

## $\alpha$ -Aminoazoles in Synthesis of Heterocycles: III.\* 4-Trifluoromethylpyrazolo[3,4-*b*]pyridines: Synthesis and Structure

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**Abstract**—Cyclocondensation of N-substituted 5-aminopyrazoles with fluorinated 1,3-diketones yielded 4-trifluoromethyl-substituted pyrazolo[3,4-*b*]pyridines as the only reaction products. The regiostructure of compounds obtained was proved by  $^1\text{H}$  and  $^{13}\text{C}$  NMR homo- and heteronuclear correlation spectroscopy. Characteristic chemical shifts in the  $^{13}\text{C}$  NMR spectra of regioisomeric pyrazolo[3,4-*b*]pyridines were established.

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Cyclocondensations of aminopyrazoles with 1,3-dielectrophiles are extensively used for preparation of bicyclic nitrogen heterocycles that are biologically active substances possessing antioxidant, enzymatic, fungicidal, antibacterial, antiphlogistic, and sedative-hypnotic actions [2–7], some among them have found application in pharmacology [8]. The problem of regiodirection of the reaction is still urgent for the molecules of 3(5)-aminopyrazoles and 1,3-dielectrophiles contain nonequivalent reaction sites.

It is known that in the reaction of N'-substituted 5-aminopyrazoles with 1,3-dielectrophiles formed substituted pyrazolo[3,4-*b*]pyridines; as bifunctional reagents 1,3-ketoesters [9, 10], symmetric 1,3-diketones, among them hexafluoroacetylacetone [10–12] were employed. However the application of unsymmetrical 1,3-diketones to the synthesis of pyrazolopyridines is poorly documented evidently because two regioisomeric products may form in the reaction. In this connection a special interest can be attracted by pyrazolopyridines containing a trifluoromethyl group capable of modifying the chemical reactivity and biological action of the heterocycle [13].

The unambiguous establishment of the regiostructure of polycyclic nitrogen heterocycles is a complex problem and as we already have stated before [1] the interpretation of experimental findings may lead to an erroneous conclusion [14, 15].

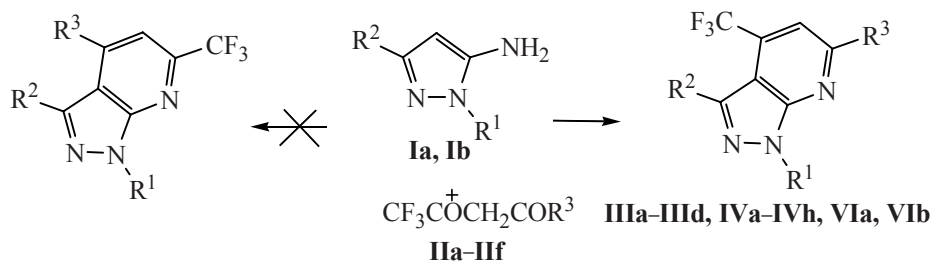
\* For communication, II see [1].

The target of this study was the investigation of the direction of reaction between N-substituted aminopyrazoles and trifluoromethyl-containing 1,3-diketones and establishing characteristic spectral distinctions of individual regioisomers.

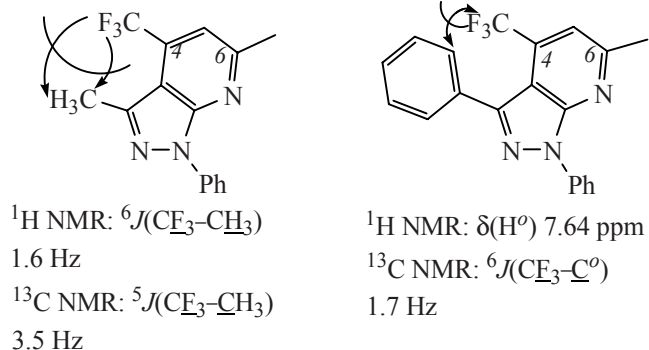
We studied the reactions of N'-substituted 5-aminopyrazoles **Ia–II** with trifluoromethyl-containing 1,3-diketones **IIa–IIc**. It was established that the reactions proceeded regiospecifically giving 4-trifluoromethyl-containing pyrazolo[3,4-*b*]pyridines notwithstanding the character of substituents at the atoms N' ( $\text{CH}_2\text{Ph}$ , Ph) and C<sup>3</sup> of aminopyrazole ( $\text{R}^2 = \text{Me}$ , Ar), and the substituent in diketone ( $\text{R}^3 = \text{Me}$ , *t*-Bu, Ar, Ht). Reaction was performed by melting or boiling in acetic acid and resulted in over 90% yield.

The structure of pyrazolo[3,4-*b*]pyridines obtained **III–VI** was proved by means of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy. The position of the trifluoromethyl group at the C<sup>4</sup> atom was unambiguously established from the observed long-range coupling constants between the fluorine atoms of the trifluoromethyl group and the protons and carbon atoms of the substituent R<sup>2</sup> ( $\text{CH}_3$ , C <sup>$\alpha$</sup> H) in the position 3 of pyrazolopyridines **IIIa–IIIc**.

