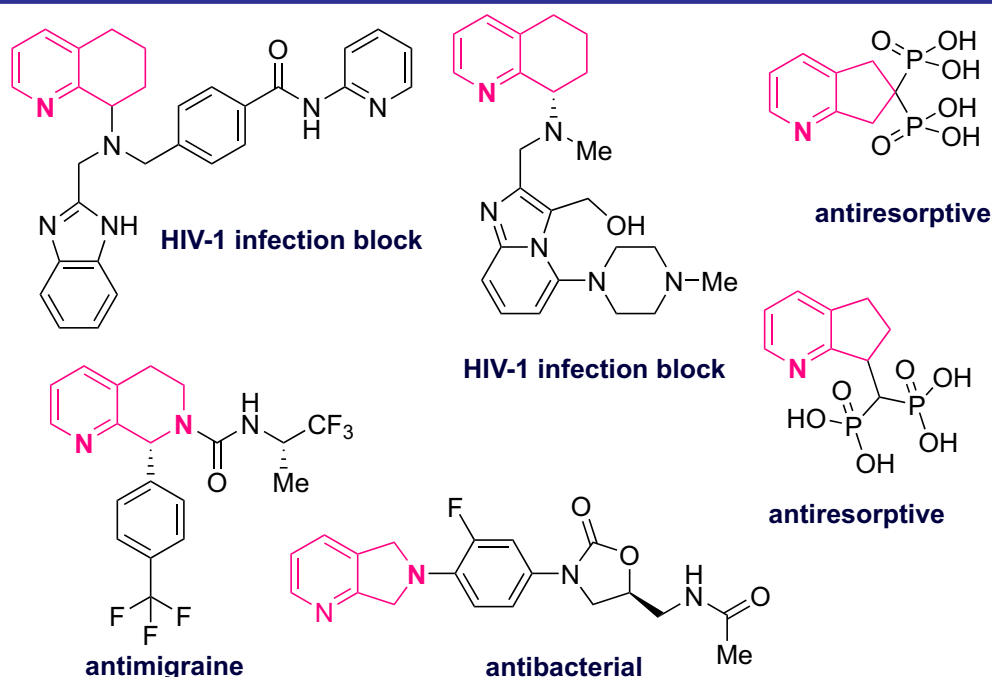


Figure 1. Examples of biologically active compounds containing a PASC moiety

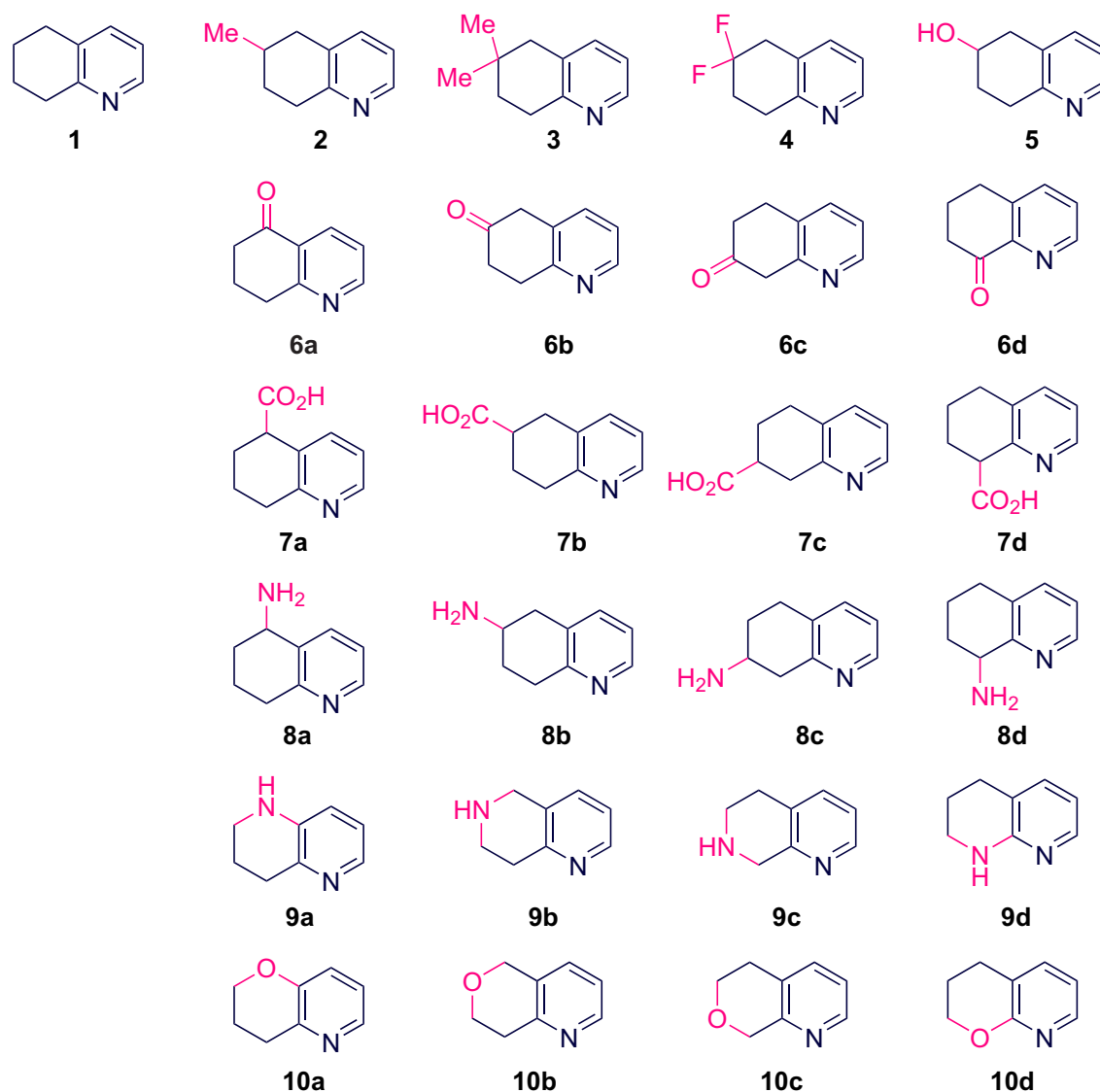


Figure 2. A representative set of PASC building blocks

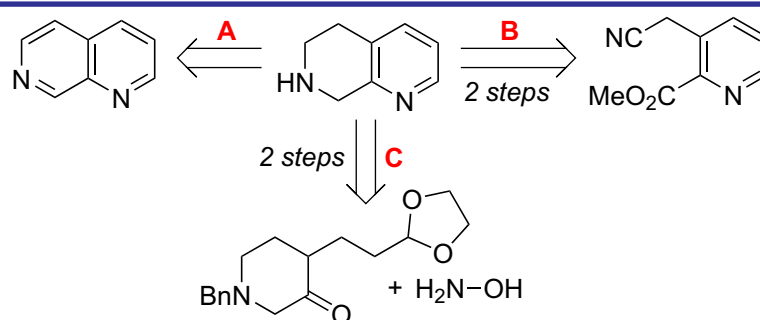


Figure 3. The retrosynthetic analysis of **9c**

pyridines fused with saturated rings bearing CHMe-, CMe₂-, CF₂-, CHOH-moieties. Propargylamine (**11**) was condensed with ketones **12–16** in the presence of anhydrous CuCl₂ to obtain the desired products (including compounds **3** and **4** previously unknown).

Although alcohol **5** was reported previously, the yield was neither good (e.g., 28%) [15] nor even reported. Our approach works much better – a one-step scalable procedure provides 58%

yield of **5**. We also attempted to oxidize alcohol **5** to obtain known [16, 17] ketone **6b** *via* the Dess-Martin oxidation. However, the yields were low (10–15%), so this way needed further optimizations. Notably, ketone **6b** can be involved in self-condensation reactions, and therefore, it should be stored in the freezer.

Ketone **6c** still remains a challenge for synthetic chemists (our attempts were unsuccessful

