Synthesis of new pyrazolo[3,4-*b*]pyridin-3-ones and pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one and study of the pyrazolic nitrogen reactivity

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Abstract

A convenient route to the synthesis of pyrazolo[3,4-*b*]pyridin-3-one and pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one *via* condensation of 3-amino-1-phenylpyrazolin-5-one with 2-pyrone derivatives followed by the alkylation of prepared compounds is described. Several reactions conditions were carefully studied.

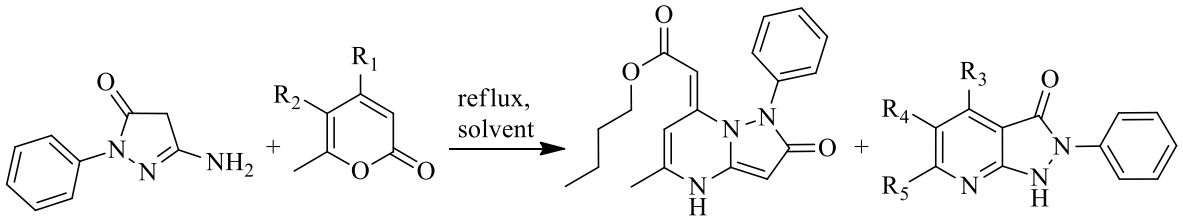
Keywords: Pyrazolone, 2-pyrone, pyrazolo[3,4-*b*]pyridin-3-one, pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one

Introduction

The interest for the synthesis of the pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine has increased in organic and pharmaceutical chemistry. These heterocyclic systems are found in a number of molecules possessing biological and/or pharmacological properties.[1-6] The literature indicates different synthetic approaches to these compounds and mentions two main processes: one reported by Kuczynski for the preparation of 3-aminopyrazolo[3,4-*b*] pyridines by reaction of 2-chloro-nicotinonitrile with some hydrazines in xylene or ethanol at reflux.[7] The same reaction was performed in the laboratory under milder conditions in the presence of copper iodide complexed with *o*-phenanthroline as catalyst, leads to excellent yields.[8] And others have been described by Quiroga on the condensation of the aminopyrazole with α,β-unsaturated

compounds. Of procedures described recently, by other authors, provide an easy method for the synthesis of pyrazolo[3,4-*b*]pyridine and pyrazolo[1,5-*a*]pyrimidine by reacting *N*-substituted or unsubstituted-pyrazol-5(4*H*)-one, aryl-oxoketene dithioacetals and alkyl amide in presence of KF-alumina as catalyst.[9]

Within the framework of our research on the development of a new route to the synthesis of polyheterocyclic compounds,[10-12] and following works already have been undertaken,[13-17-18] we report in this article the preparation of new pyrazolo[3,4-*b*]pyridin-3-ones and pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one by condensation of the 3-aminopyrazolone **1** and 2-pyrone derivative **2 (**Scheme 1).



1 **2a,b** **3** **4 -7**

R_1 = OH, CH_3
R_2 = H, $CO_2C_2H_5$

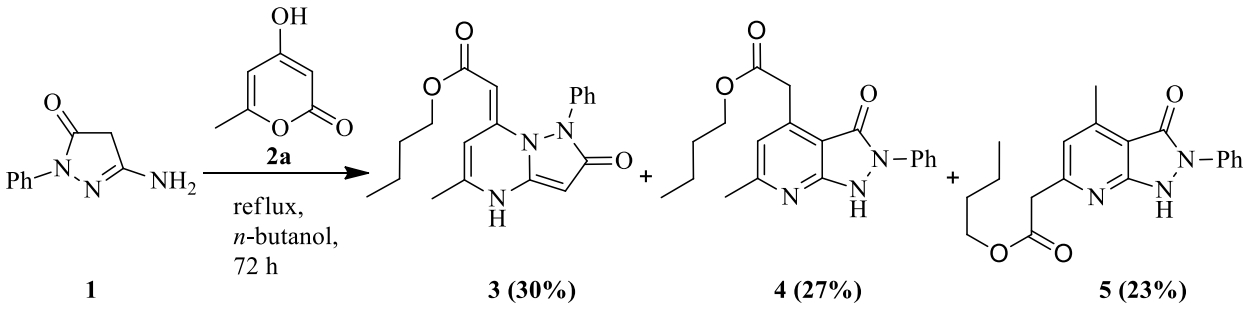
R_3 = CH_3, $CH_2CO_2C_4H_9$
R_4 = $CO_2C_2H_5$
R_5 = CH_3, $CH_2CO_2C_4H_9$