In the  $^1\text{H}$  NMR spectra of reaction products obtained from 3-methylaminopyrazoles **Ia–Ie** and trifluoromethyl-containing 1,3-diketones **IIa–IIc** appeared a quartet signal of the protons of methyl group with a coupling constant  $^6J(\text{CF}_3\text{—CH}_3)$  1.6 Hz, and in the



**I**, R<sup>1</sup> = Ph, R<sup>2</sup> = Me (**a**), 4-XC<sub>6</sub>H<sub>4</sub>, X = MeO (**b**), Me (**c**), H (**d**), Cl (**e**); R<sup>1</sup> = Bn, R<sup>2</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub> (**f**), Ph (**g**); **II**, R<sup>3</sup> = Me (**a**), *t*-Bu (**b**), C<sub>4</sub>H<sub>3</sub>S (**c**), 4-YC<sub>6</sub>H<sub>4</sub>, Y = *i*-PrO (**d**), H (**e**), Br (**f**); **III**, R<sup>1</sup> = Ph, R<sup>3</sup> = Me, R<sup>2</sup> = Me (**a**), 4-XC<sub>6</sub>H<sub>4</sub>, X = Me (**b**), H (**c**), Cl (**d**); **IV**, R<sup>1</sup> = R<sup>3</sup> = Ph, R<sup>2</sup> = Me (**a**), 4-XC<sub>6</sub>H<sub>4</sub>, X = MeO (**b**), Me (**c**), H (**d**), Cl (**e**); R<sup>1</sup> = R<sup>2</sup> = Ph, R<sup>3</sup> = 4-*i*-PrOC<sub>6</sub>H<sub>4</sub> (**f**); R<sup>1</sup> = Bn, R<sup>2</sup> = R<sup>3</sup> = Ph (**g**); R<sup>2</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>3</sup> = 4-BrC<sub>6</sub>H<sub>4</sub> (**h**); **V**, R<sup>1</sup> = Bn, R<sup>2</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>3</sup> = *t*-Bu; **VI**, R<sup>1</sup> = Ph, R<sup>3</sup> = C<sub>4</sub>H<sub>3</sub>S, R<sup>2</sup> = Me (**a**), Ph (**b**).



<sup>13</sup>C NMR spectra the carbon atom of the methyl gave rise to a quartet with a coupling constant <sup>5</sup>J(CF<sub>3</sub>-CH<sub>3</sub>) 3.5 Hz due to the through-space interaction of closely located CF<sub>3</sub> and CH<sub>3</sub> groups. In the <sup>13</sup>C NMR spectra of 3-phenylpyrazolo[3,4-*b*]pyridines a quartet signal was observed from the *ortho*-carbon atom of the phenyl group [<sup>6</sup>J(CF<sub>3</sub>-C<sup>o</sup>) 1.7 Hz] also indicating that the trifluoromethyl group was attached to C<sup>4</sup> atom of the pyridine ring.

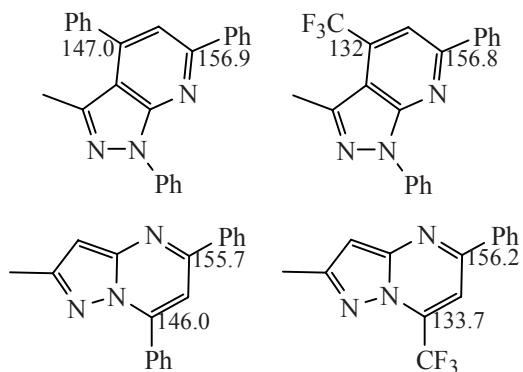
The chemical shift of the carbon atom C<sup>4</sup>CF<sub>3</sub> (fragment -C=C-CF<sub>3</sub>) is characteristic for the whole series of the trifluoromethyl-containing pyrazolo[3,4-*b*]pyridines and equals 132–133 ppm. At the same time the chemical shift of the carbon atom C<sup>6</sup>CF<sub>3</sub> [fragment -C(CF<sub>3</sub>)=N] revealed in the analysis of the <sup>13</sup>C NMR spectrum of methyl-4,6-bis(trifluoromethyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**VII**) appears significantly downfield (~147 ppm). It turned out that the chemical shifts of carbons in the fragments -C(CF<sub>3</sub>)=N- and -C=C-CF<sub>3</sub> are virtually identical for pyrazolo[3,4-*b*]pyridines, pyrazolo[1,5-*a*]pyrimidines [15], and triazolo[1,5-*a*]pyrimidines [16] and consequently they are sufficiently characteristic and can be used for elucidating the position of the CF<sub>3</sub> group in the heterocyclic compounds containing the mentioned fragments.