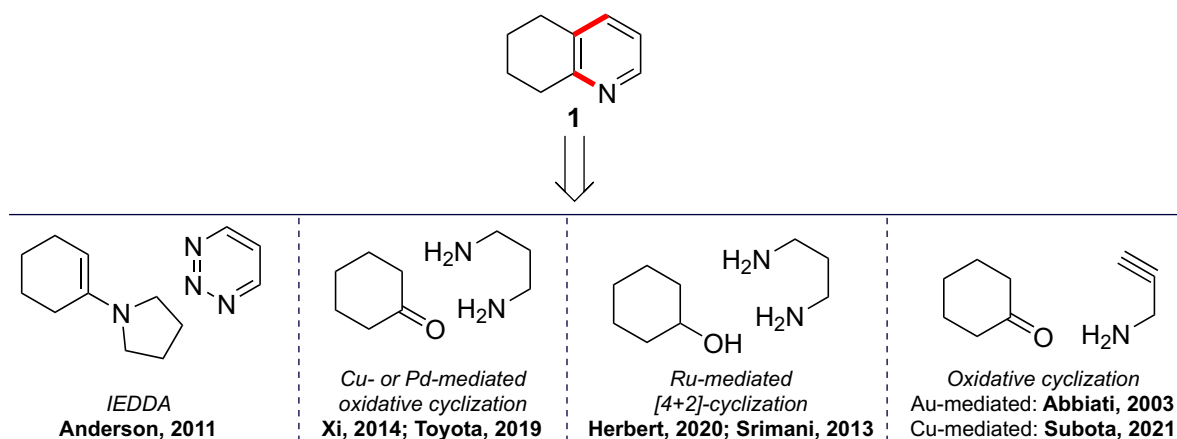
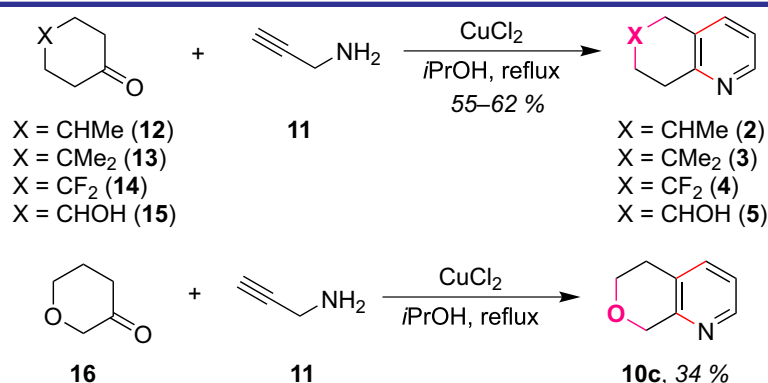


Figure 4. The known approaches for the synthesis of the pyridine ring of PASCs



Scheme 1. The synthesis of pyridines 2-5 and 10c

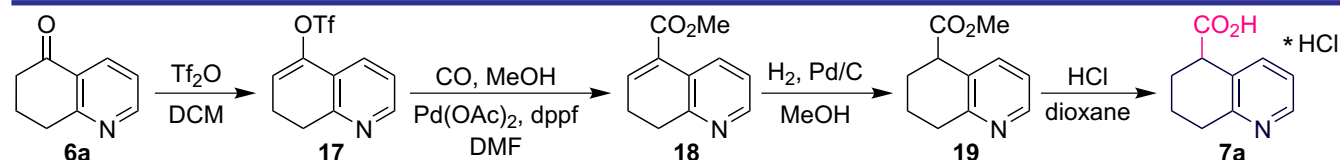
as well), while more than 20 different reactions for the synthesis of ketone **6d** were reported, even in a kilogram scale [18].

Previously, we obtained ethyl esters of carboxylic acids **7a** and **7c** as an inseparable mixture. The synthesis of **7c** in 75% *via* the Wolff-Kishner reduction was reported in 1974 [19]. Carboxylic acids **7b** and **7d** [20] were also reported. The synthesis of the previously unknown **7a** was carried out starting from ketone **6a**. At the first stage, the ketone was transformed to the enol triflate **17**, and the latter was further carbonylated with CO to form ester **18**. Compound **18** was successfully reduced to saturated acid **19**, the acidic hydrolysis of the latter led to the target acid **7a** (Scheme 2).

