DOI 10.1007/s10593-019-02603-5

Chemistry of Heterocyclic Compounds **2019**, *55*(12), 1211–1216

A convenient synthesis method of 5-oxopyrazolo[4,3-*b*]pyridine-6-carboxylic acids and their nitriles

Georgiy G. Yakovenko[1,2]*, Oleh A. Lukianov[2], Andriy V. Bol'but[2,3], Mikhailo V. Vovk[2]

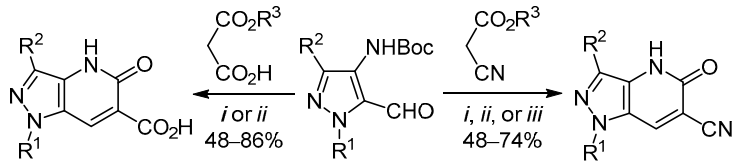
[1] *National University "Kyiv-Mohyla Academy", 2 Hrygorija Skorovody St., Kyiv 04655, Ukraine; e-mail: chemgeorge@i.ua*

[2] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska St., Kyiv 02094, Ukraine; e-mail: mvovk@ioch.kiev.ua*

[3] *Enamine Ltd., 78 Chervonotkatskaya St., Kyiv 02094, Ukraine; e-mail: bolbut@ukr.net*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2019, *55*(12), 1211–1216

Submitted June 6, 2019
Accepted August 3, 2019



R^1 = Me, Et, *t*-Bu, Ph, 2-Py; R^2 = H, OMe, Ph; R^3 = H, Me

i: pyrrolidine, Py, 45–50°C, 8–12 h (R^3 = H); *ii*: pyrrolidine, AcOH, Δ, 5–6 h (R^3 = Me)
iii: pyrrolidine, proline, MeCN, Δ, 4–6 h (R^3 = Me)

N-Boc-protected 5-formyl-1*H*-pyrazol-4-amines react with malonic acid in pyridine in the presence of pyrrolidine at 45–50°C or with malonic acid monomethyl ether in the presence of pyrrolidine in AcOH under reflux with the formation of 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylic acids. The reaction of *N*-Boc-protected 5-formyl-1*H*-pyrazol-4-amines with cyanoacetic acid in pyridine in the presence of pyrrolidine at 45–50°C leads to the formation of 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carbonitriles. The latter can also be obtained *via* cyclocondensation of *N*-Boc-protected 5-formyl-1*H*-pyrazol-4-amines with methyl cyanoacetate in AcOH under reflux in the presence of pyrrolidine or in MeCN containing pyrrolidine and a catalytic amount of proline heated under reflux.

Keywords: cyanoacetic acid, 5-formyl-1*H*-pyrazol-4-amine, malonic acid, methyl cyanoacetate, monomethyl malonate, pyrazolo[4,3-*b*]-pyridine-6-carbonitrile, pyrazolo[4,3-*b*]pyridine-6-carboxylic acid, cyclocondensation.

Derivatives of 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]-pyridine are condensed nitrogen-containing heterocyclic compounds with pronounced biological activity. Among them, inhibitors of p38 mitogen-activated protein kinases, promising agents for the treatment of viral diseases, arthritis, Alzheimer's disease and dermatitis,[1] inhibitors of bromodomain and extraterminal proteins for the treatment of autoimmune diseases, viral and inflammatory infections,[2] as well as NIK kinase inhibitors effective for the treatment and prevention of inflammatory diseases[3] were identified. There is also a report on the use of derivatives of 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]-pyridine as important intermediates in the synthesis of chemokine receptor antagonists pyrazolopiperidines.[4]

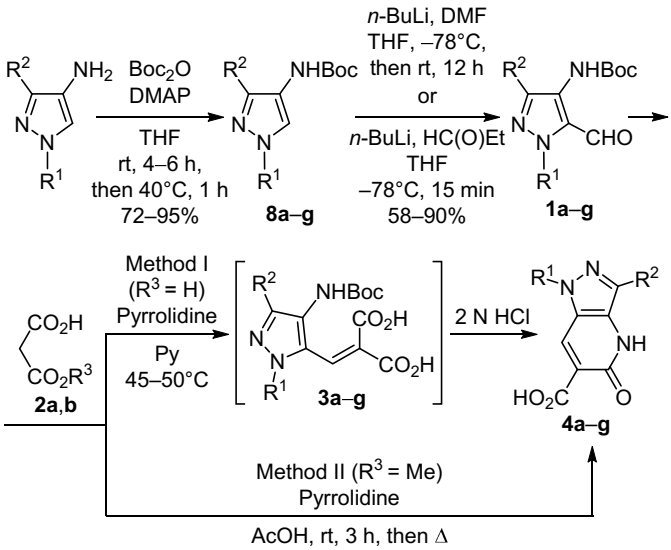
However, despite the fairly wide pharmacological profile of 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine derivatives, the known methods for their synthesis are multistage, require the use of expensive and aggressive reagents, and, as a rule, include a series of successive conversions to annulate the pyridine ring to the pyrazole.[1b,3,5] In particular, the condensation of 3,5-diacyl-1-phenyl-1*H*-pyrazol-4-amines with cyanoacetic acid proceeds in Ac_2O medium under the conditions of microwave activation with the formation of 2-cyano-*N*-(3,5-diacyl-1-phenyl-1*H*-pyrazol-4-yl)acetamides, which cyclize into 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carbonitriles only upon heating in DMF under reflux in the presence of NaOAc.[5a] In turn, intramolecular copper-catalyzed amidation of 4-iodopyrazoles does not exhibit high selectivity and leads to the formation of 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine derivatives with relatively low yields.[5b] In the context of the foregoing, it seems

reasonable to develop a preparatively convenient way to access new representatives of this heterocyclic system, additionally containing a carboxyl or nitrile functionality in the pyridine ring, which can be effectively subjected to structural modifications by pharmacophore groups. The choice of the indicated functional groups as substituents is also due to the powerful synthetic potential[6] and biological activity[7] of isostere 3-carbo-functionalized quinolin-2-ones.