The <sup>13</sup>C NMR spectrum of 3,6-dimethyl-4-trifluoromethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**IIIa**) was

registered without decoupling from protons, and it permitted the assignment of signals from all carbon atoms and unambiguous establishment of the location of two methyl (C<sup>3</sup>CH<sub>3</sub>, C<sup>6</sup>CH<sub>3</sub>) and a trifluoromethyl (C<sup>4</sup>CF<sub>3</sub>) groups. The signal of atom C<sup>3</sup>CH<sub>3</sub> at 14.77 ppm appeared as a quartet of quartets with a coupling constant <sup>5</sup>J<sub>C-F</sub> 3.6, <sup>1</sup>J<sub>C-H</sub> 128.6 Hz, and the signal of the carbon C<sup>6</sup>CH<sub>3</sub> at 25.47 ppm was observed as a quartet of doublets (<sup>1</sup>J<sub>C-H</sub> 127.9, <sup>3</sup>J<sub>C-H</sub> 4.4 Hz). The observed long-range coupling constants <sup>3</sup>J(CF<sub>3</sub>-C) for atoms C<sup>3a</sup> (109.64 ppm, <sup>3</sup>J<sub>C-F</sub> ~3 Hz) and C<sup>5</sup> (114.15 ppm, <sup>3</sup>J<sub>C-F</sub> 4.4 Hz) confirm the position of the trifluoromethyl group at the atom C<sup>4</sup> of the pyridine ring.

The chemical shifts of proton and carbon signals of groups C<sup>4</sup>CH<sub>3</sub> [fragment -C=C-CH<sub>3</sub>] and C<sup>6</sup>CH<sub>3</sub> [fragment -C(CH<sub>3</sub>)=N] were unambiguously established by an example of 3,4,6-trimethylpyrazolo[3,4-*b*]pyridine (**VIII**) by using COLOC pulse sequence. The analysis of spectra obtained demonstrated that the CH<sub>3</sub> group whose signals appeared in the <sup>1</sup>H and <sup>13</sup>C NMR spectra at δ<sub>H</sub> 2.65 and δ<sub>C</sub> 25.3 ppm was located at the atom C<sup>6</sup> (δ<sub>C</sub> 159.2 ppm), and the CH<sub>3</sub> group having chemical shifts of signals δ<sub>H</sub> 2.75 and δ<sub>C</sub> 19.4 ppm, at the atom C<sup>4</sup> (δ<sub>C</sub> 142.9 ppm). It was revealed from the <sup>13</sup>C NMR spectra of pyrazolo[3,4-*b*]pyridines **IIIa-IIIc** that the chemical shifts of carbon signals of methyl groups and pyridine ring (C<sup>6</sup>CH<sub>3</sub>) were virtually constant for all compounds **III** and coincided with the corresponding values of the C<sup>6</sup>CH<sub>3</sub> group of 3,4,6-trimethylpyrazolo[3,4-*b*]pyridine (**VIII**).

Thus the above reasoning permitted unambiguous establishing of the position of the trifluoromethyl group in compounds **III-VI** at the atom C<sup>4</sup>, and therefore the phenyl group of compounds **IVa-IVh** and the thienyl



group of compounds **VIa** and **VIb** were attached to atom  $C^6$ .

In the spectra of compounds **IVa–IVh** the chemical shift of the atom  $C^6$  [fragment  $-C^6(C_6H_5)=N$ ] is virtually identical and coincides with the chemical shift of the  $C^6$  in the spectrum of 3-methyl-1,4,6-triphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (**IX**) and also with the characteristic chemical shifts of the fragment  $C-C(Ph)=N$  of a series of pyrazolo[1,5-*a*]pyrimidines [15].

At the same time the value of the chemical shift of the carbon atom  $C^4Ph$  [147.0 ppm, fragment  $C-C(Ph)=C$ ] obtained from the  $^{13}C$  NMR spectrum of compound **VIII** differed by 10 ppm from the chemical shift of the carbon atom  $C^6C_6H_5$  [156.9 ppm, fragment  $C-C(Ph)=N$ ].

The characteristic chemical shifts of the carbon atoms of the regioisomeric pyrazolopyridines make it possible to establish unambiguously the structure of regioisomers (see the table).

Thus by cyclocondensation of *N*-substituted 5-aminopyrazoles with fluorinated 1,3-diketones we synthesized 4-trifluoromethyl-substituted pyrazolo[3,4-*b*]pyridines as the only reaction products. The characteristic chemical shifts of carbon signals in the  $^{13}C$  NMR spectra of substituted pyrazolo[3,4-*b*]pyridines were estimated permitting establishing the regioisomeric structure of the compounds.

## EXPERIMENTAL

$^1H$  and  $^{13}C$  NMR spectra were registered on a spectrometer Bruker DPX-300 (300.13 and 75.47 MHz respectively) at 22°C. Chemical shifts were measured from the signals of deuterated solvent [ $CDCl_3$  (7.28 and 76.90 ppm),  $DMCO-d_6$  (2.50 and 39.50 ppm)]. A Bruker program package for pulse sequence COLOC was used with optimization on 8 Hz.

