DOI 10.1007/s10593-019-02434-4

Chemistry of Heterocyclic Compounds **2019**, *55*(2), 167–171

Annulation of pyrrole ring in 4-acylpyridine-3,5-dicarbonitriles in the presence of ammonia

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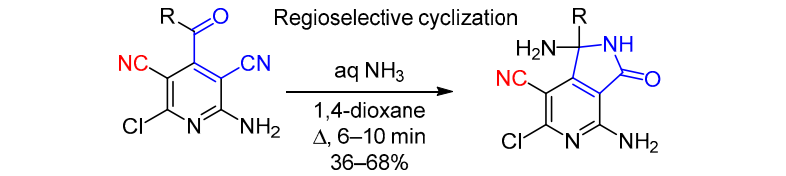
Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2019, *55*(2), 167–171

Submitted November 12, 2018
Accepted February 2, 2019



R = *t*-Bu, Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-thienyl

4-Acyl-2-amino-6-chloropyridine-3,5-dicarbonitriles underwent heterocyclization in the presence of ammonia in aqueous dioxane medium, involving the *ortho*-ketonitrile fragment while preserving the halogen atom. The pyrrole ring annulation process proceeded regioselectively with the formation of a single positional isomer.

Keywords: pyridine-3,5-dicarbonitriles, heteroannulation, rearrangement, regioselectivity.

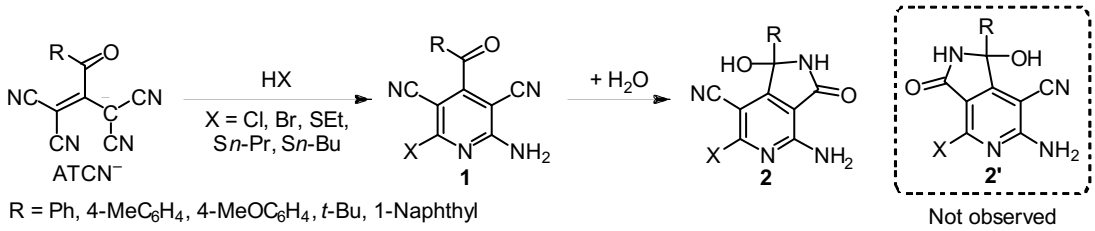
Pyridine-3,5-dicarbonitrile derivatives are of interest to researchers due to the practically useful properties discovered for some of these compounds.[1] The most valuable results have been achieved in developing selective agonists and antagonists of human adenosine receptors for the prevention and treatment of cardiovascular diseases.[2] The effectiveness of the obtained derivatives has been characterized by using mathematical methods such as QSAR, as well as experimental data.[3] Besides biologically active pyridine-3,5-dicarbonitriles, also hybrid fluorescent compounds have been described in which the pyridine ring acts as acceptor of electron density.[4] Due to the simple one-pot synthetic procedures and dense functionalization, pyridine-3,5-dicarbonitriles have been recognized as valuable precursors for fused heterocyclic compounds.[5]

We have previously reported methods for the synthesis of pyridine-3,5-dicarbonitriles **1** (X = Cl, Br, SEt, S*n*-Pr, S*n*-Bu, Scheme 1) that contain an *ortho*-ketonitrile moiety.[6] The currently widely used multicomponent syntheses starting from malononitrile[7] and cyanothioacetamide[8] do not provide access to such pyridines, therefore 2-acyl-1,1,3,3-tetracyanopropenides (ATCN) were selected as the starting materials. Halogenated derivatives **1** were obtained by using anhydrous gaseous HCl (X = Cl) or HBr (X = Br),[6a] while alkylsulfanyl-substituted pyridines (X = SEt, S*n*-Pr, S*n*-Bu) were obtained in reactions of $ATCN^-$ with aliphatic thiols in DMSO medium in the presence of NaH.[6b]

The introduction of *ortho*-ketonitrile moiety into pyridine-3,5-dicarbonitriles increases the synthetic potential of these building blocks due to the possibility of including the [*c*] bond in heteroannulation reactions. The addition of a water molecule to pyridine-3,5-dicarbonitrile **1** was used as an example to demonstrate that the cyclization process proceeded regioselectively with the formation of one of the possible positional isomers **2** (Scheme 1).[9]