Scheme 1

Results and Discussion

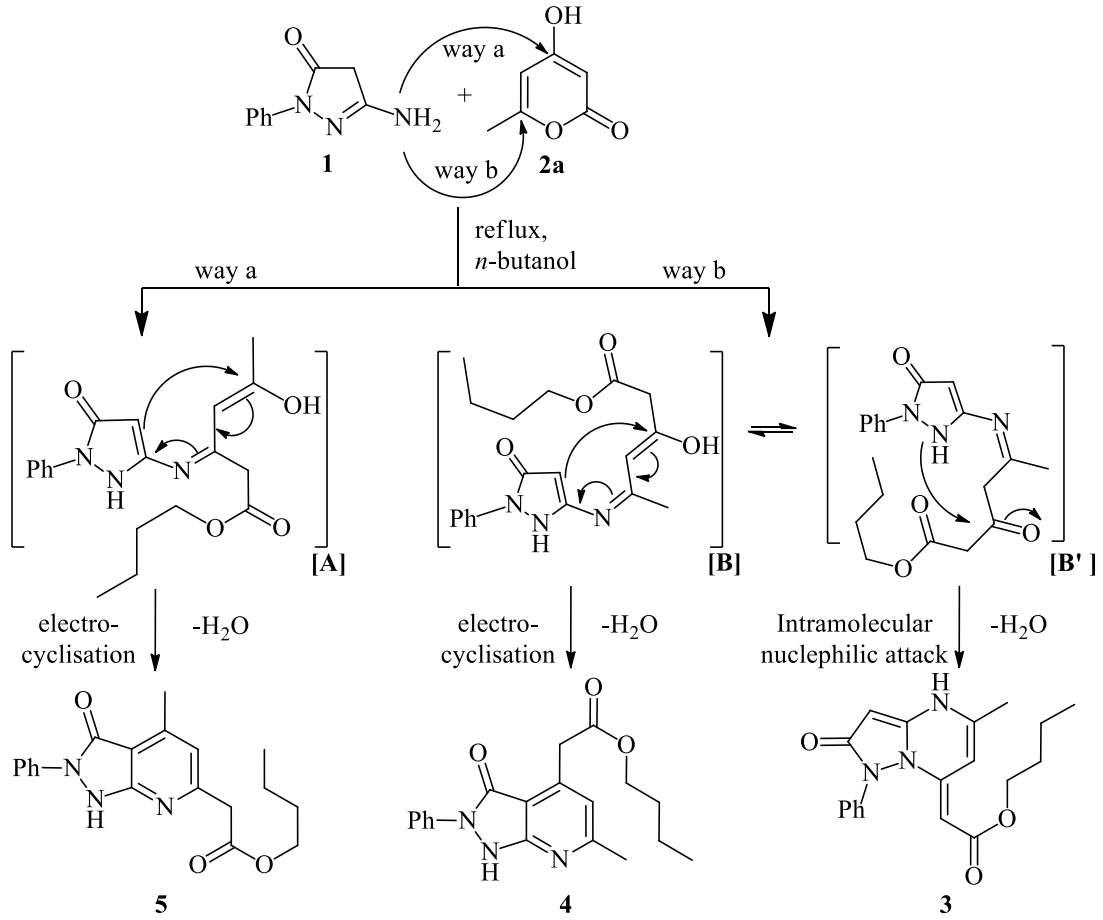
Synthesis of pyrazolo[3,4-*b*]pyridin-3-one and pyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one

Condensation of pyrazole 1 and 2-pyrone (2a). The treatment of 3-amino-1-phenylpyrazolin-5-one **1** with two equivalents of 4-hydroxy-6-methylpyran-2-one **2a**, in butanol at reflux during three days gave the compounds **3**, **4** and **5**. These products were separated by silica gel chromatography and their structures were confirmed by IR, ^{1}H NMR (250 MHz), ^{13}C NMR (62.9 MHz) and Mass spectra. After spectral analysis by NMR and masses, the compound **3** was identified as a pyrazolopyrimidinone; but the definitive identification of compounds **4** and **5** required 2D NMR-experiments (HMQC and HMC) (Scheme 2). In the case of the isomer **4**, the carbon at 157.0 ppm is assignable as the C-7a, and this carbon shows a cross-peak with the CH_2 at 3.62 ppm.



Scheme 2

Whereas, in the case of the isomer **5**, the methyl group at 2.25 ppm gives a cross-peak to carbon signal at 158.9 ppm corresponding to C-7a. The absence of CH_2 signal due to the methylene protons of the pyrazole **1** in ^{1}H NMR spectrum of the compounds **4** and **5**, shows that cyclization is carried out on the C-4 carbon of the pyrazole ring.



Scheme 3

The structure of compound **3** was confirmed by elemental analysis and spectroscopic data (^{1}H NMR, ^{13}C NMR and mass). The ^{1}H NMR spectra show the three signals, as a singlet at 4.24

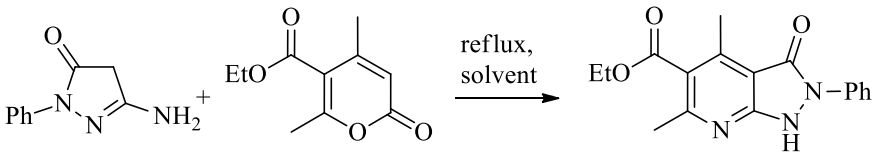
ppm, 4.83 ppm and 6.98 ppm, attributable to the olefin protons. According to these results, we propose a mechanism for the formation of compounds **3**, **4** and **5** (Scheme 3).

