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Convenient synthesis of pyrazolo[3,4-*b*]pyridin-3-ones and pyrazolo[3,4-*b*]pyridine-5-carbaldehyde using vinamidinium salts

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ABSTRACT

An expedient method for the synthesis of 2-phenyl-5-aryl-2,3-dihydropyrazolo[3,4-*b*]pyridin-3-ones and 2-phenyl-3-oxo-2,3-dihydropyrazolo[3,4-*b*]pyridine-5-carbaldehyde in a single-step via condensation of vinamidinium salts with 3-amino-1-phenyl-2-pyrazolin-5-one is described.

Heterocyclic compounds can serve as scaffolds on which pharmacophores can be arranged to yield potent and selective drugs. Pyrazolopyridines, due to their analogy with purines, have been the subject of many studies,[1,2] particularly in the context of their pharmacological properties; the four isomers [3,4-*b*], [3,4-*c*], [4,3-*c*] and [1,5-*a*] all display high biological activity.[3] Pyrazolo[3,4-*b*]pyridine derivatives have been studied as antiviral,[4] potential antimalarial agents,[5] compounds inhibiting cholesterol formation,[6] for the treatment of Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, drug and alcohol withdrawal symptoms, drug addiction and infertility.[7] They have also been reported as potent and selective inhibitors of A1 adenosine receptors[8] and phosphodiesterase 4 (PDE4) inhibitors in immune and inflammatory cells.[9] Typically, pyrazolo[3,4-*b*]pyridines are synthesized via the copper- and palladium-promoted cyclization reactions of 2-chloro-3-cyanopyridine with hydrazines,[10] the reaction of 5-aminopyrazoles with α,β-unsaturated ketones or their precursors, such as β-dimethyl-aminopropiophenones,[11] condensation reactions of 5-aminopyrazoles, dimedone, and aldehydes,[12] Friedländer-type condensation of 5-aminopyrazole-4-carbaldehydes with reactive α-methylene ketones,[13] cycloaddition reactions of pyrazolylimines with aromatic and aliphatic nitroalkenes under microwave irradiation,[14] and the reaction of dialdehydes with pyrazole and active methylene compounds under microwave irradiation.[15]

In continuation of our interest in the development of synthetic strategies to obtain functionalized heterocycles, we have concentrated our efforts on the preparation of such bioactive nitrogen-containing heterocycles, and have already reported simple and efficient procedures to synthesize interesting molecules, such as 2-pyridones[16–18] and pyrido[2,3-*d*]pyrimidines.[19]

Herein we report a novel synthetic approach for the preparation of pyrazolo[3,4-*b*]pyridine derivatives **3a–f** via the one-pot cyclocondensation of 3-amino-1-phenyl-2-pyrazolin-5-one (**1**) with vinamidinium salts **2a–f** under basic conditions (Scheme 1).

The following mechanism may be proposed for the formation of the substituted 2,3-dihydropyrazolo[3,4-*b*]pyridines **3** (Scheme 2). 3-Amino-1-phenyl-2-pyrazolin-5-one (**1**), on treatment with sodium hydride in DMF, undergoes a Michael type addition to vinamidinium salts **2** to give the intermediate enamine **4** after elimination of dimethylamine. The next step involves aza-annulation leading to the desired products **3** in good yields (Table 1). Alternatively, when the reaction was carried out using the salt **2f**[20] followed by treatment with 1 N HCl in THF, aldehyde **3f** was obtained. The aldehyde group in **3f** provides a synthetic handle for subsequent functionalization to a variety of different structures.

In conclusion, we have reported a simple and efficient method for preparing 2-phenyl-5-aryl-2,3-dihydropyrazolo[3,4-*b*]pyridin-3-ones **3a–e** and 2-phenyl-3-oxo-2,3-dihydropyrazolo[3,4-*b*]pyridine-5-carbaldehyde (**3f**) as precursors for new heterocyclic systems.

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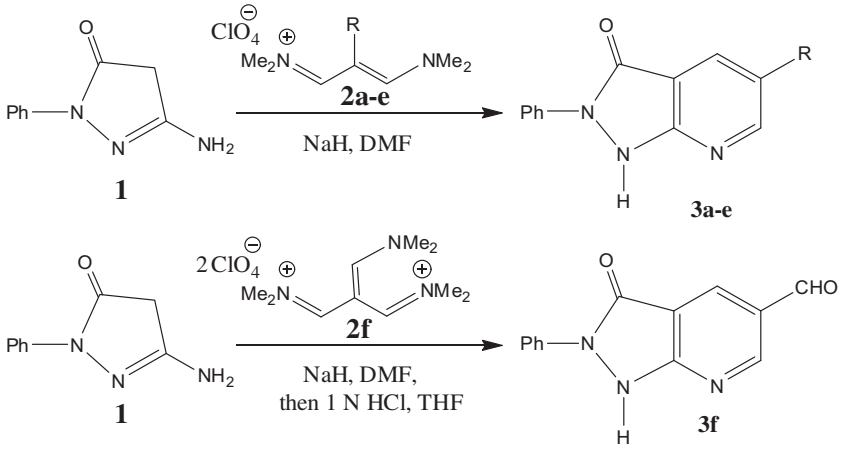
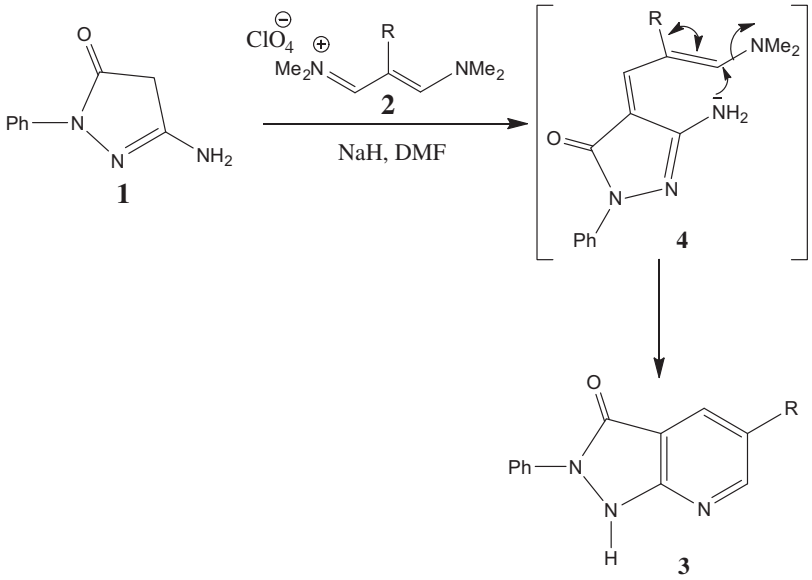