Characteristic chemical shifts of carbon atoms in  $^{13}C$  NMR spectra of pyrazolo[3,4-*b*]pyridines,  $\delta$ , ppm

Fragment	$C^6$	$CH_3$	Fragment	$C^4$	$CH_3$
$C^6(Me)=N$	~159.5	25–26	$C^4(Me)=C$	~143.5	19–20
$C^6(Ph)=N$	~157.0		$C^4(Ph)=C$	~147.5	
$C^6(CF_3)=N$	~147.5		$C^4(CF_3)=C$	~132–133	

3(5)-Aminopyrazoles **Ia–Ih** were prepared as described in [17, 18], fluorocontaining 1,3-diketones **IIa–IIc** were synthesized by procedure [19].

**Pyrazolo[3,4-*b*]pyridines.** *a.* Equimolar amounts of compounds **I** and **II** dissolved in acetic acid were mixed at 18–20°C, then the mixture was boiled for 2–4 h, the acetic acid was distilled off at a reduced pressure, and the residue was recrystallized from ethanol.

*b.* Equimolar amounts of compounds **I** and **II** were mixed and heated at 120–140°C for 10–30 min. Compounds obtained were recrystallized from ethanol.

**3,6-Dimethyl-4-trifluoromethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (IIIa).** Yield 90%, mp 61.5°C.  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 2.71 d (3H,  $C^6CH_3$ ,  $^4J_{H-H}$  1.0 Hz), 2.78 s (3H,  $C^3CH_3$ ), 7.32 c (1H,  $C^5H$ ), 7.30–8.26 m (5H,  $C_6H_5$ ).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm (reported coupling constants were obtained from the  $^{13}C$  NMR spectrum registered without decoupling from protons): 14.77 q,q ( $C^3CH_3$ ,  $^1J_{C-H}$  128.6,  $^5J_{C-F}$  3.6 Hz), 25.47 q,d ( $C^6CH_3$ ,  $^1J_{C-H}$  127.9,  $^3J_{C-H}$  4.4 Hz), 109.64 q ( $C^{3a}$ ,  $^3J_{C-F}$  ~3 Hz), 114.15 d,q,q ( $C^5$ ,  $^1J_{C-H}$  164.9,  $^3J_{C-H}$  4.3,  $^3J_{C-F}$  4.4 Hz), 122.70 q,d ( $CF_3$ ,  $^1J_{C-F}$  273.2,  $^3J_{C-H}$  5.1 Hz), 131.84 q ( $C^4CF_3$ ,  $^2J_{C-F}$  34.9 Hz), 141.36 q ( $C^3$ ,  $^2J_{C-H}$  7.5 Hz), 152.21 s ( $C^{7a}$ ), 159.48 q,d ( $C^6$ ,  $^2J_{C-H}$  5.8,  $^2J_{C-H}$  2.2 Hz), 121.07, 126.47, 129.40, 139.49 (Ph). Found, %: C 55.30; H 3.30.  $C_{15}H_{12}F_3N_3$ . Calculated, %: C 61.85; H 4.15.

**6-Methyl-3-(*p*-tolyl)-4-trifluoromethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (IIIb).** Yield 93%, mp 145°C.  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 2.48 s (3H,  $CH_3$ ), 2.83 s (3H,  $C^6CH_3$ ), 7.39 s (1H,  $C^5H$ ), 7.30–7.60, 8.30–8.33 m (9H, Ph, Ar).  $^{13}C$  NMR spectrum,  $\delta$ , ppm: 21.80 ( $CH_3$ ), 25.46 ( $C^6CH_3$ ), 109.25 ( $C^{3a}$ ), 115.40 q ( $C^5$ ,  $^3J_{C-F}$  5.0 Hz), 122.89 q ( $CF_3$ ,  $^1J_{C-F}$  273.7 Hz), 132.47 q ( $C^4CF_3$ ,  $^2J_{C-F}$  34.8 Hz), 145.43 ( $C^3$ ), 151.96 ( $C^{7a}$ ), 159.68 ( $C^6$ ), 122.38, 126.85, 129.03, 129.40, 130.08, 138.97, 139.45 (Ph, Ar). Found, %: C 68.43; H 4.59.  $C_{21}H_{16}F_3N_3$ . Calculated, %: C 68.66; H 4.39.

**6-Methyl-4-trifluoromethyl-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (IIIc).** Yield 95%, mp 125°C.

$^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.83 s (3H,  $\text{C}^6\text{CH}_3$ ), 7.39 s (1H,  $\text{C}^5\text{H}$ ), 7.34–8.33 m (9H, Ph, Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 25.48 ( $\text{C}^6\text{CH}_3$ ), 109.19 ( $\text{C}^{3a}$ ), 115.52 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  5.0 Hz), 122.73 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.7 Hz), 132.44 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.7 Hz), 145.33 ( $\text{C}^3$ ), 151.95 ( $\text{C}^{7a}$ ), 159.82 ( $\text{C}^6$ ), 122.44, 126.95, 128.32, 129.16, 129.42, 130.25, 133.87, 139.40 (Ph, Ar). Found, %: C 68.10; H 4.20.  $\text{C}_{20}\text{H}_{14}\text{F}_3\text{N}_3$ . Calculated, %: C 67.98; H 3.99.