In a previous report, we showed that the Friedlander reaction of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amines with various methylene-containing ketones can be used to obtain 5-substituted pyrazolo[4,3-*b*]-pyridines.[8] Considering these revelations, as well as the literature data on the cyclocondensation of aromatic *o*-amino-aldehydes or ketones with CH acids as an effective method for the synthesis of 3-substituted quinolones,[6a,7a,b,9] we investigated the reactions of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amines **1a**–**g** with malonic acid (**2a**), its methyl ester **2b**, and also cyanoacetic acid (**2c**) and its methyl ester **2d** in this work.

In search of the optimal conditions for cyclo-condensation of 5-formyl-1*H*-pyrazol-4-amines **1a**–**g** with malonic acid (**2a**), it was found that the use of pyridine as the solvent and an equimolar amount of pyrrolidine as the catalyst is the most effective. In this medium, the reaction is complete at 45–50°C within 8–12 h and proceeds *via* the intermediate products **3a**–**g**, which can be observed by ^{1}H NMR spectroscopy (Table 1, method I). Subsequent treatment with 2 N aqueous HCl removes the *N*-Boc protection to effect cyclization to the desired 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylic acids **4a**–**g** in 54–86% yields. Carrying out the reaction under reflux in the AcOH–pyrrolidine system, which was previously used to condense *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amines with ketones,[8] was ineffective. Thus, after carrying out the reaction of 5-formyl-1*H*-pyrazol-4-amine **1a** with acid **2a** under these conditions, it was found that the content of the target product **4a** in the reaction mixture was only 18% according to LC-M spectrometry. However, the replacement of malonic acid (**2a**) with its monomethyl ether **2b** allowed to successfully effect cyclocondensation with *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amines **1a**–**e** by stirring in AcOH–pyrrolidine at room temperature for 3 h, followed by heating under reflux for 5–6 h (method II). Most probably that under these conditions the cyclization stage proceeds noticeably faster than the competing decarboxylation reaction of the malonate carboxyl group of the crotonic condensation intermediate, although the target compounds **4a**–**e** are obtained in 4–15% lower yields than when using method I. Formation of the pyridine ring as a result of the studied cyclization is confirmed by the presence in the IR spectra of compounds **4a**–**g** of absorption bands of N–H in the 3201–3217 cm^{-1} range, carboxylic C=O in the 1721–1739 cm^{-1} range, pyridone C=O in the 1652–1665 cm^{-1} range, whereas the ^{1}H NMR spectra contained the singlet signals of protons of 7-CH at 8.70–8.97 (for compounds **4a**–**d**,**f**,**g**) and 9.63 ppm (for compound **4e**), of NH at 13.26–13.61 ppm, and of CO_2H at 15.20–15.50 ppm.

Table 1. Synthesis of 5-oxo-4,5-dihydro-1*H*-pyrazolo-[4,3-*b*]pyridine-6-carboxylic acids **4a**–**g**



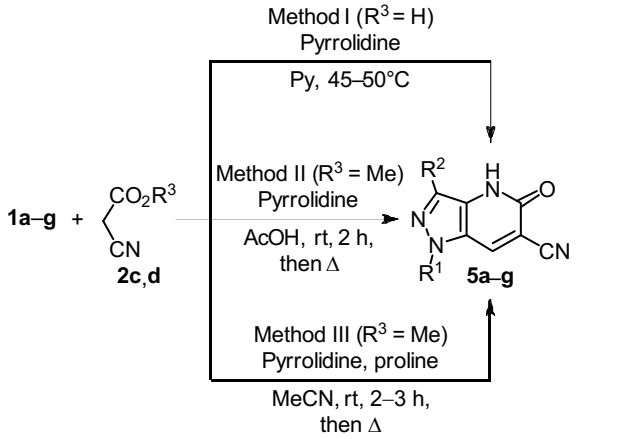
Compound	R^1	R^2	Method I		Method II	
			Time, h	Yield, %	Time, h	Yield, %
4a	Me	H	9	86	5	71
4b	Et	H	8	82	5	68
4c	*t*-Bu	H	12	62	6	58
4d	Ph	H	10	59	6	52
4e	2-Py	H	12	60	6	48
4f	Me	OMe	9	62	–	–
4g	Me	Ph	10	54	–	–

The reactivity of cyanoacetic (compound **2c**) and malonic acid (compound **2a**) with 5-formyl-1*H*-pyrazol-4-amines **1a**,**c**,**e**,**g** are practically the same. 5-Oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carbonitriles **1a**,**c**,**e**,**g** are formed as a result of this reaction in the pyridine–pyrrolidine system at 45–50°C in 48–74% yields (Table 2, method I). At the same time, methyl cyanoacetate (**2d**) does not react with 5-formyl-1*H*-pyrazol-4-amines **1a**–**g** under these conditions. A positive result, however, was achieved by carrying out the reaction in AcOH under reflux in the presence of an equimolar amount of pyrrolidine (method II).