In order to study the heterocyclization process in more detail, as well as for the purpose of developing a selective procedure for the synthesis of pyrrolo[3,4-*c*]pyridine

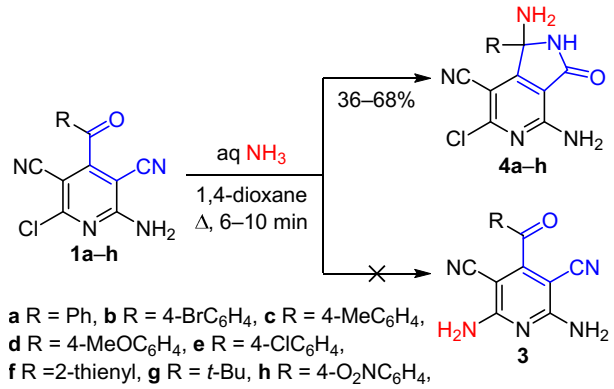
Scheme 1



systems, we are currently studying the reactions of pyridine-3,5-dicarbonitriles **1** with various types of nucleophilic reagents. In this work, we present the results obtained by using ammonia as the nucleophilic species attacking pyridine-3,5-dicarbonitriles **1** that contain a chlorine atom at position 2.

The molecules of the studied pyridine-3,5-dicarbonitriles **1a**–**h** contain several electron-withdrawing groups that facilitate nucleophilic aromatic substitution of halogen atom. Similar processes have been described in sufficient detail for structurally related compounds.[10] Therefore, we proposed that the initial stage of the reaction must be accompanied by the formation of diamine **3**. However, the analysis of reaction mixtures and the isolated products showed that the reaction followed an alternative route involving *ortho*-ketonitrile moiety, while the halogen atom remained intact. The reaction products were 1,4-diamino-1-aryl(alkyl)-6-chloro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]-pyridine-7-carbonitriles **4a**–**h** (Scheme 2).

Scheme 2



The attempts to perform targeted synthesis of diamine **3** did not give the expected result, which apparently could be explained by the insufficient nucleophilicity of ammonia in halogen substitution reaction when compounds **1** were used. Variation of reaction conditions did not provide a solution to this problem, resulting in the formation of intractable mixtures that could not be separated into individual compounds.

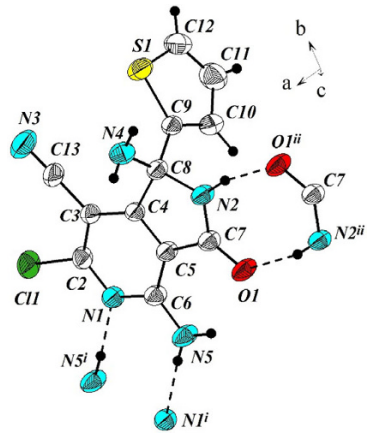


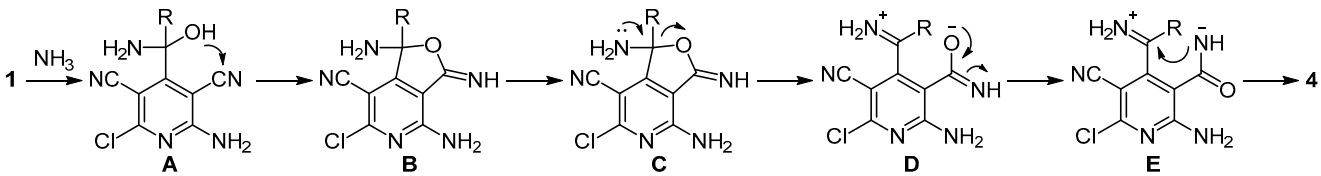
Figure 1. The molecular structure of compound **4f** with atoms represented by thermal vibration ellipsoids of 50% probability.

