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Chemistry of Heterocyclic Compounds **2017**, *53*(5), 568–574

2-Acyl(aroyl)-1,1,3,3-tetracyanopropenides

7*. Synthesis of 4-amino-1-aryl-6-halo-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles

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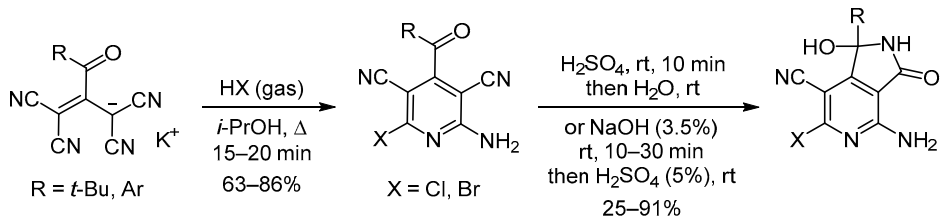


The reaction of 2-acyl(aroyl)-1,1,3,3-tetracyanopropenides with gaseous hydrogen halides was used to obtain 2-amino-3-aroyl(acyl)-6-halopyridine-3,5-dicarbonitriles, which were subsequently converted to the respective 4-amino-1-aryl-6-halo-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles by treatment with concentrated sulfuric acid, followed by aqueous workup.

Keywords: pyridines, pyrrolo[3,4-*c*]pyridines, tetracyanopropenides, annulation, iminolactone–lactam rearrangement.

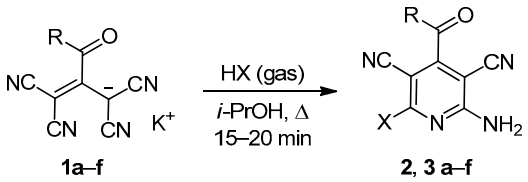
2-Acyl(aroyl)-1,1,3,3-tetracyanopropenides are relatively easily available[2] and have attracted interest as promising precursors for the synthesis of various polyfunctional heterocyclic compounds. 2-Acyl(aroyl)-1,1,3,3-tetracyanopropenides have been used as starting materials for the development of preparative methods for the synthesis of substituted furans,[3–6] pyridines,[6–9] as well as the fused ring systems of furo[3,4-*c*]pyridine[1] and thieno[2,3-*b*]-pyridine.[10] It has been noted that the interaction of propenides **1** with hydrogen halides in formic acid also resulted in the formation of 4-amino-1-aryl-6-halo-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles as by-products in low yields. Pyrrolo[3,4-*c*]-pyridines are of interest as scaffolds for the synthesis of biologically active compounds. The examples of such derivatives include ligands of serotonin 5-HT_3 receptor,[11] caspase-3 inhibitors,[12] and anthelmintic agents.[13] The 1-hydroxy-3-oxo-1-pyridylpyrrolo[3,4-*c*]pyridine fragment represents a structural feature of the INH-NAD adduct, which is formed *in vivo* from the prodrug isoniazid and NAD and suppresses the development of *Mycobacterium tuberculosis*.[14–17] Synthetic analogs of INH-NAD adduct that contain the pyrrolo[3,4-*c*]pyridine ring system in their structure have been studied as potential tuberculostatic drugs.[14–18]

In the current work, we studied the possibilities for the synthesis of pyrrolo[3,4-*c*]pyridine derivatives from propenides **1a**–**f** through 6-halopyridine intermediates **2**, **3** **a**–**f**, which were obtained according to a previously published procedure[6] by treating a solution of propenide **1a**–**f** in isopropyl alcohol with gaseous hydrogen halide (HCl, HBr) at 85°C for 15–20 min (Scheme 1, Table 1).

The transformation of pyridine derivatives **2**, **3** **a**–**f** to the respective pyrrolo[3,4-*c*]pyridines **4**, **5** **a**–**f** was

* For Communication 6, see [1].

Scheme 1



1a–f **2, 3 a–f**

Table 1. Substituents and yields of compounds **2**, **3 a**–**f**

R	Yield, %	
	X = Cl	X = Br
t-Bu	**2a** (86)	**3a** (71)
Ph	**2b** (85)	**3b** (70)
4-MeC_6H_4	**2c** (79)	**3c** (76)
4-$MeOC_6H_4$	**2d** (70)	**3d** (68)
4-BrC_6H_4	**2e** (67)	**3e** (65)
2-Thienyl	**2f** (76)	**3f** (63)

achieved by two methods. The first one (method I) was based on the reaction of pyridines **2**, **3 a**–**f** with water in the presence of a basic catalyst. A drawback of this method was the occurrence of a side reaction involving the substitution of halide with a hydroxy group with the formation of pyrrolo[3,4-*c*]pyridones **6a**–**f** as impurities (Scheme 2, Table 2), which required laborious purification of the target products and lowered their yields. The substitution of bromide was especially facile, and for that reason the yields of pyrrolo[3,4-*c*]pyridines **5 a**–**f** obtained by this method were below 15% (not presented in Table). It was established experimentally that the optimum conditions for the synthesis of pyrrolo[3,4-*c*]pyridines **4**, **5 a**–**f** involved treatment with aqueous alcohol solution of NaOH and performing the reaction at room temperature, while complete conversion to pyrrolo[3,4-*c*]pyridones **6a**–**f** was better achieved by heating at reflux in aqueous DMSO solution of NaOH. Pyridones **6** are known compounds, which were previously obtained by a reaction of 3-acyl(aroyl)-cyclopropane-1,1,2,2-tetracarbonitriles with sodium hydroxide.[19] By using this alternative method of synthesis, we were able to obtain 4-amino-1-(*tert*-butyl)-1-hydroxy-3,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (**6a**), which was not accessible *via* the direct method.