The use of the pyrrolidine–proline catalytic system, which proved to be effective when using MeCN as a solvent, is also noteworthy. Using the reaction of bifunctional pyrazoles **1a**–**d** with ester **2d** in MeCN under reflux as an example, it was demonstrated that the use of an equimolar amount of pyrrolidine and 0.1 equiv of proline leads to the desired products **5a**–**d** in 52–72% yields (Table 2, method III). It should be noted that the yields of compounds **5a**–**d** decrease by 8–11% in the absence of proline.

In the case of method III, the reaction most likely proceeds through the formation of Knoevenagel product **6**, detected by LC-M spectrometry. Subsequently, intramolecular acylation of intermediate **6** occurs by the action of pyrrolidine as a base, with the formation of intermediate

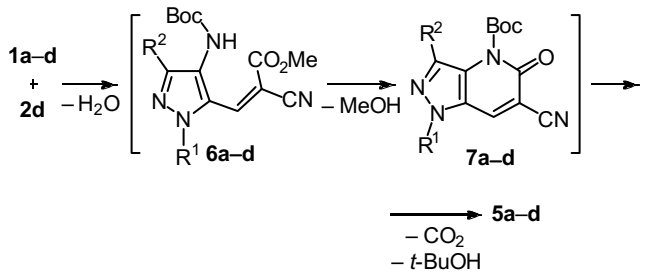
Table 2. Synthesis of 5-oxo-4,5-dihydro-1*H*-pyrazolo-[4,3-*b*]pyridin-6-carbonitriles **5a**–**g**



Compound	R^1	R^2	Method I		Method II		Method III	
			Time, h	Yield, %	Time, h	Yield, %	Time, h	Yield, %
5a	Me	H	8	74	5	67	4	56
5b	Et	H	–	–	5	69	4	52
5c	*t*-Bu	H	10	56	6	67	5	60
5d	Ph	H	8	–	6	74	6	72
5e	2-Py	H	12	48	6	70	–	–
5f	Me	OMe	–	–	5	68	–	–
5g	Me	Ph	12	49	6	61	–	–

7.[10] *N*-Boc protection is removed under the reaction conditions (elevated temperature, the presence of a base and formed H_2O), which is consistent with published data[11] (Scheme 1).

Scheme 1



Replacing the carboxyl group in acids **4a**–**g** with a cyano group affects the spectral characteristics of nitriles **5a**–**g**. Thus, in the IR spectra of products **5a**–**g**, an insignificant short-wavelength shift of the absorption bands of N–H bonds (3205–3252 cm^{-1}), a short-wavelength shift of the absorption bands of C=O bonds of pyridone (1658–1694 cm^{-1}), as well as the appearance of medium intensity absorption bands of C≡N groups in the 2220–2230 cm^{-1} range are observed. In the ^1H NMR spectra of nitriles **5a**–**g**, the chemical shifts of the 7-CH proton singlet signals are practically unchanged; however, the NH proton signal does undergo a noticeable upfield shift of 1 ppm.

To conclude, we have proposed a simple and convenient method for the synthesis of promising novel synthetic intermediates, 5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylic acids and their nitriles. This approach is based on the cyclocondensation of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4 amines with malonic or cyanoacetic acids and their esters.

Experimental

IR spectra were registered on a Bruker Vertex 70 FT-IR spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were acquired on a Varian VXR-400 spectrometer (400 and 126 MHz, respectively) in $CDCl_3$ (compounds **1b**,**f**,**g** and **9b**,**f**,**g**) or DMSO-d_6 (compounds **4a**–**g** and **5a**–**g**), with TMS as internal standard. Mass spectra were recorded on a Agilent LC/MSD SL LC-MS system equipped with a Zorbax SB-C18 column (4.6 × 150 mm, 1.8 μm), atmospheric pressure electrospray ionization, DMSO solvent. Elemental analysis was performed on a PerkinElmer Series II 2400 Elemental analyzer. Melting points were determined on a Kofler bench and are uncorrected.

The starting pyrazoles **1a**,[12] **1c**–**e**,[8] and **8b**,**f**,**g**[8] were obtained according to published methods. 1-Ethyl-1*H*-pyrazol-4-amine, 3-methoxy-1-methyl-1*H*-pyrazol-4-amine, and 1-methyl-3-phenyl-1*H*-pyrazol-4-amine used in the synthesis of *N*-Boc-protected 1-alkyl-5-formyl-1*H*-pyrazol-4-amines **1b**,**f**,**g** were supplied by Enamine Ltd.

Synthesis of *N*-Boc-substituted 1-alkyl-1*H*-pyrazol-4-amines 8b,f,g (General method).[8] DMAP (1.22 g, 0.01 mol) was added with stirring and cooling to 0°C to a solution of pyrazol-4-amine (0.257 mol) in THF (400 ml), followed by di-*tert*-butyl dicarbonate (56.8 g, 0.260 mol) over 20 min. The reaction mixture was stirred at 0°C for 1 h, then at room temperature for 4–6 h, and finally at 40°C for 1 h. The solvent was evaporated under reduced pressure, the residue was extracted with MTBE (300 ml). MTBE–hexane, 3:2 mixture (300 ml) was added to the resulting oily product. The precipitate formed after stirring was filtered off and air-dried.

