Regioisomeric 4-amino- and 6-aminopyrazolo[3,4-*b*]pyridines: synthesis and structure determination by NMR spectroscopy and X-ray diffraction

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The methods for selective synthesis of regioisomeric 4-amino- and 6-amino-1-aryl-3-R-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles were developed. Heating 4-amino-substituted pyrazolo[3,4-*b*]pyridines gave 6-amino-substituted isomers in quantitative yield. Spectral differences characteristic of both isomers were evaluated based on the ^{13}C NMR spectra.

Key words: aminopyrazoles, pyrazolo[3,4-*b*]pyridines, regioisomers, ethoxymethylidenemalononitrile.

5-Amino-1-phenylpyrazoles are the key compounds for the synthesis of novel substituted pyrazoles and pyrazolo[3,4-*b*]pyridines.[1—3] Combining pharmacophoric pyrazole and pyridine fragments in one molecule opens access to a series of nitrogen-containing polycyclic compounds with valuable biological properties. According to the published data, among pyrazolo[3,4-*b*]pyridine derivatives, compounds exhibiting antiproliferative,[4] antitumor,[5] antimicrobial and antibacterial,[6—8] antithrombotic[9] as well as antiviral[10] activity were found. Therefore, these compounds inhibit Pim kinases,[11] phosphoinositide 3-kinase,[12] and acetylcholinesterase.[13]

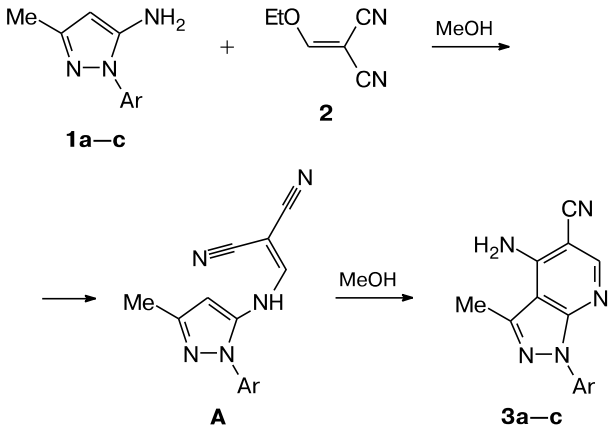
Annulation of a pyridine ring to a pyrazole rings (reaction of 1-substituted 5-aminopyrazoles with dielectrophiles)[3,14—17] and the Friedlander condensation[13,18—20] are commonly used for the synthesis of these compounds. Alternative approaches towards heterocycles containing pyrazolo[3,4-*b*]pyridine fragment are annulation of the pyrazole ring to the pyridine ring starting from 2-halogen-3-substituted pyridines (3-cyano-[21—23] and 3-acetyl-[24]) and the reaction of 2-*N*-nitroso-3-acetylpyridines[25] with hydrazines. Pyrazolo[3,4-*b*]pyridines were also obtained by regioselective procedures based on the indole[26] and benzopyrane[27] ring opening.

A wide range of biological activity of pyrazolo[3,4-*b*]-pyridines encourages the search for new compounds of these type and modification of the known synthetic methods. Cyclocondensation of 5-aminopyrazoles with 1,3-dielectrophiles can results in two regioisomeric pyrazolo[3,4-*b*]-pyridines, which differ in the position of the substituents at the C(4) and C(6). The structure of these compounds is often difficult to establish even only one regioisomer is formed. The number of publications devoted to both the synthetic procedure development and assignment of the regiostructure of the heterocycles bearing pyrazolo[3,4-*b*]pyridine moiety based on NMR spectroscopy are scares.

In continuation of our research on the reactions of N-substituted 5-aminopyrazoles with 1,3-dielectrophyles[28], in the present work with the aim of synthesizing functionalized pyrazolopyridines selectively, we studied the regioselectivity of the reactions of N-aryl-substituted 5-aminopyrazoles with ethoxymethylidenemalononitrile.

Heating a mixture of N-substituted 5-aminopyrazoles **1a—c** and ethoxymethylidenemalononitrile (**2**) in refluxing methanol for ~20 h (Scheme 1) resulted selectively in

Scheme 1



1, **3:** Ar = Ph (**a**), 3-ClC_6H_4 (**b**), 4-$EtO_2CC_6H_4$ (**c**)

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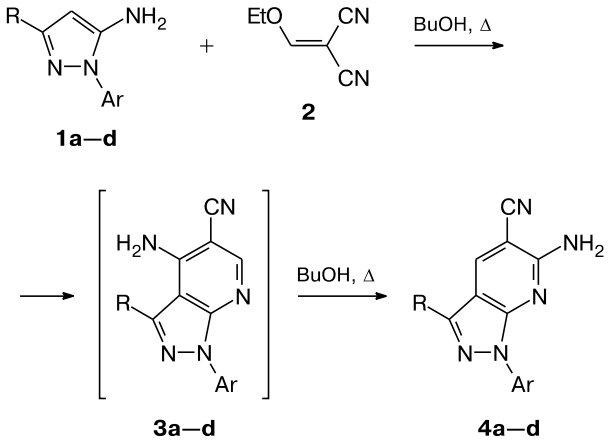
4-amino-1-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **3a**—**c** in the yields of 40—53%.[29—31]

