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A facile synthesis of regioisomeric 4-amino- and 6-amino-3-arylpyrazolo-[3,4-*b*]pyridine-5-carbonitriles

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Table of contents

Materials and methods 1
Pyrazol-5-amines **1** 2
2-[(3-Aryl-1-R-1*H*-5-pyrazol-5-yl)aminomethylidene]malononitriles **4** 3
6-Amino-1-benzyl-3-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **3** 3
4-Amino-1,3-diaryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **5** 4

Materials and methods

The NMR spectra were recorded on a spectrometer Bruker Avance II [400.1 (^{1}H), 100.6 (^{13}C), and 40.5 (^{15}N)] in DMSO-d_6. The assignment of the signals in the ^{1}H and ^{13}C spectra was based on results of methods DEPT 135, COSY, NOESY, ^{1}H-^{13}C HSQC, and ^{1}H–^{13}C, ^{1}H–^{15}N HMBC. Chemical shifts are given in the δ scale relative to the residual solvent signals (δ_H 2.50, δ_C 39.50). Elemental composition was determined by high resolution mass spectrometry (HRMS) on a Bruker Daltonics microTOF instrument employing electrospray ionization (ESI) and operating in the positive ion mode. The melting points were measured on a Boetius heating stage and were not corrected. All reagents for synthesis were commercial (Across Organics) and used without further purification.

Aminopyrazoles (**1a-g**) (*general procedure*)**.** Hydrazine hydrate (50 mmol) was added dropwise to a solution of 25 mmol of the corresponding β-keto nitrile in 50 ml of ethanol and 5 ml of acetic acid. The mixture was stirred for 2 h at 50°C, an additional 10 ml of acetic acid was added, and the mixture was heated for 5 h under reflux, cooled to room temperature, poured into 200 ml of ice water, and neutralized to pH 9 by adding aqueous ammonia. The precipitate was filtered off.

1-Benzyl-3-phenyl-1*H*-pyrazol-5-amine (**1a**). Yield 76%, mp 118-119 ºC (123-125 ºC[1]). ^{1}H NMR δ: 5.21 (s, 2H, CH_2), 5.41 (s, 2H, NH_2), 5.78 (s, 1H, CH=), 7.21-7.27, 7.31-37 (m, 8H, $H_{arom.}$), 7.71 (d, 2H, $H_{arom.}$, *J* 8.3 Hz). ^{13}C NMR δ: 49.91 (CH_2), 85.21 (CH), 124.69 (CH), 126.90 (CH), 126.98 (CH), 127.10 (CH), 128.26 (CH), 128.31 (CH), 134.18 (C), 138.06 (C), 148.25 (C), 148.59 (C).

1-Benzyl-3-(4-chlorophenyl)-1*H*-pyrazol-5-amine (**1b**). Yield 80%, mp 116-117 ºC. ^{1}H NMR δ: 5.19 (s, 2H, CH_2), 5.44 (s, 2H, NH_2), 5.76 (s, 1H, CH=), 7.19 (d, 2H, $H_{arom.}$, *J* 7.3 Hz), 7.25 (t, 1H, $H_{arom.}$, *J* 7.2 Hz), 7.33 (t, 2H, $H_{arom.}$, *J* 7.3 Hz), 7.38 (d, 2H, $H_{arom.}$, *J* 8.4 Hz), 7.69 (d, 2H, $H_{arom.}$, *J* 8.4 Hz).

1-Benzyl-3-(*p*-tolyl)-1*H*-pyrazol-5-amine (**1c**). Yield 75%, mp 115-116 ºC. ^{1}H NMR δ: 2.29 (s, 3H, Me), 5.17 (s, 2H, CH_2), 5.36 (s, 2H, NH_2), 5.69 (s, 1H, CH=), 7.13-7.34 (m, 7H, $H_{arom.}$), 7.55 (d, 2H, $H_{arom.}$, *J* 8.0 Hz).