***tert*-Butyl (1-ethyl-1*H*-pyrazol-4-yl)carbamate (8b)** was obtained from 1-ethyl-1*H*-pyrazol-4-amine (35.4 g, 0.319 mol). Yield 61.3 g (91%), light-pink powder, mp 68–69°C. IR spectrum, ν, cm^{-1}: 3376 (N–H), 1725 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.41–1.48 (12H, m, CH_3, $C(CH_3)_3$); 4.08 (2H, q, *J* = 7.2, CH_2); 6.40 (1H, br. s, NH); 7.28 (1H, s, H-5); 7.65 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.9; 27.8; 46.7; 79.5; 118.9; 121.1; 129.2; 152.8. Mass spectrum, *m*/*z* (I_{rel}, %): 212 $[M+H]^+$ (100). Found, %: C 56.39; H 8.20; N 19.68. $C_{10}H_{17}N_3O_2$. Calculated, %: C 56.85; H 8.11; N 19.89.

***tert*-Butyl (3-methoxy-1-methyl-1*H*-pyrazol-4-yl)carbamate (8f)** was obtained from 3-methoxy-1-methyl-1*H*-pyrazol-4-amine (24.9 g, 0.196 mol). Yield 42.3 g (95%), colorless crystals, mp 69–70°C. IR spectrum, ν, cm^{-1}: 3285 (N–H), 1714 (C=O). ^1H NMR spectrum, δ, ppm: 1.47 (9H, s, $C(CH_3)_3$); 3.66 (3H, s, NCH_3); 3.89 (3H, s, OCH_3); 6.08 (1H, br. s, NH); 7.48 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 28.3; 38.9; 56.3; 80.1; 105.7; 123.1; 153.1; 153.7. Mass spectrum, *m*/*z* (I_{rel}, %): 228 $[M+H]^+$ (100). Found, %: C 53.10; H 7.61; N 18.31. $C_{10}H_{17}N_3O_3$. Calculated, %: C 52.85; H 7.54; N 18.49.

***tert*-Butyl (1-methyl-3-phenyl-1*H*-pyrazol-4-yl)carbamate (8g)** was obtained from 1-methyl-3-phenyl-1*H*-pyrazol-4-amine (24.6 g, 0.142 mol). Yield 34.2 g (88%), brown powder, mp 93–94°C. IR spectrum, ν, cm^{-1}: 3301 (N–H), 1687 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (9H, s, $C(CH_3)_3$); 3.89 (3H, s, NCH_3); 7.25–7.40 (4H, m, NH, H-3,4,5 Ph); 7.67 (2H, d, *J* = 7.2, H-2,6 Ph); 7.80 (1H, s, H-5). ^{13}C NMR spectrum, δ, ppm: 27.8; 38.8; 80.0; 117.6; 122.7; 127.3; 128.5; 132.1; 140.8; 152.8. Mass spectrum, *m*/*z* (I_{rel}, %): 274 $[M+H]^+$ (100). Found, %: C 65.68; H 7.08;N 15.49. $C_{15}H_{19}N_3O_2$. Calculated, %: C 65.91; H 7.01; N 15.37.

Synthesis of *N*-Boc-protected 1-alkyl-5-formyl-1*H*-pyrazol-4-amines 1b,f,g (General method).[8] *n*-BuLi (2.5 M solution in hexane, 159 ml, 0.40 mol) was added to a cooled (–78°C) solution of carbamate **8b**,**f**,**g** (0.18 mol) in THF (600 ml) under argon atmosphere. The reaction mixture was stirred at –78°C for 2–3 h. DMF (15.4 ml, 0.20 mol) was added to the reaction mixture at –78°C, then stirring was continued at room temperature for 10–12 h. Saturated aqueous NH_4Cl (200 ml) was added to the mixture. The formed mixture was stirred for additional 20–30 min and extracted with MTBE (3×200 ml). The organic layer was washed with saturated aqueous NaCl (2×150 ml), dried over anhydrous Na_2SO_4, and filtered through a layer of silica gel. The solvent was evaporated, MTBE–hexane, 3:2 mixture (150 ml) was added to the oily residue. The precipitate formed after stirring was filtered off and air-dried.

***tert*-Butyl (1-ethyl-5-formyl-1*H*-pyrazol-4-yl)carbamate (1b)**. Yield 37.4 g (87%), light-pink powder, mp 68–69°C. IR spectrum, ν, cm^{-1}: 3376 (N–H), 1725 (C=O aldehyde), 1698 (C=O carbamate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47–1.50 (12H, m, CH_3, $C(CH_3)_3$); 4.39 (2H, q, *J* = 7.2, CH_2); 8.01 (1H, br. s, NH); 8.28 (1H, s, H-5); 9.98 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 15.5; 27.7; 45.2; 80.7; 125.0; 128.2; 129.0; 152.0; 179.0. Mass spectrum, *m*/*z* (I_{rel}, %): 240 $[M+H]^+$ (100). Found, %: C 55.38; H 7.21; N 17.49. $C_{11}H_{17}N_3O_3$. Calculated, %: C 55.22; H 7.16; N 17.56.