The reaction involves initial formation of linear structures, 2-(1-aryl-3-methyl-1*H*-5-pyrazolylaminomethylidene)malononitriles of the type **A**, arising from the nucleophilic attack of the exocyclic nitrogen atom of the aminopyrazole on the carbon atom of the ethoxymethylidene group of compound **2**. The structures of these compounds were evaluated from the analysis of the ^{1}H NMR spectra of the reaction mixtures. The reaction of aminopyrazole **1a** carried out at 20 °C in MeOH for 3 days afforded intermediate compound **A** and product **3a** in 40 and 60%, respectively. In the ^{1}H NMR spectra, the low field signals characteristic of the linear structure **A** were observed, namely, the doublets of the NH group and the neighboring =CH moiety at δ 11.12 and 8.01, respectively, with spin-spin coupling constant of 9.5 Hz. 2-[1-(3-Chlorophenyl)-3-methyl-1*H*-5-pyrazolylaminomethylidene]malononitrile **A** was obtained by three-component reaction of 5-aminopyrazole **1b**, malononitrile, and triethyl orthoformate in refluxing methanol.[32]

At the same time, heating 5-aminopyrazoles **1a**—**d** with ethoxymethylidenemalononitrile (**2**) in refluxing butyl alcohol for ~20 h gave regioisomeric 6-amino-1-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **4a**—**d** in 57—65% yields (Scheme 2).

Scheme 2

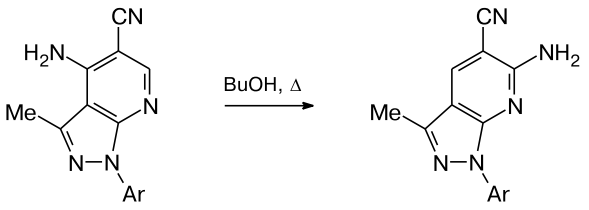


1, **3**, **4:** R = Me, Ar = Ph (**a**), 3-ClC_6H_4 (**b**), 4-$EtO_2CC_6H_4$ (**c**); R = 4-ClC_6H_4, Ar = Ph (**d**)

The similar compounds were previously obtained[13,20,33] only by the reactions of 5-amino-3-R-1-aryl-1*H*-pyrazolo-4-carbaldehydes with malononitrile. In the case of N-substituted 5-aminopyrazole **1e** (Ar = Ph, R = Bu^t), no formation of pyrazolo[3,4-*b*]pyridines **3** or **4** was detected neither refluxing the starting reactants in butyl alcohol nor at heating them in diphenyl ether at 230—235 °C. The linear structures **A** were not also found.

It was shown by special experiments that heating of compounds **3** in refluxing butyl alcohol lead to regioisomeric compounds **4** in nearly quantitative yields (Scheme 3). This reaction can also be performed in the inert solvent, diphenyl ether, at 230—235 °C.

Scheme 3



Thus, apparently, upon heating the starting reactants in refluxing butyl alcohol, initially formed pyrazolopyridines **3a**—**c** (the kinetic control products) isomerize into thermodynamically more stable compounds **4a**—**c** (see Scheme 3). This issue was confirmed by the data summarized in Table 1, which indicate selective formation of regioisomer **3** in the reaction mixture during first 30 min of the reaction, while the prolonged heating resulted in the accumulation of regioisomer **4**.

It is possible to assume that isomerization involved a reaction sequence of pyridine ring opening of compound **3** by cleavage of the C—C bond, prototropic isomerization, [1,3] shift of the —CH=C(CN)C=NH group, and the ring closure with new C—N bond formation (Scheme 4).

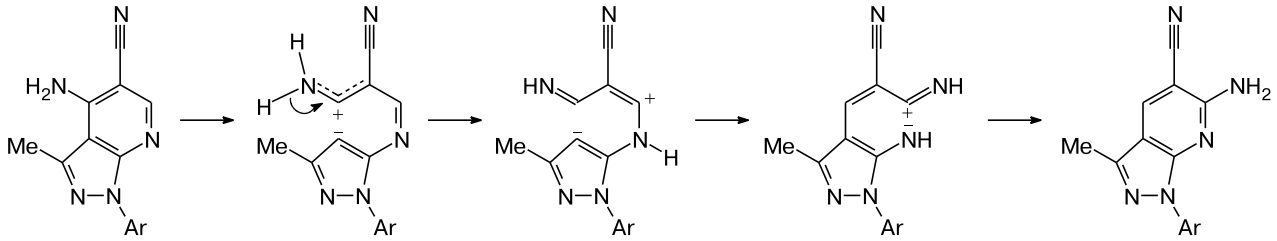
Ratios of the formed regioisomers were determined based on ^{1}H NMR spectra of the reaction mixtures. The methyne proton of the pyridine fragment and the protons of the methyl group of regioisomer **3** resonate in the stron-

Table 1. Ratio of regioisomers **3** and **4** formed at refluxing 5-aminopyrazoles **1** and ethoxymethylidenemalononitrile (**2**) in butyl alcohol depending on the reaction time (*t*)*

t/min	Ratio of regioisomers		
	3a : **4a**	**3b** : **4b**	**3c** : **4c**
30	91 : 9	94 : 6	93.5 : 6.5
100	76 : 24	50 : 50	77 : 23
160	67 : 33	31 : 69	54 : 46
250	31 : 69	11 : 89	36 : 64
330	12 : 88	6 : 94	18.5 : 81.5
400	10 : 90	3.5 : 96.5	10 : 90
550	5.5 : 94.5	1.5 : 98.5	3.5 : 96.5

* According to the ^{1}H NMR data of the samples of the reaction mixture taken upon the reaction.

