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N-Boc-4-aminopyrazole-5-carbaldehydes in Friendländer synthesis of pyrazolo[4,3-*b*]pyridines

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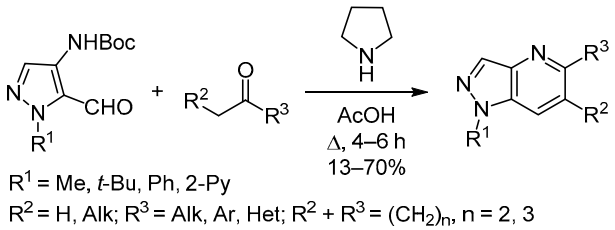


N-Boc-4-aminopyrazole-5-carbaldehydes reacted with aryl, hetaryl, alkyl, and cycloalkyl ketones containing methylene groups. The reactions were accomplished in refluxing acetic acid in the presence of pyrrolidine and resulted in the formation of 5-substituted and carbo[*b*]fused pyrazolo[4,3-*b*]pyridines.

Keywords: 4-aminopyrazole-5-carbaldehydes, ketones, pyrazolo[4,3-*b*]pyridines, Friendländer reaction.

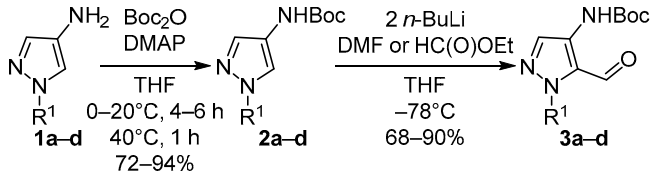
The Friendländer reaction, representing a very capable approach to the synthesis of quinolines, was discovered more than 130 years ago[1] and still has not lost its great significance in the field of organic chemistry.[2] It can be described as acid- or base-catalyzed or thermally initiated cyclocondensation of aromatic *o*-amino-substituted aldehydes or ketones with carbonyl compounds containing activated methylene groups.[3,1c] Throughout the history of its development, the applicability of Friendländer reaction has been extended to a series of nitrogen-containing heterocyclic aminocarbonyl compounds. Notable examples of the latter include aminonicotinic aldehydes that are used in the synthesis of biologically important 1,6- and 1,8-naphthyridine derivatives.[4] Performing the Friendländer reaction with some types of azolylamino aldehydes has also been described in the literature, in particular, 5-amino-4-formylimidazole,[5] 5-aminoisoxazole-4-carbaldehyde,[6] and 5-amino-1,2,3-triazole-4-carbaldehyde have been used.[7] However, the best explored among such substrates are 5-aminopyrazole-4-carbaldehydes,[8] which are used in the synthesis of pyrazolo[3,4-*b*]pyridines, some of which have been characterized as antibacterial agents,[9] as well as selective inhibitors of acetylcholinesterase[10] and chemokine receptor CCR2.[11]

In contrast to the stable 5-aminopyrazole-4-carbaldehydes, their isomers 4-aminopyrazole-5-carbaldehydes have not been isolated as individual compounds. Only 4-amino-3-*tert*-butyl-1-methylpyrazole-5-carbaldehyde has been described, after it was generated *in situ* from its 4-nitro analog, the condensation of which with acetophenone led to the respective pyrazolo[4,3-*b*]pyridine.[12] Studying this series of structures has revealed compounds with antiviral,[13] anti-inflammatory,[14] antitumor,[15] and bactericidal[16] properties. For this reason, it is of major synthetic importance to search for a simple and preparatively convenient method that would help to build pyrazolo[4,3-*b*]pyridine framework using the classical Friendländer reaction, which was also the goal of this study.

It has been previously demonstrated that some *o*-aminobenzaldehydes[17] and 3(4)-amino(iso)nicotinaldehydes[18] under the conditions of Friendländer reaction can undergo self-condensation, and for this reason, it is preferable to use their *N*-Boc-substituted derivatives. We considered it worthwhile to employ this approach also for the synthesis

of 4-aminopyrazole-5-carbaldehydes, especially because one of such compounds – 4-(Boc-amino)-1-methylpyrazole-5-carbaldehyde (**3a**) – has been described in patent literature.[19] We extended the applicability of the method proposed for its synthesis to a series of derivatives **3b**–**d** and first perfomed Boc-acylation of 4-aminopyrazoles **1b**–**d** in the presence of catalytic amounts of DMAP, followed by the formylation of *N*-Boc-substituted aminopyrazoles **2b**–**d** by the action of *n*-BuLi and DMF (in the case of compound **2b**) or *n*-BuLi and ethyl formate (in the cases of compounds **2c**,**d**).

Scheme 1



a R^1 = Me, **b** R^1 = *t*-Bu, **c** R^1 = Ph, **d** R^1 = 2-Py

The cyclocondensation reactions of *N*-Boc-aminoaryl(hetaryl) aldehydes that are described in the literature were performed with various reactants and reaction conditions: MeONa in MeOH,[18a] sequential treatment of the reaction mixtures with *t*-BuOK and HCl,[17a] CF_3COOH and NaOH,[18b,c] or by using CF_3COOH as a solvent.[18d] We optimized the Friendländer reaction of *N*-Boc-aminoformylpyrazoles and ketones using aminoaldehyde **3a** and acetophenone **4a** as the example with respect to solvents, catalysts, and reaction conditions by following the reaction progress by LC-MS analysis (Scheme 2). We found that the reaction did not proceed in EtOH, MeCN, or 1,4-dioxane as solvent in the presence of 0.1, 0.5, or 1.0 equiv of catalyst (KOH, EtONa, $AcONH_4$, H_2SO_4, piperidine) at room temperature, while resinification of the reaction mixtures started at 50°C, and was significantly accelerated at reflux. No major changes in the results were observed when using CF_3COOH as solvent and catalyst at room temperature, but formation of the respective *N*-trifluoroacetylaminoformylpyrazole occurred at reflux. The reaction gave positive results when performed in refluxing AcOH in the presence of $AcONH_4$ or organic secondary amines (Scheme 2, Table 1). Thus, refluxing reactants **3a** and **4a** for 6 h with 0.5 equiv of $AcONH_4$ resulted in 26% content of pyrazolo[4,3-*b*]-pyridine **5a** in the reaction mixture (entry 1). Doubling the amount of catalyst also doubled the yield of product **5a** (entry 2). However, the use of an equimolar amount of secondary cycloalkylamines was more effective (entries 5–7), with the best results (76% content of product **5a** at full conversion of the starting reactants) obtained when using pyrrolidine. It is important to note that adding more than 1 equiv of catalyst practically did not affect the yield of the target product.