***tert*-Butyl (5-formyl-3-methoxy-1-methyl-1*H*-pyrazol-4-yl)carbamate (1f)**. Yield 39.0 g (85%), colorless crystals, mp 76–77°C. IR spectrum, ν, cm^{-1}: 3239 (N–H), 1710 (C=O aldehyde), 1678 (C=O carbamate). ^{1}H NMR spectrum, δ, ppm: 1.49 (9H, s, $C(CH_3)_3$); 3.94 (3H, s, NCH_3); 3.98 (3H, s, OCH_3); 6.05 (1H, br. s, NH); 9.90 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 27.6; 38.7; 56.1; 80.7; 109.5; 131.5; 153.6; 154.2; 180.6. Mass spectrum, *m*/*z* (I_{rel}, %): 256 $[M+H]^+$ (100). Found, %: C 51.05; H 6.74; N 16.18. $C_{11}H_{17}N_3O_4$. Calculated, %: C 51.76; H 6.71; N 16.46.

***tert*-Butyl (5-formyl-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)carbamate (1g)**. Yield 31.4 g (58%), brown powder, mp 105–106°C. IR spectrum, ν, cm^{-1}: 3258 (N–H), 1759 (C=O aldehyde), 1671 (C=O carbamate). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (9H, s, $C(CH_3)_3$); 3.94 (3H, s, NCH_3); 7.14–7.23 (3H, m, H-3,4,5 Ph); 7.50 (2H, d, *J* = 7.6, H-2,6 Ph); 7.67 (1H, br. s, NH); 9.65 (1H, s, CHO). 13C NMR spectrum, δ, ppm: 27.6; 39.6; 80.1; 126.4; 127.5; 127.9; 131.1; 133.0; 144.2; 154.1; 179.7. Mass spectrum, *m*/*z* (I_{rel}, %): 302 $[M+H]^+$ (100). Found, %: C 63.58; H 6.40; N 13.78. $C_{16}H_{19}N_3O_3$. Calculated, %: C 63.77; H 6.36; N 13.94.

Synthesis of pyrazolo[4,3-*b*]pyridine-6-carboxylic acids 4a–g (General method). Method I. Malonic acid (**2a**) (0.62 g, 6 mmol) followed by pyrrolidine (0.5 ml, 6 mmol) was added to a solution of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amine **1a**–**g** (5 mmol) in pyridine (15 ml). The reaction mixture was heated at 45–50°C for 8–12 h. Pyridine was evaporated under reduced pressure, and the residue was treated with 2 N aqueous HCl (10 ml). The formed precipitate was filtered off, washed with H_2O (10 ml) and MTBE (10 ml), air-dried, and recrystallized from MeOH.

Method II. Monomethyl malonate (**2b**) (0.70 g, 6 mmol) followed by pyrrolidine (0.5 ml, 6 mmol) was added to a solution of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amine (5 mmol) **1a**–**e** (5 mmol) in glacial AcOH (20 ml). The reaction mixture was stirred at room temperature for 3 h, then heated under reflux for 5–6 h. The solvent was evaporated under reduced pressure, H_2O (30–40 ml) was added to the oily residue, and stirred until a loose precipitate formed. It was filtered off, washed with H_2O (10 ml) and MTBE (10 ml), air-dried, and recrystallized from MeOH.

1-Methyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylic acid (4a). Yield 0.83 g (86%, method I), 0.69 g (71%, method II), light-yellow powder, mp 264–265°C. IR spectrum, ν, cm^{-1}: 3201 (N–H), 1739 (C=O carboxylic acid), 1652 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm: 4.10 (3H, s, CH_3); 7.69 (1H, s, H-3); 8.92 (1H, s, 7-CH); 13.26 (1H, s, NH); 15.38 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 37.2; 115.2; 124.0; 127.3; 129.2; 131.4; 163.9; 165.6. Mass spectrum, *m*/*z* (I_{rel}, %): 194 $[M+H]^+$ (100). Found, %: C 49.95; H 3.57; N 21.91. $C_8H_7N_3O_3$. Calculated, %: C 49.74; H 3.65; N 21.75.

1-Ethyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylic acid (4b). Yield 0.85 g (82%, method I), 0.70 g (68%, method II), yellow powder, mp 259–261°C. IR spectrum, ν, cm^{-1}: 3214 (N–H), 1732 (C=O carboxylic acid), 1663 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, t, *J* = 7.2, CH_3); 4.50 (2H, q, *J* = 6.8, CH_2); 7.74 (1H, s, H-3); 8.97 (1H, s, 7-CH); 13.27 (1H, s, NH); 15.39 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 15.6; 44.9; 115.3; 124.3; 126.5; 129.2; 131.2; 164.0; 165.6. Mass spectrum, *m*/*z* (I_{rel}, %): 208 $[M+H]^+$ (100). Found, %: C 52.32; H 4.23; N 20.46. $C_9H_9N_3O_3$. Calculated, %: C 52.17; H 4.38; N 20.28.

1-*tert*-Butyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]-pyridine-6-carboxylic acid (4c). Yield 0.73 g (62%, method I), 0.68 g (58%, method II), beige powder, mp 261–263°C. IR spectrum, ν, cm^{-1}: 3212 (N–H), 1725 (C=O carboxylic acid), 1660 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm: 1.69 (9H, s, $C(CH_3)_3$); 7.75 (1H, s, H-3); 8.87 (1H, s, 7-CH); 13.38 (1H, s, NH); 15.39 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 30.1; 62.2; 114.7; 123.4; 125.2; 130.9; 132.2; 163.3; 165.6. Mass spectrum, *m*/*z* (I_{rel}, %): 236 $[M+H]^+$ (100). Found, %: C 55.93; H 5.65; N 17.75. $C_{11}H_{13}N_3O_3$. Calculated, %: C 56.16; H 5.57; N 17.86.