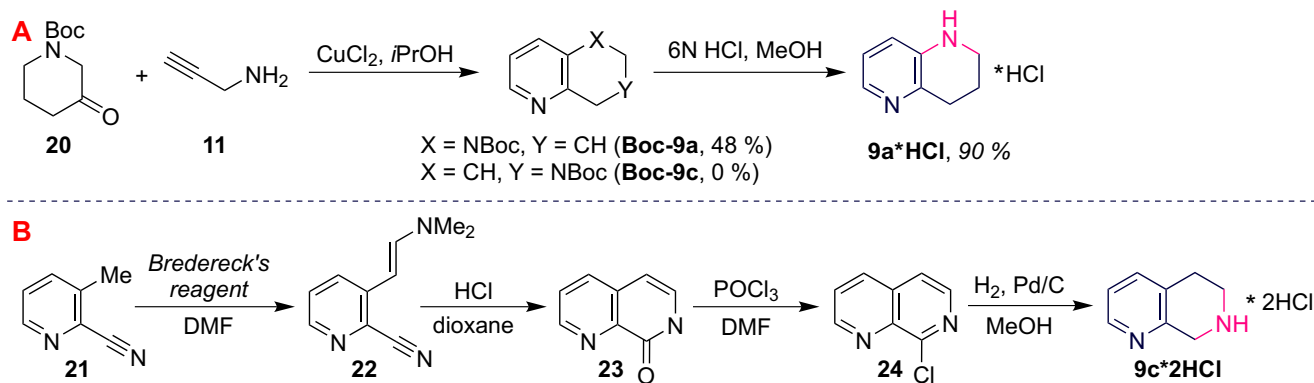
Ketone **20** reacts with propargylamine yielding pyridine **Boc-9a**, as it was described in our

previous work, and isomer **Boc-9c** were detected (Scheme 3, A). Therefore, the condensation of ketone **20** with propargylamine is not a suitable method for the synthesis of **9c**. Multistep preparations of **9c** were reported earlier [8, 9]. Alternatively, 1,7-naphtryridine partial reduction gave mixtures of isomers [7]. Hereby, we proposed an alternative 4-step way starting from nitrile **21** (Scheme 3, B).

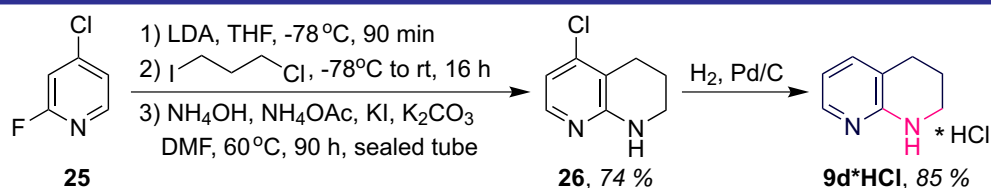
The scalable synthesis of amine **9d** from pyridine **25** was performed through an elegant route based on the construction of the piperidine ring on the b-bond of pyridine in 2-fluoro-4-chloropyridine (**25**) (Scheme 4). In contrast to the procedures previously reported [21–23], the proposed reaction sequence leads to a single isomer, consists of common organic procedures and uses available starting materials.



Scheme 2. The synthesis of carboxylic acid **7a**



Scheme 3. The synthesis of amine 9c



Scheme 4. The synthesis of amine 9d

Conclusions

A representative set of pyridines annelated with 6-membered functionalized saturated rings has been synthesized. The scope of CuCl_2 -catalyzed condensation of propargylamine with ketones has been extended. Other synthetic methods have been proposed for pyridines that cannot be obtained using this procedure. A set of novel building blocks related to medical chemistry has been created for drug development.

Experimental part

All solvents were purified according to the standard procedures. Absolute ethanol and isopropanol were used. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance 500 spectrometer (at 500 MHz for ^1H and 126 MHz for ^{13}C nuclei) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H and 101 MHz for ^{13}C nuclei). Tetramethylsilane (^1H , ^{13}C) was used as an internal standard. Mass spectra were recorded on an Agilent 5890 Series II 5972 GCMS instrument (atmospheric pressure electrospray ionization (ESI)).

The general procedure for the synthesis of pyridines 2–5 and 10c

Pyridines 2–5 and 10c were obtained according to the procedure previously developed [9].

6-Methyl-5,6,7,8-tetrahydroquinoline (2)

A brownish oil. Yield – 28 g (62%). Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}$, %: C 81.58; H 8.90; N 9.51. Found, %: C 81.38; H 9.01; N 9.59. ^1H NMR (400 MHz, Chloroform- d), δ , ppm: 1.09 (3H, d, $J = 6.5$ Hz); 1.43–1.62 (1H, m); 1.86–2.02 (2H, m); 2.43 (1H, dd, $J = 16.6, 10.5$ Hz); 2.81 (1H, dd, $J = 16.5, 5.0$ Hz); 2.90–3.04 (2H, m); 7.02 (1H, dd, $J = 7.7, 4.8$ Hz); 7.34 (1H, d, $J = 7.7$ Hz); 8.35 (1H, d, $J = 4.8$ Hz). LC-MS (ESI, positive mode), m/z : 148 $[\text{M}+\text{H}]^+$.