**6-Methyl-4-trifluoromethyl-1-phenyl-3-(4-chlorophenyl)-1H-pyrazolo[3,4-*b*]pyridine (III<sub>d</sub>).** Yield 95%, mp 122°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.83 s (3H,  $\text{C}^6\text{CH}_3$ ), 7.44 s (1H,  $\text{C}^5\text{H}$ ), 7.32–8.30 m (9H, 2Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 25.50 ( $\text{C}^6\text{CH}_3$ ), 100.98 ( $\text{C}^{3a}$ ), 115.68 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  5.0 Hz), 122.85 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.7 Hz), 132.23 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.4 Hz), 144.08 ( $\text{C}^3$ ), 151.93 ( $\text{C}^{7a}$ ), 160.04 ( $\text{C}^6$ ), 122.44, 127.12, 128.63, 129.47, 131.58, 132.05, 135.36, 139.25 (Ph, Ar). Found, %: C 62.10; H 3.60.  $\text{C}_{20}\text{H}_{13}\text{ClF}_3\text{N}_3$ . Calculated, %: C 61.95; H 3.38.

**3-Methyl-4-trifluoromethyl-1,6-diphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>a</sub>).** Yield 91%, mp 151°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.76 s (3H,  $\text{CH}_3$ ), 7.91 s (1H,  $\text{C}^5\text{H}$ ), 7.31–8.36 m (10H, 2Ph).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 14.85 ( $\text{CH}_3$ ), 110.44 ( $\text{C}^{3a}$ ), 111.14 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  4.4 Hz), 123.22 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.1 Hz), 132.53 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.3 Hz), 141.55 ( $\text{C}^3$ ), 152.37 ( $\text{C}^{7a}$ ), 157.26 ( $\text{C}^6$ ), 121.75, 126.45, 127.95, 129.42, 130.59, 138.31, 139.54 (2Ph). Found, %: C 67.69; H 4.15.  $\text{C}_{20}\text{H}_{14}\text{F}_3\text{N}_3$ . Calculated, %: C 67.98; H 3.99.

**3-(4-Methoxyphenyl)-4-trifluoromethyl-1,6-diphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>b</sub>).** Yield 95%, mp 166°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 3.92 s (3H,  $\text{CH}_3\text{O}$ ), 7.99 s (1H,  $\text{C}^5\text{H}$ ), 7.04–8.44 m (14H, 2Ph, Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 55.73 ( $\text{CH}_3\text{O}$ ), 110.08 ( $\text{C}^{3a}$ ), 112.42 q ( $\text{C}^5$ ,  $^3J_{\text{F}}$  5.1 Hz), 122.86 q ( $\text{CF}_3$ ,  $^1J_{\text{F}}$  273.0 Hz), 133.19 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.3 Hz), 145.30 ( $\text{C}^3$ ), 152.17 ( $\text{C}^{7a}$ ), 157.47 ( $\text{C}^6$ ), 113.88, 128.02, 131.56, 160.54 (Ar), 122.27, 126.84, 129.47, 139.48 ( $\text{N}^1$  Ph), 125.80, 130.72, 138.24 ( $\text{C}^6\text{Ph}$ ). Found, %: C 69.90; H 4.29.  $\text{C}_{26}\text{H}_{18}\text{F}_3\text{N}_3\text{O}$ . Calculated, %: C 70.11; H 4.07.

**3-(*p*-Tolyl)-4-trifluoromethyl-1,6-diphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>c</sub>).** Yield 91%, mp 131°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 2.50 s (3H,  $\text{CH}_3$ ), 8.00 s (1H,  $\text{C}^5\text{H}$ ), 7.34–8.45 m (14H, 2Ph, Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 21.85 (4- $\text{CH}_3$ ), 110.02 ( $\text{C}^{3a}$ ), 112.40 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  4.6 Hz), 122.96 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.5

Hz), 133.18 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.4 Hz), 145.57 ( $\text{C}^3$ ), 152.17 ( $\text{C}^{7a}$ ), 157.47 ( $\text{C}^6$ ), 126.84, 128.01, 129.12, 129.47, 130.54, 130.71, 138.24, 139.10, 139.52 (2Ph, Ar). Found, %: C 72.47; H 4.46.  $\text{C}_{26}\text{H}_{18}\text{F}_3\text{N}_3$ . Calculated, %: C 72.72; H 4.22.

**4-Trifluoromethyl-1,3,6-triphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>d</sub>).** Yield 96%, mp 164°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 8.00 s (1H,  $\text{C}^5\text{H}$ ), 7.37–8.44 m (15H, 3Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 109.18 ( $\text{C}^{3a}$ ), 111.74 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  5.1 Hz), 122.17 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.0 Hz), 132.44 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.7 Hz), 144.75 ( $\text{C}^3$ ), 151.38 ( $\text{C}^{7a}$ ), 156.82 ( $\text{C}^6$ ), 126.18, 127.27, 127.63, 127.84, 128.73, 128.50, 129.51, 130.00, 132.68, 138.64, 137.44 (3Ph). Found, %: C 55.30; H 3.30.  $\text{C}_{20}\text{H}_{13}\text{BrF}_3\text{N}_3$ . Calculated, %: C 55.57; H 3.03.