The identified optimum conditions for the synthesis of pyrazolopyridine **5a** were tested by performing Friendländer reaction of *N*-Boc-4-amino-5-formylpyrazoles **3b**–**d** with aryl(hetaryl) methyl ketones **4a**–**f**, dialkyl ketones **4g**–**j**, and cycloalkyl ketones **4k**,**l** (Scheme 3). The

Scheme 2

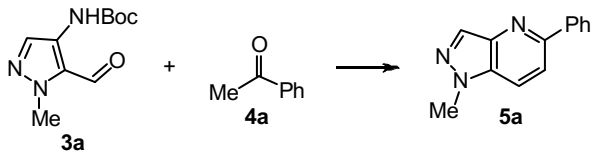


Table 1. Optimization of reaction conditions for the cyclocondensation of compounds **3a** and **4a** in refluxing AcOH*

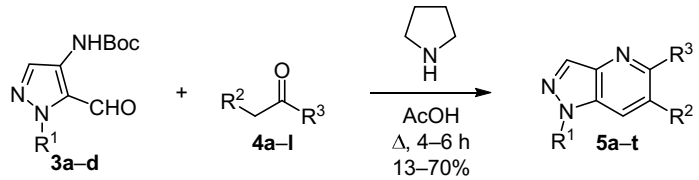
Entry	Catalyst (equiv)	Time, h	The content of compound **5a**, %**
1	$AcONH_4$ (0.5)	6	26
2	$AcONH_4$ (1.0)	6	54
3	Pyrrolidine (0.5)	6	62
4	Pyrrolidine (1.0)	2	45
5	Pyrrolidine (1.0)	4	76
6	Pyrrolidine (2.0)	4	74
7	Piperidine (1.0)	4	68
8	Morpholine (1.0)	4	65

* Compound **3a** (1.2 mmol), compound **4a** (1.21 mmol), AcOH (30 ml).
** The content of compound **5a** in the reaction mixture according to LC-MS analysis.

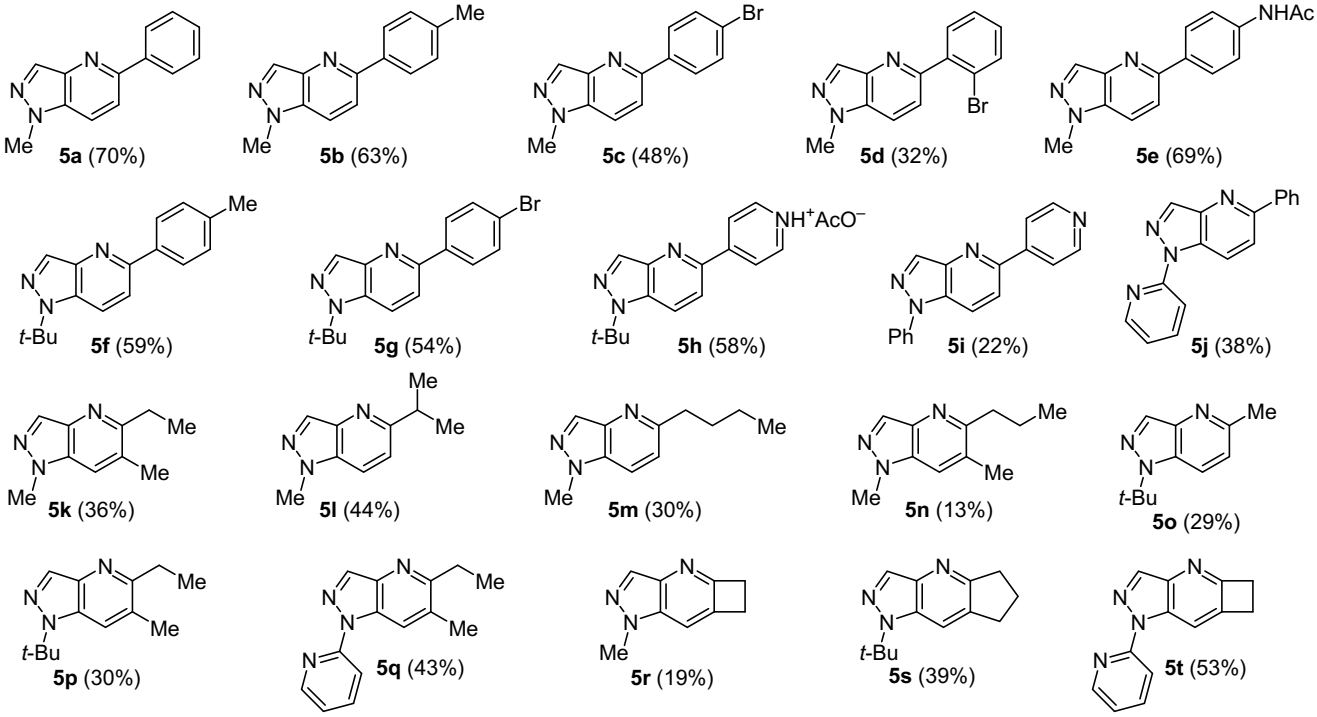
obtained results enabled us to thoroughly assess the correlation between the structure of reactant and the selectivity of the cyclocondensation processes. In particular, the best yields of the target products **5a**–**c**,**e**–**j** were observed in the reactions of 1-alkyl- and (α-pyridyl)-pyrazoles **3a**,**b**,**d** with acetophenones **4a**–**e** and isonicotinyl methyl ketone **4f**. When 4-aminoacetophenone **4e** was used in this series of experiments, *N*-acetyl derivative **5e** was isolated from the reaction mixture while acetate **5h** was obtained in the case of 4-pyridinyl methyl ketone **4f**. Comparing the yields of the isomeric products **5c** (52%) and **5d** (36%) indicated that the steric parameters of 2-bromophenyl methyl ketone **4e** had great importance for the cyclization process. The majority of reactions failed when using 1-phenyl-substituted pyrazole **3c** and only in the case of ketone **4f** it was possible to isolate pyrazolopyridine **5i** in 22% yield.