The ambivalent electrophilic nature of 2-pyrone resides on the possibility of presence, after opening the pyran ring, of three interrelated carbonyl entities, capable of modulating and accentuating the individual electronic character through inductive and tautomeric effects.[19]

In the case of α-keto esters [B'], the adjacent carboxyl moiety imparts the ketone with an enhanced electrophilic character due to its inductive withdrawal. However, this may be moderated by the presence of active protons due to keto/enol tautomerisation between [B] and [B']. The mechanism involves nucleophilic attack at two electrophilic positions. We suggest that the first attack of the primary amine of the phenylpyrazolinone to the 2-pyrone is carried out according the two pathways (a) and (b).

The intermediate [A] formed by attack at the pyranic carbon [C4] and opening of the cycle, undergo electrocyclisation at the pyrazolic carbon [C4] to lead to the pyrazolo[3,4-*b*]pyridin-3-one **5** after dehydration. In this same way, the intermediate [B] formed by reaction of the nucleophilic group at the pyranic carbon [C6] lead to the pyrazolo[3,4-*b*]pyridin-3-one **4**. On the other hand, the intermediate [B'] lead to 4,7-dihydropyrazolo[1,5-*a*]pyrimidin-2(1*H*)-one **3**, this last is attributable to the pyrazolic nitrogen attack at the C-4 position of 2-pyrone, after opening and isomerization by tautomerism. Finally, dehydration takes place, forming the product.

Condensation of pyrazole (1) and 2-pyrone (2b). The reaction of pyrazole **1** with ethyl isodehydracetate **2b** was carried out at reflux temperature of various linear aliphatic alcohols solvents for four days. These conditions allowed us to obtain in all cases the pyrazolopyridinone **6** in a range from 11-49% (Scheme 4). The best yield was obtained in butanol which presents the highest boiling point (Table 1). This fact explains the need of high temperature for the formation of compound **6**.



1 **2b** **6 (11-49%)**

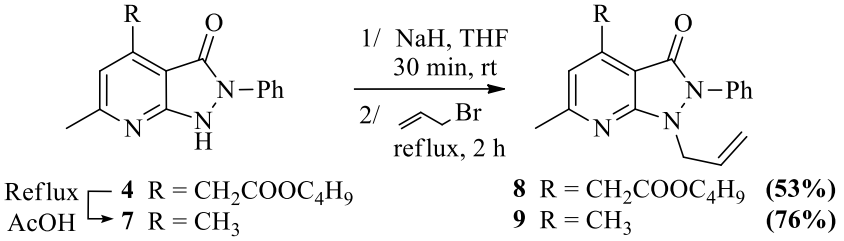
Scheme 4

Table 1. Synthesis of pyrazolo[3,4-*b*]pyridine **6** in different alcohols

Entry	Solvent	Yield (%)
1	MeOH	11
2	EtOH	18
3	BuOH	49

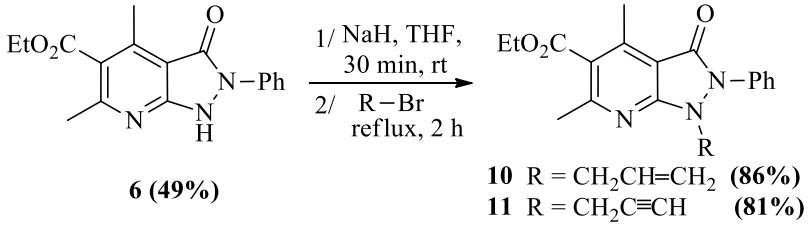
Synthesis of 1-substituted pyrazolopyridinones

The conditions used for the preparation of compound **7** were the same previously described by us for the synthesis of similar heterocyclic systems (Scheme 5).[18] The treatment of the pyrazolopyridinones **4** or **7** with allyl bromide in the presence of the sodium hydride in THF at reflux leads to the 1-allyl pyrazolopyridinones **8** or **9** respectively with moderate to good yields.