1,3-Diphenyl-1*H*-pyrazol-5-amine (**1d**). Yield 81%, mp 125-126 ºC (125-126 ºC[1], 129-130 ºC[2]). ^{1}H NMR δ: 5.41 (s, 2H, NH_2), 5.86 (s, 1H, CH=), 7.32 (t, 1H, $H_{arom.}$, *J* 7.3 Hz), 7.43 (m, 3H, $H_{arom.}$), 7.51 (d, 2H, $H_{arom.}$, *J* 7.6 Hz), 7.68 (d, 2H, $H_{arom.}$, *J* 7.6 Hz), 7.75 (d, 2H, $H_{arom.}$, *J* 8.4 Hz).

1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-5-amine (**1e**). Yield 75%, mp 170-171 ºC (172-173 ºC[2]). ^{1}H NMR δ: 2.32 (s, 3H, Me), 5.42 (s, 2H, NH_2), 5.89 (s, 1H, CH=), 7.20 (d, 2H, $H_{arom.}$, *J* 7.6 Hz), 7.33 (t, 1H, $H_{arom.}$, *J* 7.3 Hz), 7.51 (t, 2H, $H_{arom.}$, *J* 7.6 Hz), 7.66 (m, 4H, $H_{arom.}$). ^{13}C NMR δ: 20.78 (Me), 87.05 (CH=), 122.78 (CH), 124.95 (CH), 126.11 (CH), 129.01 (CH), 129.05 (CH), 130.88 (C), 136.66 (C), 139.32 (C), 148.10 (C), 150.03(C).

1,3-Bis(4-chlorophenyl)-1*H*-pyrazol-5-amine (**1f**). Yield 75%, mp 162-163 ºC. ^{1}H NMR δ: 5.42 (s, 2H, NH_2), 5.88 (s, 1H, CH=), 7.50 (m, 4H, H_{Ar}), 8.17 (d, 2H, H_{Ar}, *J* 8.3 Hz), 8.32 (d, 2H, H_{Ar}, *J* 8.3 Hz).

3-(4-Chlorophenyl)-1-(3,4-dimethylphenyl)-1*H*-pyrazol-5-amine (**1g**). Yield 75%, 139-140 ºC. ^{1}H NMR δ: 2.28 (s, 3H, Me), 2.29 (s, 3H, Me), 5.39 (s, 2H, NH_2), 5.90 (s, 1H, CH=), 7.24–7.44 (m, 5H, H_{Ar}), 7.76 (d, 2H, H_{Ar}, *J* 7.9 Hz). ^{13}C NMR δ: 18.86 (Me), 19.38 (Me), 86.70 (CH=), 120.45 (CH), 124.19 (CH), 126.62 (CH), 128.41 (CH), 129.88 (CH), 131.74 (C), 132.63 (C), 134.59 (C), 136.80 (C), 137.08 (C), 148.17 (C), 148.45 (C).

2-[(3-Aryl-1-R-1*H*-pyrazol-5-yl)aminomethylidene]malononitriles 4. A mixture of 5-amino-1-R-pyrazole **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.

2-{[1-Benzyl-3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]aminomethylidene}malononitrile 4b. Yield 90%, mp 206-207 ºC. ^{1}H NMR δ: 5.41 (s, 2H, CH_2), 6.77 (s, 1H, $CH_{pyr.}$), 7.17 (d, 2H, $H_{Ph.}$, *J* 7.3 Hz), 7.19-7.38 (m, 5H, H_{Ph}), 7.73 (d, 2H, H_{Ph}, *J* 8.2 Hz), 8.00 (br. s, 1H, CH=), 11.20 (br. s, 1H, NH). HRMS, *m/z:* 360.0999 $[M+H]^+$ (calc. for $C_{20}H_{15}ClN_5$, *m/z:* 360.1011).

2-{[1-Benzyl-3-(*p*-tolyl)-1*H*-pyrazol-5-yl]aminomethylidene}malononitrile 4c. Yield 82%, mp 186–187 ºC. ^{1}H NMR δ: 2.36 (s, 3H, Me), 5.39 (s, 2H, CH_2), 6.68 (s, 1H, $CH_{pyr.}$), 7.14-7.38 (m, 7H, $H_{Ph.}$), 7.60 (d, 2H, H_{Ph}, *J* 7.6 Hz), 8.00 (d, 1H, CH=, *J* 10.9 Hz), 11.17 (d, 1H, NH, *J* 10.9 Hz). HRMS, *m/z:* 340.1556 $[M+H]^+$ (calc. for $C_{21}H_{18}N_5$, *m/z:* 340.1557).