Scheme 4



ger field as compared with those of isomer **4**; in contrary, the NH_2 group resonates in the lower field.

This transformation was also performed in three-component version by refluxing 5-aminopyrazole **1b**, malononitrile, and triethyl orthoformate in butyl alcohol. Compound **4b** was the only product of the reaction.

Compositions and structures of the compounds synthesized were evaluated using ^1H and ^{13}C NMR spectroscopy, mass spectrometry (ESI), and X-ray diffraction.

Relative orientation of the substituents in the pyridine ring of pyrazolo[3,4-*b*]pyridines **3** and **4** (H and NH_2) was established based on the nuclear Overhauser effect observed in the 2D NOESY spectrum. In NOESY spectrum of compound **4a** in $CDCl_3$, cross peaks of high intensity for the couplings of the protons of the methyl group at δ 2.56 with the CH(4) at δ 8.12 indicate their neighboring location, which can be realized only for regioisomer **4a** but not for alternative structure **3a**. These data allowed us to identify in the ^{13}C NMR spectra the signals of the carbon atoms C(5), C(3a), C(6), C(4), and CH_3 characteristic of regioisomeric pyrazolo[3,4-*b*]pyridines **3a—d** and **4a—d** (Table 2).

The structure of compound **4b** was confirmed by a single crystal X-ray diffraction. Geometry of the molecule of **4b** is shown on Fig. 1. The hydrogen atom is bonded to the C(4) and the amino group is located at the C(6). Heteroatomic bicyclic system N(1)N(2)C(3)C(3a)C(4)-C(5)C(6)N(7)C(7a) is nearly planar, the maximum deviation from the mean plane is 0.019 Å (the C(3) atom). All formally single bonds of the pyrazolopyridine system (C—C, C—N, and N—N) are significantly shortened as compared with the standard bond lengths (1.54, 1.47, 1.45 Å, respectively)[34] indicating substantial delocalization of the π- and n-electrons.

Table 2. ^{13}C Shifts of characteristic C-atoms of pyrazolo[3,4-*b*]pyridines **3a—c** and **4a—d**

Atom	δ		
C	**3a—c**	**4a—c**	**4d**
C(5)	65.9—67.0	87.1—87.4	88.9
C(3a)	101.1—101.2	109.2—109.5	106.6
C(4)	116.0—116.3	138.3—138.5	139.2
C(6)	149.3—149.4	158.9	158.6
CH_3	16.2—16.3	11.9—12.0	—

In the crystal, molecules form centrosymmetric cyclic dimers due to interactions of the amino group hydrogens with the nitrile group nitrogens (N—H...NC—). These supramolecular associates are further connected into a three-dimensional framework by weaker contacts C(12)—H...C≡N and C(12)—H...C(5) (the shortest distances C...C are 3.308(2) and 3.380(2) Å, respectively). Besides, the second amino group hydrogen is H-bonded to the solvate acetonitrile molecule presented in a crystalline lattice. The parameters of hydrogen bonds in the compound **4b** are given below (D is donor, A is acceptor).

D—H...A	*d*/Å			Angle DHA /deg
	D—H	H...A	D...A	
N(4)—H(2N)...N(3)	0.85(2)	2.25(2)	3.079(2)	165.8(19)
N(4)—H(2M)...N(8)	0.87(2)	2.25(2)	3.103(2)	166.8(18)

In summary, varying the reaction conditions, the experimental procedures towards regioisomeric 4-amino- and 6-amino-1-aryl-3-R-1*H*-pyrazolo[3,4-*b*]pyridin-5-carbonitriles were developed. It was shown that 6-amino-substituted pyrazolo[3,4-*b*]pyridines are thermodynamically more stable than 4-amino derivatives. The characteristic spectral differences between regioisomers were determined based on the ^{13}C NMR.

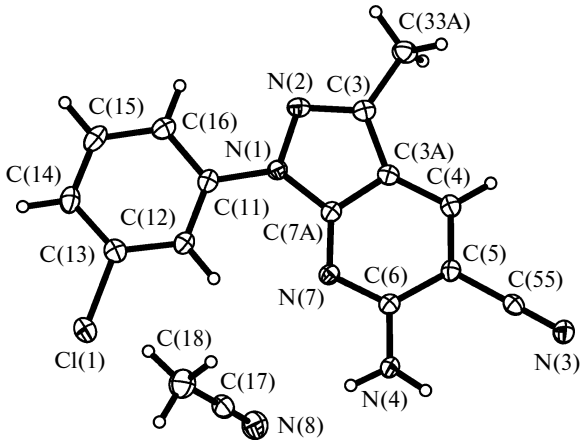


Fig. 1. Crystal structure of compound **4b**.