Compared to acetophenones, dialkyl and cycloalkyl ketones **4g**–**l** were found to be less convenient reactants in cyclocondensation with aminoaldehydes **3a**,**b**,**d**, probably due to the greater tendency toward side reactions: 5-alkylpyrazolopyridines **5k**–**q** were obtained in 13–44% yields and their carbo[*b*]fused analogs **5r**–**t** – in 19–43% yields. Remarkably, using acetone derivative **4i** allowed to isolate only the product of its condensation with pyrazole **3b**, namely, pyrazolopyridine **5o** as an individual compound in 29% yield. It should be also noted that in the case of unsymmetrical hexan-2-one (**4j**) the cyclocondensation of aminoformylpyrazole **3a** involved both the methyl and methylene groups, giving a mixture of isomers **5m** and **5n** in 43% overall yield in approximately 2.5:1 ratio. These isomers were separated by preparative liquid chromatography.

Scheme 3



4 a R^2 = H, R^3 = Ph; **b** R^2 = H, R^3 = 4-MeC_6H_4; **c** R^2 = H, R^3 = 4-BrC_6H_4; **d** R^2 = H, R^3 = 2-BrC_6H_4; **e** R^2 = H, R^3 = 4-$H_2NC_6H_4$; **f** R^2 = H, R^3 = 4-Py; **g** R^2 = Me, R^3 = Et; **h** R^2 = H, R^3 = *i*-Pr; **i** R^2 = H, R^3 = Me; **j** R^2 = H, R^3 = *n*-Bu; **k** $R^2 + R^3 = (CH_2)_2$; **l** $R^2 + R^3 = (CH_2)_3$



When discussing the possible mechanism of the studied Friendländer reaction and considering the earlier studies,[20] it appeared logical that the first stage in this process is crotonic condensation catalyzed by pyrrolidine, leading to the *E*-enone **A**, which was present in the amount of 35% in the reaction mixture when performing the condensation of compounds **3a** and **4a** in AcOH at 50°C. The subsequent acid-catalyzed isomerization of *E*-enone **A** led to the intermediate **B** having *Z*-configuration. Removal of the Boc protecting group generated the intermediate **C**, which subsequently underwent cyclodehydration, providing the target product **5**.

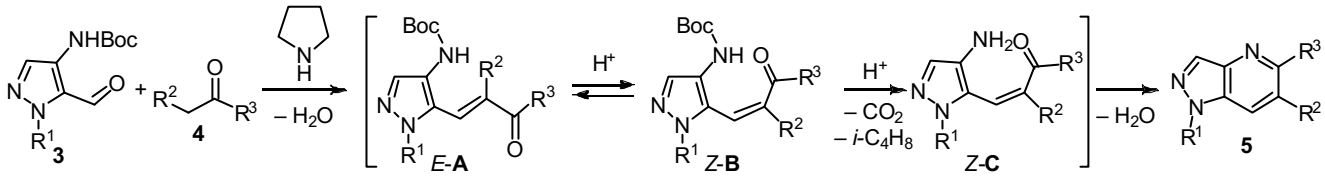
The structures of all synthesized starting compounds **3b**–**d** and products **5a**–**t** were confirmed by NMR spectroscopy and LC-MS analysis. It was important to correctly identify the structures of the regioisomeric compounds **5m**,**n** formed from the initial condensation of aminoaldehyde **3a** with hexan-2-one (**4j**) at the methyl or methylene group, respectively. ^{1}H NMR spectrum of the major isomer **5m** featured the characteristic doublet signals of H-6 and H-7 protons at 7.28 and 8.02 ppm with a spin-spin coupling constant of 8.8 Hz, while the spectrum of the minor isomer **5n** contained singlet signals of the 6-CH_3 protons at 2.55 ppm and H-7 proton at 7.80 ppm.

Thus, we have shown the possibility of performing Friendländer reaction in the series of 4-(Boc-amino)-pyrazole-5-carbaldehydes, opening a convenient synthetic access to 5-substituted and carbo[*b*]fused pyrazolo[4,3-*b*]-pyridines.

Experimental

IR spectra were recorded on a Bruker Vertex 70 FT-IR spectrometer for samples in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Varian VXR-400 instrument

Scheme 4



(400 and 126 MHz, respectively) according to pulsed Fourier technique for samples in DMSO-d_6 (compounds **3d**, **5a**–**c**,**e**–**j**,**m**–**o**,**q**,**t**) or in $CDCl_3$ (compounds **2b**–**d**, **3b**,**c**, **5d**,**k**,**l**,**p**–**s**), using TMS as internal standard. Mass spectra were recorded on an Agilent LC/MSD SL system equipped with a Zorbax SB-C_{18} column 4.6 × 15 mm, 1.8 μm (PN 82(c)75-932), the solvent was DMSO, electrospray ionization at atmospheric pressure. Preparative HPLC of compounds **5m** and **5n** was performed using a Teledyne Isco Combiflash Companion preparative liquid chromatograph (eluent MTBE–MeCN, 9:1). Elemental analysis was performed with a PerkinElmer 2400 Series CHN Analyzer at the Analytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Melting points were determined on a Kofler bench and were not corrected.