2-{[1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-5-yl]aminomethylidene}malononitrile 4e. Yield 88%, mp 273-274 ºC. ^{1}H NMR δ: 2.39 (s, 3H, Me), 6.87 (s, 1H, $CH_{pyr.}$), 7.21 (d, 2H, H_{Ph}, *J* 7.8 Hz), 7.43 (t, 1H, H_{Ph}, *J* 7.3 Hz), 7.55 (t, 2H, H_{Ph}, *J* 7.8 Hz), 7.62 (d, 2H, H_{Ph}, *J* 7.8 Hz), 7.71 (d, 2H, H_{Ph}, *J* 7.8 Hz), 8.12 (br. s, 1H, CH=), 11.25 (br. s, 1H, NH). ^{13}C NMR δ: 20.84 (Me), 53.55 (C), 98.59 (CH=), 113.45 (CN), 115.67 (CN), 123.76 (CH), 125.07 (CH), 127.70 (CH), 129.34 (CH), 129.56 (CH), 129.75 (CH), 137.72 (C), 138.35 (C), 139.93 (C), 150.46 (C), 160.27 (CH). HRMS, *m/z:* 326.1409 $[M+H]^+$ (calc. for $C_{20}H_{16}N_5$, *m/z:* 326.1401).

6-Amino-1-R-3-aryl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles 3 (general procedure). A mixture of 5-amino-1-R-pyrazole **1** (1 mmol) and ethoxymethylidenemalononitrile **2** (1 mmol) in BuOH (2 ml) was refluxed for 14 h for 5-amino-1-benzylpyrazole and 20 h for 5-amino-1-arylpyrazole. The solvent was removed *in vacuo*, the residue was recrystallized.

6-Amino-1-benzyl-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 3b. Yield 64%, mp 212-213 ºC (EtOH). ^{1}H NMR δ: 5.50 (s, 2H, CH_2), 7.25 (s, 2H, NH_2), 7.28-7.35 (m, 5H, H_{Bz}), 7.51 (d, 2H, H^m_{Ar}, *J* 8.3 Hz), 7.99 (d, 2H, H^o_{Ar}, *J* 8.3 Hz), 8.85 (s, 1H, CH=). ^{13}C NMR δ: 49.47 (CH_2), 88.63 (C^5), 105.06 (C^{3a}), 117.36 (CN), 127.27 (CH), 127.51 (CH), 128.24 (CH), 128.58 (2CH), 128.89 (CH), 130.82 (C), 133.20 (C), 137.07 (C), 139.29 (C^4H), 142.19 (C^3), 152.04 (C^{7a}), 158.53 (C^6). HRMS, *m/z:* 360.1020 $[M+H]^+$ (calc. for $C_{20}H_{15}ClN_5$, *m/z:* 360.1011).

6-Amino-1-benzyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 3c. Yield 40%, mp 182-183 ºC (BuOH). ^{1}H NMR δ: 2.36 (s, 3H, Me), 5.49 (s, 2H, CH_2), 7.19-7.33 (m, 9H, H_{Ar}, NH_2), 7.85 (d, 2H, H^o_{Ar}, *J* 7.8 Hz), 8.81 (s, 1H, CH=). ^{13}C NMR δ: 20.88 (Me), 49.37 (CH_2), 88.21 (C^5), 105.22 (C^{3a}), 117.48 (CN), 126.50 (CH), 127.24 (CH), 127.45 (CH), 128.56 (CH), 129.23 (C),

129.47 (CH), 137.22 (C), 138.09 (C), 139.33 (C^4H), 143.43 (C^3), 152.01 (C^{7a}), 158.52 (C^6). HRMS, *m/z:* 340.1572 $[M+H]^+$ (calc. for $C_{21}H_{18}N_5$, *m/z:* 340.1557).