5-Oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carboxylic acid (4d). Yield 0.74 g (59%, method I), 0.66 g (52%, method II), brown powder, mp 269–272°C. IR spectrum, ν, cm^{-1}: 3213 (N–H), 1729 (C=O carboxylic acid), 1658 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.52 (1H, t, *J* = 7.2, H-4 Ph); 7.65 (2H, t, *J* = 7.6, H-3,5 Ph); 7.76 (2H, d, *J* = 7.2, H-2,6 Ph); 8.07 (1H, s, H-3); 8.70 (1H, s, 7-CH); 13.53 (1H, s, NH); 15.20 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 116.5; 123.1; 125.8; 127.1; 128.5; 130.4; 130.8; 131.0; 138.6; 163.2; 165.3. Mass spectrum, *m*/*z* (I_{rel}, %): 256 $[M+H]^+$ (100). Found, %: C 60.98; H 3.58; N 16.33. $C_{13}H_9N_3O_3$. Calculated, %: C 61.18; H 3.55; N 16.46.

5-Oxo-1-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]-pyridine-6-carboxylic acid (4e). Yield 0.75 g (60%, method I), 0.61 g (48%, method II), brown powder, mp 284–287°C. IR spectrum, ν, cm^{-1}: 3217 (N–H), 1724 (C=O carboxylic acid), 1656 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.44 (1H, t, *J* = 7.4, H-5 Py); 7.89 (1H, d, *J* = 6.2, H-3 Py); 8.08 (1H, t, *J* = 5.4, H-4 Py); 8.14 (1H, s, H-3); 8.63 (1H, d, *J* = 5.4, H-6 Py); 9.63 (1H, s, 7-CH); 13.61 (1H, s, NH); 15.24 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 113.1; 117.0; 122.5; 125.4; 128.8; 131.9; 134.4; 140.1; 148.5; 152.5; 163.8; 165.3. Mass spectrum, *m*/*z* (I_{rel}, %): 257 $[M+H]^+$ (100). Found, %: C 56.16; H 3.22; N 21.75. $C_{12}H_8N_4O$. Calculated, %: C 56.25; H 3.15; N 21.87.

3-Methoxy-1-methyl-5-oxo-4,5-dihydro-1*H*-pyrazolo-[4,3-*b*]pyridine-6-carboxylic acid (4f). Yield 0.69 g (62%, method I), white powder, mp 264–265°C. IR spectrum, ν, cm^{-1}: 3211 (N–H), 1725 (C=O carboxylic acid), 1665 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm: 3.94 (3H, s, NCH_3); 3.97 (3H, s, OCH_3); 8.85 (1H, s, 7-CH); 13.42 (1H, s, NH); 15.50 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 36.6; 57.3; 114.2; 116.5; 128.6; 131.5; 148.1; 163.7; 165.6. Mass spectrum, *m*/*z* (I_{rel}, %): 224 $[M+H]^+$ (100). Found, %: C 48.24; H 4.01; N 18.78. $C_9H_9N_3O_4$. Calculated, %: C 48.43; H 4.06; N 18.83.

1-Methyl-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazolo-[4,3-*b*]pyridine-6-carboxylic acid (4g). Yield 0.73 g (54%, method I), brown powder, mp 290–293°C. IR spectrum, ν, cm^{-1}: 3216 (N–H), 1721 (C=O carboxylic acid), 1662 (C=O pyridone). ^{1}H NMR spectrum, δ, ppm: 4.16 (3H, s, NCH_3); 7.36–7.56 (3H, m, H-3,4,5 Ph); 7.75–7.95 (2H, m, H-2,6 Ph); 8.95 (1H, s, 7-CH); 13.28 (1H, s, NH); 15.25 (1H, s, CO_2H). ^{13}C NMR spectrum, δ, ppm: 38.8; 116.9; 128.1; 129.6; 130.8; 132.5; 133.0; 133.8; 136.6; 141.6; 166.2; 171.9. Mass spectrum, *m*/*z* (I_{rel}, %): 270 $[M+H]^+$ (100). Found, %: C 62.29; H 4.06; N 15.55. $C_{14}H_{11}N_3O_3$. Calculated, %: C 62.45; H 4.12; N 15.61.

Synthesis of pyrazolo[4,3-*b*]pyridine-6-carbonitriles 5a–g (General method). Method I. Compounds **5a**,**c**,**e**,**g** were obtained by method I of the synthesis of compounds **4a**–**g** from *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amines **1a**,**c**,**e**,**g** (5 mmol) and cyanoacetic acid (**2c**) (0.51 g, 6 mmol).

Method II. Methyl cyanoacetate (**2d**) (0.5 ml, 6 mmol) followed by pyrrolidine (0.5 ml, 6 mmol) was added to a solution of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amine **1a**–**g** (5 mmol) in AcOH (20 ml). The reaction mixture was stirred at room temperature for 2 h, then heated under reflux for 5–6 h. The solvent was evaporated under reduced pressure. H_2O (50 ml) was added to the residue, and the mixture was stirred. The formed precipitate was filtered off, washed with H_2O (10 ml) and MTBE (10 ml), air-dried, and recrystallized from MeOH.