The starting 4-aminopyrazoles **1a**–**d** were provided by Enamine Ltd. (Kyiv, Ukraine). Compounds **2a** and **3a** were synthesized according to a published procedure.[19]

Synthesis of compounds 2b–d (General method). A solution of 4-aminopyrazole **1b**–**d** (1.03 mol) in THF (1400 ml) was cooled to 0°C, then DMAP (5.03 g, 0.041 mol) was added to the stirred solution, followed by slow addition of di(*tert*-butyl) dicarbonate (229 g, 1.05 mol) over 30 min. The mixture was maintained at the indicated temperature for 1 h, allowed to warm to the room temperature, and stirred for further 4–6 h. The reaction mixture was then heated at 40°C for 1 h, evaporated, extracted with MTBE (800 ml). The obtained oily product was diluted with 3:2 MTBE–hexane mixture (300 ml), stirred, the precipitate that formed was filtered off and air-dried.

***tert*-Butyl (1-*tert*-butyl-1*H*-pyrazol-4-yl)carbamate (2b)**. Yield 230 g (93%), violet powder, mp 72–73°C. IR spectrum, ν, cm^{-1}: 3273 (N–H), 1710 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (9H, s, $C(CH_3)_3$); 1.56 (9H, s, $C(CH_3)_3$); 6.25 (1H, s, NH); 7.33 (1H, s, H-5); 7.80 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 27.9; 29.2; 58.0; 79.7; 116.6; 120.4; 128.9; 152.8. Mass spectrum, *m*/*z* (I_{rel}, %): 240 $[M+H]^+$ (100). Found, %: C 60.02; H 8.71; N 17.44. $C_{12}H_{21}N_3O_2$. Calculated, %: C 60.23; H 8.84; N 17.56.

***tert*-Butyl (1-phenyl-1*H*-pyrazol-4-yl)carbamate (2c)**.[21] Yield 193 g (72%), brown powder, mp 93–94°C. IR spectrum, ν, cm^{-1}: 3290 (N–H), 1706 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.52 (9H, s, $C(CH_3)_3$); 6.53 (1H, s, NH); 7.24 (1H, t, *J* = 7.6, H Ar); 7.42 (2H, t, *J* = 7.6, H Ar); 7.54 (1H, s, H-5); 7.66 (2H, d, *J* = 7.6, H Ar); 8.21 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 28.1; 79.0; 116; 117.8; 124.6; 125.7; 129.5; 132.4; 139.8; 152.7. Mass spectrum, *m*/*z* (I_{rel}, %): 260 $[M+H]^+$ (100). Found, %: C 64.68; H 6.72; N 16.11. $C_{14}H_{17}N_3O_2$. Calculated, %: C 64.85; H 6.61; N 16.20.

***tert*-Butyl [1-(pyridin-2-yl)-1*H*-pyrazol-4-yl]carbamate (2d)**.[22] Yield 253 g (94%), gray powder, mp 88–89°C. IR spectrum, ν, cm^{-1}: 3287 (N–H), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (9H, s, $C(CH_3)_3$); 6.43 (1H, s, NH); 7.12 (1H, t, *J* = 5.6, H Py); 7.70–7.78 (2H, m, H-5, H Py); 7.88 (1H, d, *J* = 8.4, H Py); 8.34 (1H, d, *J* = 4.0, H Py); 8.60 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 28.1; 79.1; 111.2; 114.8; 121.4; 124.8; 133.6; 139.2; 148.2; 150.9; 152.7. Mass spectrum, *m*/*z* (I_{rel}, %): 261 $[M+H]^+$ (100). Found, %: C 60.21; H 6.33; N 21.38. $C_{13}H_{16}N_4O_2$. Calculated, %: C 59.99; H 6.20; N 21.52.

Synthesis of compounds 3b–d (General method). A solution of carbamate **2b**–**d** (0.36 mol) in THF (1200 ml) was cooled to –78°C under argon atmosphere and treated by adding 2.5 M solution of *n*-BuLi in hexane (317 ml, 2.2 equiv). The reaction mixture was stirred for 2–3 h at the temperature range from –78 to –70°C. The reaction mixture was then treated at the same temperature with DMF (29.3 g, 0.4 mol, in the case of carbamate **2b**), heated to room temperature, and stirring was continued overnight. After 10–12 h, the reaction mixture was quenched with saturated aqueous solution of NH_4Cl (200 ml). In the case of carbamates **2c**,**d**, the reaction mixture was treated with ethyl formate (27 g, 0.365 mol), stirred for 0.25 h, the temperature was raised to –20°C, and saturated aqueous solution of NH_4Cl (200 ml) was added at once. In both cases, the mixture was further stirred for 20–30 min and extracted with MTBE (3×200 ml). The organic layer was washed twice with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, filtered through a layer of silica gel, and evaporated. The oily residue was taken up in 3:2 mixture of MTBE–hexane (150 ml), stirred, the obtained precipitate was then filtered off and air-dried.

***tert*-Butyl (1-*tert*-butyl-5-formyl-1*H*-pyrazol-4-yl)-carbamate (3b)**. Yield 86.8 g (90%), lilac-colored powder, mp 93–94°C. IR spectrum, ν, cm^{-1}: 3373 (N–H), 1696, 1719 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.57 (9H, s, $C(CH_3)_3$); 1.72 (9H, s, $C(CH_3)_3$); 8.00 (1H, s, H-3); 8.70 (1H, s, NH); 10.36 (1H, s, CH=O). ^{13}C NMR spectrum, δ, ppm: 25.1; 30.6; 61.2; 67.4; 116.5; 126.9; 131.2; 152.1; 180.9. Mass spectrum, *m*/*z* (I_{rel}, %): 268 $[M+H]^+$ (100). Found, %: C 58.62; H 8.07; N 15.59. $C_{13}H_{21}N_3O_3$. Calculated, %: C 58.41; H 7.92; N 15.72.