6-Amino-1,3-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 3d. Yield 52%, mp 225-226 ºC (BuOH). ^{1}H NMR δ: 7.36 (m, 3H, H_{Ar}, NH_2), 7.52 (m, 5H, H_{Ar}), 8.07 (d, 2H, H_{Ar}, *J* 7.6 Hz), 8.27 (d, 2H, H_{Ar}, *J* 8.3 Hz), 8.89 (s, 1H, CH=). ^{13}C NMR δ: 88.75 (C^5), 106.80 (C^{3a}), 117.18 (CN), 120.83 (CH), 125.98 (CH), 127.04 (CH), 128.99 (CH), 129.02 (CH), 129.11 (CH), 131.49 (C), 138.81 (C), 139.38 (C^4H), 144.62 (C^3), 151.78 (C^{7a}), 158.68 (C^6). HRMS, *m/z:* 312.1233 $[M+H]^+$ (calc. for $C_{19}H_{14}N_5$, *m/z:* 312.1244).

6-Amino-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 3e. Yield 78%, mp 242-243 ºC (BuOH). ^{1}H NMR δ: 2.40 (s, 3H, Me), 7.34 (m, 5H, H_{Ar}, NH_2), 7.55 (t, 2H, H_{Ar}, *J* 7.6 Hz), 7.97 (d, 2H, H_{Ar}, *J* 7.7 Hz), 8.27 (d, 2H, H_{Ar}, *J* 7.9 Hz), 8.87 (s, 1H, CH=). ^{13}C NMR δ: 20.90 (Me), 88.54 (C^5), 106.81 (C^{3a}), 117.17 (CN), 120.73 (CH), 125.84 (CH), 126.85 (CH), 128.68 (C), 128.95 (CH), 129.49 (CH), 138.63 (C), 138.83 (C), 139.24 (C^4H), 144.61 (C^3), 151.71 (C^{7a}), 158.62 (C^6H). HRMS, *m/z:* 326.1411 $[M+H]^+$ (calc. for $C_{20}H_{16}N_5$, *m/z:* 326.1401).

6-Amino-1,3-di(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 3f. Yield 72%, mp 263-265 ºC (BuOH). ^{1}H NMR δ: 7.46 (s, 2H, NH_2), 7.60 (m, 4H, H_{Ar}), 8.09 (d, 2H, H_{Ar}, *J* 8.3 Hz), 8.33 (d, 2H, H_{Ar}, *J* 8.3 Hz), 8.92 (s, 1H, CH=). ^{13}C NMR δ: 89.07 (C^5), 106.67 (C^{3a}), 117.16 (CN), 120.78 (C), 125.64 (CH), 126.78 (CH), 128.52 (CH), 130.03 (CH), 130.13 (C), 133.91 (C), 137.61 (C), 139.46 (C^4H), 143.80 (C^3), 151.86 (C^{7a}), 158.74 (C^6). HRMS, *m/z:* 380.0452 $[M+H]^+$ (calc. for $C_{19}H_{12}Cl_2N_5$, *m/z:* 380.0465).

6-Amino-1-(3,4-dimethylphenyl)-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 3g. Yield 56%, mp 245-246 ºC (BuOH). ^{1}H NMR δ: 2.28 (s, 3H, Me), 2.32 (s, 3H, Me), 7.27 (d, 1H, H_{Ar}, *J* 8.0 Hz), 7.34 (s, 2H, NH_2), 7.57 (d, 2H, H_{Ar}, *J* 8.3 Hz), 7.94 (d, 1H, H_{Ar}, *J* 8.0 Hz), 7.98 (s, 1H, H_{Ar}), 8.08 (d, 2H, H_{Ar}, *J* 8.3 Hz), 8.88 (s, 1H, CH=). ^{13}C NMR δ: 18.45 (Me), 19.17 (Me), 88.57 (C^5), 106.34 (C^{3a}), 116.71 (CN), 118.20 (CH), 121.78 (CH), 128.27 (CH), 128.56 (CH), 129.39 (CH), 130.19 (C), 133.33 (C), 133.89 (C), 136.29 (C), 136.53 (C), 138.49 (C^4H), 142.76 (C^3), 151.32 (C^{7a}), 158.22 (C^6). HRMS, *m/z:* 374.1179 $[M+H]^+$ (calc. for $C_{21}H_{17}ClN_5$, *m/z:* 374.1167).

