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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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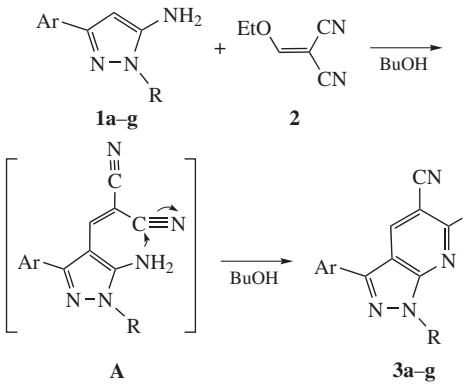
Boiling of 3-aryl-1-R-1*H*-pyrazol-5-amines with ethoxymethylidenemalononitrile in butanol affords 6-amino-3-aryl-1-R-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitriles, whereas low temperature condensation of the same reactants followed by heating to 230 °C in diphenyl ether gives the isomeric 4-amino derivatives.

Pyrazolo[3,4-*b*]pyridine pharmacophore moiety is a common fragment of physiologically active compounds.[1–7] Reactions of 1-R-5-aminopyrazoles with dielectrophiles (*e.g.*, ethoxymethylidene derivatives of malonic and cyanoacetic esters and malononitrile) lead to 4-R-pyrazolo[3,4-*b*]pyridines unsubstituted in the 6-position.[8–10] On the other hand, the Friedlander condensation of 5-aminopyrazolo-4-carbaldehydes in alkaline medium with carbonyl compounds that contain an active methylene group, affords 6-R-pyrazolo[3,4-*b*]pyridines unsubstituted in the 4-position.[11–15]

We formerly demonstrated that 5-amino-3-methyl-1-arylpyrazole regioselectively reacted with ethoxymethylidenemalononitrile in methanol to give 4-amino-1-aryl-3-methyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitriles which when boiled in butanol underwent isomerization into 6-amino-1-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles.[16] In the case of 3-*tert*-butyl-1-phenyl-1*H*-pyrazole-5-amine the formation of pyrazolo-[3,4-*b*]pyridines did not occur either by boiling the reactants in butanol or by heating in diphenyl ether at 230–235 °C.[16]

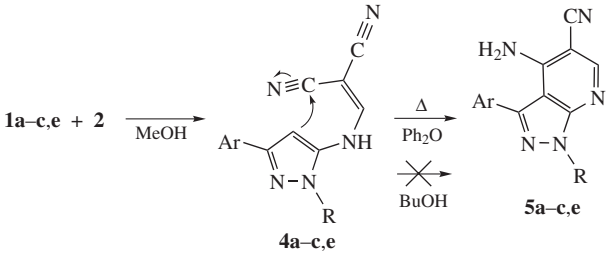
In searching the rules for the formation of regioisomeric functionalized pyrazolo[3,4-*b*]pyridines, we have studied analogous reactions of *N*-benzyl- and *N*-aryl-substituted 3-aryl-5-aminopyrazoles. By boiling *N*-substituted 5-aminopyrazoles **1a–g** with ethoxymethylidenemalononitrile **2** in butanol for ~14 h (Scheme 1),† only pyrazolo[3,4-*b*]pyridines **3a–g** were obtained.

Heating of N-substituted 5-aminopyrazoles **1a–c**,**e** with substrate **2** in methanol for ~20 h afforded only linear malononitriles




**a** Ar = Ph, R = Bn
**b** Ar = 4-ClC$_6$H$_4$, R = Bn
**c** Ar = 4-MeC$_6$H$_4$, R = Bn
**d** Ar = R = Ph
**e** Ar = 4-MeC$_6$H$_4$, R = Ph
**f** Ar = R = 4-ClC$_6$H$_4$
**g** Ar = 4-ClC$_6$H$_4$, R = 3,4-Me$_2$C$_6$H$_3$

**Scheme 1**




**Scheme 2**

**4a–c**,**e** (Scheme 2).† The reaction proceeds *via* a nucleophilic attack of the exocyclic nitrogen atom of aminopyrazole **1** on the alkene CH of compound **2** with the replacement of the ethoxy group. The structure of these compounds was established from the $^1$H and $^{13}$C NMR spectra. The downfield region of the $^1$H spectra contained characteristic doublet signals of protons of NH and alkene CH groups at $\delta$ ~11.2 and ~8.0 ppm, respectively, with a vicinal coupling constant $^3J$ ~10.6 Hz. The cyclization did not occur when compounds **4a–c**,**e** were boiled in butanol.