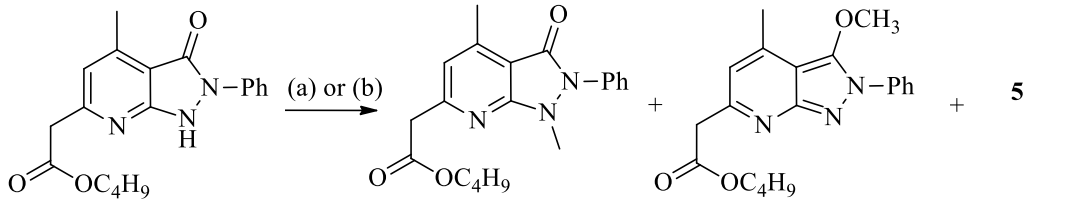
Scheme 5

The alkylation of the pyrazolo-pyridinic **6**, was prepared according the same procedure such as for the pyrazolopyridinone **4**. The pyrazolo-pyridinic **6** having two electron donating groups at the 4 and 6 positions and an electron withdrawing group at the 5 position treated with allyl or propargyl bromide led to the awaited compounds in good yield (Scheme 6).



Scheme 6

The alkylation at the first position of the pyrazolo[3,4-*b*]pyridin-3-ones **5** with iodomethane in the presence of triethylamine at room temperature, gave the desired compound **12** with a weak yield (Scheme 7). It should be noted that the followed conditions do not lead to total reaction.

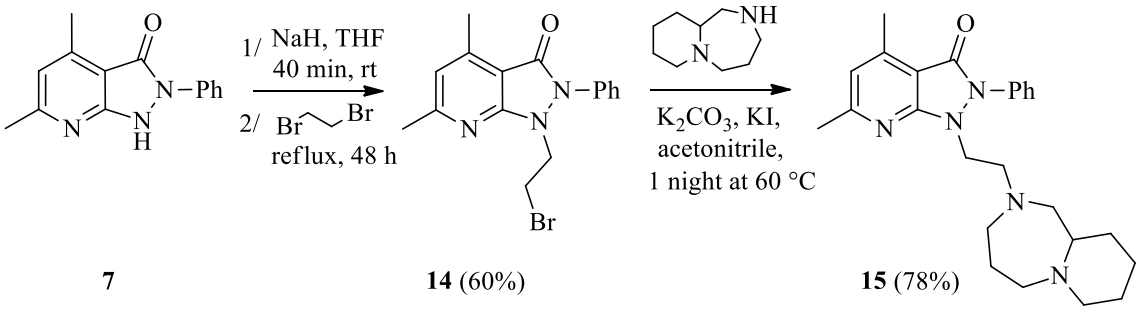


Scheme 7

On the other hand, using potassium carbonate as a base, can improve the yield of the product **12** which is around 47%. But next to the desired product, we have obtained a secondary product **13** with a yield of 21% due to *O*-methylation and tautomerization. This can be understood by considering a tautomer of the pyrazolic carbonyl by isomerization of pyridinic ring.[20]

Compounds **12** and **13** have identical molecular masses. But, the difference in chemical shifts of the methyl group makes it possible to allot the peak to 3.33 ppm in ^{1}H NMR to the compound **12** and that to 3.80 ppm to the compound **13**.

To diversify the nature of the substituent, we decide to introduce a bromoethane linker in order to incorporate a bicyclic structure such as a saturated pyridodiazepine in the pyrazolopyridinone **7**. Deprotonation of the pyrazolo[3,4-*b*]pyridin-3-one **7** with sodium hydride and further nucleophilic substitution with dibromoethane allows the alkylation at the first position of heterocyclic system isolating compound **14** in pure form with 60% yield. The substitution of the derivative **14** with the saturated pyridodiazepine [21] in acetonitrile, in the presence of potassium carbonate and a catalytic amount of potassium iodide allow us to isolate the desired compound **15** in good yield (Scheme 8).



Scheme 8

Conclusions

To summarize, we have studied the condensation of the 3-aminopyrazolone with 2-pyrone derivatives in various solvents for the synthesis of novel pyrazolo[3,4-*b*]pyridin-3-ones. Thereafter, we have shown that the *N*-1 of the pyrazolopyridinic skeleton can be easily and rapidly functionalized. In addition, the synthesized pyrazolo[3,4-*b*]pyridin-3-ones substituted by unsaturated groups, can be easily engaged in different further reactions.

Experimental Section

General. Melting points were obtained from one-end-open capillary tubes on a Büchi melting point apparatus and are uncorrected. All reagents were purchased either from Acros Organics or

Sigma Aldrich. Thin layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60 F-254). Infrared (IR) spectra were obtained on Perkin–Elmer Paragon 1000 PC FTIR. Infrared spectra were recorded using NaCl films or KBr pellets. ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a Bruker Advance DXP250 at 62.9 and 250 MHz, respectively. HMQC and HMBC data were recorded at 400 Hz (Varian-Unity 400). Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Perkin-Elmer SCIEX AOI 300 spectrometer. Elemental analysis data were taken on a Perkin–Elmer 240C elemental analytical instrument.