**4-Trifluoromethyl-3-(4-chlorophenyl)-1,6-diphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>e</sub>).** Yield 93%, mp 161–162°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 8.00 s (1H,  $\text{C}^5\text{H}$ ), 7.36–8.41 m (14H, 2Ph, Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 109.72 ( $\text{C}^{3a}$ ), 12.67 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  5.1 Hz), 122.86 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.0 Hz), 133.02 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.3 Hz), 144.26 ( $\text{C}^3$ ), 152.14 ( $\text{C}^{7a}$ ), 159.82 ( $\text{C}^6$ ), 122.33, 127.10, 128.03, 128.70, 129.52, 130.86, 131.60, 131.95, 135.47, 138.07, 139.31 (2Ph, Ar). Found, %: C 66.46; H 3.52.  $\text{C}_{25}\text{H}_{15}\text{ClF}_3\text{N}_3$ . Calculated, %: C 66.75; H 3.36.

**6-(4-Isopropoxyphenyl)-4-trifluoromethyl-1,3-diphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>f</sub>).** Yield 94%, mp 152°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 1.45 d [9H, ( $\text{CH}_3$ )<sub>2</sub>,  $J_{\text{H-H}}$  5.5 Hz], 4.69 septet [1H,  $\text{CH}(\text{CH}_3)_2$ ,  $J_{\text{H-H}}$  5.5 Hz], 7.92 s (1H,  $\text{C}^5\text{H}$ ), 7.28–8.08 m (13H, 2Ph, Ar).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 21.94 ( $\text{CH}_3$ ), 70.00 ( $\text{OCH}$ ), 108.86 ( $\text{C}^{3a}$ ), 111.40 q ( $\text{C}^5$ ,  $^3J_{\text{C-F}}$  5.6 Hz), 122.54 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  273.8 Hz), 132.50 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  31.9 Hz), 145.02 ( $\text{C}^3$ ), 151.74 ( $\text{C}^{7a}$ ), 158.85 ( $\text{C}^6$ ), 116.02, 120.71, 121.79, 126.30, 127.87, 128.71, 128.95, 129.01, 129.80, 133.14, 139.08, 160.00 (2Ph, Ar). Found, %: C 72.51; H 4.43.  $\text{C}_{28}\text{H}_{22}\text{F}_3\text{N}_3\text{O}$ . Calculated, %: C 71.03; H 4.68.

**1-Benzyl-4-trifluoromethyl-3,6-diphenyl-1H-pyrazolo[3,4-*b*]pyridine (IV<sub>g</sub>).** Yield 95%, mp 160°C.  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 5.89 s (2H,  $\text{CH}_2$ ), 7.94 s (1H,  $\text{C}^5\text{H}$ ), 7.30–7.42, 7.45–7.61, 8.21–8.23 m (14H, 3Ph).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 51.63 ( $\text{CH}_2$ ), 112.11 d.q ( $\text{C}^5$ ), 108.22 ( $\text{C}^{3a}$ ,  $J_{\text{C-H}}$  165.0,  $^3J_{\text{C-F}}$  5.0 Hz), 123.06 q ( $\text{CF}_3$ ,  $^1J_{\text{C-F}}$  274.2 Hz), 132.99 q ( $\text{C}^4\text{CF}_3$ ,  $^2J_{\text{C-F}}$  34.8 Hz), 144.32 ( $\text{C}^3$ ), 152.44 ( $\text{C}^{7a}$ ), 157.15 ( $\text{C}^6$ ), 127.96, 128.34, 128.83, 129.08, 129.00, 129.44, 130.25,



130.62, 133.80, 137.11, 138.39 (3Ph). Found, %: C 72.51; H 4.43.  $C_{26}H_{18}F_3N_3$ . Calculated, %: C 72.72; H 4.22.

**1-Benzyl-6-(4-bromophenyl)-3-(4-methoxyphenyl)-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine (IVh).** Yield 92%, mp 158°C.  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 3.89 s (3H,  $OCH_3$ ), 5.86 s (2H,  $CH_2$ ), 7.85 s (1H,  $C^5H$ ), 7.28–8.08 m (13H, 3Ar).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 51.15 ( $CH_2$ ), 55.21 ( $OCH_3$ ), 108.05 ( $C^{3a}$ ), 110.98 q ( $C^5$ ,  $^3J_{C-F}$  5.0 Hz), 122.51 q ( $CF_3$ ,  $^1J_{C-F}$  272.8 Hz), 132.32 q ( $C^4CF_3$ ,  $^2J_{C-F}$  34.8 Hz), 143.72 ( $C^3$ ), 151.88 ( $C^{7a}$ ), 155.30 ( $C^6$ ), 113.82, 124.79, 126.04, 128.33, 128.73, 129.06, 129.39, 131.43, 132.59, 137.03, 137.25, 159.93 (Ph, 2Ar). Found, %: C 72.51; H 4.43.  $C_{27}H_{19}BrF_3N_3O$ . Calculated, %: C 60.24; H 3.56.