The presumed mechanism of this reaction involved an addition of hydroxide ion to the carbonyl group, furan ring closure and subsequent iminolactone–lactam rearrangement (Scheme 2). In our opinion, the fact that this reaction proceeded under mild conditions precluded the alternative route starting from an addition of hydroxide ion to the nitrile group.

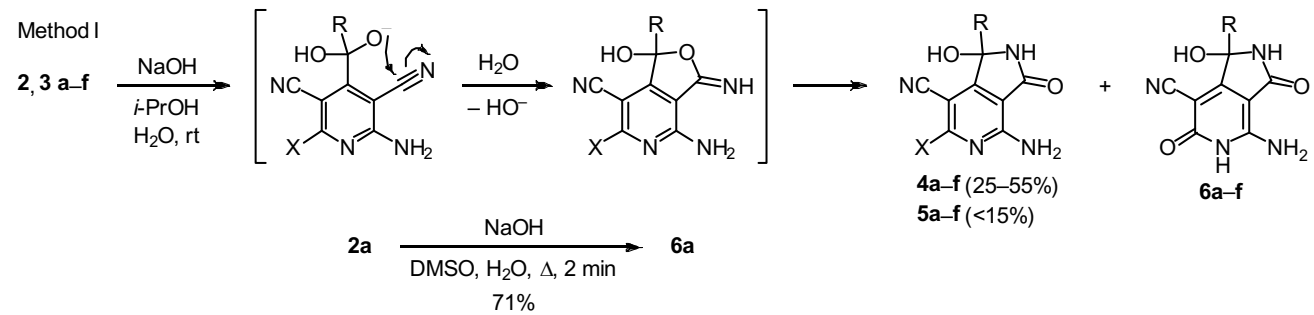
The second method (method II) was based on the use of acidic catalysis. It should be noted that acidic catalysis generally was not very effective for performing this type of process: even when pyridine **2b** was refluxed for many hours in aqueous acetic acid medium in the presence of H_2SO_4, the procedure led to the formation of only trace amounts of compound **4b**. Another method based on stepwise treatment of pyridines **2**, **3 a**–**e** first with concentrated H_2SO_4 and then with water was found to be superior. The reaction under these conditions proceeded quickly with an exothermic effect and gave high yields of compounds **4**, **5 a**–**e**. The likely sequence of reactions included the formation of cationic furopyridine intermediate **A** (Scheme 3), as the solution of pyridines **2**, **3 a**–**e** in concentrated H_2SO_4 had a bright-red color. The addition of water resulted in hydration and iminolactone–lactam rearrangement. This method was not suitable for the preparation of derivatives **4f** and **5f** containing a thiophene moiety that was unstable in the presence of H_2SO_4.

In order to confirm the proposed sequence of mechanistic steps and to exclude a possible mechanism involving Ritter cyclization, the reaction of pyridine **2b** with methanol was performed under analogous conditions. It was expected that the process in this case should stop with the formation of iminofuran **B** (Scheme 4) or pyrrolopyridine **C** (in the case of Ritter reaction), but according to the data of NMR spectra the main product was 4-amino-6-chloro-1-methoxy-3-oxo-1-phenyl-2,3-dihydro-

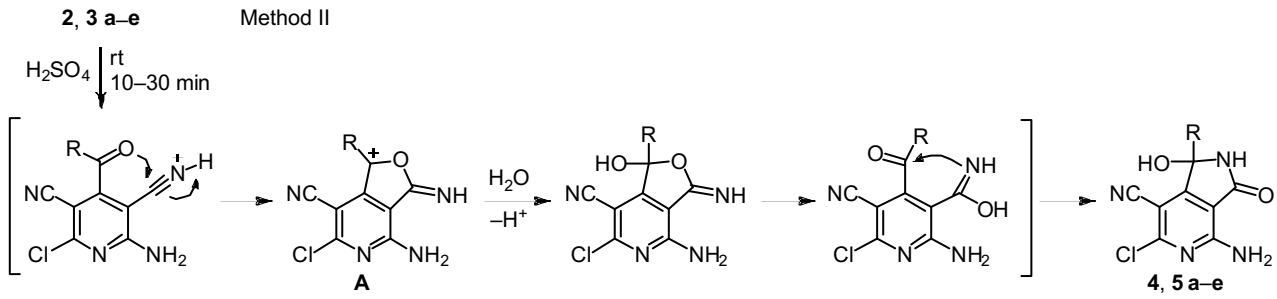
Table 2. Substituents and yields of compounds **4**, **5**

R	Yield, %		
	X = Cl		X = Br
	Method I	Method II	Method II
t-Bu	**4a** (33)	**4a** (88)	**5a** (82)
Ph	**4b** (45)	**4b** (91)	**5b** (85)
4-MeC_6H_4	**4c** (37)	**4c** (79)	**5c** (75)
4-$MeOC_6H_4$	**4d** (41)	**4d** (90)	**5d** (87)
4-BrC_6H_4	**4e** (25)	**4e** (77)	**5e** (72)
2-Thienyl	**4f** (55)	–	–