Synthesis of pyrazolo[1,5-*a*]pyrimidine and pyrazolo[3,4-*b*]pyridine

4-Hydroxy-6-methyl-pyran-2-one **2a (**720 mg, 5.71 mmol, 2 eq) was dissolved in 30 mL of *n*-butanol then 500 mg (2.86 mmol, 1 eq) of 3-amino-1-phenyl-pyrazole-5-one **1** were added. The mixture was heated at reflux during three days. After elimination of butanol under reduced pressure, the residue was then purified by column chromatography on silica gel (ethyl acetate-hexane, 4:6).

(5-Methyl-2-oxo-1-phenyl-2,4-dihydro-1*H*-pyrazolo[1,5-*a*]pyrimidin-7-ylidene)-acetic acid butyl ester (3). Yield 30%, as a white solid: m.p. 238-240 °C; IR (KBr) cm^{-1}: 1590, 1723 (CO); ^{1}H NMR (DMSO-*d_6): δ* (ppm) 0.80 (t, 3H, *J* = 7.2 Hz, CH_3), 1.11-1.25 (m, 2H, CH_2), 1.36-1.52 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 4.20 (t, 2H, *J* = 6,9 Hz, OCH_2), 4.24 (s, 1H, CH), 4.83 (s, 1H, CH), 6.98 (s, 1H, H-6), 7.13 (d, 2H, *J* = 7.5 Hz, H_{Ar}), 7.27 (t, 1H, *J* = 7.0 Hz, H_{Ar}), 7.42 (t, 2H, *J* = 7.5 Hz, H_{Ar}), 11.7 (s, 1H, NH); ^{13}C NMR (DMSO-*d_6): δ* (ppm) 13.9 (CH_3), 19.9 (CH_2), 19.9 (CH_3), 30.7 (CH_2), 62.5 (OCH_2), 72.8 (CH), 85.7 (CH), 96.4 (CH), 122.6 ($2CH_{Ar}$), 126.7 (CH_{Ar}), 129.2 ($2CH_{Ar}$), 138.1 (C_{Ar}), 141.1 (C_5), 143.5 (C_7), 151.7 (C_{3a}), 166.6 (C_2), 169.9 (CO); *m/z* (M+1) = 340. Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.35; H, 6.31; N, 12.31.

2-(6-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)-acetic acid butyl ester (4). Yield 36%, as an orange solid: m.p. 129–131 °C; IR (KBr) cm^{-1}: 1620, 1730 (CO), 3010 (NH); ^{1}H NMR ($CDCl_3$): *δ* 0.89 (t, *J* = 7.4 Hz, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 2.74 (s, 3H, CH_3), 3.62 (s, 2H, CH_2), 4.06 (t, *J* = 6.6 Hz, 2H, CH_2O), 6.86 (s, 1H, H_5), 7.26 (m, 1H, CH), 7.45 (m, 2H, CH), 7.86 (dd, *J* = 0.8, 8.4 Hz, 2H, CH), 14.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): *δ* 13.7 (CH_3), 17.3 (CH_3), 19.0 (CH_2), 30.4 (CH_2), 42.9 (CH_2), 65.2 (CH_2O), 109.5 (C_4), 119.5 (C_5), 119.7, 125.3, 129.0 (5CH), 137.1 (C_{Ar}), 150.8 (C_6), 156.7 (C_{3a}), 157.0 (C_{7a}), 159.6 (CON), 169.4 (CO); MS (EI): *m/z* 339 (M^+). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.34; H, 6.20; N, 12.44.

2-(4-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-acetic acid butyl ester (5). Yield 49%, as an orange solid: m.p. 114–116 °C; IR (KBr) cm^{-1}: 1670, 1740 (CO), 2960 (NH); ^{1}H NMR ($CDCl_3$): *δ* 0.90 (t, 3H, *J* = 7.2 Hz, CH_3), 1.36 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.15 (t, *J* = 6.6 Hz, 2H, CH_2O), 6.74 (s, 1H, H_5), 7.24 (m, 1H, CH), 7.42 (m, 2H, CH), 7.88 (dd, *J* = 0.8, 8.2 Hz, 2H, CH), 14.02 (s, 1H, NH); ^{13}C NMR

($CDCl_3$): δ 13.7 (CH_3), 19.1 (CH_2), 23.1 (CH_3), 30.5 (CH_2), 35.5 (CH_2), 65.3 (CH_2O), 108.3 (C_4), 117.9 (C_5), 120.0 (2CH), 125.4 (CH), 129.0 (2CH), 137.5 (C_{Ar}), 146.4 (C_6), 155.2 (C_{3a}), 158.9 (C_{7a}), 159.7 (CON), 169.8 (CO); MS (EI): *m/z* 339 (M^+). Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.18; H, 6.28; N, 12.40.