† Physicochemical measurements were carried out using the equipment of the resource centers of St. Petersburg University 'Methods of Substances Composition Analysis' and 'Magnetic Resonance Investigation Methods'.

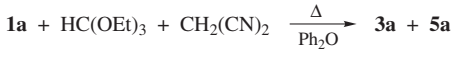
*2-[(1-Benzyl-3-phenyl-1*H*-5-pyrazol-5-yl)aminomethylidene]malononitrile* **4a**. A mixture of 5-amino-1-benzylpyrazole **1a** (1 mmol) and ethoxymethylidenemalononitrile **2** (1 mmol) in MeOH (3 ml) was boiled for 20 h. The solvent was removed *in vacuo*, the residue was recrystallized. Yield 85%, mp 188–189 °C (EtOH). $^1$H NMR, $\delta$: 5.41 (s, 2 H, CH$_2$), 6.37 (s, 1H, CH$_{pyr}$), 7.17–7.38 (m, 8 H, H$_{Ph}$, CH=), 7.73 (d, 2 H, H$_{Ph}$, *J* 7.3 Hz), 8.00 (d, 1H, CH=, *J* 10.6 Hz), 11.17 (d, 1H, NH, *J* 10.6 Hz). $^{13}$C NMR, $\delta$: 51.69 (CH$_2$), 54.00 (C), 96.33 (CH), 113.46 (CN), 115.62 (CN), 124.88 (CH), 127.26 (CH), 127.57 (CH), 127.95 (CH), 128.58 (CH), 128.72 (CH), 132.69 (C), 136.78 (C), 140.57 (C-5), 149.37 (C-3), 159.72 (CH=). HRMS, *m*/*z*: 326.1422 [M+H]$^+$ (calc. for C$_{20}$H$_{16}$N$_5$, *m*/*z*: 326.1401).

*6-Amino-1-benzyl-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile* **3a**. A mixture of compounds **1a** (1 mmol) and **2** (1 mmol) in BuOH (3 ml) was boiled for 14 h. The reaction mixture was cooled and evaporated at a reduced pressure. The dry residue was recrystallized. Yield 46%, mp 196–197 °C (EtOH). $^1$H NMR, $\delta$: 5.51 (s, 2 H, CH$_2$), 7.19 (s, 2 H, NH$_2$), 7.26 (m, 3 H, *o*-H$_{Bz}$, *p*-H$_{Bz}$), 7.33 (t, 2 H, *m*-H$_{Bz}$, *J* 7.2 Hz), 7.43 (t, 1H, *p*-H$_{Ar}$, *J* 7.2 Hz), 7.47 (t, 2H, *m*-H$_{Ar}$, *J* 7.5 Hz), 7.96 (d, 2 H, *o*-H$_{Ar}$, *J* 7.5 Hz), 8.83 (s, 1H, CH=). $^{13}$C NMR, $\delta$: 49.39 (CH$_2$), 88.40 (C-5), 105.22 (C-3a), 117.41 (CN), 126.57 (*o*-C$_{Ar}$), 127.21 (*o*-C$_{Bz}$), 127.41 (*p*-C$_{Bz}$), 128.51 (*p*-C$_{Ar}$, *m*-C$_{Bz}$), 128.84 (*m*-C$_{Ar}$), 131.97 (*i*-C$_{Ar}$), 137.13 (*i*-C$_{Bz}$), 139.27 (CH=), 143.36 (C-3), 152.02 (C-7a), 158.49 (C-6). HRMS, *m*/*z*: 326.1412 [M+H]$^+$ (calc. for C$_{20}$H$_{16}$N$_5$, *m*/*z*: 326.1401).

However, by heating for 2 h at 230 °C in diphenyl ether pyrazole[3,4-*b*]pyridines **5a**–**c**,**e** were obtained in 46–64% yields (see Scheme 2). Heating mixtures of compounds **1a** and **2** for 2 h at 230 °C in diphenyl ether produced isomeric pyrazolopyrimidines **3a** and **5a**, whereas the reaction **1e** + **2** gave an only regioisomer **3e** (Scheme 3).


**Scheme 3**

A 1 : 2 mixture of compounds **3a** and **5a** was obtained by heating the three component mixture of aminopyrazole **1a**, malononitrile, and triethyl orthoformate in diphenyl ether (Scheme 4). Additional experiments revealed that compounds **3a** and **5a** did not transform into one another by boiling either in butanol or diphenyl ether.