The structures of compounds **4a**–**h** were characterized using IR spectroscopy, ^{1}H and ^{13}C NMR spectrometry, and mass spectrometry. According to the spectral data, the transformation of pyridine-3,5-dicarbonitriles **1a**–**h** into products **4a**–**h** proceeded regioselectively, with the formation of a single positional isomer, the structure of which was determined by X-ray structural analysis in the case of compound **4f** (Fig. 1).

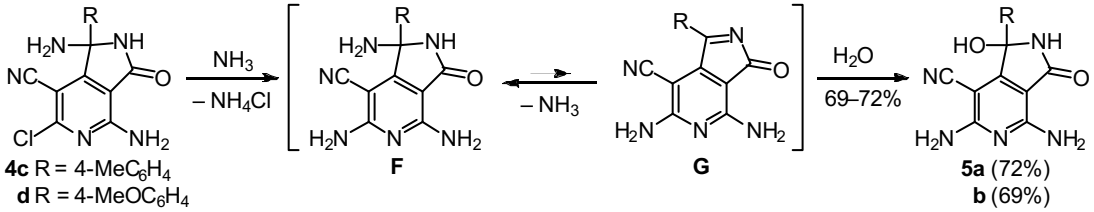
The proposed mechanism for the transformation of pyridine-3,5-dicarbonitriles **1a**–**h** into compounds **4a**–**h** includes nucleophilic addition of ammonia molecule at the carbonyl group of pyridine-3,5-dicarbonitrile **1a**–**h**, with the formation of aminal **A**. The intramolecular heterocyclization of closely positioned hydroxy and cyano groups in aminal **A** leads to the furo[3,4-*c*]pyridine derivative **B**. The molecule of the latter contains an iminolactone moiety that undergoes rearrangement under the reaction conditions (through intermediate structures **C**, **D**, **E**) into lactam **4** (Scheme 3).

In the case of compounds **4c**,**d** the substitution of chlorine atom with amino group becomes possible. However, as it was observed, this transformation was accompanied by the substitution of aminal amino group with a hydroxy group, with the formation of hydroxylactam ring in compounds **5a**,**b** (Scheme 4). The formation of intermediate products **F** and **G** was proposed by us on the

Scheme 3



Scheme 4



basis of NMR spectra of the reaction mixture. Unfortunately, we were not able to isolate these intermediates as individual compounds.

All of the synthesized pyrrolo[3,4-*c*]pyridine derivatives **4a**–**h** and **5a**,**b** had similar structures with poor solubility in many organic solvents (EtOAc, *i*-PrOH, MeCN, EtOH), therefore the formation of product mixtures created serious problems with their separation and purification. In order to avoid such problems, we performed TLC control of the reaction progress (eluent EtOAc–CH_2Cl_2, 1:1) at each step, and the products were isolated after complete conversion of the starting substrate.

Thus, we have shown that the cyclization of 4-acyl-2-amino-6-chloropyridine-3,5-dicarbonitriles in the presence of ammonia involved the *ortho*-ketonitrile moiety while the halogen atom was preserved. The cyclization reaction proceeded regioselectively with the formation of one positional isomer, the structure of which was determined by X-ray structural analysis. The substitution of halogen atom with amino group was possible after conversion of the carbonyl group. The results obtained at this stage of our study will be used for developing a selective method for the synthesis of pyrrolo[3,4-*c*]pyridine systems bearing many functional groups.

Experimental

IR spectra were recorded on an FSM-1202 FT-IR spectrometer for samples prepared as thin films (suspension in Nujol). ^{1}H and ^{13}C NMR spectra were acquired on an Agilent DDR2 400 spectrometer (400 and 101 MHz, respectively) in DMSO-d_6, using residual solvent signals as internal standard (2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei). Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI ionization, 70 eV). Elemental analysis was performed on a PerkinElmer 2400 CHN-analyzer. Melting points were determined on an OptiMelt MPA100 apparatus. The reaction progress and purity of the synthesized compounds were determined by TLC method on Sorbfil PTSKh-AF-A-UF plates (eluent EtOAc–CH_2Cl_2, 1:1), visualization under UV light (254/365 nm), in iodine vapor, or by thermal decomposition.