4,6-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid ethyl ester (6). Ethyl isodehydracetate **2b (**0.5 mL, 2.97 mmol, 1.3 eq) was introduced into a flask containing 20 mL of *n*-butanol then 400 mg (2.29 mmol, 1 eq) of 3-amino-1-phenyl-pyrazole-5-one **1** were added. The mixture was heated at reflux during four days. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica gel (ethyl acetate-hexane, 6:4). Yield 49%, as a orange solid: mp 160-162 °C; IR (KBr) cm^{-1}: 1663, 1701 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 1.38 (t, 3H, *J* = 8.8 Hz, CH_3), 2.27 (s, 3H, CH_3), 2.77 (s, 3H, CH_3), 4.39 (q, 2H, *J* = 8.8 Hz, CH_2), 7.21 (t, 1H, *J* = 9.6 Hz, H_{Ar}), 7.41 (t, 2H, *J* = 9.6 Hz, H_{Ar}), 7.86 (m, 2H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.8 (CH_3), 15.5 (CH_3), 23.0 (CH_3), 62.4 (CH_2), 109.6 (C_{3a}), 120.8 ($2CH_{Ar}$), 123.5 (C_5), 126.4 (CH_{Ar}), 129.8 ($2CH_{Ar}$), 138.0 (C_{Ar}), 151.2 (C_4), 155.0 (C_6), 158.4 (C_{7a}), 160.2 (C_3), 168.0 (CO); *m/z* (M+1) = 312. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.67; H, 5.58; N, 13.42.

(1-Allyl-6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)-acetic acid butyl ester (8). 42 mg (1.06 mmol, 1.2 eq) of sodium hydride 60% were suspended in 8 mL of THF, then 300 mg (0.88 mmol, 1 eq) of compound **4** were dissolved in 12 mL of THF and added slowly. The mixture was stirred for 30 min at room temperature. Then 0.116 mL (1.33 mmol, 1.5 eq) of allyl bromide in 3 mL of THF were added dropwise. The resulting mixture was heated at reflux for 2 hours. The THF was evaporated then the residue was taken up in water and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and were evaporated under pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexane, 4:6). Yield 53%, as a maroon solid: mp 78-80 °C; IR (KBr) cm^{-1}: 1626, 1736 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.84 (t, 3H, *J* = 7.5 Hz, CH_3), 1.20-1.33 (m, 2H, CH_2), 1.50-1.60 (m, 2H, CH_2), 2.64 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 4.08 (t, 2H, *J* = 6.6 Hz, OCH_2), 4.39 (d, 2H, *J* = 6.3 Hz, NCH_2), 4.88 (dd, 2H, *J* = 17.5 Hz, *J'* = 8.3 Hz, $=CH_2$), 5.27-5.39 (m, 1H, =CH), 6.85 (s, 1H, H_5), 7.21 (t, 1H, *J* = 6.0 Hz, H_{Ar}), 7.35-7.49 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.7 (CH_3), 17.3 (CH_3), 19.1 (CH_2), 30.6 (CH_2), 44.3 (CH_2), 51.0 (NCH_2), 65.0 (OCH_2), 109.4 (C_{3a}), 120.5 (C_5), 121.0 ($=CH_2$), 124.1 ($2CH_{Ar}$), 126.6 (CH_{Ar}), 129.1 ($2CH_{Ar}$), 129.6 (=CH), 135.0 (C_{Ar}), 149.8 (C_4), 158.7 (C_6), 160.8 (C), 161.6 (C_{7a} or C_3), 170.1 (CO); *m/z* (M+1) = 380. Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.76; H, 6.71; N, 10.95.

1-Allyl-4,6-dimethyl-2-phenyl-1,2-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-3-one (9). From the pyrazolopyridine **7** (180 mg, 0.75 mmol) and allyl bromide (0.098 mL, 1.13 mmol) following the procedure described above for compound **8** the title compound was obtained with 76% yield, as a maroon solid: mp 130-132 °C; IR (KBr) cm^{-1}: 1680 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.59 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.47 (d, 2H, *J* = 6.9 Hz, NCH_2), 4.92 (dd, 1H, *J* = 17.0 Hz, *J'* = 1.2 Hz, $=CH_2$), 5.00 (d, 1H, *J* = 10.4 Hz, $=CH_2$), 5.36-5.49 (m, 1H, =CH), 6.79 (s, 1H, H_5), 7.27-7.32 (m, 1H, H_{Ar}), 7.43-7.50 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.2 (CH_3), 25.0 (CH_3), 51.1

(NCH_2), 108.5 (C_{3a}), 120.3 (C_5), 120.9 (=CH_2), 124.1 (2CH_{Ar}), 126.5 (CH_{Ar}), 129.2 (2CH_{Ar}), 129.8 (=CH), 135.2 (C_{Ar}), 149.2 (C_4), 161.2 (C), 162.1 (C), 163.3 (C_6 or C_{7a} or C_3); *m/z* (M+1) = 280. Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.23; H, 6.21; N, 14.94.