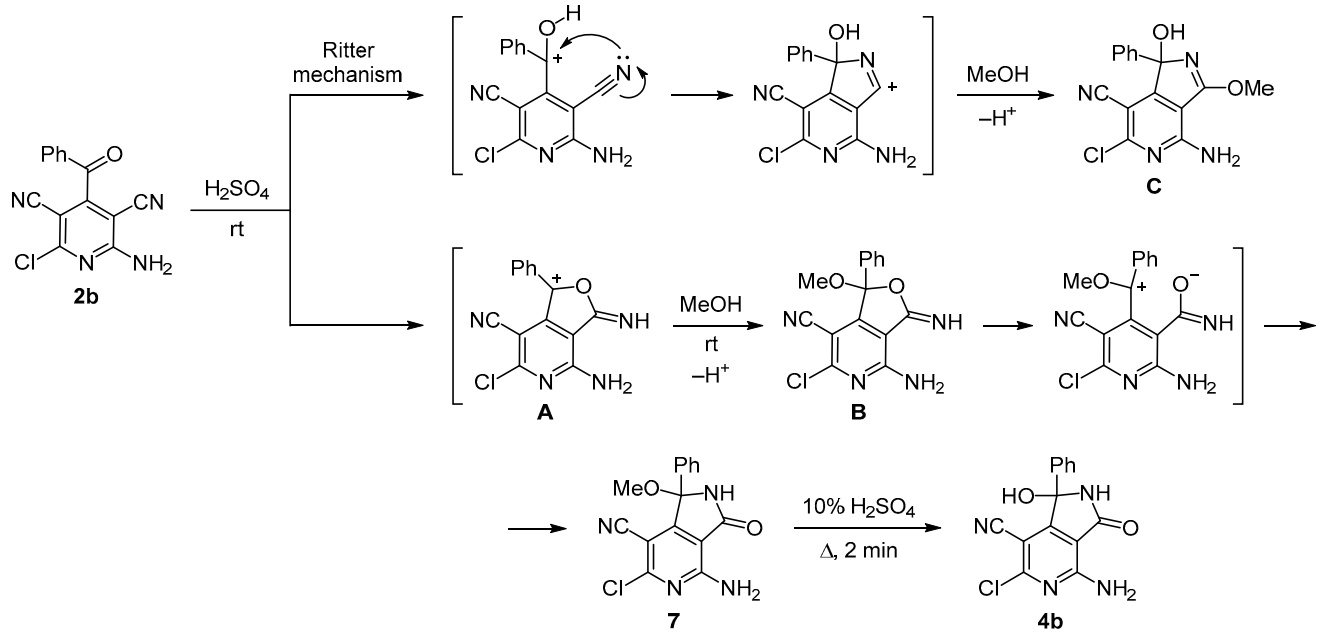
Scheme 2



Scheme 3



Scheme 4



1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (**7**) (Scheme 4). The formation of compound **7** was also confirmed by its hydrolysis leading to the formation of pyrrolo[3,4-*c*]-pyridine **4b** upon heating in dilute H_2SO_4.

Pyrrolo[3,4-*c*]pyridines **4**, **5 a**–**e** were isolated as white crystalline solids that were readily soluble in polar organic solvents. Some of them formed stable solvates with 2-propanol.

The proposed structure of the synthesized compounds was supported by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and was in agreement with IR spectral data and the results of elemental analysis. ^{1}H NMR spectra of pyrrolo[3,4-*c*]pyridines **4**, **5 a**–**e** contained two broadened singlets at 7.32–8.57 ppm, which were assigned to the amino group linked to pyridine ring. The hydroxy group proton was represented in ^{1}H NMR spectra by a singlet in the range of 6.78–8.57 ppm. The aryl substituents were observed by their characteristic signals.

The structure of pyridines **2**, **3 a**–**e** featured two nitrile groups at *ortho* position relative to the carbonyl group, and for this reason the formation of two positional isomers **4'**, **5' a**–**e** and **4''**, **5'' a**–**e** could be expected (Fig. 1). According to TLC data and NMR spectra, the reaction occurred regioselectively with the formation of only one of the possible isomers. The structure of compounds **4b** and **5a** was proved by X-ray crystallographic analysis (Figs. 2, 3). Thus, we demonstrated the general applicability of this process where the heterocyclization involved a cyano group adjacent with the amino group, leading to the formation of isomers **4'**, **5' a**–**e**.

The crystal lattice formation for both compounds was largely controlled by hydrogen bonding interactions. The crystal of compound **4b** contained molecules linked by centrosymmetric N(2)–H(2)···O(2) hydrogen bonds (2.997 Å) from one side and N(1)–H(31)···N(3) hydrogen bonds (3.039 Å) from the other side. This resulted in the formation of a chain along the crystallographic axis *b*. The adjacent

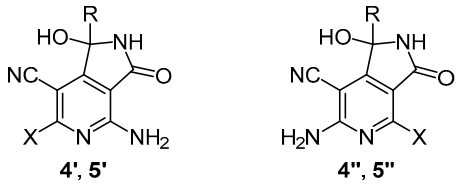


Figure 1. The possible isomers of compounds **4**, **5** with different configuration of amino group and halogen atom relative to the other groups.