***tert*-Butyl (5-formyl-1-phenyl-1*H*-pyrazol-4-yl)carbamate (3c)**. Yield 74.6 g (72%), pale-pink powder, mp 97–98°C. IR spectrum, ν, cm^{-1}: 3382 (N–H), 1701, 1722 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.54 (9H, s, $C(CH_3)_3$); 7.48–7.56 (5H, m, H Ph); 8.33 (1H, s, NH); 8.52 (1H, s, H-3); 9.89 (1H, s, CH=O). ^{13}C NMR spectrum, δ, ppm: 28.3; 81.5; 125.0; 126.0; 128.9; 129.7; 130.7; 130.8; 138.3; 152.5; 181.7. Mass spectrum, *m*/*z* (I_{rel}, %): 288 $[M+H]^+$ (100). Found, %: C 62.45; H 5.77; N 14.74. $C_{15}H_{17}N_3O_3$. Calculated, %: C 62.71; H 5.96; N 14.63.

***tert*-Butyl [5-formyl-1-(pyridin-2-yl)-1*H*-pyrazol-4-yl]-carbamate (3d)**. Yield 70.5 g (68%), beige powder, mp 82–83°C. IR spectrum, ν, cm^{-1}: 3388 (N–H), 1696, 1728 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (9H, s, $C(CH_3)_3$); 7.45 (1H, t, *J* = 5.6, H Py); 7.90 (1H, d, *J* = 8.4, H Py); 8.06 (1H, t, *J* = 6.8, H Py); 8.21 (1H, s, NH); 8.52 (1H, d, *J* = 4.4, H Pyr); 8.81 (1H, s, H-3); 10.97 (1H, s, CH=O). ^{13}C NMR spectrum, δ, ppm: 28.3; 81.5; 114.7; 122.0; 126.4; 131.9; 132.0; 138.9; 147.7; 152.6; 152.7; 186.1. Mass spectrum, *m*/*z* (I_{rel}, %): 289 $[M+H]^+$ (100). Found, %: C 58.51; H 5.74; N 19.65. $C_{14}H_{16}N_4O_3$. Calculated, %: C 58.32; H 5.59; N 19.43.

Synthesis of compounds 5a–t (General method). A solution of *N*-Boc-aminopyrazole carbaldehyde **3a**–**d**

(0.02 mol) in AcOH (100 ml) was treated by adding ketone **4a**–**l** (0.022 mol) and pyrrolidine (1.4 g, 0.02 mol), stirred for 1 h at room temperature and then refluxed for 4–6 h, while controlling the reaction progress with TLC. The mixture was cooled, the solvent was evaporated, and the obtained oily residue was diluted with H_2O (150 ml). In the case of aryl(hetaryl) ketones, the obtained precipitate was filtered off, washed with hexane (50 ml), dried, and crystallized from 1:5 mixture of MTBE–MeCN (compounds **5a**,**b**,**q**,**t**) or MeCN (compounds **5c**–**j**). In the case of dialkyl and cycloalkyl ketones, the oily product was extracted with AcOEt (2×75 ml), the organic layer was washed with aqueous $NaHCO_3$ and NaCl solutions, dried, and evaporated. The residue was diluted with 2:1 mixture of PhMe–MTBE (90 ml) and refluxed for 10 min, the solution was decanted, evaporated at reduced pressure, the obtained product was crystallized from 1:1 mixture of PhMe–MTBE (compounds **5k**,**l**,**o**,**p**,**r**,**s**).

1-Methyl-5-phenyl-1*H*-pyrazolo[4,3-*b*]pyridine (5a) was obtained from compounds **3a** and **4a**. Yield 2.93 g (70%), dark-brown powder, mp 155–156°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.94 (3H, s, CH_3); 7.44–7.51 (3H, m, H Ph); 7.99 (1H, d, *J* = 8.5, H-6); 8.14 (2H, d, *J* = 7.0, H Ph); 8.20 (1H, d, *J* = 8.5, H-7); 8.31 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 36.4; 118.8; 119.5; 127.3; 129.1; 129.2; 132.3; 133.6; 139.6; 141.7; 152.5. Mass spectrum, *m*/*z* (I_{rel}, %): 210 $[M+H]^+$ (100). Found, %: C 74.44; H 5.24; N 19.98. $C_{13}H_{11}N_3$. Calculated, %: C 74.62; H 5.30; N 20.08.

1-Methyl-5-(4-methylphenyl)-1*H*-pyrazolo[4,3-*b*]-pyridine (5b) was obtained from compounds **3a** and **4b**. Yield 2.81 g (63%), brown powder, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.36 (3H, s, CH_3); 4.09 (3H, s, CH_3); 7.30 (2H, d, *J* = 8.0, H Ar); 7.97 (1H, d, *J* = 8.0, H-6); 8.03 (2H, d, *J* = 8.0, H Ar); 8.20 (1H, d, *J* = 8.0, H-7); 8.28 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 21.3; 36.4; 118.5; 119.4; 127.2; 129.8; 132.2; 133.5; 136.8; 138.7; 141.7; 152.5. Mass spectrum, *m*/*z* (I_{rel}, %): 224 $[M+H]^+$ (100). Found, %: C 75.14; H 5.72; N 18.71. $C_{14}H_{13}N_3$. Calculated, %: C 75.31; H 5.87; N 18.82.