The starting pyridine-3,5-dicarbonitriles **1a**–**h** were obtained according to a published procedure from the respective potassium 2-acyl-1,1,3,3-tetracyanopropenides.[6a,9b]

Synthesis of 1,4-diamino-6-chloro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles 4a–**h** (General method). Aqueous 25% ammonia solution (3 ml) was added to a solution of pyridine-3,5-dicarbonitrile **1a**–**h** (1 mmol) in 1,4-dioxane (5 ml). The obtained solution was stirred and refluxed for 6–10 min in a flask equipped with a reflux condenser (control by TLC method), followed by cooling and evaporation at reduced pressure. The dry residue was purified by crystallization from MeCN.

1,4-Diamino-6-chloro-3-oxo-1-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4a). Yield 186 mg (62%), white crystals, mp 256–257°C (decomp.). IR spectrum, ν, cm^{-1}: 3396, 3145 (NH_2), 2225 (C≡N), 1689 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.10 (2H, s, NH_2); 7.32–7.47 (4H, m, 3H Ar, NH_2); 7.53–7.57 (2H, m, H Ar); 8.47 (1H, br. s, NH_2); 9.11 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 76.0; 90.3; 107.1; 113.6; 126.5; 128.3; 128.4; 138.8; 154.0; 156.2; 166.0; 166.4. Mass spectrum, *m*/*z* (I_{rel}, %): 301 $[M(^{37}Cl)]^+$ (3), 299 $[M(^{35}Cl)]^+$ (9), 285 $[M(^{37}Cl)–NH_2]^+$ (4), 283 $[M(^{35}Cl)–NH_2]^+$ (13), 256 $[M(^{37}Cl)–CONH]^+$ (3), 254 $[M(^{35}Cl)–CONH]^+$ (8), 247 $[M–Cl–NH_3]^+$ (15), 224 $[M(^{37}Cl)–Ar]^+$ (29), 222 $[M(^{35}Cl)–Ar]^+$ (82), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (3), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (9), 116 (13), 104 (44), 90 (59), 77 (100). Found, %: C 56.09; H 3.35; N 23.23. $C_{14}H_{10}ClN_5O_2$. Calculated, %: C 56.10; H 3.36; N 23.37.

1,4-Diamino-1-(4-bromophenyl)-6-chloro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4b). Yield 201 mg (53%), white crystals, mp 252–254°C (decomp.). IR spectrum, ν, cm^{-1}: 3390, 3148 (NH_2), 2220 (C≡N), 1688 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.14 (2H, s, NH_2); 7.42 (1H, br. s, NH_2); 7.48–7.52 (2H, m, H Ar); 7.55–7.60 (2H, m, H Ar); 8.49 (1H, br. s, NH_2); 9.13 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 75.6; 90.2; 107.1; 113.6; 121.8; 129.0; 131.2; 138.3; 154.6; 156.2; 165.4; 166.4. Mass spectrum, *m*/*z* (I_{rel}, %): 377 $[M]^+$ (2), 361 $[M–NH_2]^+$ (5), 224 $[M(^{37}Cl)–Ar]^+$ (18), 222 $[M(^{35}Cl)–Ar]^+$ (35), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (12), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (17), 90 (35), 71 (67), 57 (100). Found, %: C 44.32; H 2.39; N 18.46. $C_{14}H_9BrClN_5O$. Calculated, %: C 44.41; H 2.40; N 18.50.