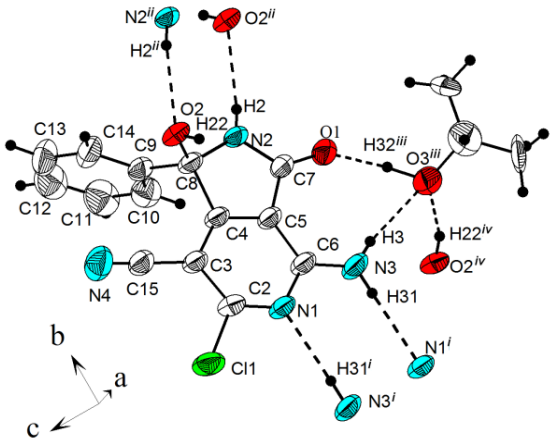


Figure 2. Molecular structure of compound **4b** solvated with 2-propanol with atoms represented by thermal vibration ellipsoids of 50% probability. Symmetry codes: (*i*) –*x*, –*y*, –*z*; (*ii*) –*x*, 1–*y*, –*z*; (*iii*) –1+*x*, *y*, –1+*z*; (*iv*) –0.5+*x*, 0.5–*y*, –0.5+*z*.

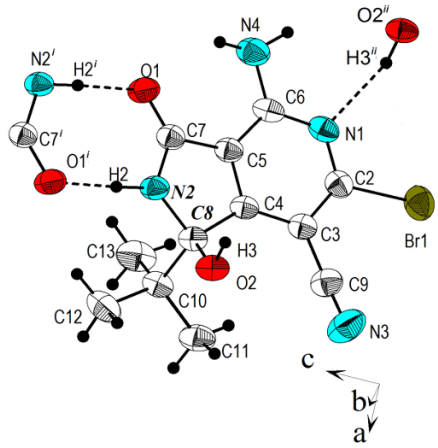


Figure 3. Molecular structure of compound **5a** according to X-ray structural analysis, with atoms represented by thermal vibration ellipsoids of 50% probability. Symmetry codes: (*i*) –*x*, 1–*y*, 1–*z*; (*ii*) –*x*, –0.5+*y*, 0.5–*z*.

chains were linked by O(3)–H(32)···O(1), O(3)–H(32)···O(2), and N(3)–H(2)···O(3) hydrogen bonds with solvated 2-propanol molecule (2.716 Å, 2.682 Å, and 3.272 Å, respectively). The molecules in crystals of compound **5a** formed centrosymmetric dimers linked by N(2)–H(2)···O(1) hydrogen bonds (2.844 Å). Besides that, O(2)–H(3)···N(1) hydrogen bond (2.860 Å) existed between the hydroxy group and the pyridine nitrogen atom.

Thus, based on the use of 2-acyl(aroyl)-1,1,3,3-tetracyanopropenides, we have developed two-step methods for the synthesis of 4-amino-1-aryl-6-halo-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles under the conditions of either acidic or basic catalysis. The compounds obtained by the method that involved treatment with concd. H_2SO_4 and then water were formed in high yields and did not contain impurities, but that method was limited to substrates lacking any acid-labile substituents. The method using basic catalysis gave lower yields, but was useful for obtaining compounds containing acid-labile substituents, for example, it was used for the synthesis of a thiophene derivative.

Experimental

IR spectra were recorded for Nujol mulls of compounds on an FSM-1202 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were acquired on an Agilent DDR2 400 instrument (400 and 101 MHz, respectively) in DMSO-d_6, using TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP2010S DI instrument (EI ionization, 70 eV). Elemental analysis was performed on a vario MICRO cube CHN-analyzer. Melting points were determined on an Electrothermal IA 9000 series II instrument. The individuality of the synthesized compounds was confirmed by TLC method on Sorbfil PTSH-AF-A-UF plates, eluent EtOAc, visualization under UV light (254 nm) or by heating. 2-Acyl(aroyl)-1,1,3,3-tetracyanopropenides **1a**–**f**[2] and 2-amino-3-aroyl(acyl)-6-halopyridine-3,5-dicarbonitriles **2a**–**c**,[6] **3b**,**c**,[6] **2d**,[7] and **3d**[7] were obtained according to published procedures.

Synthesis of 2-amino-3-aroyl(acyl)-6-halopyridine-3,5-dicarbonitriles 2, 3 a–f (General method). A suspension of propenide **1a**–**f** (5 mmol) in 2-PrOH (50 ml) was heated to reflux and, while continuing the heating and stirring, gaseous HCl or HBr was bubbled through the mixture until the reaction was complete (15–20 min). The mixture was then poured into water (200 ml), the precipitate that formed was filtered off and purified by recrystallization from a 1:4 mixture of MeCN–H_2O.