Scheme 1.



Scheme 2. A possible mechanism for the reaction shown in Scheme 1.

Table 1
Results of the reactions depicted in Scheme 1

Product[a]	R	Yield (%)
3a	Ph	92
3b	4-MeOC$_6$H$_4$	96
3c	1-Naphthyl	87
3d	4-MeC$_6$H$_4$	94
3e	4-ClC$_6$H$_4$	87
3f	CHO	81

[a] All products were characterized from their ^{1}H NMR, ^{13}C NMR and mass spectroscopic data.[20]

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20. *General procedure for the heteroannulation*: NaH (1 mmol) was suspended in DMF (8 mL), then 3-amino-1-phenyl-2-pyrazolin-5-one (**1**) (0.48 mmol) was dissolved in DMF (10 mL) and added slowly. The mixture was stirred for 30 min at 0 °C. Next vinamidinium salt **2** (0.48 mmol) was added and the resulting mixture heated at 80 °C for 6 h and the residue partitioned between CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried over Na_2SO_4, filtered and the solvents removed in vacuo. The crude residue was purified by column chromatography (10% EtOAc in hexane) to give products **3a**–**e**. For pyrazolo[3,4-*b*]pyridine **3f**, after evaporation of the solvent, THF (6 mL) and 1 N HCl (6 mL) were added. The mixture was allowed to stir at room temperature for 2 h, then neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 15 mL). Work-up and purification as above gave **3f**.

Representative spectral data of selected compounds

*2,5-Diphenyl-2,3-dihydropyrazolo[3,4-b]pyridin-3-one (**3a**)*. Yield: 92%; yellow solid; mp = 135–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.75 (s, 1H), 7.40–7.71 (m, 10H), 7.81 (d, 1H, *J* = 4.2 Hz), 8.1 (d, 1H, *J* = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 119.02, 125.99, 126.33, 127.43, 128.14, 129.13, 129.18, 129.30, 134.37, 135.38, 144.43, 150.09, 157.80, 166.06. Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.25; H, 4.56; N, 14.62. Found: C, 75.22; H, 4.54; N, 14.58. MS (EI, 30 eV): *m*/*z* = 287 (M^+).

*2-Phenyl-5-(4-methoxyphenyl)-2,3-dihydropyrazolo[3,4-b]pyridin-3-one (**3b**)*. Yield: 96%; yellow solid; mp = 141–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 6.87 (s, 1H), 7.10 (d, 2H, *J* = 8.7 Hz), 7.26 (m, 3H), 7.42 (d, 2H, *J* = 8.7 Hz), 7.83 (m, 2H), 8.19 (d, 1H, *J* = 4.3 Hz), 8.42 (d, 1H, *J* = 4.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 55.37, 114.65, 117.16, 125.72, 126.28, 126.30, 126.96, 129.53, 134.72, 136.13, 142.83, 151.49, 160.79, 162.51, 163.08. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.87; H, 4.74; N, 13.21. MS (EI, 30 eV): *m*/*z* = 317 (M^+).

*2-Phenyl-5-(4-chlorophenyl)-2,3-dihydropyrazolo[3,4-b]pyridin-3-one (**3e**)*. Yield: 87%; yellow solid; mp = 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15 (m, 3H), 7.35 (d, 2H, *J* = 8.7 Hz), 7.75 (m, 2H), 7.90 (d, 2H, *J* = 8.7 Hz), 8.20 (d, 1H, *J* = 4.3 Hz), 8.35 (s, 1H), 8.45 (d, 1H, *J* = 4.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 117.16, 125.51, 125.72, 126.28, 126.30, 128.18, 129.53, 134.13, 134.60, 135.17, 140.30, 151.38, 162.51, 163.08. Anal. Calcd for $C_{18}H_{12}N_3ClO$: C, 67.19; H, 3.76; N, 13.06. Found: C, 67.15; H, 3.72; N, 13.01%. MS (EI, 30 eV): *m*/*z* = 321 (M^+).

*2-Phenyl-3-oxo-2,3-dihydropyrazolo[3,4-b]pyridin-5-carbaldehyde (**3f**)*. Yield: 81%; yellow solid; mp = 147–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (m, 3H), 7.75 (m, 2H), 8.20 (s, 1H), 8.45 (d, 1H, *J* = 4.3 Hz), 8.96 (d, 1H, *J* = 4.3 Hz), 10.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 123.55, 125.33, 125.72, 126.28, 126.30, 128.89, 134.76, 152.59, 161.10, 162.35, 190.48.

Anal. Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.24; H, 3.77; N, 17.52. MS (EI, 30 eV): *m*/*z* = 239 (M^+).