1,4-Diamino-6-chloro-3-oxo-1-(*p*-tolyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4c). Yield 176 mg (56%), white crystals, mp 253–254°C (decomp.). IR spectrum, ν, cm^{-1}: 3379, 3148 (NH_2), 2225 (C≡N), 1692 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.29 (3H, s, CH_3); 3.05 (2H, s, NH_2); 7.15–7.19 (2H, m, H Ar); 7.39 (1H, br. s, NH_2); 7.41–7.45 (2H, m, H Ar); 8.45 (1H, br. s, NH_2); 9.07 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 25.5; 75.9; 90.3; 107.0; 113.7; 126.9; 128.8; 135.8; 137.7; 154.5; 156.2; 166.2; 166.4. Mass spectrum, *m*/*z* (I_{rel}, %): 315 $[M(^{37}Cl)]^+$ (9), 313 $[M(^{35}Cl)]^+$ (22), 299 $[M(^{37}Cl)–NH_2]^+$ (11), 297 $[M(^{35}Cl)–NH_2]^+$ (29), 261 $[M–Cl–NH_3]^+$ (15), 224 $[M(^{37}Cl)–Ar]^+$ (33), 222 $[M(^{35}Cl)–Ar]^+$ (100), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (14), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (32), 118 (40), 91 (67). Found, %: C 57.26; H 3.88; N 22.26. $C_{15}H_{12}ClN_5O$. Calculated, %: C 57.42; H 3.86; N 22.32.

1,4-Diamino-6-chloro-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4d). Yield 218 mg (66%), white crystals, mp 210–212°C (decomp.). IR spectrum, ν, cm^{-1}: 3385, 3157 (NH_2), 2223 (C≡N), 1681 (C=O). ^1H NMR spectrum, δ, ppm: 3.04 (2H, s, NH_2); 3.75 (3H, s, OCH_3); 7.39 (1H, br. s, NH_2); 7.44–7.50 (2H, m, H Ar); 7.89–7.94 (2H, m, H Ar); 8.44 (1H, br. s, NH_2); 9.05 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.2; 75.8; 90.3; 106.9; 113.6; 113.7; 127.9; 130.7; 154.5; 156.2; 159.3; 166.3; 166.4. Mass spectrum, *m*/*z* (I_{rel}, %): 331 $[M(^{37}Cl)]^+$ (1), 329 $[M(^{35}Cl)]^+$ (6), 314 $[M(^{37}Cl)–NH_2]^+$ (7), 312 $[M(^{35}Cl)–NH_2]^+$ (12), 224 $[M(^{37}Cl)–Ar]^+$ (6), 222 $[M(^{35}Cl)–Ar]^+$ (18), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (10), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (17), 153 (11), 151 (23), 90 (100). Found, %: C 54.49; H 3.69; N 21.18. $C_{15}H_{12}ClN_5O_2$. Calculated, %: C 54.64; H 3.67; N 21.24.

1,4-Diamino-6-chloro-1-(4-chlorophenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4e). Yield 197 mg (59%), white crystals, mp 287–288°C (decomp.). IR spectrum, ν, cm^{-1}: 3398, 3153 (NH_2), 2226 (C≡N), 1681 (C=O). ^1H NMR spectrum, δ, ppm: 3.15 (2H, s, NH_2); 7.40–7.46 (3H, m, 2H Ar, NH_2); 7.55–7.59 (2H, m, H Ar); 8.49 (1H, br. s, NH_2); 9.13 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 75.6; 90.2; 107.1; 113.6; 128.3; 128.7; 133.2; 137.9; 154.7; 156.3; 165.5; 166.4. Mass spectrum, *m*/*z* (I_{rel}, %): 333 $[M]^+$ (9), 316 $[M–NH_2]^+$ (16), 281 (24), 224 $[M(^{37}Cl)–Ar]^+$ (29), 222 $[M(^{35}Cl)–Ar]^+$ (100), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (13), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (33), 153 (18), 151 (45). Found, %: C 50.19; H 2.74; N 20.90. $C_{14}H_9Cl_2N_5O$. Calculated, %: C 50.32; H 2.71; N 20.96.