1-Allyl-4,6-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid ethyl ester (10). From the pyrazolopyridine **6** (130 mg, 0.42 mmol) and allyl bromide (0.055 mL, 0.63mmol) following the procedure described above for compound **8** the title compound was obtained with 86% yield, as a maroon solid: mp 86-88 °C; IR (KBr) cm^{-1}: 1666, 1706 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 1.44 (t, 3H, *J* = 6.0 Hz, CH_3), 2.63 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.45 (m, 4H, OCH_2, NCH_2), 4.92 (d, 1H, *J* = 15.0 Hz, =CH_2), 5.03 (d, 1H, *J* = 8.5 Hz, =CH_2), 5.36-5.46 (m, 1H, =CH), 7.28-7.34 (m, 1H, H_{Ar}), 7.45-7.50 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.3 (CH_3), 14.7 (CH_3), 24.1 (CH_3), 50.7 (NCH_2), 61.7 (OCH_2), 107.9 (C_{3a}), 121.2 (=CH_2), 124.4 (2CH_{Ar}), 125.6 (C_5), 126.9 (CH_{Ar}), 129.2 (2CH_{Ar}), 129.5 (=CH), 134.8 (C_{Ar}), 147.8 (C_4), 159.9 (C), 160.9 (C), 161.6 (C_6 or C_{7a} or C_3); 168.3 (CO); *m/z* (M+1) = 352. Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.47; H, 6.11; N, 11.87.

4,6-Dimethyl-3-oxo-2-phenyl-1-prop-2-ynyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid ethyl ester (11). From the pyrazolopyridine **6** (150 mg, 0.48 mmol) and propargyl bromide (0.062 mL, 0.72 mmol) following the procedure described above for compound **8** the title compound was obtained with 81% yield, as a maroon solid: mp 126-128 °C; IR (KBr) cm^{-1}: 1677, 1709 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 1.41 (t, 3H, *J* = 6.1 Hz, CH_3), 2.02 (s, 1H, ≡CH), 2.61 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.42 (m, 4H, OCH_2, NCH_2), 7.24-7.31 (m, 1H, H_{Ar}), 7.40-7.49 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): *δ (ppm)* 14.2 (CH_3), 14.6 (CH_3), 23.9 (CH_3), 48.2 (NCH_2), 61.5 (OCH_2), 70.2 (≡CH), 86.3 (C≡C), 108.4 (C_{3a}), 123.4 (2CH_{Ar}), 124.8 (C_5), 126.5 (CH_{Ar}), 128.9 (2CH_{Ar}), 135.8 (C_{Ar}), 148.8 (C_4), 160.2 (C), 161.1 (C), 162.0 (C_6 or C_{7a} or C_3), 168.6 (CO); *m/z* (M+1) = 350. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.82; H, 5.57; N, 11.92.

(1,4-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-acetic acid butyl ester (12). Potassium carbonate (90 mg, 0.65 mmol, 1.2 eq) was suspended in 8 mL of CH_2Cl_2 and 200 mg (0.59 mmol, 1 eq) of pyrazolo[3,4-*b*]pyridin-3-one **5** dissolved in 8 mL of CH_2Cl_2 were added. After 20 min of stirring at room temperature, 0.055 mL (0.88 mmol, 1.5 eq) of iodomethane in 2 mL of CH_2Cl_2 were added. The mixture was stirred for 48 hours at room temperature. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic extracts were dried on $MgSO_4$ then evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 7:3). Yield 47%, as oil; IR (NaCl) cm^{-1}: 1673, 1734 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.87 (t, 3H, *J* = 7.4 Hz, CH_3), 1.28-1.40 (m, 2H, CH_2), 1.57-1.66 (m, 2H, CH_2), 2.63 (s, 3H, CH_3), 3.33 (s, 3H, NCH_3), 4.14 (t, 2H, *J* = 6.6 Hz, OCH_2), 4.17 (s, 2H, CH_2), 6.93 (s, 1H, H_5), 7.26-7.30 (m, 1H, H_{Ar}), 7.44-7.56 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.8 (CH_3), 19.2 (CH_2), 25.2 (CH_3), 30.7 (CH_2), 35.7 (CH_2), 38.1 (NCH_3), 65.3 (OCH_2), 107.3 (C_{3a}), 120.1 (C_5), 123.9 (2CH_{Ar}), 126.6 (CH_{Ar}), 129.2 (2CH_{Ar}), 135.0 (C_{Ar}), 144.1 (C_4), 161.0 (C), 162.0 (C), 164.1 (C_6 or C_{7a} or C_3); 170.2 (CO); *m/z* (M+1) =

354. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.06; H, 6.50; N, 11.81.