Experimental

^{1}H and ^{13}C NMR spectra were run on a Bruker DPX-300 instrument (300.13 and 75.47 MHz, respectively) at 22 °C in $CDCl_3$, DMSO-d_6 or DMSO-d_6—CCl_4 (1 : 2). Chemical shifts are given in the δ scale relative to the residual solvent signals (δ_H 7.28, δ_C 76.90 ($CDCl_3$); δ_H 2.50, δ_C 39.50 (DMSO-d_6)). Elemental composition was determined by high resolution mass spectrometry on a Bruker Daltonics microTOF instrument employing electrospray ionization (ESI) and operating in the positive ion mode. Malononitrile, ethoxymethylidenemalononitrile, ethyl orthoformate (Alfa Aesar), and the solvents (produced in Russia) were used. The starting aminopyrazoles, 3-methyl-1-phenyl-1*H*-5-pyrazolamine (**1a**) (m.p. 111—112 °C (EtOH)), 3-methyl-1-(3-chlorophenyl)-1*H*-5-pyrazolamine (**1b**) (m.p. 138—139 °C (EtOH)), ethyl 4-(5-amino-3-methyl-1*H*-1-pyrazolyl)benzoate (**1c**) (m.p. 157—158 °C (EtOH)), and 1-phenyl-3-(4-chlorophenyl)-1*H*-5-pyrazolamine (**1d**) (m.p. 186—187 °C (EtOH)), were synthesized according to the known procedures.[35,36]

2-[1-(3-Chlorophenyl)-3-methyl-1*H*-5-pyrazolylaminomethylidene]malononitrile (A). A mixture of 5-aminopyrazole **1b** (1 mmol), malononitrile (1 mmol), and triethyl orthoformate (0.5 mL) in MeOH (7 mL) was refluxed for 6 h. The solvent was removed *in vacuo*, the residue was recrystallized. Yield 48%, m.p. 207—208 °C (EtOH). High resolution MS, found: *m/z* 284.0705 $[M + H]^+$. $C_{14}H_{10}ClN_5$. Calculated: 284.0697 $[M + H]^+$. ^{1}H NMR (DMSO-d_6), δ: 2.21 (s, 3 H, Me); 6.39, 6.45 (both s, 1 H, =CH, pyrazole); 7.49—7.62 (m, 4 H, H arom.); 8.04, 8.13 (both br.s, 1 H, =CH); 10.89, 11.23 (both br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 13.77 (Me); 53.54 (C(2′)); 101.29 (C(4)); 113.48, 115.72 (2 CN); 121.97, 123.98, 127.13, 130.95 (4 C, arom.); 133.54 (C(3′) arom.); 139.38, 139.59 (C(1′) arom., C(5)); 148.99 (C(3)); 160.31 (C(1′)).

Reaction of 5-aminopyrazoles 1 with ethoxymethylidenemalononitrile (2) in MeOH (general procedure). A mixture of 5-amino-1-arylpyrazole **1** (1 mmol) and ethoxymethylidenemalononitrile (**2**) (1 mmol) in MeOH (3 mL) was refluxed for 20 h. The solvent was removed *in vacuo*, the residue was recrystallized from EtOH.

4-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (3a). Yield 0.10 g (40%), m.p. 172—173 °C (from EtOH) (*cf.* Ref. 31: m.p. 192—194 °C). High resolution MS, found: *m/z* 250.1038 $[M + H]^+$. $C_{14}H_{11}N_5$. Calculated: 250.1087 $[M + H]^+$. ^{1}H NMR (DMSO-d_6), δ: 2.35 (s, 3 H, CH_3); 7.17 (br.s, 2 H, NH_2); 7.44—7.54 (m, 5 H, CH arom.); 7.97 (s, 1 H, H(6)). ^{13}C NMR ($CDCl_3$), δ: 12.56 (CH_3); 68.24 (C(5)); 101.47 (C(3a)); 115.67 (C(4)); 117.06 (CN); 124.10 (C(2′), C(6′) arom.); 129.24 (C(4′) arom.); 130.03 (C(3′), C(5′) arom.); 135.88 (C(1′) arom.); 147.15 (C(3)); 150.87 (C(6)); 151.54 (C(7a)). ^{13}C NMR (DMSO-d_6), δ: 16.27 (CH_3); 65.88 (C(5)); 101.16 (C(3a)); 116.34 (C(4)); 117.32 (CN); 124.23 (C(2′), C(6′) arom.); 128.05 (C(4′) arom.); 129.59 (C(3′), C(5′) arom.); 136.91 (C(1′) arom.); 148.49 (C(3)); 149.37 (C(6)); 151.32 (C(7a)).

4-Amino-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (3b). Yield 0.11 g (40%), m.p. 202—203 °C (from EtOH). High resolution MS, found: *m/z* 284.0648 $[M + H]^+$. $C_{14}H_{10}ClN_5$. Calculated: 284.0697 $[M + H]^+$. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 2)), δ: 2.37 (s, 3 H, CH_3); 7.12 (br.s, 2 H, NH_2); 7.35—7.50 (m, 3 H, H arom.); 7.52 (s, 1 H, H(2′) arom.); 7.90 (s, 1 H, H(6)). ^{13}C NMR (without proton decoupling, DMSO-d_6), δ: 16.16 (q, CH_3, J = 128.7 Hz); 66.55 (t, C(5), J = 1.8 Hz); 101.08 (d, C(3a), J = 1.8 Hz); 116.16 (d, C(4), ^3J = 13.2 Hz); 117.18 (d, CN, J = 8.0 Hz); 122.90 (ddd, C(6′) arom., J = 166.2 Hz, ^3J = 6.5 Hz, ^2J = 1.5 Hz); 124.10 (dt, C(2′) arom., J = 168.8 Hz, ^2J = 5.0 Hz); 127.93 (ddd, C(4′) arom., J = 167.8 Hz, ^3J = 6.0 Hz, ^2J = 1.5 Hz); 131.17 (d, C(5′) arom., J = 166.3 Hz); 133.70 (m, C(3′) arom.); 138.15 (dd, C(1′) arom., ^3J = 9.3 Hz, ^2J = 2.9 Hz); 148.92 (m, C(3)); 149.38 (d, C(6), J = 156.1 Hz); 151.47 (d, C(7a), ^3J = 5.2 Hz).