1,4-Diamino-6-chloro-3-oxo-1-(thiophen-2-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4f). Yield 162 mg (53%), white crystals, mp 215–216°C (decomp.). IR spectrum, ν, cm^{-1}: 3387, 3146 (NH_2), 2228 (C≡N), 1681 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.25 (2H, s, NH_2); 7.03 (1H, dd, ^3J = 4.7, ^3J = 3.5, H Ar); 7.27 (1H, d, ^3J = 3.5, H Ar); 7.41 (1H, br. s, NH_2); 7.51 (1H, d, ^3J = 4.7, H Ar); 8.48 (1H, br. s, NH_2); 9.31 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 74.4; 90.2; 106.3; 113.6; 126.7; 126.8; 127.3; 144.2; 154.8; 156.2; 165.2; 165.9. Mass spectrum, *m*/*z* (I_{rel}, %): 307 $[M(^{37}Cl)]^+$ (5), 305 $[M(^{35}Cl)]^+$ (11), 291 $[M(^{37}Cl)–NH_2]^+$ (8), 289 $[M(^{35}Cl)–NH_2]^+$ (23), 272 (21); 224 $[M(^{37}Cl)–Ar]^+$ (5), 222 $[M(^{35}Cl)–Ar]^+$ (12), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (6), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (16), 111 (100). Found, %: C 47.00; H 2.66; N 22.84. $C_{12}H_8ClN_5OS$. Calculated, %: C 47.14; H 2.64; N 22.91.

1,4-Diamino-1-*tert*-butyl-6-chloro-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4g). Yield 101 mg (36%), white crystals, mp 264–265°C (decomp.). IR spectrum, ν, cm^{-1}: 3396, 3142 (NH_2), 2224 (C≡N), 1680 (C=O). ^1H NMR spectrum, δ, ppm: 0.98 (9H, s, $C(CH_3)_3$); 2.63 (2H, s, NH_2); 7.35 (1H, s, NH_2); 8.32 (1H, br. s, NH_2); 8.79 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 28.1; 40.4; 81.3; 92.2; 109.1; 115.9; 155.2; 156.0; 164.9; 166.5. Mass spectrum, *m*/*z* (I_{rel}, %): 249 [M(37Cl)–CONH]$^+$ (2), 247 $[M(^{35}Cl)–CONH]^+$ (3), 224 $[M(^{37}Cl)–Ar]^+$ (36), 222 $[M(^{35}Cl)–Ar]^+$ (100), 207$[M(^{37}Cl)–Ar–NH_3]^+$ (11), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (31), 57 (93). Found, %: C 51.36; H 5.06; N 24.96. $C_{12}H_{14}ClN_5O$. Calculated, %: C 51.53; H 5.04; N 25.04.

1,4-Diamino-6-chloro-1-(4-nitrophenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (4h). Yield 234 mg (68%), white crystals, mp 239–240°C (decomp.). IR spectrum, ν, cm^{-1}: 3377, 3153 (NH_2), 2228 (C≡N), 1691 (C=O). ^1H NMR spectrum, δ, ppm: 3.30 (2H, s, NH_2); 7.48 (1H, br. s, NH_2); 7.81–7.85 (2H, m, H Ar); 8.21–8.26 (2H, m, H Ar); 8.54 (1H, br. s, NH_2); 9.24 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 75.6; 90.2; 107.3; 113.5; 123.4; 128.4; 146.1; 147.5; 154.7; 156.3; 164.8; 166.5. Mass spectrum, *m*/*z* (I_{rel}, %): 346 $[M(^{37}Cl)]^+$ (2), 344 $[M(^{35}Cl)]^+$ (6), 329 $[M(^{37}Cl)–NH_2]^+$ (15), 327 $[M(^{35}Cl)–NH_2]^+$ (25), 301 (3), 299 (8); 224 $[M(^{37}Cl)–Ar]^+$ (26), 222 $[M(^{35}Cl)–Ar]^+$ (67), 207 $[M(^{37}Cl)–Ar–NH_3]^+$ (12), 205 $[M(^{35}Cl)–Ar–NH_3]^+$ (23), 153 (23), 151 (74), 90 (100). Found, %: C 48.77; H 2.62; N 24.21. $C_{14}H_9ClN_6O_3$. Calculated, %: C 48.78; H 2.63; N 24.38.