(4,7-Dimethyl-3-oxo-2-phenyl-3,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-acetic acid butyl ester (13). This compound was obtained with compound **11** (petroleum ether-ethyl acetate, 5:5). Yield 21%, as red solid: mp 134-138 °C; IR (KBr) cm^{-1}: 1731 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.91 (t, 3H, *J* = 7.4 Hz, CH_3), 1.33-1.40 (m, 2H, CH_2), 1.56-1.66 (m, 2H, CH_2), 2.48 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.15 (t, 2H, *J* = 6.8 Hz, OCH_2), 4.27 (s, 2H, CH_2), 6.23 (s, 1H, H_5), 7.12-7.19 (m, 1H, H_{Ar}), 7.40 (t, 2H, *J* = 8.0 Hz, H_{Ar}), 8.22 (d, 2H, *J* = 8.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.3 (CH_3), 19.7 (CH_2), 20.7 (CH_3), 31.2 (CH_2), 33.1 (OCH_3), 35.3 (CH_2), 65.2 (OCH_2), 110.2 (C_{3a}), 120.1 (C_5), 120.3 ($2CH_{Ar}$), 125.1 (CH_{Ar}), 129.3 ($2CH_{Ar}$), 140.6 (C_{Ar}), 147.8 (C_4), 149.2 (C_6), 150.7 (C_{7a}), 160.7 (C_3), 170.4 (CO); *m/z* (M+1) = 354. Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.04; H, 6.48; N, 11.83.

1-(2-Bromoethyl)-4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (14). Sodium hydride 60% (60 mg, 1.51 mmol, 1.8 eq) was suspended in 8 mL of THF then 200 mg (0.84 mmol, 1 eq) of 4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **7** dissolved in 10 mL of THF were added slowly. The mixture was stirred for 40 min at room temperature. Then 0.216 mL (2.51 mmol, 5 eq) of dibromoethane in 3 mL of THF were added to drop by drop. The resulting mixture was heated at reflux for 48 hours. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and were evaporated under pressure. The residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 6.5:3.5). Yield 60%, as a maroon solid: mp 84-86 °C; IR (KBr) cm^{-1}: 1656 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.59 (s, 3H), 2.68 (s, 3H), 3.25 (t, 2H, *J* = 7.3 Hz), 4.25 (t, 2H, *J* = 7.3 Hz), 6.81 (s, 1H), 7.28-7.35 (m, 1H), 7.45-7.53 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.3 (CH_3), 25.1 (CH_3), 25.9 (CH_2), 49.2 (NCH_2), 107.7 (C), 120.6 (CH), 124.0 (2CH), 126.0 (CH), 129.4 (2CH), 135.0 (C), 149.6 (C), 160.7 (C), 162.3 (C), 163.8 (C); *m/z* (M+1) = 347. Anal. Calcd for $C_{16}H_{16}BrN_3O$: C, 55.51; H, 4.66; N, 12.14. Found: C, 55.60; H, 4.58; N, 12.23.

1-(2-(Hexahydropyrido[1,2-*a*][1,4]diazepin-2(1*H*,3*H*,7*H*)-yl)ethyl)-4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (15). Under inert atmosphere, 45 mg (0.29 mmol, 1 eq) of decahydropyrido[1,2-*a*][1,4]diazepine were put in 8 mL of acetonitril then 120 mg (0.87 mmol, 3 eq) of potassium carbonate, 7 mg (0.43 mmol, 0.15 eq) of potassium iodide and 100 mg (0.29 mmol, 1 eq) of bromoethylpyrazolo[3,4-*b*]pyridin-3-one **14** were added. The resulting mixture was stirred overnight with 60 °C. The solvent was evaporated and the residue is taken again with water and extracted with CH_2Cl_2 (3 x 20 mL). The organic phases were dried over $MgSO_4$ and evaporated under pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2-MeOH-NH_4OH, 9:1:0.5). Yield 78%, as a maroon solid: mp 94-96 °C; IR (KBr) cm^{-1}: 1683 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 1.02-1.32 (m, 4H), 1.48-1.68 (m, 5H), 1.81-1.94 (m, 2H), 2.04-2.10 (m, 1H), 2.23-2.32 (m, 1H), 2.35-2.40 (m, 4H), 2.57 (s, 3H), 2.60-2.71 (m, 8H), 4.02 (t, 2H, *J* = 6.0 Hz), 6.75 (s, 1H), 7.24-7.30 (m, 1H), 7.44-7.58 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.3 (CH_3), 24.3 (CH_2), 25.1 (CH_3), 26.0 (CH_2), 27.4 (CH_2), 31.2 (CH_2), 46.0

(CH_2), 54.0 (CH_2), 55.6 (CH_2), 55.7 (CH_2), 57.3 (CH_2), 61.1 (CH_2), 65.6 (CH), 107.3 (C), 119.5 (CH), 123.4 (2CH), 126.2 (CH), 129.2 (2CH), 135.5 (C), 149.1 (C), 161.9 (C), 162.2 (C), 162.8 (C); *m/z* (M+1) = 420. Anal. Calcd for $C_{25}H_{33}N_5O$: C, 77.57; H, 7.93; N, 16.69. Found: C, 77.68; H, 7.85; N, 16.80.

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