Method III. Methyl cyanoacetate (**2d**) (0.5 ml, 6 mmol) followed by pyrrolidine (0.5 ml, 6 mmol) and proline (6 mg, 0.5 mmol) was added to a solution of *N*-Boc-protected 1-alkyl- or 1-aryl-5-formyl-1*H*-pyrazol-4-amine **1a**–**d** (5 mmol) in anhydrous MeCN (30 ml). The reaction mixture was stirred at room temperature for 2 h, then heated under reflux for 4–6 h. The solvent was evaporated under reduced pressure. H_2O (20 ml) was added to the residue, and the mixture was stirred. The formed precipitate was filtered off, washed with H_2O (10 ml) and MTBE (10 ml), air-dried, and recrystallized from MeOH.

1-Methyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carbonitrile (5a). Yield 0.64 g (74%, method I), 0.58 g (67%, method II), 0.48 g (56%, method III), yellow powder, mp 243–245°C. IR spectrum, ν, cm^{-1}: 3251 (N–H), 2226 (C≡N), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.98 (3H, s, NCH_3); 7.52 (1H, s, H-3); 8.81 (1H, s, 7-CH); 12.32 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 39.9; 103.4; 117.1; 123.7; 125.5; 130.1; 134.6; 159.2. Mass spectrum, *m*/*z* (I_{rel}, %): 175 $[M+H]^+$ (100). Found, %: C 55.36; H 3.57; N 32.32. $C_8H_6N_4O$. Calculated, %: C 55.17; H 3.47; N 32.17.

1-Ethyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carbonitrile (5b). Yield 0.65 g (69%, method II), 0.49 g (52%, method III), beige powder, mp 251–253°C. IR spectrum, ν, cm^{-1}: 3232 (N–H), 2220 (C≡N), 1694 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.38 (3H, t, *J* = 7.2, CH_3); 4.36 (2H, q, *J* = 6.8, CH_2); 7.54 (1H, s, H-3); 8.83 (1H, s, 7-CH); 12.25 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 15.0; 44.4; 103.0; 116.7; 123.5; 124.1; 129.7; 134.1; 158.8. Mass spectrum, *m*/*z* (I_{rel}, %): 189 $[M+H]^+$ (100). Found, %: C 57.28; H 4.31; N 29.66. $C_9H_8N_4O$. Calculated, %: C 57.44; H 4.29; N 29.77.

1-*tert*-Butyl-5-oxo-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]-pyridine-6-carbonitrile (5c). Yield 0.61 g (56%, method I), 0.73 g (67%, method II), 0.65 g (60%, method III), brown powder, mp 279–281°C. IR spectrum, ν, cm^{-1}: 3244 (N–H), 2228 (C≡N), 1674 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.64 (9H, s, $C(CH_3)_3$); 7.53 (1H, s, H-3); 8.97 (1H, s, 7-CH); 12.38 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 29.9; 61.6; 117.1; 122.8; 123.1; 131.7; 136.1; 158.7; 164.6. Mass spectrum, *m*/*z* (I_{rel}, %): 217 $[M+H]^+$ (100). Found, %: C 61.03; H 5.46; N 25.75. $C_{11}H_{12}N_4O$. Calculated, %: C 61.10; H 5.59; N 25.91.

5-Oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]pyridine-6-carbonitrile (5d). Yield 0.87 g (74%, method II), 0.85 g (72%, method III), beige powder, mp 259–261°C. IR spectrum, ν, cm^{-1}: 3205 (N–H), 2230 (C≡N), 1662 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.45 (1H, t, *J* = 7.2, H-4 Ph); 7.57 (2H, t, *J* = 7.6, H-3,5 Ph); 7.71 (2H, d, *J* = 7.2, H-2,6 Ph); 7.88 (1H, s, H-3); 8.78 (1H, s, 7-CH);

12.90 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 104.8; 116.9; 122.8; 124.0; 127.2; 128.3; 130.3; 132.4; 135.2; 138.8; 159.3. Mass spectrum, *m*/*z* (I_{rel}, %): 237 $[M+H]^+$ (100). Found, %: C 65.97; H 3.45; N 23.56. $C_{13}H_8N_4O$. Calculated, %: C 66.10; H 3.41; N 23.72.

5-Oxo-1-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazolo[4,3-*b*]-pyridine-6-carbonitrile (5e). Yield 0.57 g (48%, method I), 0.83 g (70%, method II), pale-yellow powder, mp 286–287°C. IR spectrum, ν, cm^{-1}: 3247 (N–H), 2229 (C≡N), 1676 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.41 (1H, t, *J* = 7.1, H-5 Py); 7.89 (1H, d, *J* = 6.0, H-3 Py); 8.04 (1H, s, H-3); 8.06 (1H, t, *J* = 5.2, H-4 Py); 8.56 (1H, d, *J* = 5.2, H-6 Py); 9.34 (1H, s, 7-CH); 13.50 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 105.0; 112.9; 116.7; 122.4; 123.4; 128.5; 132.7; 137.5; 140.1; 145.5; 152.2; 159.0. Mass spectrum, *m*/*z* (I_{rel}, %): 238 $[M+H]^+$ (100). Found, %: C 60.55; H 2.85; N 29.43. $C_{12}H_7N_5O$. Calculated, %: C 60.76; H 2.97; N 29.52.

3-Methoxy-1-methyl-5-oxo-4,5-dihydro-1*H*-pyrazolo-[4,3-*b*]pyridine-6-carbonitrile (5f). Yield 0.69 g (68%, method II), light-beige powder, mp 252–254°C. IR spectrum, ν, cm^{-1}: 3224 (N–H), 2224 (C≡N), 1658 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.82 (3H, s, NCH_3); 3.92 (3H, s, OCH_3); 8.73 (1H, s, 7-CH); 12.30 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 36.5; 57.2; 114.7; 117.1; 127.3; 134.4; 148.8; 152.6; 159.0. Mass spectrum, *m*/*z* (I_{rel}, %): 204 $[M+H]^+$ (100). Found, %: C 52.84; H 4.01; N 27.38. $C_9H_8N_4O_2$. Calculated, %: C 52.94; H 3.95; N 27.44.