Ethyl 4-(4-amino-5-cyano-3-methyl-1*H*-pyrazolo[3,4-*b*]-pyridin-1-yl)benzoate (3c). Yield 53%, m.p. 213—214 °C. High resolution MS, found: *m/z* 322.1311 $[M + H]^+$. $C_{17}H_{15}N_5O_2$. Calculated: 322.1298 $[M + H]^+$. ^{1}H NMR (DMSO-d_6—CCl_4), δ: 1.41 (t, 3 H, Me, J = 6.9 Hz); 2.39 (s, 3 H, Me); 4.36 (q, 2 H, CH_2, J = 6.9 Hz); 7.16 (s, 2 H, NH_2); 7.64 (d, 2 H, H arom., J = 8.0 Hz); 7.93 (s, 1 H, H(6)); 8.07 (d, 2 H, H arom., J = 8.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 14.09 (Me); 16.04 (Me); 60.93 (CH_2); 67.00 (C(5)); 101.23 (C(3a)); 115.99 (C(4)); 117.01 (CN); 123.44 (C(2′)); 128.52 (C(4′)); 130.39 (C(3′)); 140.69 (C(1′)); 149.24, 149.33 (C<u>Me</u>, =CH); 151.29 (C(7a)); 164.94 (C=O).

Reaction of 5-aminopyrazoles 1 with ethoxymethylidenemalononitrile (2) in BuOH. A mixture of 5-amino-1-arylpyrazole **1** (1 mmol) and ethoxymethylidenemalononitrile (**2**) (1 mmol) in BuOH (3 mL) was refluxed for 20 h. The solvent was removed *in vacuo*, the residue was recrystallized from EtOH.

6-Amino-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (4a). Yield 65%, m.p. 193—194 °C (*cf.* Ref. 33: m.p. 226 °C; *cf.* Ref. 13: m.p. 223—225 °C). High resolution MS, found: *m/z* 250.1073 $[M + H]^+$. $C_{14}H_{11}N_5$. Calculated: 250.1087 $[M + H]^+$. ^{1}H NMR ($CDCl_3$), δ: 2.56 (s, 3 H, CH_3); 5.38 (br.s, 2 H, NH_2); 7.31 (t, 1 H, H(4′) arom., J = 8.0 Hz); 7.50 (t, 2 H, H(3′) arom., J = 8.0 Hz); 8.12 (s, 1 H, H(4)); 8.13 (d, 2 H, H(2′) arom., J = 8.0 Hz). ^{1}H NMR (DMSO-d_6), δ: 2.43 (s, 3 H, CH_3); 7.22 (br.s, 2 H, NH_2); 7.25 (t, 1 H, H(4′) arom., J = 8.0 Hz); 7.47 (t, 2 H, H(3′) arom., J = 8.0 Hz); 8.17 (d, 2 H, H(2′) arom., J = 8.0 Hz); 8.49 (s, 1 H, H(4)). ^{13}C NMR (without proton decoupling, DMSO-d_6), δ: 12.01 (q, CH_3, J = 128.7 Hz); 87.10 (t, C(5), J = 4.5 Hz); 109.21 (d, C(3a), J = 3.0 Hz); 117.36 (d, CN, J = 5.0 Hz); 119.95 (dt, C(2′) arom., J = 161.5 Hz, ^3J = 8.0 Hz); 125.28 (dt, C(4′) arom., J = 163.5 Hz, ^3J = 8.0 Hz); 128.93 (dt, C(3′) arom., J = 161.5 Hz, ^3J = 8.5 Hz); 138.44 (d, C(4), J = 169.5 Hz); 139.00 (t, C(1) arom., ^3J = 8.5 Hz); 144.18 (qd, C(3), ^2J = 7.0 Hz, ^3J = 2.0 Hz); 151.18 (d, C(7a), ^3J = 8.0 Hz); 158.87 (d, C(6), ^3J = 6.0 Hz).

6-Amino-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (4b). Yield 0.16 g (57%), m.p. 190—191 °C (from EtOH). High resolution MS, found: *m/z* 284.0688 $[M + H]^+$. $C_{14}H_{10}ClN_5$. Calculated: 284.0697 $[M + H]^+$. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 2)), δ: 2.47 (s, 3 H, CH_3); 7.01 (br.s, 2 H, NH_2); 7.18 (d, 1 H, H(4′) arom., J = 8.0 Hz); 7.44 (t, 1 H, H(5′) arom., J = 8.0 Hz); 8.27 (d, 1 H, H(6′) arom., J = 8.0 Hz); 8.30 (s, 1 H, H(2′) arom.); 8.36 (s, 1 H, H(4)). ^{13}C NMR (without proton decoupling, DMSO-d_6), δ: 11.98 (q, CH_3, J = 128.6 Hz); 87.35 (t, C(5), ^2J = 4.5 Hz); 109.32 (d, C(3a), ^2J = 3.0 Hz); 117.19 (d, CN, ^3J = 6.0 Hz); 117.73 (dt, C(6′) arom., J = 167.0 Hz, ^3J = 5.5 Hz); 118.83 (dm, C(2′) arom., J = 169.5 Hz, ^3J = 5.0 Hz); 124.72 (ddd, C(4′) arom., J = 169.0 Hz); 130.55 (d, C(5′) arom., J = 164.6 Hz); 133.38 (m, C(3′) arom.); 138.49

(d, C(4), J = 169.5 Hz); 140.15 (br.d, C(1′) arom., ^3J = 10.5 Hz); 144.84 (dq, C(3), ^2J = 7.0 Hz, ^3J = 2.5 Hz); 151.39 (d, C(7a), ^3J = 7.5 Hz); 158.95 (d, C(6), ^3J = 6.5 Hz).