6,6-Dimethyl-5,6,7,8-tetrahydroquinoline (3)

A yellowish oil. Yield – 38 g (57%). Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{N}$, %: C 81.94; H 9.38; N 8.69. Found, %: C 81.88; H 9.47; N 8.62. ^1H NMR (400 MHz, Chloroform- d), δ , ppm: 1.02 (6H, s); 1.69 (2H, t, $J = 6.9$ Hz); 2.56 (2H, s); 2.96 (2H, t, $J = 6.9$ Hz); 7.03 (1H, dd, $J = 7.6, 4.8$ Hz); 7.33 (1H, d, $J = 7.6$ Hz); 8.38 (1H, d, $J = 4.8$ Hz). LC-MS (ESI, positive mode), m/z : 162 $[\text{M}+\text{H}]^+$.

6,6-Difluoro-5,6,7,8-tetrahydroquinoline (4)

A yellowish oil. Yield – 42 g (55%). Anal. Calcd for $\text{C}_9\text{H}_9\text{F}_2\text{N}$, %: C 63.90; H 5.36; F 22.46; N 8.28. Found, %: C 63.82; H 5.45; F 22.54; N 8.17. ^1H NMR (400 MHz, DMSO- d_6), δ , ppm: 2.26–2.41 (1H, m); 3.04 (3H, t, $J = 7.1$ Hz); 3.29–3.43 (3H, m); 7.22 (1H, dd, $J = 7.8, 4.7$ Hz); 7.55 (1H, d, $J = 7.8$ Hz); 8.39 (1H, d, $J = 4.7$ Hz). ^{19}F NMR (376 MHz, DMSO- d_6) δ , ppm: -95.84. LC-MS (ESI, positive mode), m/z : 170 $[\text{M}+\text{H}]^+$.

5,6,7,8-Tetrahydroquinolin-6-ol (5)

A brown solid. Yield – 35 g (58%). M. p. 114°C. ¹H NMR corresponds to the reported previously [15]. LC-MS (ESI, positive mode), *m/z*: 150 [M+H]⁺.

5,8-Dihydro-6H-pyrano[3,4-b]pyridine (10c)

A yellowish oil. Yield – 18 g (34%). Anal. Calcd for C₈H₉NO, %: C 71.09; H 6.71; N 10.36. Found, %: C 70.97; H 6.83; N 10.29. ¹H NMR (400 MHz, Chloroform-*d*), δ , ppm: 2.90 (2H, t, *J* = 5.7 Hz); 4.00 (2H, t, *J* = 5.7 Hz); 4.82 (2H, s); 7.12 (1H, dd, *J* = 7.7, 4.9 Hz); 7.45 (1H, d, *J* = 7.7 Hz); 8.41 (1H, d, *J* = 4.8 Hz). LC-MS (ESI, positive mode), *m/z*: 136 [M+H]⁺.

The procedure for the synthesis of 5,6,7,8-tetrahydroquinoline-5-carboxylic acid hydrochloride (7a*HCl)

To 6 L round-bottomed flask dried in the oven, 7,8-dihydroquinolin-5(6*H*)-one (**6a**) (147.2 g, 1 mol, 1.0 equiv) was added. The flask was sealed and purged with argon before the addition of CH₂Cl₂ (2.8 L) and Et₃N (208 mL, 1.5 mol, 1.5 equiv). The reaction mixture was cooled to 0°C, and trifluoromethanesulfonic anhydride (242 mL, 6.2 mmol, 1.5 equiv) was added dropwise under argon atmosphere before heating to 40°C and kept at this temperature while stirring for 24 h. Upon completion of the reaction, the solution was washed with water (2×20 mL), and the organic substances were passed through a hydrophobic frit, and concentrated under reduced pressure to give compound **17** quantitatively (~279 g) as a brown oil (85–90% purity), which was used in the next step without purification.