2-Amino-4-(4-bromobenzoyl)-6-chloropyridine-3,5-dicarbonitrile (2e). White crystals, mp >275°C (decomp.). IR spectrum, ν, cm^{-1}: 3201 (NH_2), 2220 (C≡N), 1682 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.83–7.89 (2H, m, H Ar); 7.93–7.99 (2H, m, H Ar); 8.46 (1H, br. s) and 8.97 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 190.0; 160.6; 157.9; 156.0; 133.3; 132.4; 132.3; 131.5; 114.1; 113.4; 93.0; 87.0. Mass spectrum, *m/z* (I_{rel}, %): 364/362/360 $[M]^+$ (2.8/11.7/9.0), 185/183 $[C_6H_4BrCO]^+$ (98/100), 157/155 $[C_6H_4Br]^+$ (12/12). Found, %: C 46.36; H 1.70; N 15.45. $C_{14}H_6BrClN_4O$. Calculated, %: C 46.51; H 1.67; N 15.49.

2-Amino-6-chloro-4-[(thiophen-2-yl)carbonyl]pyridine-3,5-dicarbonitrile (2f). White crystals, mp 255–257°C (decomp.). IR spectrum, ν, cm^{-1}: 3211 (NH_2), 2217 (C≡N), 1662 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.38 (1H, dd, ^3J = 4.2, ^3J = 4.8, H Ar); 8.05 (1H, d, ^3J = 3.8, H Ar); 8.40 (1H, d, ^3J = 4.8, H Ar); 8.45 (1H, br. s) and 8.97 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 182.3; 160.2; 157.2; 148.3; 141.0; 140.6; 138.0; 130.4; 115.3; 113.6; 96.2; 87.1. Mass spectrum, *m/z* (I_{rel}, %): 290/288 $[M]^+$ (14/5), 116 (12), 111 $[C_4H_3SCO]^+$ (100), 83 $[C_4H_3S]^+$ (11). Found, %: C 49.98; H 1.79; N 19.51. $C_{12}H_5ClN_4OS$. Calculated, %: C 49.92; H 1.75; N 19.41.

2-Amino-6-bromo-4-pivaloylpyridine-3,5-dicarbonitrile (3a). White crystals, mp 250–252°C (decomp.). IR spectrum, ν, cm^{-1}: 3224 (NH_2), 2208 (C≡N), 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.29 (9H, s, $C(CH_3)_3$); 8.43 (1H, br. s) and 8.95 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 208.1; 160.1; 160.0; 148.4; 116.3; 114.5; 94.6; 85.3; 45.7; 27.2. Mass spectrum, *m/z* (I_{rel}, %): 308/306 $[M]^+$ (3/3), 116

(11), 57 $[C_4H_9]^+$ (100). Found, %: C 46.75; H 3.64; N 18.17. $C_{12}H_{11}BrN_4O$. Calculated, %: C 46.93; H 3.61; N 18.24.

2-Amino-6-bromo-4-(4-bromobenzoyl)pyridine-3,5-dicarbonitrile (3e). White crystals, mp >275°C (decomp.). IR spectrum, ν, cm^{-1}: 3209 (NH_2), 2221 (C≡N), 1665 (C=O). ^1H NMR spectrum, δ, ppm: 7.85–7.91 (2H, m, H Ar); 7.94–8.01 (2H, m, H Ar); 8.47 (1H, br. s) and 9.00 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 190.0; 160.2; 157.4; 148.4; 133.3; 132.4; 132.3; 131.4; 115.3; 113.5; 96.1; 87.0. Mass spectrum, *m*/*z* (I_{rel}, %): 408/406/404 $[M]^+$ (4/9/5), 185/183 $[C_6H_4BrCO]^+$ (98/100), 157/155 $[C_6H_4Br]^+$ (17/17). Found, %: C 41.32; H 1.51; N 13.77. $C_{14}H_6Br_2N_4O$. Calculated, %: C 41.41; H 1.49; N 13.80.

2-Amino-6-bromo-4-[(thiophen-2-yl)carbonyl]pyridine-3,5-dicarbonitrile (3f). White crystals, mp 270–272°C (decomp.). IR spectrum, ν, cm^{-1}: 3213 (NH_2), 2217 (C≡N), 1667 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.38 (1H, dd, ^3J = 4.0, ^3J = 4.8, H Ar); 8.07 (1H, dd, ^3J = 3.8, ^4J = 0.8, H Ar); 8.41 (1H, dd, ^3J = 4.8, ^4J = 0.8, H Ar); 8.45 (1H, br. s) and 8.97 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 182.3; 160.2; 157.2; 148.3; 141.0; 140.6; 140.0; 130.4; 115.3; 113.5; 96.2; 87.1. Mass spectrum, *m*/*z* (I_{rel}, %): 334/332 $[M]^+$ (10/10), 116 (9), 111 $[C_4H_3SCO]^+$ (100), 83 $[C_4H_3S]^+$ (13). Found, %: C 43.35; H 1.55; N 16.92. $C_{12}H_5BrN_4OS$. Calculated, %: C 43.26; H 1.51; N 16.82.

Synthesis of 4-amino-1-aryl-6-halo-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles 4, 5 a–f (General method). Method I. A suspension of pyridine **2**, **3 a–f** (1.0 mmol) and NaOH (0.1 g, 2.5 mmol) was stirred in 1:1 mixture of 2-PrOH–H_2O (3 ml) until full dissolution, then maintained until the reaction was complete (control by TLC; pyridines **2**, **3 a–f** showed yellow-green fluorescence under UV light, pyrrolo[3,4-*c*]pyridines **4**, **5 a–f** showed blue fluorescence). The reaction mixture was then diluted with H_2O (5 ml), neutralized with 5% H_2SO_4 solution, the precipitate that formed was filtered off and purified by recrystallization from 1:2 mixture of MeCN–H_2O.