5-(4-Bromophenyl)-1-methyl-1*H*-pyrazolo[4,3-*b*]-pyridine (5c) was obtained from compounds **3a** and **4c**. Yield 2.77 g (48%), orange powder, mp 174–176°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.11 (3H, s, CH_3); 7.69 (2H, d, *J* = 8.0, H Ar); 8.04 (1H, d, *J* = 8.0, H-6); 8.11 (2H, d, *J* = 8.0, H Ar); 8.25 (1H, d, *J* = 8.0, H-7); 8.32 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 36.5; 118.6; 119.7; 122.8; 129.3; 132.2; 132.4; 133.6; 138.7; 141.7; 151.2. Mass spectrum, *m*/*z* (I_{rel}, %): 290 $[M(^{81}Br)+H]^+$ (94), 288 $[M(^{79}Br)+H]^+$ (100). Found, %: C 54.37; H 3.59; N 14.47. $C_{13}H_{10}BrN_3$. Calculated, %: C 54.19; H 3.50; N 14.58.

5-(2-Bromophenyl)-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (5d) was obtained from compounds **3a** and **4d**. Yield 1.85 g (32%), light-yellow powder, mp 170–171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.12 (3H, s, CH_3); 7.38 (1H, t, *J* = 8.0, H Ar); 7.48–7.60 (3H, m, H-6, H Ar); 7.67 (1H, d, *J* = 8.0, H Ar); 7.81 (1H, d, *J* = 8.0, H-7); 8.26 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 36.5; 118.5; 122.0; 122.4; 128.3; 130.6; 132.0; 132.2; 133.4; 133.5; 141.2; 141.8; 153.9. Mass spectrum, *m*/*z* (I_{rel}, %): 290 $[M(^{81}Br)+H]^+$ (90), 288 $[M(^{79}Br)+H]^+$ (100). Found, %: C 54.04; H 3.59; N 14.49. $C_{13}H_{10}BrN_3$. Calculated, %: C 54.19; H 3.50; N 14.58.

***N*-[4-(1-Methyl-1*H*-pyrazolo[4,3-*b*]pyridinyl)phenyl]acetamide (5e)** was obtained from compounds **3a** and **4e**. Yield 3.67 g (69%), yellow powder, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.08 (3H, s, CH_3); 4.08 (3H, s, CH_3); 7.71 (2H, d, *J* = 8.0, H Ar); 7.96 (1H, d, *J* = 8.8, H-6); 8.0 (2H, d, *J* = 8.0, H Ar); 8.17 (1H, d, *J* = 8.8, H-7); 8.26 (1H, s, H-3); 10.13 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 22.5; 36.3; 118.3; 119.4; 127.6; 129.9; 133.3; 134.1; 140.4; 141.6; 144.1; 152.1; 168.9. Mass spectrum, *m*/*z* (I_{rel}, %): 267 $[M+H]^+$ (100). Found, %: C 67.44; H 5.36; N 20.91. $C_{15}H_{14}N_4O$. Calculated, %: C 67.65; H 5.30; N 21.04.

1-(*tert*-Butyl)-5-(*p*-tolyl)-1*H*-pyrazolo[4,3-*b*]pyridine (5f) was obtained from compounds **3b** and **4b**. Yield 2.67 g (59%), light-brown powder, mp 172–173°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.72 (9H, s, $C(CH_3)_3$); 2.36 (3H, s, CH_3); 7.30 (2H, d, *J* = 8.2, H Ar); 7.87 (1H, d, *J* = 8.0, H-6); 8.01 (2H, d, *J* = 8.2, H Ar); 8.26 (1H, s, H-3); 8.37 (1H, d, *J* = 8.0, H-7). ^{13}C NMR spectrum, δ, ppm: 20.8; 29.3; 60.2; 117.4; 121.2; 126.6; 128.3; 129.2; 129.4; 132.0; 134.4; 136.2; 151.5. Mass spectrum, *m*/*z* (I_{rel}, %): 266 $[M+H]^+$ (100). Found, %: C 76.79; H 7.06; N 15.99. $C_{17}H_{19}N_3$. Calculated, %: C 76.95; H 7.22; N 15.84.

5-[(4-Bromophenyl)-1-(*tert*-butyl)]-1*H*-pyrazolo[4,3-*b*]-pyridine (5g) was obtained from compounds **3b** and **4c**. Yield 3.57 g (54%), brown powder, mp 178–180°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70 (9H, s, $C(CH_3)_3$); 7.64 (2H, d, *J* =7.6, H Ar); 7.86 (1H, d, *J* = 7.8, H-6); 8.05 (2H, d, *J* = 7.6, H Ar); 8.28 (1H, s, H-3); 8.35 (1H, d, *J* = 7.8, H-7). ^{13}C NMR spectrum, δ, ppm: 29.7; 60.7; 117.9; 121.8; 122.8; 129.2; 130.6; 132.2; 136.2; 138.6; 143.0; 150.7. Mass spectrum, *m*/*z* (I_{rel}, %): 332 $[M(^{81}Br)+H]^+$ (98), 330 $[M(^{79}Br)+H]^+$ (100). Found, %: C 58.41; H 4.74; N 12.55. $C_{16}H_{16}BrN_3$. Calculated, %: C 58.19; H 4.88; N 12.72.

4-[1-(*tert*-Butyl)-1*H*-pyrazolo[4,3-*b*]pyridin-5-yl]pyridinium acetate (5h) was obtained from compounds **3b** and **4f**. Yield 2.92 g (58%), dark-brown powder, mp 180–182°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.74 (9H, s, $C(CH_3)_3$); 1.90 (3H, s, CH_3COO); 8.06 (1H, d, *J* = 8.0, H-6); 8.10 (2H, d, *J* = 5.6, H Py); 8.37 (1H, s, H-3); 8.51 (1H, d, *J* = 8.0, H-7); 8.70 (2H, d, *J* = 5.6, H Py). The pyridinium NH proton exchanged with residual water molecules in the deuterated solvent. ^{13}C NMR spectrum, δ, ppm: 21.5; 29.7; 60.9; 118.3; 121.4; 121.9; 130.9; 133.0; 143.1; 146.3; 149.2; 150.7; 172.5. Mass spectrum, *m*/*z* (I_{rel}, %): 253 $[M–AcO]^+$ (100). Found, %: C 65.12; H 6.36; N 17.82. $C_{17}H_{20}N_4O_2$. Calculated, %: C 65.37; H 6.45; N 17.94.