A solution of **17** (279 g, 1 mol) in DMF (2.2 L) was treated with methanol (1.1 L) and N,N-diisopropylethylamine (526 mL, 3 mol), and bubbled with argon for 30 min. The resulting mixture was treated with DPPF (4.5 g, 8 mmol) and palladium (II) acetate (1.8 g, 8 mmol). The resulting solution was bubbled with carbon monoxide for 30 min, and then stirred under a carbon monoxide balloon at 60°C for 6 h. After that, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting mixture was washed with 1 M aqueous HCl, twice with water, once with the saturated aqueous sodium carbonate, dried over sodium sulfate and then concentrated under vacuum to yield 147.6 g of a residue (78%, ~90% purity) as a yellowish powder. The product was used in the next step without purification.

A solution of **18** (147.6 g, 0.78 mol) in MeOH (2 L) was heated at 50°C under atmospheric pressure and bubbled with H₂ for 2 h in the presence

of 10% Pd on charcoal (10 g). After completing the reaction, Pd/C was filtered off, and the residue was evaporated under reduced pressure. The yellowish powder (~149 g, ~90% purity) obtained was used in the next step without purification.

The product **19** (95.6 g, 0.5 mol) was dissolved in the saturated solution of HCl in dioxane (1 L) and boiled until the end of the precipitate formation. Then the solid was filtered off and dried on air. The final product **7a** was obtained as a white powder in 84% yield as hydrochloride (89.8 g).

A white powder. M. p. 164°C. Anal. Calcd for C₁₀H₁₂ClNO₂, %: C 62.67; H 4.94; Cl 11.10; N 14.62. Found, %: C 62.60; H 5.03; Cl 10.97; N 14.55. ¹H NMR (DMSO-*d*₆, 500 MHz), δ , ppm: 1.55–1.86 (1H, m); 1.86–2.07 (2H, m); 2.07–2.35 (1H, m); 2.92–3.27 (2H, m); 4.06 (1H, t, *J* = 5.0 Hz); 7.81 (1H, dd, *J* = 7.8, 5.6 Hz); 8.37 (1H, d, *J* = 7.8 Hz); 8.69 (1H, d, *J* = 5.6 Hz). LC-MS (ESI, positive mode), *m/z*: 178 [M-Cl]⁺.

The procedure for the synthesis of 1,7-naphthyridin-8(7*H*)-one (23)

3-Methylpicolinonitrile (**21**) (23.62 g, 0.2 mol) and the Bredereck's reagent (69.6 g, 0.2 mmol) were dissolved in DMF (250 mL). The reaction mixture was heated at 75°C under argon for 72 h. After that, the solvent was removed *in vacuo*. Trituration with MTBE gave a brown oil **21** (~35 g, ~0.2 mol, a quantitative yield, ~85% purity). Further all 35 g of the product was used without additional purification.

The oil from the previous step was dissolved in the saturated solution of HCl in dioxane (200 mL). The reaction mixture was warmed at 45–50°C for 24 h. The reaction solution was filtered, and the filtrate was collected and dried. The light brown solid **23** (24.2 g, 83% yield) obtained was directly used in the next reaction.

A brown solid. M. p. 227°C. Anal. Calcd for C₈H₆N₂O, %: C 65.75; H 4.14; N 19.17. Found, %: C 65.64; H 4.19; N 19.28. ¹H NMR (DMSO-*d*₆, 400 MHz), δ , ppm: 6.53 (1H, d, *J* = 7.1 Hz); 7.25 (1H, d, *J* = 7.0 Hz); 7.67 (1H, dd, *J* = 8.1, 4.4 Hz); 8.10 (1H, dd, *J* = 8.1, 1.7 Hz); 8.75 (1H, dd, *J* = 4.3, 1.7 Hz); 11.50 (1H, s). LC-MS (ESI, positive mode), *m/z*: 147 [M+H]⁺.

The procedure for the synthesis of 8-chloro-1,7-naphthyridine (24)

1,7-Naphthyridin-8(7*H*)-one (**23**) (19.1 g, 0.15 mol) was dissolved in 200 mL of toluene. POCl₃ (31 g, 0.2 mol) and DIPEA (72 g, 4 mol) were added to the reaction mixture, and then it was

refluxed for 6 h. After cooling down, the mixture was diluted with EtOAc (15 mL) and washed with ice-cold water, the saturated NaHCO₃, brine. The organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by washing with *i*PrOH to give 20.2 g of a yellow solid in 82% yield.