**Scheme 4**

Therefore, the reactions of aminopyrazoles **1a**–**g** with ethoxymethylidenemalononitrile **2** possessed certain features distinguishing them from the previously studied reactions of similar type. Regioisomers **5** formed exclusively through the intramolecular cyclization of the intermediate of type **4** on heating to 230 °C in diphenyl ether, while regioisomers **3** were obtained by boiling aminopyrazoles **1** with ethoxymethylidenemalononitrile **2** in butanol, and in the case of aminopyrazole **1e**, by heating in diphenyl ether.

4-Amino-3-aryl-1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles **5** prepared in this study are stable compounds in contrast to 3-methyl-substituted analogues which readily undergo thermal isomerization into more thermodynamically stable 6-amino-1-aryl-3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles.[16]

The starting aminoazoles **1** can be regarded as 1,3-binucleophiles possessing two nonequivalent sites (C-4 and $NH_2$) capable of reacting with electrophiles without regioselectivity. It is presumed that formation of regioisomers **3** and **5** proceeds through different key intermediate structures (see Schemes 1, 2 and refs. 17, 18). In intermediate **4** (normal attack) the closure of the pyridine ring of compound **5** occurs only at high temperature as a result of the reaction of C-4 with the carbon atom of the cyano group of the dicyanomethylidene fragment. Intermediate **A** formed from attack of C-4[18] undergoes cyclization into **3** *via* the intramolecular attack of the free amino group of aminoazole on the cyano group.

Position of substituents (H and $NH_2$) in the pyridine ring in compounds **3** and **5** was deduced from NOE experiments and from long-range scalar interactions $^1H$–$^{15}N$. In the NOESY spectrum of compound **3a** in DMSO-$d_6$, a cross-peak is observed between the signals of the *ortho*-protons of the phenyl group at 7.97 ppm and the proton signal of C-4 at 8.84 ppm. The $^1H$–$^{15}N$ HMBC spectrum of compound **5a** optimized for scalar constant $J_{NH}$ 8 Hz exhibits an intensive cross-peak between the signals of protons H-6 ($\delta$ 8.44) and atom N-7 ($\delta$ 243.8) (and a weak cross-peak with the signal of the nitrogen atom of the $NH_2$ group at 89.0 ppm). This spectrum also contains cross-peaks between the signals of protons $CH_2$ ($\delta$ 5.61) and nitrogen atoms N-1 ($\delta$ 314.6) and N-7 ($\delta$ 198.9).

The formation of different individual regioisomeric compounds resulted from the change of the reaction conditions was previously observed only in the three-component reaction of N-unsubstituted 5-aminopyrazoles.[2]

Hence we have accomplished a new synthesis of two different regioisomeric derivatives of pyrazolo[3,4-*b*]pyridine by changing the nature of the solvent and the temperature of the reaction between 1-R-5-aminopyrazoles and ethoxymethylidenemalononitrile. The synthetic procedure is simple and convenient in the preparative respect and ensures high yields of substituted pyrazolo[3,4-*b*]pyridines.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.09.023.

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*4-Amino-1-benzyl-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile* **5a**. Adduct **4a** (1 mmol) was heated in diphenyl ether (2 g) at 230 °C for 2 h. The reaction mixture was diluted with 8 ml of hexane and left for a night in a refrigerator. The separated precipitate was filtered off and recrystallized. Yield 56%, mp 214–215 °C (BuOH). $^1H$ NMR, $\delta$: 5.59 (s, 2H, $CH_2$), 6.59 (s, 2H, $NH_2$), 7.28 (m, 5H, $H_{Ph}$), 7.51 (m, 3H, $H_{Ph}$), 7.62 (d, 2H, $H_{Ph}$, $J$ 7.3 Hz), 8.29 (s, 1H, CH=). $^{13}C$ NMR, $\delta$: 50.06 ($CH_2$), 84.28 (C-5), 100.11 (C-3a), 117.25 (CN), 127.63 (2CH), 128.57 (2CH), 128.97 (CH), 129.16 (CH), 132.79 (C), 136.97 (C), 144.39 (C-3), 151.95, 152.23 (C-4, C-7a), 153.27 (C-6). HRMS, *m*/*z*: 348.1237 $[M+Na]^+$ (calc. for $C_{20}H_{15}N_5Na$, *m*/*z*: 348.1220).

For the characteristics of compounds **1a**–**g**, **3b**–**g**, **4b**,**c**,**e** and **5b**,**c**,**e**, see Online Supplementary Materials.

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