Synthesis of 4,6-diamino-1-aryl-1-hydroxy-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitriles 5a,b (General method). Aqueous 25% ammonia solution (2 ml) was added to a solution of pyrrolo[3,4-*c*]pyridine **4c**,**d** (0.5 mmol) in 1,4-dioxane (2 ml). The obtained solution was stirred and refluxed for 2–3 days (control by TLC), after which the reaction mixture was cooled and evaporated at reduced pressure. The dry residue was purified by crystallization from MeCN.

4,6-Diamino-1-hydroxy-3-oxo-1-(*p*-tolyl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5a). Yield 106 mg (72%), white crystals, mp 269–270°C (decomp.). IR spectrum, ν, cm^{-1}: 3349, 3177 (NH_2, NH, OH), 2210 (C≡N), 1692 (C=O). ^1H NMR spectrum, δ, ppm: 2.29 (3H, s, CH_3); 6.67 (1H, br. s, NH_2); 6.86 (2H, s, NH_2); 7.03 (1H, br. s, NH_2); 7.13–7.17 (2H, m, H Ar); 7.30–7.34 (3H, m, H Ar, OH); 8.72 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 72.4; 86.5; 98.0; 115.3; 126.0; 128.5; 136.7; 137.3; 156.7; 162.9; 165.3; 168.1. Mass spectrum, *m*/*z* (I_{rel}, %): 295 $[M]^+$ (45), 278 $[M–OH]^+$ (25), 277 $[M–H_2O]^+$ (26), 204 $[M–Ar]^+$ (33); 186 $[M–Ar–H_2O]^+$ (41), 160 (30), 132 (56); 119 $[ArCO]^+$ (83); 91 $[Ar]^+$ (100). Found, %: C 61.02; H 4.45; N 23.92. $C_{15}H_{13}N_5O_2$. Calculated, %: C 61.01; H 4.44; N 23.72.

4,6-Diamino-1-hydroxy-1-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine-7-carbonitrile (5b). Yield 108 mg (69%), white crystals, mp 251–253°C (decomp.). IR spectrum, ν, cm^{-1}: 3424, 3340, 3146 (NH_2, NH, OH), 2209 (C≡N), 1682 (C=O). ^1H NMR spectrum, δ, ppm: 3.75 (3H, s, OCH_3); 6.68 (1H, br. s, NH_2); 6.88 (2H, s, NH_2); 6.89–6.91 (2H, m, H Ar); 6.99 (1H, s, OH); 7.35–7.37 (3H, m, H Ar, NH_2); 8.70 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.1; 72.3; 86.3; 97.9; 113.3; 115.3; 127.4; 131.5; 156.7; 159.0; 162.9; 165.4; 168.1. Mass spectrum, *m*/*z* (I_{rel}, %): 311 $[M]^+$ (22), 294 $[M–OH]^+$ (14), 293 $[M–H_2O]^+$ (18), 204 $[M–Ar]^+$ (12); 186 $[M–Ar–H_2O]^+$ (11), 135 $[ArCO]^+$ (100); 107 $[Ar]^+$ (57). Found, %: C 57.88; H 4.23; N 22.73. $C_{15}H_{13}N_5O_3$. Calculated, %: C 57.87; H 4.21; N 22.50.

X-ray structural study of compound 4f was performed on using an X-ray diffractometer Pilatus 100K STOE (MoKα radiation). Data collection, detection, and refinement of unit parameters, diffraction data processing

was carried out using the STOE X-Area program set.[11] Crystals suitable for X-ray structural analysis were obtained by slow evaporation of a solution of compound **4f** in 1,4-dioxane. The structure was solved using the SHELXS-97 software.[12] The complete X-ray structural dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1877753). The visual representation of structure was prepared using the DIAMOND program.[13]

This study received financial support from the Russian Foundation for Basic Research (project No. 18-33-01204 mol_a).

X-ray structural analysis was performed with support from M. V. Lomonosov Moscow State University development program.