Method II. A mixture of pyridine **2**, **3 a–e** (1 mmol) in concd. H_2SO_4 (1 ml) was stirred at room temperature until full dissolution (10–30 min), then diluted with H_2O (20 ml), and the white precipitate that formed was filtered off, washed with water until the washes became neutral, air-dried, and purified by recrystallization.

4-Amino-1-(*tert*-butyl)-6-chloro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4a). White crystals, mp 260–265°C (decomp.). IR spectrum, ν, cm^{-1}: 3365 (OH), 3272, 3211 (NH_2), 2225 (C≡N), 1710 (C=O). ^1H NMR spectrum, δ, ppm: 0.98 (9H, s, $C(CH_3)_3$); 6.79 (1H, br. s, OH); 7.37 (1H, br. s) and 8.41 (1H, br. s, NH_2); 8.96 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 166.9; 164.3; 156.4; 155.7; 116.2; 108.9; 93.2; 92.3; 40.8; 26.1. Mass spectrum, *m*/*z* (I_{rel}, %): 264/262 $[M–H_2O]^+$ (0.3/1), 238 (3), 179 (8), 57 $[C_4H_9]^+$ (100). Found, %: C 51.53; H 4.64; N 20.03. $C_{12}H_{13}ClN_4O_2$. Calculated, %: C 51.35; H 4.67; N 19.96.

4-Amino-6-chloro-1-hydroxy-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4b). White crystals, mp >210°C (decomp.). IR spectrum, ν, cm^{-1}: 3654 (OH), 3480, 3292 (NH_2), 2213 (C≡N), 1684 (C=O). ^1H NMR spectrum, δ, ppm: 7.31–7.40 (4H, m, H Ph, OH); 7.40–7.49 (3H, m, H Ph, NH_A); 8.55 (1H, br. s, NH_B); 9.44 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.2; 165.3; 156.5; 155.1; 138.3; 129.0; 128.6; 126.6; 113.7; 106.9; 90.3; 87.1. Mass spectrum, *m*/*z* (I_{rel}, %): 302/300 $[M]^+$ (1/2), 284/282 $[M–H_2O]^+$ (3/8), 103 $[PhCN]^+$ (16), 77 $[Ph]^+$ (32), 51 (100). Found, %: C 56.09; H 2.99; N 18.69. $C_{14}H_9ClN_4O_2$. Calculated, %: C 55.92; H 3.02; N 18.63.

Compound **4b** was also obtained by hydrolysis of 4-amino-6-chloro-1-methoxy-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (**7**). A suspension of pyrrolopyridine **7** (100 mg, 0.3 mmol) in 10% H_2SO_4 solution (2 ml) was refluxed with stirring for 2 min, then cooled, the precipitate was filtered off, washed with water, dried, and purified by recrystallization. Yield 42 mg (44%).

4-Amino-6-chloro-1-hydroxy-1-(4-methylphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4c). White crystals, mp >250°C (decomp.). IR spectrum, ν, cm^{-1}: 3633 (OH), 3481, 3277 (NH_2), 2216 (C≡N), 1689 (C=O) ^1H NMR spectrum, δ, ppm: 2.28 (3H, s, CH_3); 7.15–7.17 (2H, m, H Ar); 7.32–7.33 (2H, m, H Ar); 7.35 (1H, br. s) and 7.51 (1H, br. s, NH_2); 7.41 (1H, s, OH); 9.38 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.1; 165.5; 156.5; 155.1; 138.3; 135.5; 129.2; 126.6; 117.8; 106.8; 90.4; 87.1; 21.1. Mass spectrum, *m*/*z* (I_{rel}, %): 316/314 $[M]^+$ (0.3/1), 298/296 $[M–H_2O]^+$ (4/12), 91 $[C_6H_4CH_3]^+$ (100). Found, %: C 57.41; H 3.50; N 17.85. $C_{15}H_{11}ClN_4O_2$. Calculated, %: C 57.24; H 3.52; N 17.80.

4-Amino-6-chloro-1-hydroxy-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4d). White crystals, mp 266–268°C (decomp.). IR spectrum, ν, cm^{-1}: 3657 (OH), 3481, 3293 (NH_2), 2216 (C≡N), 1688 (C=O). ^1H NMR spectrum, δ, ppm: 3.76 (3H, s, OCH_3); 6.86–6.92 (2H, m, H Ar); 7.35–7.41 (4H, m, H Ar, OH, NH_A); 8.42 (1H, br. s, NH_B); 9.41 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.0; 165.9; 159.8; 159.5; 155.1; 130.3; 128.0 (CH); 114.2 (CH); 114.0; 106.8; 90.0; 87.0; 55.6. Mass spectrum, *m*/*z* (I_{rel}, %): 332/330 $[M]^+$ (1/2), 317/315 $[M–CH_3]^+$ (2/7), 314/312 $[M–H_2O]^+$ (5/15), 107 $[CH_3OC_6H_4]^+$ (66), 57 (100). Found, %: C 54.52; H 3.44; N 16.79. $C_{15}H_{11}ClN_4O_3$. Calculated, %: C 54.48; H 3.35; N 16.94.