1-Phenyl-5-(pyridin-4-yl)-1*H*-pyrazolo[4,3-*b*]pyridine (5i) was obtained from compounds **3c** and **4f**. Yield 1.19 g (22%), dark-brown powder, mp 192–194°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.38–7.65 (5H, m, H Ph); 7.84 (2H, d, *J* = 6.4, H Py); 8.14 (1H, s, H-3); 8.23 (1H, d, *J* = 7.6, H-6); 8.46 (1H, d, *J* = 7.6, H-7); 8.73 (2H, d, *J* = 6.4, H Py). ^{13}C NMR spectrum, δ, ppm: 107.3; 120.2; 120.9; 121.5; 122.4; 124.0; 127.7; 127.8; 130.4; 137.0; 139.2; 139.5; 150.7. Mass spectrum, *m*/*z* (I_{rel}, %): 273

$[M+H]^+$ (100). Found, %: C 75.16; H 4.59; N 20.41. $C_{17}H_{12}N_4$. Calculated, %: C 74.98; H 4.44; N 20.58.

5-Phenyl-1-(pyridin-2-yl)-1*H*-pyrazolo[4,3-*b*]pyridine (5j) was obtained from compounds **3d** and **4a**. Yield 3.06 g (38%), dark-gray powder, mp 174–175°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.36 (1H, t, *J* = 7.6, H Ph); 7.46–7.53 (3H, m, H Ph, H-6); 8.01–8.05 (2H, m, H Ph); 8.12–8.18 (3H, m, H Py); 8.59 (1H, d, *J* = 5.4, H Py); 8.71 (1H, s, H-3); 9.08 (1H, d, *J* = 8.2, H-7). ^{13}C NMR spectrum, δ, ppm: 113.0; 120.4; 121.5; 124.3; 127.4; 128.6; 129.1; 129.3; 129.5; 138.1; 139.0; 139.8; 148.6; 153.5; 154.1. Mass spectrum, *m*/*z* (I_{rel}, %): 273 $[M+H]^+$ (100). Found, %: C 74.79; H 4.38; N 20.47. $C_{17}H_{12}N_4$. Calculated, %: C 74.98; H 4.44; N 20.58.

5-Ethyl-1,6-dimethyl-1*H*-pyrazolo[4,3-*b*]pyridine (5k) was obtained from compounds **3a** and **4g**. Yield 1.36 g (36%), orange powder, mp 115–116°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 8.0, CH_3); 2.45 (3H, s, CH_3); 2.88 (2H, q, *J* = 8.0, CH_2); 4.02 (3H, s, CH_3); 7.43 (1H, s, H-7); 8.08 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 12.8; 19.9; 28.9; 35.7; 117.3; 129.3; 132.2; 132.8; 139.8; 158.1. Mass spectrum, *m*/*z* (I_{rel}, %): 176 $[M+H]^+$ (100). Found, %: C 68.72; H 7.33; N 23.81. $C_{10}H_{13}N_3$. Calculated, %: C 68.54; H 7.48; N 23.98.

5-Isopropyl-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (5l)[23] was obtained from compounds **3a** and **4h**. Yield 1.54 g (44%), beige powder, mp 110–111°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (6H, d, *J* = 6.8, $2CH_3$); 3.08 (1H, hept, *J* = 6.8, CH); 3.94 (3H, s, CH_3); 7.10 (1H, d, *J* = 8.8, H-6); 7.58 (1H, d, *J* = 8.8, H-7); 8.00 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 23.2; 35.8; 36.2; 118.9; 119.6; 132.0; 132.7; 140.9; 162.5. Mass spectrum, *m*/*z* (I_{rel}, %): 176 $[M+H]^+$ (100). Found, %: C 69.38; H 7.55; N 23.84. $C_{10}H_{13}N_3$. Calculated, %: C 68.54; H 7.48; N 23.98.

5-Butyl-1-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (5m) was obtained from compounds **3a** and **4j**. Yield 1.34 g (30%), dark-yellow oily liquid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87–0.91 (3H, m, CH_3); 1.25–1.31 (2H, m, CH_2); 1.64–1.69 (2H, m, CH_2); 2.81–2.86 (2H, m, CH_2); 4.04 (3H, s, CH_3); 7.28 (1H, d, *J* = 8.8, H-6); 8.02 (1H, d, *J* = 8.8, H-7); 8.12 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.2; 22.3; 32.1; 36.2; 37.6; 118.5; 121.0; 131.8; 132.5; 141.1; 157.7. Mass spectrum, *m*/*z* (I_{rel}, %): 190 $[M+H]^+$ (100). Found, %: C 69.65; H 8.13; N 22.08. $C_{11}H_{15}N_3$. Calculated, %: C 69.81; H 7.99; N 22.20.

1,6-Dimethyl-5-propyl-1*H*-pyrazolo[4,3-*b*]pyridine (5n) was obtained from compounds **3a** and **4j**. Yield 0.38 g (13%), orange crystals, mp 108–109°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.99 (3H, t, *J* = 7.2, CH_3); 1.62–1.69 (2H, m, CH_2); 2.55 (3H, s, CH_3); 2.68 (2H, t, *J* = 7.2, CH_2); 4.01 (3H, s, CH_3); 7.80 (1H, s, H-7); 8.04 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.2; 22.9; 23.0; 35.2; 36.1; 117.2; 132.2; 132.7; 134.0; 140.0; 153.1. Mass spectrum, *m*/*z* (I_{rel}, %): 190 $[M+H]^+$ (100). Found, %: C 69.63; H 7.92; N 22.31. $C_{11}H_{15}N_3$. Calculated, %: C 69.81; H 7.99; N 22.20.