Ethyl 4-(6-amino-5-cyano-3-methyl-1*H*-pyrazolo[3,4-*b*]-pyridin-1-yl)benzoate (4c). Yield 62%, m.p. 216—217 °C (from EtOH). High resolution MS, found: m/z 322.1272 $[M + H]^+$. $C_{17}H_{15}N_5O_2$. Calculated: M = 322.1299 $[M + H]^+$. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 2)), δ: 1.41 (t, 3 H, Me, J = 7.0 Hz); 2.48 (s, 3 H, Me); 4.34 (q, 2 H, CH_2, J = 7.0 Hz); 7.05 (s, 2 H, NH_2); 8.03 (d, 2 H, H arom., J = 8.7 Hz); 8.39 (s, 1 H, H(4)); 8.44 (d, 2 H, H arom., J = 8.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 11.92 (Me); 14.11 (Me); 60.56 (CH_2); 87.39 (C(5)); 109.50 (C(3a)); 117.06 (CN); 118.55 (C(2′) arom.); 125.68 (C(4′) arom.); 129.93 (C(3′) arom.); 138.34 (C(4)); 142.56 (C(1′) arom.); 145.25 (C(3)); 151.62 (C(7a)); 158.90 (C(6)); 165.12 (C=O).

6-Amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carbonitrile (4d). Yield 80%, m.p. 257—258 °C (from BuOH). High resolution MS, found: m/z 346.0776 $[M + H]^+$. $C_{19}H_{12}ClN_5$. Calculated: 346.0854 $[M + H]^+$. ^{1}H NMR (DMSO-d_6—CCl_4 (1 : 2)), δ: 7.05 (br.s, 2 H, NH_2); 7.28 (t, 1 H, H(4′) arom., J = 7.3 Hz); 7.48 (d, 2 H, H arom., J = 8.7 Hz); 7.50 (t, 2 H, H(3′) arom., J = 7.3 Hz); 8.04 (d, 2 H, H arom., J = 8.7 Hz); 8.29 (d, 2 H, H(2′) arom., J = 7.3 Hz); 8.75 (s, 1 H, H(4)). ^{13}C NMR (without proton decoupling, DMSO-d_6), δ: 88.88 (t, C(5), ^2J = 4.2 Hz); 106.57 (s, C(3a)); 117.09 (d, CN, ^3J = 6.0 Hz); 120.83 (dm, =CH arom., J = 162.6 Hz); 126.02 (dt, =CH arom., J = 162.6 Hz, ^3J = 8.0 Hz); 128.60 (dt, CH arom., J = 163.5 Hz, ^3J = 7.0 Hz); 128.92 (dd, CH arom., J = 161.5 Hz, ^3J = 7.5 Hz); 129.97 (dd, CH arom., J = 167.5 Hz, ^3J = 5.0 Hz); 130.27 (t, C(1′), J = 8.0 Hz); 133.70 (tt, C(4′) arom., ^3J = 11.0 Hz, ^2J = 3.0 Hz); 138.68 (td, C(1′), ^3J = 9.5 Hz, ^2J = 2.5 Hz); 139.18 (d, C(4), J = 169.6 Hz); 143.33 (m, C(3)); 151.18 (d, C(7a), ^3J = 8.0 Hz); 158.61 (d, C(6), ^3J = 6.5 Hz).

Table 3. Principal crystallographic data and parameters of the X-ray diffraction experiment for compound **4b**

Parameter	Value
Molecular formula	$C_{16}H_{13}ClN_6$
Molecular weight	324.77
T/K	100(2)
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	9.9578(3)
b/Å	7.4681(2)
c/Å	20.3407(6)
α/deg	90
β/deg	90.237(2)
γ/deg	90
V/Å^3	1512.64(8)
Z	4
d_{calc}/mg m^{-3}	1.426
μ/mm^{-1}	0.261
Crystal size/mm	0.22×0.09×0.08
Scanning range/deg	2.00—26.00
Number of measured reflections	9012
Number of independent reflections	2973 (R_{int} = 0.0244)
$R_1(I > 2\sigma)$	0.0335
$wR_2(I > 2\sigma)$	0.0819

Table 4. The principal bond distances (d) and bond angles (ω) in compound **4b**

Bond	d/Å	Angle	ω/deg
N(1)—C(7a)	1.3753(19)	C(7a)—N(1)—N(2)	110.50(12)
N(1)—N(2)	1.3961(18)	N(7)—C(7a)—N(1)	126.52(14)
N(2)—C(3)	1.310(2)	N(2)—N(1)—C(11)	118.87(12)
N(7)—C(7a)	1.332(2)	C(3)—N(2)—N(1)	106.62(12)
N(7)—C(6)	1.341(2)	C(7a)—N(7)—C(6)	114.78(13)
C(3)—C(3a)	1.423(2)	N(2)—C(3)—C(3a)	111.08(14)
C(3a)—C(4)	1.391(2)	C(4)—C(3a)—C(7a)	117.67(14)
C(4)—C(5)	1.382(2)	C(4)—C(3a)—C(3)	136.64(15)
C(5)—C(6)	1.434(2)	C(7a)—C(3a)—C(3)	105.66(14)
C(3a)—C(7a)	1.404(2)	C(5)—C(4)—C(3a)	116.93(14)
N(4)—C(6)	1.345(2)	C(4)—C(5)—C(6)	120.80(14)
N(1)—C(11)	1.413(2)	N(7)—C(6)—C(5)	122.48(14)