**1-Benzyl-6-tert-butyl-3-(4-methoxyphenyl)-4-trifluoromethyl-1H-pyrazolo[3,4-b]pyridine (V).** Yield 91%, mp 113°C.  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 1.54 s [1H, ( $CH_3$ )<sub>3</sub>], 3.87 s (3H,  $OCH_3$ ), 5.78 s (2H,  $CH_2$ ), 7.50 s (1H,  $C^5H$ ), 7.30–8.26 m (9H, Ph, Ar).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 30.11 [( $CH_3$ )<sub>3</sub>], 38.32 [ $C(CH_3)_3$ ], 51.08 ( $CH_2$ ), 55.18 ( $OCH_3$ ), 106.94 q ( $C^{3a}$ ,  $^3J_{C-F}$  ~3 Hz), 110.47 ( $C^5$ ,  $^3J_{C-F}$  5.0 Hz), 122.78 q ( $CF_3$ ,  $^1J_{C-F}$  273.2 Hz), 131.72 q ( $C^4CF_3$ ,  $^2J_{C-F}$  34.9 Hz), 143.17 ( $C^3$ ), 169.49 ( $C^6$ ), 113.26, 126.01, 127.75, 128.46, 128.59, 130.94, 136.76, 159.73 (Ph, Ar). Found, %: C 72.51; H 4.43.  $C_{25}H_{24}F_3N_3O$ . Calculated, %: C 68.32; H 5.50.

**3-Methyl-6-(2-thienyl)-4-trifluoromethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (VIa).** Yield 92%, mp 157°C.  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 2.71 s (3H,  $CH_3$ ), 7.16 m, 7.37 t ( $J_{H-H}$  7.0 Hz), 7.49 d (3H,  $C_3H_3S$ ,  $J_{H-H}$  4.8 Hz), 7.50–8.03 (5H, Ph), 7.74 c (1H,  $C^5H$ ).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 14.35 q ( $CH_3$ ,  $^3J_{C-F}$  3.3 Hz), 109.43 q ( $C^5$ ,  $J_{C-F}$  5.5 Hz), 109.80 ( $C^{3a}$ ), 122.65 q ( $CF_3$ ,  $^1J_{C-F}$  274.76 Hz), 132.02 q ( $C^4$ ,  $^2J_{C-F}$  34.3 Hz), 141.23 ( $C^3$ ), 151.38 ( $C^{7a}$ ), 151.77 ( $C^6$ ), 120.92, 128.94, 129.48, 139.06 (Ph), 125.88, 126.82, 128.30, 143.74 ( $C_4H_3S$ ). Found, %: C 59.90; H 3.55.  $C_{18}H_{12}F_3N_3S$ . Calculated, %: C 60.16; H 3.37.

**6-(2-Thienyl)-4-trifluoromethyl-1,3-diphenyl-1H-pyrazolo[3,4-b]pyridine (VIb).** Yield 93%, mp 187°C.  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 7.86 s (1H,  $C^5H$ ), 7.20–7.67 m (13H, 2Ph,  $C_3H_3S$ ).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 109.33 ( $C^{3a}$ ), 110.83 q ( $C^5$ ,  $^3J_{C-F}$  4.4 Hz), 122.30 q ( $CF_3$ ,  $^1J_{C-F}$  275.32 Hz), 132.68 q ( $C^4$ ,  $^2J_{C-F}$  33.7 Hz), 145.20 ( $C^3$ ), 151.18 ( $C^{7a}$ ), 152.12 ( $C^6$ ), 121.54, 127.94, 128.84, 129.00, 129.80, 132.92, 138.98 (2Ph), 126.41, 127.14, 128.44, 143.62 ( $C_4H_3S$ ).

Found, %: C 65.25; H 3.57.  $C_{23}H_{14}F_3N_3S$ . Calculated, %: C 65.55; H 3.35.

**3-Methyl-4,6-bis(trifluoromethyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine (VII).** Yield 89%, mp 78–79°C [10].  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 2.79 s (3H,  $CH_3$ ), 7.82 s (1H,  $C^5H$ ), 7.40–8.27 m (5H, Ph).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 14.27 ( $CH_3$ ), 109.57 ( $C^5$ ,  $^3J_{H-F}$  2.8 Hz), 113.09 ( $C^{3a}$ ), 120.00 q ( $CF_3$ ,  $^1J_{H-F}$  273.7 Hz), 120.92 ( $CF_3$ ,  $^1J_{H-F}$  273.6 Hz), 133.30 q ( $C^4CF_3$ ,  $^2J_{H-F}$  36.0 Hz), 141.31 ( $C^3$ ), 146.90 ( $C^6CF_3$ ,  $^2J_F$  36.0 Hz), 150.33 ( $C^{7a}$ ), 121.18, 126.71, 129.12, 138.28 (Ph).