1-(*tert*-Butyl)-5-methyl-1*H*-pyrazolo[4,3-*b*]pyridine (5o) was obtained from compounds **3b** and **4e**. Yield 1.09 g (29%), light-brown powder, mp 88–89°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.70 (9H, s, $C(CH_3)_3$); 2.61 (3H, s, CH_3); 7.30 (1H, d, *J* = 8.8, H-6); 8.10 (1H, s, H-3); 8.37 (1H, d, *J* = 8.8, H-7). ^{13}C NMR spectrum, δ, ppm: 23.6; 29.7; 60.7; 121.3; 122.5; 130.2; 130.5; 140.6; 153.0. Mass spectrum, *m*/*z* (I_{rel}, %): 190 $[M+H]^+$ (100). Found, %: C 69.64; H 7.81; N 22.01. $C_{11}H_{15}N_3$. Calculated, %: C 69.81; H 7.99; N 22.20.

1-(*tert*-Butyl)-5-ethyl-6-methyl-1*H*-pyrazolo[4,3-*b*]-pyridine (5p) was obtained from compounds **3b** and **4g**. Yield 1.30 g (30%), dark-brown powder, mp 92–93°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.6, CH_3); 1.72 (9H, s, $C(CH_3)_3$); 2.44 (3H, s, CH_3),; 2.88 (2H, q, *J* = 7.6, CH_2); 7.73 (1H, s, H-7); 8.08 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 12.7; 19.8; 28.4; 29.7; 60.1; 120.8; 128.8; 130.5; 131.5; 140.9; 157.1. Mass spectrum, *m*/*z* (I_{rel}, %): 218 $[M+H]^+$ (100). Found, %: C 71.99; H 8.72; N 19.18. $C_{13}H_{19}N_3$. Calculated, %: C 71.85; H 8.81; N 19.34.

5-Ethyl-6-methyl-1-(pyridin-2-yl)-1*H*-pyrazolo[4,3-*b*]-pyridine (5q) was obtained from compounds **3d** and **4g**. Yield 2.05 g (43%), brown powder, mp 108–109°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, t, *J* = 7.6, CH_3); 2.48 (3H, s, CH_3); 2.89 (2H, q, *J* =7.6, CH_2); 7.31–7.35 (1H, m, H Py); 7.98–8.03 (2H, m, H Py); 8.51 (1H, s, H-7); 8.56 (1H, d, *J* = 4.8, H Py); 8.77 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 12.5; 19.9; 28.5; 112.9; 121.2; 123.2; 131.2; 131.5; 137.4; 139.7; 141.5; 148.5; 153.8; 159.4. Mass spectrum, *m*/*z* (I_{rel}, %): 239 $[M+H]^+$ (100). Found, %: C 70.68; H 5.97; N 23.35. $C_{14}H_{14}N_4$. Calculated, %: C 70.57; H 5.92; N 23.51.

1-Methyl-5,6-dihydro-1*H*-cyclobuta[*b*]pyrazolo[3,4-*e*]-pyridine (5r) was obtained from compounds **3a** and **4k**. Yield 0.6 g (19%), yellow powder, mp 107–108°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.00–3.04 (2H, m, CH_2); 3.28–3.32 (2H, m, CH_2); 3.91 (3H, s, CH_3); 7.29 (1H, s, H-7); 7.94 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 25.3; 33.6; 36.4; 56.5; 112.4; 132.3; 134.8; 138.5; 140.6. Mass spectrum, *m*/*z* (I_{rel}, %): 160 $[M+H]^+$ (100). Found, %: C 68.11; H 5.61; N 26.57. $C_9H_9N_3$. Calculated, %: C 67.90; H 5.70; N 26.40.

1-(*tert*-Butyl)-1,5,6,7-tetrahydrocyclopenta[*b*]pyrazolo-[4,3-*e*]pyridine (5s) was obtained from compounds **3b** and **4l**. Yield 1.68 g (39%), orange powder, mp 88–89°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.73 (9H, s, $C(CH_3)_3$); 2.17–2.22 (2H, m, CH_2); 3.00–3.08 (4H, m, $2CH_2$); 7.80 (1H, s, H-7); 8.06 (1H, s, H-3). 13C NMR spectrum, δ, ppm: 24.4; 29.6; 30.8; 33.0; 60.2; 116.0; 130.9; 131.3; 135.4; 141.2; 161.7. Mass spectrum, *m*/*z* (I_{rel}, %): 216 $[M+H]^+$ (100). Found, %: C 72.71; H 7.79; N 19.43. $C_{13}H_{17}N_3$. Calculated, %: C 72.52; H 7.96; N 19.52.

1-(Pyridin-2-yl)-5,6-dihydro-1*H*-cyclobuta[*b*]pyrazolo-[4,3-*b*]pyridine (5t) was obtained from compounds **3d** and **4k**. Yield 2.36 g (53%), brown powder, mp 121–122°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18–3.22 (2H, m, CH_2); 3.41–3.45 (2H, m, CH_2); 7.33–7.37 (1H, m, H Py); 8.03 (2H, d, *J* = 4.8, H Py); 8.51 (1H, s, H-7); 8.55 (1H, d, *J* = 4.8, H Py); 8.74 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 25.6; 33.7; 113.3; 117.2; 121.4; 133.0; 137.3; 139.8; 140.5; 142.8; 148.4; 153.8; 161.9. Mass spectrum, *m*/*z* (I_{rel}, %): 223 $[M+H]^+$ (100). Found, %: C 70.52; H 4.41; N 25.07. $C_{13}H_{10}N_4$. Calculated, %: C 70.26; H 4.54; N 25.21.

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