4-Amino-1-R-3-aryl-1*H*-pyrazolo[3,4-b]pyridine-5-carbonitriles 5 (general procedure). 2-(3-Aryl-1-R-1*H*-5-pyrazol-5-ylaminomethylidene)malononitrile **A** (1 mmol) was refluxed for 2 h in diphenyl ether (3 ml). The reaction mixture was diluted with 8 ml of hexane and left over night in a refrigerator. The formed precipitate was filtered and recrystallized.

4-Amino-1-benzyl-3-(4-chlorophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 5b. Yield 66%, mp 204-205 ºC (BuOH). ^{1}H NMR δ: 5.61 (s, 2H, CH_2), 6.89 (s, 2H, NH_2), 7.30 (m, 5H,

H_{Bz}), 7.59 (d, 2H, H^{m}_{Ar}, *J* 8.3 Hz), 7.64 (d, 2H, H^{o}_{Ar}, *J* 8.3 Hz), 8.45 (s, 1H, CH=). ^{13}C NMR δ: 50.09 (CH_2), 84.50 (C^5), 100.15 (C^{3a}), 117.23 (CN), 127.61 (C^{o}_{Bz}), 128.56 (C^{p}_{Bz}, C^{m}_{Bz}), 129.07 (C^{m}_{Ar}), 130.36 (C^{o}_{Ar}), 131.56 (C^{i}_{Ar}), 133.67 (C^{i}_{Bz}), 143.36 (C^3), 151.91 (C^4), 152.33 (C^{7a}), 153.34 (C^6). HRMS, *m/z:* 360.1025 $[M+H]^+$ (calc. for $C_{20}H_{15}ClN_5$, *m/z:* 360.1011).

4-Amino-1-benzyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 5c. Yield 64%, mp 215-216 ºC (BuOH). ^{1}H NMR δ: 2.39 (s, 3H, Me), 5.60 (s, 2H, CH_2), 6.76 (s, 2H, NH_2), 7.29 (m, 5H, H_{Ar}), 7.35 (d, 2H, H_{Ar}, *J* 7.8 Hz), 7.53 (d, 2H, $H_{Ar.}$, *J* 8.3 Hz), 8.44 (s, 1H, CH=). ^{13}C NMR δ: 20.87 (Me), 50.02 (CH_2), 84.16 (C^5), 100.09 (C^{3a}), 117.26 (CN), 127.60 (2CH), 128.44 (CH), 128.54 (CH), 129.73 (CH), 129.90 (C), 137.00 (C), 138.49 (C), 144.38 (C^3), 151.94 (C^4), 152.19 (C^{7a}), 153.21 (C^6H). HRMS, *m/z:* 340.1570 $[M+H]^+$ (calc. for $C_{21}H_{18}N_5$, *m/z:* 340.1557).

4-Amino-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile 5e. Yield 56%, mp 267-268ºC (BuOH). ^{1}H NMR δ: 2.49 (s, 3H, Me), 6.81 (s, 2H, NH_2), 7.32 (t, 3H, H_{Ar}, *J* 7.3 Hz), 7.40 (d, 2H, H_{Ar}, *J* 7.8 Hz), 7.51 (t, 3H, H_{Ar}, *J* 7.8 Hz), 7.60 (d, 2H, H_{Ar}, *J* 7.8 Hz), 8.24 (d, 2H, H_{Ar}, *J* 8.0 Hz), 8.49 (s, 1H, CH=). ^{13}C NMR δ: 20.90 (Me), 85.27 (C^5), 101.65 (C^{3a}), 116.92 (CN), 121.47 (CH), 126.47 (CH), 128.56 (CH), 129.00 (CH), 129.42 (C), 129.75 (CH), 138.47 (C), 138.91 (C), 145.65 (C^3), 151.86, 151.95 (C^4, C^{7a}), 153.54 (C^6H). HRMS, *m/z:* 326.1414 $[M+H]^+$ (calc. for $C_{20}H_{16}N_5$, *m/z:* 326.1401).

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