Three-component reaction of aminopyrazole 1b, malononitrile, and ethyl orthoformate. A mixture of aminopyrazole **1b** (1 mmol), malononitrile (1 mmol), and ethyl orthoformate (0.5 mL) in butyl alcohol was refluxed for 18 h. The solvent was removed *in vacuo*, the residue was recrystallized from BuOH. 6-Amino-1-(3-chlorophenyl)-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**4b**) was obtained in the yield of 50%.

Isomerization of regioisomers 3 into regioisomers 4. General procedure *A*. A mixture of compounds **3a—c** (1 mmol) and diphenyl ether (1.5 g) was heated at 230—235 °C for 0.5 h. The reaction mixture was diluted with hexane (6 mL), the precipitate formed was filtered off. Compounds **4a—c** were obtained in the yields of 100% (according to the ^{1}H NMR spectral data).

General procedure *B*. A mixture of compounds **3a—c** (1 mmol) in BuOH (3 mL) was refluxed for 10 h. The reaction mixture was cooled to ambient temperature, the solvent was removed *in vacuo*. Compounds **4a—c** were obtained in the yields of 100% (according to the ^{1}H NMR spectral data).

X-ray diffraction analysis. Single crystal of compound **4b** was obtained by slow concentration of a solution in MeCN at 20 °C. For the X-ray diffraction, the crystal was immersed in cryo-oil and mounted on a Nylon loop. The X-ray diffraction data were collected on a Bruker AXS Smart ApexII diffractometer at 100(2) K (monochromator, Mo-Kα radiation (λ = 0.71073 Å)). The cell parameters were refined by APEX2 program.[37] The structure was solved by the direct method using SHELXS-97 software[38] and WinGX graphical interface.[39] Absorption correction were applied using SADABS v.2.10 program[40]. The hydrogen atoms of the amine group were located in difference Fourier maps and refined isotropically. The positions of the remained hydrogen atoms were calculated and refined using the riding model. The crystal of compound **4b** contains the acetonitrile solvation molecule. The crystal structure parameters and experimental details are given in Table 3, selected bond lengths and angles are listed in Table 4. The atomic coordinates and displacement parameters for compound **4b** were deposited with the Cambridge Crystallographyc Data Center (http://ccdc.cam.ac.uk; CCDC 817502).