A yellow solid. M. p. 89°C. Anal. Calcd for C₈H₅ClN₂, %: C 58.38; H 3.06; Cl 21.54; N 17.02. Found, %: C 58.27; H 3.11; Cl 21.47; N 16.95. ¹H NMR (Chloroform-*d*, 400 MHz), δ, ppm: 7.65 (1H, d, *J* = 5.6 Hz); 7.71 (1H, dd, *J* = 8.4, 4.2 Hz); 8.23 (1H, dd, *J* = 8.4, 1.7 Hz); 8.41 (1H, d, *J* = 5.6 Hz); 9.16 (1H, dd, *J* = 4.2, 1.7 Hz). LC-MS (ESI, positive mode), *m/z*: 165 [M+H]⁺.

The procedure for the synthesis of 5,6,7,8-Tetrahydro-1,7-naphthyridine dihydrochloride (9c*2HCl)

A solution of 8-chloro-1,7-naphthyridine (**24**) (16.5 g, 0.1 mol) in MeOH (300 mL) was placed into the autoclave and heated at 50°C under 10 atm pressure of H₂ for 6 h in the presence of 10% Pd on charcoal (5 g). After completing the reaction, Pd/C was filtered off, and the residue was evaporated under reduced pressure. Then the crude substrate was dissolved in the saturated solution of HCl in dioxane. The yellowish powder (~12.3 g, 87% yield) was obtained as a dihydrochloride after simple filtration.

A yellow solid. M. p. 210°C (decomp.). Anal. Calcd for C₈H₁₂Cl₂N₂, %: C 46.40; H 5.84; Cl 34.23; N 13.53. Found, %: C 46.34; H 5.93; Cl 34.18; N 13.44. ¹H NMR (400 MHz, DMSO-*d*₆), δ, ppm: 3.12 (1H, t, *J* = 6.2 Hz); 3.40 (1H, q, *J* = 6.4 Hz); 4.38 (1H, t, *J* = 4.5 Hz); 7.55 (1H, dd, *J* = 7.8, 5.1 Hz); 8.58 (1H, d, *J* = 5.1 Hz); 10.02 (1H, s). LC-MS (ESI, positive mode), *m/z*: 135 [M-HCl-Cl]⁺.

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5-Chloro-1,2,3,4-tetrahydro-1,8-naphthyridine (26)

The synthesis was performed from 4-chloro-2-fluoropyridine (**25**) according to the procedure reported [24].

A yellow solid. Yield – 21 g (74%). M. p. 97°C. Anal. Calcd for C₈H₉ClN₂, %: C 56.98; H 5.38; Cl 21.02; N 16.61. Found, %: C 57.05; H 5.33; Cl 20.94; N 16.66. ¹H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.94 (3H, pent, *J* = 6.2 Hz); 2.78 (3H, t, *J* = 6.5 Hz); 3.32–3.43 (3H, m); 6.56 (1H, d, *J* = 5.5 Hz); 7.74 (1H, d, *J* = 5.5 Hz). LC-MS (ESI, positive mode), *m/z*: 169 [M+H]⁺.

The procedure for the synthesis of 1,2,3,4-tetrahydro-1,8-naphthyridine (9d*HCl)

The reduction of 5-chloro-1,2,3,4-tetrahydro-1,8-naphthyridine (**26**) was performed by the seminal procedure used for preparation of amine **9c**. Amine **9d** was obtained in 85% yield as a yellow powder in a hydrochloride form (28 g).

A yellow solid. M. p. 71°C. Anal. Calcd for C₈H₉ClN₂, %: C 56.98; H 5.38; Cl 21.02; N 16.61. Found, %: C 57.08; H 5.24; Cl 20.93; N 16.66. ¹H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.94–1.87 (2H, pent, *J* = 6.2 Hz); 2.71 (2H, t, *J* = 6.3 Hz); 3.29–3.64 (2H, m); 6.47 (1H, dd, *J* = 7.1, 5.0 Hz); 7.12 (1H, d, *J* = 7.1 Hz); 7.84 (1H, d, *J* = 4.4 Hz). LC-MS (ESI, positive mode), *m/z*: 135 [M+H]⁺.

Acknowledgments

The authors thank Prof. Serhiy V. Ryabukin for his encouragement and support, the UOS Lab (www.en.uoslab.com) for providing high pressure reactors, and Tetiana V. Druzhenko for her help with the manuscript preparation.

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