4-Amino-1-(4-bromophenyl)-6-chloro-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4e). White crystals, mp >210°C (decomp.). IR spectrum, ν, cm^{-1}: 3652 (OH), 3485, 3286 (NH_2), 2218 (C≡N), 1682 (C=O). ^1H NMR spectrum, δ, ppm: 7.41–7.48 (3H, m, H Ar, OH); 7.52 (1H, br. s) and 8.57 (1H, br. s, NH_2); 7.57–7.59 (2H, m, H Ar); 9.47 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.0; 164.8; 156.5; 155.2; 137.8; 131.6; 129.0; 122.4; 113.7; 106.9; 90.1; 86.7. Mass spectrum, *m*/*z* (I_{rel}, %): 364/362/360 $[M–H_2O]^+$ (2/8/6), 185/183 $[C_6H_4BrCO]^+$ (26/27), 157/155 $[C_6H_4Br]^+$ (30/31), 43 (100). Found, %: C 44.40; H 2.10; N 14.79. $C_{14}H_8BrClN_4O_2$. Calculated, %: C 44.30; H 2.12; N 14.76.

4-Amino-6-chloro-1-hydroxy-3-oxo-1-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4f). White crystals, mp >190°C (decomp.). IR spectrum, ν, cm^{-1}:

3627 (OH), 3479, 3281 (NH_2), 2219 (C≡N), 1688 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.99–7.05 (1H, m, H Ar); 7.12 (1H, dd, ^3J = 4.8, ^3J = 1.0, H Ar); 7.48 (1H, br. s) and 8.52 (1H, br. s, NH_2); 7.54 (1H, dd, ^3J = 5.0, ^3J = 1.0, H Ar); 7.63 (1H, s, OH); 9.64 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.0; 164.1; 156.5; 147.4; 144.0; 127.1; 126.3; 125.1; 112.8; 105.1; 93.6; 86.6. Found, %: C 47.08; H 2.33; N 18.22. $C_{12}H_7ClN_4O_2S$. Calculated, %: C 46.99; H 2.30; N 18.27.

4-Amino-6-bromo-1-(*tert*-butyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5a). White crystals, mp >270°C (decomp.). IR spectrum, ν, cm^{-1}: 3366 (OH), 3275, 3211 (NH_2), 2225 (C≡N), 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.98 (9H, s, $C(CH_3)_3$); 6.78 (1H, br. s, OH); 7.37 (1H, br. s) and 8.42 (1H, br. s, NH_2); 8.94 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.1; 163.9; 156.3; 148.1; 117.4; 109.0; 95.6; 93.2; 40.8; 26.2. Mass spectrum, *m*/*z* ($I_{rel.}$, %): 308/306 $[M–H_2O]^+$ (1/1), 278 (3), 222 (8), 116 (20), 57 $[C_4H_9]^+$ (100). Found, %: C 44.41; H 4.13; N 17.21. $C_{12}H_{13}BrN_4O_2$. Calculated, %: C 44.33; H 4.03; N 17.23.

4-Amino-6-bromo-1-hydroxy-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5b). White crystals, mp >270°C (decomp.). IR spectrum, ν, cm^{-1}: 3649 (OH), 3482, 3275 (NH_2), 2217 (C≡N), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.32–7.40 (5H, m, H Ph, OH, NH_A); 7.42–7.49 (2H, m, H Ph); 8.53 (1H, br. s, NH_B); 9.40 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.2; 165.0; 156.5; 147.3; 138.3; 129.0; 128.6; 126.6; 114.9; 107.0; 93.7; 87.1. Mass spectrum, *m*/*z* (I_{rel}, %): 346/344 $[M]^+$ (1/1), 328/326 $[M–H_2O]^+$ (11/11), 103 $[PhCN]^+$ (25), 77 $[Ph]^+$ (30), 51 (100). Found, %: C 48.81; H 2.72; N 16.09. $C_{14}H_9BrN_4O_2$. Calculated, %: C 48.72; H 2.63; N 16.23.

4-Amino-6-bromo-1-hydroxy-1-(4-methylphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5c). White crystals, mp >270°C (decomp.). IR spectrum, ν, cm^{-1}: 3642 (OH), 3479, 3293 (NH_2), 2217 (C≡N), 1678 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.30 (3H, s, CH_3); 7.17–7.20 (2H, m, H Ar); 7.31–7.38 (3H, m, H Ar, OH); 7.40 (1H, br. s) and 8.54 (1H, br. s, NH_2); 9.38 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.2; 165.1; 156.5; 147.3; 138.3; 135.3; 129.2; 126.2; 114.9; 106.9; 93.7; 87.1; 21.1. Mass spectrum, *m*/*z* (I_{rel}, %): 360/358 $[M]^+$ (1/1), 342/340 $[M–H_2O]^+$ (9/9), 91 $[C_6H_4CH_3]^+$ (100). Found, %: C 50.24; H 3.17; N 15.47. $C_{15}H_{11}BrN_4O_2$. Calculated, %: C 50.16; H 3.09; N 15.60.