**3,4,6-Trimethyl-1-phenyl-1H-pyrazolo[3,4-b]pyridine (VIII).** Yield 87%, mp 127–128°C [9].  $^1H$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 2.65 s (3H,  $C^6CH_3$ ), 2.68 s (3H,  $C^3CH_3$ ), 2.75 s (3H,  $C^4CH_3$ ), 7.23–8.31 m (5H,  $C_6H_5$ ).  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm (reported coupling constants were obtained from the  $^{13}C$  NMR spectrum registered without decoupling from protons): 15.76 q ( $C^3CH_3$ ,  $^1J_{C-H}$  128.8 Hz), 19.36 q.d ( $C^4CH_3$ ,  $^1J_{C-H}$  127.1,  $^3J_{C-H}$  4.1 Hz), 25.28 q.d ( $C^6CH_3$ ,  $^1J_{C-H}$  127.1,  $^3J_{C-H}$  2.1 Hz), 114.99 s ( $C^{3a}$ ), 119.02 m ( $C^5$ ), 142.83 q ( $C^3$ ,  $^2J_{C-H}$  8.7 Hz), 142.93 q ( $C^4$ ,  $^2J_{C-H}$  8.0 Hz), 151.75 C ( $C^{7a}$ ), 159.20 q ( $C^6$ ,  $^2J_{C-H}$  8.0 Hz), 122.20, 125.57, 129.32, 140.22 (Ph).

**3-Methyl-1,4,6-triphenyl-1H-pyrazolo[3,4-b]pyridine (IX).** Yield 70%, mp 148°C.  $^{13}C$  NMR spectrum ( $CDCl_3$ ),  $\delta$ , ppm: 15.80 ( $CH_3$ ), 114.22 ( $C^5$ ), 115.72 ( $C^{3a}$ ), 142.90 ( $C^3$ ), 146.99 ( $C^4$ ), 152.07 ( $C^{7a}$ ), 156.86 ( $C^6$ ), 121.37, 125.75, 128.01, 128.76, 129.14, 129.20, 129.37, 129.47, 129.85, 138.27, 139.58, 140.24 (3Ph). Found, %: C 82.91; H 5.47.  $C_{25}H_{19}N_3$ . Calculated, %: C 83.08; H 5.30.

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## REFERENCES

- Emelina, E.E., Petrov, A.A., and Firsov, A.V., *Zh. Org. Khim.* 2001, vol. 37, p. 899.
- Hardy, C.R., *Adv. Heterocycl. Chem.*, 1984, vol. 36, p. 343.
- Elnagdi, M.H., Elmoghayar, M.R.H., and Elgemeie, G.E.H., *Adv. Heterocycl. Chem.*, 1987, vol. 41, p. 319.
- Abu, Almaati, T.M. and El-Taweel, F.M., *J. Heterocycl. Chem.*, 2004, vol. 41, p. 109.
- Maretina, I.A., *Zh. Org. Khim.* 2005, vol. 41, p. 9.
- De Mello, H., Echevarria, A., Bernardino, A.M., Cantocava-lheiro, M., and Leon, L.L., *J. Med. Chem.*, 2004, vol. 47, p. 5427.

7. Straub, A., Benet-Buckholz, J., Frode, R., Kern, A., Kohlsdorfer, C., Schmitt, P., Schwarz, T., Siefert, H-M., and Stasch, J-P., *Bioorg. Med. Chem.*, 2002, vol. 10, p. 1711.
8. George, C.F.P., *Lancet*, 2001, vol. 357, p. 1623.
9. Grandberg, I.I., *Zh. Obshch. Khim.*, 1961, vol. 31, p. 2307.
10. Linch, B.M., Khan, M.A., Teo, H.Ch., and Pedrotti, F., *Canad. J. Chem.*, 1988, vol. 66, p. 420.
11. Nam, N.L., Grandberg, I.I., and Sorokin, V.I., *Khim. Geterotsikl. Soedin.*, 2003, p. 1080.
12. Nam, N.L., Grandberg, I.I., and Sorokin, V.I., *Khim. Geterotsikl. Soedin.*, 2002, p. 1555.
13. Silvester, M.J., *Adv. Heterocycl. Chem.*, 1994, vol. 59, p. 1; Erian, A.W., *J. Heterocycl. Chem.*, 2001, vol. 38, p. 793.
14. Balicki, R., *Polich J. Chem.*, 1981, vol. 55, p. 1995.
15. Singh, S.P., Naithani, R., Aggarawal, R., and Prakash, O., *Synth. Commun.*, 2004, vol. 34, p. 4359.
16. Zayzev, V., Kolehmainen, E., Laihia, K., Mansikkamäki, H., Petrov, A., and Emelina, E., Abstracts of Papers, *III Molodezhnaia shkola-konferentsiia po organicheskomu sintezu (YSCOS-3)* (Youth Conference on Organic Synthesis), St. Petersburg, 2002, p. 106.
17. German Patent 145750, 1981; *Chem. Abstr.*, 1981, vol. 95, 80952m.
18. Grandberg, I.I., Din, Vei-Py, and Kost, A.N., *Zh. Obshch. Khim.*, 1961, vol. 31, p. 2311; Takahashi, M., Nagaoaka, H., and Inoue, K. J., *J. Heterocycl. Chem.*, 2004, vol. 41, p. 525.
19. Henne, A.L., Newman, M.S., Quill, L.L., and Stamford, R.A., *J. Am. Chem. Soc.*, 1947, vol. 69, p. 819.