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References

1. J. Elguero, *Comprehensive Heterocyclic Chemistry*, Eds A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Pergamon, New York, 1996.
2. J. Elguero, P. Goya, N. Jagerovic, A. M. S. Silva, *Targets Heterocycl. Syst.*, 2002, **6**, 52.
3. V. A. Chebanov, K. A. Gura, S. M. Desenko, *Top. Heterocycl. Chem.*, 2010, **23**, 41.
4. J. Shi, G. Xu, W. Zhu, H. Ye, S. Yang, Y. Luo, J. Han, J. Yang, R. Li, Y. Wei, L. Chen, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 4273.
5. N. R. Mohamed, N. Y. Khaireldin, A. F. Fahmy, A. A. El-Sayed, *Pharma Chemica*, 2010, **2**, 400.
6. M. S. M. Carla, M. R. S. A. Carlos, R. R. Carlos, J. B. Eliezer, *J. Mol. Struct. (Theochem.)*, 2002, **579**, 31.
7. B. Leal, I. F. Afonso, C. R. Rodrigues, P. A. Abreu, R. Garrett, L. C. S. Pinheiro, A. R. Azevedo, J. C. Borges, P. F. Vegi, C. C. C. Santos, F. C. A. da Silveira, L. M. Cabral, I. C. P. P. Frugulhetti, A. M. R. Bernardino, D. O. Santos, H. C. Castro, *Bioorg. Med. Chem.*, 2008, **16**, 8196.
8. F. A. Goda, A. A.-M. Abdel-Aziz, O. A. Attef, *Bioorg. Med. Chem.*, 2004, **12**, 1845.
9. R. B. Geraldo, M. L. Bello, L. R. S. Dias, M. A. F. Vera, T. Nagashima, P. A. Abreu, M. B. Santos, M. G. Albuquerque, L. M. Cabral, A. C. C. Freitas, M. V. Kalil, C. R. Rodrigues, H. C. Castro, *J. Atheroscler. Thromb.*, 2010, **17**, 730.
10. D.-S. Su, J. J. Lim, E. Tinney, B.-L. Wan, M. B. Young, K. D. Anderson, D. Rudd, V. Munshi, C. Bahnck, P. J. Felock, M. Lu, M.-T. Lai, S. Touch, G. Moyer, D. J. DiStefano, J. A. Flynn, Y. Yuexia Liang, R. Sanchez, R. Perlow-Poehnelt, M. M. Miller, J. P. Vacca, T. M. Williams, N. J. Anthony, *J. Med. Chem.*, 2009, **52**, 7163.
11. G. A. Nishiguchi, G. Atallah, C. Bellamacina, M. T. Burger, Y. Ding, P. H. Feucht, P. D. Garcia, W. Han, L. Klivansky, M. Lindvall, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6366.
12. S. T. Staben, T. P. Heffron, D. P. Sutherlin, S. R. Bhat, G. M. Castanedo, I. S. Chuckowree, J. Dotson, A. J. Folkes, L. S. Friedman, L. L. Lee, J. Lesnick, C. Lewis, J. M. Murray, J. Nonomiya, A. G. Olivero, E. Plise, J. Pang, W. W. Wei Prior, L. L. Salphati, L. L. Rouge, D. D. Sampath, V. V. Tsui, N. C. N. C. Wan, S. S. Wang, C. C. Weismann, P. Wu, B.-Y. Zhu, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6048.
13. E. J. Barreiro, C. A. Camara, H. Verli, L. Brazil-Más, N. G. Castro, W. M. Cintra, Y. Aracava, C. R. Rodrigues, C. A. M. Fraga, *J. Med. Chem.*, 2003, **46**, 1144.
14. F. Shi, Q. Wang, S. Tu, J. Zhou, B. Jiang, C. Li, D. Zhou, Q. Shao, L. Cao, *J. Heterocycl. Chem.*, 2008, **45**, 1103.
15. C.-L. Shi, D.-Q. Shi, S. H. Kim, Z.-B. Huang, S.-J. Ji, M. Ji, *Tetrahedron*, 2008, **64**, 2425.
16. A. Shaabani, M. Seyyedhamzeh, A. Maleki, M. Behnam, F. Rezazadeh, *Tetrahedron Lett.*, 2009, **50**, 17.
17. J. Quiroga, J. Portilla, H. Serrano, R. Abonia, B. Insuasty, M. Nogueras, J. Cobo, *Tetrahedron Lett.*, 2007, **48**, 1987.
18. Z. Airong, Z. Wei, P. Jinhui, *Synth. Commun.*, 2006, **36**, 1549.
19. M. N. Jachak, A. B. Avhale, V. J. Medhane, R. B. Toche, *J. Heterocycl. Chem.*, 2006, **43**, 1169.
20. R. B. Toche, D. C. Bhavsar, M. A. Kazi, S. M. Bagul, M. N. Jachak, *J. Heterocycl. Chem.*, 2010, **47**, 287.
21. N. A. Hamdy, A. M. Gamal-Eldeen, *Eur. J. Med. Chem.*, 2009, **44**, 4547.
22. G. Lavecchia, S. Berteina-Raboin, G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 6633; G. Lavecchia, S. Berteina-Raboin, G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 2389.
23. S. G. Cottis, P. B. Clarke, H. Tieckelmann, *J. Heterocycl. Chem.*, 1965, **2**, 192.
24. L. Revesz, E. Blum, F. E. Di Padova, T. Buhl, R. Feifel, H. Gram, P. Hiestand, U. Manning, U. Neumann, G. Rucklin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 262; G. L. Beutner, J. K. Kuethe, M. M. Kim, N. Yasuda, *J. Org. Chem.*, 2009, **74**, 789.
25. G. P. Sagitullina, L. A. Lisitskaya, M. A. Vorontsova, S. Reva, R. S. Sagitullin, *Mendeleev Commun.*, 2007, **17**, 192.
26. S. Lee, S. B. Park, *Org. Lett.*, 2009, **11**, 5214.
27. H. Stankovičová, A. Gáplovský, M. Lácová, J. Chovancová, A. Puchała, *J. Heterocycl. Chem.*, 2006, **43**, 843.
28. E. E. Emelina, A. A. Petrov, S. I. Selivanov, D. V. Filyukov, *Zh. Org. Khim.*, 2008, **44**, 259 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2008, **44**, 251].
29. A. M. Hussein, T. I. El-Emary, *J. Chem. Res. S*, 1998, 20.
30. B. M. Lynch, M. A. Khan, N. C. Teo, F. Pedrotti, *Can. J. Chem.*, 1988, **66**, 420.
31. S. M. Al-Mousawi, K. Kaul, M. A. Mohammad, M. H. Elnagdi, *J. Chem. Res. M*, 1997, 2026.
32. T. I. El-Emary, *J. Chin. Chem. Soc. (Taipei)*, 2007, **46**, 585.
33. V. K. Ahluwalia, B. Goyal, *Synth. Commun.*, 1996, **26**, 1341.
34. A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.
35. I. I. Granberg, N. F. Krokhina, *Khim.-Farm. Zh.*, 1968, 16 [*Pharm. Chem. J. (Engl. Transl.)*, 1968, 12].
36. N. L. Nam, I. I. Granberg, V. I. Sorokin, *Khim. Geterotsikl. Soedin.*, 2000, 342 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2000, **36**, 281]; C. Alberti, C. Tironi, *Farmaco*, 1964, **19**, 618; J. Portilla, E. G. Mata, M. Nogueras, J. Cobo, J. N. Low, C. Glidewell, *Acta Crystallogr., Sect. C*, 2007, **63**, O21.
37. *Bruker AXS, APEX2 — Software Suite for Crystallographic Programs*, Bruker AXS, Madison (USA), 2009.
38. G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.
39. L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
40. G. M. Sheldrick, *SADABS — Bruker AXS Scaling and Absorption Correction*, Bruker AXS, Madison (USA), 2008.

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