4-Amino-6-bromo-1-hydroxy-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5d). White crystals, mp 270–272°C (decomp.). IR spectrum, ν, cm^{-1}: 3651 (OH), 3478, 3294 (NH_2), 2216 (C≡N), 1694 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.75 (3H, s, CH_3); 6.88–6.93 (2H, m, H Ar); 7.32–7.44 (4H, m, H Ar, OH, NH_A); 8.49 (1H, br. s, NH_B); 9.36 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.0; 165.6; 159.8; 156.5; 155.1; 130.1; 128.0 (CH); 113.9 (CH); 113.8; 106.8; 90.2; 87.0; 55.6. Mass spectrum, *m*/*z* (I_{rel}, %): 376/374 $[M]^+$ (1/1), 361/359 $[M–CH_3]^+$ (5/5), 358/356 $[M–H_2O]^+$ (16/16), 107 $[CH_3OC_6H_4]^+$ (56), 43 (100). Found, %: C 48.12; H 3.04; N 14.81. $C_{15}H_{11}BrN_4O_3$. Calculated, %: C 48.02; H 2.96; N 14.93.

4-Amino-6-bromo-1-(4-bromophenyl)-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5e). White crystals, mp >210°C (decomp.). IR spectrum, ν, cm^{-1}: 3650 (OH), 3491, 3274 (NH_2), 2220 (C≡N), 1683 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.38–7.41 (4H, m, H Ar, OH, NH_A); 7.55–7.57 (2H, m, H Ar); 8.56 (1H, br. s, NH_B); 9.43 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.2; 164.4; 156.5; 147.3; 137.8; 131.6; 129.0; 122.4; 114.9; 107.0; 93.5; 86.7. Mass spectrum, *m*/*z* (I_{rel}, %): 408/406/404 $[M–H_2O]^+$ (5/10/5), 185/183 $[C_6H_4BrCO]^+$ (16/16), 157/155 $[C_6H_4Br]^+$ (24/25), 43 (100). Found, %: C 39.80; H 1.98; N 13.12. $C_{14}H_8Br_2N_4O_2$. Calculated, %: C 39.65; H 1.90; N 13.21.

4-Amino-1-(*tert*-butyl)-1-hydroxy-3,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (6a). Pyridine **2a** (260 mg, 1 mmol) was added to a solution of NaOH (100 mg, 2.5 mmol) in a 1:1 mixture of DMSO–H_2O (2 ml). The mixture was refluxed for 2 min, then cooled, treated with H_2O (5 ml), neutralized with 5% H_2SO_4 solution, the precipitate that formed was filtered off and purified by recrystallization from a 1:5 MeCN–EtOH mixture. Yield 186 mg (71%), white crystals, mp 238–240°C (decomp.). IR spectrum, ν, cm^{-1}: 3602 (OH), 3270, 3212 (NH_2), 2222 (C≡N), 1705, 1691 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.99 (9H, s, $C(CH_3)_3$); 6.52 (1H, s, OH); 7.35 (2H, br. s, NH_2); 8.50 (1H, s, NH); 11.40 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 168.6; 165.2; 162.1; 151.3; 115.8; 92.3; 89.1; 79.2; 40.7; 26.2. Found, %: C 55.04; H 5.40; N 21.31. $C_{12}H_{14}N_4O_3$. Calculated, %: C 54.96; H 5.38; N 21.36.

4-Amino-6-chloro-1-methoxy-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (7). A mixture of pyridine **2c** (280 mg, 1 mmol) and concd. H_2SO_4 (1 ml) was stirred until full dissolution. Then MeOH (10 ml) was added, the white precipitate that formed was filtered off, washed with water until the washes became neutral, air-dried, and purified by recrystallization from a 1:4 mixture of MeCN–H_2O. Yield 198 mg (63%), white crystals, mp >210°C (decomp.). IR spectrum, ν, cm^{-1}: 3461, 3255 (NH_2), 2224 (C≡N), 1682 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.20 (3H, s, OCH_3); 7.34–7.44 (3H, m, H Ph); 7.46–7.49 (2H, m, H Ph); 7.53 (1H, br. s) and 8.68 (1H, br. s, NH_2); 9.40 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 167.5; 161.8; 156.5; 155.7; 137.2; 129.4; 128.8; 126.7; 113.6; 108.0; 91.5; 90.2; 50.9. Found, %: C 57.14; H 3.57; N 17.71. $C_{15}H_{11}ClN_4O_2$. Calculated, %: C 57.24; H 3.52; N 17.80.

X-ray structural study of compounds 4b, **5a**. Crystals suitable for X-ray structural analysis were obtained by slow evaporation of solvent at room temperature: compound **4b** – from a 1:1 mixture of MeCN–2-PrOH, compound **5a** – from MeCN. Crystallographic studies were performed on a STOE diffractometer with Pilatus100K detector, focussing mirror collimation, CuKα-radiation (λ 1.54186 Å). Unit cell parameters and tables of structure factors were obtained by using the STOE X-Area (STOE&Cie GmbH) software.[20] The compound structures were solved by direct method and refined by using the SHELX software.[21] The positions and thermal parameters of non-hydrogen atoms were refined in full-matrix anisotropic approximation. The

hydrogen atom positions were calculated or determined from difference Fourier syntheses and refined according to the "rider" model or freely in isotropic approximation. Visualization was performed with the DIAMOND program.[22] The complete X-ray structural dataset was deposited at the Cambridge Crystallographic Data Center (deposits CCDC 1523242 (compound **4b**) and CCDC 1523243 (compound **5a**)).

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