1-Methyl-5-oxo-3-phenyl-4,5-dihydro-1*H*-pyrazolo-[4,3-*b*]pyridine-6-carbonitrile (5g). Yield 0.61 g (49%, method I), 0.76 g (61%, method II), white powder, mp 285–288°C. IR spectrum, ν, cm^{-1}: 3252 (N–H), 2230 (C≡N), 1671 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.07 (3H, s, NCH_3); 7.38 (1H, t, *J* = 7.2, H-4 Ph); 7.47 (2H, t, *J* = 8.0, H-3,5 Ph); 7.85–8.08 (2H, m, H-2,6 Ph); 8.85 (1H, s, 7-CH); 12.15 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 37.0; 116.9; 126.8; 127.1; 128.5; 129.2; 129.9; 131.3; 136.9; 155.1; 159.9; 167.7. Mass spectrum, *m*/*z* (I_{rel}, %): 251 $[M+H]^+$ (100). Found, %: C 67.41; H 4.09; N 22.30. $C_{14}H_{10}N_4O$. Calculated, %: C 67.19; H 4.03; N 22.39.

References

1. (a) Arora, N.; Billedeau, R. J.; Dewdney, N. J.; Gabriel, T.; Goldstein, D. M.; O'Yang, C.; Soth, M. US Patent 20050197340. (b) Arora, N.; Billedeau, R. J.; Dewdney, N. J.; Gabriel, T.; Goldstein, D. M.; O'Yang, C.; Soth, M.; Trejo-Martin, T. A. WO Patent 2007023105.
2. Duffy, B. C.; Liu, S.; Quinn, J. F.; Wang, R.; Jiang, M. X.; Martin, G. S.; Wagner, G. S.; Young, P. R. WO Patent 2015002754.
3. Blaquiere, N.; Burch, J.; Castanedo, G.; Feng, J. A.; Hu, B.; Staben, S.; Wu, G.; Yuen, P.-W. WO Patent 2015025025.
4. Betageri, R.; Cook, B. N.; Disalvo, D.; Harcken, C.; Kuzmich, D.; Liu, P.; Lord, J.; Mao, C.; Razavi, H. WO Patent 2012087782.
5. (a) Ibrahim, H. M.; Behbehani, H.; Makhseed, S.; Elnagdi, M. N. *Molecules* **2011**, *16*, 3723. (b) Nag, S.; Nayak, M.; Batra, S. *Adv. Synt. Catal.* **2009**, *351*, 2715.
6. (a) Turkman, N.; Shavrin, A.; Ivanov, R. A.; Rabinovich, B.; Volgin, A.; Gelovani, J. G.; Alauddin, M. M. *Bioorg. Med. Chem.* **2011**, *19*, 5698. (b) del Mar Blanco, M.; Avendaño, C.; Cabezas, N.; Menéndez, J. C. *Heterocycles* **1993**, *36*, 1387. (c) El-Sayed, O. A.; Aboul-Enein, H. Y. *Arch. Pharm.* **2001**, *334*, 117. (d) El-Sayed, O. A.; Al-Bassam, B. A.; Hussein, M. E. *Arch. Pharm.* **2002**, *335,* 403.
7. (a) Desos, P.; Lepagnol, J. M.; Morain, P.; Lestage, P.; Cordi, A. A. *J. Med. Chem.* **1996**, *39*, 197. (b) Shi, J.; Xiao, Z.; Ihnat, M. A.; Kamat, C.; Pandit, B.; Hu, Z.; Li, P.-K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1187. (c) Tedesco, R.; Shaw, A. N.; Bambal, R.; Chai, D.; Concha, N. O.; Darcy, M. G.; Dhanak, D.; Fitch, D. M.; Gates, A.; Gerhardt, W. G.; Halegoua, D. L.; Han, C.; Hoffmann, G. A.; Johnston, V. K.; Kaura, A. C.; Liu, N.; Keenan, R. M.; Lin-Goerke, J.; Sarisky, R. T.; Wiggall, K. J.; Zimmerman, M. N.; Duffy, K. J. *J. Med. Chem.* **2006**, *49*, 971. (d) Pathuri, G.; Li, Q.; Mohammed, A.; Gali, H.; Pento, J. T.; Rao, C. V. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1380.
8. Yakovenko, G. G.; Lukianov, O. A.; Bol'but, A. V.; Vovk, M. V. *Chem. Heterocycl. Compd.* **2019**, *55*, 379. [*Khim. Geterotsikl. Soedin.* **2019**, *55*, 379.]
9. Watson, B. T.; Christiansen, G. E. *Tetrahedron Lett.* **1998**, *39*, 9839.
10. Dagar, A.; Biswas, S.; Samanta, S. *RSC Adv.* **2015**, *5*, 52497.
11. El Kazzouli, S.; Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 8575.
12. Yamanaka, T.; Ohki, H.; Ohgaki, M.; Okuda, S.; Toda, A.; Kawabata, K.; Inoue, S.; Misumi, K.; Itoh, K.; Satoh, K. WO Patent 2004101571.