References

1. (a) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko A. *Org. Lett.* **2006**, *8*, 899. (b) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Yu.; Magedov, I. V.; Kornienko A. *J. Org. Chem.* **2007**, *72*, 3443.
2. (a) Louvel, J.; Guo, D.; Soethoudt, M.; Mocking, T. A. M.; Lenselink, E. B.; Mulder-Krieger, T.; Heitman, L. H.; IJzerman, A. P.; *Eur. J. Med. Chem.* **2015**, *101*, 681. (b) Meibom, D.; Albrecht-Kupper, B.; Diedrichs, N.; Hubsch, W.; Kast, R.; Kramer, T.; Krenz, U.; Lerchen, H.-G.; Mittendorf, J.; Nell, P. G.; Susmeier, F.; Vakalopoulos, A.; Zimmermann, K. *ChemMedChem* **2017**, *12*, 728.
3. (a) Mais, F.-J.; Heilman, W.; Olenik, B.; Keil, B.; Becker, G.; Meibom, D.; Kuhlmann, T. US Patent 20180155336A1. (b) Rodríguez, D.; Gao, Z.-G.; Moss, S. M.; Jacobson, K. A.; Carlsson, J. *J. Chem. Inf. Model.* **2015**, *55*, 550.
4. (a) Soumya, T. V.; Muhammed Ajmal, C.; Bahulayan, D. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 450. (b) Bardasov, I. N.; Alekseeva, A. U.; Chunikhin, S. S.; Tafeenko, V. A.; Ershov, O. V. *Tetrahedron Lett.* **2017**, *58*, 3919.
5. Ibrahim, D. A.; Ismail, N. S. M. *Eur. J. Med. Chem.* **2011**, *46*, 5825.
6. (a) Karpov, S. V.; Kayukov, Ya. S.; Bardasov, I. N.; Kayukova, O. V.; Lipin, K. V.; Nasakin, O. E. *Russ. J. Org. Chem.* **2011**, *47*, 1492. [*Zh. Org. Khim.* **2011**, *47*, 1492.] (b) Grigor'ev, A. A.; Karpov, S. V.; Kayukov, Ya. S.; Belikov, M. Yu.; Nasakin, O. E. *Tetrahedron Lett.* **2015**, *56*, 6279. (c) Grigor'ev, A. A.; Karpov, S. V.; Kayukov, Ya. S.; Nasakin, O. E.; Gracheva, Iu. A.; Tafeenko, V. A. *Chem. Heterocycl. Compd.* **2017**, *53*, 230. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 230.] (d) Karpov, S. V.; Grigor'ev, A. A.; Kayukov, Ya. S.; Karpova, I. V.; Nasakin, O. E.; Tafeenko, V. A. *J. Org. Chem.* **2016**, *81*, 6402.
7. Grigor'ev, A. A.; Shtyrlin, N. V.; Gabbasova, R. R.; Zeldi, M. I.; Grishaev, D. Yu.; Gnezdilov, O. I.; Balakin, K. V.; Nasakin, O. E.; Shtyrlin, Yu. G. *Synth. Commun.* **2018**, *48*, 2288.
8. Attia, A. M. E.; Ismail, A. E.-H. A. A. *Tetrahedron* **2003**, *59*, 1749.
9. (a) Grigor'ev, A. A.; Karpov, S. V.; Kayukov, Ya. S.; Gracheva, Iu. A.; Tafeenko, V. A. *Synlett* **2017**, 1592. (b) Kayukov, Ya. S.; Karpov, S. V.; Grigor'ev, A. A.; Nikiforova, A. L.; Nasakin, O. E.; Shchegravina, E. S.; Kayukova, O. V.; Tafeenko, V. A. *Chem. Heterocycl. Compd.* **2017**, *53*, 568. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 568.]
10. Maksimova, V. N.; Ershov, O. V.; Lipin, K. V.; Eremkin, A. V.; Nasakin, O. E. *Russ. J. Org. Chem.* **2012**, *48*, 426. [*Zh. Org. Khim.* **2012**, *48*, 429.]
11. Stoe & Cie, X-AREA, version 1.30. Stoe & Cie GmbH: Darmstadt, Germany, 2005.
12. Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *A64*, 112.
13. Brandenburg, K. *DIAMOND*, *Release 2.1d*; Crystal Impact GbR: Bonn, 2000.